A STUDY OF HETEROAROMATIC ENEDIYNE AND SUBSTITUTED BENZOTHIOPHENE SYNTHESIS WITH A STUDY OF UNUSUAL ^{1}H NMR SIGNALS IN NEOMENTHYL HALIDES

A Thesis

Presented to

The Faculty of Graduate Studies

of

Lakehead University

by

KAI YLIJOKI

In partial fulfillment of requirements

for the degree of

Master of Science

January 12, 2004

Your file Votre référence
ISBN: 0-612-92263-4
Our file Notre référence
ISBN: 0-612-92263-4

ABSTRACT

A STUDY OF HETEROAROMATIC ENEDIYNE AND SUBSTITUTED BENZOTHIOPHENE SYNTHESIS WITH A STUDY OF UNUSUAL ^{1}H NMR SIGNALS IN NEOMENTHYL HALIDES

Kai Ylijoki
Lakehead University

Supervisor:
Dr. C. Gottardo

The synthesis of a number of heteroaromatic enediynes has been examined using the Sonogashira coupling reaction. Alkynes were coupled to 2,3-dibromothiophene to yield a number of hetero- and homo-disubstituted enediynes. Both thermal and photochemical Bergman cyclizations were attempted with these enediynes in an attempt to produce substituted fused bicyclic heteroaromatic products. Through this method, benzothiophene was prepared. The enediyne functionality and its cyclization is of synthetic interest given that a variety of naturally occurring compounds containing this unit demonstrate the ability to cleave DNA.

In addition, a solvent effect study on neomenthyl halides was undertaken. In this study, the effect of various solvents on the ^{1}H NMR spectra of neomenthyl halides was investigated. During the course of the study an unusual low field proton resonance was discovered.

ACKNOWLEDGEMENTS

I would like to thank Dr. G. Spivak and Dr. S. Kinrade for the help in understanding the low field ^{1}H NMR signal as well as Dr. C. MacKinnon for assistance with the theoretical calculations. I would also like to thank A. Raitsakas for running my GCMS samples and help with the FTIR, K. Prignitz for running my NMR samples and A. Bharath and D. Leach for the endless assistance in repairing whatever equipment failure we encountered. Finally, I would especially like to thank Dr. C. Gottardo, without whom I never would have been able to complete this work. I was very close to quitting for a while, but your understanding and support carried me through some pretty rough times. You will never understand how much it truly meant to me and I will always be grateful.

TABLE OF CONTENTS

PAGE

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

cd	carbon distance
1,4-CHD	1,4-cyclohexadiene
Δ	heat
DMF	N,N-dimethylformamide
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
eq.	equivalent
Et_3N	triethylamine
FID	flame ionization detector
FTIR	Fourier transform infrared
GCMS	gas chromatography mass spectrometry
GLC	gas-liquid chromatography
hν	light
IR	infrared
MS	mass spectrum
NIST	National Institute of Standards and Technology
NMR	nuclear magnetic resonance
ppm	parts per million

R_F	retardation factor
RT	retention time
SERM	selective estrogen receptor modulator
SSHB	short, strong hydrogen bond
TEMPO	2,2,6,6-tetramethyl-1-piperdinyloxy
THF	tetrahydrofuran
THP	tetrahydropyran
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMS	trimethylsilyl/tetramethylsilane

CHAPTER ONE: A SYNTHETIC AND MECHANISTIC REVIEW OF ENEDIYNE CHEMISTRY

1.1 Introduction

Recently there has been a surge in the attention that enediynes have received in the literature. This pique in interest is due to the discovery of the enediyne antitumour antibiotics,[1] a class of naturally occurring compounds which have demonstrated a great deal of potential for use in the fight against cancer. Presently, research is being conducted to develop synthetic analogs of these compounds, as well as investigations on their mode of action, in order to control better their activity. However, the use of enediyne chemistry remains a relatively untapped resource in the synthesis of compounds outside the sphere of the anticancer agents.

In this thesis, reviews of anticancer agents and bicyclic heteroaromatic fused ring systems will be presented, followed by reviews of synthetic methodology most commonly employed in their synthesis and cycloaromatization reactions which they can undergo. The preliminary stages of extending the use of enediyne chemistry in the synthesis of heteroaromatic fused ring systems will be presented in Chapter Two.

1.2 Enediyne Anticancer Agents

Enediyne chemistry was first studied in detail as far back as 1972, when Bergman conducted a study on the thermal cyclization of simple (Z)-enediynes.[2] However, the work did not receive much attention and the Bergman cyclization (*vide infra*) was relegated to the status of a *curio* in the realms of physical organic chemistry. Then, in 1987, a new class of anticancer

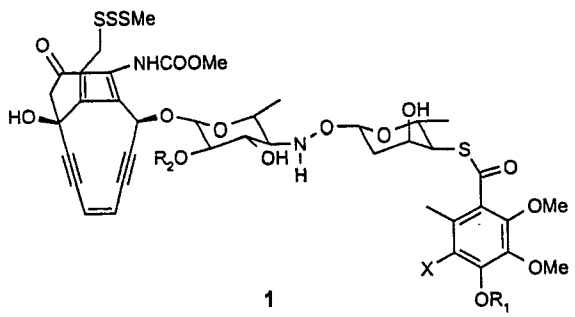
agent was discovered which revitalized interest in the Bergman cyclization.[1] These two novel compounds had an enediyne core which was the cause of their striking cytotoxicity. Since then, more examples have been found, with a total of seven families having been classified. These families are calicheamicins (**1**),[1] esperamicins (**2**),[1] dynemicins (**3**),[1] neocarzinostatin chromophore (**4**),[1] kedarcidin chromophore (**5**),[1] C-1027 chromophore (**6**)[1] and, most recently, shishijimicins (**7**)[3] (Figure 1). Today, enediyne anticancer agents are considered to be the most potent class of antitumour antibiotic yet discovered.

1.2.1 Mode of Action

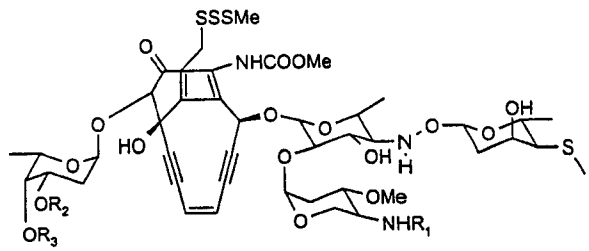
The extreme cytotoxicity of these compounds arises from their unique mode of action.[1] These agents are capable of abstracting hydrogen atoms from the sugar-phosphate backbone of double strand DNA. The radicals which result from this abstraction react further, resulting in eventual DNA strand cleavage, leading to cell death. This cleavage is achieved through cyclization of the enediyne moiety of the anticancer agent, forming a benzenoid diradical intermediate. This intermediate has the ability to abstract hydrogen atoms from the DNA backbone causing the fatal reaction sequence. The product of enediyne cyclization is an aromatic ring. The mechanisms by which this cyclization may occur will be discussed in Section 1.4.

In order for these compounds to be effective, there are a number of different structural components which must be in place in addition to the enediyne functionality itself. One of these is the chelating unit, which is the portion of the molecule that recognizes certain DNA sequences and causes the agent to associate with the DNA strand.[1] In this fashion, the enediyne portion of the molecule is brought into a region where the cyclization intermediate will be capable of

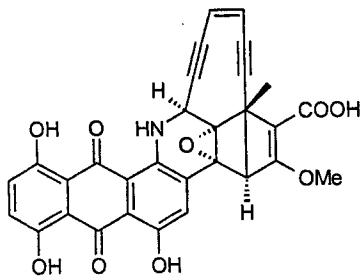
Figure 1



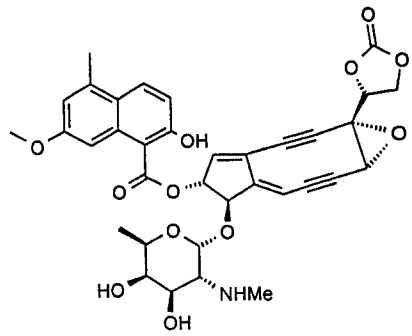
1



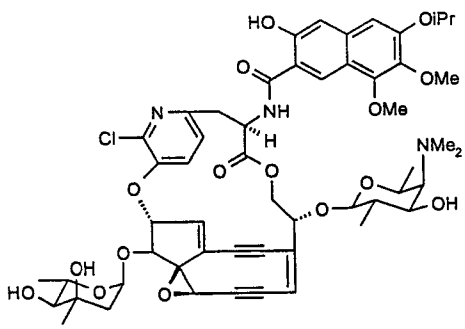
2



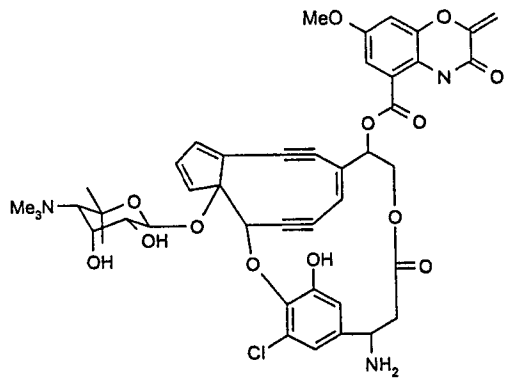
3



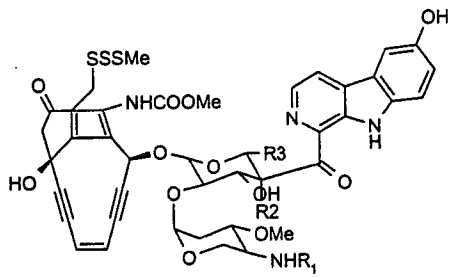
4



5



6



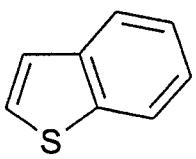
7

abstracting hydrogen atoms. The other critical unit is the triggering device which, when chemically reacted, will allow cyclization to occur. Until then, the ends of the enediyne are kept far enough apart that reaction is not possible. This way, it is ensured that reaction will only occur at the desired time and location. All attempts at developing synthetic analogs must keep these vital factors in mind.

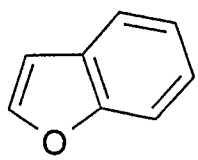
1.3 Benzothiophenes, Benzofurans and Indoles

Benzothiophenes (**8**), benzofurans (**9**) and indoles (**10**) are bicyclic heteroaromatic fused ring systems. All three consist of a six-membered aromatic ring which is fused to a five-membered aromatic ring. The only major difference between the three classes is the nature of the heteroatom. It is this structural similarity which results in the three compounds generally being studied together.

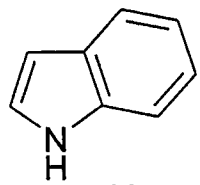
Figure 2



8



9

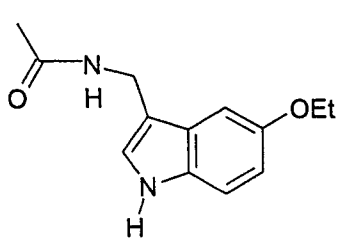


10

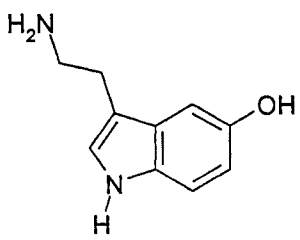
The fused ring systems of benzothiophenes, benzofurans and indoles provide the core of many naturally occurring, biologically active compounds. One of the simplest and highly studied of these is melatonin (**11**).[4] Melatonin is a compound which has the heterocyclic indole core and has been found to have a variety of biological functions at very low doses. In frogs which have been treated with this compound, the skin tends to lighten.[4] This effect is caused by doses far

below those needed by the next most active agents that have the same biological activity. Melatonin has also been linked to the functioning of sleep mechanisms in a variety of different organisms. Another very important biological compound having the indole core is serotonin (**12**), which has been shown to have a variety of neurological effects.[4] The far reaching biological importance of indoles is evident when the structure of tryptophan (**13**), a standard amino acid, is examined. Tryptophan, which is an important component of proteins, is also the synthetic precursor for melatonin and seratonin.[5]

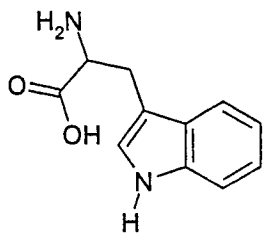
Figure 3



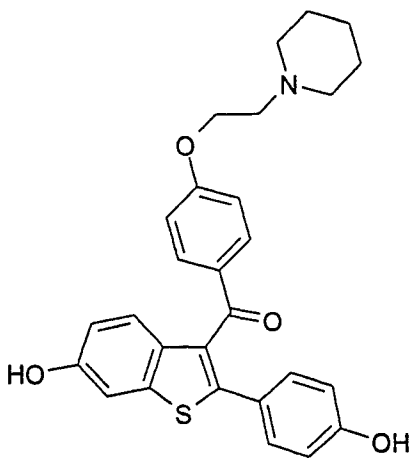
11



12



13



14

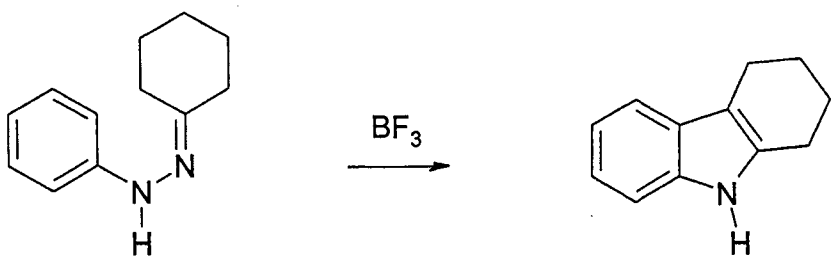
Benzothiophenes occur naturally in coal and shale oil products but have also been found to

have biological significance. Raloxifene (**14**), a natural benzothiophene derivative, is a compound known as a selective estrogen receptor modulator (SERM).[6] These compounds bind to estrogen receptors and can influence biochemical processes in positive or negative fashions. A number of them have been made available for clinical treatment and others are under investigation for post-menopausal diseases such as osteoporosis. Benzofuran derivatives such as SK-951, have been linked to serotonin activity. It has been found that they bind to serotonin S-HT3 and S-HT4 receptor sites.[7]

1.3.1 The Fischer Indole Synthesis

One of the first methods used for the synthesis of these fused ring systems was developed by Emil Fischer and is now known as the *Fischer Indole Synthesis*.[8] This process involves the reaction of a phenylhydrazone, usually of an aldehyde or ketone, with a catalytic amount of BF_3 (Scheme 1). The result of this reaction is the formation of a substituted indole, **16**.

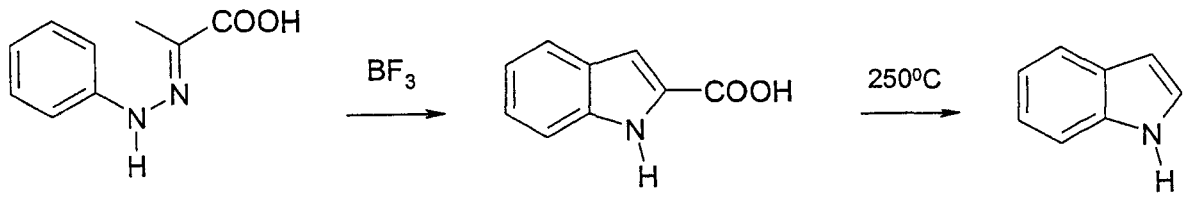
Scheme 1



15 **16**

In order to make an unsubstituted indole, it is necessary to use the phenylhydrazone of pyruvic acid (**17**). The resulting indole (**18**) will have a carboxylic acid functionality which allows it to be decarboxylated to yield the unsubstituted product (**19**) (Scheme 2).[8] This decarboxylation will only take place at temperatures of 250°C. Such extreme reaction temperatures make this synthesis difficult to perform. Another drawback of this method is that it could only be used to synthesize indoles; benzothiophenes and benzofurans still had to be isolated from natural compounds. Since the structure of the three are identical but for the heteroatoms, it would be advantageous to develop a synthetic strategy using the same method to synthesize all three.

Scheme 2

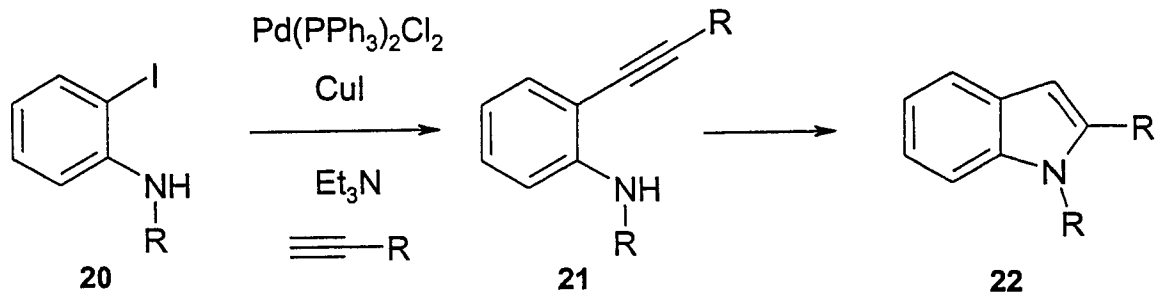


17 **18** **19**

1.3.2 Modern Methods of Benzothiophene, Benzofuran and Indole Synthesis

Using organometallic catalysts, a system useful for the synthesis of all three classes of compounds has been developed.[9,10] In order to perform these syntheses, an *ortho*-substituted halobenzene starting material is used (**20**), where the nature of the substituent depends on the class of compound which is desired. A carbon-carbon cross coupling reaction is performed in order to substitute the halogen with an acetylene. The resulting product (**21**) can then spontaneously cyclize with the substituent in order to form the heterocylic ring of the final product (**22**)

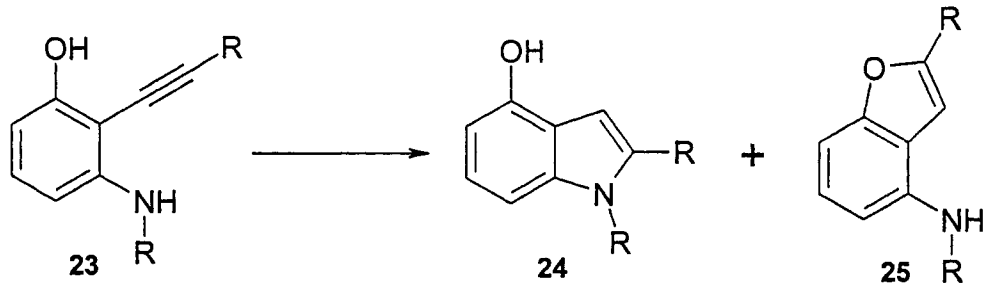
Scheme 3



(Scheme 3).[9,10] If the desire is to form benzothiophenes, the substituent used would be a thiol. Similarly, if benzofurans or indoles are the compounds of interest, a hydroxyl or amine functionality would be used. This technique has had much research devoted to it. A recent modification consists of the initial benzene reagent being bound to a resin to allow for solid phase synthesis.

Good yields (>99%) can be obtained through this[9] and other methods,[10] but the technique does have a major drawback. When a benzothiophene, benzofuran or indole is fully formed, it is difficult to perform substitutions on the benzene portion of the ring system. This is due to the much greater reactivity of the carbons in the heterocyclic ring. If the desired product has substituents in the benzo positions, it is necessary that they be present in the initial starting material. This can lead to problems. If the substituent is very bulky, it may be difficult for the acetylene to substitute the halogen which will keep the reaction from proceeding. Even more problematic, is the possibility of getting a cyclization to the wrong substituent (Scheme 4). If the desired substituent is an additional site to which a cyclization can occur, like an alcohol or amine group, and is located in an appropriate position, cyclization may occur to it rather than to the desired site. This would result in the formation of undesired product. It is these shortcomings

Scheme 4



that the work described herein is designed to overcome.

