Synthesis of Single Isomer Trisubstituted and Tetrasubstituted Olefins from *E*-β-Chloro-α-Iodo-α,β-Unsaturated Esters and Bergman Cycloaromatizations With and Without a Radical Trapping Agent

by

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Table of Contents

List of Figures

List of Schemes

List of Tables

List of Abbreviations

Ac	acetyl
AcOH	acetic acid
Ar	aryl
Bn	benzyl
Boc	*tert*-butyloxycarbonyl
br	broad
Bu	butyl
Bz	benzoyl
CI	chemical ionization
Cy	cyclohexyl
d	doublet
D	deuterium
DABCO	1,4-diazabicyclo[2.2.2]octane
DavePhos	2'dicyclohexylphosphino-2'-(N,N-dimethylamino)biphenyl
dba	dibenzylideneacetone
DCE	1,2-dichloroethane
DCM	dichloromethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DEPT	distortionless enhanced proton transfer
DIPEA	diisopropylethylamine

DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMSO	dimethysulfoxide
DNA	deoxyribonucleic acid
dppf	1,1'-bis(diphenylphosphino)ferrocene
dt	doublet of triplets
dq	doublet of quartets
EI	Electron Impact Ionization
Et	ethyl
EtOAc	ethyl acetate
eq	equivalents
h	hours
HOMO	highest occupied molecular orbital
HRMS	high resolution mass spectrometry
Hz	Hertz
i-PrOH	isopropanol
IR	infrared spectroscopy
m	multiplet
M^+	molecular ion
Me	methyl
MeOH	methanol
mmol	millimoles
min	minutes
MS	mass spectroscopy

n-BuLi	*n*-butyl lithium
nM	nanomolar
NMR	nuclear magnetic resonance spectroscopy
ph	phenyl
ppm	parts per million
q	quartet
r.t.	room temperature
s	singlet
SOMO	singly occupied molecular orbital
SPhos	2-dicyclohexylphosphino-2',6'-dimethoxybiphenyl
t	triplet
TBS	*tert*-butyldimethyl silyl
THF	tetrahydrofuran
TLC	thin layer chromatography
UV	ultraviolet

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Abstract

Optimized methods for the regioselective and stereospecific synthesis of both trisubstituted and tetrasubstituted olefins as single isomers from *E*-β-chloro-α-iodo-α,β-unsaturated esters have been developed from previous work done in the Ogilvie lab. These optimized methods have led to the synthesis of *trans* isomeric enediynes that can be photoisomerized to their respective *cis* isomers and subsequently undergo microwave-assisted Bergman cycloaromatizations. Furthermore, both *cis* and *trans* isomeric enediynes that have propargyl ether substituents have been found to be able to undergo photoactivated Bergman cyclizations without the need for an intermolecular hydrogen donor. A mechanism study has confirmed that the Bergman cyclization products that form without the presence of an intermolecular hydrogen donor undergo a series of 1,5-hydrogen shifts as intermediates. A series of optimizations to these reactions were carried out, in part by utilizing electron-donating or electron-withdrawing functional groups to help stabilize the resulting radicals that form on the intermediates, and thus increase the yield of the associated Bergman cyclization products.

Chapter 1

1.1 Introduction

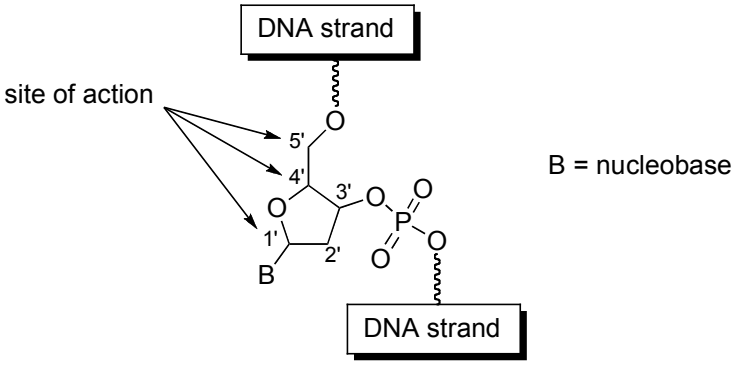
Chemotherapy is generally the initial form of treatment for many types of cancer, and the American Cancer Society reports that there are currently more than 100 drugs that are used for chemotherapy. These drugs are either used alone, or in combination with other drugs or treatments and vary widely in both their chemical composition, and the specific forms of cancer that they can treat. Most anticancer drugs target cell division or DNA synthesis, and the development of effective anticancer medications requires a deep knowledge of the drug action mechanism at both the cellular and molecular levels.[1] In recent decades, much has been learned about DNA-drug interactions, and these interactions can generally be classified as follows.[2]

1. The formation of non-covalent complexes that are the result of intercalation, insertion between base pairs, or groove binding.
2. The formation of a covalent bond between the DNA and the anticancer drug.
3. The initial binding to the DNA molecule via a particular mechanism, followed by the cleavage of the DNA backbone.

Enediyne antibiotics are a class of highly potent anticancer compounds that interact with DNA through the third method, by positioning themselves within the minor groove of the DNA molecule in such a way as to be able to abstract two

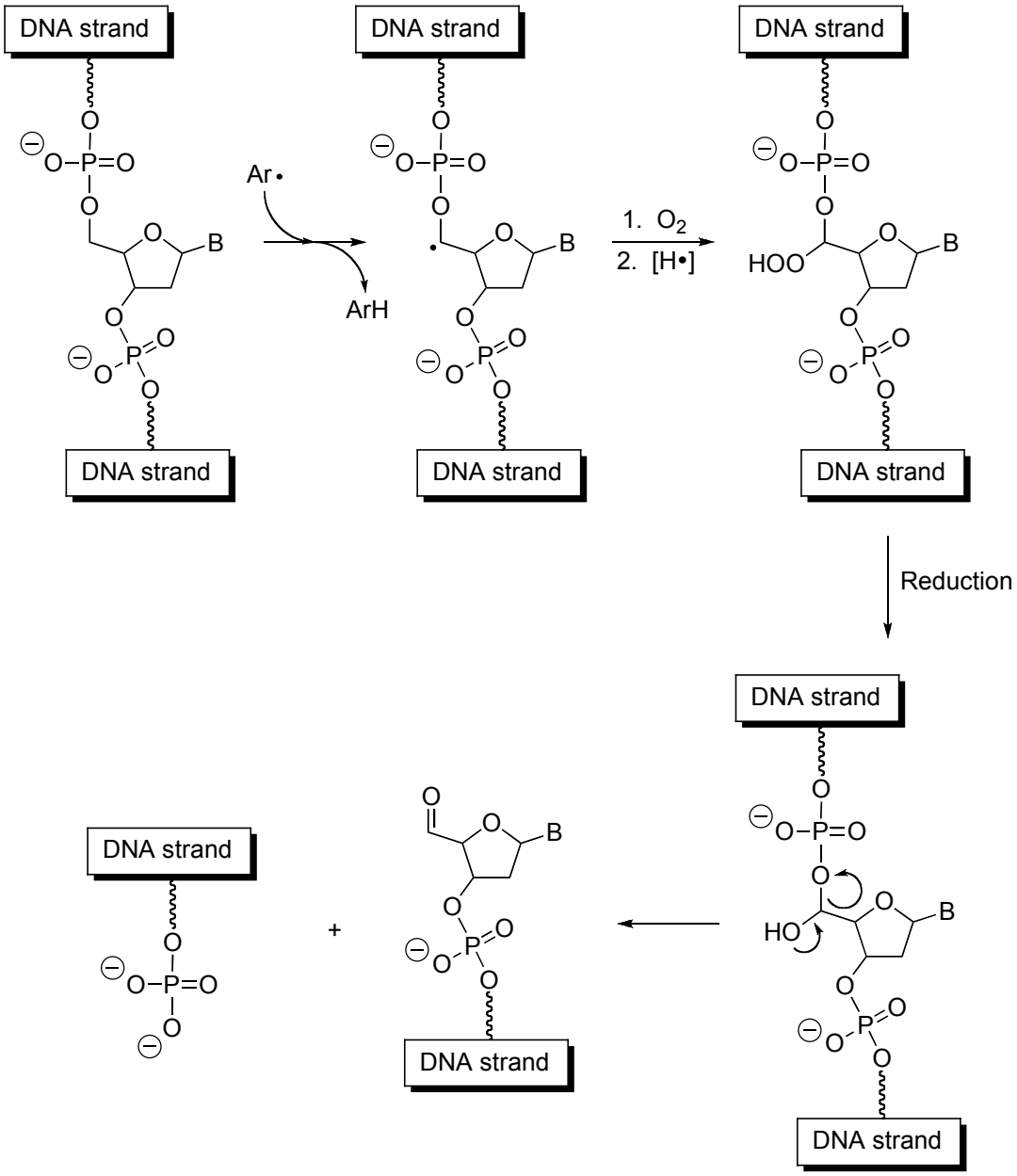
hydrogen atoms from sugars on the backbones of opposite DNA strands (**Figure I-1**).[3]

Figure I-1: Site of Action of an Enediyne Antibiotic



As can be seen immediately above, there are three sites on the sugar portion of the sugar-phosphate backbone of a DNA strand from which a hydrogen atom can be abstracted by the active form of the enediyne antibiotic. The most common site of attack involves hydrogen atom abstraction from the C(5') of deoxyribose, followed by reaction with molecular oxygen. This leads to the cleavage of the DNA strand, and to the formation of a C(5')-aldehyde, as shown in **Scheme I-1**.[3]

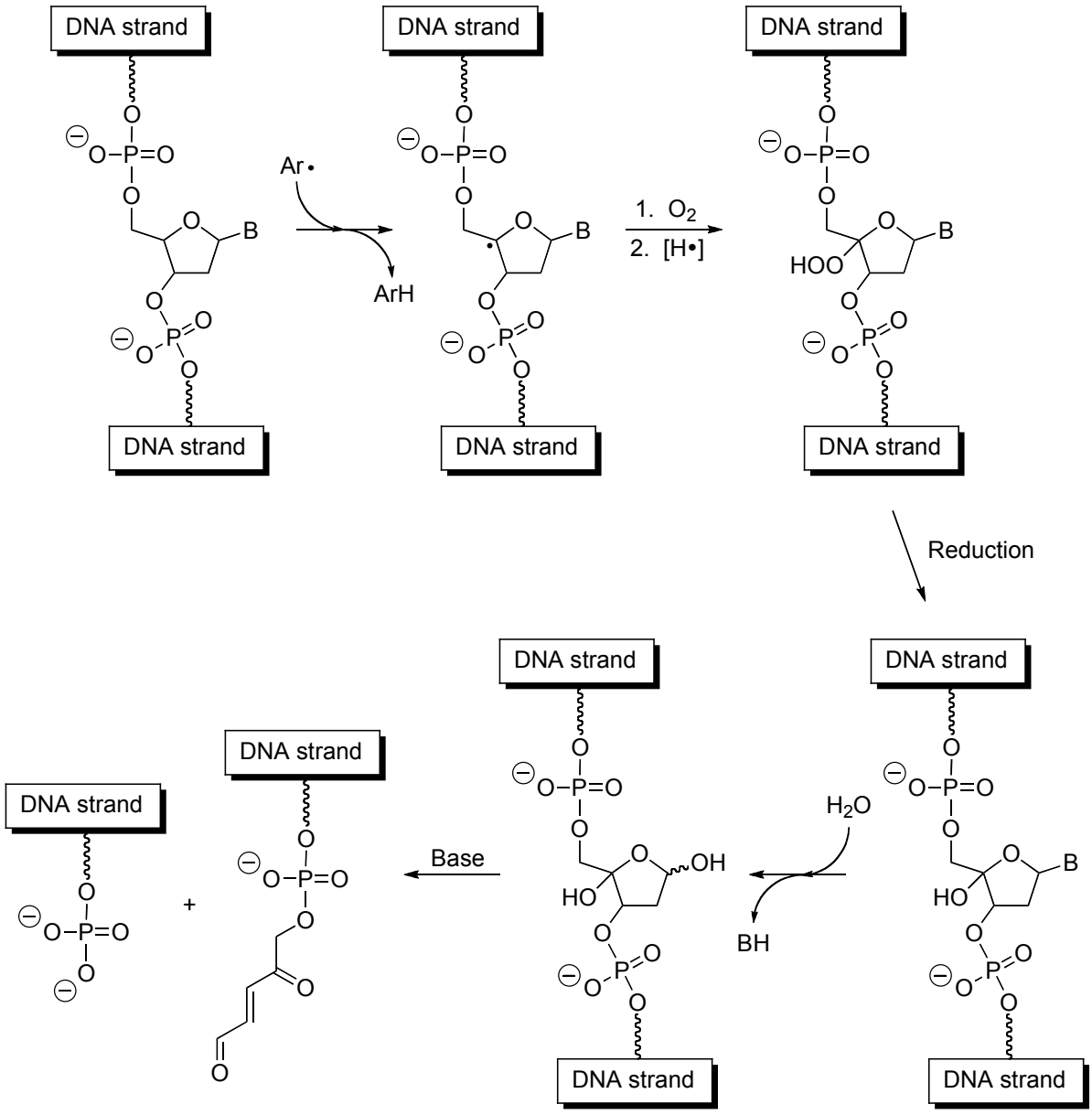
Scheme I-1: DNA Cleavage by C(5') Hydrogen Atom Abstraction



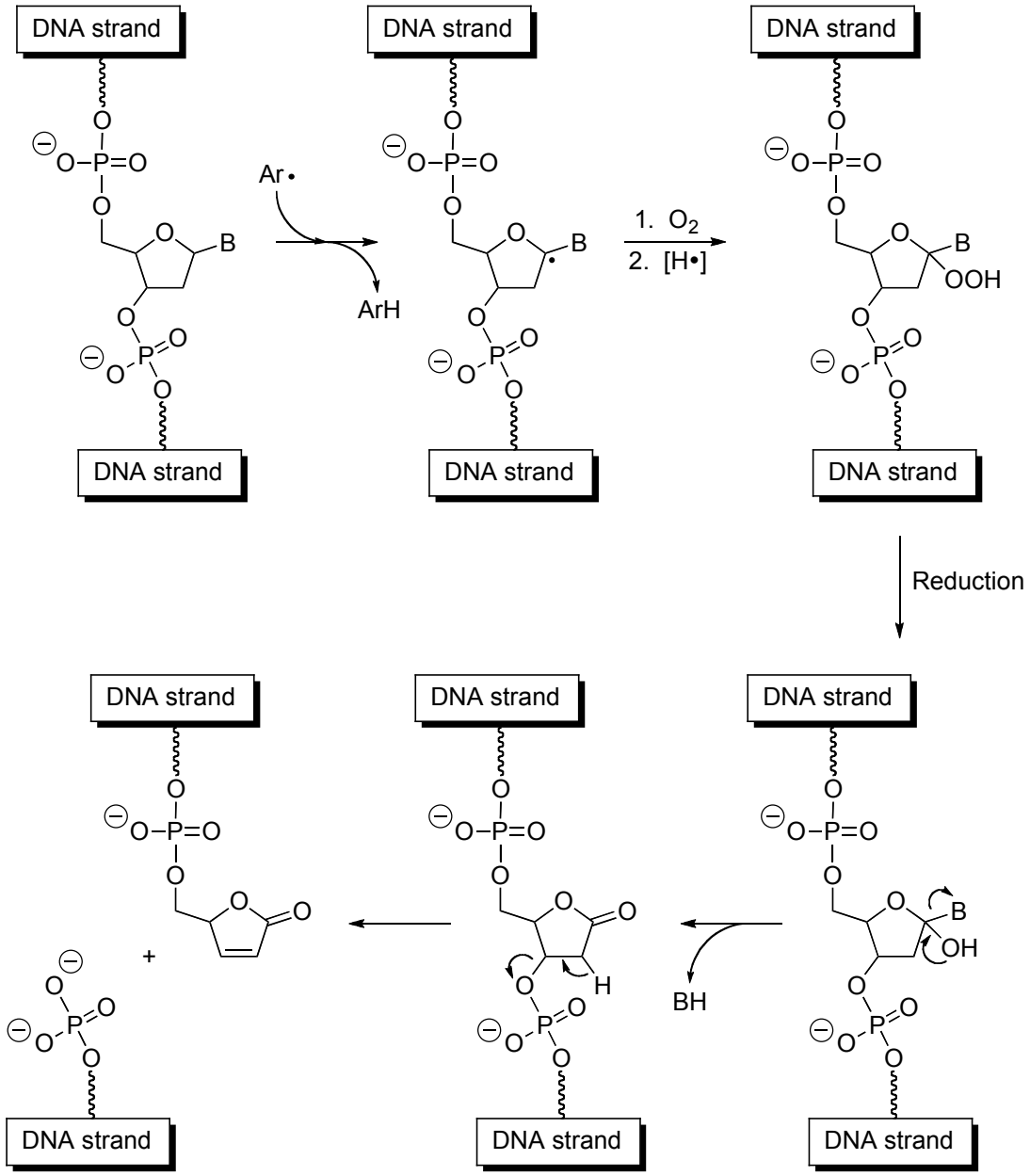
Less common sites of attack involve hydrogen atom abstraction from either the C(4') or C(1') of deoxyribose, again followed by reaction with molecular oxygen.

Both of these sites of abstraction lead to cleavage of the DNA strand, and are shown in **Scheme I-2** and **Scheme I-3**, respectively.[3]

Scheme I-2: DNA Cleavage by C(4') Hydrogen Atom Abstraction



Scheme I-3: DNA Cleavage by C(1') Hydrogen Atom Abstraction

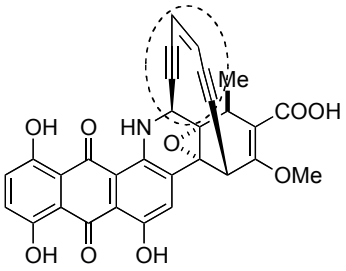


1.2 Structure and Mechanism of Action of Enediyne Antibiotics

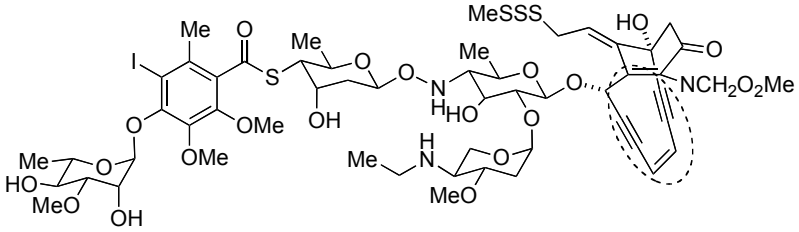
Enediyne antibiotics are a relatively new class of anticancer agents, having been discovered in the mid-1980s. Since then, this class of compounds has been

the focus of intense research, as enediynes possess both a unique mode of action as well as a high potency.[1, 3, 4] Enediyne natural products have been isolated from various bacteria, and include dynemicin A (**I-1**), calicheamicin γ_1^I (**I-2**), neocarzinostatin chromophore (**I-3**), and kedarcidin chromophore (**I-4**) (**Figure I-2**).[3]

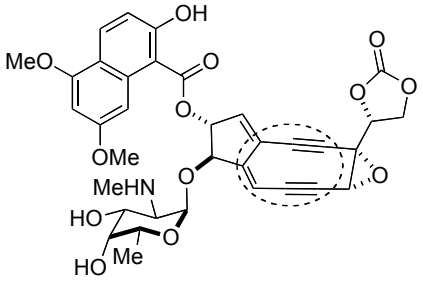
Figure I-2: Macrocyclic Anticancer Agents Containing Enediyne Moieties Isolated From Various Bacteria



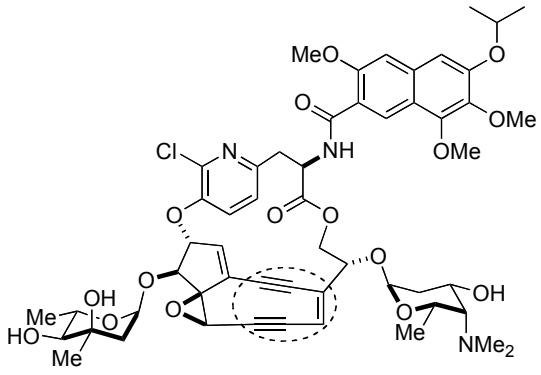
I-1
Dynemicin A



I-2
Calicheamicin γ_1^I



I-3
Neocarzinostatin Chromophore

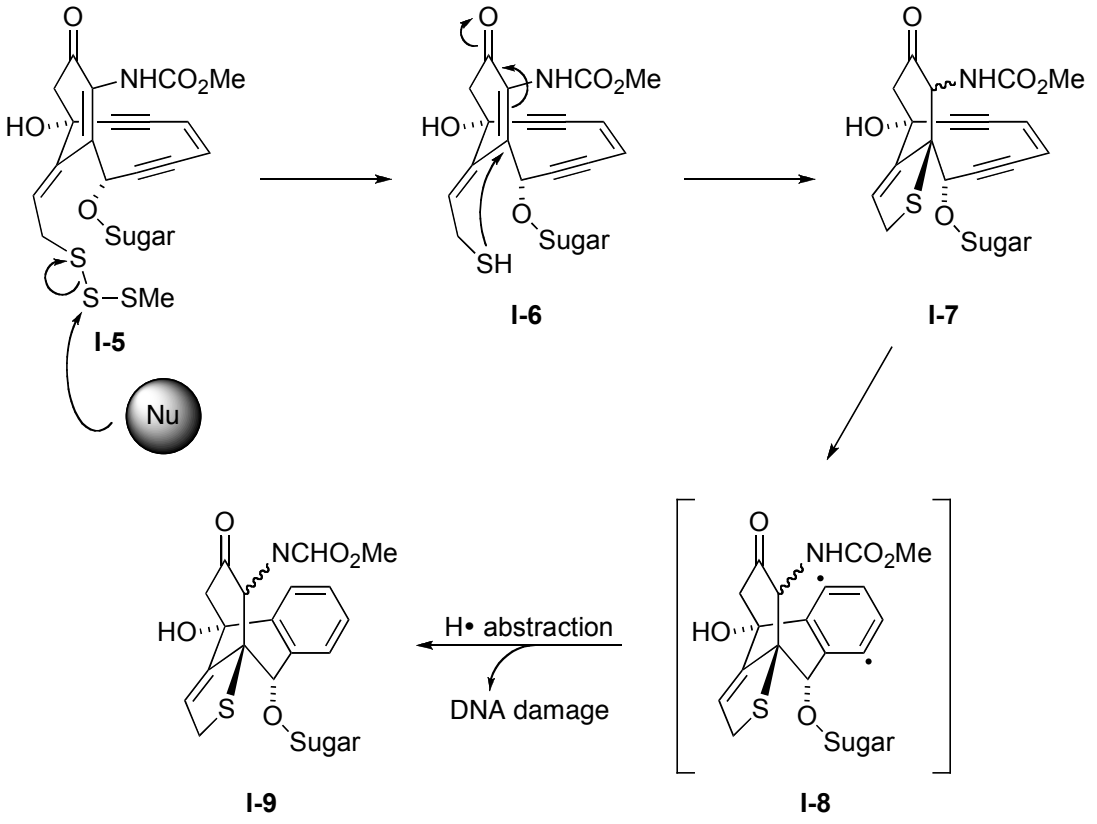


I-4
Kedarcidin Chromophore

As highlighted above, the common structural motif among enediyne natural products is an enediyne moiety (*Z*-hexa-1,5-diyne-3-ene) that is found positioned within a 9-membered or 10-membered ring. It is this enediyne moiety that can act

as a “warhead” and cleave DNA strands by a unique chemical process. After docking in the minor groove of the DNA molecule, each of the natural products shown in **Figure I-2** can undergo an electrophilic condensation that induces a specific set of structural changes whereby the diyne moieties reach a critical distance from each other, and thus initiate a Bergman cyclization. For example, the calicheamicin family of enediynes was the first of the enediyne antibiotics whose mechanism of activation was elucidated in greater detail, and these compounds are characterized by the presence of an allylic trisulfide group. As shown in **Scheme I-4**, the mechanism for DNA cleavage, with respect to the calicheamicin family of enediynes, is initiated by a nucleophilic attack on the allylic trisulfide goup **I-5** to form the thiol **I-6**. This thiol **I-6** serves as an intramolecular nucleophile for a Michael addition in order to produce the dihydrothiophene **I-7**. The structural changes that are induced by this process reduce the distance between the diyne moieties, and allow for the cycloaromatization, known as a Bergman cyclization, of the dihydrothiophene **I-7** to form the highly reactive aromatic 1,4-diradical **I-8** as an intermediate. It is this reactive 1,4-diradical **I-8**, while positioned within the minor groove of the DNA molecule, that is able to abstract a hydrogen atom from the sugar-phosphate backbone of each strand, resulting in cleavage of the DNA double helix.[1, 3]

Scheme I-4: Triggering Mechanism for the Activation of the Calicheamicin Family of Enediyne Antibiotics

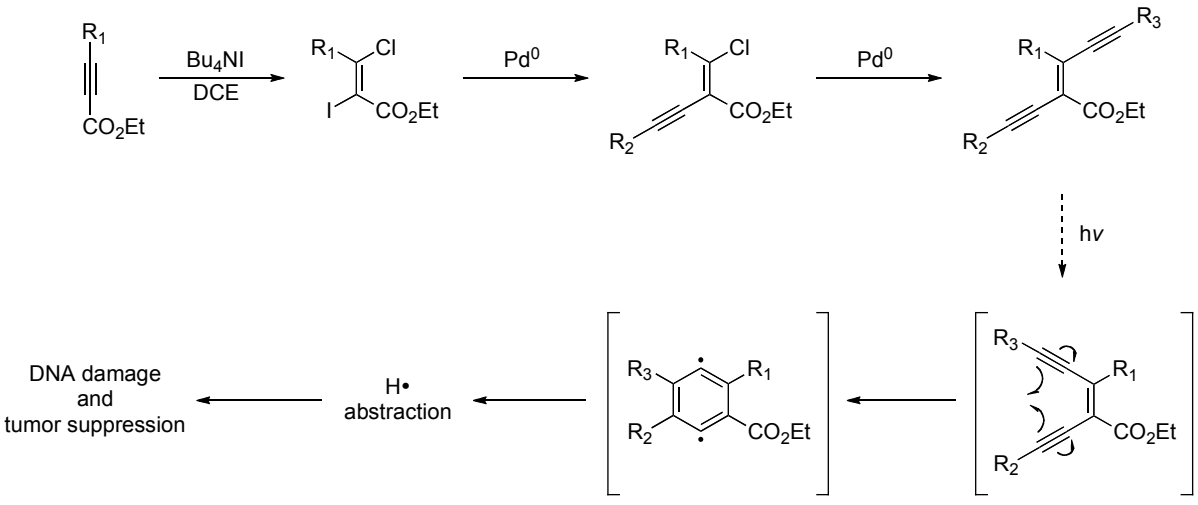


Although enediyne natural products are very effective at cleaving DNA strands, they are also highly cytotoxic. It is for this reason that there is a need for new enediyne-related derivatives that show maximum toxicity towards tumor cells, while being minimally destructive towards healthy, non-cancer cells. As well, enediyne natural products tend to be both structurally complex, as well as synthetically challenging. Ideally, future enediyne analogs, in addition to being less cytotoxic to healthy cells, would also be synthetically more accessible. These demands on the characteristics of future enediyne-related derivatives open the door

for the development of synthetic compounds that will be able to better discriminate between tumor cells and healthy, normal cells, all the while still showing the potent anticancer properties of enediyne natural products.[1, 5]

Work done previously in the Ogilvie lab has led to the development of a stereo- and regio-specific methodology for the synthesis of tetrasubstituted olefins as single isomers.[6] It is through the use of this new methodology that a new class of photoactivated enediyne analogs can be envisioned. As shown in **Scheme I-5**, these new compounds would be synthesized in the *trans* isomeric form, and thus be unreactive towards a cycloaromatization. However, upon the local application of a light source of an appropriate wavelength, photoisomerization would generate the reactive *cis* isomeric form that could then undergo a Bergman cyclization resulting in hydrogen atom abstraction and tumor cell DNA cleavage.

Scheme I-5: Methodology for the Development of a New Class of Enediyne Antibiotics



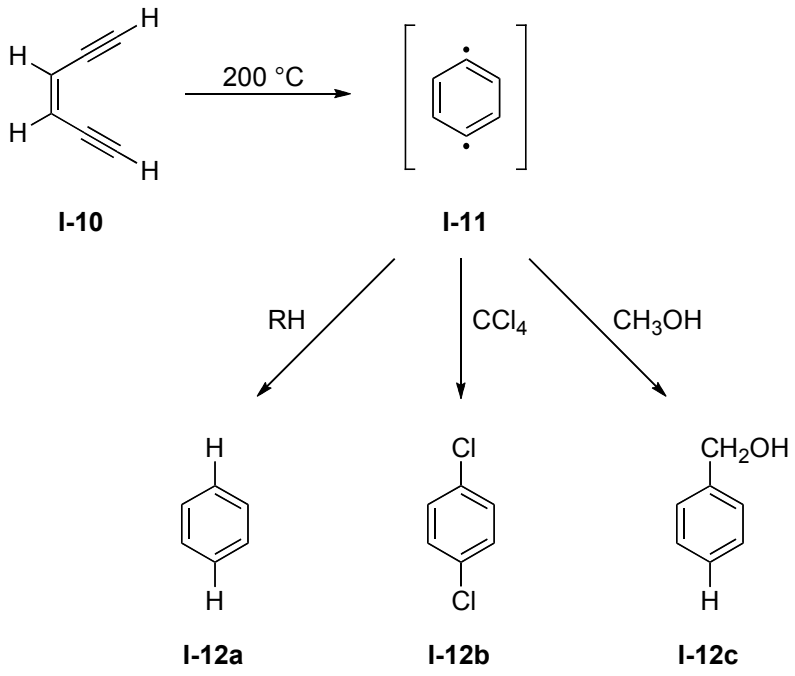
The key to helping to avoid the cytotoxicity to non-tumor cells would lie with the fact that these new enediyne analogs could be administered as part of a localized phototherapy and thereby specifically target cancer cells. Any of the inactive *trans* isomeric form of these enediyne compounds that came into contact with healthy cells would not be targeted by the light source and thus remain in the inactive form resulting in no DNA strand cleavage of these healthy cells. This thesis will thus present the work performed towards the creation of these new enediyne compounds. However, an introduction to the Bergman cyclization, as well as advances in enediyne research will be discussed first.

1.3 Bergman Cycloaromatization

In 1972, Robert Bergman reported the first in-depth study on the unique behaviour of acyclic, *cis* isomeric enediynes upon thermal activation.[7, 8] It was determined that the simple enediyne **I-10** produced benzene-related derivatives **I-12a-c** upon heating in solution, with the exact structure of these compounds being dependent upon the solvent used (**Scheme I-6**). Bergman realized the importance of the highly reactive 1,4-diradical **I-11** in this reaction, and that this was the intermediate that was responsible for the abstraction of two atoms from an available donor, such as the reaction solvent, leading to the stable benzene-related analogs **I-12a-c**. Initially, the Bergman cycloaromatization garnered the interest of only physical organic and theoretical chemists, however, with the discovery of enediyne anticancer antibiotics in the mid-1980s and their ability to cleave double stranded DNA, the reaction attracted the attention of the synthetic organic community and became the focus of intense research. Since this time, the total syntheses of

enediyne natural products such as Dynemicin A and Calicheamicin γ_1^I have been achieved, and further research into the reactivity of this class of compounds is ongoing.[9, 10]

Scheme I-6: Formation of Benzene-Related Derivatives From the Thermolysis of a Simple *Cis* Isomeric Enediyne (I-10)

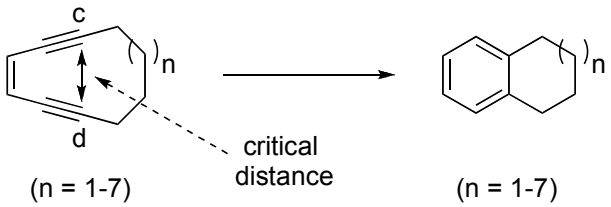


I-10 **I-11** **I-12a** **I-12b** **I-12c**

Both experimental and computational studies have determined that the Bergman cycloaromatization of *cis* isomeric enediynes is heavily influenced by a number of factors. These include the following: (1) the critical distance between the two terminal acetylenic carbon atoms; (2) the difference in strain energy between the enediyne and the transition state; (3) the concentration of the radical trapping agent; and (4) substituent effects.[1, 11]

With respect to the critical distance between the two terminal acetylenic carbon atoms, Nicolaou and coworkers synthesized several simple, relatively strain-free enediyne systems in order to effectively model the ten-membered cyclic enediynes that are present in natural products such as the calicheamicin and dynemicin families of antibiotics. A key finding in these studies was that at room temperature the cyclic enediynes **I-13** with n = 2 to n = 7 were all found to be stable, but cyclodec-3-ene-1,5-diyne (n = 1) was able to undergo a Bergman cyclization (**Scheme I-7**). From the observations on the reactivities of these compounds, Nicolaou was able to conclude that the cyclization became faster as the critical distance decreased, and that this critical distance was paramount to the ease with which an enediyne underwent a cyclization. Furthermore, Nicolaou determined that the ten-membered cyclic enediynes were of optimal size for a spontaneous Bergman cyclization to proceed at room temperature, and that the critical distance for this cyclization to occur at this temperature was 3.2 Å to 3.3 Å. Enediynes with interatomic acetylenic distances greater than 3.3 Å were found to be thermodynamically stable to Bergman cyclizations at 25 °C.[12]

Scheme I-7: Critical Distance Required for a Bergman Cycloaromatization in Simple Cyclic Enediynes (I-13)



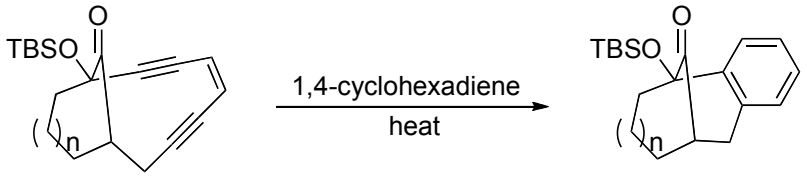
(n = 1-7) (n = 1-7)

I-13 **I-14**

These pioneering studies by Nicolaou were supported by further studies that utilized similar models. Kraka and Cremer, through the use of *ab initio* methods, computationally determined that the critical distance for a Bergman cycloaromatization to occur at 25 °C was 3.0 Å.[13]

Magnus, through experimental means, and Snyder, through *ab initio* computational methods, both independently suggested that the crucial factor governing the reactivity of strained enediynes is not the critical distance between the two terminal acetylenic carbon atoms, but the difference in the strain energy between the enediyne and the transition state that leads to the 1,4-diradical intermediate. Magnus and coworkers demonstrated this relationship through the study of bicyclic enediyne systems (**Table I-1**).[11, 14]

Table I-1: Correlation Between Strain Energy and Enediyne Reactivity



I-15a (n = 0)
I-15b (n = 1)

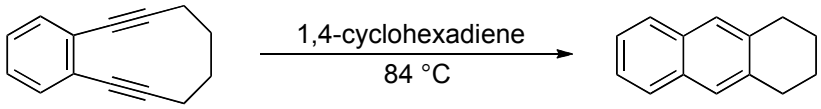
I-16a (n = 0)
I-16b (n = 1)

Compound	n	Critical Distance (Å)	Strain Energy (kcal/mol)	Temperature (°C)	Rate (s^{-1})
I-15a	0	3.37	19.6	124	2.08×10^{-5}
I-15b	1	3.39	15.1	71	1.07×10^{-4}

The data shows that both enediynes **I-15a** and **I-15b** have almost identical critical distances, but that the less strained bicyclic system **I-15b** with n = 1 is able to undergo a Bergman cyclization at only 71 °C. This compares to the more strained bicyclic system **I-15a** with n = 0 which undergoes cycloaromatization at 124 °C. Assuming that the transition state of the Bergman cyclization is product-like, Magnus was able to show, through the use of models of Bergman cyclization products, that the calculated strain energies of these cyclized products could be used to make predictions about the reactivity of bicyclic enediynes. Magnus concluded that the smaller the strain energy of the Bergman cyclization product, the more reactive the corresponding bicyclic enediyne.[11]

Semmelhack and coworkers investigated the effects that the concentration of a radical trapping agent had on a Bergman cycloaromatization. As shown in **Table I-2**, it was demonstrated that the reactivity towards a Bergman cyclization of the cyclic enediyne **I-17** was dependent upon the concentration of the radical trapping agent, 1,4-cyclohexadiene. As the concentration of the radical trapping agent increased, the half-life of the cyclic enediyne **I-17** decreased substantially. A ten-fold increase in the concentration of 1,4-cyclohexadiene resulted in a greater than ten-fold decrease in the half-life of the cyclic enediyne starting material **I-17**.[11, 15, 16]

Table I-2: Inverse Correlation Between Concentration of the Radical Trapping Agent and the Half-life of the Enediyne Starting Material (I-17)

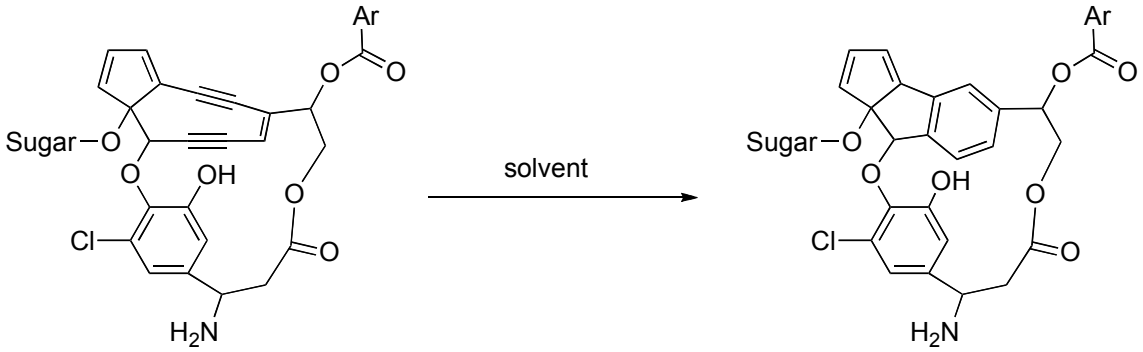


I-17 **I-18**

Concentration of 1,4-cyclohexadiene (M)	Solvent	$t_{1/2}$ (h)
0	C_6D_6	129
0.25	C_6D_6	39
0.5	C_6D_6	24
10.5	neat	10.5

In addition, Yoshida and coworkers examined the kinetics of the Bergman cycloaromatization of enediyne **I-19** using different solvents and reported a significant kinetic isotope effect (**Table I-3**). This implies that the rate of cyclization of the enediyne **I-19** is, in fact, affected by the concentration of the radical trapping agent. As well, it implies that the hydrogen abstraction from the hydrogen donor may be the rate-determining step.[11, 17] The experiments conducted by both Semmelhack and Yoshida indicate that the concentration of the radical trapping agent must be considered when comparing the results from different Bergman cycloaromatization experiments.

Table I-3: Kinetic Isotope Effect of the Bergman Cycloaromatization



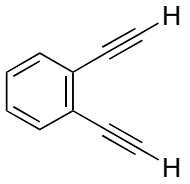
I-19 **I-20**

Solvent	k_H/k_D
dioxane/dioxane-d_6	2.9
CH_3OH/CH_3OD	1.1
CH_3OH/CD_3OD	2.8

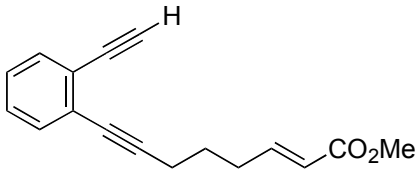
Finally, with regards to the influence of substituent effects on the Bergman cycloaromatization, it has been established that the cyclization is sensitive to both steric and electronic effects on the acetylenic substituents. Grissom and coworkers conducted studies on acyclic aromatic enediynes in which the ene portion of the compound was part of an aromatic ring (**Table I-4**). The activation energies of the enediynes **I-21**, **I-22**, and **I-23** were compared and the alkyl substituents on the terminal acetylenic carbons were found to cause a decrease in Bergman cyclization reactivity. It should be noted that in this particular instance, the differences in the reactivity between the three enediynes **I-21**, **I-22**, and **I-23** cannot be due to the

influence of strain factors, since the three substrates all have similar strain energies, as do their respective transition states.[11, 18, 19]

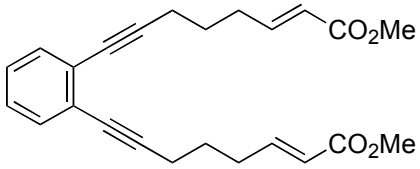
Table I-4: Effect of Alkyl Substituents on the Activation Energy Required for a Bergman Cycloaromatization



I-21



I-22



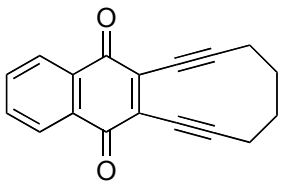
I-23

Enediyne	E_a (kcal/mol)
I-21	25.1 ± 0.08
I-22	28.1 ± 0.08
I-23	34.0 ± 0.3

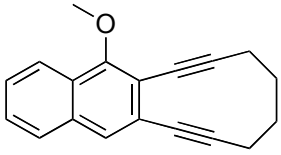
The effects of substituents on the ene portion of an enediyne system were investigated by Semmelhack and coworkers. As shown in **Table I-5**, Semmelhack found that there was an increased Bergman cyclization reactivity when the ene portion of the enediyne system was part of a quinone ring **I-24**, as opposed to when it was part of an aromatic ring **I-25**. This result advanced the likelihood that the olefinic or aromatic character of the ene unit of the enediyne system did, in fact, affect the reactivity with respect to a Bergman cyclization.[16] Interestingly, this was in direct contrast to investigations conducted by Grissom and coworkers, who

observed that substituents on the ene portion of the enediyne had minimal effect on Bergman cyclization reactivity.[18, 19]

Table I-5: Substituents on the Ene Portion of an Enediyne System and Their Effect on Bergman Cyclization Reactivity



I-24



I-25

Enediyne	$t_{1/2}$ (h)	T (°C)
I-24	88	40
I-25	168	120

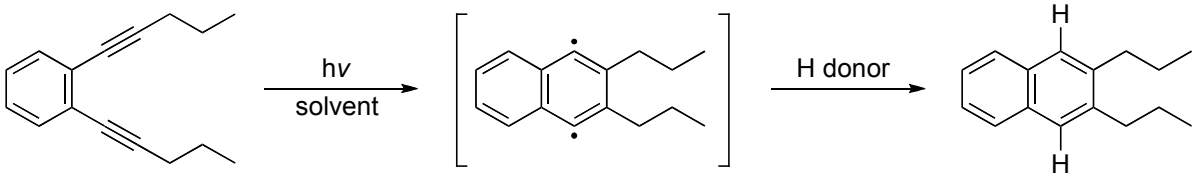
When investigating the influence of substituent electronic effects, several groups have shown that both electron withdrawing and electron donating substituents can help to increase the reactivity of a particular enediyne system with respect to a Bergman cyclization. In each case, the substituent electronic effect helped to stabilize the transition state, which resulted in an increased rate of cycloaromatization. In summary, the electronic effects of particular substituents can influence each enediyne system in a unique way, which ultimately results in a delicate balance between the promotion and inhibition of cyclization. Although accurate predictions can be produced through the use of computational methods,

the control of Bergman cyclization reactivity of particular enediyne systems is not a trivial task.[11]

1.4 Photoactivated Bergman Cycloaromatization

Unfortunately, one of the most important and challenging obstacles to enediyne cyclizations is the high temperature that is required to promote the ring closure of acyclic systems. Turro and coworkers produced the first direct photoactivated Bergman cyclization of an enediyne as an alternative to the classical method of thermolysis. When the aromatic enediyne **I-26** was irradiated in the presence of various hydrogen donors, the naphthalene derivative **I-27** was formed (**Table I-6**). The results of these experiments were consistent with the intermediacy of a 1,4-diradical, which is similar to the intermediate present in thermal Bergman cyclizations.[20]

Table I-6: The First Reported Photoactivated Bergman Cycloaromatization

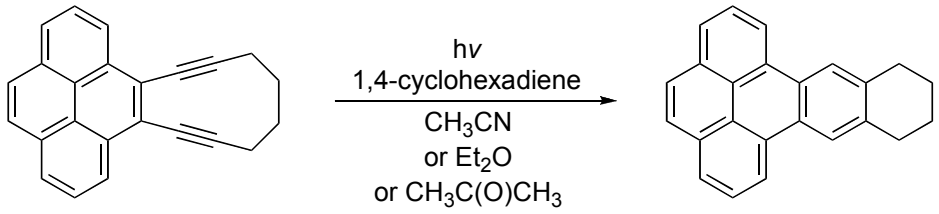


I-26 **I-27**

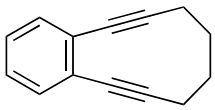
Solvent	Yield (%)
C_6H_6/benzhydrol	40
i-PrOH	25

Following the pioneering work by Turro, Funk and coworkers conducted an extensive investigation into photoactivated Bergman cycloaromatizations, which led to the development of a new class of photoactivated aromatic enediynes. It was envisaged that these polycyclic aromatic enediynes would have both facile synthetic pathways, as well as being able to intercalate into DNA were they would then be photochemically activated as opposed to thermally activated. Of the five enediynes that were synthesized, four were able to successfully undergo a photoactivated Bergman cyclization (**Scheme I-8**). The most successful of these was the aromatic enediyne **I-28**, which produced Bergman cyclization product **I-29** in quantitative yield, after being exposed to sunlight. The dialkynylphenanthrene **I-33** also performed well under identical conditions and experienced an overall conversion of 82 %. Funk also investigated the reaction rate with respect to the concentration of the radical trapping agent, 1,4-cyclohexadiene. It was observed that the photoactivated Bergman cyclization proceeded more slowly if a lesser quantity of the radical trapping agent was used, or not at all in the absence of any hydrogen donor. This last result is, in fact, consistent with a reversible cycloaromatization.[21]

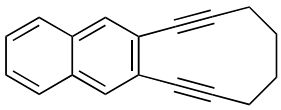
Scheme I-8: Most Successful Aromatic Enediyne Analog Capable of Undergoing a Photoactivated Bergman Cyclization



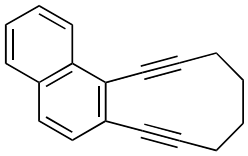
I-28 **I-29**



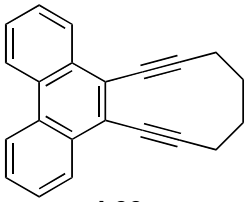
I-30
15% conversion



I-31
no conversion



I-32
38% conversion

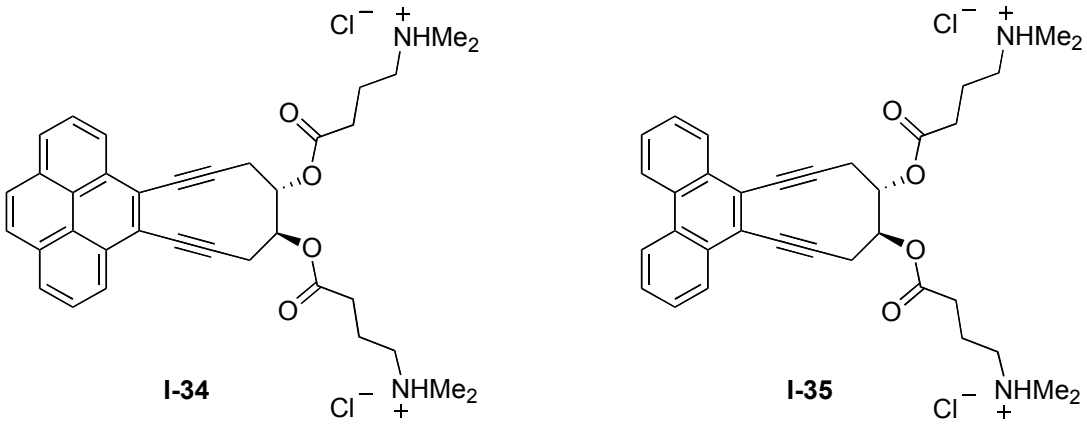


I-33
82% conversion

Building further on this work, Funk and coworkers synthesized water-soluble analogs of both **I-28** and **I-33** in order to investigate the DNA photocleaving properties of these aromatic enediynes. As shown in **Figure I-3**, the resulting water-soluble enediynes **I-34** and **I-35** were hypothesized to be able to intercalate with DNA, and upon photoirradiation initiate hydrogen atom abstraction and DNA strand cleavage. DNA photocleavage by aromatic enediynes **I-34** and **I-35** was tested using supercoiled plasmid pUC19 DNA. Primarily single stranded DNA breaks were observed, with the dialkynylpyrene **I-34** being more effective than the

dialkynylphenanthrene **I-35**. This was likely due to the fact that the dialkynypyrene **I-34** was both a better intercalator and had more efficient photochemistry than the dialkynylphenanthrene **I-35**.[21]

Figure I-3: Water Soluble Aromatic Enediynes With DNA Photocleaving Properties

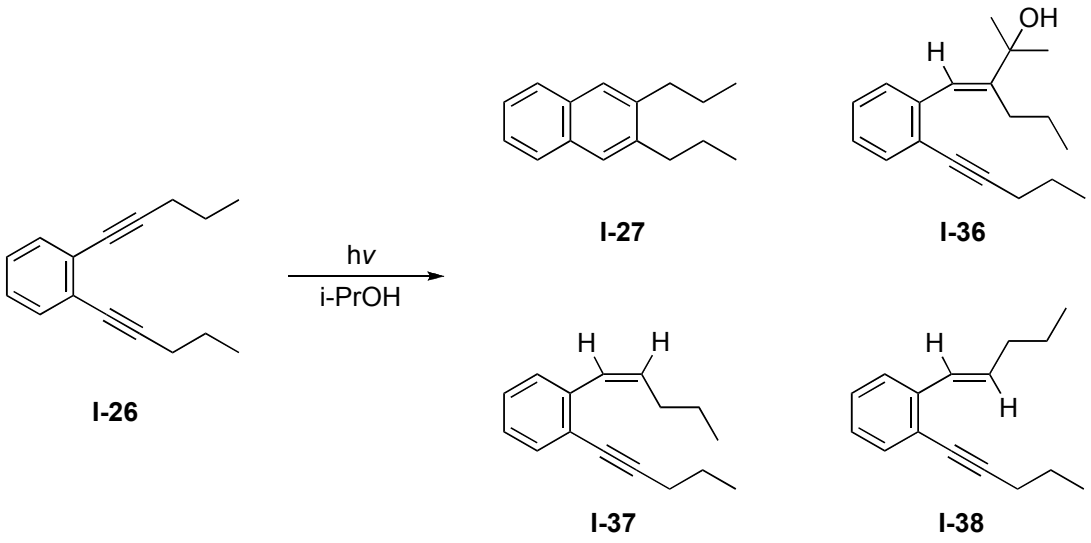


I-34 **I-35**

In 1998, Evenzahav and Turro reported further investigations on the photoactivation of aromatic enediynes. Photolysis of the aromatic enediyne **I-26** in 2-propanol, without the presence of a radical trapping agent, produced the products **I-27**, **I-36**, **I-37**, and **I-38** in a 2 : 4 : 2 : 1 ratio (**Scheme I-9**). When the reaction was carried out to 50 % conversion of enediyne **I-26**, a yield of 25 % for the cyclized product **I-27**, and a mass balance of 80 % were realized. When the experiment was repeated in the presence of the radical trapping agent 1,4-cyclohexadiene, the photolysis of **I-26** produced only the cyclized product **I-27**, as well as an additional uncharacterized product. It was observed that when the reaction was run with a

triplet sensitizer such as xanthone or acetophenone, the conversion of aromatic enediyne **I-26** increased significantly, but the yield of cyclized product **I-27**, as well as the mass balance, decreased dramatically.[22]

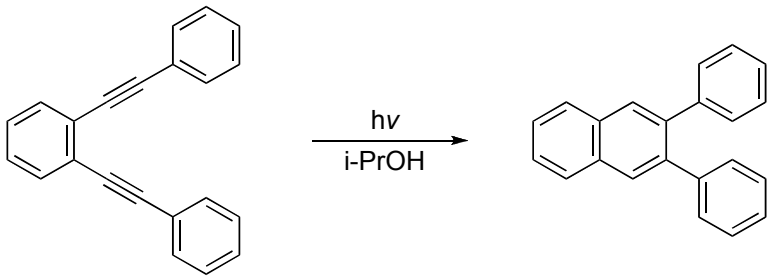
Scheme I-9: Photoirradiation of an Aromatic Enediyne and the Unexpected Photoreduction Side Products



Furthermore, the aromatic enediyne **I-39** was photolyzed in 2-propanol, without the presence of a radical trapping agent, and produced only the cyclized product **I-40**, with a mass balance of 75 % (**Scheme I-10**). The reduced side products, such as those seen above in **Scheme I-9**, were not formed in any detectable amount. Interestingly, when the experiment was repeated in the presence of the radical trapping agent 1,4-cyclohexadiene, photochemical conversion of **I-39** did occur, but produced no product that was detectable by gas chromatography, which suggests that the formation of an uncharacterized polymeric

material occurred. When the reaction was run with the triplet sensitizer xanthone, no conversion of the enediyne **I-39** was observed.[22]

Scheme I-10: Photoirradiation of an Aromatic Enediyne With Phenyl Alkynyl Substituents

