A REACTIVITY STUDY OF THE PALLADIUM CROSS-COUPLING SYNTHESIS OF ENEDIYNES

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ABSTRACT

A REACTIVITY STUDY OF THE PALLADIUM CROSS-COUPLING SYNTHESIS OF ENEDIYNES

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A reactivity study looking at various aspects of the palladium catalyzed (Sonogashira) reaction for the synthesis of enediynes was performed. Alkynes were coupled to 1,2-dichloro-, 1,2-dibromo- and 1,2-diiodobenzene. From this, four conclusions were drawn. It was determined that the carbon-iodine bond is the most reactive towards coupling though it is usually harder to obtain the second substitution in comparison to chlorine and bromine. It was found that alkynes bearing TMS and $C(CH_3)_2OH$ or moderately bulky (TBDMS, TIPS) groups couple to form disubstituted enediynes while alkynes containing THP do not. It was determined that this palladium cross-coupling reaction does not exhibit much if any solvent effect. The order of addition for the reaction mixture was only important if a reactive alkyne was used. In cases such as this, the alkyne should be added last to minimize homocoupling. Additionally, successful photochemical cyclizations were performed on three of the four enediynes synthesized.

ACKNOWLEDGEMENTS

There are a number of people I wish to thank for their help and guidance throughout this project, for without them, this thesis would not have been possible. First and foremost, I would like to thank Dr. C. Gottardo for taking me on as her first graduate student. Without her supportive and invaluable direction and guidance, I could never have even completed a fraction of this thesis. I would also like to thank Dr. J. Banks, not only for the use of his GLC, but for his help and insight into the reactivity study yield calculations. Additionally, I would like to thank Ainsley for his GLC help and expertise and Ain for running all of my GCMS samples. Finally, I wish to thank Rob Leach for his understanding and his patience through my entire university career, but, especially over the last couple of years.

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1,4-CHD	1,4-cyclohexadiene
DMAP	4-(N,N-dimethyl)aminopyridine
DMF	N,N-dimethylformamide
eq.	equivalent
Δ	heat
GCMS	gas chromatography mass spectrometry
GLC	gas-liquid chromatography
hν	light
RT	room temperature
TBDMS	t-butyldimethylsilyl
t-BOC	t-butoxycarbonyl
THF	tetrahydrofuran
THP	tetrahydropyran
Et_3N	triethylamine
TIPS	triisopropylsilyl
TMS	trimethylsilyl

CHAPTER ONE: A SYNTHETIC AND MECHANISTIC REVIEW OF ENEDIYNE CHEMISTRY

1.1 Introduction

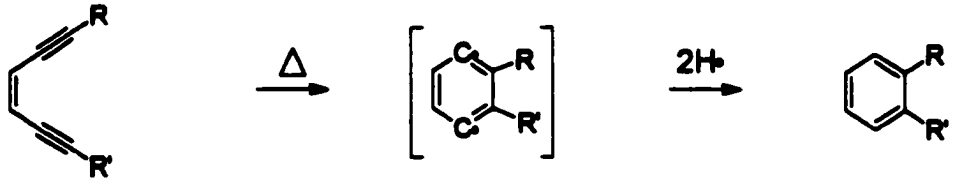
The discovery of the extremely potent natural product enediyne antitumor antibiotics has sparked a plethora of interest in chemical, biological and medical research. In particular, chemical researchers are involved in determining the way in which the novel molecular enediyne structure of these antitumor antibiotics acts to control both their biological activity and their mode of action[1] which causes cell death. Investigations are also underway to develop more selective and stable analogs of these antibiotics which will function just as well if not better than their natural counterparts.[2]

In this thesis, reviews of both enediyne antitumor antibiotics and the cyclization reactions they can undergo will be presented, followed by a review of the palladium cross-coupling reaction that has been used to synthesize enediynes. A reactivity study of the palladium cross-coupling reaction for enediyne synthesis will be introduced in Chapter Two of this thesis along with a brief look at the photochemical reactivity of the enediynes synthesized during the study.

1.2 Enediyne Antitumor Antibiotics

Enediynes and their chemistry have been studied since the mid-1960s and, in 1972, Bergman performed the first detailed study of the thermal cyclization of simple acyclic (Z)-enediynes (Scheme 1).[3] Bergman's work was interesting from a physical organic viewpoint, but, for the most part, it was forgotten for some time. It was not until 1987 when two novel antitumor antibiotics with cyclic enediyne cores were reported,[2] that the work of Bergman and others in this area gained renewed interest.

Scheme 1



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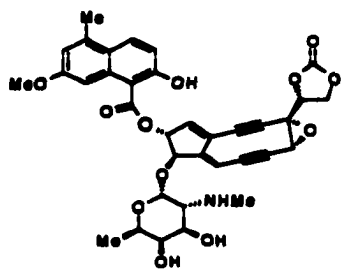
Presently, there are several known families of naturally occurring enediynes with more being discovered at a steady rate. Of these families, there are six which have been most extensively researched, namely, neocarzinostatin chromophore 4, calicheamicins 5, esperimicins 6, dynemicin 7, kedarcidin chromophore 8, and C-1027 chromophore 9 (Figure 1).[2] Except for neocarzinostatin chromophore, which has an enyne-cumulene core, all of the other families contain a conjugated enediyne core.[4] This enediyne or enyne-cumulene core is often called the warhead of the antibiotic molecule because it is the portion of the molecule which exercises its biological activity. In addition to this warhead core, the structure of each of these antitumor antibiotics must contain a delivery system which allows

for both the conveyance and the binding of the antibiotic to its target, DNA. Furthermore, these enediynes need an associated triggering device so that once the molecule has been delivered and bound to its target DNA, it can be activated to function.

Figure 1



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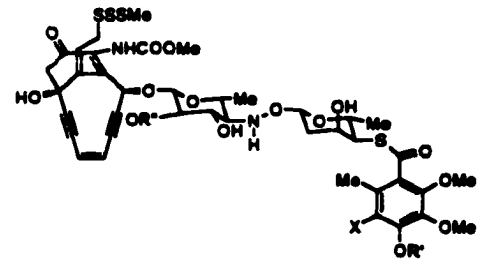

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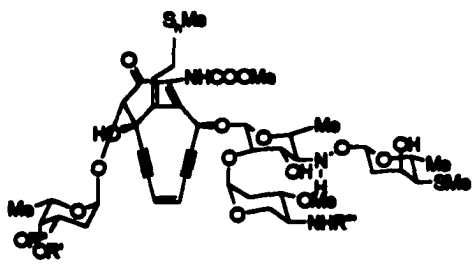

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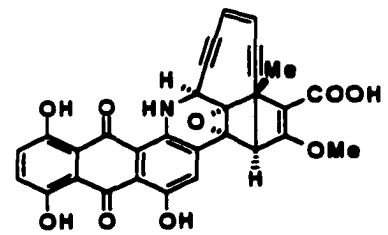

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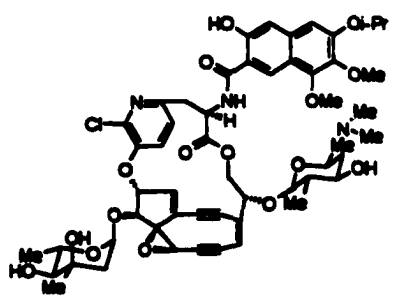

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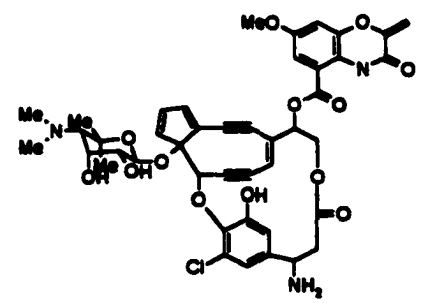

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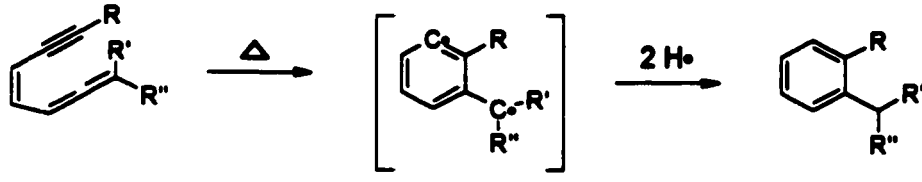
1.2.1 Mode of Action