1.4 Cycloaromatization

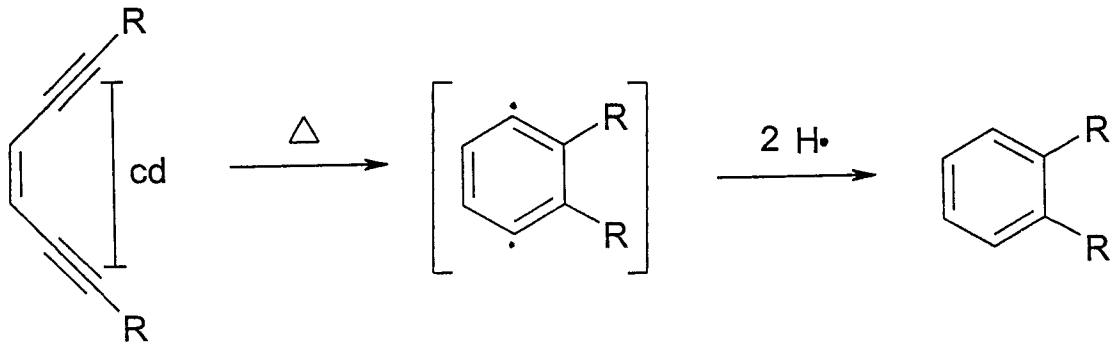
As previously discussed, the cyclization of the enediyne moiety gives the enediyne anticancer agents their extreme potency.[1] This being the case, an understanding of the mechanisms by which this cyclization can occur is critical to the development and harnessing of the potential of these drugs. The reaction which has received the bulk of the attention in the literature is the Bergman cyclization[2] since almost all of the natural anticancer agents that have been discovered function through this mechanism. However, there are other cycloaromatization pathways that have been elucidated. They are the Myers-Saito cyclization,[11] the Schmittel cyclization[12,13] and the tandem cyclization.[1,14]

1.4.1 Bergman Cyclization

In 1972, Jones and Bergman published a paper on a reaction which has since come to be known as the Bergman cyclization.[2] In the course of their research, it was found that when an enediyne was exposed to heat, a thermal cyclization would occur. The mechanism that Bergman

proposed for this cyclization involved the formation of a biradical intermediate that would then abstract hydrogens from a hydrogen atom donor, yielding the final aromatic product (Scheme 5). Since then, a great deal of research has been conducted to determine the factors which influence the reactivity of these compounds. In spite of all the research that has been conducted on this reaction, there is no direct evidence to support the existence of the biradical intermediate. However, indirect evidence such a radical trapping experiments using TEMPO, do support its existence.[15]

Scheme 5



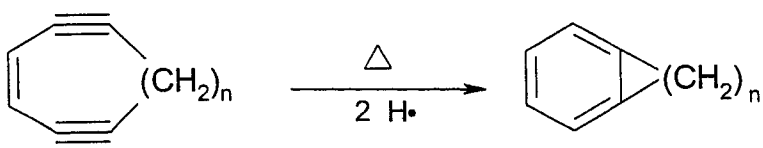
26 **27** **28**

As previously mentioned, the natural enediynes have a trigger mechanism which, when in place, keeps the ends of the enediyne far enough apart that they cannot react. Upon removal, the ends are brought together close enough that reaction can occur. In order to determine what this critical distance is, Nicolaou studied a series of enediynes which had the ends tethered by hydrocarbon chains varying in length.[16] By varying the length of the tether, the distance between the ends of the two alkynes (cd) can be changed. Then, by performing a series of cyclization experiments, the distances at which cyclization occurs can be determined. The results of this experiment showed that in order to achieve cyclization at room temperatures, the separation must

be in the range of 3.20 - 3.31 Å. If the separation of the ends is outside this range, the reaction must be driven by the addition of thermal energy.

However, a more recent study by Schreiner,[17] on compounds similar to those studied by Nicolaou (**29a-f**) (Scheme 6), has shown that the critical range may actually be extended beyond the Nicolaou limits. The cd for **29c** (n = 3) and **29d** (n = 4), the only compounds to cyclize, were calculated as being 2.924 Å and 3.413 Å respectively. These distances fall outside of the Nicolaou limits. It is interesting to note that **29e** (n = 5) does not cyclize even though cd is only slightly higher than that of **29d** (3.588 Å) so a definite critical point is reached in between these two distances.

Scheme 6



29a-f
(n=1-6)

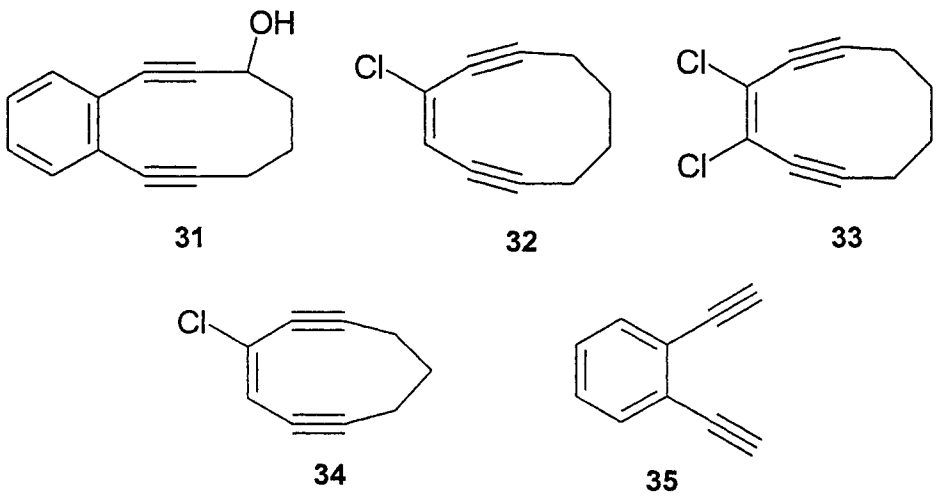
30a-f

The finding that the distance between the terminal alkynyl carbons plays an important role in the reactivity of these compounds is supported by studying substituent effects. Grissom has found that the addition of one alkyl unit on a terminal carbon causes the activation energy to be raised from 25.1 kcal/mol to 28.1 kcal/mol.[18] When a second alkyl unit was added the activation barrier was raised to 34.0 kcal/mol. This result is in accordance with the hypothesis that cd is a critical factor in cyclization. The large alkyl groups would result in steric interactions, which would subsequently push the ends further apart.

In addition to alkyl substitution, the effects of other groups have been studied. If an

electron withdrawing group is located in a proximal position to the alkynyl carbon (**31**), there appears to be a rate accelerating effect.[19] Vinyl substitution has also been studied and the results appear to indicate that electron withdrawing groups lower the rate of reaction by increasing the activation energy (**32**,**33**,**34**).[20,21] Various studies[18,22,23,24] have also employed benzannulated enediynes (**35**) and their results indicate that this alteration of the nature of the double bond has little to no effect on the reaction rate, although it may cause a change in the rate limiting step.[23,25]

Figure 4

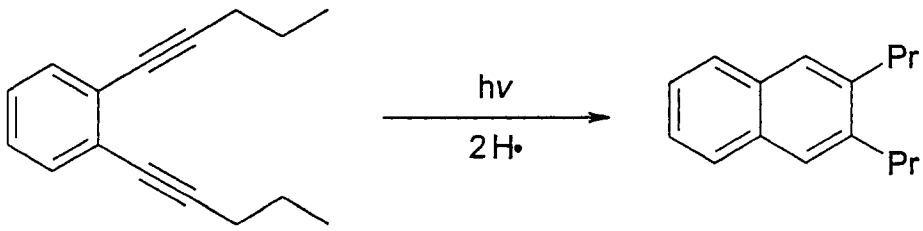


31 **32** **33**

34 **35**

Many organic reactions which proceed through thermal mechanisms have been found to proceed through photochemical mechanisms as well. A photochemical Bergman cyclization was not reported until 1994 when Evenzahav and Turro reported the cyclization of **36**.[26] By irradiating this compound in a number of solvents, it was found that the expected Bergman cyclization product was formed (**37**) (Scheme 7). This work also provides evidence that the reaction proceeds through the same biradical intermediate.

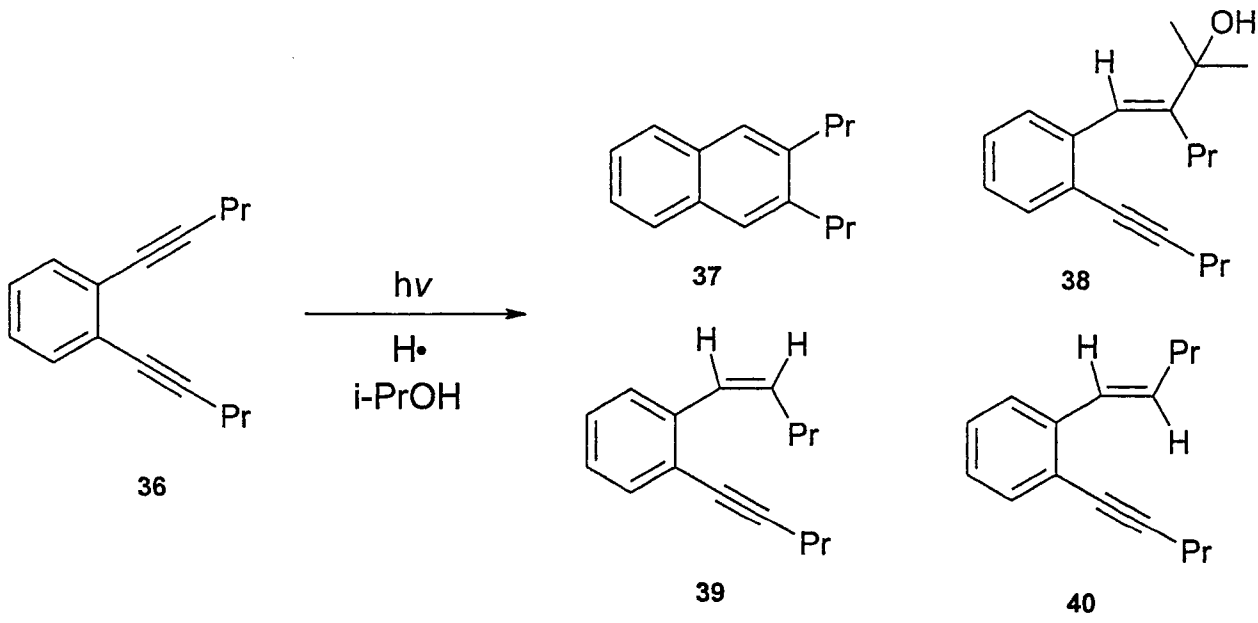
Scheme 7



36 **37**

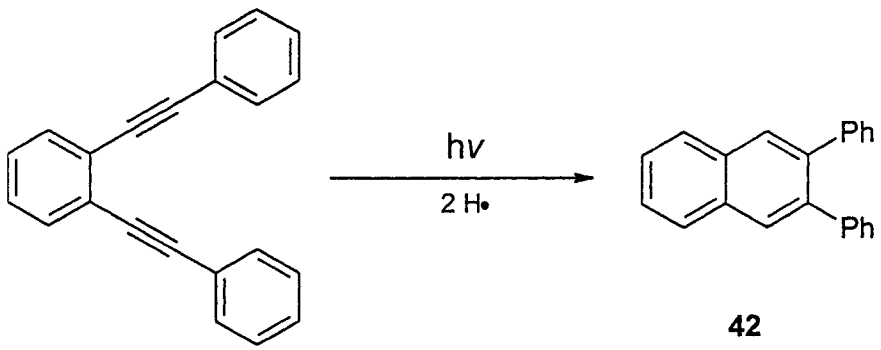
In a more recent study,[27] the same group has reported another successful photochemical Bergman cyclization along with a more in-depth study of their previous success. The cyclization of **36** was found to yield four different products, one of which is the Bergman cyclization product (**37**), and the others being various photoreduction products (**38-40**) (Scheme 8). The cyclization of **41** yielded only the Bergman cyclization product **42** (Scheme 9).

Scheme 8



36 **37** **38** **39** **40**

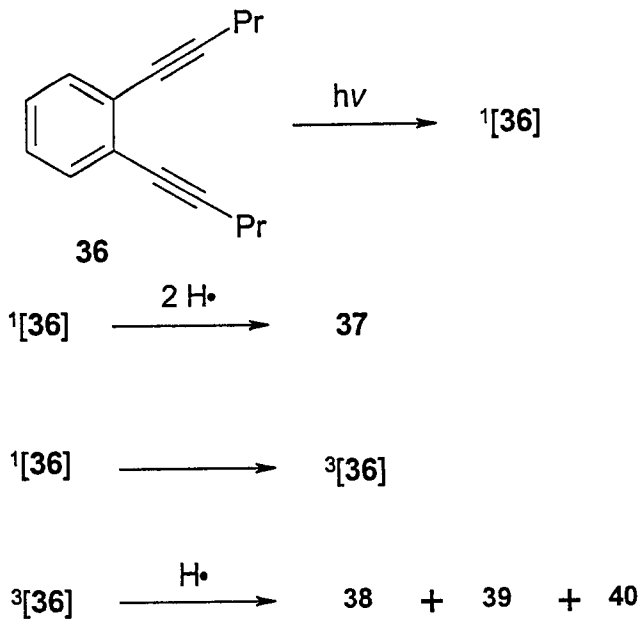
Scheme 9



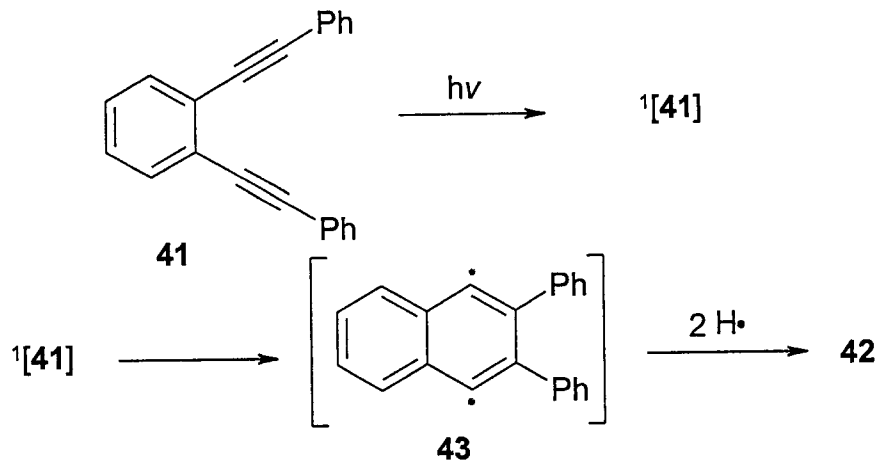
41 **42**

In an attempt to explain these and their past results, a mechanism for this cyclization was proposed. This mechanism assumes that cyclization occurs from the singlet excited state and that photoreduction occurs from the triplet excited state. This assumption is based on the theory that the quantum yield of fluorescence depends on the rigidity of the molecule.[28] The less rigid the molecule, the higher the chance that other modes of deactivation, such as intersystem crossing, will occur. The benzene groups on **41** would make the compound more rigid, preventing intersystem crossing from the first excited singlet state to the first excited triplet state. Since photoreduction occurs from the triplet state, this would explain why **41** forms only cyclization products (Scheme 10). Since **36** is less rigid, intersystem crossing is more likely, allowing for more photoreduction to occur (Scheme 11).

Scheme 10



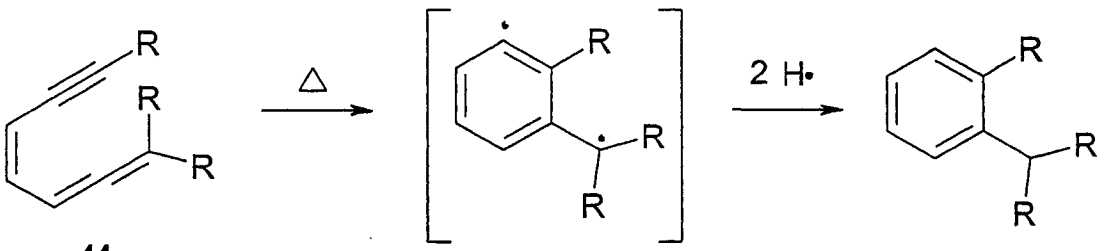
Scheme 11



1.4.2 Myers-Saito Cyclization

When the structure of neocarzinostatin chromophore (**4**) is examined, it can be seen that it does not have an enediyne core and can therefore not react through the Bergman cyclization. However, this compound still exhibits the same ability to cleave DNA strands. Another form of cycloaromatization is the Myers-Saito cyclization which occurs in eneyne-allene systems (**44**).[11] The mechanism is believed to be analogous to the Bergman cyclization (Scheme 12). However, the biradical formed in the Myers-Saito reaction is less reactive than the benzenoid biradical formed in the Bergman reaction. Eneyne-allenes also tend to cyclize much more readily than their enediyne counterparts due to the exothermic nature of the Myers-Saito cyclization.[1]

Scheme 12



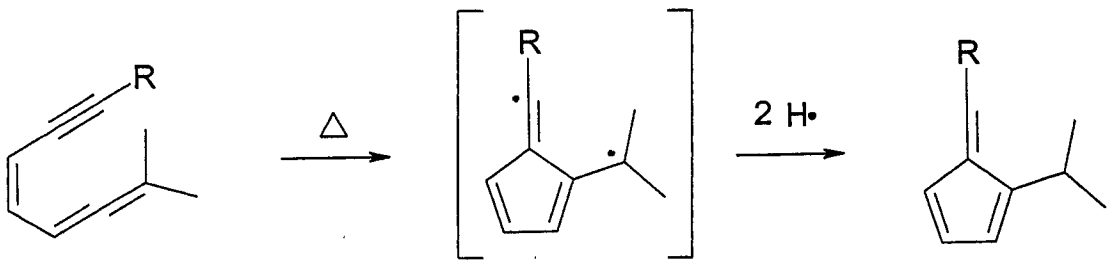
44 **45** **46**

1.4.3 Schmittel Cyclization

The Schmittel cyclization is a special case of the Myers-Saito cyclization.[12] In this reaction, the substituent on the alkyne terminus of the eneyne-allene system causes the cyclization to result in a five-membered rather than a six-membered ring (Scheme 13). The reaction generally proceeds most readily when the substituent is an aromatic group, however, it has been found that the reaction can be forced to occur through steric effects alone (R=t-Bu, TMS). When an

aromatic group is in place, the developing biradical can be best stabilized if it is in the vinylic position adjacent to the aromatic ring, resulting in this C2-C6 cyclization.

Scheme 13



47 48 49

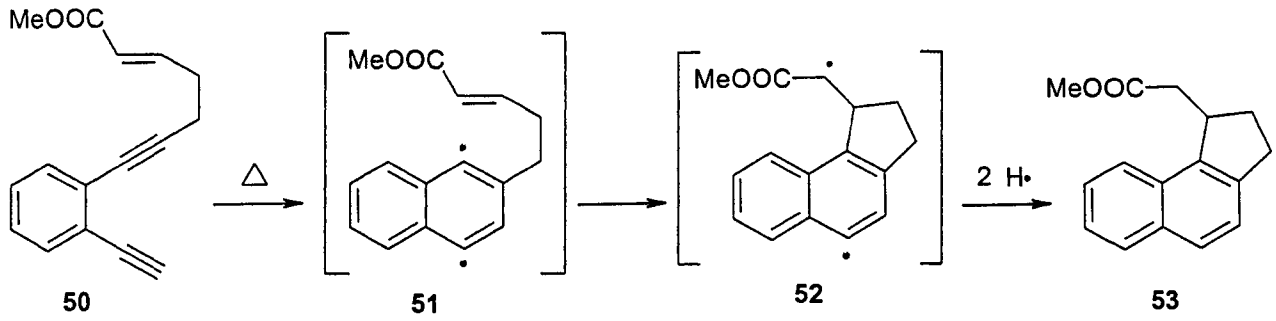
1.4.4 Tandem Cyclization

The biradical intermediate which is proposed to form in Bergman and Myers-Saito cyclizations can potentially react further before abstracting hydrogen atoms from a donor source. This principle has led to the interesting and synthetically useful reaction known as the tandem cyclization.[1,14,15,18] In this system, radical accepting tethers are placed on the termini of the conjugated system. Once cyclization has taken place, these tethers can react to form additional rings. These reactions can be done on both enediyne systems (Scheme 14) and eneyne-allene systems (Scheme 15).

