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Synthesis of Metal-Coordinating Arenediynes And Study Of Their Reactivity in Bergman Cyclization

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SYNTHESIS OF METAL-COORDINATING ARENEDIYNES AND STUDY OF THEIR REACTIVITY IN BERGMAN CYCLIZATION

by

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ABSTRACT

Synthesis of Metal-Coordinating Arenediynes and Their Reactivity in Bergman Cyclization, Salma Al-Karmi, Ryerson University, 2009, Master of Science in Molecular Science

The Bergman cycloaromatization (BC) in which a cis-alkene-1,2-diyne (enediyne) cyclizes to form a *p*-benzyne diradical, typically is a very endothermic reaction, requiring a substantial amount of energy (i.e. high temperature) for it to proceed. This reaction received very little attention until a decade after its discovery, when the natural enediynes were isolated and shown to be the most active antitumor agents ever discovered. Having BC at the heart of their mode of action, these natural enediynes have been very challenging to mimic from synthetic standpoints. Of particular interest is to be able to design and synthesize an enediyne that is stable at room temperature, while also being capable of being triggered to undergo BC under ambient conditions. Although a relatively new concept, metal-induced BC reactions have generally been known to decrease the demanding energy barrier.

The work presented here describes several synthetic strategies towards arenediyne crown ethers and the synthesis of several arenediyne hydrazone/Schiff base ligands with extended π-systems. These synthesized enediynes are useful ligands, capable of metal-coordination and hence potentially decreasing the BC energy barrier. BC reactions of enediyne intermediates are also reported.

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LIST OF ABBREVIATIONS

AcOH : acetic acid

BC: Bergman cyclization

n-$BuNH_2$: *n*-butylamine

cd: critical distance

1,4- CHD = 1,4-cyclohexadiene

1,2-DBB: 1,2-dibromobenzene

DCM: methylene chloride

DFT: density functional theory

DIPA : diisopropylamine

DMF: N,N- dimethylformamide

DMSO: dimethyl sulfoxide

DNPH: 2,4-dinitrophenylhydrazine

DSC: differential scanning calorimetry

EDG: electron-donating group

Et_3N : triethylamine

GS: ground state

TS: transition state

p-TSA : *p*-toluene sulfonic acid

PADA: propiolaldehyde diethyl acetal

PCC: pyridinium chlorochromate

R_f: retention factor

THF: tetrahydrofuran

TLC: thin-layer chromatography

TFA: trifluroacetic acid

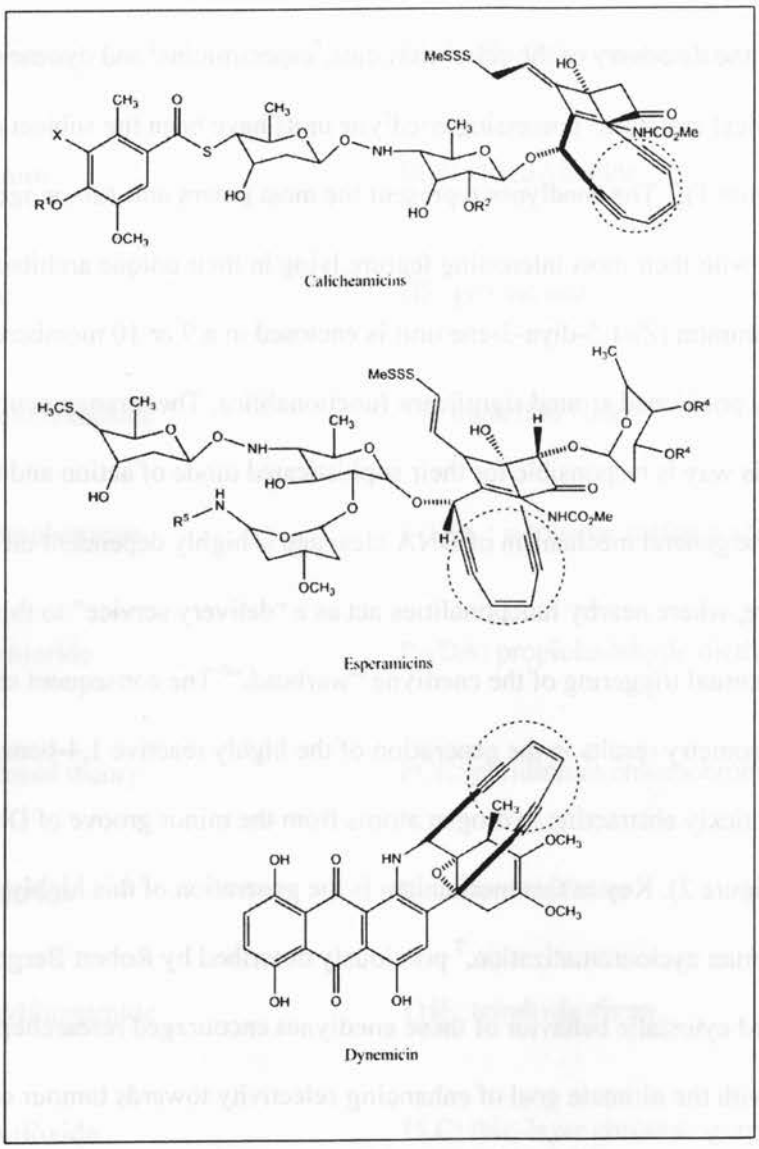
TMSA: trimethylsilyl acetylene

1. INTRODUCTION

1.1 The Enediyne Antibiotics

Ever since the discovery of the calicheamicins,[1] esperamicins[2] and dynemicins [3] in the late 1980s, chemical structures possessing enediyne units have been the subject of avid scientific research (figure 1).[4] The enediynes represent the most potent anti-tumor agents ever discovered [5] with their most interesting feature lying in their unique architectural scaffold, where the common (*Z*)-1,5-diyn-3-ene unit is enclosed in a 9 or 10 membered ring, conveniently positioned around significant functionalities. The arrangement of the enediyne moiety in this way is responsible for their sophisticated mode of action and high degree of potency.[6] The general mechanism of DNA cleavage is highly dependent on this enediyne infrastructure, where nearby functionalities act as a "delivery service" to the target DNA and allow for eventual triggering of the enediyne "warhead."[6] The consequent change in molecular geometry results in the generation of the highly reactive 1,4-benzenoid radical, capable of quickly abstracting hydrogen atoms from the minor groove of DNA, prompting cell death (figure 2). Key to this mechanism is the generation of this highly unstable biradical via the Bergman cycloaromatization,[7] previously described by Robert Bergman (scheme 1). The advanced cytostatic behavior of these enediynes encouraged researchers to design new enediynes, with the ultimate goal of enhancing selectivity towards tumour cells and minimizing toxicity towards healthy cells. Of particular interest is to be able to design an enediyne that is stable at room temperature, while still being capable of being triggered under physiological conditions.

***Figure 1**- The natural enediyne antibiotics.*



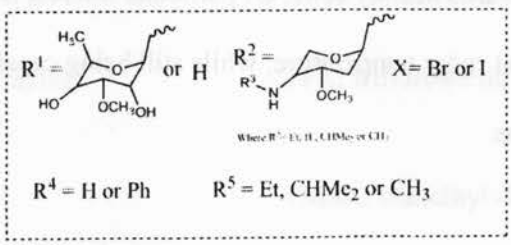
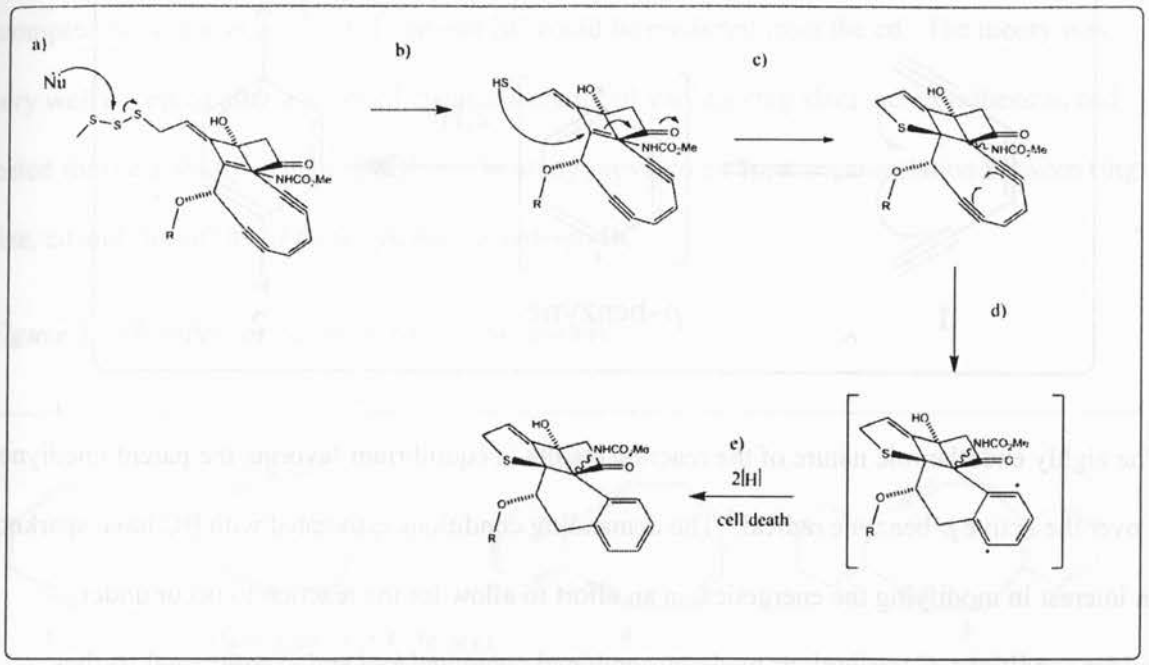


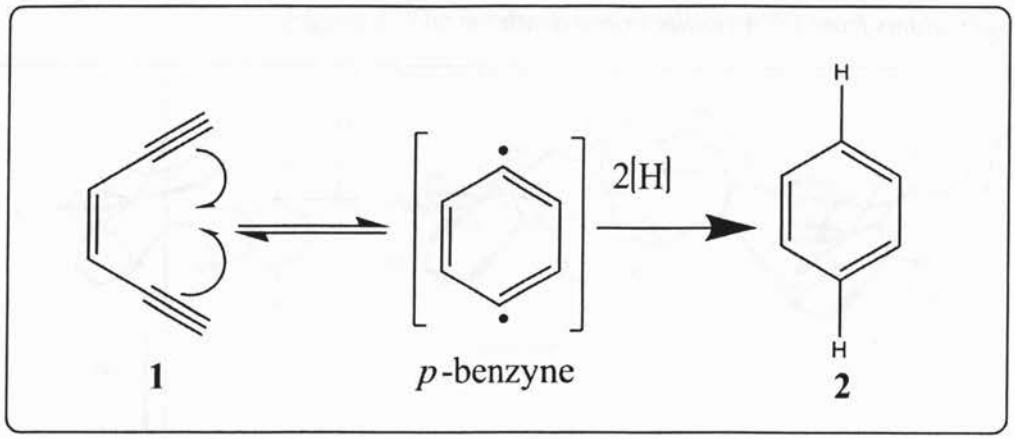
***Figure 2**- General mechanism of DNA cleavage by the calicheamicin family a) attack by a nucleophile at the trisulfide bridge generates a thiol b) intramolecular Micheal addition facilitates a cascade of conformational events c) intramolecular cyclization promotes enediyne strain d) BC generates a highly unstable benzyne radical e) abstraction of hydrogen atoms from DNA results in cell death.*



1.2 The Bergman Cycloaromatization (BC)

The Bergman cyclization (BC) was first reported in a study by Robert Bergman in 1972, where he noted the unique action of acyclic *Z*-enediynes upon thermal activation.[7] Under pyrolytic conditions, the parent 3-ene-1,5-diyne was converted to a stable benzene structure through a highly unstable *p*-benzyne diradical intermediate in the presence of a hydrogen-donor solvent (scheme 1).

Scheme 1- The *Bergman cycloaromatization.*



The highly endothermic nature of the reaction results in equilibrium favoring the parent enediyne **1** over the active *p*-benzyne radical.[8] The demanding conditions associated with BC have sparked an interest in modifying the energetics, in an effort to allow for the reaction to occur under milder conditions. Contributions made by combined computational and experimental studies have shown that four main factors influence the reactivity of *Z*-enediynes[9]:

- The distance between the terminal acetylenic carbons (i.e. the"critical distance", hereafter referred to as "cd").
- Variation in strain energy between the ground and the transition states.
- Substituent effects.
- The concentration of trapping agents/ hydrogen donors.

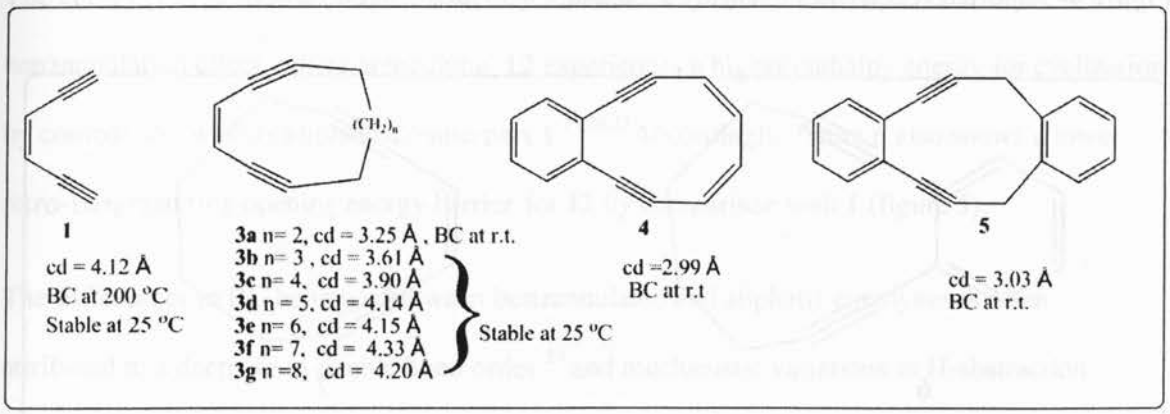
1.2.1 Designed Enediynes

i) The Critical distance

With BC being at the heart of triggering this biological cascade of events (see figure 2), many studies have focused on devising means by which to manipulate and influence the process. [9-11]

The first generation of synthetic enediynes[12] were designed with the intention of allowing for a clearer understanding of the factors that influence BC (figure 3). The geometry change associated with the enediyne moiety with an accompanied rapid BC in the natural products prompted Nicolaou *et al.*[14] to believe that BC could be predicted from the cd. The theory was very well accepted after a series of cyclic enediynes of varying ring sizes were synthesized and tested for their ability to undergo BC.[12] The study provided an apparent correlation between ring size, cd and the ability of these systems to undergo BC.

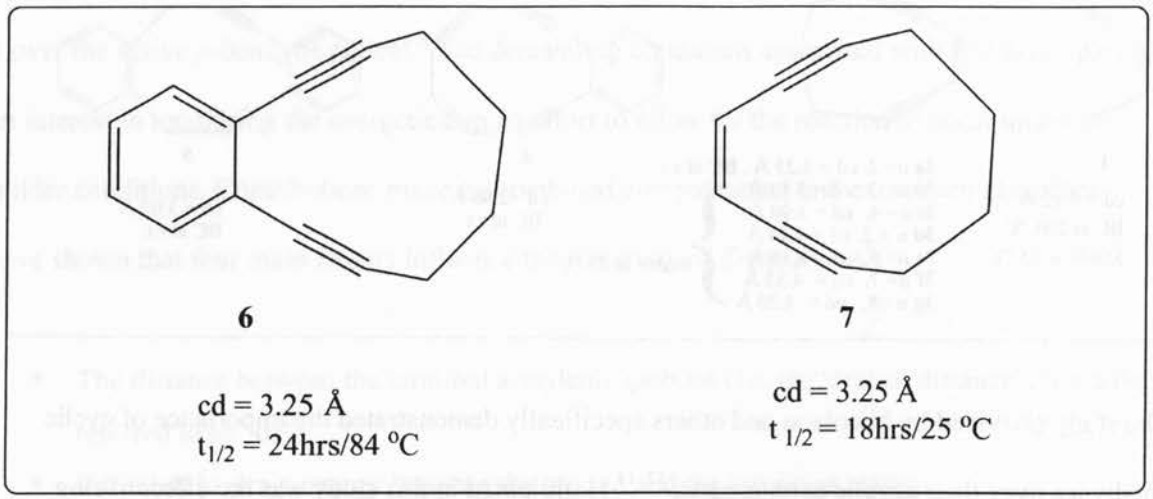
***Figure 3** - The effect of cd on the rate of cyclization.*



The study provided by Nicolaou and others specifically demonstrated the importance of cyclic enediynes over their acyclic counterparts. [12, 14] Highlighted in this study was the effect of ring size. The 10-membered ring **3a** was found to spontaneously cyclize by comparison with larger rings (**3b-3g**) which were found to be stable. This difference in behavior was correlated to cd, where a shorter cd promoted an increase in ring strain.[4] This concept was emphasized in earlier studies where other known systems demonstrated similar behavior.[14-16] Similarly, arenediynes **4** and **5** cyclize readily and this was additionally correlated to optimum cd. The cd range whereby spontaneous cyclization occurs was defined as < 3.31 Å.[16]

The cd theory is regarded as a rough estimation in assessing the overall stability of the enediyne and is not always definite, as demonstrated by various mechanistic studies.[17,18] For example, the arenediyne **6** exhibits an identical cd to its aliphatic counterpart **7** (figure 4), but both display very different BC behavior.[13,20] Thus the alternate theory put forth by Magnus and Snyder [17,20] describing the strain energy difference between GS and TS has become more widely accepted and is regarded as a more accurate representation of enediyne reactivity. Nonetheless, contemporary DFT calculations [21] show a definite correlation between cd and BC reactivity and in the majority of cases, it has provided a good means of predicting BC activation.

Figure 4- *Reported reactivities of enediynes **6** and **7** with identical cd values.*



ii) Substituent effects and structural variations within the enediyne core

a) Arenediynes vs. Aliphatic enediynes

The benzannulation effect on BC has been reported many times in literature as being an inhibitory factor in BC activation with an accompanied increase in activation energy by comparison with their aliphatic counterparts.[22, 23] This is also exemplified in figure 4, where cd is

clearly not responsible for the dramatic differences in thermal behavior of **6** and **7**. In one study, Nicolaou *et al.* [24] noted a dramatic change in BC behavior in redox benzoquinone /hydroquinone enediynes (scheme 2), where **8** exhibits a slower BC by comparison with **9**. These findings have led the authors to suggest that benzannulation is a clear disadvantage (with the electronic properties also clearly varying dramatically). One year later, Nicolaou *et al.* [25] demonstrated a variation in the thermodynamics of their synthesized benzannulated dynemicin derivatives, where the benzannulation effect is more pronounced in **11** by comparison to **10**, resulting in an increase in activation energy of BC.

The energy profile shown in figure 6 clearly illustrate the physical consequence of this benzannulation effect, where arenediyne **12** experiences a higher enthalpy energy for cyclization by comparison with its aliphatic counterpart **1**.[19,26,27] Accordingly, figure 6 also shows a lower retro-Bergman ring opening energy barrier for **12** by comparison with **1** (figure 5).

The differences in BC behavior between benzannulated and aliphatic enediynes is often attributed to a decrease in double bond order [23] and mechanistic variations in H-abstraction abilities.[28] In the latter case, the slower (higher energy) H-abstraction in arenediynes has led to a lower activation barrier for the retro-Bergman, unrelated to singlet-triplet splittings.[28] It was clear that benzannulation offered a dramatic increase in the endothermicity of BC and even changed the overall rate-determining step of the reaction[29,30] (where aliphatic enediynes experience a rate determining step in cyclization rather than the slow H-abstraction step experienced by arenediynes). In such cases, the concentrations of H-donors become important.[31]

Scheme 2- *The effect of bennzannulation on BC rates in redox-controlled systems a) hydroquinone b) quinone derivatives.*

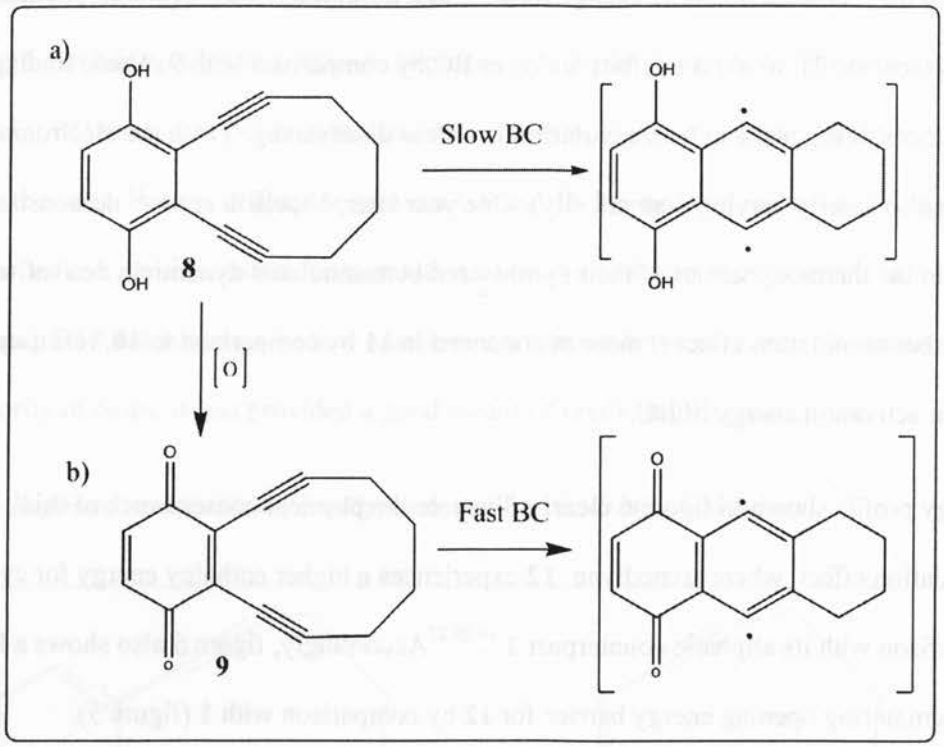
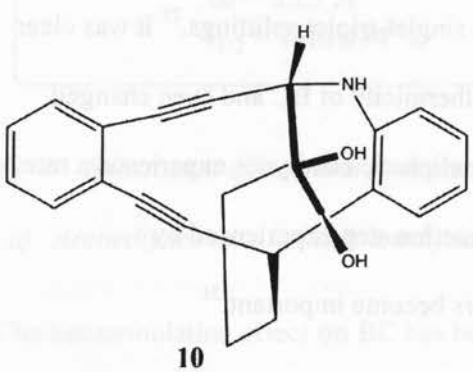
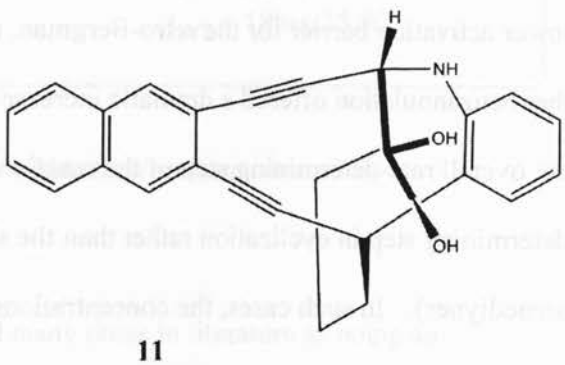


Figure 5- *The effect of benzannulation on BC thermodynamics for synthesized benzannulated dynemicin derivatives*



10

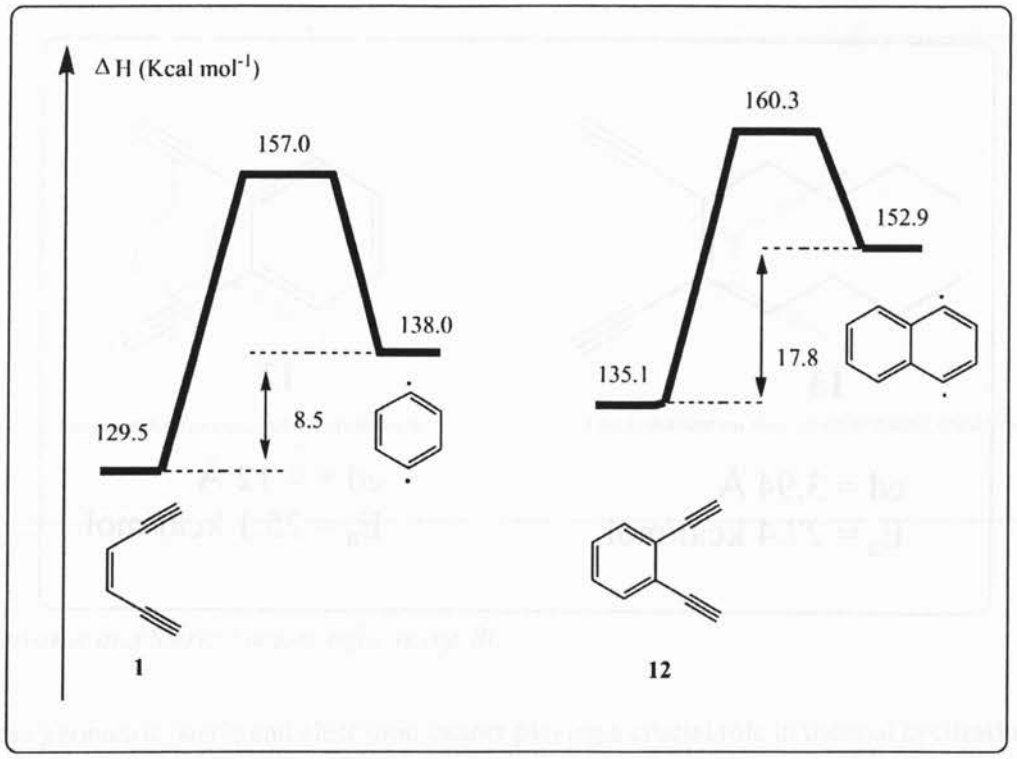
$\Delta G^{\ddagger}$= 22.6kcal/mol, 30 °C



11

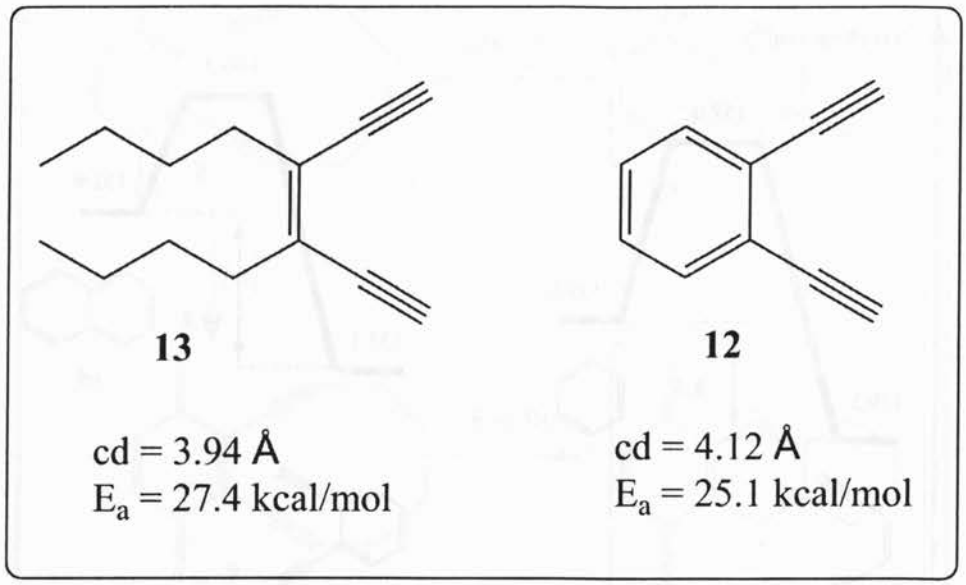
$\Delta G^{\ddagger}$= 25.7kcal/mol, 37 °C

Figure 6- *Energy profiles for aliphatic enediyne **1** and arenediyne **12** as calculated by Roth et al.*[20, 27, 32]



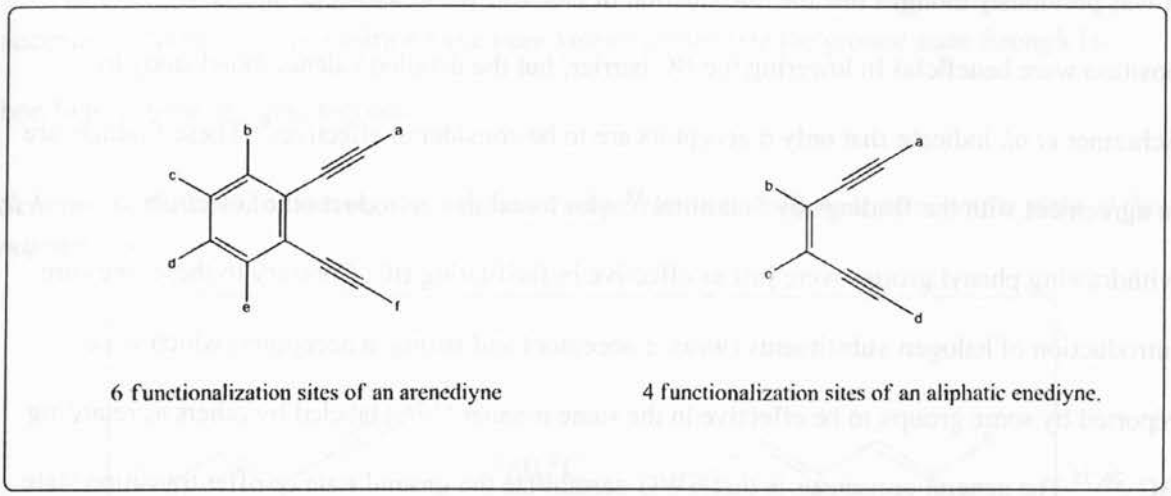
The situation is further complicated with studies that suggest that benzannulation itself is not enough to promote lower enediyne cyclization rates. The activation energy profiles of the cyclization of several acyclic enediynes established by Grissom *et al.* [33] demonstrate this well with the arenediyne **12** cyclizing more readily than the nonaromatic counterpart **13** (it is also of importance to note the cd values). Through this study and others like it, [34, 35] it becomes apparent the benzannulation effect is more pronounced in cyclic enediynes , where the ring strain effect may play an important role.

***Figure** 7- The activation energies of enediynes **13** and **12** and associated cd.*



Despite these observations, benzannulated systems offer some advantages. Although arenediynes are incapable of being substituted at the vinyl end which have been known to influence BC dramatically,[23,26] arenediynes are attractive synthetic candidates that offer additional functionalization sites (figure 8). This permits extended capacities to electronically and sterically manipulate enediyne cyclization. Evidently, the ultimate goal is to synthesize a drug candidate that does not experience a limited shelf-life, a limitation that is likely with the aliphatic enediynes where polymerization, isomerization, retro-Bergman rearrangements and potential premature activation become concerning and likely events.

***Figure 8**- The functionilization potentials of arenediynes and aliphatic enediynes.*



6 functionalization sites of an arenediyne

4 functionalization sites of an aliphatic enediyne.

b) Electronic and Steric Factors influencing BC

With the geometric, steric and electronic factors playing a crucial role in thermal cyclization of the enediynes, it soon became obvious that BC control and manipulation can be achieved through appropriate functionalization at key positions of the enediyne motif. Thermal BC activation can often be controlled through the introduction of strain or manipulation of electronic factors.[26,37]

Substitution within and surrounding the enediyne functionality is fragile, where the slightest structural modifications present a dramatic change in BC activation.[36] Not surprisingly, substituents promoting radical stabilization are critical, especially in the case of highly unstable sigma-type radicals such as the *p*-benzyne radical intermediate involved in BC. Substitution at the alkyne termini is often damaging, where often times, variation of electronic and steric properties at this position leads to increased thermal activation temperatures.[33] A few exceptions

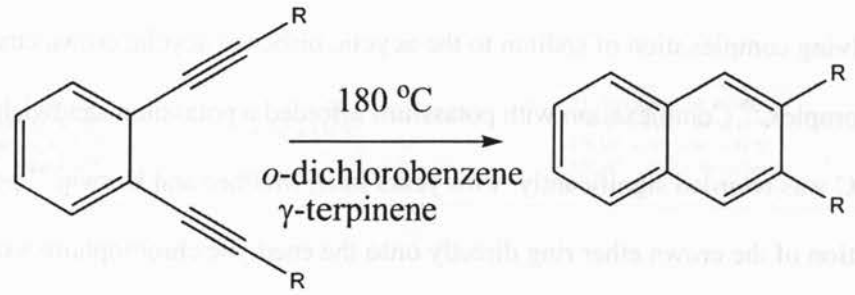
exist with the dibromo and dichloro enediynes which were able to cyclize at much lower temperatures (180 °C) with modest yields [38] (scheme 3).

It was previously thought that the introduction of electron-withdrawing groups (EWG) at this position were beneficial in lowering the BC barrier, but the detailed valence-bond study by Schreiner *et al.* indicate that only σ acceptors are to be considered effective.[40] These findings are in agreement with the findings by Schmittel [39] who found that introduction of electron withdrawing phenyl groups were just as effective in facilitating BC. Contrary to these finds are introduction of halogen substituents (weak σ acceptors and strong π acceptors) which were reported by some groups to be effective in the same manner [23] but labeled by others as retarding BC .[26, 35] The general consensus is that EWG destabilize the ground state or offer transition state stabilization.[23] For the same reason, electron-donating groups (EDG) at this position retard BC dramatically.[23]

In the case of arenediynes, the introduction of 4,5-substituents has led to some dispute in the effect of EDG on BC activation. While many authors have claimed that the introduction of EDG at this position is accompanied by an increase in the BC barrier,[39, 41] Bowles *et al.*[36] have exhibited an increase in the overall yield of the reaction with their systems. Alabugin *et al.* have claimed that the nature of substituents at this position do not offer a grave effect on BC cyclization rates.[42] This point was emphasized by various other authors,[43] suggesting that these substituents are too remote from radical formation to have a direct influence on cyclization rates. This promoted the notion that 3, 6- substituents close to the enediyne moiety and therefore in proximal positions to radical formation, are significant in facilitating thermal reactivity. Alabugin *et al.* have shown that the nature of the substituent at this position is critical on

deciding the overall fate of BC.[8,26] Interestingly, the introduction of repulsive (or steric) substituents have been shown to decrease the BC barrier by providing repulsion between the substituent and the in-plane alkyne orbitals with an accompanied decrease in the cd.[26] H-bond acceptors or donors at this position have been known to stabilize the ground state through H-bonding with the in plane π-bonds.[26]

Scheme 3- *The effect of varying the electronic properties at the alkyne termini on the yield of the naphthalene.*[36]



14a-d

Cpd	R	% Yield
a	Cl	90
b	Br	85
c	C(O)Me	0
d	CCTMS	0

1.2.2 Metal-induced BC reactions: The Metalloenediynes

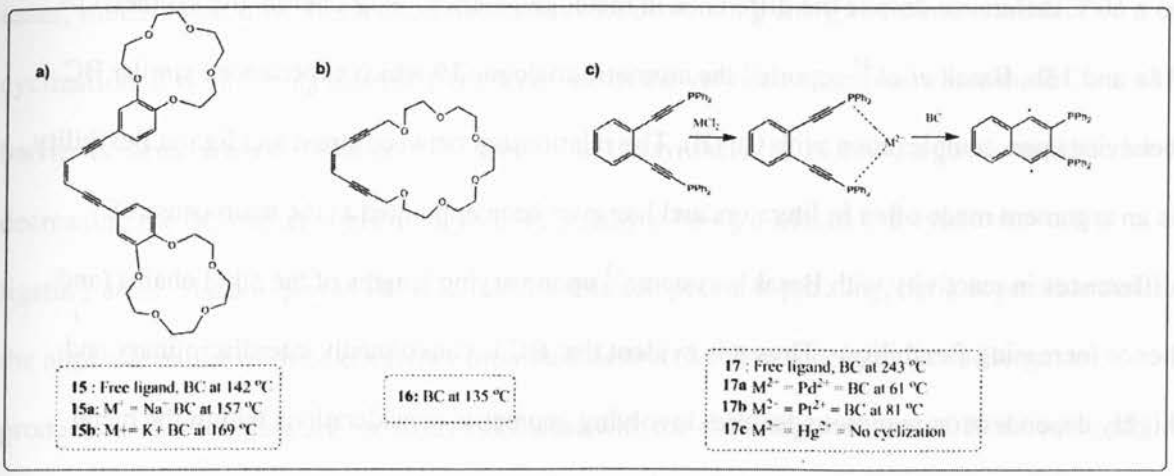
The dramatic influence of electronic factors imposed particularly at the acetylenic positions spawned the design of enediynes through the revolutionary development of the metalloenediynes. The concept behind the use of metals to lower BC activation barriers was not

exploited until relatively recently, with Konig and McPhee's efforts to decrease the BC barrier through their prepared enediyne crown ethers [35, 44] (figure 9a). The rationale behind metalloenediyne design is quite elementary; these enediynes are defined by the possession of ligating systems at the acetylenic or propargylic positions resulting in an anticipated increase in thermal cyclization upon metal chelation. The enhanced BC reactivity is the result of what Basak *et al.* [45] refer to as the generation of a "metallocycle", where the metal facilitates the formation of a "cyclic network." The complexity of this notion was emphasized when in some cases, metal-coordination afforded a detrimental effect on BC activation.[45]

Studies involving complexation of sodium to the acyclic bisbenzo acyclic crown ether **15** led to a bissodium complex.[35] Complexation with potassium afforded a potassium sandwich.[35] In both these cases, BC was retarded significantly. Two years later, McPhee and Kerwin [44] postulated that incorporation of the crown ether ring directly onto the enediyne chromophore would dramatically facilitate BC. They reported the synthesis of **16** and its strong binding affinity towards alkali metals, but did not include comparative BC studies. Soon after, Buchwald reported the synthesis of the bisphosphino ligand **17** (figure 9c) where the importance of the metal center was emphasized through complexation studies with platinum, palladium and mercury.[46] This study, like many succeeding ones, demonstrated that metals facilitating the formation of strained square planar complexes resulted in a decrease in cd which translated to an increase in BC reactivity by comparison with the free ligand.[23] By contrast, metals forming tetrahedral geometries often result in noteworthy stability by comparison to the free ligand.[23] Many cited examples now show that metal center geometry is accountable for stark differences in BC reactivities.[47] Since then, a number of different ligands have been synthesized including bipyridal, amino and diimino enediynes [46] (see figures 10, 11 and 12) In recent years, many

groups have worked at determining the factors involved in facilitating BC through metal coordination.