It is the unique way in which the enediyne antitumor antibiotics function that has brought them to the forefront of research in many areas. These molecules irreversibly cleave double-stranded DNA through a series of reactions.[1,2] Once the enediyne has been introduced into a cell, the molecule recognizes and binds to a specific sequence of DNA which is characteristic of that enediyne system.[2,4] Then, the triggering device in the enediyne system is set off, removing the blocking device, activating the enediyne system towards cyclization.[5] Cyclization follows, which for the enediyne core is a Bergman cyclization (Scheme 1) and for the enyne-cumulene core is a type of Myers-Saito cyclization (Scheme 2).[4] It is believed that both types of cyclizations occur through a benzenoid-type diradical

Scheme 2



10 11 12

intermediate which proceeds to abstract hydrogen from the sugar phosphate backbone of the target DNA.[6,7,8] The ring closure and the hydrogen abstraction may or may not occur simultaneously.[2,9] Regardless, the removal of hydrogen from the DNA backbone leaves DNA radicals which react with molecular oxygen to cleave the DNA,[1] eventually resulting in cell death. The potency of these enediyne systems is quite amazing. In fact, they are

among some of the most potent antitumor agents known.[10]

1.2.2 Calicheamicins and Esperimicins

In taking a closer look at the natural product enediynes, it can be seen that the calicheamicins 5 and esperimicins 6 contain the same enediyne bicyclic core. Both families also contain polysaccharide fragments, their delivery system, which shape the molecules in such a way that they can bind into the minor groove of DNA. This binding occurs at TCCT sites for calicheamicins and at less specific sites for esperimicins with preference shown for T>C>A>G.[1] In addition, these two families of enediynes contain the same triggering device, a trisulphide moiety. A nucleophile attacks the middle sulphur atom of the trisulphide forming a thiolate which proceeds to attack the α,β-unsaturated ketone in the adjacent 6-membered ring converting the sp^2 carbon at the point of attack to an sp^3 carbon.[11] This removes the blocking device present, the bridgehead double bond, triggering cyclization.[6,10] Bergman cyclization is then believed to proceed as previously outlined. Presently, there are 20 calicheamicins and 7 esperimicins known.

1.2.3 Dynemicin

Compared to the calicheamicins and esperimicins, there are relatively few dynemicin antibiotics known. In fact, there are only two, dynemicin A (7) and deoxydynemicin A.[2] The dynemicins are a unique family of enediyne antitumor antibiotics in that they are the only ones that lack carbohydrate residues.[12] Instead, they combine a 10-membered enediyne

bridge with the anthraquinone chromophore of the anthracycline anticancer antibiotics.[1] Dynemicins also intercalate the minor groove of DNA, but unlike the calicheamicins and esperimicins, they bind through their anthraquinone component and they show binding preference to sites with the DNA bases G and to a lesser extent A.[1] Once bound, dynemicins are activated by a two-electron bioreduction by the anthraquinol to form a quinone methide. This bioreduction and rearrangement occurs simultaneously with an opening of the epoxide (the blocking device) on the 10-membered enediyne ring allowing for cyclization to commence.[5] As before, Bergman cyclization proceeds as previously detailed.

1.2.4 Neocarzinostatin Chromophore

Since the neocarzinostatin (NCS) chromophore 4 has an enyne-cumulene core instead of an enediyne core, the mode of action of this antibiotic is slightly different than the other enediynes. The structural differences between the NCS chromophore and many of the other enediyne systems do not end with the enyne-cumulene core. Unlike the enediyne systems discussed so far, the NCS chromophore is associated with an apoprotein when isolated from nature. The NCS chromophore performs all of the biological activity of the antibiotic while the apoprotein helps to transport and stabilize the NCS chromophore.[1] Though this apoprotein may be the delivery system for the NCS chromophore, it does not double as the DNA binding site. Instead, the structural feature of the NCS chromophore that binds it into the minor groove of DNA is its naphthoate group which preferentially binds to sites with A and T residues. The NCS chromophore is then usually activated by thiol attack on the

epoxide causing both the epoxide to open and the ring skeleton to rearrange forming a diradical comparable to 11 through a Myers-Saito type cyclization. This diradical acts in a similar manner to the 1,4-diradical formed in the Bergman cyclization and abstracts hydrogen from the DNA to which it is bound, causing strand cleavage and cell death.

1.2.5 Analogs

These natural product enediyne antitumor antibiotics are quite unique and sophisticated in both their biological function and their mode of action. Unfortunately, many of these natural enediynes are also so toxic they cannot be used in clinical trials.[7] Much research has been dedicated to developing analogs of these natural enediyne systems.[1,2,4,5,7,8,10,13] Analogs should be designed to have a number of desirable characteristics. Firstly, they should be chemically stable under neutral conditions but be able to cyclize upon suitable activation. Secondly, analogs should be structurally simple with many of the non-essential functional groups from the analogous natural product structure removed, allowing for easier synthesis. Thirdly, analogs must still have enough suitable functionality in order to attach to appropriate delivery systems and other required moieties such as initiators and deactivators. Initiators and deactivators are included to allow for the activation and modulation of the biological functioning of the enediyne antitumor analog.[2,8] The goal in making enediyne analogs is to maximize biological activity while keeping the molecular complexity at a minimum. To this end, it has been reported that some analogs have not only shown the usual DNA cleavage, but they have also shown an impairment of the ability to

synthesize DNA, RNA and proteins in some tumor cells.[14] From this example and others, it is apparent that progress has been made in designing and synthesizing analogs or prodrugs for natural enediyne antitumor antibiotics. There are many more approaches which need to be investigated to bring a better understanding of this field to the scientific community.

1.3 Cyclization Reactions

The cyclization reactions that enediyne antitumor antibiotics undergo is another area of research which has received an enormous amount of attention recently. In designing analogs, it is important that a good understanding of the cyclization process exists in order to impart proper or improved biological activity to the synthetic molecule. There are four types of enediyne or enyne-cumulene/allene cyclizations which have received the most attention, the Bergman cyclization,[3] the Myers-Saito cyclization,[4] the Schmittel or C2-C6 cyclization[15,16] and tandem cyclizations.[2,17,18,19]

1.3.1 Bergman Cyclization

Of the enediyne-type cyclizations, the Bergman cyclization (Scheme 1) has been researched the most. Though a lot of time has been invested in studying this reaction since Bergman first discovered it, there is no direct proof of the biradical intermediate.[2] Although some experiments have arisen to challenge the existence of this intermediate,[2] the original mechanism (discussed previously) Bergman proposed still stands.[2] This is due to the fact that there is enough indirect proof of a radical intermediate to support Bergman's

mechanism. As further proof, experiments have been performed showing that a well known radical trapping agent (TEMPO) reacts with intermediates of this cyclization[17] lending further support to Bergman's work.

In addition to studying the actual mechanism of the Bergman cyclization, the reactivity of this reaction has been investigated in some detail. A couple of important factors that affect the cyclization reactivity are strain effects and substituent effects. Strain effects exert enormous amounts of influence on the reactivity of enediynes. For simple enediyne systems, a straightforward method of predicting the cyclization reactivity has been developed based on the strain effects associated with the acetylenic carbon (cd) distance. For cyclizations of cyclic systems to rapidly occur at room temperature, the cd distance should be less than 3.20Å. If the cd distance of a system falls within the range of 3.20-3.35Å, the compound will show limited thermal stability at room temperature, while an enediyne system with a cd distance of greater than 3.35Å is thermally stable at room temperature.[14,20,21] A similar but more complicated method of predicting enediyne reactivity has also been developed for strained enediynes. This method uses the difference in strain energies of the transition state and the ground state (ΔSE). Based on the literature assumption that the transition state is product-like,[6] ΔSE is the difference between the strain energy of the cyclized product and the strain energy of the ground state enediyne system.[6] The larger the ΔSE value, the more thermally stable the compound. This results in less strained enediyne systems being more reactive than more strained ones.[2] These calculated ΔSE values correlate fairly well with known enediyne reactivities.[10]

Substituent effects can also play a major role in influencing the reactivity of enediyne systems. Sterically, large bulky groups on the terminal acetylenic carbons of enediynes tend to increase the cd distance, causing the enediyne to be less reactive to cyclization. Electronically, alkyl substituents on the terminal acetylenic carbons have been shown to decrease the reactivity of cyclization,[2] while electron withdrawing groups such as hydroxyl, alkoxyl and carboxyl groups, even at the propargylic position of cyclic systems, seem to increase the cyclization reactivity.[10] Substituent effects have also been studied on the enediyne double bond showing that cyclization reactivity correlates well with the bond order of this double bond.[10] In many instances, researchers include the enediyne double bond in an aromatic ring. This change in the format of the double bond has been found to show little effect on the cyclization reactivity of the enediyne system.[2]

