ALKYLATIONS OF 1,2-ALTERNATE CALIX[4]ARENE

Thesis

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DEDICATION

I would like to thank my family and friends who have helped me along the way, especially my wife who has been there for me throughout my college years. A special thanks also goes to Dr. M. T. Blanda who gave me confidence and drive to accomplish this goal and to Dr. D. A. Feakes who gave me the passion to pursue chemistry as a life-long career.

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ABSTRACT

A 1,2-alternate calix[4]arene conformer (25, 26-dibenzoyloxy-27, 28-dihydroxy calix[4]arene) was synthesized from the more common 1,3-dibenzoyloxy flattened cone conformer. The 1,2-alternate conformer was exhaustively alkylated with methyl, ethyl, and *n*-propyl tosylate. The 1,2-alternate conformation was conserved during methylation while in the ethylation and propylation, the products were a 1,3-alternate 1,3-diester and a partial cone 1,3-diester.

The 1,2 alternate calix[4]arene was also alkylated in a stepwise fashion to find the pathway for the exhaustive alkylation process. Methyl and *n*-propyl tosylate were used as the alkylating agents in the first alkylation of the 1,2-alternate conformer. The 1,2-alternate diester stereochemistry was retained with the methyl tosylate, however, in the case of the *n*-propyl tosylate, the reaction yielded 1,2-dibenzoyloxy calix[4]arene in cone and partial cone conformations. The second methylation stayed in the 1,2-alternate 1,2-diester orientation, as in the exhaustive alkylation. Likewise, the second propylation yielded the same 1,3-alternate diester and 1,3-diester partial cone conformations as did in the exhaustive alkylations.

It was determined that size of the electrophile determines whether migration of the ester will happen. In the case of the methyl tosylate, no

migration occurred, where as in the case of the ethyl and *n*-propyl tosylate, migration did occur. However, in the alkylation of ethyl and propyl, the 1,2-diester orientation was preserved after the first alkylation, but during the second alkylation, there was a migration of the 1,2-diester to the 1,3-diester.

1.0 INTRODUCTION

1.1 Background of Calixarenes

Phenol-aldehyde condensations generally result in the formation of a very complex mixture of oligomeric products, [1] however, under specific reaction conditions some phenols yield macrocyclic products. [2] Under these conditions, phenols bearing alkyl groups in the para position give mainly tetra-, hexa-, and octameric macrocycles (see **Figure 1.1**). [3] These macrocyclic compounds range in size with the number of repeating phenol units determining the size (4-20). [4] Of all the known macrocycles, the tetrameric macrocycle is by far the most studied and applied. [5]

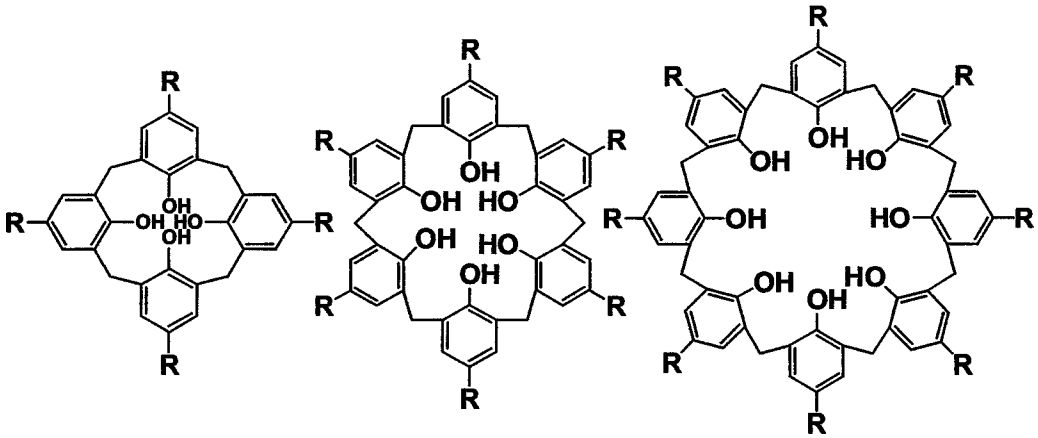


Figure 1.1: Diagrams of a (1a) tetrameric, (1b) hexameric and (1c) octameric calixarenes.

In 1966, Dr. David Gutsche, who is responsible for the major initial advancements in the calixarene field, [4,5] coined the name 'calix[4]arene' after looking at the CPK molecular model of the cyclic tetramer. [6] The name is derived for the Latin *calix* because of the vase-like structure that these macrocycles assume when all the aromatic rings are oriented in the same direction and *arene* which indicates the presence of aryl groups. [6] This name was extended to all of the larger known macrocycles. The bracketed number between calix and arene represents the number of repeating phenol units in the macrocycle. For example, the cyclic tetramer obtained from *p*-t-butylphenol is named *p*-t-butylcalix[4]arene.

These macrocycles were discovered in an era when supramolecular chemistry was in its growing phase. Calixarenes filled a great need of easily available and synthetically versatile building blocks for the construction of receptor molecules able to perform specific supramolecular functions. One attraction was the basket shaped cavity containing a lipophilic interior made up of aromatic nuclei. This structural feature helped to better understand weak intermolecular forces such as cation/π and CH/π interactions. [3]

More recently, the calixarene cavity has been exploited as an additional binding site for apolar groups in receptors which use the strategy of multipoint interactions in the recognition of polyfunctional guest. [7] Other applications of their Host-Guest complexing ability, [8] recognition of neutral molecules in solution and in gas phase, [9] spherical metal ion recognition, [10] hosts for quaternary cations, [11] anion receptors, [12] self-assembly, [13] and catalytic systems. [14]

1.2 Representations of Calixarenes

Calixarenes are big in size, thus the difficulty in naming and numbering the compounds. Calixarenes were first referred to as cyclischenmehrker-n-methylene-phenolverbindungen. According to the Chemical Abstracts, calix[4]arenes are named based on the numbering system in **Figure 1.2**. For example, calix[4]arenes with *t*-butyl groups at the para positions is named 5,11,17,23-tetra-*tert*-butyl-25,26,27,28-tetrahydroxycalix[4]arene.

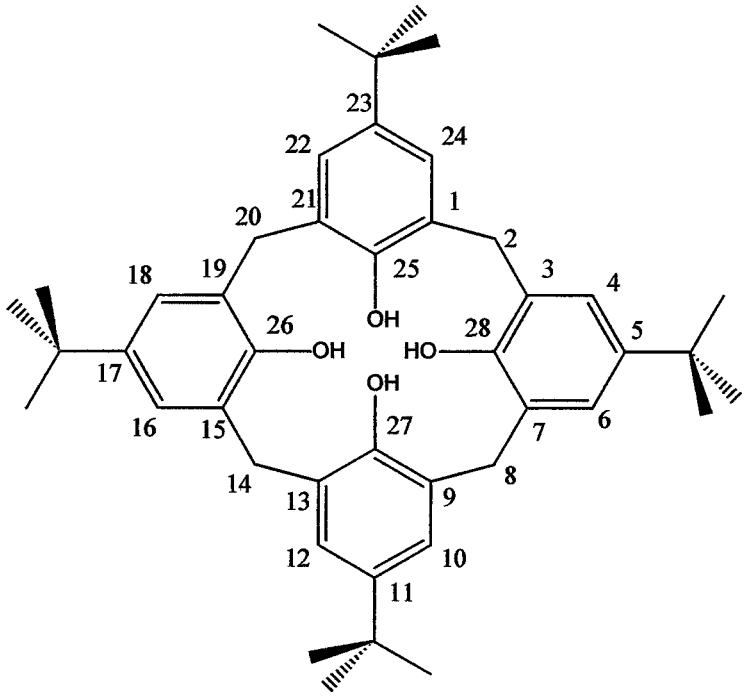


Figure 1.2: Numbering pattern for calix[4]arene.

Calix[n]arenes are generally depicted with the oxygenated aryl carbons oriented downward and the para carbons oriented upward. The region represented

by the hydroxyl groups in **Figure 1.3** is referred to as the *lower rim* and the region represented by the *tert*-butyl groups is referred to as the *upper rim.* [15]

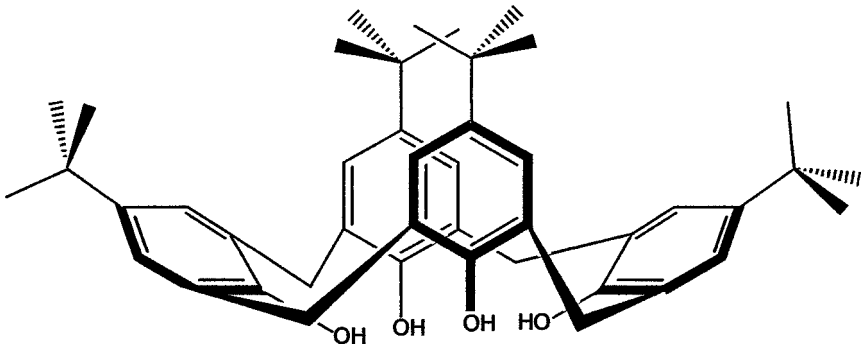


Figure 1.3: Face designation of calix[4]arenes.

Many procedures have been developed to synthesize calixarenes throughout the years. However, the most general and useful procedure is the one-step, base-induced condensations of *p*-substituted phenols and formaldehyde. [3] With base variations, such as counter ions and molar equivalence, this method gives good yields of the even numbered calixarene products (calix[n]arenes where n = 4,6,8), especially with phenols substituted at the para positions with t-butyl groups. [16] An advantage of having the alkyl groups at the para positions, is that they can be easily removed giving the unsubstituted calix[n]arenes, thus allowing the introduction of other functional groups on the aromatic nuclei at the upper rim.

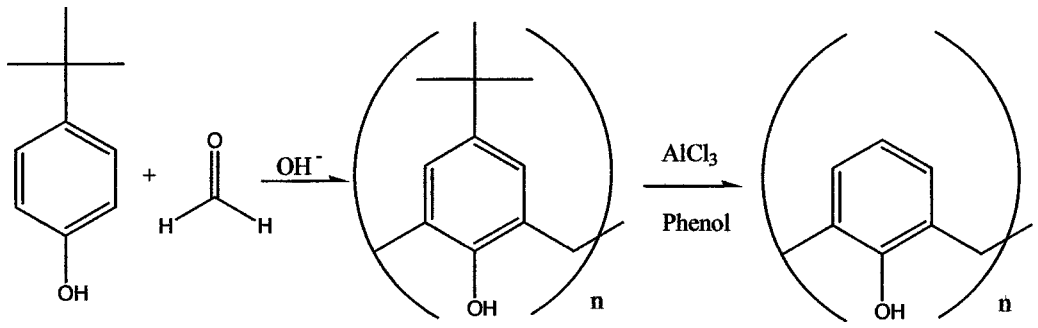


Figure 1.4: General reaction scheme for synthesis of calix[n]arene.

Calix[4]arenes are well known for their conformational mobility. The mobility of calix[4]arenes is due to the phenolic residue undergoing ring inversion by passing the oxygen atom through the annulus of the macrocycle. Due to the inversion, calix[4]arenes have four different conformations. The four conformers are cone, partial cone, 1,2-alternate, and 1,3-alternate (see **Figure 1.5**). In the cone conformation, all R groups, para to the hydroxyl groups, are oriented in the same plane and is represented as (u, u, u, u). Partial cone occurs when one of the R groups is oriented in a different plane than the other three R groups (u, u, u, d). In the case of 1,2-alternate, two adjacent (proximal) R groups are oriented in the same plane while the remaining two R groups are oriented in a different plane (u, u, d, d). The 1,3-alternate conformer is similar, however, two nonadjacent (distal) R groups are in a different plane than the other two distal R groups (u, d, u, d), see **Figure 1.5**.

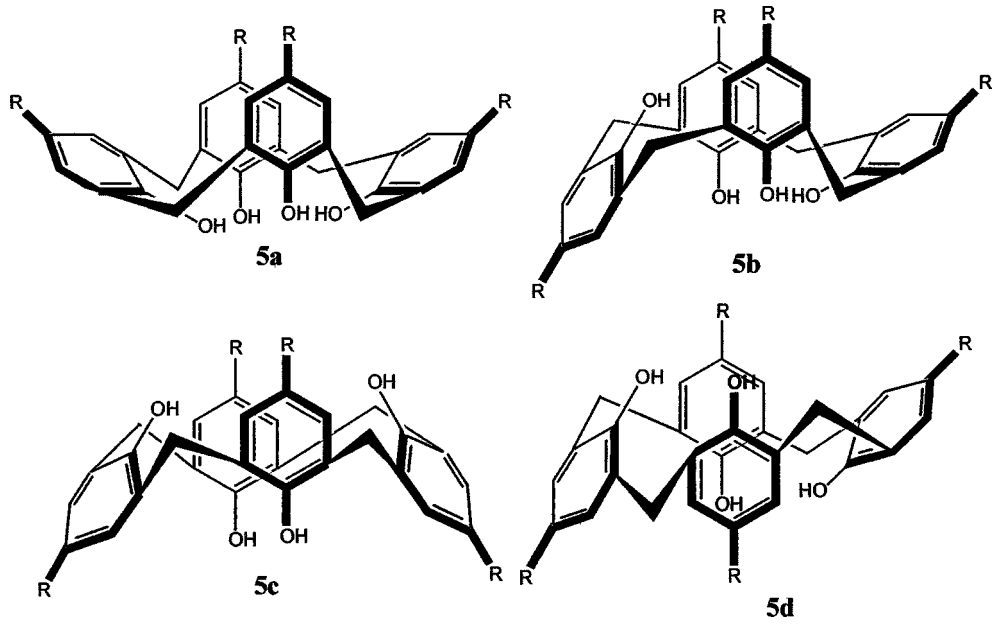


Figure 1.5: The four conformers of calix[4]arene: Cone (5a), Partial Cone (5b), 1,3-Alternate (5c), 1,2-Alternate (5d).

The conformation of calix[4]arenes can be identified by NMR spectroscopy via the de Mendoza rule. [17] The methylene carbons that connect two adjacent phenolic residues have distinct NMR patterns. There are two orientations that the four methylene carbons can have, *syn* orientation and *anti* orientation (see **Figure 1.6**). When two adjacent R groups are in the same plane, the orientation is *syn*. [11A] When two adjacent R groups are in opposite planes, the orientation is *anti*. [11A]

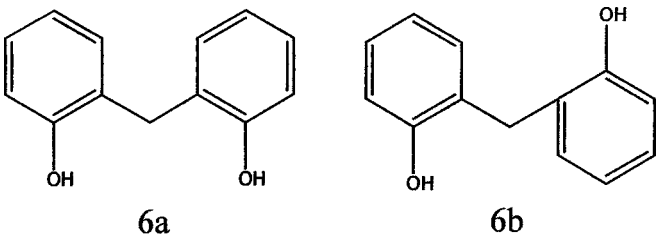


Figure 1.6: Representation of *Syn* Orientation (6a) and *Anti* Orientation (6b).

In the ^{1}H-NMR spectra of the cone conformation of an non-alkylated calix[4]arene, a pair of doublets between 3 and 4.5 ppm illustrates that the two methylene hydrogens are diastereotopic. In the ^{13}C-NMR spectra, the $ArCH_2Ar$ carbons exhibit one singlet signal at approximately 31 ppm. For the 1,3-alternate conformer, the ^{1}H-NMR spectra exhibits a singlet at 3.8 ppm while in the ^{13}C NMR spectra, one singlet signal appears at approximately 38 ppm. For the ^{1}H-NMR and ^{13}C-NMR spectra of partial cone and 1,2-alternate, very similar spectra are obtained in the methylene region (31-38 ppm). In the case of the ^{1}H-NMR spectrum, the two pairs of doublets signals and a singlet signal appear at 4.1 ppm, 3.2 ppm, and 3.8 ppm respectively. In the ^{13}C-NMR spectra, two singlet signals appear at approximately 30 and 37 ppm. The signal at 37 ppm denotes the two *anti* methylene groups and the signal at 30 ppm denotes the two *syn* methylene groups.

1.3 Functionalization of Calix[4]arenes

1.3.1 Functionalization at the Phenolic Hydroxy Groups (Lower Rim)

Functionalization of the phenolic hydroxy groups represent an excellent method for the introduction of groups which modify the shape and the complexing properties of these molecules. [2]

1.3.1.1 Complete Functionalization

The complete functionalization of the phenolic hydroxy groups has been performed using a variety of alkylating agents and in different reaction conditions.

Depending on the reaction conditions, selective conformations of calix[4]arenes can be obtained as well as mixtures of cone, partial cone, 1,2-alternate, and 1,3-alternate stereoisomers. [3] However, the alkylating groups have to be larger than ethyl, otherwise inversion will occur due to the rotation of the small group though the annulus.