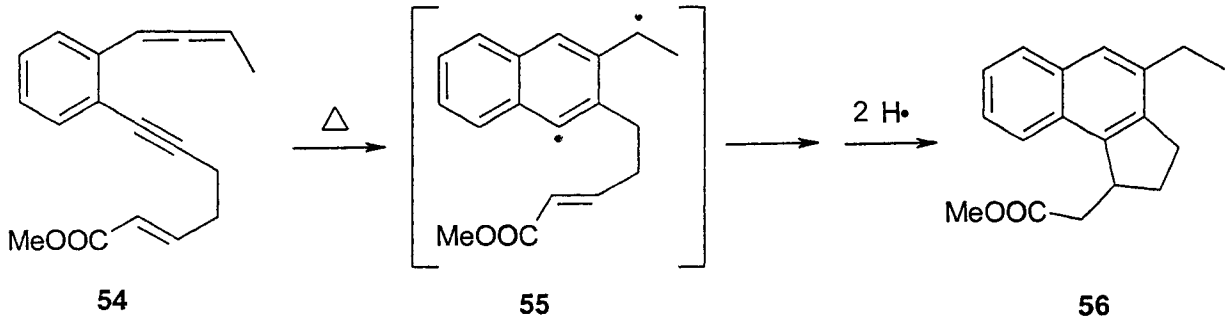
1.5 Carbon-Carbon Cross Coupling Reactions

The most common methods used for the synthesis of enediynes and compounds used in the formation of benzothiophenes, benzofurans and indoles involve carbon-carbon cross coupling of vinyl or arylhalides with acetylenes. Reactions of this type have been investigated since the

Scheme 14



Scheme 15

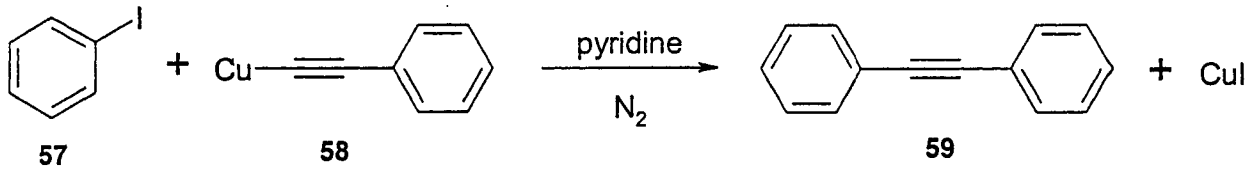


early 1960's and have been improved upon dramatically in recent times.

1.5.1 Stephens-Castro Coupling

In 1963, Stephens and Castro did some of the earliest work involving coupling of alkynes with arylhalides.[29] The coupling was accomplished by synthesizing cuprous acetylides which would then undergo a substitution reaction with the arylhalide (Scheme 16). The general trend for the reactivity was found to be that I>Br>Cl (with fluorine not observed to react at all) and with reactions proceeding better if electron withdrawing groups or poorly electron donating groups are

Scheme 16



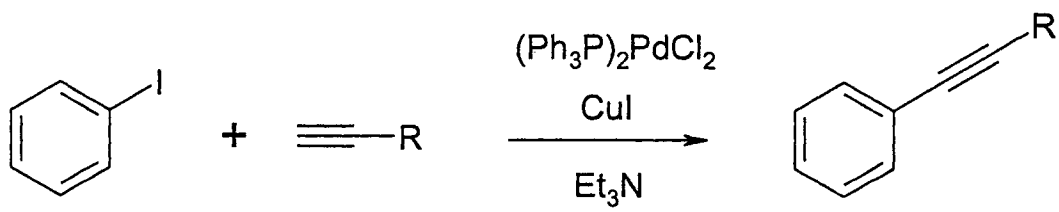
57 58 59

attached to the arylhalide (NO_2>H>MeO). The main difficulty with this reaction is that the cuprous acetylides can be very difficult to form and can exhibit a high degree of instability.

1.5.2 Sonogashira Coupling

The Sonogashira coupling[30] makes improvements on the Stephens-Castro coupling by using a palladium catalyst, which makes the reaction proceed at much milder and easier to achieve conditions. The classic Sonogashira reaction involves the use of $PdCl_2$, PPh_3, CuI and an amine solvent, usually triethylamine (Scheme 17). The $PdCl_2$ functions as the catalyst while the other three reagents are needed as cocatalysts. The phosphine adds to the palladium metal, allowing for the electronics and the sterics of the catalyst to be adjusted. The amine is used to remove the acidic material that is produced in the reaction while the role of the CuI is not completely

Scheme 17

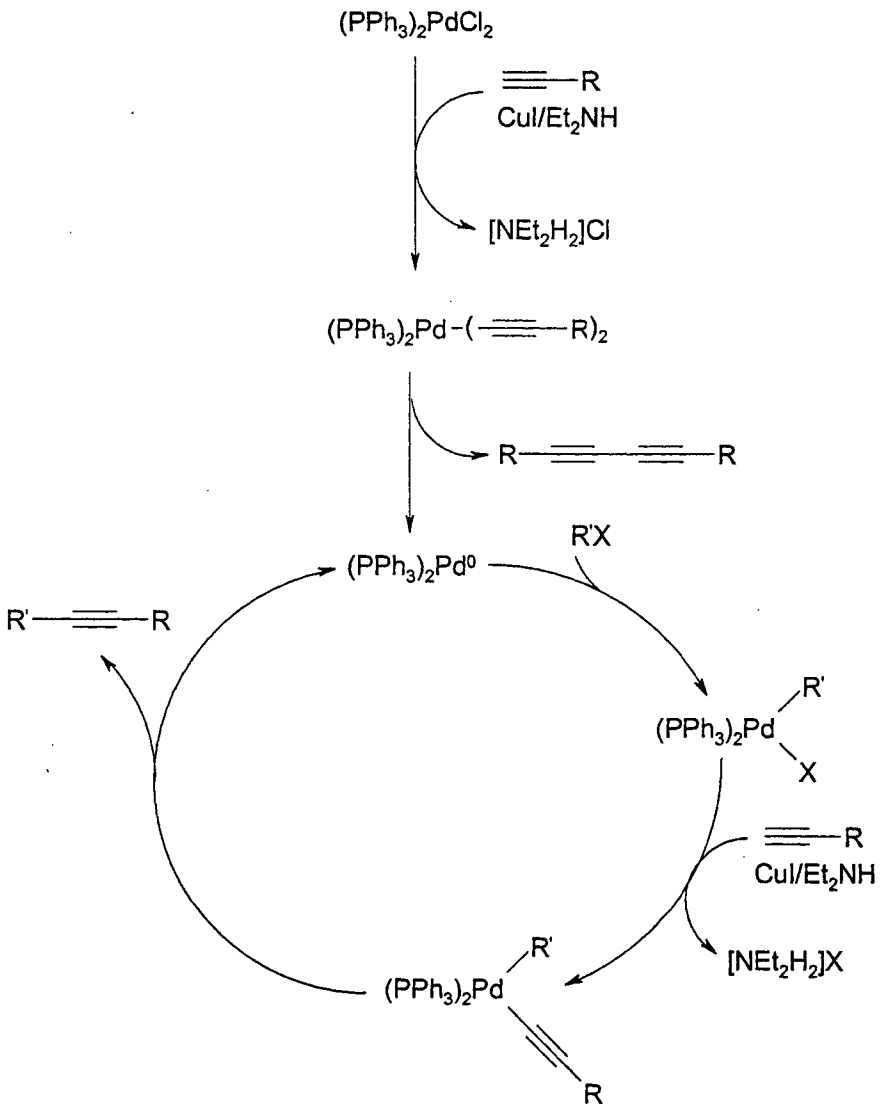


57 60

understood. The reaction has been found to proceed in it's absence, albeit very slowly. When the CuI is added the rate is significantly increased.[31,32]

To date, the mechanism for this reaction has not been elucidated, however the most accepted one is that which was proposed by Sonogashira (Scheme 18). In this proposed mechanism, the first step is a reduction of the catalyst from a Pd(II) state to Pd(0). The reaction then proceeds through a series of oxidative addition and reductive elimination reactions. Although the addition of CuI has been found to be necessary, this mechanism does not indicate what role it plays in the reaction.

Scheme 18



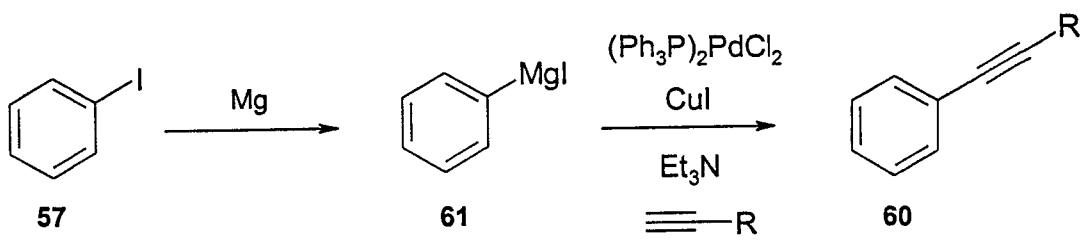
Improvements that have been made on this scheme mainly involve the catalyst and the solvent. The most common catalysts used are $Pd(PPh_3)_4$ and $PdCl_2(PPh_3)_2$ although some procedures have used a Pd/C catalyst. It is interesting to note that both the Pd^0 and Pd^{2+} catalysts are effective in this reaction; the reasons for this are not yet understood. In addition, Thorand and Krause have suggested that a better choice of solvent is THF,[33] the reason being that it appears to aid in minimizing the amount of Glaser coupling (oxidative homocoupling of the alkyne) that will occur if oxygen is not completely excluded from the reaction system. The general reactivity observed for this coupling is the same as the Stephens-Castro coupling with I>Br>Cl and the presence of electron donating groups hindering the activity while electron withdrawing groups promote the reaction.

1.5.3 Grignard-Sonogashira Coupling

A very recent improvement on the Sonogashira reaction conditions is performing the coupling with an alkyne and an aryl Grignard in place of an aryl halide (Scheme 19).[34] By making this modification, it has been found that good to excellent yields can be obtained even when electron donating substituents are present. The most interesting consideration in this result is that the acidic nature of hydrogens attached to *sp* hybridized carbons tends to interfere with Grignard reagents. Therefore, the expected result of the reaction would be a deprotonation of the alkyne with no coupling occurring (Scheme 20). However, this deprotonation reaction only occurs to sparing degrees with the main product being that which would be expected from a standard Sonogashira coupling.

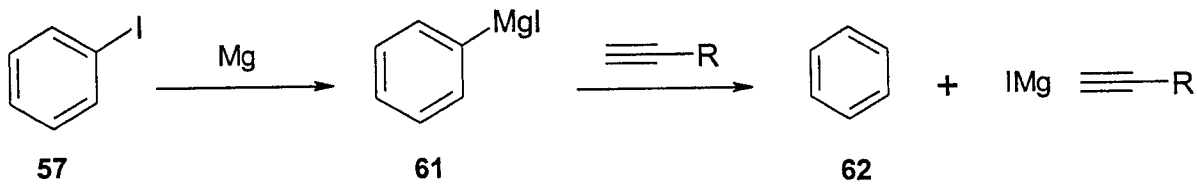
From this literature review, it can be seen that even though enediyne chemistry has

Scheme 19



57 61 60

Scheme 20



57 61 62

become a useful tool in the synthesis of novel compounds,[35] the potential of enediynes has been overlooked in the synthesis of heteroaromatic systems. In this thesis, the combination of carbon-carbon cross coupling reactions and Bergman cyclizations will be examined as a potential means of synthesizing substituted benzothiophenes. In Chapter Two, an outline for a novel approach to benzothiophene synthesis will be presented along with the preliminary steps taken to applying this methodology. This will be followed, in Chapter Three, by an additional study performed on neomenthyl halides to determine the effects of Lewis basic solvents on their NMR spectra and the discovery of an unusually low field proton resonance.

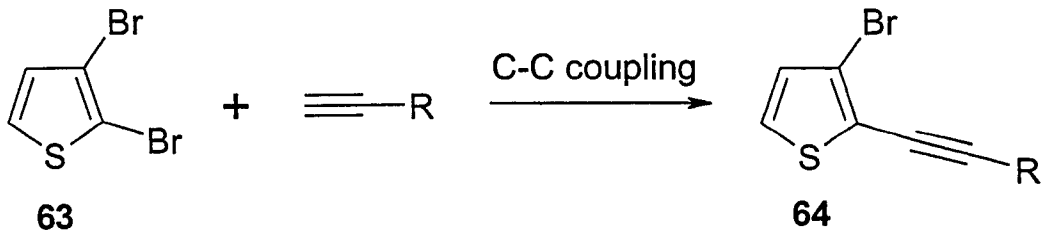
CHAPTER TWO: A STUDY OF SUBSTITUTED BENZOTHIOPHENE SYNTHESIS

2.1 Introduction

In Chapter One, a review of enediyne chemistry was presented along with synthetic methodology used for their syntheses, as well as synthetic methods for the preparation of fused bicyclic heteroaromatic systems. It has been noted that the present methods used for the synthesis of the heteroaromatic systems is lacking in a number of ways and that the utility of enediynes as synthetic tools in the formation of compounds other than anticancer agents remains relatively unexplored. It is these shortcomings that this research begins to address.

In this chapter, the initial stages of a novel methodology of synthesizing substituted benzothiophenes is presented. By harnessing the potential of enediynes to form aromatic rings, it may be possible to achieve substitution on the six-membered ring of the benzothiophene system. The first stage of this novel reaction scheme consists of performing a Sonogashira coupling reaction between an alkyne and 2,3-dibromothiophene (Scheme 21). Due to the heteroatom, the reactivity at C-2 is much higher than the reactivity at C-3. This permits the reaction to be stopped

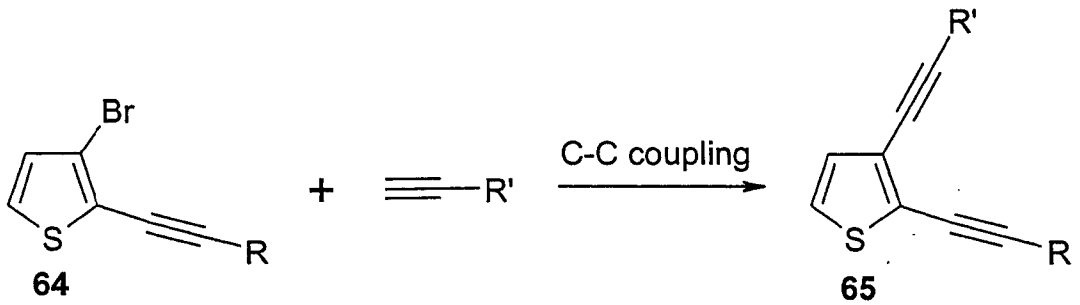
Scheme 21



63 **64**

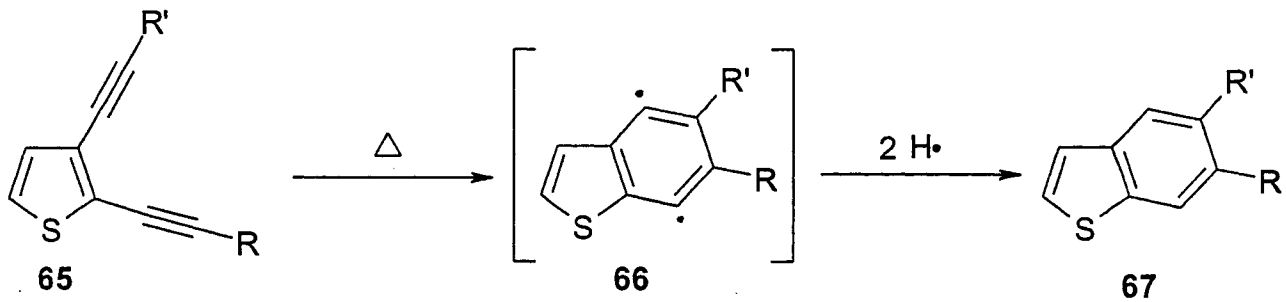
after only one coupling has taken place. Compound **64** can then be isolated and subjected to another Sonogashira reaction (Scheme 22). The ability to conduct each coupling reaction individually allows for a change of alkyne, thereby providing a means of introducing differing substituents into the system.

Scheme 22



Upon completion of the second coupling reaction, the 1,5-diyne-3-ene functionality is fully formed (**65**). A Bergman cyclization can then be performed to close the ring and generate the substituted benzothiophene (Scheme 23). It can be seen that the nature of the substituents on

Scheme 23

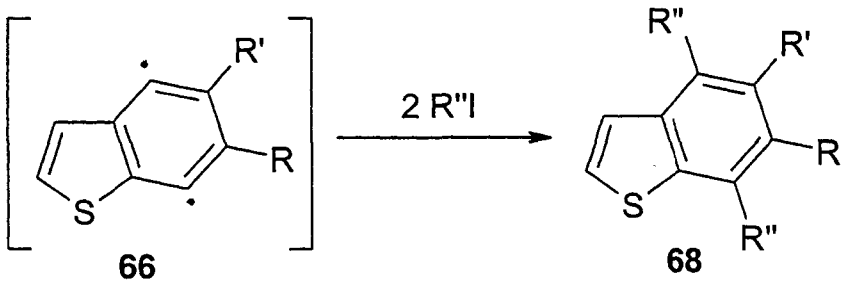


the benzene portion of the ring system is determined by the initial alkynes used in the cross-couplings. Since the Bergman cyclization is known to proceed through both thermal and photochemical reaction pathways, this provides a means of performing the cyclization under

different conditions, as necessary.

The substituents on C-6 and C-7 of the final product are determined by the substituents on the alkyne termini of the enediyne. If substitution is desired at C-5 and C-8, it would be possible to utilize the biradical intermediate to introduce substituents at these locations (Scheme 24).

Scheme 24



Substituents on the five-membered ring of the system can either be present in the initial 2,3-dibromothiophene reagent or can be easily introduced upon completion of the scheme. Given the similarity of structure between benzothiophenes, benzofurans and indoles, it is believed that the same methodology can be applied to the synthesis of all three. This study focuses on benzothiophenes due to the commercial availability of the 2,3-dibromothiophene (**63**) starting material, and the timeframe of the research project.