For cyclic enediynes, both the ring size and the degree of strain in the ring play a large part in the rate of cyclization. For example, rings that are 9- or 10-membered have been shown to cyclize spontaneously at room temperature[10,22] while larger rings do not. Other factors which affect both cyclic and acyclic systems include the state of hybridization, the presence of heteroatoms and the complexation of metal ions.[23] In addition, it is important to note that there is a difference in the rates of cyclization between cyclic and acyclic systems. Cyclic systems usually require cyclization temperatures at, or below, physiological levels (37°C) while acyclic systems usually need high temperatures to cyclize (upwards of 160°C). This may be due to the fact that the rate determining step for cyclic systems is hydrogen abstraction,[24] while the rate determining step for acyclic systems is the formation

of the radical intermediate. This indicates there may be a large energy difference from ground state to the transition state of acyclic systems in comparison to cyclic systems.[24]

All of the above information on the Bergman cyclization has been obtained through thermal reactivity studies. There is now evidence for a photochemical Bergman cyclization.[25] From this initial study, it appears as though the mechanism for the photochemical cyclizations is similar to the thermal one and the enediyne cyclizes through a 1,4-diradical intermediate. The major difference between the thermal and photochemical cyclizations is that the thermal cyclizations arise from a conjugative effect of the entire enediyne functionality whereas it has been proposed that photochemical cyclizations arise from excitation of the acetylenic units of the enediyne.

1.3.2 Myers-Saito Cyclization

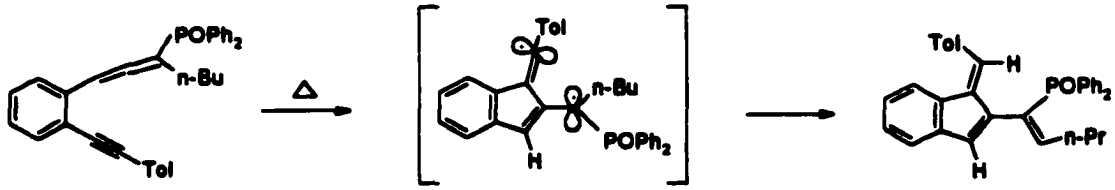
The Myers-Saito cyclization[4] (Scheme 2) is similar to the Bergman cyclization in many ways. There are three major differences between the two types. Firstly, as stated earlier, the Myers-Saito cyclization involves the cyclization of an enyne-allene rather than an enediyne. Secondly, the Myers-Saito cyclization goes through a less reactive σ,π-biradical from the enyne-allene starting material whereas the Bergman cyclization has a very reactive σ,σ-biradical intermediate. Cyclizations from enyne-cumulenes are similar to those from enyne-allenes except that they go through σ,σ-biradical intermediates. Finally, Bergman cyclizations are moderately endothermic and so heating is often required for cyclization to occur whereas Myers-Saito cyclizations are quite exothermic.[1,2] As a result,

enyne-allene and enyne-cumulene analogs have received more attention than their corresponding enediynes simply because they are easier to cyclize.

1.3.3 Schmittel Cyclization

The Schmittel cyclization is a special type of Myers-Saito cyclization in which substituent effects cause an enyne-allene system to cyclize into a 5- and not a 6-membered ring (Scheme 3).[15,16] Specifically, if an aryl or other bulky radical stabilizing substituent is on the terminal acetylenic carbon of the enyne-allene, upon cyclization a short-lived benzofulvene biradical intermediate 14 is formed which is stabilized at the vinylic radical centre by the attached radical stabilizing substituent group. This biradical intermediate then proceeds to form benzofulvene or benzofluorene derivatives 15 in fairly high yields.[15] This

Scheme 3



13 14 15

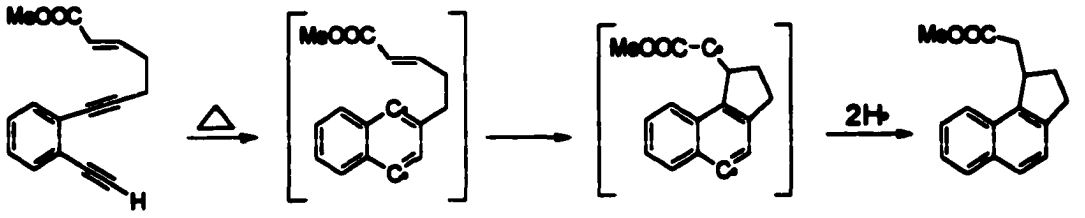
cyclization appears to be a general thermal reaction of enyne-allenes.

1.3.4 Tandem Cyclizations

As mentioned previously, Bergman and Myers-Saito cyclizations proceed through a biradical intermediate. This biradical intermediate can undergo subsequent intramolecular

radical cyclizations to form bi- and polycyclic systems.[2,17,18,19] These subsequent cyclizations are termed tandem cyclizations. Tandem cyclizations via the Bergman reaction (Scheme 4)

Scheme 4



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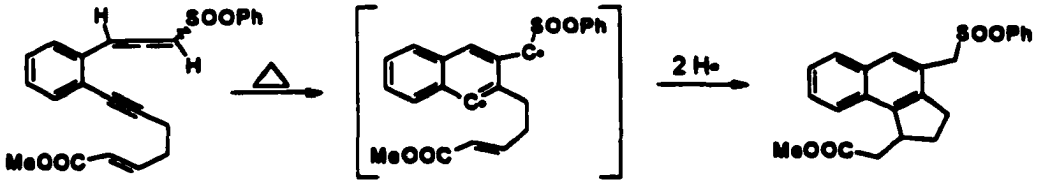
have been well documented, but they require high temperatures (150-200°C) which can sometimes decompose the enediyne starting material. Since, in general, Bergman cyclizations require such high temperatures and Myers-Saito cyclizations do not, tandem cyclizations have now been done on enyne-allene systems which occur at physiological temperature (37°C) (Scheme 5).

Scheme 5



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1.4 Palladium Cross-coupling Reaction

In order to prepare the enediyne antitumor antibiotic analogs or to synthesize the

actual natural products, a reliable method is needed to construct the enediyne core. A number of methods have been studied and employed to make enediynes including Norrish Type II reactions on a diyne to form the double bond portion of the molecule,[26] the dehydration of prop-2-ynyl alcohols to selectively form (Z)-enediynes,[27] and the use of a Diels-Alder reaction to introduce the double bond in a diyne.[2] Still, the most common standard method of enediyne formation is a palladium-catalyzed cross-coupling reaction.

1.4.1 Stephens-Castro Coupling

A palladium cross-coupling reaction used for enediyne synthesis today was first investigated by Stephens and Castro in 1963.[28] These researchers coupled cuprous acetylides with aryl iodides, in pyridine, to produce enynes in relatively high yields. This Stephens-Castro coupling was also shown to react well when alkenyl halides were used as starting materials. In fact, it was concluded that the coupling reaction will only take place if the displaced halogen is attached to an sp^2 carbon atom. It was also found that for both alkenyl and aromatic systems, the ease of displacement of the halogen was I>Br>Cl with no replacement of F at all.[29,30] Unfortunately, the cuprous acetylides can require vigorous reaction conditions and can be difficult to synthesize. A modified method of this coupling has been developed, called the Sonogashira coupling reaction.[31]

1.4.2 Sonogashira Coupling

Instead of using cuprous acetylides, the Sonogashira coupling reaction uses cuprous

iodide and a palladium catalyst in an amine solvent under mild conditions. Originally, Sonogashira *et al*[31] coupled iodoarenes, bromoalkenes and bromopyridines with acetylenes at room temperature in relatively high yields (80-98%). Due to the numerous applications recently found for this reaction, especially in natural product syntheses, a fair amount of research is being put into optimizing this reaction. Bleicher *et al*[32] found that coupling a bromopyridine with TMS acetylene did not go to completion and that the starting materials were difficult to separate from products. They developed a different protocol for the cross-coupling reaction. Instead of using expensive palladium catalysts they used palladium on carbon (Pd/C) with triphenylphosphine, cuprous iodide and potassium carbonate as the base in dimethoxyethane and water. They found this worked quite well with yields ranging from 92% to 98%. Thorand and Krause[33] also had problems with the typical Sonogashira reaction conditions, having difficulties reproducing the high yields reported in the literature. They believed these difficulties were due to a number of factors. To begin with, there is a low reactivity of coupling with aryl bromides resulting in some harsh reaction conditions. Conversely, aryl iodides couple extremely well due to the rich chemistry of the I-C(sp^2) bond[34] but they are expensive and difficult to prepare. In addition, Glaser coupling (oxidative homocoupling of the alkyne) occurs if oxygen is not completely excluded, wasting alkyne, and often causing difficulties in separation from the desired products. So, Thorand and Krause tried different solvents for the Sonogashira coupling and found that tetrahydrofuran (THF) works well, increasing the reactivity of the reaction while decreasing Glaser coupling when combined with a slow addition of the alkyne. This decrease in Glaser

coupling by slow addition of the alkyne was previously noted by Xu *et al.*[35] Thorand and Krause then did a reactivity study with different substituted aryl bromides and different alkynes with yields ranging between 80% to 95%.