Alkylation of calix[4]arenes using sodium hydride as the base and N,N-dimethyl-formamide (DMF) or tetrahydrofuran (THF)/DMF as the solvent system will predominately give the cone conformation as the product. [18] In this example, the proximal (adjacent phenoxy nuclei) 1,2-dialkylated products are considered to be intermediates with the sodium cation acting as the template. [19] If the base is changed to cesium carbonate and the solvent to acetonitrile, the 1,3-alternate conformer is produced in relatively high yields. [20] To obtain the partial cone conformer in mediocre yields, potassium t-butoxide is used as the base with benzene as the solvent. [18] Up until five years ago, the 1,2-alternate conformer was not synthesized in high yield. In 1997, Ungaro *et. al* reported the 1,2-alternate conformation in high yield due to a template effect involving a larger and "softer" cation that can coordinate with the two "soft" aromatic walls thus giving a preference to the rare 1,2-alternate conformer. [21] This mechanistic picture for the formation of the four different stereoisomers is rather complex due to the many different factors influencing the stereochemical outcome of these reactions. [18] Although, to increase the formation of the cone conformer over all other conformers, it is possible to generalize of all the factors by increasing the

rate of alkylation (substrate, solvent, cation, alkylating agent, temperature, etc.) or decrease the rate of ring inversion (templating cation, solvent, etc.). [2]

1.3.1.2 Selective Functionalization

In the past two decades, many synthetic methods have been developed for the selective functionalization of calix[4]arenes at the lower rim. [2] **Figure 1.7** gives the solvent and base conditions to successfully arrive at the desired functionalized calix[4]arene conformer. [2]

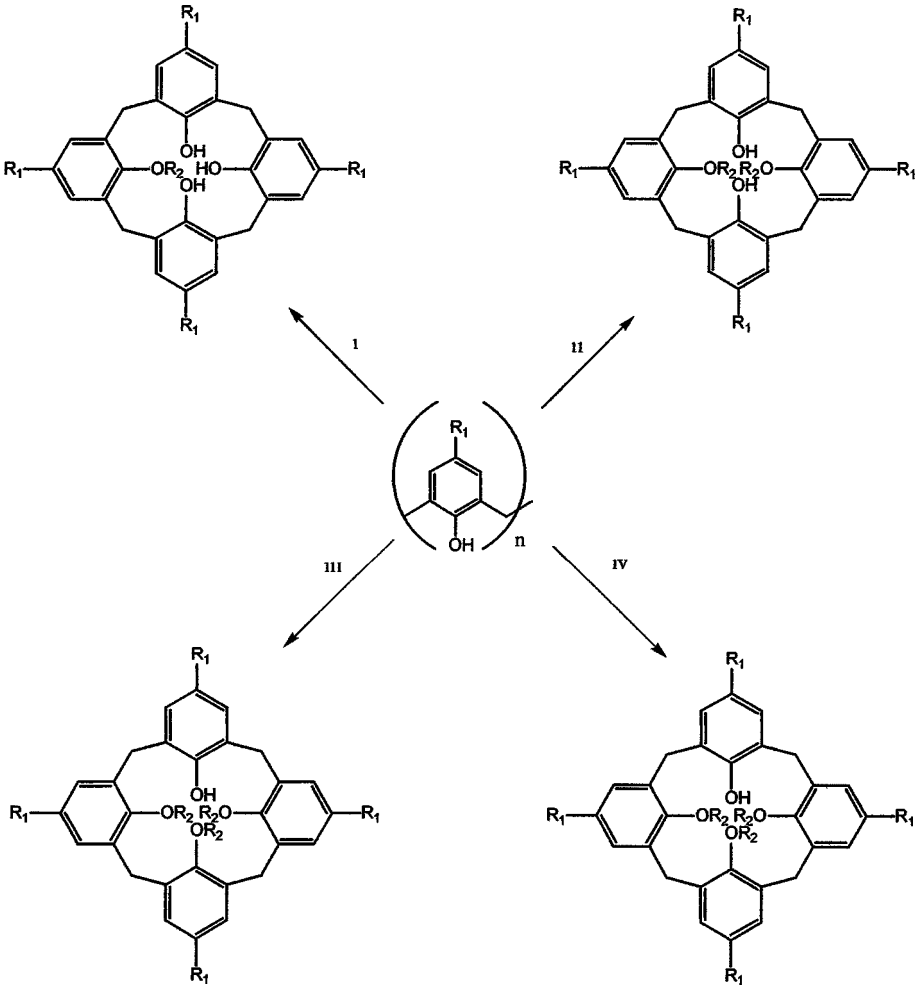


Figure 1.7: Reaction wheel for the selective functionalization. (i) CsF, DMF (ii) K_2CO_3, MeCOMe or MeCN (iii) BaO, $Ba(OH)_2$, DMF (iv) NaH, DMF.

There is great difficulty in selective alkylation of calixarenes at the lower rim because with each alkylation, the pK_a for the calixarene increases (9-12). It is difficult to obtain accurate pK_a values due to the apolar solvents that these reactions are usually performed in. However, with the current available data on water-soluble calixarenes, it has been concluded that the first hydroxy group is much more acidic than the others. [2] It is thought that the conjugate anion can be stabilized by two intramolecular hydrogen bonds and the second dissociation occurs at the distal position. By using 1.2 molar equivalence of a weak base in DMF or MeCN and an excess of alkylating agent a good yield of monoalkylated calixarene can be obtained. [22] For the functionalization of the distal 1,3-alternate calix[4]arene, a slight excess of a weak base, cesium carbonate, and a slight excess of the alkylating agent in acetonitrile will produce the conformer in high yield. The direct dialkylation of proximal 1,2-alternate calix[4]arene has been achieved by using NaH in DMF and 2.2 equivalence of the alkylating agent. [19] While in the case of the trialkylated calix[4]arene, alkyl halides in the presence of BaO-$Ba(OH)_2$ as the base are used. [23]

1.3.2 Functionalization at the Aromatic Nuclei (Upper Rim)

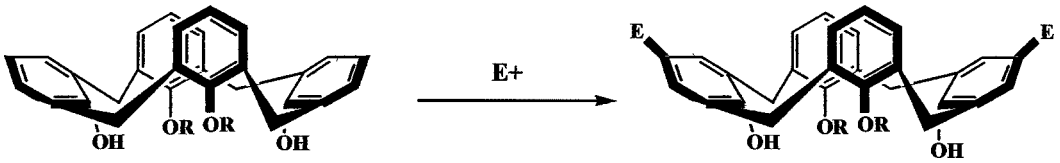
Functionalization of calix[4]arenes can also be accomplished at the upper rim of the molecules. The *t*-butyl groups of the *p-t*-butyl calix[4]arenes can be easily removed from the upper rim by transalkylation using $AlCl_3$ and an acceptor solvent such as toluene. [2]

1.3.2.1 Complete Functionalization

The complete functionalization can be performed to introduce new hydrophilic groups on the aromatic nuclei, such as $SO_3^-Na^+$, $CH_2NMe_3^+$, or even $CH_2PO(ONa)_2$, to deepen the lipophilic cavity for the inclusion of neutral molecules. More recent upper rim functionalizations (reaction conditions provided by Gutsche), include nitration, sulfonation, bromination, iodination, acylation, and chloromethylation. [15]

1.3.2.2 Selective Functionalization

The selective upper rim functionalizations on specific phenol rings of calixarenes builds on its reputation as being versatile in molecular recognition. Differences in reactivity of phenols and phenol ethers in aromatic transformations and in oxidation processes play a vital role in the selective functionalization. [24] Examples of 1,3-(diametrical) substitutions are reported in **Figure 1.8.**



E=Br, NO_2, CH_2NMe_2, CHO, etc

Figure 1.8: Selective 1,3 (diametrical) substitution.

Selective removal of the *p-t*-butyl groups from the phenolic nuclei is another approach to selective functionalization. Starting with 1,3-dialkoxy-*p-t*-butyl calix[4]arene (see **Figure 1.9**), *para* position of the phenols are available for functionalization with mild $AlCl_3$ conditions. [24]

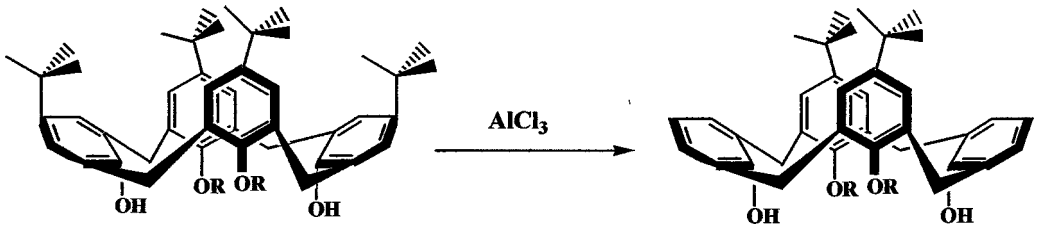


Figure 1.9: Selective removal of 1,3 (diametrical) *t*-butyl groups.

1.4 Synthesis of 1,2-Alternate Conformer

As reported earlier, a template effect of a "soft" cation governs the synthesis of the proximal 1,2-alternate conformer. Blanda *et. al* reported that a "soft" cesium ion, from a carbonate base promotes the conversion of a 1,3-benzoate ester in cone conformation to the 1-2-alternate conformer via rearrangement. [25] The theory is that the carbonate base generates the phenolate ion(s) necessary to initiate the rearrangement according to the mechanism shown in **Figure 1.10**. [25] In the mechanism, the key step is the formation of the tetrahedral intermediate **B**, which has been implicated in similar intramolecular migrations. [26]

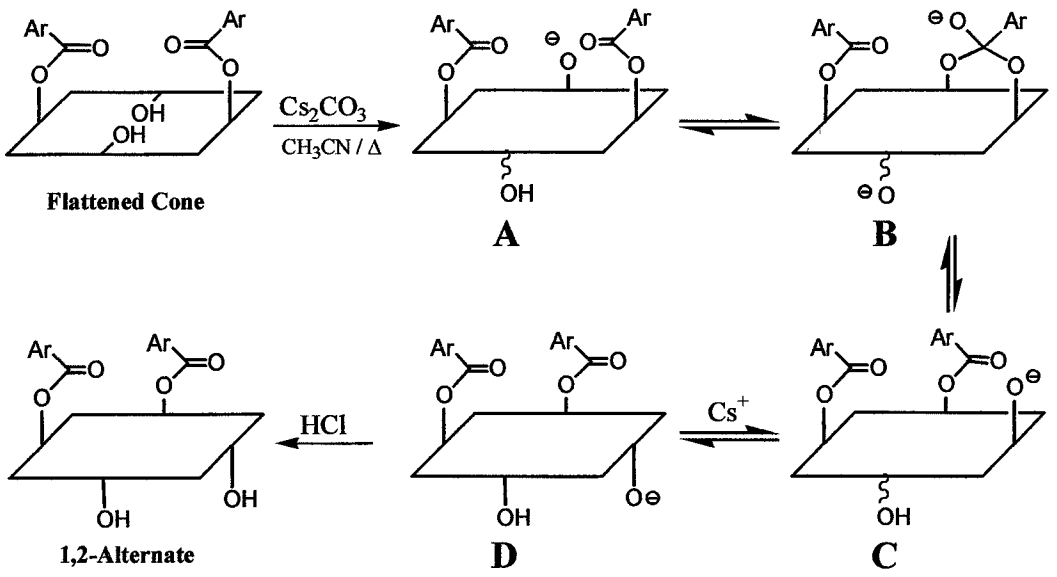
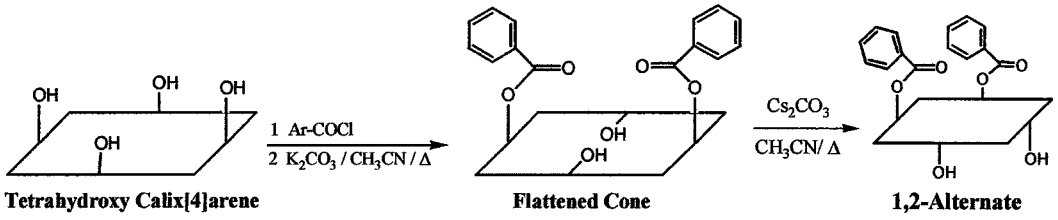


Figure 1.10: Mechanism showing the formation of the 1,2-alternate conformer from the more common flattened cone.

In route to the 1,2-alternate conformer (**Figure 1.11**), synthesis of the flattened cone (**11B**) was completed by suspending tetrahydroxy calix[4]arene (**11A**) in refluxing acetonitrile in the presence of potassium carbonate and benzoyl chloride. Within two hours of reaction time, high stereoselectivity of the flattened cone was obtained in high yield. The product existed in the flattened cone conformation in solution and was verified by ^{1}H and ^{13}C NMR. In the spectrum, a doublet of doublets for the *endo* and *exo* methylenes of the Ar-CH_2-Ar protons at 3.90-3.49 ppm confirmed the structure due to its C_{2V} symmetry. [25] Due to an addendum to the de Mendoza rule, [17] the singlet signal of the methylenes of the Ar-CH_2-Ar carbons at 32 ppm in the ^{13}C spectrum was verified.

Synthesis of 1,2-alternate was completed by suspending the 1,3-alternate flattened cone conformer in refluxing acetonitrile with 10 molar equivalents of cesium carbonate for 24 hours. The ^{13}C NMR data for the methylenes of the Ar-

CH_2-Ar showed to have the signal patterns for the known *anti* and *syn* oriented carbons, respectively at 37.08, 30.78, and 29.52 ppm. [25]



Tetrahydroxy Calix[4]arene **Flattened Cone** **1,2-Alternate**

11A **11B** **11C**

Figure 1.11: Synthetic procedure for 1,2-alternate calix[4]arene.

2.0 EXPERIMENTAL

2.1 Materials

All solvents were purchased from EM Scientific and were used as received. All reagents used in synthesis were purchased from Aldrich and were used without further purification, including the starting material, 4-*tert*-butyl calix[4]arene. All reactions were carried out in flame dried round-bottom flasks and under a dry argon atmosphere. For identification characterizations, analytical thin layer chromatography (TLC) was performed on precoated silica gel plates (Silica Gel 1B2-F) as the solid support. For purification purposes, column chromatography was used with silica gel (Silica Gel IB2-F, 60-200 Mesh [75-250 micron]). For structural identification, a 400 MHz Varian NMR was used to obtain ^{1}H-NMR and ^{13}C-NMR spectra. Chloroform-*d* ($CDCl_3$) was the solvent used with tetramethylsilane (TMS) as the internal standard. The chemical shifts (δ) were reported relative to the internal standard and the residual chloroform signals and are expressed in ppm.

2.2 Synthesis

2.2.1 Synthesis of 25, 26, 27, 28-tetrahydroxy calix[4]arene (1)

To a flame dried two-neck, 2 L round-bottom flask, equipped with a mechanical stirrer, 4-*tert*-butyl calix[4]arene (25.15 g, 0.03814 mol) was dissolved in 1 L of toluene. To the solution, phenol (21.91 g, 0.2326 mol) was added along with aluminum chloride (41.39 g, 0.3101 mol). The aluminum chloride was added slowly in small portions. The reaction was allowed to stir under argon at room temperature for 72 h. Approximately 500 mL of 2 N HCl was added to the round-bottomed flask to quench to the solution. After 30 min., the solution was transferred to a 2 L separatory funnel. The organic layer was isolated in the separatory funnel and washed two more times with 2 N HCl (2x 150 mL). The organic layer was isolated, dried over anhydrous magnesium sulfate and filtered. The solution was concentrated under reduced pressure to approximately 50 mL. The concentrate was poured slowly into approximately 700 mL of stirring methanol to precipitate the product. The precipitate was filtered via vacuum filtration to give 15.81 g (96%) of compound **1**, a fine white powder. **^{1}H-NMR** ($CDCl_3$) δ: 3.50 (d, 4H), 3.96 (d, 4H), 5.50 (s, 2H), 6.69 (t, 2H), 6.78 (t, 2H), 6.89 (d, 2H), 7.02 (d, 4H), 7.51 (t, 4H), 7.69 (t, 2H), 8.34-8.36 (d, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 31.683, 122.226, 128.219, 128.955, 148.739.

2.2.2 Synthesis of 25, 27-dibenzoyloxy-26, 28-dihydroxy calix[4]arene (2)

To a three-neck, 1 L round-bottom flask, equipped with a reflux condenser, 10.0 g (23.6 mmol) of compound **1** were suspended in 500 mL of acetonitrile. To the suspension, 5.75 mL (50.0 mmol) of benzoyl chloride was added via syringe along with 3.59 g of potassium carbonate (25.9 mmol). The reaction mixture was stirred at reflux for 3 h under argon. After 3 h, the reaction was cooled to room temperature. To the reaction flask, 400 mL of 2 N HCl was added to quench the solution and precipitate the product. After 0.5 h of stirring, compound **2** was collected via vacuum filtration and washed with 500 mL of methanol to yield 12.24 g (82%) of a fine white powder. **^{1}H-NMR** ($CDCl_3$) δ: 3.50 (d, 4H), 3.96 (d, 4H), 5.50 (s, 2H), 6.69 (t,2H), 6.78 (t, 2H), 6.89 (d, 2H), 7.02 (d, 4H), 7.51 (t, 4H), 7.69m (t, 2H), 8.34-8.36 (d, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 32.449, 119.898, 126.664, 128.105, 128.940, 129.122, 129.213, 130.533, 132.285, 133.893, 145.432, 152.797, 164.541.

2.2.3 Synthesis of 25, 26-dibenzoyloxy-27, 28-dihydroxy calix[4]arene (3)

To a two-neck, 2 L round-bottom flask, equipped with a reflux condenser, 10.0 g (15.8 mmol) of compound **2** was suspended in 1 L of acetonitrile. To the suspension, 3.09 g (31.6 mmol) of cesium carbonate was added. The suspension was stirred at reflux for 2 h under argon. The mixture was allowed to cool to room temperature. The solvent was reduced to dryness under reduced pressure. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 150 ml)

with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered, and reduced to approximately 50 mL under reduced pressure. The concentrate was slowly poured into approximately 700 mL of hexanes to precipitate the product. The product **3** was then filtered via vacuum filtration and washed with 200 mL of hexanes to yield 8.37 g (83%) of a fine white powder. **^{1}H-NMR** ($CDCl_3$) δ: 3.50 (d, 1H), 3.51 (d, 1H), 3.91 (d, 2H), 3.92 (d. 1H), 4.00 (d, 2H), 4.05 (d, 1H), 6.22 (s, 2H), 6.50 (t-2H), 6.70 (d, 2H), 6.88 (t, 4H), 7.14-7.31 (m, 12H), 7.42-7.45 (m, 2H): **^{13}C-NMR** ($CDCl_3$) δ: 29.346, 30.734, 37.197, 120.686, 125.306, 126.770, 127.916, 127.984, 128.151, 128.227, 128.811, 129.220, 129.395, 129.949, 130.047, 131.557, 132.308, 132.710, 134.697, 147.153, 151.583, 165.124.

