EFFORTS TOWARDS THE MODULAR SYNTHESIS OF ORGANIC NANOTUBES

BY

RYAN JAMES DENMAN

B.S., University of Central Florida, 2009

A thesis submitted to the

Faculty of the Graduate School of the University of Colorado

in partial fulfillment of the requirement for the degree of

Master of Materials Chemistry

Department of Chemistry and Biochemistry

2013

This thesis entitled:

Efforts Towards the Modular Synthesis of Organic Nanotubes

written by Ryan James Denman

has been approved for the Department of Chemistry and Biochemistry

_____

Dr. Wei Zhang

_____

Dr. Doug Gin

Date_____

The final copy of the this thesis has been examined by the signatories, and we find that both the content and the form meet acceptable presentation standards of scholarly work in the above mentioned discipline.

Denman, Ryan James (MS, Organic/Materials Chemistry, Department of Chemistry and Biochemistry)

Efforts Towards the Modular Synthesis of Organic Nanotubes

Thesis directed by Assistant Professor Wei Zhang

Organic nanotubes are desirable for their wide array of applications. We show here experimental efforts toward the modular construction of organic nanotubes, in which nanotubes of controlled size and chemical functionality were attempted through dynamic covalent chemistry (imine metathesis) and living polymerization (ring opening metathesis polymerization). The methods explored here outline several key concepts that are believed to be essential to the covalent assembly of organic nanotubes.

I dedicate this thesis and the work in it to those who never stopped believing in me.

Table of Contents

Chapter 1

Introduction: Organic Nanotubes

1.1 Carbon Nanotubes: Inspiration for Organic Nanotubes

Carbon nanotubes (CNTs) are unique structures found in the insoluble material remaining from arc-burned graphite rods, among other methods of creation.[1] CNTs are one of the allotropes of carbon and they have many intrinsic properties (electronic, optic, etc.) which open up their use in a variety of applications.[1] The structural properties of CNTs are also desirable, since they can be used as scaffolding for composite materials.[1] CNTs, however, have some principle disadvantages that complicate their use. Among these are the multiple isomers that can be formed, which have different properties. Further difficulty arises in the creation of a single type of CNT and purifying different isomers.[1] Another challenge is creating a single walled CNT versus a multi-walled CNT, or nested CNT.[1] The next complication of CNTs is their solubility and finally, functionalization. CNTs are not soluble in water or organic solvents without some sort of functionalization. In doing so, there are many reactions that can be performed on a CNT, but control of where these reactions occur and the density of attached functional groups on a CNT is a matter dictated by statistics.[1]

Inspired by the wealth of applications for CNTs, chemists have been trying to overcome the complications associated with controlled CNT synthesis. Organic nanotubes (ONTs) present themselves as a solution to the disadvantages of using CNTs. This is primarily achieved through intelligent design in building the nanotube "bottom up" and with functionalities incorporated into the building blocks used. Variation in the building blocks will dictate properties such as the

solubility, functional groups, and reactive sites of the ONTs. More specifically, the density of the reactive sites can be controlled, the location of the reactive sites can be tuned for interior versus exterior selectivity, and finally, the size parameters, which consist of the diameter, pore size, and length of the ONT, can be controlled. Additionally, any other properties that are inherent to the molecules used to build the tubes, which include, but are not limited to: robust structure, electronic, transport, and host-guest interactions, can be included by variation of the building blocks.

If ONTs are the cure to the disadvantages of CNTs, how is this cure to be administered? An ONT is a structure that can have dimensions similar to or larger than a CNT, which typically has a 1 nm diameter with variable length. Since they are made up of smaller organic molecules, there needs to be a way to hold the tubes together through intermolecular interactions or a large number of covalent bonds. The ONTs that have been developed include single molecules that coil into tubular shapes, stacking of macrocycles, and amphiphilic assemblies. The early advances were highlighted in a previous review article.[2] These early examples of nanotubes demonstrated excellent progress towards realizing their practical applications. All of these examples were based on weak intermolecular forces and solvent interactions, so the ONT formed lacked the robustness which will be required for practical ONT applications. The solution for minimizing the structural dependence on solvent and intermolecular forces is covalent bonding. However, it introduces a complicated element which raises the question: How can many covalent bonds be made, while still producing ONTs in reasonable yields? We shall review recent advances in the field of ONTs first for a solution to this conundrum.

1.2 Types of Organic Nanotubes

The types of ONTs that will be discussed here will be classified based on their construction methods. The discussion will begin by introducing macrocycles that stack to adopt a nanotubular shape, followed by amphiphilic assemblies, bottlebrush copolymers, and finally, conclude with looking at discrete molecules that come together to form porous ONTs.

1.2.1 Stacked Macrocycles

The first strategy for designing ONT involves stacking and polymerizing macrocycles. The first method, used by Morin *et. al.* and illustrated in *Figure 1.1,* consists of stringing the macrocycles along a polymer core, crosslinking the outer rim of the macrocycles and then removing the templating polymer.[3]

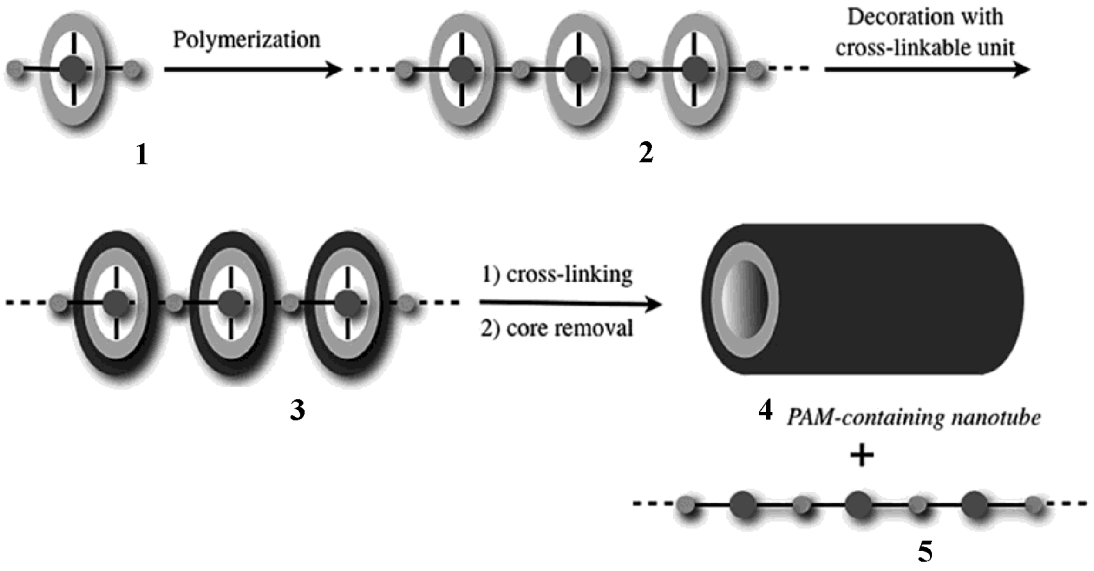
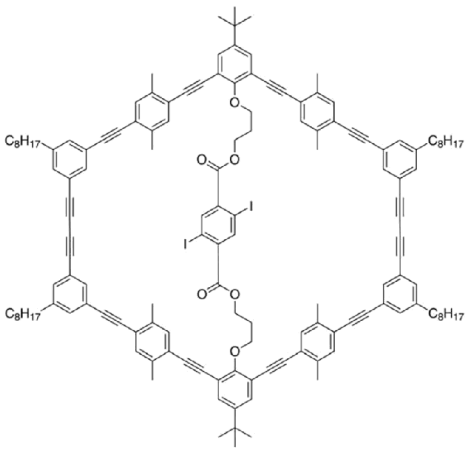
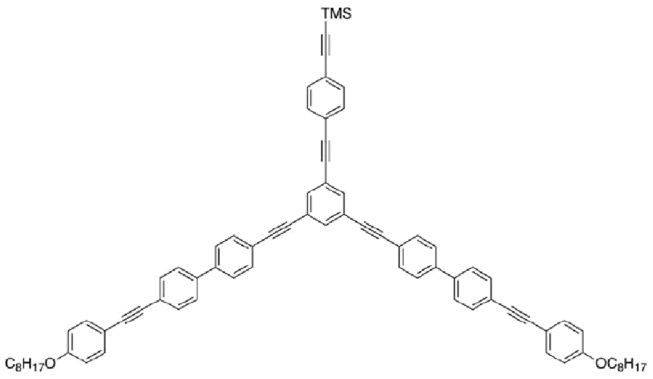


Figure 1.1: *Schematic representing the construction of an ONT using a polymer core as a template.*[3]

The stepwise synthesis yielded **6** shown in *Figure 1.2* in eight steps with a 12% overall yield. Two other macrocycles were attempted with Boc-protected amines, instead of the four alkyl chains in **6**, but both had low solubility in organic solvents and could not be used for the final coupling to form the polymer **2** shown in *Figure 1.1*.

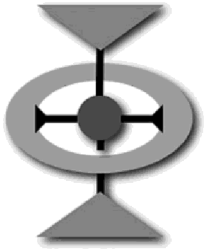


6



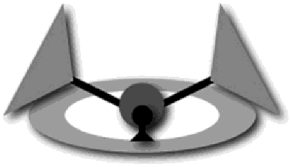
7

Figure 1.2: *Phenylacetylene macrocycle (PAM)* ***6*** *with central aryl diiodo core for polymerization of the macrocycles by the Sonogashira coupling. Bulky end group used to create a [2] rotaxane by the Sonogashira coupling.* [3]



Desired pseudorotaxane conformation

8



Undesired conformation

9

Figure 1.3: *Two possible structures resulting from the Sonogashira reaction of* ***6*** *with 7. In the desired conformation* ***8*** *the two bulky end groups are on opposite sides of the macrocycle and the undesired structure* ***9*** *comes from both bulky groups being on the same side of the macrocycle.*[3]

Unfortunately, complications arose with the synthesis of the PAMs, as well as an uncertainty as to whether the bonds forming at the core of the macrocycle were on the same side of the macrocycle or on opposite sides, as shown in *Figure 1.3*, with the former representing desired result. The polymer formed should be threaded through all of the macrocycles so they can be crosslinked to form the nanotube. Therefore, although the concept is valid and holds promise, further work is needed to make it a reality. Instead of installing crosslinkable groups to the macrocycles, another approach for constructing robust stacks is to polymerize the macrocycle backbones directly. This has been demonstrated by topochemical polymerization of diacetylenes. Lauher *et. al.* sought out a very robust ONT with a continuous network of covalent bonds.[4] For this to be achieved with diacetylenes, an ideal distance of 4.9 Å between the macrocycles must be present. Macrocycle **10**, shown in *Figure 1.4*, was designed for this reaction and formed in three steps with a 34% overall yield. Growing crystals was an important step in the synthesis of this ONT because it resulted in the ideal distance between the polymerizable diacetylenes. To form the crystals, a 1:1 solution of methylene chloride and hexanes was slowly evaporated yielding monoclinic crystals with a repeat distance of 5.09 Å. Crystal growth in the same solvent combination at 40 ^{o}C yielded triclinic crystals with a repeat distance of 4.84 Å. A sample of the latter crystal structure was slowly annealed at 40 ^{o}C over many days and after three days, polymerization occurred. The amount of polymer increased steadily until day 35 and then an increase in scattering was seen in the X-ray diffraction which indicated a loss in the ordered structure of the ONT.

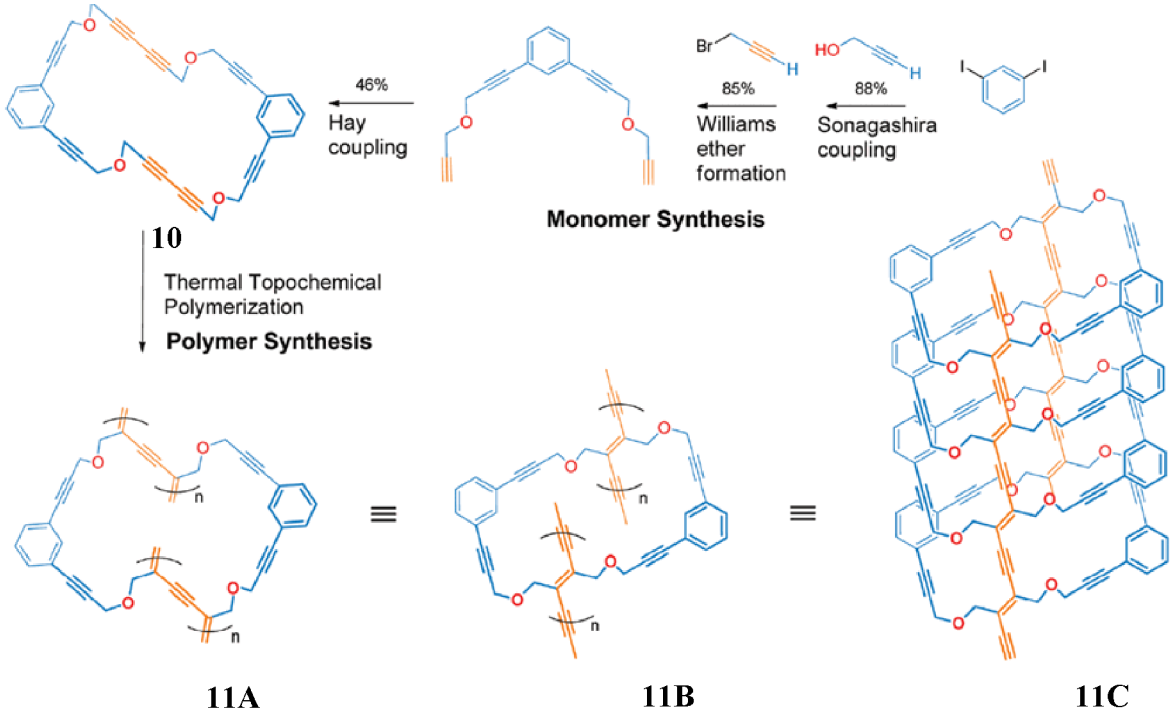
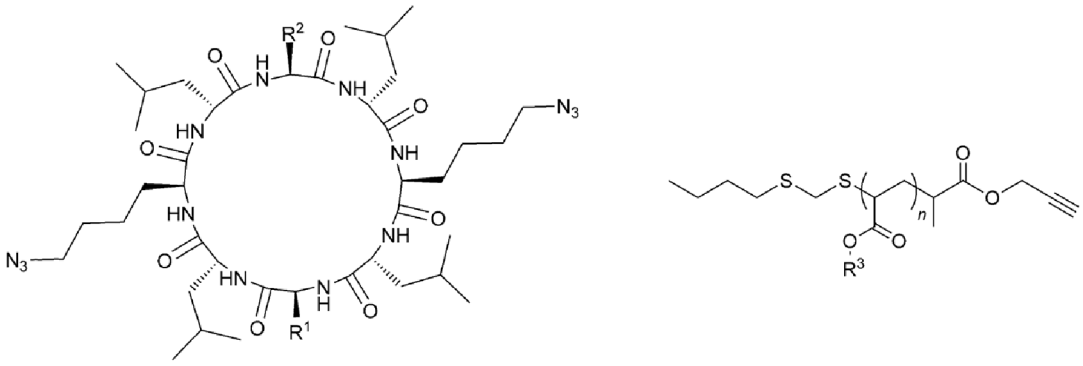


Figure 1.4: *Synthesis and polymerization of a diacetylene macrocycle to yield an ONT. Structures **11A** and **11B** can be identified by single-crystal X-ray diffraction.*[4]

The last example of a macrocycle stack forming an ONT is based on the conjugation of polymers to cyclic peptides. Jolliffe *et. al.* demonstrated that cyclic peptides with pendant azide groups can form ONTs through self-aggregation in solution, and polymers substituted with terminal acetylenes can be covalently attached to the ONTs through click chemistry shown in *Figure 1.5.*[5] The cyclic peptides had 2, 3, or 4 azide groups and the copper catalyzed triazole reaction produced 100% conversion for the peptides with 2 and 3 azides. The tubes were characterized by TEM and had dimensions between 50-100 nm in length and 8-12 nm in diameter. Complete hydrolysis of the polymer linker and the peptide could be performed by heating them in a 9:1 mixture of DMF and TFA.



12 **13**

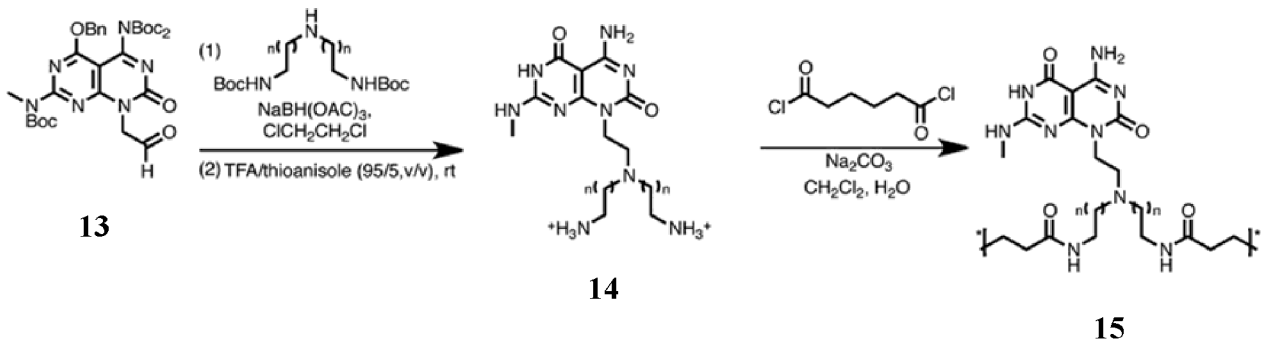
Figure 1.5: *Cyclic octapeptide* ***12*** *(R^1 and R^2 could be azides), and alkyne containing acrylate polymer* ***13****. When* ***12*** *and* ***13*** *are reacted by a copper-catalyzed azide-alkyne cycloaddition, they produced a water soluble ONT.*[5]

A pH-responsive modification was created by using a polymer composed of poly(acrylic acid) (PAA) which contained additional alkyne groups to conjugate to the peptides. When the pH of an aqueous solution is below 5, the carboxylic acid groups on the polymers are protonated and formation of the tube is possible. If the pH is raised, deprotonation occurs and the negatively charged polymers repel each other and therefore cannot hold the peptides together. This method of forming ONT shows great promise for bio-ONTs due to the water solubility of the product due to the synthetically simple nature of the method; it would also be favorable for large scale production.

1.2.2 Stacked Rosettes

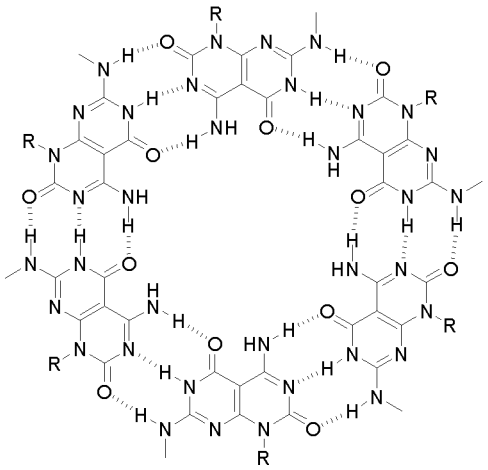
Another method for nanotube formation that is related to the "stacking and polymerization" approach is to form macrocycles first from rosettes and followed by covalent linkage of the rosette rings. This was demonstrated by Fenniri *et. al.* using a heterobicyclic molecule that has behaviors of both guanine and cytosine in terms of hydrogen bond donors and

acceptors.[6] The synthesis of the molecule is illustrated in *Figure 1.6*, along with the reaction with adipoyl chloride, which links all of the rosette pieces together in a nylon-type polymer.



13 **14** **15**

Figure 1.6: *Synthesis and polymerization of rosette* ***14*** *to form an ONT* ***16****. Two different rosettes were created where n=1 and n=2.*[6]



17

Figure 1.7: M*acrocycle assembled from six rosette pieces. Dashed lines indicate hydrogen bonding.*

The nanotube formed has a diameter of 3.4 ± 0.2 nm and has an indeterminate length. The promise this work holds is in the facile synthesis of the rosette pieces, their potential customizability which affects the inner and outer functionalities of the tube, and the self-assembly behavior in the construction of the tube.

1.2.3 Self-Assembled Amphiphiles

The next class of nanotubes comes from self-assembled amphiphiles. A large portion of the work advanced in this field has been reported by Masuda *et. al.*[7] The basic concept underlying their work is the construction of the relatively simple amphiphilic molecules that have alkyl chains with *cis* double bonds and a polar head group. A recent example is shown in *Figure 1.8*.[8]

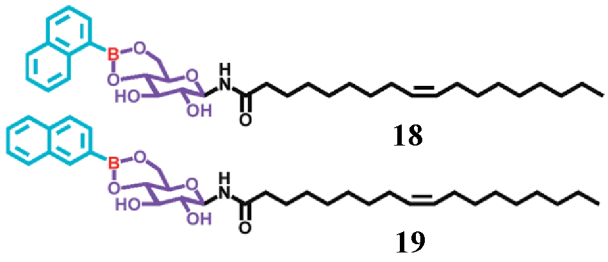


Figure 1.8: *Amphiphilic monomer used to construct bilayer nanotapes **18** and nanotubes **19**.*[8]

The goal of this work was to construct a light harvesting scaffold. To achieve this goal, a glycolipid and naphthalene-boronic acid were coupled and the location of the borate ester linkage on the naphthalene determined the self-assembly of the structure. Structure **18** yielded bilayer nanotapes and **19** yielded the desired nanotubes. Once the nanotube was assembled, it can act as a host for anthracene. Anthracene was chosen as a guest because its absorption band overlapped with the fluorescence band from the naphthalene contained in the nanotube wall. The naphthalene groups in the nanotube were excited with light at a wavelength of 280 nm and emission occurred at 350 nm. When the guest was inside the nanotube, the same 280 nm excitation resulted in a redshift of the emission to 400 nm, representative of fluorescence from anthracene which demonstrated energy transfer between the two species. Fluorescence experiments also revealed that anthracene in the bulk solution, and not in the nanotube channel,

would not show energy transfer between naphthalene and anthracene. This transfer of energy between ONTs and their guest species holds great promise for potential applications in light harvesting for solar energy. Another possible application this type of nanotube could be used for the separation and conduction of electron/hole pairs, where one would travel along the surface of the tube and the other along the guest in the nanotube cavity.

A second novel advancement in the area of amphiphile nanotubes is based on the host-guest interaction of an α-cyclodextrin as an end group on a poly(caprolactone) (PCL) with a single *trans*-azo capped PAA.[9] These short polymers can be combined in water to yield nanotubes with the PCL chains on the interior of a bilayer, which composes the wall of a tubby (1.5 nm < length/diameter < 3.0 nm) nanotube shown in *Figure 1.9*. The nanotube was shown to have reversible assembly/disassembly behavior in response to the isomerization of the *trans*-azo group to *cis*-azo when irradiated with 365 nm light. This would enable the release of a guest from the nanotube with a photo trigger.

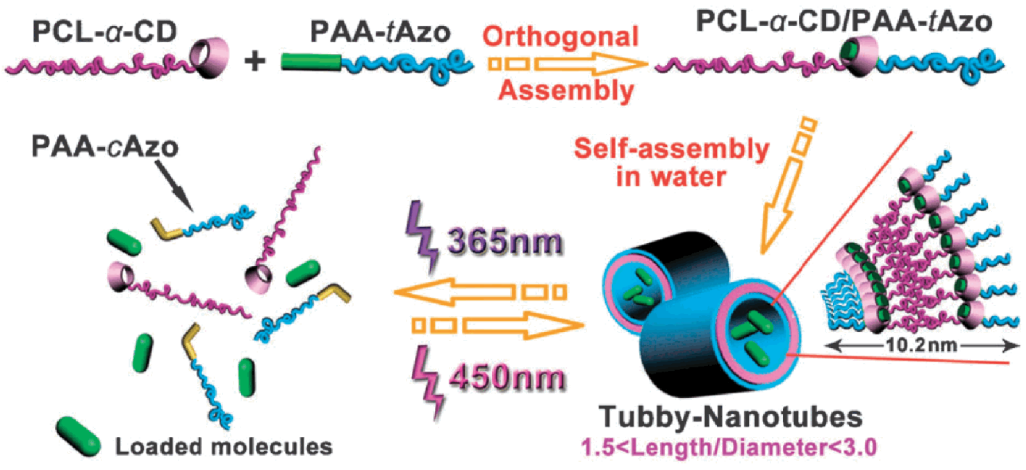
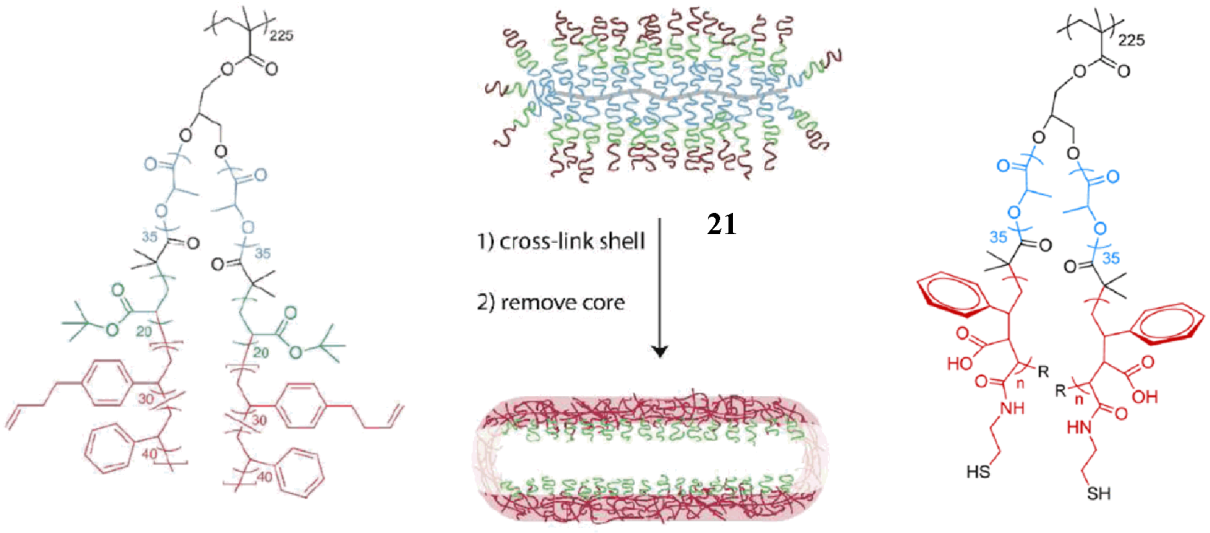


Figure 1.9: *Schematic depicting the reversible assembly and disassembly of the amphiphilic nanotube with a guest.*[9]

1.2.4 Bottlebrush Copolymers

The next type of ONTs comes from bottlebrush copolymers which are composed of long polymeric backbones with densely grafted, shorter polymer chains. The density of the grafted chains leads to the overall shape of the polymer in solution.[10] Two examples of nanotubes constructed by this method are shown in *Figure 1.10*. The first is constructed with an inner polylactide (PLA) block, a middle block of poly(*t*-butyl acrylate) to control functionality on the interior of the tube, and an outer poly(styrene-*ran*-(4-(3-butenyl)styrene)) block. Crosslinking occurs at the outer block by reaction of the styrene groups with a Grubbs catalyst. Once crosslinked, the core of the bottlebrush polymer was removed by acidic hydrolysis of the PLA block. At the same time, the *t*-butyl groups were deprotected, which left the newly formed cavity coated with acrylic acid groups and thus rendering the interior of the tube hydrophilic.