In a review of the literature for the synthesis of enediynes, it was found that most researchers use the Sonogashira coupling reaction or slight modifications of it. The majority of coupling reactions are performed on *cis*-1,2-dichloroethylene [21,22,19,32,36] though quite a few are also performed with 1,2-dibromobenzene[23,37,38,39] and 1,2-diiodobenzene.[17,18,19] In choosing the alkyne, most researchers prefer TMS acetylene,[18,19,36,37,40,41] propargyl alcohol[23,19,37] or protected versions of the alcohol using THP [32,42] or other protecting groups such as silyl ethers.[35] The solvent of preference still seems to be an organic base,[23,21,35,37,38,43] usually either n-butylamine, n-propylamine or triethylamine, though quite a few are also using benzene[17,18,19,44] and some have started using THF.[18,19,45] As with most reactions, there is even some choice in the palladium catalyst used. Usually it is either $Pd(PPh_3)_4$ [21,22,32,37,42,45] or $PdCl_2(PPh_3)_2$.[19,41,43] Depending on various and, as yet undetermined, aspects of the reaction conditions, these syntheses can be completed using both the Pd(0) catalyst[46] and the Pd(II) catalyst.[47] The only constant in all of the literature procedures is the use of CuI as a co-catalyst which speeds up the rate of the reaction considerably.[32,37] It is important to note that almost all of the literature reactions were done to produce monosubstituted products.

From this review of the literature it is apparent that a comprehensive study of this palladium-catalyzed cross-coupling reaction has not been done. For example, there are no comparisons available which look at the coupling reaction in terms of halide replacement for

iodine, bromine and chlorine on aromatic rings or the ease of coupling for monosubstitution compared to disubstitution or the reactivity differences in various solvents which are not amines. This thesis will address all of these issues and more in Chapter Two.

CHAPTER TWO: A REACTIVITY STUDY OF ENEDIYNE SYNTHESIS

2.1 Introduction

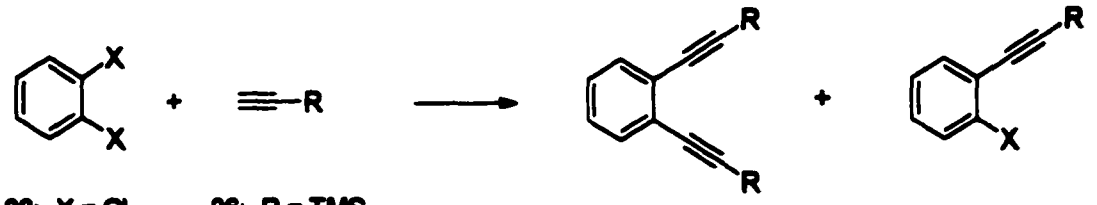
In Chapter One, a review of procedures used to date for the Sonogashira coupling reaction were described. With well-known applications in the synthesis of enediynes, it would be expected that more detailed information would be available. We noticed a number of voids in the literature including those mentioned at the conclusion of Chapter One.

In this chapter, four of the informational voids were addressed in the form of a reactivity study of the Sonogashira reaction. Firstly, the ease of halide replacement was considered by using iodo-, bromo- and chloro-substituted arenes. Secondly, by comparing mono- and disubstituted percent yields from reaction mixtures set up for disubstitution, the ease of mono- and disubstitution was evaluated. Thirdly, the effects of polar and nonpolar solvents were examined by comparing percent yields of mono- and disubstituted alkynes for each type of solvent. Fourthly, the method or rather, order of addition of the reagents, was investigated to determine if it had any effect.

2.2 Reactivity Study

The reactivity study (Scheme 6) was set up to evaluate all four voids efficiently and effectively. The focus of the study was in completing the disubstitution to a symmetrical enediyne in one step. As such, although monosubstituted products were obtained, they were not further reacted to form disubstituted products. First of all, the reagents were chosen. Tetrakis(triphenylphosphine)palladium(0) was chosen as the catalyst since it was more prevalent in the literature. Cuprous iodide was used as the co-catalyst. Triethylamine was decided on for the base since it has been used frequently,[19,33,34,42] it was readily available and the nature of the amine has not been deemed to be critical to the reaction.[37] The arenes

Scheme 6



23: X = Cl
24: X = Br
25: X = I

26: R = TMS
27: R = CH_2OTIPS
28: R = $CH_2OTBDMS$
29: R = CH_2OTHP
30: R = $C(CH_3)_2OH$

31 - 35

36 - 50

Starting Materials		Product	
X	R	di	mono
Cl	TMS	31	36
Br	TMS	31	37
I	TMS	31	38
Cl	TIPS	32	39
Br	TIPS	32	40
I	TIPS	32	41
Cl	TBDMS	33	42
Br	TBDMS	33	43
I	TBDMS	33	44
Cl	THP	34	45
Br	THP	34	46
I	THP	34	47
Cl	$C(CH_3)_2OH$	35	48
Br	$C(CH_3)_2OH$	35	49
I	$C(CH_3)_2OH$	35	50

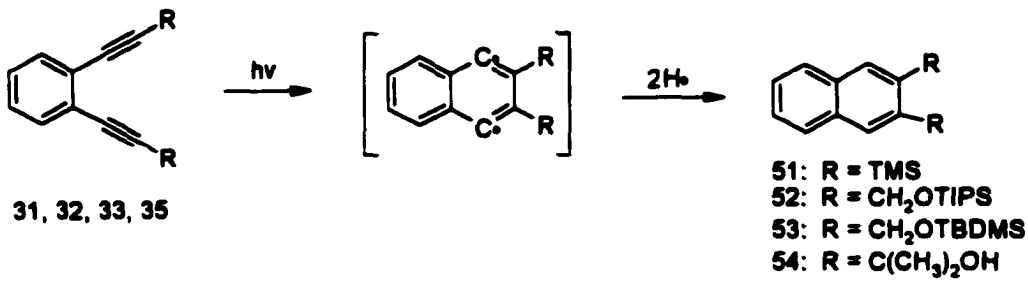
chosen were the 1,2-dihalosubstituted benzenes: 1,2-dichlorobenzene, 23, 1,2-dibromobenzene, 24, and 1,2-diiodobenzene, 25, because they are relatively simple having no heteroatoms or substitutions present to influence reactivity. The alkynes chosen were those most commonly used in the literature: TMS acetylene, 26, TIPS, 27, TBDMS, 28 and THP, 29, protected propargyl alcohol and 2-methyl-3-butyn-2-ol, 30. All reactions were performed using identical amounts of each reactant in the ratios: 1 equivalent of the 1,2-dihalobenzene, 2.5 equivalents of the alkyne, 0.06 equivalents of $Pd(PPh_3)_4$, 0.2 equivalents of CuI and 6 equivalents of Et_3N. Benzene was chosen as the nonpolar solvent and THF as a moderately polar solvent because they had both been shown to work well in the literature. Finally, the two methods of addition that were chosen were taken from the literature, one in which the 1,2-dihalobenzene was added last[42] and the other in which the alkyne was added last.[19]

The reactivity study then entailed combining each of the three 1,2-dihalobenzenes with each of the five alkynes in turn, in both benzene and THF, using both addition methods, in duplicate. The combinations attempted involved a total of 120 reactions. These reactions were divided up into four groups: Method A, Method B, Method C and Method D (see Chapter Three).