2.2.4 Synthesis of 25,26-dibenzoyloxy-27-28-dimethoxy calix[4]arene (4)

To a 500 mL round-bottom flask, 2.00 g (3.16 mmol) of compound **3** was added along with 300 mL of acetonitrile and 4.12 g (12.6 mmol) of cesium carbonate. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 15 min. Once at reflux, 1.91 mL (12.6 mmol) of methyl *p*-toluenesulfonate was added to the reaction mixture via syringe. After 4 h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under vacuum. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 150 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude material was analyzed by TLC and the separation

of compounds **4A** and **4B** (85% and 5% yield, respectively) was achieved by column chromatography on silica gel (100 % Dichloromethane). **4A**. **^{1}H-NMR** ($CDCl_3$) δ: 3.00 (s, 6H), 3.23 (d,2H), 3.39 (d, 1H), 3.59 (d, 2H), 3.76 (d, 2H), 4.19 (d, 1H), 6.58 (d, 3H), 6.69 (t, 3H), 6.86 (t, 4H), 7.02 (t, 4H), 7.16 (m, 8H), 7.33 (m, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 28.557, 29.794, 37.311, 59.970, 122.848, 124.722, 127.840, 128.113, 128.507, 128.758, 128.826, 129.387, 129.569, 130.389, 132.543, 132.596, 132.725, 133.461, 135.653, 147.790, 157.348, 165.405.

2.2.5 Synthesis of 25, 27-dibenzoyloxy-26, 28-diethoxy calix[4]arene (5)

To a 500 mL round-bottom flask, 2.00 g (3.16 mmol) of compound **3** was added along with 300 mL of acetonitrile and 4.12 g (12.6 mmol) of cesium carbonate. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 15 min. Once at reflux, 2.53 g (12.6 mmol) of compound **10** was added to the reaction mixture. After 4 h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under reduced pressure. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 150 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude material was observed on TLC and the separation of compounds **5A**, and **5B** (45% and 30% yield, respectively) was achieved by column

chromatography on silica gel (100% Chloroform). **5A** (1,3-Alternate). **^{1}H-NMR** ($CDCl_3$) δ: 1.23-1.27 (m, 6H), 3.36 (d, 4H), 3.64-3.73 (m, 8H), 6.33 (t, 2H), 6.48 (d, 4H), 6.91 (t, 2H), 7.10 (d, 4H), 7.50 (t, 4H), 7.68 (t, 2H), 7.82 (d, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 15.555, 37.046, 66.668, 121.650, 124.062, 127.992, 128.993, 130.525, 131.140, 131.458, 132.953, 133.529, 133.886, 147.775, 156.871, 164.892. **5B** (Partial Cone). **^{1}H-NMR** ($CDCl_3$) δ: 0.72 (t, 3H), 1.33 (t, 3H), 3.05 (d, 2H), 3.45 (d, 2H), 3.70-3.80 (m, 8H), 6.42 (d, 2H), 6.64 (t, 2H), 6.81-6.90 (m, 2H), 6.99-7.03 (m, 6H), 7.53 (t, 4H), 7.64 (t, 2H), 6.28 (d, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 14.774, 15.821, 31.197, 36.484, 67.662, 67.996, 121.559, 122.833, 124.123, 28.348, 128.507, 129.084, 129.463, 129.850, 130.662, 131.238, 132.839, 133.590, 134.273, 136.548, 146.288, 154.860, 157.591, 165.283.

2.2.6 Synthesis of 25, 27-dibenzoyloxy-26, 28-dipropyloxy calix[4]arene (6)

To a 500 mL round-bottom flask, 1.50 g (2.37 mmol) of compound **3** was added along with 300 mL of acetonitrile and 3.09 g (9.48 mmol) of cesium carbonate. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 15 min. Once at reflux, 2.03 g (9.48 mmol) of compound **11** was added to the reaction mixture via syringe. After 4 h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under vacuum. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 150 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to

dryness. The crude material was analyzed using TLC and the separation of compounds **6A** and **6B** (31% and 48% yield, respectively) was achieved by column chromatography on silica gel (100% Chloroform). **6A** (1,3-Alternate). **^{1}H-NMR** ($CDCl_3$) δ: 0.89 (t, 6H), 1.73 (t, 4H), 3.60 (d, 4H), 3.58-3.68 (m, 8H), 6.33 (t, 2H), 6.47 (d, 4H), 6.88 (t, 2H), 7.10 (d, 4H), 7.50-7.54 (m, 5H), 7.84-7.87 (m, 5H): **^{13}C-NMR** ($CDCl_3$) δ: 10.245, 23.589, 6.85, 73.465, 121.506, 124.017, 127.992, 128.143, 128.386, 128.424, 128.697, 129.031, 129.167, 130.237, 130.510, 131.246, 131.534, 132.915, 133.567, 133.704, 147.715, 157.197, 164.494. **6B** (Partial Cone). **^{1}H-NMR** ($CDCl_3$) δ: 0.47 (t, 3H), 0.98 (t, 3H), 1.36 (m, 2H), 1.82-1.89 (m, 2H), 3.07 (d, 2H), 3.74-3.53 (m, 4H), 3.71-3.75 (m, 6H), 6.35 (d, 2H), 6.62 (t, 2H), 6.83 (t, 1H), 6.95 (t, 1H), 7.00-7.06 (m, 6H), 7.55 (t, 4H), 7.66 (t, 2H), 8.26 (d, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 9.016, 10.541, 21.851, 23.953, 31.341, 36.166, 74.390, 74.717, 121.301, 122.659, 124.130, 128.416, 128.447, 129.251, 129.494, 129.653, 130.556, 130.654, 131.162, 132.816, 133.620, 134.166, 136.457, 146.425, 155.338, 157.963, 65.321.

2.2.7 Synthesis of 25, 26-dibenzoyloxy-27-methoxy-28-hydroxy calix[4]arene (7)

To a three neck, 1 L round-bottom flask, 2.00 g (3.16 mmol) of compound **4** was added along with 500 mL of acetonitrile and 0.93 g (2.8 mmol) of cesium carbonate. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 20 min. Once at reflux, 0.95 mL (6.3 mmol) of methyl *p*-toluenesulfonate was added to the reaction

mixture via syringe. After 4 h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under vacuum. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 150 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude material was analyzed using TLC and the separation of compounds **7A** (or **7B**) and **7C** (80% and 10% yield, respectively) was achieved by column chromatography on silica gel (100% Dichloromethane). **7A** or **7B**. **^{1}H-NMR** ($CDCl_3$) δ: 3.24 (s, 1H), 3.46-3.59 (m, 5H), 3.86-4.10 (m, 6H), 6.34 (t, 2H), 6.63-7.51 (m, 21H): **^{13}C-NMR** ($CDCl_3$) δ: 29.035, 31.220, 37.888, 37.979, 60.850, 119.935, 125.010, 125.450, 125.663, 127.764, 127.809, 128.128, 128.257, 128.310, 128.416, 128.507, 129.084, 129.463, 129.562, 129.782, 129.933, 130.548, 132.209, 132.588, 152.994. **7C**. **^{1}H-NMR** ($CDCl_3$) δ: 3.31-3.84 (m, 11H), 6.50-8.43 (m, 24H): **^{13}C-NMR** ($CDCl_3$) δ: 32.373, 37.402, 56.063, 119.708, 125.109, 125.541, 125.951, 127.734, 127.779, 128.083, 128.439, 128.788 128.197, 129.091, 129.152, 129.236, 129.463, 129.569, 130.290, 130.434, 130.753, 130.889, 131.087, 131.261, 132.535, 132.846, 133.165, 133.453, 133.559, 133.651, 133.742, 146.668, 152.782, 164.426.

2.2.8 Synthesis of 25, 26-dibenzoyloxy-27-propyloxy-28-hydroxy calix[4]arene (8)

To a three neck, 1 L round-bottom flask, 5.00 g (7.90 mmol) of compound **4** was added along with 500 mL of acetonitrile and 2.30 g (7.11 mmol) of cesium

carbonate. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 20 min. Once at reflux, 3.40 g (15.8 mmol) of compound **11** was added to the reaction mixture via syringe. After 4 h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under reduced pressure. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 150 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude material was analyzed using TLC and the separation of compounds **8A** and **8B** (33% and 45% yield, respectively) was achieved by column chromatography on silica gel (90% Dichloromethane and 10% Hexanes). **8A**. **^{1}H-NMR** ($CDCl_3$) δ: 0.51 (t, 3H), 1.01-1.11 (m, 1H), 1.23-1.31 (m, 1H), 3.42 (m, 4H), 3.81-3.93 (m, 2H), 6.46 (t, 2H), 6.58 (t, 2H), 6.63 (t, 2H), 6.80-6.89 (m, 5H), 7.06-7.27 (m, 10H): **^{13}C-NMR** ($CDCl_3$) δ: 9.578, 21.912, 29.050, 31.501, 37.569, 38.161, 74.747, 119.890, 124.532, 125.109, 125.405, 127.582, 127.696, 127.734, 127.802, 128.022, 128.151, 128.257, 128.295, 128.515, 128.909, 129.311, 129.402, 129.562, 129.653, 129.683, 129.789, 130.108, 130.108, 130.578, 131.481, 131.564, 132.209, 132.262, 132.551, 133.696, 133.886, 134.584, 146.455, 147.426, 152.706, 153.214, 164.737, 165.427. **8B**. **^{1}H-NMR** ($CDCl_3$) δ: 0.53 (t, 3H), 1.03 (m, 2H), 3.23-3.55 (m, 6H), 3.94-4.25 (m, 4H), 6.43-6.74 (m, 9H), 7.02-7.43 (m, 10H), 7.79 (d, 2H), 8.69 (d, 2H): **^{13}C-NMR** ($CDCl_3$) δ: 10.465, 22.276, 30.044, 30.484, 31.152, 31.372, 78.805, 118.987, 124.669, 124.798, 125.981, 127.225, 127.764, 127.976, 128.090,

128.356, 128.378, 128.826, 128.947, 129.016, 129.046, 129.372, 129.600, 130.138, 131.784, 131.845, 131.959, 132.884, 133.233, 133.431, 133.673, 135.524, 136.010, 145.408, 147.123, 152.076, 153.275.

2.2.9 Synthesis of 25, 27-dibenzoyloxy-26, 28-dimethoxy calix[4]arene (4A)

To a 100 mL round-bottom flask, 0.23 g (0.36 mmol) of compound **7A** was added along with 0.23 g (0.72 mmol) of cesium carbonate and 50 mL of acetonitrile. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 0.5 h. Once at reflux, 0.10 mL (0.72 mmol) of compound **11** was added to the reaction mixture via syringe. After 4 h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under vacuum. The residue was then taken up in 100 mL of dichloromethane and transferred to a 500 mL separatory funnel. The organic layer was washed three times (3x 50 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to approximately 10 mL and poured slowly into stirring 300 mL of cold methanol for precipitation. The precipitate (**4A**) was filtered via vacuum filtration to give 78% yield of an off white powder. **4A**. **^{1}H-NMR** ($CDCl_3$) δ: 3.00 (s, 6H), 3.23 (d, 2H), 3.39 (d, 1H), 3.59 (d, 2H), 3.76 (d, 2H), 4.19 (d, 1H), 6.58 (d, 3H), 6.69 (t, 3H), 6.86 (t, 4H), 7.02 (t, 4H), 7.16 (m, 8H), 7.33 (m, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 28.557, 29.794, 37.311, 59.970, 122.848, 124.722, 127.840, 128.113, 128.507, 128.758, 128.826,

129.387, 129.569, 130.389, 132.543, 132.596, 132.725, 133.461, 135.653, 147.790, 157.348, 165.405.

2.2.10 Synthesis of 25,27-dibenzoyloxy-26, 28-dipropyloxy calix[4]arene (6A) (1,3-Alternate)

To a 250 mL round-bottom flask, 1.25 g (1.85 mmol) of compound **8A** was added along with 0.90 g (3.70 mmol) of cesium carbonate and 125 mL of acetonitrile. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 0.5 h. Once at reflux, 0.60 g (3.70 mmol) of compound **11** was added to the reaction mixture via syringe. After 4h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under vacuum. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 100 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude material was analyzed using TLC and the isolation of compound **6A** (60% yield) was achieved by column chromatography on silica gel (95% Dichloromethane and 5% Hexanes). **6A** (1,3-Alternate). **^{1}H-NMR** ($CDCl_3$) δ: 0.89 (t, 6H), 1.73 (t, 4H), 3.60 (d, 4H), 3.58-3.68 (m, 8H), 6.33 (t, 2H), 6.47 (d, 4H), 6.88 (t, 2H), 7.10 (d, 4H), 7.50-7.54 (m, 5H), 7.84-7.87 (m, 5H): **^{13}C-NMR** ($CDCl_3$) δ: 10.245, 23.589, 6.85, 73.465, 121.506, 124.017, 127.992, 128.143, 128.386, 128.424, 128.697, 129.031, 129.167, 130.237, 130.510, 131.246, 131.534, 132.915, 133.567, 133.704, 147.715, 157.197, 164.494.

2.2.11 Synthesis of 25, 27-dibenzoyloxy-26, 28-dipropyloxy calix[4]arene (6B) (Partial Cone)

To a 250 mL round-bottom flask, 1.25 g (1.85 mmol) of compound **8B** was added along with 0.90 g (2.8 mmol) of cesium carbonate and 125 mL of acetonitrile. The reaction mixture was stirred under argon and heated until the reaction reached refluxing temperature, approximately 0.5h. Once at reflux, 0.60 g (2.8 mmol) of compound **11** was added to the reaction mixture via syringe. After 4 h, the heat was turned off and the reaction was allowed to cool for 15 min. The solvent was reduced to dryness under vacuum. The residue was then taken up in 250 mL of dichloromethane and transferred to a 1 L separatory funnel. The organic layer was washed three times (3x 100 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude material was observed on TLC and the isolation of compound **6B** (75% yield) was achieved by column chromatography on silica gel (90% Chloroform and 10% Petroleum ether). **6B**. **^{1}H-NMR** ($CDCl_3$) δ: 0.47 (t, 3H), 0.98 (t, 3H), 1.36 (m, 2H), 1.82-1.89 (m, 2H), 3.07 (d, 2H), 3.74-3.53 (m, 4H), 3.71-3.75 (m, 6H), 6.35 (d, 2H), 6.62 (t, 2H), 6.83 (t, 1H), 6.95 (t, 1H), 7.00-7.06 (m, 6H), 7.55 (t, 4H), 7.66 (t, 2H), 8.26 (d, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 9.016, 10.541, 21.851, 23.953, 31.341, 36.166, 74.390, 74.717, 121.301, 122.659, 124.130, 128.416, 128.447, 129.251, 129.494, 129.653, 130.556, 130.654, 131.162, 132.816, 133.620, 134.166, 136.457, 146.425, 155.338, 157.963, 165.321.

2.2.12 Rearrangement Control Studies (3) and (9).

To a 500 mL round bottom flask, 2.00 g (3.16 mmol) of **3** was added to the flask along with 300 mL of acetonitrile. To the suspension, 4.12 g (12.6 mmol) of Cs_2CO_3 was added and brought up to reflux. The reaction was allowed to run for 24 h. After 24 h, the reaction was allowed to cool down to room temperature, approximately 20 min, followed by the addition of 30 mL of 2N HCl. The reaction mixture stirred for 15 min. The solution was reduced to dryness under vacuum and the residue was taken up in 100 mL of dichloromethane. The solution was then transferred to a 500 mL separatory funnel and washed three times (3x 50 mL) with 2 N HCl. The organic layer was dried over magnesium sulfate, filtered and reduced to dryness. The crude material was observed on TLC and the isolation of compounds **3** and **9** (80% and 5% yield, respectively) was achieved by column chromatography on silica gel (100% Dichloromethane). **3**. **^{1}H-NMR** ($CDCl_3$) δ: 3.50 (d, 1H), 3.51 (d, 1H), 3.91 (d, 2H), 3.92 (d. 1H), 4.00 (d, 2H), 4.05 (d, 1H), 6.22 (s, 2H), 6.50 (t-2H), 6.70 (d, 2H), 6.88 (t, 4H), 7.14-7.31 (m, 12H), 7.42-7.45 (m, 2H): **^{13}C-NMR** ($CDCl_3$) δ: 29.346, 30.734, 37.197, 120.686, 125.306, 126.770, 127.916, 127.984, 128.151, 128.227, 128.811, 129.220, 129.395, 129.949, 130.047, 131.557, 132.308, 132.710, 134.697, 147.153, 151.583, 165.124. **9**. **^{1}H-NMR** ($CDCl_3$) δ: 3.68-3.92 (m, 4H), 6.34 (t, 2H), 6.72 (t, 2H), 6.86 (d, 4H), 6.99 (d, 4H), 7.03-7.08 (m, 6H), 7.15 (d, 4H): **^{13}C-NMR** ($CDCl_3$) δ: 31.326. 34.300. 120.975. 121.862. 127.324. 128.136. 128.174. 128.242. 128.568. 128.788. 128.970. 129.903.

129.971. 131.246. 131.542. 132.642. 133.157. 133.362. 133.992. 149.216. 150.764. 164.123.