20 **22** **23**

Figure 1.10: *Two bottlebrush copolymers **20** and **23**. Crosslinking of the outer shell is by alkene metathesis for **20** and disulfide exchange for **23**. A bottlebrush copolymer **21**, which is*

crosslinked, then the core is removed by acidic or basic hydrolysis of the PLA inner block to yield the nanotube ***22****.*[10,11]

The experiment shown in *Figure 1.11* demonstrated the selectivity of the nanotubes for binding positively charged, water soluble dyes. The positively charged dye, methylene blue (**MB)**, was observed in the chloroform layer in the presence of ONT with the hydrophilic interior. The same mixing experiment was repeated with a negatively charged dye, alizarin red S (**ARS)**, which resulted in an absence of the dye in the cavity of the tube as indicated by the color of the chloroform layer.

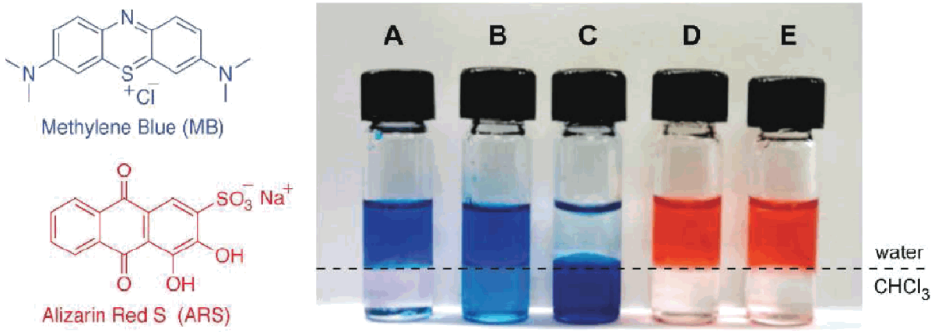


Figure 1.11: *(A) [MB]/$CHCl_3$, (B) [MB]/[ONT without PAA], (C) [MB]/ONT with PAA, (D) [ARS]/$CHCl_3$, (E) [ARS]/ONT with PAA. Each vial was shaken for 5 minutes with all components of the solution present.*[10]

A similar bottlebrush copolymer was created by reductive crosslinking thiol groups to form disulfide groups on the exterior of the nanotube.[11] These nanotubes have the same host-guest properties as the previously mentioned tubes, but the principle difference between them is the biodegradability. These tubes were composed of the same PLA core, but now contained a poly(styrene-co-maleic anhydride) shell. Reaction of the anhydride with cysteamine converted ~30% of the anhydrides to thiols. Oxidation of the thiol groups crosslinked the outer shell of the

polymer forming the initial structure of the nanotube. Hydrolysis removed the core of the bottlebrush polymer and converted the remaining anhydrides to carboxylic acids, resulting in a nanotube that was water soluble. The nanotube was stable for days in an aqueous medium, but upon the introduction of a reducing agent, dithiothreitol (DTT), the disulfide linkages were broken and the tube degraded into small molecules. The potential for biodegradability comes from the naturally reducing environments of endosomes, lysosomes, and cytosol.[12, 13]

1.2.5 Porous Network Materials

The final type of ONT to be discussed is a network polymer that self-assembles into a rare, template free nanotube structure.[14] The porous network was assembled from the 1:2 ratio of tetra(4-ethynylphenyl)methane and *N,N'*-di(4-iodophenyl)-4,4'-bipyridinium dichloride building blocks through a Sonogashira coupling in 3:2:2 toluene, methanol, triethylamine solution as shown in *Figure 1.12*.

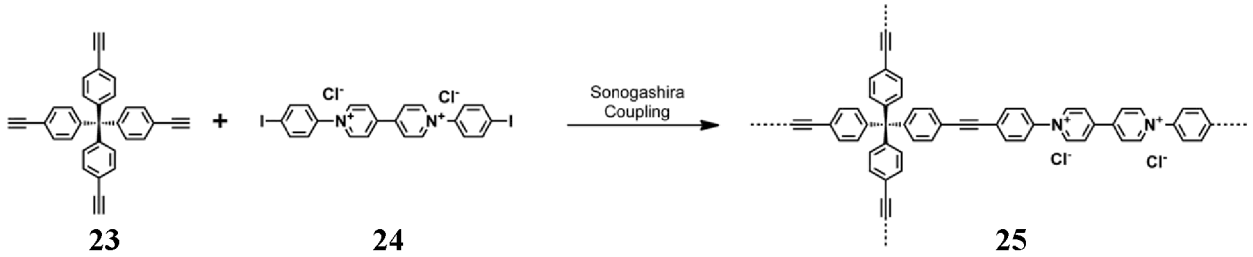


Figure 1.12: *Polymerization reaction to form the porous organic nanotube.*[14]

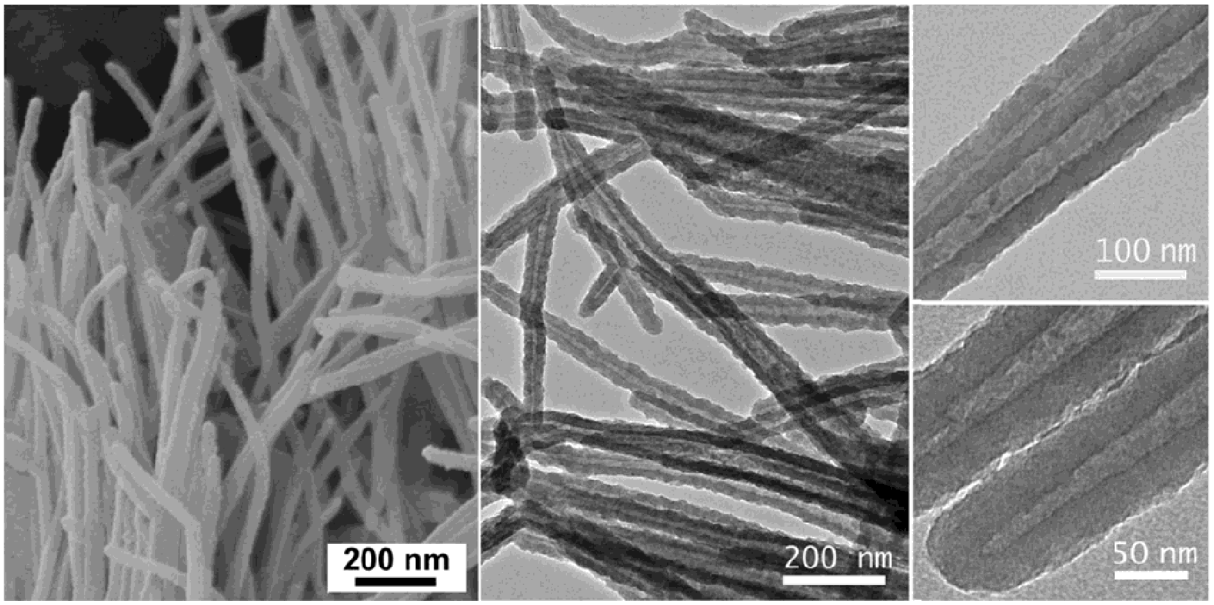


Figure 1.13: *Left: SEM image of porous ONTs. Center, right top and right bottom: TEM images of porous ONTs.*[14]

The average diameter and thickness of the tubes created was 92 ± 19 nm and 31 ± 4 nm, respectively. The mechanism by which these structures are formed is not clear, however the solvent combination and charges on the pyridinium component were found to be essential to the reaction. When only toluene or methanol was used, in addition to the triethylamine, only amorphous powders were produced. Porous structures like this have found application in gas storage and separation. Additionally, they can be used as templates for inorganic materials, especially given the unique structure of the tube. The ONT was reacted with iron carbonyl to uniformly coat the porous surface with iron and then was combusted to remove all of the organic material, resulting in a porous iron oxide nanotube. The inorganic nanotube demonstrated excellent properties as an anode material for a lithium ion battery. This method breaks away from the conventional use of an ONT, but is important in expanding the possible applications of ONTs.

1.3 Conclusions

Let us return to the question posed at the beginning, "How can many covalent bonds be made, while still producing ONTs in reasonable yields?" The best examples of nanotubes presented here make use of two concepts to deliver materials in high yield. First, a self-assembly method is used to place all components into the desired nanotube shape. Self-assembly characteristics are built into the molecules used for the construction of ONTs. Second, various reactions are used to connect or cross link all of the components with covalent bonds in high yields, which resulted in robust ONT structures. Out of the work discussed here, the methods that adhere best to these two concepts are ONTs from cyclic peptides, stacked rosettes, amphiphiles, bottlebrush copolymers, and porous network materials. The cyclic peptides, rosettes, and amphiphiles both follow a two-step process of self-assembly, followed by covalent bonding. Bottlebrush copolymers skip the self-assembly stage by having all of the nanotube components linked together initially in a polymer. Crosslinking yielded excellent secondary bond formation and removal of the polymer core produced the ONT. The porous nanotube combines both of these concepts into one step by simultaneous self-assembly and covalent linkage. A third concept which was not addressed by all ONT types was control of the nanotube length. This is also an essential component to the overall ONT picture. All of these methods demonstrated good formation of the target nanotubes and the facile nature of their synthesis would allow for large scale production of the nanotubes. ONTs offer a wealth of applications and approaches that solve some of the major issues encountered with CNTs.

Chapter 2

Attempted Synthesis of ONTs Containing a Rigid Linker

2.1 Introduction

We wish to achieve controlled synthesis of Organic Nanotubes (ONT), due to the wide scope of existing and theoretical applications which have been reviewed in chapter 1. ONT are modeled after carbon nanotubes (CNT), but have several advantages over them. Namely, our proposed method addresses three aspects of ONT design which determine the properties of the nanotubes, thus the applications they can be used for. The first aspect that we seek to the control is the length and diameter of the tube. Secondly, control over the chemical functionality in terms of the solubility of the nanotube (organic or aqueous). Finally, tailoring the chemical environment inside and outside of the tube.

2.2 Nanotube Design

The ONT design which was pursued here utilized the stacked macrocycle motif. The path taken to achieve the nanotubes has two underlying concepts which need to be understood before we can advance to the work completed: (1) living polymerization and (2) preorganization of the polymerizable groups.[15] The first is the living polymerization of the norbornene groups, which gives control over the molecular weight and also the polydispersity index (PDI). The second element is the preorganization of the norbornene groups to allow polymerization to take place without defects or branching along the polymer backbone. Defects would be most prevalent for the second norbornene group on the opposite side of the macrocycle.

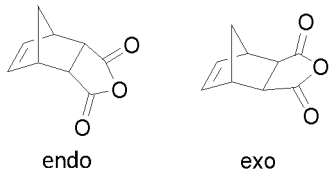


Figure 2.1: *Stereochemistries of the Diels-Alder reaction for producing norbornene dicarboxylic anhydride.*

The preorganization can be affected by several factors. First, the stereochemistry of the norbornene groups must be pure endo or exo to achieve the best packing of the macrocycles. The Diels-Alder reaction used to create the starting material can produce two products with either endo or exo stereochemistry as shown in *Figure 2.1*. The exo product is thermodynamically more stable; however, the endo product is kinetically favored. Therefore, the endo product forms faster. The next aspect affecting preorganization is how the norbornene is connected to the macrocycle. The best way to connect the norbornene groups, as professed by Luh *et.al.*,[15] is by an aryl amine due to the π-π stacking of the aryl ring. On the opposite side of the aryl ring is an ester group and this, though not explicitly stated as important, will also have an effect on the preorganization of the norbornene group for polymerization.

The molecules used to construct the nanotubes are shown in *Figure 2.2*. There are four methods to construct ONTs via the complimentary half macrocycles used. These methods are shown in *Figure 2.3*. The first method is the formation of the macrocycles through imine condensation/metathesis, followed by a polymerization of the macrocycles. The second method involves polymerizing one half of the macrocycle first, either the amine or the aldehyde monomer, mixing in the complimentary half and polymerizing the second norbornene group to "zip up" the nanotube. The third approach polymerizes the monomers separately and then covalently assembles the two complementary polymers into a tubular structure through imine condensation reaction. The final method of creating the nanotube entails two different

polymerizable groups on the macrocycle. The first step would be forming the macrocycle, then polymerizing one side of the macrocycle, and finally polymerizing the remaining side of the macrocycle. This final method would require two orthogonal polymerizable groups.

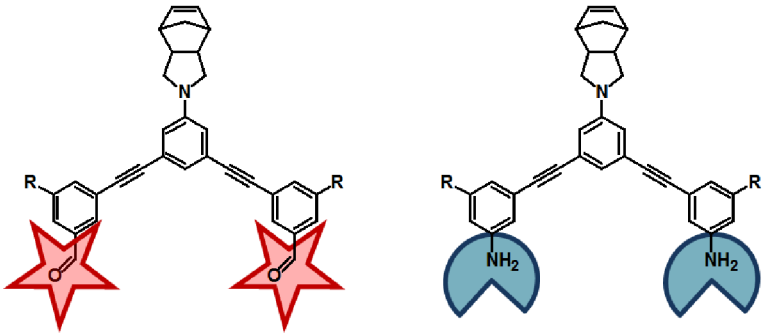


Figure 2.2: *Monomers designed for nanotube formation.*

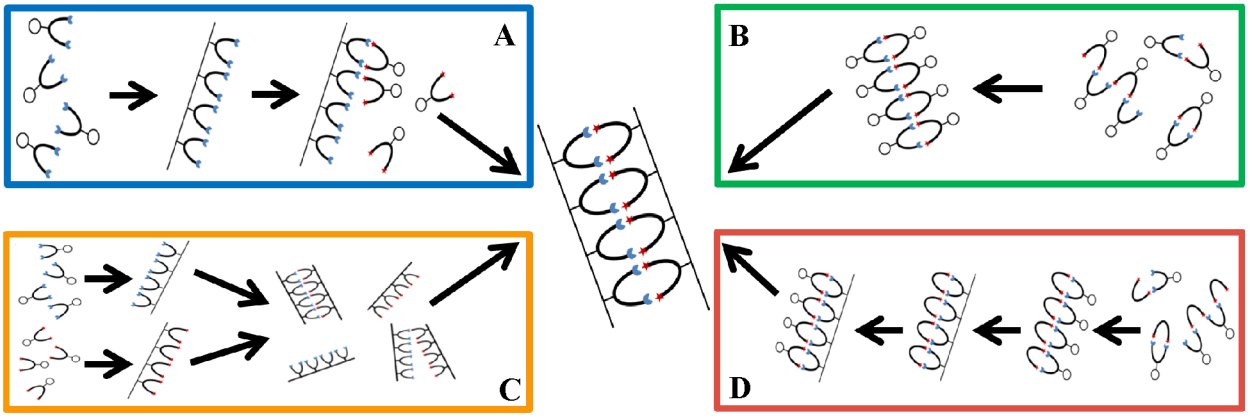


Figure 2.3: *Proposed methods for nanotube formation. Method **A** = Polymer + Monomer. Method **B** = Monomer + Monomer. Method **C** = Polymer + Polymer. Method **D** = Orthogonal Polymerization.*

2.3 Building Block Synthesis

The synthesis of the macrocycles was accomplished by making two macrocycle halves, one containing two amines and the other with two aldehydes. Each half of the macrocycle is prepared from two types of building blocks. The first component is the rigid centerpiece (RCP) which contains the norbornene group. The second components are two end pieces which

contains either an amino or a formyl group. The synthesis of the RCP is shown in *Figure 2.4*. The syntheses of the end pieces are shown in *Figure 2.5*.

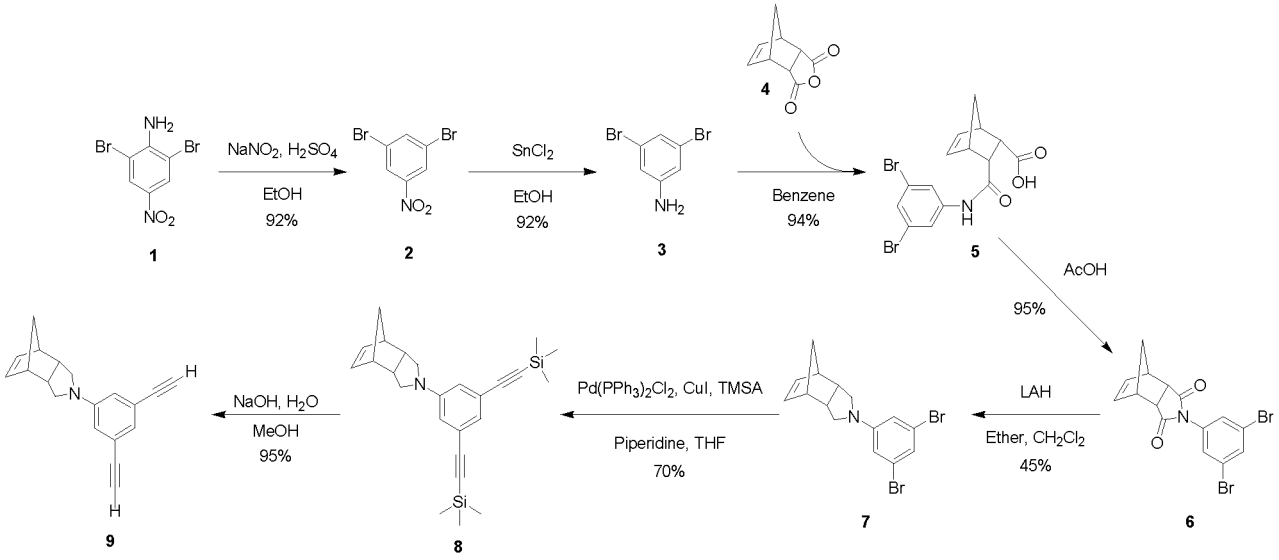


Figure 2.4: *Synthesis of the Rigid Center Piece (RCP).*

The synthesis of the RCP began with the deamination of 2,6-dibromo-4-nitroaniline with $NaNO_2$, and H_2SO_4 in refluxing ethanol to form **2** in excellent yield.[16] The orange-brown solid was then subjected to a $SnCl_2$ reduction to produce 3,5-dibromoaniline in high yield after purification by silica gel chromatography.[17] For the next reaction, both **3** and **4** were dissolved in benzene and the polar amido acid **5** precipitated out.[18] In the original procedure for this reaction, the reaction proceeded at r.t. and took 4-7 days to complete. At the end of the reaction, both starting materials were still present, which was confirmed by NMR, so the reaction mixture was concentrated and saved for future use. The yield was 42% for the first trial, but subsequent trials achieved high yields. This is due to having a pre-saturated solution of benzene. It was common to begin the reaction with undissolved starting materials in the solution, which would gradually dissolve as product precipitated. After sufficient product was created in the reaction, the solid was collected by filtration, washed with benzene, and **5** was collected in high yield. In the next

step, the off-white solid was dissolved in acetic acid and refluxed overnight.[18] The yield was high for the reaction and no purification was necessary.

After closing the amido acid to the imide **6**, lithium aluminum hydride (LAH) was used to reduce it to a tertiary amine.[18] This reaction required optimization due to reduction of the aryl bromides by LAH. The debrominated side product had very little polarity difference from the desired product, and could not be separated by column chromatography. The first few trials did not rigorously separate the side product and purification was delayed until after the Sonogashira reaction. Strict adherence to the reaction time prevented debromination of **7**. Reacting for 40 minutes at r.t. from the time the starting material was added to when the quenching began was enough time to ensure complete reaction without reducing the aryl bromides. When purifying the product by column chromatography, the highest yield achieved was 60%, even though the crude product ^{1}H NMR showed only the desired product in the optimized trials. The cause of the product loss was never identified, but it is believed to arise from the alumina residues complexing with the amine, and thus resulting in the polar complex binding to the silica. Neither washing the column with a polar solvent nor soaking the silica gel overnight in a polar solvent recovered any additional product. Given the purity of the product by NMR, one trial was not purified at this step and used directly for the Sonogashira coupling. This reaction still suffered from an unusually low yield, so pure product was used for future reactions. The next step in the synthesis is a Sonogashira coupling with trimethylsilylacetylene (TMSA), CuI, piperidine, and $Pd(PPh_3)_2Cl_2$ in THF, which produced the protected diacetylene in good yield after column chromatography.[19] The last step for the creation of the RCP was deprotection of the TMS group by sodium hydroxide in methanol.[20] A final column separation produced pure diacetylene **9** in good yield.

Synthesis of the amine and aldehyde end pieces was the next step towards the ONT. The amine end piece was made from 3-bromo-5-iodobenzoic acid via the Curtius rearrangement.[21] The aldehyde end piece was made from the same starting material by first reducing the carboxylic acid **10** to alcohol **11** with borane in THF, followed by Swern oxidation of **11** to aldehyde **12**.[22,23] These reactions are shown in *Figure 2.5*.

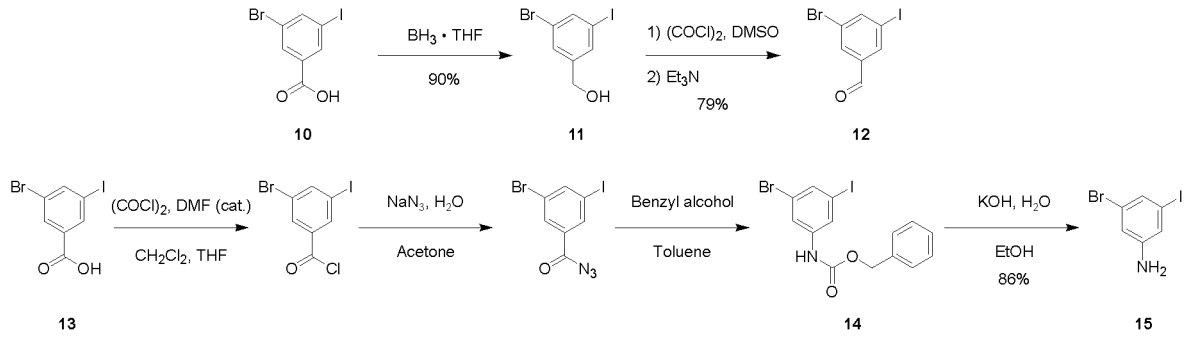


Figure 2.5: *Synthesis of amine (Am) and aldehyde (Al) end pieces.*

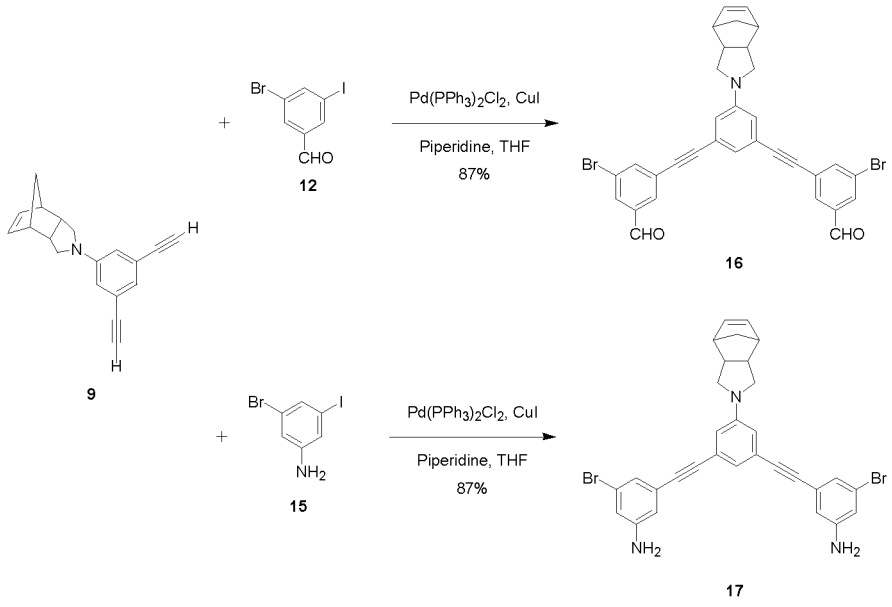
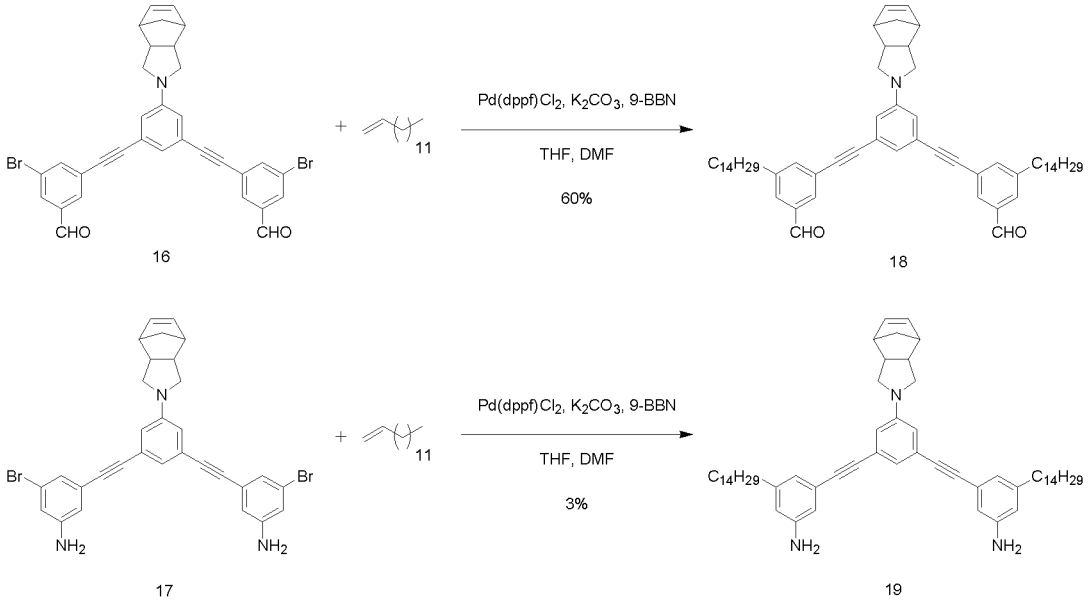


Figure 2.6: *Synthesis of dialdehyde (DAl) and diamine (DAm) monomers.*

The next stage of the synthesis is to combine the RCP with each of the end pieces through Sonogashira couplings to produce **16** (dialdehyde, DAl) and **17** (diamine, DAm) as shown in *Figure 2.6*.[19]

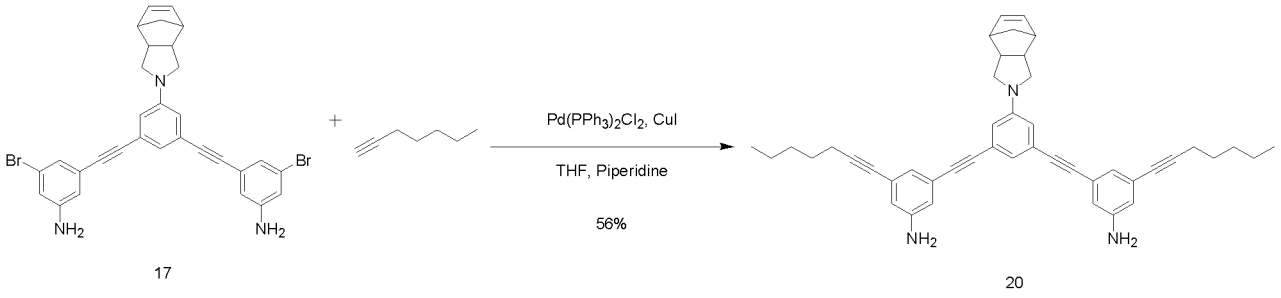
2.4 Attempted Nanotube Synthesis

Once the DAl and DAm monomers were prepared, preliminary studies of polymerization and macrocyclization were performed. Polymerization of both DAm and DAl, in addition to the macrocyclization reactions, created precipitates which indicated that the polymers and macrocycles were not sufficiently soluble. This result was anticipated. The available aryl bromide on both of the amine and aldehyde end pieces was then coupled to an alkyl chain to increase solubility. A Suzuki coupling was used to install two tetradecyl chains on both DAl and DAm monomers ($Pd(dppf)Cl_2$, K_2CO_3, and 9-BBN in a THF/DMF mixture) as shown in *Figure 2.7*.[24] The DAl monomer reacted well to make **18** (DAlTd), but the DAm monomer did not produce the alkylated product. It was not certain whether the Suzuki coupling conditions selected would work on this particular substrate, so to make further progress towards nanotube formation, a different solubilizing chain was chosen. The DAm monomer was reacted with 1-heptyne in a Sonogashira coupling to produce **20** in moderate yield seen in *Figure 2.8*. After continued trials, the Suzuki coupling produced the desired product **19**, but the reaction was still fraught with low yields. To remedy this problem, the Curtius rearrangement was stopped at the carbamate stage **14** and the deprotection was done after the alkylation as shown in *Figure 2.9*.