In addition to this reactivity study, the photochemical cyclizations of the enediynes synthesized were examined (Scheme 7). These were done to determine if the enediynes from the study would also cyclize through a photo-Bergman cyclization to form substituted

naphthalenes. The procedure for the photochemical cyclizations was modified from the literature.[25]

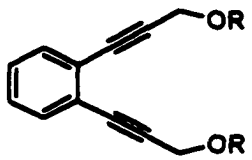
Scheme 7



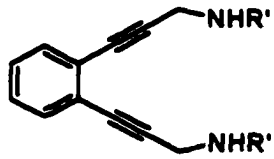
2.3 Rationale for the Reactivity Study

In Chapter One the natural enediynes were discussed in some detail. In looking closely at their structures (Figure 1) it is apparent that they all have a heteroatom located close to their enediyne portion. Yet, much research has focused on preparing and cyclizing carbon containing systems. The original focus of this thesis proposed that heteroatom enediynes are closer in structure to the naturally occurring ones. With that said, enediynes containing heteroatoms provide more accurate models for the natural enediynes. A number of heteroatom systems were then proposed (Scheme 8) and the syntheses of many of them were attempted to be followed by both thermal and photochemical cyclizations. The two types of experiments were proposed in order to compare both the ease of cyclization between the two methods, as well as the ease of cyclization between carbon and heteroatom containing enediynes.

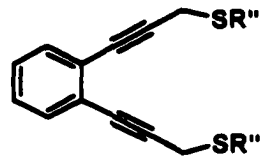
Scheme 8



55: R = H
56: R = CH=CH$_2$
57: R = CH$_2$CH=CH$_2$



58: R' = t-BOC
59: R' = TBDMS
60: R' = H
61: R' = CH$_3$
62: R' = CH=CH$_2$



63: R" = COCH$_3$
64: R" = H
65: R" = CH$_3$
66: R" = CH$_2$Ph
67: R" = CH=CH$_2$
68: R" = CH$_2$CH=CH$_2$

With this in mind, the syntheses of a number of the heteroatom enediynes (Scheme 8) were attempted using 23 as the 1,2-dihalobenzene. To begin with, the syntheses of 58, 59 and 60 were tried using both Methods A and D of the reactivity study (see Chapter Three). In all cases, no products were formed. Then, reactions were performed to make 63 and 66 using both Methods A and D and Method D, respectively, also to no avail. Much frustration arose from the fact that 55 had been synthesized in the literature from 24,[37] but these results were not reproducible when 23 was substituted for 24. Not only was 55 unattainable from the coupling reactions tried, but, by preparing the protected enediynes, 32, 33, and 34 and attempting their deprotection by various methods, 55 was still elusive.

Instead of continuing with the frustrating attempts of synthesizing the heteroatom enediynes that were proposed, it was decided that a more detailed attempt should be made to look into why these experiments had failed. The reactivity study contained in this thesis is the result.

2.4 Results and Discussion

The results of the reactivity study are presented in terms of percent yields for each reaction (Table 1). There are a number of obvious trends within the yields obtained. Firstly, the 1,2-diiodobenzene showed the best coupling, though in addition to the desired disubstituted product, it generally produced significant amounts of the monosubstituted product as well. This is probably due to the fact that of the three halides used **23**, **24**, and **25**, the carbon-iodine bond is both the longest and the most polarizable.[48] This indicates that of the three, the carbon-iodine bond is the most reactive. Additionally, the longer bond distance allows for a less hindered attack on the arene by the catalyst to form **69**. Both of these factors combine to produce the higher yields seen. This is not to say that **23** and **24** do not react at all, though for many of the reactions this is the case. It appears that when **23** and **24** do react, they react to completion forming primarily the disubstituted products with very little monosubstituted product. These results with dichloride and dibromide show a marked difference with respect to other work where the diiodobenzene was used. For example, coupling of the 1,2-diiodobenzene with propargyl alcohol (1.2 eq.) has been reported to give the monoalkyne in a 52% yield with none of the di-alkyne reported.[19] In our reactions, for example, the 1,2-diiodobenzene, **25**, and the TMS acetylene, **26**, it appears as if the mono alkyne, **38**, forms preferentially (see Table 1) and is then converted in the presence of excess alkyne to the disubstituted product, **31**. Furthermore, it should be noted that the stepwise addition of alkynyl substituents to 1,2-diiodobenzenes has been performed to give *bis*-1,2-

Table 1: Reactivity Study Yields

	Method A			Method B			Method C			Method D		
Alkyne	23	24	25	23	24	25	23	24	25	23	24	25
26 di	0%[a]	0%	20%	0%	0%	36%	0%	0%	15%	0%	0%	24%
mono	0%	0%	53%	0%	0%	56%	0%	0%	49%	0%	0%	60%
27 di	24%	24%	13%	19%	20%	13%	12%	16%	21%	15%	21%	22%
mono	0%	0%	15%	1%	1%	19%	0%	0%	13%	1%	1%	18%
28 di	16%	19%	6%	5%	6%	9%	16%	27%	12%	14%	16%	14%
mono	0%	0%	10%	0%	1%	24%	0%	1%	19%	0%	1%	16%
29 di	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%	0%
mono	0%	0%	37%	0%	0%	34%	0%	0%	21%	0%	0%	23%
30 di	0%	0%	53%	0%	0%	24%	0%	0%	3%	0%	0%	5%
mono	0%	2%	47%	0%	1%	69%	0%	1%	54%	0%	1%	54%

a) Yields determined by GLC

dialkynylbenzenes in an overall yield of 73% using 3 equivalents of the alkyne.[17] This is most likely due to the fact that with both the chlorine and bromine atoms quite tightly bound, when substitution does occur at one site, neighbouring group participation may occur to facilitate the second substitution.[30] In cases where an electron-withdrawing group is in the para-position with respect to a monobromide, the reactivity is not affected, with yields ranging from 65-99%.[33] It is more likely that the more electronegative chloride and bromide

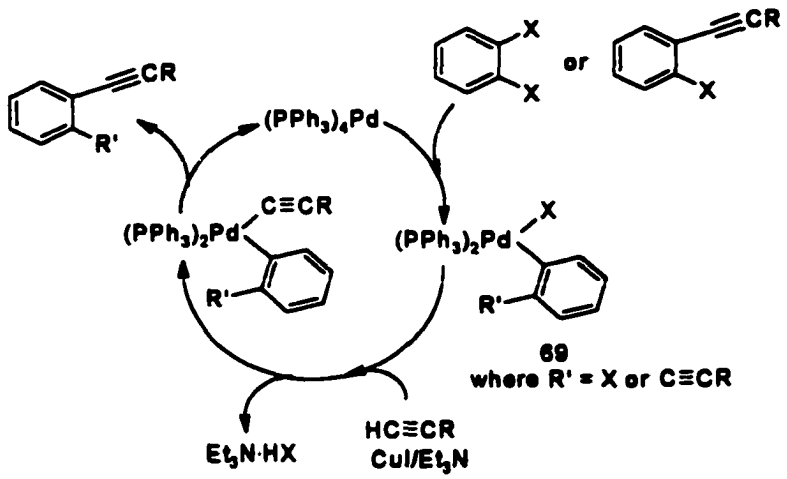
relative to the iodide result in an inductive effect which decreases the reactivity rather than a direct neighbouring group participation. Once one of the chlorides or bromides has been replaced, the second substitution occurs more easily due to the presence of the electron-donating alkyne.