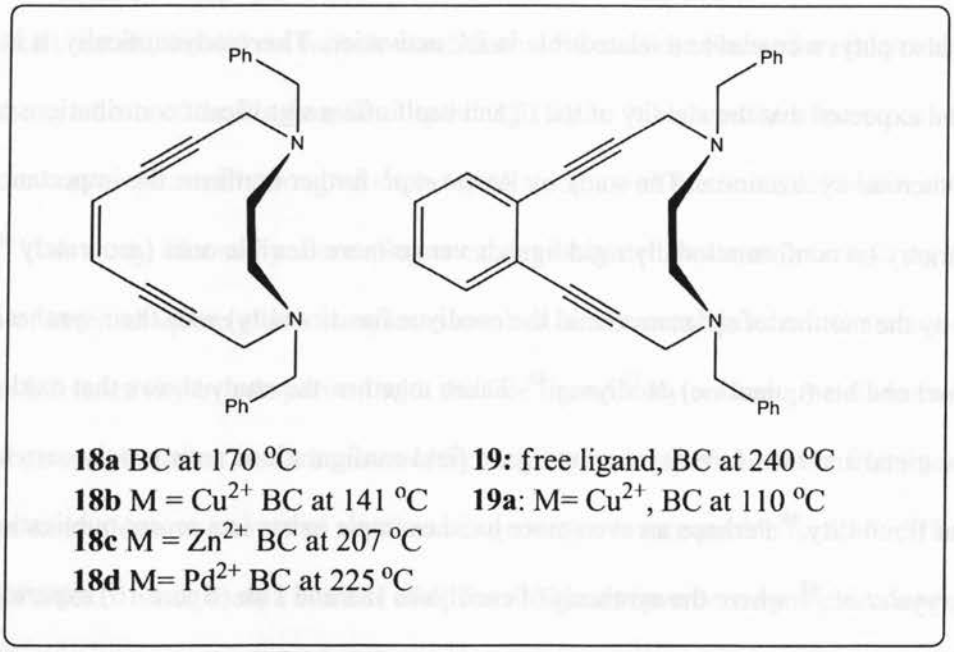
***Figure 9**- Metalloenediyne ligands previously synthesized a) bis acyclic crown ether prepared by Konig et al. b) cyclic aliphatic crown ether prepared by McPhee and Kerwin c) bis phosphino ligand prepared by Buchwald et al.*



With the metal center geometry being crucial in BC reactivity, it becomes clear that ligand flexibility also plays a crucial and related role in BC activation. Thermodynamically, it is obvious and expected that the rigidity of the ligand itself offers significant contributions to the control of thermal cyclizations. The study by Rawat *et al.* further confirms the importance of metal geometry on conformationally rigid ligands versus more flexible ones (accurately identified by the number of sp^3 atoms amid the enediyne functionality) with their synthesized bis(pyridine) and bis (quinoline) enediynes.[48] Taken together, the study shows that oxidation state of the metal and therefore its inherent ligand field configurations are strongly correlated with ligand flexibility.[48] Perhaps an even more lucid example exists in a recent publication by Bhattacharyya *et al.*,[47] where the synthesis of enediynes **18a** and **18b** (figure 10) experienced additional strain provided by the incorporated ethylenediamine bridge, facilitating a decrease in

cd . Interestingly, the study demonstrates that the cd for all metals tested (Zn(II), Cu(II) and Pd(II) were strangely similar irrespective of the metal's geometric preference, which in conformationally more flexible ligands would lead to dramatic cd variations.[23] While the cd remained remarkably unchanged, comparisons in BC behavior between Cu (II) and Zn (II) lead to a 60°C difference despite the difference in metal geometries. Years before the synthesis of **18a** and **18b**, Basak *et al.*[49] reported the aromatic analogue **19** which experienced similar BC behavior upon complexation with Cu (II). The relationship between strain and ligand flexibility is an argument made often in literature and has even been appointed as the main cause of differences in reactivity with Basak's systems[13] upon varying lengths of the alkyl chains (and hence increasing flexibility) Thus it is evident that BC is convolutedly interdisciplinary and highly dependent on numerous features involving geometric considerations within the metal center, ligand flexibility and steric bulk at the acetylenic positions.

***Figure 10**- Conformationally rigid enediyne ligands.*



18a BC at 170 °C
18b M = Cu^{2+} BC at 141 °C
18c M = Zn^{2+} BC at 207 °C
18d M= Pd^{2+} BC at 225 °C

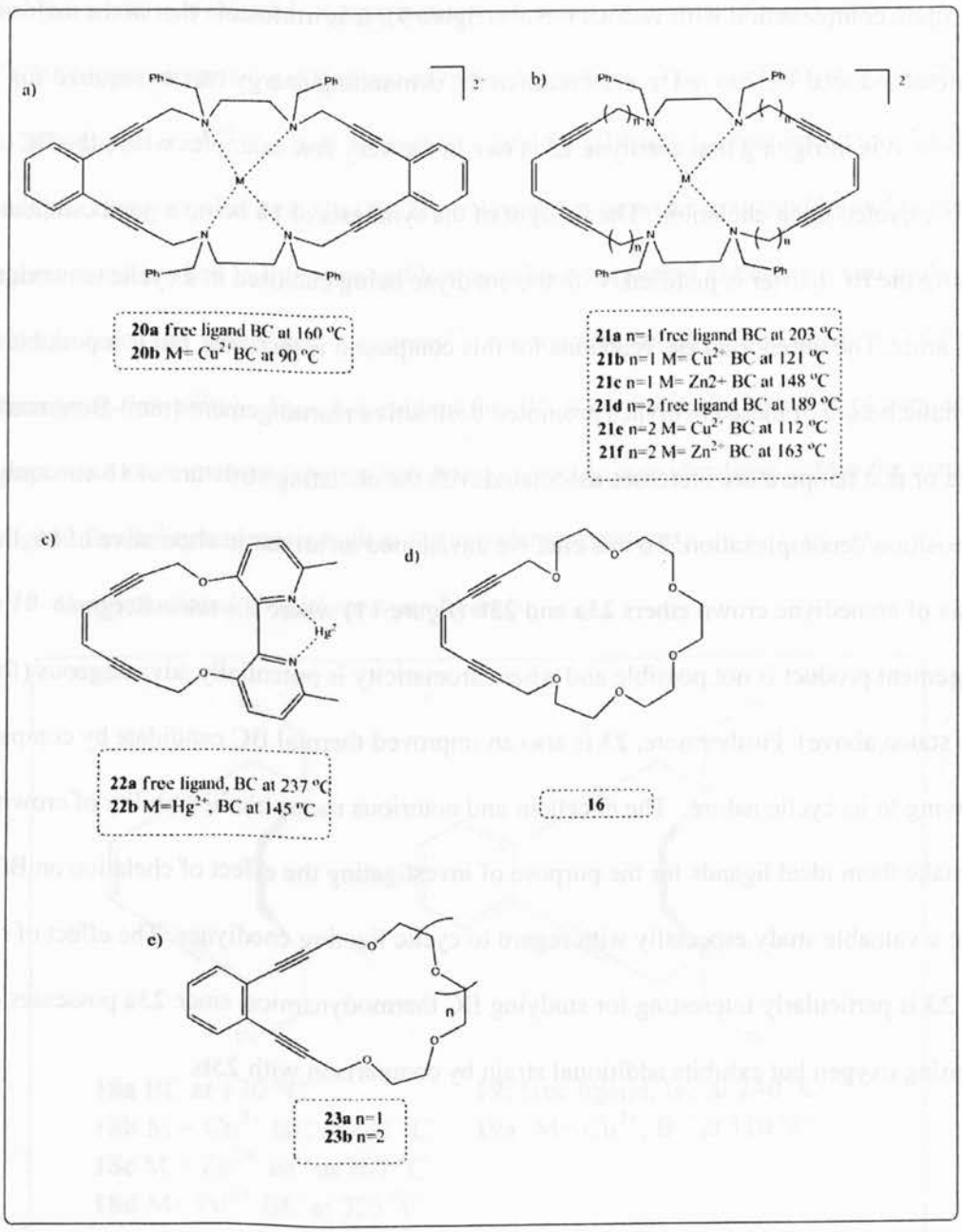
19: free ligand, BC at 240 °C
19a: M= Cu^{2+}, BC at 110 °C

1.2 Thesis objectives

a) Arenediyne crown ethers

Some enediyne macrocycles have been prepared previously with the intention of decreasing BC barriers upon complexation with various metals (figure 9). It is irrefutable that in the majority of cases, metal-induced BC has led to a decrease in the demanding energy barrier required for cyclization. It is intriguing that enediyne **15** is one of the very few examples where the BC barrier is elevated upon chelation. The thought of the synthesis of **16** being a good candidate for decreasing the BC barrier is justified, with the enediyne being enclosed in a cyclic network of ligating arms. The unreported BC reactions for this compound is puzzling, but it is possible that the aliphatic nature of these enediynes promoted destructive rearrangement (retro-Bergman) products or that temperature increases associated with the chelating structure of **16** encouraged decomposition/decomplexation. To this end, we envisioned an aromatic alternative of **16**, the synthesis of arenediyne crown ethers **23a** and **23b** (figure 11) where the retro-Bergman rearrangement product is not possible and where aromaticity is potentially advantageous (for the reasons stated above). Furthermore, **23** is also an improved thermal BC candidate by comparison to **15** owing to its cyclic nature. The excellent and notorious metal-binding ability of crown ethers make them ideal ligands for the purpose of investigating the effect of chelation on BC barriers; a valuable study especially with regard to cyclic ligating enediynes. The effect of ring size on **23** is particularly interesting for studying BC thermodynamics, since **23a** possesses one less ligating oxygen but exhibits additional strain by comparison with **23b**.

Figure 11 *– Some enediyne macrocycles previously prepared in literature a) tetraazearenediyne ligand prepared by Basak et al.[49,01] b) tetraazenediyne ligand prepared by Zaleski et al.[51] c) bipyridine macrocycle prepared by Konig et al.[52] d) enediyne crown ether by McPhee et al.[44] e)our proposed arenediynes.*

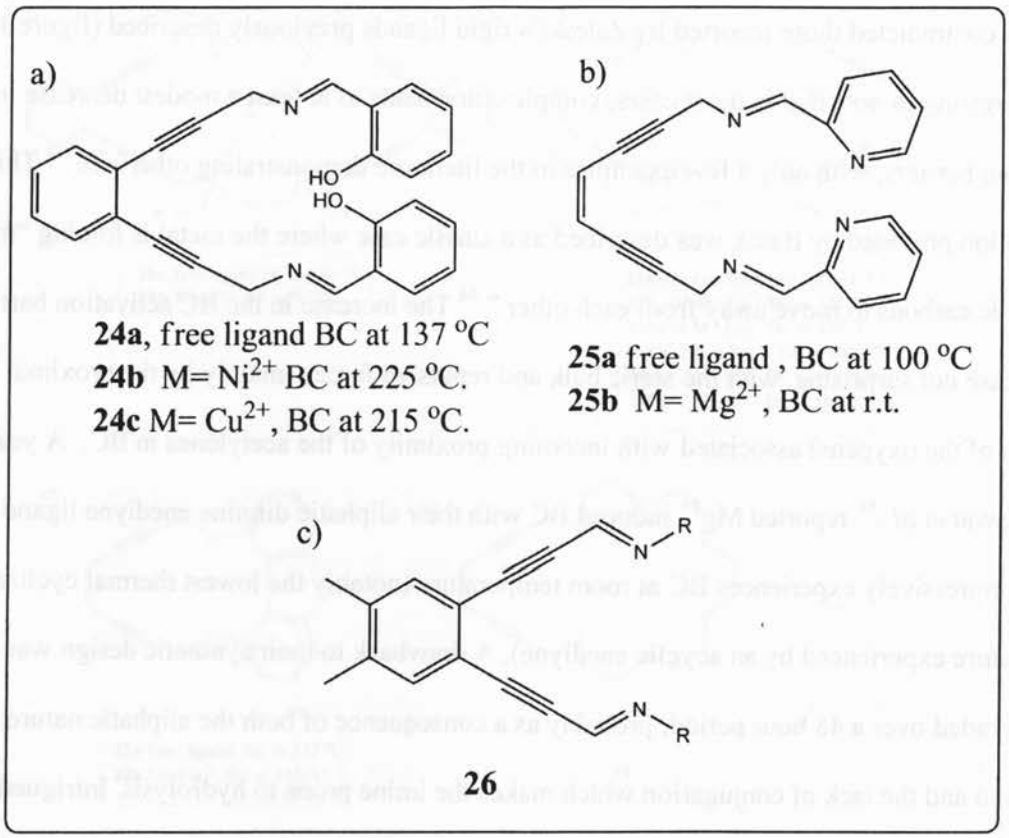


b) Arenediyne Imines and Hydrazones

In 2000, Basak reported the interesting behavior of his benzannulated diimine ligands upon complexation with Ni(II) and Cu (II) (figure 12, **24b** and **24c** respectively), where a significant increase in BC onset temperatures were reported by comparison with the free ligand.[53] These findings contradicted those reported by Zaleski's rigid ligands previously described (figure 10). It is interesting to note that in most cases, complexation leads to at least a modest decrease in BC activation barriers, with only a few examples in the literature demonstrating otherwise.[53] This explanation provided by Basak was described as a classic case where the metal is forcing "the acetylenic carbons to move away from each other." [54] The increase in the BC activation barrier is in this case not surprising, with the steric bulk and repulsive forces (mainly by the proximal position of the oxygens) associated with incoming proximity of the acetylenes in BC. A year later, Rawat *et al*.[54] reported Mg^{2+} induced BC with their aliphatic diimine enediyne ligand **25a** which impressively experiences BC at room temperature (notably the lowest thermal cyclization temperature experienced by an acyclic enediyne). A drawback to their synthetic design was that **25a** degraded over a 48 hour period, probably as a consequence of both the aliphatic nature of the ligand and the lack of conjugation which makes the imine prone to hydrolysis. Intrigued by the fascinating outcomes of these experiments, we wanted to prepare arenediyne Schiff bases with the general structure shown in figure 12 (structure **26**). Our design varies from **25a** in that the extended π system is likely to provide additional stability and favourable π-cation interactions upon chelation. Additionally, the sp^2 hybridization on the ligating nitrogen provides accompanying ligand rigidity, of vital importance especially with regard to acyclic enediyne ligands. Of particular interest is to observe the thermal BC behavior of these imines in the

presence and absence of metals and to see whether our imines are comparative to those previously synthesized.

***Figure 12**- Diimine ligands previously synthesized in literature a) arenediyne diimine prepared by Basak et al. [53] b) diimine ligand prepared by Rawat et al. [54] c) general structure for our arenediyne diimines*



In relation to this, the synthesis of hydrazone **27** is very attractive in that it could display self-quenching properties which we believe to be feasible through the existence of a structurally similar known persistent stable radical. The *p*-benzyne radical intermediate in BC has been very mysterious, with very few experimental data related to it, owing to its sharp lifetime.[27] Self-quenching enediynes have been known to exist, with donor subsituents being positioned in the ortho position[8] and in the 1,6 positions[33] (figure 13). The asymmetrical substitution in **28** and **29**

makes self-quenching feasible from only one end of the generated *p*-benzyne radical and an external hydrogen donor (i.e. 1,4-cyclohexadiene) is required to quench the opposite end. Our design should permit self-quenching from both ends intramolecularly. The kinetics of this is intriguing and should in our opinion, provide a more accurate quantitative study of these radicals.

***Scheme 4**- Proposed self-trapping mechanism for hydrzone 27.*

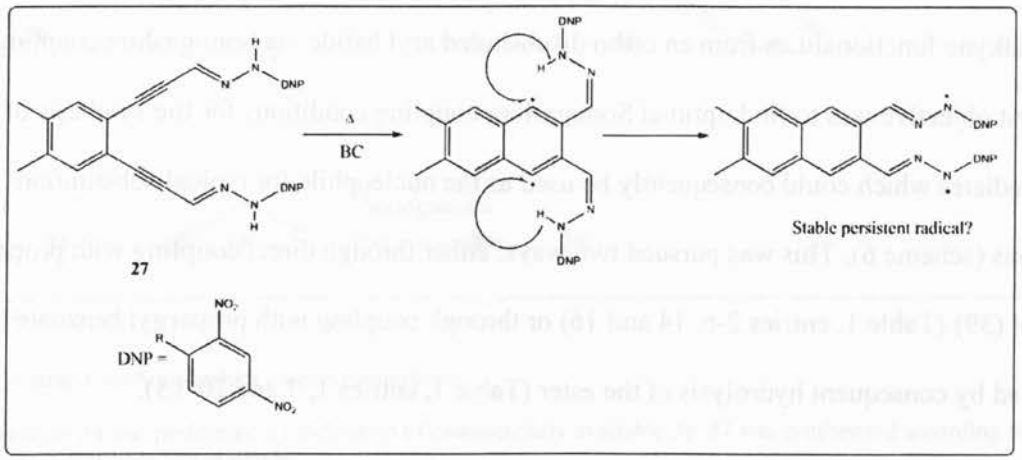
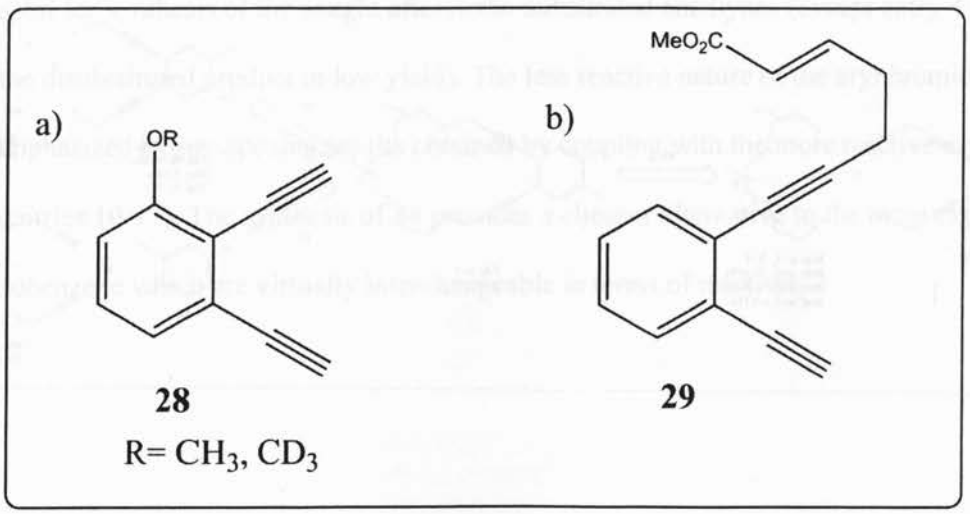


***Figure 13**- Self-trapping arenediynes previously synthesized.*

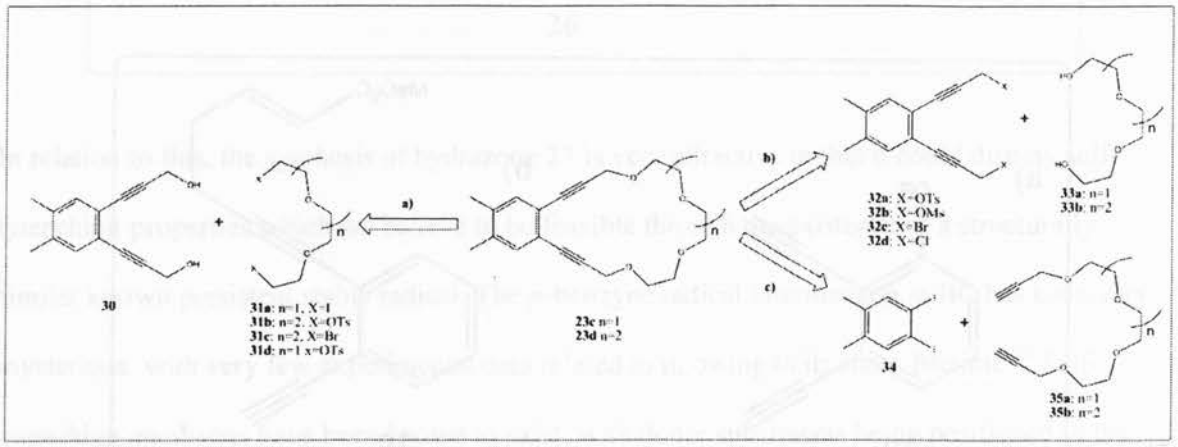


2. RESULTS AND DISCUSSION

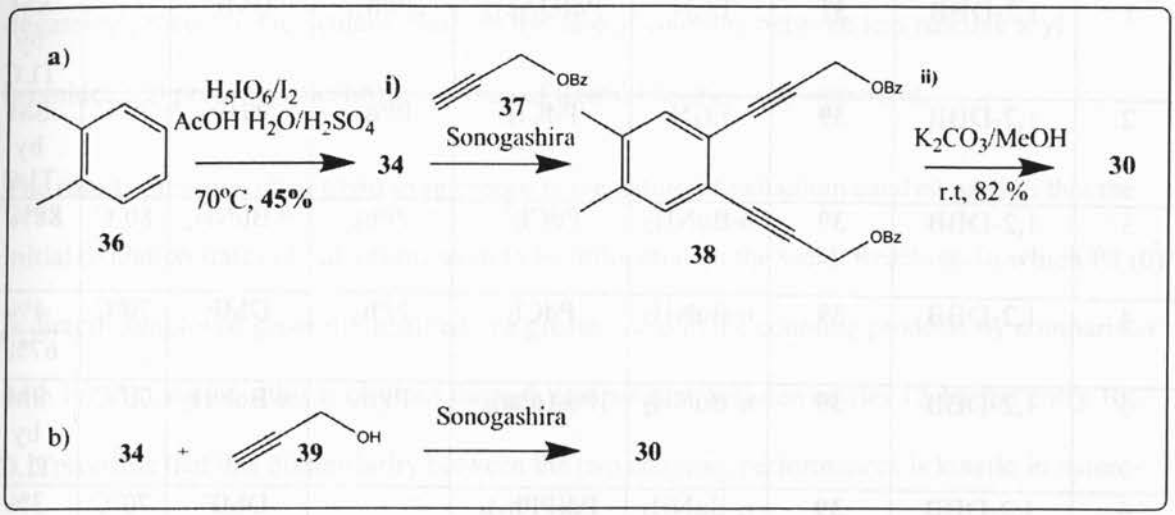
2.1 Crown Ether synthesis

Scheme 5 shows the initial one pot synthesis routes investigated for the synthesis of desired arenediyne crown ethers **23c** and **23d**. The arenediynes synthesized originated from introduction of the alkyne functionalities from an ortho disubsituted aryl halide via Sonogashira coupling.[55] The first objective was to find optimal Sonogashira coupling conditions for the synthesis of diol intermediates which could consequently be used as the nucleophile for typical substitution reactions (scheme 6). This was pursued two ways: either through direct coupling with propargyl alcohol (**39**) (Table 1, entries 2-6, 14 and 16) or through coupling with propargyl benzoate (**37**), followed by consequent hydrolysis of the ester (Table 1, entries 1, 7 and 10-13).

***Scheme 5**- Three disconnections investigated for the one pot synthesis of arenediyne crown ethers **23c** and **23d**: a) S_N2 subsitution where the arenediyne is the nucleophile b) S_N2 substitution where the arenediyne is the electrophile c) tandem Sonogashira coupling.*



Scheme 6- *Synthesis of diol intermediate used for nucleophilic substitution reactions a) i) synthesis of disubsituted ester through Sonogashira coupling [a] ii) hydrolysis of diester to give diol 30 b) Direct Sonogashira coupling[a] with commercially available 39 [b].*



a refer to table 1 for Sonogashira coupling conditions.

b Synthesis of **34** was performed by iodination of commercially available **36**. **37** was synthesized according to procedures in materials and methods.

Table 1 shows the Sonogashira coupling conditions for the synthesis of various arenediyne intermediates. Coupling with 1,2-dibromobenzene as the aryl halide (entries 1-8) proved to be unsuccessful for synthesis of the sought after *ortho*-substituted enediynes (except entry 4 that yielded the disubstituted product in low yield). The less reactive nature of the aryl bromides is further emphasized by juxtaposing results obtained by coupling with the more reactive aryl iodides (entries 10-17). The synthesis of **34** provides a cheaper alternative to the more expensive 1,2-diiodobenzene which are virtually interchangeable in terms of reactivity.

***Table 1**- Sonogashira Coupling reactions for the synthesis of various disubstiuted arenediyne intermediates*

Entry	Aryl halide	Alkyne	Base	Pd catalyst[a]	Ligand	Solvent	T(°C)	% Yield
1	1,2-DBB	**37**	Et_3N	$Pd(OAc)_2$	PPh_3	DMF	r.t.	SM by TLC
2	1,2-DBB	**39**	Et_3N	$PdCl_2$	PPh_3	THF	70°C	SM by TLC
3	1,2-DBB	**39**	*n*-$BuNH_2$	$PdCl_2$[b]	PPh_3	*n*-$BuNH_2$	80°C	88%[c]
4	1,2-DBB	**39**	*n*-$BuNH_2$	$PdCl_2$	PPh_3	DMF	70°C	4%
								67%[c]
5	1,2-DBB	**39**	*n*-$BuNH_2$	$Pd_2(dba)_3$	PPh_3	*n*-$BuNH_2$	70°C	SM by TLC
6	1,2-DBB	**39**	*n*-$BuNH_2$	$Pd(PPh_3)_4$	-	DMF	70°C	3%
								70%[c]
7	1,2-DBB	**37**	Et_3N	$Pd(PPh_3)_4$	-	DMF	70°C	SM by TLC
8	1,2-DBB	TMSA	Et_3N	$PdCl_2$	PPh_3	THF	60°C	SM by TLC
9	**34**	TMSA	Et_3N	$PdCl_2$	PPh_3	THF	40°C	SM by TLC
10	**34**	**37**	Et_3N	$PdCl_2$	PPh_3	Et_3N	60°C	23%
11	**34**	**37**	Et_3N	$PdCl_2$	PPh_3	Toluene	60°C	16%
12	**34**	**37**	Et_3N	$Pd(PPh_3)_4$	-	Et_3N	60°C	65%
13	**34**	**37**	DIPA	$Pd(PPh_3)_4$	-	DIPA	60°C	45%
14	**34**	**39**	Et_3N	$Pd(PPh_3)_4$	-	Et_3N	70°C	82%
15	**34**	**37**	Et_3N	$Pd(PPh_3)_4$	-	Et_3N	60°C	80%[d]
16	**34**	**39**	Et_3N	$Pd(PPh_3)_4$	-	Et_3N	r.t.	90%
17	1,2-DBB	**39**	Et_3N	$PdCl_2$	H-P(*t*-Bu)$_3BF_4$	THF	r.t.	25%[c]

[a] unless otherwise stated, CuI was used as a copper cocatalyst.; [b] $Cu(OAc)_2.H2O$ was used as co-catalyst [c] isolated monosubstituted product; [d] freeze-pump-thaw technique. 1,2-DBB = 1,2-dibromobenzene, TMSA = trimethylsilyl acetylene.

The result in entry 9 is perplexing, but failure to generate any product is likely due to the high vapour pressure of TMS acetylene where entry into the gas phase is facilitated by the preliminary degassing process in the Schlenk flask. In the case of coupling between less reactive aryl bromides and propargyl alcohol the choice of ligand becomes very important.[56]

The results present a clear trend in reference to the nature of palladium catalyst used in that the initial oxidation states of palladium seem to be influential on the yield. Reactions in which Pd (0) is directly employed generally resulted in a greater yield in the coupling products by comparison with Pd (II) catalysts (this is obvious through comparisons between entries 12-16 and entry 10). It is probable that this dissimilarity between the two coupling performances is kinetic in nature- where the Pd(0) experiences a faster oxidative addition step by comparison with Pd(II), which needs to be reduced before being converted to the active catalytic species. This could be enough to facilitate the Glaser coupling, [57] where the coupling between the alkynes generates a homo coupled product, thereby exhausting the alkyne and copper resources in the reaction mixture. In the addition of the PPh_3 ligands separately *in situ*, the assumption that all existing palladium sources will be reduced is tentative. While there have been many examples of Pd (II) catalyzed Sonogashira coupling reactions, the choice of ligand has also changed invariably to promote higher yields. Once again, varying electronic and steric properties of the ligand through introduction of the bulkier ligand seem to promote an increase in the yield. The relationship between varying ligand properties and efficiency of coupling remains unclear, but it is presumed that sterically hindered phosphane ligands promote facile oxidative addition and reductive elimination steps.[56]

Many preceding studies, such as the study by Gelman and Buchwald [58] have eliminated copper co-catalysts altogether, when they found that CuI either inhibited the reaction or decreased the yields significantly. This is likely due to an increased rate in the Glaser homo coupling, which is known to be facilitated by the presence of these copper catalysts and is more specifically problematic for less reactive aryl halides (aryl chlorides and to some extent, the aryl bromides) which exert stronger influences on reaction rates.[56] This is perhaps a contributing factor to the low yields in some entries, but this effect if present, is not considered substantial since without exclusion of CuI, entries 14-17 are able to generate excellent yields. Entry 3 is unusual in that a copper (II) promoter was able to achieve effective coupling, a very unconventional choice in Sonogashira coupling where copper (I) promoters are traditionally used. In this case, it is questionable whether modification of coupling conditions, such as ratio of alkyne to aryl halide could promote higher yields of *ortho* substituted products.

The best results were attained when amines were used neat in accordance with original Sonogashira coupling conditions.[55] With reductive elimination being the rate determining step and with the amine/base having an integral role in this phase of the mechanism, it becomes clear that the choice of base (more specifically amines) is critical kinetically.[59] The use of triethylamine as the solvent afforded higher yields than when *n*-$BuNH_2$ (entries 3 and 4) and diisopropylamine (DIPA) (entry 13) were used as the solvent. Previous studies have reported high coupling yields with the use of both *n*-$BuNH_2$ and DIPA [75] and the kinetic mechanistic studies by Tougerti *et al.* suggests that the use of secondary amines promote an accelerating effect in the oxidative addition step.[59] In the latter study, piperidine was found as a great model amine, which evidently mirrors the basicity of triethylamine, *n*-$BuNH_2$ and DIPA. It is difficult to perform a comparative study between the amines used, since the aryl halide was varied in

entries with *n*-$BuNH_2$, which is a likely reason for the decelerating effect of the reaction. In spite of this, it is assumed and likely that under similar conditions (i.e. use of the aryl iodide), *n*-$BuNH_2$ is expected to generate results similar to when Et_3N was used. The use of DIPA is noticeably responsible for the decrease in yield when comparing entries 12 and 13 where only the base was varied.

Despite success with the use of this base in previous Sonogashira coupling conditions, DIPA is not ideal for the coupling reactions shown. Given the basicity and nature of DIPA (i.e being a secondary amine) the reason for the poor yields is perplexing. Table 1 also shows that using alternative solvents results in appreciably lower yields. The importance of deaerated reaction conditions is emphasized when entries 12 and 15 are compared, where the latter entry ensured inert conditions through the use of the "freeze-pump- thaw" technique (generating a 15% increase in the yield).

The majority of the reactions were performed with the application of heat, but performing the reaction at room temperature proved to be valuable (comparison between entries 14 and 16). Increasing reaction temperature has been linked to dramatically facilitating the Glaser coupling side reaction, which could account for the lower yield in entry 14. Only slight % yield differences were found between the two entries. Thus it would be premature to suggest that temperature changes are detrimental in the coupling reactions shown, especially when considering entry 16 where a high yield was obtained.

The synthesis of crown ethers have for sometime been very challenging and often inefficient due to competing side-reactions.[62] Currently, three general synthetic strategies have been devised to minimize this effect and promote cyclization:

1. The high dilution principle, whereby carrying the reaction out under dilute conditions prevents/minimizes intermolecular interactions.[62]
2. The template effect, whereby an incorporated metal encourages intramolecular cyclization.[62]
3. The cesium effect, where electronic variations promote cyclization.[62,63]

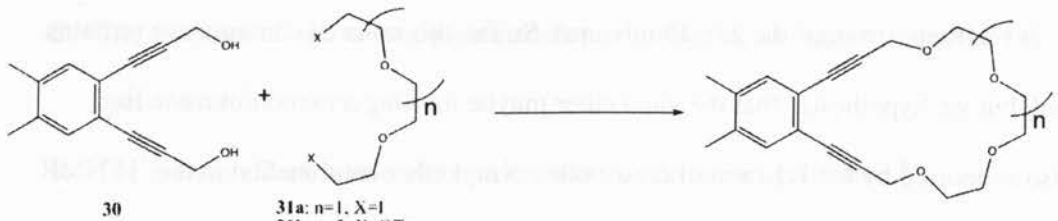
Conventional crown ether syntheses through typical nucleophilic substitution via deprotonation of 30 were unsuccessful for the synthesis of the desired crown ethers **23c** and **23d**. Table 2 shows the conditions used when **30** is used as a nucleophile. In all cases, starting material was recovered, with the exception of entries 9 and 10 where **23c** was synthesized in low yields. Initially, we attempted the synthesis of **23c** and **23d** with synthesized ditosylates **31b** and **31d**, but this resulted in complicated mixtures and unidentified products, in accordance with McPhee and Kerwin's findings.[44] The authors attributed this to the instability of the enediyne in the strongly basic conditions necessary for alkylation which is strongly supported by the fact that the enediynes undergo isomerization to more reactive allene-eneynes through Myers-Saito cyclizations under such conditions.[64] The recovery of starting material is puzzling, but it is likely attributable to consumption of the electrophiles in elimination side-reactions, where the basic conditions seem to be predominantly promoting elimination, leading to vinyl ether synthesis. Treatment with Cs_2CO_3 (entry 7) was carried out to facilitate ring closure after reports claimed the use of cesium salts afforded higher yields in crown ether synthesis.[63] This had no effect on the outcome of the reaction. The low yield afforded by entries 9 and 10 could be credited to the iodide's leaving group ability which is manifested kinetically. Unfortunately, the reaction generated vinyl elimination by-product **40** which could not be chromatographically separated from arenediyne crown ether **23c** (mass spectrometry confirms the presence of both species).

Interestingly, **40** was isolated in its pure form and exhibited very different TLC behavior to the crown ether/vinyl ether combination, possibly suggesting an affinity between the two (figure 14 shows the ^{1}H NMR spectrum of the **23c/40** mixture). So far, this unusual consequence remains unexplained, but we hypothesize that the vinyl ether maybe forming a pseudorotaxane like species (also supported by the 1:1 ratio of crown ether: vinyl ether combination in the ^{1}H NMR spectrum, figure 14).

Our findings encouraged us to investigate alternate routes towards the synthesis of arenediyne crown ethers **23**. Consequently, we attempted conversion of **30** to electrophiles **32a-e**, (scheme 5b) which we envisioned could be reacted with glycols **33a** and **33b** under similar conditions. Ditosylate **32a** could not be isolated in its pure form, though ^{1}H NMR showed the presence of characteristic tosylate peaks. The crude mixture was allowed to react in a substitution reaction, but resulted in complicated mixtures by TLC. Synthesis of mesylate **32b** was performed with the intention of bromination to **32c**. Procedures towards the step-wise synthesis was identical to Basak's methodology,[49] but attempts at synthesizing **32b** were unsuccessful resulting in only starting material and/or monosubstituted bromo/mesylate products.

Attempts at synthesizing and isolating **32d** failed, with the generation of what initially appeared to be the disubstituted dichloride **32d** by ^{1}H NMR, but was later found to be inconsistent with the m/z peaks. Instead, the mass spectrum was indicative of a structure that possessed additional chlorides (m/z =320 and m/z= 285/287) which was confirmed to be Bergman products **41** and **42** (scheme 7). The reaction generated these products through quenching of the *p*-benzyne radicals with chlorine atoms (presumably supplied by thionyl chloride), at just 70 °C, very different thermal behavior from when diol **30** was heated directly at comparatively elevated temperatures with 1,4-CHD as the quencher (see following paragraphs for a discussion of BC of diol **30**).

Table 2- Attempted one-pot S_N2 substitution for the generation of crown ethers 23c and 23d when diol 30 is the nucleophile.



30

31a: n=1, X=I
31b: n=2, X=OTs
31c: n=2, X=Br
31d: n=1 x=OTs

23c n=1
23d n=2

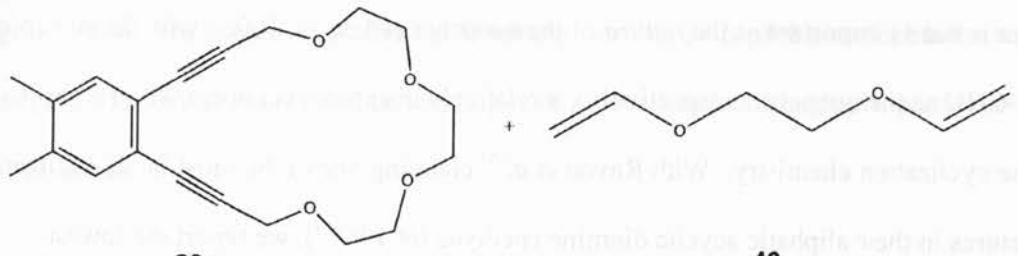
Entry	Electrophile	Base	T (°C)	Solvent	Concentration (M)	% Yield
1	**31b**	NaH	80	THF	0.15	SM by TLC[a]
2	**31b**	NaH	80	THF	0.10	SM by TLC[a]
3	**31b**	NaH	80	THF	0.03	SM by TLC
4	**31b**	KO-t-Bu	40	t-BuOH/dioxane	0.03	SM by TLC[a]
5	**31b**	KO-t-Bu	40	t-BuOH/dioxane	0.36	SM by TLC[a]
6	**31b**	KO-t-Bu	70	t-BuOH/dioxane	0.05	SM by TLC[a]
7	**31b**	NaH/Cs_2CO_3[b]	90	THF	0.03	SM by TLC
8	**31b**	NaH	80	DMF	1.00	SM by TLC
9	**31d**	NaH	80	THF	0.24	4%[c]
10	**31d**	NaH	80	THF	0.30	6%[c]
11	**31c**	NaH	75	THF	0.20	SM by TLC

[a] additional spots were present by TLC, but could not be identified by NMR.