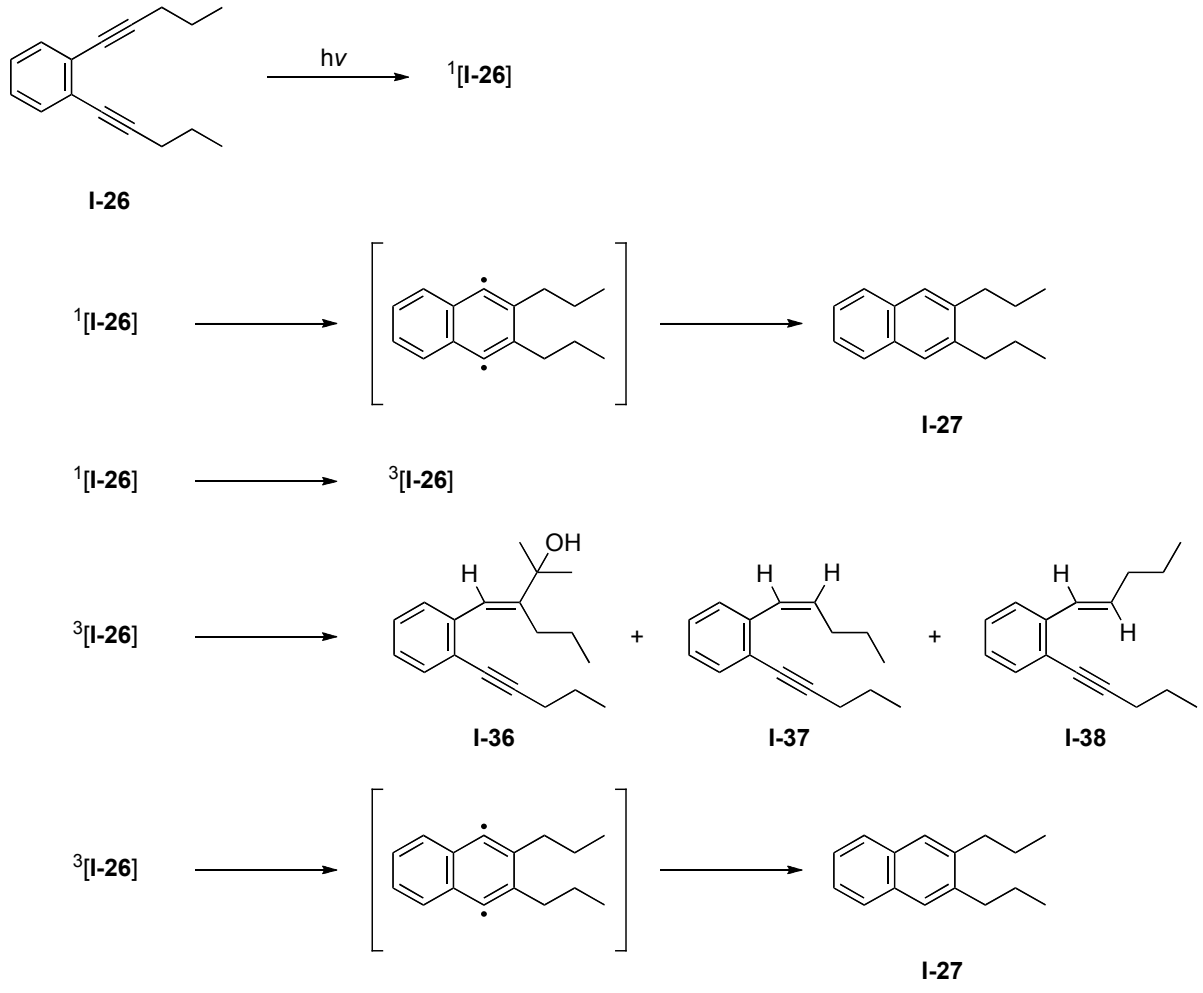


I-39 **I-40**

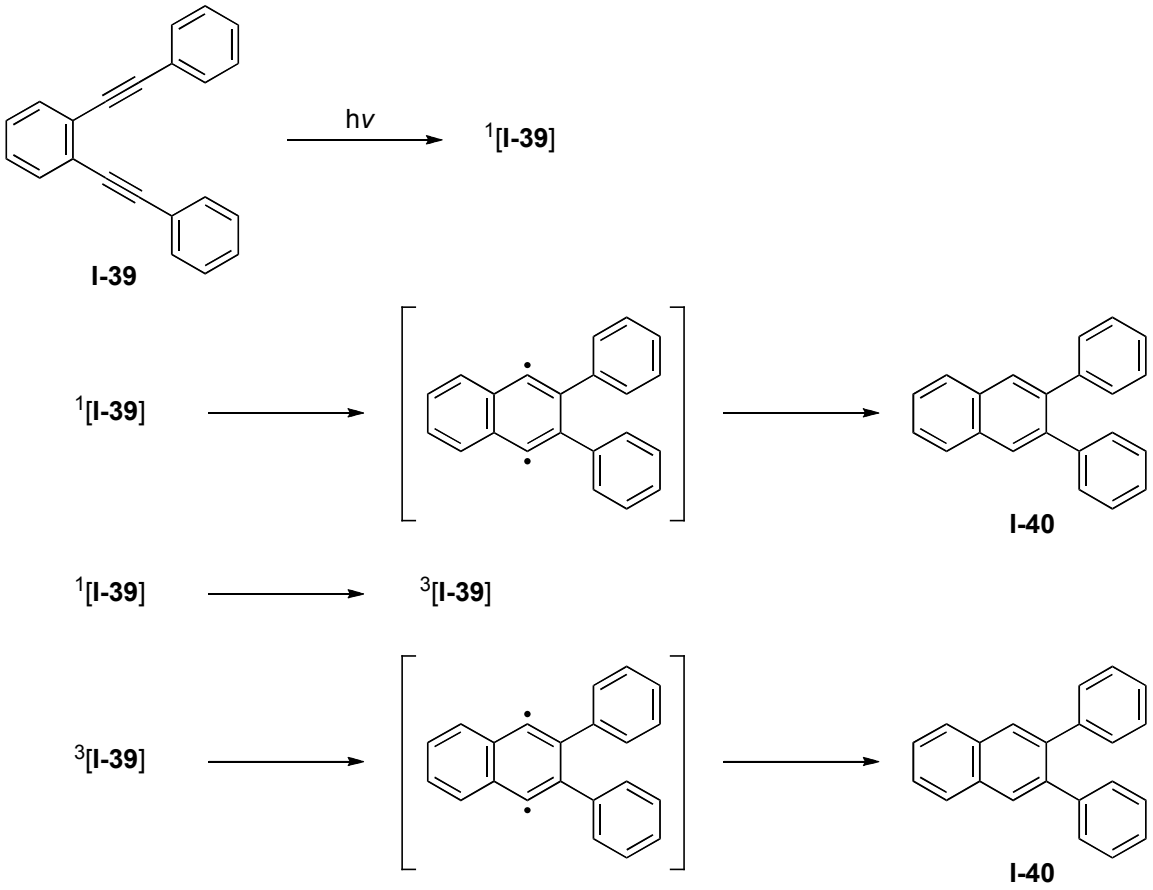
These photolysis experiments supported the hypothesis that the aromatic enediynes **I-26** and **I-39** can react under photochemical conditions to give a product identical to that formed from a Bergman cycloaromatization. Evenzahav and Turro postulated that the reactivity of the enediynes **I-26** and **I-39** arose from the excitation of the acetylenic units as opposed to the conjugated enediyne system. As shown in **Scheme I-11** and **Scheme I-12**, the initial photoexcitation of the enediynes **I-26** and **I-39** to the singlet state would induce the formation of cyclized products **I-27** and **I-40**, by a mechanism similar to that for the thermal Bergman cyclization. An intersystem crossing from the singlet state to the triplet state could also be responsible for the production of the cyclized products **I-27** and **I-40**. However, for the photoexcited enediyne **I-26**, it was this intersystem crossing to the triplet state that was responsible for the production of the acetylene photoreduction products **I-**

36, **I-37**, and **I-38**. Although similar photoreduction products were theoretically possible after the photoexcited enediyne **I-39** underwent an intersystem crossing to the triplet state, these products were not experimentally observed. A likely explanation for this would be that the phenyl substituents on the aromatic enediyne **I-39** might result in an increase in the rigidity of the molecule through both steric hindrance as well as π-stacking interactions, which would decrease the efficiency of an intersystem crossing from the singlet state to the triplet state.[22]

Scheme I-11: Photoexcitation of an Aromatic Enediyne (I-26) and the Resulting Intersystem Crossing



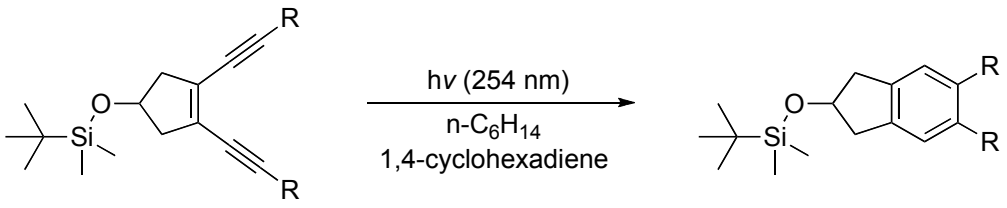
Scheme I-12: Photoexcitation of an Aromatic Enediyne (I-39) and the Resulting Intersystem Crossing



Up until this point, all photoactivated Bergman cyclizations had been performed on arene-fused enediynes. In 1999, Hirama and coworkers reported the photoactivated Bergman cyclization of several aliphatic enediynes. As shown in **Table I-7**, the initial investigations on aliphatic enediynes involved 1,2-diethynylcyclopentene derivatives. The enediyne **I-41a**, with R = H, was irradiated for 6 hours in which time, the starting material completely disappeared, but the cyclized product **I-42a** was formed in only a very low yield of 3 %. However, the

photolysis of the enediyne **I-41b**, with R = Me, produced the cyclized product **I-42b** in the high yield of 71 %. As well, photoreduction products similar to those reported by Evenzahav and Turro were not observed. Photolysis of the enediyne **I-41b** was then repeated in [D_8]THF (99.5 atom % D), which produced the deuterated product **I-42b** in 14 % yield. These results provide substantial evidence that the photocyclization of enediyne **I-41b** progresses through a 1,4-diradical intermediate.[23]

Table I-7: Photoactivated Bergman Cycloaromatizations of 1,2-diethynyl-cyclopentene Derivatives (I-41a and I-41b)



I-41a (R = H)
I-41b (R = Me)

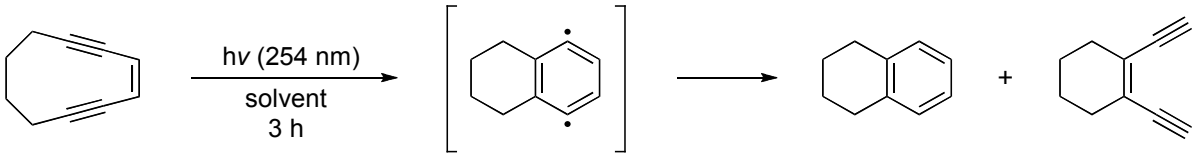
I-42a (R = H)
I-42b (R = Me)

Enediyne	Time (h)	Yield (%)
I-41a	6	3
I-41b	18	71

Hirama and coworkers then investigated the cycloaromatization of the ten-membered cyclic enediyne **I-43** in a variety of solvents (**Table I-8**). After irradiation of the starting material for three hours, the cyclized tetrahydronaphthalene product **I-45** was obtained, along with a considerable amount of the enediyne 1,2-

diethynylcyclohexene **I-46**, which was formed in all solvents except *i*-PrOH. The formation of the enediyne **I-46** was interesting, as it should have arisen from the retro-Bergman cyclization of the 1,4-diradical intermediate **I-44**, and because the enediyne **I-46** had never been isolated in a thermal Bergman cycloaromatization of the starting material **I-43**.[23]

Table I-8: Photoactivated Bergman Cycloaromatizations of Cyclodeca-1,5-diyn-3-ene (I-43)



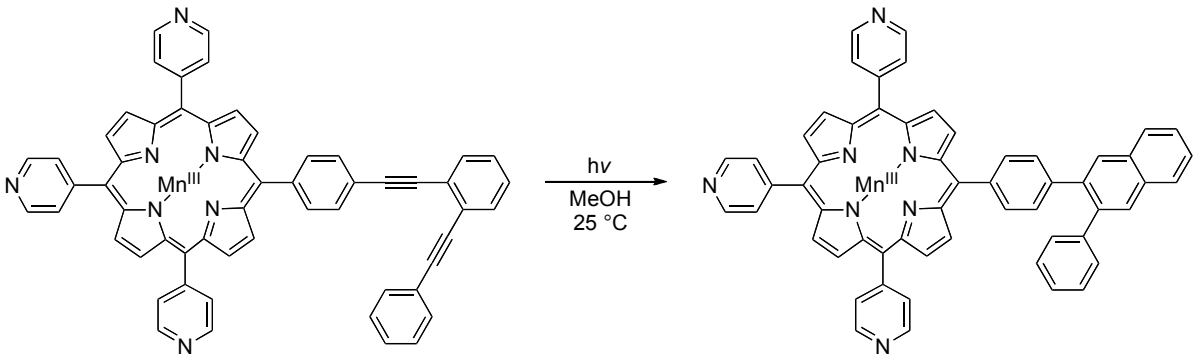
I-43 **I-44** **I-45** **I-46**

Solvent	Yield of **I-45** (%)	Yield of **I-46** (%)
hexane	29	6
cyclohexane	26	20
CH_3CN	12	24
i-PrOH	3	0

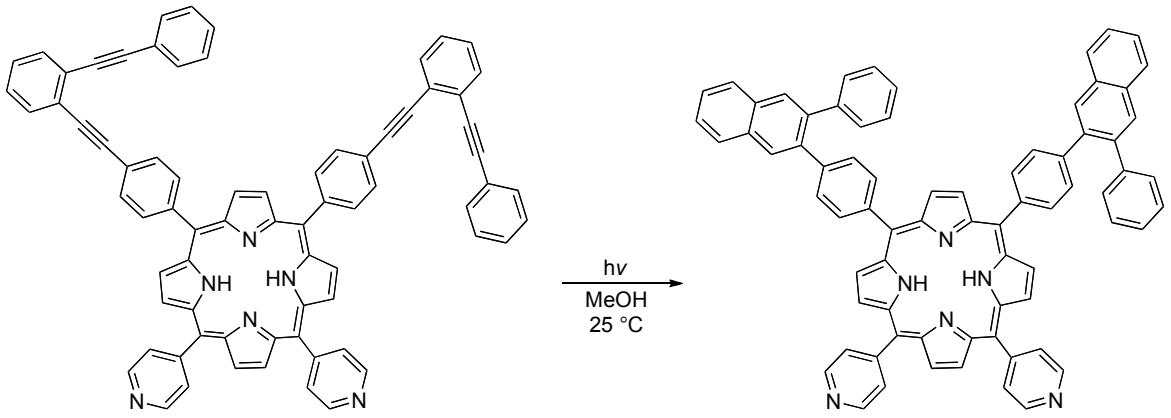
In 2004, Jones and coworkers reported the photoactivated Bergman cyclizations of various chimeric enediynes that were composed of one or more aromatic enediyne units coupled to either a porphyrin or a spiroalcohol. The Jones group was particularly interested in the development of chimeras with the following characteristics: (1) potential for cellular uptake; and (2) the potential to effect selective binding to specific nucleic acid sequences. Specific porphyrins have the

ability to accumulate in rapidly dividing tumor cells with a degree of selectivity, which makes an enediyne-porphyrin chimera the beneficiary of targeted delivery. As shown in **Table I-9**, Jones and coworkers were able to synthesize two enediyne-porphyrin chimeras that were able to undergo photoactivated Bergman cyclizations.[24]

Table I-9: Photoactivated Bergman Cyclizations of Enediyne-porphyrin Chimeras (I-47 and I-49)



I-47 **I-48**

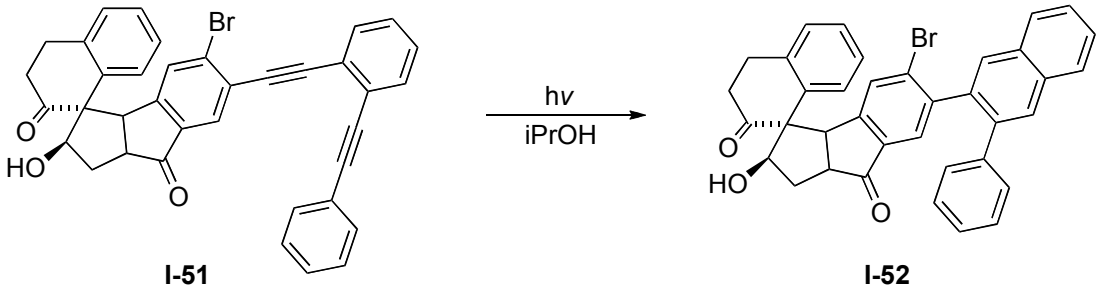


I-49 **I-50**

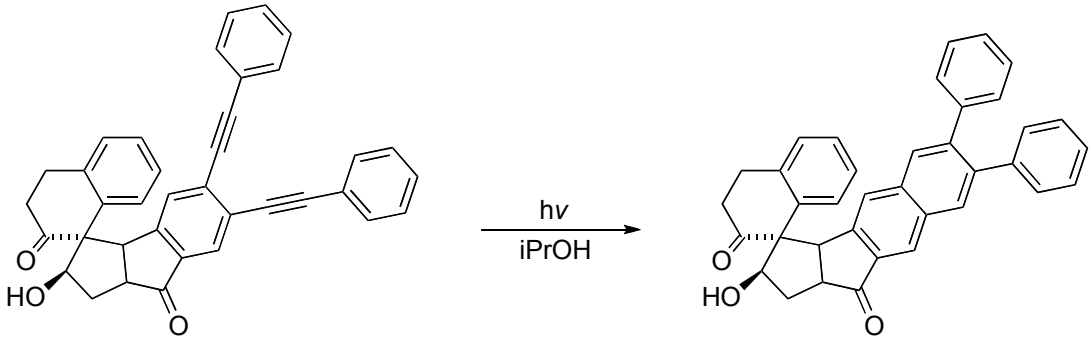
Enediyne	Yield (%)
I-47	30
I-49	20

The Jones group also investigated the photoactivated Bergman cyclizations of enediyne-spiroalcohol chimeras as particular spiroalcohols can have up to nM affinities for bulged DNA microenvironments. This is of significance, as bulged DNA microenvironments have been implicated in frame-shift mutagenesis, imperfect homologous recombination, and as the cause of numerous human neurodegenerative genetic diseases. As shown in **Table I-10**, Jones and coworkers were able to synthesize two enediyne-spiroalcohol chimeras that were able to undergo photoactivated Bergman cyclizations.[24]

Table I-10: Photoactivated Bergman Cyclizations of Enediyne-sprioalcohol Chimeras (I-51 and I-53)



I-51 **I-52**



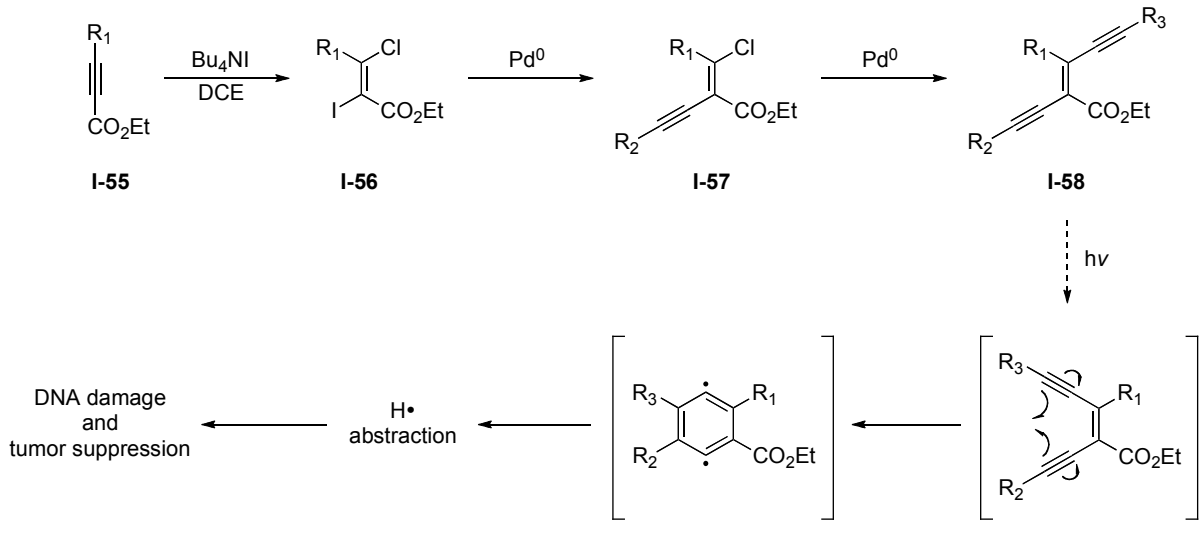
I-53 **I-54**

Enediyne	Yield (%)
I-51	25
I-53	17

1.5 Research Goal

The primary goal of this research project was to create a new class of photoactivated enediyne antibiotics using a methodology developed in the Ogilvie laboratory.[6] As shown in **Scheme I-13**, this approach begins by synthesizing a single isomer *E*-β-chloro-α-iodo-α,β-unsaturated ester **I-56** by exposure of a 2-alkynyl ester **I-55** to Bu_4NI in refluxing dichloromethane. Subsequent Sonogashira couplings at both the α-iodo and the β-chloro positions of the olefin template will afford the tetrasubstituted olefin **I-58** in *trans* isomeric form. Only upon irradiation of light of an appropriate wavelength would the unreactive *trans* isomer be photoisomerized to the reactive *cis* isomer and then undergo a Bergman cyclization, which would result in hydrogen atom abstraction and tumor cell DNA cleavage.

Scheme I-13: The Development of a New Class of Photoactivated Enediyne Antibiotics as the Project Goal



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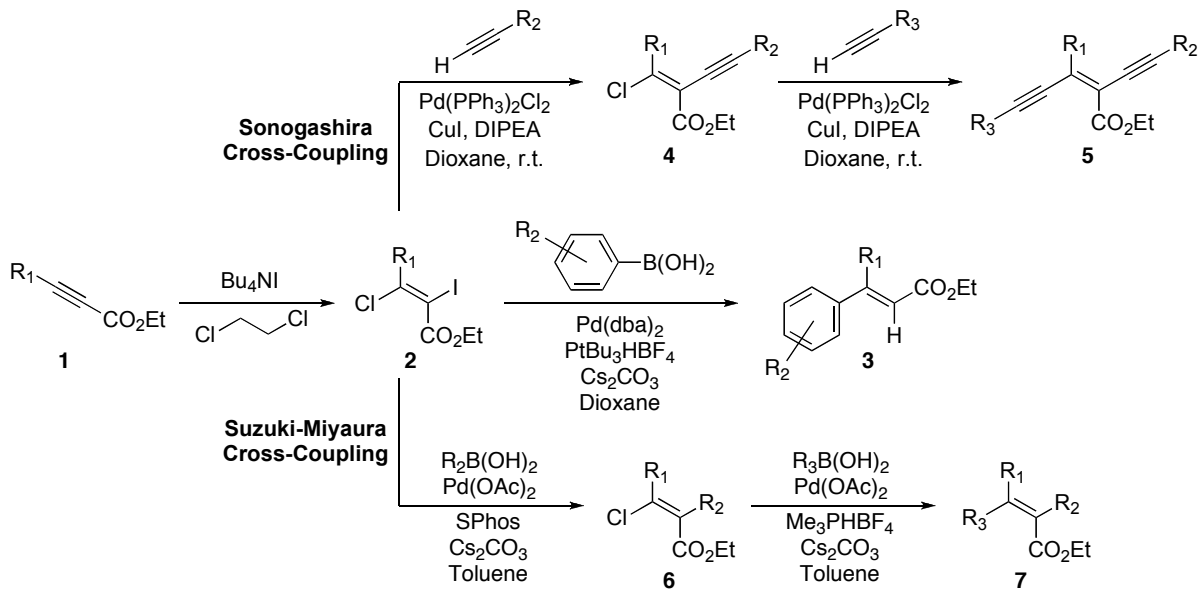
Chapter 2

2.1 Results and Discussion: Synthesis of Single Isomer Trisubstituted and Tetrasubstituted Olefins from *E*-β-Chloro-α-Iodo-α,β-Unsaturated Esters and Bergman Cycloaromatizations With a Radical Trapping Agent

2.2 Previous Work

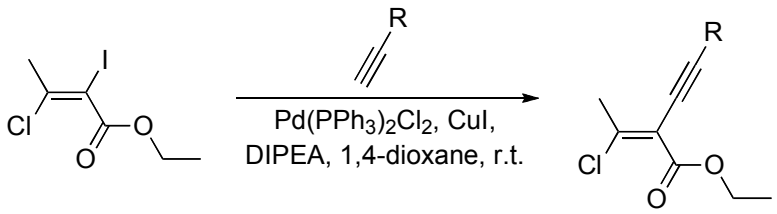
Recently, a major area of research in the Ogilvie group has involved the synthesis of both trisubstituted and tetrasubstituted olefins using an *E*-β-chloro-α-iodo-α,β-unsaturated ester template.[1] The olefin template used in this pathway is very distinct from other templates that are employed to make such substituted products. The principle feature is the presence of two different halogen functional groups that can selectively undergo either Sonogashira[2] or Suzuki-Miyaura[3] cross coupling reactions (**Scheme 1**). A 2-alkynyl ester **1** is exposed to Bu_4NI in refluxing DCE to produce a single isomer *E*-β-chloro-α-iodo-α,β-unsaturated ester **2**. This α,β-unsaturated ester can then undergo a Suzuki-Miyaura cross coupling reaction with an arylboronic acid to form a trisubstituted olefin **3**. Furthermore, it was also shown that both trisubstituted and tetrasubstituted olefins[4] could be synthesized through a series of Sonogashira cross couplings, with a variety of partners, to produce **4** or **5** as single isomers, or through a series of Suzuki-Miyaura cross couplings to produce **6** or **7**, also as single isomers. This is of significance as there are currently few methods that construct acyclic tetrasubstituted olefins[5, 6], and the synthesis of olefins containing four distinct carbon substituents are uncommon.[5, 7]

Scheme 1: Previous Synthesis of Trisubstituted and Tetrasubstituted Olefins in the Ogilvie Group

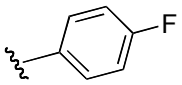
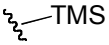
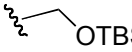
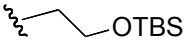


The initial studies aimed at optimizing the cross couplings to synthesize trisubstituted **4** and tetrasubstituted **5** olefins, from the *E*-β-chloro-α-iodo-α,β-unsaturated ester template **2**, were performed as part of the Ph.D. thesis of Dr. Alison Flynn.[8] The conditions initially developed by Flynn for the Sonogashira cross coupling at the α-iodo position of the olefin template, produced a mixture of mono-addition and double-addition products. As well, isomerization of the olefin product was observed. Further study led to optimized conditions that produced single isomer trisubstituted olefins in favorable yields (**Table 1**). This primary coupling had a large scope and showed a tolerance for a variety of substituents, including alkynyl groups with aryl (**9a *trans*** and **9b *trans***), silyl (**9c *trans***), alkyl (**9d *trans***), and tethered silyl ether (**9e *trans*** and **9f *trans***) functions.

Table 1: Optimized Conditions for the Sonogashira Cross Coupling Reaction at the α-Iodo Position of (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (8)



8 **9**

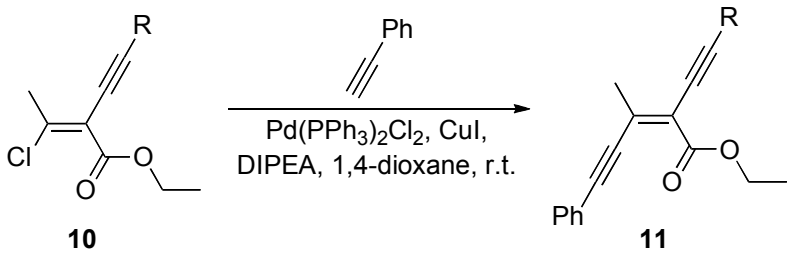
Entry[a]	R	Product	Yield (%)[b]
1		**9a *trans***	78
2		**9b *trans***	77
3		**9c *trans***	68
4		**9d *trans***	74
5		**9e *trans***	76
6		**9f *trans***	72

[a] Conditions: 0.10 eq. of $Pd(PPh_3)_2Cl_2$, 0.15 eq. of CuI, 3.0 eq. of alkyne, 3.0 eq. of DIPEA, dioxane (0.1 M), 23 °C, 2 h.

[b] Isolated yield.

These conditions were not as successful with regards to the Sonogashira cross coupling at the β-chloro position of the olefin template, and produced single isomer tetrasubstituted olefins in moderate yields (**Table 2**).

Table 2: Initial Conditions for the Sonogashira Cross Coupling Reaction at the β-Chloro Position of (*Z*)-ethyl 3-chloro-2-alkynylbut-2-enoate (10)



10 **11**

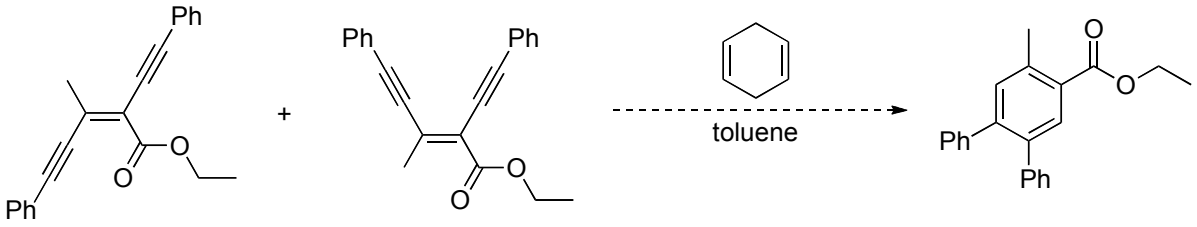
Entry[a]	R	Product	Yield (%)[b]
1	Ph	**11a *trans***	55
2	TMS	**11b *trans***	42

[a] Conditions: 0.10 eq. of $Pd(PPh_3)_2Cl_2$, 0.15 eq. of CuI, 3.0 eq. of alkyne, 3.0 eq. of DIPEA, dioxane (0.1 M), 23 °C, 2 h.
[b] Isolated yield.

The first studies that were performed to see if a tetrasubstituted enediyne would undergo a Bergman cyclization were carried out as part of the Honours thesis of Katarina Vulic.[9] It was decided that the tetrasubstituted olefin **11a *trans*** would be tested for reactivity towards a Bergman cyclization, since it was readily available. Since enediyne **11a *trans*** contained two identical alkynyl substituents, a one-pot Sonogashira cross coupling reaction of compound **8** was performed over an

extended reaction time (12 h), with excess phenylacetylene (6 eq.). This produced a 1.2 : 1 mixture of *trans* (**11a *trans***) to *cis* (**11a *cis***) isomers in similar yield to the overall recovery from sequential cross couplings (40 %). Although the synthesis of the single *trans* isomer **11a *trans*** was possible through sequential cross couplings, the one-pot method permitted direct access to a mixture of *cis* (**11a *cis***) and *trans* (**11a *trans***) enediynes, which could then immediately be tested for Bergman cyclization reactivity, following a set of reaction conditions developed by O'Connor and coworkers (**Table 3**).[10]

Table 3: Attempted Bergman Cyclization of (*Z/E*)-ethyl 3-methyl-5-phenyl-2-(phenylethynyl)pent-2-en-4-ynoate (11a *trans* and 11a *cis*)



11a *trans* **11a *cis*** **12**

1.2 : 1

Entry[a]	Reaction Conditions	Yield (%)
1	r.t.	no reaction
2	hν (350 nm)	no reaction
3	reflux	*trans* isomer (**11a *trans***) recovered + decomposition products
4	reflux, hν (350 nm)	*trans* isomer (**11a *trans***) recovered + decomposition products

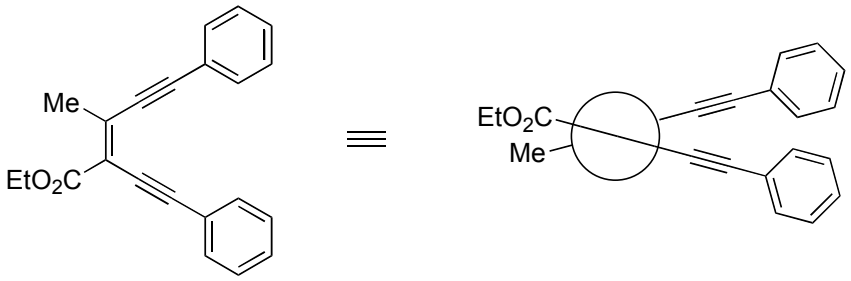
[a] Conditions: 5 eq. 1,4-cyclohexadiene, 12 h.

No spontaneous Bergman cyclization was observed at room temperature (Entry 1), so an attempt to photolyze ($h\nu$ = 350 nm) the mixture of isomers was then made (Entry 2). Again, no Bergman cyclization was observed. A third attempt, and one that was more inline with the classical route to a Bergman cyclization, involved the thermolysis of the isomeric mixture (Entry 3), by refluxing in toluene (111 °C). Although both qualitative TLC, and NMR indicated the disappearance of the *cis* isomer **11a *cis***, there was no observation of a Bergman cyclization product, and only the *trans* isomer **11a *trans*** was recovered, along with decomposition products. The final attempt (Entry 4), involved the simultaneous thermolysis and photolysis of the isomeric mixture. It was hoped that through Le Châtelier's principle, the *trans* isomer **11a *trans*** would continuously isomerize to the *cis* isomer **11a *cis***, while the *cis* isomer **11a *cis*** reacted and underwent a Bergman cyclization. This would result in the complete conversion of both **11a *trans*** and **11a *cis*** to form compound **12**, and make for easier characterization of the product. Unfortunately, although both qualitative TLC, and NMR again indicated the disappearance of the *cis* isomer **11a *cis***, there was no observation of a Bergman cyclization, and only the *trans* isomer **11a *trans*** was recovered, along with decomposition products.

It was hypothesized, but not confirmed, that due to the high degree of steric congestion of the *cis* isomer **11a *cis***, the molecule does not lie fully planar. This deviation from planarity had been previously reported for other acyclic tetrasubstituted olefins as a means of decreasing unfavorable steric interactions (**Scheme 2**).[11] This planar deviation would increase the distance between the

acetylene carbons and therefore make a Bergman cyclization with the *cis* enediyne **11a *cis*** more difficult.

Scheme 2: Possible Deviation From Planarity for the Sterically Congested Enediyne (*E*)-ethyl 3-methyl-5-phenyl-2-(phenylethynyl)pent-2-en-4-ynoate (11a *cis*)



11a *cis* **11a *cis***

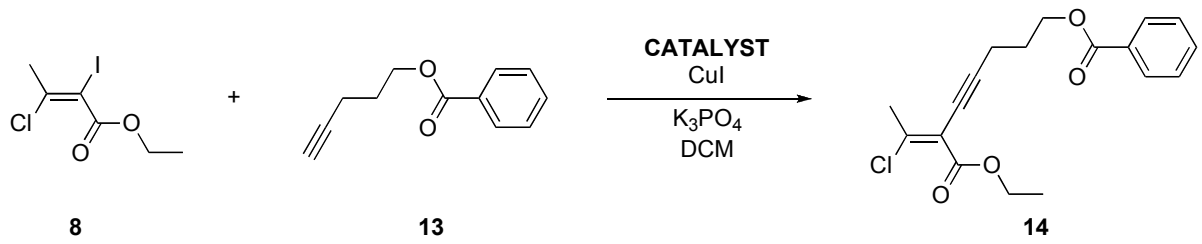
In order to test this hypothesis, and decrease the deviation from planarity, an enediyne would need to be synthesized that contained less steric interactions surrounding the acetylene carbons. This could be achieved by the Sonogashira cross coupling of an alkyl acetylene substituent at both the α-iodo position and the β-chloro position of the olefin template. However, as previously illustrated (**Table 2**), only two enediynes had been synthesized with this methodology, and both in moderate yield. As well, the Sonogashira cross couplings, under the current conditions, were not scalable past 50 mg. Due to the modest yields of the Sonogashira cross couplings at the β-chloro position, as well as their lack of scalability, the research direction of this project shifted towards finding the optimal

conditions for synthesizing enediynes with alkyl acetylene substituents at both the α-iodo position as well as the β-chloro position of the olefin template, in order that they be tested for Bergman cyclization reactivity.

2.3 Optimization of the Sonogashira Cross Coupling With Respect to Alkyl Acetylene Substituents at the α-Iodo Position of the Olefin Template

In order to make for a more facile purification, pent-4-ynyl benzoate **13**, which contains a three-carbon linker followed by a benzoate group, was chosen. The reasoning for this was that the trisubstituted olefin **14** produced from this substrate would have a considerably smaller R_f value than that of the starting material **8**. This optimization process began with an experiment to determine a suitable catalyst for the cross coupling (**Table 4**), while using K_3PO_4 as the base, and DCM as the solvent. A variety of catalysts were tested and $Pd(PPh_3)_2Cl_2$ (Entry 1), was found to give the highest yield (72 %). Similarly, the catalyst $Pd(dppf)_2Cl_2$ (Entry 2), which contains the large, sterically hindered, bidentate dppf ligand, also gave a good yield (71 %). Other palladium catalysts containing bulky, electron donating bidentate ligands such as SPhos (Entry 3) and DavePhos (Entry 4) gave poor yields. The remaining palladium catalysts containing monodentate phosphine ligands (Entry 5 through Entry 8), all gave yields of less than 20 %. It should be noted that a cross coupling reaction, under the aforementioned conditions, with the optimal catalyst $Pd(PPh_3)_2Cl_2$ (Entry 1), was scalable to at least 1000 mg.

Table 4: Determining a Suitable Catalyst for the Sonogashira Cross Coupling Reaction at the α-Iodo Position



8 **13** **14**

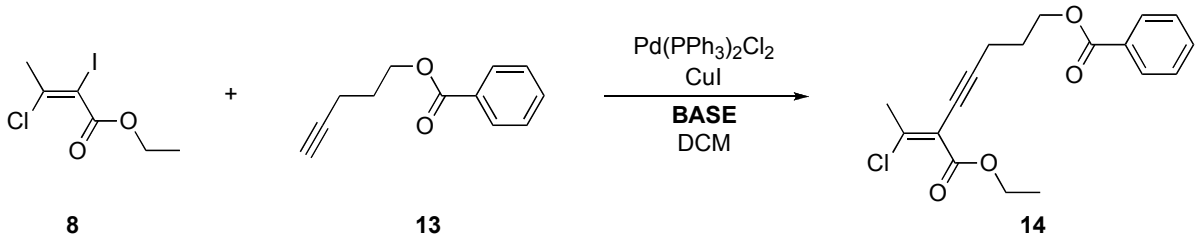
Entry[a]	Catalyst	Yield (%)[b]
1	**$Pd(PPh_3)_2Cl_2$**	**72**
2	$Pd(dppf)_2Cl_2$	71
3	$Pd(OAc)_2$ + SPhos	25
4	$Pd(OAc)_2$ + DavePhos	9
5	$Pd(OAc)_2$ + PEt_3	10
6	$Pd(OAc)_2$ + P^tBu_3	13
7	$Pd(OAc)_2$ + P^tBu_2Me	17
8	$Pd(OAc)_2$ + PMe_3	11

[a] Conditions: 0.10 eq. of CATALYST, 0.15 eq. of CuI, 3.0 eq. of K_3PO_4, DCM (0.05 M), 23 °C, 36 h.
[b] Isolated yield.

With $Pd(PPh_3)_2Cl_2$ identified as the optimal catalyst, attention was turned to exploring the influence of different bases on the cross coupling reaction (**Table 5**). The initial base used, K_3PO_4 (Entry 1), provided a good yield (72 %), however the influence of water in $K_3PO_4 \bullet H_2O$ (Entry 2) resulted in a drastically reduced yield (6 %). Of all the bases tested, Cs_2CO_3 proved to provide the best yield. However, the

degree of purity of the Cs_2CO_3 was vital to the success of the reaction. Relatively high purity Cs_2CO_3 (99 %) (Entry 3), gave only a modest yield of 43 %, whereas Cs_2CO_3 (99.995 %) (Entry 4) gave the highest yield of the study at 78 %. The final inorganic base tested, K_2CO_3 (Entry 8), gave a moderate yield of 54 %. Among the amine bases, NEt_3 (Entry 5) and DABCO (Entry 7) provided very poor yields. Only DIPEA (Entry 6) provided a modest yield of 44 %.

Table 5: Determining a Suitable Base for the Sonogashira Cross Coupling Reaction at the α-Iodo Position



8 **13** **14**

Entry[a]	BASE	Yield (%)[b]
1	K_3PO_4	72
2	$K_3PO_4 \bullet H_2O$	6
3	Cs_2CO_3 (99 %)	43
4	**Cs_2CO_3 (99.995 %)**	**78**
5	NEt_3	10
6	DIPEA	44
7	DABCO	5
8	K_2CO_3	54

[a] Conditions: 0.10 eq. of $Pd(PPh_3)_2Cl_2$, 0.15 eq. of CuI, 3.0 eq. of BASE, DCM (0.05 M), 23 °C, 36 h.
[b] Isolated yield.

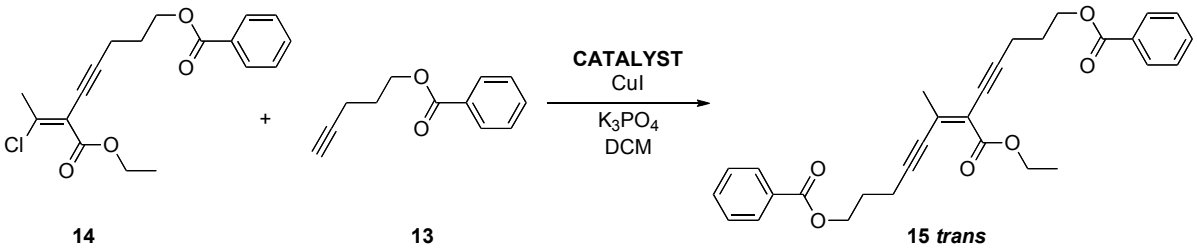
The final optimized conditions for a Sonogashira cross coupling with respect to an alkyl acetylene substituent at the α-iodo position of the olefin template were determined to include $Pd(PPh_3)_2Cl_2$ as the catalyst, and Cs_2CO_3 (99.995 %) as the base. Again, it was determined that under these conditions, the reaction was scalable to at least 1000 mg.

2.4 Optimization of the Sonogashira Cross Coupling With Respect to Alkyl Acetylene Substituents at the β-Chloro Position of the Olefin Template

With the optimized conditions for the synthesis of a trisubstituted olefin having been determined above, attention was then turned to the optimization of a Sonogashira cross coupling between an alkyl acetylene and the chloro position of the olefin template. Again, in order to allow for an easier purification, pent-4-ynyl benzoate **13** was chosen, with the reasoning mirroring that for the Sonogashira cross coupling at the iodo position. As in the earlier optimization process, the cross coupling at the chloro position began with an experiment to determine a suitable catalyst (**Table 6**), while using K_3PO_4 as the base, and DCM as the solvent. A series of catalysts identical to those used before were tested, and $Pd(OAc)_2$ + DavePhos (Entry 4) was found to give the highest yield (84 %). The palladium catalysts containing bulky, electron donating bidentate ligands such as dppf (Entry 2) and SPhos (Entry 3) gave modest yields of 41 % and 36 % respectively. The remaining palladium catalysts containing monodentate phosphine ligands (Entry 1, and Entry 5 through Entry 8) all gave moderate yields of less than 60 %. It should be noted that a cross coupling reaction, under the aforementioned conditions, with

the optimal catalyst $Pd(OAc)_2$ + DavePhos (Entry 4), was scalable to at least 1000 mg.

Table 6: Determining a Suitable Catalyst for the Sonogashira Cross Coupling Reaction at the β-Chloro Position



14 **13** **15 *trans***

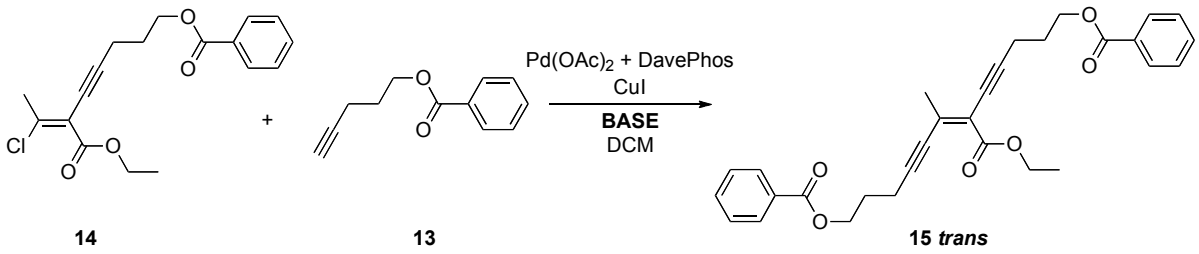
Entry[a]	Catalyst	Yield (%)[b]
1	$Pd(PPh_3)_2Cl_2$	45
2	$Pd(dppf)_2Cl_2$	41
3	$Pd(OAc)_2$ + SPhos	36
4	**$Pd(OAc)_2$ + DavePhos**	**84**
5	$Pd(OAc)_2 + PEt_3$	51
6	$Pd(OAc)_2 + P^tBu_3$	29
7	$Pd(OAc)_2 + P^tBu_2Me$	56
8	$Pd(OAc)_2 + PMe_3$	43

[a] Conditions: 0.10 eq. of CATALYST, 0.15 eq. of CuI, 3.0 eq. of K_3PO_4, DCM (0.05 M), 23 °C, 72 h.
[b] Isolated yield.

Similar to the previous catalyst scan, once $Pd(OAc)_2$ + DavePhos had been identified as the optimal catalyst, attention was focused on exploring the influence of different bases on the cross coupling (**Table 7**). A series of bases identical to those used in the initial cross coupling at the α-iodo position were tested. The initial base used, K_3PO_4 (Entry 1), in fact, proved to give the best yield (84 %), however, as before, the influence of water in $K_3PO_4 \bullet H_2O$ (Entry 2) resulted in a drastically reduced yield (8 %). The remaining inorganic bases used in the scan gave moderate to good yields with Cs_2CO_3 (99.995 %) giving the highest (74 %). Among the amine bases used, all three gave moderate yields with DIPEA being the highest (67 %).

The final optimized conditions for a Sonogashira cross coupling with respect to an alkyl acetylene substituent at the β-chloro position of the olefin template were determined to include $Pd(OAc)_2$ + DavePhos as the catalyst, and K_3PO_4 as the base. Again, it was determined that under these conditions, the reaction was scalable to at least 1000 mg.

Table 7: Determining a Suitable Base for the Sonogashira Cross Coupling Reaction at the β-Chloro Position



14 **13** **15 *trans***

Entry[a]	BASE	Yield (%)[b]
1	**K_3PO_4**	**84**
2	$K_3PO_4 \bullet H_2O$	8
3	Cs_2CO_3 (99 %)	39
4	Cs_2CO_3 (99.995 %)	74
5	NEt_3	56
6	DIPEA	67
7	DABCO	55
8	K_2CO_3	46

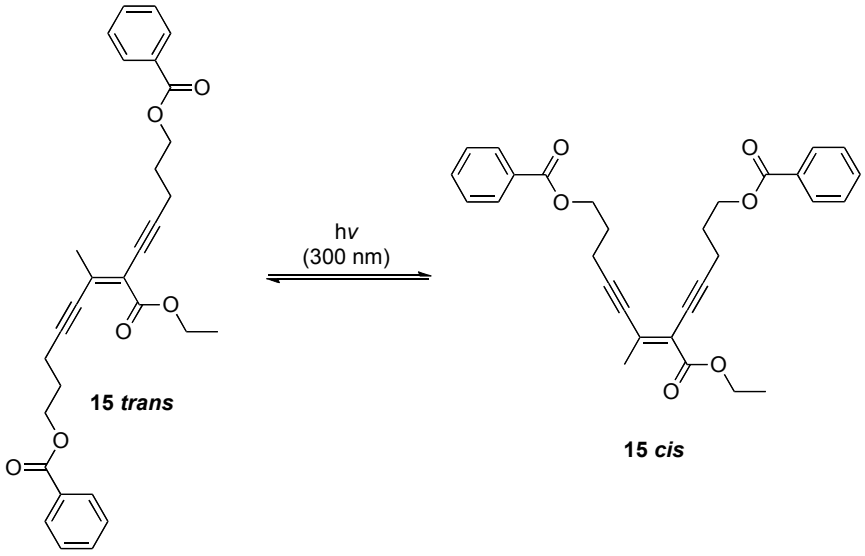
[a] Conditions: 0.10 eq. of $Pd(OAc)_2$ + DavePhos, 0.15 eq. of CuI, 3.0 eq. of BASE, DCM (0.05 M), 23 °C, 72 h.
[b] Isolated yield.

2.5 Photoisomerization of the *Trans* Enediyne to a *Trans-Cis* Enediyne Mixture

Photochemical *trans-cis* isomerization[12] of the alkene (**Scheme 3**) played a very important role in the attempt to get the newly synthesized enediyne **15 *trans*** to undergo a Bergman cyclization, as *trans* enediynes have generally proven to be

both thermally and photochemically inert to cyclization. In order to photoisomerize the *trans* enediyne **15 *trans*** to its *cis* isomer **15 *cis***, UV light of approximately 300 nm wavelength was required. The previously synthesized *trans* enediyne **15 *trans*** was dissolved in freshly distilled DCM, and the solution was photolyzed using a UV lamp (300 nm) for 20 h to produce a mixture of both *cis* (**15 *cis***) and *trans* (**15 *trans***) isomers.

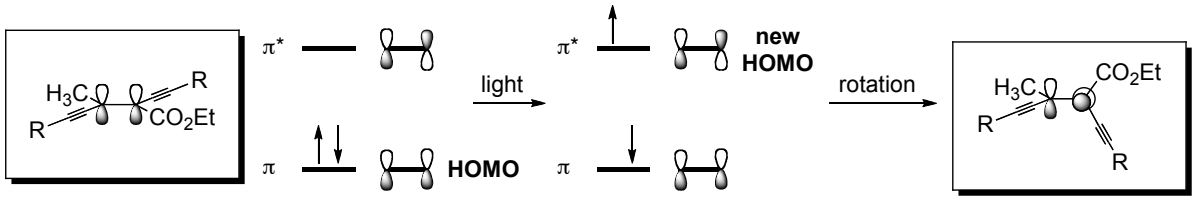
Scheme 3: Photoisomerization of the *Trans* Enediyne Isomer



Since *cis* and *trans* isomers show different absorption maxima, the isomerization of one of the isomers will occur at a faster rate than that for the other isomer, and its concentration will decrease until the point in time at which a photostationary state is reached. It is at this photostationary state that the rate of *trans* to *cis* isomerization is equal to the rate of *cis* to *trans* isomerization.

Photoisomerization occurs when the alkene absorbs a photon, and an electron is promoted from the π orbital to the π^* orbital. The resulting species then undergoes rotation to an excited state in which the sp^2 carbons are twisted 90° with respect to each other. This perpendicular rearrangement is believed to be the minimum-energy geometry that reduces the electron repulsion between the SOMO orbitals. Continued rotation allows the possibility of returning to either the *cis* or *trans* ground states (**Scheme 4**).

Scheme 4: Photochemical Isomerization of Enediynes

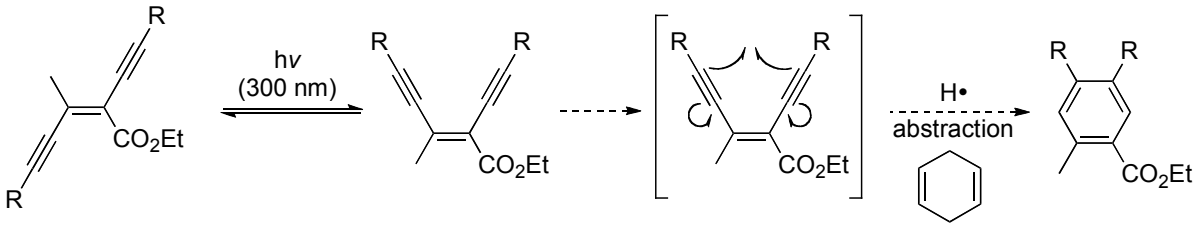


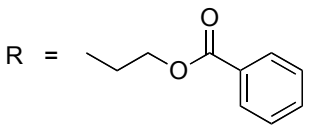
The desired *cis* enediyne isomer **15 *cis*** was observed, along with the *trans* enediyne isomer **15 *trans***, as a separable mixture, in a 43 : 57 ratio. The fact that the observed isomeric ratio was not 50 : 50 can be attributed to the *cis* isomer **15 *cis*** being less thermodynamically stable, as the two largest substituents across the double bond are in the same orientation, and thus result in an increase in the steric hindrance for the enediyne. UV-Vis spectroscopy indicated an absorption peak for *trans* isomer **15 *trans*** at λ = 286.1 nm and for *cis* isomer **15 *cis*** at λ = 290.2 nm.

2.6 Attempts at a Photoactivated Bergman Cyclization

Once both enediyne isomers **15 *trans*** and **15 *cis*** had been synthesized, their reactivity with respect to a Bergman cyclization was investigated (**Table 8**). Using 1,4-cyclohexadiene as the radical trapping agent, and UV light of approximately 300 nm wavelength, a variety of conditions were tested. Initially, only the *trans* isomer **15 *trans*** was used as the starting material, in an attempt to determine whether or not the *trans* enediyne **15 *trans*** could be photoisomerized to its *cis* isomer **15 *cis***, and then have the *cis* isomer **15 *cis*** subsequently undergo a Bergman cyclization.