Secondly, there are two noticeable trends involved in looking specifically at the alkynes used in coupling. The first trend to note is that 26 and 30 coupled the best in terms of 1,2-diiodobenzene conversion to either mono- or disubstituted products, with conversions ranging from 58-100%. It is important to note that both 26 and 30 were also the only alkynes to show Glaser coupling (homocoupling of the alkyne). This indicates that these two alkynes were the most reactive towards coupling of the five that were chosen. So reactive in fact, that they only had a chance to react with the most reactive arene before homocoupling occurred. Also, since Glaser coupling occurs because oxygen has not been excluded, our nitrogen atmosphere was not sufficient to exclude oxygen. The second trend deals with reactivity, where 27 and 28 reacted with all three 1,2-dihalobenzenes to produce disubstituted products but with starting material conversions that were substantially lower (5-40%). These two alkynes do not exhibit Glaser coupling and, therefore, were present in the reaction mixture long enough to react with all three arenes. It was expected that 27 and 28 should react similarly because they have similar structures which include bulky groups four atoms removed from the point of reaction. From the results, it appears that these bulky groups cause some steric hindrance allowing less of the starting materials to be converted to

products. The noticeable trend from the reactivity study data concerning the nature of the alkyne, was the fact that no disubstituted product with 29 was obtained, even though the THP group was four atoms removed from the reaction site. This is most likely due to steric factors. Futhermore, THP may have acted as a Lewis base, coordinating the metal catalysts and removing reactivity from the system. On the other hand, the silicon-based protecting groups, particularly with large R groups, are often used to limit the coordination of the oxygen atoms.[49]

Thirdly, the different solvents had small to moderate effects on the coupling yields with the majority of the reactions working better in benzene. The only major exception to this was that the coupling of 28 with all three 1,2-dihalobenzenes showed better yields in THF. From these results, we can conclude that the solubility of the alkynes did not differ significantly in the solvents chosen. The rate of a reaction may also be affected by changes in solvent. A mechanism (Scheme 9) was proposed by Sonogashira *et al*[51] in 1975 which is still deemed valid. To date, the nature of the Pd species (69) has not been ascertained. If species 69 has more ionic-like bonds than covalent and formation of the Pd species is rate limiting, an increase in the reactivity should occur in more polar solvents. The results from our study do not help to shed light on this mechanism because the polarity difference between the two solvents, THF and benzene, was not large enough to influence reactivity. Furthermore, without varying the relative concentrations of the starting materials,determining the rate limiting step is problematic.

Scheme 9



Fourthly, the method of addition had some effect on the coupling yields. In general, the method in which the 1,2-dihalobenzene was added last gave slightly higher yields than the method adding the alkyne last. Also, adding the alkyne last usually produced more monosubstituted products, but often seemed to decrease, if only slightly at times, the amount of Glaser coupling observed by GLC.

From this reactivity study, a number of conclusions can be drawn. 1) 1,2-diiodobenzene is the best arene with which to couple. 2) Sequential monosubstitutions should be performed to maximize the amount of starting materials converted to the disubstituted product. 3) Benzene should be used as the solvent. 4) If very reactive alkynes are used, the procedure should entail adding the alkyne last to minimize homocoupling. If alkynes with moderate reactivity are used, this is not necessary, and the arene should be added last since this gave the better yields.

The photochemical cyclizations proceeded with moderate success for three of the four synthesized enediynes. The percent conversions are contained in Table 2. The TMS and $C(CH_3)_2OH$ containing alkynes cyclized with similar percent conversions indicating that their cd distance is adequate for light-initiated cyclization at temperatures slightly elevated from room temperature. These two enediynes also showed the formation of side products which

Table 2: Photochemical Cyclization Conversions

Enediyne	% Cyclized	% Starting Material	% Alkyne Reduction Products
31	11%[a]	54%	35%
32	0%	100%	0%
33	14%	86%	0%
35	10%	61%	29%

a) Yields determined by GLC

from GCMS were determined to be products resulting primarily from the reduction of one of the alkynes to an alkene[25] by the proton source of the reaction, 1,4-CHD. The enediyne with the TBDMS group also cyclized, with a slightly higher conversion rate and without the production of any reduction side products. This may indicate that the bulkiness of the group is far enough removed to allow cyclization to proceed while sterically hindering the attack of 1,4-CHD on the alkyne inhibiting formation of any reduction products. On the other hand, the TIPS group on an enediyne must be sufficiently bulky enough to inhibit both cyclization and reduction reactions since neither cyclized product nor any other product was

observed.

2.5 Future Work

This reactivity study has attempted to answer some of the reactivity considerations of this palladium cross-coupling reaction. Experiments should be done to couple other alkyne groups that have not yet been tried, such as, propargylamine and propargyl thiol. Also, other solvents like methanol or DMF should be investigated to determine if they have more of an affect on the conversion of starting material to product. Highly polar solvents may also provide some insight into the reaction mechanism and the nature of the Pd species (69). Then, the coupling reaction should be optimized for both mono- and disubstitution. Recent reports by Yu *et al*[50] shiow increased monosubstitution yields when a larger amount of Pd catalyst is used. This may be one way to optimize the reaction; however, Pd catalysts are expensive resulting in a decrease of the cost effectiveness.

Finally, much work is needed for the cyclization reactions. In addition to the photochemical cyclizations, the thermal cyclizations of these compounds should be performed with the "new" alkynes to verify that those which are not already reported in the literature do indeed occur. The photochemical and thermal cyclizations should then be optimized. To this end, quantum yields of the photochemical reactions should be done to compare the efficiencies of cyclization. Once this is done, a comparative study on the similarities and differences between the two cyclizations should be undertaken to get a better understanding of their mechanisms and the factors that affect reactivity in cyclizations.

CHAPTER THREE: EXPERIMENTAL

3.1 Experimental

3.1.1 General Experimental Techniques, Instrumentation and Materials

Analytical gas chromatography (GLC) was performed on a Hewlett Packard 5890 equipped with a flame ionization detector (FID) using a 30 m by 0.25 mm DB-5HT column of (5% phenyl) methylpolysiloxane. The carrier gas used was helium with a flow rate of 2.0 mL/min. All reaction yields for the coupling reactions were reported by GC. Molecules with the same empirical formula as the coupled products were used to calculate response factors.[51] Gas chromatography-mass spectrometry (GCMS) was used to determine the identity of the GC peaks. GCMS was performed on a Hewlett Packard 5890 Series II gas chromatograph also using a DB-5HT column and helium as the carrier gas. The linear velocity in this system was 35 cm/s. The gas chromatograph was attached to a VG Micromass AutoSpec mass spectrometer which measured the mass spectra of the samples between 52 and 510 mass units with a resolution of 3000 at 70 e.V. ionizing energy. Mass spectral data are presented in the following form: parent ion (relative intensity), *m/e* of significant fragments (relative intensity).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured at 200 MHz on a Bruker AC-E 200 spectrometer. The solvent used was $CDCl_3$. Chemical shifts are reported in parts per million (ppm) from an internal standard of tetramethylsilane (TMS)

unless otherwise noted. ^{13}C NMR were also recorded in $CDCl_3$ with $CDCl_3$ as the internal standard (δ 77.0) on the same spectrometer. The NMR data are reported as follows: chemical shift (for ^1H NMR signals; multiplicity, the coupling constants in Hertz, and integration).

Infrared spectra were measured on a Bruker IFS 66 Fourier transform infrared (FTIR) spectrometer without solvent (neat) and the data are reported in reciprocal centimetres. Ultraviolet spectra were determined using a Perkin-Elmer Lambda 11 spectrometer, in CH_2Cl_2 and the wavelengths of maximum absorption are reported in nanometres with corresponding molar absorptivities (ϵ).

All experiments were run under a positive pressure of nitrogen in flasks that were oven dried. Air and moisture sensitive reagents were transferred by syringe and introduced to the reaction flasks through rubber septa.

Photochemical cyclizations were performed by irradiating the sample, in CH_2Cl_2 in a quartz cuvette, with a Hanovia 200 W medium pressure Hg arc lamp at 25±1°C.

Excess solvents were removed *in vacuo* at pressures obtained by a water aspirator drawing on a Buchi rotary evaporator. All compounds were stored in the refrigerator under N_2 at a temperature of 4°C.

Tetrahydrofuran was distilled from potassium. Benzene was rendered anhydrous by stirring over $CaCl_2$ for four hours followed by storage over 4Å molecular sieves. All other solvents were used as received.

Analytical thin layer chromatography (TLC) was performed on silica gel of 5-17 μm

particle size, 60Å pore size, with a thickness of 250 μm, containing a 254 nm fluorescent indicator. The solvents used for the chromatography are indicated in parentheses in the procedure and the relative concentrations are calculated by volume. Spots were viewed using ultraviolet light and treatment with 10% aqueous sulphuric acid followed by heating on a hot plate. Liquid chromatography was used to purify the reaction mixtures. The chromatography was accomplished using 230-400 mesh recycled silica gel and the solvent systems were determined by analytical TLC.

Tetrakis(triphenylphosphine)palladium(0) and 2-[(Prop-1-ynyl)oxy]tetrahydro-2H-pyran **29** were synthesized using previously described methods.[52,53] All other chemicals for which procedures are not listed, were purchased from Aldrich. Compounds **31**,[38] **32**,[37] **33**,[37] **34**,[37] **35**,[38] **38**,[16,38] **39**,[19,37] **40**,[37] **41**,[19] **43**,[37] **44**,[19] **47**,[19] **49**,[38] **50**[38] and **53**[54] were compared to previously reported literature values.