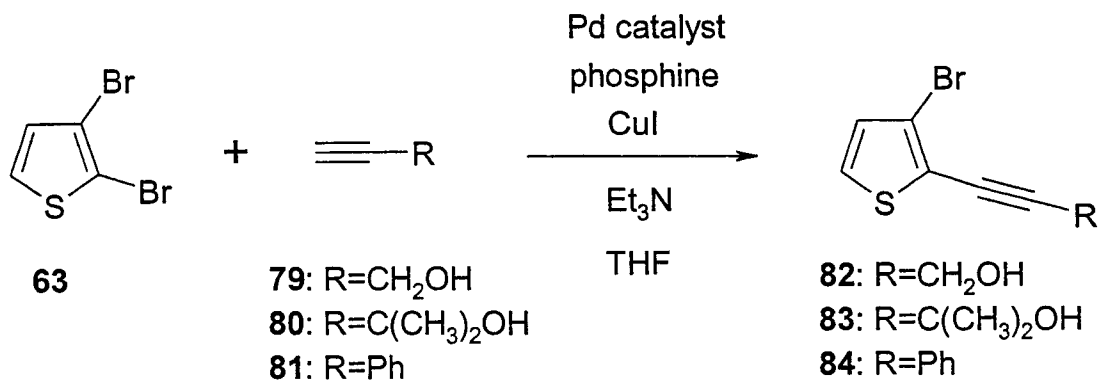
2.2 Synthetic Studies on Substituted Benzothiophenes

2.2.1 Optimization of the Catalyst/Alkyne System

Before the reactions detailed in the above methodology could be attempted, it was first necessary to determine which catalyst system would be most effective in the cross coupling

reaction and which alkynes would give the best results. In an effort to determine this, a study of the Sonogashira coupling reaction was performed where different combinations of palladium catalyst, phosphine ligand and alkyne were used (Scheme 25). The six palladium catalysts used were palladium(II) chloride ($PdCl_2$)(**69**), *tetrakis*(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$) (**70**), palladium(II) acetate ($Pd_3(OAc)_6$) (**71**), palladium(II) acetylacetonate (Pd(acac)) (**72**),

Scheme 25



63

79: R=CH_2OH
80: R=$C(CH_3)_2OH$
81: R=Ph

82: R=CH_2OH
83: R=$C(CH_3)_2OH$
84: R=Ph

1,1-bis(diphenylphosphinoferrocene)dichloropalladium(II) [(dppf)$PdCl_2$] (**73**) and [1,2-bis(diphenylphosphino)ethane]dichloropalladium(II) [(dppe)$PdCl_2$] (**74**). The four different phosphines studied were triphenylphosphine (PPh_3) (**75**), tricyclohexylphosphine (PCy_3) (**76**), tri-n-butylphosphine ($P(n\text{-}Bu)_3$) (**77**), and tri-t-butylphosphine ($P(t\text{-}Bu)_3$) (**78**) and were chosen since successful procedures employing them have been reported in the literature or were readily available. The three alkynes utilized were propargyl alcohol (**79**), 2-methyl-3-butyn-2-ol (**80**) and phenylacetylene (**81**) due to availability and literature precedents. The amine chosen was triethylamine since it was used most frequently in the literature and the solvent was THF due to the findings of Thorand and Krause[33] and ease of use (over solvents such as dioxane). CuI was

used as in accordance with the classic Sonogashira reaction conditions. The results are tabulated in Table 1. Many of the products could not be separated from a side product by chromatography and, therefore, the results are presented as a ratio of product to starting thiophene.

When the results of the reactivity study are examined, it can be seen that the most effective catalyst systems are the combination of $Pd(PPh_3)_4$ (**69**) with PPh_3 (**75**), and [(dppf)$PdCl_2$] (**73**) with P(t-Bu)$_3$ (**78**). These results are in good agreement with the literature.[30,36] It would not be expected that **69** would need to have additional phosphine added to the system. However, reactions conducted in the absence of the phosphine were found to result in slightly lower yields (40% vs. 42%). Even though this addition provides us with elevated yields, the final products prove extremely difficult to purify due to the added triphenylphosphineoxide that is generated as a side product. Therefore, subsequent reactions were conducted in the absence of additional phosphine. The method by which the extra phosphine aids the reaction is not understood but we have postulated that it may function as an oxygen scavenger, thereby preventing catalyst degradation and Glaser coupling. It may also be that the excess phosphine aids in catalyst regeneration and extends the number of turnovers that are possible.

Propargyl alcohol (**79**) does not appear to be active in the coupling reaction. This result is most likely due to interference from the hydroxyl group. However, the high yields were obtained when 2-methyl-3-butyn-2-ol (**80**) was used as the alkyne. It may be that in this alkyne, the tertiary hydroxyl group is sufficiently shielded by the two adjacent methyl groups, thereby preventing any difficulties which could potentially arise. The most effective phosphines appear to be PPh_3 and P(t-Bu)$_3$ with PCy_3 and P(n-Bu)$_3$ exhibiting little to no reactivity. On the basis of this study, it was decided that the catalyst to use for subsequent reactions would be $Pd(PPh_3)_4$ and the alkynes

Table 1: Reactivity Study Yields

Phosphine	Palladium Catalyst						Alkyne
	69	**70**	**71**	**72**	**73**	**74**	
PPh_3 (**75**)	0	0	0	0	0	0	**79**
	0.104[a]	0.398	0.092	0.084	0.119	0	**80**
	0.116	0.939	0	0	1.309	0	**81**
PCy_3 (**76**)	0	0	0	0	0	0	**79**
	0	0	0	0	0	0	**80**
	0.026	0.203	0	0	0.131	0	**81**
$P(n\text{-}Bu)_3$ (**77**)	0	0	0	0	0	0	**79**
	0	0	0	0	0	0	**80**
	0	0	0	0	0	0	**81**
$P(t\text{-}Bu)_3$ (**78**)	0	0	0	0	0	0	**79**
	0.206	0	0.023	0	0.581	0	**80**
	3.837	0	0.109	9.463	6.119	0	**81**

[a] Values are expressed as ratios of product peak area vs. starting material peak area as determined by GLC

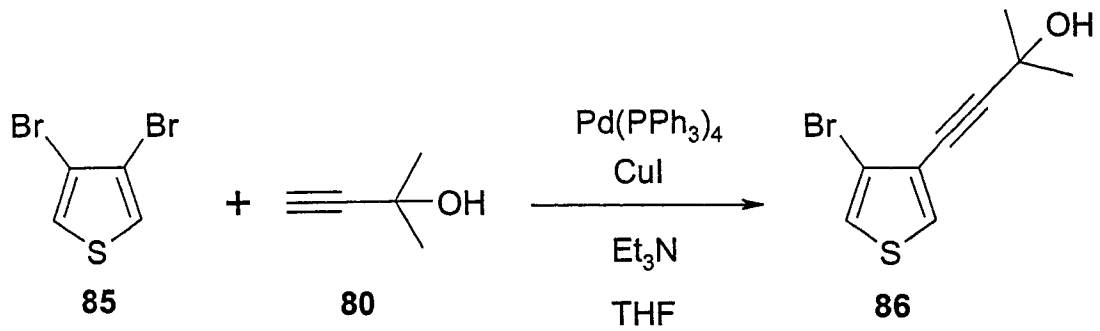
with the most promise were 2-methyl-3-butyn-2-ol and phenylacetylene. Phenylacetylene demonstrated an excellent propensity towards coupling, however, the products proved extremely difficult to purify. With this knowledge, the first stage of the proposed synthetic scheme could be undertaken.

2.2.2 Formation of Monocoupled Products

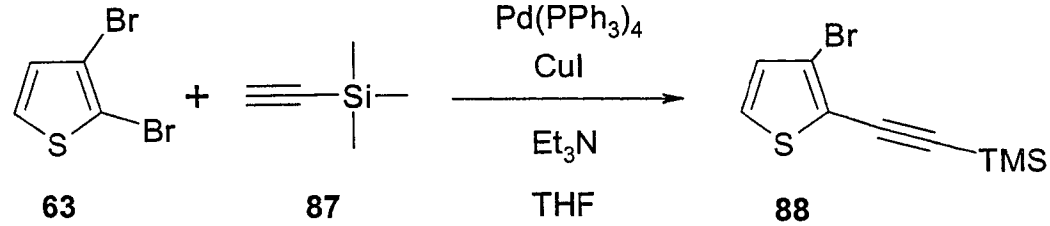
The first stage of the proposed synthetic scheme is a Sonogashira coupling reaction employed to yield a product with one alkyne at the C-2 position (Scheme 21). With the above reactivity study completed, it was known that compounds **83** and **84** can be successfully synthesized. The main byproducts of these reactions are triphenylphosphineoxide and the homocoupled product resulting from Glaser coupling. Compound **83** forms very easily at room temperature and can be separated from the reaction mixture readily in good yields (80% after further optimization). The fact that the Glaser coupled product has two hydroxyl groups on it, versus one on the monocoupled product, allows for facile separation of the two by column chromatography. For compound **84**, however, the Glaser coupled product and the desired monocoupled product have similar polarities and retardation factors (R_F) in most solvents and, as a result, cannot be separated from each other. This unfortunately prevents accurate yields from being determined for these results.

In order to ensure that we were correct in assuming that the first coupling occurs at C-2, an identical reaction as that portrayed in Scheme 25 was attempted using 3,4-dibromothiophene (**85**) as the starting material (Scheme 26). In this material, the only coupling which is possible would be at a C-3 position. When the reaction was attempted, it was found that product **86** was not formed. This supports our supposition that coupling is only occurring at the C-2 position. With the coupling reactions performed successfully for the two most promising alkynes from the reactivity study, attempts were made to generate additional monocoupled products. In the literature, a very popular alkyne used in these reactions is trimethylsilylacetylene (**87**). Again, the same reaction was performed using this alkyne (Scheme 27) and gas chromatography-mass

Scheme 26



Scheme 27



spectrometry (GCMS) analysis showed a new product corresponding to **88**. Unfortunately, when purification was attempted on this product, it was again found that it was not possible to separate the Glaser product from **88**.

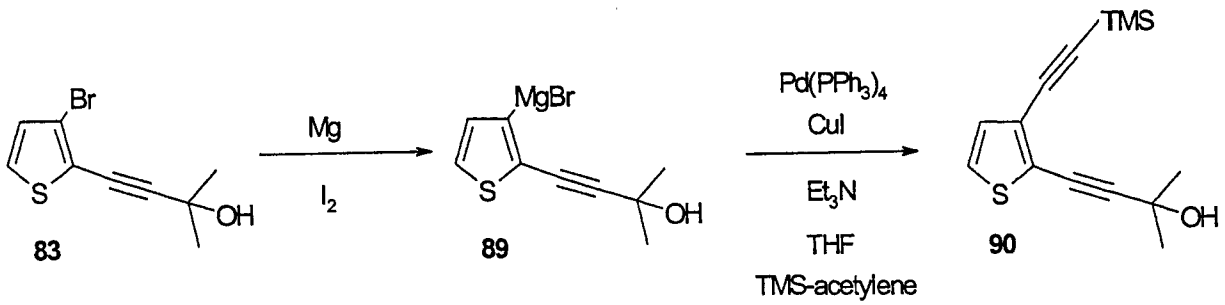
With a number of successfully synthesized monocoupled products in hand, it was possible to begin the synthesis of the enediyne. This stage of the synthetic scheme would prove to be the most challenging step in the enediyne synthesis.

2.2.3 Formation of the Enediyne

When coupling reactions were attempted on 3,4-dibromothiophene, no products were

formed (Scheme 26). This indicates that under standard Sonogashira coupling conditions, it is not possible to achieve substitution at the C-3 position. Therefore, it was necessary to employ a different method to achieve this second coupling. The first reaction attempted was the Grignard-Sonogashira coupling (Scheme 26).[34] Since the Grignard-Sonogashira reaction has been found to

Scheme 28

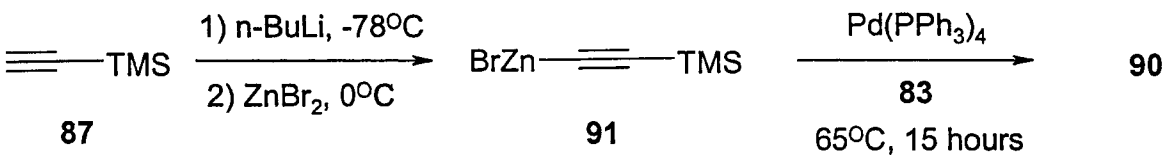


be capable of giving better yields than standard Sonogashira reactions, even in systems where electron donating substituents have lowered the reactivity, it was hoped that this modification would boost the reactivity of C-3 enough to permit coupling to occur. The choice of starting material was based on the fact that compound **83** is the most easily synthesized and purified of the three successfully formed monocoupled products. The first attempt was unsuccessful with no desired products being formed. It is believed that the Grignard reagent did not form adequately at the temperature at which the experiment was run (40°C). Therefore, to help drive the reaction, the formation of the Grignard was done at reflux conditions for 6 hours. Then, the coupling catalysts and alkyne were added. Gas-liquid chromatography (GLC) indicated the appearance of a new product with a retention time (RT) of 16 minutes. This RT is reasonable for the expected product **90,** given that **83** has a RT of 13 minutes. GCMS confirmed that this new peak has the desired mass of 262.08 g/mol (exact mass, actual value from GCMS was 262.095 g/mol). However, the

reaction did not proceed very efficiently. When the GLC chromatogram is examined, the ratio of the product peak area to starting material peak area is 0.099, indicating that very little starting material was converted to product. Given the very low yield of the reaction, no further attempts to characterize this compound were made. This result does indicate that it is possible to generate the heterodisubstituted enediynes which are critical to the success of our proposed methodology.

To find a more efficient means of enediyne synthesis, attention was now turned to a transmetallation coupling reported by Collins *et al.*[37] They report the ability to perform a coupling reaction between (2-bromophenylethynyl)trimethylsilane and 1,3,5-tribromobenzene by first performing a lithiation reaction on the alkyne, followed by a transmetallation and then a palladium catalyzed cross-coupling. In order to adapt this method to our purposes, the reaction in Scheme 29 was attempted. By taking advantage of the acidic nature of the hydrogen on the *sp* hybridized carbon of the alkyne, it was believed that the same lithiation/transmetallation/cross-coupling sequence can be achieved. Unfortunately, the reaction scheme did not yield any

Scheme 29

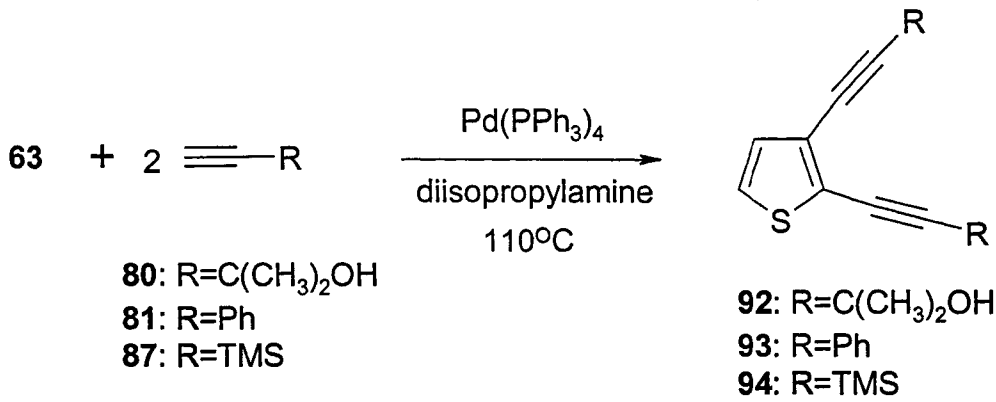


products. Since the original citation dealt with a lithiation/transmetallation/cross-coupling on a brominated starting material, the reaction was attempted again, using 2,3-dibromothiophene as the starting reagent and triisopropylsilyl(TIPS)acetylene. The reaction was not performed on any of the monocoupled products in the interest of not wasting starting materials. When this reaction was performed, the monocoupled product could be observed on GLC (confirmed by GCMS). No

dicoupled products could be observed. This may be due to the regular palladium catalyzed Sonogashira reaction taking place with no influence from the transmetallation conditions. Again, the conversion to monocoupled product was poor (ratio of product to starting material peak areas was 0.032) so no further characterization or purification was attempted on this reaction. In general, this reaction is rather difficult to perform and, even if it had been successful, would not be a desirable technique.

The solution to synthesizing enediynes arose through a method that was much more facile than the techniques attempted previously. It was found that through the use of high temperature reactions in sealed tubes,[38] it would be possible to force a coupling reaction to occur at C-3 (Scheme 30). Our first successful reaction utilizing this technique was done with 2,3-dibromothiophene and 2-methyl-3-butyn-2-ol, resulting in **92**. Compound **92** can be separated from the reaction mixture very easily and in very good yields (84%). Following this success,

Scheme 30

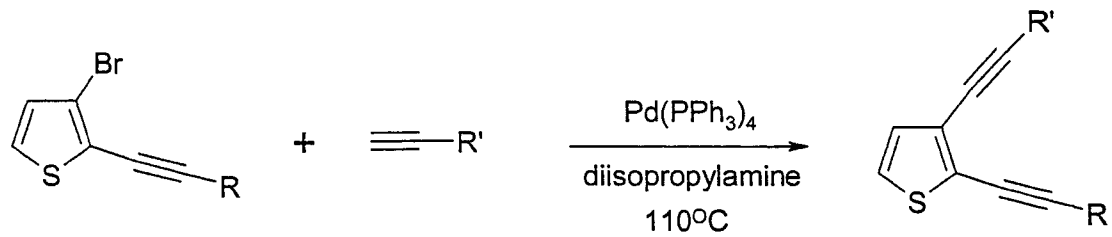


93 was synthesized using phenylacetylene as the alkyne, and it too proved to be very easily isolated in good yields (80%). Again, these two alkynes are the ones which demonstrated the greatest promise in the original reactivity study. As with monocoupling, the reaction was

extended to include TMS-acetylene which resulted in compound **94**. Unfortunately, **94** did not prove as easy to purify as **92** and **93**, resulting in an inability to determine a yield for this reaction.

This success demonstrates that it is possible to synthesize enediynes using the heteroaromatic starting material. However, all of these compounds are homodisubstituted while the objective is to be able to synthesize heterodisubstituted enediynes as well. This can be accomplished by performing the high temperature/sealed tube reactions using a monocoupled thiophene in place of 2,3-dibromothiophene (Scheme 31). The first reaction attempted using this scheme employed **83** as the starting material and TMS-acetylene. Through this reaction it was

Scheme 31



83: R=$C(CH_3)_2OH$
84: R=Ph

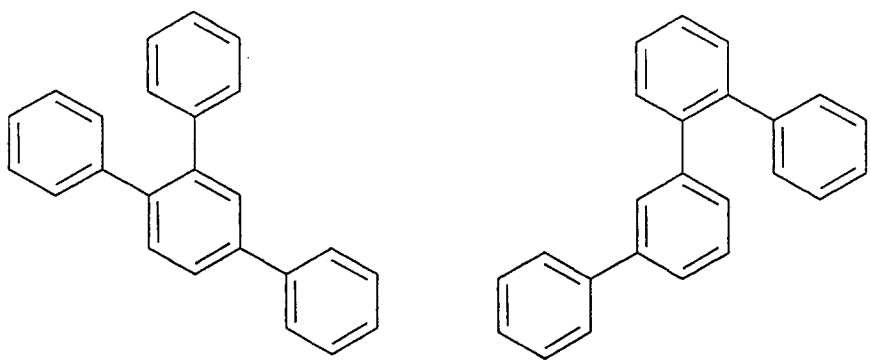
80: R'=$C(CH_3)_2OH$
81: R'=Ph
87: R'=TMS

90: R=$C(CH_3)_2OH$
R'=TMS
95: R=$C(CH_3)_2OH$
R'=Ph
96: R=Ph
R'=$C(CH_3)_2OH$

possible to synthesize compound **90**, which had been made earlier using the Grignard-Sonogashira coupling conditions, in a 90% yield. This compound was very easily isolated in high enough quantities to allow for a complete structural characterization. In addition, compound **95** was also successfully synthesized and isolated. In this case however, the synthesis did not proceed as effectively as for **90**, resulting in a 57% yield. The reason for this low yield is that the majority of the phenylacetylene appears to react with itself to generate what seems to correspond to

tetraphenyl compounds 1,2,4-triphenylbenzene (**97**) and 2,3'-diphenyl-1,1'-biphenyl (**98**) (Figure 5). This judgement is made on the basis of the mass spectral analysis of the sample. This tendency of the alkyne to react with itself consumes starting material in an unproductive fashion, resulting in low yields. It is interesting to note that these side products do not appear in the formation of **93**. It may be that, with the monocoupled starting material (**83**) used, the substituent causes steric hindrance and slows the rate of reaction for the second substitution, thereby allowing the alkyne sufficient time to react and form these side products. During the formation of **93**, the substituent is not in place, allowing for a higher reaction rate and preventing the loss of alkyne to undesired products.

Figure 5



97 **98**

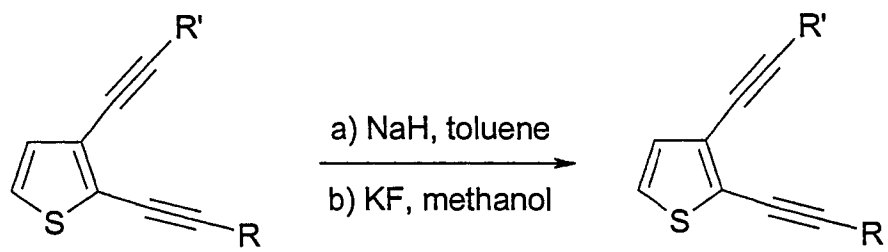
With the successful synthesis of heterodisubstituted compounds **90** and **95**, attempts were made to synthesize other enediynes using the monosubstituted product **84**. Employing the reaction used in Scheme 31, it was expected that compound **96** would be easily formed since it is very similar in structure to **95**. However, when the reaction was attempted, no products were formed. It may be possible that the Ph group causes too much steric hindrance to allow another

reaction to occur once it is already in place. The alkynes which are being used in this study are all rather large and would be expected to have significant steric interactions with one another. The tertiary alcohol used in the synthesis of **90** and **95** may be small enough to permit another alkyne to react, thus allowing these enediynes to be prepared.