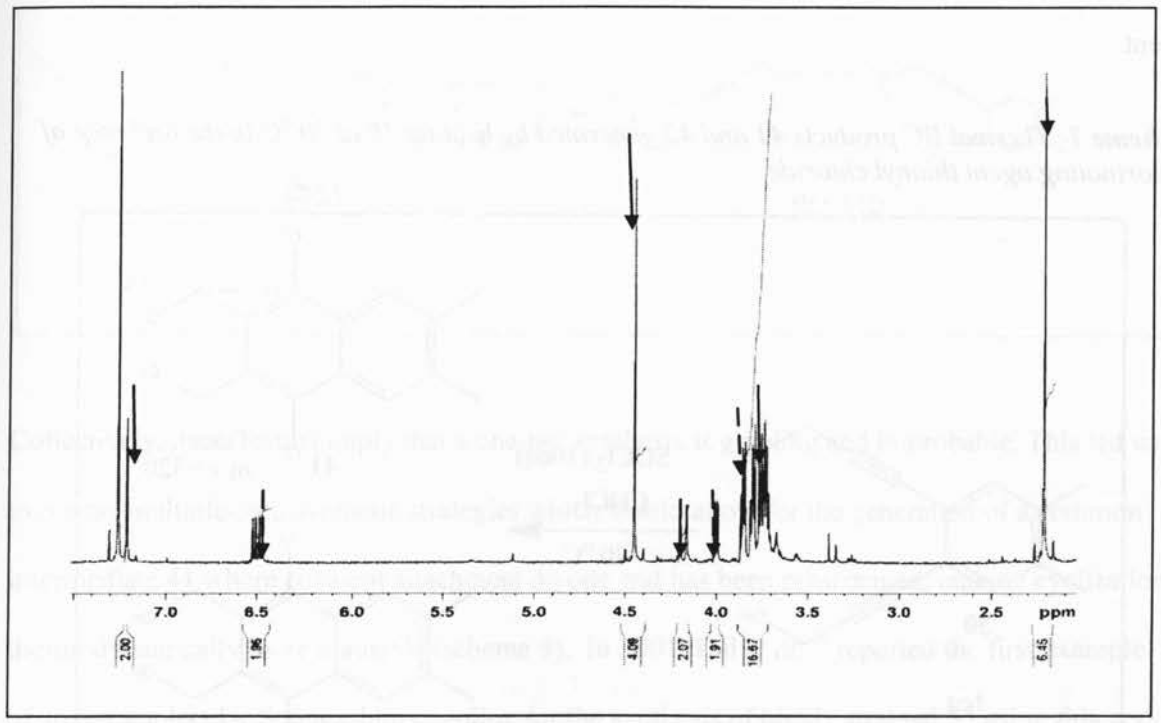
[b] NaH: Cs_2CO_3 = 2:1

[c] isolated product could not be obtained, yield based on a combination of vinyl ether **40** and crown ether **23c** (see figure 14).

Figure 14- *^{1}H NMR spectrum of crown ether **23c** and vinyl by-product **40** (isolated in a 1:1). Protons corresponding to **40** are shown with dashed arrows and solid arrows denote protons in **23c**.*



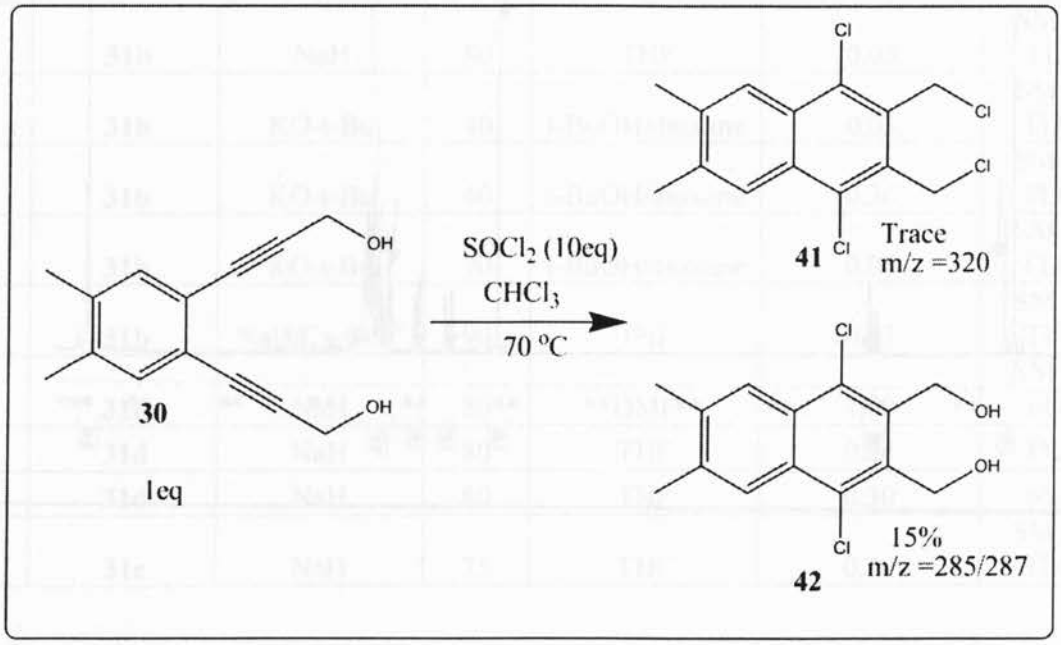
23c **40**



BC product **41** illustrates a classic example where variation of electronic properties at the acetylenic positions allows for dramatic influences in thermal behavior. The presence of **42** as the dominant product is captivating (as indicated by relative abundances) because failure of chlorination at the acetylenic position preserves the electronic properties of **30**.

This result (by comparison with direct BC attempts with **30**) possibly indicates a discriminatory effect in relation to the quencher involved. It may also indicate that the concentration of quencher is not as important as the *nature* of the quencher (10 eq vs. 100eq with thionyl chloride and 1,4-CHD as the quenchers respectively), a relatively unexplored concept with respect to enediyne cyclization chemistry. With Rawat *et al.*[65] claiming one of the most facile cyclization temperatures in their aliphatic acyclic diamine enediyne (at 106°C), we report the lowest temperature to date for a non-coordinated acyclic enediyne with an unconventional trapping agent.

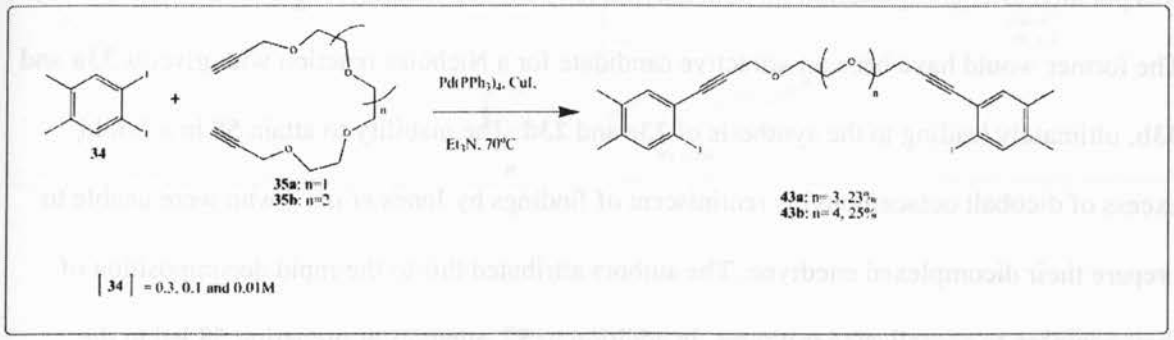
***Scheme** 7- Thermal BC products **41** and **42** generated by heating **30** at 70 °C in the presence of chlorinating agent thionyl chloride.*



Tandem Sonogashira attempts through coupling of **34** with synthesized diynes **35a** and **35b** resulted in arylation on both ends to give the structures **43a** and **43b** respectively. We proposed that dramatically diluting the reaction would result in mono arylation, but this continued to preferentially generate **43a** and **43b** and prevented the synthesis of the desired product. Attempts

at cyclization through this method were attempted again, where Na_2CO_3 was strategically chosen to facilitate cyclization through an assumed metal-template effect (data not shown). This led to analogous results. The presence of identical leaving groups on **34** is problematic, but the results also suggest that cyclization is more demanding making cyclization through this particular method doubtful.

***Scheme 8**- Attempted Tandem Sonogashira coupling gave products **43a** and **43b**, with no evidence of any formation of intramolecular cyclization products **23c** and **23d**.*

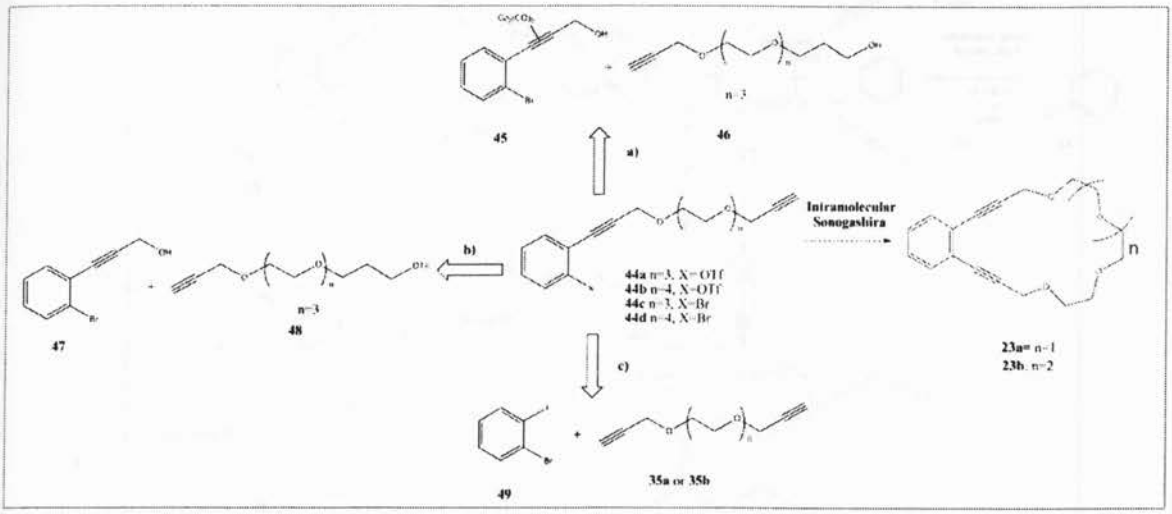


Collectively, these results imply that a one-pot synthesis is grueling and improbable. This led us to pursue multiple-step synthetic strategies which would allow for the generation of a common intermediate **44** where covalent attachment on one end has been prearranged, making cyclization thermodynamically more plausible (scheme 9). In 2001, Dai *et al.* [66] reported the first example of an intramolecular Sonogashira coupling for the synthesis of highly strained **53** using this very ideology (scheme 10). We speculated that under very dilute conditions, we would be able to optimize conditions for the synthesis of **23a-b**, which fortunately do not possess the strain exhibited by **53**. Initially, we attempted a Sonogashira coupling using a 4-fold excess of diynes **35a** and **35b** , in hope of synthesizing **44e** (scheme 11). Regrettably, the synthesis of **44e** could not be achieved through this method and instead, resulted in the synthesis of **43c** and **43d**. This result was surprising given the reaction conditions (i.e. excess diyne). For further investigation,

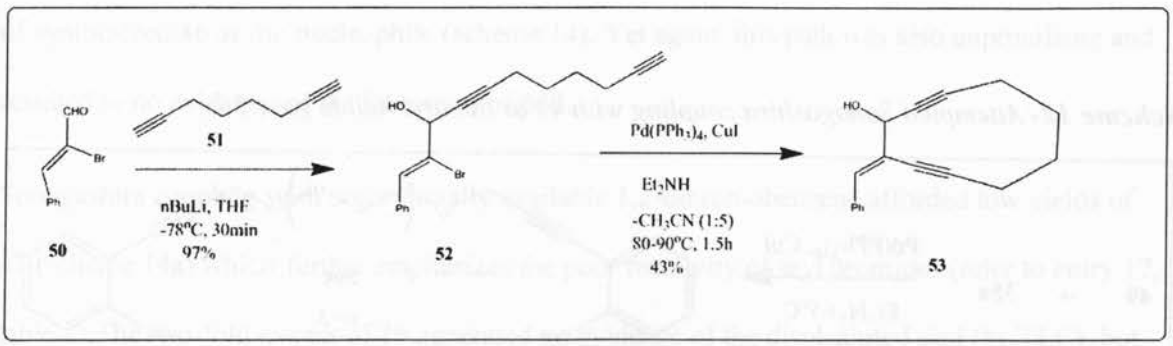
we attempted a similar route through Sonogashira coupling with **49** (scheme 9c). As before, the diarylated product **56e** was the only product isolated and identified (scheme 12). Consequently, the proposed synthetic strategy proposed in scheme 11 and 12 showed no promise and was abandoned.

With the Nicholas reaction being predominantly used in the synthesis of the enediyne antibiotics,[67] we attempted a Nicholas reaction between **45** and **46** (path a, scheme 9). This route was pursued after complexation on both alkynes (**57**) could not be derived from **30** (scheme 13). The former would have been an attractive candidate for a Nicholas reaction with glycols **33a** and **33b**, ultimately leading to the synthesis of **23c** and **23d**. The inability to attain **58** in a 5-fold excess of dicobalt octacarbonyl is reminiscent of findings by Jones *et al.*,[34] who were unable to prepare their dicomplexed enediyne. The authors attributed this to the rapid decomposition of their complex to complicated mixtures. In addition to **57**, attempts at preparing **58** led to the isolation of various compounds that could not be identified by NMR spectroscopy. The instability reported by Jones *et al.* is difficult to account for since introduction of $Co_2(CO)_6$ at the acetylenic positions have in previous literature sources accounted for reduced strain and even promoted stability by comparison to unbound counterparts.[68] For this reason, failure to prepare **58** is not likely steric-related. Dramatic variation of electronic properties of the conjugated system through complexation at one end is perhaps a more valid explanation. Literature examples where complexation is carried out on both ends of the enediyne are scarce.[67]

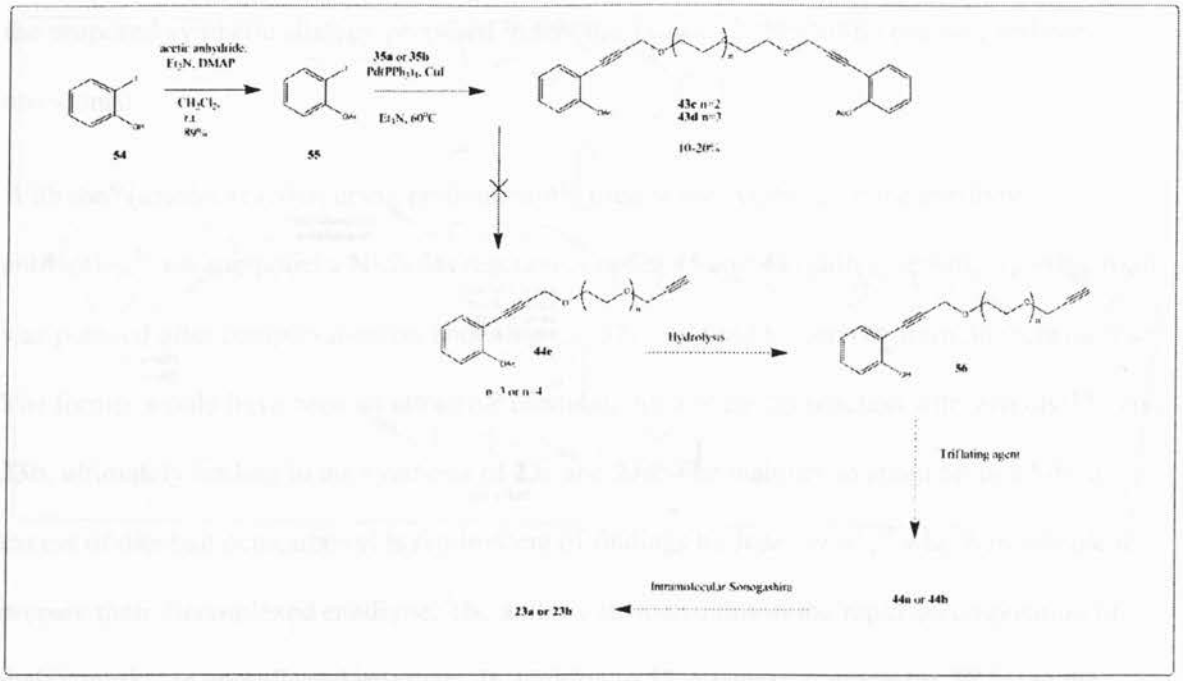
***Scheme 9**- Disconnections explored for the step-wise synthesis of crown ether **23** via common intermediate **44** a) Nicholas reaction for the generation of **44c** and **44d** b) S_N2 where **48** is the electrophile. d) direct Sonogashira with **49**.*



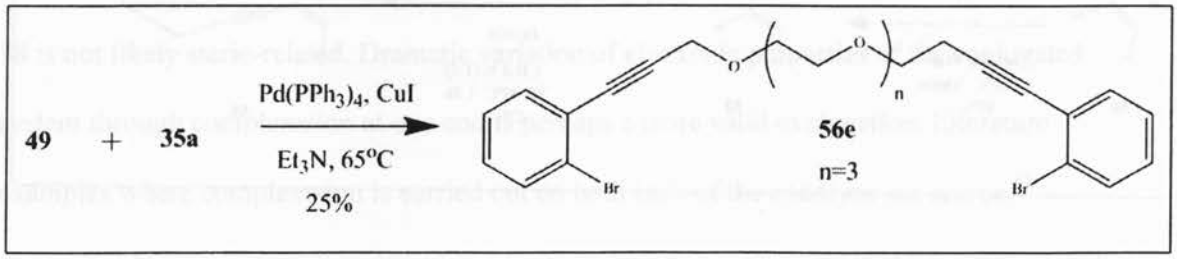
***Scheme 10**- Two-step synthesis of a highly strained deca-1,5-diyne **53** via intramolecular Sonogashira coupling, as reported by Dai.et al.* [66]



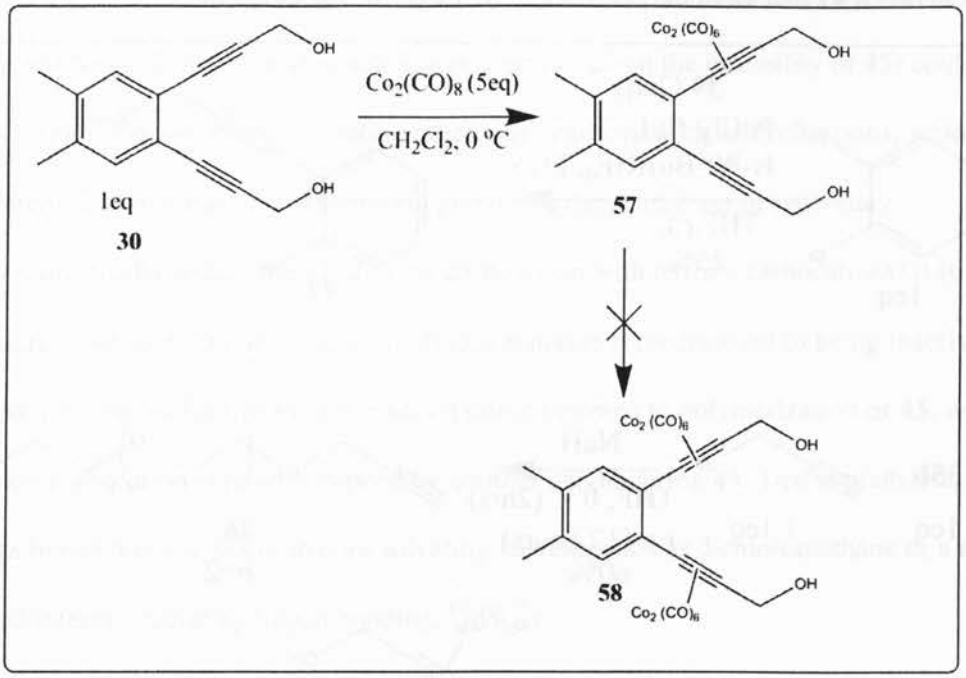
***Scheme 11**- Attempted synthesis of **44e** was unsuccessful via Sonogashira coupling with acetate 51. Dashed arrows represent planned synthetic strategy toward **23a** or **23b** given the successful synthesis of **44e**.*



***Scheme 12**- Attempted Sonogashira coupling with **49** as the aryl halide gave **56e**.*



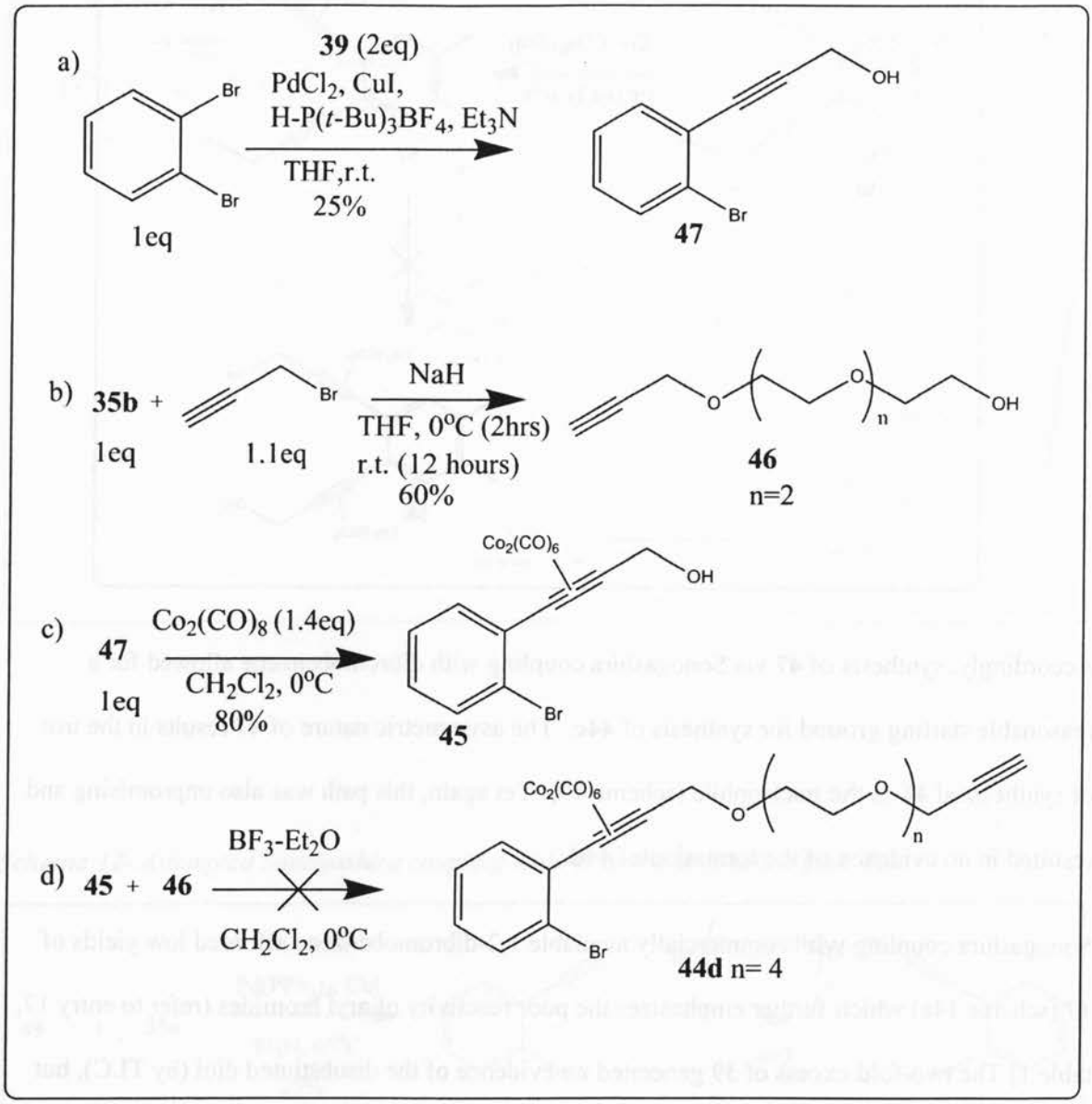
***Scheme 13**- Treatment of **30** with dicobalt octacarbonyl led to formation of **57** with no further complexation to **58**.*



Accordingly, synthesis of **47** via Sonogashira coupling with dibromobenzene allowed for a reasonable starting ground for synthesis of **44c**. The asymmetric nature of **47** results in the use of synthesized **46** as the nucleophile (scheme 14). Yet again, this path was also unpromising and resulted in no evidence of the formation of **44d**.

Sonogashira coupling with commercially available 1,2-dibromobenzene afforded low yields of **47** (scheme 14a) which further emphasizes the poor reactivity of aryl bromides (refer to entry 17, table 1).The two-fold excess of **39** generated no evidence of the disubstiuted diol (by TLC), but other species with considerably low R_f's (which also happened to stain $KMNO_4$) suggests the consumption of **39** in polymerization as a more favourable route under these experimental conditions.

Scheme 14- *Route towards the synthesis of 43d a) preparation of* ***47*** *via Sonogashira coupling b) Synthesis of propargyl ether* ***46*** *c) complexation with* $Co_2(CO)_8$ *to give* ***45*** *d) Attempted Nicholas reaction between* ***45*** *and* ***46*** *in the presence of* BF_3-Et_2O *as the Lewis acid.*



Complexation to give **45** (scheme 14c) was undemanding, but it soon became obvious that **45** was easily prone to decomplexation to **47**. This behaviour is atypical of derived complexed cobalt carbonyl propargyl species, since they have been previously known to be conveniently air stable.[68] Attempted Nicholas reaction (scheme 14d) with **45** and **46** resulted in **47** and other

complicated mixtures that could not be identified by NMR, with no evidence of the formation of the alkylated alkyne **44d**. The presence of the alkyne functionality in **46** could be a reason for this, where residual cobalt carbonyl in solution (especially given the instability of **45**) could have resulted in further complexation, promoting other side-reactions such as cyclizations, which have been documented in literature.[67] Furthermore, given that the generation of secondary carbocations drastically reduce the yield [67] (by comparison with tertiary carbocations) it is likely that the nature of **45** as a primary reactant in this case makes it predisposed to being inactive. The complicated mixtures isolated from this reaction could be owed to polymerization of **45**, where the generated carbocation is rapidly trapped by another neighbouring **45**. This is plausible, given that this has been known to occur in poor solvating solvents such as dichloromethane as a result of promoted intermolecular hydrogen bonding. [67, 69-71]

Preparation of **44d** via a typical substitution reaction with **47** as the nucleophile and **48** as the electrophile were unsuccessful (scheme 9c). It is notable that **47** was recovered in good % recovery, reminiscent of results obtained by scheme 5a. With time, tosylate **48** was consumed, probably in the formation of a vinyl elimination product which is facilitated by the strongly basic conditions, and the labile nature of the leaving group.

2.2. Synthesis of Arenediyne Schiff Base and Hydrazone Podands

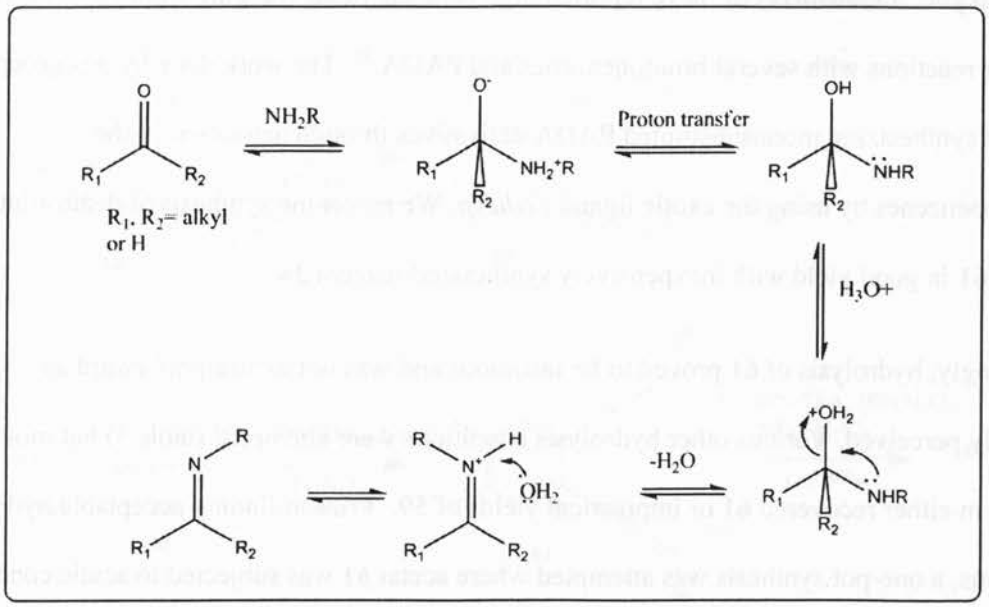
Imine synthesis is usually a reversible acid catalyzed process and with optimized conditions, can lead to versatile and high-yielding syntheses (scheme 15).[72] Often times, nucleophilic attack is a slow process with equilibrium favouring the parent carbonyl being of particular concern.[72] The challenge lies in finding the appropriate conditions, since the presence of acid is required for the formation of the iminium ion (through protonation of the hydroxyl) but conversely, in a highly

acidic environment, nucleophilic addition can be prevented from occurring.[72] At the same time, the chemistry of the carbonyl functionality can be taken advantage of, with the electronegativity of the attached oxygen and the trigonally hybridized carbon making the carbon prone to nucleophilic attack .[73] This point is especially valid for aldehydes, where reactivity is enhanced through obvious electronic and steric properties.

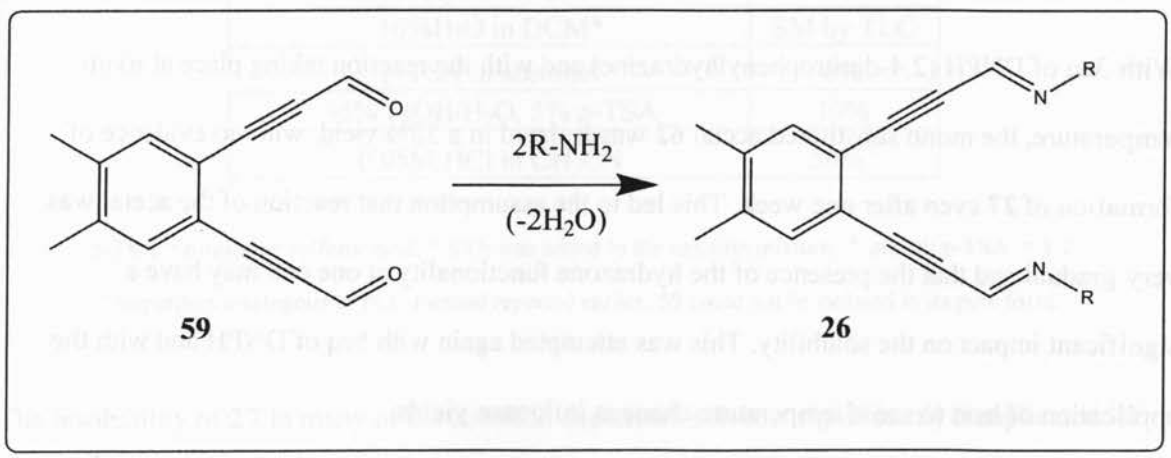
While nitrogen based enediynes have been extensively synthesized [49-52,54,74,75] the enediyne diimines **24a** and **25a** aforementioned are the only known disubstiuted imino ligands synthesized in literature. As previously mentioned, the sp^3 hybridized carbon disconnecting the sp^2 hybridized nitrogen can have severe consequences both thermodynamically and especially in relation to stability. The authors have synthesized their enediynes through a condensation reaction where the enediyne is the amine. We envisioned a synthesis of diimine ligands with extended π-systems through an enediyne aldehyde **59** in which a simple condensation with various amines would give a diimine with the general structure in **26** (scheme 16). This design is also advantageous in relation to metal-induced thermal activations, where π-complexation usually results in geometric and electronic influences manifested through a decreased the thermal activation barrier.[54]

Initially, synthesis of **59** was attempted through mild oxidation of **30** with PCC (scheme 17a). The reaction afforded a 28% yield of **59**. The low yield and the considerable mass of polymeric material generated by this method persuaded us to pursue additional routes towards **59**. Furthermore, this method prevented **59** from being isolated in its pure form, with persistent impurities visible by ^{1}H NMR spectroscopy.

Scheme 15- *Mechanism for acid-catalyzed nucleophilic addition reaction for the formation of an imine.*



Scheme 16- *A general condensation reaction for the synthesis of diimine ligands with the general structure* ***59*** *through a vital enediyne dialdehyde precursor* ***59****.*



Sonogashira coupling with commercially available propiolaldehyde diethyl acetal (PADA) (**60**) was used to synthesize a diacetal intermediate **61** , which was then hydrolyzed to **59** using the conditions shown in scheme 17b. Noteworthy is the impressive yield obtained in the synthesis of

59 with exactly 2eq of **60**, since the Sonogashira coupling conditions denoted in table 1 required excess alkyne. Lemhadri *et al.* have reported high isolated yields (ranging from 70-94%) for coupling reactions with several bromobenzenes and PADA.[76] The work done by this group was aimed at synthesizing monosubstituted PADA derivatives through activation of the dibromobenzenes by using the exotic ligand *Tedicyp*. We report the synthesis of disubstituted product **61** in good yield with inexpensively synthesized reagent **34**.

Surprisingly, hydrolysis of **61** proved to be fastidious and was not as straightforward as originally perceived. Various other hydrolysis conditions were attempted (table 3) but mostly resulted in either recovered **61** or impractical yields of **59**. Prior to finding acceptable hydrolysis conditions, a one-pot synthesis was attempted where acetal **61** was subjected to acidic conditions in the presence of the hydrazine/amine This route was based on the assumption that **61** could be converted directly to **26**, with the release of ethanol from the acetal, rather than water from the aldehyde **59**. Scheme 18 shows our efforts to synthesize hydrazone **27** in this fashion.

With 3eq of DNPH (2,4-dinitrophenylhydrazine) and with the reaction taking place at room temperature, the mono substituted acetal **62** was isolated in a 58% yield, with no evidence of formation of **27** even after one week. This led to the assumption that reaction of the acetal was very gradual and that the presence of the hydrazone functionality at one end may have a significant impact on the solubility. This was attempted again with 5eq of DNPH and with the application of heat to see if temperature changes influence yields.

***Scheme 17**- Synthesis of **59** a) via oxidation with PCC b) **61** was synthesized via Sonogashira with commercially available **60**, followed by hydrolysis of **61**.*

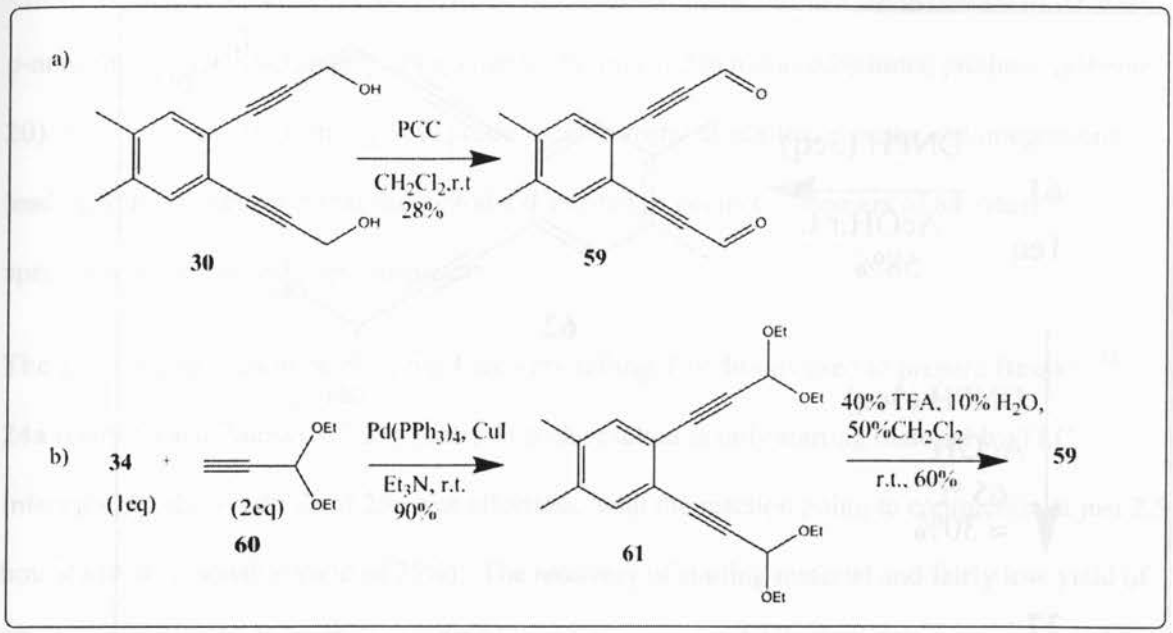


***Table 3**- Hydrolysis conditions for the conversion of **61** to **59**.*

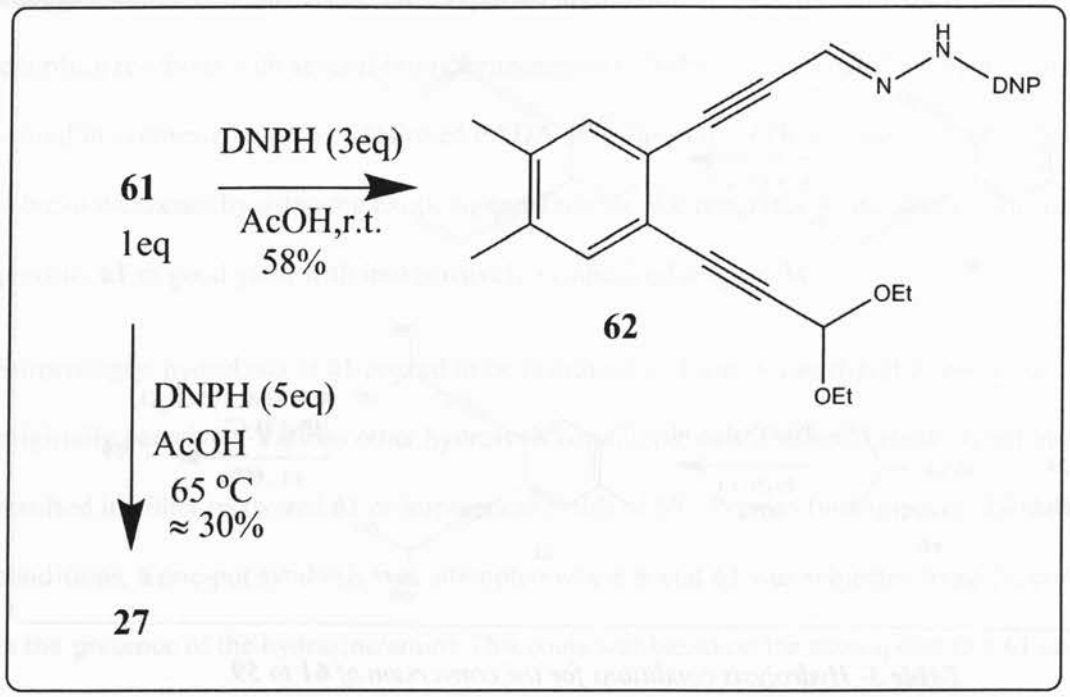
Hydrolysis conditions	% yield of 59
10%H_2O in DCM*	SM by TLC
p-TSA in acetone[a]	6%
95% EtOH/H_2O, 5% p-TSA	10%
0.05M HCl in CH_3CN	50%[b]

p-TSA = p-toluene sulfonic acid, * SiO_2 was added to the reaction mixture, [a] acetal: p-TSA = 1:2

[b] impurities analogous to PCC method reported earlier, **59** could not be isolated in its pure form.