3.2 Preparations

3-triisopropylsiloxypropyne 27

Propargyl alcohol (0.6928 g, 0.72 mL, 12.4 mmol), triisopropylsilyl chloride (2.9886 g, 3.3 mL, 15.5 mmol) and DMAP (1.8936 g, 15.5 mmol) in CH_2Cl_2 (35 mL) were stirred overnight at room temperature. The reaction mixture was washed with water (3x20 mL). The aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The organic phases were combined and dried over $NaSO_4$. The solvent was removed *in vacuo*. The product was not

purified further.

^{1}H NMR ($CDCl_3$): δ 4.37 (d, J=2.4, 2H), 2.38 (t, J=2.4, 1H), 1.05-1.10 (m, 21H).

^{13}C NMR ($CDCl_3$): δ 82.3, 72.5, 51.7, 25.7, 17.8, 11.9.

3-tert-butyldimethylsiloxypropyne 28

Propargyl alcohol (0.6928 g, 0.72 mL, 12.4 mmol), tert-butyldimethylsilyl chloride (2.3363 g, 15.5 mmol) and DMAP (1.8936 g, 15.5 mmol) in CH_2Cl_2 (35 mL) were stirred overnight at room temperature. The reaction mixture was washed with water (3x20 mL). The aqueous phase was extracted with CH_2Cl_2 (3x20 mL). The organic phases were combined and dried over $NaSO_4$. The solvent was removed *in vacuo*. The product was not purified further.

^{1}H NMR ($CDCl_3$): δ 4.30 (d, J=2.4, 2H), 2.38 (t, J=2.4, 1H), 0.91 (s, 9H), 0.13 (s, 6H).

^{13}C NMR ($CDCl_3$): δ 82.3, 72.8, 51.3, 25.7, 18.1, -5.3.

General Procedures for Enediynes

For all methods listed below, after completion of the reaction, the excess solvents were removed *in vacuo*. The crude mixture was dissolved in CH_2Cl_2, gravity filtered and the excess solvent was again removed *in vacuo*.

Method A: Et_3N (6 eq.), CuI (0.2 eq.), $Pd(PPh_3)_4$ (0.06 eq.) and the alkyne (2.5 eq.) were dissolved in anhydrous benzene (10 mL). Then 1,2-dihalobenzene (1 eq.) was added via syringe at 0°C. The reaction was stirred overnight at room temperature.

Method B: 1,2-dihalobenzene (1 eq.) was dissolved in anhydrous benzene (10 mL). Et_3N (6 eq.) and $Pd(PPh_3)_4$ (0.06 eq.) were added and the mixture allowed to stir for 10 min.

CuI (0.2 eq.) was added and the reaction mixture was stirred for another 10 min. The alkyne was added slowly via syringe and the reaction was left to stir overnight at room temperature.

Method C: Et_3N (6 eq.), CuI (0.2 eq.), $Pd(PPh_3)_4$ (0.06 eq.) and the alkyne (2.5 eq.) were dissolved in anhydrous THF (10 mL). Then 1,2-dihalobenzene (1 eq.) was added via syringe at 0°C. The reaction was stirred overnight at room temperature.

Method D: 1,2-dihalobenzene (1 eq.) was dissolved in anhydrous THF (10 mL). Et_3N (6 eq.) and $Pd(PPh_3)_4$ (0.06 eq.) were added and the mixture allowed to stir for 10 min. CuI (0.2 eq.) was added and the reaction mixture was stirred for another 10 min. The alkyne was added slowly via syringe and the reaction was left to stir overnight at room temperature.

1,2-*bis*-(trimethylsilylethynyl)benzene 31

Using the four above listed methods, **31** was synthesized using Et_3N (0.6071 g, 0.84 mL, 6 mmol), CuI (0.0381 g, 0.2 mmol), $Pd(PPh_3)_4$ (0.0693 g, 0.06 mmol), trimethylsilylacetylene **26** (0.2456 g, 0.35 mL, 2.5 mmol) and each of three 1,2-dihalobenzene compounds, namely 1,2-dichlorobenzene **23** (0.1470 g, 0.11 mL, 1 mmol), 1,2-dibromobenzene **24** (0.2359 g, 0.12 mL, 1 mmol) and 1,2-diiodobenzene **25** (0.3299 g, 1 mmol).

TLC (20% Et_2O in hexane): $R_f = 0.65$.

IR (neat): 3068, 2159, 1574, 1457, 1412, 1251, 1128, 1035, 846, 748.

UV (CH_2Cl_2): $\lambda_{max} = 278$ (ϵ=580), 270 (620), 260 (950), 248 (990), 232 (1000).

^1H NMR ($CDCl_3$): δ 7.44-7.39 (m, 2H), 7.20-7.16 (m, 2H), 0.26 (s, 18H).

^{13}C NMR ($CDCl_3$): δ 132.2, 127.9, 125.8, 88.2, 85.6, 0.0.

MS: 270 (M^+, 55), 255 (74), 227 (8), 195 (16), 167 (19), 120 (28), 73 (100).

Percent yields Method A) **23**: 0% **31**, 0% **36**; **24**: 0% **31**, 0% **37**; **25**: 20% **31**, 53% **38**.

Method B) **23**: 0% **31**, 0% **36**; **24**: 0% **31**, 0% **37**; **25**: 36% **31**, 56% **38**.

Method C) **23**: 0% **31**, 0% **36**; **24**: 0% **31**, 0% **37**; **25**: 15% **31**, 49% **38**.

Method D) **23**: 0% **31**, 0% **36**; **24**: 0% **31**, 0% **37**; **25**: 24% **31**, 60% **38**.

1,2-*bis*-(3-triisopropylsiloxypropynyl)benzene **32**

Using the four above listed methods, **32** was synthesized using Et_3N (0.6071 g, 0.84 mL, 6 mmol), CuI (0.0381 g, 0.2 mmol), $Pd(PPh_3)_4$ (0.0693 g, 0.06 mmol), 3-triisopropylsiloxypropyne **27** (0.5310 g, 2.5 mmol) and each of three 1,2-dihalobenzene compounds, namely 1,2-dichlorobenzene **23** (0.1470 g, 0.11 mL, 1 mmol), 1,2-dibromobenzene **24** (0.2359 g, 0.12 mL, 1 mmol) and 1,2-diiodobenzene **25** (0.3299 g, 1 mmol).

TLC (20% Et_2O in hexane): R_f= 0.72.

IR (neat): 3068, 2944, 2875, 2867, 2133, 1574, 1459, 1259, 1096, 1069, 883, 751.

UV (CH_2Cl_2): λ_{max} = 270 (ε=690), 260 (720), 248 (710), 228 (1100).

^1H NMR ($CDCl_3$): δ 7.40-7.36(m, 2H), 7.17-7.12 (m, 2H), 4.42 (s, 4H), 1.05-1.10 (m, 42H).

^{13}C NMR ($CDCl_3$): δ 132.4, 128.0, 124.8, 77.5, 69.0, 52.2, 17.7, 11.9.

MS: 379 (26), 337 (100), 295 (60), 265 (18), 223 (15), 75 (30).

Percent yields Method A) **23**: 24% **32**, 0% **39**; **24**: 24% **32**, 0% **40**; **25**: 13% **32**, 15% **41**.

Method B) 23: 19% 32, 1% 39; 24: 20% 32, 1% 40; 25: 13% 32, 19% 41.

Method C) 23: 12% 32, 0% 39; 24: 16 % 32, 0% 40; 25: 21% 32, 13% 41.

Method D) 23: 15% 32, 1% 39; 24: 21% 32, 1% 40; 25: 22% 32, 18% 41.

1,2-*bis*-(3-tert-butyldimethylsiloxypropynyl)benzene 33

Using the four above listed methods, 33 was synthesized using Et_3N (0.6071 g, 0.84 mL, 6 mmol), CuI (0.0381 g, 0.2 mmol), $Pd(PPh_3)_4$ (0.0693 g, 0.06 mmol), 3-tert-butyldimethylsiloxypropyne 28 (0.4258 g, 2.5 mmol) and each of three 1,2-dihalobenzene compounds, namely 1,2-dichlorobenzene 23 (0.1470 g, 0.11 mL, 1 mmol), 1,2-dibromobenzene 24 (0.2359 g, 0.12 mL, 1 mmol) and 1,2-diiodobenzene 25 (0.3299 g, 1 mmol).