2.2.13 Synthesis of ethyl *p*-toluenesulfonate (10)

To a 1 L Erlenmeyer flask, 30.0 g (157 mmol) of *p*-toluenesulfonyl chloride was added to 500 mL of pyridine. The solution was stirred until all *p*-toluenesulfonyl chloride dissolved. Once dissolved, 8.30 mL (143 mmol) of ethanol was added to the solution. The Erlenmeyer flask was then covered with parafilm and placed in a freezer for 72 h. The flask was removed from the freezer and the pyridine hydrochloride crystals were removed via vacuum filtration. The mother liquor was slowly added to 1.2 L of stirring iced water. The tosylate **(10)** precipitated out of solution. After the ice was completely melted, the reaction mixture was transferred to a 2 L separatory funnel and 400 mL of diethyl ether was added. The layers were separated and two more extractions were completed using 200 mL of diethyl ether for each extraction. All organic layers were collected and washed three times with 150 mL of cold 6 N HCl. All aqueous layers were combined and extracted two more times with 150 mL of diethyl ether for each extraction. All organic layers were combined and dried over magnesium sulfate, filtered and reduced to dryness under reduced pressure to yield **(10)** an oil (91%). **10**. **^{1}H-NMR** ($CDCl_3$) δ: 1.20 (t, 3H), 2.36 (s, 3H), 4.01 (q, 2H), 7.27 (d, 2H), 7.71 (d, 2H): **^{13}C-NMR** ($CDCl_3$) δ: 14.387, 21.275, 66.661, 127.498, 129.615, 132.794, 144.521.

2.2.14 Synthesis of *n*-propyl *p*-toluenesulfonate (11)

To a 1 L Erlenmeyer flask, 30.0 g (157 mmol) of *p*-toluenesulfonyl chloride was added to 500 mL of pyridine. The solution was stirred until all *p*-toluenesulfonyl chloride dissolved. Once dissolved, 10.71 mL (0.143 mol) of *n*-propanol was added to the solution. The Erlenmeyer flask was then covered with parafilm and placed in a freezer for 72 h. The flask was removed from the freezer and the pyridine hydrochloride crystals were removed via vacuum filtration. The mother liquor was slowly added to 1.2 L of stirring iced water. The tosylate **(11)** precipitated out of solution. After the ice was completely melted, the reaction mixture was transferred to a 2 L separatory funnel and 400 mL of diethyl ether was added. The layers were separated and two more extractions were completed using 200 mL of diethyl ether for each extraction. All organic layers were collected and washed three times with 150 mL of cold 6 N HCl. All aqueous layers were combined and extracted two more times with 150 mL of diethyl ether for each extraction. All organic layers were combined and dried over magnesium sulfate, filtered and reduced to dryness under reduced pressure to yield **(11)** an oil (95%). **11**. ^{1}H-NMR ($CDCl_3$) δ: 0.89 (t, 3H), 1.66 (q, 2H), 2.44 (s, 3H), 3.98 (t, 2H), 7.35 (d, 2H), 7.78 (d, 2H): **^{13}C-NMR** ($CDCl_3$) δ: 9.676, 21.290, 22.018, 71.263, 127.529, 129.600, 132.892, 144.483.

3.0 RESULTS

3.1 Synthesis and Characterization

3.1.1 Synthesis of 25, 26, 27, 28-tetrahydroxy calix[4]arene (1).

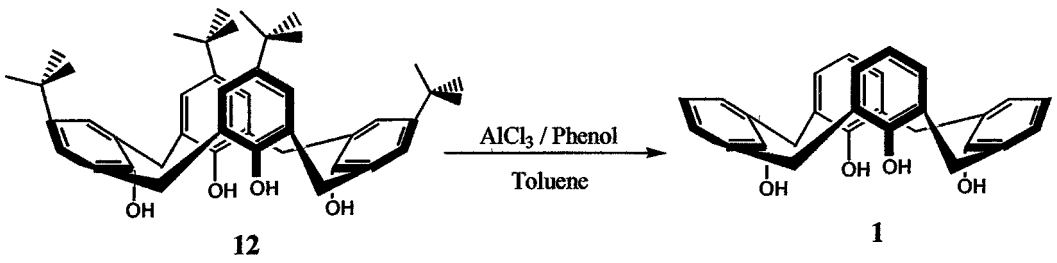


Figure 3.1: Synthesis of 25, 26, 27, 28-tetrahydroxy (cone) calix[4]arene (1).

The synthesis of compound **1** was accomplished by a reverse Friedel Crafts alkylation reaction. The de-*tert*-butylation was catalyzed by aluminum chloride to produce **1** in 96% yield. Dealkylating **12** provided a conformationaly mobile compound, **1**, as evidence by broad signals at 3.5 and 4.2 ppm in the ^{1}H-NMR spectrum for the hydrogens of the Ar-CH_2-Ar moieties. [5] In solution, **1** exists primarily in the cone conformation. Further evidence of the cone conformation was provided by a signal at 31.68 ppm in the ^{13}C-NMR spectrum, which indicated the presence of only one type of *syn* Ar-CH_2-Ar carbon. [5] Compound **1** served as the principle starting material for all subsequent synthesis.

3.1.2 Synthesis of 25, 27-dibenzoyloxy-26, 28-dihydroxy calix[4]arene (2).

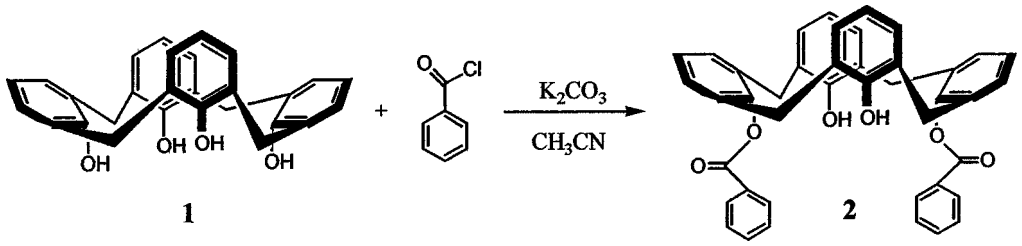


Figure 3.2: Synthesis of 25, 27-dibenzoyloxy-26, 28-dihydroxy (cone) calix[4]arene (2).

The lower rim of **1** was functionalized using benzoyl chloride because of its high reactivity and for the unique migration ability of the benzoyloxy groups.[25] Two molar equivalents of base and acylating agent were used in the synthetic reaction. These reaction conditions optimized the formation of distal phenolate ions and ultimately 1,3 selective substitution at the lower rim of **1**. The 1,3-diester, **2**, was obtained in 82% yield after recrystallization of the crude reaction mixture. The conformation of **2** was determined to be a flatted cone due to the lone signal at 32.45 ppm for the Ar-CH_2-Ar carbons in the 13-NMR spectrum.

3.1.3 Synthesis of 25, 26-dibenzoyloxy-27, 28-dihydroxy calix[4]arene (3).

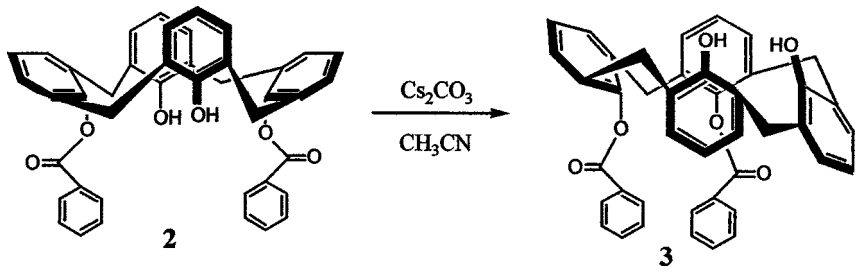


Figure 3.3: Synthesis of 25, 26-dibenzoyloxy-27, 28-dihydroxy (1,2-alternate) calix[4]arene (3).

The rearranged *syn* 1,2 diester **3** was prepared by treatment of the syn 1,3-diester with two molar equivalence of Cs_2CO_3 in refluxing acetonitrile. Compound **3** was isolated in 83% yield after recrystallization of the crude mixture. The 1,2-alternate structural conformation of **3** was verified by ^{13}C-NMR spectroscopy. The spectrum contained one signal at 37.20 ppm and two signals at 30.73 and 29.35 ppm in a 2:1:1 ratio for the *anti* and *syn* methylene groups respectively.

3.2 Background Rearrangement Studies

Prior to alkylation of **3**, a control experiment was conducted to determine the stability of the 1,2-alternate conformation in refluxing acetonitrile in the presence of Cs_2CO_3. Compound **3** was maintained under these conditions for a period of 24 h followed by the addition of HCl. The crude reaction mixture was analyzed by ^{13}C-NMR spectroscopy and was found to contain **3** as the major product with a small amount of **9**. Compounds **3** and **9** were isolated via column chromatography in 80% and 5% yield, respectively (see **Table 3.1**). This experiment indicated that **3** is stable under the reaction conditions and that rearrangement is correlated to the alkylation process.

3.3 Alkylations of 3

In the quest of finding the pathways for alkylations of **3**, two different reaction protocols were employed. The first set of experiments involved a exhaustive alkylation of **3** in which a four molar excess of Cs_2CO_3 and alkyl

tosylate (R = Me, Et and *n*-Pr) were used. The second set of experiments involved a stepwise alkylation of **3** wherein the first step utilized 0.9 molar equivalents of base and 2 molar equivalents of alkyl tosylate to yield the monoalkylated products **7** and **8** (see **Table 3.1**). In the second step, **7** and **8** were treated with 2 molar equivalents of base and tosylate to provide the dialkylated products **4** – **6** (see **Table 3.1**).

Experiment	Compound	^{13}C Chemical Shifts of Ar-CH_2-Ar	Relative Orientation of Ester Groups	Conformation	% Yield
Exhaustive alkylation					
R=Methyl	**4A**	37.31, 29.79, 28.56	Syn 1,2	1,2-Alternate	85
	4B		Syn 1,3		5
R=Ethyl	**5A**	37.05	Syn 1,3	1,3-Alternate	45
	5B	36.48, 31.20	Syn 1,3	Partial Cone	30
R=Propyl	**6A**	36.99	Syn 1,3	1,3-Alternate	31
	6B	36.17, 31.34	Syn 1,3	Partial Cone	48
1st Stepwise Monoalkylation					
R=Methyl	**7A**	37.98, 37.89, 31.22, 29.04	Syn 1,2	1,2-Alternate	80
	or 7B	37.98, 37.89, 31.22, 29.04	Syn 1,2	Partial Cone	80
	7C	37.30, 32.27	Syn 1,2	Partial Cone	10
R=Propyl	**8A**	38.16, 37.57, 31.50, 29.05	Syn 1,2	Partial Cone	33
	8B	31.37, 31.15, 30.48, 30.04	Syn 1,2	Cone	45
2nd Stepwise Monoalkylation					
R=Methyl	**4A**	37.35, 29.90, 28.62	Syn 1,2	1,2-Alternate	78
R=Propyl	**6A**	36.84	Syn 1,3	1,3-Alternate	60
R=Propyl	**6B**	35.92, 31.10	Syn 1,3	Partial Cone	75
Rearrangement Control Studies					
	3	37.07, 30.61, 29.22	Syn 1,2	1,2-Alternate	80
	9	31.33		Flattened Cone	5

Table 3.1: Compound number, ^{13}C-NMR shifts, relative orientation of ester groups, conformation and percent yields of alkylation reactions.

3.3.1 Exhaustive alkylation

3.3.1.1 Synthesis of 25, 26-dibenzoyloxy-27, 28-dimethoxy calix[4]arene (4).

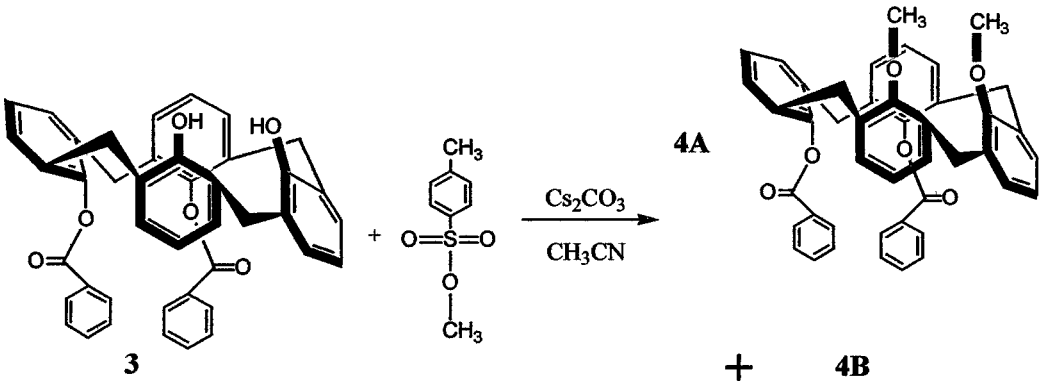


Figure 3.4: Synthesis of 25, 26 dibenzoyloxy-27, 28-dimethoxy (1,2-alternate) calix[4]arene (**4A**) and (**4B**).

Two products (**4A** and **4B**) were formed during the alkylation of **3** with methyl tosylate (see **Figure 3.4**), which were isolated in 85% and 5% yields, respectively (see **Table 3.1**). The conformation of **4A** was determined to be 1,2-alternate in which the benzoyloxy groups remained in a *syn* 1,2-orientation (see **Table 3.1**) as evidenced by the presence of signals at 37.31, 29.79 and 28.56 ppm in a 2:1:1 ratio. The conformation of **4B** was not determined due to the broadened ^{13}C-NMR signals. However, the small amount of **4B** was figured to be rearranged and 1,3-diester.

3.3.1.2 Synthesis of 25, 27-dibenzoyloxy-26, 28-diethoxy calix[4]arene (5) and 26, 28-di-n-propyloxy calix[4]arene (6).

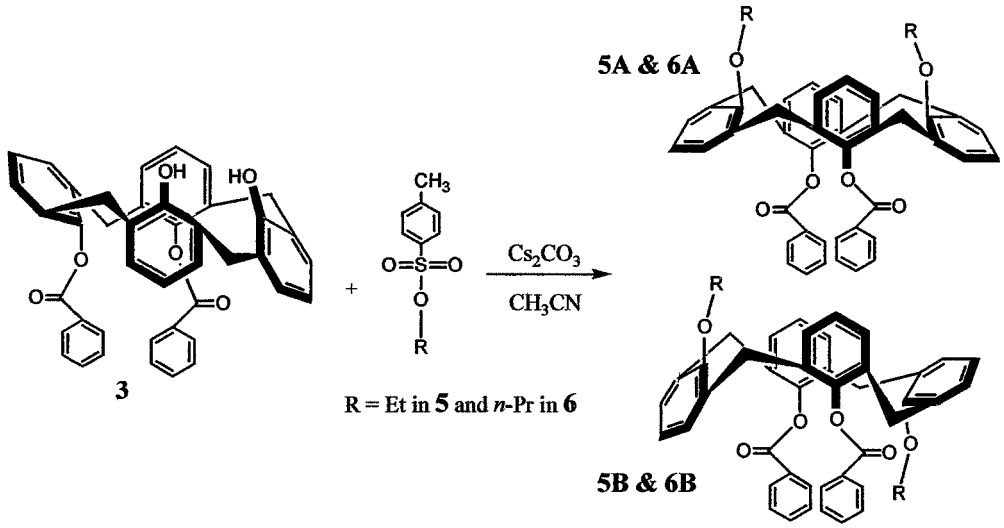


Figure 3.5: Synthesis of 25, 27-dibenzoyloxy-26, 28-diethoxy calix[4]arene (**5**) and 26, 28-di-n-propyloxy calix[4]arene (**6**).

When the alkyl tosylate was changed to ethyl and *n*-propyl, two products were isolated in each case. In the alkylation of **3** with ethyl tosylate, the major product, **5A**, was isolated in 45% yield while the minor component, **5B**, was isolated in 30 % yield after column chromatography (see **Figure 3.5**). Analogously, when propyl tosylate was used, the major component, **6B**, was isolated in 45% yield, and the minor product, **6A**, was isolated in 30% yield after column chromatography (see **Table 3.1**).

Compounds **5A** and **6A** were determined to have 1,3-alternate conformation in which the ester groups were in a *syn* 1,3-orientation as evidence by the presence of only one signal in the ^{13}C-NMR spectra around 37 ppm corresponding to *anti* oriented Ar-CH_2-Ar groups (see **Table 3.1**). Compounds

5B and **6B** were found to have partial cone conformation with *syn* 1,3 ester groups as indicated by the presence of one signal around 37 ppm and one signal around 31 ppm with a 1:1 relative intensity for the *anti* and *syn* oriented Ar-CH_2-Ar groups, respectively (see **Table 3.1**).

3.3.2 Stepwise alkylations

3.3.2.1 Monoalkylations of 3

3.3.2.1.1 Synthesis of 25, 26-dibenzoyloxy-27-methoxy-28 hydroxy calix[4]arene (7).

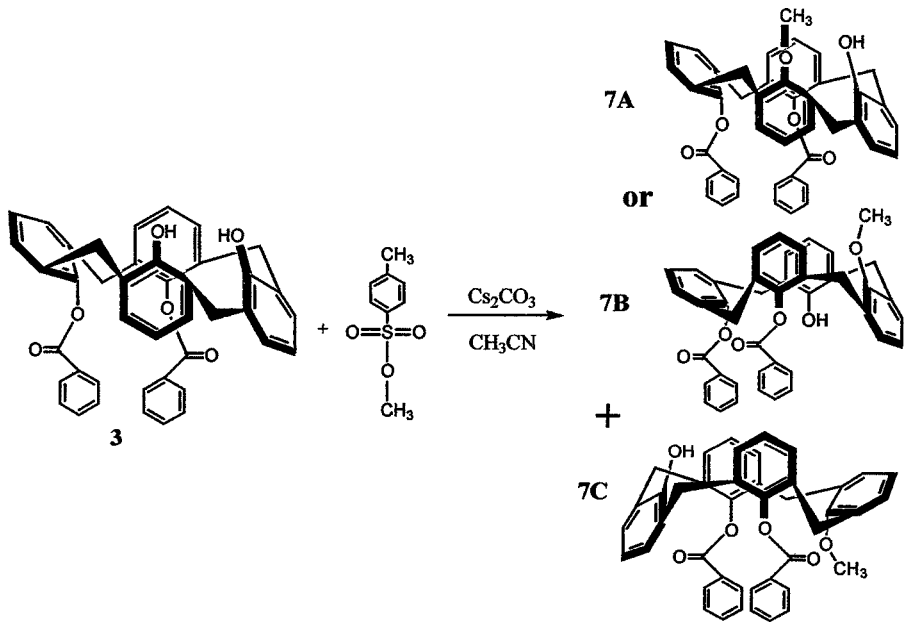


Figure 3.6: Products of monomethylation of **3**.