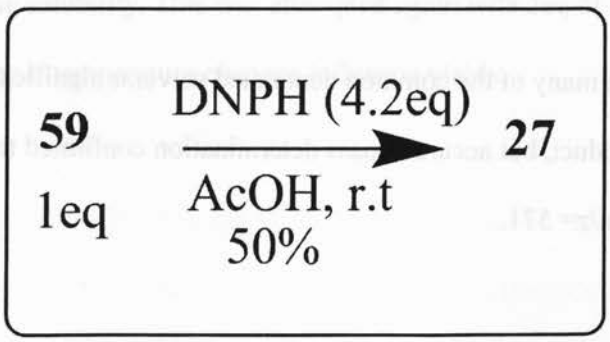
The insolubility of **27** in many of the common deuterated solvents significantly complicated ^1H NMR of the isolated product, but accurate mass determination confirmed the presence of **27** through a MH^+peak at m/z= 571.

***Scheme 18**- One-pot synthesis of 27 via acetal intermediate 61.*



Synthesis of **27** by direct condensation with **59** afforded **27** in a 50% yield (scheme 19). No heat was applied, but the 20% increase in yield indicates the reaction occurs at milder conditions through **59**. The isolated hydrazone from this reaction was also confirmed by accurate mass determinations.

***Scheme 19**- Synthesis of 27 via dialdehyde 59.*

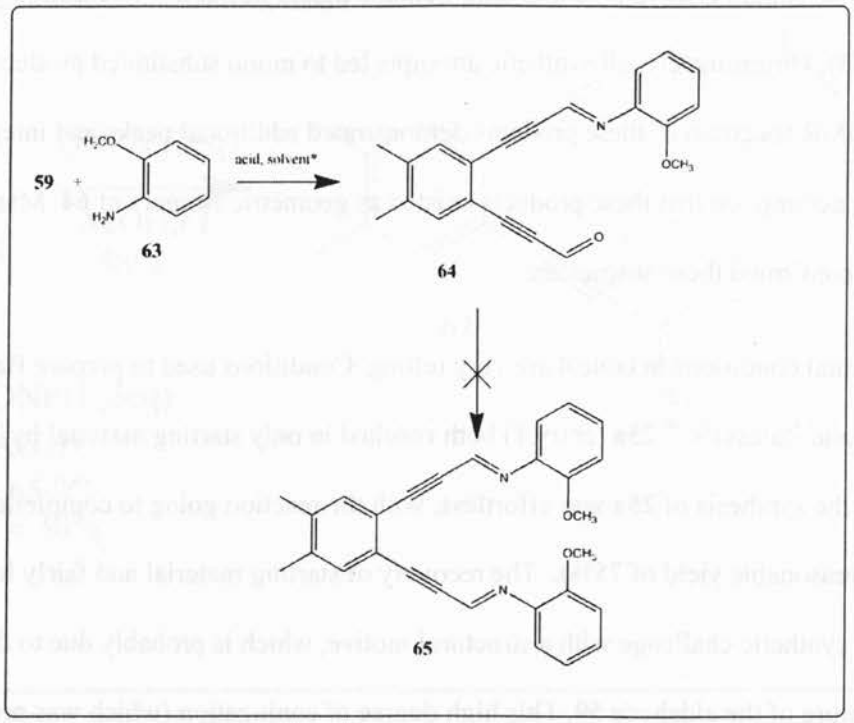


Asymmetrical substitution was also encountered when the synthesis of **65** was attempted. Enediyne **65** was sought after as potential tetra-dendate ligand through condensation of **59** with *o*-anisidine (**63**). Unfortunately, all synthetic attempts led to mono substituted products (scheme 20). The ^{1}H NMR spectrum of these products demonstrated additional peaks and integrations, leading to the assumption that these products existed as geometric isomers of **64**. Mass spectrometry confirmed these suspicions.

The experimental conditions in table 4 are very telling. Conditions used to prepare Basak's [53] **24a** (entry 5) and Zaleski's [54] **25a** (entry 1) both resulted in only starting material by TLC. Interestingly, the synthesis of **25a** was effortless, with the reaction going to completion at just 2.5 hours(with a reasonable yield of 75%). The recovery of starting material and fairly low yield of **64** suggests a synthetic challenge with a structural motive, which is probably due to the highly conjugated nature of the aldehyde **59**. This high degree of conjugation (which was previously described as an evident advantage in the synthetic design of these imine enediynes) is also a disadvantage, since this extended π system in **59** can cause substantial stability and lower the overall energy of the molecule. This is manifested here with themodynamic consequences.

For this reason, the sp^3 hybridized carbon on the imine nitrogens separating the enediyne functionality in both **24a** and **25a** is synthetically more attainable through their respective enediyne amines. Furthermore, in the synthesis of these imines, nucleophilic addition is expected to happen twice within the same molecule, adding to the difficulty of synthesis. It is apparent through the entries in table 4 that the introduction of acetic acid (as a catalyst) encourages some synthetic manipulations, but is not enough to promote synthesis of desired **65**. This is also evident through the increase in yield experienced when acetic acid was used as a solvent for synthesis of **59**.

***Scheme 20-** Attempted synthesis of **65** led to monosubstituted product **64**.*



* see table 4 for conditions used

***Table 4-** conditions used for attempted synthesis of **65** and % yield of **64**.*

Entry	Solvent	Acid	T (°C)	% Yield of 64
1	CH_2Cl_2	none	r.t.	SM by TLC
2	CH_2Cl_2	AcOH[a]	r.t.	23%
3	EtOH	AcOH[a]	70	15%
4	EtOH	none	r.t.	SM by TLC
5	EtOH	none	70	SM by TLC

[a] 6 drops of acetic acid was introduced to the reaction.

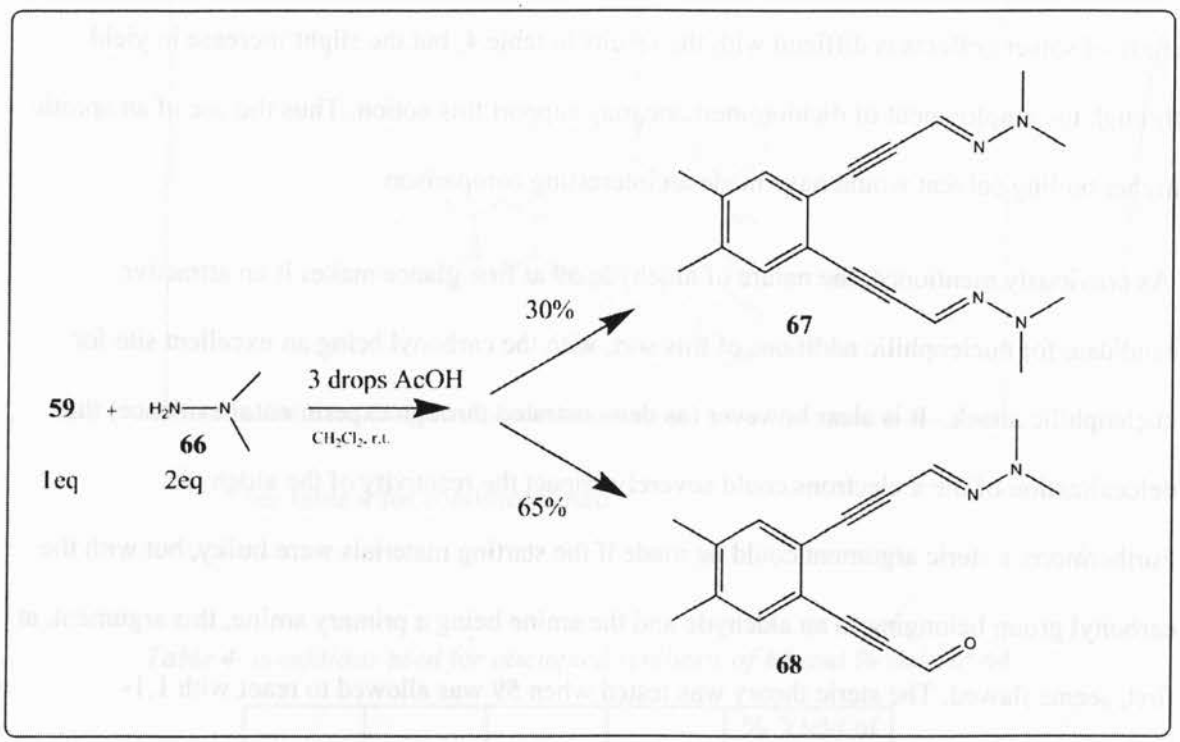
In all cases, reactants **59**:**63** were mixed in a 1:2 ratio

The increase in yield of the latter in excess of DNPH persuaded the introduction of a 5-fold excess of **63** (entry not shown on table) but resulted only in complicated mixtures. The use of ethanol decreased yields and could perhaps be attributed to intermolecular hydrogen bond interactions. These solvent effects are also encountered in previous studies, where it was shown that alcohols as solvents were beneficial in the synthesis of low-melting soluble derivatives, while less soluble compounds required less polar solvents such as chloroform.[77] A comparative study of solvent effects is difficult with the results in table 4, but the slight increase in yield through the employment of dichloromethane may support this notion. Thus the use of an aprotic higher boiling solvent would have made an interesting comparison.

As previously mentioned, the nature of aldehyde **59** at first glance makes it an attractive candidate for nucleophilic additions of this sort, with the carbonyl being an excellent site for nucleophilic attack. It is clear however (as demonstrated through experimental evidence) that delocalization of the π electrons could severely impact the reactivity of the aldehyde. Furthermore, a steric argument could be made if the starting materials were bulky, but with the carbonyl group belonging to an aldehyde and the amine being a primary amine, this argument, at first, seems flawed. The steric theory was tested when **59** was allowed to react with 1,1-dimethylhydrazine **66** to allow for a synthesis of hydrazone **67**, in our eyes, a less sterically demanding molecule. The theme of asymmetry is persistent, with **59** appearing to be fastidious, but notable is the dramatic increase in monosubstituted product (**68**) and gradual increase of disubstituted product **67**. This emphasizes that low yields and lack of reactivity is perhaps partially steric related, but it is also sensible to assume that the prime reason is as a result of the substantial stability of **59**. Reactions involving **63** could perhaps result in a more sterically demanding tetrahedral transition state, given the bulkiness of the phenyl ring and the methoxy

substituent. Nucleophilic attack is therefore more challenging with **63** as a nucleophile. This theory would have been strongly supported with the use of other, less bulkier amines for a valuable comparison. The ability to synthesize hydrazone **27** in modest yields could be attributed to the solvent used, where the abundance of acid are more promising for the synthesis.

***Scheme 21**- Condensation reaction between **59** and **65** led to both hydrazones **67** and **68**.*

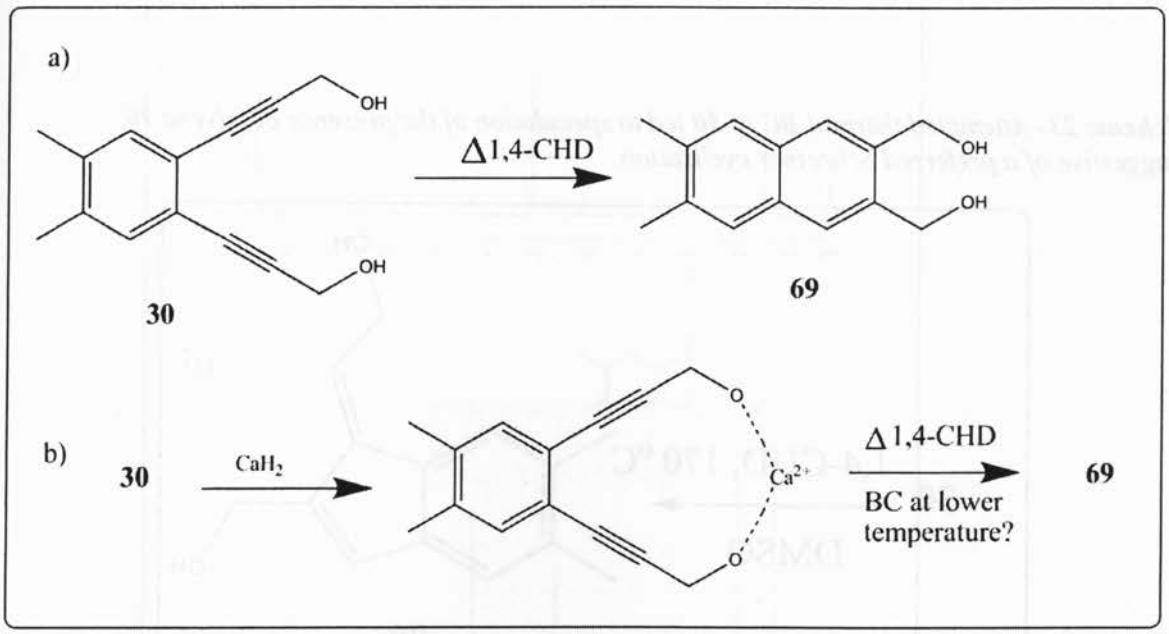


2.3 Related BC reactions

The high-yielding and relatively cheap synthesis of diol **30** encouraged its use as a substrate for some preliminary BC reactions. In particular, we were interested in comparing the BC behavior of **30** as a free ligand (scheme 22a) and in metal-induced BC with calcium hydride serving the dual role as a base and source of Ca^{2+} (scheme 22b). Initial experiments involving γ-terpinene as the hydrogen-donor generated a new spot by TLC with additional observed peaks in the aromatic

region of the ^{1}H NMR spectrum. This product however could not be isolated despite chromatographic efforts, possibly due to contamination with *p*-cymene (aromatized γ-terpinene). Consequently, we could not accurately appoint these peaks to the BC product **69**, due to significant complications in the spectrum. The employment of 1,4-CHD as the quencher would result in the generation of benzene upon hydrogen abstraction, a lower boiling solvent that could be easily removed *in vacuo*.

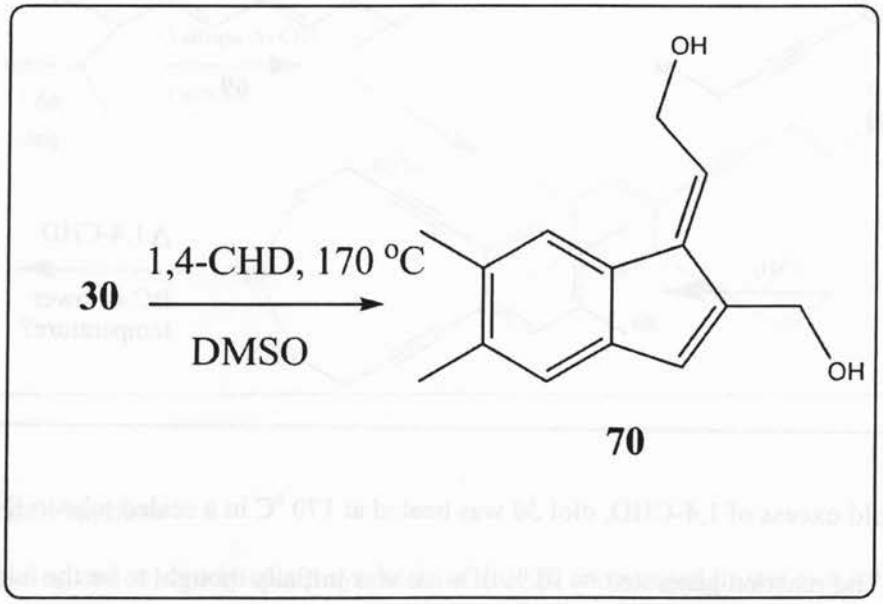
***Scheme 22**-a) thermal BC of **30** as a free ligand b) metal-induced BC of **30** in the presence of Ca^{2+}.*



Using a 40-fold excess of 1,4-CHD, diol **30** was heated at 170 °C in a sealed tube in DMSO (scheme 23).The reaction generated ≈ 10 % of what was initially thought to be the naphthalene derivative **69**. The ^{1}H NMR spectrum of the isolated product was suggestive of a Schreiner cyclization product (fulvene **70**) evident through the two additional peaks in the vinylic region at ≈ 5.2 and 5.6 ppm (figure 15). This finding is remarkable since this type of cyclization is common within eneyneallene type systems, with only a few examples in literature supporting

enediynes cyclizing to fulvenes.[78] This is because the generation of the fulvenic radical intermediate is extremely endothermic, with an activation barrier of ≈ 30-35 kcal/mol, resulting in this process being ≈ 10 kcal/mol more endothermic than generation of the *p*-benzyne radical.[27,78] The existence of **70** suggests that H-abstraction rates were variable. It is already established that trapping of the *p*-benzyne radical does not occur simultaneously, with the first H-abstraction step being 1 kcal/mol more endothermic than the second,[31] but this usually results in the formation of the naphthalene BC product. Unfortunately, a valid carbon spectrum confirming the presence of **70** could not be obtained as a result of insufficient product recovery.

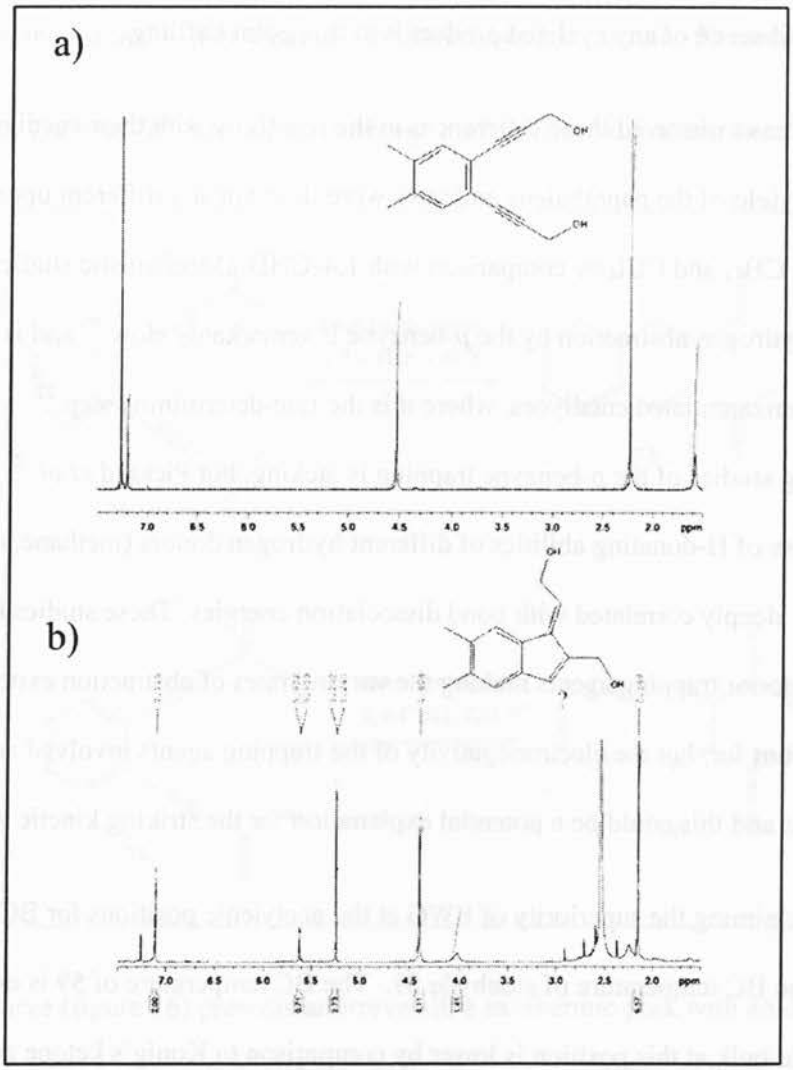
***Scheme 23**- Attempted thermal BC of **30** led to speculation of the presence of fulvene **70**, suggestive of a preferred Schreiner cyclization.*



Thermal BC of **30** was attempted again, this time at 160 °C with a 100-fold excess of 1,4-CHD. After 48 hours of heating, the reaction showed no signs of new product. Instead, **30** was

recovered and ^{13}C NMR ruled out a potential deceptive ^{1}H NMR spectrum, with the acetylenic carbons still intact (that is, the spectrum was identical to that of **30**).

***Figure 15**- a) ^{1}H NMR spectrum of **30** b) ^{1}H NMR spectrum of suspected **70**.*



At this juncture, the results are perplexing, especially when juxtaposed with the findings depicted in scheme 7, where quenching was obtainable at just 70 °C with only 10eq of $SOCl_2$. The result of the latter experiment suggests the formation of the *p*-benzyne radical at a much lower

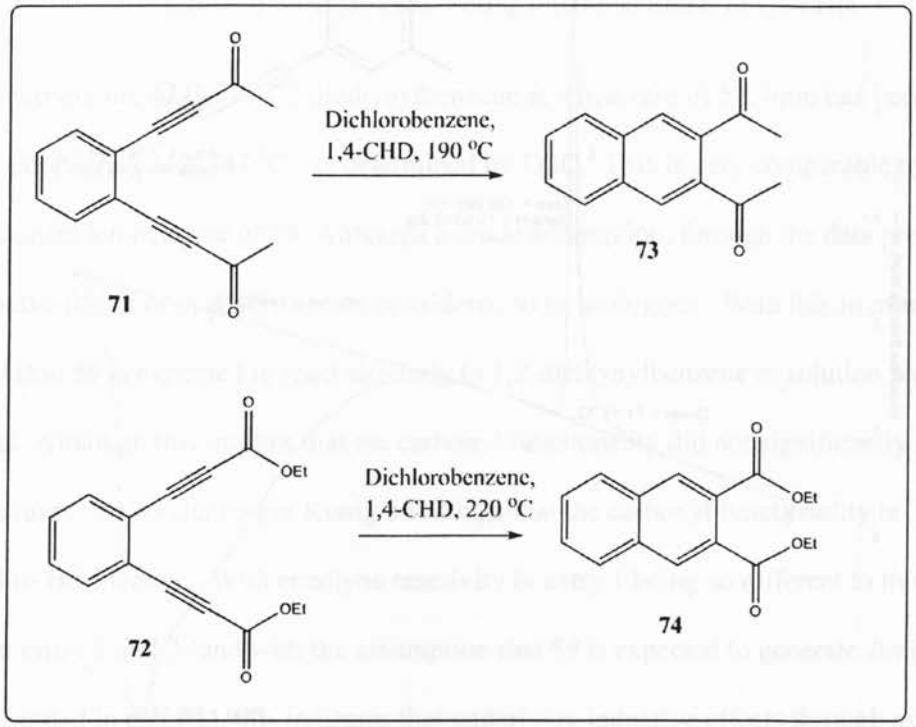
temperature than when heated at 160 °C (a significant 90 °C difference). This implies that abstraction of chlorine is more exothermic than abstraction with hydrogen [31] and is therefore thermodynamically more attainable. Given the 100-fold excess of 1,4-CHD and the established relation between quencher concentration and enediyne reactivity (especially with regard to arenediynes) [31,79] the absence of any cyclized product is at this point baffling.

Semmelhack *et al.* [79] have observed these differences in the reactivity with their enediyne systems, where both yield of the naphthalene and rates were dramatically different upon heating with trapping agents CBr_4 and CCl_4 by comparison with 1,4-CHD. Mechanistic studies have already shown that hydrogen abstraction by the *p*-benzyne is remarkably slow [80] and is especially challenging for the benzannulated enediynes, where it is the rate-determining step.[22] Comparative trapping studies of the *p*-benzyne trapping is lacking, but Pickard *et al.* [27] have shown that the success of H-donating abilities of different hydrogen donors (methane, methanol and 1,4-CHD) were deeply correlated with bond dissociation energies. These studies have been limited to hydrogen donor trapping agents making the varying rates of abstraction experienced here difficult to account for, but the electronegativity of the trapping agents involved are remarkably divergent and this could be a potential explanation for the striking kinetic variations.

With many studies claiming the superiority of EWG at the acetylenic positions for BC, we were curious to observe the BC temperature of aldehyde **59**. The BC temperature of **59** is especially attractive, since steric bulk at this position is lower by comparison to Konig's ketone analogue **71** (scheme 24). This provides a useful comparison with Konig's carbonyl and carboxyl systems, [35] since inductive effects through electron donation to the carbonyl is not experienced in **59** by comparison to **71** and **72**, dramatically varying the electronics between the two systems.

The thermal behavior of **59** was investigated by DSC since sample sizes were not as demanding as those required in solution-phase experiments, vital since the synthesis of acetal precursor **61** was costly. For this reason, comparisons in the thermal behavior of the two systems are tricky and are to be regarded as approximate. Additionally, the absence of solution phase studies does not confirm the mechanism of thermal cyclization, but it is assumed **59** reacted through BC.

***Scheme 24**- Thermal BC for Konig's carbonyl and carboxyl-substiuted enediynes.*



The DSC curve (figure 16) presents an irreversible exothermic peak with an onset temperature at ≈ 150°C. By comparison, solution phase studies have shown 70% and 90% yields at temperatures of 190 and 220°C for **71** and **72** respectively in the presence of 100-fold 1,4-CHD. Konig has compared BC temperatures of **71** and **72** with that of 1,2-diethynlbenzene (table 5). The latter served as a model enediyne, so as to imply that any differences in BC behavior were

attributed to the carbonyl functionality. This led the authors to assume that terminal carbonyl substituted enediynes did not correspond to an increase in thermal reactivity and that it essentially had a detrimental effect on BC.

Figure 16- *DSC curve showing thermal cyclization of* ***59*** *at a heating rate of 5 °C/min.*

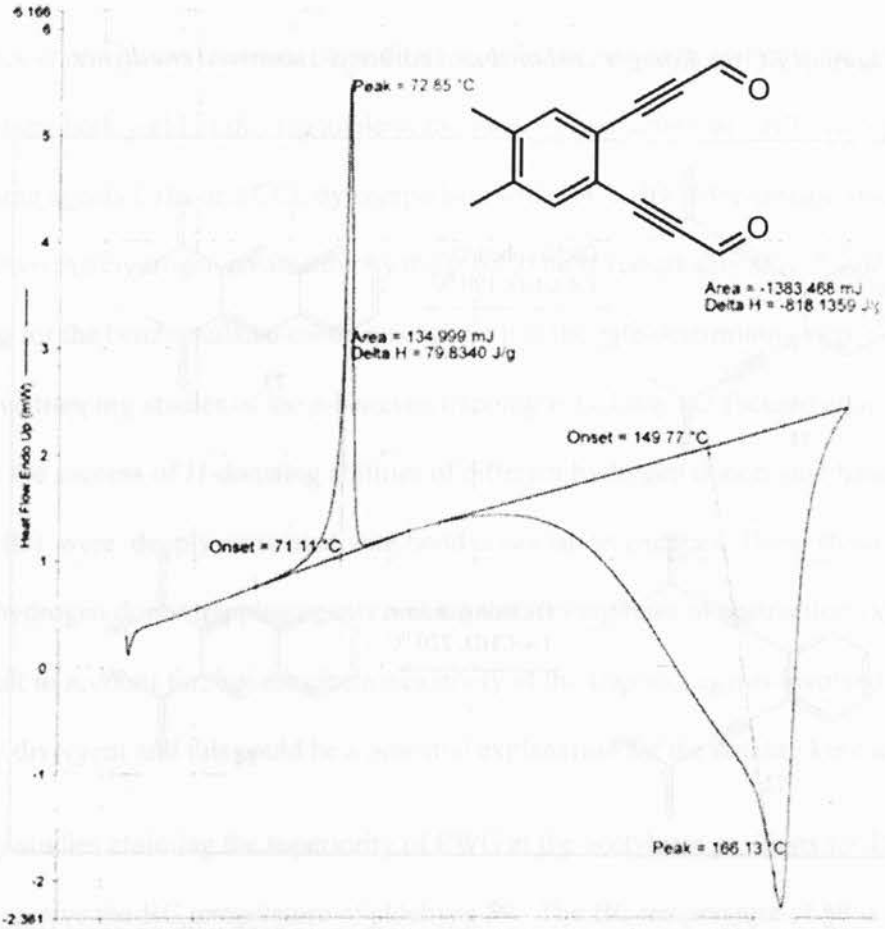
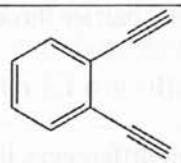


Table 5- *Solution-phase BC kinetic comparisons between 71,72 and 1,2-diethynylbenzene, as calculated by Konig et al.*[3]

Entry	Enediyne	T(°C)	Half-life (min)[a]
1	 1,2-diethynylbenzene	162	29
2	**71**	162	481
3	**72**	162	660

[a] half-lives were determined using a 100-fold excess of 1,4-CHD

The onset temperature of BC of 1,2-diethynylbenzene at a heat rate of 5°C/min has been previously established as ≈ 147 °C , as determined by DSC.[8] This is very comparable to the determined onset temperature of **59**. Although a crude assumption, through the data presented, thermal reactivities of both enediynes are considered to be analogous. With this in mind, it can be assumed that **59** is expected to react similarly to 1,2-diethynylbenzene in solution phase experiments. Although this implies that the carbonyl functionality did not significantly impact BC temperatures, it also challenges Konig's findings that the carbonyl functionality is detrimental to BC kinetics. With enediyne reactivity in entry 1 being so different to those presented in entry 2 and 3 (and with the assumption that **59** is expected to generate similar results to those presented in entry 1), this indicates that underlying inductive effects through associated methyl and ethoxy groups (or related steric factors) are the cause of dramatic changes in BC kinetics, rather than the carbonyl functionality itself. Solution-phase studies of **59** are needed to confirm these suspicions.

The thermal reactivity of **59** in the presence of metals was of interest. The strong σ-donating ability of the carbonyl makes it a very attractive candidate for the study but it also poses a

challenge given the reactive nature of aldehydes. To our knowledge, metal-binding BC studies via metal-coordination through a carbonyl ligand have never been studied. To this end, we wanted to observe the influence of metals on the BC barrier through comparable DSC measurements. Dialdehyde **59** was mixed with $ZnBr_2$ in a 1:1 ratio in diethyl ether. The ^{1}H NMR spectrum for this complex demonstrated ≈ 0.1 ppm differences in chemical shifts compared to that of uncoordinated **59** (figure 17). Figure 18 shows the DSC curve of **59** upon assumed coordination with Zn^{2+}. The DSC curve is unusual in that it displays two exothermic dips, with onset temperatures at ≈ 105 °C and ≈ 121 °C. If the trend presented in figure 16 is followed (i.e BC occurs after endothermic melting) then the second exothermic peak can be regarded as the thermal activation temperature. The additional exothermic peak could be as a result of decomposition of the metal-aldehyde complex. Although the exact mechanism is currently unknown, the change brought about by the metal has led to a ≈ 30°C difference in thermal activation temperatures. Descriptions pertaining to the exact orientation of the metal-ligand cannot be addressed until a crystal structure of the coordinated species is obtained.

More telling physical manipulations were witnessed when attempted coordination of **59** to Cu^{2+} was tried (data not shown). Over time, the ^{1}H NMR spectrum showed the presence of an additional peak at δ 10.4 ppm. In view of the fact that the aldehyde protons for naphthalene dialdehyde coincidentally appear at this same chemical shift, BC was attempted by heating the sample at 150 °C, in the presence of 50-fold excess of 1,4-CHD and with periodic inspection *via* ^{1}H NMR spectroscopy. No significant changes in peak integrations led to the conclusion that BC was not the reason for the sudden appearance of the additional peak. Instead, we propose that Cu^{2+} assisted oxidation of the aldehyde, causing the formation of the respective carboxylic acid

(where the acidic proton is also expected to at $\delta \approx 10.4$ ppm). The physical manipulation is more pronounced with Cu^{2+} because of its strength as an oxidizing agent.

Figure 17- *^1H NMR expansions for a) dialdehyde **59** b) upon assumed coordination with Zn^{2+}*

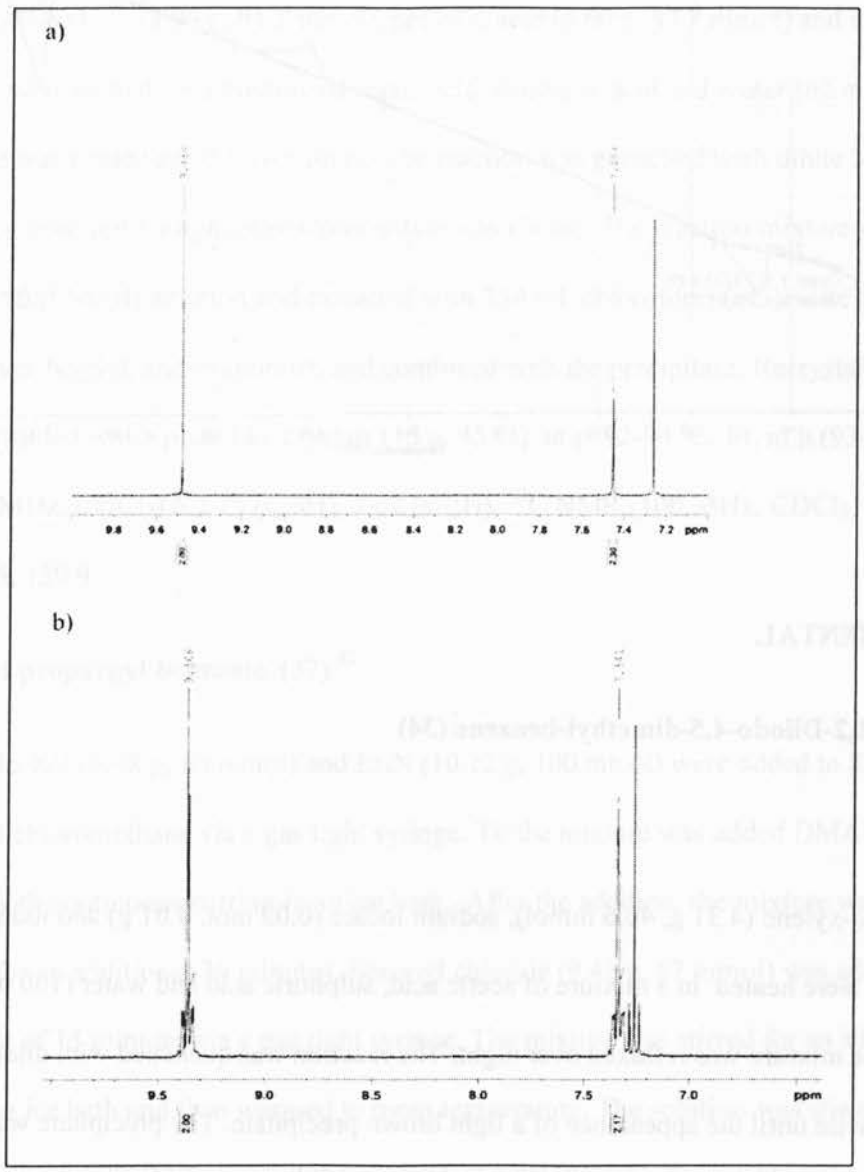
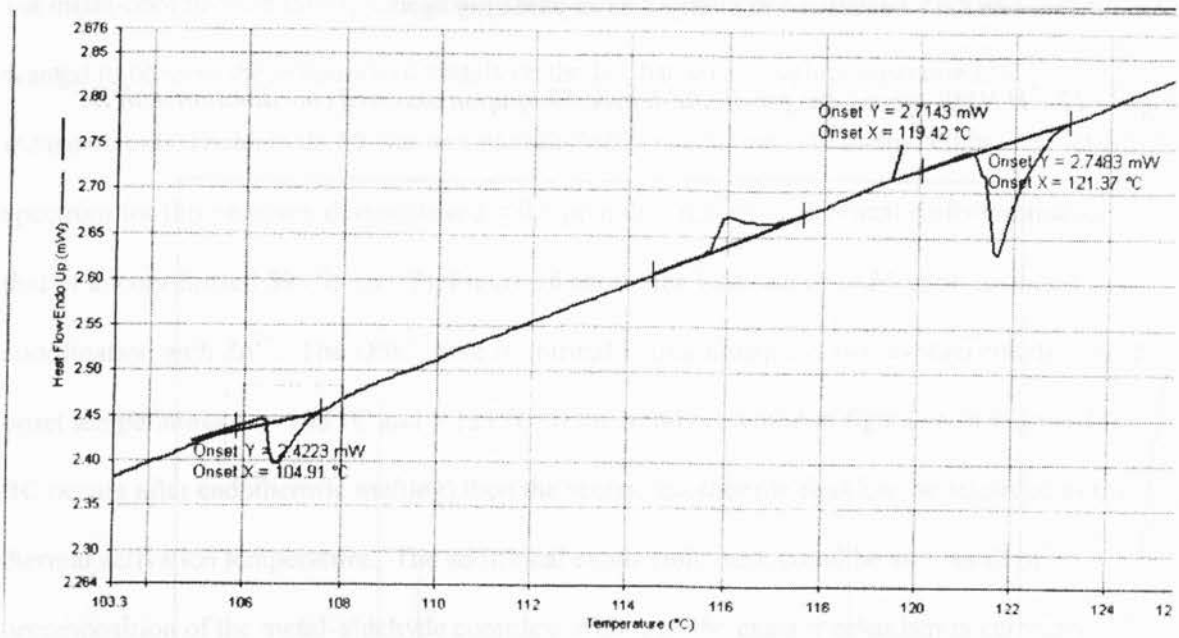


***Figure 18**- DSC curve of **59** through assumed coordination with Zn^{2+}.*



3. EXPERIMENTAL

Synthesis of 1,2-Diiodo-4,5-dimethyl-benzene (34)

Method 1:

A mixture of *o*-xylene (4.31 g, 40.6 mmol), sodium iodate (0.02 mol, 4.01 g) and iodine (0.04 mol, 11.34 g) were heated in a mixture of acetic acid, sulphuric acid and water (160 mL, 100:20:3). The mixture was refluxed over night. The reaction was quenched with dilute Na_2SO_3 solution dropwise until the appearance of a light brown precipitate. The precipitate was filtered and the solution was extracted with 100 mL dichloromethane (×3). The combined organic extracts were neutralized and extracted with 0.5 M NaOH and then dried over Na_2SO_4, evaporated and combined with the precipitate. The residue was redissolved in methanol and

charcoal was added to remove remaining coloured impurities. The mixture was recrystallized in methanol to afford white crystals (3.63 g, 25 %)

Method 2 [81]:

A mixture of *o*-xylene (9.99 g, 94.2 mmol), periodic acid (8.60 g, 37.7 mmol) and iodine (21 g, 84.8 mmol) were heated in a mixture of acetic acid, sulphuric acid and water (62 mL, 100:20:3). The mixture was heated at 70°C overnight. The reaction was quenched with dilute Na_2SO_3 solution drop wise until a light brown precipitate was visible. The reaction mixture was poured into 45 mL 10M NaOH solution and extracted with 350 mL chloroform (×3). The organic phase was dried over Na_2SO_4 and evaporated and combined with the precipitate. Recrystallization in methanol afforded white plate-like crystals (15 g, 45 %). m.p. 92-94 °C, lit. m.p (93-94 °C). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.15 (s, 6H), 7.62 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 18.9, 103.8, 138.5, 139.9.