16 18 17 19

Figure 2.7: *Synthesis of dialdehyde with tetradecyl chain (DAlTd) and diamine with tetradecyl chain (DAmTd) monomers.*



17 20

Figure 2.8: *Synthesis of diamine monomer with heptyne alkyl chain (DAmHy).*

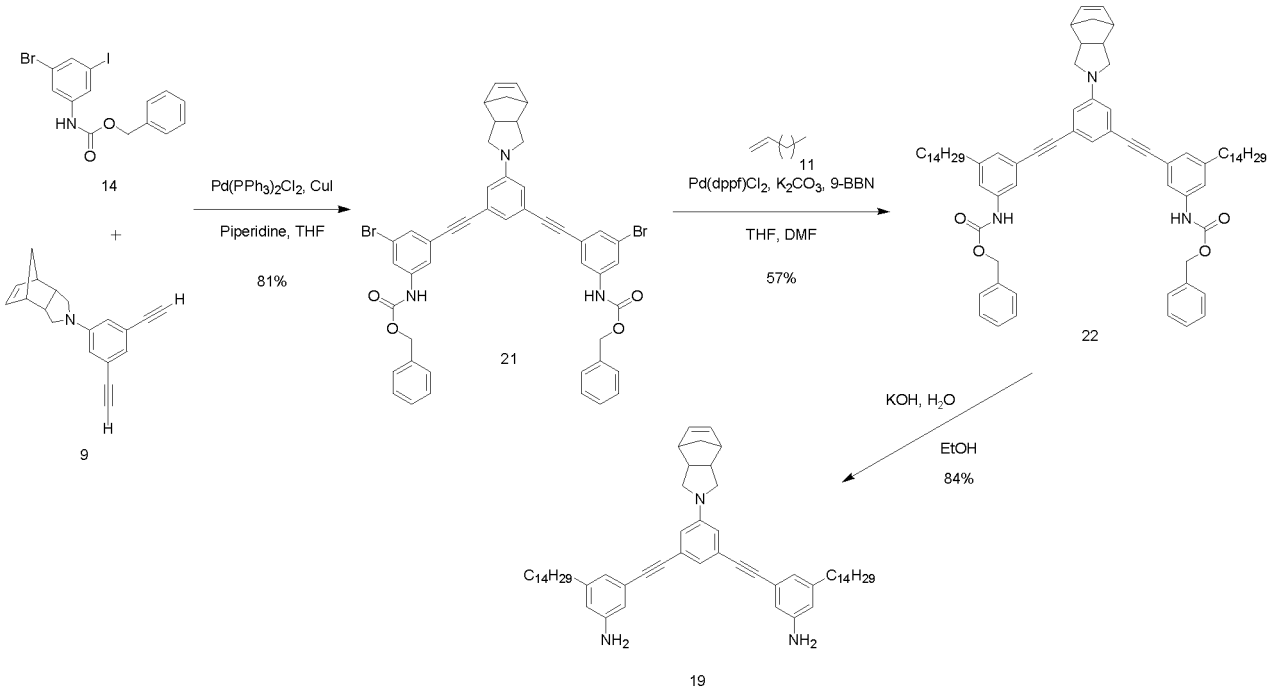


Figure 2.9: *Alternate synthesis of DAmTd monomer.*

Now with the two monomers containing alkyl chains, prepared, the first method explored for the nanotube formation was the Polymer + Monomer (Method **A**) shown in *Figure 2.3*. Grubbs' alkene metathesis catalysts were used for all polymerizations and several types are shown in *Figure 2.10*.[25] Both Grubbs' 2nd generation and Grubbs-Hoveyda 2nd generation catalysts were tested and both resulted in significant amounts of precipitates formed during the reactions. The 1st generation catalyst was then used exclusively for all of the polymerizations after getting better Gel Permeation Chromatography (GPC) results from both monomers. Both DAl and DAm were polymerized independently to gauge if one monomer was a better candidate for the "polymer" portion of the nanotube and the general scheme for the reaction is shown in *Figure 2.11*. The GPC traces for both reactions are shown in *Figure 2.12*. The diamine for both the heptyne and the tetradecyl monomers appeared to react slower, but produced polymers of similar molecular weights.

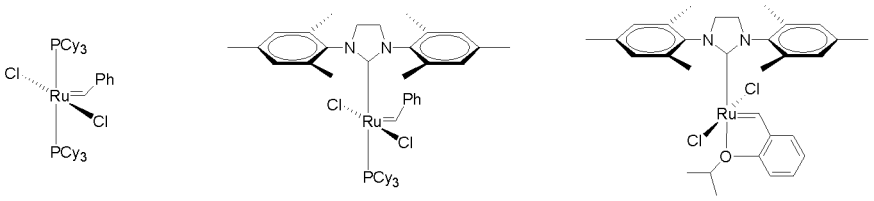


Figure 2.10: *Several types of alkene metathesis catalysts. From left to right: Grubbs' first generation, second generation, and Grubbs-Hoveyda second generation catalysts.*[26]

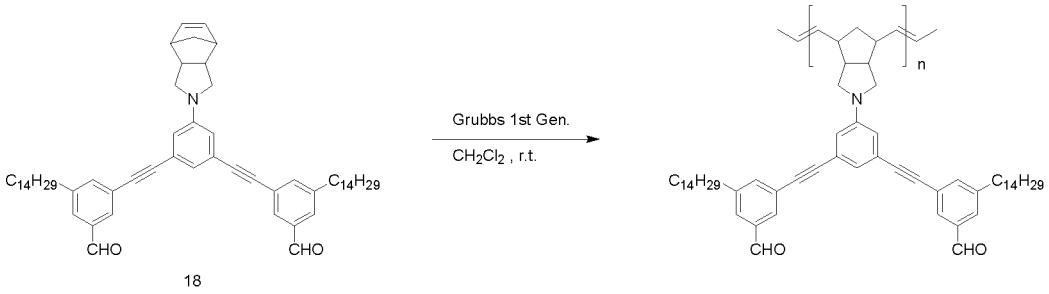


Figure 2.11: *General polymerization conditions for the Polymer + Monomer method.*

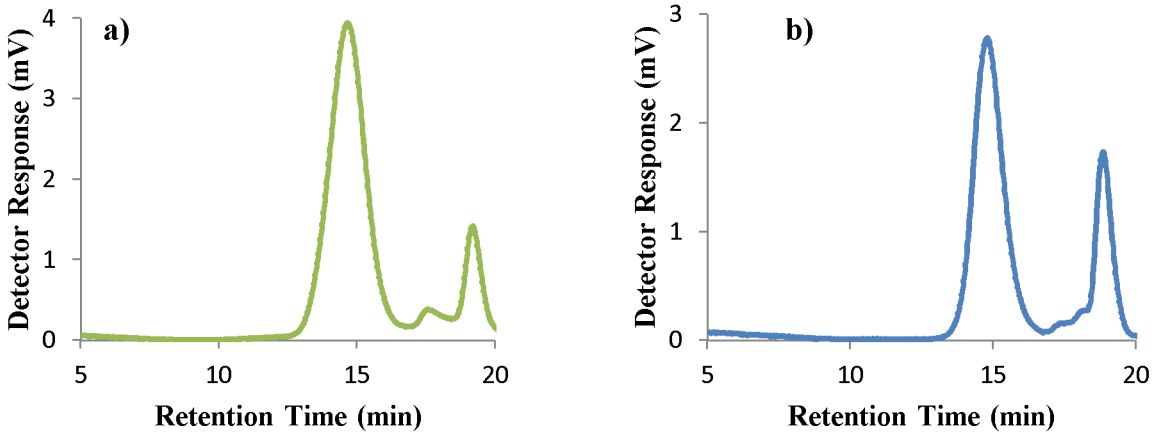


Figure 2.12: *Polymerizations with Grubbs first generation catalyst. a) DAmTdP retention time = 14.68 min, Mn = 10,755, Mw = 12,124, PDI = 1.127. b) DAlTdP retention time = 14.82 min, Mn = 9,724, Mw = 10,531, PDI = 1.081*

The next step was to react the polymers of DAlTd and DAmTd, DAlTdP and DAmTdP, respectively, with the complimentary monomers. The polymer and complimentary monomer

were dissolved in chloroform with a catalytic amount of scandium triflate (or TFA) and the reaction was stirred at r.t. for 1-24 hours. Both of the reactions, using either DAlTdP or DAmTdP, did not work as expected.

GPC was used to determine whether or not the reaction was proceeding. The GPC trace for the imine metathesis reaction between DAlTdP and DAmTd is shown in *Figure 2.13*. The doubling of the molecular weight of the polymer was not observed, which was the anticipated result of a successful reaction sequence at this step.

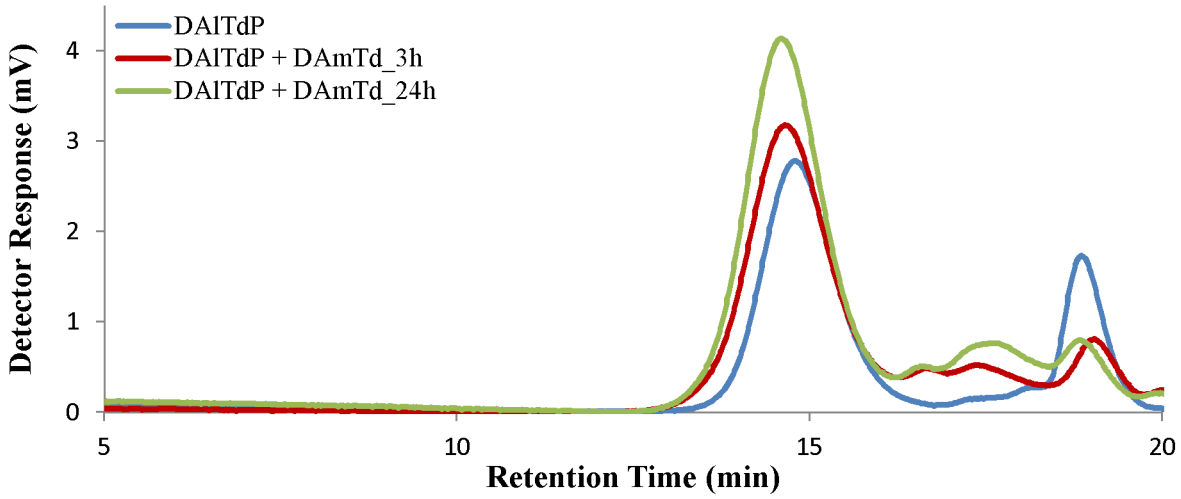


Figure 2.13: *Polymer + Monomer approach using a polymer of **18** with **17** under standard imine metathesis conditions seen in Figure 2.15.*

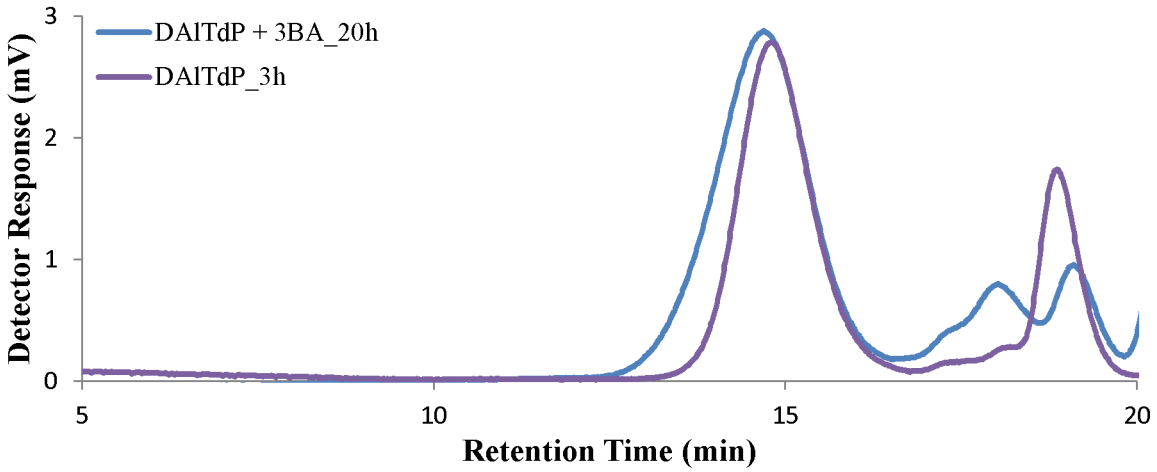


Figure 2.14: *Model reaction with DAlTdP and 3-bromoaniline.*

^{1}H NMR was unable to confirm if the reaction worked either. After several attempts, including variation of conditions for this reaction, with the amine and aldehyde polymers, simplified model reactions were conducted, in which 4-bromobenzaldehyde and 3-bromoaniline were reacted with DAmTdP and DAlTdP, respectively, under the same reaction condition as previously used. The GPC trace for the imine metathesis reaction between DAlTdP and 3-bromoaniline is shown in *Figure 2.14*. There was no detectable change in the molecular weight by GPC nor was there an appearance of an imine peak in the ^{1}H NMR spectrum. The conclusion drawn at this point was that while the polymer was formed, there was some unknown factor which hid or deactivated the reactive sites of the polymer, thus preventing it from reacting with the complimentary amine or aldehyde. The unidentified factor could take the form of intermolecular reactions between polymer chains or conformations adopted by the individual polymers. Based on the poor results of the Polymer + Monomer approach, it was believed that the Polymer + Polymer (*Figure 2.3*, Method **C**) approach would be less likely to be successful. Since the Orthogonal Polymerization (*Figure 2.3*, Method **D**) approach would take a significant amount of new synthetic work, focus was turned towards the Monomer + Monomer approach.

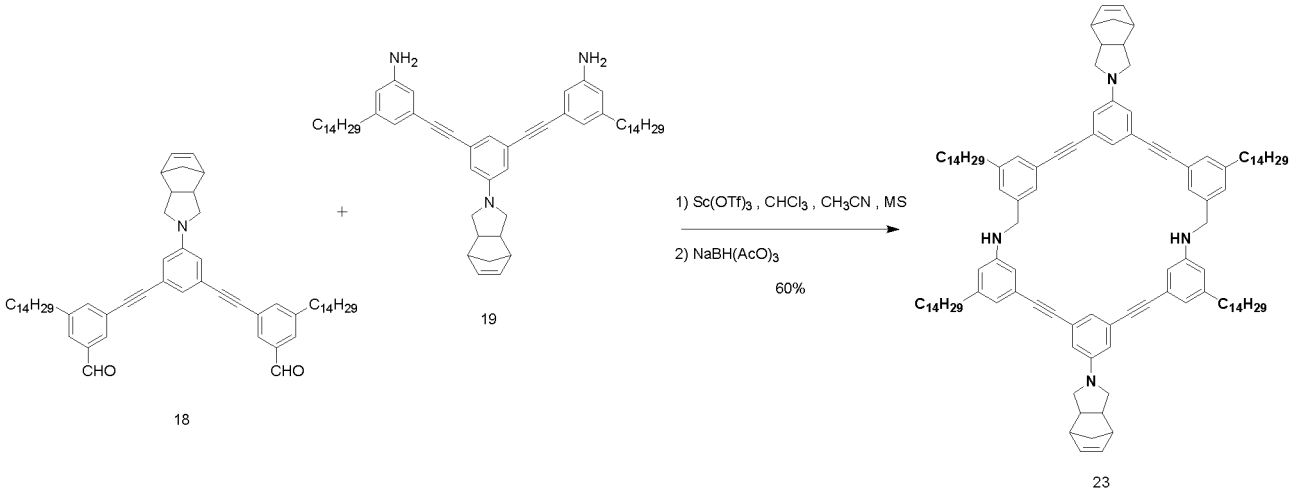


Figure 2.15: *Imine formation and metathesis of DAlTd and DAmTd monomers which initially forms the imine macrocycle (IMC) catalyzed by scandium triflate. The amine macrocycle (AMC) is formed after reduction with sodium triacetoxy borohydride.*

The Monomer + Monomer approach utilized both DAlTd and DAmTd and first assembled them through imine metathesis/condensation into a macrocycle.[27] The formation of the macrocycle was facile. The initial macrocycle formed contained an imine linker connecting the two halves of the macrocycle and could be reduced into the more robust amine. The shape and conformation of the macrocycle is very important to the success of this method, because it determines how closely the norbornene groups can come to one another, especially since parallel polymerization of adjacent norbornene groups is desired.

The amine macrocycle (AMC) was initially chosen for polymerization because it is more stable in the presence of water and more soluble in organic solvents. Several attempts to polymerize the AMC were not successful. An investigation into the conformational behavior of the AMC was necessary to determine if conformation was a factor preventing nanotube formation. Two studies were pursued to aid in understanding the differences between the IMC and the AMC: Spartan calculations and an NMR aggregation study. The former entailed

building each of the macrocycles, less the tetradecyl solubilizing chains, and calculating the thermodynamic equilibrium conformation at each macrocycle's lowest energy conformation. The calculations were performed at the PM3 level on Spartan '04. *Figure 2.16* shows the resulting calculations for the side view, (a) and (b), and the top view, (c) and (d), of the AMC and IMC, respectively.

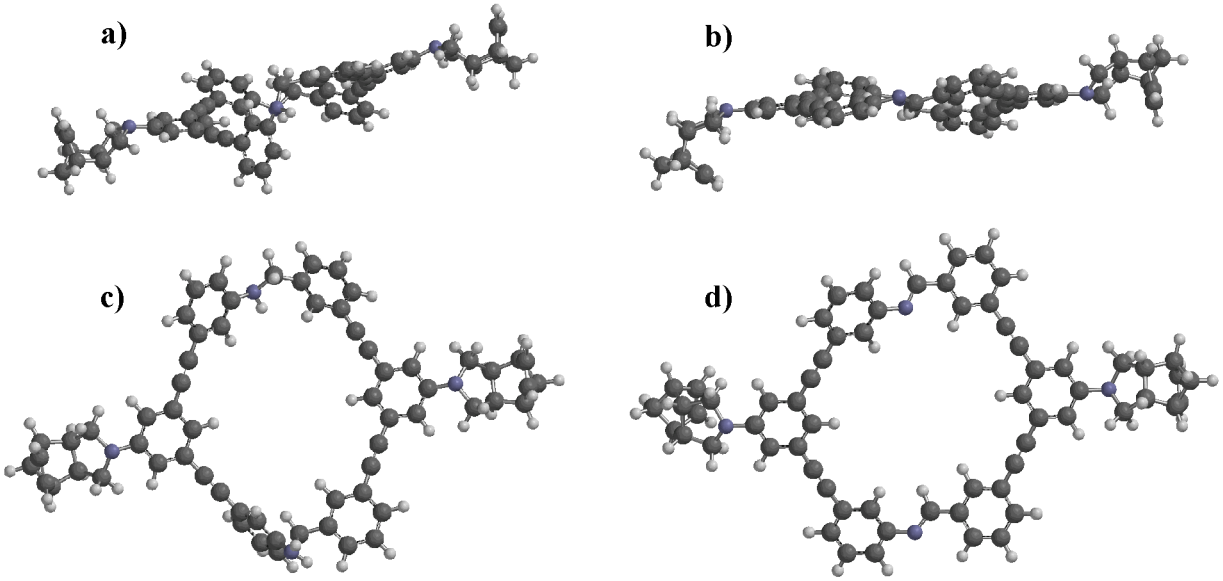


Figure 2.16: *a) AMC side view, b) IMC side view, c) AMC top view, d) IMC top view.*

From the Spartan calculations, both macrocycles appear to have a twist in the conformation, with the twist in the AMC being more predominant. Based on this data, it would appear that the IMC would be a better candidate to form a stack of macrocycles, and ultimately produce the ONT. The NMR study was performed at r.t. in $CDCl_3$ and 6 different concentrations were investigated for both the AMC and IMC. The AMC had a downfield shift of 0.006 ppm as the concentration was varied from 0.15 mM to 12 mM. The IMC was measured from 0.175 mM to 14 mM and an upfield shift of 0.052 ppm was seen as indicated in the plots for *Figure 2.17*. This confirmed the data from the Spartan calculations, which suggested that the AMC may not aggregate to a significant extent. Based on these results, isolation and reaction of the IMC was

sought out as the ideal way to form the nanotube. Isolation of the IMC was attempted, but it was not successful due to solubility and its susceptibility to hydrolysis. Several attempts were made to polymerize the imine macrocycle directly after formation and in the same reaction flask, but they failed. Further attempts were made to polymerize the AMC and those were also unsuccessful.

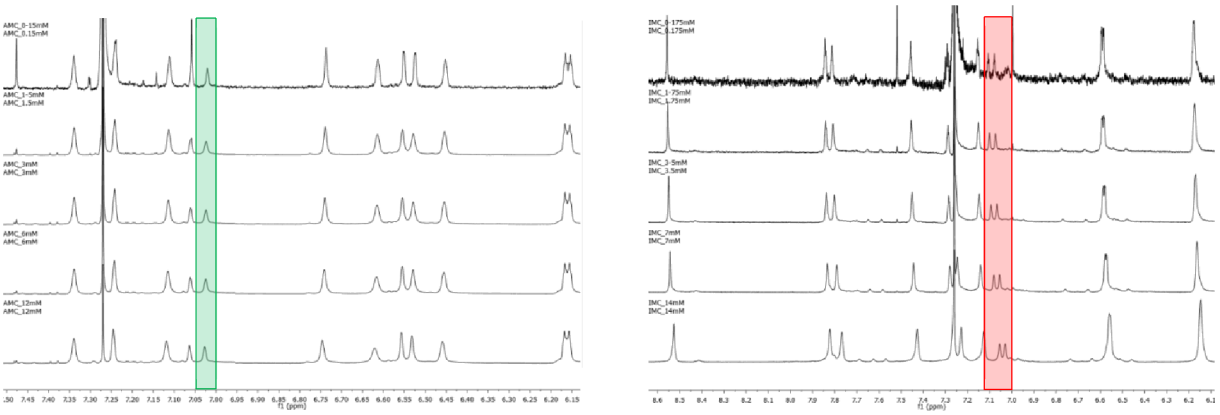


Figure 2.17: *a) AMC, The peak at 7.020 ppm (green) shifts downfield to 7.027 ppm as the concentration changes from 0.15 mM to 12 mM. b) IMC, The peak at 7.106 ppm (red) shifts upfield to7.054 ppm as the concentration changes from 0.175 mM to 14 mM. All spectra were taken in $CDCl_3$ at r.t.*

At this point in the research, it was discovered that the norbornene being used was not a pure isomer and the synthesis was repeated to produce pure endo-norbornene monomers and macrocycles. This did not provide successful trials.

2.5 Conclusion

From here it was thought that another parameter, specifically the flexibility in between the norbornene group and the macrocycle, played an essential role in the formation the ONT. If the polymer backbone was too rigidly connected to the macrocycle, which would distort the stacking, the norbornene groups on the opposite side of the forming tube would lose their

preorganization. This loss of order could lead to crosslinking or other defects in the nanotubes. Adding more flexibility in between the macrocycle and norbornene group would help the formation of the nanotubes. To pursue this goal, new synthetic pathways were created which introduce additional atoms in between the two regions of the monomers.

2.6 Experimental Section

The following section contains experimental procedures and ^{1}H NMR data for the compounds shown.

2.6.1 General Methods

Reagents and solvents were purchased for commercial suppliers and used without further purification, unless otherwise indicated. Ether, tetrahydrofuran, toluene, CH_2Cl_2, and DMF were purified by a MBRAUN solvent purification system. Reagent grade chloroform was purchased from Mallinckrodt Chemicals, and anhydrous acetonitrile was purchased from Sigma-Aldrich.