In the monomethylations of **3**, 0.9 molar equivalents of base and 2 molar equivalents of methyl tosylate were used in the preparation of the monoalkylated products **7A-C**, as shown in **Figure 3.6**. Compound **7A** (or **7B** see discussion

section) and **7C** were isolated in 80 % and 10% yields, respectively, via column chromatography (see **Table 3.1**). The structure of the major product could not be unambiguously identified because both **7A** and **7B** have identical patterns for the Ar-CH_2-Ar in their ^{13}C-NMR spectra. Nonetheless, **7A** or **7B** must assume either 1,2-alternate or partial cone conformation with *syn* 1,2-ester groups based on the appearance of two signals around 38 ppm (1:1 relative intensity) and two signals around 29 - 31 ppm (1:1 relative intensity) for the two types of *anti* and *syn* Ar-CH_2-Ar groups. On the other hand, **7C** must assume a partial cone conformation wherein the ester groups have migrated to a *syn* 1,3-orientation based on the presence of one signal around 37 ppm and one signal around 31 ppm in a 1:1 relative intensity (see **Table 3.1**).

3.3.2.1.2 Synthesis of 25, 26-dibenzoyloxy-27-propyloxy-28-hydroxy calix[4]arene (8).

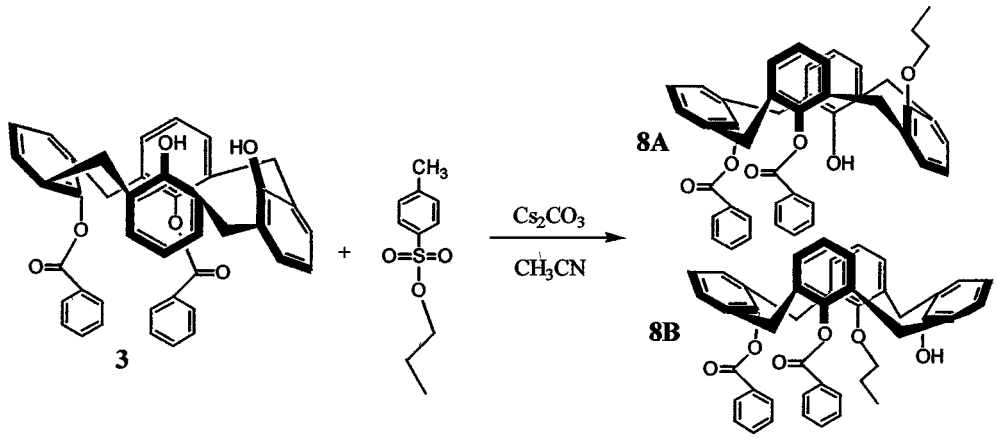


Figure 3.7: Mono-*n*-propylation of **3**.

As in the synthesis of monomethylated compounds **7A-C**, 0.9 molar equivalents of base was used and two molar equivalents of alkyl tosylate were used in the synthesis of 25, 26-dibenzoyloxy-27-propyloxy-28-hydroxy

calix[4]arene. These reaction conditions produced two major products **8A** and **8B** (see **Figure 3.7**) in 33% yield and 45% yield, respectively after column chromatography (see **Table 3.1**). The partial cone conformation of **8A** was determined by the presence of two signals around 37 ppm (1:1 relative intensity) and two signals around 31 ppm (1:1 relative intensity) for the *anti* and *syn* oriented Ar-CH_2-Ar groups (see **Table 3.1**). The cone conformation of the major product, **8B**, was verified by the presence of four signals between 30 – 31 ppm (1:1:1:1 relative intensity) in the ^{13}C-NMR spectrum indicating the presence of four different *syn* oriented Ar-CH_2-Ar groups (see **Table 3.1**). Furthermore, both **8A** and **8B** must have the ester groups in an unrearranged *syn* 1,2-orientation because their observed ^{13}C-NMR spectral pattern could not be produced by any *syn* 1,3-diester products.

3.3.2.2 Monoalkylation of 7 and 8

3.3.2.2.1 Synthesis of 25,27-dibenzoyloxy-26, 28-dimethoxy calix[4]arene 4A.

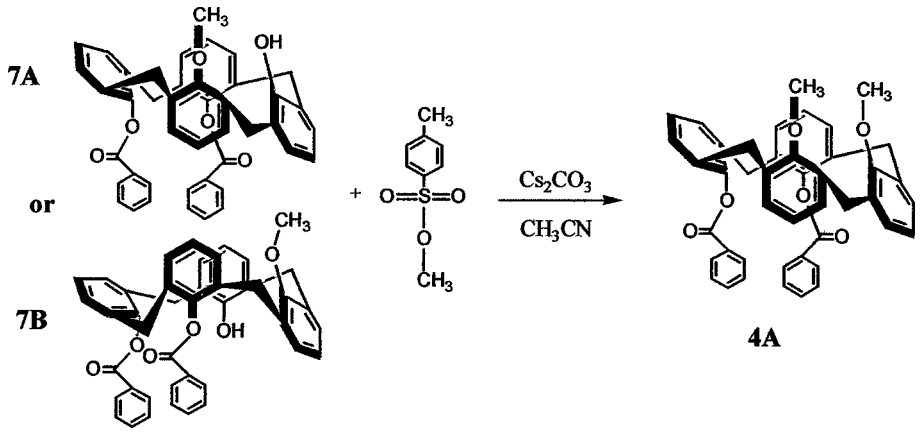


Figure 3.8: Synthesis of **4A**.

In the second monomethylation of **7A** (or **7B**), 2 molar equivalents of base and methyl tosylate were used in the preparation of **4A** (see **Figure 3.1**). Compound **4A** was obtained in 78% yield after recrystallization of the crude reaction mixture (see **Table 3.1**). The conformation of **4A** via stepwise alkylation was determined by its identical ^{13}C-NMR spectrum to that of **4A** via exhaustive alkylation. Thus the conformation of **4A** was 1,2-alternate where the benzoyloxy groups remained in a *syn* 1,2-orientation, as evidenced by the presence of one *anti* signal at 37.35 ppm and two *syn* signals at 29.90 and 28.62 ppm in a 2:1:1 relative intensity representing the Ar-CH_2-Ar groups (see **Table 3.1**). Further corroboration of the conformation is due to the one signal at 59.99 ppm, which represents the methyl group next to the oxygen of the phenol. This lone signal is due to the symmetry of **4A**.

3.3.2.2.2 Synthesis of 25,27-dibenzoyloxy-26, 28-dipropyloxy calix[4]arene 6A and 6B.

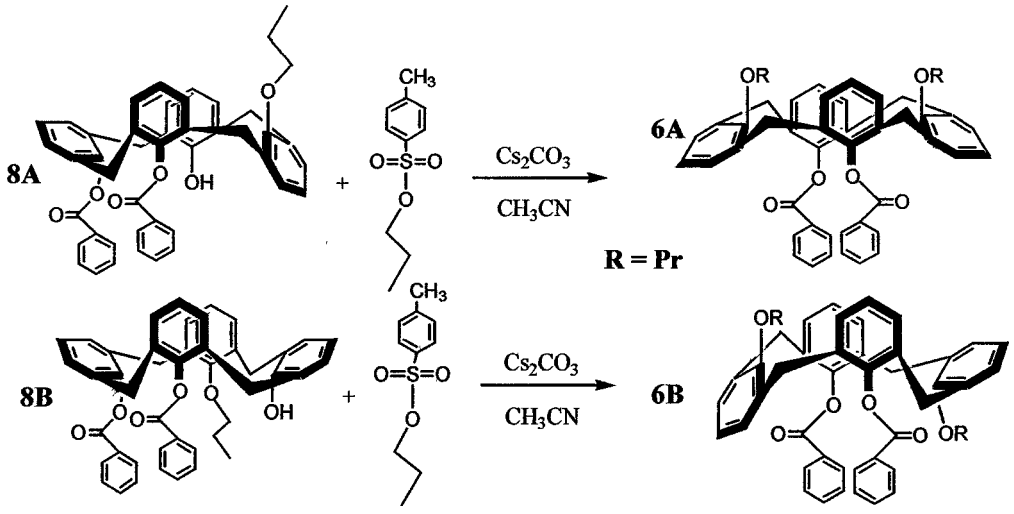


Figure 3.9: Synthesis of **6A** and **6B**.

As in the second monomethylation of **7A** (or **7B**), 2 molar equivalents of base and propyl tosylate were used in the preparation of **6A** and **6B** (see **Figure 3.9**). These reaction conditions produced one major product for each respective reaction. Compounds **6A** and **6B** were produced in 60% and 75 % yields after column chromatography, respectively (see **Table 3.1**). The 1,3-alternate conformation of **6A** and the partial cone conformation of **6B** via stepwise alkylation were verified in the same manner as **6A** and **6B** via exhaustive alkylation, respectively. Further corroboration of **6A** is with only one set of signals that arise for the alkyl groups, due to the symmetry. The lone signal at 73.27 ppm (see **Table 3.1**) denotes the methylene carbons of the alkyl groups that are next to the oxygens of the phenols. Due to the non-symmetry of **6B**, two sets of signals for the propyl groups appear. For the methylene carbons next to the oxygens of the phenols, two signals appear at 74.40 and 74.13 ppm (see **Table 3.1**).

4.0 DISCUSSION

4.1 Proposed Pathway for Stepwise Alkylation

Our previously reported preliminary results of exhaustive alkylations of **3** indicated that the 1,2-alternate conformation was conserved to a high degree when methyl tosylate was used, but a mixture of conformers was produced during propylation and benzylation. [25] We therefore embarked on a systematic study to identify factors which control the final stereochemical outcome in the alkylated products (e.g. solvent, base, temperature and electrophile). Assuming the monoalkylated products were precursors to the dialkylated products, we devised the pathway summarized in **Figure 4.1**.

When **3** was treated with 0.9 equivalents of base and excess methyl or *n*-propyl tosylate, the major products were found to be the monoalkylated unrearranged syn 1,2-diesters **7A** (or **7B**) and **8A** and **8B,** respectively. The key reaction intermediate, **3B**, is assumed to be strongly favored due to intramolecular hydrogen bonding. Furthermore, the barrier to conversion to **3C** has been estimated to be very high even though the energy difference was estimated to be small (1-2 kcal/mol). [29]

The exact conformation of the monomethylated product could not be unambiguously assigned since **7A** and two partial cone forms of **7B** would have similar ^{13}C-NMR signal patterns for the Ar-CH_2-Ar groups. Likewise, the same

uncertainty arose for one of the monopropylated products, **8A**, however, the conformation of the other monopropylated product **8B** could be assigned the cone conformation with a high degree of certainty. All the monoalkylated products, with the exception of the rearranged syn 1,3-diester **7C**, are inherently chiral (albeit racemic) calix[4]arenes of the AABC variety. [15]

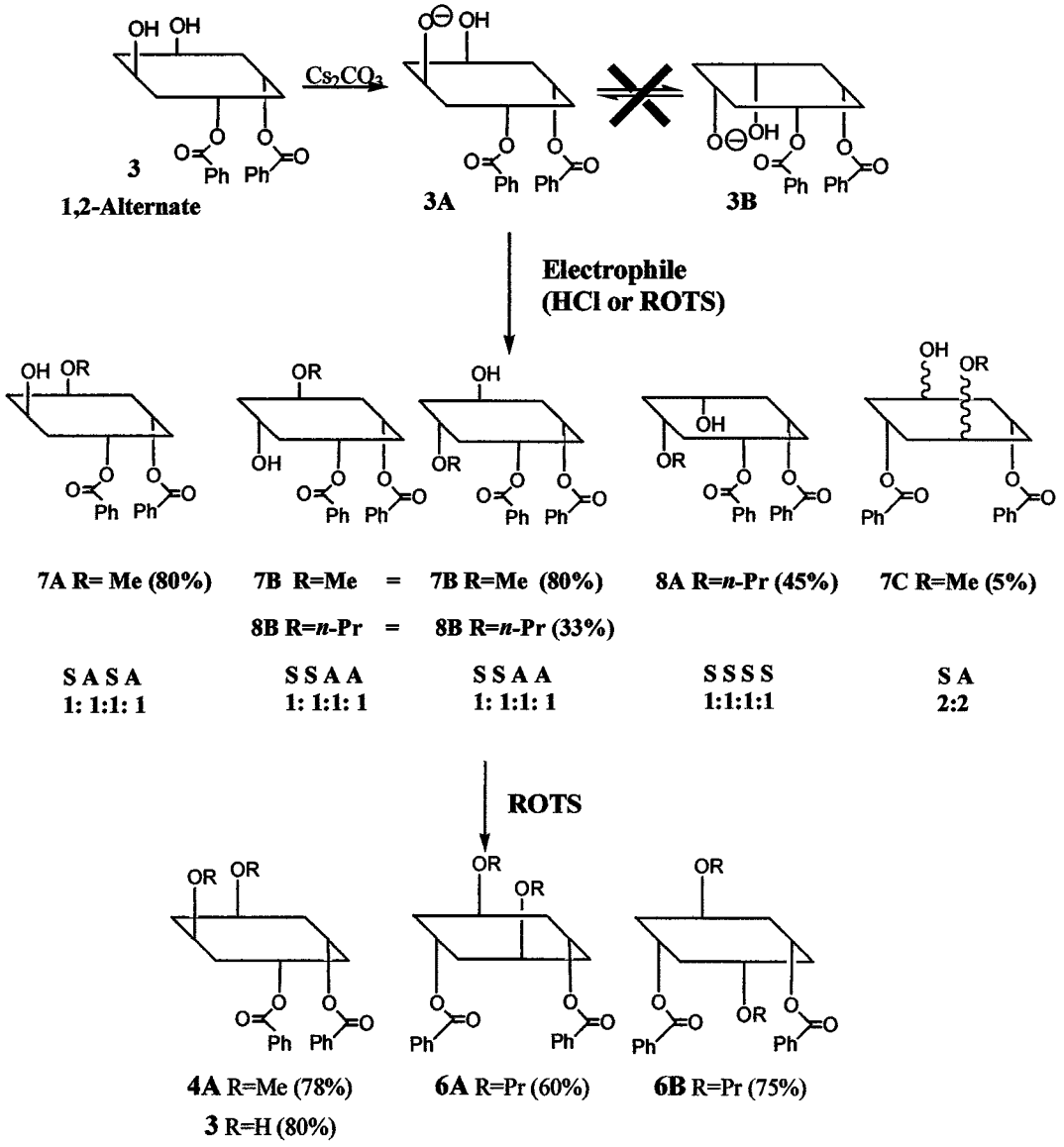


Figure 4.1: Proposed pathway for stepwise alkylation of **3**.

Subsequent alkylation of the monoalkylated products provided the dialkylated products **4-6** in good yields. The high yield of the 1,2-alternate conformer **4A** was anomalous because the reaction conditions employed typically result in formation of 1,3-alternate and partial cone conformers. [30] Based on the abundance of **4A** (85%) in the reaction mixture, we believe that **7A** was the most likely monomethylated intermediate. The small amount of the rearranged isomer **4B** (5%) probably came from **7C**.

When the monopropylated product **8A** (partial cone) was treated with excess Cs_2CO_3 and *n*-propyl tosylate, the rearranged *syn* 1,3-diester **6A** (1,3-alternate) was isolated in high yield. Based on the 1,3-alternate conformation of **6A**, we believe the most likely structure for **8A** has the propyl group *anti* to the two ester groups. On the other hand when the cone isomer **8B** was further alkylated, compound **6B** (partial cone) was the principle product. This assignment is consistent with the fact that at least one propyl group must be *syn* to the two ester groups. The conformational outcome was not noteworthy since it is known that 1,3-alternate and partial cone conformations are favored in calix[4]arenes when the alkylation reactions are carried out in acetone or acetonitrile with metal carbonate bases. [30] However, the *syn* 1,3 substitution pattern of the ester groups indicated that a migration had occurred similar to that which was exploited in the synthesis of **3** from a flatted cone precursor. [25] Furthermore, it can be concluded that the first alkylation step occurs prior to the migration process and ultimately the second alkylation step determines the final conformation.

4.2 Exhaustive Alkylation

In order to check the validity of the above-mentioned proposed stepwise pathway, we performed exhaustive alkylations on **3**. The reaction protocol involved treatment of **3** with an excess of base followed by equilibration prior to introduction of the alkyl tosylate (thermodynamic control). When an aliquot of the reaction mixture was quenched with HCl, the major product was unadulterated **3** that indicated that the monoanion **3B** was formed. Similarly, when an excess of methyl tosylate was added to the reaction mixture, **4A** was isolated in high yield and a small amount of **4B** was produced. Conversely when ethyl or propyl tosylate was added to the reaction, two major compounds (**5A** & **B** and **6A** & **B**) were produced in each case. Because exhaustive alkylation provided identical products as the stepwise alkylation process, we believe our proposed pathway to be operative. Moreover, the competition between ester migration vs. alkylation appears to be closely related to the size of the second incoming electrophilic group. For example, the rate of protonation and methylation are greater than ester migration where as ethylation and propylation, ester migration is faster.