TLC (20% Et_2O in hexane): $R_f = 0.66$.

IR (neat): 3068, 2929, 2857, 2123, 1574, 1458, 1435, 1255, 1128, 1093, 1036, 837, 750.

UV (CH_2Cl_2): $\lambda_{max} = 270$ (ϵ=1400), 260 (1400), 244 (1500), 228 (2200).

^1H NMR ($CDCl_3$): δ 7.55-7.43 (m, 2H), 7.17-7.12 (m, 2H), 4.37 (s, 4H), 0.91 (s, 18H), 0.11 (s, 12H).

^{13}C NMR ($CDCl_3$): δ 133.7, 128.4, 124.9, 77.6, 69.2, 52.0, 25.7, 18.2, -5.2.

MS: 281 (43), 251 (4), 225 (41), 195 (26), 147 (100), 97 (42), 75 (100).

Percent yields Method A) 23: 16% 33, 0% 42; 24: 19% 33, 0% 43; 25: 6% 33, 10% 44.

Method B) 23: 5% 33, 0% 42; 24: 6% 33, 1% 43; 25: 9% 33, 24% 44.

Method C) 23: 16% 33, 0% 42; 24: 27% 33, 1% 43; 25: 12% 33, 19% 44.

Method D) **23**: 14% **33**, 0% **42**; **24**: 16% **33**, 1% **43**; **25**: 14% **33**, 16% **44**.

1,2-*bis*-[3-(tetrahydro-4H-2-pyranoxy)propynyl]benzene **34**

Using the four above listed methods, **34** was synthesized using Et_3N (0.6071 g, 0.84 mL, 6 mmol), CuI (0.0381 g, 0.2 mmol), $Pd(PPh_3)_4$ (0.0693 g, 0.06 mmol), 2-[(Prop-1-ynyl)oxy]tetrahydro-2H-pyran **29** (0.3479 g, 2.5 mmol) and each of three 1,2-dihalobenzene compounds, namely 1,2-dichlorobenzene **23** (0.1470 g, 0.11 mL, 1 mmol), 1,2-dibromobenzene **24** (0.2359 g, 0.12 mL, 1 mmol) and 1,2-diiodobenzene **25** (0.3299 g, 1 mmol).

Percent yields Method A) **23**: 0% **34**, 0% **45**; **24**: 0% **34**, 0% **46**; **25**: 0% **34**, 37% **47**.

Method B) **23**: 0% **34**, 0% **45**; **24**: 0% **34**, 0% **46**; **25**: 0% **34**, 34% **47**.

Method C) **23**: 0% **34**, 0% **45**; **24**: 0% **34**, 0% **46**; **25**: 0% **34**, 21% **47**.

Method D) **23**: 0% **34**, 0% **45**; **24**: 0% **34**, 0% **46**; **25**: 0% **34**, 23% **47**.

1,2-*bis*-(3-hydroxy-3-methylbut-3-ynyl)benzene **35**

Using the four above listed methods, **35** was synthesized using Et_3N (0.6071 g, 0.84 mL, 6 mmol), CuI (0.0381 g, 0.2 mmol), $Pd(PPh_3)_4$ (0.0693 g, 0.06 mmol), 2-methyl-3-butyn-2-ol **30** (0.2103 g, 0.24 mL, 2.5 mmol) and each of three 1,2-dihalobenzene compounds, namely 1,2-dichlorobenzene **23** (0.1470 g, 0.11 mL, 1 mmol), 1,2-dibromobenzene **24** (0.2359 g, 0.12 mL, 1 mmol) and 1,2-diiodobenzene **25** (0.3299 g, 1 mmol).

TLC (20% Et_2O in hexane): $R_f = 0.0$

UV (CH_2Cl_2): λ_{max} = 274 (ϵ=11500), 260 (12700), 236 (21200).

^{1}H NMR ($CDCl_3$): δ 7.38-7.33 (m, 2H), 7.20-7.16 (m, 2H), 4.13 (br.s, 2H), 1.63 (s, 12H).

^{13}C NMR ($CDCl_3$): δ 131.2, 127.6, 125.4, ,98.1, 80.6, 65.4, 31.3.

MS: 242 (M^+, 6), 209 (100), 195 (24), 180 (25), 165 (67), 126 (19), 75 (6).

Percent yields Method A) **23**: 0% **35**, 0% **48**; **24**: 0% **35**, 2% **49**; **25**: 53% **35**, 47% **50**.

Method B) **23**: 0% **35**, 0% **48**; **24**: 0% **35**, 1% **49**; **25**: 24% **35**, 69% **50**.

Method C) **23**: 0% **35**, 0% **48**; **24**: 0% **35**, 1% **49**; **25**: 3% **35**, 54% **50**.

Method D) **23**: 0% **35**, 0% **48**; **24**: 0% **35**, 1% **49**; **25**: 5% **35**, 54% **50**.

General Procedure for Photochemical Cyclizations

A solution of 1,4-cyclohexadiene (1,4-CHD) (20 eq.) and the enediyne (1 eq.) in CH_2Cl_2 was degassed using N_2 and irradiated for 5 hours. Separation and purification of the products was performed by liquid chromatography. Percent conversions were determined using GC with an internal standard of biphenyl.

Photolysis of 31

Using the above listed method, 1,4-CHD (0.5930 g, 0.70 mL, 7.4 mmol) and **31** (0.1000 g, 0.4 mmol) were brought to volume (3 mL) with CH_2Cl_2.

Percent yield: 11% **51**, 35% alkyne reduction products.

TLC (20% Et_2O in hexane): R_f= 0.73.

IR (neat): 3028, 1609, 1589, 1475, 1250, 888, 842, 759.

^{1}H NMR ($CDCl_3$): δ 7.60-7.57 (m, 2H), 7.51-7.43 (m, 2H), 7.30-7.22 (m, 2H), 0.26 (s, 18H).

^{13}C NMR ($CDCl_3$): δ 129.6, 128.7, 127.1, 126.7, 125.7, 0.0.

MS: 257 (8), 241 (31), 199 (68), 183 (30), 169 (25), 145 (5), 73 (100).

Photolysis of 32

Using the above listed method, 1,4-CHD (0.3205 g, 0.38 mL, 4.0 mmol) and 32 (0.1008 g, 0.2 mmol) were brought to volume (3 mL) with CH_2Cl_2.

Percent yield: 0% 52.

Photolysis of 33

Using the above listed method, 1,4-CHD (0.3846 g, 0.45 mL, 4.8 mmol) and 33 (0.1006 g, 0.2 mmol) were brought to volume (3 mL) with CH_2Cl_2.

Percent yield: 14% 53.

TLC (20% Et_2O in hexane): R_f= 0.55.

IR (neat): 2930, 2858, 1493, 1256, 1126, 1092, 837, 779, 750.

^1H NMR ($CDCl_3$): δ 7.45-7.41 (m, 2H), 7.21-7.06 (m, 4H), 4.32 (s, 4H), 0.91 (s, 18H), 0.11 (s, 12H)

^{13}C NMR ($CDCl_3$): δ 131.8, 130.0, 128.8, 127.1, 125.6, 52.0, 25.7, 18.2, -5.2.

MS: 167 (40), 149 (31), 137 (100), 75 (85).

Photolysis of 35

Using the above listed method, 1,4-CHD (0.6651 g, 0.79 mL, 8.3 mmol) and 35 (0.1000 g, 0.4 mmol) were brought to volume (3 mL) with CH_2Cl_2.

Percent yield: 10% 54, 29% alkyne reduction products.

TLC (20% Et_2O in hexane): R_f= 0.13.

IR (neat): 3387, 3026, 2978, 2924, 1632, 1601, 1452, 1375, 1184, 909, 894, 757.

^1H NMR ($CDCl_3$): δ 7.43-7.39 (m, 2H), 7.30-7.22 (m, 2H), 7.16-7.10 (m, 2H), 4.81 (br.s, 2H), 1.67 (s, 12H).

^{13}C NMR ($CDCl_3$): δ 135.9, 131.9, 129.3, 126.7, 125.5, 65.4, 31.3.

MS: 226 (3), 211 (34), 193 (12), 183 (32), 168 (100), 153 (74), 128 (58), 91 (9), 77 (12).

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