2.2.4 Deprotection of Enediynes

The enediynes **90, 92** and **95** not only provide proof that it is possible to form enediynes through our proposed methodology, they also provide the means of synthesizing further enediynes through their deprotection. It is possible to remove the tertiary alcohol and TMS groups from these compounds in order to generate the product, **99**, which would have been the result of using ethyne as the original starting reagent (Scheme 32). Since ethyne is a gas at room temperature, performing syntheses with it prove more difficult. Both 2-methyl-3-butyn-2-ol (**80**) and

Scheme 32



90: R=$C(CH_3)_2OH$
R'=TMS
92: R=R'=$C(CH_3)_2OH$

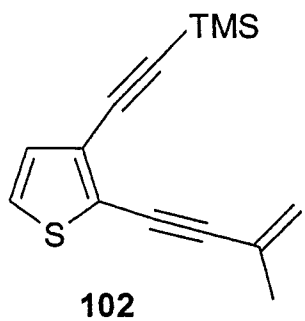
99: R=R'=H
100: R=H
R'=TMS
101: R=$C(CH_3)_2OH$
R'=H

a) conditions for removal of $C(CH_3)_2OH$
b) conditions for removal of TMS

TMS-acetylene (**87**) are liquids at room temperature, therefore, providing a much more convenient means of achieving the same ends.

The first deprotection attempted was on **92** and proceeded very smoothly with a 53% isolated yield of **99**. No further purification was performed upon the product. Given the ease of this reaction, it was believed that the same reaction should be possible to perform upon **90**; however, when it was attempted, GCMS indicated that a very sparing amount of desired product was formed. The main product of the reaction appeared to be the product expected of a dehydration (**102**) (Figure 6). This was believed to be the case since GCMS indicated the product had a mass of 244.067 g/mol which is 18 mass units lighter than the original starting material (262.444 g/mol). Further support for this was sought through NMR of the crude sample, however, a vinylic peak could not be observed. Since this product was undesired, no further characterization or purification was attempted. Deprotection of the TMS group on **90** was

Figure 6



102

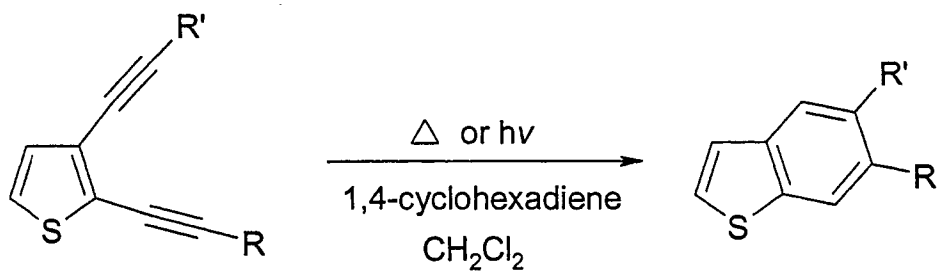
not attempted since it was not possible to gather enough of the material given the time frame of the project. Also, due to the previously mentioned difficulties involved in the synthesis of **95**, it was not possible to gather enough product to attempt deprotection of this compound.

2.2.5 Cyclizations

As mentioned previously, the Bergman cyclization is known to proceed through both thermal and photochemical pathways. Therefore, in attempts to generate substituted benzothiophenes from the enediynes that were successfully synthesized, both types of cyclization were attempted (Scheme 33). For all thermal and photochemical reactions attempted, 1,4-cyclohexadiene was used as the hydrogen atom source. Compound **92** was the first to be synthesized and was therefore the first to be subjected to the cyclization conditions. Unfortunately, no cyclization was observed in either the thermal or photochemical reactions. In fact, **92** demonstrated remarkable stability with no degradation products detected. As reported by Evenzahav and Turro,[27] photochemical reduction products can be observed when the photochemical Bergman cyclization is attempted. No such products were detected in this case. The lack of cyclization is not surprising given that the Bergman cyclization is dependant on cd. The tertiary alcohol groups of **92** would result in a great deal of steric interaction, forcing the alkyne ends apart, thereby preventing reaction.

The next set of cyclizations were attempted on **93**. Again, the enediyne demonstrated a great deal of stability under both sets of reaction conditions with no cyclized products forming, nor any thermal degradation or photoreduction products. Given the bulk of the Ph substituents, cd would be expected to be large and therefore the lack of thermal cyclization is not surprising. However, one of the compounds for which Evenzahav and Turro report successful photocyclization is an enediyne with Ph substituents (**41**).[27] The lack of reactivity displayed by **93** under photochemical conditions is disappointing. It may be that cd in **93** is slightly larger than that of **41** due to the five-membered ring having smaller internal angles. In addition, the

Scheme 33



90: R=$C(CH_3)_2OH$
R'=TMS
92: R=R'=$C(CH_3)_2OH$
93: R=R'=Ph
94: R=R'=TMS
95: R=$C(CH_3)_2OH$
R'=Ph
99: R=R'=H
101: R=$C(CH_3)_2OH$
R'=H

103: R=$C(CH_3)_2OH$
R'=TMS
104: R=R'=$C(CH_3)_2OH$
105: R=R'=Ph
106: R=R'=TMS
107: R=$C(CH_3)_2OH$
R'=Ph
8: R=R'=H
108: R=$C(CH_3)_2OH$
R'=H

heteroaromatic nature of this ring may alter the electronics enough that photochemical excitation does not readily occur.

The same lack of reactivity under both thermal and photochemical conditions was observed for all of the substituted enediynes synthesized. In an effort to determine if the substituents were the cause of this, attention was focused on **99**. Since this compound has no substituents on the enediyne termini, it should have the most potential to cyclize. When thermal cyclizations were attempted, no products, degradation or otherwise were observed. On the basis of this result, it can be concluded that the substituents are not preventing cyclizations from occurring in the other enediynes. When the photochemical conditions were attempted, it appears that a successful, though inefficient reaction was achieved. When GLC was performed on the crude products, a new, extremely small peak appears at a RT of 6.4 minutes. When this sample is

analyzed by GCMS, and the results compared to the spectral library, the peak is a perfect match for the library spectrum of benzothiophene (**8**), the product expected of a Bergman cyclization. To provide additional evidence that this new peak is indeed a result of successful photochemical Bergman cyclization, a standard sample of pure benzothiophene was analyzed by GLC and the RT time compared with that found for the reaction product. The benzothiophene standard results in a RT of 6.4 minutes, the same as that found previously. Using the response factor method for determining product yields via GLC, the yield of this reaction was found to be 0.024%. Due to the extremely small yield, isolation was not possible. No photoreduction products were observed.

Evenzahav and Turro report a solvent dependance in the photochemical Bergman reaction where ethanol results in the best product yields.[27] Photochemical cyclization on **99** was attempted again, this time using ethanol as the solvent rather than dichloromethane. No products were formed under these conditions. As discussed earlier, it is believed that photochemical Bergman cyclization occurs from the singlet excited state while photoreduction occurs from the triplet state. These results are supported by studies using triplet sensitizers, which result in higher yields of reduced products versus unsensitized reactions. To examine if this was the case, cyclization of **99** was attempted in the presence of acetophenone. Surprisingly, no products, reduced or otherwise, could be detected. It appears that **99** is not as susceptible to photoreduction as the corresponding nonheteroaromatic enediynes. However, the fact that the previously observed Bergman cyclization is suppressed, appears to lend support to the proposed photocyclization mechanism (Scheme 10).

To rationalize the results found during the above cyclizations, the cd distances for the various enediynes were calculated theoretically at both the MOPAC and MM2 levels. The results

are reported in Table 2. It can be seen that all of the results fall outside of the critical ranges determined by Nicolaou and Schreiner by approximately 1 Å. This could explain the lack of reactivity since the cyclization of these compounds would have to be driven by adding a significant amount of heat energy. Due to the equipment at our disposal, it was not possible to safely attempt these cyclizations at temperatures higher than 170°C. It is interesting to note that **99** also falls outside of the range, yet was observed to cyclize under photochemical conditions. It may be that the lack of substituents in this case result in a less strained transition state, which permits product formation. Cyclization of the other compounds would have a significant strain due to the 1,2 relationship of the large substituents.

It is interesting to note that when theoretical calculations are done on **36** and **41**, the compounds which Evenzahav and Turro report successful photochemical cyclizations of,[27] the cd distances are again found to be outside of the critical range established by Nicolaou[16] and Schreiner[17] (**36**: 4.059 Å by MOPAC and 4.051 Å by MM2, **41**: 4.082 Å by MOPAC and 4.078 Å by MM2). In Schreiner's study, it was found that the range is very precise given that some compounds, even though only slightly outside the range, do not cyclize. Given Evenzahav and Turro's results, it appears that the critical range is not as large a factor in the photochemical cyclization as in the thermal mechanism. However, their values are much closer to the critical range than the compounds investigated here, which may provide some indication as to why **36** and **41** cyclize while our heteroaromatic enediynes do not.

Table 2: Theoretical Calculations for the cd Distance

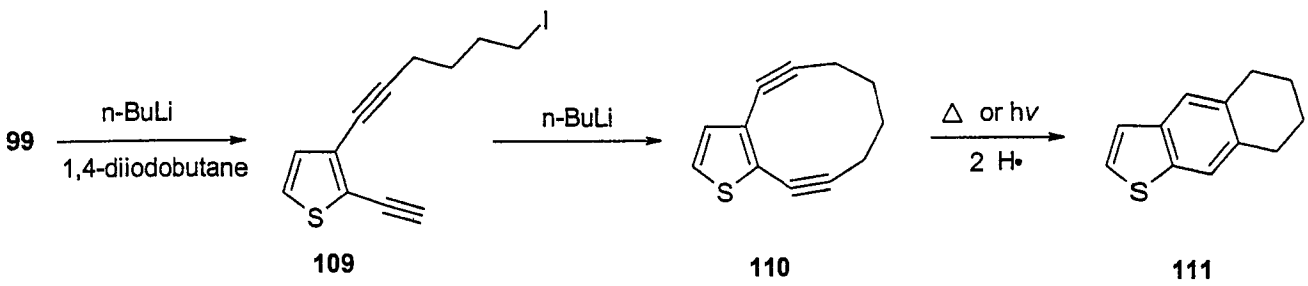
Enediyne	MOPAC (Å)	MM2 (Å)
90	4.406	4.381
92	4.392	4.392
93	4.373	4.408
94	4.400	4.400
95	4.399	4.399
99	4.473	4.409
101	4.418	4.396

2.2.6 Formation of Cyclic Enediynes

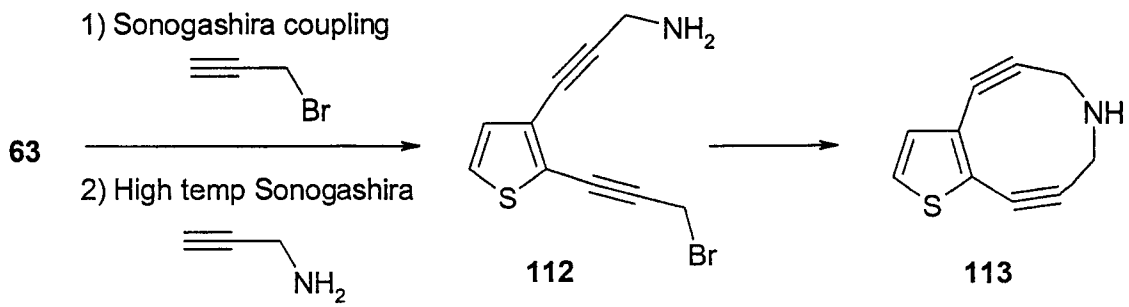
Due to the failure to cyclize any of the enediynes synthesized save one, and that sparingly, the possibility of forming cyclic enediynes was examined as a means of increasing the reactivity of the compounds. As discussed in Section 1.4.1, cyclic enediynes undergo Bergman cyclizations readily, with nine and ten-membered rings exhibiting the greatest reactivity. It was first proposed that the hydrogens on the *sp* hybridized carbons of **99** could be used as a means of converting this compound into a cyclic enediyne which could then be cyclized (Scheme 34). When the reaction was performed, no products could be observed. It is not understood why the reaction would not proceed, given that S_N2 reactions of this type are well documented.

To circumvent the difficulty presented in using **99** as the starting material to form cyclic enediynes, the use of propargyl bromide and propargyl amine to synthesize a new enediyne was proposed (Scheme 35). By using the same methodology developed previously, **112** could be formed which could then undergo an intramolecular cyclization to give the cyclic enediyne **113**.

Scheme 34

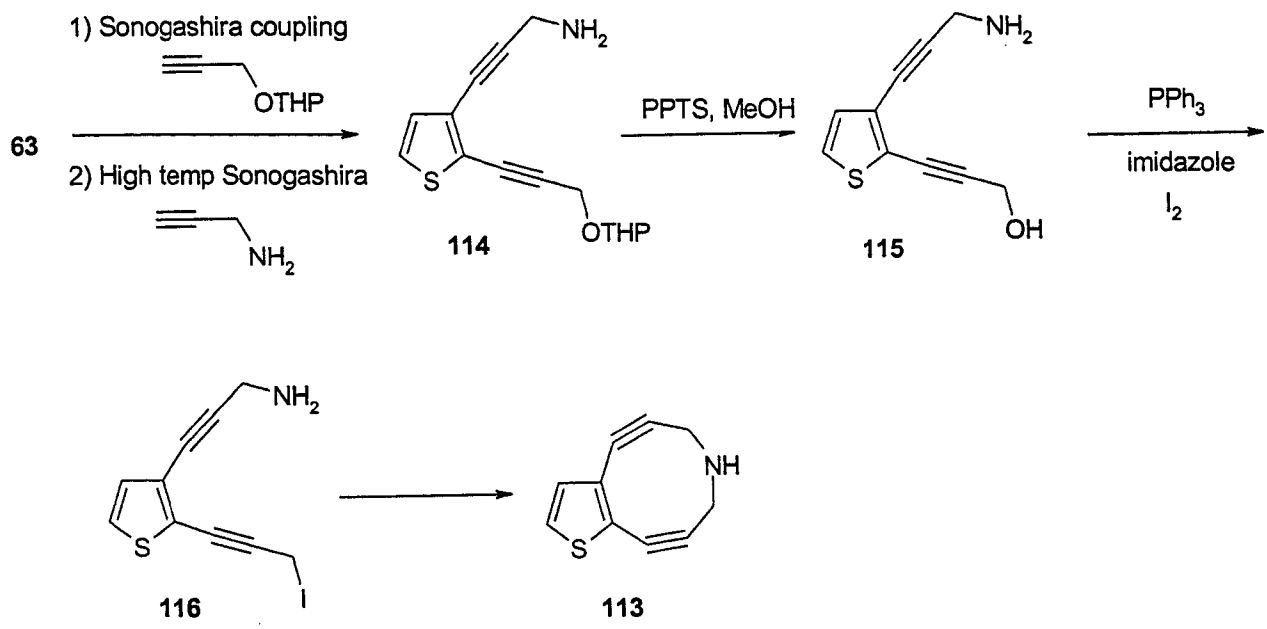


Scheme 35



However, when the first coupling with propargyl bromide was attempted, no product was formed. It may be possible that the Br is interfering with the reaction in a fashion similar to propargyl alcohol. In order to overcome this difficulty, the method shown in Scheme 36 was proposed using propargyl alcohol. Due to the observed lack of reactivity of propargyl alcohol, it would first be necessary to add a protecting group. When the coupling reaction with this protected alcohol was attempted, it was again noted that the reaction yielded no products. This lack of reactivity of the THP protected propargyl alcohol has been previously noted in our group.[39] Coupling with it is only possible when the halogen being substituted is iodine. The possibility of using these schemes to synthesize cyclic enediynes is a field which still requires a great deal of investigation.

Scheme 36



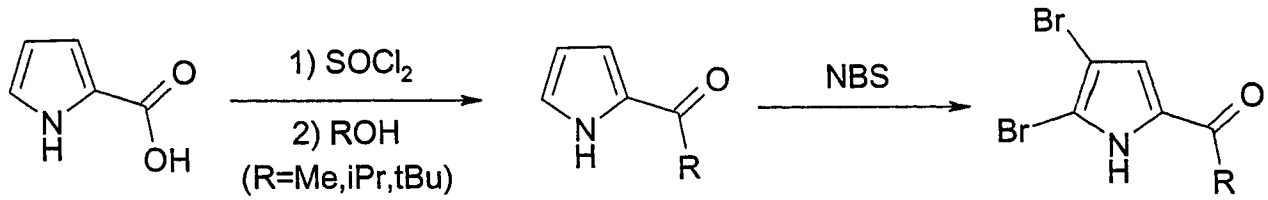
2.3 Synthesis of 2,3-Dibromopyrrole

The above study focused on using 2,3-dibromothiophene as the starting material because of its commercial availability. In order to extend the above work to the synthesis of benzofurans and indoles, it would first be necessary to develop a protocol for the synthesis of the dibrominated or diiodinated starting materials. The initial stages of the development of such a protocol for 2,3-dibromopyrrole was undertaken and the preliminary results are reported in this section.

As noted earlier, the carbons in the C-2 and C-5 positions of thiophene are the most reactive. The same reactivity is observed for pyrrole, so if bromination was attempted, the expected product would be 2,5-dibromopyrrole. By using pyrrole-2-carboxylic acid (**117**) as the base starting material, one of these reactive sites is occupied and will not interfere with the bromination. If **117** was converted into an ester, it may provide enough steric hindrance to

prevent bromination at the C-3 position (Scheme 37). It is this possibility which was investigated in this brief study.

Scheme 37



117

118: R=Me
119: R=iPr
120: R=tBu

121: R=Me
122: R=iPr
123: R=tBu

The first ester to be synthesized and brominated was **118**. GLC indicated that four distinct products were formed in this reaction. According to GCMS analysis, these four products correspond to two different monobrominated products, a dibrominated product and a tribrominated product (peak area ratio is approximately 3:8:1:3 respectively). Attempts at separating them to allow for further characterization were unsuccessful. It seems that bromination at C-3 was not suppressed as hoped. Due to the inability to separate the products from one another, it is not known whether the dibrominated compound is the desired **121** or not. The existence of two distinct monobrominated compounds of the exact same mass (202.973 g/mol, the mass expected for monobromination of **118**) is curious. Given that C-5 has the highest reactivity, and is the least sterically crowded, it would be expected that bromination would occur at that site preferentially. Ester **119** was synthesized in anticipation that the larger group would provide more hindrance. Again, the same four product distribution resulted from the bromination (peak area ratio approximately 2:4:1:6); all attempts to separate the products were unsuccessful. The most interesting result of this reaction is that the formation of the tribominated product was not

hindered as expected; rather, it appears to have been facilitated by the larger ester group. This raises the possibility that the bromination may actually be occurring on the ester substituent and is not localized to the ring carbons as expected. Attempts at synthesizing ester **120** were unsuccessful. It may be that the tertiary butyl group is too large to allow for esterification to occur. This reaction may proceed if it were to be attempted again at higher temperatures and increased reaction times.

2.4 Future Work

It has been demonstrated that the Sonogashira coupling reaction can be applied very effectively to the synthesis of both homo- and heterodisubstituted enediynes. Additional work must be performed in order to extend the range of enediynes which can be made. Other commercially available alkynes, such as propargyl amine, should be studied. In addition, the potential of **90**, **92** and **95** to permit further functionalization must be investigated. **90** in particular may allow for a large range of functionalization since it may be possible to deprotect and functionalize each alkyne terminus separately, owing to the differing protecting groups used. The formation of cyclic enediynes must also be studied further, not only to improve cyclization, but to provide a route for the synthesis of novel compounds outside the bicyclic system studied here.