Table 8: Attempted Bergman Cyclization of (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl Dibenzoate (15 *trans*)





Entry[a]	Solvent	Reflux Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	DCM	23	yes	19	81	0
2	toluene	111	yes	19	81	0
3	toluene	111	no	0	100	0
4	mesitylene	164	yes	19	81	0
5	mesitylene	164	no	0	100	0
6	nitrobenzene	211	yes	decomposition	decomposition	0
7	nitrobenzene	211	no	decomposition	decomposition	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 2 h.

The first trial (Entry 1) was used to determine whether or not the *trans* isomer **15 *trans*** could be photoisomerized with UV light to the *cis* isomer **15 *cis***, and then, in the presence of a radical trapping agent (1,4-cyclohexadiene), have the *cis* isomer **15 *cis*** spontaneously undergo a Bergman cyclization at room temperature. Unfortunately, after two hours, only a mixture of *trans* (**15 *trans***) and *cis* (**15 *cis***) isomers was recovered in an 81 : 19 ratio. It was then decided to determine whether or not the reaction was thermodynamically accessible, either with or without the assistance of a UV light source. The second trial (Entry 2) consisted of simultaneously refluxing the *trans* isomer **15 *trans*** in toluene, while irradiating the solution with approximately 300 nm UV light. This experiment again resulted in the formation of a mixture of *trans* (**15 *trans***) and *cis* (**15 *cis***) isomers in an 81 : 19 ratio. The third experiment (Entry 3) determined whether or not the *trans* isomer **15 *trans*** could thermodynamically undergo a Bergman cyclization, with no UV light source. As expected, it did not undergo a cyclization, and only the *trans* isomer **15 *trans*** was recovered. Toluene has a reflux temperature of 111 °C, and at this point it was decided to make use of a solvent with a significantly higher boiling point in order to determine whether or not the reaction was thermodynamically accessible. It was decided upon the use of mesitylene, as its reflux temperature is 164 °C, which could possibly provide enough thermal energy to force the enediyne **15 *trans*** to undergo a Bergman cyclization. Similar experiments were run to the trials that were done in toluene, and unfortunately, both experiments (Entry 4 and Entry 5) did not provide a Bergman cyclization, but gave similar results as before (Entry 2 and Entry 3). The final step, in this series of experiments, consisted of making use of a high-boiling

solvent with a reflux temperature in excess of 200 °C. Nitrobenzene was used in the final two trials (Entry 6 and Entry 7). After the starting material **15** ***trans*** was subjected to reflux for two hours while being irradiated by UV light, only decomposition products were isolated. Similarly, only decomposition products remained after the *trans* enediyne **15** ***trans*** was exposed to refluxing nitrobenzene, without irradiation from any UV light source.

At this point, it was decided that an increased reaction time might be necessary to induce a Bergman cyclization. The previous experiments were repeated, but for reaction lengths of four hours or six hours (**Table 9**). The results were similar to above, in regards to the fact that no Bergman cyclization was observed. The sole difference between the results from the extended reaction times and those from the previous reactions lay in the fact that a greater percentage of the *cis* isomer **15** ***cis*** formed. This can be explained simply by the fact that a greater reaction time allows for more of the *trans* isomer **15** ***trans*** to be photoisomerized to the *cis* isomer **15** ***cis***, as the reaction mixture had not yet reached a photostationary state.

Table 9: Attempted Bergman Cyclization of (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl Dibenzoate (15 *trans*) Using Extended Reaction Times

Entry[a]	Solvent	Reflux Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	DCM	23	yes	27	73	0
2	toluene	111	yes	27	73	0
3	toluene	111	no	0	100	0
4	mesitylene	164	yes	27	73	0
5	mesitylene	164	no	0	100	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 4 h.

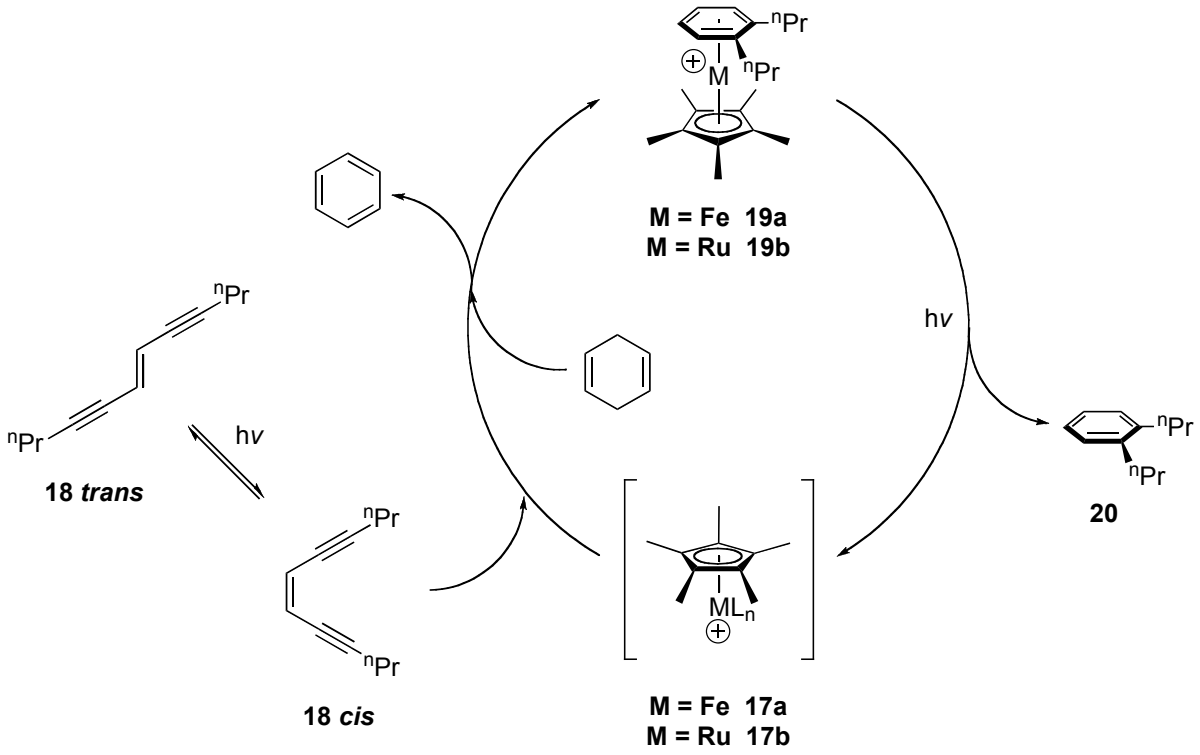
Entry[a]	Solvent	Reflux Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	DCM	23	yes	34	66	0
2	toluene	111	yes	34	66	0
3	toluene	111	no	0	100	0
4	mesitylene	164	yes	34	66	0
5	mesitylene	164	no	0	100	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 6 h.

2.7 Transition-Metal-Catalyzed Enediyne Cycloaromatization

In 2005, O'Connor and coworkers published the first transition-metal-catalyzed Bergman cycloaromatization (**Scheme 5**).[10] This was particularly useful for *trans* enediynes, which had previously been inert to both thermal and photochemical Bergman cyclizations.

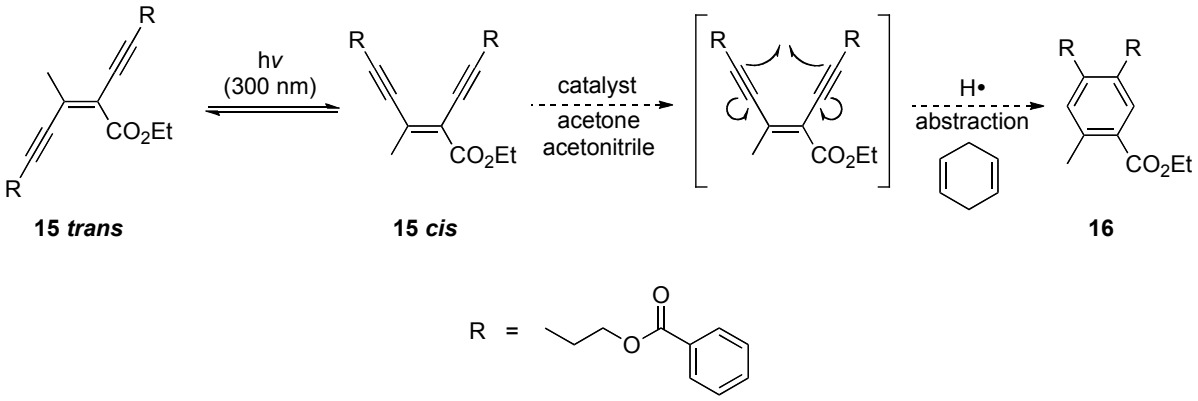
Scheme 5: Catalytic Cycle for Transition-Metal-Catalyzed Enediyne Cycloaromatization



The use of the catalysts $[(\eta^5\text{-}C_5Me_5)Ru(CH_3CN)_3]OTf$ or $[(\eta^5\text{-}C_5Me_5)Fe(CH_3CN)_3]PF_6$ in the presence of 1,4-cyclohexadiene as the radical trapping agent, resulted in the enediyne **18** ***trans*** undergoing a Bergman cyclization while under UV light irradiation. The Bergman cyclization product **20** formed in 74 % yield with the ruthenium based catalyst, and in 83 % yield with the iron based catalyst. This was significant as it represented the first transition-metal-catalyzed Bergman cycloaromatization reaction. The simultaneous use of a transition metal and UV light overcame the previous stereochemical requirement of a *cis* enediyne geometry. The fact that the previously synthesized enediyne **15** ***trans*** was both

acyclic and of *trans* geometry lent itself to the possibility that a Bergman cyclization could be catalyzed by similar conditions to those that were reported by O'Connor and coworkers (**Table 10**).

Table 10: Attempted Bergman Cyclization of (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl Dibenzoate (15 *trans*) Using a Transition-Metal-Catalyst



Entry[a]	Solvent	Catalyst	Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	acetone	$[\eta^5\text{-}C_5Me_5)Ru(CH_3CN)_3]OTf$	23	yes	43	57	0

[a] Conditions: 0.25 eq. of catalyst, 2.5 eq. of acetonitrile, 5 eq. 1,4-cyclohexadiene, concentration (0.02 M), 6 d.

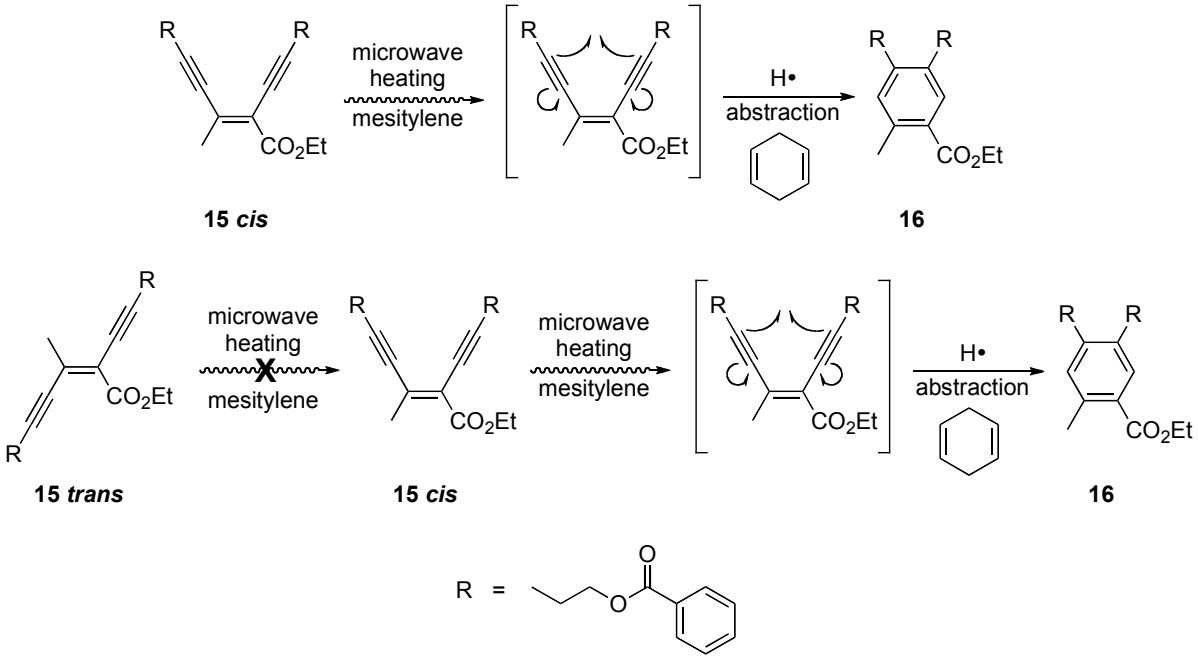
An experiment using the method developed by O'Conner and coworkers was set up using **15 *trans*** as the starting material (**Table 10**). The catalyst $[(\eta^5\text{-}C_5Me_5)Ru(CH_3CN)_3]OTf$ was used, along with UV light of approximately 300 nm wavelength. After photolyzing the reaction for six days, a mixture of *cis* (**15 *cis***) and

trans (**15 *trans***) isomers of the starting material **15 *trans*** was recovered, in a 43 : 57 ratio. No Bergman cyclization product was observed. At this point, no further attempts were made to catalyze the reaction with a transition metal catalyst. Instead, the project proceeded towards investigating the effects of using microwave heat on both the *cis* (**15 *cis***) and *trans* (**15 *trans***) enediynes.

2.8 Microwave-Assisted Enediyne Cycloaromatization

All previous thermal, photochemical, or transition-metal-catalyzed attempts to induce a Bergman cyclization had been unsuccessful, and had either resulted in the recovery of one or both of the isomers **15 *cis*** and **15 *trans***, or in decomposition of the starting material. It was then decided to attempt a microwave-assisted Bergman cyclization, as a solvent such as mesitylene can be superheated to 250 °C[13, 14], in order to determine whether or not the reaction was indeed thermally accessible. Similar procedures were followed as to those shown before (**Table 8**), but in this instance, only single isomers of the starting material **15 *cis*** or **15 *trans*** where used in the reaction, and neither isomer **15 *cis*** or **15 *trans*** was irradiated with UV light (**Table 11**).

Table 11: Microwave-Assisted Bergman Cyclization of (*Z*/*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl Dibenzoate (15 *trans* and 15 *cis*)



Entry[a]	Initial Isomer	Microwave Temperature (°C)	Recovered Isomer		Bergman Product Yield (%)[b]
			Cis (%)	*Trans* (%)	
1	*cis*	200	59	—	0
2	*cis*	250	0	—	31
3	*cis*	225	0	—	36
4	*trans*	225	—	44	0
5	*trans*	250	—	35	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, mesitylene (0.05 M), 2 h.
[b] Isolated yield.

The initial microwave experiment (Entry 1) consisted of microwaving the *cis* isomer **15 *cis*** and the radical trapping agent 1,4-cyclohexadiene in mesitylene for two hours at 200 °C. No Bergman cyclization product **16** was observed, but slightly

more than half of the starting material **15 *cis*** was recovered (59 %). This significant loss in the starting material **15 *cis*** can be attributed to its likely decomposition due to the extreme temperature of the reaction. Despite this fact, further attempts at initiating a Bergman cyclization using **15 *cis*** as the starting material were made. The second experiment (Entry 2) was run under nearly identical conditions to the previous experiment, but the temperature of the reaction was raised to 250 °C. This proved to be successful, as the Bergman cyclization product **16** was isolated in 31 % yield. No starting material **15 *cis*** was recovered, however a significant amount of decomposition products formed, which can again be attributed to the very high temperature involved in this reaction. A third and final attempt at a microwave-assisted Bergman cyclization with the *cis* isomer **15 *cis*** was made by moderating the temperature to 225 °C (Entry 3), in hopes of increasing the reaction yield. The Bergman cyclization product **16** was once again observed, but with an increased yield of 36 %. The lower temperature for this experiment likely resulted in less decomposition of the starting material **15 *cis***, which then resulted in a higher yield.

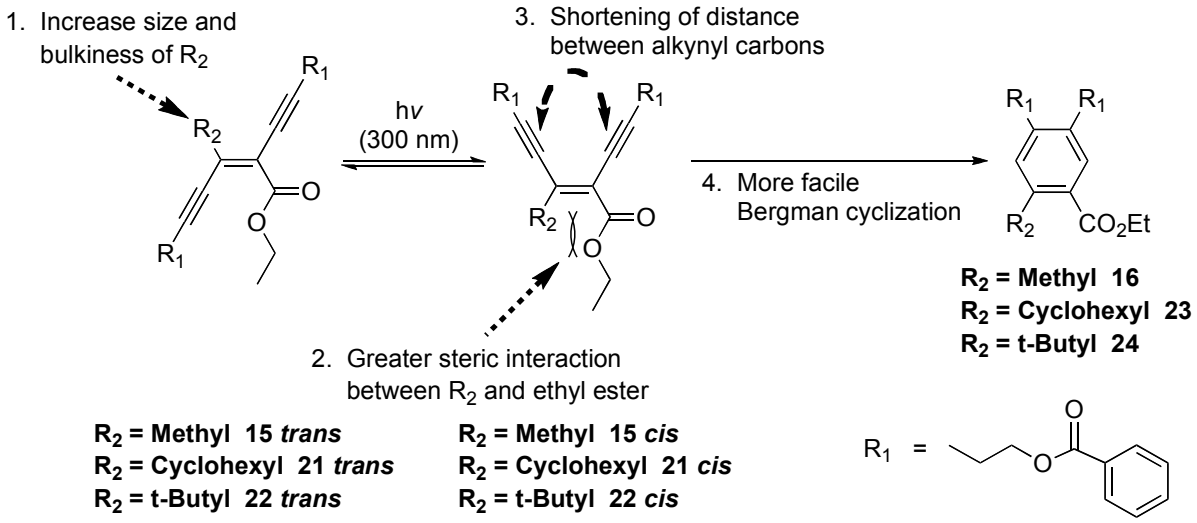
Two final attempts at Bergman cyclizations were made, but this time using the *trans* isomer **15 *trans*** as the starting material. It was thought that given the extreme temperature involved in these microwave experiments, that the *trans* isomer **15 *trans*** may thermally isomerize[15, 16] to the *cis* isomer **15 *cis***, and then undergo a Bergman cyclization as before. The initial microwave experiment using the *trans* isomer **15 *trans*** (Entry 4) was again carried out under similar conditions to the previous experiments, and at a temperature of 225 °C. Neither the Bergman cyclization product **16**, nor the *cis* isomer **15 *cis*** was observed as products of this

reaction. Only 44 % of the *trans* isomer **15 *trans*** starting material was recovered, along with decomposition products. One final attempt at forcing the *trans* isomer **15 *trans*** to undergo a microwave-assisted Bergman cyclization was made (Entry 5). This trial consisted of heating the compound **15 *trans*** to a temperature of 250 °C. Again, neither the Bergman cyclization product **16**, nor the *cis* isomer **15 *cis*** was observed as products of this reaction. The *trans* isomer **15 *trans*** was again recovered (35 %), along with decomposition products. As expected, the higher microwave temperature led to a greater degree of decomposition of the starting material **15 *trans***.

2.9 Altering a Functional Group on the Alkene of the Enediyne

Given the two successful microwave-assisted enediyne cycloaromatizations above, it was decided to attempt to change the methyl functional group on the alkene of the enediyne **15 *trans***. The reasoning for this was that a larger, bulkier functional group, such as a cyclohexyl or a t-butyl, may be able to help decrease the distance between the alkynyl carbons, when the enediyne was in its *cis* isomeric form (**Scheme 6**). When in the *cis* isomeric form, there would be a large steric interaction between the functional group at the R_2 position and the ethyl ester. This large steric interaction on one side of the enediyne may help to force the alkynyl carbons on the opposite side of the enediyne closer together. This would be desirable, as decreasing this distance would likely make a Bergman cyclization of the enediyne more feasible.

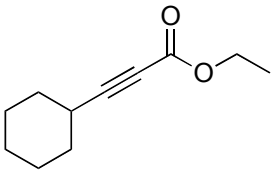
Scheme 6: Attempt to Decrease the Distance Between the Alkynyl Carbons of the Enediyne



2.10 Synthesizing an Enediyne With a Cyclohexyl Functional Group at the R_2 Position

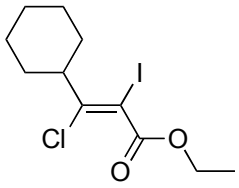
The initial attempt at increasing the size and bulkiness of the R_2 functional group from **Scheme 6** involved the synthesis of a cyclohexyl alkynyl ester and its corresponding *E*-β-chloro-α-iodo-α,β-unsaturated ester (**Figure 1**). The synthesis was straightforward,[8] and produced the desired alkynyl ester **25** in excellent yield (99 %). This compound was then utilized in the synthesis of the *E*-β-chloro-α-iodo-α,β-unsaturated ester **26** following a nearly identical procedure[8] to that shown in **Scheme 1**.

Figure 1: Cyclohexyl Alkynyl Ester (25) and Its Corresponding *E*-β-chloro-α-iodo-α,β-unsaturated Ester (26)



25

yield = 99 %

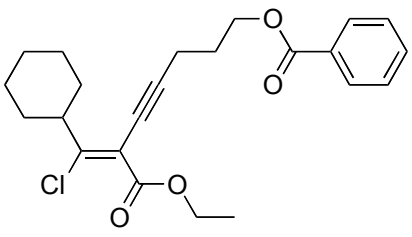


26

yield = 68 %

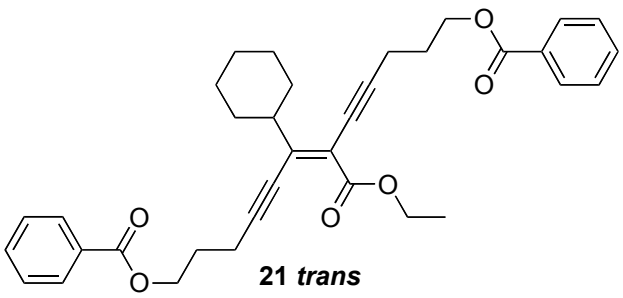
Once the *E*-β-chloro-α-iodo-α,β-unsaturated ester **26**, with a large, bulky R_2 group had been synthesized, it was then used in a series of Sonogashira cross coupling reactions similar to the optimized trials shown in **Table 4** through **Table 7**. These sequential cross couplings produced the trisubstituted olefin **27**, followed by the tetrasubstituted olefin **21 *trans***, as shown in **Figure 2**, both in moderate to good yield.

Figure 2: Cyclohexyl Trisubstituted Olefin (27) and Cyclohexyl Tetrasubstituted Olefin (21 *trans*)



27

yield = 60 %



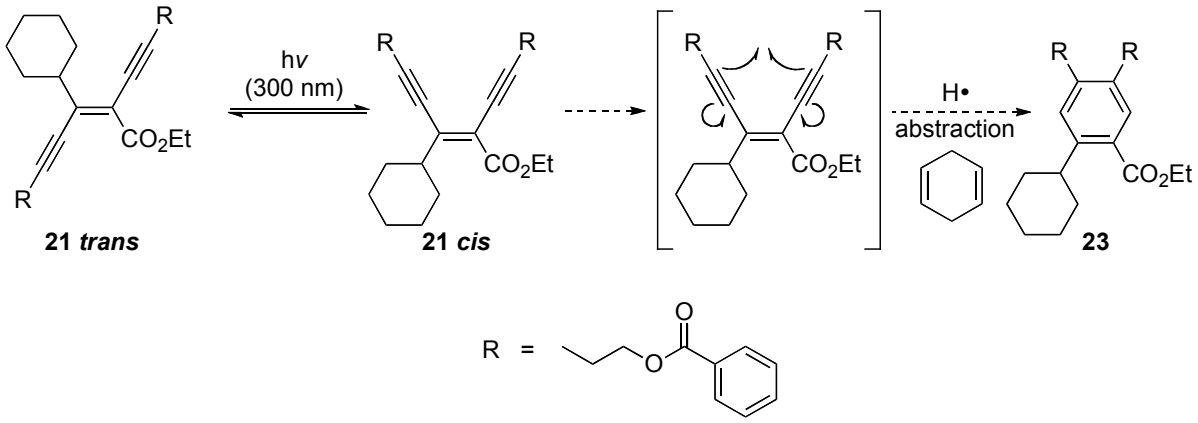
21 *trans*

yield = 76 %

2.11 Attempts at a Photoactivated Bergman Cyclization

With the desired enediyne containing the cyclohexyl functional group at the R_2 position having been synthesized as the *trans* isomer **21 *trans***, the compound's reactivity towards a Bergman cyclization was investigated in order to determine whether or not the large, bulky cyclohexyl group would help to make the reaction more accessible, by helping to force the alkynyl carbons closer together when in the *cis* isomeric form **21 *cis*** (**Table 12**). Using 1,4-cyclohexadiene as the radical trapping agent, and UV light of approximately 300 nm wavelength, a variety of conditions similar to those tested previously (**Table 8**) were tried. Initially, only the *trans* isomer ***21 trans*** was used as the starting material, in an attempt to determine whether or not the *trans* enediyne **21 *trans*** could be photoisomerized to its *cis* isomer **21 *cis***, and then have the *cis* isomer **21 *cis*** subsequently undergo a Bergman cyclization.

Table 12: Attempted Bergman Cyclization of (*Z*)-6-cyclohexyl-7-(ethoxycarbonyl)dodeca-6-en-4,8-diyne-1,12-diyl Dibenzoate (21 *trans*)



Entry[a]	Solvent	Reflux Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	DCM	23	yes	17	83	0
2	toluene	111	yes	17	83	0
3	toluene	111	no	0	100	0
4	mesitylene	164	yes	17	83	0
5	mesitylene	164	no	0	100	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 2 h.

The first trial (Entry 1) was used to determine whether or not the *trans* isomer **21 *trans*** could be photoisomerized with UV light to the *cis* isomer **21 *cis***, and then, in the presence of a radical trapping agent (1,4-cyclohexadiene), have the *cis* isomer **21 *cis*** spontaneously undergo a Bergman cyclization at room temperature. Unfortunately, after two hours, only a mixture of *trans* (**21 *trans***) and *cis* (**21 *cis***) isomers was recovered in an 83 : 17 ratio. It was then decided to determine whether or not the reaction was thermodynamically accessible, either with or without the

assistance of a UV light source. The second trial (Entry 2) consisted of simultaneously refluxing the *trans* isomer **21 *trans*** in toluene, while irradiating the solution with approximately 300 nm UV light. This experiment again resulted in the formation of a mixture of *trans* (**21 *trans***) and *cis* (**21 *cis***) isomers in an 83 : 17 ratio. The third experiment (Entry 3) was utilized to determine whether or not the *trans* isomer **21 *trans*** could thermodynamically undergo a Bergman cyclization, with no UV light source. As expected, it did not undergo a cyclization, and only the *trans* isomer **21 *trans*** was recovered. As discussed before concerning the previous attempts at a Bergman cyclization (**Table 8**), toluene has a reflux temperature of only 111 °C, so it was decided to make use of a solvent with a significantly higher boiling point in order to determine whether or not the reaction was thermodynamically accessible. Again mesitylene was utilized, as its reflux temperature is 164 °C, which could possibly provide enough thermal energy to force the enediyne **21 *trans*** to undergo a Bergman cyclization. Similar experiments were run to the trials that were done in toluene, and unfortunately, both experiments (Entry 4 and Entry 5) did not provide a Bergman cyclization, but gave similar results to before (Entry 2 and Entry 3). Due to the decomposition of the enediyne **15 *trans*** in refluxing nitrobenzene during the previous series of experiments (**Table 8**), it was decided against attempting a Bergman cyclization of the compound **21 *trans*** with that solvent. However, like before, it was thought that an increased reaction time might be necessary to induce a Bergman cyclization. The previous experiments were repeated, but for reaction lengths of four hours or six hours (**Table 13**). The results were similar to those previous, in regards to the fact that no Bergman

cyclization product **23** was observed. Again, the sole difference between the results from the extended reaction times and those from the previous reactions lay in the fact that a greater percentage of the *cis* isomer **21 *cis*** formed. This can be explained simply by the fact that a greater reaction time allows for more of the *trans* isomer **21 *trans*** to be photoisomerized to the *cis* isomer **21 *cis***, as the reaction mixture had not yet reached a photostationary state.

Table 13: Attempted Bergman Cyclization of (*Z*)-6-cyclohexyl-7-(ethoxycarbonyl)dodeca-6-en-4,8-diyne-1,12-diyl Dibenzoate (21 *trans*) Using Extended Reaction Times

Entry[a]	Solvent	Reflux Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	DCM	23	yes	25	75	0
2	toluene	111	yes	25	75	0
3	toluene	111	no	0	100	0
4	mesitylene	164	yes	25	75	0
5	mesitylene	164	no	0	100	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 4 h.

Entry[a]	Solvent	Reflux Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	DCM	23	yes	33	67	0
2	toluene	111	yes	33	67	0
3	toluene	111	no	0	100	0
4	mesitylene	164	yes	33	67	0
5	mesitylene	164	no	0	100	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 6 h.

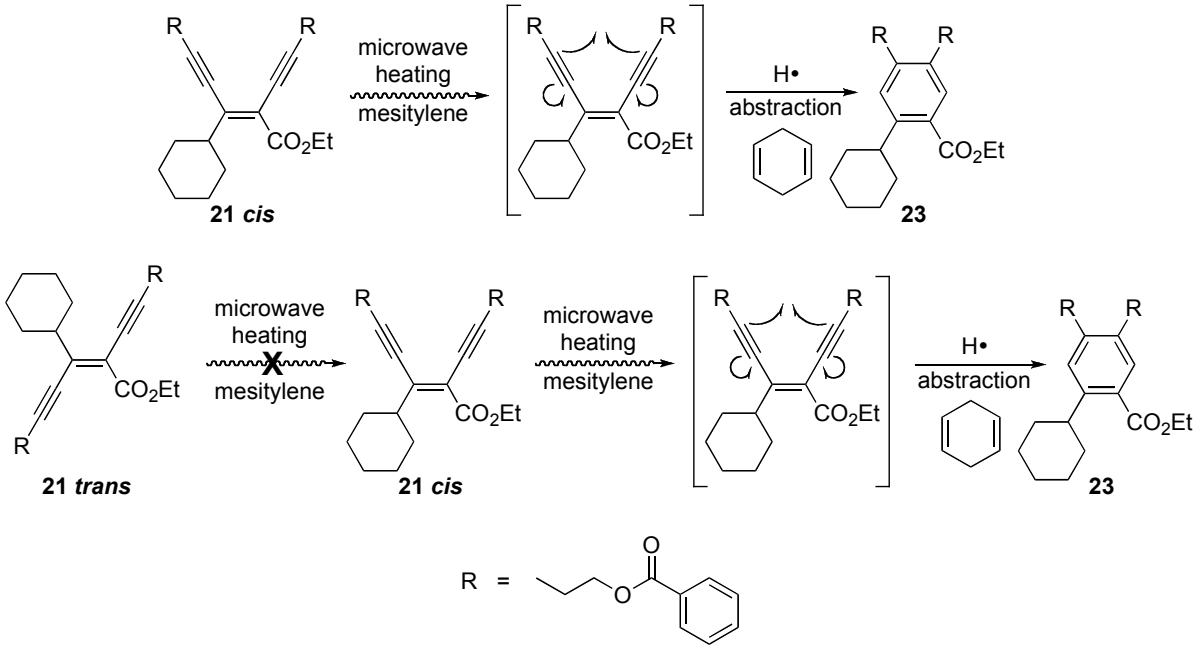
Unfortunately, including the large, bulky cyclohexyl group at the R_2 position did not help to induce a Bergman cyclization of enediyne **21 *trans*** in lower boiling solvents. As was done previously with both isomers **15 *cis*** and **15 *trans***, the project

proceeded towards investigating the effects of using microwave heat on both the *cis* (**21 *cis***) and *trans* (**21 *trans***) enediynes.

2.12 Microwave-Assisted Enediyne Cycloaromatization

As was the case with **15 *trans***, up to this point all previous thermal, and photochemical attempts at a Bergman cyclization of enediyne **21 *trans*** had been unsuccessful and had resulted in the recovery of either one or both of the isomers **21 *cis*** and **21 *trans***. Similar to before, it was then decided to attempt a microwave-assisted Bergman cyclization by superheating mesitylene to 250 °C, in order to determine whether or not the reaction was indeed thermally accessible. Similar procedures were followed as to those shown before (**Table 12**), but again, for this new series of microwave-assisted reactions, only single isomers of the starting material **21 *cis*** or **21 *trans*** where used in the reaction, and neither isomer **21 *cis*** or **21 *trans*** was irradiated with UV light (**Table 14**).

Table 14: Microwave-Assisted Bergman Cyclization of (*Z/E*)-6-cyclohexyl-7-(ethoxycarbonyl)dodeca-6-en-4,8-diyne-1,12-diyl Dibenzoate (21 *trans* and 21 *cis*)



Entry[a]	Initial Isomer	Microwave Temperature (°C)	Recovered Isomer		Bergman Product Yield (%)[b]
			Cis (%)	*Trans* (%)	
1	*cis*	200	56	—	0
2	*cis*	250	0	—	30
3	*cis*	225	0	—	31
4	*trans*	225	—	40	0
5	*trans*	250	—	34	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, mesitylene (0.05 M), 2 h.
[b] Isolated yield.

In the initial series of microwave experiments (**Table 11**), the enediyne **15 *cis*** was unable to undergo a Bergman cyclization at 200 °C, so the first trial (Entry 1) in this new series of microwave experiments was used to determine whether or not the

cyclohexyl group at the R_2 position of enediyne **21** ***cis*** would help to induce a Bergman cyclization. Unfortunately, a Bergman cyclization was not observed at this temperature, but as before, a little more than half of the starting material **21** ***cis*** was recovered (56 %), with the loss of much of the starting material **21** ***cis*** being attributed to decomposition due to the extreme temperature of the reaction. Like before, further attempts were made to force **21** ***cis*** to undergo a Bergman cyclization. The second experiment (Entry 2) consisted of raising the reaction temperature to 250 °C, which proved to be successful, as the Bergman cyclization product **23** was isolated in 30 % yield. No starting material **21** ***cis*** was recovered, but significant amounts of decomposition products did form. In the initial series of microwave experiments, **15** ***cis*** was also able to undergo a microwave-assisted Bergman cyclization at 250 °C, but in 31 % yield. The nearly identical yields for the Bergman cyclization products **23** and **16** produced by the enediynes **21** ***cis*** and **15** ***cis*** at 250 °C did not lend support to the hypothesis that the cyclohexyl group in **21** ***cis*** would be more favorable to inducing a Bergman cyclization than would the methyl group in **15** ***cis***. A third and final attempt at a microwave-assisted Bergman cyclization with the *cis* isomer **21** ***cis*** was made by moderating the temperature to 225 °C (Entry 3), in hopes of increasing the reaction yield. The Bergman cyclization product **23** was once again observed, but with a marginally higher yield of 31 %, along with decomposition products. This was slightly less than the 36 % yield that was observed for the Bergman cyclization product **16** from the enediyne **15** ***cis*** at 225 °C. Like the yield for the Bergman cyclization product **23** at 250 °C, the yield at

225 °C was not supportive of the hypothesis that the cyclohexyl group on enediyne **21** ***cis*** assists in making the reaction more facile.

As was done with the microwave experiments before with enediyne **15** ***trans***, two final microwave-assisted reactions were run using the *trans* isomer **21** ***trans*** as the starting material. The reasoning for this was to determine whether or not the extreme temperature in the microwave would be able to isomerize[15, 16] the *trans* isomer **21** ***trans*** to the *cis* isomer **21** ***cis***, which would then undergo a Bergman cyclization as before. The initial microwave experiment using the *trans* isomer **21** ***trans*** (Entry 4) was again carried out under similar conditions to the previous experiments, and at a temperature of 225 °C. Neither the Bergman cyclization product **23**, nor the *cis* isomer **21** ***cis*** was observed as products of this reaction. Only 40 % of the *trans* isomer **21** ***trans*** starting material was recovered, along with decomposition products. This is similar to the amount of starting material recovered from the microwave-assisted experiments on **15** ***trans***. One final attempt at forcing the *trans* isomer **21** ***trans*** to undergo a microwave-assisted Bergman cyclization was made (Entry 5). This trial consisted of heating the compound **21** ***trans*** to a temperature of 250 °C. Again, neither the Bergman cyclization product **23**, nor the *cis* isomer **21** ***cis*** was observed as products of this reaction. The *trans* isomer **21** ***trans*** was again recovered (34 %), along with decomposition products. As expected, the higher microwave temperature led to a greater degree of decomposition of the starting material **21** ***trans***.

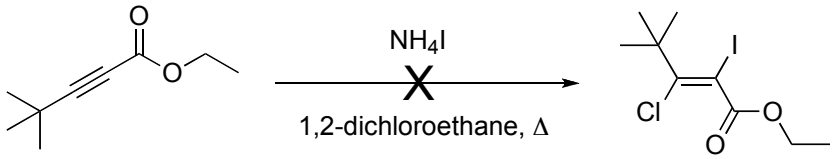
Overall, the yields of Bergman cyclization product **23** were slightly lower than those for Bergman cyclization product **16**. This is not supportive of the idea that the

large cyclohexyl group on either isomer **21** ***cis*** or **21** ***trans*** aids in making the reaction more readily accessible. However, further attempts were made in order to test the hypothesis that the size of the R_2 group on the enediyne is directly correlated to the ease of formation of the Bergman cyclization product.

2.13 Further Modifications to the Functional Groups on the Alkene of the Enediyne

A further attempt at increasing the size and bulkiness of the R_2 functional group shown in **Scheme 6** involved the synthesis of a t-butyl alkynyl ester and the attempted synthesis of its corresponding *E*-β-chloro-α-iodo-α,β-unsaturated ester (**Scheme 7**). The synthesis of the alkynyl ester was straightforward, and produced the desired compound **28** in excellent yield (88 %). This compound was then utilized in the attempted synthesis of an *E*-β-chloro-α-iodo-α,β-unsaturated ester **29** following a nearly identical procedure to that shown in **Scheme 1**. Unfortunately, all attempts at the chloro-iodination of the t-butyl alkynyl ester **28** were unsuccessful.

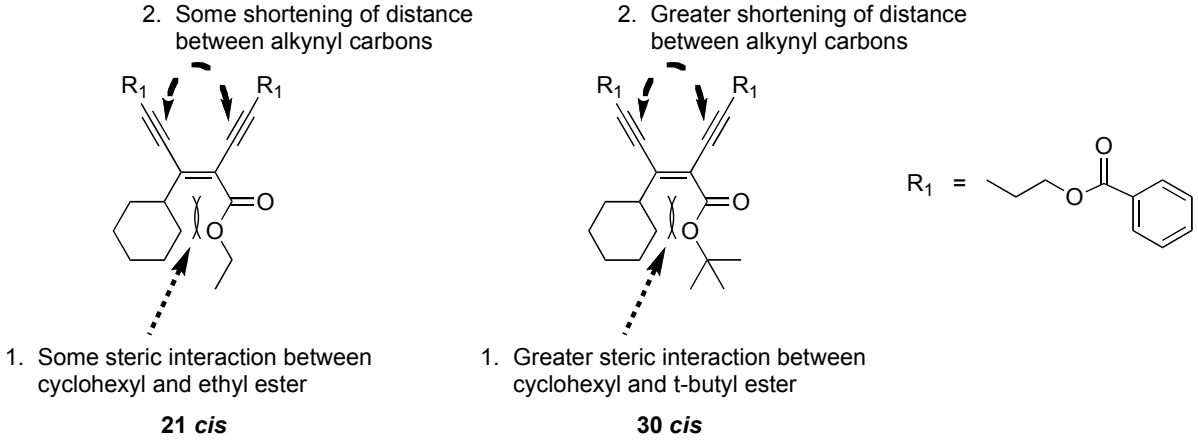
Scheme 7: t-Butyl Alkynyl Ester (28) and the Attempted Synthesis of Its Corresponding *E*-β-chloro-α-iodo-α,β-unsaturated Ester (29)



28 **29**

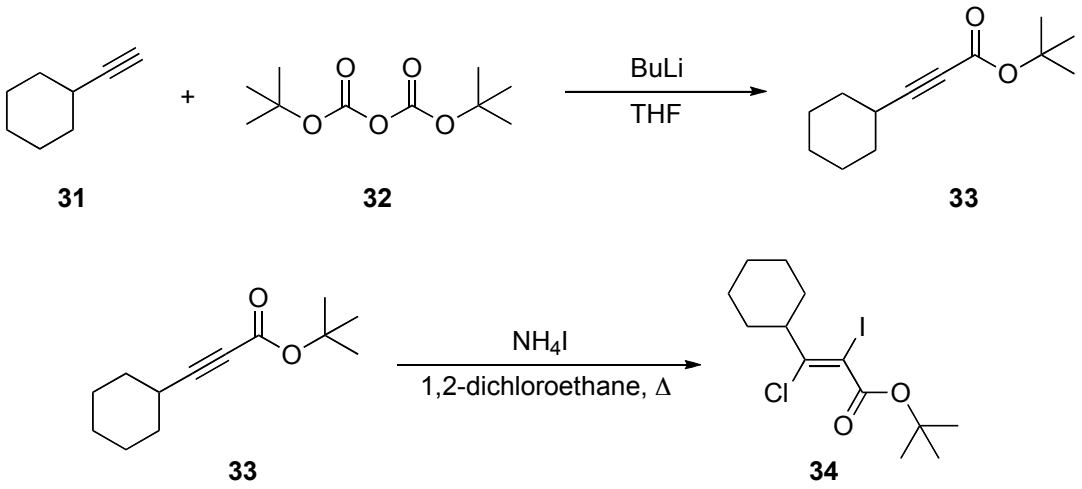
Given the difficulties associated with synthesizing the *E*-β-chloro-α-iodo-α,β-unsaturated ester **29**, it was decided to again utilize a cyclohexyl group at the R_2 position of the enediyne, but to also substitute the ethyl ester function for a t-butyl ester group (**Scheme 8**). It was thought that by increasing the size of the ester group on the enediyne, a larger degree of steric interaction would exist between the cyclohexyl group at the R_2 position, and the t-butyl ester, than between the cyclohexyl group at the R_2 position, and the ethyl ester, as existed in enediyne **21** ***cis***. Again, this large steric interaction on one side of the *cis* enediyne **30** ***cis*** may help to force the alkynyl carbons on the opposite side of the *cis* enediyne **30** ***cis*** closer together, and thus make a Bergman cyclization more accessible.

Scheme 8: Further Attempt to Decrease the Distance Between the Alkynyl Carbons of the Enediyne



This third attempt at increasing the steric interaction between the R_2 functional group and the ester function began with the synthesis of a cyclohexyl alkynyl ester **33** and its *E*-β-chloro-α-iodo-α,β-unsaturated ester **34** (**Scheme 9**).

Scheme 9: Synthesis of Cyclohexyl Alkynyl Ester (33) and Its Corresponding *E*-β-chloro-α-iodo-α,β-unsaturated Ester (34)

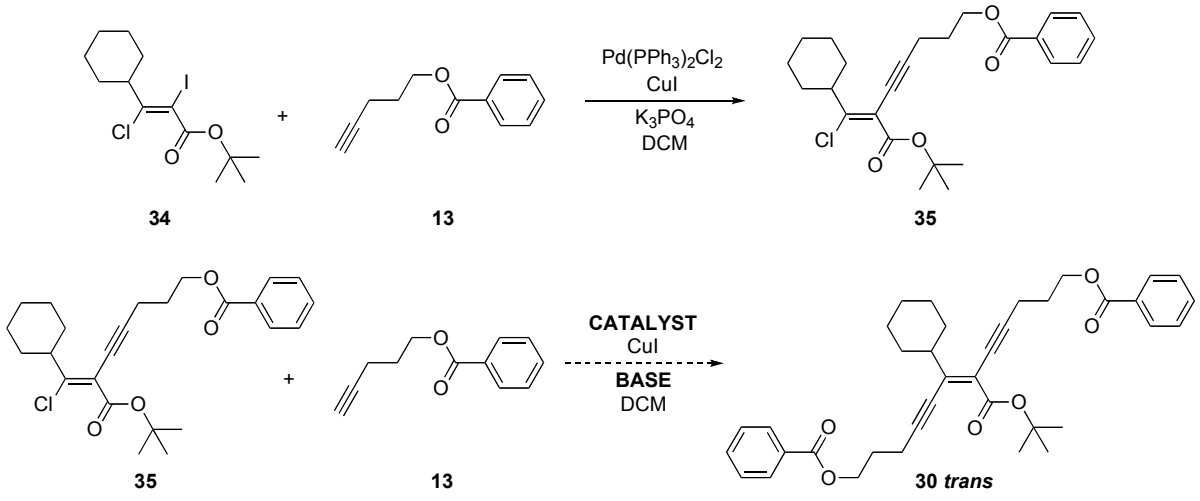


31 **32** **33** **33** **34**

The synthesis of the cyclohexyl alkynyl ester **33** was relatively straight forward, and the desired product was produced in 87 % yield. This alkynyl ester was then utilized in the synthesis of the *E*-β-chloro-α-iodo-α,β-unsaturated ester **34**, following a nearly identical procedure to that shown in **Scheme 1**, which produced the compound in 52 % yield. With the *E*-β-chloro-α-iodo-α,β-unsaturated ester **34** in hand, it was then used in a Sonogashira cross coupling at the iodo position followed by an attempted Sonogashira cross coupling at the chloro position of the alkene (**Scheme 10**). With respect to the cross coupling at the iodo position, a reaction

similar to the optimized trials shown in **Table 4** and **Table 5** was run, and this produced the trisubstituted olefin **35** in a modest 37 % yield. Possible reasons for this modest yield include the large degree of steric hindrance produced by the t-butyl ester interfering with the cross coupling at the nearby iodo position. This trisubstituted olefin **35** then underwent an attempted Sonogashira cross coupling at the chloro position of the alkene. Cross coupling reactions similar to the optimized trials shown in **Table 6** and **Table 7** were run, but were unsuccessful, and none of the expected product was synthesized. This led to a number of different cross coupling trials similar to those done in **Table 6** and **Table 7**. Unfortunately, none of the desired tetrasubstituted olefin **30** ***trans*** was successfully produced from any of these attempted cross couplings. This could be attributed to the large t-butyl ester interfering with the cross coupling occurring at the adjacent chloro position.

Scheme 10: Cyclohexyl Trisubstituted Olefin (35) and the Attempted Synthesis of a Cyclohexyl Tetrasubstituted Olefin With a t-Butyl Ester (30 *trans*)



Given the lack of success in synthesizing enediyne **30** ***trans*** as well as the poorer overall yields of the Bergman cyclizations associated with **21** ***cis*** as compared to those for **15** ***cis***, a change in direction of the project was decided upon. Instead of trying to force the alkynyl carbons of a *cis* enediyne closer together via strong steric interactions on the opposite side of the alkene, as shown in **Scheme 6** and **Scheme 8**, it was decided to incorporate the use of metal cations as a way of shortening the distances between the alkynyl carbons, and thus make the Bergman cyclization reactions more accessible.

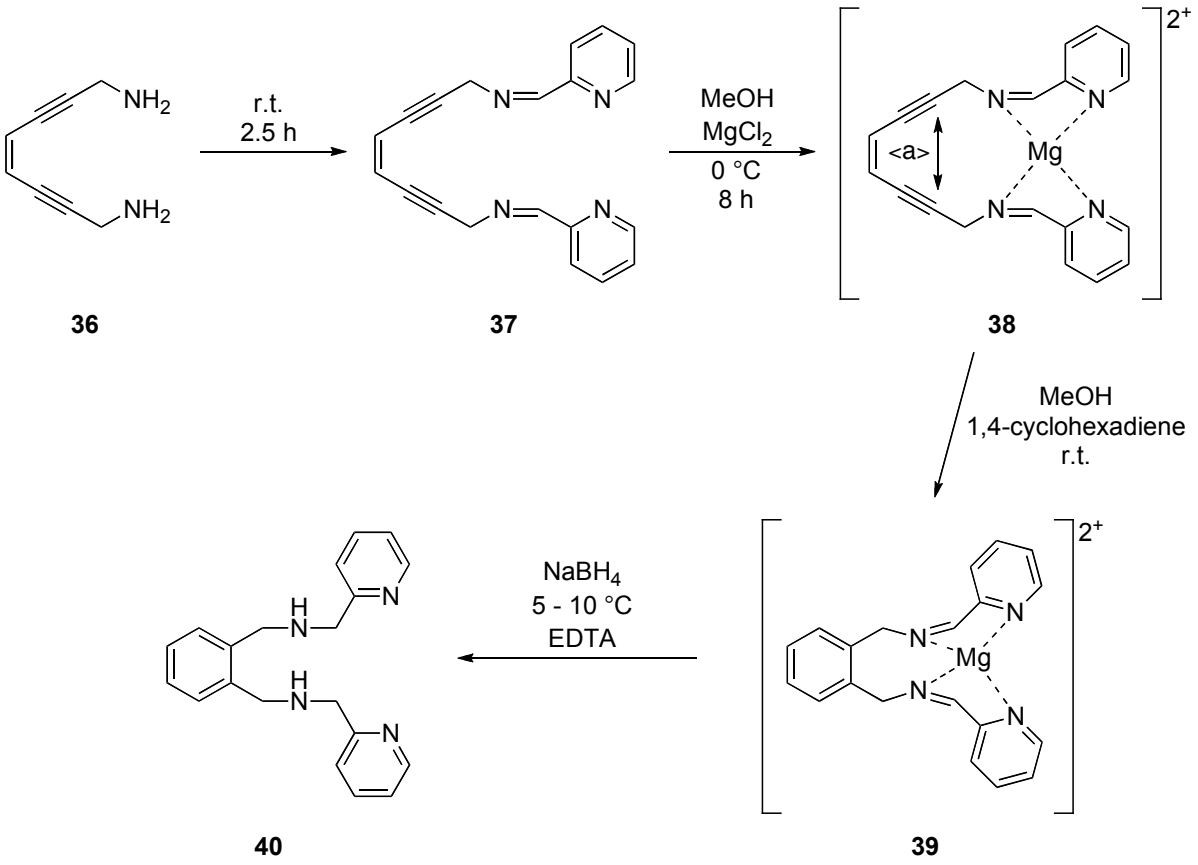
2.14 Metal Cation Induced Bergman Cyclizations

Beginning in 2000, J. M. Zaleski and coworkers used metal cations in order to promote the thermal Bergman cyclization of a bis(pyridine)enediyne at ambient temperature (**Scheme 11**).[17, 18] The major theme from their contribution to thermal enediyne cyclizations showed that metal center geometry, ligand flexibility, and steric bulk adjacent to the alkyne termini could have a significant impact on the temperature required for a Bergman cyclization. Their use of magnesium cations (Mg^{2+}) was particularly appealing for biological applications, as it employed an in vivo metal, which is typically less toxic than other metal cations.

The key step to their reported Bergman cyclization involved the formation of a bis(pyridine)enediyne ligand **37**, and the corresponding Mg^{2+} complex **38**. Synthesis of the bis(pyridine)enediyne ligand **37** involved the reaction of the bis(amino)enediyne **36** with pyridine-2-carboxaldehyde. The Mg^{2+} complex **38** was prepared by incubation of **37** with $MgCl_2 \bullet 6H_2O$ in MeOH at 0 °C for 8 h. Upon warming the Mg^{2+} complex **38** to room temperature in the presence of a methanol

solution containing 20 equivalents of the radical trapping agent 1,4-cyclohexadiene, the Bergman cyclized product **39** formed. This contrasts radically to the temperature required to induce a thermal Bergman cyclization for the non-Mg^{2+} complexed enediyne **37**. With no Mg^{2+} cations present, the enediyne **37** required a temperature of 100 °C in order to thermally cyclize.