Synthesis of propargyl benzoate (37) [82]

Propargyl alcohol (4.48 g, 80 mmol) and Et_3N (10.12 g, 100 mmol) were added to 83 mL of anhydrous dichloromethane via a gas tight syringe. To the mixture was added DMAP (0.80 g, 6.7 mmol) with continuous stirring in an ice bath. After the addition, the mixture was stirred in an ice bath for an additional 30 minutes. Benzoyl chloride (9.42 g, 67 mmol) was added slowly over a period of 15 minutes via a gas tight syringe. The mixture was stirred for an additional 30 minutes in an ice bath and then warmed to room temperature. The solution was stirred vigorously at room temperature for 15 hours and then quenched with 100 mL of ice cold water. The reaction mixture was extracted with 100 mL 1M HCl (× 2) and washed with 100 mL portions of

distilled water and brine. The organic phase was dried over sodium sulphate and concentrated *in vacuo* to funish a colourless oil (11.02 g, 86 %).

Synthesis of 3,3'-(4,5-dimethyl-1,2-phenylene)bis(prop-2-yne-3,1-diyl) dibenzoate (38)

34 (2.22 g, 6.2 mmol) and propargyl benzoate (2.18 g, 13.6 mmol) were added to a Schlenk flask containing freshly distilled degassed Et_3N (57 mL). Deaerated conditions were ensured via the "freeze-pump-thaw" technique. $Pd(PPh_3)_4$ (0.22 g, 0.31 mmol) and CuI (0.12 g, 0.61 mmol) were added to the mixture and the flask was evacuated and backfilled with argon (× 3). The reaction mixture was heated at 60 °C overnight, diluted with 40 mL dichloromethane and filtered through a pad of Celite™. The reaction mixture was extracted with 80 mL aq NH_4Cl solution and again with 100 mL dichloromethane (× 3). The organic phase was dried over $MgSO_4$ and the solvent was removed by rotary evaporation. The crude mixture was dry packed on silica and purified by column chromatography (20 % EtOAc/Hexanes) to afford a light yellow solid (2.10 g, 85 %). ^1H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 6H), 5.16 (s,4H), 7.42 (t, J = 7.12Hz, 4H), 7.56 (t, J = 7.75Hz, 2H), 8.08 (d, J=7.60Hz, 4H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.54, 53.44, 85.06, 86.07, 122.32, 128.39, 129.67, 133.18, 133.19, 137.61, 165.89.

Synthesis of 3,3'-(4,5-dimethyl-1,2-phenylene)diprop-2-yn-1-ol (30)

Method 1- Methanolysis of benzoate **38**: K_2CO_3 (0.92 mmol, 0.127 g) was added to a stirred solution of **38** (1 mmol, 0.422 g) in methanol (5 mL). The mixture was stirred at room temperature overnight, filtered and the methanol was removed by rotary evaporation. The crude mixture was purified by column chromatography (50 % EtOAc/Hexanes) and concentrated *in vacuo* to afford a peach coloured solid (0.18 g, 82%).

Method 2: Sonogashira coupling : **34** (0.36 g, 1 mmol), $Pd(PPh_3)_4$ (0.06 g ,0.05 mmol) and CuI (0.02 g, 0.1 mmol) were added to degassed Et_3N (10 mL) under a stream of argon. The mixture was evacuated and backfilled with argon (× 3) and stirred at room temperature for 15 minutes. Propargyl alcohol (0.39 g, 6.7 mmol) was added via syringe under a stream of argon and the flask was evacuated and backfilled (× 3). The flask was sealed and heated at 60 °C over night. The reaction mixture was diluted with dichloromethane and filtered through a pad of Celite™. The crude product was purified by column chromatography (50 % EtOAc/Hexanes) and concentrated *in vacuo* to afford the diol as a peach coloured solid (0.19 g, 89 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.58 (s, 2H), 2.22 (s, 6H), 4.53 (d, 4H), 7.20 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.16, 51.72, 84.61, 90.54, 122.57, 132.38, 137.25.

Synthesis of 3,3'-(4,5-dimethyl-1,2-phenylene)bis(prop-2-yne-3,1-diyl) dimethanesulfonate (32b)

Mesyl chloride (0.23 g, 2 mmol) was added to a stirring solution of Et_3N (0.20 g, 2 mmol) in anhydrous dichloromethane (1 mL) at 0°C. Diol **30** (0.17 g,0.8 mmol) was added slowly with continuous stirring and the solution was stirred at 0 °C for 30 minutes and at room temperature for 2 hours. The reaction mixture was filtered and evaporated to give a white solid. The mesylate could not be synthesized according to literature protocol.[49]

Synthesis of crown (23c) and 1,2-bis(allyloxy)ethane (40)

Diol **30** (0.48 mmol, 0.103 g) was dissolved in 1 mL dry THF and added slowly to a stirred suspension of NaH (40 % mineral oil, 0.04 g,0.96 mmol) in dry THF (1 mL). **31a** (0.17 g, 0.48 mmol) was added after the disappearance of evolving gas and the reaction mixture was refluxed overnight at 80 °C. The reaction mixture was quenched with methanol, filtered and purified by

column chromatography (30 % EtOAc/hexanes) to furnish a pale orange oil (≈ 4 %). The crown ether could not be isolated in its pure form, and afforded a 1:1 mixture with the vinyl ether. **23c** ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.22 (s, 6H), 3.79-3.85 (m, 12H), 4.45 (s, 4H), 7.21 (s, 2H). **40**: 3.79-3.85 (m, 4H), 4.00 (dd, J_1 = 14.2 Hz, J_2 = 2.00 Hz, 2H), 4.18 (dd, J_1 = 6.81 Hz, J_2 = 2.10 Hz, 2H), 6.50 (dd, J_1 = 14.2 Hz, J_2 = 6.81 Hz, 2H). 54,122.57, 132.38, 137.25. TOF MS EI$^+$calc for $C_{20}H_{24}O_4$ Na^+: 351.1566, found: 351.1569.

Synthesis of 1,2-bis(3,3-diethoxyprop-1-ynyl)-4,5-dimethylbenzene (61)

34 (2.24 g, 6.3 mmol), $Pd(PPh_3)_4$ (0.36 g, 0.31 mmol) and CuI (0.12 g,0.62 mmol) were added to a Schlenk flask containing freshly distilled degassed Et_3N (20 mL). The flask was sealed and stirred at room temperature for 15 minutes and PADA (**60**) (1.61 g, 12.6 mmol) was added under a stream of argon. The reaction vessel was sealed and stirred at 60 °C overnight. The reaction mixture as diluted with dichloromethane (30 mL), extracted with 1 M HCl (15 mL) and the organic phase was dried over Na_2SO_4. The crude mixture was purified by column chromatography (10 % EtOAc/hexanes) and concentrated *in vacuo* to afford a blue/black oil (2.00 g, 90 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.21 (t, J = 7.21 Hz, 12H), 2.19 (s, 6H), 3.61-3.70 (m, 4H), 3.79-3.86 (m, 4H), 5.47 (s, 2H), 7.23 (s, 2H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 15.23, 60.89, 83.72, 83.80, 91.84, 122.0, 133,35, 137.55. TOF EI$^+$ calc. for $C_{22}H_{30}O_4$ 358.2144, found: 358.2134.

Synthesis of 3,3'-(4,5-dimethyl-1,2-phenylene)dipropiolaldehyde (59)

Method 1: oxidation of **30** using PCC

Diol **30** (0.02 g, 0.1 mmol) was diluted with dry dichloromethane (0.3 mL) and added dropwise to a stirring solution of PCC in (0.11 g, 0.5 mmol) in dry dichloromethane (0.3 mL). The reaction

was stirred at room temperature overnight after which it was diluted with 5 mL of Et_2O, washed with 10 mL 0.1 M NaOH (× 2), 0.1 M HCl (× 2) and saturated $NaHCO_3$ solution (× 2). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford an orange solid (6.0 mg, 28%).

Method 2: Hydrolysis of **61**

Acetal **61** (0.35 g,0.97 mmol) was added to a 40 %TFA/10 % H_2O/50 %DCM solution and stirred at room temperature overnight. The reaction mixture was diluted with 30 mL of dichloromethane, extracted with 20 mL saturated $NaHCO_3$ (× 2), dried over Na_2SO_4 and concentrated *in vacuo*. The crude mixture was passed through a silica gel column eluted with dichloromethane to afford the dialdehyde **59** as an orange solid (12.2 mg, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.32 (s, 6H), 7.45 (s, 2H), 9.48 (s, 2H); ^{13} C NMR (100 MHz, $CDCl_3$) δ 19.87, 91.60, 91.95, 120.90, 135.03, 141.04, 176.47. TOF MS EI^+ calc for $C_{14}H_{10}O_2$: 210.0681, found: 210.068

Synthesis of (E)-1-(3-(2-(3,3-diethoxyprop-1-ynyl)-4,5-dimethylphenyl)prop-2-ynylidene)-2-(2,4-dinitrophenyl)hydrazine (62)

2,4-Dinitrophenylhydrazine (30 % water) (0.06 g, 0.3 mmol) was added to a stirred solution of **61** (0.04 g, 0.1 mmol) in acetic acid (1 mL). The reaction mixture was stirred at r.t. for 48 hours and extracted with 10 mL saturated $NaHCO_3$ (× 3). The organic phase was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude mixture was purified by column chromatography (50 % hexanes/dichloromethane) to afford a peach coloured solid (58 %, 0.139 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 1.22 (t, J = 7.09 Hz, 6H), 2.22 (s, 3H), 2.25 (s,3H), 3.62-3.69 (m, 2H), 3.76-3.84 (m, 2H), 5.49 (s, 1H), 7.05 (s, 1H), 7.54 (s, 1H), 8.00 (d, J = 9.81 Hz, 1H),

8.37 (dd, J_1= 9.81 Hz, J_2 = 2.35Hz, 1H), 9.17 (d, J = 2.35 Hz, 1H), 12.17 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.73, 19.81, 22.68, 23.91, 30.71, 60.93, 82.67, 88.48, 91.75, 102.24, 104.00, 117.20, 120.26, 123.27, 130.03, 133.87, 139.92, 176.50, 206.99. TOF MS EI+ calc for $C_{24}H_{24}N_4O_6Na^+$: 487.1588, found: 487.1583.

Synthesis of (E)-3-(2-(3-(2-methoxyphenylimino)prop-1-ynyl)-4,5-dimethylphenyl)propiolaldehyde (64a)

59 (0.03 g, 0.15 mmol) was dissolved in 1:1 dichloromethane/acetic acid solution (2 mL) containing molecular sieves (4 Å). **63** (0.04 g, 0.3 mmol) was added to the stirring solution and the reaction was left stirring overnight at r.t. The reaction mixture was diluted with 20 mL dichloromethane, filtered through Celite™ and extracted with 10 mL saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude mixture was purified by column chromatography (30 % EtOAc/hexanes) and concentrated *in vacuo* to afford a red solid (11.1 mg, 23 %).

Synthesis of (2E,2'E)-2,2'-(3,3'-(4,5-dimethyl-1,2-phenylene)bis(prop-2-yne-3-yl-1-ylidene))bis(1,1-dimethylhydrazine) (67)

1,1-dimethylhydrazine was added to the stirring solution of dialdhyde **59** (0.02g, 0.06mmol) in dichloromethane (1mL) containing 7 drops of acetic acid.The reaction was stirred at r.t. overnight. The mixture was diluted with dichloromethane (15 mL) and extracted with 5mL saturated $NaHCO_3$. The organic phase was dried over Na_2SO_4, the solvent was removed via rotary evaporation and the crude mixture was purified by column chromatography (20% EtOAc/Hexanes) and concentrated *in vacuo* to afford a brown solid (5.28 mg, 30%) ^{1}H NMR

(400 MHz, $CDCl_3$) δ 2.20 (s, 6H), 3.00 (s, 6H), 3.00 (s, 6H), 6.54 (s, 2H), 7.26 (s,2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.54, 42.44, 88.31, 90.08, 113.25, 122.70, 132.91, 136.69.

(E)-3-(2-(3-(2,2-dimethylhydrazono)prop-1-ynyl)-4,5-dimethylphenyl)propiolaldehyde (68) was isolated as a yellow solid (65 %, 9.84 mg)^1H NMR (400 MHz, $CDCl_3$) δ 2.24 (s, 3H), 2.25 (s, 3H), 3.03 (s, 6H), 6.48 (s, 1H), 7.32 (s, 1H), 7.34 (s, 1H), 9.47 (s, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 19.51, 19.90, 42.42, 86.70, 91.22, 92.21, 94.89, 111.46, 118.61, 125.46, 133.11, 134.57, 137.07, 140.67, 176.90.

Synthesis of (2E,2'E)-2,2'-(3,3'-(4,5-dimethyl-1,2-phenylene)bis(prop-2-yne-3-yl-1-ylidene))bis(1-(2,4-dinitrophenyl)hydrazine) (27)

Method 1:

2,4- dinitrophenylhydrazine (30 % water) (0.04 g, 0.02 mmol) was added to a stirred solution of **59** (0.01 g, 0.05 mmol) in acetic acid (2 mL). The mixture was stirred at room temperature overnight. The reaction mixture was diluted in dichloromethane (10 mL) and extracted with 5 mL saturated $NaHCO_3$ (× 3). The organic phase was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude was purified by column chromatography (30% EtOAc/hexanes) and concentrated *in vacuo* to afford the dihydrazine as a crystalline red/orange solid (0.014 g, 50 %).

Method 2:

Acetal **61** (0.04 g,0.12 mmol) was heated in acetic acid (1 mL) at 60 °C for 20 minutes. The solution was allowed to cool to room temperature and 2,4-dinitrophenylhydrazine (0.12 g, 0.6 mmol) was added to the mixture, sealed and heated at 65 °C overnight. The reaction mixture was diluted with dichloromethane (20 mL) and extracted with $NaHCO_3$ (× 3), dried over Na_2SO_4 and

the mixture was concentrated *in vacuo* to afford a red solid (1 mg, 15 %). ESI-MS Calc for $C_{26}H_{18}N_8O_8$ MH^+ 571.1288, found: 571.1288. A valid NMR spectrum could not be obtained due to insolubility of the product.

Tosylation of diol (32a)

Diol **30** (0.24 g, 1.1 mmol) was dissolved in a mixture of Et_3N (6.0 mmol, 0.61g) and THF (2 mL) in an ice bath. The mixture was stirred for 30 minutes at 0 °C. TsCl (0.42 g, 2.2 mmol) was added slowly and the reaction mixture was stirred for an additional 20 minutes. The reaction mixture was filtered through silica. The tosylate could not be purified despite chromatographic efforts.

Synthesis of tetraethylene glycol ditosylate (31b) [83]

Tetraethylene glycol (17.6 g, 35 mmol) was diluted in THF (20 mL) and added to an aqueous solution of NaOH (20 % w/v). The mixture was stirred in an ice bath and a solution of tosyl chloride (14.5 g, 76 mmol) in 20 mL THF was added slowly drop wise *via* an additional funnel over a 2 hour period. After addition, the mixture was stirred for an additional hour in an ice bath and poured into an ice-water mixture (25 g/25 mL). The reaction mixture was stirred at room temperature until the ice melted and the THF was removed by rotary evaporation. The residue was dissolved in 10 mL dichloromethane and extracted against 10 mL of distilled water (× 3). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford a colourless oil (13.7 g, 93 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.45 (s, 6H), 3.57 (s, 8H), 3.68 (t, J = 4.7 Hz, 4H), 4.16 (t, J = 4.7 Hz, 4H), 7.35 (d,J = 8.2 Hz, 4H), 7.80 (d, J = 8.2 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.6, 68.7, 70.5, 70.7, 72.4, 128.0, 129.8, 133.0, 144.9.

Synthesis of 1-bromo-2-(2-(2-(2-bromoethoxy)ethoxy)ethoxy)ethane (31c) [84]

NaBr (0.82 g, 8 mmol) was added to a stirred solution of **31b** (0.94 g, 2 mmol) in dry DMF (5 mL) and the reaction was heated at 80 °C overnight. The reaction mixture was filtered and concentrated *in vacuo* to afford a clear oil (71 %, 1.82 g).

Synthesis of triethylene glycol ditosylate (31d) [83]

Triethylene glycol (16.0 g, 35 mmol) was diluted in THF (20 mL) and added to an aqueous solution of NaOH (20 % w/v). The mixture was stirred in an ice bath and a solution of TsCl (14.5 g, 76 mmol) in 20 mL THF was added slowly drop wise via an additional funnel over a 2 hour period. After addition, the mixture was stirred for an additional hour in an ice bath and poured into an ice-water mixture (25 g/25 mL). A white precipitate was formed and isolated by vacuum filtration (6.34 g, 75 %). m.p 78-81 °C ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.34 (s, 6H), 3.47 (s, 4H), 3.54 (t, J = 4.0 Hz, 4H), 4.01 (t, J = 4.0 Hz, 4H), 7.25 (d, J = 8.0 Hz, 4H), 7.67 (d, J = 8.0 Hz, 4H). ^{13}C NMR (100 MHz, $CDCl_3$) 21.56, 70.34, 70.47, 71.20, 127.82, 129.87, 132.72 144.92.

Synthesis of 4,7,10,13-tetraoxahexadeca-1,15-diyne [85] **(35a)**

Propargyl alcohol (1.12 g, 40 mmol) was diluted in 3 mL dry THF and added slowly drop wise via an addition funnel to a stirring suspension of NaH (60% mineral oil, 1.60 g, 40 mmol) in dry THF (50 mL). The mixture was stirred at room temperature for 20 minutes. A solution of triethylene glycol ditosylate (4.58 g, 10 mmol) in 20 mL dry THF was added slowly to the mixture via an addition funnel over a period of 2 hours. After addition, the reaction mixture was refluxed at 80 °C over night. The reaction mixture was filtered through Celite™ and the THF was removed by rotary evaporation. The residue was diluted with 30 mL dichloromethane and

extracted with 30 mL of water (× 3). The organic phase was dried over Na_2SO_4 and evaporated to give a light orange oil (1.47 g, 65 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.40 (t, J = 2.5 Hz, 2H), 3.63-3.72 (m, 12H), 4.18 (d, J = 2.5 Hz 4H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.21, 58.05, 68.77, 70.26, 74.35, 79.39.

Synthesis of 4,7,10,13,16-pentaoxanonadeca-1,18-diyne [85] (35b)

Propargyl alcohol (1.12 g, 40 mmol) was diluted in 3 mL dry THF and added slowly drop wise via an addition funnel to a stirring suspension of NaH (60% mineral oil, 1.60 g,40 mmol) in dry THF (50 mL). The mixture was stirred at room temperature for 20 minutes. A solution of **31c** (5.02 g, 10 mmol) in 20 mL dry THF was added slowly to the mixture via an addition funnel over a period of 2 hours. After addition, the reaction mixture was refluxed at 80 °C over night. The reaction mixture was filtered through Celite™ and the THF was removed by rotary evaporation. The residue was diluted with 30 mL dichloromethane and extracted with 30 mL of water (× 3). The organic phase was dried over Na_2SO_4 and evaporated to give a pale orange oil (1.54 g, 57 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.37 (t, J = 2.4 Hz, 2H), 3.53-3.63 (m, 16H), 4.10 (d, J = 2.4 Hz, 4H) ^{13}C NMR (100 MHz, $CDCl_3$) δ 53.21, 58.11, 68.83, 70.13, 70.33, 74.38, 79.43.

Synthesis of 1,16-bis(2-iodo-4,5-dimethylphenyl)-4,7,10,13-tetraoxahexadeca-1,15-diyne (43a)

34 (1 mmol, 0.358 g), $Pd(PPh_3)_4$ (0.05 mmol, 57.8 mg), and CuI (0.1 mmol, 19.0 mg) were added to degassed freshly distilled Et_3N(3.3 mL) in a Schlenk flask under inert atmosphere. The reaction was stirred at room temperature for 5 minutes, followed by the addition of **35a** (1 mmol, 0.226 g). The reaction vessel was sealed and heated at 60°C overnight. The reaction mixture was

filtered through Celite™, diluted with dichloromethane (30 mL) and extracted with 1M HCl (10 mL, × 3). The organic phase was dried over Na_2SO_4 and the solvent was removed by rotary evaporation. The crude was purified by column chromatography (20 % EtOAc/hexanes) and concentrated *in vacuo* to afford and orange/brown oil (0.161 g, 25 %). ^{1}H NMR (400MHz, $CDCl_3$) δ 2.17 (s, 6H), 2.20 (s, 6H), 3.67-3.84 (m, 12H), 4.47 (s, 4H), 7.21 (s, 2H), 7.58 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 19.29, 29.71, 59.11, 69.15, 70.51, 70.63, 87.80, 88.25, 96.95, 126.42, 133.80, 136.63, 139.22, 139.33. One aromatic carbon was not observed.

Synthesis of 1,19-bis(2-iodo-4,5-dimethylphenyl)-4,7,10,13,16-pentaoxanonadeca-1,18-diyne (43b)

43b was synthesized in accordance with methodology for **43a**, (0.182 g, 25 %).

Synthesis of 3-(2-bromophenyl)prop-2-yn-1-ol [49,50] (47)

1,2-dibromobenzene (3.0 mmol, 0.70 g) and Et_3N (7.2 mmol, 1.0 mL) were added to a Schlenk flask containing a degassed solution of Palladium (II) chloride (0.09 mmol, 0.015 g), *$HP(t\text{-}Bu)_3BF_4$* (0.21 mmol, 0.06 g) and CuI (0.09 mmol, 0.017 g) in THF (6mL). The mixture was stirred at r.t. under inert conditions for 5 minutes. Propargyl alcohol (6.0 mmol, 0.34 g) was added by syringe and the flask was sealed and stirred at r.t. for 14 hours. The reaction mixture was filtered through Celite™ and purified by column chromatography (20 % EtOAc/hexanes) to afford a brown oil (25 %, 0.19 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.61 (s, 1H), 4.56 (s, 2H), 7.13-7.25 (m, 1H), 7.13-7.17 (m, 1H), 7.46 (dd, J_1 = 7.61 Hz, J_2 = 1.77 Hz), 7.56 (dd, J_1 = 8.10 Hz, J_2 = 1.25 Hz) ^{13}C NMR (100 MHz, $CDCl_3$) δ 51.62, 84.14, 91.95, 124.68, 125.43, 127.04, 128.67, 132.40, 133.58.

Synthesis of 3-(2-bromophenyl)prop-2-yn-1-ol hexacarbonyl dicobalt (45)

Dicobalt octacarbonyl (0.49 mmol, 0.19 g) was added slowly to a solution of **47** (0.35 mmol, 0.07 g) in dry dichloromethane (3 mL) at 0 °C. The reaction was stirred at 0°C for 2 hours and at r.t. for 14 hours after which the reaction mixture was filtered through Celite™ and concentrated *in vacuo* to give a blue-black solid (76 %, 0.14 g). ^{1}H NMR (400 MHz, $CDCl_3$) δ2.15 (br s, 1H), 5.13 (s, 2H), 7.19 -7.35 (br, 2H), 7.58-7.64 (br, 2H). Valid carbon spectra could not be obtained due to shimming problems associated with accumulated cobalt carbonyl.

Synthesis of 3,6,9,12-tetraoxapentadec-14-yn-1-ol [87] (46)

NaH (60 % w/w in mineral oil, 29 mmol, 1.17 g) was added to a stirring solution of tetra(ethylene glycol) (26.5 mmol, 5.14 g) in THF (100mL) at 0 °C and after 15 minutes of stirring, propargyl bromide (80 % in toluene, 29 mmol, 4.33 g) was added slowly to the mixture via an addition funnel at 0 °C for 2 hours. The reaction was then stirred for an additional 3 hours at r.t. The reaction mixture was quenched with methanol, filtered through Celite™ and the THF was removed by rotary evaporation. The mixture was passed through silica gel (neat EtOAc) and concentrated *in vacuo* to afford a clear oil (4.42 g, 60 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.94 (s, 1H), 2.40 (t, J = 2.4 Hz, 1H), 2.75 (br.s, 1H), 3.56 (t, J = 4.4 Hz, 2H), 3.56 (t, J = 4.4 Hz, 2H), 3.61-3.65 (m, 14H), 4.16 (d, J = 2.4 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 58.27, 61.60, 68.99, 70.28, 72.43, 74.47, 76.68, 76.93, 77.00, 77.32, 79.53.

Synthesis of 3,6,9,12-tetraoxapentadec-14-ynyl 4-methylbenzenesulfonate [87] (48)

TsCl (3.1 mmol, 0.59 g) , DMAP (0.10 mmol, 12.2 mg) and **46** (2.59 mmol, 1.00 g) were added to a 1:1 dichloromethane:pyridine solution (6 mL) and stirred in an ice bath. After two hours, the solution was allowed to stir at room temperature overnight. The reaction was poured into ice cold

water (12 mL) and extracted with dichloromethane (20 mL, × 3). The organic phase was washed with portions of brine (10 mL), aqueous NH_4Cl (10 mL) and dried over Na_2SO_4 The crude was purified by column chromatography (50 % EtOAc/hexanes) and concentrated *in vacuo* to yield the tosylate as a clear oil (72 %, 0.72 g). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 2.40 (t, J = 2.4 Hz, 1H), 2.54 (s, 3H), 3.70-3.55 (m, 14H), 4.16 (t, J = 7.8 Hz, 2H), 4.19 (d, J = 2.4 Hz, 2H), 7.26 (d, J = 8.4 Hz, 2H), 7.75 (d, J = 8.4 Hz,2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.64, 58.40, 68.69, 70.41, 70.60, 74.48, 127.99, 129.81, 133.02, 144.78.

2-iodophenyl acetate [88,89] **(55)**

2-Iodophenol (5.00 g, 22.7 mmol) was added to a mixture of acetic anhydride (113 mmol, 10.7 mL) and Et_3N (113 mmol,11 mL) in anhydrous dichloromethane (43 mL). After 5 minutes of stirring, DMAP (0.83 g) was added and the reaction mixture was stirred at room temperature for 24 hours. The reaction mixture was diluted with 200 mL of dichloromethane, extracted with 100 mL portions of 1M HCl (× 3) and washed with 100 mL of sat. $NaHCO_3$ (× 3). The organic phase was dried over Na_2SO_4 and the solvent was removed by rotarary evaporation. The crude was purified by filtering through silica eluted with hexanes and concentrated *in vacuo* to afford a pale yellow oil (5.29 g, 89 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.23 (s, 3H), 6.94 (dt, J_1 = 8.01 Hz, J_2=1.50 Hz 1H), 7.11 (dd , J_1 = 8.01 Hz, J_2 = 1.50 Hz) , 7.33 (dt, J_1 = 8.10 Hz, J_2=1.5 Hz,1H), 7.82 (dd, J_1 = 8.10 Hz, J_2 = 1.50 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.29, 90.92, 123.53, 127.51, 128.0, 139.4, 151.3, 168.4.

1,16-bis(2-bromophenyl)-4,7,10,13-tetraoxahexadeca-1,15-diyne (56e)

1-bromo-2-iodobenzene (2 mmol, 0.56 g), **35a** (1.83 mmol, 0.41 g) and $Pd(PPh_3)_4$ (0.022 mmol, 25.0 mg) were added to freshly distilled, degassed Et_3N (3 mL) under inert atomosphere. The

mixture was stirred at room temperature for 5 minutes, followed by the addition of CuI (0.022 mmol, 4.15 mg). The Schlenk flask was sealed and the reaction was heated at 65 °C overnight. The reaction mixture was diluted with dichloromethane, filtered through a pad of Celite™ and the solvent was removed by rotary evaporation. The crude mixture was purified by column chromatography (20 % EtOAc/hexanes) and concentrated *in vacuo* to furnish a clear oil (0.275 g, 25 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.67-3.80 (m, 12H), 4.44, (s,4H), 7.10-7.14 (td, J_1 = 7.70 Hz, J_2 = 1.70 Hz, 2H), 7.19-7.21 (td, J_1 = 7.70 Hz, J_2 = 1.17 Hz, 2H), 7.43 (dd, J_1 = 7.70 Hz, J_2 = 1.70 Hz), 7.52 (dd, J1 = 6.78 Hz, J2 = 1.17 Hz, 2H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 59.43, 69.16, 70.47, 70.55, 84.83, 89.92, 124.79, 126.67, 127.25, 129.61, 132.37, 133.54.

Synthesis of 3,3'-(4,5-dimethyl-1,2-phenylene)diprop-2-yn-1-ol hexacarbonyldicobalt (57)

Dicobalt octacarbonyl (1.4 mmol, 0.53 g) was added gradually to a stirring solution of diol **30** (0.28 mmol, 0.06 g) in dry DCM (3 mL) at 0°C. The reaction mixture was stirred at 0 °C for 2 hours and then at r.t for 3 hours. The reaction mixture was filtered through a pad of Celite™ and purified by column chromatography (20 % EtOAc/hexanes) to afford a purple solid (34.3 mg, 53 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.22 (s, 3H), 2.29 (s, 3H), 4.54 (br s, 2H), 5.15 (br s, 2H), 7.22 (s, 1H), 7.31 (s, 1H). ^{13}C NMR (400 MHz, $CDCl_3$) δ 19.33, 19.89, 29.70, 51.90, 65.00, 85.62, 88.47, 92.60, 98.51, 118.42, 133.91, 134.75, 136.25, 137.04, 138.64, 199.44. TOF MS EI^+ calc for $C_{14}H_{13}OCo_2$ 314.9606, found: 314.9624

Synthesis of (1,4-dichloronaphthalene-2,3-diyl)dimethanol (42) (BC of **30**)

Thionyl chloride (10mmol, 1.19g) was carefully added to a stirring solution of diol **30** (1mmol, 0.214g) in chloroform (5mL) containing 1 drop of DMF in an ice bath. After addition, the mixture was refluxed at 70°C overnight. The reaction mixture was diluted with 50mL

chloroform, extracted with ice-cold NaCl solution, dried over MgSO4 and the solvent was removed by rotary evaporation. The crude was purified by column chromotagraphy (hexanes) and concentrated *in vacuo* to afford a white solid (38.7 mg, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 (s, 6H), 5.13 (s, 4H), 8.10 (s, 2H). ^{13}C NMR (100MHz, $CDCl_3$) δ 20.37, 29.70, 40.97, 125.30, 130.28, 130.92, 131.92, 139.40.

Synthesis of 1-azido-2-(2-(2-(2-azidoethoxy)ethoxy)ethoxy)ethane [90] (73)

Tetraethylene glycol ditosylate (0.94 g, 2 mmol) was diluted with anhydrous DMF (5 mL) and sodium azide was added periodically (0.52 g, 8 mmol) with stirring. After addition of the azide, the reaction was heated at 80 °C overnight. The reaction mixture was diluted with 5 mL of distilled water and extracted with 30 mL of EtOAc (× 3) and washed with water (10 mL) and brine (20 mL). The organic phase was dried over Na_2SO_4 and concentrated *in vacuo* to afford a light yellow oil (0.347 g, 71 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.38-3.41(m, 4H), 3.67-3.70 (m, 12H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 50.9, 70.2, 70.9

Synthesis of 2,2'-(2,2'-oxybis(ethane-2,1-diyl)bis(oxy))diethanamine [91] (74)

The diazide (0.35 g, 1.4 mmol) was diluted with 3mL anhydrous THF and added drop wise to a stirred suspension of LAH (0.32 g, 8.4 mmol) in THF. The reaction mixture was refluxed at 80°C overnight and quenched slowly the following day with saturated sodium sulphate solution. The precipitate was filtered and washed with acetone and evaporated to give a pale orange oil (0.245 g, 91 %).

Synthesis of propargyl tosylate [92] (75)

Propargyl alcohol (0.56 g, 10 mmol) and TsCl (2.28 g, 12 mmol) were dissolved in 20 mL of ether at room temperature. The mixture was cooled in an ice bath and finely powdered KOH was added in small portions slowly over a 25 minute period. After addition of KOH, the mixture was stirred in an ice bath for an additional 30 minutes and poured slowly into 20 mL of ice-cold water. The mixture was extracted with 20 mL of ether (× 3). The organic phase was dried over magnesium sulphate and evaporated to afford the tosylate as a clear oil (1.81 g, 86 %) ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.47 (s,3H), 2.48 (t, J = 2.5 Hz, 1H), 4.65 (d, J = 2.5 Hz, 2H), 7.32 (d, J = 8.0 Hz, 2H), 7.77 (d, J = 8.0 Hz, 2H).

4. CONCLUSION

The experimental work presented here emphasizes the synthetic challenges associated with the synthesis and design of the enediynes. For some time, the electronic and geometric factors associated with the Bergman cyclization has been the center of extensive study, but minor structural variations within or surrounding the enediyne core commonly results in diverse thermal reactivities.

We have reported the existence of the first arenediyne crown ether (achievable through a one-pot synthesis) but attempts at increasing yields and other methods of purification are necessary. Difficulties are experienced when a two-step synthesis is attempted, mainly because the route towards a common prearranged intermediate has posed a challenge. Synthetic attempts *via* intramolecular Sonogashira reactions towards an arenediyne crown ether (whether they be one-

pot or step-wise) resulted in diarylated species, suggesting that cyclization is not favorable under the experimental conditions and that tandem substitution is a likely outcome.

Various novel arenediynes have been synthesized that could potentially serve as important intermediates and building blocks towards more complicated structures. Among them were diacetal and dialdehyde arenediynes, which were used to synthesize novel hydrazone arenediynes with extended π systems. These hydrazones have the potential to be good metal-coordinating ligands, which could promote a decrease in the thermal activation barrier. In relation to this, we have reported the thermal reactivity of the dialdehyde intermediate with coordination to a metal, which promoted a ≈ 30 °C temperature decrease in thermal cyclization temperatures by comparison with the non-coordinated species. Coupled with previous carbonyl-based experimental data from the literature, our results suggest that the carbonyl functionality is not detrimental to BC kinetics (as previously stated in literature) but that other steric or electronic effects are to be considered as the prime cause for a decrease in thermal reactivity.

Experimental data pertaining to additional thermal BC of our diol intermediate implies that BC is not only dependent on the concentration of the quencher, but is also highly dependent on the nature of the quencher. Notable is that when thionyl chloride is used as a quencher, BC occurs at a much lower temperature than with the conventional 1,4-cyclohexadiene, where quenching is achieved at a much lower concentration. These results possibly suggest that the *p*-benzyne radical exists at a lower temperature and this could potentially support the theory that hydrogen abstraction is a rate-determining step.