The cyclization of these compounds requires much more investigation. The thermal cyclizations should be attempted at higher temperatures than those investigated here. Lack of equipment which could safely withstand high temperatures and pressures prevented a full study of this mode of cyclization. Temperatures as high as 245^{o}C have been used in the literature to

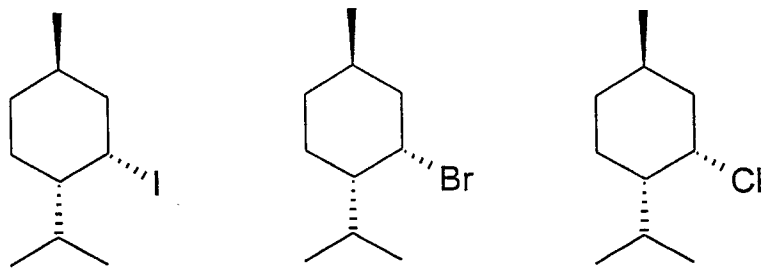
achieve these reactions. Once the cyclization has been optimized, it is necessary to attempt the use of radical trapping agents other than 1,4-cyclohexadiene to see if the proposed method of introducing substituents detailed in Scheme 24 is viable.

CHAPTER THREE: AN NMR STUDY OF THE NEOMENTHYL HALIDES

3.1 Introduction

It has been found that neomenthyl iodide (**125**), exhibits a very high field proton resonance (-0.16 ppm), whose origins are not yet understood.[40] In an attempt to provide some insight into the existence of this odd shift, the effect of varying solvents on the NMR spectra of **125**, as well as neomenthyl bromide (**126**) and neomenthyl chloride (**127**), were examined. In the course of this study, an unusually low field proton resonance was discovered, whose shift varies as a function of concentration.

Figure 7



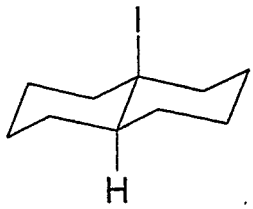
125 **126** **127**

3.2 Unusual Chemical Shifts in the ^{1}H NMR of *trans*-9-Halodecalins

In 1987, Schrumpf *et al.* reported the discovery of an unusually high field proton (-0.34 ppm) in *trans*-9-iododecalin (**128**).[41] They suggested this unusual shift may be due to the electronegativity of the halide, or possibly steric crowding. Similar studies were conducted upon *trans*-9-bromodecalin. In this case, there was still a shifting of the H-10 proton signal, but it was

much less extreme (0.84 ppm). Therefore, the less electronegative atom caused the highest degree of shielding. Schrumpf also proposed that the types of steric crowding which have been demonstrated to cause large shifts are not present in the *trans*-9-halodecalins. Schneider *et al.* also investigated this usual characteristic of the *trans*-9-halodecalins and proposed that the unusual shifting is caused by a tertiary halide interacting with a tertiary carbon atom, since none of the secondary carbon atoms exhibit any unusual shifts.[42]

Figure 8



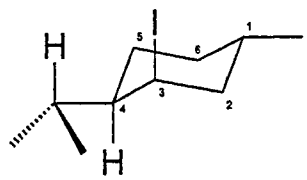
128

3.3 Unusual Chemical Shifts in the ^{1}H NMR of Neomenthyl Halides

In 1990, Lange and Gottardo first reported the existence of an unusual chemical shift (-0.16 ppm) in the ^{1}H NMR spectrum of neomenthyl iodide.[40] It was determined that **125** is predominately in a chair conformation with a staggered isopropyl group (Figure 9). Through decoupling experiments, the unusual signal was assigned to H-4. This proton is in a β antiperiplanar arrangement with respect to the iodide, as was observed in the case of *trans*-9-iododecalin. In addition, the ^{13}C NMR spectrum was determined, but it did not exhibit any unusual carbon signals.

Contrary to the proposal of Schneider, the unusual chemical shift in this case cannot be attributed to a tertiary proton interacting with a tertiary iodide, considering the iodide is a

Figure 9



129

secondary one here. However, only tertiary hydrogens have exhibited the unusual shielding effect. In neomenthyl iodide, C-2, although it is β antiperiplanar to the iodide, does not exhibit any unusual shifting. Lange and Gottardo proposed that the unusual shift is due to the large size of the iodide coupled with its good leaving group ability.[43] The large size of the iodide would be expected to cause distortion to the ring, resulting in increased shielding of H-4 due to the formation of a "ring" of protons around it.

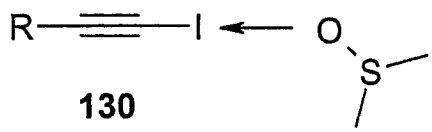
3.4 Unusual Solvent Effects on the ^{13}C NMR of Iodoalkynes

In a recent study by Goroff *et al*,[44] a surprising solvent effect on the ^{13}C NMR of iodoalkynes was observed. Iodoalkynes tend to have a C-1 carbon resonance around 0 ppm. However, when strongly Lewis basic solvents are employed, this signal shifts as much as 15 ppm downfield. When DMSO was used as the solvent, the C-1 signal of 1-iodo-2-phenylethyne shifted from 6.2 ppm to 17.7 ppm. Similarly, pyridine resulted in a shift to 19.4 ppm. The magnitude of this shift is very surprising given that solvent effects are rarely observed in ^{13}C NMR spectroscopy.[44]

Iodoalkynes have been shown to be good Lewis acids.[45] When a simple model of Lewis base activity is employed (Figure 10), it would be expected that the solvent would cause an

increase of electron density at the carbon atom. Therefore, the carbon signal would be expected to shift upfield. Considering this is not the observed result, the direction of this shift is as surprising as the magnitude.

Figure 10



130

To understand better the origins of this unusual solvent effect, theoretical calculations were performed for the cases of 1-iodo-2-phenylethyne and 2-cyano-1-iodoethyne.[46] The results indicate that the shift arises from a polarization of the C-I σ bond toward the carbon. The alkyne is also polarized by the Lewis base, causing a shifting of the electron cloud around C-1 towards C-2. This results in a significant deshielding of the C-1 nucleus.

^{1}H NMR spectroscopy has shown that unusual chemical shifts can be exhibited by tertiary protons when they are in a β antiperiplanar arrangement with an iodide. Since Lewis basic solvents have been shown to have profound effects on the NMR spectra of iodoalkynes, it may be possible to observe similar effects on the spectra of neomenthyl halides. Therefore, the effects of different solvents on both the ^{1}H NMR and ^{13}C NMR spectra of **125-127** were determined in an attempt to shed light on the origins of the unusual chemical shift of H-4.

3.5 A Solvent-Effects Study on Neomenthyl Halides

3.5.1 Results

Neomenthyl iodide (**125**), neomenthyl bromide (**126**) and neomenthyl chloride (**127**) were

prepared and their ^{1}H NMR and ^{13}C NMR spectra were determined in chloroform-*d* ($CDCl_3$). Comparison to literature results indicated excellent agreement.[40] The solvents chosen for the solvent effects study range in Lewis basicity. They are dichloromethane-d_2 (CD_2Cl_2), tetrahydrofuran-d_8 (THF), acetone-d_6, dimethylformamide-d_7 (DMF), dimethylsulfoxide-d_6 (DMSO), pyridine-d_5, toluene-d_8, benzene-d_6 and aniline-d_{11}. The results of the study are reported in Tables 3-8. It can be seen that the general trend is that Lewis bases cause a downfield shift of H-4 while aromatic compounds cause an upfield shift. These results are most apparent for **125**, less noticeable for **126** and the trend is difficult to observe in **127** spectra.

3.5.2 Discussion

The proposal made by Lange and Gottardo which claims the low field proton signal is the result of a bridged hydride[43] would predict that Lewis bases would result in a downfield shift. Lewis bases would be expected to coordinate with the relatively acidic proton in the H-4, thereby facilitating the dissociation of the proton. This trend is observed in the results of the study: Lewis bases cause a downfield shift of the proton signal. Aromatic compounds such as benzene and toluene are poor Lewis bases, hence they should not influence the shift of the H-4 signal. This prediction is not supported by the results. Aromatic compounds tend to result in an upfield shift of the H-4 signal with the most extreme result being for benzene which caused a shift from -0.16 ppm to -0.46 ppm in the case of **125**. To determine which of the factors causing shifts bears the most weight, pyridine and aniline, both Lewis basic aromatic compounds were investigated. In both cases, a significant upfield shift was observed. Pyridine, being the stronger Lewis base, shifted the H-4 signal to -0.22 ppm while aniline caused a shift to -0.41 ppm, a shift

Table 3: ^{1}H NMR Results for Neomenthyl Iodide (125) (ppm)

Proton	$CDCl_3$	CD_2Cl_2	THF	Acetone	DMF	DMSO[a]	Pyridine	Toluene	Benzene	Aniline
1	1.97	1.96	1.97	1.96	1.91	1.94	1.97	1.86	1.96	1.95
2α	1.36	1.37	1.40	1.43	1.46	1.39	1.27	1.27	1.27	1.25
2β	2.22	2.18	2.16	2.17	2.14	2.16	2.13	2.05	2.05	2.05
3	4.77	4.75	4.77	4.80	4.86	4.76	4.71	4.52	4.52	4.58
4	-0.16	-0.15	-0.12	-0.09	-0.06	-0.13	-0.22	-0.41	-0.46	-0.41
5α	1.77	1.74	1.74	1.75	1.71	1.75	1.66	1.58	1.57	1.62
5β	1.23	1.27	1.26	1.26	1.20	1.26	1.19	1.23	1.21	1.20
6α[b]	0.96	0.96	0.96	0.98	1.01	0.97	0.91	0.96	0.75	0.98
6β	1.74	1.74	1.74	1.75	1.77	1.75	1.66	1.58	1.57	1.59
7-Me	0.92	0.92	0.91	0.91	0.90	0.90	0.85	0.92	0.80	0.88
8	1.28	1.28	1.26	1.26	1.23	1.26	1.19	1.23	1.30	1.28
9-Me[c]	0.88	0.87	0.88	0.88	0.88	0.87	0.83	0.88	0.78	0.80
10-Me[c]	0.96	0.95	0.96	0.96	0.96	0.96	0.89	0.95	0.84	0.89

[a]Due to solubility difficulties, DMSO runs were performed as a mixture with $CDCl_3$ (approx. 4:1 $CDCl_3$:DMSO).
[b]Partially buried in methyl doublet resonances.
[c]Assignments in the same column may be interchanged.

Table 4: ^{13}C NMR Results for Neomenthyl Iodide (125) (ppm)

Carbon	$CDCl_3$	CD_2Cl_2	THF	Acetone	DMF	DMSO[a]	Pyridine	Toluene	Benzene	Aniline
1	28.8	28.8	29.0	28.9	29.1	28.4	28.6	28.6	28.6	28.9
2	45.6	45.4	45.7	45.6	45.5	45.0	45.2	45.3	45.2	45.2
3	46.3	46.4	46.3	46.6	48.1	46.5	46.5	45.5	45.9	46.6
4	49.6	49.4	49.6	49.4	49.2	48.9	49.0	49.2	49.2	49.1
5	27.0	26.9	27.2	27.1	27.2	26.6	26.8	26.8	26.8	26.9
6	35.2	35.0	35.3	35.1	35.0	34.6	34.8	34.9	34.9	34.8
7	22.0	21.7	21.8	21.7	21.7	21.5	21.6	21.7	21.7	21.7
8	34.1	33.9	34.3	34.1	34.4	33.6	33.8	33.8	33.9	34.0
9[b]	20.7	20.4	20.5	20.5	20.4	20.3	20.3	20.4	20.4	20.3
10[b]	20.3	20.0	20.1	20.0	19.9	19.8	19.9	19.9	20.0	19.9

[a]Due to solubility difficulties, DMSO runs were performed as a mixture with $CDCl_3$ (approx. 4:1 $CDCl_3$:DMSO).
[b]Assignments in the same column may be interchanged.

Table 5: ^{1}H NMR Results for Neomenthyl Bromide (126) (ppm)

Proton	$CDCl_3$	CD_2Cl_2	THF	Acetone	DMF	DMSO[a]	Pyridine	Toluene	Benzene	Aniline
1	1.96	1.96	1.95	1.95	1.91	1.91	1.93	1.94	1.96	1.93
2α	1.44	1.46	1.47	1.51	1.53	1.49	1.36	1.48	1.13	1.35
2β	2.16	2.16	2.12	2.12	2.09	2.10	2.08	2.00	2.02	2.00
3	4.67	4.66	4.65	4.70	4.73	4.71	4.63	4.40	4.43	4.49
4	0.78	0.80	0.81	b	b	0.88	0.70	0.50	0.49	0.55
5α	1.75	1.75	1.73	1.75	1.73	1.71	1.64	1.67	1.60	1.58
5β	1.37	1.38	1.36	1.38	1.33	1.33	1.46	1.14	1.36	1.19
6α	b	b	b	b	b	b	b	0.75	0.73	0.77
6β	1.75	1.75	1.73	1.75	1.73	1.71	1.64	1.67	1.60	1.58
7-Me	0.90	0.88	0.88	0.87	0.87	0.88	0.80	0.78	0.83	0.78
8	1.50	1.47	1.48	1.53	1.42	1.43	1.48	1.33	1.52	1.48
9-Me	0.93	0.92	0.93	0.96	0.93	0.92	0.93	0.85	0.86	0.84
10-Me	0.93	0.92	0.93	0.96	0.93	0.92	0.93	0.85	0.86	0.84

[a]Due to solubility difficulties, DMSO runs were performed as a mixture with $CDCl_3$ (approx. 4:1 $CDCl_3$:DMSO).
[b]Completely buried in methyl doublet resonances.

Table 6: ^{13}C NMR Results for Neomenthyl Bromide (126) (ppm)

Carbon	$CDCl_3$	CD_2Cl_2	THF	Acetone	DMF	DMSO[a]	Pyridine	Toluene	Benzene	Aniline
1	27.0	27.1	27.3	27.2	27.2	26.5	27.0	26.9	26.9	26.8
2	44.1	44.2	44.4	44.3	44.1	43.5	44.0	44.0	43.9	43.6
3	60.3	61.0	60.3	60.7	61.4	60.9	61.0	59.8	60.0	60.2
4	49.4	49.5	49.6	49.4	49.1	48.5	49.1	49.2	49.2	48.7
5	25.3	25.4	25.6	25.5	25.5	24.8	25.4	25.2	25.3	25.1
6	35.1	35.1	35.4	35.2	35.0	34.4	34.9	35.0	34.9	34.6
7	22.0	21.9	22.0	21.9	21.8	21.6	21.9	21.9	21.9	21.8
8	31.6	31.7	31.6	31.8	31.8	31.1	31.6	31.5	31.5	31.4
9[b]	20.9	20.7	20.8	20.8	20.7	20.5	20.7	20.3	20.7	20.5
10[b]	20.3	20.2	20.2	20.2	20.0	19.8	20.1	20.1	20.1	19.9

[a]Due to solubility difficulties, DMSO runs were performed as a mixture with $CDCl_3$ (approx. 4:1 $CDCl_3$:DMSO).
[b]Assignments in the same column may be interchanged.

Table 7: ^{1}H NMR Results for Neomenthyl Chloride (127) (ppm)

Proton	$CDCl_3$	CD_2Cl_2	THF	Acetone	DMF	DMSO[a]	Pyridine	Toluene	Benzene	Aniline
1	1.91	1.95	1.93	1.93	1.93	1.85	1.98	1.87	1.92	1.74
2α	1.35	1.38	1.39	1.55	1.38	1.35	1.30	1.24	1.21	1.13
2β	2.06	2.19	2.00	2.00	1.98	1.98	2.15	1.87	1.92	1.89
3	4.51	4.52	4.49	4.55	4.59	4.53	4.45	4.25	4.29	4.37
4	1.04	1.06	1.10	1.08	1.05	1.03	b	1.05	1.03	0.88
5α	1.72	1.71	1.69	1.72	1.71	1.68	1.61	1.55	1.58	1.58
5β	1.39	1.32	1.33	1.40	1.23	1.26	1.21	1.55	1.47	1.43
6α	0.88	0.79	0.80	0.78	0.77	0.74	0.79	0.79	0.76	0.75
6β	1.76	1.62	1.63	1.63	1.62	1.61	1.58	1.55	1.55	1.48
7-Me	0.88	0.79	0.82	0.78	0.77	0.76	0.84	0.79	0.76	0.75
8	1.55	1.58	1.55	1.56	1.34	1.57	1.37	1.37	1.40	1.33
9-Me	0.91	0.88	0.87	0.88	0.86	0.87	0.88	0.83	0.82	0.82
10-Me	0.94	0.93	0.91	0.90	0.89	0.90	0.97	0.95	0.93	0.88

[a]Due to solubility difficulties, DMSO runs were performed as a mixture with $CDCl_3$ (approx. 4:1 $CDCl_3$:DMSO).
[b]Completely buried in methyl doublet resonances.

Table 8: ^{13}C NMR Results for Neomenthyl Chloride (127) (ppm)

Carbon	$CDCl_3$	CD_2Cl_2	THF	Acetone	DMF	DMSO[a]	Pyridine	Toluene	Benzene	Aniline
1	25.8	26.0	26.6	26.1	24.8	25.6	25.8	26.0	26.0	26.0
2	43.4	43.6	43.8	43.7	43.5	42.8	43.4	43.4	43.3	42.9
3	63.2	63.8	63.7	63.8	64.4	63.4	63.9	63.0	63.1	64.1
4	49.0	49.2	49.4	49.2	48.9	48.1	48.8	49.0	49.0	48.4
5	24.3	24.6	24.0	24.9	24.8	24.0	24.6	24.6	24.6	24.4
6	34.9	35.0	35.4	35.4	35.2	34.5	34.9	35.0	34.9	34.6
7	21.9	22.0	22.1	22.6	22.6	22.3	21.9	22.0	22.0	22.4
8	30.1	30.4	30.7	30.7	30.6	29.8	30.3	30.3	30.3	30.2
9[b]	20.8	20.9	21.0	20.9	20.8	20.6	20.8	20.8	20.8	20.7
10[b]	20.2	20.2	20.3	20.3	20.2	19.9	20.2	20.2	20.2	20.1

[a]Due to solubility difficulties, DMSO runs were performed as a mixture with $CDCl_3$ (approx. 4:1 $CDCl_3$:DMSO).
[b]Assignments in the same column may be interchanged.