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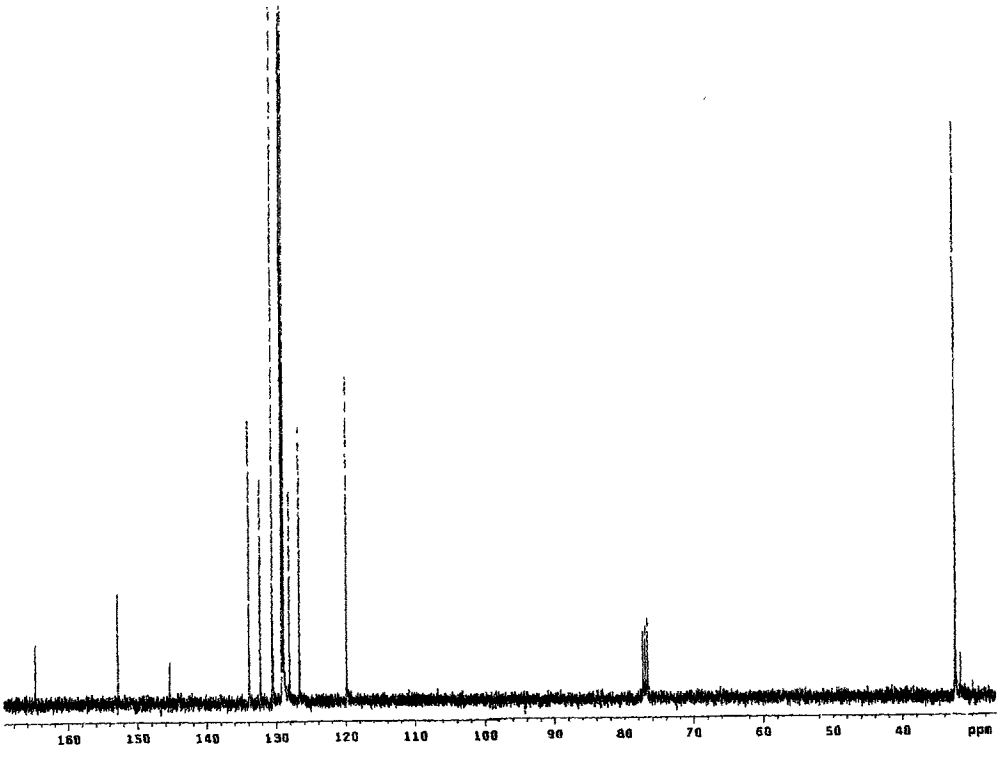
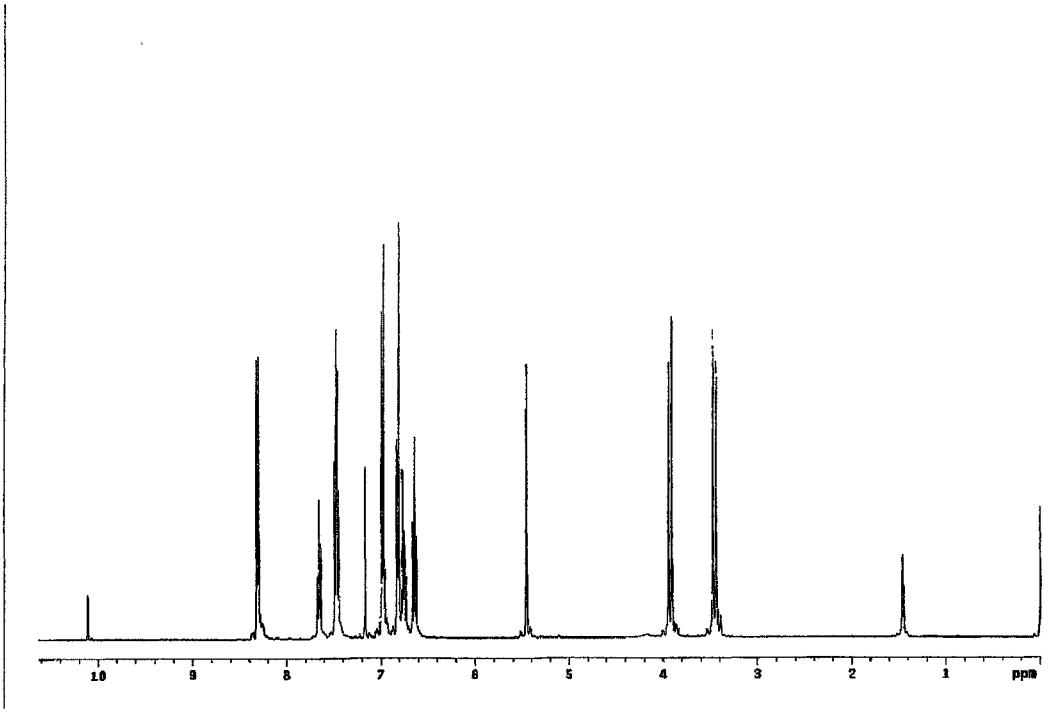
APPENDIX: NMR SPECTRA



Spectrum 1. ^{13}C-NMR of Compound 2



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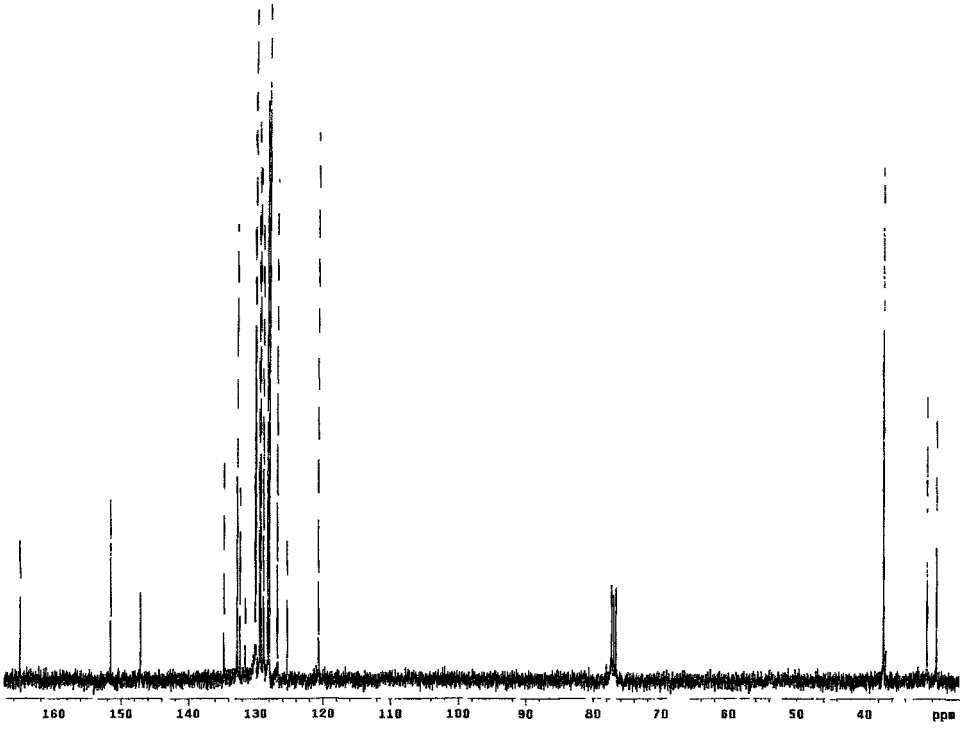

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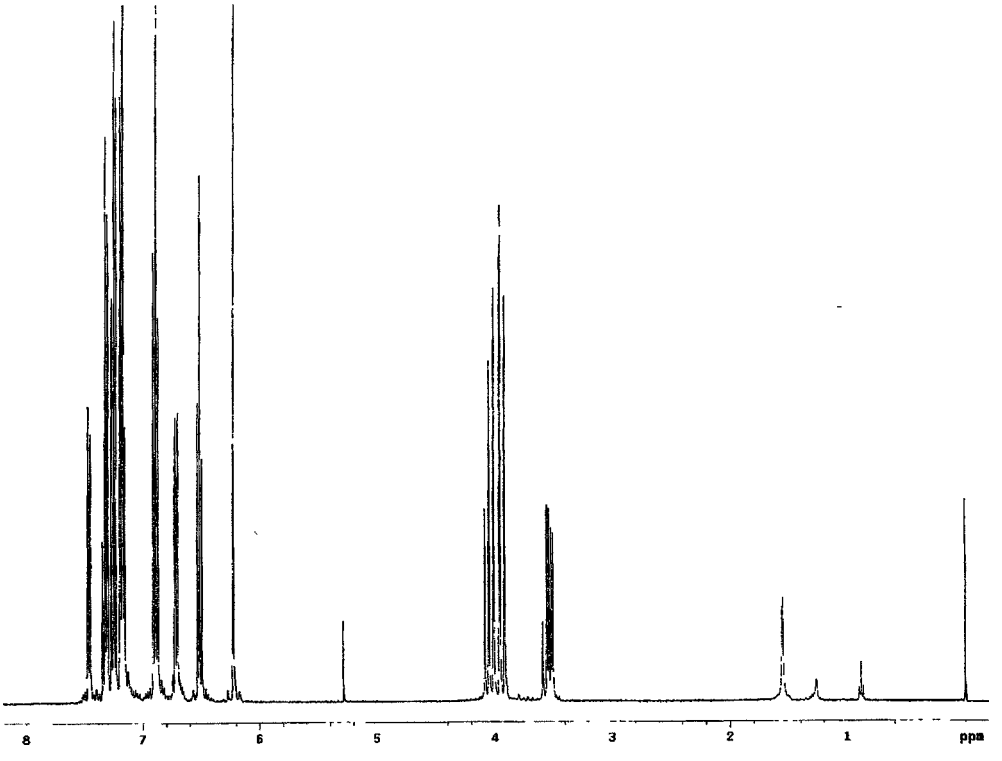

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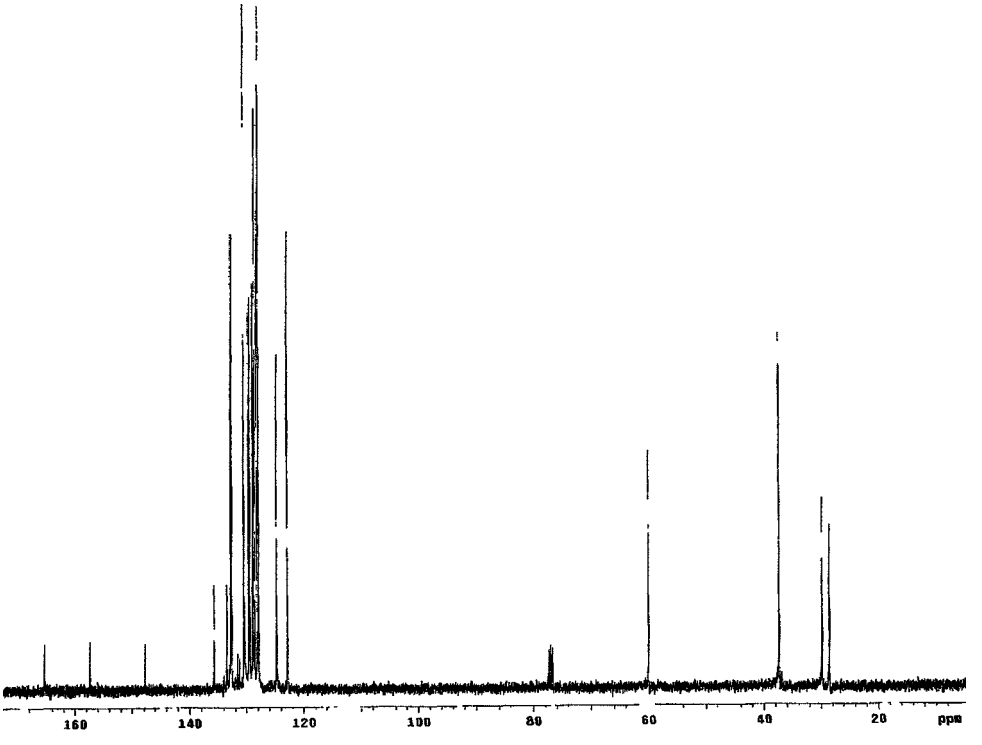
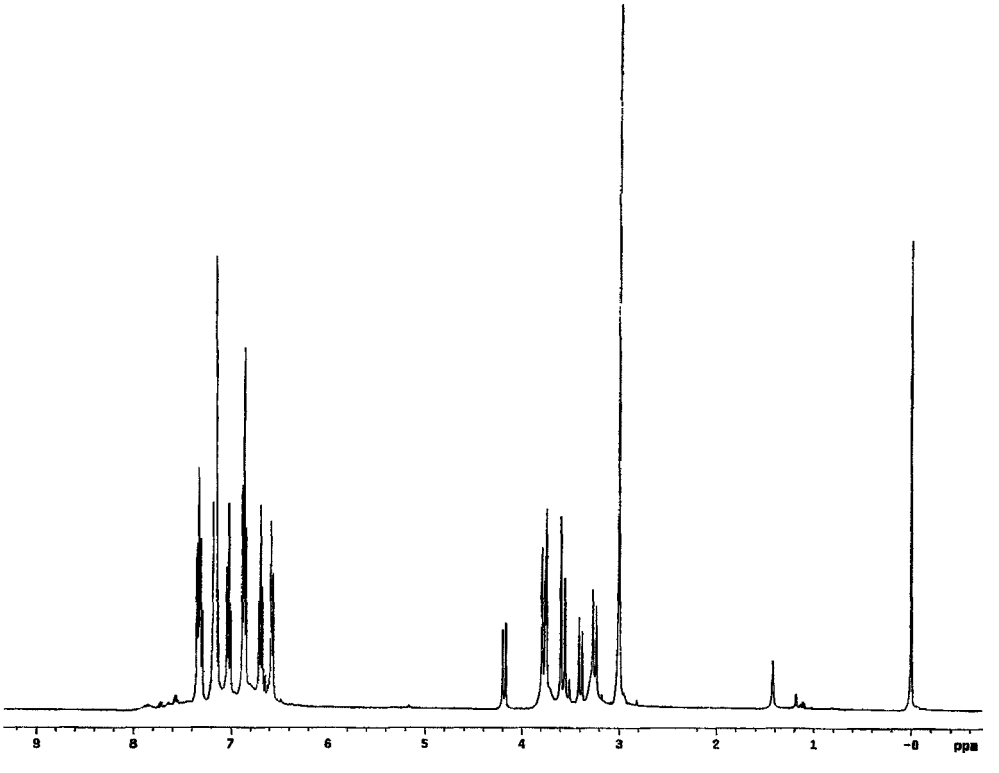


Spectrum 5. ^{13}C-NMR of Compound 4A



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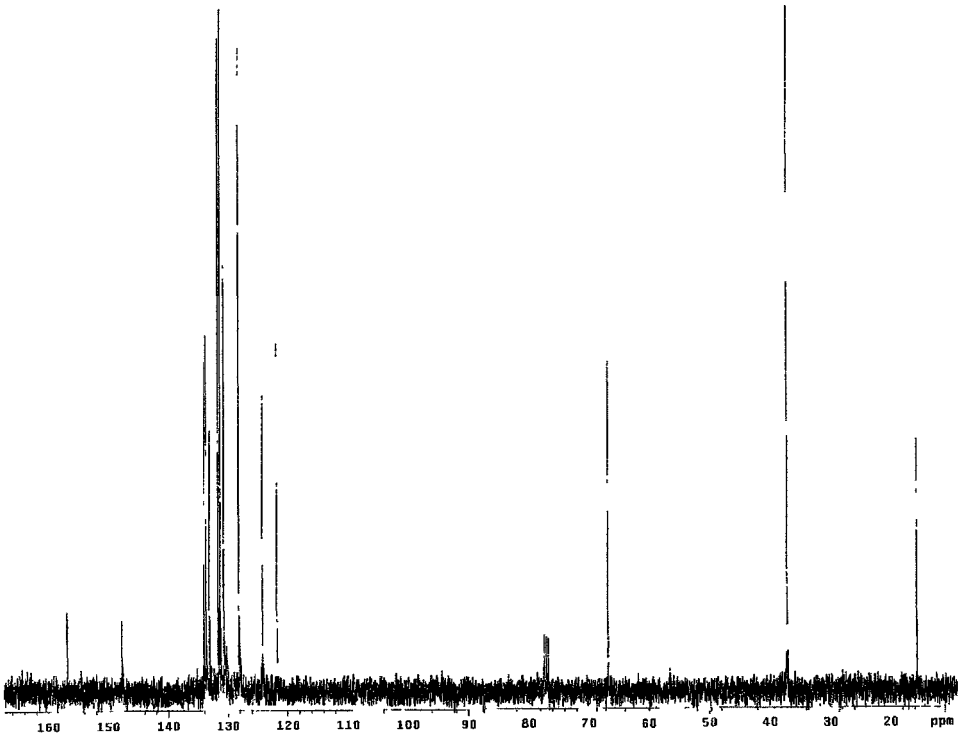