All reactions, except those performed in aqueous solvent, or otherwise noted, were conducted under dry nitrogen atmosphere in flame-dried glassware. Solvents were removed via rotary evaporator, unless specified.

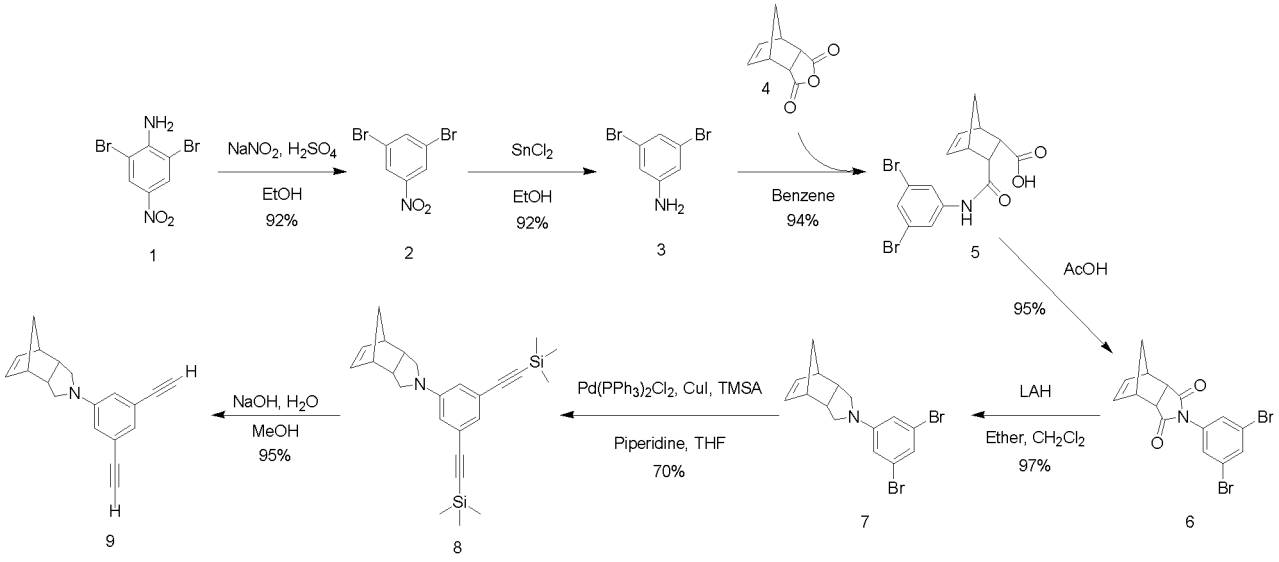
The purity of all compounds was $\geq$ 95% based on integration of the ^{1}H NMR spectrum, unless otherwise noted.

Flash chromatography was performed by using a 100-150 times weight excess of flash silica gel 32-63 μm from Dynamic Absorbants Inc. Fractions were analyzed by thin layer chromatography (TLC) using TLC silica gel F254-250 μm precoated-plates from Dynamic Absorbants Inc.

NMR spectra were taken on Inova 400 and Inova 500 spectrometers. $CDCl_3$ (7.26 ppm) was used as an internal reference in ^1H NMR, and $CDCl_3$ (77.23 ppm) for ^{13}C NMR. ^1H NMR data were reported in order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants (J, Hz), and assignments.

All microwave reactions were conducted under dry nitrogen in oven-dried glass tube using Discover SP microwave from CEM.

2.6.2 Syntheses



2: SM (**1**) (1.0196 g, 3.429 mmol) and 1.6 mL of sulfuric acid were added to 16 mL of ethanol in a RBF with a reflux condenser and refluxed at 90 °C. $NaNO_2$ (0.0816 g, 10.985 mmol) was added slowly to the top of the reflux condenser and 5 mL of ethanol was used to rinse the $NaNO_2$ into the reaction mixture The mixture was refluxed for 3 h. The mixture was cooled to r.t. and poured into 150 mL of ice water. Precipitate was collected by vacuum filtration and washed thrice with 5 mL portions of water, shiny yellow-orange crystals resulted. No other purification was necessary. Yield was 92%. ^1H NMR (400 MHz, CDCl3) δ 8.33 (d, J = 1.7 Hz, 2H), 8.00 (t, J = 1.7 Hz, 1H).

3: SM **2** (0.8860 g, 3.154 mmol) and $SnCl_2$ (3.3652g, 17.747 mmol) were added to 100 mL of ethanol. The mixture was refluxed at 90 °C for 3 h, then cooled to r.t. and poured into 75 mL of ice. 50 mL of 20% NaOH was added slowly, resulting in a pH of ~12.5. Extraction was performed with ether in three portions of 50 mL. The organic layer was washed with 50 mL of brine, and dried over sodium sulfate. A gradient column was run with hexanes, 2.5% EtOAc in

hexanes, 5.0%, and 7.5%. The silica was wet packed with hexanes. The product was dark, red-brown solid. Yield was 92%. ^{1}H NMR (400 MHz, CDCl3) δ 7.01 (s, 1H), 6.74 (s, 2H), 4.12 (q, J = 7.1 Hz, 1H), 3.77 (s, 2H), 2.05 (s, 1H), 1.31 – 1.20 (m, 1H).

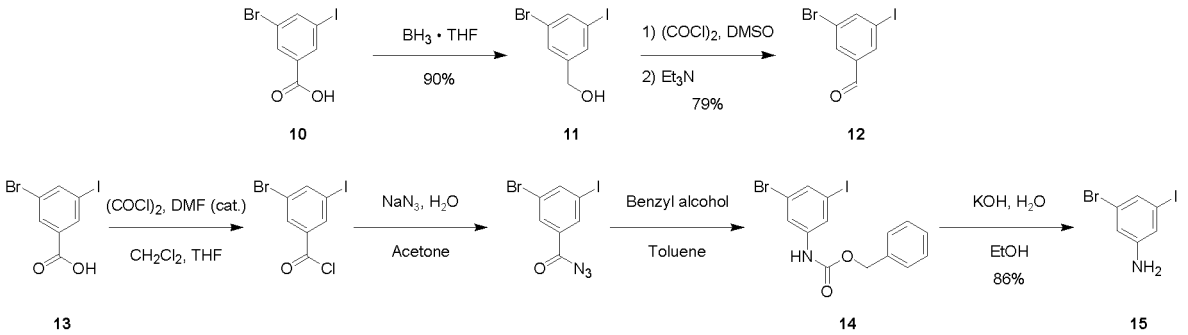
5: The original synthesis used two steps to form **6**, but was later modified to form **6** in one step. Therefore, the data for **5** are not shown.

6: SM **3** (2.4172 g, 17.884 mmol) and **4** (3.2294 g, 19.672 mmol) were added to a 35 mL microwave tube along with 20 mL of glacial acetic acid. The reaction mixture was heated to 125 °C for 3 hours. The reaction mixture was poured into a separatory funnel along with 150 mL of ethyl acetate. The organic layer was rinsed with water (50 mL x10) and the water was drained off without shaking the funnel. The organic layer was rinsed with brine and dried over sodium sulfate. The crude product was pure by NMR and used directly for the next step. Yield was 92.5%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.29 (s, 2H), 6.28 (s, 2H), 3.52 (s, 2H), 3.45 (s, 2H), 1.81 (d, J = 8.9 Hz, 1H), 1.63 (d, J = 8.9 Hz, 1H).

7: LAH (2.3655 g, 64.024 mmol) was added to a RBF along with 100 mL of ethyl ether to make a slurry, which was then cooled to 0 °C. SM **6** (4.2122 g, 10.608 mmol) was added slowly in CH_2Cl_2 (35 mL), and the reaction mixture was removed from the ice bath and stirred for 45 min. *Reduction of the aryl bromines will occur if the reaction is stirred for more than 45 min. A Fieser workup was used: 2.3655 g of LAH was quenched slowly with 2.3655 mL of DI H_2O at 0°C. Then, 2.3655 mL of 25% aqueous NaOH was added, followed by 3(2.3655) mL of DI H_2O, and the mixture was stirred for 1 hour. The solid was filtered off and the organic solvent was dried over sodium sulfate. Yield was 97.1%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, J = 1.7 Hz, 18H), 7.30 – 7.23 (m, 97H), 6.29 (dt, J = 3.7, 1.9 Hz, 41H), 4.12 (q, J = 7.1 Hz, 25H), 3.58 (dd, J = 3.0, 1.6 Hz, 3H), 3.56 – 3.40 (m, 82H), 2.18 (d, J = 2.0 Hz, 4H), 2.05 (s, 38H), 1.84 – 1.75 (m, 21H), 1.65 – 1.54 (m, 153H), 1.26 (t, J = 7.1 Hz, 41H).

8: $Pd(PPh_3)_2Cl_2$ (0.1489 g, 0.212 mmol) and CuI (0.0135 g, 0.071 mmol) were added to a sealed tube. The SM (**7**) was dissolved in a minimum of THF (~14 mL) and added to the sealed tube along with 10 mL of piperidine. The tube was vacuum/refilled with N_2 three times. TMSA (3.998 mL, 28.288 mmol) was added while under nitrogen. The reaction mixture was heated to 65°C for 14 hours. The mixture was concentrated and purified by column, with no extraction performed. Yield was 70%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.48 (s, 1H), 6.13 (s, 1H), 3.20 (s, 1H), 3.06 (s, 1H), 2.96 (s, 1H), 2.89 (d, J = 9.7 Hz, 1H), 1.58 (s, 1H), 1.51 (s, 1H), 0.23 (s, 1H).

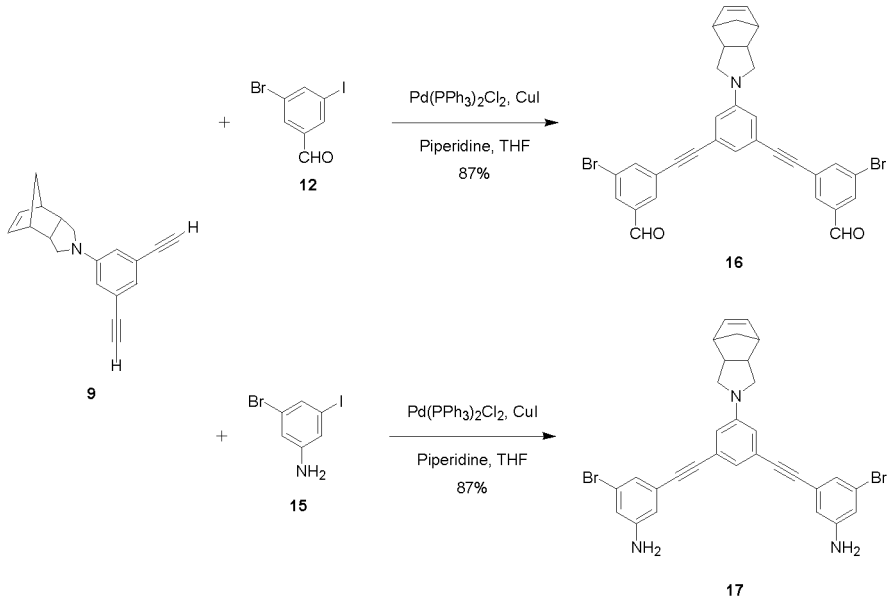
9: SM (0.8202 g, 2.0317 mmol) was dissolved in 6.5 mL of THF, then 75 mL of methanol was added to the RBF. A solution of NaOH (0.8127 g, 20.317 mmol) in 3 mL of H_2O was added dropwise. The reaction mixture was stirred at r.t. for 50 min, and TLC showed the reaction as complete. After removing the solvent, extraction was performed with 25 mL of ethyl acetate and 25 mL of water, washed three times with ethyl acetate, once with brine, and dried over sodium sulfate. The crude product was purified by column, hexanes, 1% EtOAc, 2% EtOAc, 3% EtOAc. Yield was 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.90 (s, 1H), 6.54 (s, 2H), 6.15 (s, 2H), 3.21 (s, 2H), 3.08 (s, 2H), 3.00 (s, 2H), 2.97 (s, 2H), 2.89 (d, J = 9.6 Hz, 2H), 1.61 (d, J = 8.3 Hz, 1H), 1.51 (d, J = 8.3 Hz, 1H).



11: SM (**10**) (1.0336 g, 3.162 mmol) was added to 10 mL of dry THF and cooled to 0 °C with an ice bath. 8 mL of BH_3·THF (8.0 mmol, 1.0 M) solution was added drop wise at 0 °C. The mixture was stirred at 0 °C for 2h and at r.t. for 20h. Reaction was quenched slowly by adding 20 mL of 1:1 THF:H_2O. Extraction was performed with three washings of CH_2Cl_2 and one with brine followed by drying over sodium sulfate. No purification was performed, since the material was used directly for the next step. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.65 (s, 1H), 7.48 (s, 1H), 4.64 (d, J = 5.7 Hz, 2H), 3.74 (ddd, J = 6.7, 4.2, 2.5 Hz, 1H), 1.90 – 1.81 (m, 1H), 1.75 (t, J = 6.0 Hz, 1H), 1.56 (s, 1H), 1.43 (s, 1H), 1.25 (s, 1H).

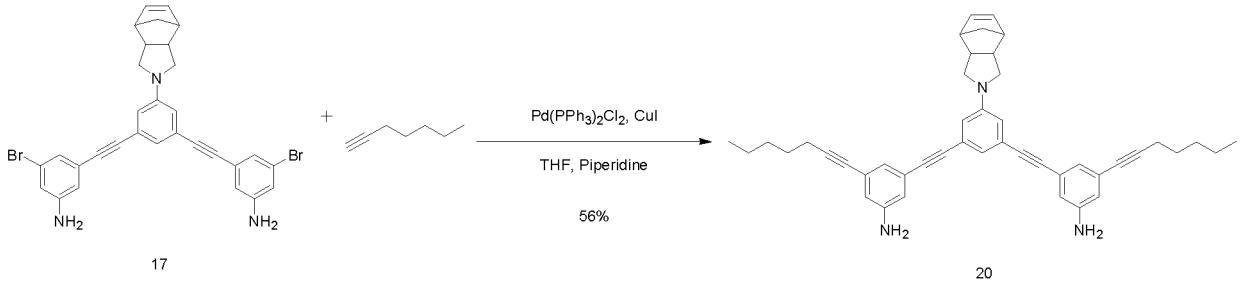
12: DMSO (0.91 mL, 12.784 mmol) was added to 10 mL of CH_2Cl_2 at -30 °C. Oxalyl chloride added drop wise followed by stirring for 15 min at -30 °C. The reaction mixture was cooled to -60 °C, and SM (**11**) (1.0000 g, 3.196 mmol) was dissolved in 15 mL of CH_2Cl_2 before added. The reaction was stirred at -78 °C for 3 h, then Et_3N (2.59 mL, 25.568 mmol) was added as the mixture was allowed to warm up to r.t. Extraction was performed by adding 25 mL of H_2O, washing thrice with 25 mL of CH_2Cl_2, washing with 25 mL of brine, and drying over sodium sulfate. TLC showed several spots. Column chromatography was used to purify. Silica was dry packed and the solvent gradient contained hexanes, 1% ethyl acetate in hexanes, and 2% ethyl acetate. Yield was 79%. ^{1}H NMR (400 MHz, CDCl3) δ 9.87 (s, 1H), 8.13 (t, J = 1.4 Hz, 1H), 8.12 – 8.10 (m, 1H), 7.97 – 7.96 (m, 1H), 1.55 (s, 5H), 1.25 (s, 3H).

15: SM (**13**) (1.0031 g, 3.068 mmol) was added to 20 mL of CH_2Cl_2 and 4 mL of THF and cooled to 0 °C in a RBF. Oxalyl chloride (0.78 mL, 9.205 mmol) was added dropwise to the mixture followed by 4 drops of DMF. The mixture was allowed to warm to r.t. and stirred for one hour. After one hour, the solvent was removed. 20 mL of acetone was added to the solid, and cooled to 0 °C. Sodium azide (0.6003 g, 9.205 mmol) dissolved in 2 mL of water was added dropwise. The mixture was stirred for 30 min at 0 °C. Solvent was removed and extraction performed with 50 mL of H_2O and ethyl acetate (3x 50 mL). The azide formed was added with toluene (20 mL) to a sealed tube. Benzyl alcohol (0.953 mL, 9.205 mmol) was added and the mixture was stirred at 95 °C for 90 min. Ethyl acetate was added to the sealed tube, and the reaction mixture was washed with 1M HCl (2 x 50 mL), saturated $NaHCO_3$ (2 x 50 mL), and brine (50 mL). The dry product was dissolved in 55 mL of ethanol, to which was added KOH (2.65 g, 46.026 mmol) dissolved in 5.5 mL of H_2O. The reaction mixture was stirred at 95 °C for 1 hour. The solvent was removed and extracted with 50 mL of H_2O, EtOAc (3 x 50 mL), washed with brine, and dried over sodium sulfate. A gradient column was run with 5% EtOAc in hexanes, 7%, 10%, and 12%. Yield was 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (s, 1H), 6.96 (s, 1H), 6.78 (s, 1H), 3.74 (s, 2H).

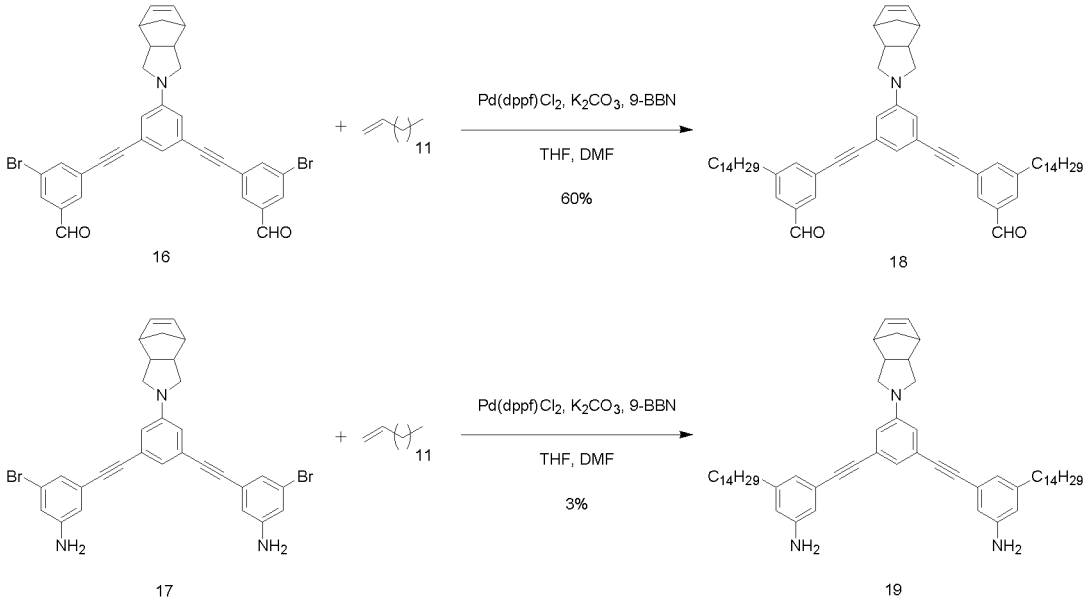


16: $Pd(PPh_3)_2Cl_2$ (0.0592 g, 0.0843 mmol) and CuI (0.0054 g, 0.0281 mmol) were added to a sealed tube. SM (**9**) (0.3643 g, 1.4047 mmol) was dissolved in a minimum of THF (~5 mL) as well as **12** (0.9608 g, 3.0903 mmol) (dissolved in ~20 mL of THF) and was added to the sealed tube along with 6 mL of piperidine. The tube was vacuum/refilled with N_2 three times. The reaction mixture was stirred at room temperature overnight. The mixture was filtered after adding ethyl acetate, and a column was run to purify. The column was packed with 10% CH_2Cl_2 in hexanes, followed by the gradient: 25%, 40%, 40%, 50%, 65%, 80%, 80%, and 100%. Yield was 71%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.93 (s, 1H), 6.80 (s, 1H), 6.74 (s, 1H), 6.55 (s, 1H), 6.16 (s, 1H), 3.73 (s, 4H), 3.24 (s, 1H), 3.09 (s, 1H), 2.98 (s, 1H), 2.92 (d, J = 8.1 Hz, 1H), 1.61 (d, J = 8.2 Hz, 1H), 1.52 (d, J = 8.6 Hz, 2H), 1.29 – 1.17 (m, 4H).

17: $Pd(PPh_3)_2Cl_2$ (41.9 mg, 0.0597 mmol) and CuI (3.8 mg, 0.0199 mmol) were added to a sealed tube. SM (**9**) (0.2580 g, 0.9946 mmol) was dissolved in a minimum of THF (~5 mL) as well as **15** (0.6519 g, 2.188 mmol) (dissolved in ~20 mL of THF) and was added to the sealed tube along with 6 mL of piperidine. The tube was vacuum/refilled with N_2 three times. The reaction mixture was stirred at room temperature overnight. The mixture was filtered after adding ethyl acetate, and a column was run to purify. Column chromatography was run with 30% CH_2Cl_2 in hexanes and followed the gradient: 30%, 35%, 40%, 45%, 50%, 55%, 60%, 65%, 70%, and 75%. Yield was 79%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.97 (s, 1H), 7.97 (s, 1H), 7.95 (s, 1H), 7.91 (s, 1H), 6.99 (s, 1H), 6.61 (s, 1H), 6.19 (s, 1H), 3.28 (s, 1H), 3.13 (s, 1H), 3.01 (s, 1H), 2.96 (d, J = 9.6 Hz, 1H), 1.64 (d, J = 8.1 Hz, 1H), 1.54 (d, J = 8.1 Hz, 1H), 1.26 (s, 1H).



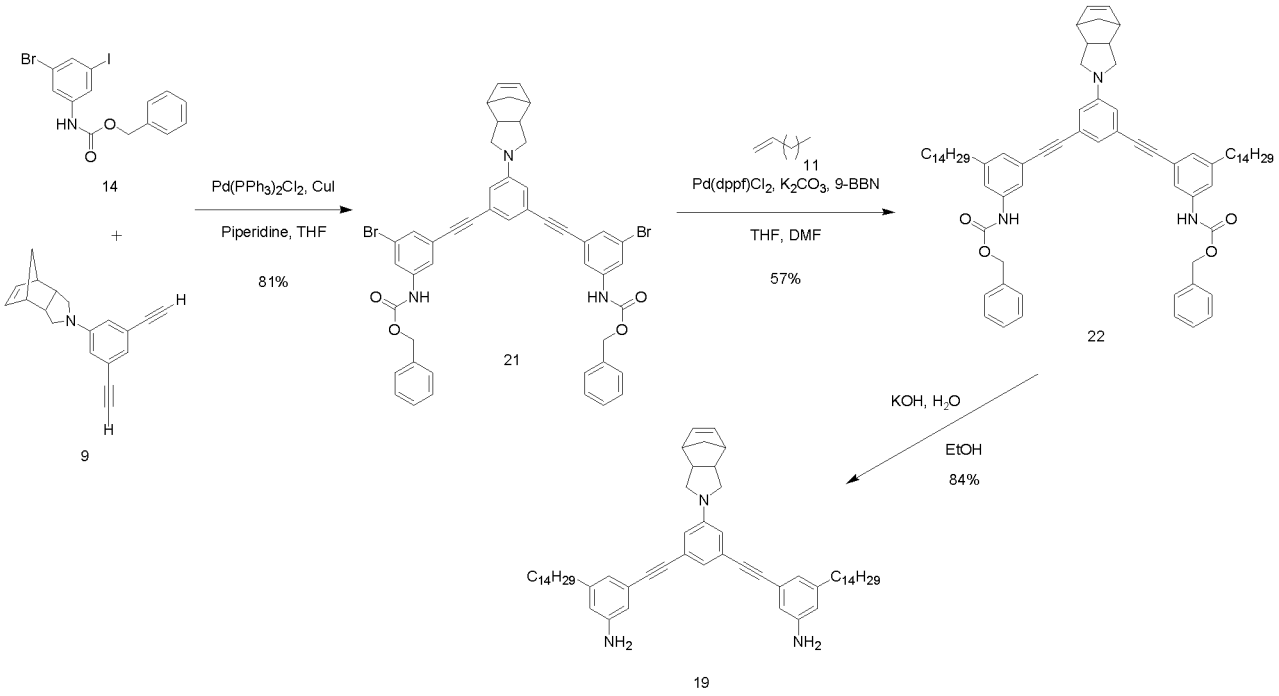
20: $Pd(PPh_3)_2Cl_2$ (5.6 mg, 0.008 mmol) and CuI (0.5 mg, 0.003 mmol) were added to a sealed tube. Diamine **17** (80.8 mg, 0.135 mmol) was dissolved in a minimum of THF (~1.7 mL) and added to the sealed tube along with 0.5 mL of piperidine. The tube was vacuum/refilled three times with N_2. Heptyne (0.07 mL, 0.539 mmol) was added and the reaction mixture was stirred at 65 °C for 16h. The mixture was filtered after adding ethyl acetate, and a column was run to purify. The column was packed with 10% CH_2Cl_2 in hexanes, followed by the gradient: 25%, 40%, 40%, 50%, 65%, 80%, 80%, and 100%. Yield was 56%. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.05 (s, 1H), 6.93 (s, 1H), 6.80 (s, 1H), 6.74 (s, 1H), 6.55 (s, 1H), 6.16 (s, 1H), 3.73 (s, 4H), 3.24 (s, 1H), 3.09 (s, 1H), 2.98 (s, 1H), 2.92 (d, J = 8.1 Hz, 1H), 1.61 (d, J = 8.2 Hz, 1H), 1.52 (d, J = 8.6 Hz, 2H), 1.29 – 1.17 (m, 4H).



18: Tetradecene (0.18 mL, 0.716 mmol) was added to a sealed tube under N_2 along with 0.5 mL of THF and cooled to 0° C. 9-BBN solution in THF (1.43 mL , 0.5 M) was added dropwise and the mixture was stirred at 0° C for 10 min then allowed to warm to r.t. The reaction mixture was stirred at r.t. for 6 h. $Pd(dppf)Cl_2$ (11.9 mg, 0.016 mmol), K_2CO_3 (179.8 mg, 1.301 mmol) and **16** (101.7 mg, 0.163 mmol) were added via a glass funnel to the sealed tube. 7 mL of DMF was used to rinse the reagents into the tube. The reaction mixture was heated to 65 °C for 16 hours. The column was packed with 25% CH_2Cl_2 in hexanes, followed by the gradient: 25%, 30%, 35%, 40%, 45%, and 50%. Yield was 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.00 (s, 2H), 7.85 (s, 2H), 7.67 (s, 2H), 7.61 (s, 2H), 7.03 (s, 1H), 6.63 (s, 2H), 6.19 (s, 2H), 3.28 (s, 1H), 3.12 (s, 2H), 3.00 (s, 2H), 2.96 (d, J = 9.4 Hz, 2H), 2.73 – 2.66 (m, 4H), 2.05 (d, J = 7.8 Hz, 3H), 1.26 (s, 162H), 0.89 (s, 33H).