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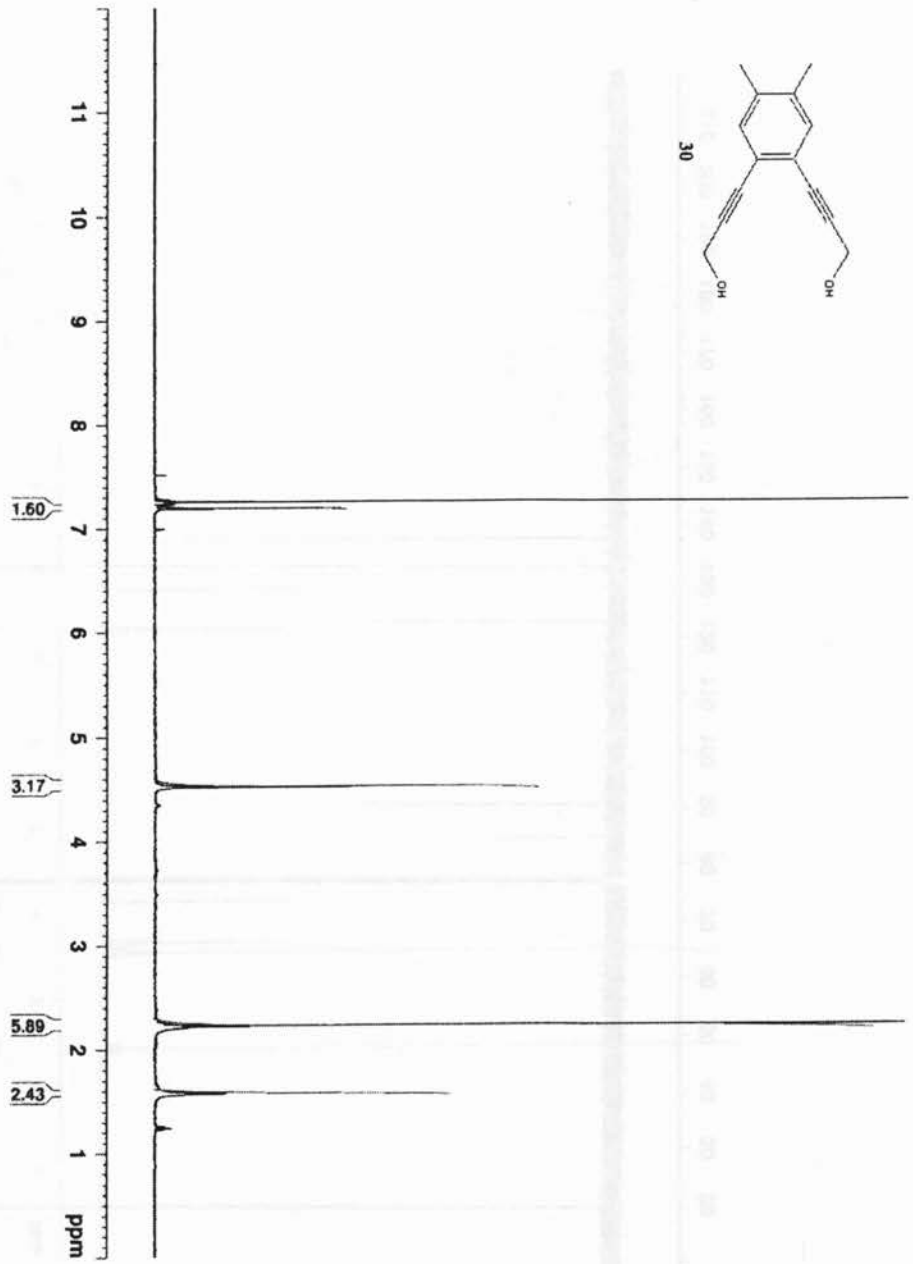
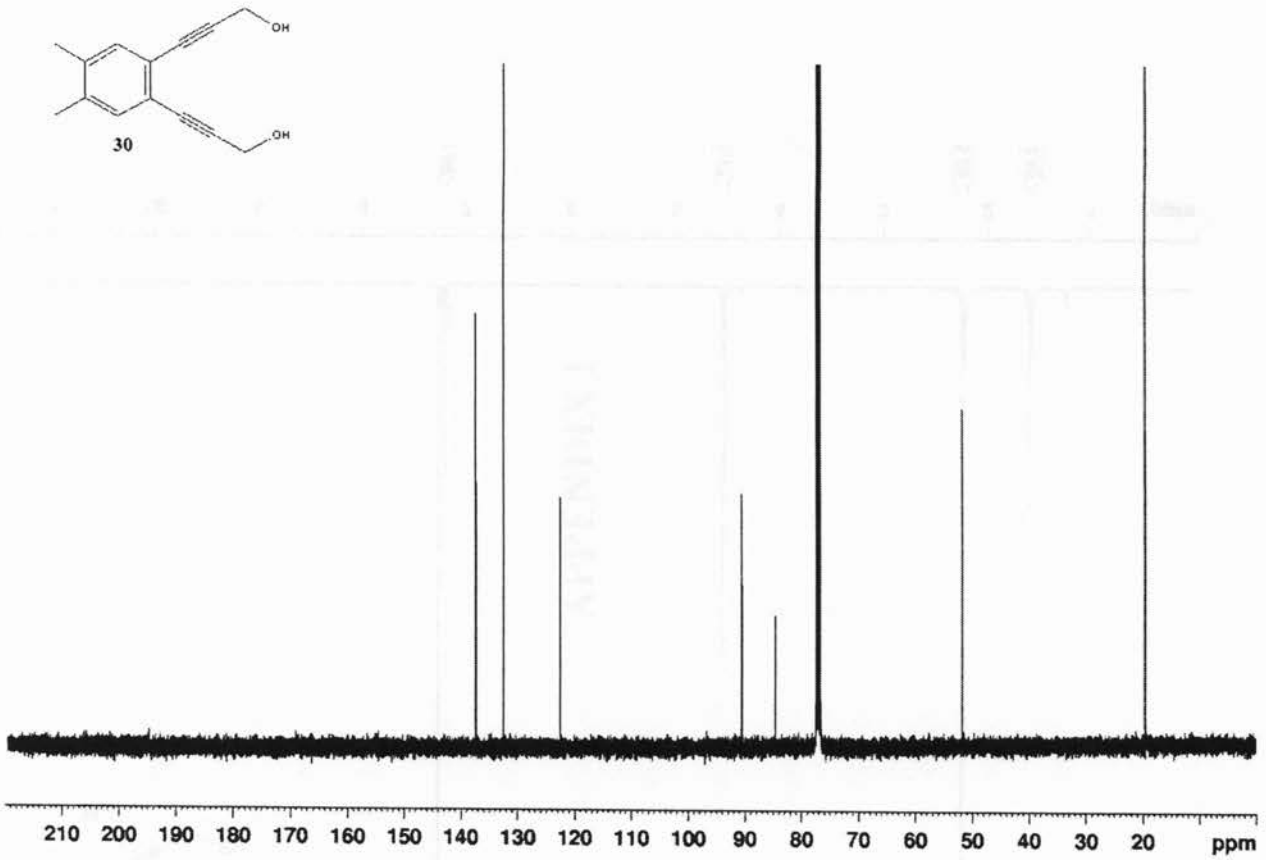
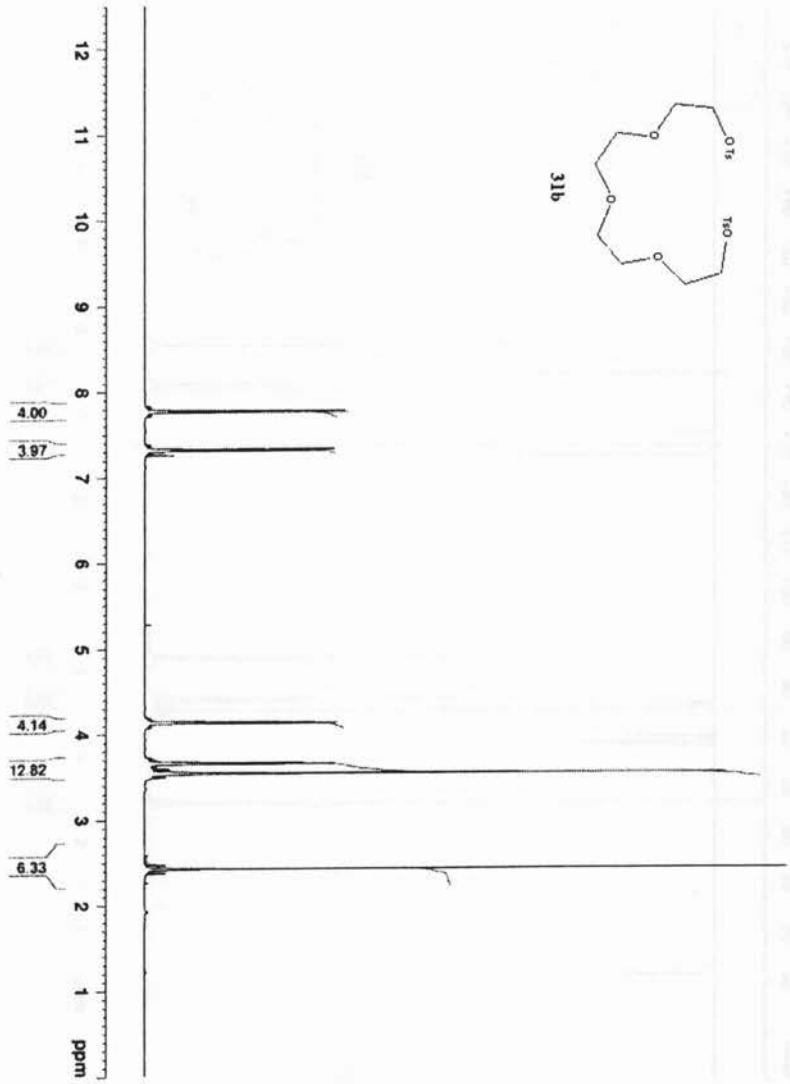
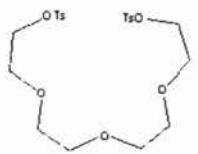
APPENDIX I


30
OH
OH
1.60
3.17
5.89
2.43
11
10
9
8
7
6
5
4
3
2
1
ppm


OH
OH
30
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

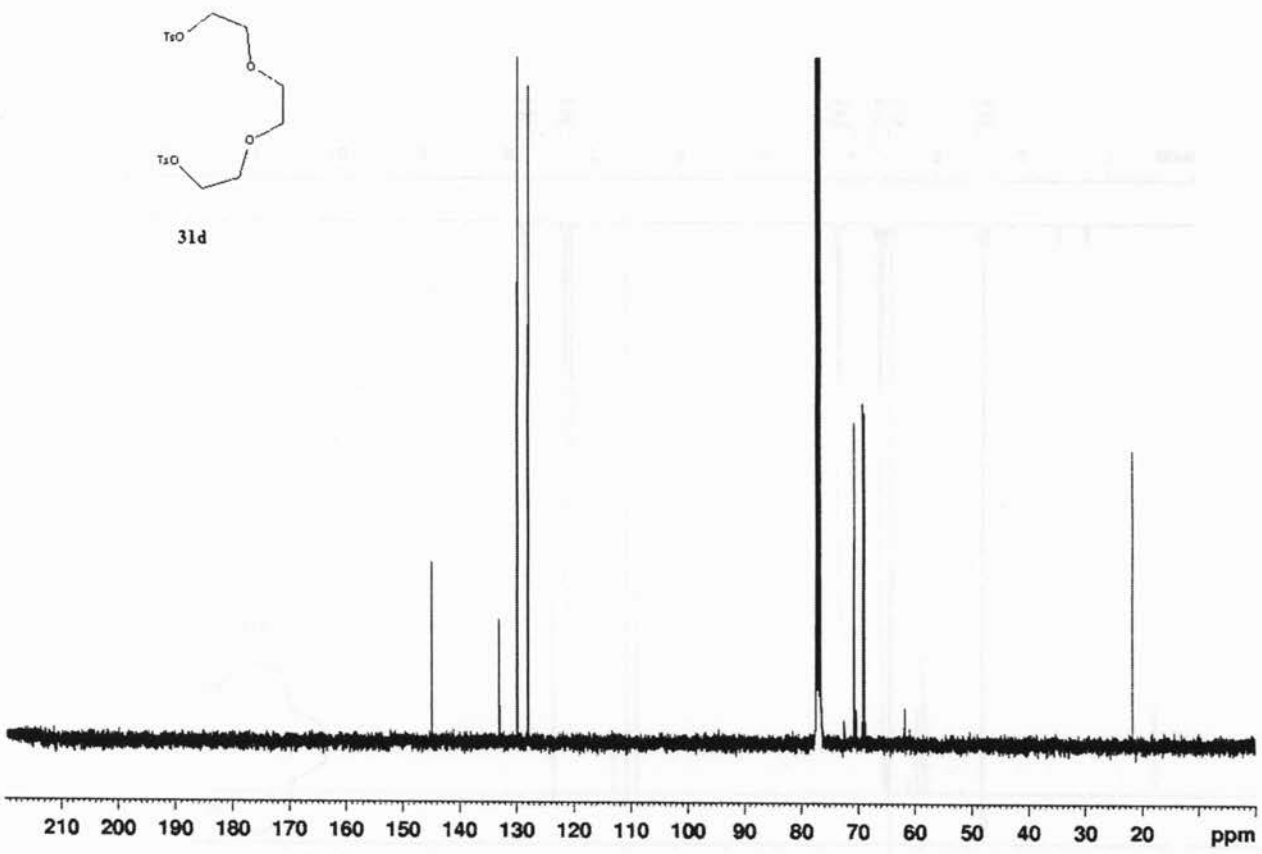

4.00
3.97
4.14
12.82
6.33
12
11
10
9
8
7
6
5
4
3
2
1
ppm
31b
OTs
TsO

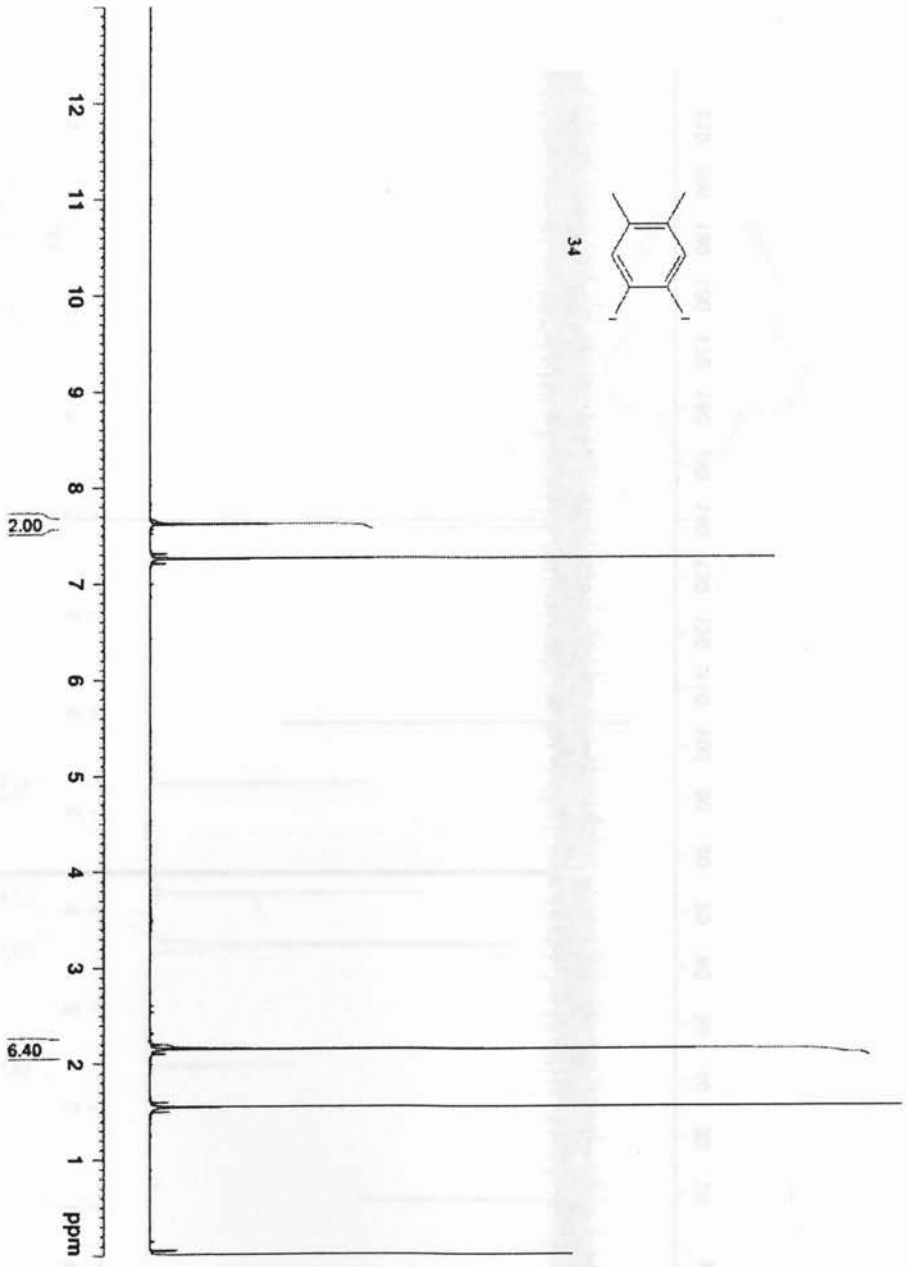

OTs
TsO
O
O
O

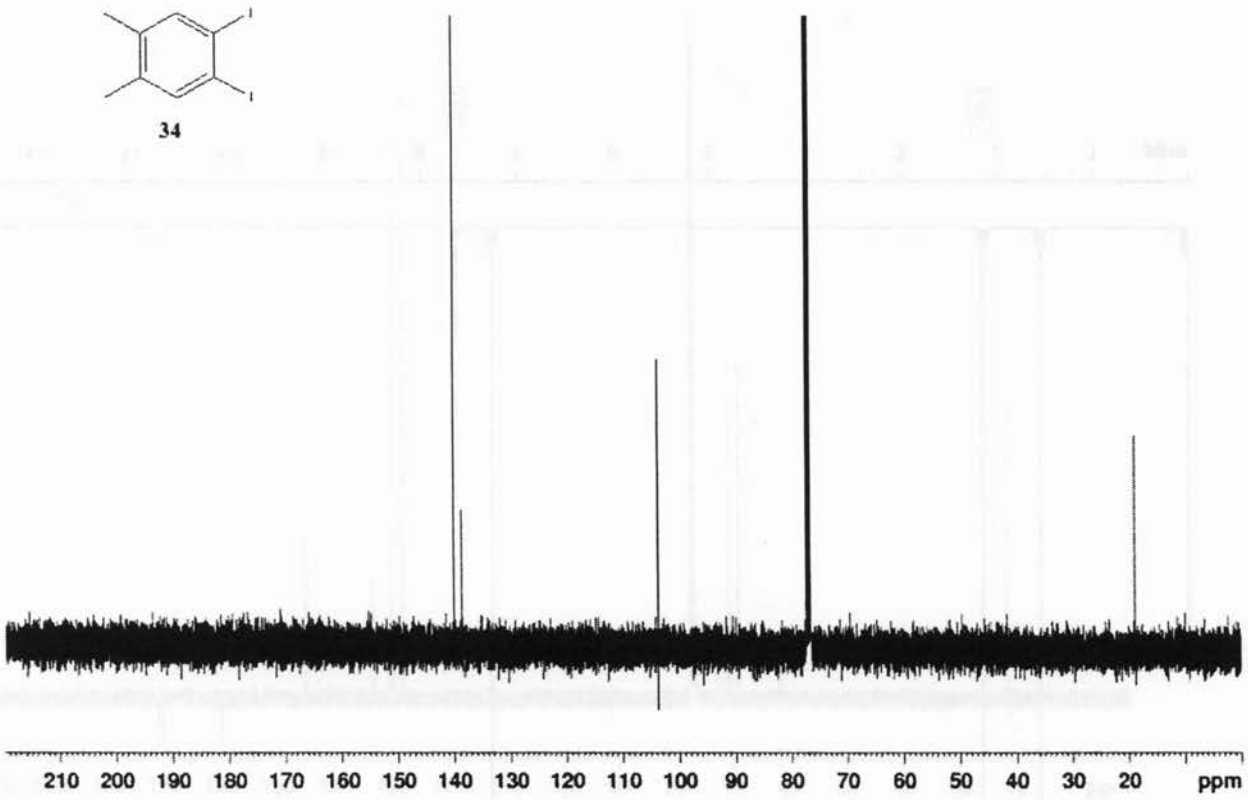
31b

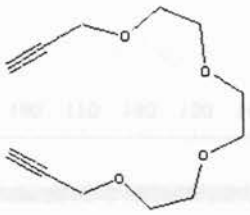
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