Scheme 11: Mg^{2+}-Induced Thermal Enediyne Cyclization at Ambient Temperature

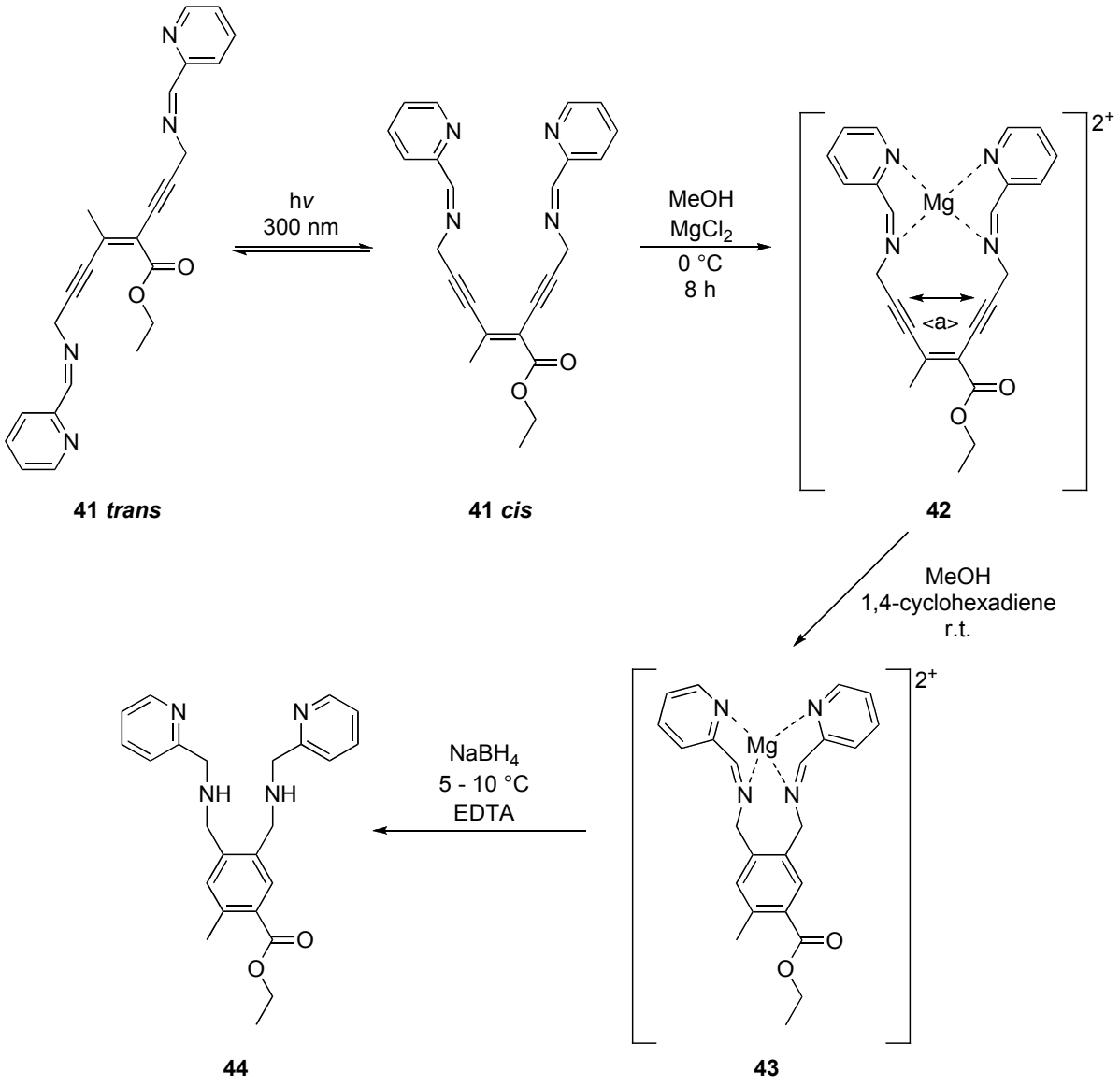


36 **37** **38** **39** **40**

The cation Mg^{2+} is electrophilic, and frequently forms six-coordinate structures[19] in the presence of anionic ligands and coordinating solvents. Computational studies done by J. M. Zaleski and coworkers suggested that in a coordinating solvent, such as methanol, the Mg^{2+} complex **38** is best described as a six-coordinate structure. The facile thermal reactivity of complex **38** results from the ability of Mg^{2+} to coordinate to both the pyridine and the imine nitrogens. Due to the poor basicity of the imine nitrogens, the Mg^{2+} metal center must adopt additional ligands in order to satisfy its Lewis acidity, and in this case the Mg^{2+} acquires two MeOH ligands from the surrounding solvent. This increase in coordination number helps to reduce the alkyne termini separation of complex **38** and to thus lower the barrier to thermal Bergman cyclization.

Given the success achieved by J. M. Zaleski and coworkers with respect to the Mg^{2+} metal complex **38**, it was decided to attempt a Bergman cyclization on a similar enediyne, but with the added step of photoisomerizing the initial, unreactive *trans* isomer **41** ***trans*** to the reactive *cis* isomer **41** ***cis*** before the cyclization occurred (**Scheme 12**).

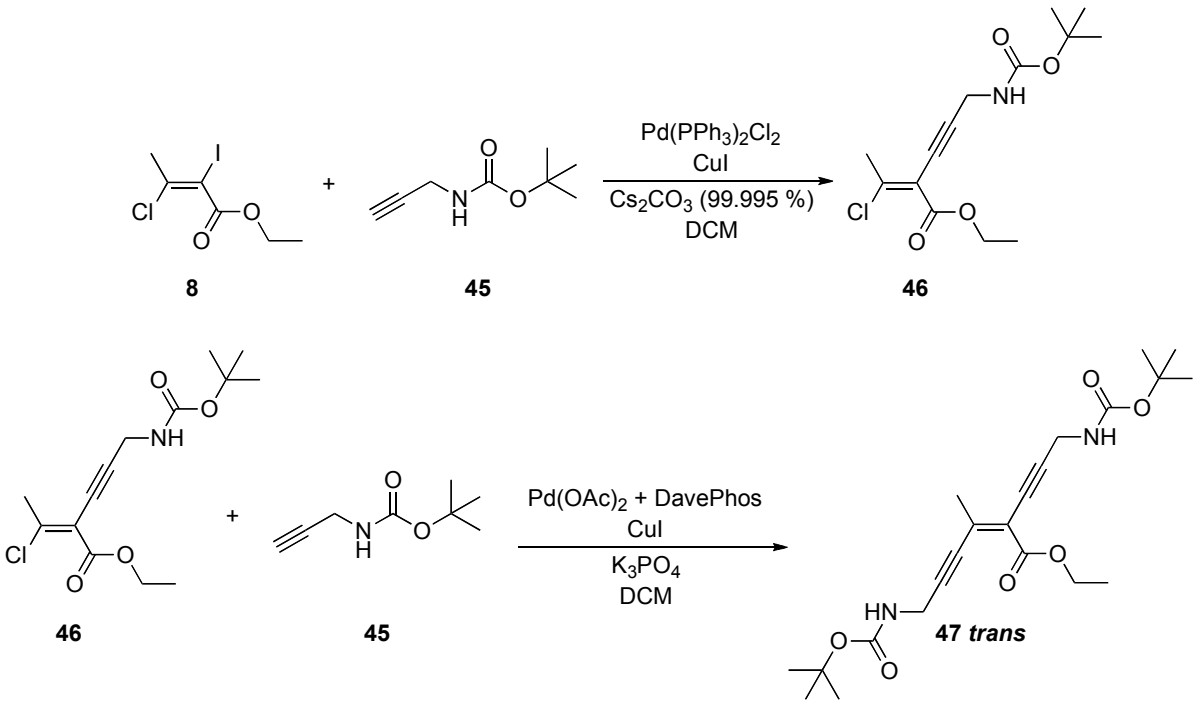
Scheme 12: Mg^{2+}-Induced Thermal Enediyne Cyclization at Ambient Temperature With *Trans*-*Cis* Photoisomerization Activation Step



Given the fact that the bis(pyridine)enediyne **37** is stable for only 12 hours at room temperature before starting to degrade slowly over a 48 hour period, it was not feasible to simply perform a series of Sonogashira cross couplings between the *E*-β-

chloro-α-iodo-α,β-unsaturated ester **8** and an alkynyl substituent similar to that present in the bis(pyridine)enediyne **37**. Instead, a less direct synthesis of *trans* enediyne **41** ***trans*** was proposed that made use of a bis(carbamate)enediyne (**Scheme 13**).

Scheme 13: Synthesis of a *Trans* Bis(carbamate)enediyne (47 *trans*)



8 **45** **46**

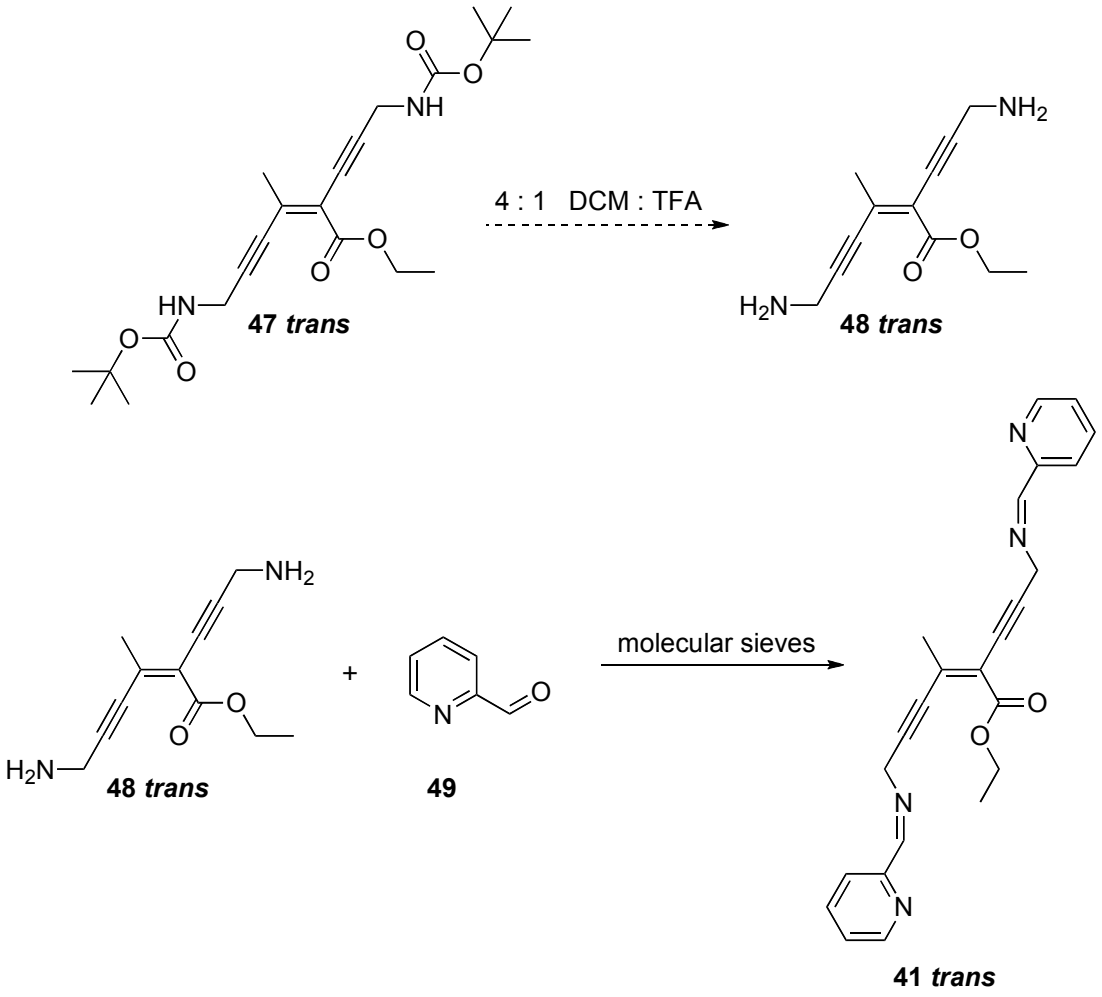
46 **45** **47 *trans***

The synthesis of the bis(carbamate)enediyne **47** ***trans*** was straightforward and utilized similar reaction conditions to the previous Sonogashira cross couplings shown in **Table 4** through **Table 7**. Initially, the *E*-β-chloro-α-iodo-α,β-unsaturated ester **8** was coupled to the BOC-protected propargyl amine **45** to yield the trisubstituted olefin **46** in good yield (70 %). This trisubstituted olefin **46** was then

used in a second Sonogashira cross coupling to produce the tetrasubstituted olefin and bis(carbamate)enediyne **47 *trans***, also in good yield (74 %).

With the desired bis(carbamate)enediyne **47 *trans*** in hand, the next steps in the attempted synthesis of bis(pyridine)enediyne **41 *trans*** involved the removal of the BOC protecting groups to form the bis(amino)enediyne **48 *trans***, and then reacting this enediyne with pyridine-2-carboxaldehyde **49** (**Scheme 14**).

Scheme 14: Attempted Synthesis of a *Trans* Bis(pyridine)enediyne (41 *trans*)



47 *trans* **48 *trans*** **48 *trans*** **49** **41 *trans***

Unfortunately, none of the attempted BOC deprotections of **47 *trans*** resulted in the recovery of the deprotected bis(amino)enediyne **48 *trans***. Different deprotection conditions were tried (**Table 15**), but all resulted in neither the starting material **47 *trans*** nor the desired product **48 *trans*** being recovered.

Table 15: Attempted BOC Deprotection of *Trans* Bis(carbamate)enediyne (47 *trans*)

Entry	Deprotection Conditions[a]	Time	Yield (%)
1	4 : 1 DCM : TFA	10 min	no product or starting material recovered
2	4 : 1 DCM : TFA, 2 eq. anisole	10 min	no product or starting material recovered
3	12 M HCl, EtOAc	10 min	no product or starting material recovered
4	8 eq. potassium tert-butoxide, 2 eq. H_2O	4 hours	no product or starting material recovered

[a] Conditions: concentration (0.05 M)

Standard BOC deprotection conditions were initially used.[20] In the first attempt (Entry 1), a 4 : 1 DCM : TFA ratio was used. Qualitative TLC indicated the disappearance of the BOC protected starting material **47 *trans***, but the desired product **48 *trans*** was not recovered. The second attempt (Entry 2) was similar to the first, but with the addition of anisole as a scavenger in order to react with the tert-butyl carbocation. Unfortunately, this too resulted in the disappearance of the starting material **47 *trans***, but none of the bis(amino)enediyne **48 *trans*** was recovered. A third attempt (Entry 3) made use of different acidic deprotection conditions (12 M HCl in EtOAc), but the results were identical to the previous two entries. Finally, an unorthodox method of deprotecting the primary BOC groups was

attempted using the alkaline conditions reported by N. J. Tom and coworkers in 2003 (Entry 4).[21] This consisted of stirring the starting material **47** ***trans*** for three hours in a solution of THF containing eight equivalents of potassium tert-butoxide. This was followed by the addition of two equivalents of water before refluxing the solution for one hour. Upon cooling, the reaction was quenched with citric acid and then extracted with EtOAc. Although the starting material **47** ***trans*** was consumed in this reaction, no product **48** ***trans*** could be recovered.

A speculative reason for the failure to recover the bis(amino)enediyne **48** ***trans*** could be attributed to the potential for the free amino groups on the deprotected amines to react with the ethyl ester functional group on the alkene. This type of reaction could have potentially occurred repeatedly, and resulted in the formation of a long chain of repeating enediyne units or lactams, which would have been extremely difficult to isolate and characterize.

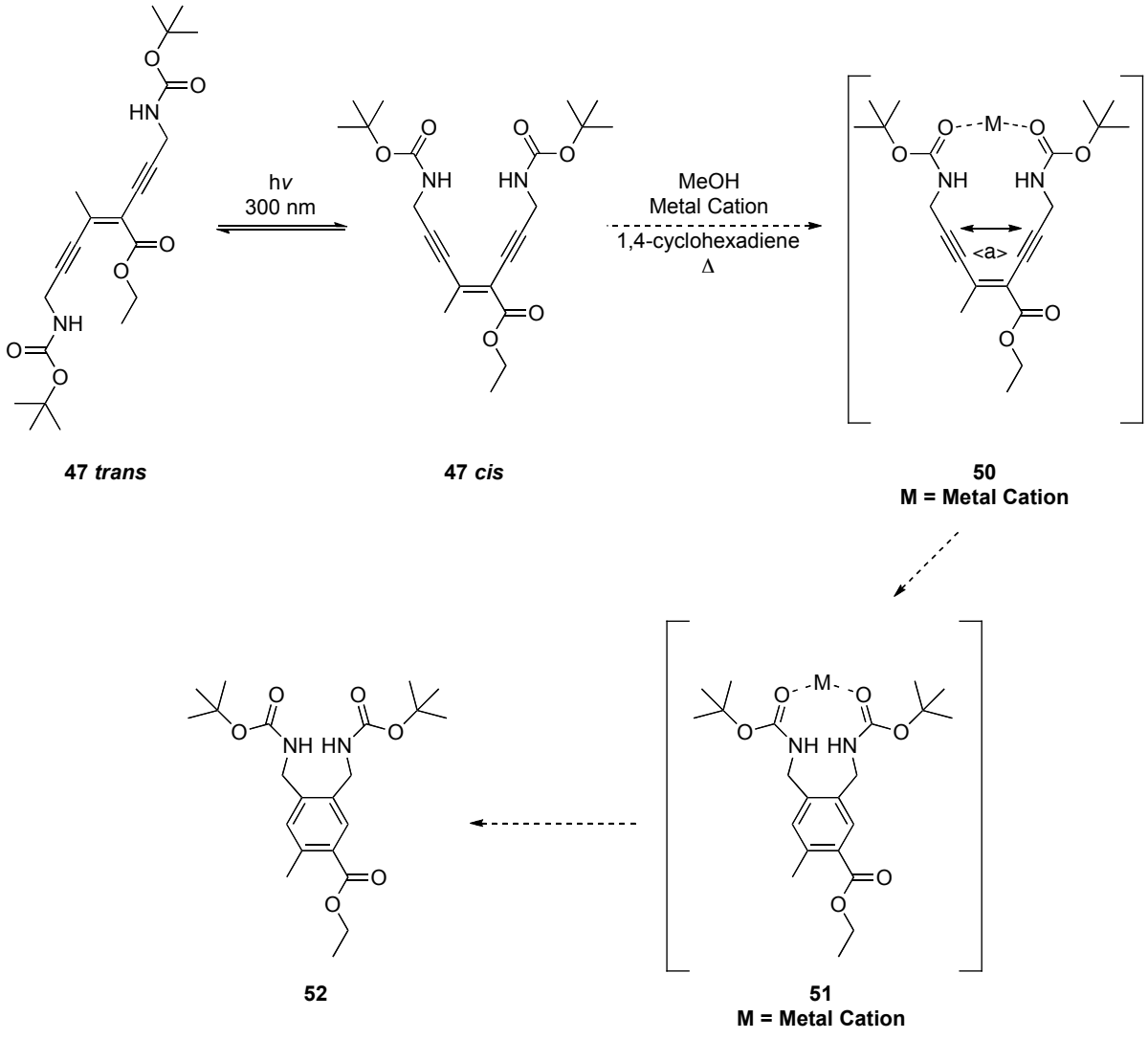
Due to the difficulties in deprotecting the bis(carbamate)enediyne **47** ***trans***, the synthesis of the bis(pyridine)enediyne **41** ***trans*** was halted and the direction of the project with respect to metal cation induced Bergman cyclizations was changed.

2.15 Further Attempts at Metal Cation Induced Bergman Cyclizations

Given the fact that the bis(carbamate)enediyne **47** ***trans*** had been synthesized in good yield, it was decided to attempt a metal cation induced Bergman cyclization on this enediyne with both BOC protecting groups still attached to the compound (**Scheme 15**). The reasoning for this was that the oxygen atom in each carbamate carbonyl might be Lewis basic enough to coordinate to a metal cation. The coordination from both of these oxygen atoms to the metal cation center

may help to reduce the alkyne termini separation of complex **50** and thus lower the barrier to a thermal Bergman cyclization.

Scheme 15: Attempted Metal Cation Induced Thermal Enediyne Cyclization With *Trans-Cis* Photoisomerization Activation Step



A variety of different metal cations that could act as Lewis acids were employed in the attempt to get the bis(carbamate)enediyne **47 *trans*** to undergo a

Bergman cyclization (**Table 16**). The hardest of these Lewis acids was Al^{3+} ($AlCl_3$), which was utilized for its compact charge density. The other hard Lewis acid used was Mg^{2+} ($MgCl_2$, $MgBr_2$, $MgBr_2 \bullet O(C_2H_5)_2$), as the previous thermal enediyne cyclization reported by J. M. Zaleski and coworkers was induced by Mg^{2+} cations. As well, an intermediate Lewis acid, Zn^{2+} ($ZnCl_2$), was also employed. In the initial series of experiments, methanol was used as the reaction solvent, but later reactions made use of toluene or mesitylene in order to see if a Bergman cyclization was thermally accessible. All attempts at getting the bis(carbamate)enediyne **47** ***trans*** to undergo a Bergman cyclization were carried out while irradiating the reaction mixture with UV light of approximately 300 nm.

The first series of experiments (Entry 1 through Entry 5) were performed in methanol at room temperature. No Bergman cyclization product was observed, and only a mixture of *cis* (**47** ***cis***) and *trans* (**47** ***trans***) isomers were recovered in a 37 : 63 ratio. The second series of experiments (Entry 6 through Entry 10) were also carried out in methanol, but this time the reaction was heated to reflux. Again, no Bergman cyclization product was observed, and a similar isomeric mixture was recovered to that of the previous experiment. The final two series of experiments were done in toluene (Entry 11 through Entry 15) and mesitylene (Entry 16 through Entry 20). Both reactions were heated to reflux for a period of two hours, but produced no Bergman cyclization product. As before a mixture of *cis* (**47** ***cis***) and *trans* (**47** ***trans***) isomers were recovered, in a 17 : 83 ratio. No further attempts were made to induce the enediyne **47** ***trans*** to undergo a Bergman cyclization, as unidentifiable decomposition products began to form while refluxing in mesitylene.

Table 16: Summary of Metal Cations Used in Attempted Thermal Enediyne Cyclization With *Trans*-*Cis* Photoisomerization Activation Step

Entry[a]	Metal Reagent	Solvent	Reflux Temperature (°C)	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	$MgCl_2$	Methanol	23	37	63	0
2	$MgBr_2$	Methanol	23	37	63	0
3	$MgBr_2•O(C_2H_5)_2$	Methanol	23	37	63	0
4	$ZnCl_2$	Methanol	23	37	63	0
5	$AlCl_3$	Methanol	23	37	63	0

[a] Conditions: 1 eq. metal reagent, 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 12 h.

Entry[a]	Metal Reagent	Solvent	Reflux Temperature (°C)	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
6	$MgCl_2$	Methanol	65	37	63	0
7	$MgBr_2$	Methanol	65	37	63	0
8	$MgBr_2•O(C_2H_5)_2$	Methanol	65	37	63	0
9	$ZnCl_2$	Methanol	65	37	63	0
10	$AlCl_3$	Methanol	65	37	63	0

[a] Conditions: 1 eq. metal reagent, 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 12 h.

Entry[a]	Metal Reagent	Solvent	Reflux Temperature (°C)	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
11	$MgCl_2$	Toluene	111	17	83	0
12	$MgBr_2$	Toluene	111	17	83	0
13	$MgBr_2•O(C_2H_5)_2$	Toluene	111	17	83	0
14	$ZnCl_2$	Toluene	111	17	83	0
15	$AlCl_3$	Toluene	111	17	83	0

[a] Conditions: 1 eq. metal reagent, 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 2 h.

Entry[a]	Metal Reagent	Solvent	Reflux Temperature (°C)	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
16	$MgCl_2$	Mesitylene	164	17	83	0
17	$MgBr_2$	Mesitylene	164	17	83	0
18	$MgBr_2•O(C_2H_5)_2$	Mesitylene	164	17	83	0
19	$ZnCl_2$	Mesitylene	164	17	83	0
20	$AlCl_3$	Mesitylene	164	17	83	0

[a] Conditions: 1 eq. metal reagent, 20 eq. 1,4-cyclohexadiene, concentration (0.05 M), 2 h.

2.16 Conclusions

In summary, the optimized conditions for the sequential Sonogashira cross couplings between an acetylene substituent and either the α-iodo or the β-chloro position of the *E*-β-chloro-α-iodo-α,β-unsaturated ester templates **8** or **26**, produce the desired trisubstituted or tetrasubstituted olefins in good yield. The *cis* isomer enediynes **15** ***cis*** and **21** ***cis*** were both found to be able to undergo microwave-assisted Bergman cyclizations at 225 °C or higher, via the superheating of mesitylene. The size of the functional group at the R_2 position of each respective enediyne seemed to have no effect in making a Bergman cyclization more facile. The addition of various metal cations did not allow the bis(carbamate)enediyne **47** ***trans*** to undergo a Bergman cyclization at 164 °C, despite the irradiation of UV light.

2.17 References

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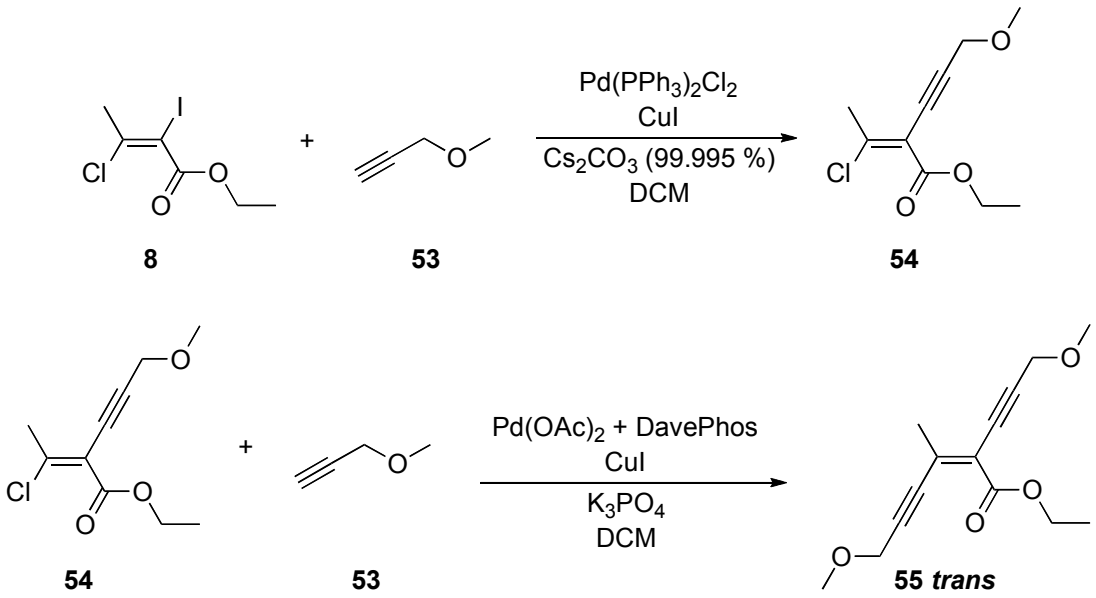
Chapter 3

3.1 Results and Discussion: Synthesis of Single Isomer Trisubstituted and Tetrasubstituted Olefins from *E*-β-Chloro-α-Iodo-α,β-Unsaturated Esters and Bergman Cycloaromatizations Without a Radical Trapping Agent

3.2 Synthesis of a Less Sterically Congested Enediyne

Building further on the work of J. M. Zaleski and coworkers[1, 2], it was decided to synthesize an enediyne with minimal steric bulk adjacent to the alkyne termini in order to determine if this would allow a Bergman cyclization to be more accessible. The goal was again to make use of a photoactivation step in which the unreactive *trans* isomer was isomerized to the reactive *cis* isomer before the Bergman cyclization occurred. As shown in **Scheme 16**, in order to help minimize the steric bulk adjacent to the alkyne termini, methyl propargyl ether **53** was used in a Sonogashira cross coupling with the *E*-β-chloro-α-iodo-α,β-unsaturated ester **8** to give the trisubstituted olefin **54** in good yield (76 %). This trisubstituted olefin **54** was then used in a second Sonogashira cross coupling to produce the tetrasubstituted olefin **55** ***trans***, in excellent yield (81 %). Both Sonogashira cross couplings made use of the optimized conditions developed previously in **Table 4** through **Table 7**.

Scheme 16: Synthesis of a *Trans* Enediyne With Minimal Steric Bulk Adjacent to the Alkyne Termini (55 *trans*)



8 **53** **54** **54** **53** **55 *trans***

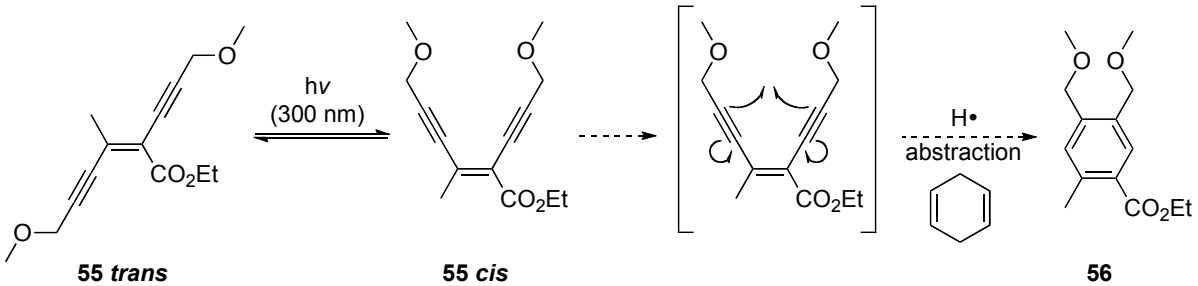
3.3 Attempts to Achieve a Photoactivated Bergman Cyclization

With the less sterically congested enediyne **55 *trans*** having been synthesized as the *trans* isomer, the compound's reactivity towards a Bergman cyclization was investigated in order to determine whether or not the smaller degree of steric bulk adjacent to the alkyne termini would help to lower the temperature required for a Bergman cyclization, and thus make the reaction more accessible (**Table 17**).

A similar format to previous attempts (**Table 8** and **Table 12**) at achieving a Bergman cyclization was followed. The radical trapping agent 1,4-cyclohexadiene, and UV light of approximately 300 nm wavelength were utilized. Initially, only the *trans* isomer **55 *trans*** was used as the starting material, in an attempt to determine

whether or not this *trans* enediyne **55 *trans*** could be photoisomerized to its *cis* isomer **55 *cis***, and then have this *cis* isomer **55 *cis*** subsequently undergo a Bergman cyclization.

Table 17: Attempted Bergman Cyclization of (*Z*)-ethyl 6-methoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (55 *trans*)



55 *trans* **55 *cis*** **56**

Entry[a]	Solvent	Reflux Temperature (°C)	Photolysis	Recovered Isomeric Ratio *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)
1	DCM	23	yes	22	78	0
2	toluene	111	yes	22	78	0
3	toluene	111	no	0	100	0
4	mesitylene	164	yes	22	78	0
5	mesitylene	164	no	0	100	0
6	tetrahydronaphthalene	207	yes	22	78	0
7	tetrahydronaphthalene	207	no	0	100	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, 1 eq. DIPEA, concentration (0.05 M), 2 h.

As was investigated before with enediynes **15 *trans*** and **21 *trans***, the first trial (Entry 1) was used to determine whether or not the newly synthesized enediyne **55 *trans*** could be photoisomerized to the reactive *cis* isomer **55 *cis***, which would subsequently undergo a Bergman cyclization at room temperature. After two hours,

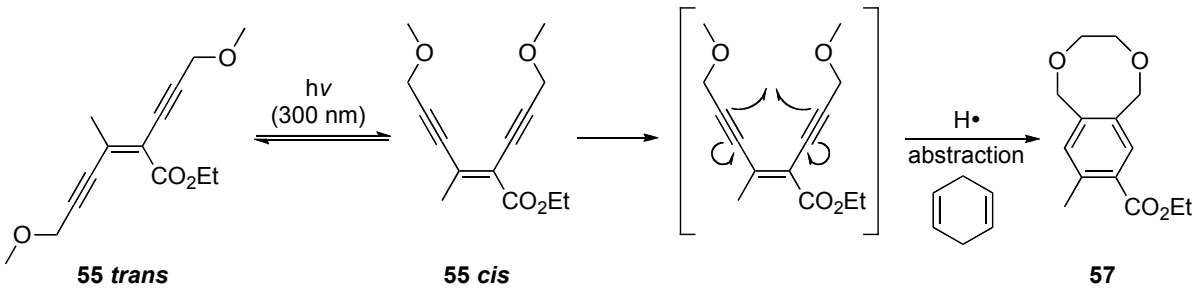
no Bergman cyclization product **56** was observed, and only a mixture of *trans* (**55 *trans***) and *cis* (**55 *cis***) isomers was recovered in a 78 : 22 ratio. As before, further experiments were conducted to determine whether or not the reaction was thermodynamically accessible, either with or without the assistance of a UV light source. The second trial (Entry 2) consisted of simultaneously refluxing the *trans* isomer **55 *trans*** in toluene, while irradiating the solution with approximately 300 nm UV light. This experiment again resulted in the formation of a mixture of *trans* (**55 *trans***) and *cis* (**55 *cis***) isomers in a 78 : 22 ratio. The third experiment (Entry 3) confirmed that the *trans* isomer **55 *trans*** could not undergo a Bergman cyclization without irradiation from a UV light source, and only the *trans* isomer **55 *trans*** starting material was recovered. The higher boiling solvent, mesitylene, was then used in a series of experiments similar to the trials conducted in toluene. Both experiments (Entry 4 and Entry 5) did not provide a Bergman cyclization, and the experiment (Entry 4) in which the *trans* enediyne **55 *trans*** was simultaneously refluxed in mesitylene while being irradiated with UV light resulted in another mixture of *trans* (**55 *trans***) and *cis* (**55 *cis***) isomers, in the same ratio as before. The trial (Entry 5) in which the *trans* enediyne **55 *trans*** was refluxed in mesitylene without being irradiated with UV light resulted in only the starting material **55 *trans*** being recovered. In the series of experiments conducted in **Table 8**, the *trans* enediyne **15 *trans*** underwent decomposition while refluxing in nitrobenzene. Given this fact, the high boiling solvent tetrahydronaphthalene was used in place of nitrobenzene in order to determine whether or not the reaction was thermodynamically accessible. Two final experiments (Entry 6 and Entry 7) were conducted, similar to the trials run in both toluene and mesitylene. Neither trial produced the expected Bergman

cyclization product **56**, but a similar mixture of *trans* (**55 *trans***) and *cis* (**55 *cis***) isomers was recovered after the experiment (Entry 6) in which the solution was irradiated with UV light. For the last trial (Entry 7), the lack of irradiation with UV light resulted in the recovery of only the *trans* isomer **55 *trans***. It should be noted that for both of the last two trials (Entry 6 and Entry 7), unidentifiable decomposition products formed from refluxing in tetrahydronaphthalene, which can be attributed to the extreme temperature of the reaction.

3.4 Photoactivated Bergman Cyclization Using 1-methylnaphthalene as the Reaction Solvent

At this point, all previous thermal and photochemical attempts at getting the *trans* enediyne **55 *trans*** to undergo a Bergman cyclization had proven unsuccessful, and had resulted in the recovery of one or both isomers **55 *cis*** and **55 *trans***. Instead of attempting a microwave-assisted[3-7] enediyne cycloaromatization, it was decided to attempt a Bergman cyclization similar to that shown in **Table 17**, but with 1-methylnaphthalene as the reaction solvent. Due to this solvent's very high boiling point (243 °C), it was thought that after the *trans* isomer **55 *trans*** had been photoisomerized to the reactive *cis* isomer **55 *cis***, enough thermal energy would be provided to force the enediyne **55 *cis*** to undergo a Bergman cyclization. As shown in **Table 18**, the *trans* isomer **55 *trans*** was subjected to these new reaction conditions with some very interesting, and unexpected results.

Table 18: Initial Bergman Cyclization of (*Z*)-ethyl 6-methoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (55 *trans*)



55 *trans* **55 *cis*** **57**

Entry[a]	Photolysis	Time (h)	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]
1	yes	1	0	15	13
2	no	1	0	35	0
3	yes	2	0	0	10
4	no	2	0	17	0
5	yes	3	0	0	8
6	no	3	0	10	0

[a] Conditions: 20 eq. 1,4-cyclohexadiene, 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C).

[b] Isolated yield.

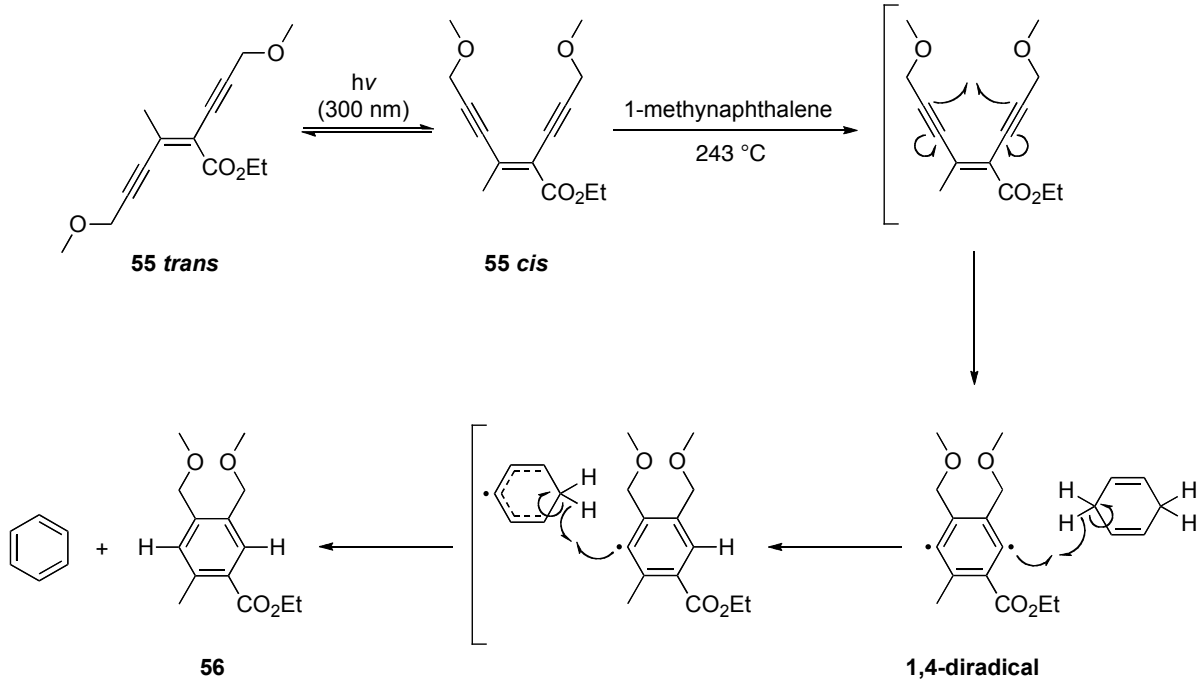
The initial experiment (Entry 1), using 1-methylnaphthalene as the reaction solvent and the irradiation of UV light of approximately 300 nm, provided the unexpected cyclization product **57** in 13 % yield. None of the expected Bergman cyclization product **56** was observed, and 15 % of the unreacted starting material **55 *trans*** was recovered. There was no *cis* isomer **55 *cis*** present at the end of the reaction. This unique Bergman cyclization product **57** consisted of a six-membered aromatic ring fused to an eight-membered ring that contained two oxygen atoms. The structure of cyclization product **57** was confirmed through a combination of ^{1}H

NMR, DEPT-135, and mass-spectrum analysis. Before further examination of this unforeseen product **57** was carried out, a series of other reactions were performed in an attempt to optimize the reaction yield. The second experiment (Entry 2) was run in order to determine if the extreme reaction temperature was sufficient to thermally isomerize the starting material **55** ***trans*** to the reactive *cis* isomer **55** ***cis***, absent the irradiation of UV light. No Bergman cyclization was observed, and only 35 % of the *trans* isomer starting material **55** ***trans*** was recovered, along with unidentifiable decomposition products. Given the fact that at the end of the first experiment (Entry 1), some of the *trans* isomer **55** ***trans*** starting material remained, longer reaction times were investigated in an attempt to fully react the starting material **55** ***trans*** and boost the yield of the new Bergman cyclization product **57**. The third trial (Entry 3) utilized reaction conditions identical to those from the first experiment (Entry 1), but the reaction time was extended to two hours. This produced the Bergman cyclization product **57** in 10 % yield, and neither isomer **55** ***trans*** or **55** ***cis*** was recovered. A similar experiment (Entry 5) increased the reaction time to three hours and gave the Bergman cyclization product **57** in 8 % yield. Again, neither isomer **55** ***trans*** or **55** ***cis*** was recovered. Two further trials (Entry 4 and Entry 6) again showed that an increased reaction time would not cause the starting material **55** ***trans*** to thermally isomerize to the *cis* isomer **55** ***cis***. No Bergman cyclization product **57** was observed, and less than 20 % of the trans isomer **55** ***trans*** starting material was recovered after each experiment.

3.5 Further Examination of the Novel Bergman Cyclization Product (57)

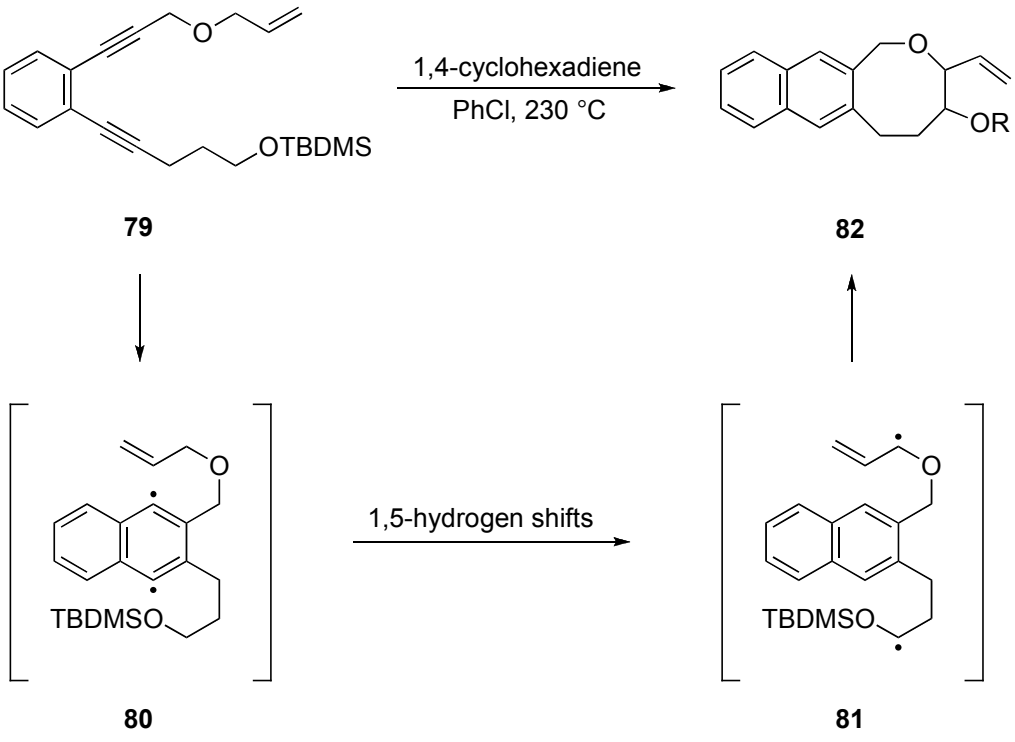
Attention was now turned to the Bergman cyclization product **57** that had formed during the last series of reactions (**Table 18**). As stated previously, this was not the intended product **56**, and further investigation focused on determining the reasons as to why this unexpected product **57** formed. As can be seen in **Scheme 17**, a Bergman cycloaromatization consists of the formation of a highly reactive 1,4-diradical intermediate species, which can be quenched by a hydrogen donor[8, 9] such as 1,4-cyclohexadiene.

Scheme 17: Reaction Mechanism for the Formation of the Expected Bergman Cyclization Product (56)



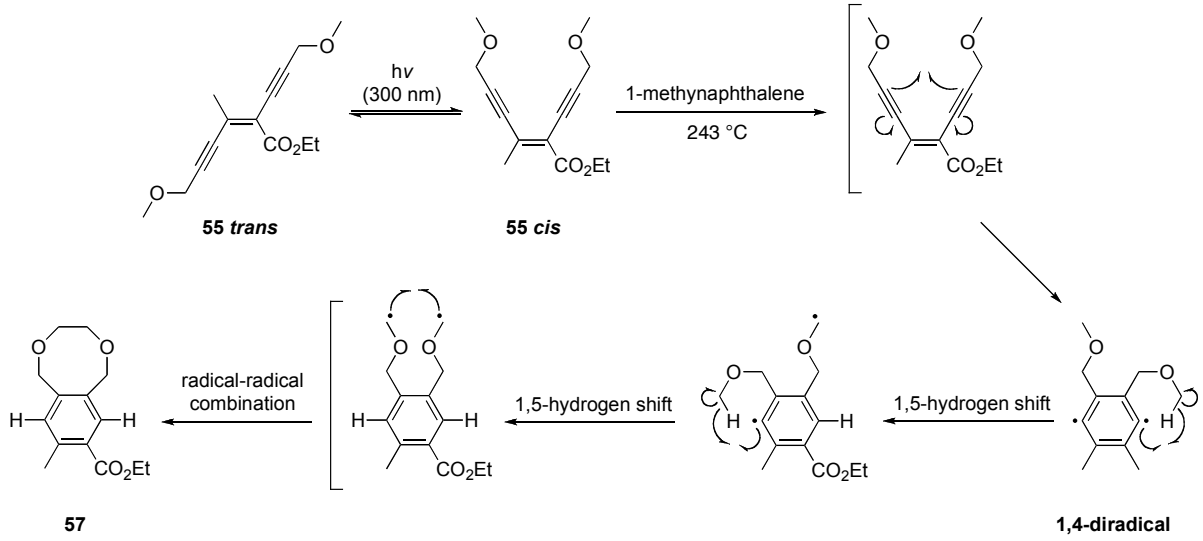
What made Bergman cyclization product **57** both unexpected and very interesting was the presence of the second eight-membered ring that was fused to the benzene moiety. In 1994, Grissom and coworkers reported the unexpected formation of a similar eight-membered ring after the thermolysis of the acyclic aromatic enediyne **79** (**Scheme 18**).[10] Grissom speculated that thermolysis results in the cyclization of enediyne **79** to form the 1,4-diradical **80**, which can then undergo two 1,5-hydrogen shifts to form the stabilized diradical **81**, followed by recombination to give the cyclic ether **82**.

Scheme 18: Cyclic Ether Reported by Grissom and Coworkers



With respect to cyclization product **57**, it was speculated that the reactive *cis* isomer **55** ***cis*** could act as its own hydrogen donor via a series of 1,5-hydrogen shifts in order to quench the highly reactive 1,4-diradical. A speculative mechanism was proposed as shown in **Scheme 19**.

Scheme 19: Speculative Reaction Mechanism for the Formation of the Unexpected Bergman Cyclization Product (57)



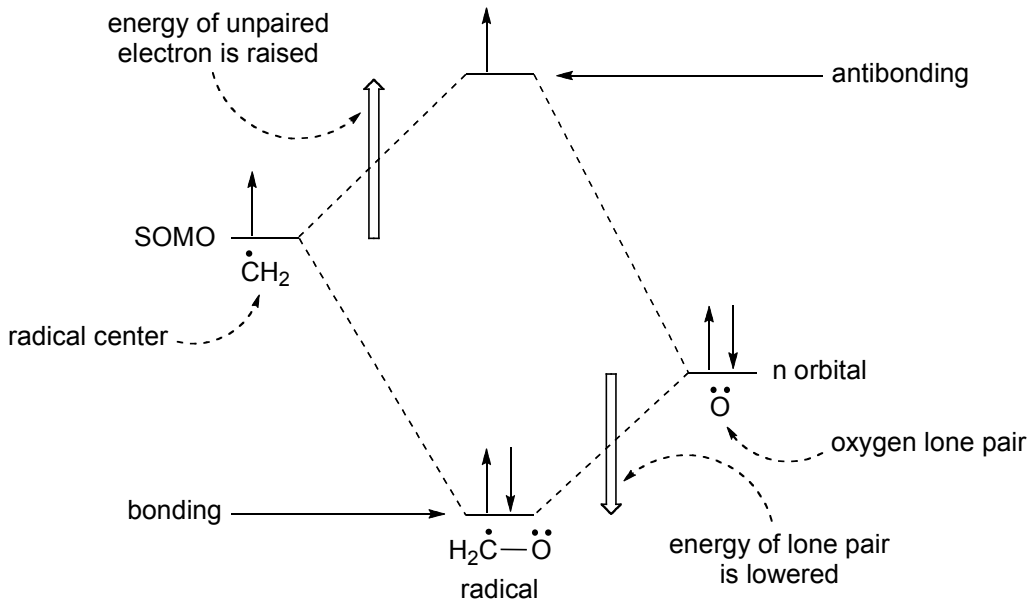
According to this speculative reaction mechanism (**Scheme 19**), after the starting material **55** ***trans*** photoisomerizes to the *cis* isomer **55** ***cis***, the highly reactive 1,4-diradical forms as an intermediate. This 1,4-diradical species is quenched via two 1,5-hydrogen shifts, forming another intermediate diradical species in which each of the terminal carbons adjacent to the oxygen atoms is a radical. The final step to form Bergman cyclization product **57** would involve a

radical-radical combination between the two aforementioned terminal carbon radicals to form an eight-membered ring.

3.6 Radical Stabilization Via Adjacent Functional Groups

Although only speculative at this point, the fact that a series of 1,5-hydrogen shifts likely occur in order to quench the reactive 1,4-diradical, shown in **Scheme 19**, can be attributed to the weakening of the C-H bonds that are adjacent to electron-donating groups such as ethers. In the specific case pertaining to the *cis* isomer **55** ***cis***, these C-H bonds are weakened due to the fact that the adjacent electron-donating ether functional groups can help to stabilize the resulting radicals and thus make them easier to form.[11-13] This stabilization process can be better explained via molecular orbital (MO) theory and the overall energy of the radical (**Scheme 20**).

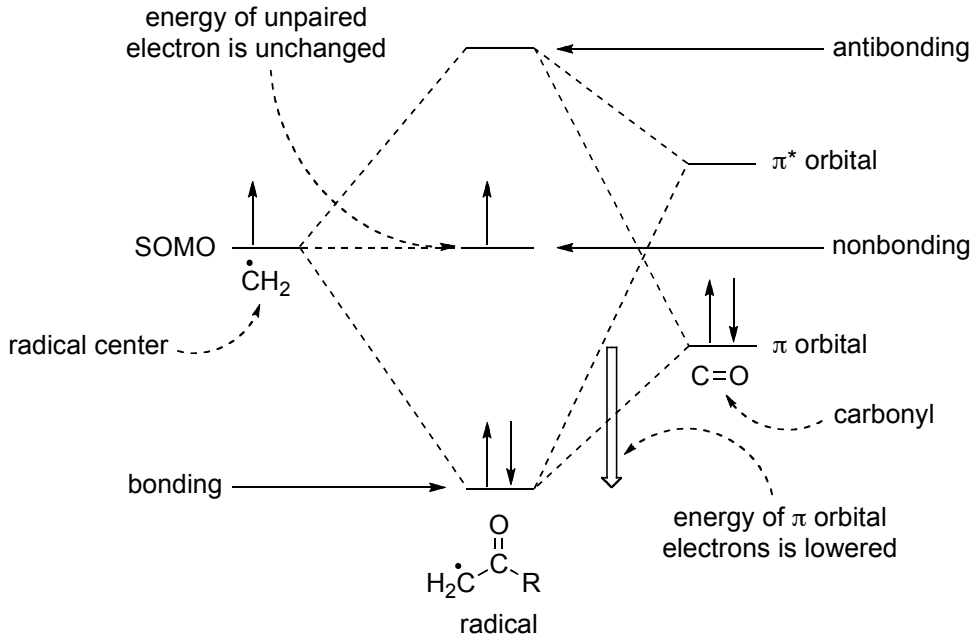
Scheme 20: Radical Stabilization Via an Electron-Donating Group



The above diagram (**Scheme 20**) shows a three-electron interaction between the lone pair of the adjacent oxygen atom and the unpaired electron at the carbon radical center. The interaction between the relatively high-energy filled n orbital from the lone pair on the oxygen atom and the SOMO of the radical center produce new bonding and antibonding molecular orbitals, which can then be filled by the three electrons. In order to fill these new molecular orbitals, the two electrons from the lone pair on oxygen are lowered in energy in order to fill the bonding orbital, whereas the single electron from the SOMO of the radical center is raised in energy in order to fill the antibonding orbital. In summary, two electrons were lowered in energy, whereas only one electron was raised in energy, which contributes to an overall stabilization of the radical system.

The theory behind the stabilization of a radical system, such as the one shown above (**Scheme 20**), can be extended to electron withdrawing functional groups that are adjacent to the radical center. The C-H bonds adjacent to an electron-withdrawing functional group, such as a carbonyl, will also weaken due to the overall stabilization that an electron-withdrawing functional group provides to the resulting radical system (**Scheme 21**).

Scheme 21: Radical Stabilization Via an Electron-Withdrawing Group

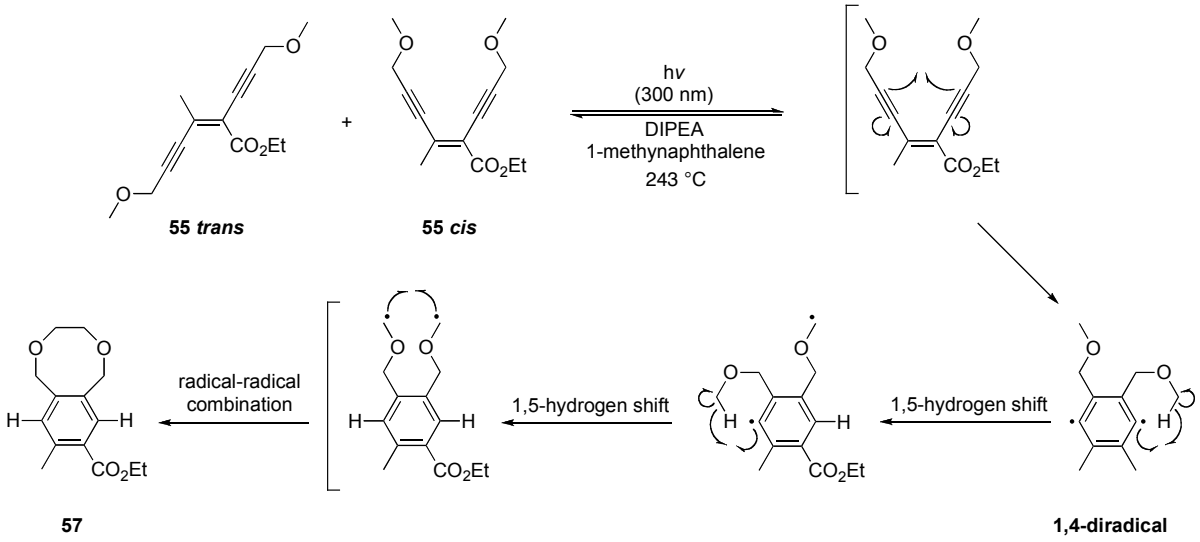


The above diagram (**Scheme 21**) shows a three-electron interaction between the orbitals of a carbonyl π-acceptor group and the unpaired electron at the carbon radical center. In this case, the interaction produces new bonding and antibonding molecular orbitals, as well as a nonbonding molecular orbital. In order to fill these new molecular orbitals, the two electrons from the π orbital are lowered in energy in order to fill the bonding orbital, whereas the single electron from the SOMO of the radical center remains unchanged in energy by entering the nonbonding orbital. In summary, there is a net two-electron stabilization of this system via the lowering in energy of two of the electrons, which contributes to the overall stabilization of the radical system.