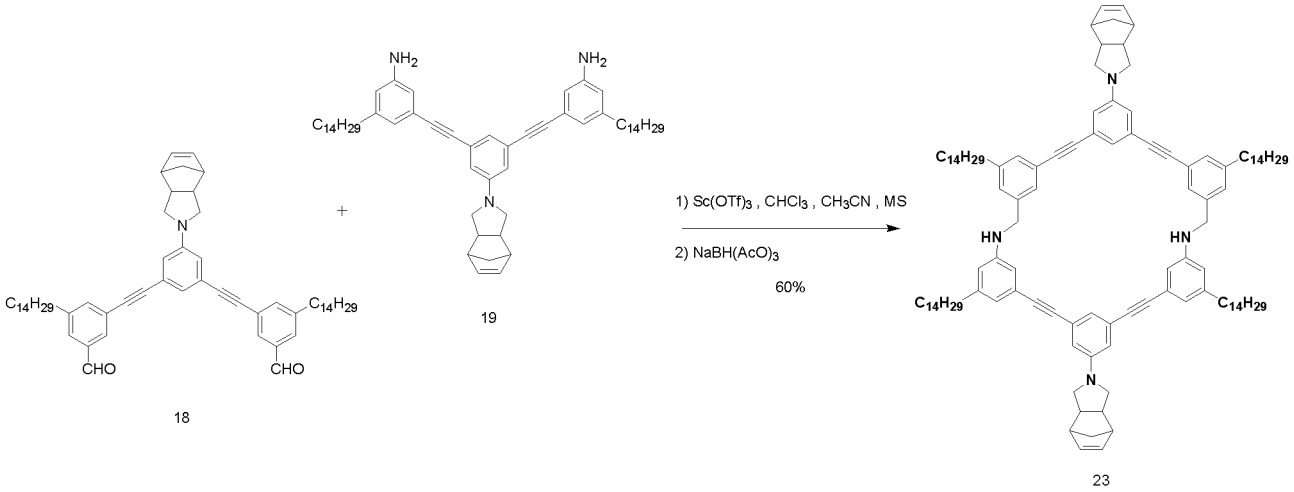
19: Tetradecene (1.038 mL, 4.072 mmol) was added to a sealed tube under N_2 along with 1.5 mL of THF and cooled to 0° C. 9-BBN solution in THF (8.2 mL , 0.5 M) was added dropwise and the mixture was stirred at 0° C for 10 min then allowed to warm to r.t. The reaction mixture was stirred at r.t. for 6 h. $Pd(dppf)Cl_2$ (67.7 mg, 0.093 mmol), K_2CO_3 (1.0232 mg, 7.403 mmol) and **17** (554.7 mg, 0.925 mmol) were added via a glass funnel to the sealed tube. 15 mL of DMF was used to rinse the reagents into the tube. The reaction mixture was heated to 85 °C 20 hours.

The column was packed with 1% TEA in Ch_2Cl_2, followed by the gradient: 1% EtOAc + 1% TEA in CH_2Cl_2, 2% + 1%, 3% + 1%, 4% + 1%, 5% + 1%. Yield was 3%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.99 (s, 1H), 6.79 (s, 2H), 6.68 (s, 2H), 6.58 (s, 2H), 6.50 (s, 2H), 6.18 (s, 2H), 3.67 (s, 3H), 3.27 (s, 2H), 3.09 (s, 2H), 2.99 (s, 2H), 2.92 (d, J = 11.0 Hz, 2H), 2.54 – 2.47 (m, 4H), 1.57 (s, 41H), 1.26 (s, 47H), 0.88 (t, J = 7.0 Hz, 7H).

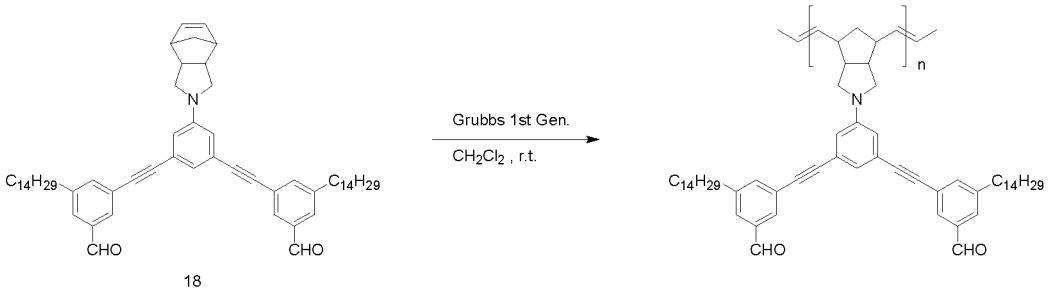


21: Procedure same as **17**. Column: 50% CH_2Cl_2 in hexanes (3 column volumes), 75% (5cv). Yield was 81%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (s, 2H), 7.45 (s, 2H), 6.99 (s, 1H), 6.66 (s, 4H), 6.20 (s, 2H), 5.23 (s, 4H), 3.30 (s, 1H), 3.13 (s, 2H), 3.00 (s, 2H), 2.93 (d, J = 9.6 Hz, 2H), 1.65 (d, J = 9.1 Hz, 1H).

22: Procedure same as **19**. Column: 50% CH_2Cl_2 in hexanes. Yield was 57%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 – 7.34 (m, 12H), 7.24 (s, 2H), 7.09 (s, 2H), 6.99 (s, 1H), 6.71 (s, 2H), 6.58 (s, 2H), 6.18 (s, 2H), 5.23 (s, 4H), 3.25 (s, 2H), 3.10 (s, 2H), 3.00 (s, 2H), 2.94 (d, J = 9.7 Hz, 2H), 2.58 (s, 4H), 1.62 (t, J = 7.5 Hz, 5H), 1.53 (d, J = 8.0 Hz, 1H), 1.30 (d, J = 17.8 Hz, 45H), 0.90 (s, 6H).



20: **18** (100 mg, 0.120 mmol) and **19** (103.2 mg, 0.120 mmol) were dissolved in dry $CHCl_3$ and added to a sealed tube along with 4 angstrom MS, $Sc(OTf)_3$ (8.3 mg, 0.0168 mmol) catalyst was dissolved in CH_3CN (0.4 mL) and added dropwise. The reaction mixture was stirred at r.t. for 18h. Completion of the reaction was determined by the imine peak (8.57 ppm). $NaBH(AcO)_3$ (508.5 mg, 2.399 mmol) was added and the reaction mixture was stirred at r.t. for 6 hours. Quenched with sat. $NaHCO_3$. Work up: add H_2O (50 mL) and wash with EtOAc (3x 50 mL), brine (50 mL), and dry over Na_2SO_4. Column: 50% CH_2Cl_2 in hexanes. ^1H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.34 (s, 2H), 7.24 (s, 2H), 7.11 (s, 2H), 7.06 (s, 1H), 7.02 (s, 1H), 6.74 (s, 2H), 6.61 (s, 2H), 6.55 (s, 2H), 6.52 (s, 2H), 6.45 (s, 2H), 6.16 (d, J = 6.1 Hz, 4H), 4.36 (s, 4H), 4.14 (s, 1H), 3.24 (d, J = 7.9 Hz, 3H), 3.08 (s, 4H), 2.97 (s, 4H), 2.92 (t, J = 9.4 Hz, 4H), 2.62 – 2.55 (m, 4H), 2.54 – 2.46 (m, 4H), 1.60 (d, J = 6.6 Hz, 9H), 1.53 (s, 3H), 1.26 (s, 144H), 0.88 (s, 21H).



Polymer: **18** (25 mg, 0.029 mmol) was added to a 4 mL vial and transferred to a glove box with Ar atmosphere, then dissolved in 2.5 mL of CH_2Cl_2. Grubbs first generation catalyst (1.7 mg, 0.002 mmol) was dissolved in CH_2Cl_2 (0.5 mL) and added dropwise to the reaction mixture. The reaction was stirred at r.t. for 3h and quenched with vinyl ethyl ether (0.2 mL). Mn = 9,724 Mw = 10,531 PDI = 1.081.

Chapter 3

Attempted Synthesis of ONTs Containing a Flexible Linker

3.1 Introduction

Given the failures experienced in the polymerization of the norbornene groups and the idea that the current Center Piece was probably too "rigid", plans for introducing flexibility into the linker between the norbornene groups and the macrocycle were developed, in which.one or more sp^3 hybridized atoms need to be added into the linker. A three carbon ester was used to achieve flexibility in the ladder polymers reported by Luh *et. al.* (*Figure 3.1*). Based on their work with ladder polymers, the polymerization of two norbornene groups on opposite ends of a molecule should be completed in 1 hour at room temperature in CH_2Cl_2 using the Grubbs' first generation catalyst.[25] Ideally, flexibility would prevent the deformation of one side of the ladder. Such deformation may disrupt the preorganization of the norbornene groups on the other side of the macrocycle causing defects in the nanotube.

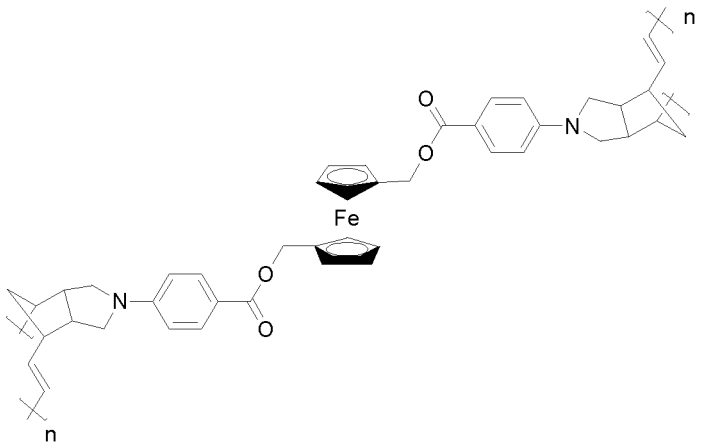


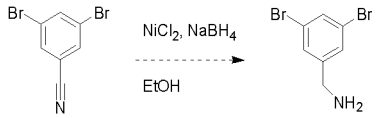
Figure 3.1: *Double-stranded norbornene, ladder polymer.*[25]

3.2 Building Block Synthesis

Synthetic methods used for the development of the flexible linkers follow the same synthetic steps as seen in *Figure 2.4*. Each flexible centerpiece attempted, unless otherwise stated, created a different amine to couple to norbornene dicarboxylic anhydride and proceeded through imide reduction by LAH, Sonogashira coupling with TMSA and deprotection with sodium hydroxide in methanol/THF.

3.2.1 Flexible Centerpiece 1 (FCP1): Aliphatic Amine

The first flexible centerpiece attempted added one methylene group between the nitrogen and aromatic ring of the RCP. The synthesis started with the reduction of an aromatic cyano to form an amine in the presence of nickel (II) chloride and sodium borohydride in dry ethanol as shown in *Figure 3.1*.[28] This reaction was tried several times and did not work.



24 25

Figure 3.2: *Cyano reduction with nickel (II) chloride and sodium borohydride*

Another approach used a benzyl bromide that was reacted with sodium azide.[29,30] The next step involved the Staudinger reaction with triphenyl phosphine to produce the amine in good yield.[30] The reactions that followed repeated the same synthetic steps as previously described in section 2.3: reaction with norbornene dicarboxylic anhydride to produce the imide, reduction by LAH to the amine, Sonogashira coupling with TMSA, and deprotection to the terminal alkyne.[18,19,20] During the course of the synthesis, the products became increasingly more difficult to purify by column chromatography. For the deprotection step conversion in the NMR spectra was 75%, but no pure product was isolated. It was believed that the greater basicity of the aliphatic amine, compared to the aryl amine, led to the deprotonation of the alkyne

and subsequent decomposition of the product. The Sonogashira coupling with **12** was attempted but the NMR of the crude product could not confirm the success of the reaction (*Figure 3.3)*. Luh *et. al.* mentioned in one of their papers that the aryl amine is an important component to the preorganization of the norbornene groups.[25] With this in mind, a new synthesis was devised using an ether linker consisting of a phenylene and a methylene moiety.

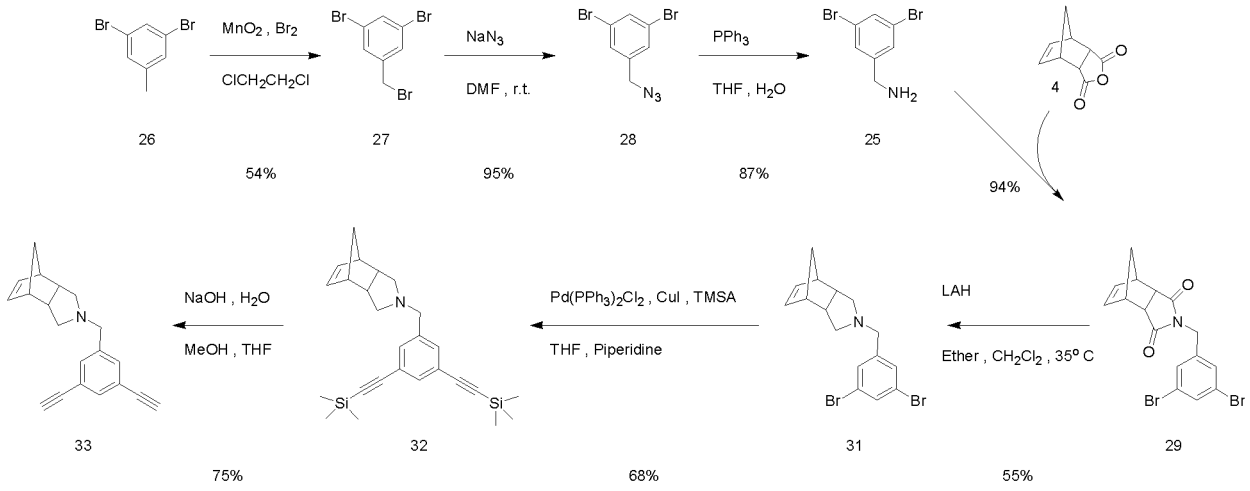


Figure 3.3: *Synthesis of **FCP1** with an aliphatic amine and one methylene group.*

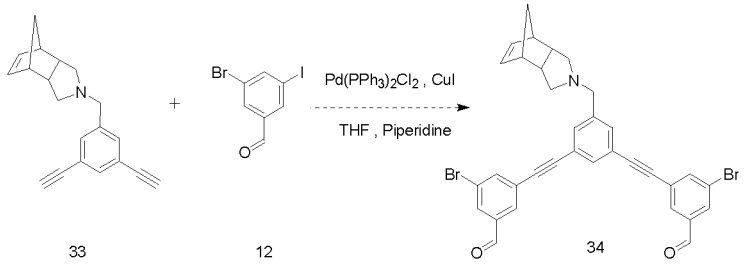


Figure 3.4: *Attempted synthesis of the dialdehyde monomer from **FCP1.***

3.2.2 Flexible Centerpiece 2 (FCP2): Ether

The synthetic routes for the ether linker are shown in *Figure 3.5 and 3.6.* The first route taken to synthesize the ether linker used amino anisole that reacted with norbornene dicarboxylic anhydride to form the amido acid, first, and then the imide, second. The next step was LAH reduction of the imide to form the amine. The deprotection of the methoxy group with boron

tribromide, to form the phenol, also resulted in an unexpected side reaction of the norbornene double bond .[31] An alternative method to deprotect the methoxy group used trimethylsilyl chloride (TMSCl) to generate trimethylsilyl iodide (TMSI) *in situ*, which then forms a silyl ether.[32] Lithium iodide, TMSCl, **34**, and acetonitrile were added to a sealed tube and heated to 50 °C. The ^{1}H NMR of the reaction product after 3 hours showed the starting material consumed, but peaks corresponding to the desired product **42** were not observed. It was thought that oxidation of the phenol was occurring, and a one pot reaction was set up to react the phenol immediately with the benzyl bromide **27**. The procedure for the first step was the same, after 3 hours the reaction was stopped and solvent was removed, then potassium carbonate, DMF, and **27** were added and the reaction was heated to 50 °C for 3 hours. The NMR of the reaction mixture after 3 hours showed no peaks corresponding to the desired product **43**. The reaction didn't work possibly due to incomplete formation of TMSI in the first step, and a side reaction occurred to consume the starting material. The same reaction was run several more times with commercially available TMSI, and the desired product was still not produced.[33] This route arrived at a dead end and developing a new approach was necessary. By evaluating a different starting material, the direction of the synthesis was revitalized. Aminophenol was reacted with norbornene dicarboxylic anhydride to make the imide, but at the same time, it also reacts with the phenol to form an ester. To ensure all of the aniline converted into amido acid, two equivalents of the **4** were used. The ring was closed to form the imide via refluxing in acetic acid, and further reduced with LAH. This last reaction reduced the imide to an amine and the phenolic ester to an alcohol, leaving it ready to react with benzyl bromide to form the ether linkage. However, the electron rich phenols are very susceptible to oxidation, especially in the anionic form, and the product was not isolated from the work up. A different approach was to

first react **37** with **27** by dissolving both in DMF, adding potassium carbonate, and heating to 70 ^{o}C for 1 hour. The amino phenol is very sensitive to oxidation and the color of the reaction can indicate whether the oxidation has taken place. The greenish-brown color of the un-oxidized species is desired, but when the amino phenol is oxidized, a red or purple color appears. **44** was formed in excellent yield. Reaction of **44** and **4** also worked well, but the ring closing reaction to form the imide did not produce the desired result. Acid is needed to catalyze the closing of the ring, yet under the same reaction conditions necessary for the ring closure, the ether linkage would cleave. Cleavage of the ether occurred faster than the imide formation, and based on these results, the ether linkage approach was abandoned. A ketone linker was the next to be pursued.

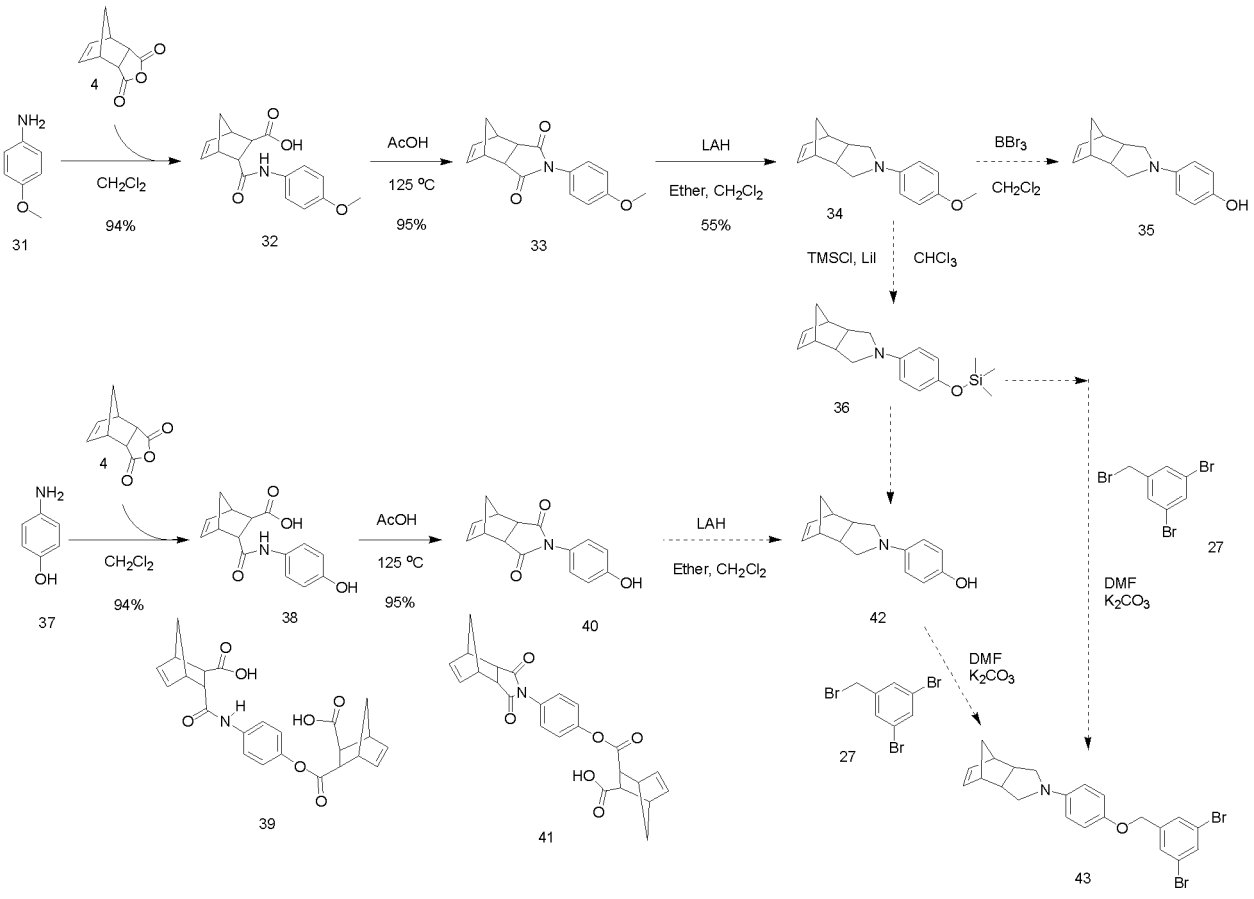


Figure 3.5: *Attempted synthetic routes for* ***FCP2*** *which contains an ether linkage. Dotted arrows represent unsuccessful reactions.*

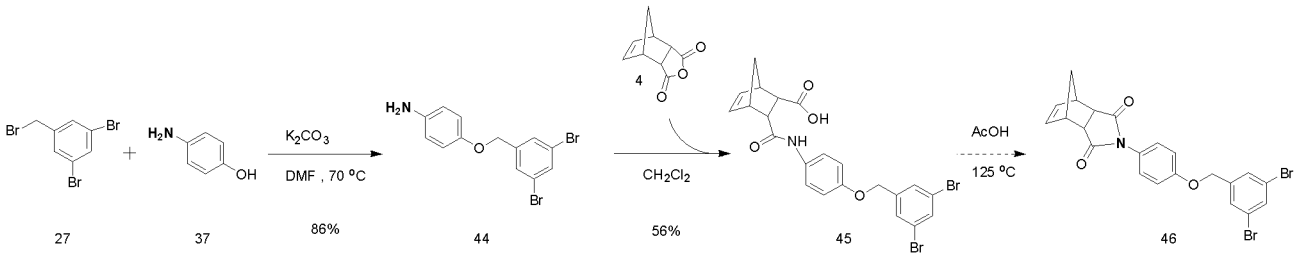


Figure 3.6: *Attempted synthetic routes for* ***FCP2*** *which contains an ether linkage. The reaction to produce* ***46*** *was not successful.*

3.2.3 Flexible Centerpiece 3 (FCP3): Ketone

The ketone linker route began with *p*-nitroacetophenone **47** as the starting material, and then it was reduced by tin chloride in refluxing ethanol to form amino acetophenone.[17] **48** was reacted with norbornene dicarboxylic anhydride in a microwave reactor at 125 ^{o}C with acetic acid as the solvent. Complete conversion to the imide was achieved in 3 hours; this showed a dramatic improvement over the two step reaction used previously. Reduction with LAH followed and the reaction was worked up by the Fieser method.[34] This resulted in a pure product, therefore no further purification was necessary. The secondary benzylic alcohol was oxidized first by the Swern oxidation, which did not produce the desired product; instead an NMR of the product indicated that a styrene derivative formed.[23] The next method attempted for oxidation was pyridinium chloro chromate (PCC).[35] This reaction did not produce the desired product **51** either. The last oxidation method, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in 1,4-dioxane at r.t. for 1 hour, yielded the desired ketone in excellent yield.[36]

Two pathways were taken with **51** to produce **52**. The first involved an acid catalyzed aldol condensation, followed by selective reduction of the α, β-alkene.[37] The aldol condensation in this sequence did not work as expected, which was determined by the ^{1}H NMR of the crude

product, therefore the reduction reaction was not pursued further. The second pathway utilized an enolate alkylation with benzyl bromide **27**.[38] The enolate was formed using lithium diisopropyl amide (LDA) (commercial solution in heptane), followed by the addition of dibromobenzyl bromide. The product obtained from the reaction was double alkylated, resulting from the formation of a second enolate after initial alkylation. Maintaining low temperatures throughout the reaction sequence could not control the over alkylation, therefore it is presumed that the formation of the second enolate is faster than alkylation of the first. This exhausted the possible routes with the ketone linker. The next flexible linker involved an ester linking the norbornene group and the macrocycle.