31d
TsO
OTs
4.00
3.96
4.03
5.65
3.75
6.22
ppm

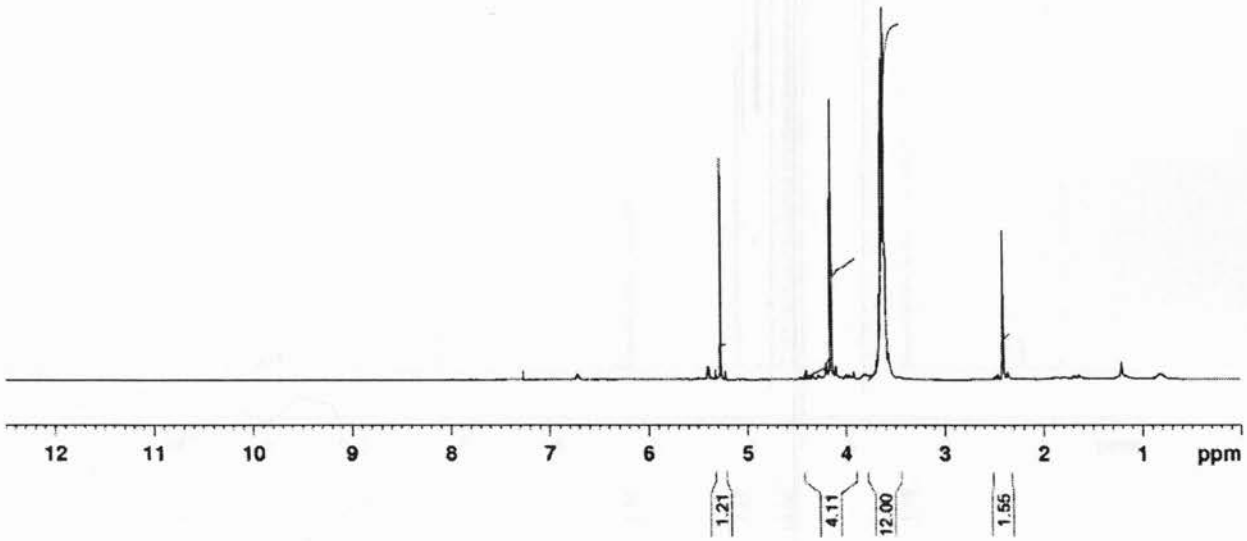

TsO
O
O
TsO
31d
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

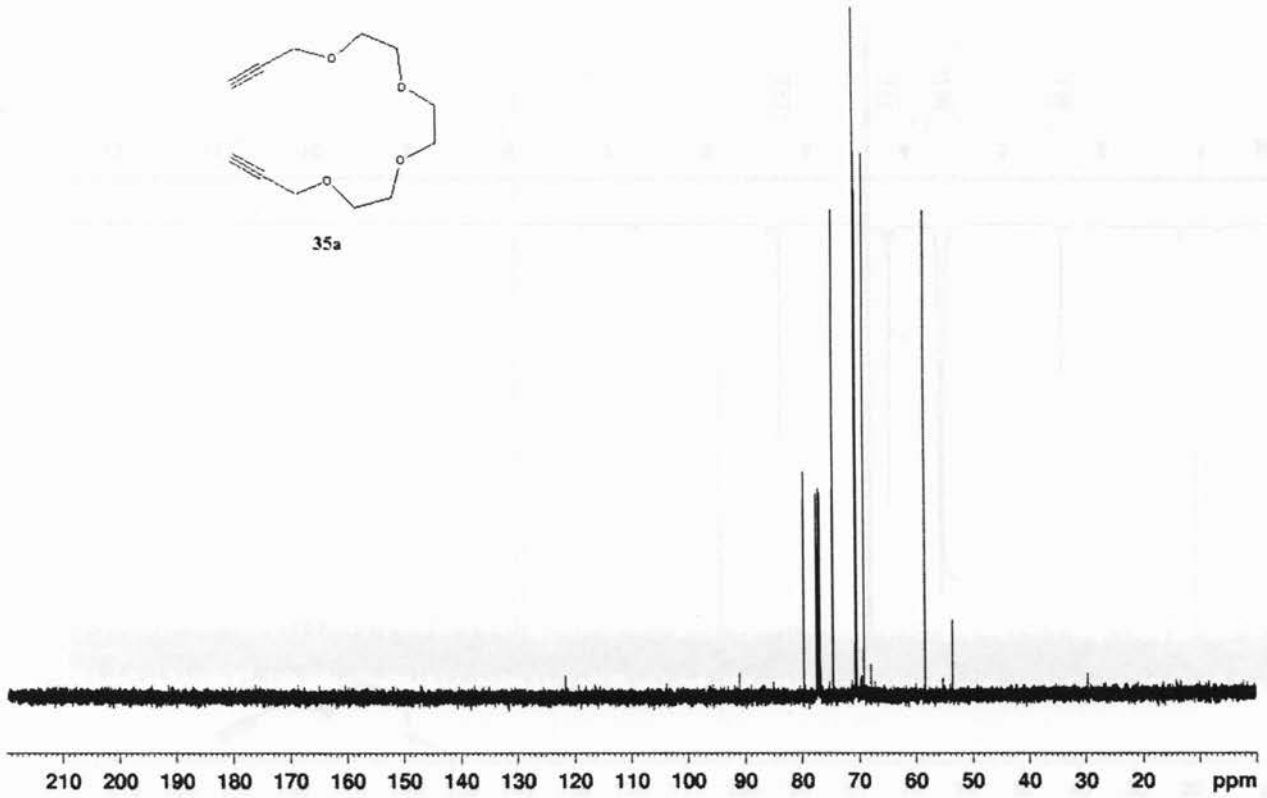

34
2.00
6.40
12
11
10
9
8
7
6
5
4
3
2
1
ppm


I
I
34
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

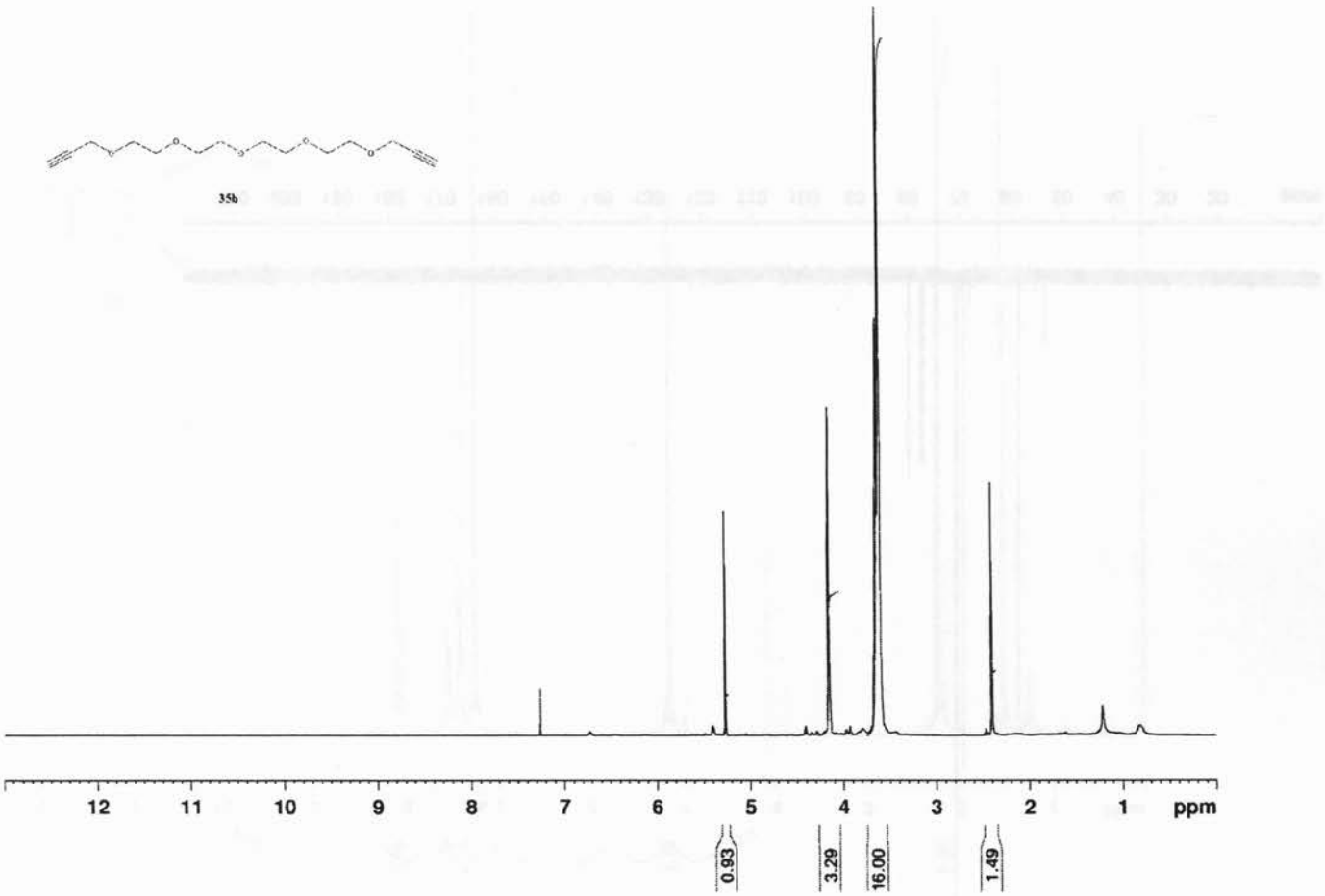


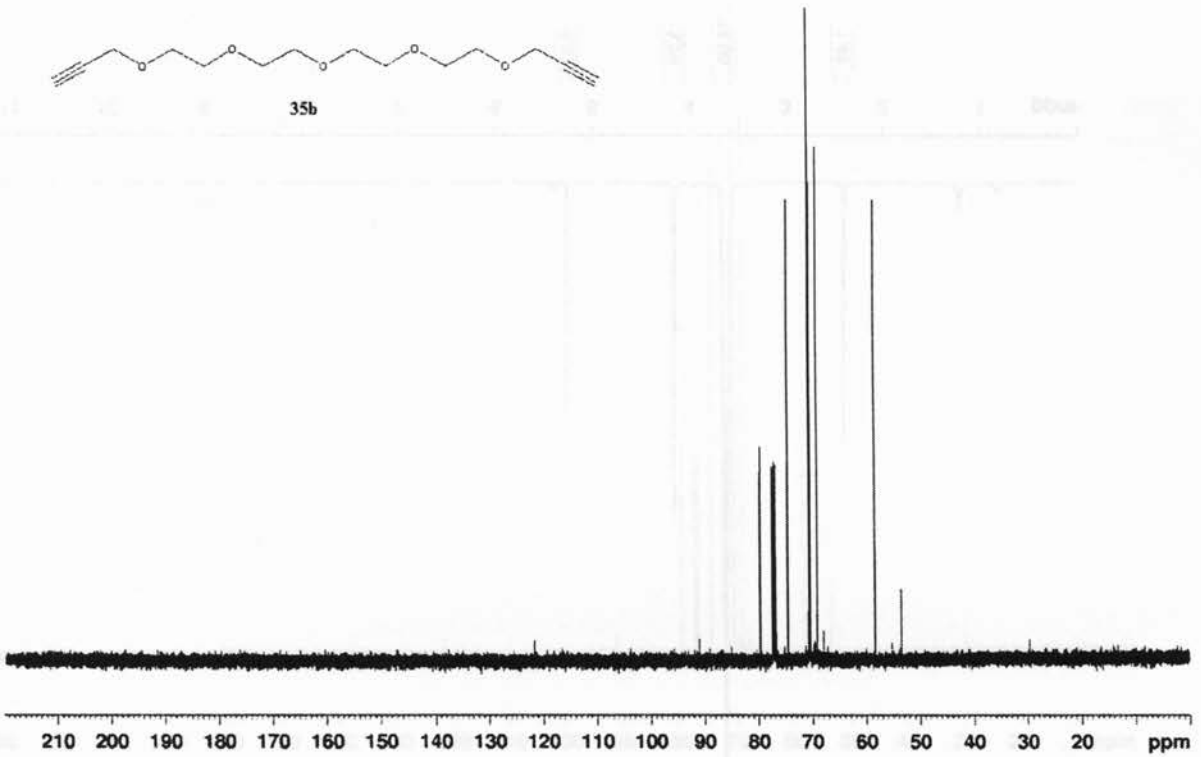
35a

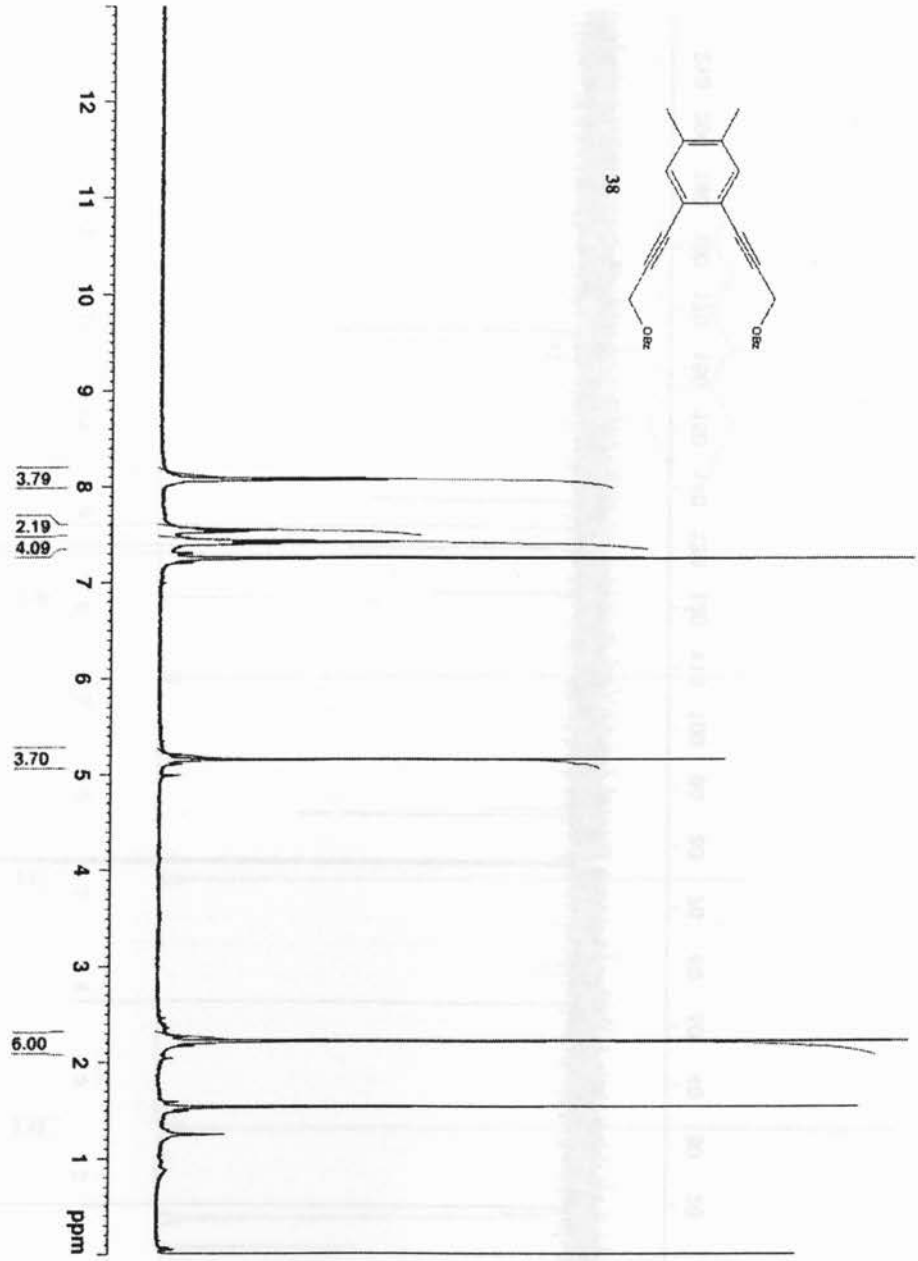


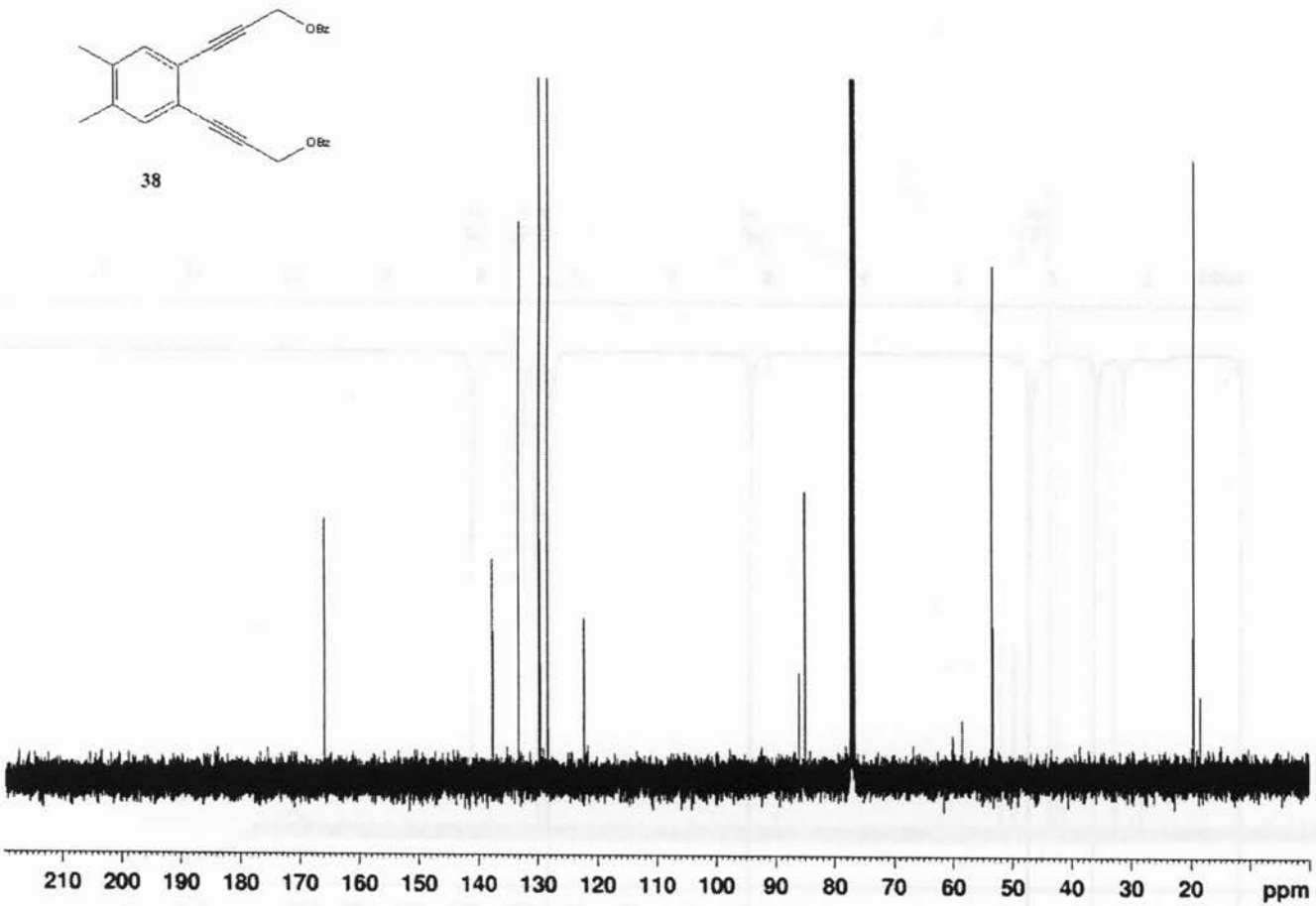

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

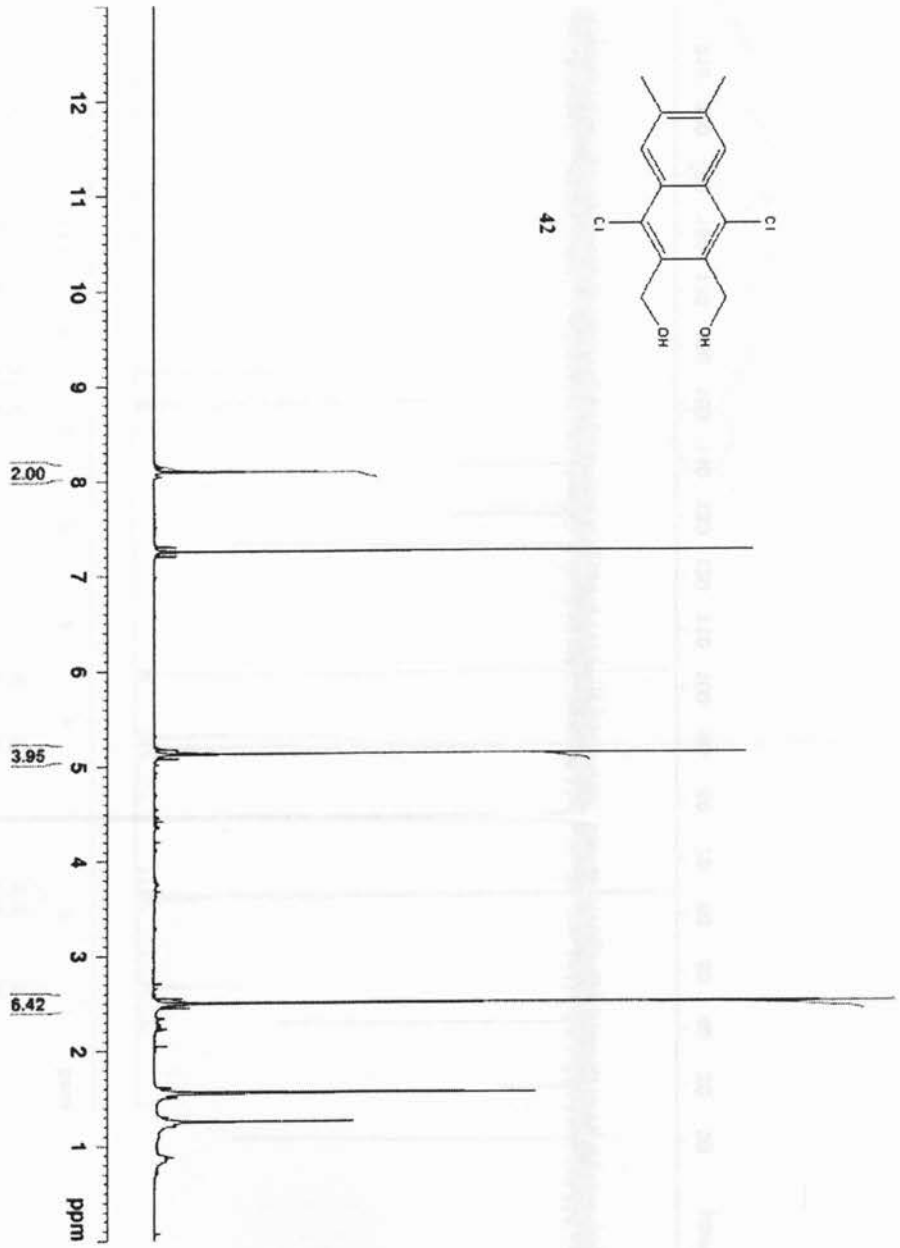
35a


35b
12
11
10
9
8
7
6
5
4
3
2
1
ppm
0.93
3.29
16.00
1.49

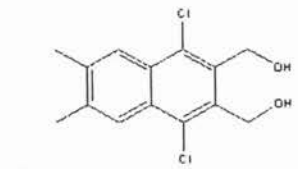

35b
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


38
OBz
OBz
3.79
2.19
4.09
3.70
6.00
12
11
10
9
8
7
6
5
4
3
2
1
ppm


OBz
OBz
38
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

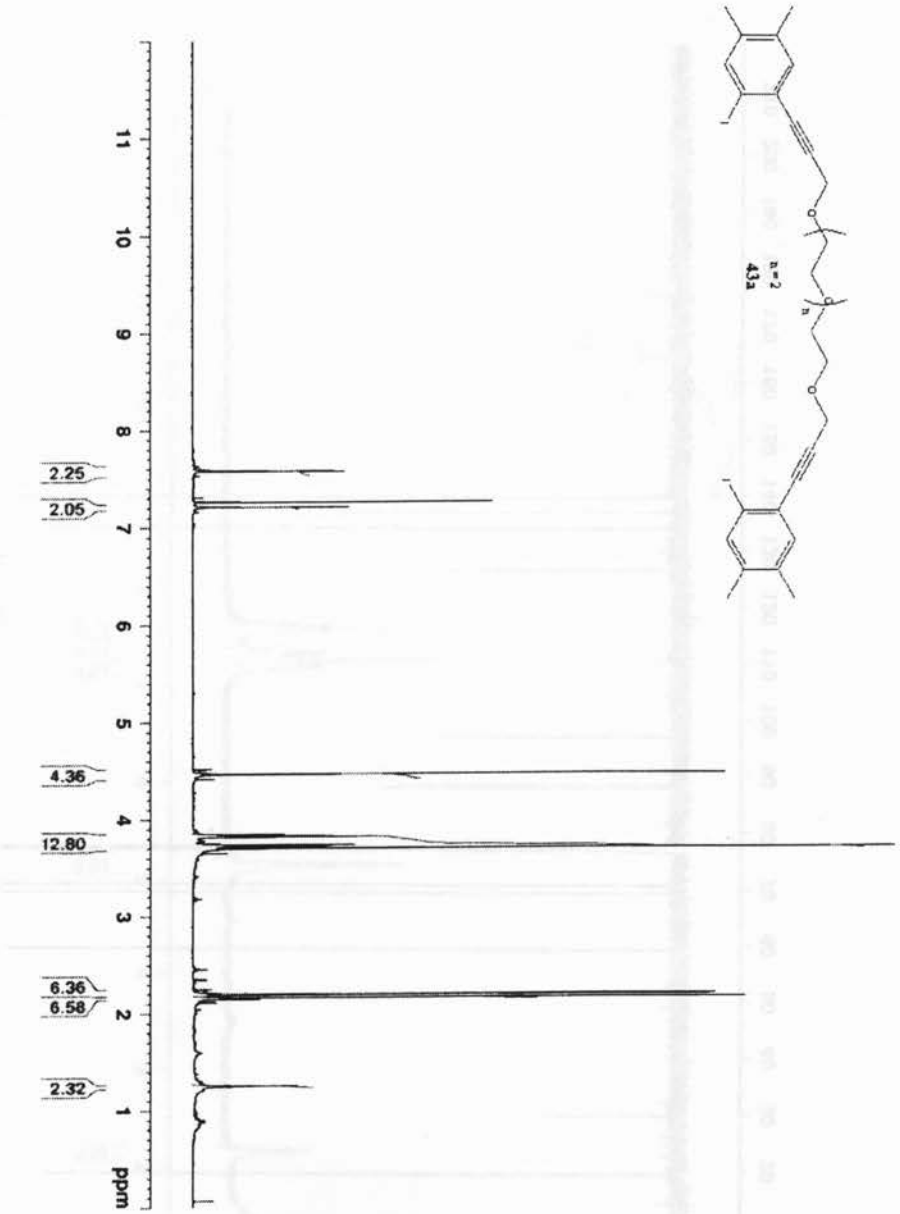


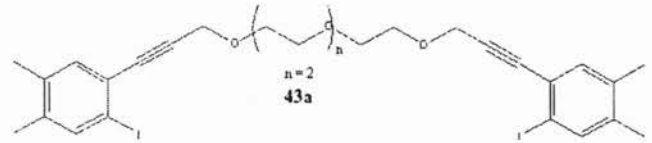
42

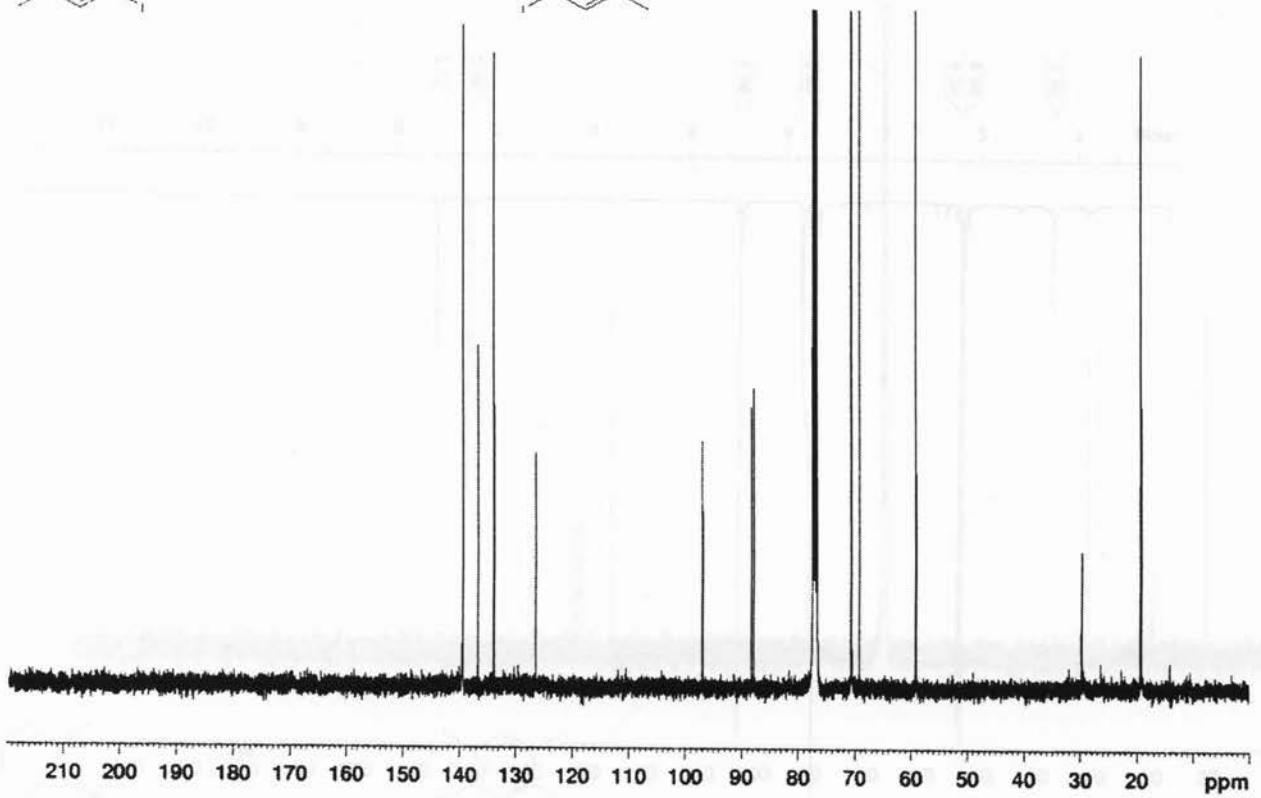

Cl
OH
OH
Cl

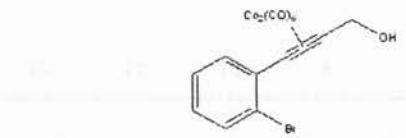
42

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

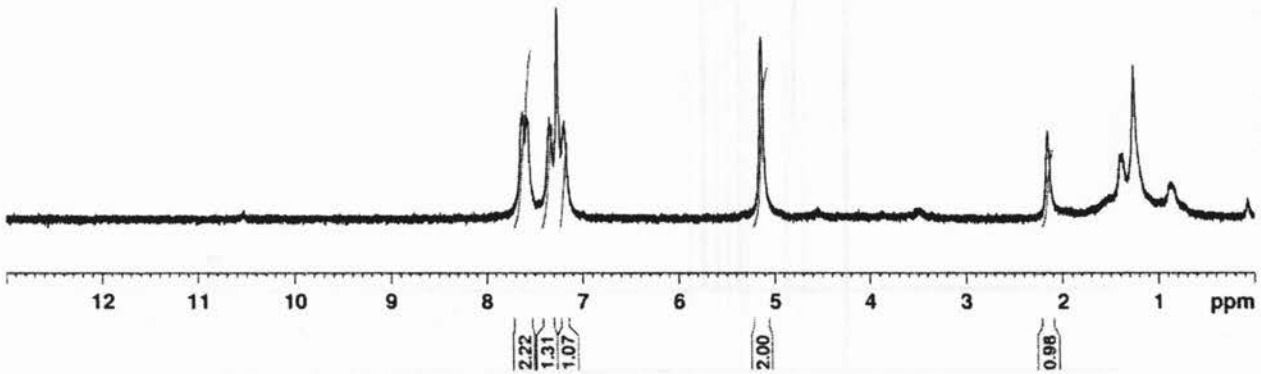

2.25
2.05
4.36
12.80
6.36
6.58
2.32
ppm
n = 2
43a

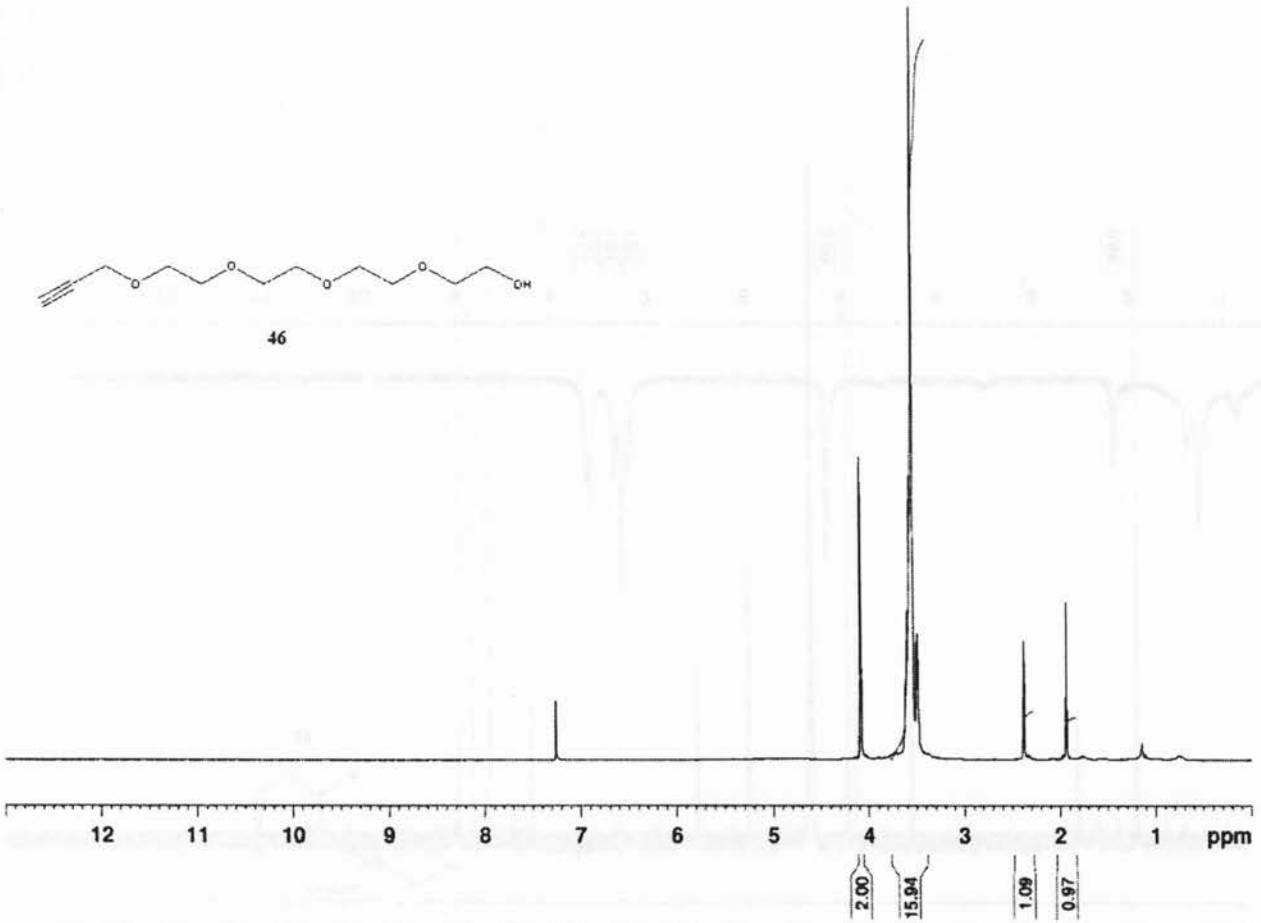

n = 2
43a


210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

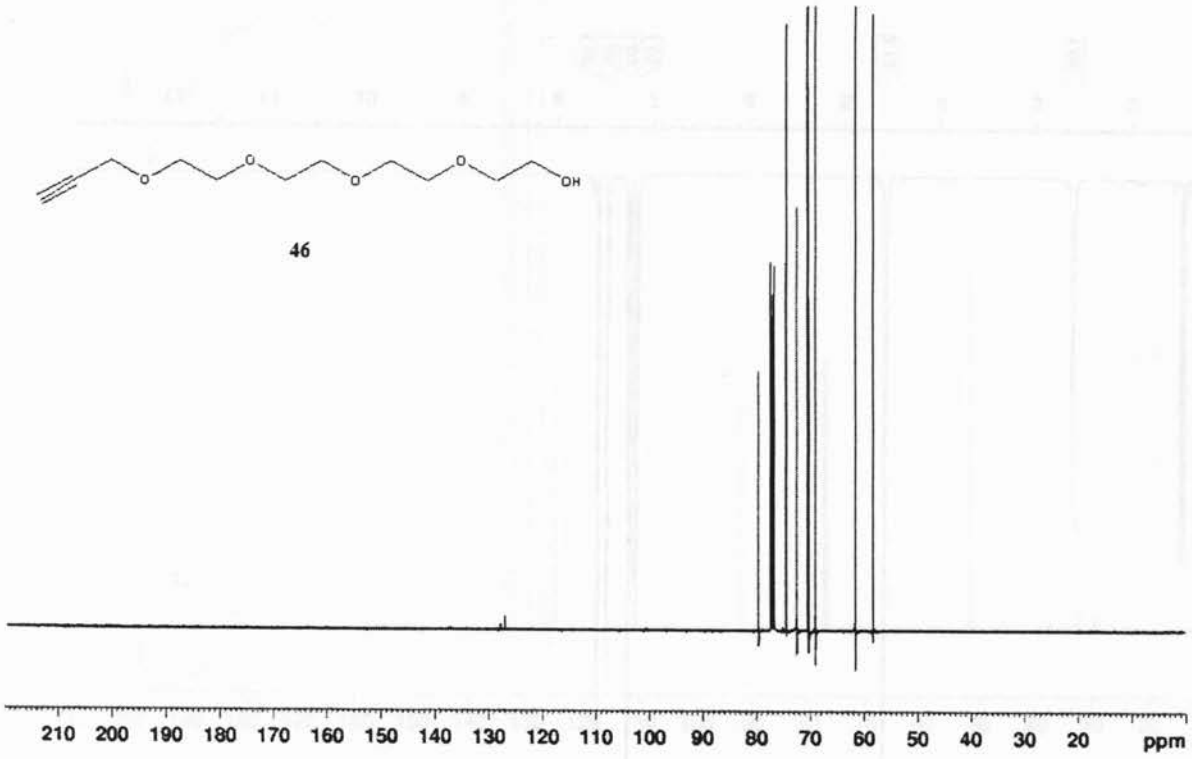


45

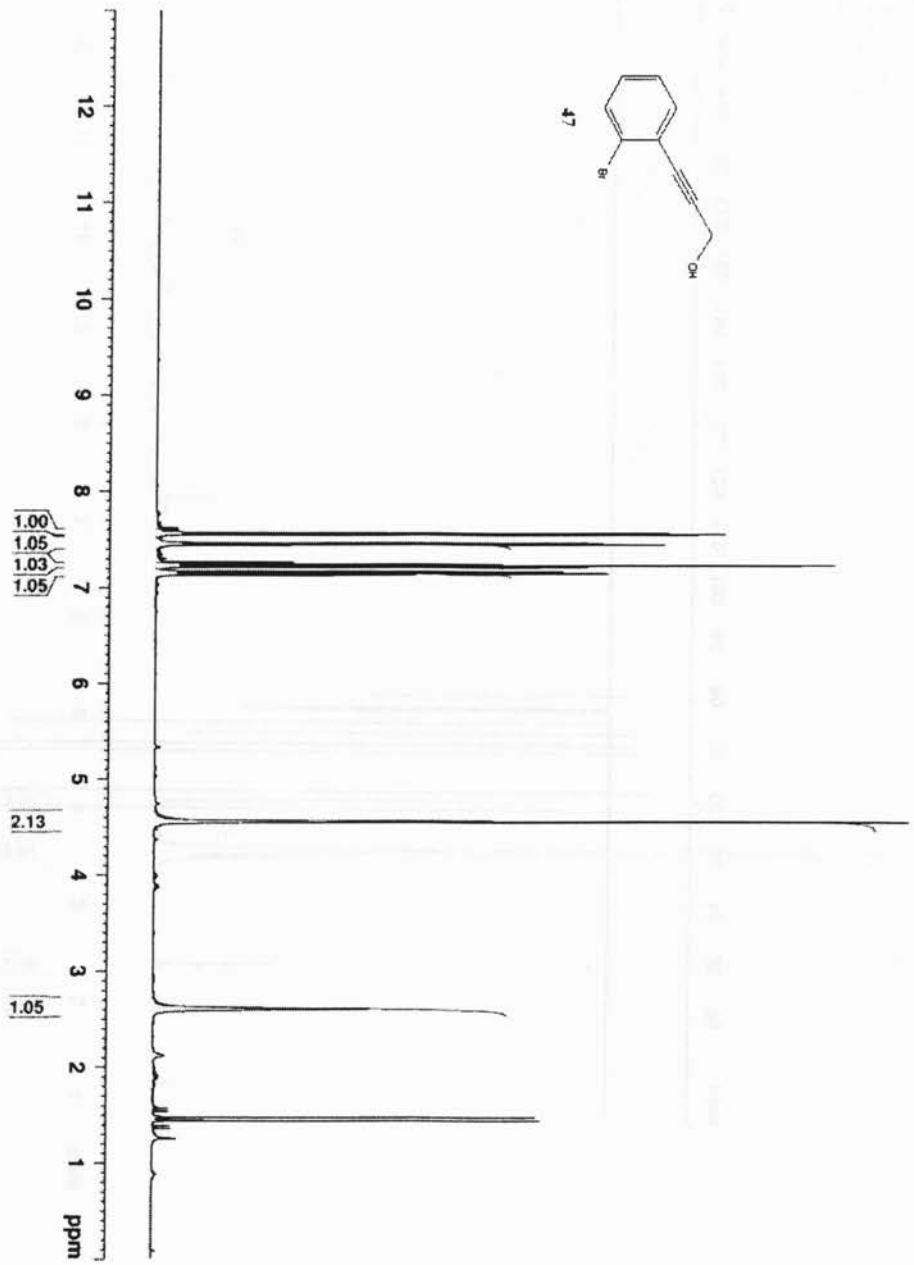


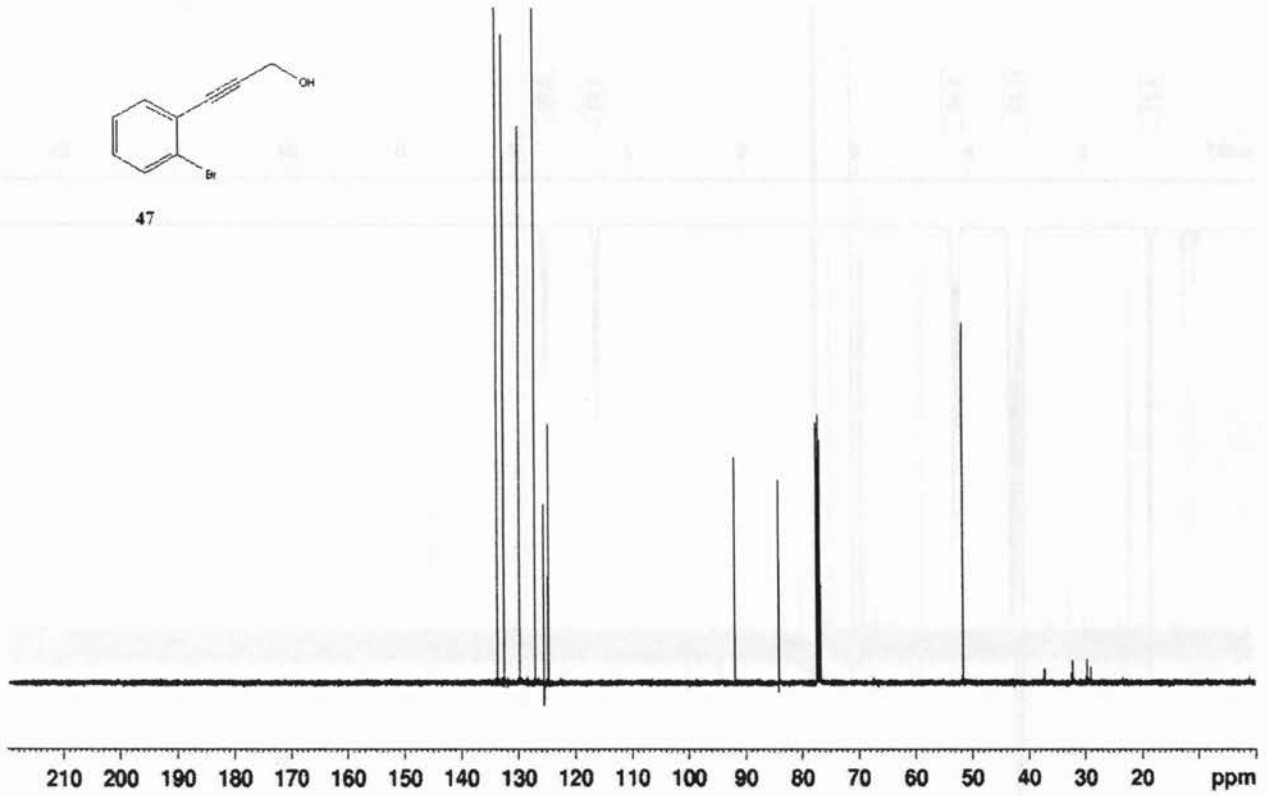


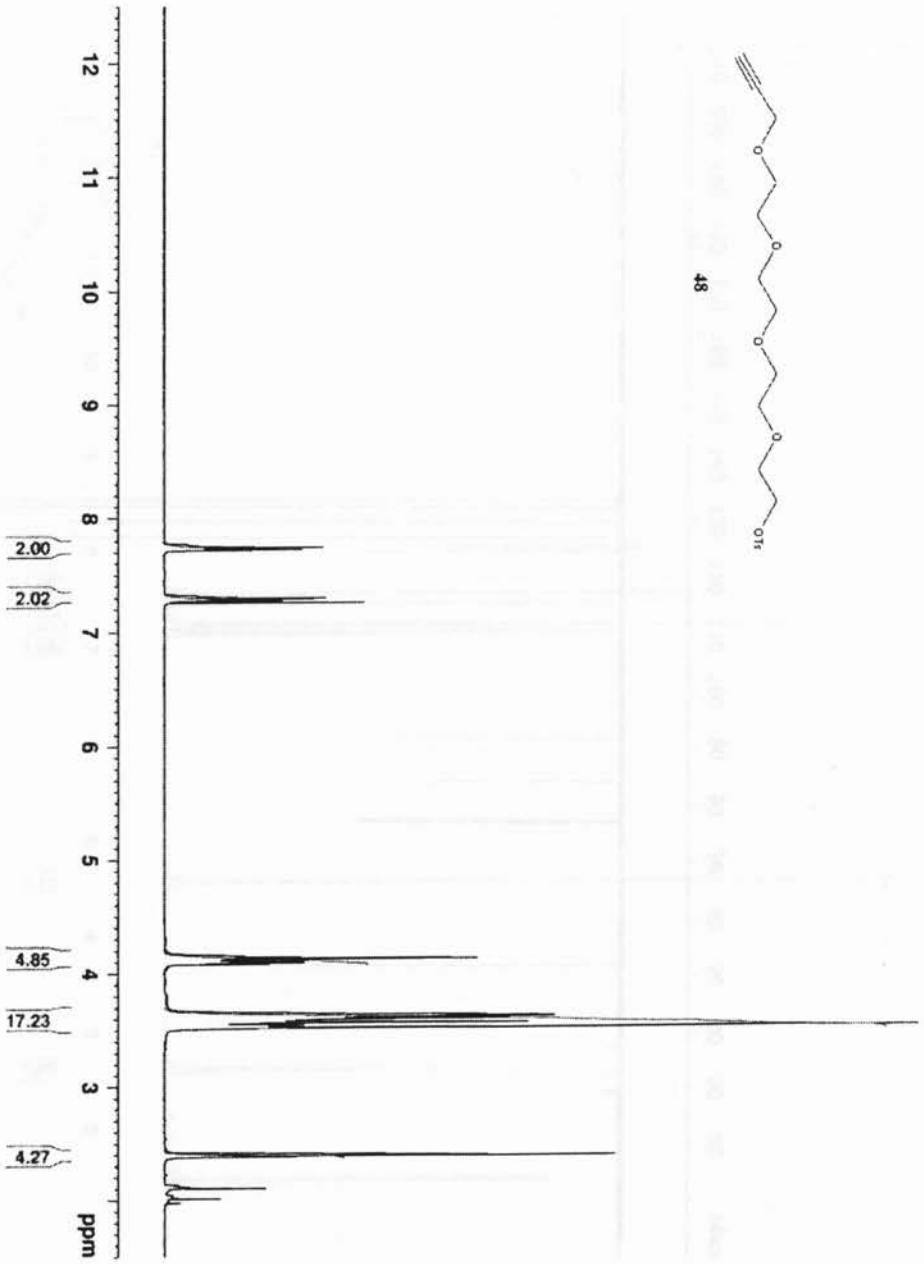
46


O
O
O
O
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

46

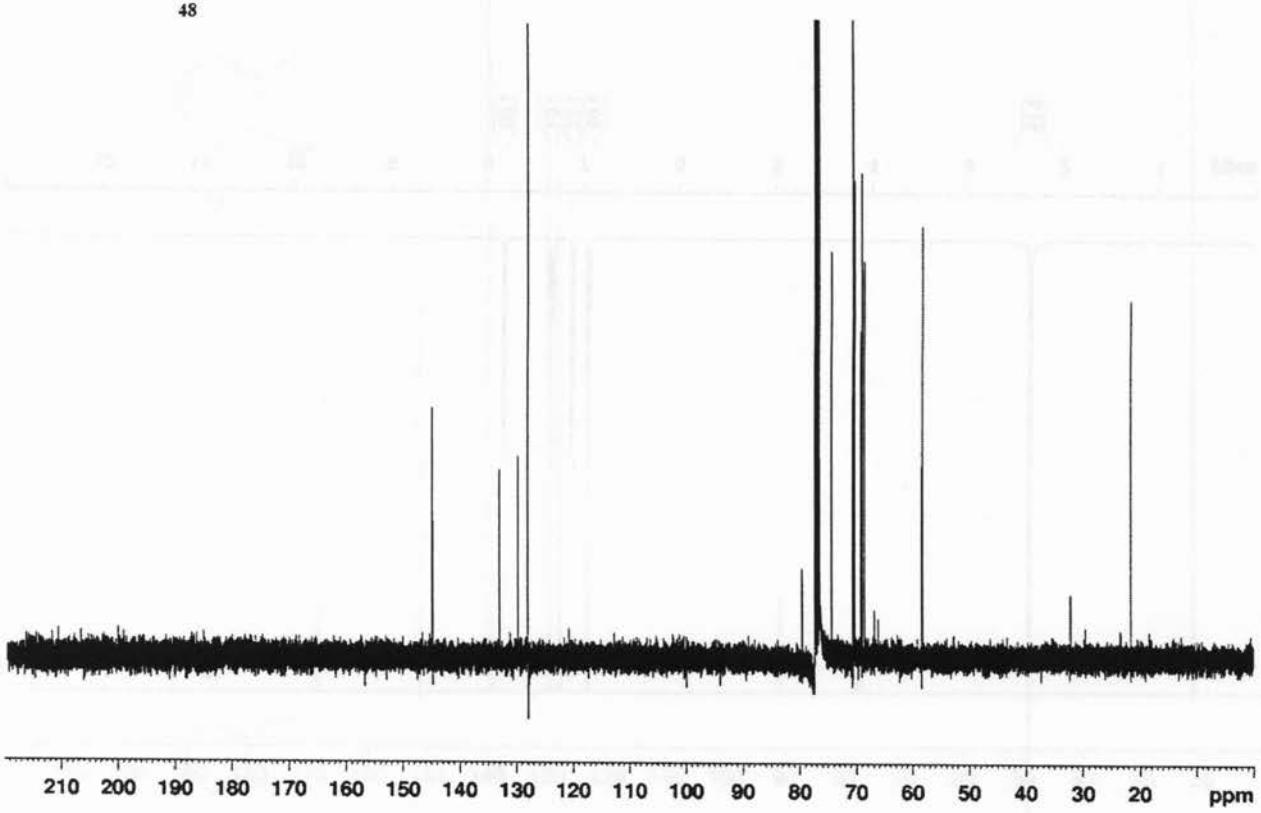

47
Br
OH
1.00
1.05
1.03
1.05
2.13
1.05
12
11
10
9
8
7
6
5
4
3
2
1
ppm

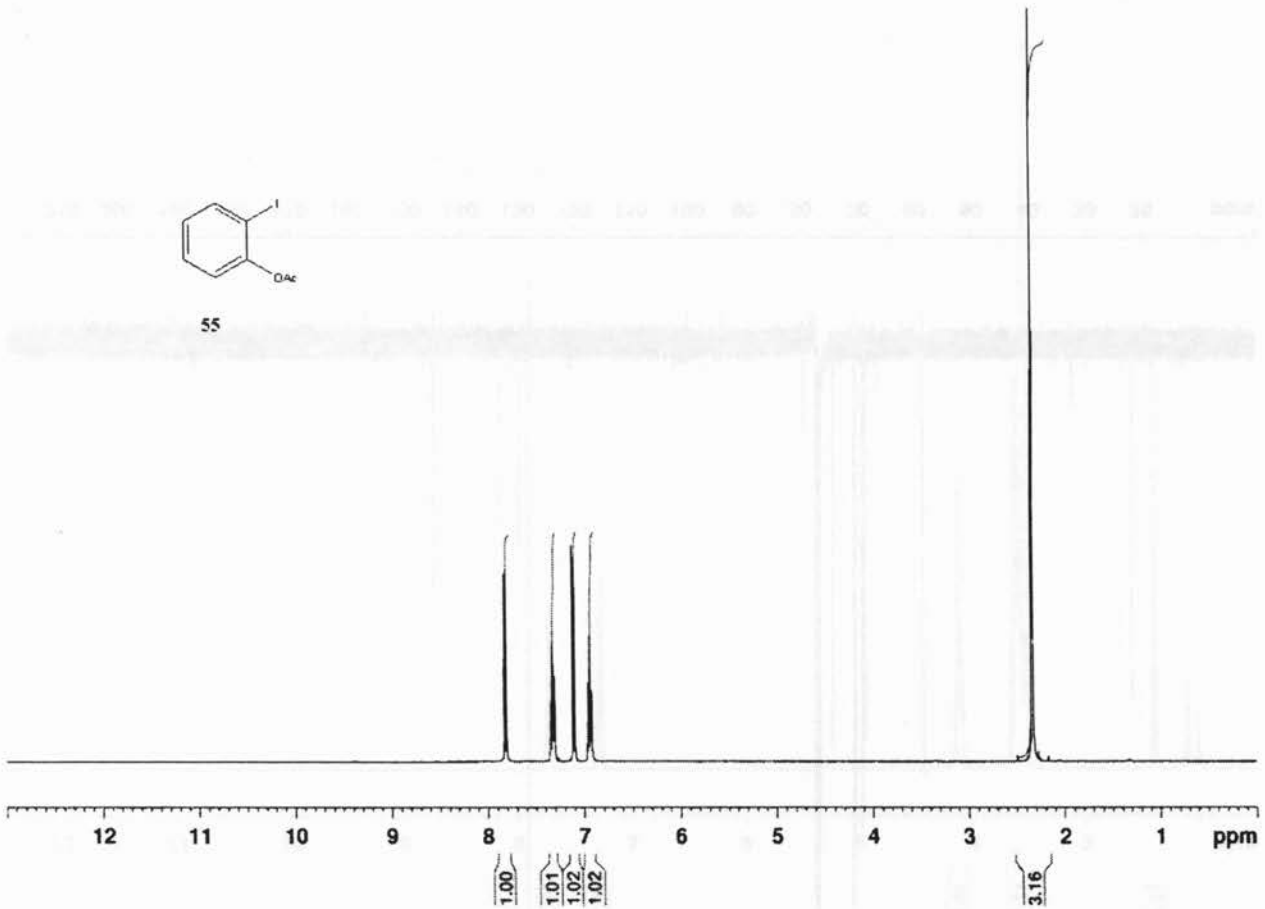

OH
Br
47
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


12
11
10
9
8
7
6
5
4
3
ppm
2.00
2.02