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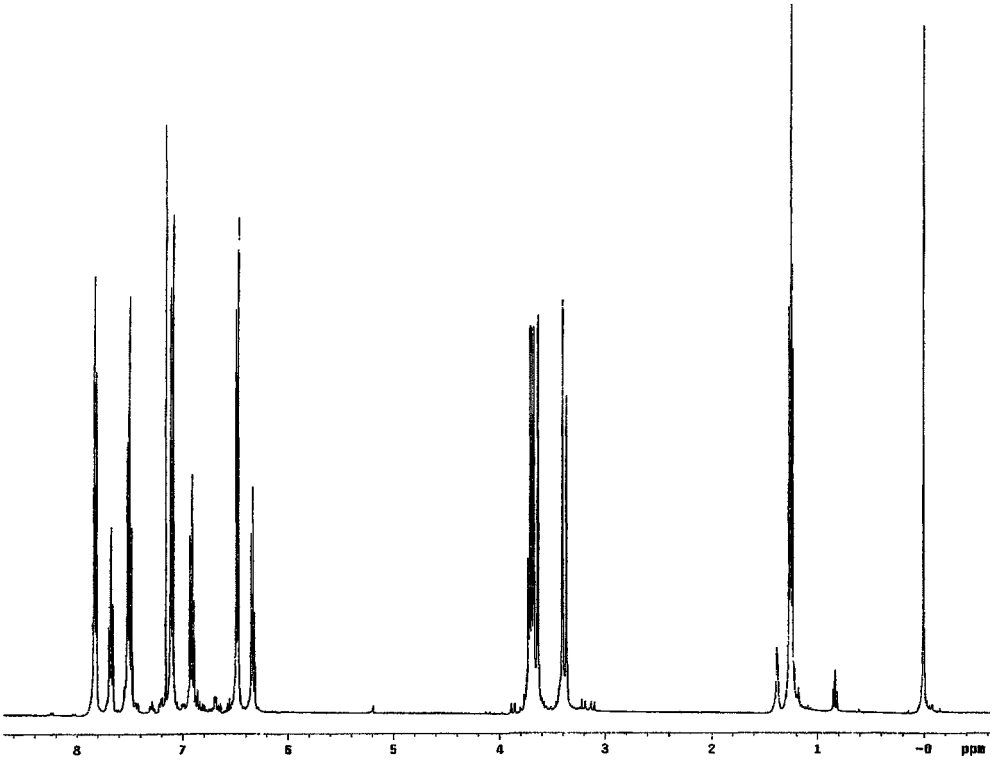

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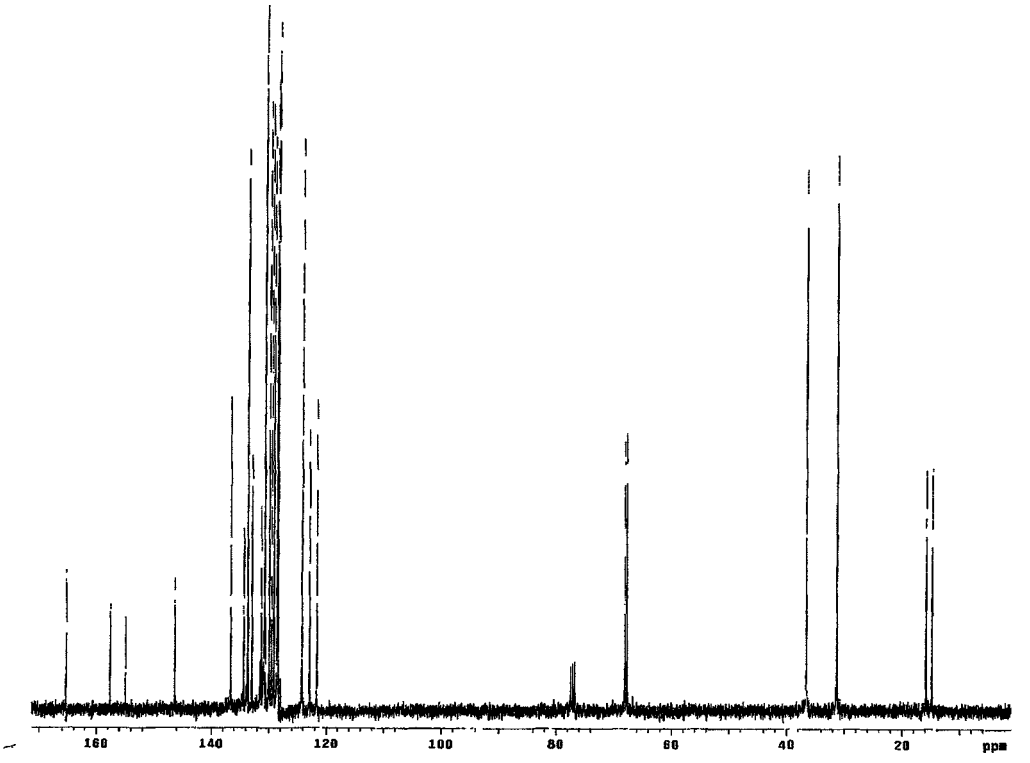

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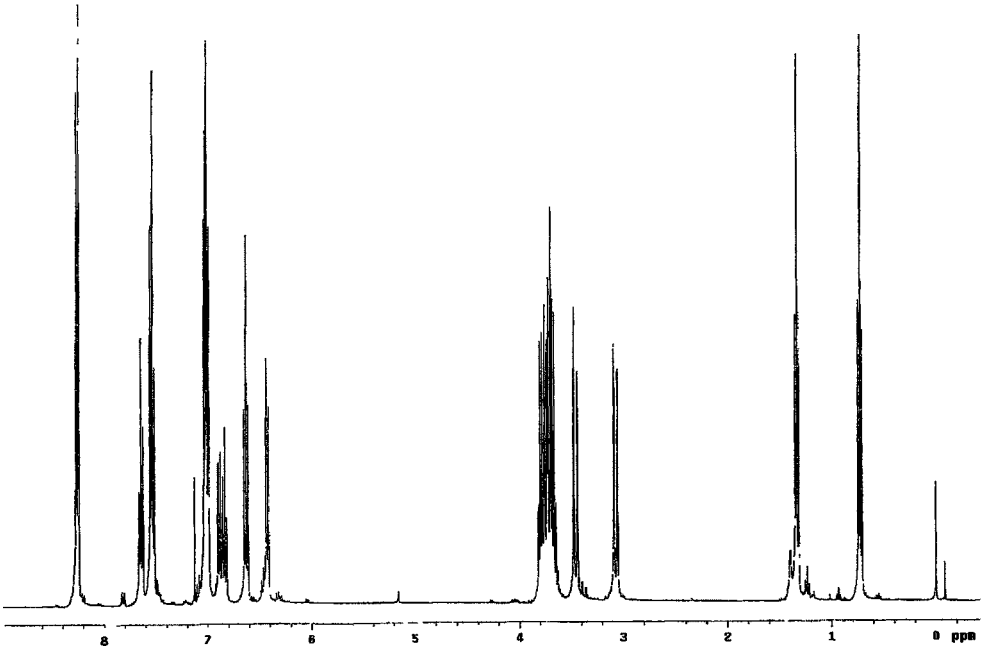
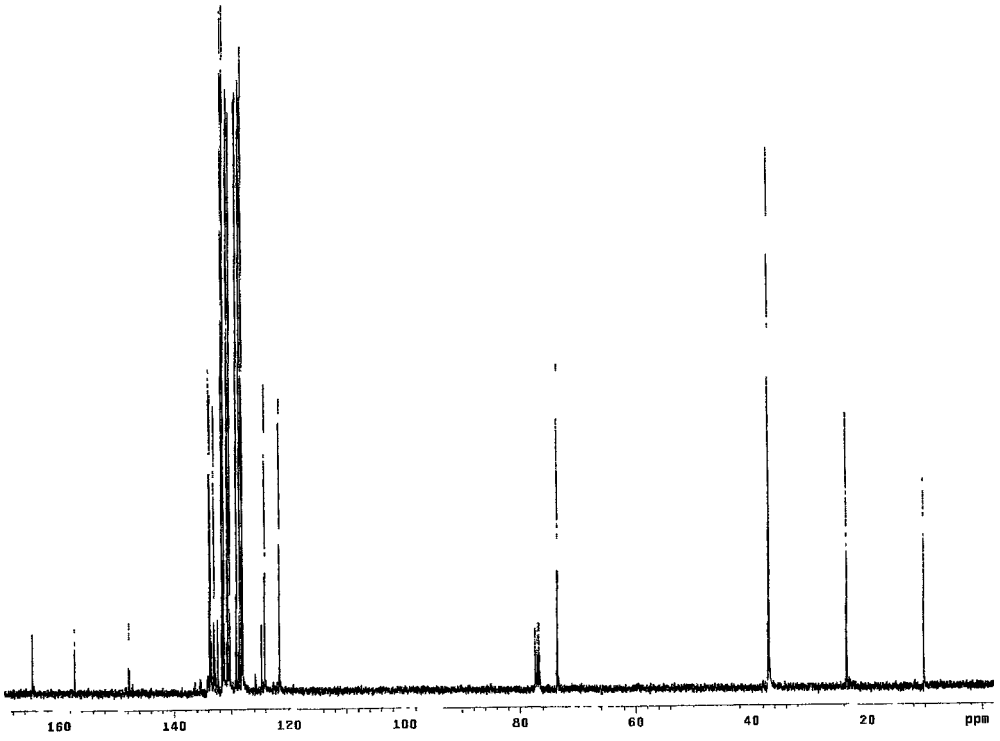
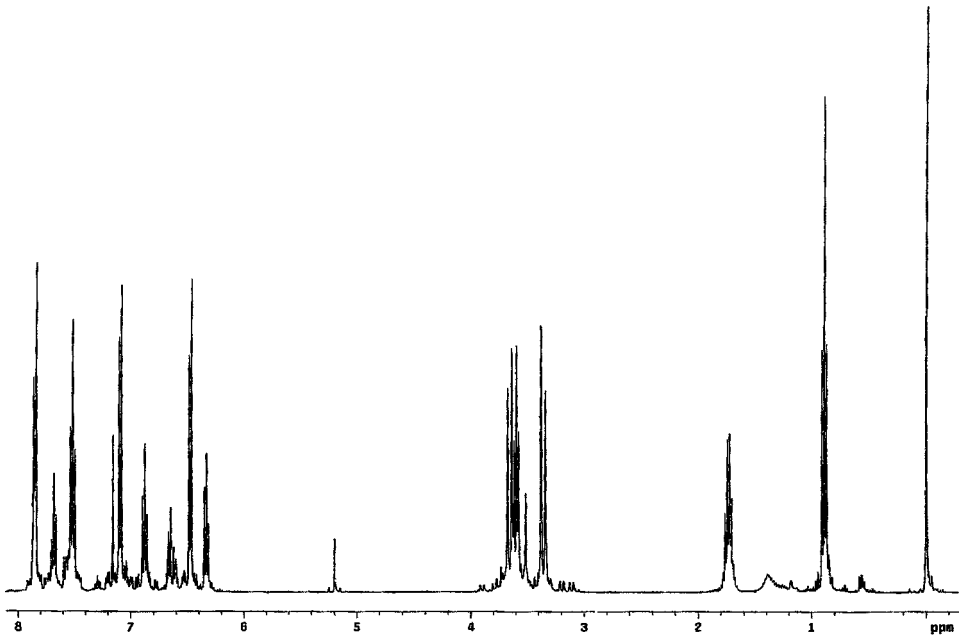