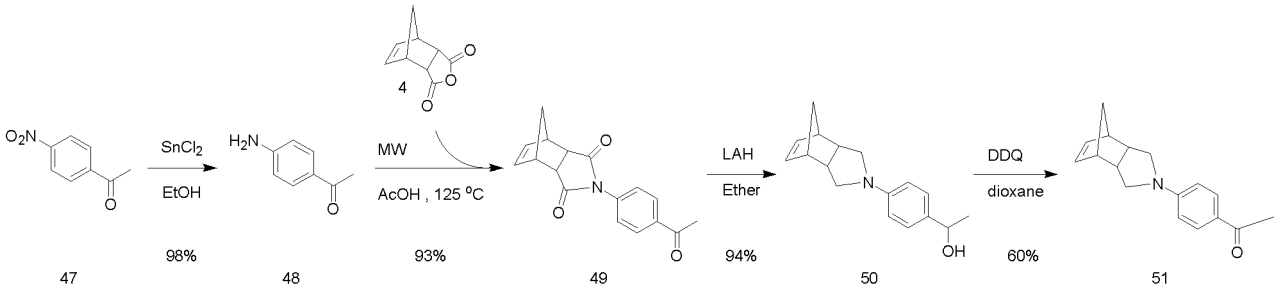


Figure 3.7: *Synthesis of norbornene moiety containing a ketone for* ***FCP3***

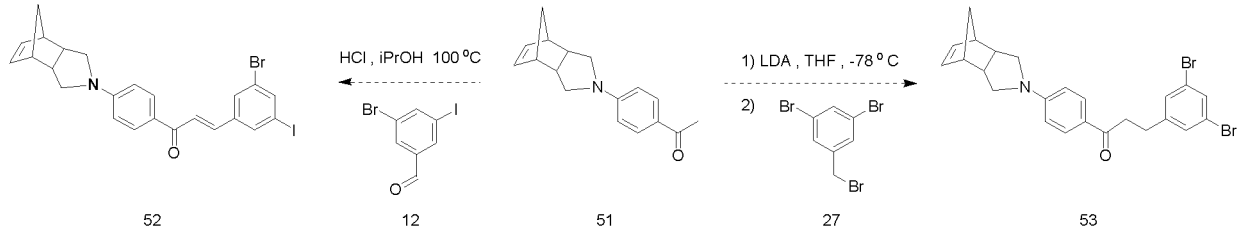


Figure 3.8: *Two attempted syntheses for connecting the ketone to an aryl ring. Left: acid catalyzed aldol condensation. Right: enolate alkylation.*

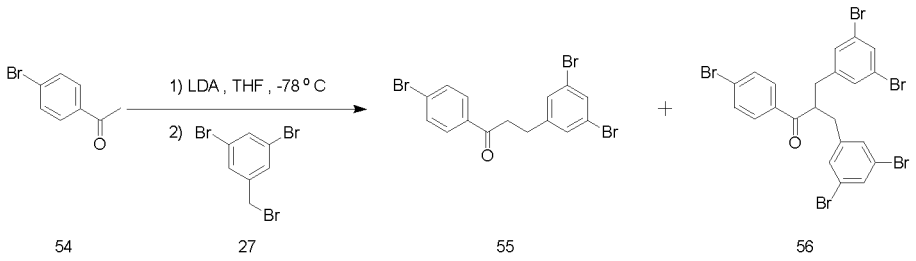


Figure 3.9: *Model reaction for enolate alkylation. Desired product **55** did not form, only the double alkylated product **56** was observed.*

3.2.4 Flexible Centerpiece 4 (FCP4): Ester

One possible synthetic route for the ester linker was explored by oxidizing **51** to carboxylic acid **63**, then couple it to 3,5-dibromobenzyl alcohol.[39] The oxidation was run in a microwave reactor with bleach and sodium hydroxide in a mixture of water and isopropanol. A yellow crystalline material remained after the reaction, which NMR showed to be the starting material. The oxidation did not work, so another route was pursued with nitrobenzoic acid. The first reaction was esterification in a microwave reactor at 110 °C with methanol as the solvent and catalyzed with sulfuric acid. The reaction was completed in 1 hour and the yield was quantitative. The next step that followed was a reduction of the nitro group with tin (II) chloride in refluxing ethanol. After column purification, the amine **59** was reacted with norbornene dicarboxylic anhydride in a microwave reactor at 125 °C with acetic acid as the solvent to form the imide **60**. Both the imide and the methyl ester were reduced by LAH in the next step to give an amine and benzyl alcohol on **61** in high yield.

Two possible routes were investigated from here to make the ester linker. The first involved oxidation of the benzyl alcohol **61** to carboxylic acid **63**. To make the oxidation as mild as possible, it was performed in two steps to prevent reaction of the norbornene double

bond with strong oxidants. The first choice to oxidize the benzyl alcohol to aldehyde was PCC. The NMR of the crude product showed an undesired product had formed. DDQ was the next choice and worked well. Once at the aldehyde stage, a Pinnick oxidation was performed, but did not yield the desired product.[40] No other oxidation methods were investigated. Instead, the benzyl alcohol was used to make an ester with 3,5-dinitrobenzoic acid **64**.

Several methods were attempted to synthesize the ester, though none of them appeared to yield the correct product. The first method utilized diisopropylcarbodiimide (DIC), a catalytic amount of 4-dimethylaminopyridine (DMAP), and was run at r.t. in CH_2Cl_2.[41] The method did not yield the ester as the major product, but instead favored a coupling between diisopropylurea and the benzoic acid to yield **65**. Several different ratios of the reagents were used and all produced the same major product. The second method was a Mitsunobu coupling with diisopropyl azodicarboxylate (DIAD), triphenyl phosphine, and was run in THF as the solvent.[42] The third method used oxalyl chloride to form an acid chloride from the benzoic acid first, and then couple it with the benzyl alcohol in the presence of triethylamine.[43] The final method which demonstrated the most promise of yielding the product used dicyclohexylcarbodiimide (DCC), a catalytic amount of DMAP, and CH_2Cl_2 as the solvent.[44] The products of the methods 2, 3, and 4 each produced crude ^1H NMRs which all agreed. The product had very low solubility and it was not isolated. Column chromatography was attempted to purify the products obtained from each method, but no pure product was isolated. A similar product, with a benzoate ester and two aromatic nitro groups, was found in literature.[45] That compound was worked up and purified by a column under much less polar conditions than was used for **66**. With one sample from the acid chloride method, the next reaction, a tin chloride reduction, was attempted on the crude product. NMR spectra of the product showed no peaks that would correspond to the desired product;

subsequent purification did not produce any product. A model reaction (*Figure 3.12*) was run with a simple benzoic acid **67** and **61** to test whether the ester reaction was problematic or the substrates being used. One hour at r.t. yield the ester **68** under the same conditions listed above. The dinitrobenzoic acid appears to be responsible for the failure of the reaction. Given the failed trials with this method, focus was turned to a simple flexible linker that did not contain any functional groups.

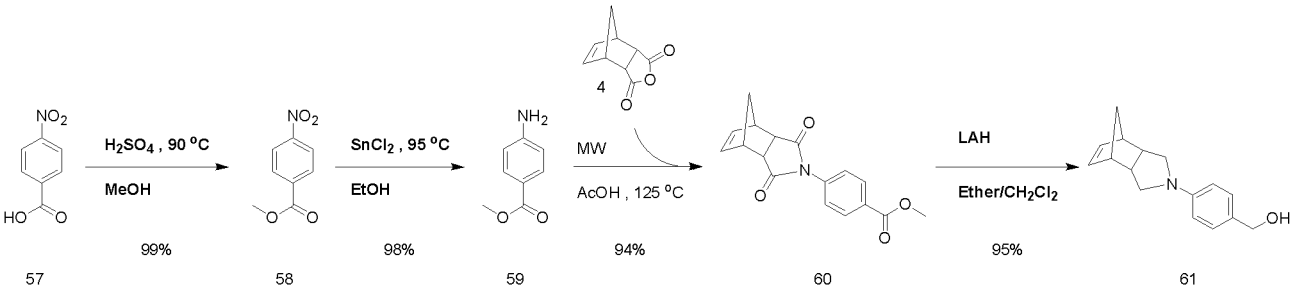


Figure 3.10: *Synthesis of a norbornene moiety containing a benzylic alcohol.*

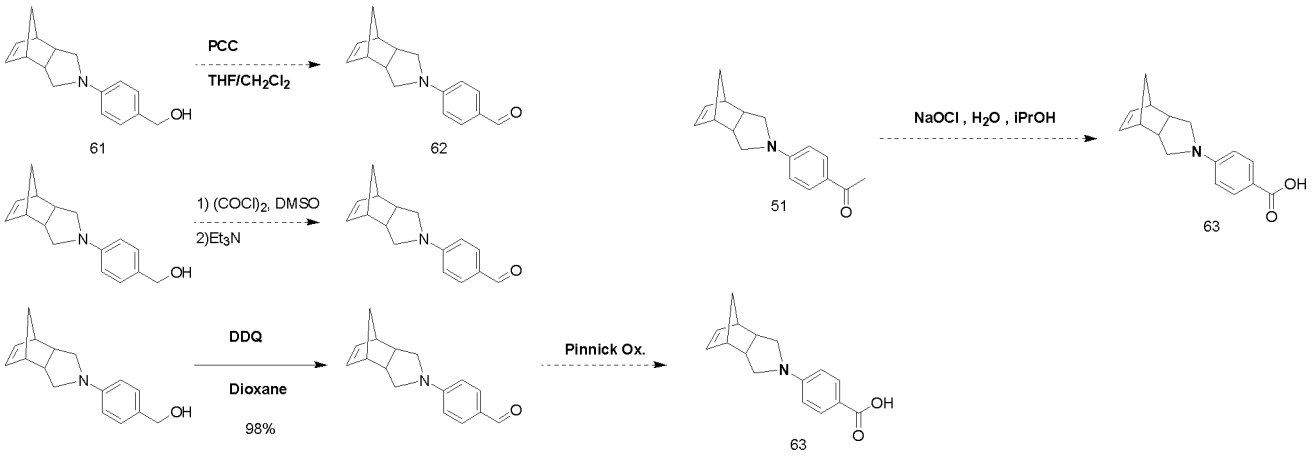


Figure 3.11: *Attempted synthesis of a norbornene moiety containing a carboxylic acid*

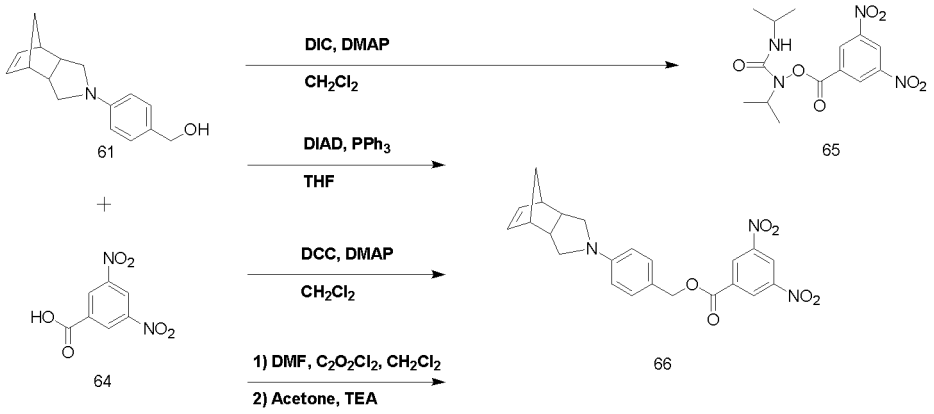


Figure 3.12: *Attempted routes for ester synthesis with **61**. None of the shown reactions yielded the desired product **66**.*

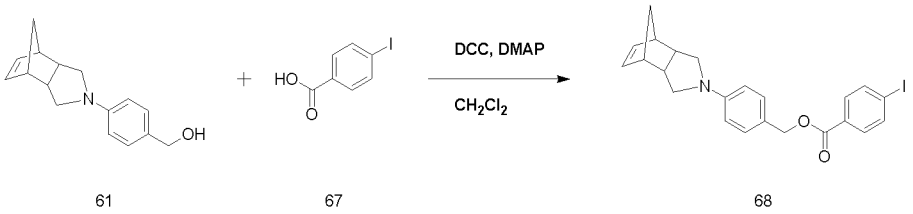


Figure 3.13: *Model reaction for ester formation.*

3.2.5 Flexible Centerpiece 5 (FCP5): Alkyl

The most successful attempt out of all of the flexible linkers involved a two carbon, ethylene linker. The synthesis began with 4-nitrobenzyl bromide and 3,5-dibromobenzylbromide. The former was converted into an organozinc compound, mixed with copper (I) cyanide, and lithium chloride to form the active reagent.[46] The benzyl bromide **27** was added in the next step of the reaction. Following work up and purification, the yield was high at 92%. The next steps employed a tin chloride reduction, imide formation with **4**, a LAH reduction, Sonogashira coupling with TMSA, and deprotection of the alkyne to yield the Flexible Centerpiece (FCP5) **75**. It was reacted with the amine **78** and aldehyde **12** end pieces by a Sonogashira coupling. The amine end piece was modified from **15** to avoid large losses from alkylation by the Suzuki

coupling.[47] Flexible dinitro with decoxy solubilizing chains (FDNoDo) **79** was reduced by tin chloride to give **81** (FDAmDo) and flexible dialdehyde (FDAl) **80** had a tetradecyl alkyl chain installed through a Suzuki coupling to yield **82** (FDAlTd). Preliminary polymerization studies were conducted for both monomers, but difficulties in the synthesis prevented sufficient quantities of materials on hand to fully discover the feasibility of the ethylene linker in the overall nanotube synthesis.

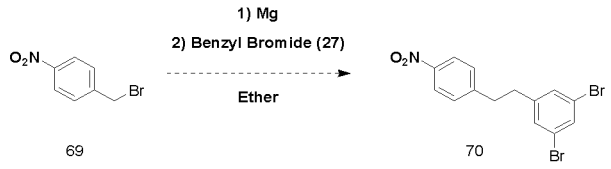


Figure 3.14: *Attempted synthesis of an ethylene linker for the flexible centerpiece*

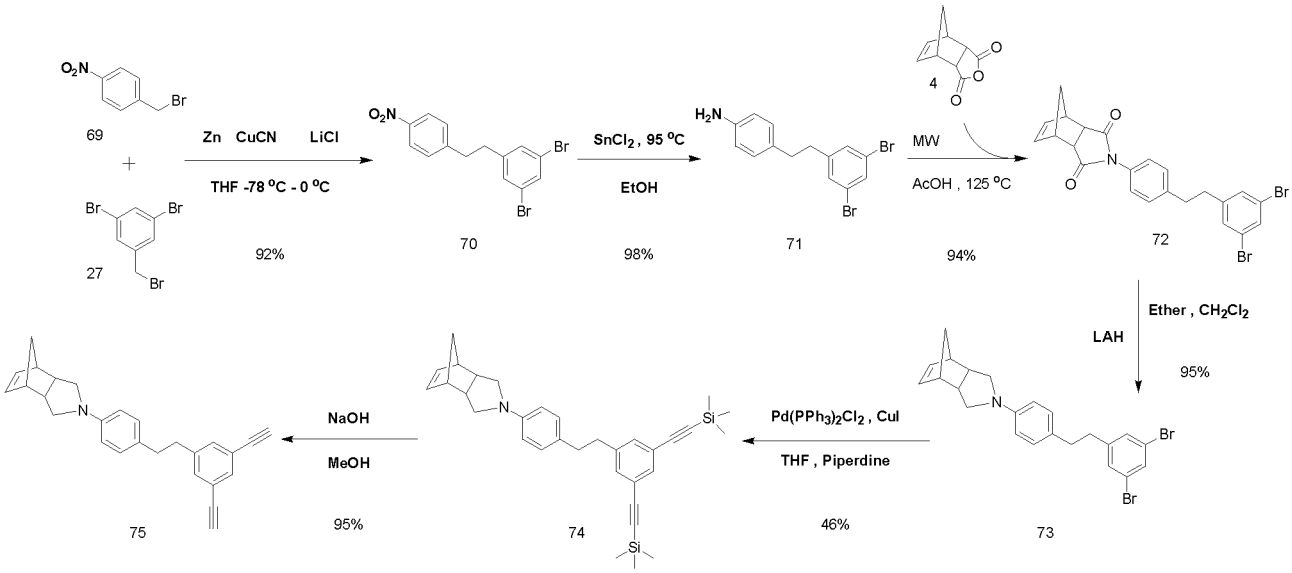


Figure 3.15: *Synthesis of Flexible Centerpiece 5 (**FCP5**).*

Figure 3.16: *Synthesis of new amine precursor to replace bromoiodoaniline **15**.*

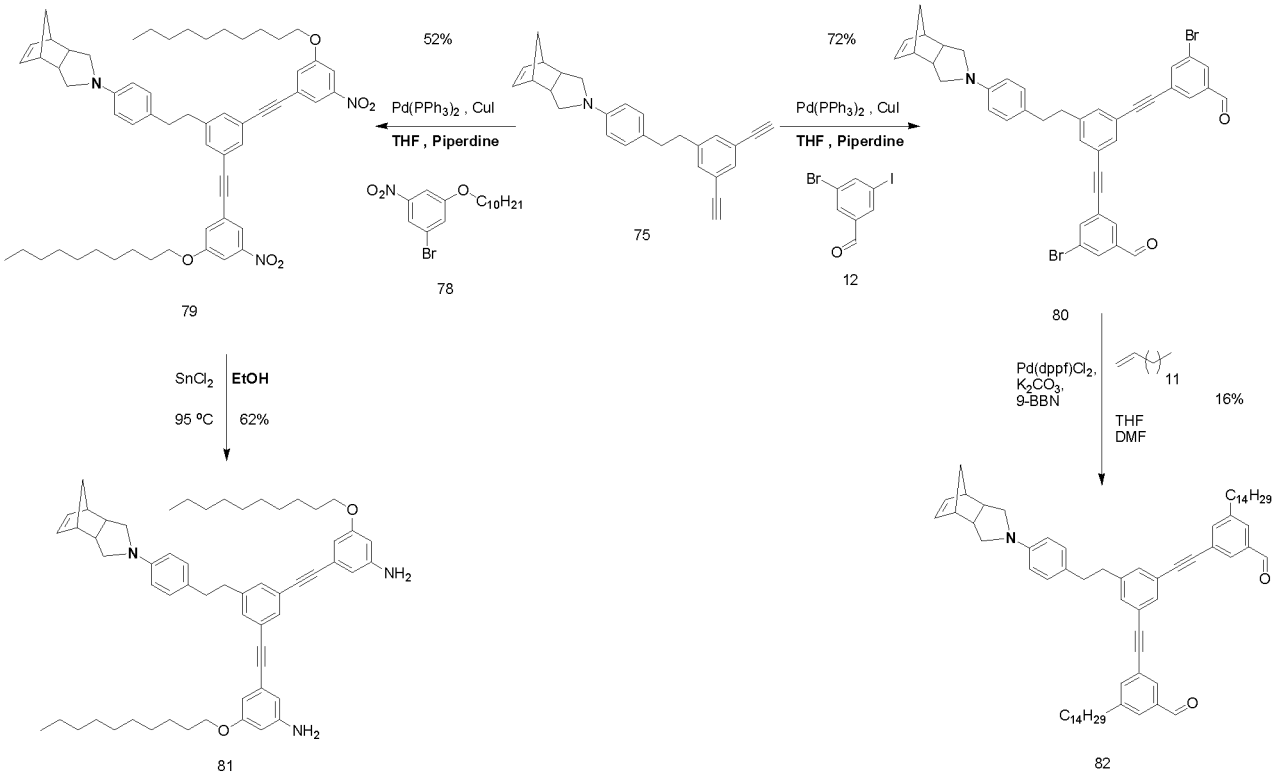


Figure 3.17: *Synthesis of monomers FDAmDo* ***(81)*** *and FDAlTd* ***(82)****.*

3.3 Conclusions

This is the end of the research work completed. Unfortunately it has shed more light on the reactions and methods that have not worked. Several points should be taken away from the research: (1) the macrocycle conformation resulting from imine or amine connections may affect the formation of the nanotube, the imine seems to be the best candidate, (2) the aryl amine connection for the norbornene group in necessary, and (3) flexibility, with sp^3 hybridized atoms, should exist between the norbornene group and the macrocycle. There is still more waiting to be explored with the methods out lined in the past two chapters. The work presented here has created a solid base of information from which further work can be done to one day realize the desired ONTs.

3.4 Experimental Section

The following section contains experimental procedures and ^{1}H NMR data for the compounds shown.

3.4.1 General Methods

Reagents and solvents were purchased for commercial suppliers and used without further purification, unless otherwise indicated. Ether, tetrahydrofuran, toluene, CH_2Cl_2, and DMF were purified by a MBRAUN solvent purification system. Reagent grade chloroform was purchased from Mallinckrodt Chemicals, and anhydrous acetonitrile was purchased from Sigma-Aldrich.

All reactions, except those performed in aqueous solvent, or otherwise noted, were conducted under dry nitrogen atmosphere in flame-dried glassware. Solvents were removed via rotary evaporator, unless specified.

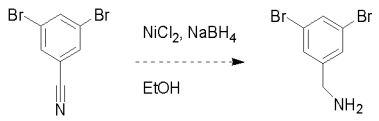
The purity of all compounds was $\geq$ 95% based on integration of the ^{1}H NMR spectrum, unless otherwise noted.

Flash chromatography was performed by using a 100-150 times weight excess of flash silica gel 32-63 μm from Dynamic Absorbants Inc. Fractions were analyzed by thin layer chromatography (TLC) using TLC silica gel F254-250 μm precoated-plates from Dynamic Absorbants Inc.

NMR spectra were taken on Inova 400 and Inova 500 spectrometers. $CDCl_3$ (7.26 ppm) was used as an internal reference in ^{1}H NMR, and $CDCl_3$ (77.23 ppm) for ^{13}C NMR. ^{1}H NMR data were reported in order: chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), number of protons, coupling constants (J, Hz), and assignments.

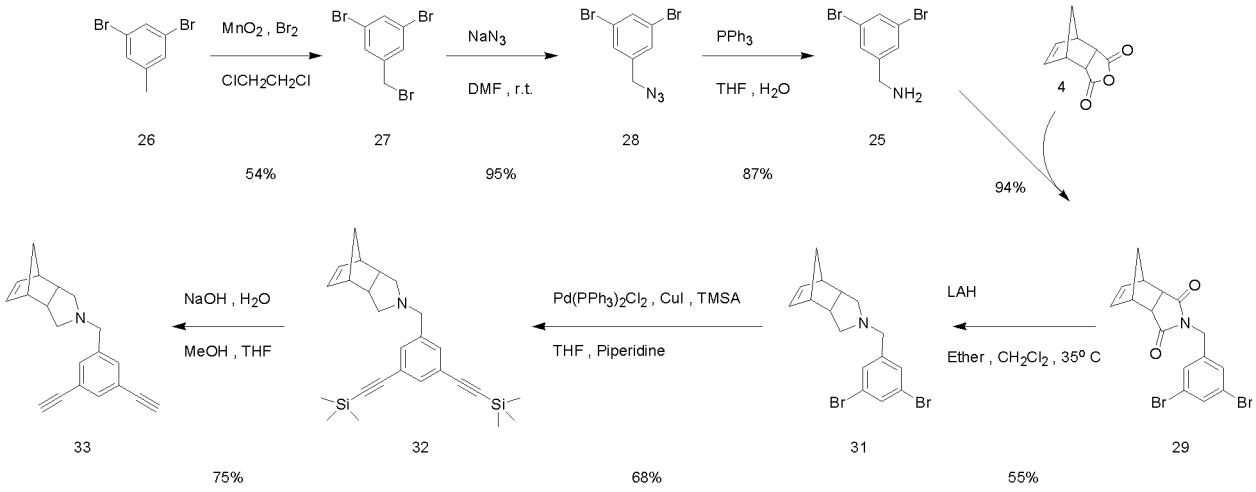
The microwave reactor used was a Discovery-S microwave reactor manufactured by CEM Corporation.

3.4.2 Syntheses



24 25

25: **24** (500 mg, 1.916 mmol) and $NiCl_2$ (248.4 mg, 1.916 mmol) were added to a sealed tube with 10 mL of ethanol dried with 4 angstrom MS. The reaction mixture was stirring at r.t. when the $NaBH_4$ (217.4 mg, 5.749 mmol) was added and rinsed into the tube with 5 mL of dry ethanol. The reaction was stopped after 40min and filtered through a Celite pad. Work up with EtOAc (3x50mL), H_2O (50 mL), washed with brine (50 mL), and dried over Na_2SO_4. Column: 25% CH_2Cl_2 in hexanes, 35%, 45%, 55%, 65%. No product isolated. No NMR of pure product.



27: **26** (5.000 g, 20.006 mmol), MnO_2 (1.7393 g, 20.006 mmol), and dichloroethane (10 mL) were added to a sealed tube, then Br_2 (1.03 mL, 22.006 mmol) was added dropwise. The reaction was heated to 100 ^{o}C for 18h. Solids were filtered and rinsed with CH_2Cl_2 to dissolve all product. The solvent was removed and the orange solid was scraped on to a filter funnel. Rinsed with several portions of cold methanol, and the off-white solid is pure **27**. No further purification necessary. Yield was 54%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.49 (s, 2H), 4.37 (s, 2H).

28: SM (497.8 mg, 1.52 mmol) and DMF (20 mL) were added to a sealed tube, then NaN_3 (150.7 mg, 2.281 mmol) was added and the reaction was stirred at r.t. for 1h. NMR showed complete conversion. Work up: added EtOAc (70 mL) and H_2O (50 mL) to the rxn mixture, washed the organic layer with H_2O (50 mL x2), brine (50 mL), and dried with Na_2SO_4. No purification done

as product was used directly for the next step. Yield was 95%. Crude NMR: ^{1}H NMR (400 MHz, CDCl3) δ 7.64 (s, 1H), 7.41 (s, 2H), 4.33 (s, 2H).

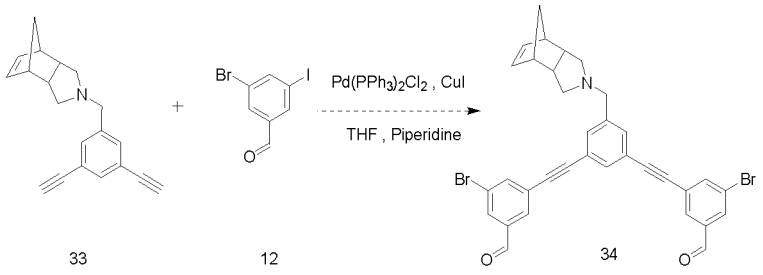
25: Azide **28** (442.5 mg, 1.521 mmol), PPh_3 (598.0 mg, 2.281 mmol), THF (15 mL), and H_2O (4.5 mL) were added to a sealed tube, which was heated to 75 °C for 1h. Work up: remove solvent, add EtOAc (50 mL) and H_2O (50 mL), and wash aqueous layer with EtOAc (3x 50 mL), wash organic layer with brine (50 mL), then dry over Na_2SO_4. Column: $CHCl_3$, 1% MeOH in $CHCl_3$, 2%, 3%, 4%, 5%. Yield was 87%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.46 (s, 2H), 3.88 (s, 2H).

29: Procedure same as **6**. No purification performed. Yield was 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.37 (s, 2H), 6.00 (t, J = 1.7 Hz, 2H), 4.43 (s, 2H), 3.41 (s, 2H), 3.32 (s, 2H), 1.74 (d, J = 8.9 Hz, 1H), 1.55 (d, J = 8.8 Hz, 1H).

31: Procedure same as **7**, except heated to 35 °C. Column: 10% EtOAc in CH_2Cl_2, 14%, 18%, 22%, 26%, 33%. 1% TEA used in solvent mixtures throughout column. Yield was 55%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (s, 1H), 7.37 (s, 2H), 6.16 (s, 2H), 3.43 (s, 2H), 2.90 (s, 2H), 2.80 (s, 2H), 2.74 (s, 2H), 1.97 (s, 2H), 1.66 (d, J = 8.1 Hz, 1H), 1.53 (d, J = 8.1 Hz, 1H).