4.85
17.23
4.27
48

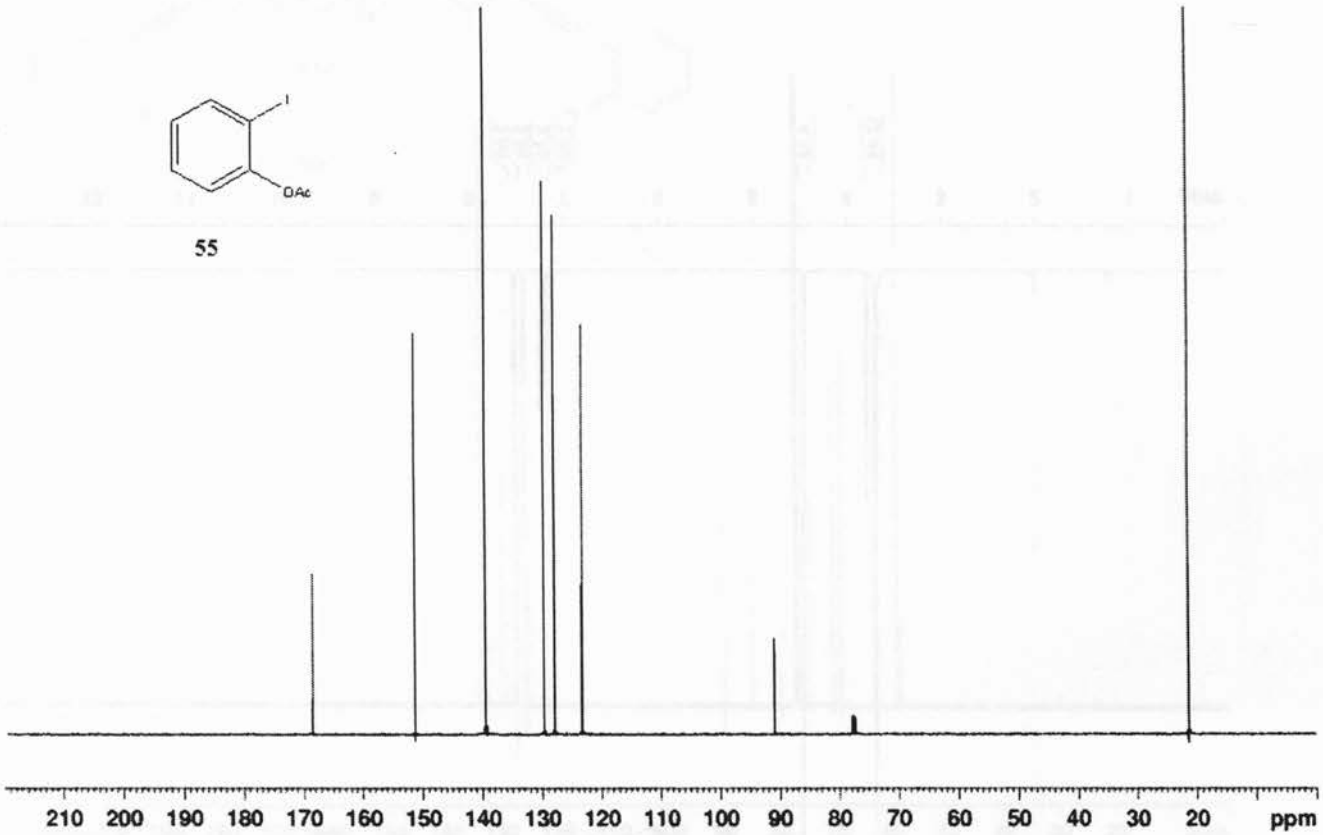

OTs

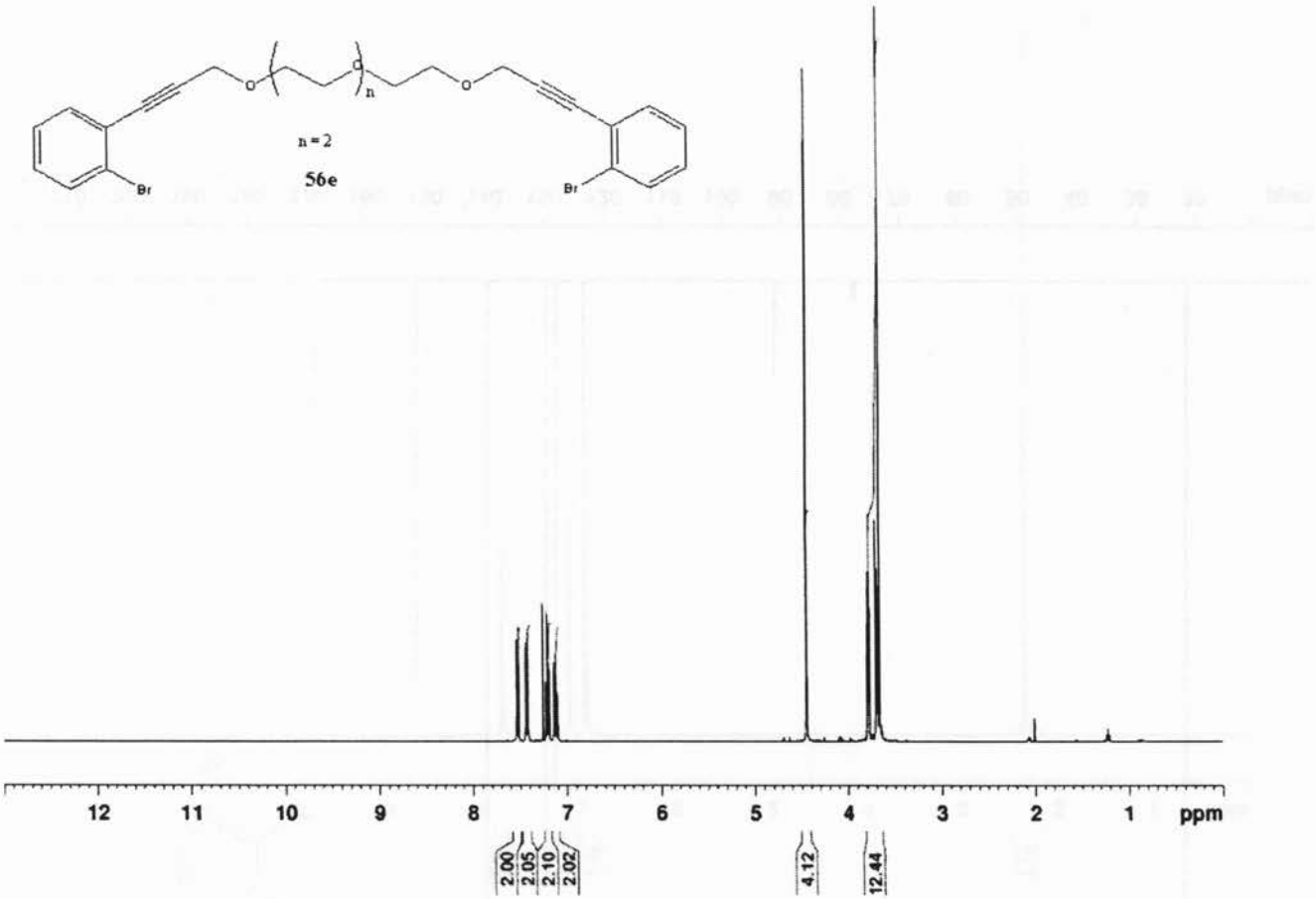
48

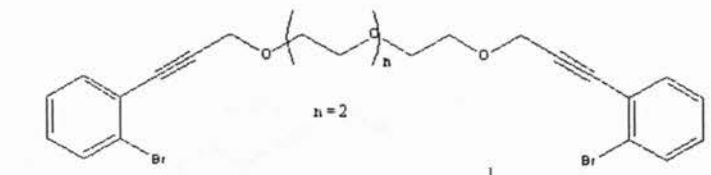

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm



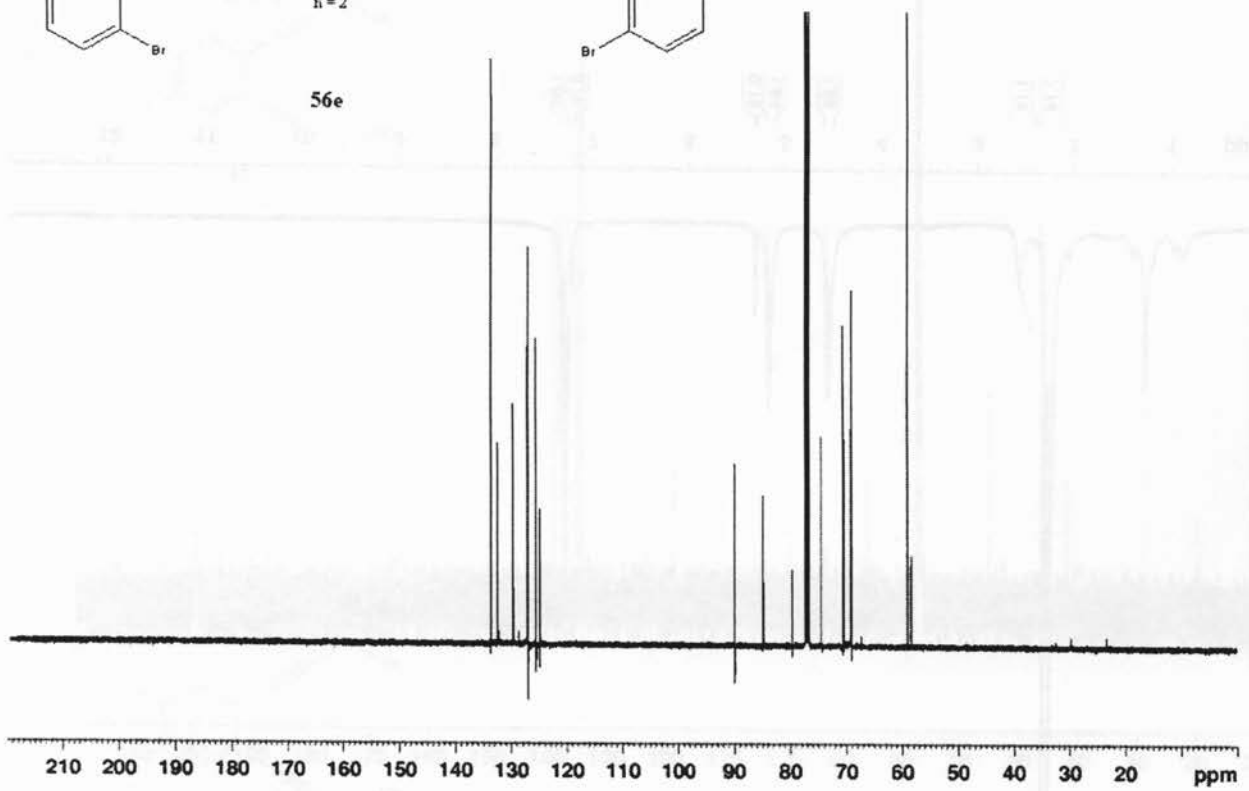
55

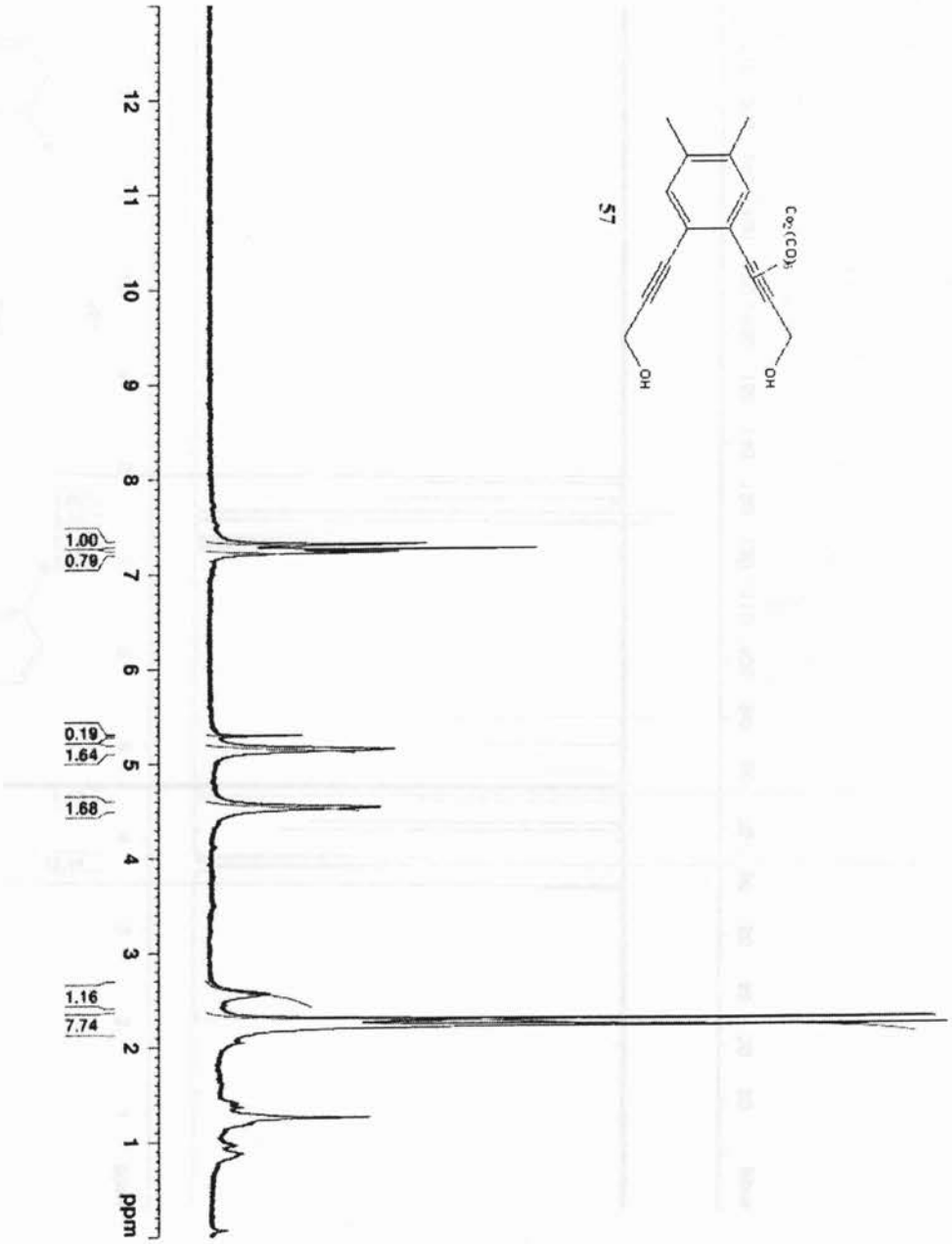

I
OAc
55
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

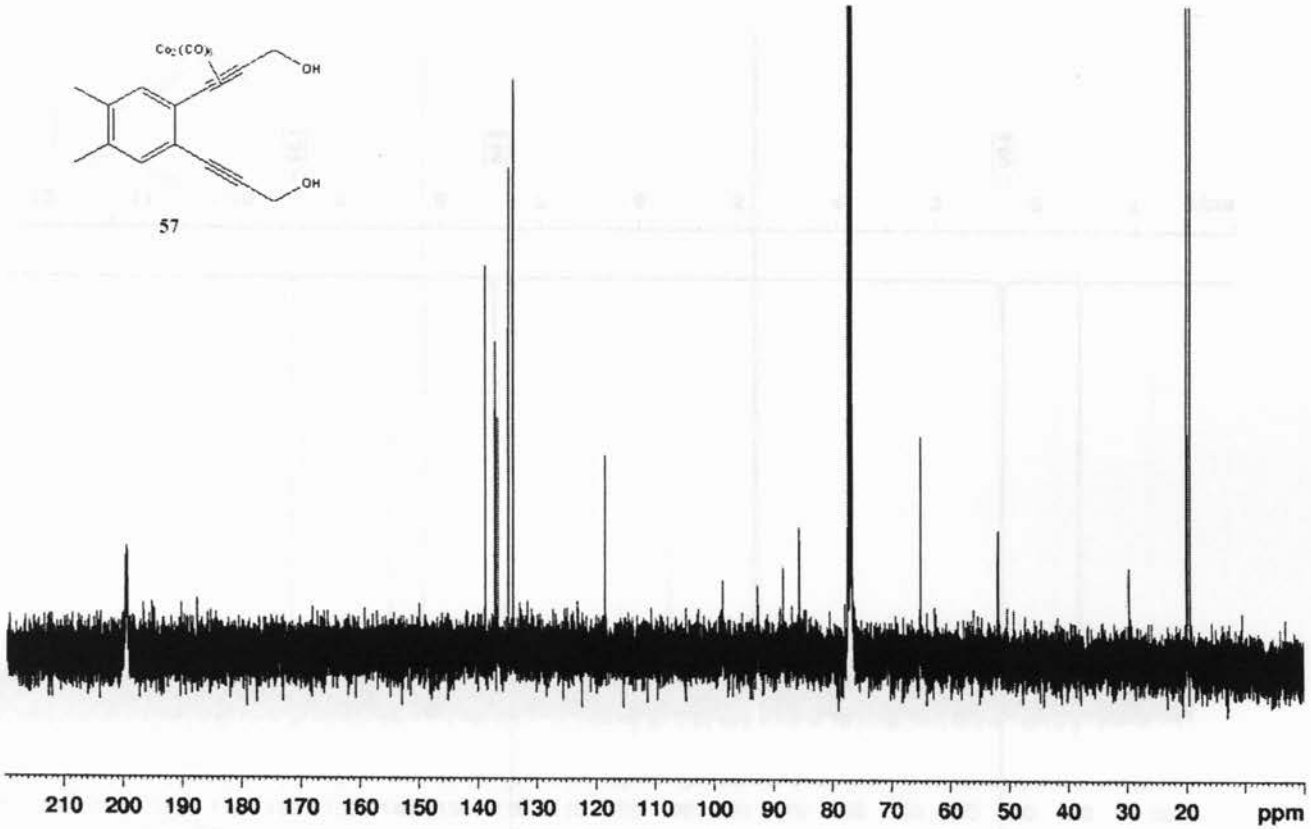

n = 2
56e
Br
Br
12
11
10
9
8
7
6
5
4
3
2
1
ppm
2.00
2.05
2.10
2.02
4.12
12.44


n = 2
Br
Br

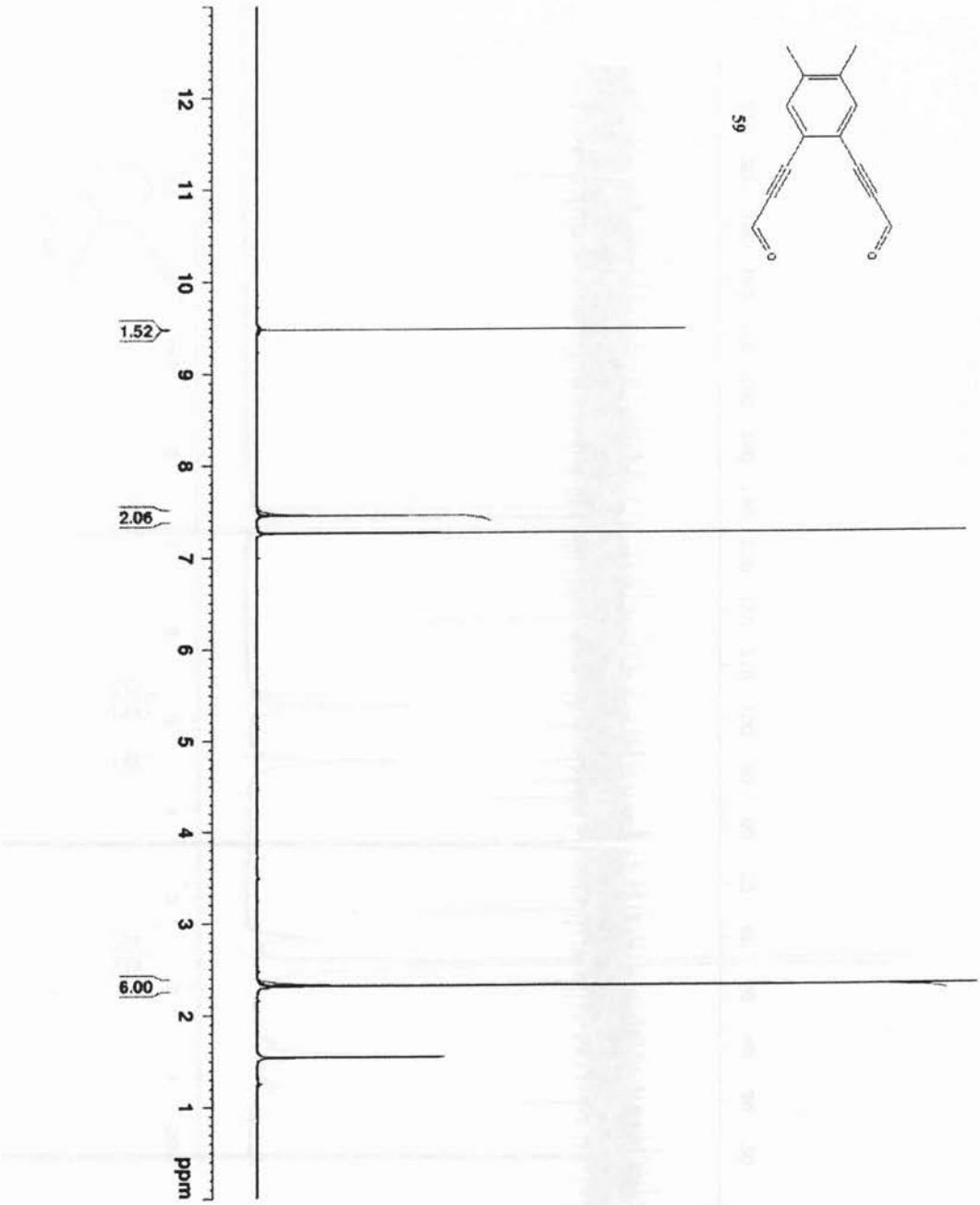
56e

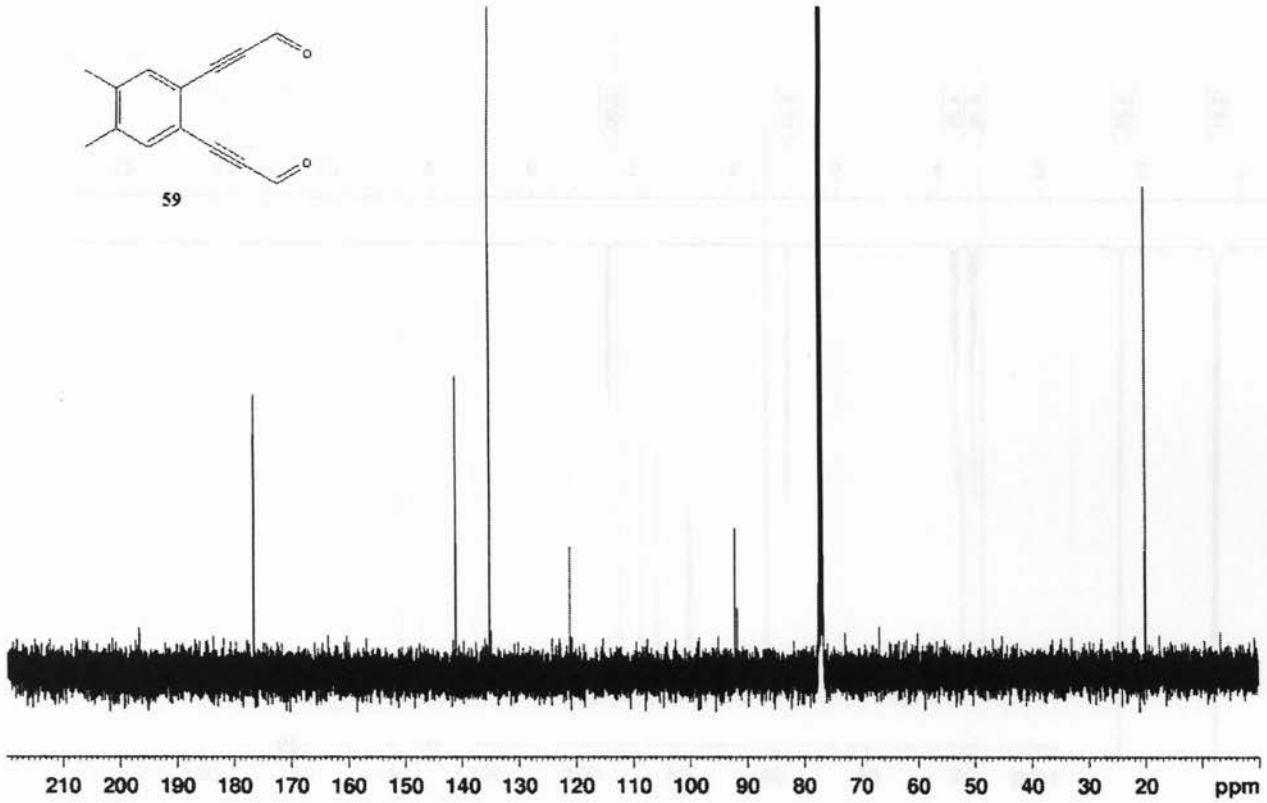

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


57
Co2(CO)6
HO
HO
1.00
0.79
0.19
1.64
1.68
1.16
7.74
12
11
10
9
8
7
6
5
4
3
2
1
ppm


Co2(CO)6
OH
OH
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

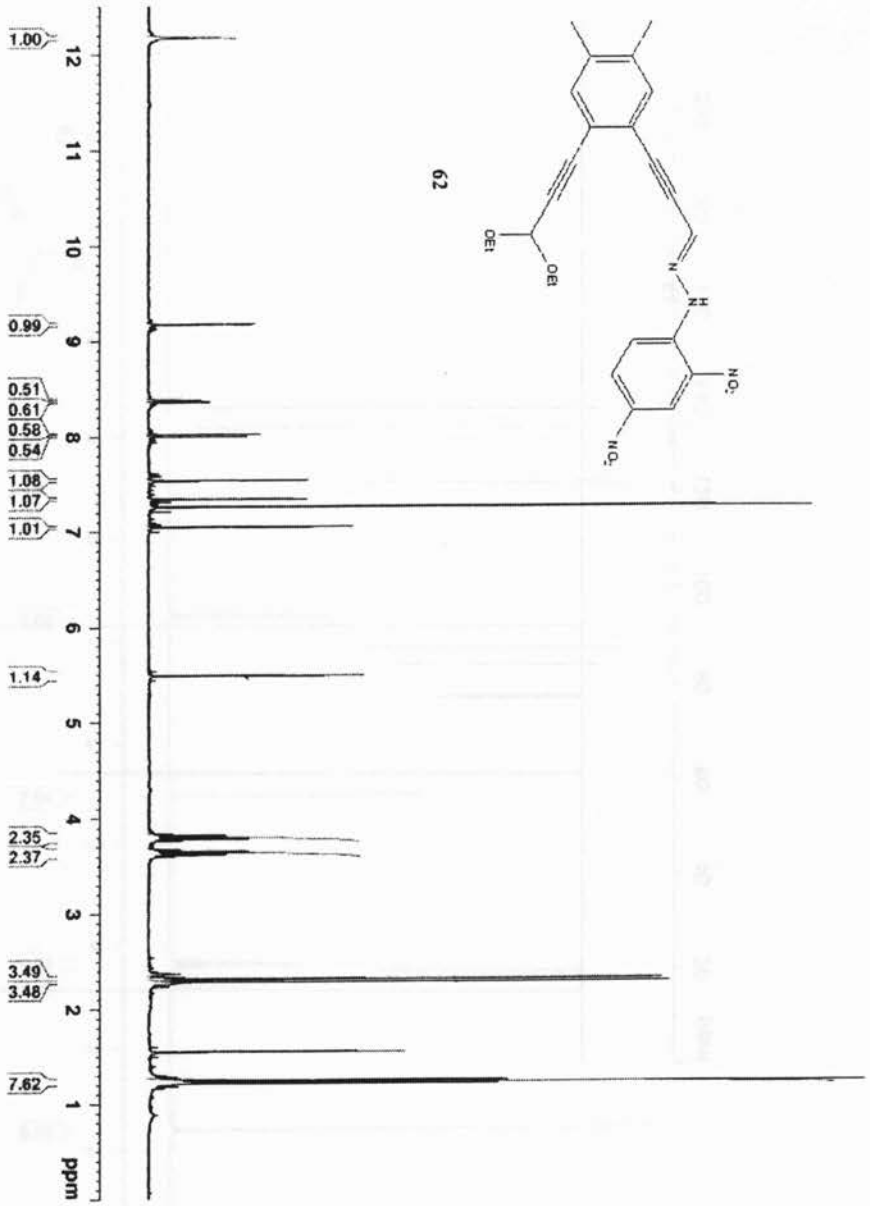
57

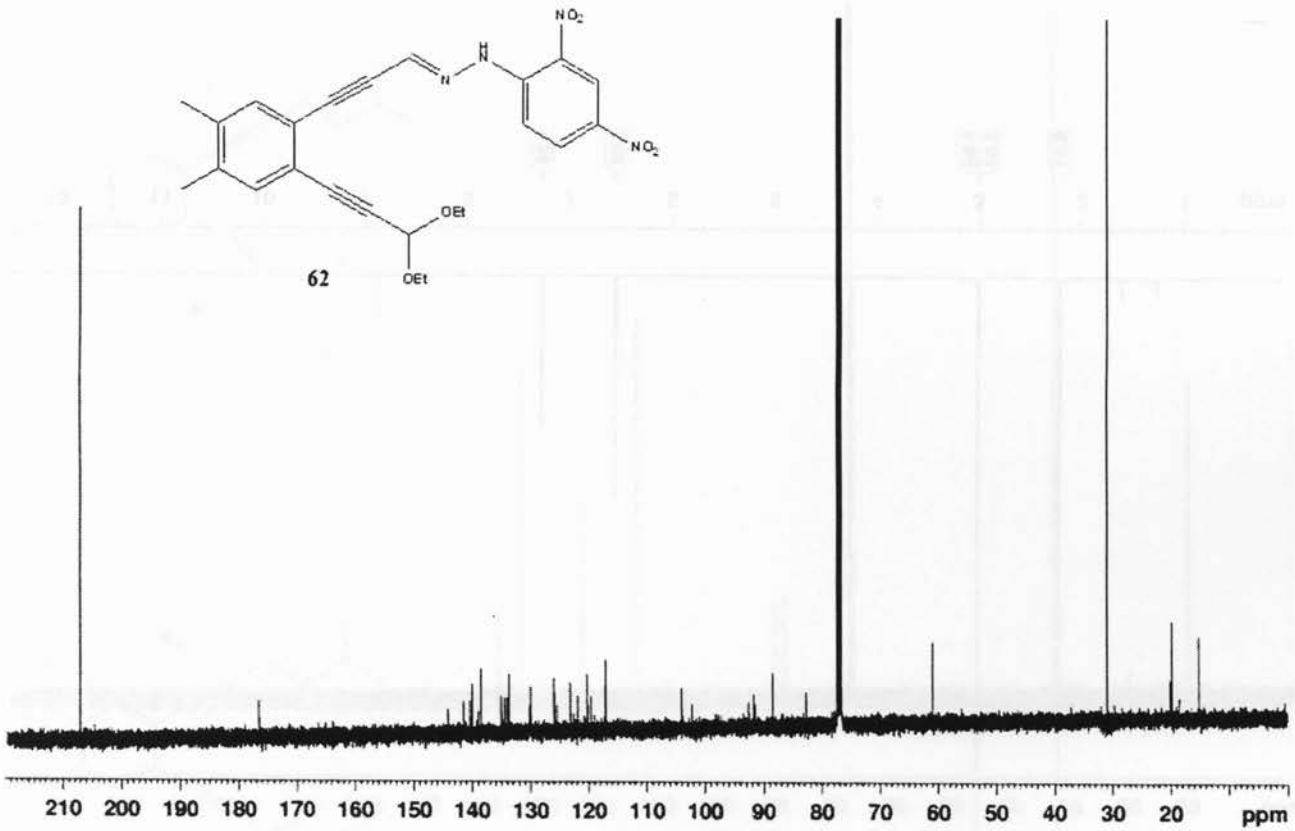

59
O
O
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.52
2.06
6.00

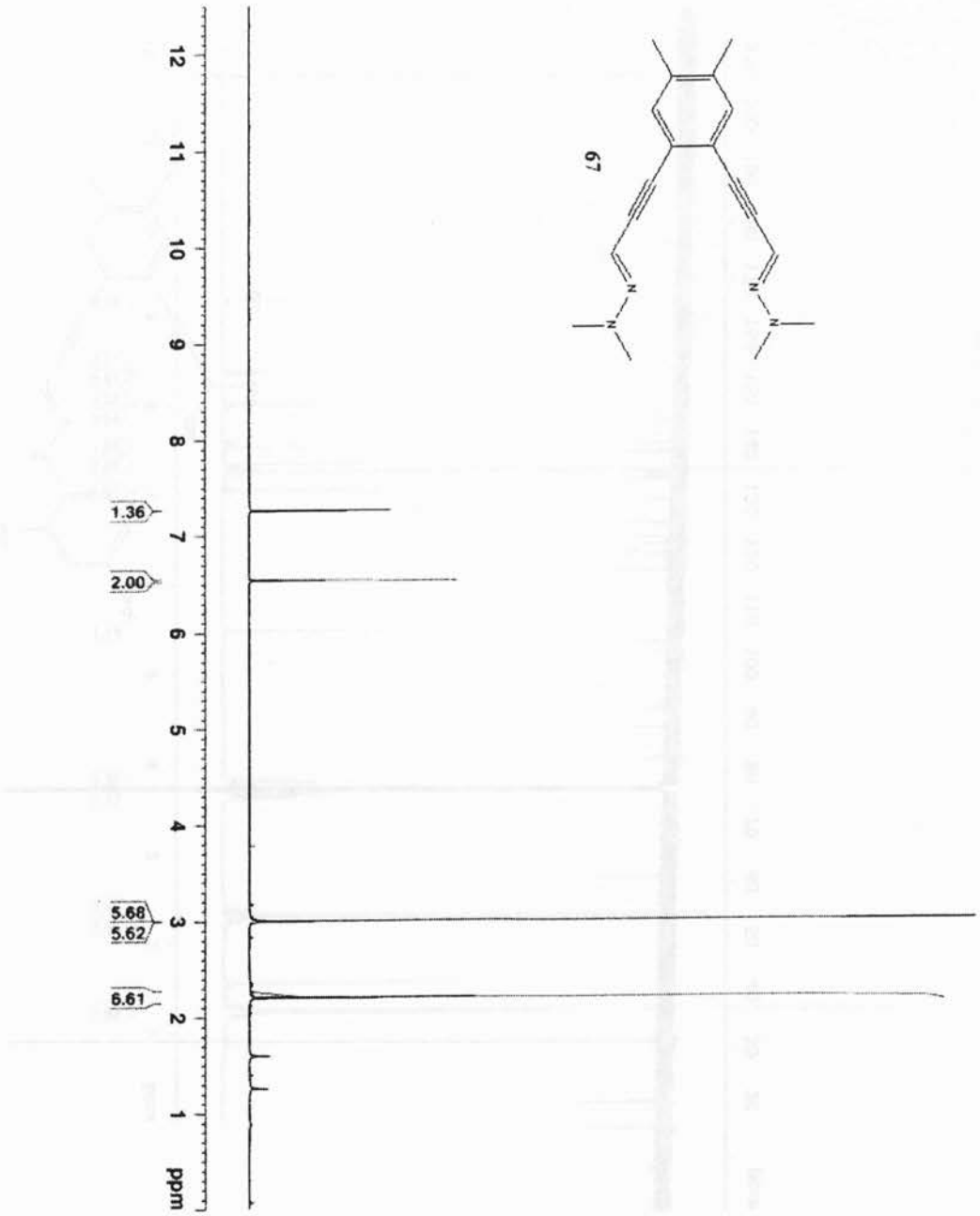

O
O
59
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm

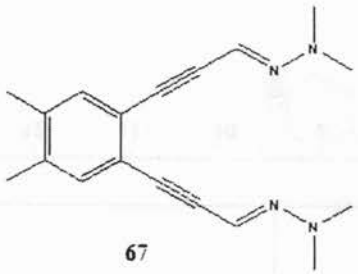
61
OEt
OEt
OEt
OEt
2.00
2.04
4.26
4.38
6.28
12.91
ppm

200
180
160
140
120
100
80
60
40
20
ppm
OEt
OEt
OEt
OEt


1.00
0.99
0.51
0.61
0.58
0.54
1.08
1.07
1.01
1.14
2.35
2.37
3.49
3.48
7.62
12
11
10
9
8
7
6
5
4
3
2
1
ppm
62
OEt
OEt
N
NH
NO2
NO2

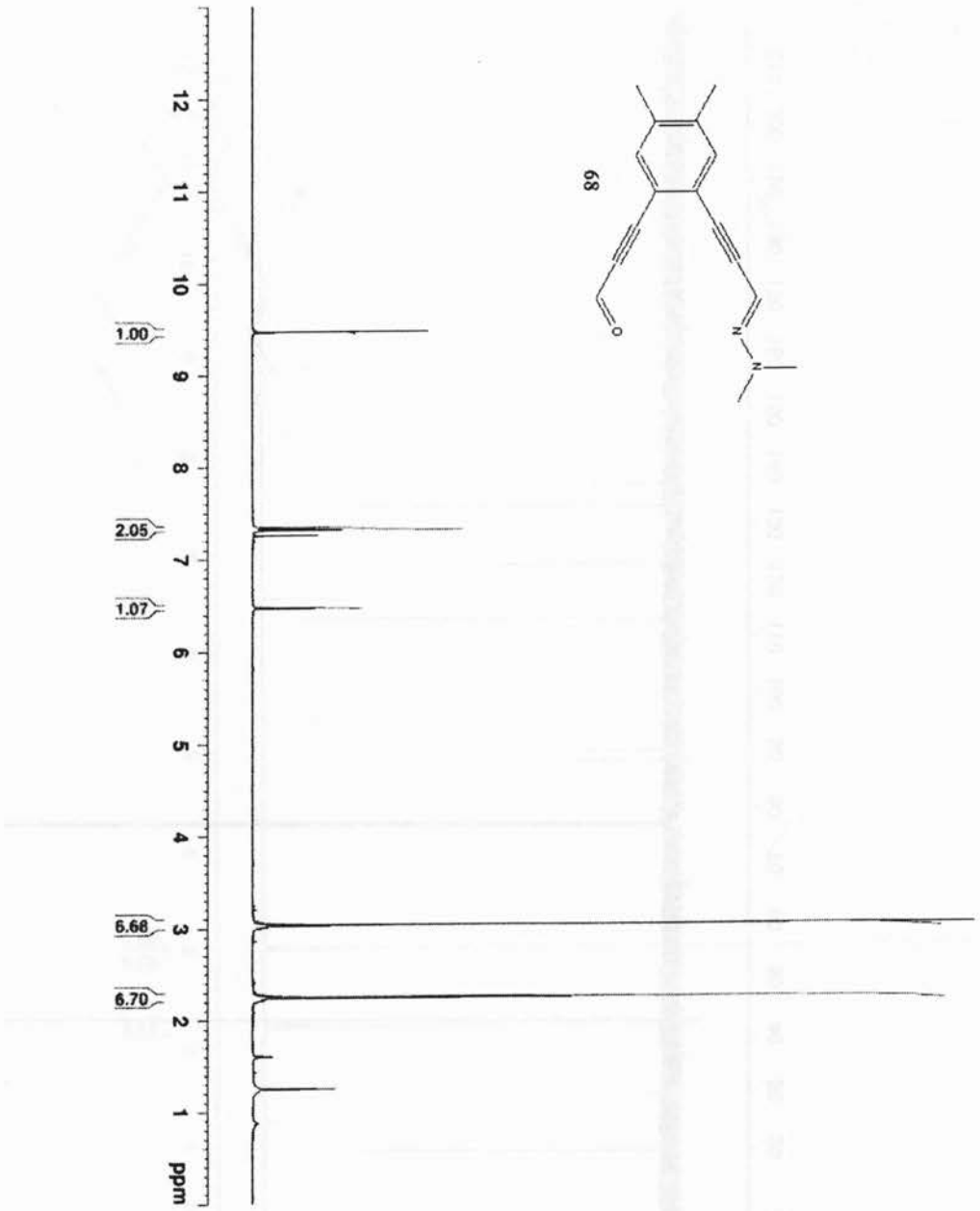

NO2
NO2
N
H
N
OEt
OEt
62
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


67
1.36
2.00
5.68
5.62
6.61
12
11
10
9
8
7
6
5
4
3
2
1
ppm

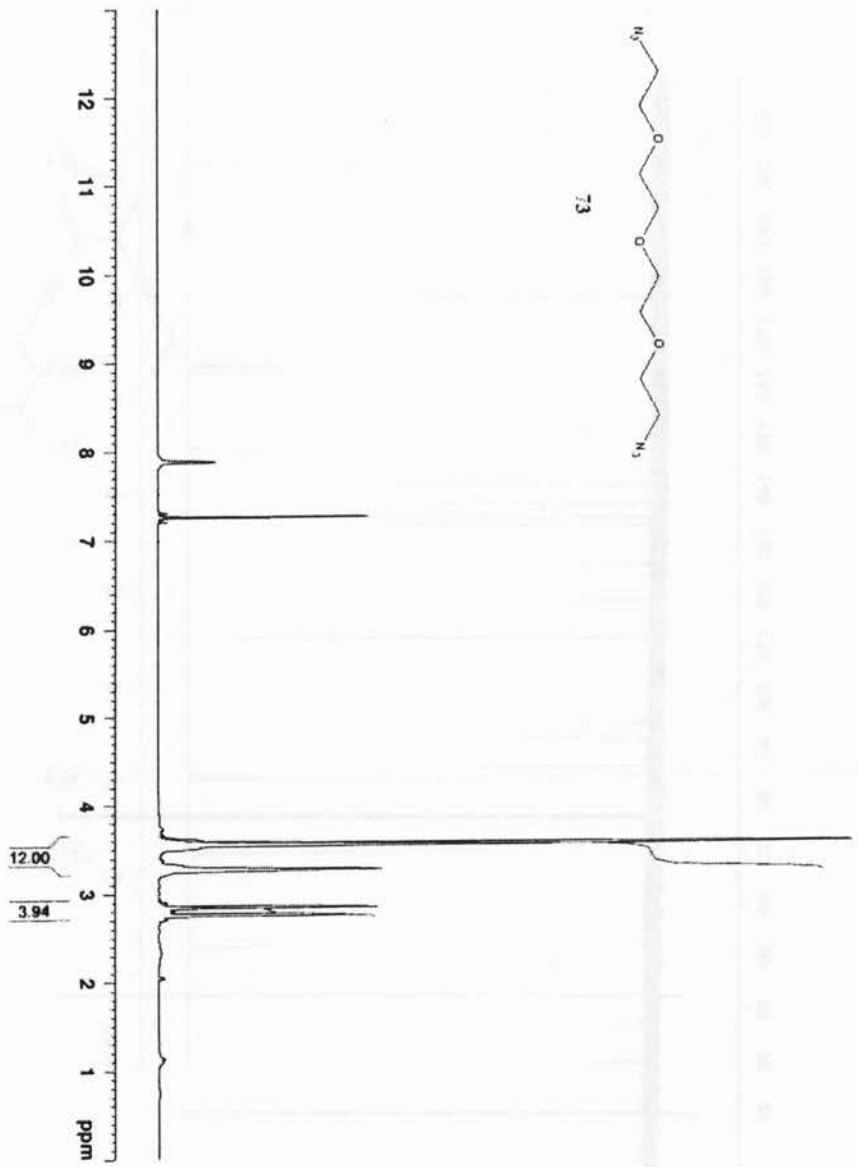


67

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


68
O
N
N
12
11
10
9
8
7
6
5
4
3
2
1
ppm
1.00
2.05
1.07
6.68
6.70

210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
ppm
68
O
N
N



73

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