3.7 Verification of the Lack of Necessity for an Intermolecular Hydrogen Donor and the Optimization of the Reaction Conditions

Given the speculative mechanism and the reasons for it that were discussed above (**Chapter 3.4** and **Chapter 3.5**), it was decided to confirm the lack of necessity for an intermolecular hydrogen donor, such as 1,4-cyclohexadiene, for the reaction shown previously in **Scheme 19**. Essentially, since 1,4-cyclohexadiene is often used as a radical trapping agent for the quenching of the intermediate 1,4-diradical species formed during a Bergman cyclization, a series of experiments were run similar to those shown in **Table 18**, but without the presence of 1,4-cyclohexadiene. As well, it was thought that further optimizations could be developed for this reaction in order to help increase the reaction yield. One of the first optimizations used was to modify the reaction to include some of the *cis* isomer **55 *cis*** as the starting material. Using a procedure similar to that for **Scheme 3**, the *trans* isomer **55 *trans*** starting material was photolyzed using UV light of approximately 300 nm for 20 h. This produced an inseparable mixture of *cis* (**55 *cis***) and *trans* (**55 *trans***) isomers in a 40 : 60 ratio. It was this mixture of isomers that was used as the starting material in the new series of optimization reactions (**Table 19**).

Table 19: Optimization of the Reaction Conditions for Bergman Cyclization Product (57)



Entry[a]	Time (min)	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]	Bergman Product Yield (%)[c]
1	60	0	0	26	65
2	45	0	19	26	65
3	30	0	20	30	75
4	15	0	25	15	38

[a] Conditions: 40 : 60 ratio of *cis* (**55 *cis***) : *trans* (**55 *trans***) isomers as starting material, 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), h*v* (300 nm).

[b] Isolated yield based on total starting material.

[c] Isolated yield based on *cis* isomer.

The initial experiment (Entry 1), using the 40 : 60 ratio of *cis* (**55 *cis***) : *trans* (**55 *trans***) isomers as the starting material, and no intermolecular radical trapping agent (1,4-cyclohexadiene), produced the Bergman cyclization product **57** in 26 % yield. Neither isomer of the starting material **55 *cis*** or **55 *trans*** was recovered at the end of the reaction. Given the lack of recovery of any starting material, the

second experiment (Entry 2) consisted of reducing the reaction time from 60 minutes to 45 minutes, in an attempt to boost the reaction yield since the extreme temperature of the reaction may have been decomposing both the starting material **55** ***cis*** and **55** ***trans***, and the cyclization product **57**. This trial produced the Bergman cyclization product **57**, again in 26 % yield, but with 19 % of the *trans* isomer **55** ***trans*** starting material being recovered. Further reductions in reaction time were investigated, with the third experiment (Entry 3) being run for 30 minutes. This trial again produced the Bergman cyclization product **57**, but in 30 % yield, a slight improvement from the previous two experiments. As well, 20 % of the *trans* isomer **55** ***trans*** starting material was recovered. The final experiment (Entry 4) reduced the reaction time to 15 minutes. This again produced Bergman cyclization product **57**, but only in 15 % yield. However, there was the largest recovery of starting material for this series of experiments, as 25 % of the *trans* isomer **55** ***trans*** remained. It should be noted, that of the four trials run, none of the *cis* isomer **55** ***cis*** starting material was found to remain after each reaction was completed. In summary, a reaction time of 30 minutes produced the greatest yield of the Bergman cyclization product **57**, when a 40 : 60 mixture of *cis* (**55** ***cis***) : *trans* (**55** ***trans***) isomers were used as the starting material. As well, the formation of the Bergman cyclization product **57** in each of these experiments confirmed the lack of necessity for an intermolecular radical trapping agent, such as 1,4-cyclohexadiene, and lent further evidence to the hypothesis that the reactive *cis* isomer **55** ***cis*** could act as its own hydrogen donor via a series of 1,5-hydrogen shifts.

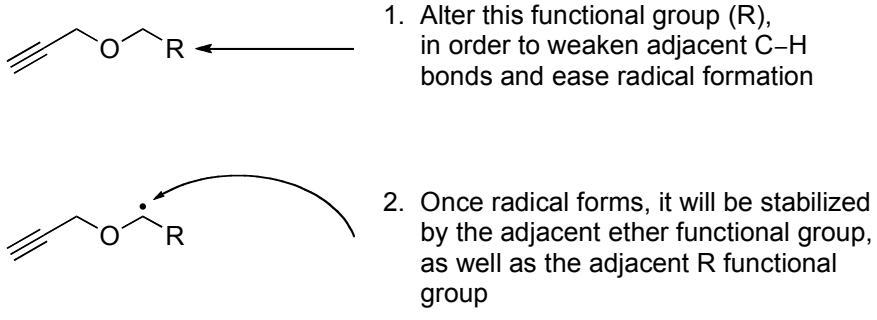
The success in improving the reaction yields for this series of Bergman cyclizations led to an investigation on methods of better stabilizing the resulting

radicals that are formed on the carbon atoms immediately adjacent to the ether functional groups.

3.8 Increasing Radical Stabilization as a Means of Increasing Bergman Cyclization Product Reaction Yields

As was previously discussed in **Chapter 3.6**, electron-donating or electron-withdrawing functional groups that are adjacent to C-H bonds help to weaken these C-H bonds, and to stabilize any resulting radical. Given this, it was decided to alter the functional groups adjacent to the radical bearing carbons in enediyne **55** ***trans***, as a way of trying to further stabilize the radicals that form, and thus, potentially increase the yield of any Bergman cyclization products (**Scheme 22**).

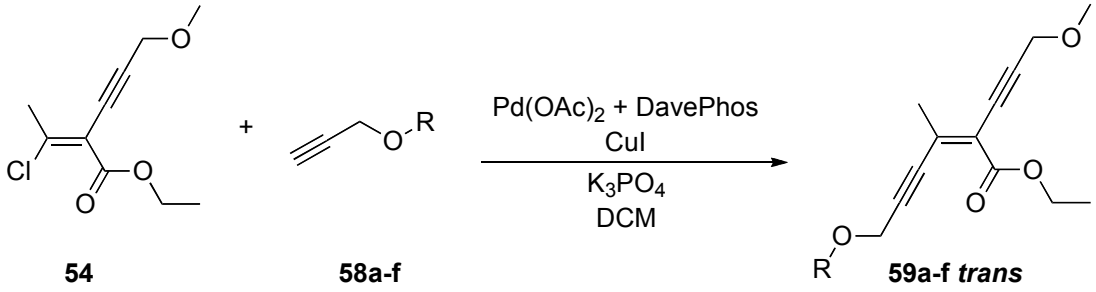
Scheme 22: Altering the Functional Groups on a Propargyl Ether Substituent In Order to Increase Radical Stabilization



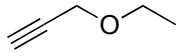
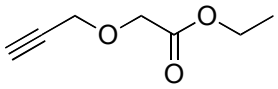
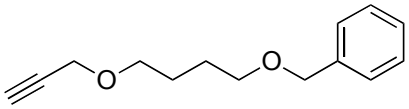
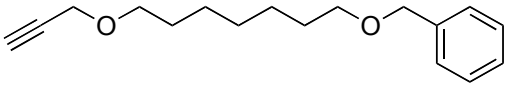
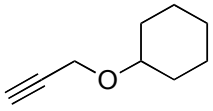
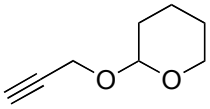
In order to simplify the process of synthesizing a variety of different enediynes, it was decided that the majority of the enediynes synthesized would contain the alkynyl substituent methyl propargyl ether **53** at the α-iodo position of the *E*-β-chloro-α-iodo-α,β-unsaturated ester template **8**. This resulting trisubstituted

olefin **54**, would then undergo a series of Sonogashira cross couplings with a variety of different propargyl ether substituents **58a-f**, that contained one or more radical stabilizing functional groups, to form a set of tetrasubstituted olefins **59a-f *trans*** that could then be tested for increased Bergman cyclization product yields (**Table 20**).

Table 20: Synthesis of Enediynes Containing Additional Radical Stabilizing Functional Groups (59a-f *trans*)



54 **58a-f** **59a-f *trans***

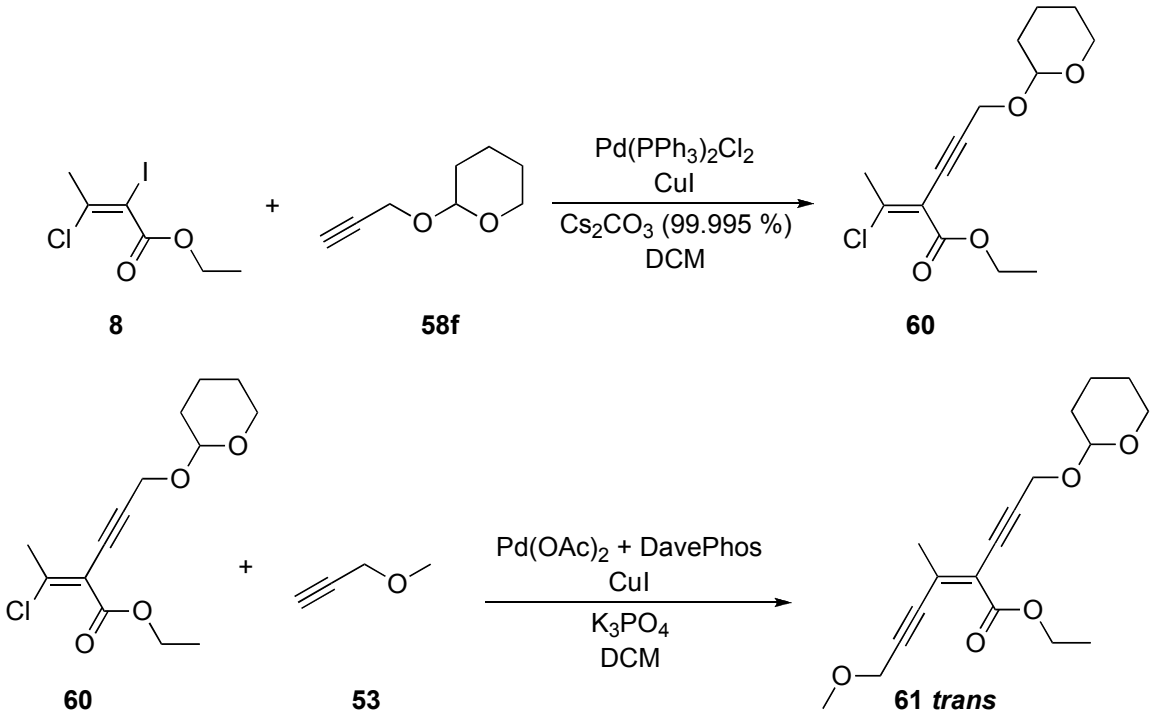
Entry[a]	R	Product	Yield (%)[b]
1	 **58a**	**59a *trans***	76
2	 **58b**	**59b *trans***	82
3	 **58c**	**59c *trans***	85
4	 **58d**	**59d *trans***	85
5	 **58e**	**59e *trans***	78
6	 **58f**	**59f *trans***	71

[a] Conditions: 0.10 eq. of $Pd(PPh_3)_2Cl_2$, 0.15 eq. of CuI, 3.0 eq. of alkyne, 3.0 eq. of K_3PO_4, DCM (0.05 M), 23 °C, 72 h.

[b] Isolated yield.

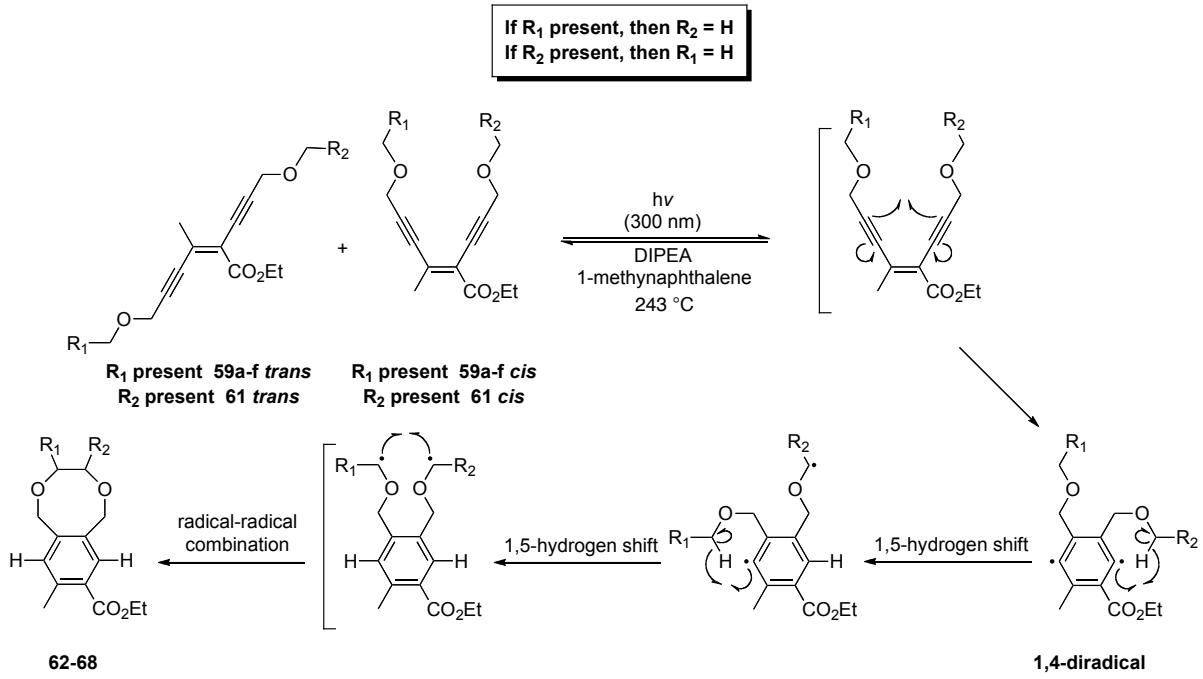
One further enediyne was synthesized for this series of Bergman cyclization reactions, similar to enediyne **59f *trans***, but with the alkyne substituent **58f** at the α-iodo position of the olefin template, and the alkyne substituent methyl propargyl ether **53** at the β-chloro position (**Scheme 23**). The reasoning for this was to determine whether or not reversing the position of the respective alkynes on the olefin template would influence the yield of any Bergman cyclization product that formed. The initial Sonogashira cross coupling produced the trisubstituted olefin **60**, which was used immediately in a second Sonogashira cross coupling to give the desired tetrasubstituted olefin **61 *trans***, in good yield (68 %).

Scheme 23: Synthesis of a *Trans* Enediyne With Alkynyl Substituents Cross Coupled in Reverse Order (61 *trans*)



With this new group of enediynes **59a-f *trans*** and **61 *trans*** that contained various radical stabilizing functional groups having been successfully synthesized, work proceeded towards investigating the influence these functional groups had on the yields of any Bergman cyclization products that formed. As had been discovered previously (**Table 19**), using some of the *cis* isomer **55 *cis*** as the starting material helped to increase the yields of the Bergman cyclization product **57** over that formed when only the *trans* isomer **55 *trans*** was used as the starting material. Given this, it was decided to photoisomerize each of the newly synthesized *trans* enediynes **59a-f *trans*** and **61 *trans*** to a mixture of both *cis* and *trans* isomers. Following a nearly identical procedure to that for **Scheme 3**, each of these *trans* isomers **59a-f *trans*** and **61 *trans*** was photolyzed using UV light of approximately 300 nm for 20 h. This produced various ratios of *cis* (**59a-f *cis*** and **61 *cis***) : *trans* (**59a-f *trans*** and **61 *trans***) isomers ranging from a 37 : 63 ratio to a 43 : 57 ratio. It was these varying mixtures of isomers that were used as the starting material in the new series of Bergman cyclization reactions (**Table 21**) in an attempt to synthesize a set of new Bergman cyclization products (**Figure 3**). Furthermore, given the results from **Table 19**, two reactions were run for each mixture of enediyne isomers. The first reaction was run for 30 minutes, as this reaction time produced the greatest overall yield of the Bergman cyclization product **57**, whereas the second reaction was run for 60 minutes, as this was the minimum reaction time required to consume all the *trans* isomer **55 *trans***.

Table 21: Bergman Cyclizations and Attempts at Bergman Cyclizations With Enediynes Possessing Radical Stabilizing Functional Groups (59a-f *trans* and 61 *trans*) and (59a-f *cis* and 61 *cis*)



Entry[a]	Enediyne	Starting Isomeric Ratio *Cis* (%)	*Trans* (%)	Time (min)	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]	Bergman Product Yield (%)[d]
1	**59a**	41	59	30	0	18	unconfirmed (< 35)[c]	unconfirmed (< 85)[c]
2	**59a**	41	59	60	0	0	unconfirmed (< 30)[c]	unconfirmed (< 73)[c]
3	**59b**	40	60	30	0	16	35	88
4	**59b**	40	60	60	0	0	28	70
5	**59c**	37	63	30	0	19	unconfirmed (< 35)[c]	unconfirmed (< 95)[c]
6	**59c**	37	63	60	0	0	unconfirmed (< 30)[c]	unconfirmed (< 81)[c]
7	**59d**	39	61	30	0	20	33	85
8	**59d**	39	61	60	0	0	27	69
9	**59e**	38	62	30	0	11	decomposition	decomposition
10	**59e**	38	62	60	0	0	decomposition	decomposition
11	**59f**	40	60	30	0	15	decomposition	decomposition
12	**59f**	40	60	60	0	0	decomposition	decomposition
13	**61**	41	59	30	0	14	decomposition	decomposition
14	**61**	41	59	60	0	0	decomposition	decomposition

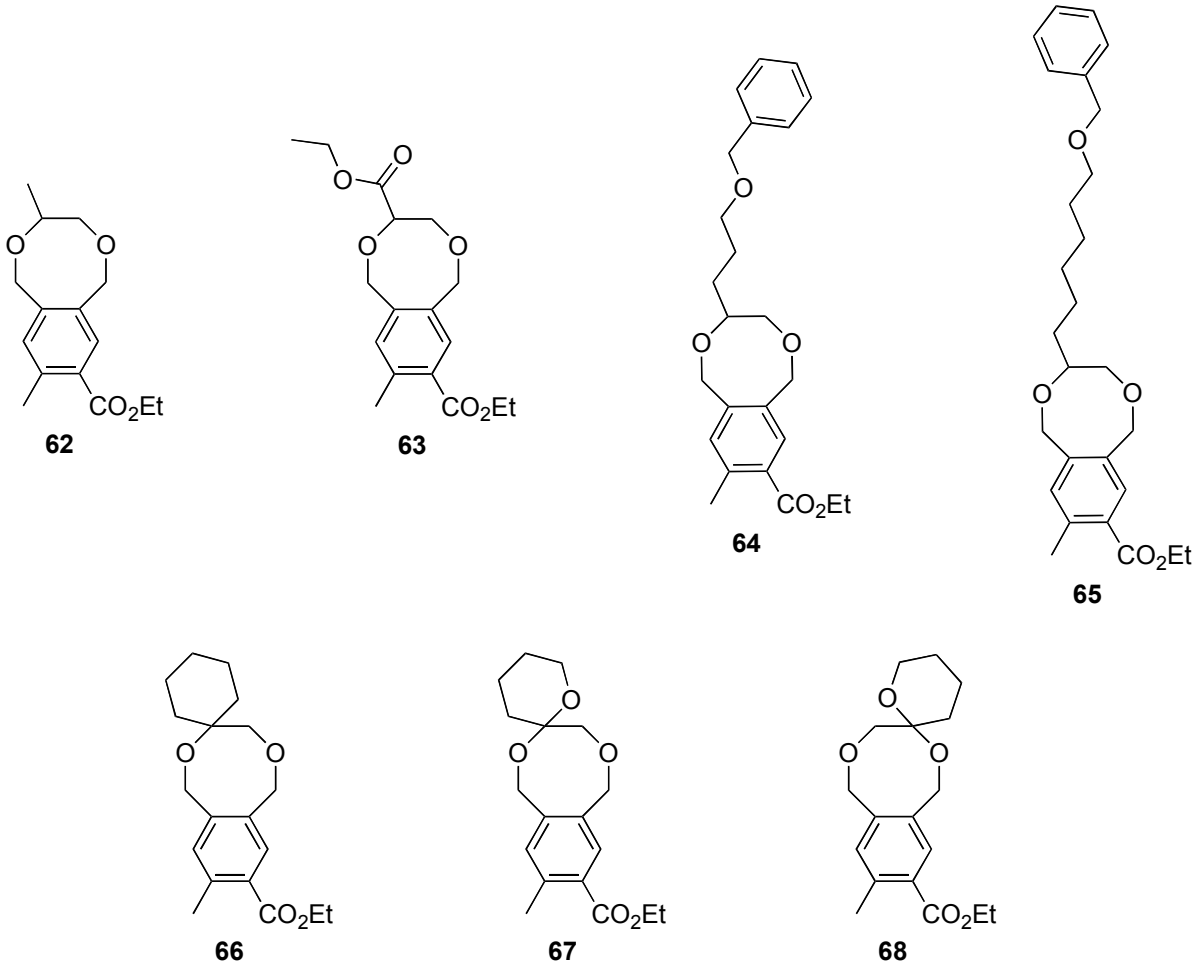
[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), h*v* (300 nm).

[b] Isolated yield based on total starting material.

[c] Unconfirmed product. Approximate yield based on molecular weight of expected product.

[d] Isolated yield based on *cis* isomer.

Figure 3: Expected Bergman Cyclization Products (62 – 68)



The initial experiment (Entry 1) in **Table 21** employed a mixture of isomers of the enediyne **59a**. This enediyne had the alkynyl substituent ethyl propargyl ether **58a** cross coupled at the β-chloro position of the olefin template, which was thought to be able to further stabilize any radical that formed due to the slight electron-donating effects of the additional $-CH_3$ group adjacent to the radical center. Using a 41 : 59 ratio of *cis* (**59a *cis***) : *trans* (**59a *trans***) isomers as the starting material, the reaction was run for 30 minutes, and produced a product that could not be confirmed

as the expected Bergman cyclization product **62** due to difficulties in its purification. Both preparatory plate chromatography, as well as HPLC (50 : 50 acetonitrile : water) were employed in multiple unsuccessful purification attempts. Although two singlets characteristic of the expected Bergman cyclization product **62** were present in the ^{1}H NMR, additional peaks mid- and up-field were present that were inconsistent with this expected product **62**. As was similar to the experiments run in **Table 19**, 18 % of the *trans* isomer **59a *trans*** starting material was recovered. A second experiment (Entry 2) was run with nearly identical reaction conditions to the first (Entry 1), but for an increased reaction time of 60 minutes. This again produced a product that could not be confirmed as the expected Bergman cyclization product **62**, despite repeated attempts at purification. None of the starting material **59a *cis*** and **59a *trans*** was recovered after this reaction. The second enediyne tested was **59b**, which contained the alkynyl substituent **58b** cross coupled at the β-chloro position of the olefin template. The ethyl ester present on this enediyne **59b** was thought to be able to help stabilize any adjacent radical that formed due to the electron-withdrawing effects of the ester functional group. For this third experiment (Entry 3), a 40 : 60 ratio of *cis* (**59b *cis***) : *trans* (**59b *trans***) isomers was used as the starting material, and the reaction produced the desired Bergman cyclization product **63**, in 35 % yield. Only 16 % of the *trans* isomer **59b *trans*** starting material was recovered. The fourth experiment (Entry 4) consisted of increasing the length of the previous reaction to 60 minutes, and this again produced the desired Bergman cyclization product **63**, but in 28 % yield. No starting material **59b *cis*** or **59b *trans*** was observed after this reaction. This was the first confirmed Bergman cyclization using an enediyne containing an additional radical stabilizing functional group. This

Bergman cyclization product **63** had a slightly larger yield for both reaction times, than that produced for Bergman cyclization product **57**. This can likely be attributed to the increase in radical stabilization brought about by the electron-withdrawing ethyl ester functional group prior to the radical-radical combination step (**Table 21**). The third enediyne tested was **59c**, which contained the alkynyl substituent **58c** cross coupled at the β-chloro position of the olefin template. This alkynyl substituent **58c** contained a four-carbon linker followed by a benzyl ether group, and it was thought that the carbon atom in the linker that was adjacent to the radical center could help to stabilize that radical via electron-donating effects. The fifth experiment (Entry 5) employed a 37 : 63 ratio of *cis* (**59c *cis***) : *trans* (**59c *trans***) isomers as the starting material, and produced a product that could not be confirmed as the desired Bergman cyclization product **64**. This unidentifiable product did have two singlets in the aromatic region of the ^{1}H NMR, but it also contained another singlet that was characteristic of an aldehyde. As well, 19 % of the starting material **59c *trans*** was recovered at the end of the reaction. A sixth experiment (Entry 6) was run, similar to before, but for a duration of 60 minutes. The same unidentifiable compound as before was produced, and none of the expected Bergman cyclization product **64** could be confirmed. As in previous reactions of this length, none of the starting material **59c *cis*** or **59c *trans*** was recovered at the end of the reaction. Given the difficulties in identifying this unknown compound with the apparent aldehyde functional group, but still wanting to test the radical stabilizing effects from an adjacent electron-donating carbon, it was decided to increase the length of the linker to seven carbons, from the present four, on the chance that the four-carbon linker was simply too short and was somehow interfering with the Bergman cyclization

reaction to produce the unexpected, and unidentifiable product. Therefore, the fourth enediyne tested was **59d**, which contained the alkynyl substituent **58d** cross coupled at the β-chloro position of the olefin template. This alkynyl substituent **58d** differed from the previous one **58c**, only in the fact that the linker was longer and seven carbons in length. The seventh experiment (Entry 7) made use of a 39 : 61 ratio of *cis* (**59d *cis***) : *trans* (**59d *trans***) isomers as the starting material, and produced the desired Bergman cyclization product **65**, in 33 % yield. Similar to previous reactions of this length, 20 % of the *trans* isomer **59d *trans*** starting material was recovered. The eighth experiment (Entry 8), with a 60 minute reaction time, again produced the desired Bergman cyclization product **65**, but in a 27 % yield. However, consistent with previous reactions of this length, none of the starting material **59d *cis*** or **59d *trans*** was recovered. This was the second confirmed Bergman cyclization using an enediyne containing an additional radical stabilizing functional group. The yields for both reaction times for this Bergman cyclization product **65**, was slightly larger than that for Bergman cyclization product **57**. Again, this would be consistent with an increase in stabilization of the radical prior to the radical-radical combination step, that would be brought about by the electron-donating effects from the carbon atom in the linker that was adjacent to the radical center (**Table 21**). The fifth enediyne tested was **59e**, and contained the alkynyl substituent **58e** cross coupled at the β-chloro position of the olefin template. The cyclohexyl group present on this enediyne **59e** was thought to potentially be able to significantly stabilize the radical center since there would be a total of three functional groups adjacent to the radical when it formed. Namely, there would be

the electron-donating oxygen from the ether functional group, as well as two separate adjacent carbon atoms from the cyclohexyl group, both of which would be electron donating. Since tertiary radicals are more stable relative to secondary or primary radicals,[14] it was hoped that this cyclohexyl group would help to significantly boost the yields of the Bergman cyclization product **66**. The ninth experiment (Entry 9) consisted of a 38 : 62 ratio of *cis* (**59e *cis***) : *trans* (**59e *trans***) isomers as the starting material. Unfortunately, only unidentifiable decomposition products, and 11 % of the *trans* isomer **59e *trans*** starting material were recovered at the end of the reaction. The tenth experiment (Entry 10) gave similar results, with the exception being that none of the starting material **59e *cis*** or **59e *trans*** was observed after the reaction. The fact that the cyclohexyl functional group did not seem to aid in increasing the yield of the Bergman cyclization product **66** was disappointing, and could possibly be attributed to the cyclohexyl group simply being too large and bulky to permit the final radical-radical combination shown in **Table 21**. Although speculative, if this were the case, the 1,4-diradical would have formed, followed by two 1,5-hydrogen shifts, but the final radical-radical combination to form the second ring would not have occurred, again possibly due to the steric interactions of the large cyclohexyl group. Despite the lack of success with enediyne **59e**, a sixth enediyne **59f** was tested, which contained the alkynyl substituent **58f** cross coupled at the β-chloro position of the olefin template. This enediyne **59f** contained a tetrahydropyran functional group, which was thought to potentially be able to stabilize any radical that formed to an even greater extent than the stabilization from the cyclohexyl functional group present in enediyne **59e**. In this case, the resulting radical would be stabilized by three adjacent functional groups, two of which would

be electron-donating oxygen atoms. The remaining functional group would be an electron-donating carbon atom from inside the ring of the tetrahydropyran system. It was thought that the additional electron-donating oxygen atom inside the tetrahydropyran system, would give an even greater degree of radical stabilization than for that from the cyclohexyl system previously. The eleventh experiment (Entry 11) was run using a 40 : 60 ratio of *cis* (**59f *cis***) : *trans* (**59f *trans***) isomers as the starting material. As with the case previous, only unidentifiable decomposition products, and 15 % of the *trans* isomer **59f *trans*** starting material were recovered at the end of the reaction. The twelfth experiment (Entry 12) gave similar results, with the exception being that none of the starting material **59f *cis*** or **59f *trans*** was observed after the reaction. Given the similarity in size between the tetrahydropyran functional group and the cyclohexyl functional group from the previous experiments (Entry 9 and Entry 10), it is not surprising that none of the expected Bergman cyclization product **67** was isolated, and could possibly be attributed to the tetrahydropyran group simply being too large and bulky to permit the final radical-radical combination shown in **Table 21**. The seventh, and final, enediyne tested was **61**. It was this enediyne that had its alkynyl substituents cross coupled in reverse order to the olefin template, relative to the previous enediyne **59f** synthesized in this group. This enediyne **61** contained the tetrahydropyran functional group at the α-iodo position of the olefin template, in an attempt to determine if the position of the respective alkynes would influence the yield of any Bergman cyclization product that formed. The thirteenth experiment (Entry 13) was run using a 41 : 59 ratio of *cis* (**61 *cis***) : *trans* (**61 *trans***) isomers as the starting material. Similar to the two cases immediately previous, only unidentifiable

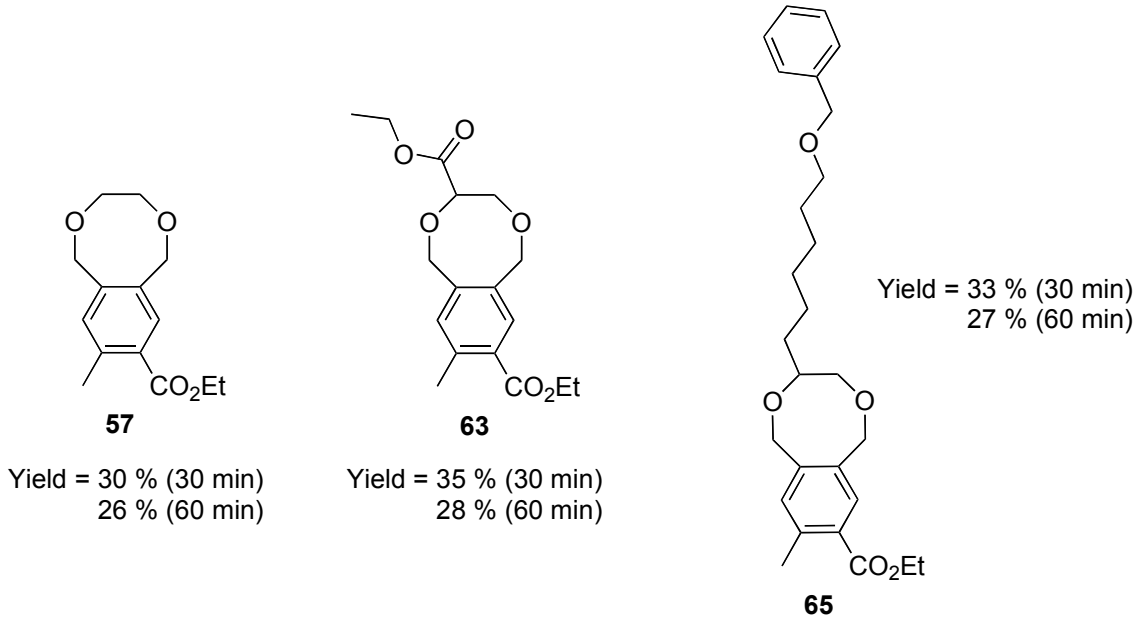
decomposition products, and 14 % of the *trans* isomer **61** ***trans*** starting material were recovered at the end of the reaction. The fourteenth, and final, experiment (Entry 14) gave unidentifiable decomposition products as well, and none of the starting material **61** ***cis*** or **61** ***trans*** was recovered after the reaction. This was not surprising, given the failure of the previous enediyne **59f** to successfully produce a Bergman cyclization product.

3.9 Summary of Successful Bergman Cyclizations Without the Use of an Intermolecular Hydrogen Donor

In summary, a total of three enediynes successfully underwent Bergman cyclizations without the use of an intermolecular hydrogen donor, such as 1,4-cyclohexadiene (**Figure 4**). The initial enediyne isomers to do so were **55** ***cis*** and **55** ***trans***, which produced the Bergman cyclization product **57** in 30 % yield over 30 minutes and in 26 % yield over 60 minutes. The inclusion of a radical stabilizing functional group such as an electron-withdrawing ethyl ester or an electron-donating carbon atom seemed to provide for a slight increase in the Bergman cyclization product yields. In the case of the enediyne isomers containing the ethyl ester **59b** ***cis*** and **59b** ***trans***, the electron-withdrawing effects from the ester functional group seemed to stabilize the resulting radical such that there was a slight improvement in the yield of the associated Bergman cyclization product **63**. This Bergman cyclization product **63** was produced in 35 % yield over 30 minutes and in 28 % yield over 60 minutes. In the case of the enediyne containing the seven carbon linker **59d** ***cis*** and **59d** ***trans***, the electron-donating effects from the carbon atom inside the linker seemed to stabilize the resulting radical such that there was again a slight

improvement in the overall yields for the associated Bergman cyclization product **65**, which was produced in 33 % yield over 30 minutes and in 27 % yield over 60 minutes.

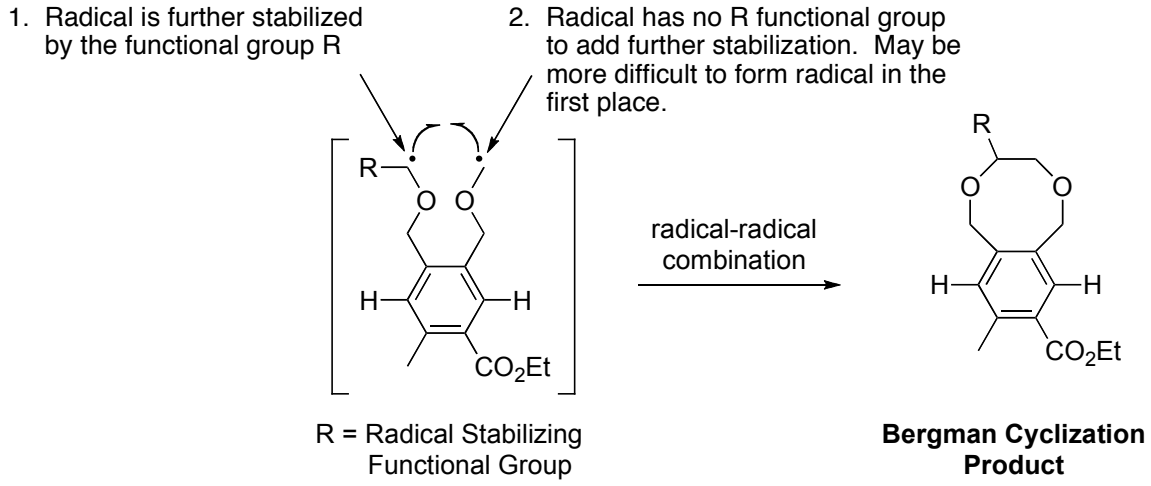
Figure 4: Successful Bergman Cyclization Products and Their Corresponding Yields (57), (63), and (65)



However, despite the use of a radical stabilizing functional group on one of the alkynyl substituents for each of the enediynes above (**Table 21**), the improvement in yields for Bergman cyclization products **63** and **65** over that for the initial Bergman cyclization product **57**, was 5 % or less. A compelling reason as to why the yield improvement was not greater lies in the fact that a radical stabilizing functional group was used on only one of the alkynyl substituents for each of the enediynes (**Scheme 24**). What this means is that during the series of 1,5-hydrogen

shifts that occur after the formation of the 1,4-diradical, one of the radicals forms on the terminal carbon adjacent to the oxygen atom of the ether functional group. Since this is a primary radical, it may not have been very stable, despite the adjacent oxygen atom, and may have been more difficult to form than if an additional radical stabilizing functional group had been present. Had there, in fact, been another radical stabilizing functional group present on this alkynyl substituent as well, the yields of the associated Bergman cyclization product may have been significantly higher.

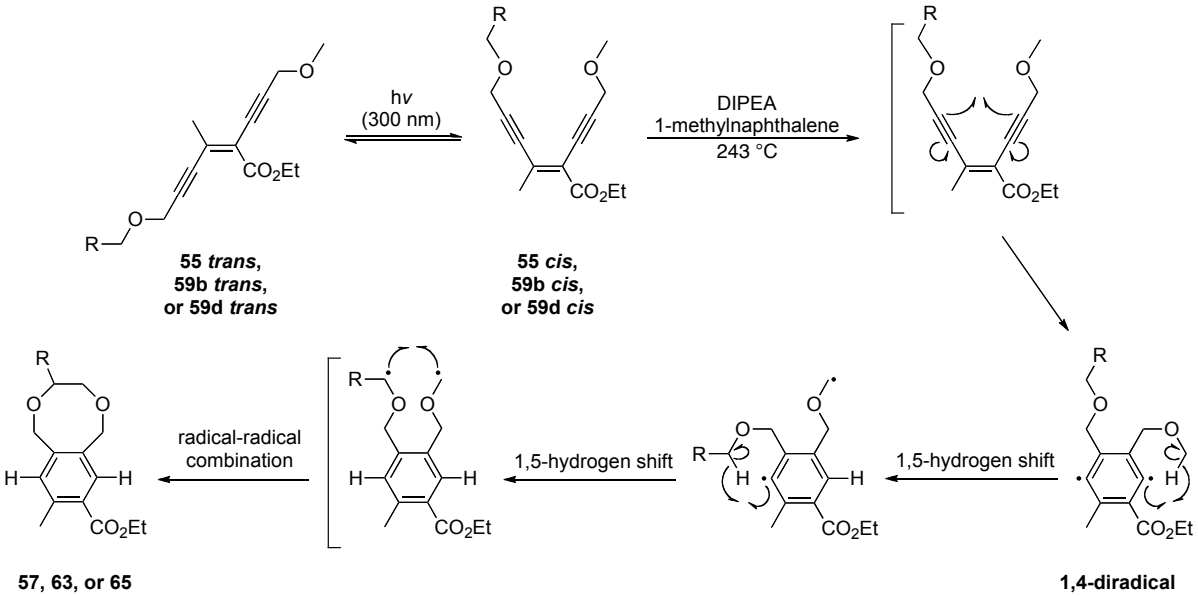
Scheme 24: Increased Radical Stabilization on Only One Alkynyl Substituent of the Enediyne



3.10 Photoactivated Bergman Cyclizations Using Only *Trans* Isomer Enediynes

Given the success in synthesizing the Bergman cyclization products shown above in **Figure 4**, it was decided that further attempts at Bergman cyclization products **63** and **65** would be made using only the *trans* isomer of their respective enediynes. This was carried out in order to satisfy the original goal of the project in which the unreactive *trans* isomer of an enediyne was photoisomerized to the reactive *cis* isomer, which could then subsequently undergo a Bergman cyclization. As well, the degree to which the yields of the Bergman cyclization products **63** and **65** are improved, over that for **57**, by the different radical stabilizing functional groups that are present in both enediynes **59b *trans*** and **59d *trans*** could be determined. As shown in **Table 22**, the enediynes **55 *trans***, **59b *trans***, and **59d *trans*** were subjected to similar reaction conditions to that shown previously in **Table 19**.

Table 22: Photoactivated Bergman Cyclizations Using Only a *Trans* Isomer Enediyne as the Starting Material (55 *trans*), (59b *trans*), and (59d *trans*)



Entry[a]	Enediyne	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]
1	**55 *trans***	0	12	13
2	**59b *trans***	0	5	20
3	**59d *trans***	0	5	16

[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), h*v* (300 nm), 60 min.

[b] Isolated yield.

The initial experiment (Entry 1) utilized the enediyne **55 *trans***, which contained no radical stabilizing functional group beyond the ether oxygen atoms. After a reaction time of 60 minutes, the desired Bergman cyclization product **57** was produced in 13 % yield, with only 12 % of the *trans* isomer **55 *trans*** starting material being recovered. The second experiment (Entry 2) made use of the enediyne **59b**

trans, which contained the electron withdrawing ethyl ester functional group. The desired Bergman cyclization product **63** was produced in 20 % yield, and in this case, 5 % of the *trans* isomer **59b *trans*** starting material was recovered. The final experiment (Entry 3) in this series of *trans* isomer reactions employed the enediyne **59d *trans***, which contained a seven carbon linker followed by a benzyl ether group. This reaction also produced the desired Bergman cyclization product **65**, but in 16 % yield. Similar to the experiment immediately previous (Entry 2), only 5 % of the *trans* isomer **59d *trans*** starting material was recovered.

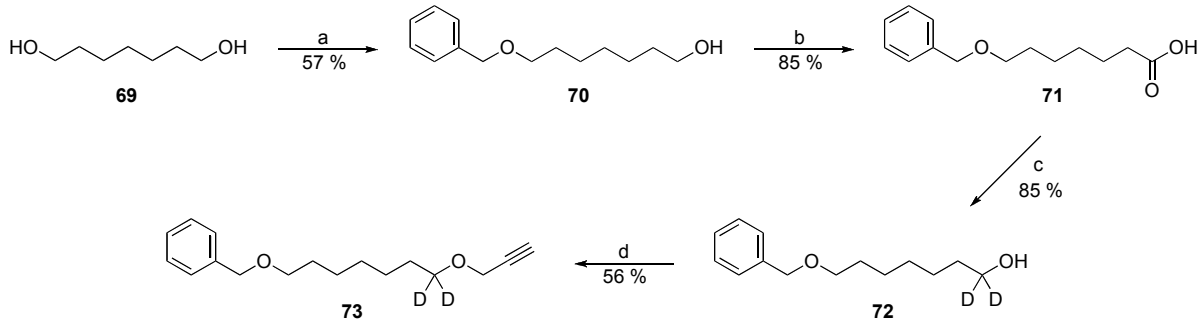
Overall, the two *trans* isomer enediynes with additional radical stabilizing functional groups **59b *trans*** and **59d *trans*** produced their respective Bergman cyclization products **63** and **65** in slightly better yield than the enediyne **55 *trans*** was able to produce Bergman cyclization product **57**. This is consistent with the results from the experiments conducted previously in **Table 21** as both the electron-withdrawing ethyl ester of **59b *trans*** and the electron-donating carbon atom of **59d *trans*** seem to help provide enough radical stabilization such that there is a slight increase in the respective Bergman cyclization product yields over that of Bergman cyclization product **57**.

3.11 Mechanism Study: Verification of the Series of 1,5-hydrogen Shifts

The final series of reactions involving the absence of an intermolecular hydrogen donor, such as 1,4-cyclohexadiene, was used in order to perform a mechanism study that would conclusively verify the occurrence of the sequence of two 1,5-hydrogen shifts before the formation of the Bergman cyclization product. Incorporated into this mechanism study was the deuterated alkynyl substituent **73**,

which was similar to the previously used alkyne **58d**, with the exception being that the first carbon in the seven-carbon linker was bonded to two deuterium atoms instead of two hydrogen atoms (**Scheme 25**). Initially, 1,7-heptanediol was selectively monoprotected using benzyl bromide[15] to provide **70**, which was then oxidized to the carboxylic acid **71**, in good yield.[16] The carboxylic acid **71** was then reduced to an alcohol **72** via the introduction of two deuterium atoms by using lithium aluminum deuteride as the reducing agent, in a modified procedure by W. G. Brown and coworkers.[17] The final step in the synthesis consisted of reacting the deuterated alcohol **72** with propargyl bromide to produce the desired alkyne **73**.

Scheme 25: Synthesis of Deuterated Alkyne (73)

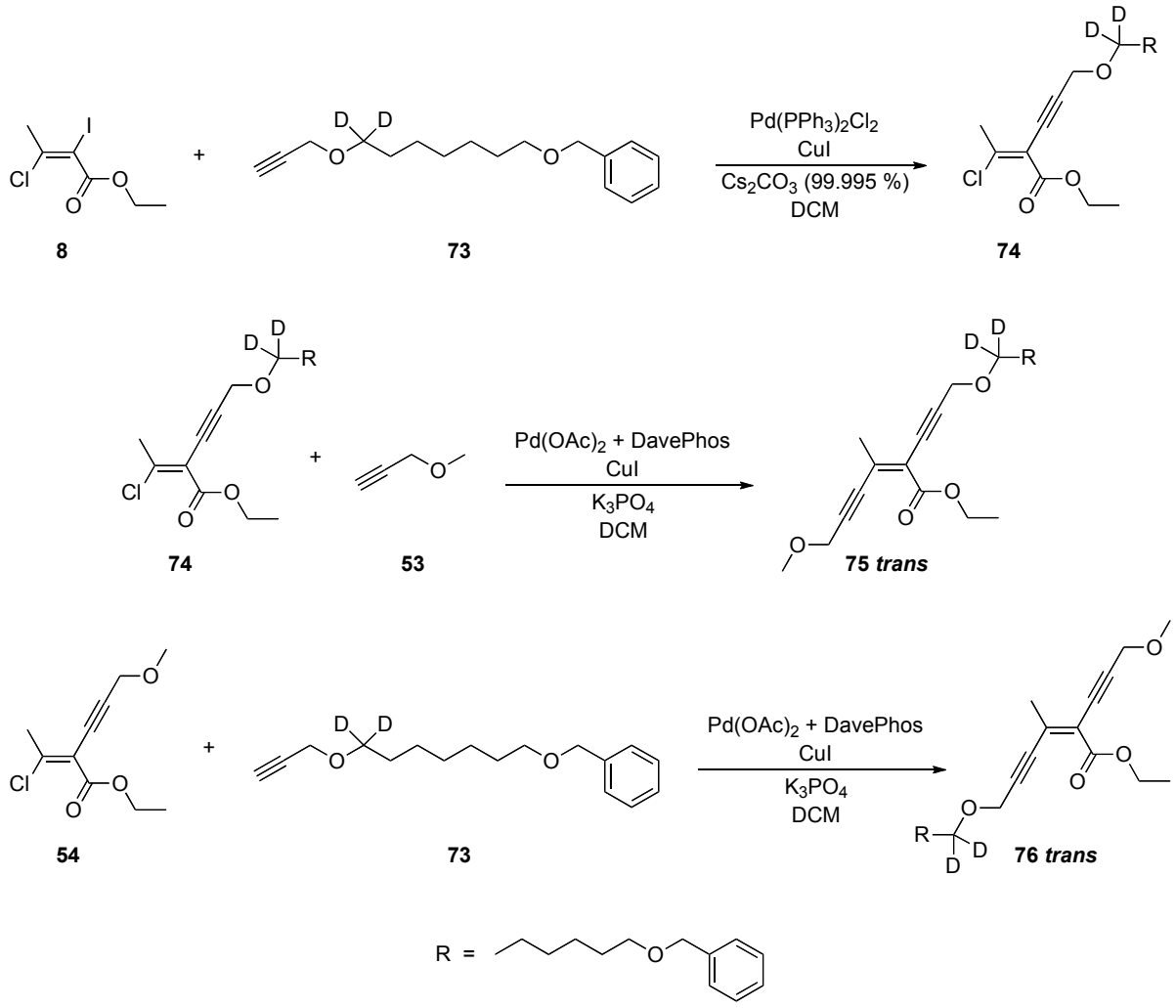


(a) Benzyl Bromide, NaH, Bu_4NI, THF (b) TEMPO, Na_3PO_4, $NaClO_2$/NaOCl, MeCN (c) $LiAlD_4$, THF (d) Propargyl Bromide, NaH, Bu_4NI, THF

Once the deuterated alkyne **73** was successfully synthesized, it was utilized in the synthesis of two additional enediynes. As shown in **Scheme 26**, a series of Sonogashira cross couplings were employed utilizing the optimized conditions

developed previously in **Table 4** through **Table 7**. The initial deuterated *trans* enediyne **75** ***trans*** contained the deuterated alkynyl substituent at the α-iodo position of the olefin template, and was synthesized in 82 % yield. In the case of the second deuterated *trans* enediyne **76** ***trans***, the yield was also 82 %, however, the deuterated alkynyl substituent was instead cross coupled to the β-chloro position of the olefin template.

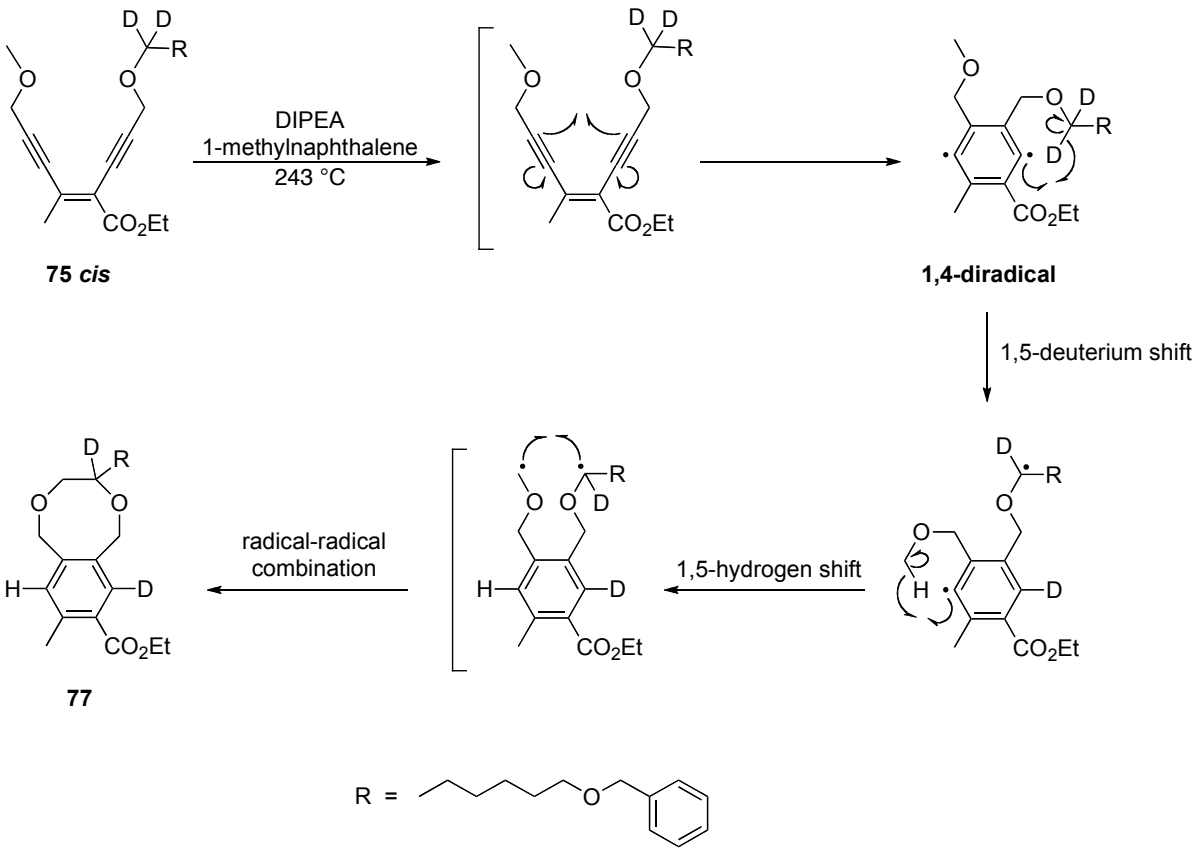
Scheme 26: Synthesis of Deuterated *Trans* Enediynes (75 *trans*) and (76 *trans*)



The two deuterated *trans* enediynes **75 *trans*** and **76 *trans*** were then photolyzed using UV light of approximately 300 nm for 20 h, from a procedure similar to that for **Scheme 3**. This produced a separable mixture of *cis* (**75 *cis***) and *trans* (**75 *trans***) isomers for the initial deuterated enediyne, as well as *cis* (**76 *cis***) and *trans* (**76 *trans***) isomers for the second deuterated enediyne. Both mixtures of *cis* : *trans* isomers were produced in a 39 : 61 ratio.

Using only the *cis* isomer of the initial deuterated enediyne **75 *cis***, the first Bergman cyclization in the mechanism study on the 1,5 hydrogen shifts was carried out (**Table 23**). No UV light was used to irradiate the enedyine **75 *cis***, since it was already in the reactive *cis* isomeric form. The reaction was run for 15 minutes, after which the desired Bergman cyclization product **77** was produced in 37 % yield. None of the *cis* isomer **75 *cis*** starting material was recovered. As confirmed by ^{1}H NMR, a 1,5-deuterium shift had indeed taken place, in which a deuterium atom had been transferred from the carbon atom immediately adjacent to the ether oxygen atom, to the carbon atom inside the aromatic ring. This was followed by the radical-radical combination step to form the eight-membered ring that contained the two oxygen atoms.