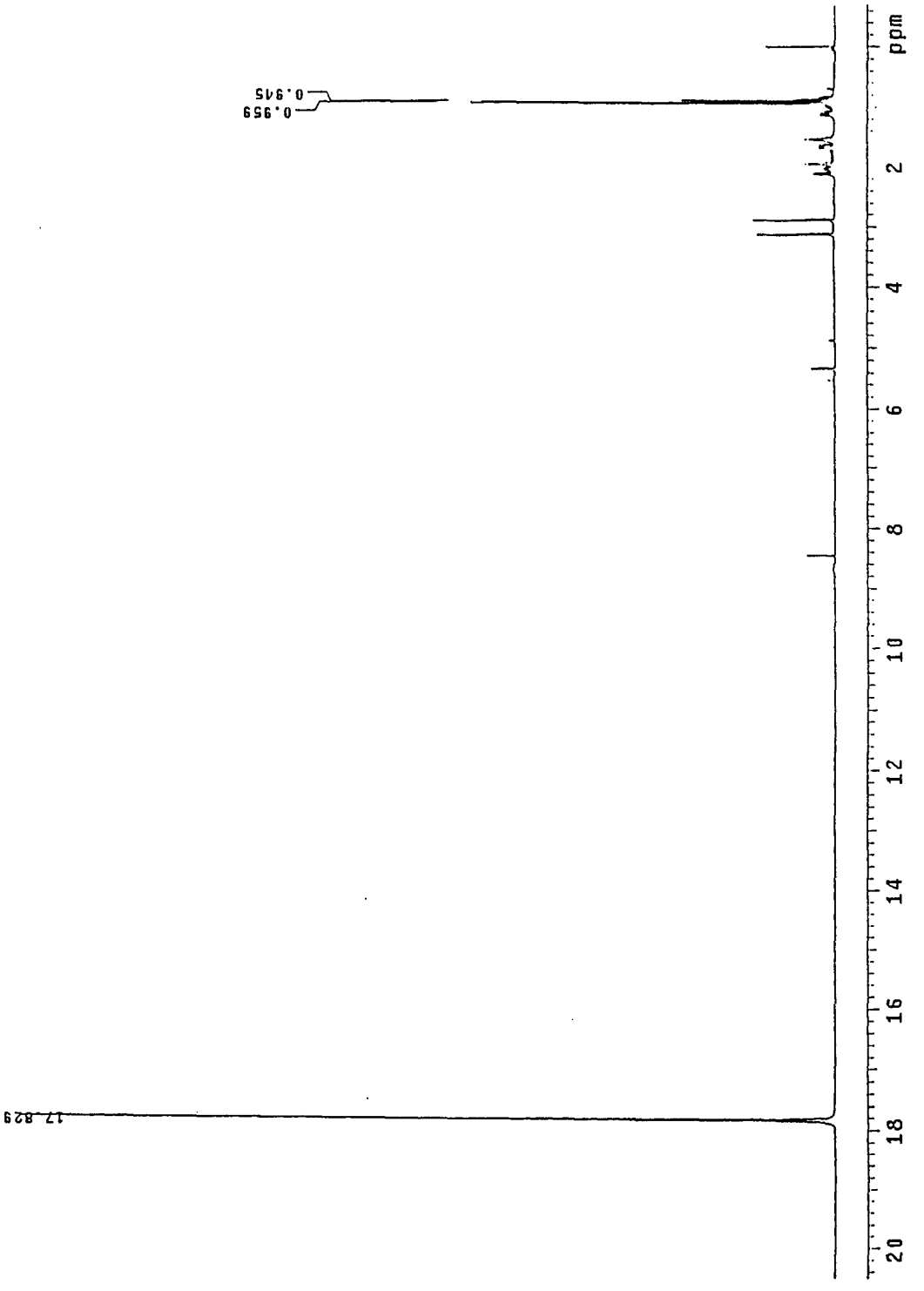
almost as great as that observed for benzene. Since Lewis bases are exhibiting this trend, it is likely that a similar case of bond polarization as that observed by Goroff is taking place. Polar compounds have also been shown to cause chemical shifts to change by as much as 0.3 ppm,[47] therefore, the results may be due to this effect. Aromatic compounds have been observed to cause shifts in NMR signals by as much as 1 ppm due to the magnetic field which these compounds can generate from their ring current.[47] They have the ability to solvate areas of low electron density and cause shielding with their anisotropic field. It could be that the shifting observed with these solvents is due to this effect.

In the proposition put forth by Lange and Gottardo to explain the shifts observed in the neomenthyl halides, it would also be expected that a shift of the C-4 and C-5 signals would be observed. This would be because of the developing double bond character at these positions. This effect is not observed, and given that the ^{1}H NMR signals do not exhibit the expected trend, this proposition is likely incorrect.

3.6 An Unusual Low Field Proton in Neomenthyl Iodide

During the course of the above NMR study, it was found that after a sample of **125** had been allowed to sit in DMF for a period of three days, the high field H-4 proton signal would disappear and a new extremely low field signal would emerge, the first instance being at 17.9 ppm (Figure 11). Common ^{1}H NMR signals for organic compounds tend to only range as high as 12 ppm. In these cases, the cause for the high signal is hydrogen bonding. This signal of almost 18 ppm is well beyond the range of common organic signals. In a search of the literature to determine the cause of this unusual shift, it was found that proton signals in this range have been

Figure 11



observed as the result of short, strong hydrogen bonds (SSHB) in active sites of enzymes.[48] Signals in this range have also been observed during proton bonding to 1,8-bis(dialkylamino)-naphthalenes.[49] However, in both of these cases, the signal is extremely broad (approximately 1 ppm) and very weak. The signal which was determined in our studies, although broad (approximately 0.2 ppm), is not nearly as broad as those observed in the previous cases. In addition, the signal being observed here is extremely strong.

3.6.1 The Effect of the Solvent

Since this signal had only been observed for the case of DMF, it was first necessary to determine if this same result could be obtained from any of the other solvents employed in the NMR study. Since DMF is a Lewis basic solvent, the solvent which would be expected to yield similar results is pyridine. When a pyridine sample was prepared in an identical fashion to that used for DMF, no anomalus peaks emerged on the NMR spectrum. The same was attempted for diisopropylamine, in anticipation that the greater Lewis basicity of this solvent would provide better results. However, it was again found that no new signals emerged on the spectrum. It appears that this effect is specific to DMF.

3.6.2 The Effect of Concentration

When attempts were being made to reproduce the low field signal after it's first discovery, it was noticed that the signal did not always appear in exactly the same position. Rather, it was observed to migrate from 17.9 ppm to 17.4 ppm to 16.5 ppm. This tendency of the signal to change position was unexpected and could not be immediately accounted for. In the studies

Table 9: Concentration Study Results

Concentration (mg/ml)	Chemical Shift (ppm)	Peak Shape
20	9.1	Weak, broad
40	12.2	Weak, very broad
60	15.1	Strong, sharp
80	15.8	Strong, sharp
100	16.3	Strong, sharp

conducted on 1,8-bis(dialkylamino)naphthalenes,[49] it was found that depending on the concentration of the acid, the signal observed for the hydrogen bonding varied between 12-18 ppm. The possibility that this same effect could be occurring here was investigated by performing a concentration study with concentrations ranging from 20-100 mg **125**/ml of DMF. The results of this study are reported in Table 9. At low concentrations, the unusual signal appears at a much lower shift (9 ppm) and the signal is very weak and broad, somewhat similar to the proton signals observed in the hydrogen bonding cases cited above. As the concentrations are increased, the signal shifts further downfield while becoming stronger and sharper until at 100 mg/ml the signal has shifted to 16.3 ppm (an increase of over 7 ppm). Therefore, it can be concluded that this unusual proton signal does not appear at a consistent chemical shift, rather it is concentration dependant.

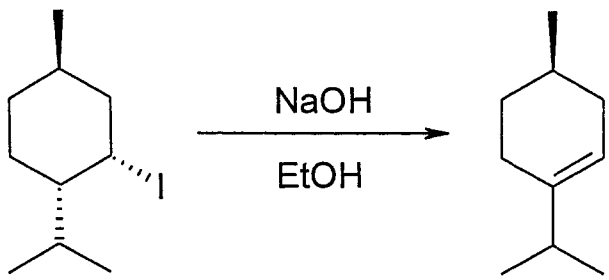
3.6.3 Neomenthyl Iodide as a Proton Source

The results of the concentration study undertaken above agree very well with the results found in the studies of 1,8-bis(dialkylamino)naphthalenes. In this study, the low field proton signals were achieved through the use of acetic acid and triflouroacetic acid as proton sources. In

the case of neomenthyl iodide, it may be that H-4 functions as a source of protons which can coordinate with the nitrogen of DMF. If this were the case, it would be expected that any proton source in combination with DMF should yield similar results. Therefore, a mixture of DMF and acetic acid was prepared and allowed to stir overnight. When the ^{1}H NMR spectrum of this solution was determined, it could be seen that there were no unusual proton signals. Therefore, it is not simply the ability of **125** to function as an acid that gives rise to this unusual signal.

As stated earlier, when the ^{1}H NMR spectra of these reactions are examined, it can be seen that the unusual high field proton signal of **125** disappears over time. This supports the idea that **125** is being deprotonated. The product of deprotonation would be expected to be **131**. This too is supported by the ^{1}H NMR by the emergence of a signal in the alkene region (5.34 ppm). In order to compare spectra, a sample of **131** was prepared from neomenthyl iodide (Scheme 38).

Scheme 38



125 **131**

However, the spectra do not compare well, indicating that the product of the reaction between **125** and DMF is not **131**. This result is supported by GLC. The RT for **131** was found to be 2.3 minutes, however, the RT for the main product peak of this reaction is 7.7 minutes, the same RT as for neomenthyl iodide. This result is curious since NMR spectroscopy indicates the

product is no longer neomenthyl iodide. GCMS indicates that this product has a similar structure to **125**, unfortunately, a parent peak cannot be captured due to the labile nature of the substituent.When neomenthyl bromide was allowed to sit in DMF for an equivalent length of time, no reaction was observed. It appears that the nature of the halide does influence the formation of this unusual signal, either through steric or electronic effects.

3.6.4 Other Considerations

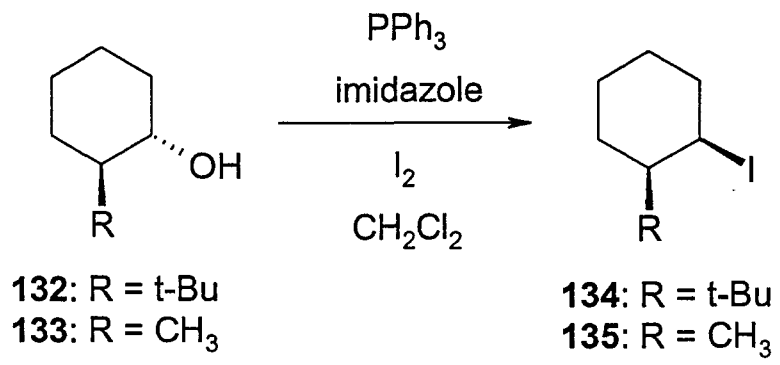
Two very curious features of this new signal are that it is a strong singlet and that the integration does not remain consistent between different concentrations. In the early runs performed with very high concentrations to get the shifts of 18 ppm, the signal integrates to 16H in comparison with the emerging alkene peak. In other lower concentration runs it corresponds to 3H and in others still, 2H. This inconsistency of the integration indicates that at high concentrations, there are more protons involved in generating the signal than there is at low concentrations.

The fact that the signal exhibits no multiplicity is quite perplexing. This would indicate that the molecule responsible for the signal is of very high symmetry or of a very simple structure. Low temperature ^{1}H NMR spectroscopy was performed to ensure that the signal is truly a singlet. At low temperatures (-41^{o}C in DMF), the signal did not resolve into a multiplet. Given that the signal integrates to a high as 16H, it cannot be assumed that the structure is simple. Therefore, it must be a very symmetric compound or -41^{o}C is not a low enough temperature to freeze out any dynamics in the molecule.

3.7 Formation of Other Iodides with a β Anitperiplanar Arrangement

To develop a better understanding of the nature of the unusual proton signals detailed above, the formation of other iodides with the β anitperiplanar arrangement was attempted (Scheme 39). By altering the substituent, the effect of steric crowding on the chemical shift

Scheme 39



132: R = t-Bu
133: R = CH_3

134: R = t-Bu
135: R = CH_3

could be determined. It would be expected that if steric crowding plays an important role in the unusual shift of the tertiary proton at C-4, **134** would exhibit a larger shift than that found for **125** while **135** would exhibit less of one. Unfortunately, it was not possible to synthesize **134**, most likely due to the steric effect of the t-Bu group preventing iodination from occurring. The reaction was attempted at both room and reflux (THF) temperatures with no product forming. Compound **135** was successfully prepared, and when the ^1H NMR spectrum was examined, there was a relatively low shift signal at 0.70 ppm. This signal is in the range observed for neomenthyl bromide. Therefore, it does appear that steric hindrance plays an important role in the appearance of the unusual high field proton signal in the compounds with β antiperiplanar formations. When **135** was allowed to sit in DMF for extended periods of time no unusual low field signals emerged. It would appear that the steric effect of the substituent plays an important role in the formation of

both the unusual low field signal discovered here and the unusual high field signal reported for neomenthyl halides. It may be that the steric crowding causes the proton on C-4 to be more acidic, allowing strain to be relieved by its removal. This would also be assisted by the good leaving group ability of iodide. Upon dissociation, it may be that a complex between DMF and the dissociation product forms.

To better understand the origins of these unusual shifts, a useful model compound would be (α,β,α)-2,4-dimethylisopropylcyclohexane. Given that a methyl group is comparable in size to an iodide,[43] it would be possible to determine if it is the leaving group ability of the iodide that is active in these cases, or rather its large size. In addition, the synthesis of compound **134** should be further investigated. Since **135** displayed the expected H-4 shift, **134** would provide definitive evidence that steric effects are the critical factor in the formation of these unusual signals.

CHAPTER FOUR: EXPERIMENTAL

4.1 Experimental

4.1.1 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 capillary column of (5% phenyl)methylpolysiloxane. The carrier gas was helium or nitrogen with a flow rate of 2.0 mL/min and a column head pressure of 21 psi. The temperature program used was the following: initial temperature = 80°C, initial time = 5 minutes, rate = 10°C/minute, final temperature = 280°C, final time = 10 minutes. Gas chromatography-mass spectrometry (GCMS) was performed on a Hewlett Packard 5890 Series II gas chromatograph equipped with a 30 m by 0.25 mm Supelco SPB-5 capillary column. The carrier gas was helium with a linear velocity of 35 cm/s at 80°C and a column head pressure of 15 psi. The temperature program used was the following: initial temperature = 80°C, initial time = 2 minutes, rate = 10°C/minute, final temperature = 280°C, final time = 15 minutes. The gas chromatograph was connected to a Micromass VG Autospec which measured the mass of samples between 52 and 510 mass units with a resolution of 3000 and an ionizing potential of 70 eV at 260°C and accelerating voltage of 7600 V. Mass spectral data are reported in the following fashion: parent ion(relative intensity), *m/e* of significant fragments(relative intensity).

Proton nuclear magnetic resonance (^{1}H NMR) spectra were measured on a Varian AS500 using the ^{UNITY}INOVA NMR spectrometer system, VNMR 6.1C software and a switchable PF6 NMR probe at room temperature (unless otherwise indicated). The solvent used was $CDCl_3$

unless otherwise stated. Chemical shifts are reported in parts per million (ppm) from an internal standard of tetramethylsilane (TMS). ^{13}C NMR were also recorded using $CDCl_3$ as the solvent unless otherwise stated and TMS as the internal standard on the same spectrometer. The NMR data are reported as follows: chemical shift(for ^1H NMR signals: multiplicity, coupling constant in Hertz, integration).

Infrared (IR) spectra were measured on either a Perkin Elmer 1320 IR spectrometer or a Bruker IFS-66 Fourier transform infrared (FTIR) spectrometer with a resolution of 4 cm^{-1}. All spectra were determined without solvent (neat) unless otherwise noted, in the transmission mode using KBr plates and are reported as wavenumbers. Ultraviolet spectra were measured using a Perkin-Elmer Lambda 11 spectrometer, in ether or dichloromethane using a quartz cuvet, and are reported as wavelength of maximum absorption (in nm) with the corresponding molar absorptivity (ϵ).

Photocyclizations were performed by irradiating the sample, in CH_2Cl_2, in a quartz reaction tube sealed with a rubber septum and parafilm, with a Hanovia 200 W medium pressure Hg arc lamp at 25±1°C.

All experiments were run under a positive pressure of either nitrogen or argon in flasks that were either flame or oven dried. Air and moisture sensitive reagents were transferred by syringe and introduced to the reaction flasks through rubber septa. Excess solvents were removed *in vacuo* at pressures obtained by a water aspirator drawing on a Buchi rotary evaporator. All compounds were stored at room temperature under atmospheric conditions unless noted otherwise. Tetrahydrofuran (THF) was distilled from potassium. Toluene was distilled from calcium chloride. CH_2Cl_2 was rendered anhydrous by storing 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 chromatography are indicated in parentheses in the procedures and the relative concentrations are calculated by volume. Spots were viewed using ultraviolet light. Column chromatography was used to purify the reaction mixtures and was accomplished using 230-400 mesh silica gel and the solvent systems were determined by analytical TLC.

Tetrakis(triphenylphosphine)palladium(0) (**70**)[50] and 2-[(prop-1-ynyl)oxy]tetrahydro-2H-pyran[51] were synthesized using previously described methods. All other chemicals for which procedures are not listed were purchased from Aldrich. Compounds **125**,[40] **126**,[40] and **127**[40] were compared to previously reported literature values. Compounds **118**, **119** and **132** were compared to the National Institute of Standards and Technology (NIST) library mass spectra and found to be perfect matches.

4.2 Preparations

4.2.1 Experimental for Chapter Two

3-bromo-2-(3-hydroxy-3-methylbut-3-ynyl)thiophene **83**

2,3-Dibromothiophene (0.112 mL, 241 mg, 1.0 mmol), **70** (23.1 mg, 0.02 mmol), CuI (7.6 mg, 0.04 mmol) and triethylamine (0.146 mL, 106 mg, 1.05 mmol) were combined in THF (5.0 mL). To this, 2-methyl-3-butyn-2-ol (0.291 mL, 286 mg, 3.0 mmol) was added dropwise over 30 minutes. After the addition was complete, the mixture was allowed to stir overnight. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the

product purified by column chromatography (20% diethylether/hexanes). An 80% yield of **83** was obtained as determined by GLC.

TLC(10% diethylether/hexanes): R_F: 0.09.

IR(neat): 3350, 2975, 2925, 2210, 1715, 1500, 1450, 1245, 1160, 965, 855, 710.

^{1}H NMR($CDCl_3$): δ 7.18(d, J = 5.5, 1H, H-3), 6.94(d, J = 5.5, 1H, H-4), 2.17(s, 1H, OH), 1.64-1.25(m, 6H, CH_3).

^{13}C NMR($CDCl_3$): δ 129.9, 126.9, 120.2, 116.2, 101.5, 74.0, 65.8, 31.2, 29.7.

MS: 246(36), 229(100), 188(54), 165(58), 122(26), 107(18), 63(43), exact mass calcd for C_9H_9OSBr *m/z* 243.996, obsd *m/z* 243.952.

3-bromo-2-phenylethynylthiophene **84**

2,3-Dibromothiophene (0.112 mL, 241 mg, 1.0 mmol), **70** (23.1 mg, 0.02 mmol), CuI (7.6 mg, 0.04 mmol) and triethylamine (0.146 mL, 106 mg, 1.05 mmol) were combined in THF (5.0 mL). To this, phenylacetylene (0.329 mL, 306 mg, 3.0 mmol) was added dropwise over 30 minutes. After the addition was complete, the mixture was allowed to stir overnight. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (100% hexanes). Yield could not be determined.

TLC(100% hexanes): R_F: 0.22.

IR(neat): 1595, 1489, 1445, 1070, 1025, 915, 860, 753, 685.

^{1}H NMR($CDCl_3$): δ 7.51-7.21(m, 5H, Ph), 6.95(d, J = 5.0, 1H, H-3), 6.86(d, J = 5.5, 1H, H-4).

^{13}C NMR($CDCl_3$): δ 132.4, 131.4, 130.1, 129.1, 128.7, 128.3, 127.0, 121.7, 114.0, 111.3.

MS: 264(100), 183(6), 139(94), 86(6), exact mass calcd for $C_{12}H_7SBr$ *m/z* 261.945, obsd *m/z*

261.959.

3-bromo-2-trimethylsilylethynylthiophene **85**

2,3-Dibromothiophene (0.112 mL, 241 mg, 1.0 mmol), **70** (23.1 mg, 0.02 mmol), CuI (7.6 mg, 0.04 mmol) and triethylamine (0.146 mL, 106 mg, 1.05 mmol) were combined in THF (5.0 mL). To this, trimethylsilylacetylene (0.177 mL, 123 mg, 1.25 mmol) was added dropwise over 30 minutes. After the addition was complete, the mixture was allowed to stir overnight. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (20% diethylether/hexanes). Yield could not be determined.

TLC(100% hexanes): R_F: 0.24.

IR(neat): 2980, 2160, 1255, 1120, 855, 765, 705.

^{1}H NMR($CDCl_3$): δ 7.14(d, J = 5.0, 1H, H-3), 6.91(d, J = 5.0, 1H, H-4), 0.18(m, 9H, $Si(CH_3)_3$).

^{13}C NMR($CDCl_3$): δ 130.4, 127.5, 121.2, 117.1, 103.9, 96.1, 0.39.