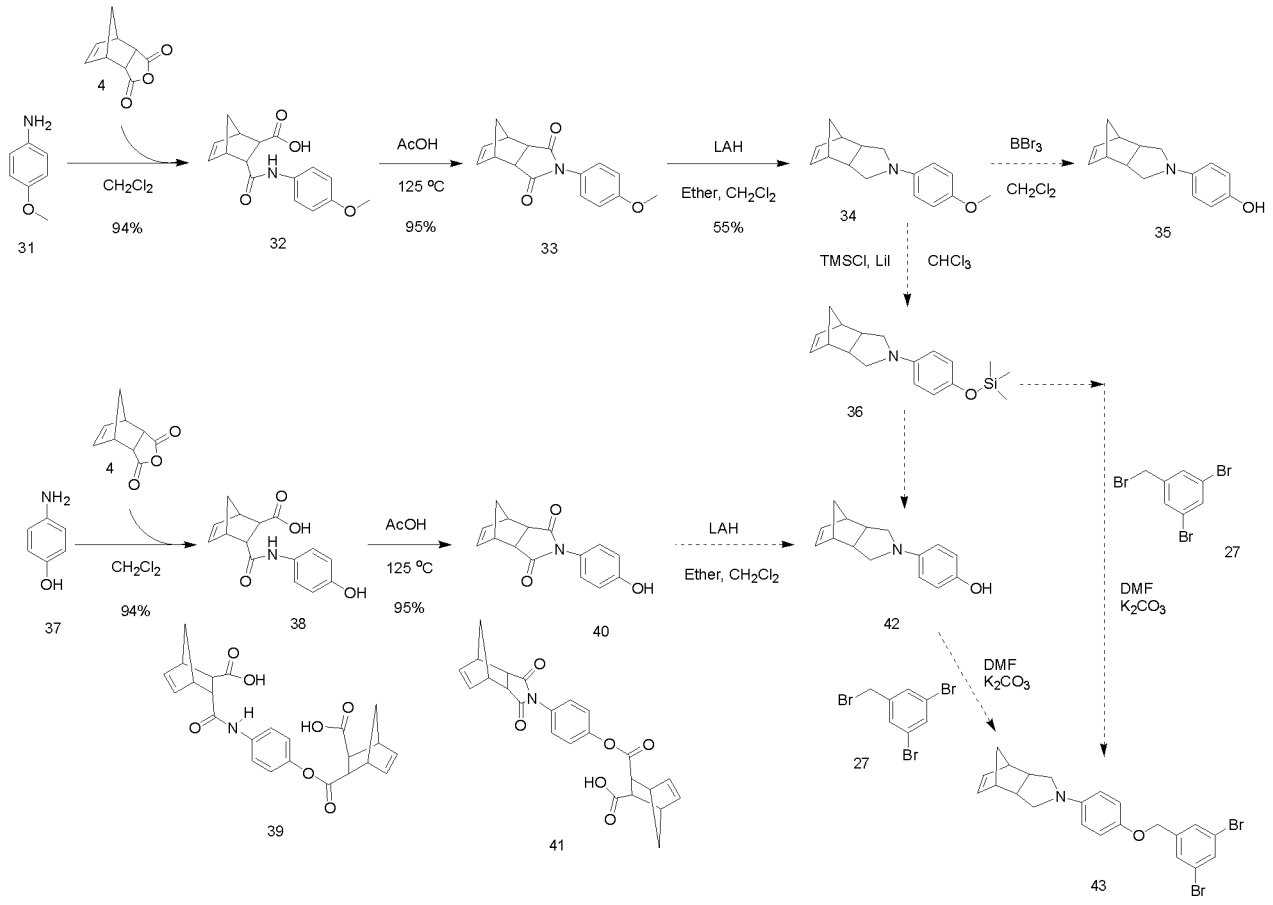
32: Procedure same as **8**. Silica gel plug run with EtOAc directly after reaction. Yield was 68%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.34 (s, 2H), 6.15 (t, J = 1.8 Hz, 2H), 3.42 (s, 2H), 3.13 (s, 12H), 2.91 (s, 2H), 2.78 (s, 4H), 1.89 (s, 15H), 1.68 (s, 9H), 1.54 (d, J = 8.1 Hz, 1H).

33: Procedure same as **9**. Column: 1% MeOH in CH_2Cl_2, 2%, 3%, 5%, 7%, 10%. 1% TEA used in solvent mixtures throughout column. Yield was estimated to be 75%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (s, 1H), 7.40 (s, 1H), 6.16 (s, 2H), 3.44 (s, 2H), 3.06 (s, 1H), 2.90 (s, 2H), 2.77 (d, J = 16.9 Hz, 4H), 1.94 (s, 2H), 1.66 (d, J = 8.1 Hz, 1H), 1.53 (d, J = 8.1 Hz, 1H).



33 12 34

34: Procedure same as **16**. Expected product did not form.



33: Procedure same as **6**. No purification performed. Yield was 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (s, 1H), 6.49 (s, 2H), 6.13 (s, 2H), 3.20 (s, 3H), 3.06 (s, 2H), 2.96 (s, 2H), 2.89 (d, J = 9.6 Hz, 2H), 1.60 (d, J = 8.3 Hz, 1H), 1.50 (d, J = 8.2 Hz, 1H).

34: Procedure same as **7**. Column: CH_2Cl_2. Yield = 55% ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.82 (d, J = 9.0 Hz, 2H), 6.43 (d, J = 9.0 Hz, 2H), 6.16 (s, 2H), 3.74 (s, 3H), 3.20 (s, 2H), 3.06 (s, 2H), 2.96 (s, 2H), 2.84 (d, J = 9.2 Hz, 2H), 1.61 (d, J = 8.1 Hz, 1H), 1.52 (d, J = 8.0 Hz, 1H).

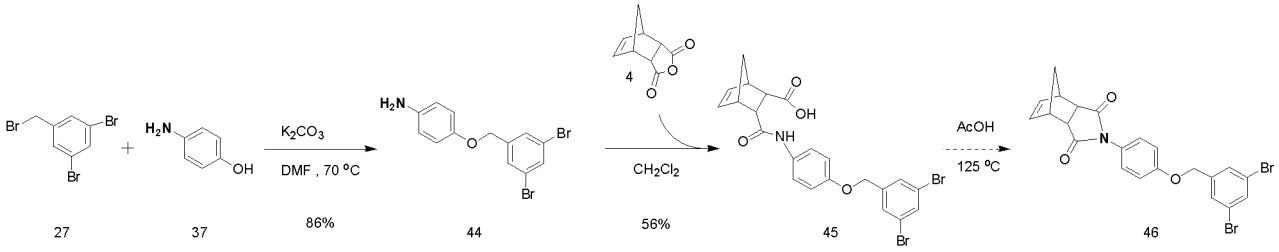
35: SM (394 mg, 1.633 mmol) dissolved in CH_2Cl_2 (6 mL) and cooled to 0° C. BBr_3 (0.46 mL, 4.898 mmol) added dropwise and the reaction was stirred for 30 min. Reaction warmed to r.t. and stirred for 1 h. Quenched with saturated $NaHCO_3$ (5 mL). Extract with CH_2Cl_2 (30 mL x4), water (50 mL), brine (40 mL), and dry over Na_2SO_4. ^{1}H NMR shows norbornene double bond is destroyed.

36: Lithium iodide (332.8 mg, 2.486 mmol) and CH_3CN (17 mL) were added to a sealed tube. TMSCl (0.31 mL, 2.486 mmol) and SM (500.0 mg, 2.072 mmol) were added and the reaction was heated to 50° C for 3h. The reaction was cooled to 0° C and quenched with MeOH. ^{1}H NMR showed the starting material consumed, but peaks corresponding to the desired product were not seen.

41: Procedure same as **6**. No purification performed. Yield was 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (d, *J* = 8.8 Hz, 2H), 6.82 (d, *J* = 8.8 Hz, 2H), 6.26 (s, 2H), 3.51 (s, 2H), 3.43 (s, 1H), 1.79 (d, *J* = 8.9 Hz, 1H), 1.62 (d, *J* = 8.8 Hz, 1H).

42: Procedure same as **7**. No product obtained.

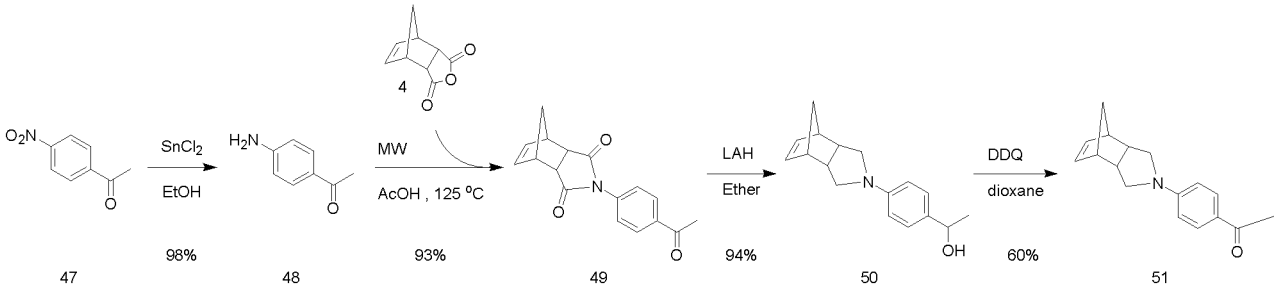
43: The procedure from **36** was used, but after heating for 3h, the solvent was removed. K_2CO_3 (1.4317 g, 10.359 mmol), **27** (817.5 mg, 2.486 mmol), and DMF (15 mL) were added the sealed tube, and the reaction was heated at 50 °C for 3h. ^{1}H NMR did not show peaks corresponding to the desired product.



44: Aminophenol (0.9994 g, 9.123 mmol), potassium carbonate (2.5218 g, 18.247 mmol), and DMF (20 mL) were added to a sealed tube and stirred at 70 °C for 1h. **27** (1.000 g, 3.041 mmol) was added to the sealed tube and stirred for 1h. Work up with water and CH_2Cl_2 wash with brine and dry over sodium sulfate. No purification performed. Yield was 86%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (s, 1H), 7.46 (s, 2H), 6.72 (d, *J* = 8.8 Hz, 2H), 6.49 (d, *J* = 8.8 Hz, 2H), 4.24 (s, 2H).

45: **44** (1.8482 g, 5.176 mmol) and **4** (1.0210 g, 6.212 mmol) were added to a RBF with EtOAc (15 mL) and stirred at r.t. for 2d. The reaction was filtered to yield a white solid (**45**). No purification was performed. Yield was 56%. ^{1}H NMR (500 MHz, CD_3OD) δ 7.59 (t, *J* = 1.6 Hz, 1H), 7.39 (d, *J* = 1.6 Hz, 2H), 6.97 (d, *J* = 8.7 Hz, 2H), 6.79 (t, *J* = 8.0 Hz, 2H), 6.28 (dd, *J* = 5.5, 3.0 Hz, 1H), 6.19 (dd, *J* = 5.5, 2.9 Hz, 1H), 4.76 (d, *J* = 2.5 Hz, 2H), 3.26 (dt, *J* = 7.0, 3.2 Hz, 1H), 3.04 (s, 1H), 2.92 (s, 1H), 2.85 (dd, *J* = 10.0, 3.5 Hz, 1H), 1.30 (d, *J* = 8.5 Hz, 1H), 1.12 (d, *J* = 8.5 Hz, 1H).

46: **45** (3.4868 g, 6.690 mmol) was added to a sealed tube with AcOH (70 mL) and heated to 125 °C for 16h. ^{1}H NMR revealed the ether had cleaved. Many other methods were attempted for this reaction, including one step reactions from **44** and **4**. After many trials, it was discovered that acid is needed to catalyze the reaction, and the amount required is greater than the amount required to cleave the ether linkage.

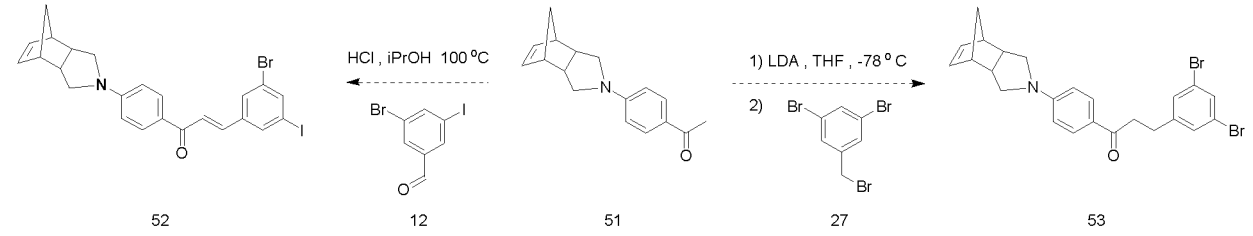


48: Procedure same as **3**. Yield was 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, J = 8.6 Hz, 2H), 6.66 (d, J = 8.6 Hz, 2H), 4.13 (s, 2H), 2.52 (s, 3H).

49: Procedure same as **6**. Yield was 93%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 8.8 Hz, 4H), 7.38 – 7.25 (m, 7H), 6.30 (dd, J = 9.0, 7.2 Hz, 5H), 4.14 (q, J = 7.1 Hz, 1H), 3.67 – 3.44 (m, 10H), 2.61 (d, J = 7.6 Hz, 6H), 2.24 (s, 1H), 2.09 (d, J = 16.2 Hz, 5H), 1.83 (d, J = 8.9 Hz, 3H), 1.65 (d, J = 10.2 Hz, 4H), 1.28 (t, J = 7.1 Hz, 2H).

50: Procedure same as **7**. Yield was 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 (d, J = 8.6 Hz, 2H), 6.44 (d, J = 8.7 Hz, 2H), 6.15 (t, J = 1.9 Hz, 2H), 3.23 (t, J = 9.2 Hz, 2H), 3.07 (dd, J = 7.3, 3.7 Hz, 2H), 3.00 – 2.95 (m, 2H), 2.91 (dd, J = 9.5, 2.9 Hz, 2H), 1.47 (d, J = 6.4 Hz, 3H).

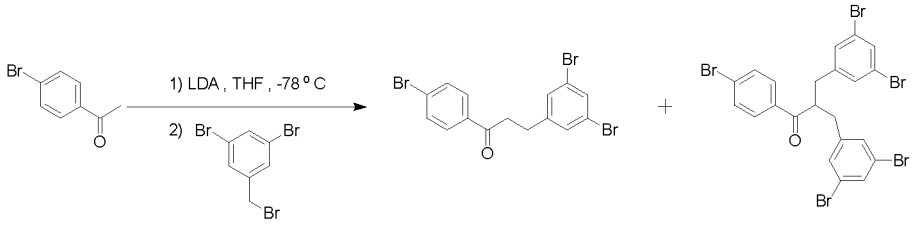
51: SM (200.0 mg, 0.783 mmol) was transferred in CH_2Cl_2 to a RBF and the solvent was removed. Dioxane (4 mL) and DDQ (177.8 mg, 0.783 mmol) were added to the flask and the reaction was stirred at r.t. for 1h. Solvent was removed and CH_2Cl_2 was added to disperse the solid and then it was filtered and washed with CH_2Cl_2 until no color was seen in the solvent coming out of the filter funnel. Column: CH_2Cl_2 (x2), 2% EtOAc in CH_2Cl_2 (x2), 4% EtOAc (x2), 10% EtOAc (x2). Yield was 60%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (d, J = 9.0 Hz, 1H), 6.40 (d, J = 9.0 Hz, 1H), 6.17 (t, J = 1.9 Hz, 1H), 3.32 (dd, J = 10.6, 8.9 Hz, 1H), 3.11 (dd, J = 7.3, 3.8 Hz, 1H), 3.03 – 2.96 (m, 2H), 2.49 (s, 2H), 1.63 (dt, J = 8.2, 1.7 Hz, 1H), 1.53 (d, J = 8.3 Hz, 1H).



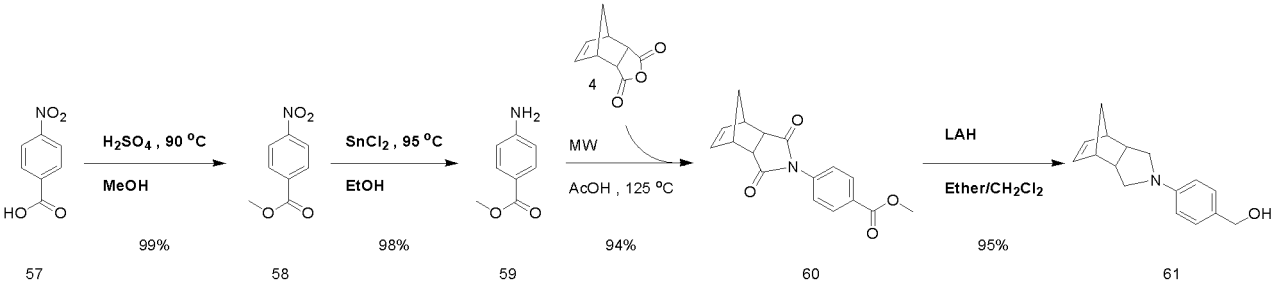
52: **51** (200 mg, 0.789 mmol) and **12** (245.5 mg, 0.789 mmol) were added to a microwave tube, then dissolved in isopropanol, and then 1 drop of conc. HCl. The reaction mixture was heated to 100 °C for 8h. No peaks corresponding to the desired product were seen in the crude ^{1}H NMR.

53: Dry THF was added to a sealed tube and cooled to -78 °C. An LDA solution (Aldrich, 2.0M in heptane) was added, followed by dropwise addition of the ketone **51**. The solution was stirred for 1.5h while the acetone bath was allowed to warm, reaching a temperature of -20 °C. The

reaction mixture was cooled back to -78 °C for dropwise addition of the electrophile **27**. The reaction mixture was stirred for 15min then allowed to warm to 0 °C and stirred for 1h. The reaction was quenched with saturated aqueous ammonium chloride. *Only starting materials were seen in the NMR indicating the enolate did not form.



55/56: Procedure same as **53** but with **54** as the ketone. ^{1}H NMR showed double alkylation.



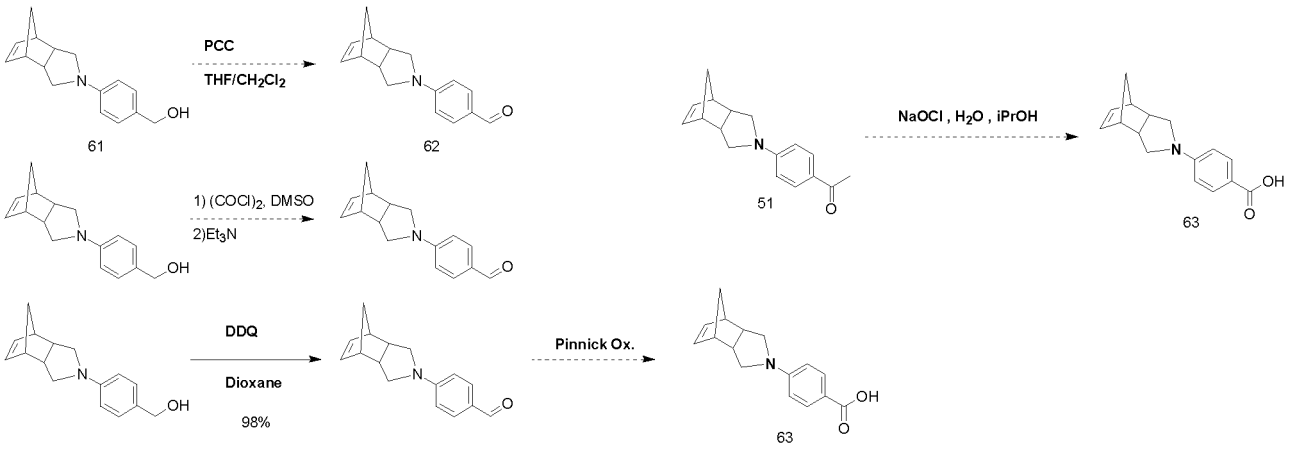
58: **57** (500 mg, 2.992 mmol) and methanol (2.5 mL) were added to a 10 mL microwave tube followed by dropwise addition of sulfuric acid (10 drops). The reaction was heated to 90 °C for 1h. The reaction mixture was worked up with ethyl acetate, water, aqueous sodium bicarbonate, washed with brine, and dried over sodium sulfate. No purification necessary. Yield was 99.4%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 1.4 Hz, 1H), 7.32 (s, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.40 (d, *J* = 8.4 Hz, 2H), 6.15 (s, 2H), 3.21 (t, *J* = 8.9 Hz, 2H), 3.06 (d, *J* = 5.0 Hz, 5H), 2.97 (s, 2H), 2.89 (d, *J* = 12.1 Hz, 3H), 2.79 (d, *J* = 5.6 Hz, 6H), 1.60 (d, *J* = 7.4 Hz, 1H), 1.51 (d, *J* = 8.5 Hz, 2H).

59: Procedure same as **3**. No purification performed. Yield was 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 1.4 Hz, 1H), 7.32 (s, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.40 (d, *J* = 8.4 Hz, 2H), 6.15 (s, 2H), 3.21 (t, *J* = 8.9 Hz, 2H), 3.06 (d, *J* = 5.0 Hz, 5H), 2.97 (s, 2H), 2.89 (d, *J* = 12.1 Hz, 3H), 2.79 (d, *J* = 5.6 Hz, 6H), 1.60 (d, *J* = 7.4 Hz, 1H), 1.51 (d, *J* = 8.5 Hz, 2H).

60: Procedure same as **6**. Column: CH_2Cl_2, 3% EtOAc in CH_2Cl_2, 4%, 5%, 6%, 8, 10%. Yield was 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (t, *J* = 1.4 Hz, 1H), 7.32 (s, 2H), 7.01 (d, *J* = 8.4 Hz, 2H), 6.40 (d, *J* = 8.4 Hz, 2H), 6.15 (s, 2H), 3.21 (t, *J* = 8.9 Hz, 2H), 3.06 (d, *J* = 5.0 Hz, 5H), 2.97 (s, 2H), 2.89 (d, *J* = 12.1 Hz, 3H), 2.79 (d, *J* = 5.6 Hz, 6H), 1.60 (d, *J* = 7.4 Hz, 1H), 1.51 (d, *J* = 8.5 Hz, 2H).

61: Procedure same as **7**. No purification performed. Yield was 96%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, *J* = 8.5 Hz, 2H), 6.45 (d, *J* = 7.5 Hz, 2H), 6.16 (s, 2H), 4.55 (s, 2H), 3.24 (t, *J*

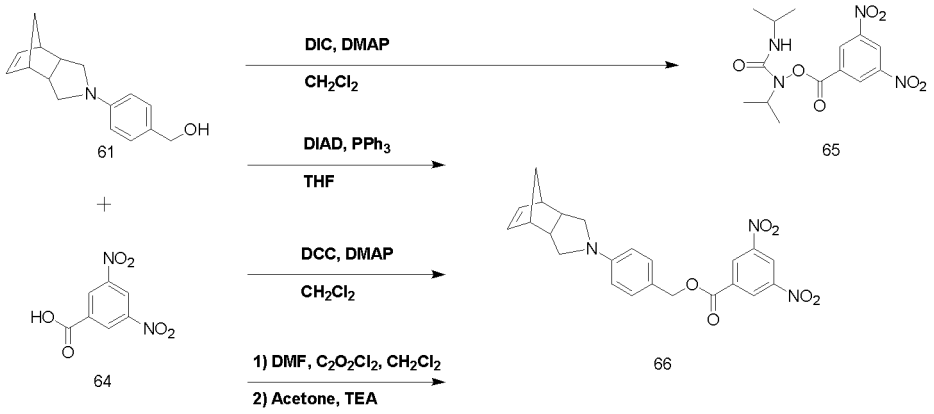
= 8.2 Hz, 2H), 3.08 (d, J = 4.0 Hz, 2H), 3.00 – 2.95 (m, 2H), 2.93 – 2.88 (m, 2H), 1.61 (d, J = 8.2 Hz, 1H), 1.52 (d, J = 8.2 Hz, 1H).



62: Procedure same as **51**. No purification performed. Yield was 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.5 Hz, 2H), 6.45 (d, J = 7.5 Hz, 2H), 6.16 (s, 2H), 4.55 (s, 2H), 3.24 (t, J = 8.2 Hz, 2H), 3.08 (d, J = 4.0 Hz, 2H), 3.00 – 2.95 (m, 2H), 2.93 – 2.88 (m, 2H), 1.61 (d, J = 8.2 Hz, 1H), 1.52 (d, J = 8.2 Hz, 1H). Pyridinium chloro chromate and Swern oxidations were also tried, but did not yield the desired product.

63 (Pinnick Oxidation): **62** (100 mg, 0.209 mmol), sodium phosphate mono-basic dihydrate (328.0 mg, 1.045 mmol), sodium chlorate (116 mg, 0.627 mmol), and t-BuOH (5 mL) were added to a RBF and stirred at r.t. *3 mL of CH_2Cl_2 was added to solubilize the starting material, since it was not soluble in t-BuOH. This created two phases in the RBF, and the stirring was turned up high to emulsify the reaction mixture. After 16h of stirring the ^{1}H NMR showed a stoichiometric aldehyde peak and an asymmetric norbornene double bond which indicates the opening/oxidation of the amine.

63 (Bleach Oxidation): **51** (200 mg, 0.789 mmol), KOH (34.7 mg, 0.868 mmol), and MeOH (2 mL) were added to a sealed tube. Bleach (Clorox, 6.15% NaOCl, 4.2 mL, 3.395 mmol) was added and the reaction was heated to 60 ^{o}C for 3h. **51** was not soluble in MeOH and after 3h, solids were visible floating in the solution. The organic solvent was taken off and isopropanol was added. Heating again to 60 ^{o}C resulted in yellow crystals in the solution. Upon analysis by NMR, these crystals were only starting material.

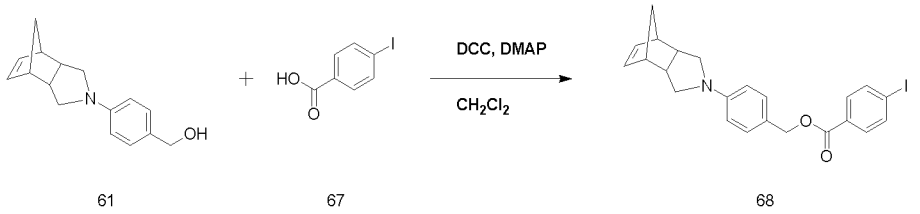


Ester (66) formation by Diisopropylcarbodiimide: **61** (50 mg, 0.207 mmol), **64** (65.9 mg, 0.311 mmol), DMAP (27.8 mg, 0.228 mmol), and CH_2Cl_2 (4 mL) were added to a sealed tube, then diisopropylcarbodiimide (64 µL, 0.414 mmol) was added dropwise and the reaction was stirred at r.t. The acid starting material reacted with the diisopropylurea formed from the reaction and the desired product did not for in a significant amount. Instead, **65** was isolated as the major product.