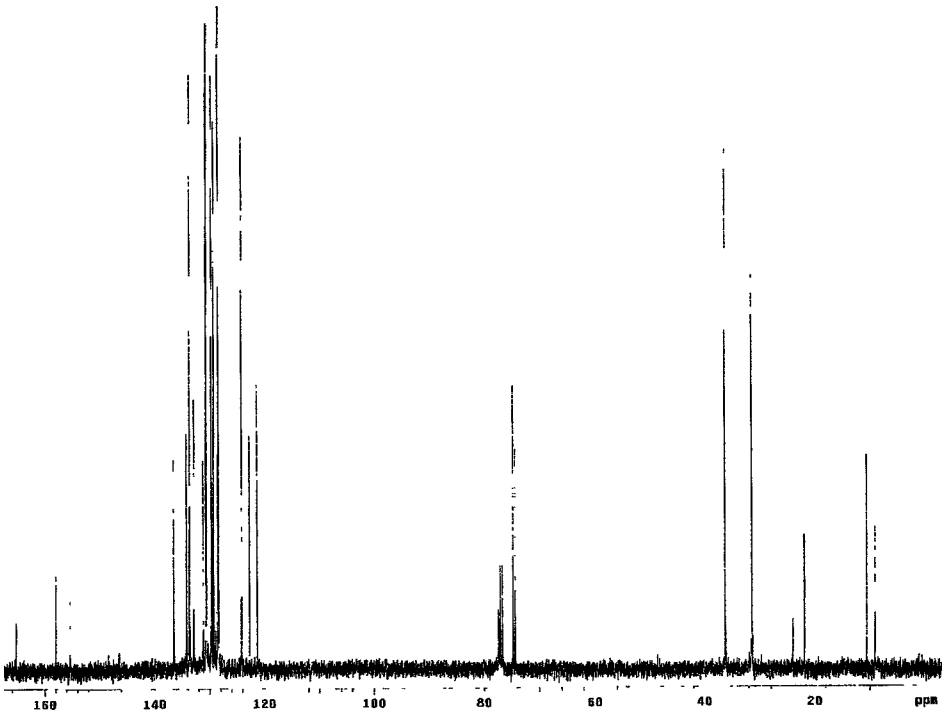
Spectrum 10. ^{1}H-NMR of Compound 5B



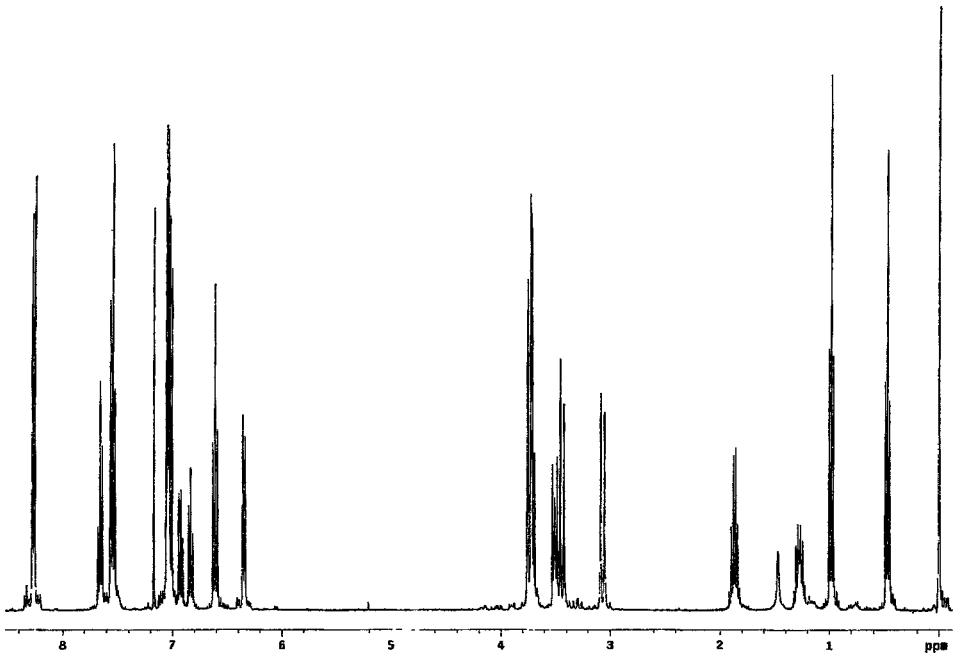
Spectrum 11. ^{13}C-NMR of Compound 6A



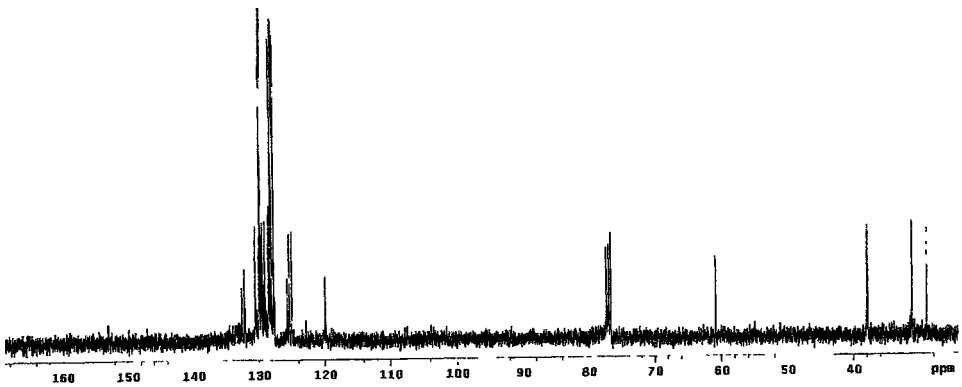
Spectrum 12. ^{1}H-NMR of Compound 6A



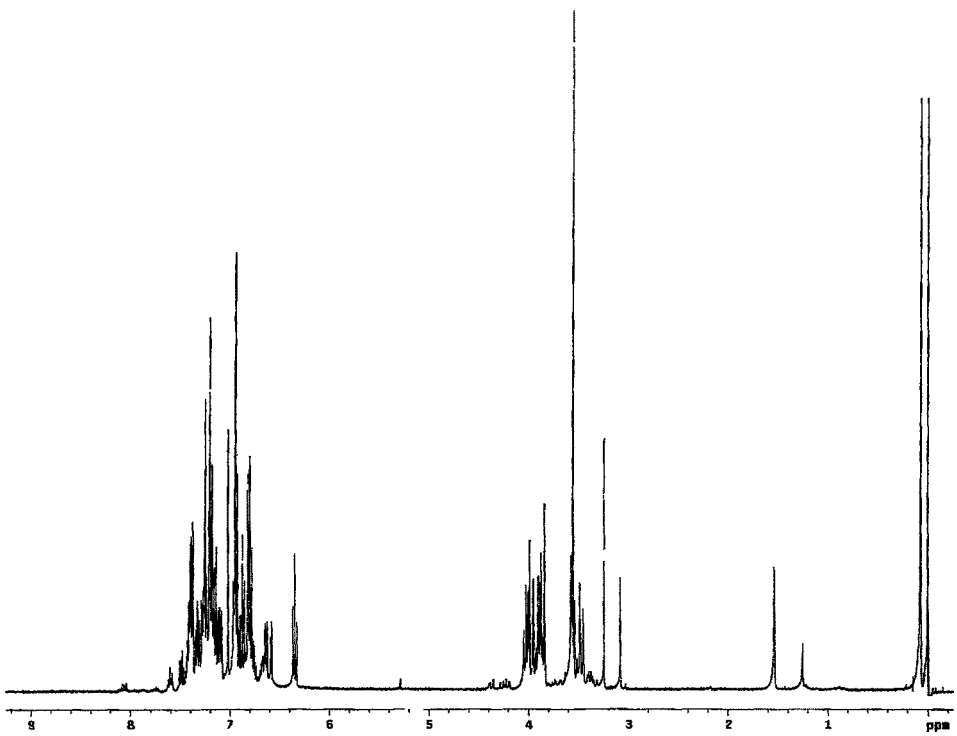
Spectrum 13. ^{13}C-NMR of Compound 6B



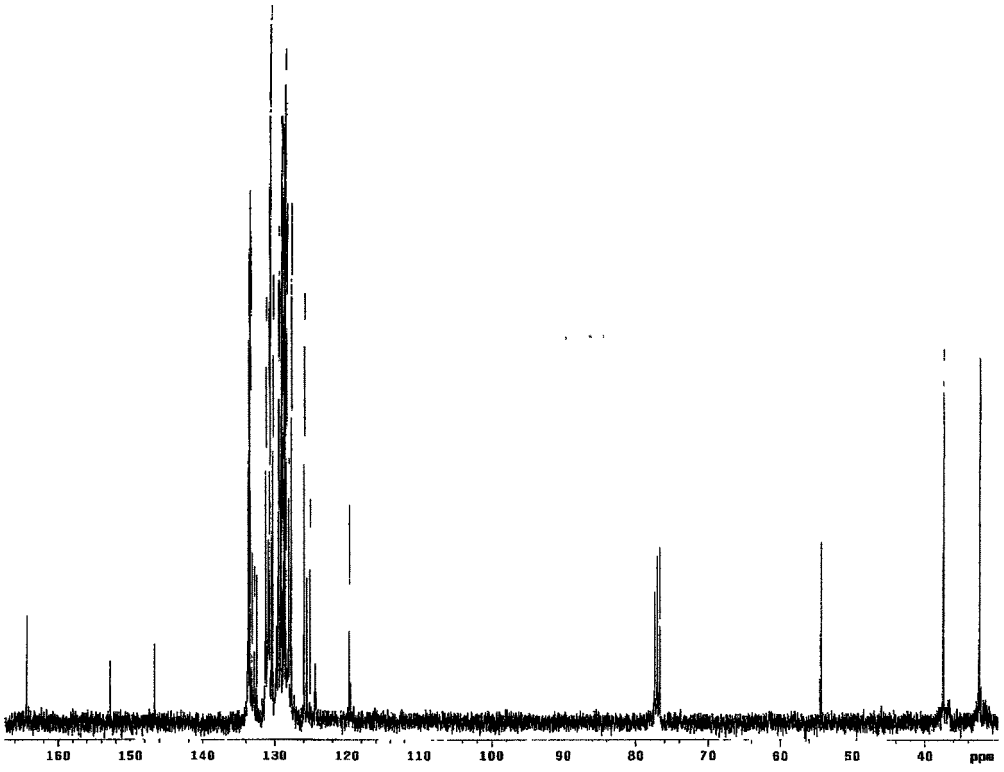
Spectrum 14. ^{1}H-NMR of Compound 6B



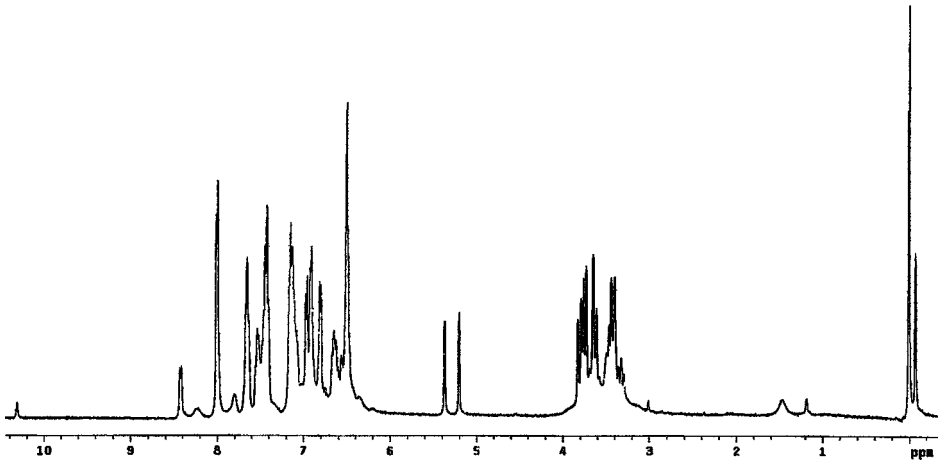
Spectrum 15. ^{13}C-NMR of Compound 7A or 7B



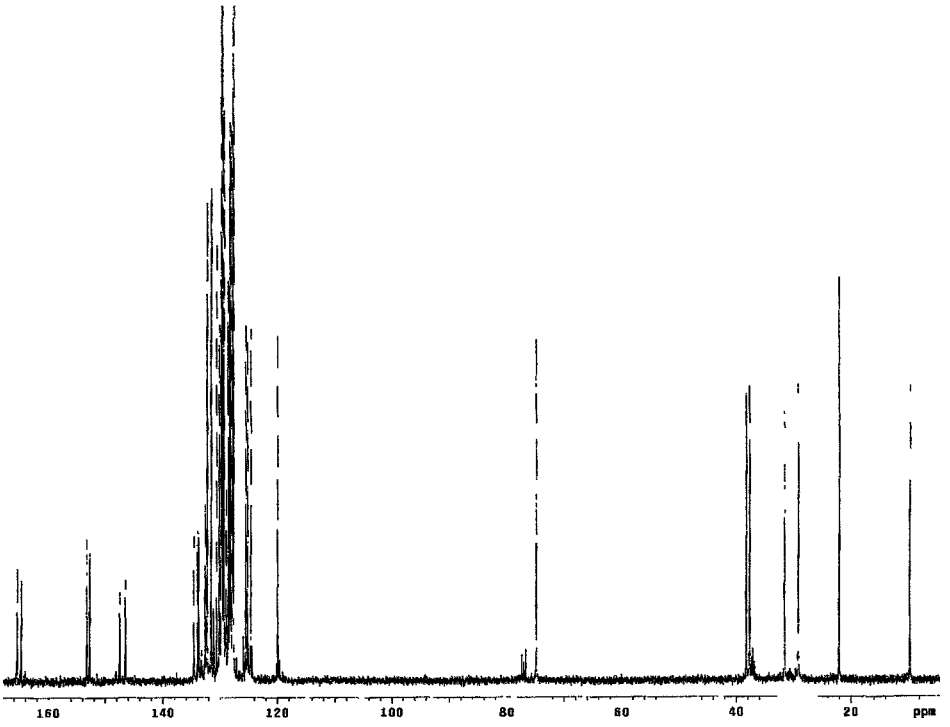
Spectrum 16. ^{1}H-NMR of Compound 7A or 7B



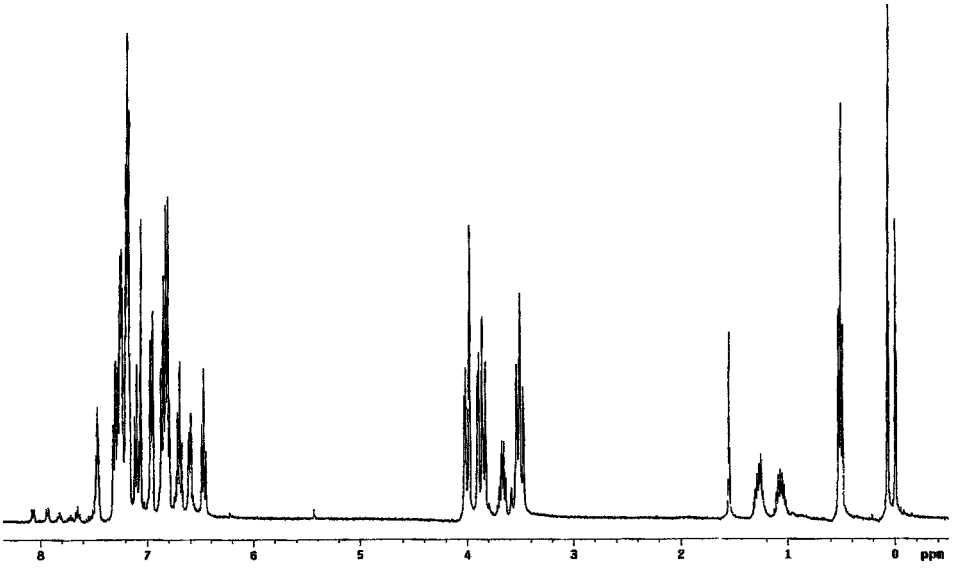
Spectrum 17. ^{13}C-NMR of Compound 7C



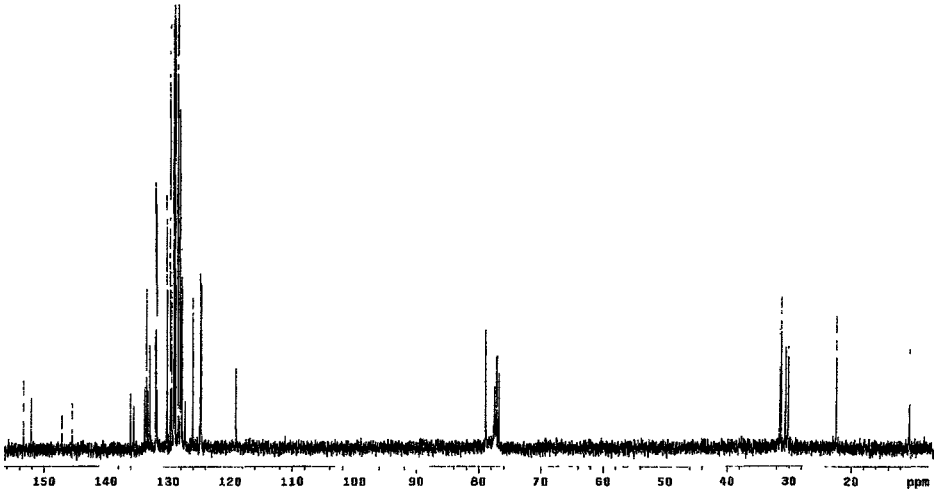
Spectrum 18. ^{1}H-NMR of Compound 7C



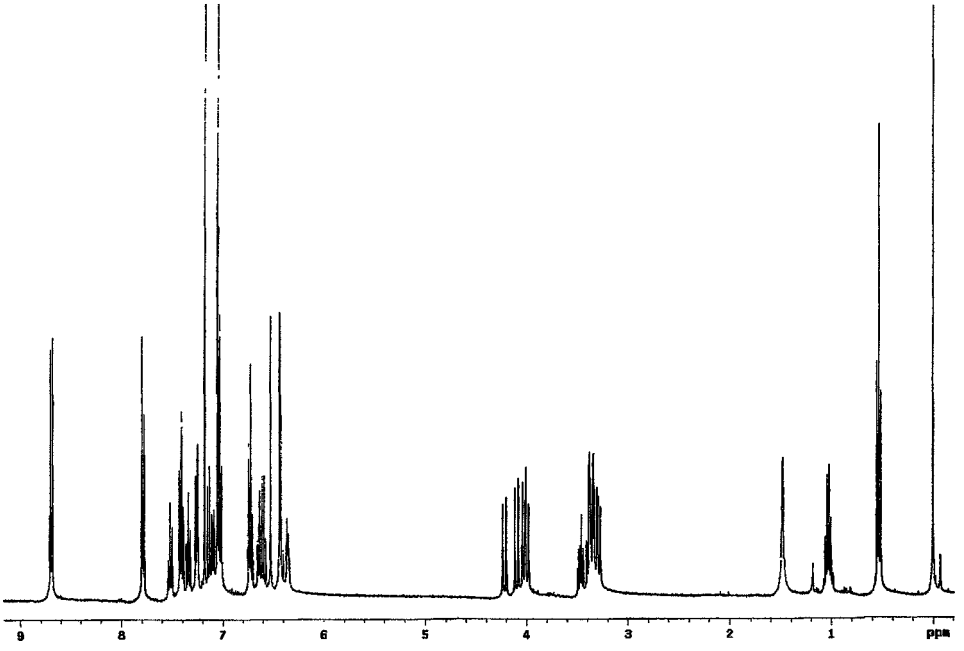
Spectrum 19. ^{13}C-NMR of Compound 8A



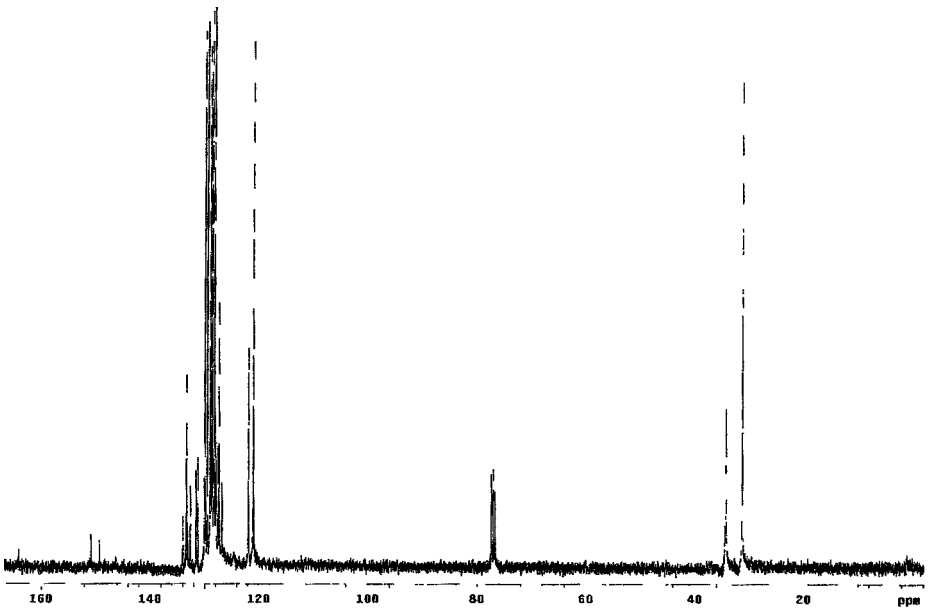
Spectrum 20. ^{1}H-NMR of Compound 8A



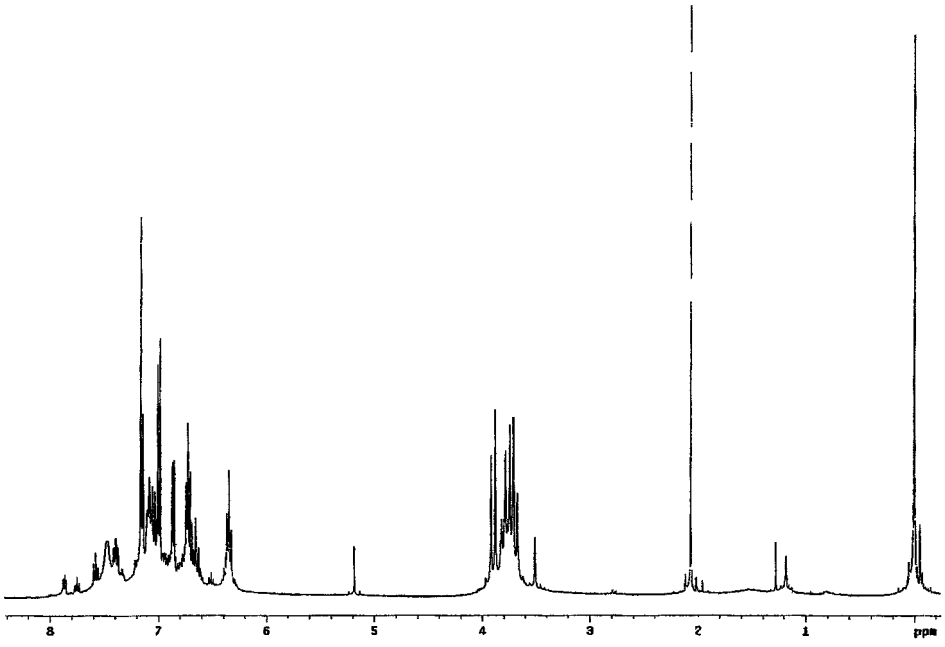
Spectrum 21. ^{13}C-NMR of Compound 8B



Spectrum 22. ^{1}H-NMR of Compound 8B



Spectrum 31. ^{13}C-NMR of Compound 9



Spectrum 32. ^{1}H-NMR of Compound 9

VITA

Abelardo H. Rodriguez II was born in Alice, Texas, on September, 28 1977, the son of Abelardo I. Rodriguez and Angelita H. Rodriguez, and brother to Belinda R. Smith, Beverly R. Mendez, Anna B. Trejo, and Andres H. Rodriguez. After completing his work at San Diego High School, Texas, in 1996, he entered Southwest Texas State University in San Marcos, Texas. He received the degree of Bachelor of Science in Chemistry from Southwest Texas State University in May, 2000. In the Fall semester of 2000, he entered graduate school at Southwest Texas State University. On November 24, 2000, he married Tracy M. Ruiz. On December 21, 2002, he graduated with his Master of Science in Chemistry from Southwest Texas State University.