MS: 260(48), 245(100), 122(8), exact mass calcd for $C_9H_{11}SSiBr$ *m/z* 257.953, obsd *m/z* 257.927.

2-(3-hydroxy-3-methylbut-3-ynyl)-3-(trimethylsilylethynyl)thiophene **90**

Grignard-Sonogashira Method

Magnesium (9.8 mg, 0.4 mmol), **83** (100.0 mg, 0.4 mmol) and a catalytic amount of iodine were combined in THF (2.0 ml) and refluxed for 8 hours. The septum was temporarily removed to add **70** (9.2 mg, 0.008 mmol), CuI (3.0 mg, 0.016 mmol) and triethylamine (0.044 mL, 32 mg, 0.6 mmol). After stirring for 10 minutes, trimethylsilylacetylene was added dropwise (0.057 mL,

40 mg, 0.4 mmol) over 10 minutes. This mixture was stirred for 4 hours, quenched with 4 mL of water, extracted with diethylether (3 x 10 mL), washed with 5 mL of water, 5 mL of brine, dried over magnesium sulphate, filtered and concentrated. No yield determined.

High Temperature/Sealed Tube Method

83 (100 mg, 0.4 mmol) and **70** (9.2 mg, 0.008 mmol) were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 10 minutes. Trimethylsilylacetylene (0.114 mL, 79 mg, 0.8 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 100-110°C for 13 hours. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (15% diethylether/hexanes) to give 122.2 mg (90%) of **90** as a brown liquid.

TLC(10% diethylether/hexanes): R_F: 0.07.

UV(CH_3OCH_3): λ_{max} = 227 (ϵ = 9200), 286 (7800).

IR(neat): 3290, 3100, 2990, 1510, 1370, 1250, 1165, 1120, 970, 840, 760.

^{1}H NMR($CDCl_3$): δ 7.19-6.90(m, 2H, H-3, H-4), 4.42(s, 1H, OH), 1.56(s, 3H, CH_3), 1.49(s, 3H, CH_3), 0.18(s, 9H, $Si(CH_3)_3$).

^{13}C NMR($CDCl_3$): δ 129.8, 129.7, 126.7, 126.0, 102.2, 100.3, 76.5, 75.0, 60.0, 31.7, 29.2, 0.30.

MS: 262(80), 247(100), 229(20), 204(21), 189(82), 171(13), 116(13), 73(94), exact mass calcd for $C_{14}H_{18}OSSi$ *m/z* 262.084, obsd *m/z* 262.104.

2,3-*bis*-(3-hydroxy-3-methylbut-3-ynyl)thiophene **92**

2,3-Dibromothiophene (0.112 mL, 241 mg, 1.0 mmol) and **70** (12 mg, 0.01 mmol) were

combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 10 minutes. 2-methyl-3-butyn-2-ol (0.242 mL, 210 mg, 2.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 100-110°C for 13 hours. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (20% diethylether/hexanes). 83.6% yield as determined by GLC.

TLC(10% diethylether/hexanes): R_F: 0.00.

UV(CH_3OCH_3): $\lambda_{max} = 284$ ($\epsilon = 2400$)

IR(neat): 3343, 2982, 2933, 2223, 1377, 1363, 1160, 950, 728.

^{1}H NMR($CDCl_3$): δ 7.11(d, J = 5.5, 1H, H-4), 6.93(d, J = 5.0, 1H, H-3), 1.63-1.53(m, 12H, CH_3).

^{13}C NMR($CDCl_3$): δ 129.2, 126.8, 126.2, 125.9, 102.1, 98.2, 84.2, 76.7, 74.8, 65.9, 31.2, 31.5.

MS: 248(40), 215(100), 200(27), 187(28), 172(41), 147(16), 132(17), exact mass calcd for $C_{14}H_{16}O_2S$ *m/z* 248.087, obsd *m/z* 248.118.

1,2-(diphenylethynyl)thiophene **93**

2,3-Dibromothiophene (0.112 mL, 241 mg, 1.0 mmol) and **70** (12 mg, 0.01 mmol) were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 10 minutes. Phenylacetylene (0.275 mL, 256 mg, 2.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 100-110°C for 13 hours. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (100% hexanes) to give 227 mg (80%) of **93** as a brown liquid.

TLC(100% hexanes): R_F: 0.11.

UV(CH_2Cl_2): $\lambda_{max} = 277$ ($\epsilon = 900$).

IR(neat): 3105, 3080, 3058, 2924, 2200, 1596, 1486, 1443, 1070, 1027, 755, 689.

^{1}H NMR($CDCl_3$): δ 7.55-7.31(m, 10H, Ph), 7.18(d, J = 5.0, 1H, H-4), 7.08(d, J = 5.0, 1H, H-3).

^{13}C NMR($CDCl_3$): δ 130.4, 128.4, 127.4, 125.2, 122.1, 121.8, 96.6, 92.6, 83.0, 81.0.

MS: 284(100), 239(9), exact mass calcd for $C_{20}H_{12}S$ *m/z* 284.066, obsd *m/z* 284.057.

Anal. Calcd for $C_{20}H_{12}S$: C, 84.47; H, 4.25. Found: C, 83.75; H, 4.68.

1,2-*bis*-(trimethysilylethynyl)thiophene **94**

2,3-Dibromothiophene (0.112 mL, 241 mg, 1.0 mmol) and **70** (12 mg, 0.01 mmol) were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 10 minutes. Trimethylsilylacetylene (0.353 mL, 245 mg, 2.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 100-110°C for 13 hours. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (100% hexanes). Yield could not be determined.

TLC(10% diethylether/hexanes): R_F: 0.48.

UV(CH_2Cl_2): λ_{max} = 279 (ε = 400).

IR(CH_3OH): 2965, 1650, 1505, 1420, 1350, 1258, 1020, 845, 760, 710.

^{1}H NMR($CDCl_3$): δ 7.10(d, J = 5.0, 1H, H-4), 6.97(d, J = 5.0, 1H, H-3), 0.27 (s, 9H, $Si(CH_3)_3$), 0.23(s, 9H, $Si(CH_3)_3$).

MS: 276(66), 261(71), 233(7), 201(12), 173(13), 123(25), 73(100), exact mass calcd for $C_{14}H_{20}SSi_2$ *m/z* 276.083, obsd *m/z* 276.110.

2-(3-hydroxy-3-methylbut-3-ynyl)-3-(phenylethynyl)thiophene **95**

83 (100 mg, 0.4 mmol) and **70** (9.2 mg, 0.008 mmol) were combined in diisopropylamine (4.0 mL) in a dry pressure tube. The system was degassed with argon for 10 minutes. Phenylacetylene (0.165 mL, 153 mg, 1.5 mmol) was added. The tube was sealed and allowed to stir in an oil bath at 100-110°C for 13 hours. The mixture was filtered through Celite with diethylether. Excess solvent was removed *in vacuo* and the product purified by column chromatography (5% diethylether/hexanes) to give 60.4 mg (57%) of **95** as a brown liquid.

TLC(10% diethylether/hexanes): R_F: 0.11

UV(CH_3OCH_3): λ_{max} = 264 (ϵ = 7500), 306 (5800).

IR(neat): 3385, 2975, 2925, 2850, 2210, 1150, 760, 695.

^{1}H NMR($CDCl_3$): δ 7.52-7.25(m, 5H, Ph), 7.16(d, J = 5.5, 1H, H-4), 7.05(d, J = 5.5, 1H, H-3), 2.19(s, 1H, OH), 1.65(s, 6H, CH_3).

^{13}C NMR($CDCl_3$): δ 131.6, 129.3, 128.4, 128.2, 127.9, 127.0,125.9, 123.1, 101.9, 93.3, 83.7, 74.8, 65.9, 31.4.

MS: 266(100), 251(30), 233(20), 221(44), 208(85), 189(19), 179(21), 163(38), exact mass calcd for $C_{17}H_{14}OS$ *m/z* 266.077, obsd *m/z* 266.085.

2,3-(diethynyl)thiophene **99**

Sodium hydride (19 mg, 0.8 mmol) and **92** (100 mg, 0.4 mmol) were combined in toluene (3 ml) and refluxed for 20 minutes. The mixture was then quenched with water, extracted with ether, washed with water and then brine and dried over magnesium sulphate. Excess solvent was removed *in vacuo* to give 27.8 mg (53%) of **99** as a brown liquid.

TLC(10% diethylether/hexanes): R_F: 0.36.

UV(CH_3OCH_3): λ_{max} = 214 (ϵ = 6300), 275 (4000).

IR(neat): 3289, 2977, 2928, 2103, 1659, 1377, 1166, 949, 728.

^{1}H NMR($CDCl_3$): δ 7.17(d, J = 5.0, 1H, H-4), 7.03(d, J = 5.5, 1H, H-3), 3.61(s, 1H, CCH), 3.33(s, 1H, CCH).

^{13}C NMR($CDCl_3$): δ 141.8, 130.0, 126.7, 119.8, 85.6, 81.4, 77.7, 75.8, 31.7, 29.9.

MS: 132(100), 93(6), 87(8), 69(13), 62(6), exact mass calcd for C_8H_4S *m/z* 132.003, obsd *m/z* 132.004.

General Procedure for Thermal Cyclizations

The enediyne (1 eq.), 1,4-cyclohexadiene (1,4-CHD) (20 eq.) and dichlorobenzene (8 mL) were combined in a pressure tube. The system was purged with argon for 20 minutes and then the tube was sealed and placed in an oil bath at 170-180^{o}C for 5 hours. The crude mixture was run through a silica plug to remove the solvent.

General Procedure for Photochemical Cyclizations

The enediyne (1 eq.), 1,4-CHD (20 eq.) and dichloromethane (3 mL) were combined in a quartz tube. The system was purged with argon for 10 minutes, then the tube was sealed with a septum and parafilm and irradiated with UV light for 10 hours. Excess solvent was removed *in vacuo*.

Photocyclization of **99** to Yield Benzothiophene **8**

99 (100 mg, 0.78 mmol), 1,4-CHD (1.43 mL, 1.21 g, 15.14 mmol) and CH_2Cl_2 (3 mL) were combined and irradiated for 10 hours in UV light to give 0.024% yield of **8** as determined by GLC.

MS: 134(100), 89(10), 79(15), 67(8), exact mass calcd for C_8H_6S *m/z* 134.019, obsd *m/z* 134.014.

4.2.2 Experimental for Chapter Three

Neomenthyl Iodide **125**

A solution of imidazole (1.02 g, 15.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol), and iodine (3.81 g, 15.0 mmol) in dichloromethane (15.0 mL) was prepared. To this solution, menthol (1.56 g, 10.0 mmol) in dichloromethane (5.0 mL) was added and stirred for 3 hours. The product was isolated by short column chromatography (100% hexanes) and excess solvent was removed *in vacuo* to give 1.32 g (50%) of **125** as a clear, colourless liquid.

Neomenthyl Bromide **126**

A solution of imidazole (1.02 g, 15.0 mmol), triphenylphosphine (3.93 g, 15.0 mmol), and bromine (0.774 mL, 2.40 g, 15.0 mmol) in dichloromethane (15.0 mL) was prepared. To this solution, menthol (1.56 g, 10.0 mmol) in dichloromethane (5.0 mL) was added and stirred for 3 hours. The product was isolated by short column chromatography (100% hexanes) and excess solvent was removed *in vacuo* to give 0.96 g (42%) of **126** as a clear, colourless liquid.

Neomenthyl Chloride **127**

A solution of imidazole (0.41 g, 6.0 mmol), triphenylphosphine (1.60 g, 6.0 mmol), and carbon tetrachloride (10.0 mL) was prepared. To this solution, menthol (0.78 g, 5.0 mmol) was added and stirred for 6 hours. The product was isolated by short column chromatography (100% hexanes) and excess solvent was removed *in vacuo* to give 0.31 g (18%) of **127** as a clear, colourless liquid.

cis-1-iodo-2-methylcyclohexane **136**

A solution of imidazole (0.51 g, 7.5 mmol), triphenylphosphine (1.96 g, 7.5 mmol), and iodine (1.90 g, 7.5 mmol) was prepared in dry CH_2Cl_2 (10 mL). To this solution, *trans*-2-methylcyclohexanol (0.62 mL, 0.57 g, 5.0 mmol) was added and stirred for 3 hours. The product was immediately isolated by short column chromatography (100% hexanes) and excess solvent was removed *in vacuo*.

TLC(100% hexanes): R_F: 0.23.

IR(neat): 2950, 2875, 1460, 1385, 1360, 1265, 1180, 925, 760, 640.

^{1}H NMR($CDCl_3$): δ 4.65(s, 1H), 2.20-1.40(m, 7H), 1.30(m, 1H), 0.92-0.87(m, 3H), 0.70(m, 1H).

^{13}C NMR($CDCl_3$): δ 37.7, 36.7, 31.7, 30.7, 25.2, 24.1, 22.8.

MS: 223(8), 127(17), 98(100), 81(59), 69(92), exact mass calcd for $C_7H_{13}I$ *m/z* 224.006, obsd *m/z* 223.985.

REFERENCES

1. Grissom, J.W.; Gunawardena, G.U.; Klingberg, D.; Huang, D. *Tetrahedron.* **1996**, *52*, 6453 and references cited therein.
2. Jones, R.R.; Bergman, R.G. *J. Am. Chem. Soc.* **1972**, *94*, 660.
3. Oku, N.; Matsunaga, S.; Fusetani, N. *J. Am. Chem. Soc.* **2003**, *125*, 2044.
4. Barchas, J.; DaCosta, F.; Spector, S. *Nature.* **1967**, *214*, 919.
5. Voet, D.; Voet, J. *Biochemistry.* John Wiley and Sons: New York, 1995.
6. Goldstein, S. *Hum. Reprod. Update.* **2000**, *6*, 212.
7. Takeha, M.. *Jpn. J. Pharmacol.* **1999**, *79*, 203.
8. Streitweiser, A., Jr.; Heathcock, C.H. *Introduction to Organic Chemistry.* 3rd Ed. Macmillan Publishing Company: New York, 1985.
9. Fagnola, M.C.; Candiani, I.; Visentin, G.; Cabri, W.; Zarini, F.; Mongelli, N.; Bedeschi, A. *Tetrahedron Lett.* **1997**, *38*, 2307 and references cited therein.
10. Candiani, I.; DeBernardinis, S.; Cabri, W.; Marchi, M.; Bedeschi, A.; Penco, S.; Erba, F.C. *Synlett.* **1993**, 269.
11. Saito, I.; Nakatani, K. *Bull. Chem. Jpn.* **1996**, *69*, 3007 and references cited therin.
12. Schmittel, M.; Strittmatter, M.; Kiau, S. *Tetrahedron Lett.* **1995**, *36*, 4975.
13. (a) Schmittel, M.; Maywald, M. *J. Chem. Soc., Chem. Commun.* **2001**, 155. (b) Schmittel, M.; Steffen, J.-P.; Auer, D.; Maywald, M. *Tetrahedron Lett.* **1997**, *38*, 6177. (c) Schmittel, M.; Strittmatter, M.; Kiau, S. *Angew. Chem. Int. Ed. Engl.* **1996**, *35*, 1843.
14. (a) Grissom, J.W.; Calkins, T.L. *Tetrahedron Lett.* **1992**, *33*, 2315. (b) Grissom, J.W.;

Calkins, T.L.; McMillen, H.A. *J. Org. Chem.* **1993**, *58*, 6556.

15. Grissom, J.W.; Calkins, T.L.; Egan, M. *J. Am. Chem. Soc.* **1993**, *115*, 11744.
16. Nicolaou, K.C.; Zuccarello, G.; Ogawa, Y.; Schweiger, E.J.; Kumazawa, T. *J. Am. Chem. Soc.* **1988**, *110*, 4866.
17. Schreiner, P.R. *J. Chem. Soc., Chem. Commun.* **1998**, 483.
18. Grissom, J.W.; Calkins, T.L.; McMillen, H; Jiang, Y. *J. Org. Chem.* **1994**, *59*, 5833.
19. Boger, D.L.; Zhou, J. *J. Org. Chem.* **1993**, *58*, 3018.
20. Jones, G.B.; Plourde, G.W. *Org. Lett.* **2000**, *2*, 1757.
21. Jones, G.B.; Warner, P.M. *J. Am. Chem. Soc.* **2001**, *123*, 2134.
22. Singh, R.; Just, G. *Tetrahedron Lett.* **1990**, *31*, 185.
23. Semmelhack, M.F.; Neu, T.; Foubelo, F. *Tetrahedron Lett.* **1992**, *33*, 3277.
24. Nicolaou, K.C.; Liu, A.; Zheng, Z.; McComb, S. *J. Am. Chem. Soc.* **1992**, *114*, 9279.
25. Kaneko, T.; Takahashi, M.; Hirama, M. *Tetrahedron Lett.* **1999**, *40*, 2015.
26. Turro, N.J.; Evenzahav, A.; Nicolaou, K.C. *Tetrahedron Lett.* **1994**, *35*, 8089.
27. Evenzahav, A.; Turro, N.J. *J. Am. Chem. Soc.* **1998**, *120*, 1835.
28. Turro, N.J. *Modern Molecular Photochemistry*; The Benjamin/Cummings Publishing Co.: Menlo Park, CA, 1978.
29. Stephens, R.D.; Castro, C.E. *J. Org. Chem.* **1963**, *28*, 3313.
30. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467.
31. Just, G.; Singh, R. *Tetrahedron Lett.* **1987**, *28*, 5981.
32. Bleicher, L.S.; Cosford, N.D.P.; Herbaut, A.; McCallum, J.S.; McDonald, I.A. *J. Org. Chem.* **1998**, *63*, 1109.
33. Thorand, S.; Krause, N. *J. Org. Chem.* **1998**, 63, 8551.

34. Gottardo, C.; Aguirre, A. *Tetrahedron Lett.* **2002**, *43*, 7091.

35. Bowles, D.M.; Palmer, G.J.; Landis, C.A.; Scott, J.L.; Anthony, J.E. *Tetrahedron.* **2001**, *57*, 3753.

36. Hundertmark, T.; Littke, A.F.; Buchwald, S.L.; Fu, G.C.; *Org. Lett.* **2000**, *2*, 1729.

37. Collins, S.K.; Yap, G.P.A.; Fallis, A.G. *Org. Lett.* **2002**, *4*, 11.

38. Kim, C.S.; Russell, K.C. *J. Org. Chem.* **1998**, *63*, 8229.

39. Leach, D. Master's Thesis. Lakehead University, 1999.

40. Lange, G.L.; Gottardo, C. *Magn. Reson. Chem.* **1990**, *28*, 659.

41. Schrumpf, G.; Sanwald, W.; Machinek, R. *Magn. Reson. Chem.* **1987**, *25*, 11.

42. Schneider, H.J.; Jung, M. *Magn. Reson. Chem.* **1988**, *26*, 679.

43. Gottardo, C. Master's Thesis. University of Guelph, 1990.

44. Gao, K.; Goroff, N.S. *J. Am. Chem. Soc.* **2000**, *122*, 9320.

45. Laurence, C.; Queignec-Cabanetos, M.; Dziembowska, T.; Queignec, R.; Wojtkowiak, B. *J. Am. Chem. Soc.* **1981**, *103*, 2567.

46. Rege, P.D.; Malkina, O.L.; Goroff, N.S. *J. Am. Chem. Soc.* **2002**, *3*, 370.

47. Williams, D.H.; Fleming, I. *Spectroscopic Methods in Organic Chemistry,* 4th ed; McGraw-Hill: London, 1987.

48. Viragh, C.; Harris, T.K.; Reddy, P.M.; Massiah, M.A.; Mildvan, A.S.; Kovach, I.M. *Biochemistry.* **2000**, *39*, 16200.

49. De Groot, R.L.; Sikkema, D.J. *Rec. Trav. Chim. des Pays-Bas.* **1976**, *95*, 10.

50. Heck, R.F. *Palladium Reagents in Organic Synthesis*; Academic Press: New York, 1985.

51. Savoia, D.; Tagliavini, E.; Trombini, C.; Umani-Ronchi, A. *J. Org. Chem.* **1981**, *46*, 5340.