Table 23: Initial Bergman Cyclization of the 1,5-hydrogen Shift Mechanism Study (77)



Entry[a]	Enediyne	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]
1	**75 *cis***	0	0	37

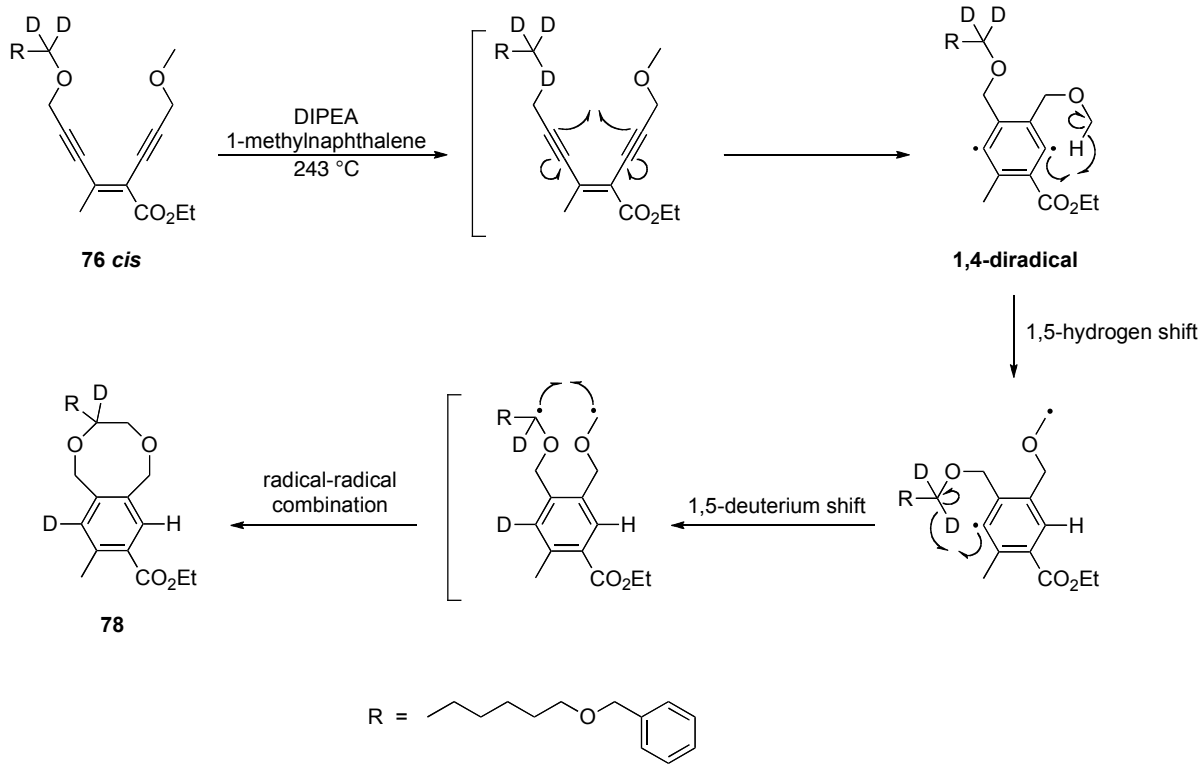
[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), 15 min.

[b] Isolated yield.

Using only the *cis* isomer of the second deuterated enediyne **76 *cis***, the second Bergman cyclization in the mechanism study on the 1,5 hydrogen shifts was carried out (**Table 24**). The reaction was run under identical conditions to those

immediately previous, and the desired Bergman cyclization product **78** was produced in 36 % yield. None of the *cis* isomer **76** ***cis*** starting material was recovered. As in the previous reaction, ^{1}H NMR confirmed that a 1,5-deuterium shift had taken place, and a deuterium atom had been transferred from the carbon atom immediately adjacent to the ether oxygen atom, to the carbon atom inside the aromatic ring. This was followed by the radical-radical combination step to form the eight-membered ring that contained the two oxygen atoms. It should be noted that at 6.99 ppm in the ^{1}H NMR of Bergman cyclization product **78**, there is a singlet that integrates to 0.38. This can be attributed to a likely kinetic isotope effect and the fact that the initial starting material **76** ***cis*** was not completely deuterated. This would result in a hydrogen atom being transferred to the carbon atom inside the aromatic ring and being detected in the subsequent ^{1}H NMR. Furthermore, some of the signal at 6.99 ppm can be attributed to the fact one of the radicals in the resulting 1,4-diradical is *ortho* to a methyl substituent. The methyl substituent would stabilize this radical and allow it to abstract a hydrogen atom from some other hydrogen source, possibly intermolecularly.

Table 24: Second Bergman Cyclization of the 1,5-hydrogen Shift Mechanism Study (78)



Entry[a]	Enediyne	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]
1	**76 *cis***	0	0	36

[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), 15 min.

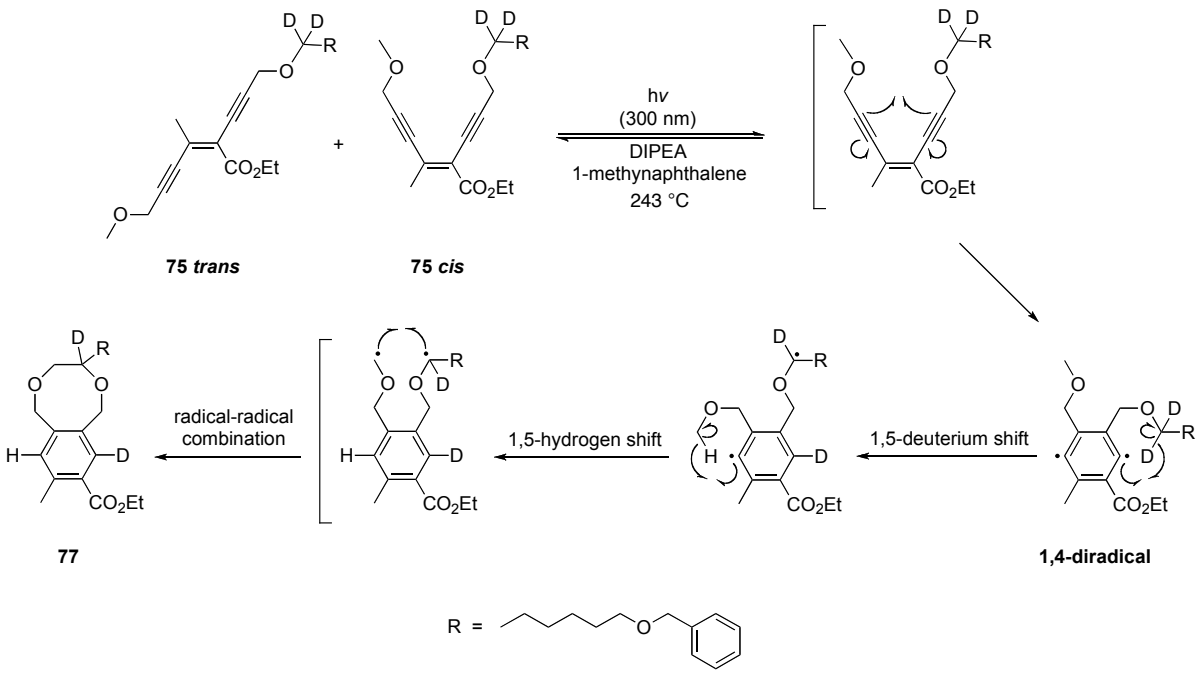
[b] Isolated yield.

At this point, it was decided to test a mixture of *cis* and *trans* isomers of the two deuterated enediynes **75 *cis*** and **75 *trans***, as well as **76 *cis*** and **76 *trans***, for Bergman cyclization reactivity under identical conditions to the enediynes utilized in **Table 19** and **Table 21**. The primary reason for this was to determine if the deuterated enediynes performed differently in terms of their reaction yields, as

compared to the previous non-deuterated enediynes, when UV light was utilized in the reaction. As well, it could also be determined whether or not the reversing of the position of the deuterated alkynyl substituent on the olefin template had any significant influence on the yield of the Bergman cyclization products that formed under these conditions.

Using a 39 : 61 ratio of *cis* (**75 *cis***) : *trans* (**75 *trans***) isomers, two Bergman cyclization reactions were carried out, as shown in **Table 25**. The initial reaction (Entry 1) was run for 30 minutes, and produced the desired Bergman cyclization product **77** in 34 % yield. Only 18 % of the *trans* isomer **75 *trans*** starting material was recovered. The second reaction (Entry 2) was run for 60 minutes, and again produced Bergman cyclization product **77**, but in 27 % yield. In this instance however, none of the starting material **75 *cis*** or **75 *trans*** was recovered. It should be noted that the Bergman cyclization yields from this set of reactions, with the deuterated enediyne isomers **75 *cis*** and **75 *trans***, are similar to that for the non-deuterated enediyne isomers **59d *cis*** and **59d *trans*** from **Table 21**.

Table 25: First Bergman Cyclization With a Deuterated Enediyne Using a Mixture of *Cis* and *Trans* Isomers (75 *cis*) and (75 *trans*)



Entry[a]	Starting Isomeric Ratio *Cis* (%)	*Trans* (%)	Time (min)	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]	Bergman Product Yield (%)[c]
1	39	61	30	0	18	34	87
2	39	61	60	0	0	27	69

[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), hν (300 nm).

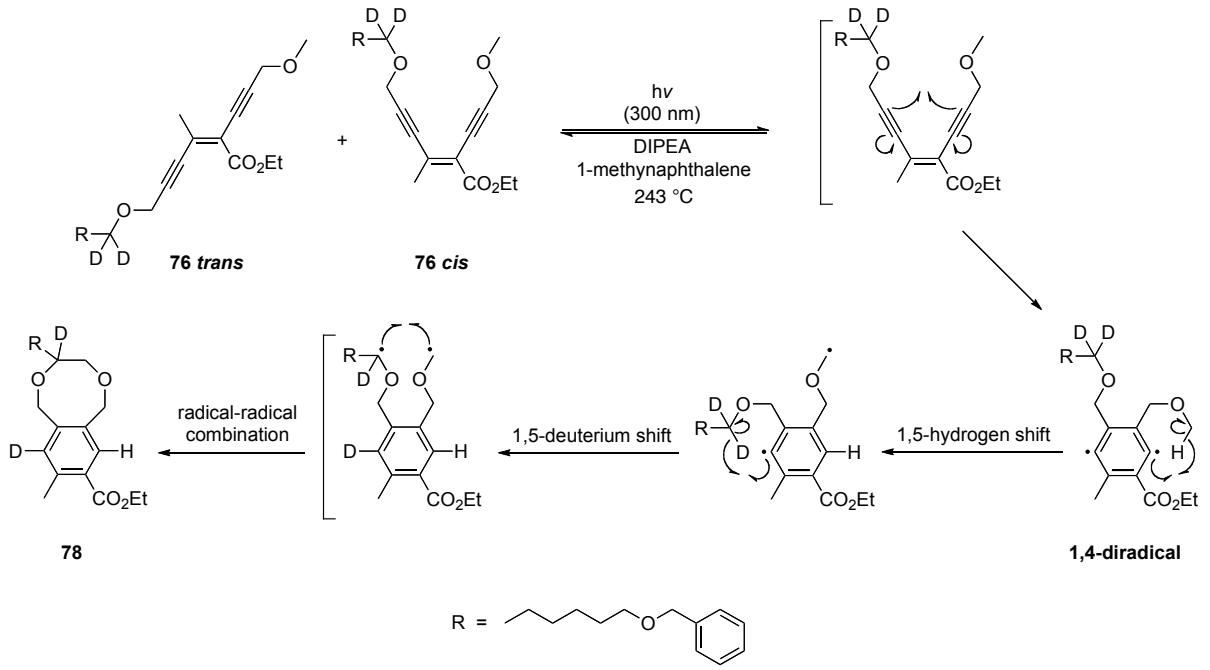
[b] Isolated yield based on total starting material.

[c] Isolated yield based on *cis* isomer.

Similar to the reactions immediately previous, a 39 : 61 ratio of *cis* (**76 *cis***) : *trans* (**76 *trans***) isomers were used in the two Bergman cyclization reactions shown in **Table 26**. As before, the initial reaction (Entry 1) was run for 30 minutes, however, the desired Bergman cyclization product **78** was produced in 32 % yield,

with 21 % of the *trans* isomer **76** ***trans*** starting material being recovered. The second reaction (Entry 2) was run for 60 minutes, and likewise produced Bergman cyclization product **78**, but in 26 % yield. Similar to previous reactions of this length, none of the starting material **76** ***cis*** or **76** ***trans*** was recovered. The Bergman cyclization yields from this set of reactions with the deuterated enediyne isomers **76** ***cis*** and **76** ***trans*** are similar to that for both the non-deuterated enediyne isomers **59d** ***cis*** and **59d** ***trans*** from **Table 21**, as well as the deuterated enediyne isomers **75** ***cis*** and **75** ***trans*** from **Table 25**. At least in this instance, it appears that reversing the position of the alkynyl substituent on the olefin template does not, in fact, significantly affect the yield of the Bergman cyclization product.

Table 26: Second Bergman Cyclization With a Deuterated Enediyne Using a Mixture of *Cis* and *Trans* Isomers (76 *cis*) and (76 *trans*)



Entry[a]	Starting Isomeric Ratio *Cis* (%)	*Trans* (%)	Time (min)	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]	Bergman Product Yield (%)[c]
1	39	61	30	0	21	32	82
2	39	61	60	0	0	26	67

[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), h*v* (300 nm).

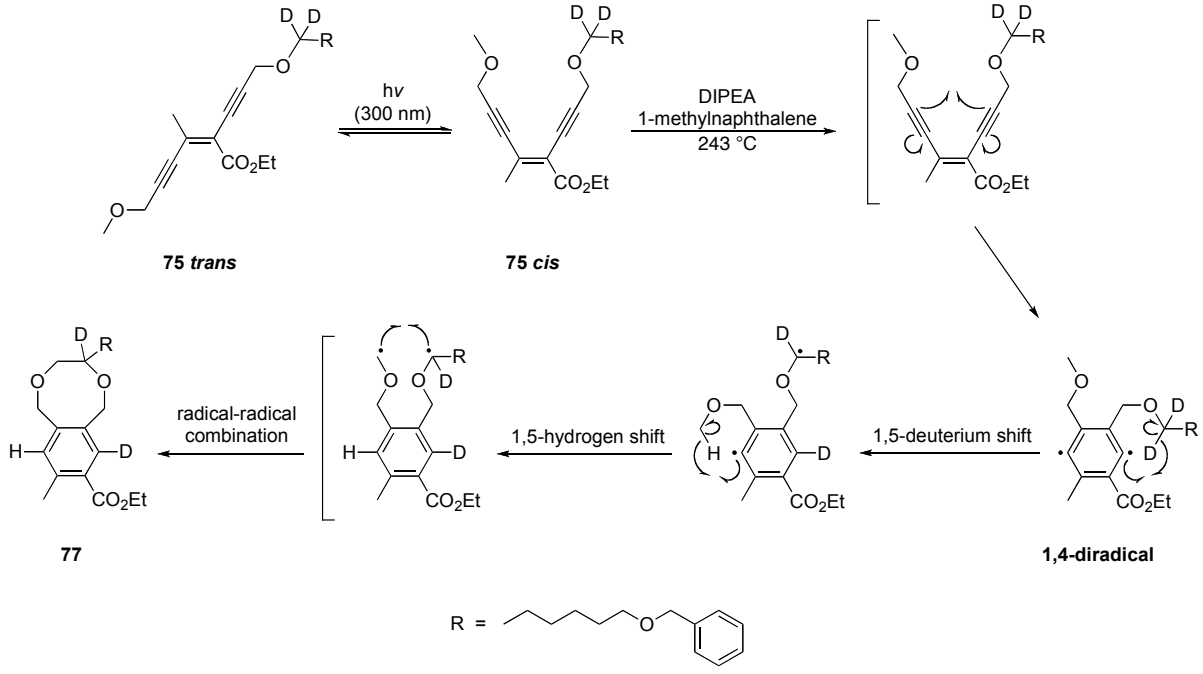
[b] Isolated yield based on total starting material.

[c] Isolated yield based on *cis* isomer.

The final set of reactions with the two deuterated enediynes consisted of utilizing only the *trans* isomer of each respective compound **75 *trans*** and **76 *trans*** in a series of Bergman cyclization reactions. As before, this was to satisfy the original goal of the project in which the unreactive *trans* isomer of an enediyne was photoisomerized to the reactive *cis* isomer, which could then subsequently undergo

a Bergman cyclization. As well, it could be determined whether or not reversing the position of the alkynyl substituent on the olefin template had any effect on the Bergman cyclization yield when only the *trans* isomer was used as the starting material. As shown in **Table 27**, the *trans* isomer of the initial deuterated enediyne **75 *trans*** was subjected to Bergman cyclization conditions that were identical to those used previously on the *trans* enediynes in **Table 22**.

Table 27: Photoactivated Bergman Cyclization Using Only a Deuterated *Trans* Isomer Enediyne as the Starting Material (75 *trans*)



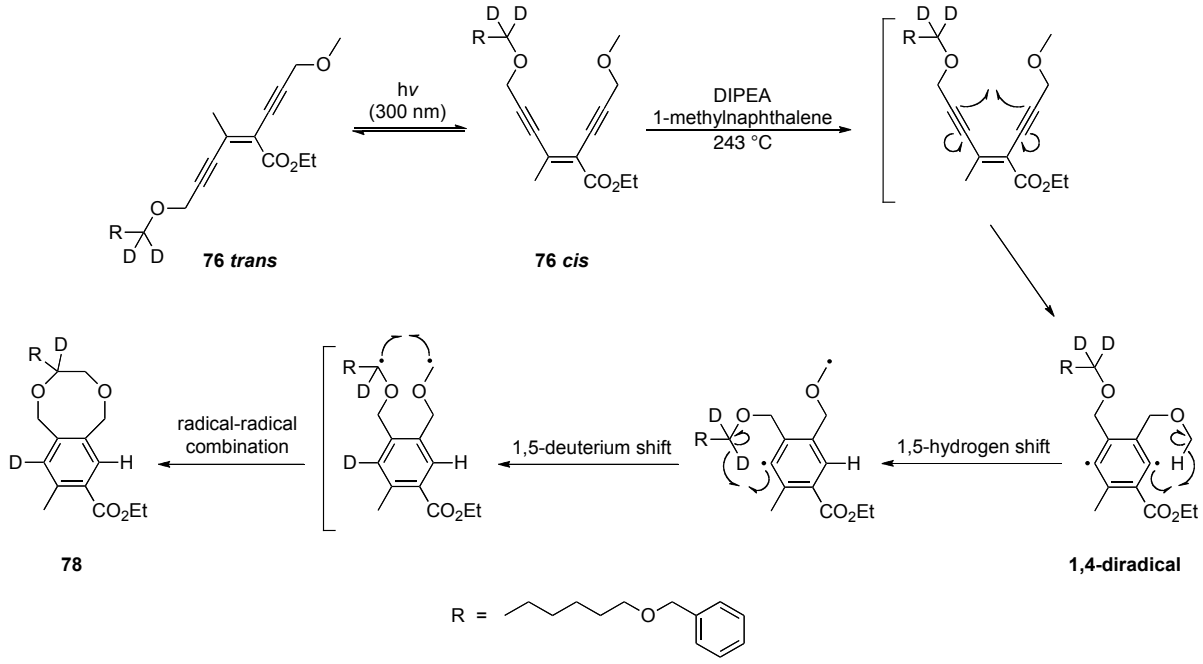
Entry[a]	Enediyne	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]
1	**75 *trans***	0	7	16

[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), h*v* (300 nm), 60 min.

[b] Isolated yield.

The Bergman cyclization reaction using only the *trans* isomer **75 *trans*** produced the desired Bergman cyclization product **77** in 16 % yield, with only 7 % of the starting material **75 *trans*** being recovered. This result was almost identical to that for the non-deuterated *trans* isomer **59d *trans*** shown above in **Table 22**. The final reaction, shown in **Table 28**, utilized the *trans* isomer of the second deuterated enediyne **76 *trans*** under identical conditions to the reaction immediately previous (**Table 27**).

Table 28: Photoactivated Bergman Cyclization Using Only a Deuterated *Trans* Isomer Enediyne as the Starting Material (76 *trans*)



Entry[a]	Enediyne	Recovered Isomer (by weight) *Cis* (%)	*Trans* (%)	Bergman Product Yield (%)[b]
1	**76 *trans***	0	9	15

[a] 1 eq. DIPEA, 1-methylnaphthalene (0.05 M), reflux (243 °C), NO RADICAL TRAPPING AGENT (1,4-cyclohexadiene), h*v* (300 nm), 60 min.

[b] Isolated yield.

The Bergman cyclization reaction using only the *trans* isomer **76** ***trans*** produced the desired Bergman cyclization product **78** in 15 % yield, with only 9 % of the starting material **76** ***trans*** being recovered. Again, this result was almost identical to that for the non-deuterated *trans* isomer **59d** ***trans*** shown above in **Table 22**. As well, the result was similar to that for the initial deuterated *trans* isomer **75** ***trans***. Again, it appears that reversing the position of the alkynyl substituent on the olefin template does not, in fact, affect the yield of the Bergman cyclization product.

3.12 Conclusions

In summary, the less sterically congested enediyne **55** ***trans*** was found to be able to undergo a Bergman cyclization without the need for an intermolecular hydrogen donor, such as 1,4-cyclohexadiene. Yields of the resulting Bergman cyclization product **57** were increased by the inclusion of some of the *cis* isomer starting material **55** ***cis*** in the reaction. Various radical stabilizing functional groups were used in an attempt to help stabilize the resulting radicals, and it was found that there was a slight increase in the Bergman cyclization product yields from the use of the electron-withdrawing ethyl ester functional group and the electron-donating seven-carbon linker. The *trans* enediyne isomers that contained the radical stabilizing functional groups **59b** ***trans*** and **59d** ***trans*** were also found to be able to undergo photoactivated Bergman cyclizations upon irradiation of UV light of approximately 300 nm, with product yields reaching up to 20 %. Finally, a mechanism study was conducted that conclusively proved the existence of a series of intramolecular 1,5-hydrogen shifts in the formation of the various Bergman cyclization products that did not require an intermolecular hydrogen donor.

3.13 References

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Claims to Original Research

1. Optimized a method for the regioselective and stereospecific synthesis of trisubstituted olefins as single isomers from *E*-β-chloro-α-iodo-α,β-unsaturated esters.

2. Optimized a method for the regioselective and stereospecific synthesis of tetrasubstituted olefins as single isomers from *E*-β-chloro-α-iodo-α,β-unsaturated esters.

3. Prepared and characterized 32 trisubstituted or tetrasubstituted olefin derivatives.

4. Developed a method for microwave-assisted Bergman cyclization reactions.

5. Developed a method for Bergman cyclization reactions using either *cis* or *trans* enediynes without the use of an intermolecular hydrogen donor.

6. Prepared and characterized seven Bergman cyclization derivatives.

7. Investigated in detail the mechanism of a Bergman cyclization forming cyclic diether compounds without the use of an intermolecular hydrogen donor.

Chapter 4

4.1 Experimental

4.2 General Experimental Procedure

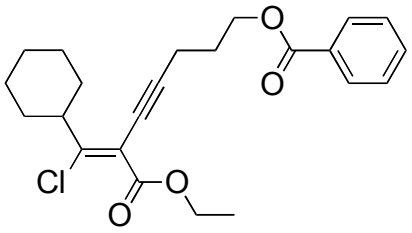
Reactions were performed using oven- or flame-dried round bottom flasks or vials under nitrogen atmosphere. Glassware was equipped with a magnetic stir bar and rubber septum or screw cap with specialized septa. All solvents were distilled prior to use: THF over sodium/benzophenone; DCM, toluene, DMF, and triethylamine over calcium hydride. Reagents were purchased from Sigma-Aldrich, Strem Chemical, GFS Chemicals, TCI America, and Acros Organics. Reactions were monitored by thin layer chromatography, using silica gel 60 F_{254} pre-coated 0.25 mm thick aluminum plates. TLCs were visualized using ultraviolet light, or developed by heating after treatment with potassium permanganate. When necessary, products were purified using flash column chromatography on silica gel 60 (230-400 mesh), or preparatory TLC glass plates pre-coated with silica gel (Si250F). Solvents were evaporated on rotary evaporators.

^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance 300 MHz (^{1}H) and 75 MHz (^{13}C) spectrometer, a Bruker Avance 400 MHz (^{1}H) and 100 MHz (^{13}C) spectrometer, or a Bruker Avance 500 MHz (^{1}H) and 125 MHz (^{13}C) spectrometer. Chemical shifts are reported in ppm δ units relative to chloroform (7.26 ppm for ^{1}H NMR, 77.0 ppm for decoupled ^{13}C NMR), benzene (7.16 ppm for ^{1}H NMR, 128.06 ppm for decoupled ^{13}C NMR), DMSO (2.50 ppm for ^{1}H NMR, 39.52 ppm for

decoupled ^{13}C NMR), or acetone-d_6 (2.05 ppm for ^{1}H NMR, 33.0 ppm for decoupled ^{13}C NMR) as internal standards. Infrared spectra were recorded as neat films on a sodium chloride cell using a Bomem Michaelson 100 FTR spectrometer. Mass spectra were obtained using a Kratos IIH instrument using either CI or EI ionization techniques.

Synthesis of Trisubstituted Olefins

General Procedure for the Sonogashira Cross-Coupling of (*E*)-β-chloro-α-iodo-α,β-unsaturated esters:



27

(*Z*)-7-chloro-7-cyclohexyl-6-(ethoxycarbonyl)hept-6-en-4-ynyl benzoate (27)

To an oven dried vial, equipped with a Teflon-coated stir bar, was added (*E*)-ethyl 3-chloro-3-cyclohexyl-2-iodoacrylate (**26**) (122.5 mg, 0.358 mmol) under a nitrogen atmosphere. Freshly distilled dichloromethane (2.0 mL) was added, followed by CuI (20.5 mg, 0.107 mmol) and Cs_2CO_3 (350.0 mg, 1.074 mmol), and the solution was sparged for 10 minutes. To a second oven dried vial, equipped with a Teflon-coated stir bar, were added pent-4-ynyl benzoate (**13**) (202.1 mg, 1.074 mmol) followed by freshly distilled dichloromethane (1.0 mL). The resulting solution was sparged for 10 minutes before being transferred under nitrogen to the first vial via canula.

$Pd(PPh_3)_2Cl_2$ (50.3 mg, 0.072 mmol) was then added to the first vial and the solution was further sparged for 10 minutes, before being stirred for 36 hours at room temperature. The solution was then diluted with Et_2O and washed with water. The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product (**27**) (86.5 mg, 0.215 mmol, 60 %) was obtained as a yellow oil by flash chromatography (5 % EtOAc in hexanes).

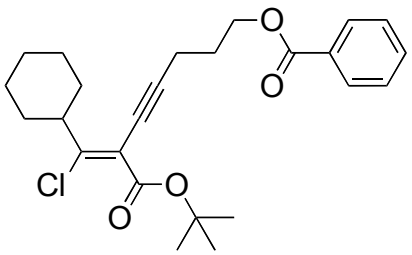
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.59 – 7.54 (m, 1H), 7.46 – 7.42 (m, 2H), 4.44 (t, J = 6.4 Hz, 2H), 4.26 (q, J = 6.8 Hz, 2H), 3.15 – 3.08 (m, 1H), 2.60 (t, J = 6.8 Hz, 2H), 2.08 – 2.01 (m, 2H), 1.82 – 1.78 (m, 2H), 1.69 – 1.66 (m, 3H), 1.55 – 1.45 (m, 2H), 1.36 – 1.11 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 164.3 (C), 154.7 (C), 133.0 (CH), 130.1 (C), 129.5 (CH), 128.4 (CH), 113.6 (C), 96.5 (C), 75.0 (C), 63.4 (CH_2), 61.6 (CH_2), 45.0 (CH), 29.9 (CH_2), 27.7 (CH_2), 25.7 (CH_2), 25.5 (CH_2), 16.7 (CH_2), 14.1 (CH_3);

IR (neat) 2225, 1723, 712 cm^{-1};

MS (EI) 402.2 (M^+);

HRMS calcd for $C_{23}H_{27}O_4Cl$ (M^+) 402.1598, found 402.1577.



35

(*Z*)-6-(*tert*-butoxycarbonyl)-7-chloro-7-cyclohexylhept-6-en-4-ynyl benzoate (35)

Prepared from (*E*)-*tert*-butyl 3-chloro-3-cyclohexyl-2-iodoacrylate (**34**) (60 mg, 0.162 mmol) and pent-4-ynyl benzoate (**13**) (91.5 mg, 0.486 mmol), using a procedure similar to that described above for (*Z*)-7-chloro-7-cyclohexyl-6-(ethoxycarbonyl)hept-6-en-4-ynyl benzoate (**27**), that provided the title compound (**35**) (25.8 mg, 0.060 mmol, 37 %) as a yellow oil after flash chromatography (5 % EtOAc in hexanes).

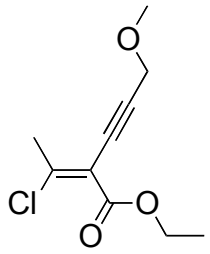
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.03 (m, 2H), 7.59 – 7.54 (m, 1H), 7.46 – 7.42 (m, 2H), 4.44 (t, J = 6.4 Hz, 2H), 3.11 – 3.03 (m, 1H), 2.59 (t, J = 7.0 Hz, 2H), 2.08 – 2.01 (m, 2H), 1.81 – 1.77 (m, 2H), 1.68 – 1.65 (m, 3H), 1.54 – 1.43 (m, 11H), 1.35 – 1.14 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.4 (C), 163.5 (C), 152.8 (C), 133.0 (CH), 130.2 (C), 129.5 (CH), 128.4 (CH), 115.0 (C), 96.1 (C), 82.5 (C), 75.3 (C), 63.5 (CH_2), 44.8 (CH), 30.0 (CH_2), 28.0 (CH_3), 27.8 (CH_2), 25.8 (CH_2), 25.6 (CH_2), 16.7 (CH_2);

IR (neat) 2223, 1723, 1600, 712 cm^{-1};

MS (EI) 357.1 (M^+ -$OC(CH_3)_3$);

HRMS calcd for $C_{21}H_{22}O_3Cl$ (M^+ -$OC(CH_3)_3$) 357.1258, found 357.1261.



54

(*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (54)

Prepared from (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (**8**) (66.3 mg, 0.242 mmol) and methyl propargyl ether (**53**) (50.9 mg, 0.726 mmol), using a procedure similar to that described above for (*Z*)-7-chloro-7-cyclohexyl-6-(ethoxycarbonyl)hept-6-en-4-ynyl benzoate (**27**), that provided the title compound (**54**) (39.8 mg, 0.184 mmol, 76%) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

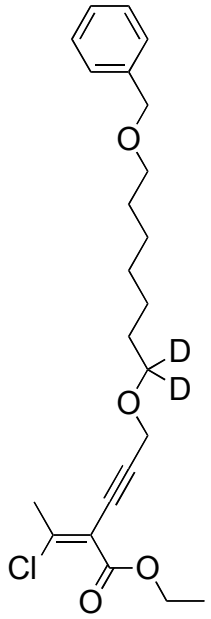
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.31 – 4.24 (m, 4H), 3.41 (s, 3H), 2.44 (s, 3H), 1.33 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (C), 147.9 (C), 114.6 (C), 92.8 (C), 80.2 (C), 61.7 (CH_2), 60.3 (CH_2), 57.7 (CH_3), 26.3 (CH_3), 14.1 (CH_3);

IR (neat) 2202, 1734, 665 cm^{-1};

MS (EI) 216.1 (M^+);

HRMS calcd for $C_{10}H_{13}O_3Cl$ (M^+) 216.0553, found 216.0557.



74

(*Z*)-ethyl 5-(7-(benzyloxy)-1,1-dideuteroheptyloxy)-2-(1-chloroethylidene)pent-3-ynoate (74)

Prepared from (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (**8**) (71.1 mg, 0.259 mmol) and ((7,7-dideutero-7-(prop-2-ynyloxy)heptyloxy)methyl)benzene (**73**) (203.9 mg, 0.777 mmol), using a procedure similar to that described above for (*Z*)-7-chloro-7-cyclohexyl-6-(ethoxycarbonyl)hept-6-en-4-ynyl benzoate (**27**), that provided the title compound (**74**) (78.5 mg, 0.192 mmol, 74%) as a yellow oil after flash chromatography (8 % EtOAc in hexanes).

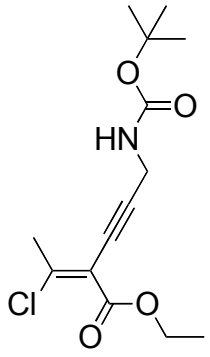
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36 – 7.22 (m, 5H), 4.48 (s, 2H), 4.29 – 4.22 (m, 4H), 3.44 (t, J = 6.6 Hz, 2H), 2.41 (s, 3H), 1.62 – 1.54 (m, 4H), 1.42 – 1.26 (m, 9H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.3 (C), 147.6 (C), 138.6 (C), 128.3 (CH), 127.5 (CH), 127.4 (CH), 114.7 (C), 93.4 (C), 79.7 (C), 72.8 (CH_2), 70.4 (CH_2), 61.7 (CH_2), 58.6 (CH_2), 29.7 (CH_2), 29.27 (CH_2), 29.24 (CH_2), 26.3 (CH_3), 26.1 (CH_2), 26.0 (CH_2), 14.1 (CH_3);

IR (neat) 2170, 1737, 779 cm^{-1};

MS (EI) 408.2 (M^+);

HRMS calcd for $C_{23}H_{29}D_2O_4Cl$ (M^+) 408.2036, found 408.2062.



46

(*Z*)-ethyl 5-(*tert*-butoxycarbonylamino)-2-(1-chloroethylidene)pent-3-ynoate (46)

Prepared from (*E*)-ethyl 3-chloro-2-iodobut-2-enoate (**8**) (53.5 mg, 0.195 mmol) and *tert*-butyl prop-2-ynylcarbamate (**45**) (90.8 mg, 0.585 mmol), using a procedure similar to that described above for (*Z*)-7-chloro-7-cyclohexyl-6-(ethoxycarbonyl)hept-6-en-4-ynyl benzoate (**27**), that provided the title compound (**46**) (40.7 mg, 0.135 mmol, 69%) as a yellow oil after flash chromatography (8 % EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.77 (br s, 1H), 4.25 (q, J = 7.2 Hz, 2H), 4.09 (d, J = 4.4 Hz, 2H), 2.40 (s, 3H), 1.44 (s, 9H), 1.31 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.4 (C), 155.2 (C), 147.6 (C), 114.6 (C), 93.3 (C), 80.1 (C), 76.8 (C), 61.7 (CH_2), 31.2 (CH_2), 28.3 (CH_3), 26.1 (CH_3), 14.0 (CH_3);

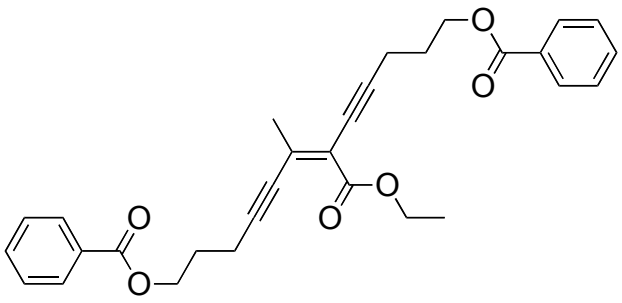
IR (neat) 2210, 1724, 781 cm^{-1};

MS (EI) 228.0 (M^+ -$OC(CH_3)_3$);

HRMS calcd for $C_{10}H_{11}NO_3Cl$ (M^+ -$OC(CH_3)_3$) 228.0422, found 228.0402.

Synthesis of Tetrasubstituted Olefins

General Procedure for the Sonogashira Cross-Coupling of (*Z*)-β-chloro-α-alkynyl-α,β-unsaturated esters:



15 *trans*

(*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (15 *trans*)

To an oven dried vial, equipped with a Teflon-coated stir bar, was added (*Z*)-7-chloro-6-(ethoxycarbonyl)oct-6-en-4-ynyl benzoate (**14**) (36.6 mg, 0.109 mmol) under a nitrogen atmosphere. Freshly distilled dichloromethane (2.0 mL) was added, followed by CuI (3.1 mg, 0.016 mmol) and K_3PO_4 (69.6 mg, 0.328 mmol), and the resulting solution was sparged for 10 minutes. To a second oven dried vial, equipped with a Teflon-coated stir bar, were added pent-4-ynyl benzoate (**13**) (61.7 mg, 0.328 mmol) followed by freshly distilled dichloromethane (1.0 mL). The resulting solution was sparged for 10 minutes before being transferred under nitrogen to the first vial via canula. $Pd(OAc)_2$ (7.4 mg, 0.011 mmol) and DAVE-PHOS (8.6 mg, 0.022 mmol) were then added to the first vial and the solution was further sparged with nitrogen for 10 minutes, before being stirred for 72 hours at room temperature. The solution was then diluted with Et_2O and washed with water.

The organic phase was dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product (**15 *trans***) (44.9 mg, 0.092 mmol, 84 %) was obtained as a yellow oil by flash chromatography (10 % EtOAc in hexanes).

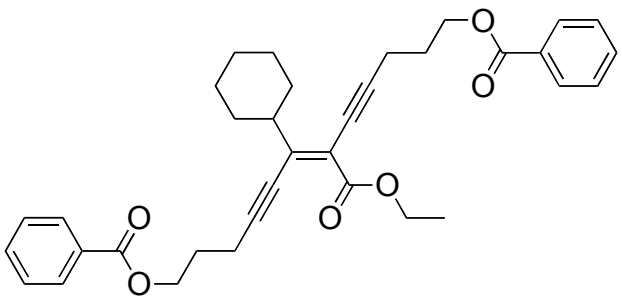
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.02 (m, 4H), 7.57 – 7.52 (m, 2H), 7.45 – 7.41 (m, 4H), 4.47 – 4.43 (m, 4H), 4.23 (q, J = 7.2 Hz, 2H), 2.67 – 2.62 (m, 4H), 2.16 (s, 3H), 2.09 – 2.02 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.5 (C), 164.3 (C), 136.6 (C), 132.93 (CH), 132.90 (CH), 130.20 (C), 130.18 (C), 129.55 (CH), 129.53 (CH), 128.33 (CH), 128.31 (CH), 120.06 (C), 104.2 (C), 100.01 (C), 99.96 (C), 81.6 (C), 63.6 (CH_2), 63.5 (CH_2), 61.1 (CH_2), 27.9 (CH_2), 27.7 (CH_2), 24.4 (CH_3), 17.2 (CH_2), 16.8 (CH_2), 14.2 (CH_3);

IR (neat) 2225, 1719 cm^{-1};

MS (EI) 486.2 (M^+);

HRMS calcd for $C_{30}H_{30}O_6$ (M^+) 486.2042, found 486.2037.



21 *trans*

(*Z*)-6-cyclohexyl-7-(ethoxycarbonyl)dodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (21 *trans*)

Prepared from (*Z*)-7-chloro-7-cyclohexyl-6-(ethoxycarbonyl)hept-6-en-4-ynyl benzoate (**27**) (70.7 mg, 0.175 mmol) and pent-4-ynyl benzoate (**13**) (98.8 mg, 0.525 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**21 *trans***) (73.3 mg, 0.132 mmol, 76 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

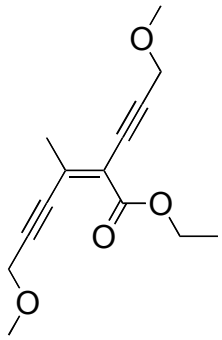
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.03 (m, 4H), 7.56 – 7.52 (m, 2H), 7.44 – 7.40 (m, 4H), 4.48 – 4.44 (m, 4H), 4.22 (q, J = 6.8 Hz, 2H), 2.94 – 2.87 (m, 1H), 2.70 – 2.62 (m, 4H), 2.10 – 2.02 (m, 4H), 1.77 – 1.74 (m, 2H), 1.67 – 1.64 (m, 3H), 1.49 – 1.39 (m, 2H), 1.34 – 1.13 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.33 (C), 166.31 (C), 164.7 (C), 146.1 (C), 132.84 (CH), 132.82 (CH), 130.1 (C), 129.46 (CH), 129.45 (CH), 128.25 (CH), 128.24 (CH), 118.69 (C), 105.3 (C), 99.3 (C), 78.8 (C), 76.7 (C), 63.5 (CH_2), 63.4 (CH_2), 61.0 (CH_2), 44.3 (CH), 30.7 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 26.0 (CH_2), 25.6 (CH_2), 17.1 (CH_2), 16.8 (CH_2), 14.1 (CH_3);

IR (neat) 2225, 1719 cm^{-1};

MS (EI) 554.3 (M^+);

HRMS calcd for $C_{35}H_{38}O_6$ (M^+) 554.2668, found 554.2635.



55 *trans*

(*Z*)-ethyl 6-methoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (55 *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (72.2 mg, 0.333 mmol) and methyl propargyl ether (**53**) (70.0 mg, 0.999 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**55 *trans***) (67.6 mg, 0.270 mmol, 81 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

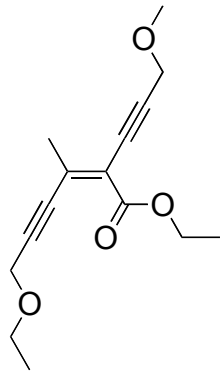
^{1}H NMR (400 MHz, $CDCl_3$) δ 4.36 (s, 2H), 4.34 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 4.431 (s, 3H), 4.427 (s, 3H), 2.24 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (C), 137.1 (C), 120.2 (C), 100.9 (C), 96.6 (C), 86.2 (C), 81.7 (C), 61.4 (CH_2), 60.6 (CH_2), 60.5 (CH_2), 57.8 (CH_3), 57.7 (CH_3), 24.3 (CH_3), 14.2 (CH_3);

IR (neat) 2202, 1726 cm^{-1};

MS (EI) 205.1 (M^+ -OCH_2CH_3);

HRMS calcd for $C_{12}H_{13}O_3$ (M^+ -OCH_2CH_3) 205.0859, found 205.0836.



59a *trans*

(*Z*)-ethyl 6-ethoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59a *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (62.2 mg, 0.287 mmol) and ethyl propargyl ether (**58a**) (72.4 mg, 0.861 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**59a *trans***) (57.6 mg, 0.218 mmol, 76 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

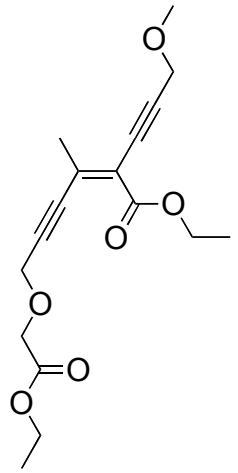
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (s, 2H), 4.32 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.60 (q, J = 7.2 Hz, 2H), 3.40 (s, 3H), 2.22 (s, 3H), 1.30 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (C), 137.0 (C), 120.1 (C), 101.3 (C), 96.5 (C), 85.7 (C), 81.6 (C), 65.5 (CH_2), 61.2 (CH_2), 60.4 (CH_2), 58.7 (CH_2), 57.4 (CH_3), 24.1 (CH_3), 14.9 (CH_3), 14.1 (CH_3);

IR (neat) 2199, 1728 cm^{-1};

MS (EI) 264.1 (M^+);

HRMS calcd for $C_{15}H_{20}O_4$ (M^+) 264.1362, found 264.1363.



59b *trans*

(*Z*)-ethyl 6-(2-ethoxy-2-oxoethoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59b *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (61.8 mg, 0.285 mmol) and ethyl 2-(prop-2-ynyloxy)acetate (**58b**) (121.6 mg, 0.855 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**59b *trans***) (75.4 mg, 0.234 mmol, 82 %) as a yellow oil after flash chromatography (20 % EtOAc in hexanes).

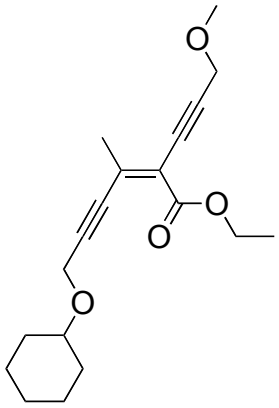
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.56 (s, 2H), 4.33 (s, 2H), 4.27 – 4.18 (m, 6H), 3.41 (s, 3H), 2.22 (s, 3H), 1.32 – 1.25 (m, 6H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 (C), 163.5 (C), 136.7 (C), 120.5 (C), 99.5 (C), 96.8 (C), 87.0 (C), 81.5 (C), 66.2 (CH_2), 61.3 (CH_2), 60.9 (CH_2), 60.4 (CH_2), 59.1 (CH_2), 57.6 (CH_3), 24.0 (CH_3), 14.14 (CH_3), 14.09 (CH_3);

IR (neat) 2202, 1751, 1728 cm^{-1};

MS (EI) 322.1 (M^+);

HRMS calcd for $C_{17}H_{22}O_6$ (M^+) 322.1416, found 322.1436.



59e *trans*

(*Z*)-ethyl 6-(cyclohexyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59e *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (73.0 mg, 0.337 mmol) and cyclohexyl propargyl ether (**58e**) (139.7 mg, 1.011 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**59e *trans***) (83.7 mg, 0.263 mmol, 78 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

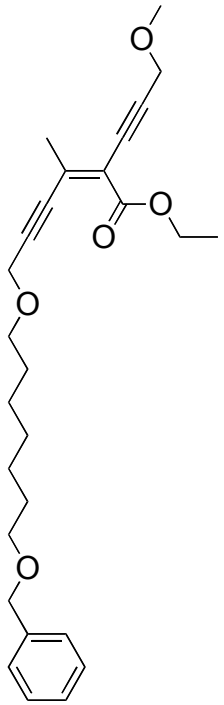
^{1}H NMR (300 MHz, $CDCl_3$) δ 4.43 (s, 2H), 4.33 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.58 – 3.47 (m, 1H), 3.42 (s, 3H), 2.23 (s, 3H), 1.99 – 1.88 (m, 2H), 1.79 – 1.68 (m, 2H), 1.59 – 1.49 (m, 1H), 1.37 – 1.17 (m, 8H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C), 137.3 (C), 120.0 (C), 102.1 (C), 96.4 (C), 85.2 (C), 81.7 (C), 76.7 (CH), 61.3 (CH_2), 60.4 (CH_2), 57.6 (CH_3), 55.9 (CH_2), 31.9 (CH_2), 25.7 (CH_2), 24.2 (CH_3), 24.0 (CH_2), 14.1 (CH_3);

IR (neat) 2199, 1728 cm^{-1};

MS (EI) 318.2 (M^+);

HRMS calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1847.



59d *trans*

(*Z*)-ethyl 6-(7-(benzyloxy)heptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59d *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (75.5 mg, 0.348 mmol) and ((7-(prop-2-ynyloxy)heptyloxy)methyl)benzene (**58d**) (271.8 mg, 1.044 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**59d *trans***) (130.5 mg, 0.296 mmol, 85 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

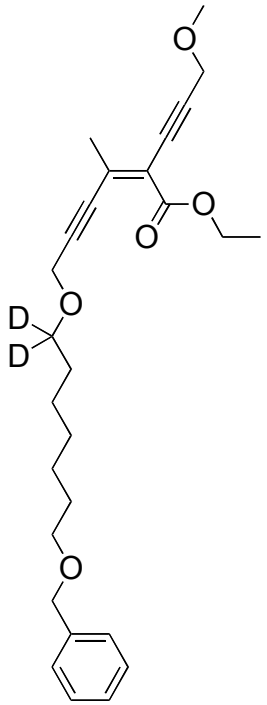
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 4.5 (s, 2H), 4.38 (s, 2H), 4.34 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.54 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.43 (s, 3H), 2.24 (s, 3H), 1.65 – 1.55 (m, 4H), 1.42 – 1.28 (m, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (C), 138.7 (C), 137.2 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 120.1 (C), 101.5 (C), 96.5 (C), 85.8 (C), 81.7 (C), 72.8 (CH_2), 70.4 (CH_2), 70.3 (CH_2), 61.3 (CH_2), 60.5 (CH_2), 59.0 (CH_2), 57.6 (CH_3), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.13 (CH_2), 26.06 (CH_2), 24.2 (CH_3), 14.1 (CH_3);

IR (neat) 2200, 1727 cm^{-1};

MS (EI) 440.3 (M^+);

HRMS calcd for $C_{27}H_{36}O_5$ (M^+) 440.2563, found 440.2582.



76 *trans*

(*Z*)-ethyl 6-(7-(benzyloxy)-1,1-dideuteroheptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (76 *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (81.5 mg, 0.376 mmol) and ((7,7-dideutero-7-(prop-2-ynyloxy)heptyloxy)methyl)benzene (**73**) (296.0 mg, 1.128 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**76 *trans***) (136.3 mg, 0.308 mmol, 82 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

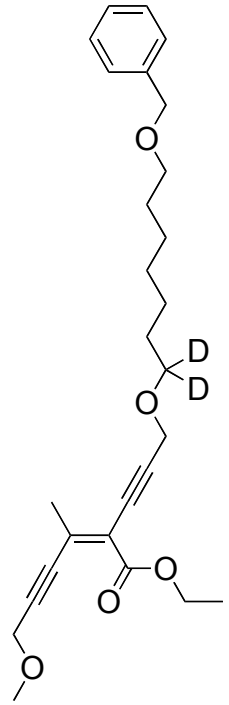
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 4.50 (s, 2H), 4.38 (s, 2H), 4.34 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.43 (s, 3H), 2.24 (s, 3H), 1.66 – 1.55 (m, 4H), 1.42 – 1.28 (m, 9H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.7 (C), 138.7 (C), 137.2 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 120.1 (C), 101.5 (C), 96.5 (C), 85.7 (C), 81.7 (C), 72.8 (CH_2), 70.4 (CH_2), 61.3 (CH_2), 60.5 (CH_2), 58.92 (CD_2), 58.89 (CH_2), 57.6 (CH_3), 29.7 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 24.2 (CH_3), 14.1 (CH_3);

IR (neat) 2198, 1727 cm^{-1};

MS (EI) 442.3 (M^+);

HRMS calcd for $C_{27}H_{34}D_2O_5$ (M^+) 442.2688, found 442.2682.



75 *trans*

(*Z*)-ethyl 2-(3-(7-(benzyloxy)-1,1-dideuteroheptyloxy)prop-1-ynyl)-6-methoxy-3-methylhex-2-en-4-ynoate (75 *trans*)

Prepared from (*Z*)-ethyl 5-(7-(benzyloxy)-1,1-dideuteroheptyloxy)-2-(1-chloroethylidene)pent-3-ynoate (**74**) (160.5 mg, 0.392 mmol) and methyl propargyl ether (**53**) (82.4 mg, 1.176 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**75 *trans***) (142.4 mg, 0.322 mmol, 82 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

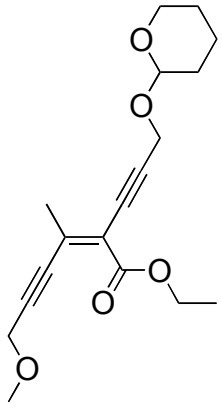
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36 – 7.25 (m, 5H), 4.50 (s, 2H), 4.37 (s, 2H), 4.35 (s, 2H), 4.25 (q, J = 7.2 Hz, 2H), 3.47 – 3.42 (m, 5H), 2.23 (s, 3H), 1.64 – 1.54 (m, 4H), 1.42 – 1.27 (m, 9H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7 (C), 138.7 (C), 136.9 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 120.3 (C), 100.7 (C), 97.2 (C), 86.2 (C), 81.2 (C), 72.8 (CH_2), 70.4 (CH_2), 61.3 (CH_2), 60.6 (CH_2), 58.7 (CH_2), 57.7 (CH_3), 29.7 (CH_2), 29.27 (CH_2), 29.24 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 24.2 (CH_3), 14.1 (CH_3);

IR (neat) 2170, 1728 cm^{-1};

MS (EI) 442.3 (M^+);

HRMS calcd for $C_{27}H_{34}D_2O_5$ (M^+) 442.2688, found 442.2667.



61 *trans*

(*Z*)-ethyl 6-methoxy-3-methyl-2-(3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-ynyl) hex-2-en-4-ynoate (61 *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-(tetrahydro-2*H*-pyran-2-yloxy)pent-3-ynoate (**60**) (80.7 mg, 0.281 mmol) and methyl propargyl ether (**53**) (59.1 mg, 0.843 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**61 *trans***) (61.3 mg, 0.191 mmol, 68 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

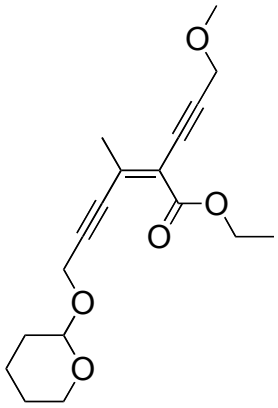
^{1}H NMR (300 MHz, C_6D_6) δ 4.93 (t, J = 3.3 Hz, 1H), 4.39 (d, J = 2.4 Hz, 2H), 4.06 – 3.99 (m, 4H), 3.73 – 3.65 (m, 1H), 3.39 – 3.31 (m, 1H), 3.25 (s, 3H), 2.10 (s, 3H), 1.75 – 1.52 (m, 3H), 1.38 – 1.16 (m, 3H), 0.98 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, C_6D_6) δ 163.6 (C), 137.0 (C), 121.3 (C), 101.7 (C), 97.8 (C), 96.7 (CH), 86.7 (C), 81.7 (C), 61.5 (CH_2), 61.2 (CH_2), 60.5 (CH_2), 57.4 (CH_3), 54.8 (CH_2), 30.6 (CH_2), 25.8 (CH_2), 24.0 (CH_3), 19.2 (CH_2), 14.2 (CH_3);

IR (neat) 2201, 1726 cm^{-1};

MS (EI) 320.2 (M^+);

HRMS calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1606.