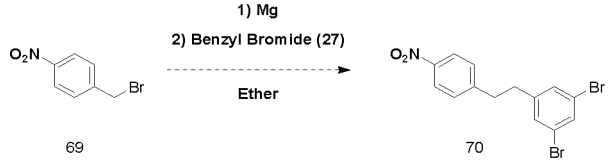
Ester (66) formation by Mitsunobu Coupling: **61** (50 mg, 0.207 mmol), **64** (41.0 mg, 0.269 mmol), PPh_3 (76.1 mg, 0.290 mmol), and THF (2 mL) were added to a RBF, then diisopropyl azodicarboxylate (53 µL, 0.269 mmol) was added dropwise and the reaction was stirred at r.t. *After stirring for 16h, the starting material is consumed and replaced with peaks that correspond to the desired product. Column: prewash column with TEA (5% in CH_2Cl_2); CH_2Cl_2, 5% EtOAc in CH_2Cl_2 (x2), 19% (x2), 40% EtOAc + 10% MeOH (x2), 60% EtOAc + 10% MeOH + 5% TEA (x2), 60% EtOAc + 10% MeOH (x4). The material isolated from the column was no longer soluble in the common NMR solvents and could not be characterized.

Ester (66) formation by Dicyclohexylcarbodiimide: **61** (51.7 mg, 0.214 mmol), **64** (48.9 mg, 0.321 mmol), DMAP (2.6 mg, 0.021 mmol), and CH_2Cl_2 (2 mL) were added to a RBF and the reaction was stirred at r.t. for 16h. ^{1}H NMR after 16h showed agreement with the Mitsunobu and acid chloride methods. Work up: filter the insoluble dicyclohexylurea side product, wash solid with CH_2Cl_2. *After storing dry overnight in a stoppered flask in the fridge, the crude product was no longer soluble in common NMR solvents.

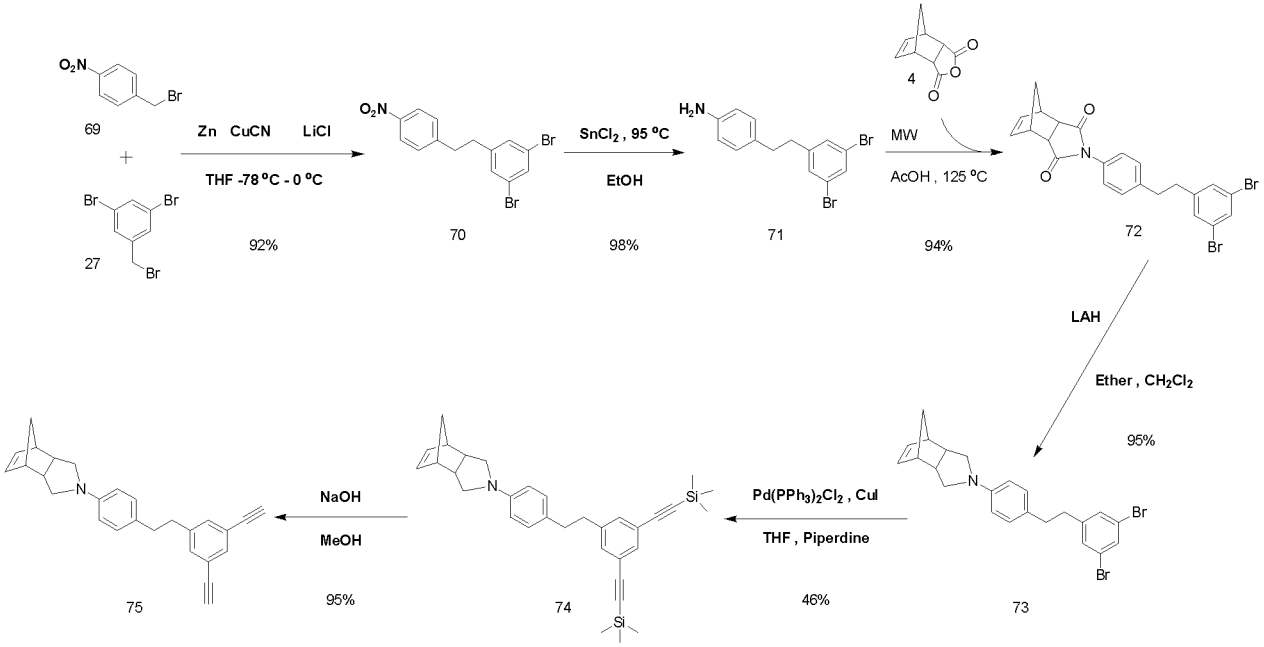
Ester (66) formation by Acid Chloride: **64** (34.7 mg, 0.228 mmol). THF (0.28 mL), and CH_2Cl_2 (1.4 mL) were added to a RBF and cooled to 0 °C. Oxalyl chloride (58 µL, 0.684 mmol) was added dropwise then 1 drop of DMF and the reaction was allowed to warm to r.t. and stirred for 1h. The solvent was removed and THF (2 mL) was added and the reaction was cooled to 0 °C. **61** (50 mg, 0.207 mmol) was added in THF (0.5 mL) dropwise and TEA (45 µL, 0.314 mmol) was added and the reaction was stirred at 0 °C. The ^{1}H NMR shows peaks that correspond to the product which match the results from the Mitsunobu and DCC methods. A column was run but no material was isolated that was soluble after concentrating fractions.



68: Procedure same as **66 DCC**. This was a model reaction to test success of ester forming method. Work up: wash with H_2O, 0.1 M HCl, brine, and dry over Na_2SO_4. No purification performed. No yield recorded. ^{1}H NMR (500 MHz, Acetone-d_6) δ 7.92 (d, J = 8.6 Hz, 2H), 7.76 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.7 Hz, 2H), 6.45 (d, J = 8.7 Hz, 2H), 6.17 (t, J = 1.9 Hz, 2H), 5.21 (s, 2H), 3.48 (s, 2H), 3.26 – 3.17 (m, 2H), 3.12 (dd, J = 7.1, 3.9 Hz, 2H), 3.01 – 2.96 (m, 2H), 2.94 (dd, J = 9.7, 2.9 Hz, 2H).



70: Magnesium turnings (22.5 mg, 0.926 mmol) were added to a sealed tube. THF (2 mL) and I_2 (one small crystal) were then added and the mixture was heated to 40 °C for 15min. **69** (200 mg, 0.926 mmol) was added dropwise in THF (1 mL) and then the reaction mixture was heated to 40 °C for 1h. The mixture was then transferred by syringe to a second sealed tube and **27** (253.7 mg, 0.771 mmol) was added dropwise in THF (1 mL) at 0 °C. ^{1}H NMR showed only starting materials, thus the Grignard reagent did not form.



70: Zinc dust (97 mg, 0.732 mmol) was added to a sealed tube, then cooled to 0 °C. **27** (400 mg, 0.608 mmol) in dry THF (1.4 mL) was added dropwise, then the reaction mixture was stirred at 0

°C for 2h. Half of the above solution (0.7 mL) was transferred to a solution of CuCN (50.4 mg, 0.282 mmol) and dried LiCl (51.6 mg, 0.608 mmol) at -78 °C in dry THF (1.25 mL). The solution was allowed to warm to -20 °C over 30min, then cooled back down to -78 °C. **69** (97 mg, 0.225 mmol) in dry THF (0.25 mL) was added dropwise. The reaction mixture was allowed to slowly warm to r.t. over 18h. Column: 15 % CH_2Cl_2 in hexanes, 20%, 25%, 30%, 35%, 40%, 50%. Yield was 92%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.7 Hz, 2H), 7.53 (t, *J* = 1.9 Hz, 1H), 7.30 (d, *J* = 8.7 Hz, 2H), 7.24 (dd, *J* = 3.4, 1.7 Hz, 3H), 3.02 (dd, *J* = 9.2, 6.5 Hz, 2H), 2.90 (dd, *J* = 9.2, 6.5 Hz, 2H), 2.83 (s, 1H).

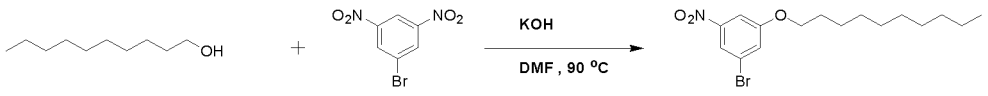
71: Procedure same as **3**. No purification performed. Yield was 98%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (t, *J* = 1.7 Hz, 1H), 7.25 (d, *J* = 1.7 Hz, 2H), 6.96 (d, *J* = 7.9 Hz, 2H), 6.62 (d, *J* = 6.3 Hz, 2H), 2.80 (s, 4H), 1.59 (s, 7H).

72: Procedure same as **6**. Column: 80 % CH_2Cl_2 in hexanes (x2), CH_2Cl_2 (x3), 2% EtOAc in CH_2Cl_2 (x2), 4% (x2). Yield was 94%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.52 (t, *J* = 1.7 Hz, 1H), 7.29 (d, *J* = 1.7 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 7.10 – 7.05 (m, 2H), 6.27 (t, *J* = 1.8 Hz, 2H), 3.52 (dt, *J* = 4.7, 1.7 Hz, 2H), 3.44 (dd, *J* = 2.9, 1.6 Hz, 2H), 2.93 – 2.82 (m, 4H), 1.80 (dt, *J* = 8.9, 1.6 Hz, 1H), 1.62 (d, *J* = 8.8 Hz, 1H).

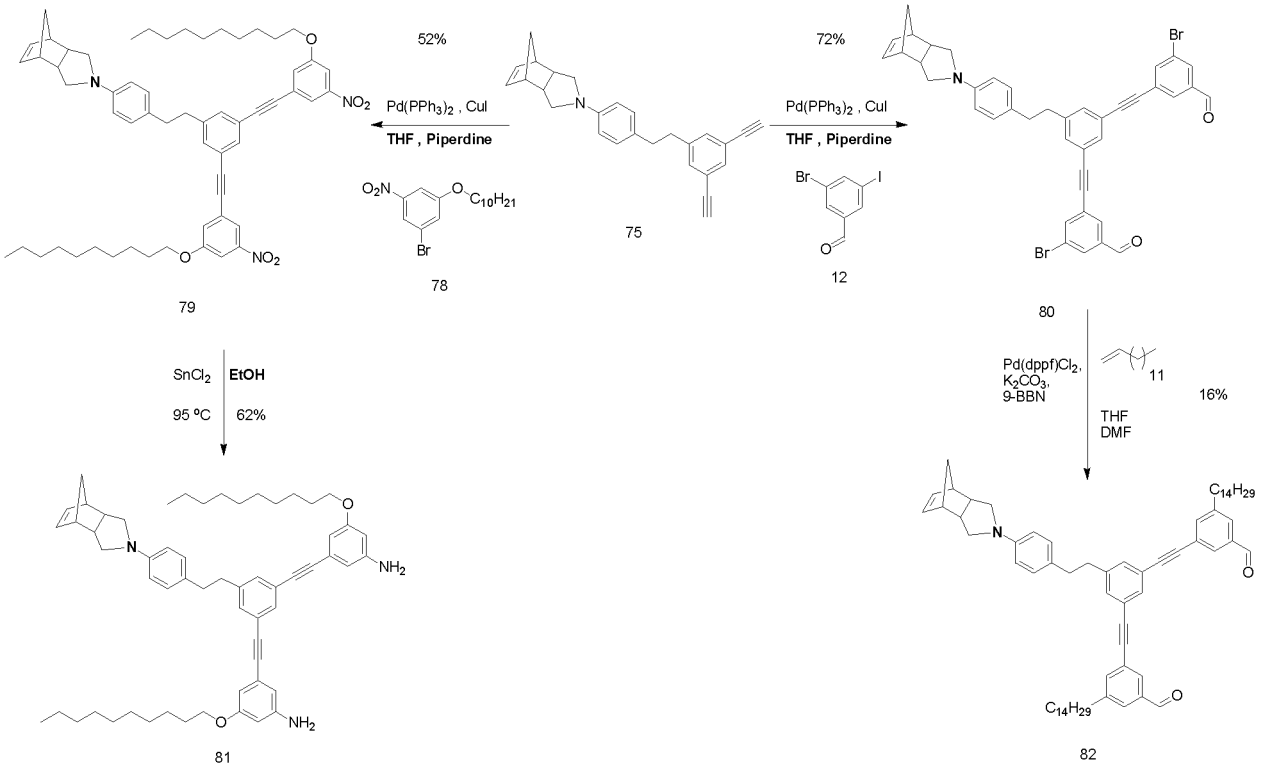
73: Procedure same as **7**. No purification performed. Yield was 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 3.21 (t, *J* = 8.7 Hz, 1H), 3.07 (s, 1H), 2.96 (s, 1H), 2.88 (d, *J* = 10.4 Hz, 1H), 2.78 (s, 2H), 1.59 (s, 1H), 1.51 (d, *J* = 8.2 Hz, 1H).

74: Procedure same as **8**. Column: 20% CH_2Cl_2 in hexanes, 24% (x2), 28% (x2), 30% (x2). Yield was 46%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (s, 1H), 6.99 (d, *J* = 8.4 Hz, 1H), 6.40 (d, *J* = 8.3 Hz, 1H), 6.15 (s, 1H), 3.21 (t, *J* = 8.7 Hz, 1H), 3.07 (s, 1H), 2.96 (s, 1H), 2.88 (d, *J* = 10.4 Hz, 1H), 2.78 (s, 2H), 1.59 (s, 1H), 1.51 (d, *J* = 8.2 Hz, 1H).

75: Procedure same as **9**. No purification performed. Column: 25% CH_2Cl_2 in hexanes, 29%, 33%, 37%, 41%, 45%, 50%. Yield was 95%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.46 (s, 1H), 7.32 (s, 2H), 7.01 (d, *J* = 8.5 Hz, 2H), 6.40 (d, *J* = 8.6 Hz, 2H), 6.15 (s, 2H), 3.21 (t, *J* = 8.0 Hz, 2H), 3.06 (d, *J* = 4.8 Hz, 4H), 2.97 (s, 2H), 2.88 (dd, *J* = 9.4, 3.0 Hz, 2H), 2.79 (d, *J* = 5.1 Hz, 5H), 1.60 (d, *J* = 8.1 Hz, 1H), 1.51 (d, *J* = 8.2 Hz, 1H).



76 77 52% 78



78: **77** (2.7096 g, 10.970 mmol), powdered KOH (1.2557 g, 22.379 mmol), decanol (4.25 mL, 22.269 mmol), and DMF (50 mL) were added to a sealed tube. The mixture was heated to 90 °C for 19h. Work up: dilute reaction mixture with EtOAc and rinse with water (500 mL) without shaking separatory funnel. Column: 8% CH_2Cl_2 in hexanes, 13% (x2), 21% (x2), 30% (x2). Yield was 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.95 (t, J = 1.8 Hz, 1H), 7.67 (t, J = 2.2 Hz, 1H), 7.39 – 7.34 (m, 1H), 4.02 (t, J = 6.5 Hz, 2H), 1.85 – 1.77 (m, 2H), 0.89 (t, J = 7.0 Hz, 4H).
79: Procedure same as **17**, except reaction temperature was 65 °C. Column: 25% CH_2Cl_2, 30%, 35%, 40%, 45%, 50%, 55%. Yield was 52%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 – 7.95 (m, 1H), 7.71 (t, J = 2.2 Hz, 1H), 7.58 (t, J = 1.4 Hz, 1H), 7.41 (s, 1H), 7.35 (dd, J = 2.4, 1.3 Hz, 1H), 7.08 – 7.00 (m, 1H), 6.43 (d, J = 8.3 Hz, 1H), 6.15 (s, 1H), 4.06 (t, J = 6.5 Hz, 2H), 3.22 (t, J = 7.8 Hz, 1H), 3.07 (s, 1H), 2.97 (s, 1H), 2.93 – 2.80 (m, 4H), 1.90 – 1.78 (m, 3H), 0.89 (t, J = 6.9 Hz, 5H).

80: Procedure same as **16**. Column: 45% CH_2Cl_2 in hexanes, 50%, 55%, 60%, 65%, 70%, 75%. Yield was 72%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.98 (s, 2H), 8.00 – 7.98 (m, 2H), 7.96 (t, J = 1.4 Hz, 2H), 7.92 (t, J = 1.7 Hz, 2H), 7.56 (s, 1H), 7.40 (s, 2H), 7.04 (d, J = 8.5 Hz, 2H), 6.43 (d, J = 8.4 Hz, 2H), 6.15 (s, 2H), 3.22 (t, J = 8.8 Hz, 2H), 3.10 – 3.02 (m, 2H), 2.97 (s, 2H), 2.86 (tdd, J = 12.4, 9.7, 2.5 Hz, 7H), 1.60 (d, J = 8.2 Hz, 1H), 1.52 (d, J = 8.2 Hz, 2H).

81: Procedure same as **3**. Column: CH_2Cl_2, 0.3% EtOAc in CH_2Cl_2, 0.6%, 0.9%, 1.2%, 1.5%, 2%. Yield was 62.3%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (s, 1H), 7.33 (s, 1H), 7.05 (d, J = 3.5 Hz, 2H), 6.50 (s, 2H), 6.49 – 6.46 (m, 2H), 6.42 (s, 2H), 6.25 (t, J = 2.1 Hz, 2H), 6.16 (s, 1H), 4.13 (q, J = 7.1 Hz, 1H), 3.93 (t, J = 6.6 Hz, 4H), 3.69 (s, 3H), 3.22 (s, 1H), 3.07 (s, 1H), 2.96 (s, 2H), 2.86 (d, J = 26.3 Hz, 6H), 2.06 (s, 1H), 1.81 – 1.72 (m, 4H), 0.89 (t, J = 6.9 Hz, 7H).

82: Procedure same as **18**. Column: 25% CH_2Cl_2 in hexanes, 30%, 35%, 40%, 45%, 50%, 55%. Yield was 16.2%. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.01 (s, 2H), 7.86 (s, 2H), 7.68 (s, 2H), 7.62 (s, 2H), 7.58 (s, 1H), 7.40 (s, 1H), 7.04 (s, 1H), 6.43 (d, J = 8.3 Hz, 1H), 6.15 (s, 1H), 3.65 (t, J = 6.6 Hz, 4H), 3.22 (t, J = 8.6 Hz, 1H), 3.06 (d, J = 3.2 Hz, 1H), 2.96 (s, 2H), 2.88 (dd, J = 16.2, 7.6 Hz, 7H), 2.73 – 2.66 (m, 5H), 1.26 (s, 118H), 0.88 (td, J = 7.0, 3.2 Hz, 19H).

Bibliography

1. V. N. Popov, P. Lambin and North Atlantic Treaty Organization., *Carbon nanotubes : from basic research to nanotechnology*. (Springer, Dordrecht, 2006).
2. M. A. B. Block, C. Kaiser, A. Khan and S. Hecht, Top Curr Chem **245**, 89-150 (2005).
3. K. Cantin, A. Lafleur-Lambert, P. Dufour and J. F. Morin, Eur J Org Chem (27), 5335-5349 (2012).
4. T. J. Hsu, F. W. Fowler and J. W. Lauher, Journal of the American Chemical Society **134** (1), 142-145 (2012).
5. R. Chapman, G. G. Warr, S. Perrier and K. A. Jolliffe, Chem-Eur J **19** (6), 1955-1961 (2013).
6. B. L. Deng, R. L. Beingessner, R. S. Johnson, N. K. Girdhar, C. Danumah, T. Yamazaki and H. Fenniri, Macromolecules **45** (17), 7157-7162 (2012).
7. N. Kameta, H. Minamikawa and M. Masuda, Soft Matter **7** (10), 4539-4561 (2011).
8. N. Kameta, K. Ishikawa, M. Masuda, M. Asakawa and T. Shimizu, Chem Mater **24** (1), 209-214 (2012).
9. Q. Yan, Y. Xin, R. Zhou, Y. W. Yin and J. Y. Yuan, Chem Commun **47** (34), 9594-9596 (2011).
10. K. Huang and J. Rzayev, Journal of the American Chemical Society **133** (42), 16726-16729 (2011).
11. K. Huang, M. Johnson and J. Rzayev, Acs Macro Lett **1** (7), 892-895 (2012).
12. E. P. Feener, W. C. Shen and H. J. P. Ryser, J Biol Chem **265** (31), 18780-18785 (1990).
13. J. Yang, H. Chen, I. R. Vlahov, J. X. Cheng and P. S. Low, P Natl Acad Sci USA **103** (37), 13872-13877 (2006).
14. N. Kang, J. H. Park, J. Choi, J. Jin, J. Chun, I. G. Jung, J. Jeong, J. G. Park, S. M. Lee, H. J. Kim and S. U. Son, Angew Chem Int Edit **51** (27), 6626-6630 (2012).
15. T. Y. Luh, Accounts Chem Res **46** (2), 378-389 (2013).
16. G. H. Coleman and W. F. Talbot, Org Synth **13**, 96-98 (1933).
17. K. Onitsuka, M. Fujimoto, H. Kitajima, N. Ohshiro, F. Takei and S. Takahashi, Chemistry – A European Journal **10** (24), 6433-6446 (2004).
18. I. N. Tarabara, A. O. Kas'yan, O. V. Krishchik, S. V. Shishkina, O. V. Shishkin and L. I. Kas'yan, Russ J Org Chem+ **38** (9), 1299-1308 (2002).
19. S. Thorand and N. Krause, J Org Chem **63** (23), 8551-8553 (1998).
20. W. B. Austin, N. Bilow, W. J. Kelleghan and K. S. Y. Lau, The Journal of Organic Chemistry **46** (11), 2280-2286 (1981).
21. M. Schulze, Synthetic Commun **40** (10), 1461-1476 (2010).
22. U. Lehmann and A. D. Schlüter, Eur J Org Chem **2000** (20), 3483-3487 (2000).
23. A. J. Mancuso and D. Swern, Synthesis-Stuttgart (3), 165-185 (1981).
24. N. Miyaura, T. Ishiyama, H. Sasaki, M. Ishikawa, M. Satoh and A. Suzuki, Journal of the American Chemical Society **111** (1), 314-321 (1989).
25. C. M. Chou, S. L. Lee, C. H. Chen, A. T. Biju, H. W. Wang, Y. L. Wu, G. F. Zhang, K. W. Yang, T. S. Lim, M. J. Huang, P. Y. Tsai, K. C. Lin, S. L. Huang, C. H. Chen and T. Y. Luh, Journal of the American Chemical Society **131** (35), 12579-12585 (2009).
26. J. A. Love, J. P. Morgan, T. M. Trnka and R. H. Grubbs, Angew Chem Int Edit **41** (21), 4035-4037 (2002).

27. Y. H. Jin, B. A. Voss, R. D. Noble and W. Zhang, Angew Chem Int Edit **49** (36), 6348-6351 (2010).
28. N. A. Lozinskaya, S. E. Sosonyuk, M. S. Volkova, M. Y. Seliverstov, M. V. Proskurnina, S. E. Bachurin and N. S. Zefirov, Synthesis-Stuttgart (2), 273-276 (2011).
29. K. M. Mathew, S. Ravi, V. K. P. Unny and N. Sivaprasad, J Labelled Compd Rad **49** (8), 699-705 (2006).
30. K. Tomaya, M. Takahashi, N. Minakawa and A. Matsuda, Org Lett **12** (17), 3836-3839 (2010).
31. M. V. Bhatt and S. U. Kulkarni, Synthesis-Stuttgart (4), 249-282 (1983).
32. G. A. Olah, S. C. Narang, B. G. B. Gupta and R. Malhotra, J Org Chem **44** (8), 1247-1251 (1979).
33. T. L. Ho and G. A. Olah, Synthesis-Stuttgart (6), 417-418 (1977).
34. L. F. Fieser, M. Fieser and T.-L. Ho, *Reagents for organic synthesis*. (Wiley, New York, 1967).
35. E. J. Corey and J. W. Suggs, Tetrahedron Lett (31), 2647-2650 (1975).
36. H. D. Becker, A. Bjork and E. Adler, J Org Chem **45** (9), 1596-1600 (1980).
37. V. Tomar, G. Bhattacharjee, Kamaluddin, S. Rajakumar, K. Srivastava and S. K. Puri, European Journal of Medicinal Chemistry **45** (2), 745-751 (2010).
38. D. Seebach, H. Bossler, H. Grundler, S. Shoda and R. Wenger, Helv Chim Acta **74** (1), 197-224 (1991).
39. J. Palecek, R. Zweigerdt, R. Olmer, U. Martin, A. Kirschning and G. Drager, Org Biomol Chem **9** (15), 5503-5510 (2011).
40. S. Roesner, J. M. Casatejada, T. G. Elford, R. P. Sonawane and V. K. Aggarwal, Org Lett **13** (21), 5740-5743 (2011).
41. Y. M. Angell, C. Garciaecheverria and D. H. Rich, Tetrahedron Lett **35** (33), 5981-5984 (1994).
42. R. Dembinski, Eur J Org Chem (13), 2763-2772 (2004).
43. C. Marti and E. M. Carreira, Journal of the American Chemical Society **127** (32), 11505-11515 (2005).
44. R. J. Smith, R. A. Capaldi, D. Muchmore and F. Dahlquist, Biochemistry-Us **17** (18), 3719-3723 (1978).
45. X. Garcia-Mera, J. E. Rodriguez-Borges, M. L. C. Vale and M. J. Alves, Tetrahedron **67** (37), 7162-7172 (2011).
46. A. Krasovskiy, V. Malakhov, A. Gavryushin and P. Knochel, Angew Chem Int Edit **45** (36), 6040-6044 (2006).
47. R. Kandre, K. Feldman, H. E. H. Meijer, P. Smith and A. D. Schluter, Angew Chem Int Edit **46** (26), 4956-4959 (2007).

Vita

Ryan Denman served four years in the United States Air Force as a Satellite Operations Analyst. During his service he acquired an Associate in Applied Science from the Community College of the Air Force and an Associate in the Arts from Brevard Community College in 2007. After being Honorably Discharged from military service, he continued his education with a Bachelors of Science in Chemistry at the University of Central Florida, which he completed in 2009. He pursued a MS in Materials Chemistry at the University of Colorado at Boulder under the guidance of Prof. Wei Zhang. His research focused on construction of covalent organic nanotubes via dynamic covalent chemistry methods.