59f *trans*

(*Z*)-ethyl 2-(3-methoxyprop-1-ynyl)-3-methyl-6-(tetrahydro-2*H*-pyran-2-yloxy) hex-2-en-4-ynoate (59f *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (75.2 mg, 0.347 mmol) and 2-(prop-2-ynyloxy)tetrahydro-*2H*-pyran (**58f**) (145.9 mg, 1.041 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**59f *trans***) (79.0 mg, 0.246 mmol, 71 %) as a yellow oil after flash chromatography (10 % EtOAc in hexanes).

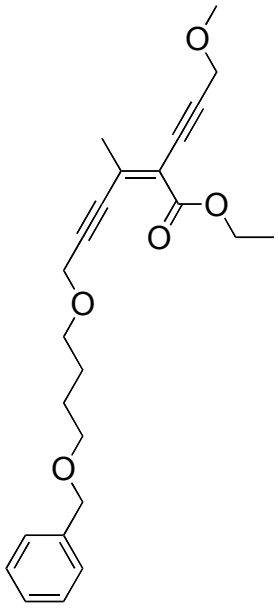
^{1}H NMR (300 MHz, $(CD_3)_2CO$) δ 4.87 (t, J = 3.6 Hz, 1H), 4.48 (s, 2H), 4.33 (s, 2H), 4.21 (q, J = 7.2 Hz, 2H), 3.85 – 3.77 (m, 1H), 3.53 – 3.45 (m, 1H), 3.37 (s, 3H), 2.20 (s, 3H), 1.82 – 1.48 (m, 6H), 1.28 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $(CD_3)_2CO$) δ 164.0 (C), 136.6 (C), 121.4 (C), 101.5 (C), 98.2 (C), 97.2 (CH), 86.3 (C), 81.4 (C), 62.3 (CH_2), 61.8 (CH_2), 60.7 (CH_2), 57.6 (CH_3), 54.9 (CH_2), 31.0 (CH_2), 26.2 (CH_2), 23.9 (CH_3), 19.8 (CH_2), 14.4 (CH_3);

IR (neat) 2201, 1726 cm^{-1};

MS (EI) 320.2 (M^+);

HRMS calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1603.



59c *trans*

(*Z*)-ethyl 6-(4-(benzyloxy)butoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59c *trans*)

Prepared from (*Z*)-ethyl 2-(1-chloroethylidene)-5-methoxypent-3-ynoate (**54**) (83.9 mg, 0.387 mmol) and ((4-(prop-2-ynyloxy)butoxy)methyl)benzene (**58c**) (253.4 mg, 1.161 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**59c *trans***) (131.2 mg, 0.329 mmol, 85 %) as a yellow oil after flash chromatography (15 % EtOAc in hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 4.50 (s, 2H), 4.38 (s, 2H), 4.34 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.62 – 3.53 (m, 2H), 3.52 – 5.47 (m, 2H), 3.42 (s, 3H), 2.23 (s, 3H), 1.74 – 1.65 (m, 4H), 1.31 (t, J = 7.2 Hz, 3H);

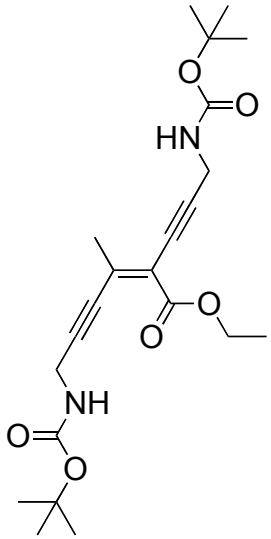
^{13}C NMR (75 MHz, $CDCl_3$) δ 163.6 (C), 138.6 (C), 137.1 (C), 128.3 (CH), 127.5 (CH), 127.4 (CH), 120.1 (C), 101.4 (C), 96.5 (C), 85.8 (C), 81.6 (C), 72.8 (CH_2), 70.0

(CH_2), 69.0 (CH_2), 61.3 (CH_2), 60.4 (CH_2), 58.9 (CH_2), 57.6 (CH_3), 26.4 (CH_2), 26.3 (CH_2), 24.2 (CH_3), 14.1 (CH_3);

IR (neat) 2199, 1728 cm^{-1};

MS (EI) 398.2 (M^+);

HRMS calcd for $C_{24}H_{30}O_5$ (M^+) 398.2093, found 398.2070.



47 trans

(*Z*)-ethyl 6-(*tert*-butoxycarbonylamino)-2-(3-(*tert*-butoxycarbonylamino)prop-1-ynyl)-3-methylhex-2-en-4-ynoate (47 *trans*)

Prepared from (*Z*)-ethyl 5-(*tert*-butoxycarbonylamino)-2-(1-chloroethylidene)pent-3-ynoate (**46**) (59.1 mg, 0.196 mmol) and *tert*-butyl prop-2-ynylcarbamate (**45**) (91.3 mg, 0.588 mmol), using a procedure similar to that described above for (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***), that provided the title compound (**47 *trans***) (60.9 mg, 0.270 mmol, 74 %) as a yellow oil after flash chromatography (20 % EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 4.80 (br s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 4.18 – 4.13 (m, 4H), 2.16 (s, 3H), 1.44 (s, 18H), 1.31 (t, J = 7.2 Hz, 3H);

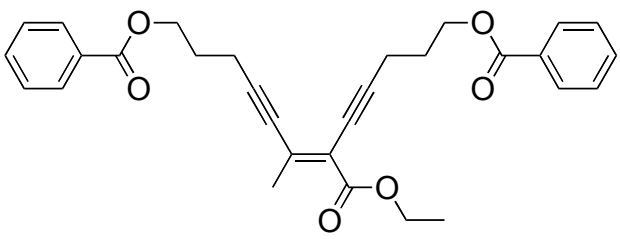
IR (neat) 2208, 1725;

MS (EI) 420.2 (M^+);

HRMS calcd for $C_{22}H_{32}N_2O_6$ (M^+) 420.2260, found 420.2254.

Photoisomerization of Tetrasubstituted Olefins

General Procedure for the Photoisomerization of Tetrasubstituted Olefins:



15 *cis*

(*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (15 *cis*)

To an oven dried round bottom flask, equipped with a Teflon-coated stir bar, was added (*Z*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *trans***) (49.8 mg, 0.102 mmol) under a nitrogen atmosphere. Freshly distilled dichloromethane (5.1 mL) was added, and the solution was sparged for five minutes, before being stirred at room temperature for 20 hours while simultaneously being irradiated by 300 nm light. The dichloromethane was removed *in vacuo*, and the *E* isomer (**15 *cis***) (21.4 mg, 0.044 mmol, 43 %) and *Z* isomer (**15 *trans***) (28.4 mg, 0.058 mmol, 57 %) were separated by flash chromatography (8 % EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.01 (m, 4H), 7.56 – 7.51 (m, 2H), 7.43 – 7.39 (m, 4H), 4.48 – 4.43 (m, 4H), 4.22 (q, J = 7.2 Hz, 2H), 2.66 – 2.60 (m, 2H), 2.24 (s, 3H), 2.07 – 2.00 (m, 4H), 1.30 (t, J = 7.2 Hz, 3H);

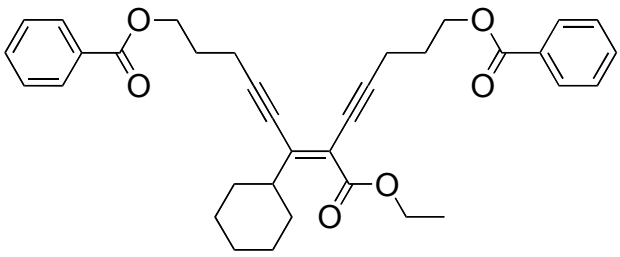
^{13}C NMR (100 MHz, $CDCl_3$) δ 166.40 (C), 166.38 (C), 165.1 (C), 138.7 (C), 132.91 (CH), 132.85 (CH), 130.2 (C), 130.1 (C), 129.49 (CH), 129.48 (CH), 128.30 (CH),

128.28 (CH), 119.1 (C), 100.7 (C), 94.4 (C), 83.6 (C), 78.6 (C), 63.6 (CH_2), 63.5 (CH_2), 61.1 (CH_2), 27.8 (CH_2), 27.7 (CH_2), 21.4 (CH_3), 16.9 (CH_2), 16.6 (CH_2), 14.1 (CH_3);

IR (neat) 2212, 1720 cm^{-1};

MS (EI) 486.2 (M^+);

HRMS calcd for $C_{30}H_{30}O_6$ (M^+) 486.2042, found 486.2028.



21 *cis*

(*E*)-6-cyclohexyl-7-(ethoxycarbonyl)dodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (21 *cis*)

Prepared from (*Z*)-6-cyclohexyl-7-(ethoxycarbonyl)dodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**21 *trans***) (36.5 mg, 0.066 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided a mixture of *E* isomer (**21 *cis***) (14.6 mg, 0.026 mmol, 40 %) and *Z* isomer (**21 *trans***) (21.9 mg, 0.040 mmol, 60 %) that were separated by flash chromatography (10 % EtOAc in hexanes).

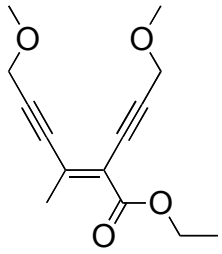
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.01 (m, 4H), 7.56 – 7.52 (m, 2H), 7.44 – 7.39 (m, 4H), 4.48 – 4.44 (m, 4H), 4.23 (q, J = 6.8 Hz, 2H), 3.15 – 3.08 (m, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.62 (t, J = 6.8 Hz, 2H), 2.09 – 1.99 (m, 4H), 1.75 – 1.72 (m, 2H), 1.67 – 1.64 (m, 3H), 1.47 – 1.38 (m, 2H), 1.33 – 1.12 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.44 (C), 166.41 (C), 165.2 (C), 147.4 (C), 132.93 (CH), 132.88 (CH), 130.2 (C), 130.1 (C), 129.53 (CH), 129.51 (CH), 128.34 (CH), 128.32 (CH), 118.4 (C), 101.9 (C), 94.2 (C), 80.3 (C), 78.9 (C), 63.6 (CH_2), 63.5 (CH_2), 61.1 (CH_2), 40.7 (CH), 31.7 (CH_2), 27.9 (CH_2), 25.9 (CH_2), 25.7 (CH_2), 16.9 (CH_2), 16.7 (CH_2), 14.1 (CH_3);

IR (neat) 2210, 1719 cm^{-1};

MS (EI) 554.3 (M^+);

HRMS calcd for $C_{35}H_{38}O_6$ (M^+) 554.2668, found 554.2660.



55 *cis*

(*E*)-ethyl 6-methoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (55 *cis*)

Prepared from (*Z*)-ethyl 6-methoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**55 *trans***) (60.0 mg, 0.240 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided an inseparable mixture of *E* isomer (**55 *cis***) (24.0 mg, 0.096 mmol, 40 %) and *Z* isomer (**55 *trans***) (36.0 mg, 0.144 mmol, 60 %).

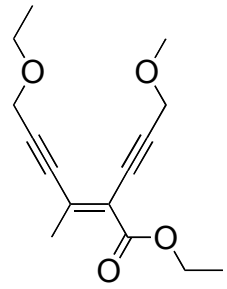
^{1}H NMR (*E* isomer, 400 MHz, $CDCl_3$) δ 4.33 (s, 2H), 4.31 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.43 (s, 3H), 3.42 (s, 3H), 2.31 (s, 3H), 1.32 (t, J = 7.2 Hz, 3H);

^{13}C NMR (*E* isomer, 75 MHz, DMSO) δ 163.7 (C), 138.0 (C), 119.0 (C), 97.9 (C), 91.9 (C), 87.2 (C), 82.7 (C), 61.2 (CH_2), 59.48 (CH_2), 59.45 (CH_2), 56.9 (CH_3), 56.8 (CH_3), 20.9 (CH_3), 13.96 (CH_3);

IR (neat) 2202, 1702 cm^{-1};

MS (EI) 250.1 (M^+);

HRMS calcd for $C_{14}H_{18}O_4$ (M^+) 250.1205, found 250.1209.



59a *cis*

(*E*)-ethyl 6-ethoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59a *cis*)

Prepared from (*Z*)-ethyl 6-ethoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59a *trans***) (42.7 mg, 0.162 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided an inseparable mixture of *E* isomer (**59a *cis***) (17.5 mg, 0.066 mmol, 41 %) and *Z* isomer (**59a *trans***) (25.2 mg, 0.096 mmol, 59 %).

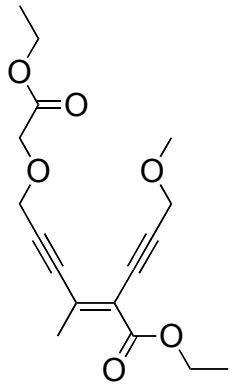
^{1}H NMR (*E* isomer, 300 MHz, $CDCl_3$) δ 4.36 (s, 2H), 4.29 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.61 (q, J = 7.2 Hz, 2H), 3.42 (s, 3H), 2.30 (s, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.22 (t, J = 7.2 Hz, 3H);

^{13}C NMR (*E* isomer, 75 MHz, $CDCl_3$) δ 164.4 (C), 139.3 (C), 119.3 (C), 97.4 (C), 91.0 (C), 87.4 (C), 83.3 (C), 65.5 (CH_2), 61.3 (CH_2), 60.3 (CH_2), 58.5 (CH_2), 57.3 (CH_3), 21.2 (CH_3), 15.0 (CH_3), 14.1 (CH_3);

IR (neat) 2202, 1726 cm^{-1};

MS (EI) 264.1 (M^+);

HRMS calcd for $C_{15}H_{20}O_4$ (M^+) 264.1362, found 264.1375.



59b *cis*

(*E*)-ethyl 6-(2-ethoxy-2-oxoethoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59b *cis*)

Prepared from (*Z*)-ethyl 6-(2-ethoxy-2-oxoethoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59b *trans***) (60.7 mg, 0.188 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided an inseparable mixture of *E* isomer (**59b *cis***) (24.3 mg, 0.075 mmol, 40 %) and *Z* isomer (**59b *trans***) (36.4 mg, 0.113 mmol, 60 %).

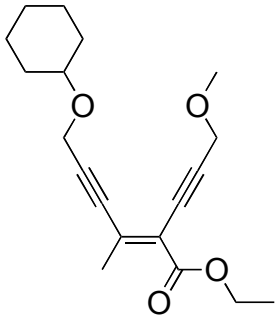
^{1}H NMR (*E* isomer, 400 MHz, $CDCl_3$) δ 4.54 (s, 2H), 4.30 (s, 2H), 4.26 – 4.19 (m, 6H), 3.41 (s, 3H), 2.29 (s, 3H), 1.33 – 1.26 (m, 6H);

^{13}C NMR (*E* isomer, 75 MHz, $CDCl_3$) δ 169.8 (C), 164.3 (C), 138.7 (C), 119.7 (C), 95.4 (C), 91.4 (C), 88.7 (C), 83.2 (C), 66.1 (CH_2), 61.4 (CH_2), 60.9 (CH_2), 60.3 (CH_2), 58.9 (CH_2), 57.4 (CH_3), 21.0 (CH_3), 14.2 (CH_3), 14.1 (CH_3);

IR (neat) 2205, 1751, 1725 cm^{-1};

MS (EI) 322.1 (M^+);

HRMS calcd for $C_{17}H_{22}O_6$ (M^+) 322.1416, found 322.1415.



59e *cis*

(*E*)-ethyl 6-(cyclohexyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59e *cis*)

Prepared from (*Z*)-ethyl 6-(cyclohexyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59e *trans***) (75.5 mg, 0.237 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided an inseparable mixture of *E* isomer (**59e *cis***) (28.7 mg, 0.090 mmol, 38 %) and *Z* isomer (**59e *trans***) (46.8 mg, 0.147 mmol, 62 %).

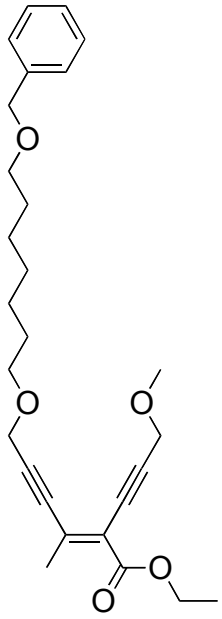
^{1}H NMR (*E* isomer, 300 MHz, $CDCl_3$) δ 4.40 (s, 2H), 4.31 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.56 – 3.46 (m, 1H), 3.43 (s, 3H), 2.30 (s, 3H), 1.98 – 1.85 (m, 2H), 1.80 – 1.68 (m, 2H), 1.59 – 1.47 (m, 1H), 1.39 – 1.18 (m, 8H);

^{13}C NMR (*E* isomer, 75 MHz, $CDCl_3$) δ 164.5 (C), 139.4 (C), 119.2 (C), 98.3 (C), 91.0 (C), 86.9 (C), 83.3 (C), 76.6 (CH), 61.3 (CH_2), 60.4 (CH_2), 57.3 (CH_3), 55.7 (CH_2), 31.9 (CH_2), 25.7 (CH_2), 24.0 (CH_2), 21.3 (CH_3), 14.1 (CH_3);

IR (neat) 2202, 1723 cm^{-1};

MS (EI) 318.2 (M^+);

HRMS calcd for $C_{19}H_{26}O_4$ (M^+) 318.1831, found 318.1825.



59d *cis*

(*E*)-ethyl 6-(7-(benzyloxy)heptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59d *cis*)

Prepared from (*Z*)-ethyl 6-(7-(benzyloxy)heptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59d *trans***) (80.5 mg, 0.183 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided a mixture of *E* isomer (**59d *cis***) (31.4 mg, 0.071 mmol, 39 %) and *Z* isomer (**59d *trans***) (49.1 mg, 0.112 mmol, 61 %) that were separated by flash chromatography (15 % EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 4.50 (s, 2H), 4.36 (s, 2H), 4.30 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.53 (t, J = 6.8 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.42 (s, 3H), 2.77 (s, 3H), 1.65 – 1.56 (m, 4H), 1.42 – 1.30 (m, 9H);

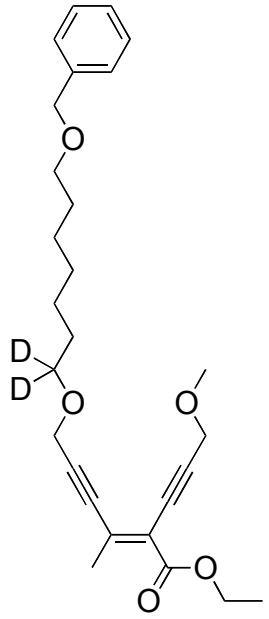
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C), 139.3 (C), 138.7 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 119.3 (C), 97.5 (C), 91.1 (C), 87.4 (C), 83.3 (C), 72.8 (CH_2), 70.4

(CH_2), 70.3 (CH_2), 61.3 (CH_2), 60.4 (CH_2), 58.8 (CH_2), 57.4 (CH_3), 29.7 (CH_2), 29.5 (CH_2), 29.3 (CH_2), 26.17 (CH_2), 26.12 (CH_2), 21.3 (CH_3), 14.2 (CH_3);

IR (neat) 2209, 1719 cm^{-1};

MS (EI) 349.2 (M^+ -OC_7H_7);

HRMS calcd for $C_{20}H_{29}O_4$ (M^+ -OC_7H_7) 349.2015, found 349.2014.



76 *cis*

(*E*)-ethyl 6-(7-(benzyloxy)-1,1-dideuteroheptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (76 *cis*)

Prepared from (*Z*)-ethyl 6-(7-(benzyloxy)-1,1-dideuteroheptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**76 *trans***) (44.4 mg, 0.100 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided a mixture of *E* isomer (**76 *cis***) (16.4 mg, 0.037 mmol, 37 %) and *Z* isomer (**76 *trans***) (28.0 mg, 0.063 mmol, 63 %) that were separated by flash chromatography (10 % EtOAc in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 4.50 (s, 2H), 4.36 (s, 2H), 4.30 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 3.42 (s, 3H), 2.31 (s, 3H), 1.64 – 1.54 (m, 4H), 1.42 – 1.28 (m, 9H);

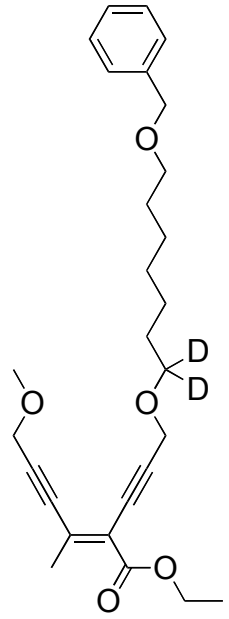
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.5 (C), 139.3 (C), 138.7 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 119.3 (C), 97.6 (C), 91.0 (C), 87.4 (C), 83.3 (C), 72.9 (CH_2), 70.4

(CH_2), 61.3 (CH_2), 60.4 (CH_2), 58.72 (CD_2), 58.69 (CH_2), 57.4 (CH_3), 29.7 (CH_2), 29.29 (CH_2), 29.27 (CH_2), 26.1 (CH_2), 26.0 (CH_2), 21.3 (CH_3), 14.1 (CH_3);

IR (neat) 2209, 1720 cm^{-1};

MS (EI) 442.3 (M^+);

HRMS calcd for $C_{27}H_{34}D_2O_5$ (M^+) 442.2688, found 442.2686.



75 *cis*

(*E*)-ethyl 2-(3-(7-(benzyloxy)-1,1-dideuteroheptyloxy)prop-1-ynyl)-6-methoxy-3-methylhex-2-en-4-ynoate (75 *cis*)

Prepared from (*Z*)-ethyl 2-(3-(7-(benzyloxy)-1,1-dideuteroheptyloxy)prop-1-ynyl)-6-methoxy-3-methylhex-2-en-4-ynoate (**75 *trans***) (52.8 mg, 0.119 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided a mixture of *E* isomer (**75 *cis***) (20.1 mg, 0.045 mmol, 38 %) and *Z* isomer (**75 *trans***) (32.7 mg, 0.074 mmol, 62 %) that were separated by flash chromatography (10 % EtOAc in hexanes).

^{1}H NMR (*E* isomer, 400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 4.50 (s, 2H), 4.33 (s, 2H), 4.32 (s, 2H), 4.23 (q, J = 7.2 Hz, 2H), 3.47 – 3.42 (m, 5H), 2.31 (s, 3H), 1.66 – 1.54 (m, 4H), 1.43 – 1.27 (m, 9H);

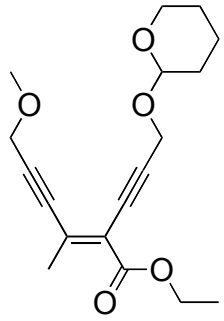
^{13}C NMR (*E* isomer, 100 MHz, $CDCl_3$) δ 164.5 (C), 139.0 (C), 136.9 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 119.5 (C), 96.8 (C), 91.7 (C), 87.9 (C), 82.7 (C), 72.8

(CH_2), 70.4 (CH_2), 61.3 (CH_2), 60.3 (CH_2), 58.7 (CH_2), 57.6 (CH_3), 29.7 (CH_2), 29.31 (CH_2), 29.29 (CH_2), 26.13 (CH_2), 26.06 (CH_2), 21.2 (CH_3), 14.1 (CH_3);

IR (neat) 2173, 1720 cm^{-1};

MS (EI) 442.3 (M^+);

HRMS calcd for $C_{27}H_{34}D_2O_5$ (M^+) 442.2688, found 442.2648.



61 *cis*

(*E*)-ethyl 6-methoxy-3-methyl-2-(3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-ynyl) hex-2-en-4-ynoate (61 *cis*)

Prepared from (*Z*)-ethyl 6-methoxy-3-methyl-2-(3-(tetrahydro-2*H*-pyran-2-yloxy)prop-1-ynyl)hex-2-en-4-ynoate (**61 *trans***) (74.1 mg, 0.231 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided a mixture of *E* isomer (**61 *cis***) (30.4 mg, 0.095 mmol, 41 %) and *Z* isomer (**61 *trans***) (43.7 mg, 0.136 mmol, 59 %) that were separated by flash chromatography (10 % EtOAc in hexanes).

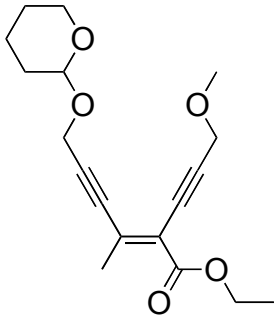
^{1}H NMR (300 MHz, C_6D_6) δ 5.06 (t, J = 3.3 Hz, 1H), 4.44 (dd, J = 15.9 Hz, 21.3 Hz, 2H), 4.05 (s, 2H), 3.94 (q, J = 7.2 Hz, 2H), 3.70 – 3.62 (m, 1H), 3.38 – 3.30 (m, 1H), 3.22 (s, 3H), 2.29 (s, 3H), 1.76 – 1.53 (m, 3H), 1.39 – 1.13 (m, 3H), 0.93 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, C_6D_6) δ 164.5 (C), 139.5 (C), 120.4 (C), 97.8 (C), 96.2 (CH), 92.4 (CH), 88.4 (C), 83.4 (C), 61.3 (CH_2), 61.2 (CH_2), 60.3 (CH_2), 57.3 (CH_3), 54.6 (CH_2), 30.6 (CH_2), 25.8 (CH_2), 21.3 (CH_3), 19.1 (CH_2), 14.1 (CH_3);

IR (neat) 2209, 1720 cm^{-1};

MS (EI) 320.2 (M^+);

HRMS calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1634.



59f *cis*

(*E*)-ethyl 2-(3-methoxyprop-1-ynyl)-3-methyl-6-(tetrahydro-2*H*-pyran-2-yloxy) hex-2-en-4-ynoate (59f *cis*)

Prepared from (*Z*)-ethyl 2-(3-methoxyprop-1-ynyl)-3-methyl-6-(tetrahydro-2*H*-pyran-2-yloxy)hex-2-en-4-ynoate (**59f *trans***) (78.1 mg, 0.244 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided a mixture of *E* isomer (**59f *cis***) (31.2 mg, 0.098 mmol, 40 %) and *Z* isomer (**59f *trans***) (46.9 mg, 0.146 mmol, 60 %) that were separated by flash chromatography (10 % EtOAc in hexanes).

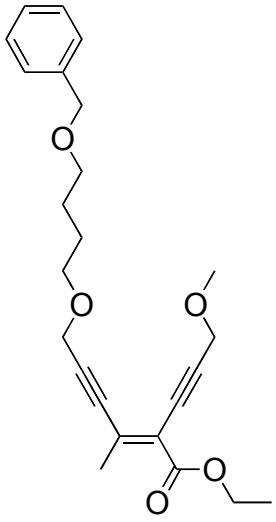
^{1}H NMR (300 MHz, acetone-d_6) δ 4.90 (t, J = 3.6 Hz, 1H), 4.43 (s, 2H), 4.35 (s, 2H), 4.22 (q, J = 7.2 Hz, 2H), 3.83 – 3.75 (m, 1H), 3.52 – 3.45 (m, 1H), 3.39 (s, 3H), 2.26 (s, 3H), 1.85 – 1.45 (m, 6H), 1.29 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, acetone-d_6) δ 164.8 (C), 138.9 (C), 120.6 (C), 98.2 (C), 96.8 (CH), 92.6 (C), 88.0 (C), 83.1 (C), 62.1 (CH_2), 61.9 (CH_2), 60.5 (CH_2), 57.6 (CH_3), 54.7 (CH_2), 31.0 (CH_2), 26.2 (CH_2), 21.2 (CH_3), 19.7 (CH_2), 14.4 (CH_3);

IR (neat) 2207, 1723 cm^{-1};

MS (EI) 320.2 (M^+);

HRMS calcd for $C_{18}H_{24}O_5$ (M^+) 320.1624, found 320.1640.



59c *cis*

(*E*)-ethyl 6-(4-(benzyloxy)butoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (59c *cis*)

Prepared from (*Z*)-ethyl 6-(4-(benzyloxy)butoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59c *trans***) (68.0 mg, 0.171 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided a mixture of *E* isomer (**59c *cis***) (25.2 mg, 0.063 mmol, 37 %) and *Z* isomer (**59c *trans***) (42.8 mg, 0.108 mmol, 63 %) that were separated by flash chromatography (10 % EtOAc in hexanes).

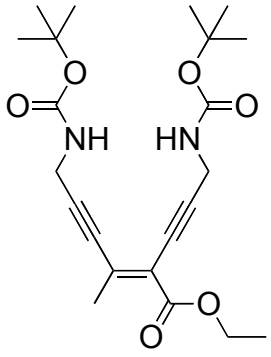
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 – 7.24 (m, 5H), 4.50 (s, 2H), 4.36 (s, 2H), 4.30 (s, 2H), 4.24 (q, J = 7.2 Hz, 2H), 3.60 – 3.53 (m, 2H), 3.52 – 3.47 (m, 2H), 3.42 (s, 3H), 2.30 (s, 3H), 1.73 – 1.65 (m, 4H), 1.32 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 164.5 (C), 139.3 (C), 138.6 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 119.3 (C), 97.4 (C), 91.1 (C), 87.5 (C), 83.3 (C), 72.8 (CH_2), 70.0 (CH_2), 69.9 (CH_2), 61.3 (CH_2), 60.4 (CH_2), 58.7 (CH_2), 57.4 (CH_3), 26.4 (CH_2), 26.3 (CH_2), 21.2 (CH_3), 14.1 (CH_3);

IR (neat) 2110, 1719 cm^{-1};

MS (EI) 398.2 (M^+);

HRMS calcd for $C_{24}H_{30}O_5$ (M^+) 398.2093, found 398.2102.



47 *cis*

(*E*)-ethyl 6-(*tert*-butoxycarbonylamino)-2-(3-(*tert*-butoxycarbonylamino)prop-1-ynyl)-3-methylhex-2-en-4-ynoate (47 *cis*)

Prepared from (*Z*)-ethyl 6-(*tert*-butoxycarbonylamino)-2-(3-(*tert*-butoxycarbonylamino)prop-1-ynyl)-3-methylhex-2-en-4-ynoate (**47 *trans***) (30.0 mg, 0.071 mmol), using a procedure similar to that described above for (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15 *cis***), that provided an inseparable mixture of *E* isomer (**47 *cis***) (11.1 mg, 0.026 mmol, 37 %) and *Z* isomer (**47 *trans***) (18.9 mg, 0.045 mmol, 63 %).

^{1}H NMR (*E* isomer, 400 MHz, $CDCl_3$) δ 4.80 (br s, 2H), 4.26 – 4.08 (m, 6H), 2.25 (s, 3H), 1.44 (s, 18H), 1.30 (t, J = 7.2 Hz, 3H);

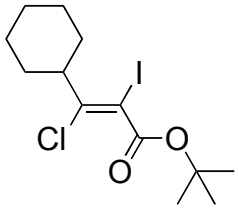
IR (neat) 2114, 1720 cm^{-1};

MS (EI) 420.2 (M^+);

HRMS calcd for $C_{22}H_{32}N_2O_6$ (M^+) 420.2260, found 420.2264.

Chloroiodination of Alkynes

General Procedure for the Halogenation of Alkynes Using Bu_4NI/DCE



34

(*E*)-*tert*-butyl 3-chloro-3-cyclohexyl-2-iodoacrylate (34)

A solution of *tert*-butyl 3-cyclohexylpropiolate (**33**) (810.6 mg, 3.892 mmol) and tetrabutylammonium iodide (4.312 g, 11.675 mmol) in dichloroethane (45 mL) was heated at reflux for 72 hours. The reaction mixture was cooled, diluted with Et_2O, and washed with saturated $NaHSO_3$, $NaHCO_3$, and brine. The organic phase was then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product (**34**) (1115.3 mg, 3.009 mmol, 77 %) was obtained as a yellow oil by flash chromatography (1 % Et_2O in hexanes).

^{1}H NMR (400 MHz, $CDCl_3$) δ 2.96 – 2.87 (m, 1H), 1.83 – 1.78 (m, 2H), 1.71 – 1.67 (m, 3H), 1.55 – 1.43 (m, 11H), 1.38 – 1.12 (m, 3H);

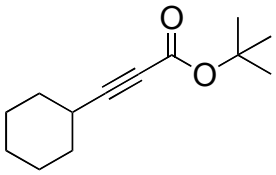
^{13}C NMR (100 MHz, $CDCl_3$) δ 164.2 (C), 140.9 (C), 83.3 (C), 80.5 (C), 48.1 (CH), 29.6 (CH_2), 27.8 (CH_3), 25.6 (CH_2), 25.5 (CH_2);

IR (neat) 1726, 1617, 669 cm^{-1};

MS (EI) 370.0 (M^+);

HRMS calcd for $C_{13}H_{20}O_2ClI$ (M^+) 370.0197, found 370.0194.

Synthesis of Alkynes



33

***tert*-butyl 3-cyclohexylpropiolate (33)**

To a solution of cyclohexylacetylene (**31**) (0.500 g, 4.622 mmol) in THF (45 mL) at -78 °C was added a solution of butyllithium (2.5 M, 2.04 mL, 5.084 mmol) dropwise over 30 minutes. After stirring for one hour, a solution of Boc_2O (**32**) (2.017 g, 9.244 mmol) in THF (5 mL) was added slowly over 10 minutes. After 12 hours at room temperature, the reaction was quenched by the careful addition of 10 % HCl solution. The mixture was diluted with Et_2O, and the organic layer was dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The pure product (**33**) (810.6 mg, 3.892 mmol, 84 %) was obtained as a yellow oil by flash chromatography (1 % Et_2O in hexanes).

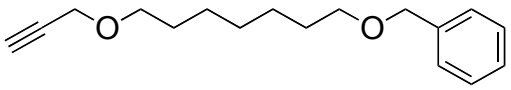
^{1}H NMR (400 MHz, $CDCl_3$) δ 2.50 – 2.43 (m, 1H), 1.87 – 1.80 (m, 2H), 1.78 – 1.67 (m, 2H), 1.55 – 1.44 (m, 13H), 1.35 – 1.27 (m, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 153.2 (C), 90.4 (C), 82.8 (C), 74.3 (C), 31.6 (CH_2), 28.9 (CH), 28.0 (CH_3), 25.6 (CH_2), 24.7 (CH_2);

IR (neat) 2228, 1701 cm^{-1};

MS (EI) 135.1 (M^+ -$OC(CH_3)_3$);

HRMS calcd for $C_9H_{11}O$ (M^+ -$OC(CH_3)_3$) 135.0804, found 135.0800.



58d

((7-(prop-2-ynyloxy)heptyloxy)methyl)benzene (58d)

To an oven dried round bottom flask, equipped with a Teflon-coated stir bar, was added NaH (60 % dispersion in mineral oil, 1.266 g, 31.650 mmol) under a nitrogen atmosphere. Freshly distilled THF (60 mL) was added, followed by heptane-1,7-diol (3.800 g, 28.770 mmol), and the resulting solution was then stirred for one hour. Benzyl bromide (5.410 g, 31.650 mmol) and tetrabutylammonium iodide (531.4 mg, 1.439 mmol) were then added, before heating the solution at reflux for 12 hours. The reaction mixture was then cooled, diluted with a 1:1 mixture of Et_2O and H_2O, and extracted. The aqueous layer was washed with Et_2O (three times). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product 7-(benzyloxy)heptan-1-ol (4.541 g, 20.430 mmol, 71 %) was obtained as a clear oil by flash chromatography (25 % EtOAc in hexanes), and was immediately used in the following reaction. To an oven dried round bottom flask, equipped with a Teflon-coated stir bar, was added NaH (60 % dispersion in mineral oil, 980.4 mg, 24.510 mmol) under a nitrogen atmosphere. Freshly distilled THF (60 mL) was added, followed by the 7-(benzyloxy)heptan-1-ol (4.541 g, 20.430 mmol), and the resulting solution was then stirred for one hour. Propargyl bromide (4.375 g, 36.774 mmol) and tetrabutylammonium iodide (377.3 mg, 1.022 mmol) were then added, and stirring was continued at room temperature for 12 hours. The reaction mixture was then diluted with a 1:1 mixture of Et_2O and H_2O and extracted. The aqueous layer was washed with Et_2O (three times). The

combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product (**58d**) (2.926 g, 11.240 mmol, 55 %) was obtained as a clear oil by flash chromatography (25 % EtOAc in hexanes).

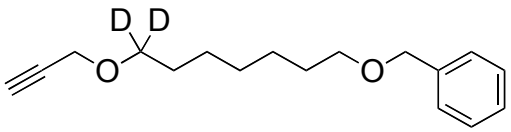
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.35 – 7.23 (m, 5H), 4.48 (s, 2H), 4.11 (d, J = 2.4 Hz, 2H), 3.48 (t, J = 6.8 Hz, 2H), 3.44 (t, J = 6.8 Hz, 2H), 2.39 (t, J = 2.4 Hz, 1H), 1.63 – 1.54 (m, 4H), 1.41 – 1.27 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 80.0 (C), 74.0 (CH), 72.8 (CH_2), 70.4 (CH_2), 70.2 (CH_2), 58.0 (CH_2), 29.7 (CH_2), 29.4 (CH_2), 29.2 (CH_2), 26.1 (CH_2), 26.0 (CH_2);

IR (neat) 2116, 1101 cm^{-1};

MS (EI) 260.2 (M^+);

HRMS calcd for $C_{17}H_{24}O_2$ (M^+) 260.1776, found 260.1773.



73

((7,7-dideutero-7-(prop-2-ynyloxy)heptyloxy)methyl)benzene (73)

To an oven dried round bottom flask, equipped with a Teflon-coated stir bar, was added 7-(benzyloxy)heptan-1-ol (4.680 g, 21.050 mmol), TEMPO (296.0 mg, 1.890 mmol), acetonitrile (125 mL), and potassium phosphate buffer (0.67 M, 47 mL, 31.490 mmol). Separate solutions of $NaClO_2$ (5.510 g in 25 mL water, 60.900 mmol) and NaOCl (637 μL in 11.4 mL water) were then prepared. The first reaction mixture was stirred and heated to 35 °C, upon which 20 % of the $NaClO_2$ solution was added, immediately followed by 20 % of the NaOCl solution. The remaining portions of both the $NaClO_2$ and the NaOCl solutions were then added simultaneously over two hours by syringe pump, followed by stirring the reaction mixture for 12 hours at 35 °C. The reaction mixture was cooled, diluted with water, and the pH was adjusted to 8.0 by the addition of NaOH solution (6.3 g in 13 mL water, 157.500 mmol), before being poured into a solution of cold Na_2SO_3 (12.2 g in 200 mL water, 85.891 mmol) and stirred for 30 minutes. The aqueous solution was then washed with Et_2O before being acidified with 12 M HCl until the pH was 1.0. The aqueous layer was then extracted with Et_2O (three times). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product 7-(benzyloxy)heptanoic acid (4.228 g, 17.893 mmol, 85 %) was obtained as a white solid that was immediately used in the following reaction. To an oven dried round bottom flask, equipped with a Teflon-coated stir

bar, was added 7-(benzyloxy)heptanoic acid (4.228 g, 17.893 mmol) under a nitrogen atmosphere. Freshly distilled THF (8 mL) was added, followed by $LiAlD_4$ (826.5 mg, 19.682 mmol) and the resulting solution was stirred for 12 hours at room temperature. The reaction mixture was then diluted with a 1:1 mixture of Et_2O and H_2O, followed by the addition of potassium sodium tartrate. After stirring for 15 minutes, the organic layer was extracted with Et_2O (three times), and the organic phase was then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product 7-(benzyloxy)-1,1-dideuteroheptan-1-ol (3.412 g, 15.209 mmol, 85 %) was obtained as a clear oil that was immediately used in the following reaction. To an oven dried round bottom flask, equipped with a Teflon-coated stir bar, was added NaH (60 % dispersion in mineral oil, 730.0 mg, 18.251 mmol) under a nitrogen atmosphere. Freshly distilled THF (60 mL) was added, followed by 7-(benzyloxy)-1,1-dideuteroheptan-1-ol (3.412 g, 15.209 mmol), and the resulting solution was then stirred for one hour. Propargyl bromide (3.257 g, 27.376 mmol) and tetrabutylammonium iodide (280.9 mg, 0.760 mmol) were then added, and the resulting solution was stirred at room temperature for 12 hours. The reaction mixture was then diluted with a 1:1 mixture of Et_2O and H_2O, and the phases were separated. The aqueous layer was washed with Et_2O (three times). The combined organic extracts were then dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The pure product (**73**) (2.235 g, 8.517 mmol, 56 %) was obtained as a clear oil by flash chromatography (25 % EtOAc in hexanes).

^{1}**H NMR** (400 MHz, $CDCl_3$) δ 7.37 – 7.25 (m, 5H), 4.50 (s, 2H), 4.13 (d, J = 2.4 Hz, 2H), 3.46 (t, J = 6.8 Hz, 2H), 2.41 (t, J = 2.4 Hz, 1H), 1.65 – 1.56 (m, 4H), 1.41 – 1.30 (m, 6H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.7 (C), 128.3 (CH), 127.6 (CH), 127.4 (CH), 80.0 (C), 74.0 (CH), 72.8 (CH_2), 70.4 (CH_2), 57.93 (CD_2), 57.90 (CH_2), 29.7 (CH_2), 29.22 (CH_2), 29.18 (CH_2), 26.1 (CH_2), 26.0 (CH_2);

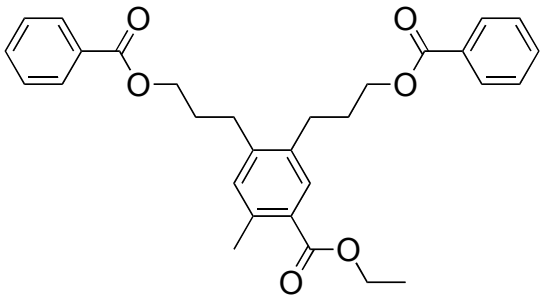
IR (neat) 2116, 1100 cm^{-1};

MS (EI) 262.2 (M^+);

HRMS calcd for $C_{17}H_{22}D_2O_2$ (M^+) 262.1902, found 262.1911.

Bergman Cycloaromatizations

General Procedure for the Bergman Cycloaromatizations Using 1,4-Cyclohexadiene as the Radical Trapping Agent



16

3,3'-(4-(ethoxycarbonyl)-5-methyl-1,2-phenylene)bis(propane-3,1-diyl) dibenzoate (16)

To an oven dried microwavable vial, equipped with a carboflon stir bar, was added (*E*)-6-(ethoxycarbonyl)-7-methyldodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**15** ***cis***) (51.1 mg, 0.105 mmol). Dry mesitylene (3 mL) was then added, and the solution was sparged with nitrogen for five minutes before 1,4-cyclohexadiene (126.2 mg, 1.575 mmol) was added to the vial. The reaction mixture was then heated at 225 °C using microwave for two hours, after which time the pure product (**16**) (18.5 mg, 0.038 mmol, 36 %) was obtained as a yellow oil by gradient silica gel chromatography (100 % hexanes to 10 % EtOAc in hexanes), followed by preparatory thin layer chromatography (100 % DCM).

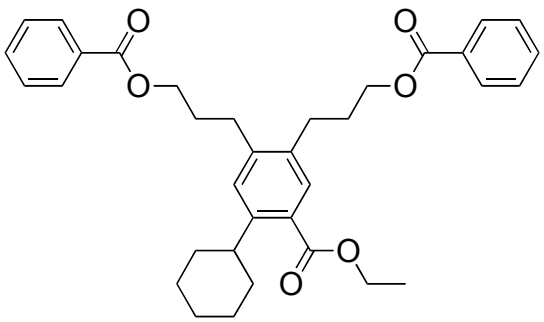
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 – 8.00 (m, 4H), 7.76 (s, 1H), 7.57 – 7.53 (m, 2H), 7.45 – 7.41 (m, 4H), 7.06 (s, 1H), 4.37 – 4.30 (m, 6H), 2.83 – 2.79 (m, 4H), 2.53 (s, 3H), 2.10 – 2.05 (m, 4H), 1.37 (t, J = 7.2 Hz, 3H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 167.6 (C), 166.5 (C), 143.3 (C), 138.0 (C), 136.4 (C), 132.98 (CH), 132.95 (CH), 132.7 (CH), 131.6 (CH), 130.22 (C), 130.17 (C), 129.5 (CH), 128.4 (CH), 127.9 (C), 64.3 (CH_2), 60.6 (CH_2), 30.0 (CH_2), 29.9 (CH_2), 29.0 (CH_2), 28.5 (CH_2), 21.3 (CH_3), 14.3 (CH_3);

IR (neat) 1717 cm^{-1};

MS (EI) 443.2 (M^+ -OCH_2CH_3);

HRMS calcd for $C_{28}H_{27}O_5$ (M^+ -OCH_2CH_3) 443.1853, found 443.1810.



23

3,3'-(4-cyclohexyl-5-(ethoxycarbonyl)-1,2-phenylene)bis(propane-3,1-diyl) dibenzoate (23)

Prepared from (*E*)-6-cyclohexyl-7-(ethoxycarbonyl)dodeca-6-en-4,8-diyne-1,12-diyl dibenzoate (**21** ***trans***) (50.7 mg, 0.091 mmol), using a procedure similar to that described above for 3,3'-(4-(ethoxycarbonyl)-5-methyl-1,2-phenylene)bis(propane-3,1-diyl) dibenzoate (**16**), that provided the title compound (**23**) (15.8 mg, 0.028 mmol, 31 %) as a yellow oil after gradient silica gel chromatography (100 % hexanes to 10 % EtOAc in hexanes), followed by preparatory thin layer chromatography (100% DCM).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.04 – 8.01 (m, 4H), 7.58 – 7.53 (m, 3H), 7.45 – 7.41 (m, 4H), 7.17 (s, 1H), 4.37 – 4.31 (m, 6H), 3.30 – 3.24 (m, 1H), 2.85 – 2.78 (m, 4H), 2.12 – 2.04 (m, 4H), 1.85 – 1.72 (m, 5H), 1.45 – 1.19 (m, 8H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 168.4 (C), 166.53 (C), 166.49 (C), 146.5 (C), 142.8 (C), 136.1 (C), 133.0 (CH), 132.9 (CH), 130.8 (CH), 130.23 (C), 130.21 (C), 129.5 (CH), 128.4 (CH), 127.9 (CH), 64.4 (CH_2), 64.3 (CH_2), 60.8 (CH_2), 39.9 (CH), 34.4 (CH_2), 30.0 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 28.5 (CH_2), 27.0 (CH_2), 26.2 (CH_2), 14.3 (CH_3);

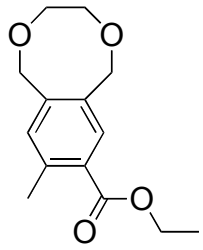
IR (neat) 1717 cm^{-1};

MS (EI) 511.2 (M^+ -OCH_2CH_3);

HRMS calcd for $C_{33}H_{35}O_5$ (M^+ -OCH_2CH_3) 511.2484, found 511.2485.

Bergman Cycloaromatizations

General Procedure for the Bergman Cycloaromatizations Using No Radical Trapping Agent



57

ethyl 9-methyl-1,3,4,6-tetrahydrobenzo[*f*][1,4]dioxocine-8-carboxylate (57)

To an oven dried round bottom flask, equipped with a Teflon-coated stir bar, was added a mixture of (*E*)-ethyl 6-methoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**55** ***cis***) and (*Z*)-ethyl 6-methoxy-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**55** ***trans***) (13.5 mg, 0.054 mmol). 1-methylnaphthalene (4 mL) and DIPEA (0.1 mL) were then added, and the solution was sparged with nitrogen for 10 minutes, before being heated to reflux for one hour while simultaneously being irradiated with 300 nm light. The pure product (**57**) (3.5 mg, 0.014 mmol, 26 %) was obtained as a yellow oil by gradient silica gel chromatography (100 % hexanes to 10 % EtOAc in hexanes), followed by preparatory thin layer chromatography (20 % EtOAc in hexanes).

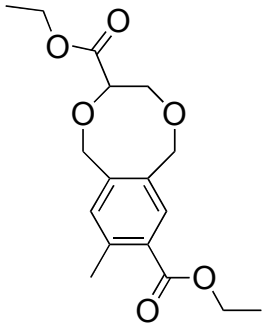
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 (s, 1H), 7.04 (s, 1H), 4.95 (s, 2H), 4.92 (s, 2H), 4.35 (q, J = 7.2 Hz, 2H), 3.83 – 3.77 (m, 4H), 2.58 (s, 3H), 1.39 (t, J = 7.2 Hz, 3H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.1 (C), 140.0 (C), 139.1 (C), 134.2 (C), 132.8 (CH), 132.7 (CH), 129.3 (C), 72.2 (CH_2), 71.9 (CH_2), 71.2 (CH_2), 70.1 (CH_2), 60.8 (CH_2), 21.3 (CH_3), 14.3 (CH_3);

IR (neat) 1720 cm^{-1};

MS (EI) 250.1 (M^+);

HRMS calcd for $C_{14}H_{18}O_4$ (M^+) 250.1205, found 250.1195.



63

diethyl 9-methyl-1,3,4,6-tetrahydrobenzo[f][1,4]dioxocine-3,8-dicarboxylate (63)

Prepared from an inseparable mixture of (*E*)-ethyl 6-(2-ethoxy-2-oxoethoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59b *cis***) and (*Z*)-ethyl 6-(2-ethoxy-2-oxoethoxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59b *trans***) (14.1 mg, 0.044 mmol), using a procedure similar to that described above for ethyl 9-methyl-1,3,4,6-tetrahydrobenzo[*f*][1,4]dioxocine-8-carboxylate (**57**), that provided the title compound (**63**) (3.9 mg, 0.012 mmol, 28 %) as a yellow oil after gradient silica gel chromatography (100 % hexanes to 10 % EtOAc in hexanes), followed by preparatory thin layer chromatography (20 % EtOAc in hexanes).

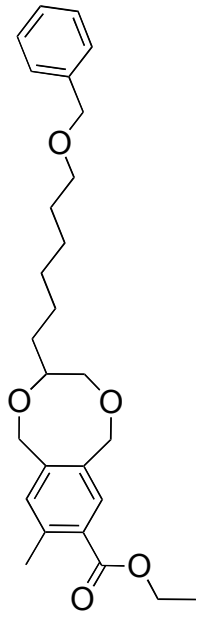
^{1}H NMR (400 MHz, acetone-d_6) δ 7.73 (s, 1H), 7.16 (s, 1H), 5.25 (d, J = 14.4 Hz, 1H), 5.09 (d, J = 13.2 Hz, 1H), 4.86 (d, J = 14.4 Hz, 1H), 4.78 (d, J = 13.2 Hz, 1H), 4.33 (q, J = 7.2 Hz, 2H), 4.27 (dd, J = 2.8 Hz, 7.2 Hz, 1H), 4.17 (q, J = 7.2 Hz, 2H), 3.98 (dd, J = 2.8 Hz, 12.8 Hz, 1H), 3.83 (dd, J = 7.2 Hz, 12.8 Hz, 1H), 2.55 (s, 3H), 1.36 (t, J = 7.2 Hz, 3H), 1.25 (t, J = 7.2 Hz, 3H);

^{13}C NMR (125 MHz, acetone-d_6) δ 170.4 (C), 167.4 (C), 142.3 (C), 140.2 (C), 135.1 (C), 133.4 (CH), 133.3 (CH), 130.1 (C), 79.7 (CH), 72.9 (CH_2), 72.0 (CH_2), 70.7 (CH_2), 61.4 (CH_2), 61.3 (CH_2), 21.2 (CH_3), 14.6 (CH_3), 14.5 (CH_3);

IR (neat) 1751, 1725 cm^{-1};

MS (EI) 322.1 (M^+);

HRMS calcd for $C_{17}H_{22}O_6$ (M^+) 322.1416, found 322.1425.



65

ethyl 3-(6-(benzyloxy)hexyl)-9-methyl-1,3,4,6-tetrahydrobenzo[f][1,4]dioxocine-8-carboxylate (65)

Prepared from a mixture of (*E*)-ethyl 6-(7-(benzyloxy)heptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59d *cis***) and (*Z*)-ethyl 6-(7-(benzyloxy)heptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**59d *trans***) (13.9 mg, 0.032 mmol), using a procedure similar to that described above for ethyl 9-methyl-1,3,4,6-tetrahydrobenzo[*f*][1,4]dioxocine-8-carboxylate (**57**), that provided the title compound (**65**) (3.8 mg, 0.009 mmol, 27 %) as a yellow oil after gradient silica gel chromatography (100 % hexanes to 10 % EtOAc in hexanes), followed by preparatory thin layer chromatography (20 % EtOAc in hexanes).

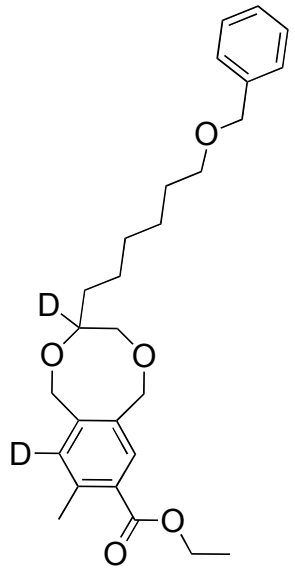
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.36 – 7.24 (m, 5H), 6.99 (s, 1H), 5.06 (d, J = 14 Hz, 2H), 4.88 (d, J = 14.8 Hz, 1H), 4.84 (d, J = 14.8 Hz, 1H), 4.50 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.79 (dd, J = 2 Hz, 12.4 Hz, 1H), 3.58 – 3.61 (m, 1H), 3.48 – 3.40 (m, 3H), 2.56 (s, 3H), 1.65 – 1.58 (m, 2H), 1.49 – 1.27 (m, 11H);

^{13}C NMR (125 MHz, $CDCl_3$) δ 167.2 (C), 141.7 (C), 139.8 (C), 138.6 (C), 134.2 (C), 132.6 (CH), 132.1 (CH), 128.8 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 81.1 (CH), 74.1 (CH_2), 72.9 (CH_2), 72.8 (CH_2), 72.6 (CH_2), 70.4 (CH_2), 60.7 (CH_2), 32.3 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 21.4 (CH_3), 14.4 (CH_3);

IR (neat) 1717 cm^{-1};

MS (EI) 440.3 (M^+);

HRMS calcd for $C_{27}H_{36}O_5$ (M^+) 440.2563, found 440.2535.



78

ethyl 3-(6-(benzyloxy)hexyl)-3,10-dideutero-9-methyl-1,3,4,6-tetrahydrobenzo [f][1,4]dioxocine-8-carboxylate (78)

Prepared from a mixture of (*E*)-ethyl 6-(7-(benzyloxy)-1,1-dideuteroheptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**76** ***cis***) and (*Z*)-ethyl 6-(7-(benzyloxy)-1,1-dideuteroheptyloxy)-2-(3-methoxyprop-1-ynyl)-3-methylhex-2-en-4-ynoate (**76** ***trans***) (11.5 mg, 0.026 mmol), using a procedure similar to that described above for ethyl 9-methyl-1,3,4,6-tetrahydrobenzo[*f*][1,4]dioxocine-8-carboxylate (**57**), that provided the title compound (**78**) (3.0 mg, 0.007 mmol, 26 %) as a yellow oil after gradient silica gel chromatography (100 % hexanes to 10 % EtOAc in hexanes), followed by preparatory thin layer chromatography (20 % EtOAc in hexanes).

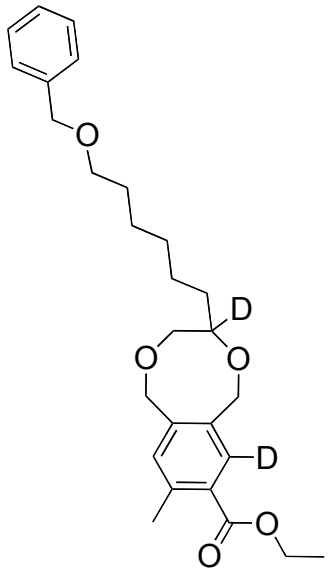
^{1}H NMR (300 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.37 – 7.25 (m, 5H), 5.06 (d, J = 10.5 Hz, 2H), 4.86 (m, 2H), 4.50 (s, 2H), 4.34 (q, J = 6 Hz, 2H), 3.78 (d, J = 9.3 Hz, 1H), 3.44 (m, 3H), 2.56 (s, 3H), 1.66 – 1.56 (m, 4H), 1.45 – 1.28 (m, 9H);

^{13}C NMR (125 MHz, DMSO) δ 166.6 (C), 142.34 (C), 142.26 (C), 138.8 (C), 138.5 (C), 134.5 (CD), 131.9 (CH), 131.8 (C), 128.3 (CH), 127.5 (CH), 127.4 (CH), 73.3 (CH_2), 72.1 (CH_2), 71.9 (CH_2), 71.8 (CH_2), 69.7 (CH_2), 69.6 (CD), 60.6 (CH_2), 31.7 (CH_2), 29.2 (CH_2), 29.0 (CH_2), 25.7 (CH_2), 25.1 (CH_2), 20.7 (CH_3), 14.3 (CH_3);

IR (neat) 1720 cm^{-1};

MS (EI) 442.3 (M^+);

HRMS calcd for $C_{27}H_{34}D_2O_5$ (M^+) 442.2688, found 442.2685.



77

ethyl 4-(6-(benzyloxy)hexyl)-4,7-dideutero-9-methyl-1,3,4,6-tetrahydrobenzo [f][1,4]dioxocine-8-carboxylate (77)

Prepared from a mixture of (*E*)-ethyl 2-(3-(7-(benzyloxy)-1,1-dideuteroheptyloxy)prop-1-ynyl)-6-methoxy-3-methylhex-2-en-4-ynoate (**75** ***cis***) and (*Z*)-ethyl 2-(3-(7-(benzyloxy)-1,1-dideuteroheptyloxy)prop-1-ynyl)-6-methoxy-3-methylhex-2-en-4-ynoate (**75** ***trans***) (11.8 mg, 0.027 mmol), using a procedure similar to that described above for ethyl 9-methyl-1,3,4,6-tetrahydrobenzo[*f*][1,4]dioxocine-8-carboxylate (**57**), that provided the title compound (**77**) (3.2 mg, 0.007 mmol, 27 %) as a yellow oil after gradient silica gel chromatography (100 % hexanes to 10 % EtOAc in hexanes), followed by preparatory thin layer chromatography (20 % EtOAc in hexanes).

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 – 7.25 (m, 5H), 7.00 (s, 1H), 5.07 – 4.84 (m, 4H), 4.98 (s, 2H), 4.34 (q, J = 7.2 Hz, 2H), 3.83 (d, J = 12.3 Hz, 1H), 3.48 – 3.40 (m, 3H), 2.57 (s, 3H), 1.66 – 1.56 (m, 2H), 1.42 – 1.28 (m, 11H);

^{13}C NMR (75 MHz, $CDCl_3$) δ 167.2 (C), 141.0 (C), 139.6 (C), 138.7 (C), 134.7 (C), 132.6 (CH), 128.8 (C), 128.3 (CH), 127.6 (CH), 127.5 (CH), 77.2 (CD), 75.3 (CH_2), 73.3 (CH_2), 72.9 (CH_2), 72.1 (CH_2), 70.4 (CH_2), 60.7 (CH_2), 32.1 (CH_2), 29.7 (CH_2), 29.5 (CH_2), 26.1 (CH_2), 25.6 (CH_2), 21.3 (CH_3), 14.4 (CH_3);

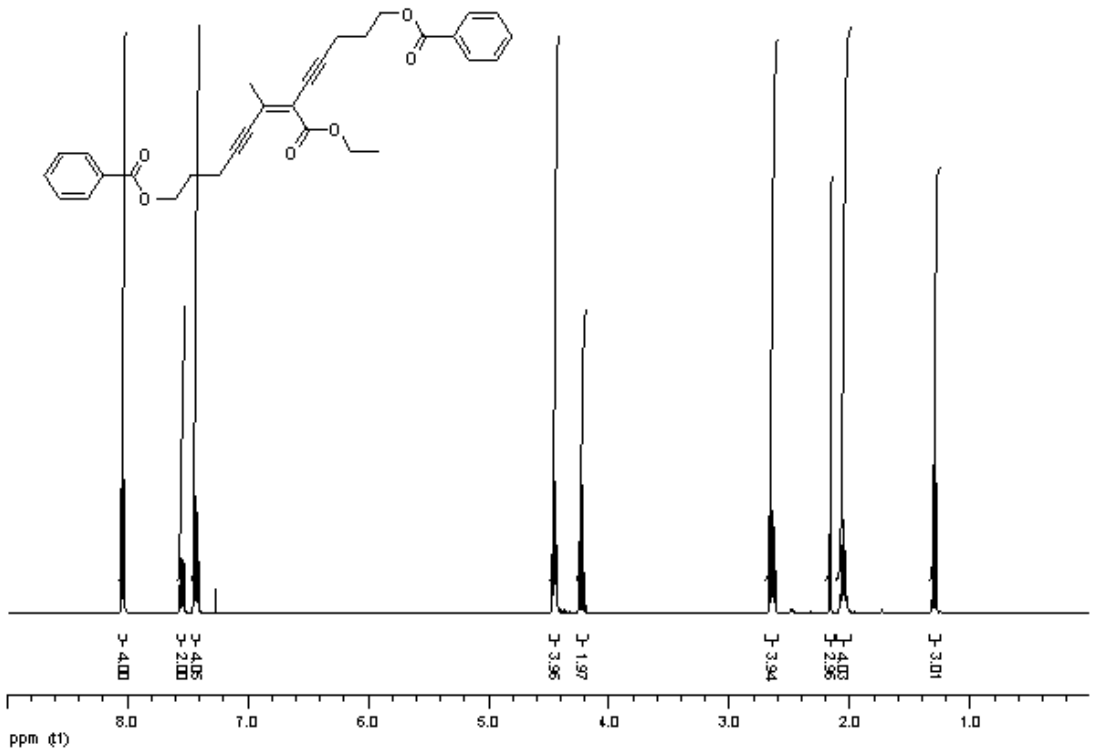
IR (neat) 1720 cm^{-1};

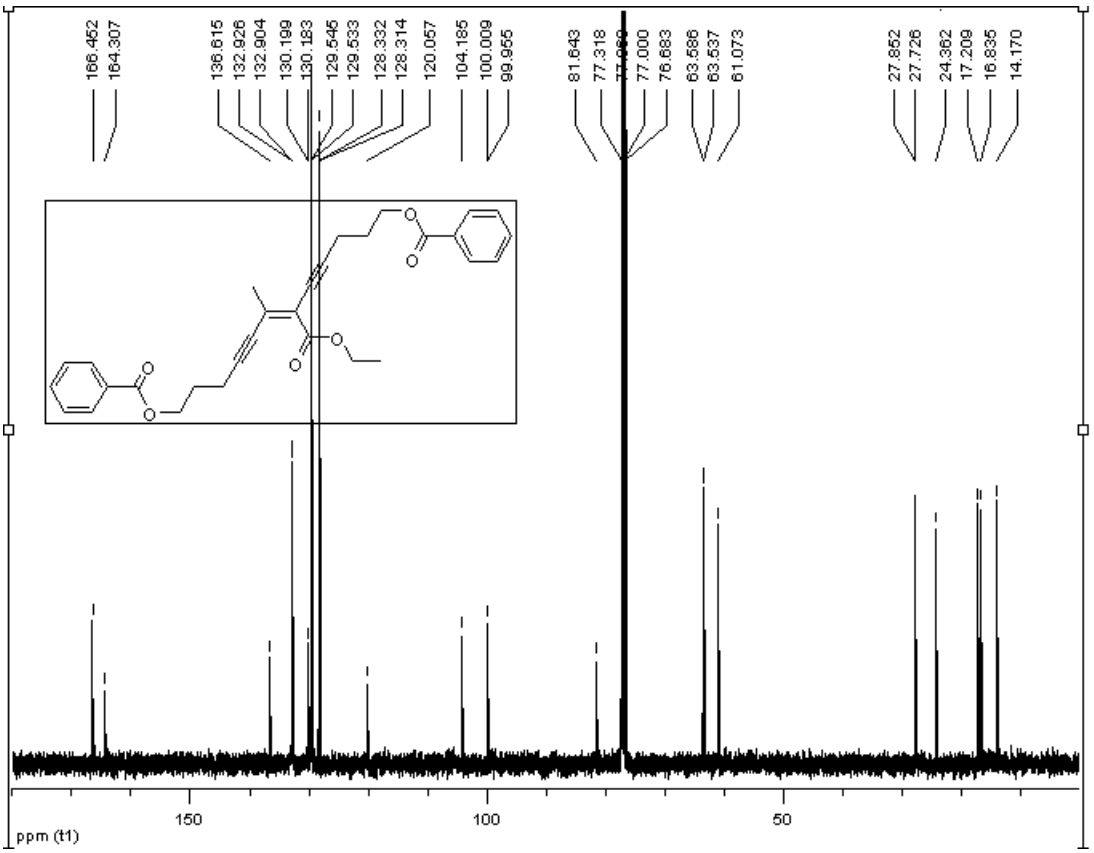
MS (EI) 442.3 (M^+);

HRMS calcd for $C_{27}H_{34}D_2O_5$ (M^+) 442.2688, found 442.2687.

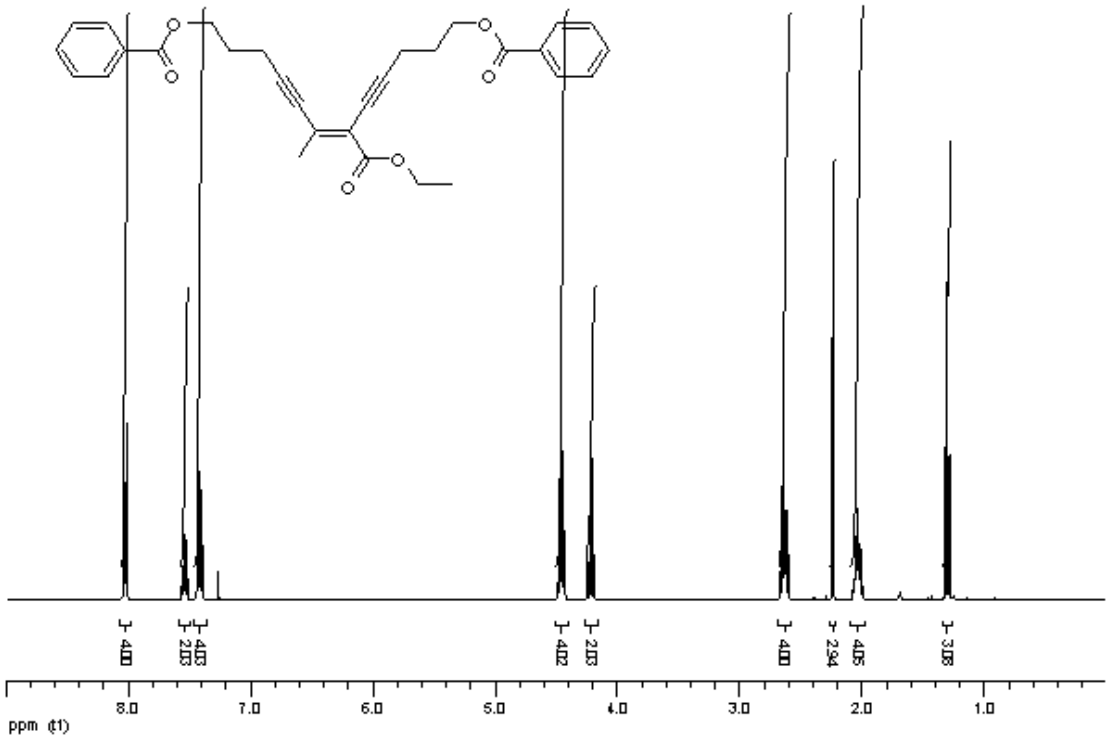
Appendix – NMR and UV-Vis Spectra

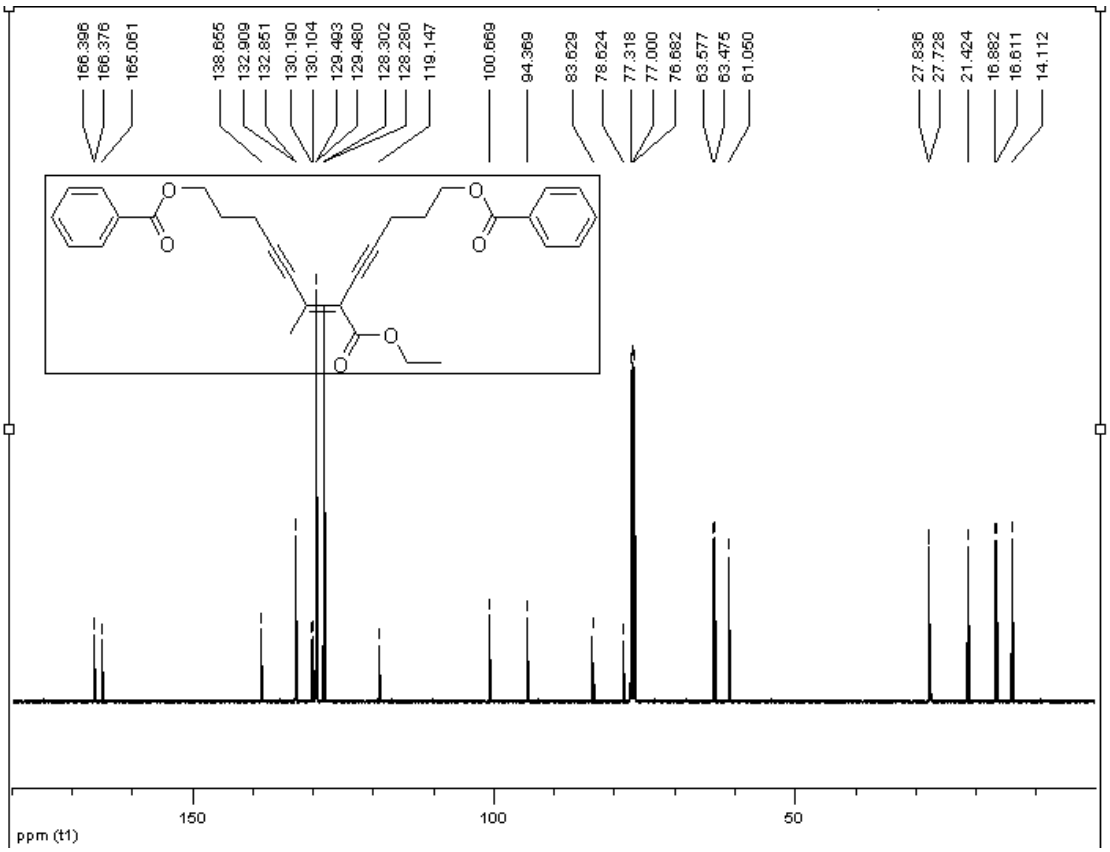
15 *trans*


4.00
2.00
4.05
3.96
1.97
3.94
2.00
4.03
3.01
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

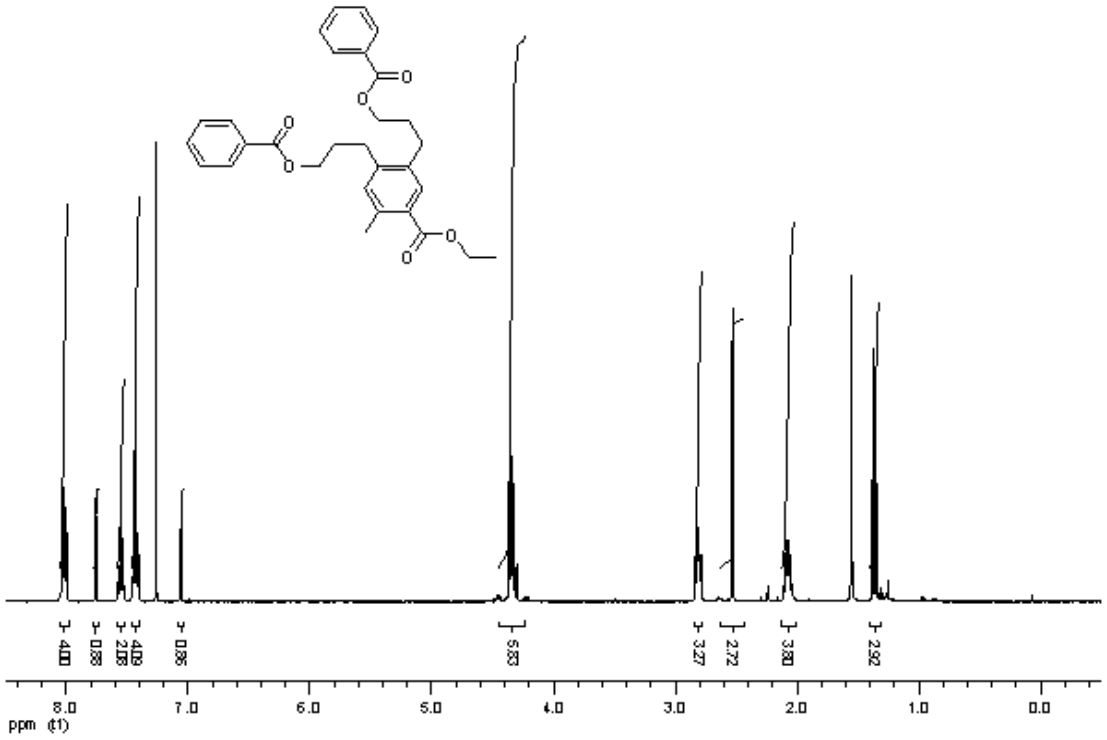

166.452
164.307
136.615
132.926
132.904
130.199
130.183
129.545
129.533
128.332
128.314
120.057
104.185
100.009
99.955
81.643
77.318
77.000
76.683
63.586
63.537
61.073
27.852
27.726
24.362
17.209
16.835
14.170
150
100
50
ppm (t1)

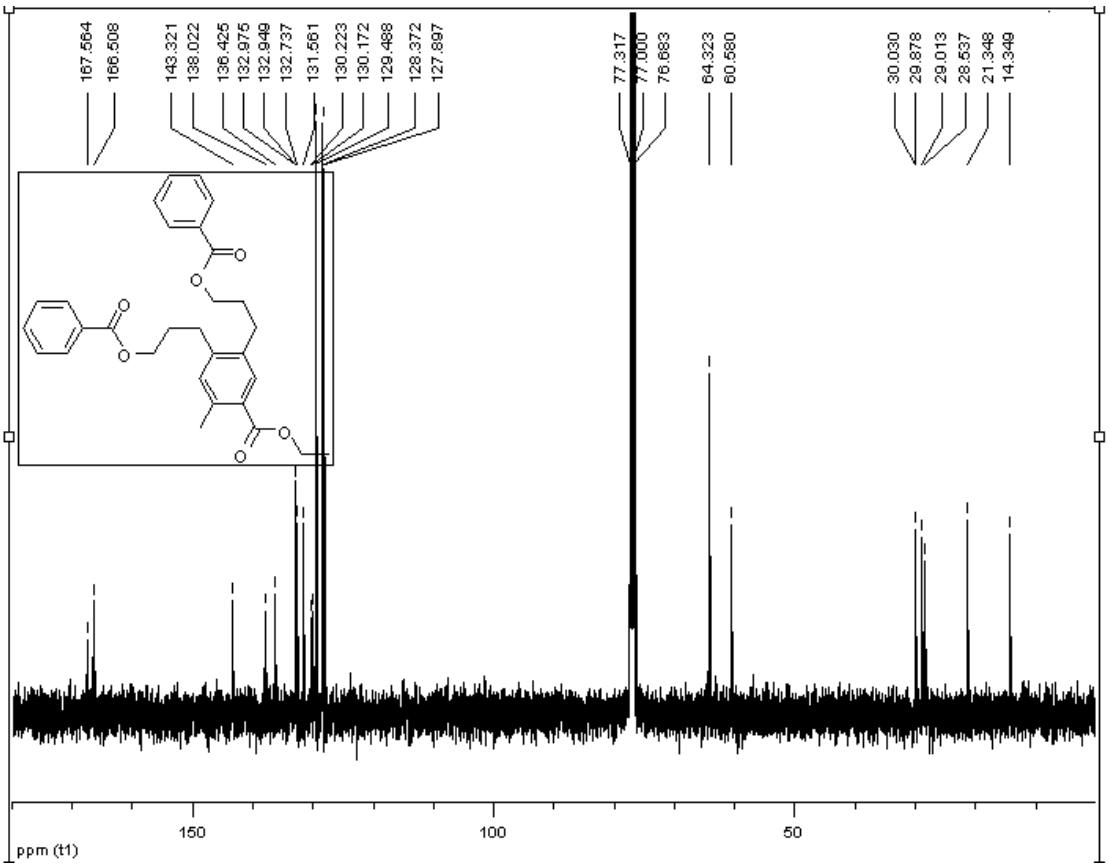
15 *cis*


4.00
2.15
3.15
4.02
2.15
4.00
2.34
4.05
3.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

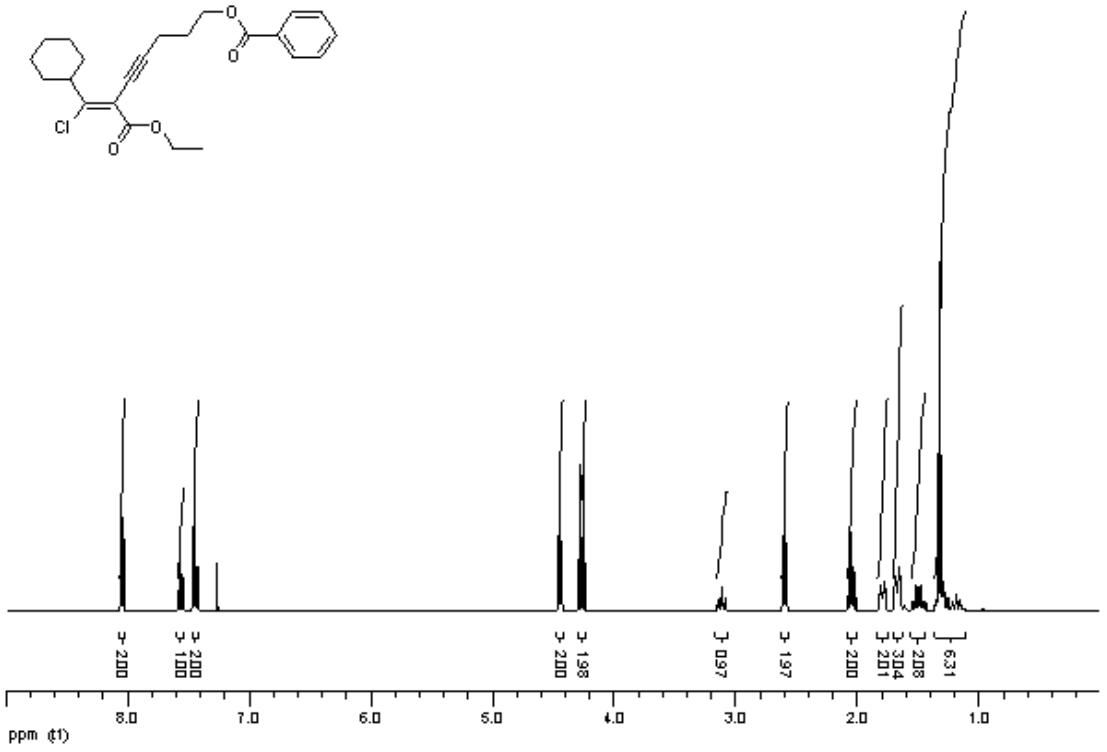

166.396
166.376
165.061
138.655
132.909
132.851
130.190
130.104
129.493
129.480
128.302
128.280
119.147
100.669
94.369
83.629
78.624
77.318
77.000
76.682
63.577
63.475
61.050
27.836
27.728
21.424
16.882
16.611
14.112
150
100
50
ppm (t1)

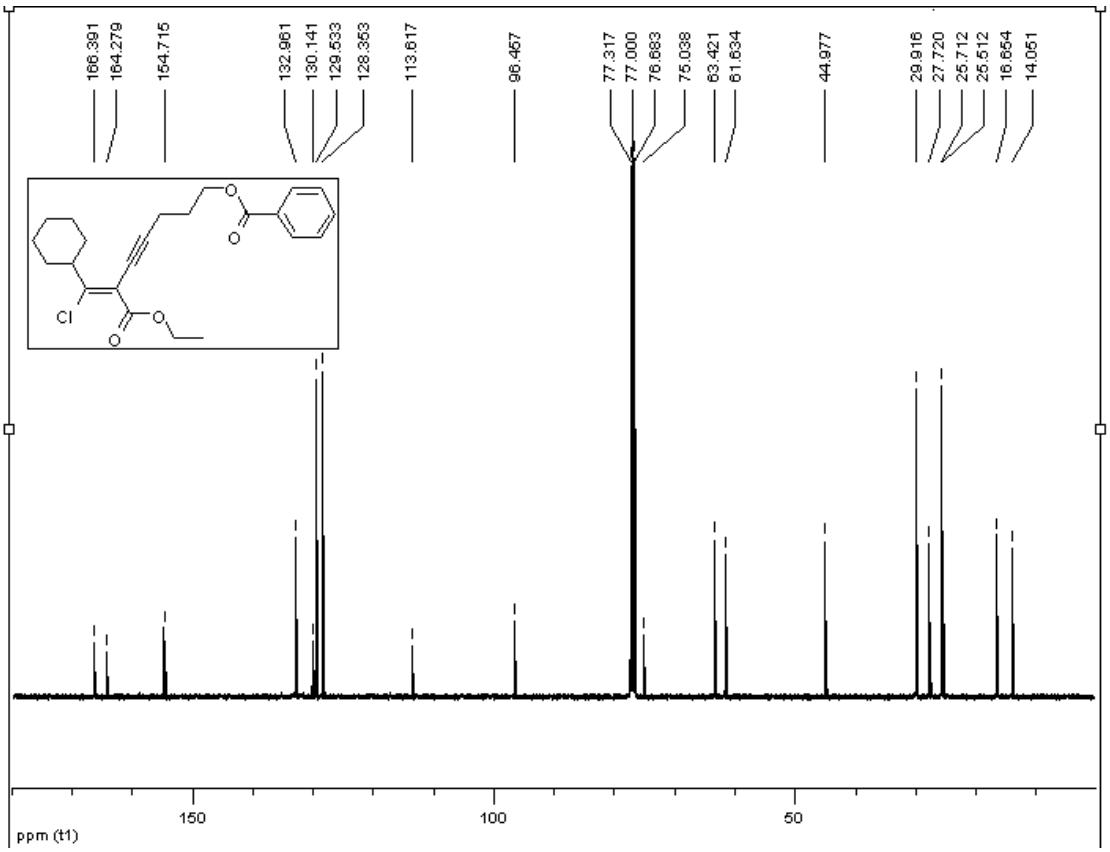
16


1.00
0.88
2.08
4.00
3.00
5.83
3.27
2.22
3.88
2.32
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

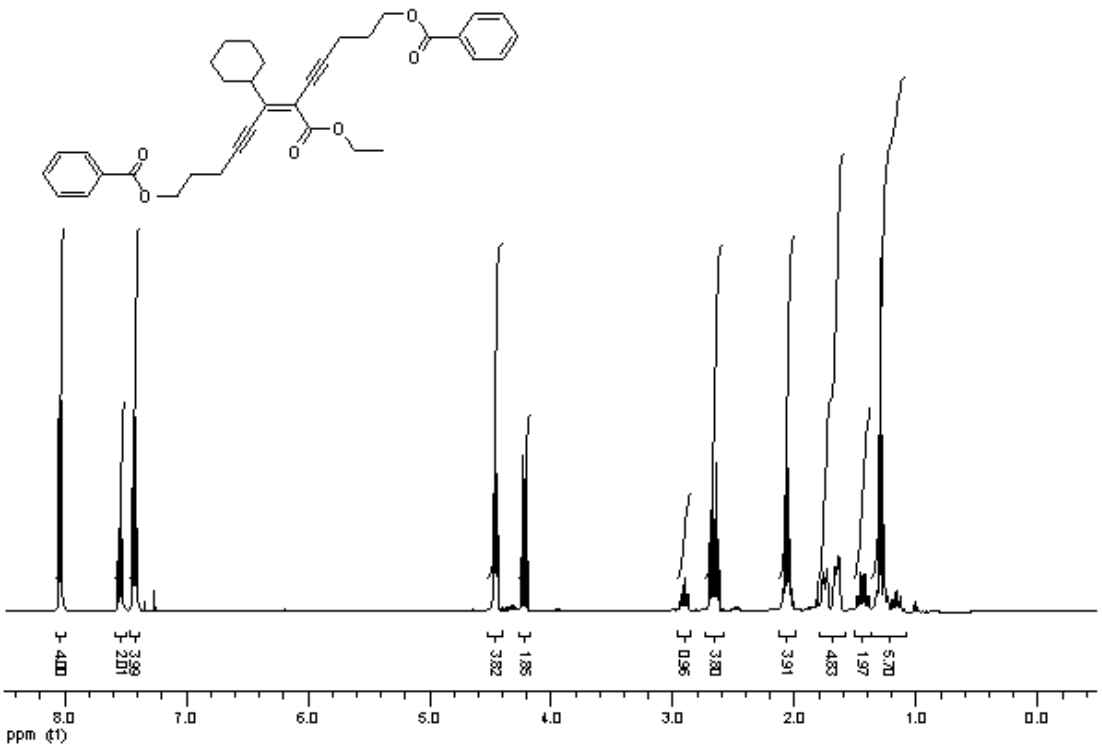

167.564
166.508
143.321
138.022
136.425
132.975
132.949
132.737
131.561
130.223
130.172
129.488
128.372
127.897
77.317
77.000
76.683
64.323
60.580
30.030
29.878
29.013
28.537
21.348
14.349
150
100
50
ppm (t1)

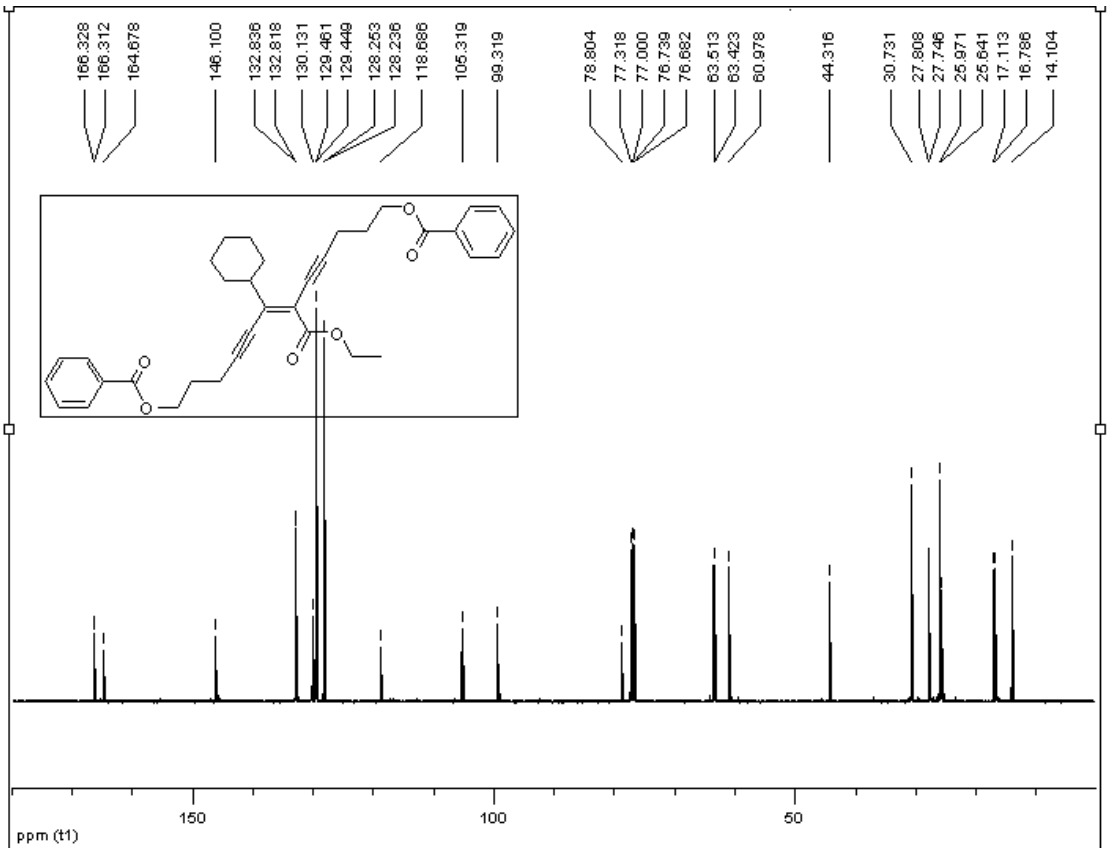
27


Cl
O
O
O
O
2.00
2.01
2.00
1.98
0.97
1.97
2.00
3.44
3.01
2.08
6.31
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)

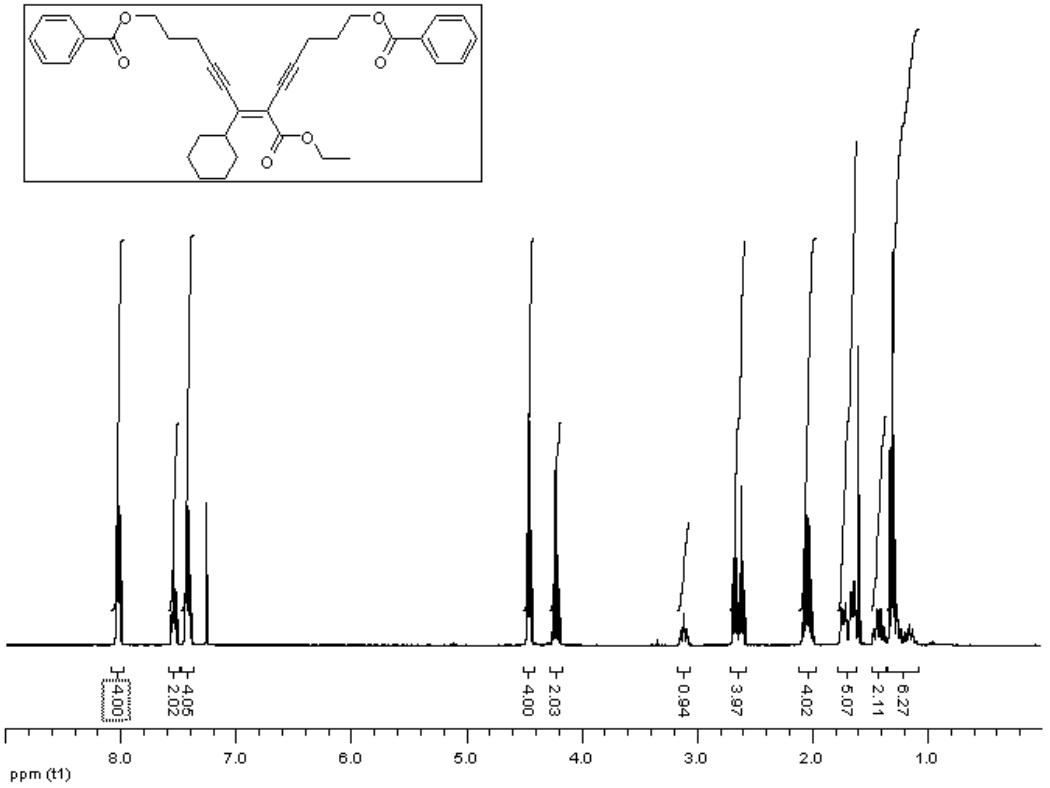

166.391
164.279
154.715
132.961
130.141
129.533
128.353
113.617
96.467
77.317
77.000
76.683
75.038
63.421
61.634
44.977
29.916
27.720
25.712
25.512
16.654
14.051
Cl
O
O
O
O
150
100
50
ppm (t1)

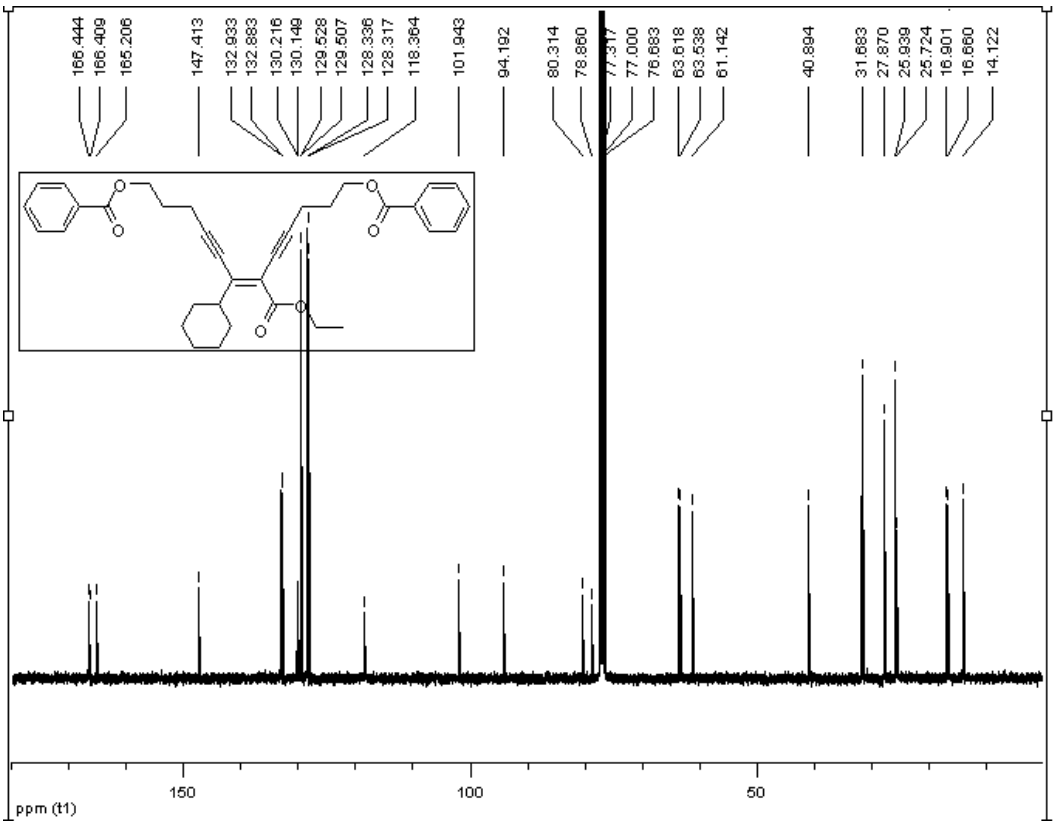
21 *trans*


4.00
2.01
3.69
3.82
1.85
0.96
3.38
3.91
4.82
1.97
5.70
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

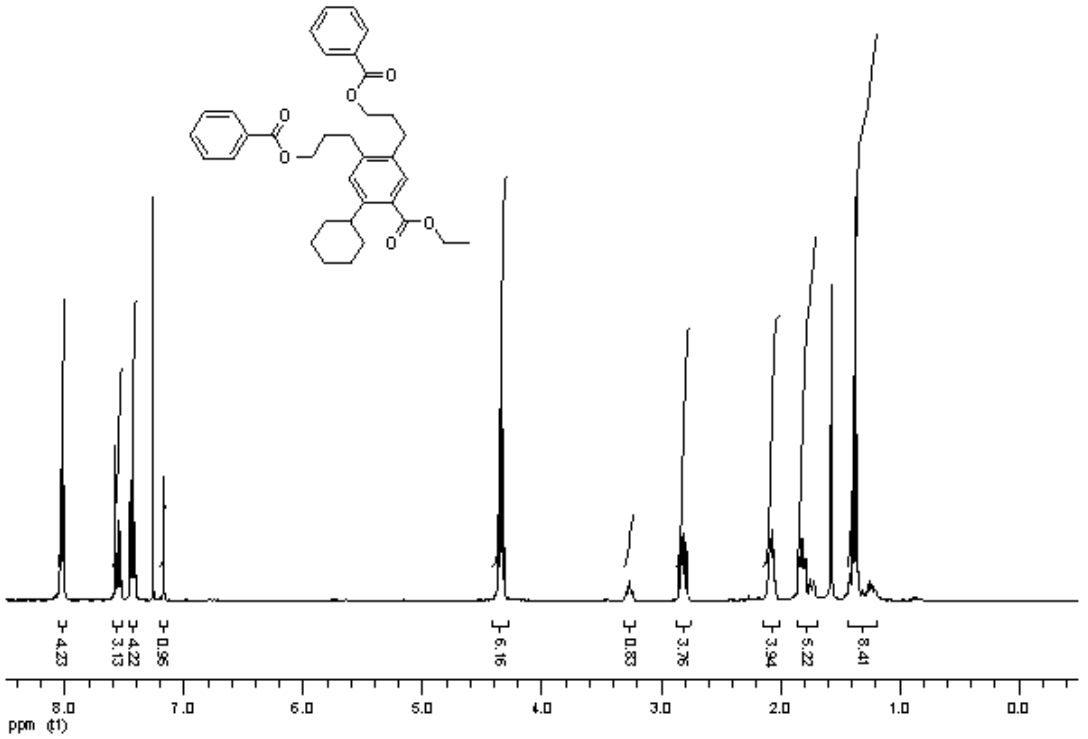

166.328
166.312
164.678
146.100
132.836
132.818
130.131
129.461
129.449
128.253
128.236
118.686
105.319
99.319
78.804
77.318
77.000
76.739
76.682
63.513
63.423
60.978
44.316
30.731
27.808
27.746
25.971
25.641
17.113
16.786
14.104
150
100
50
ppm (t1)

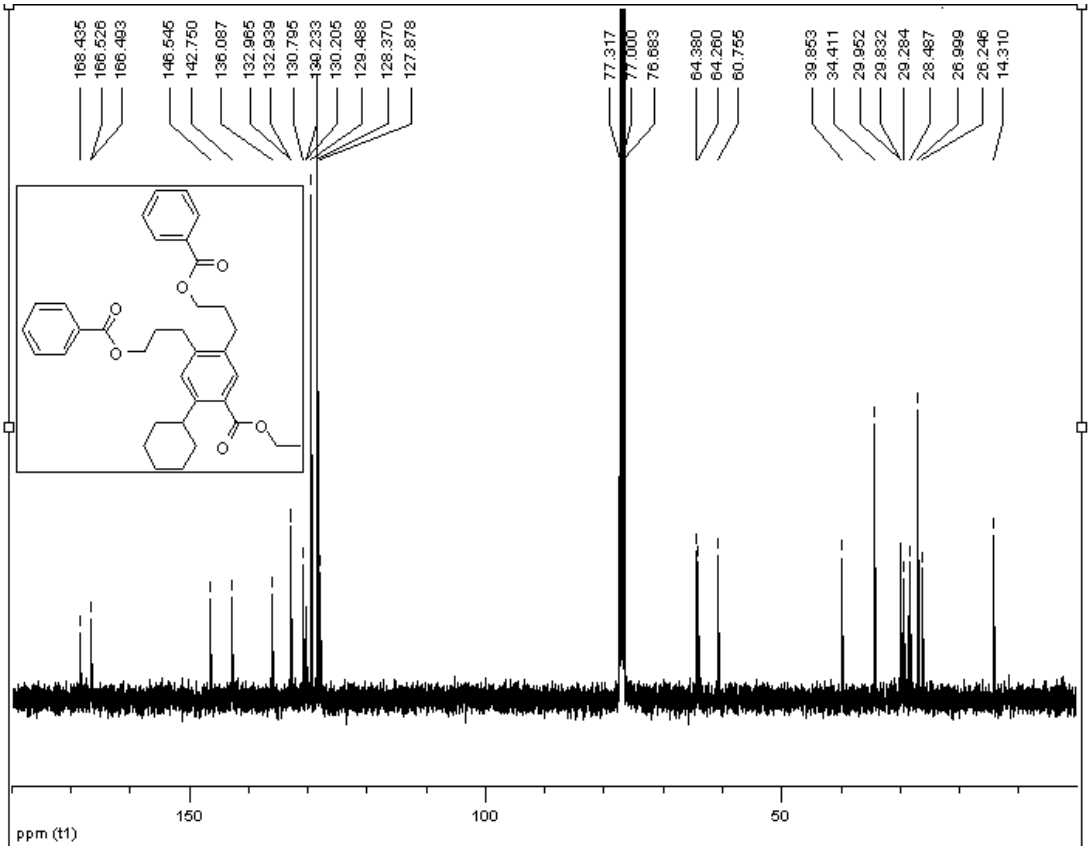
21 *cis*


4.00
2.02
4.05
4.00
2.03
0.94
3.97
4.02
5.07
2.11
6.27
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
ppm (t1)


166.444
166.409
165.206
147.413
132.933
132.883
130.216
130.149
129.528
129.507
128.336
128.317
118.364
101.943
94.192
80.314
78.860
77.317
77.000
76.683
63.618
63.538
61.142
40.894
31.683
27.870
25.939
25.724
16.901
16.660
14.122
150
100
50
ppm (t1)

23


4.23
3.13
4.22
0.96
6.16
0.83
3.36
3.94
5.22
8.41
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


168.435
166.526
166.493
146.545
142.750
136.087
132.965
132.939
130.795
130.233
130.205
129.488
128.370
127.878
77.317
77.000
76.683
64.380
64.260
60.755
39.853
34.411
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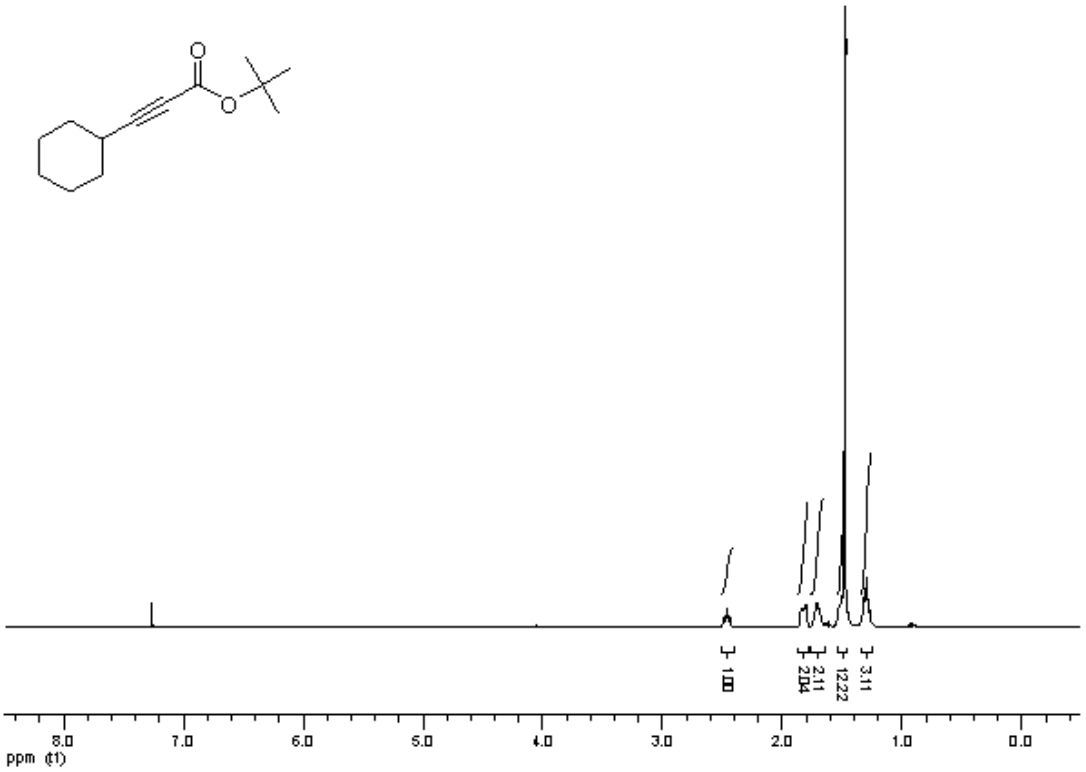
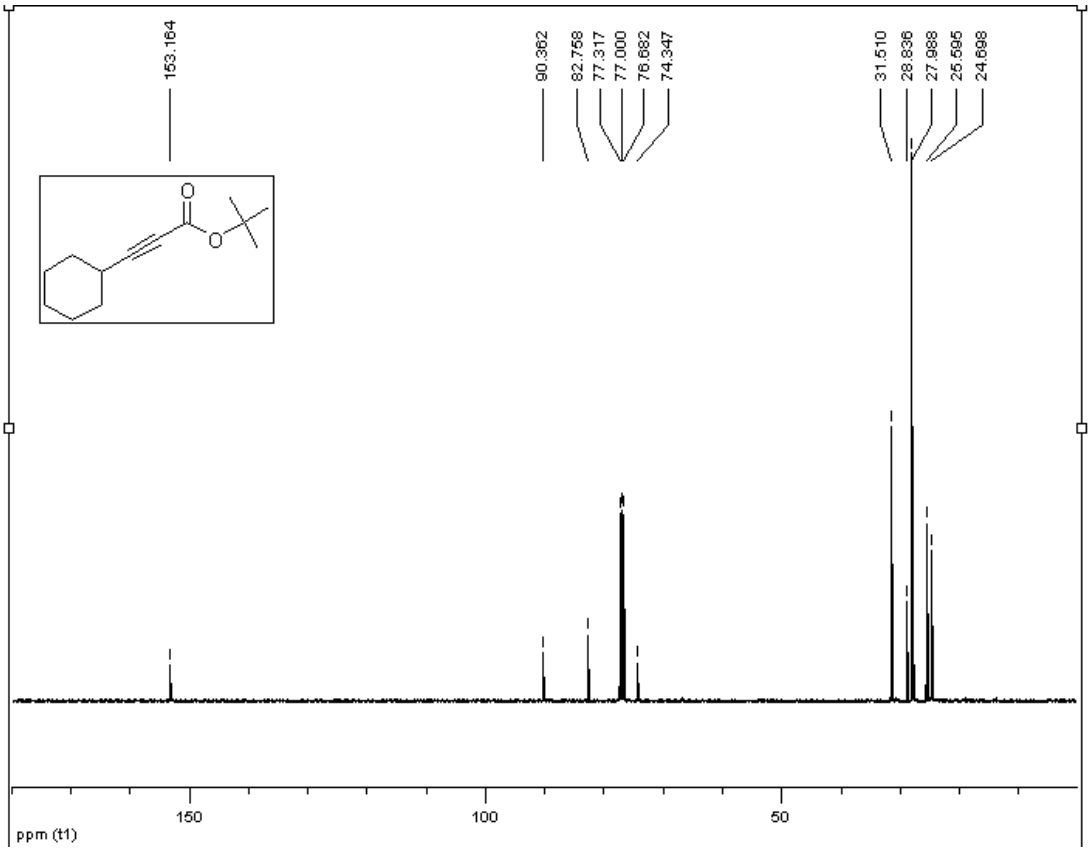
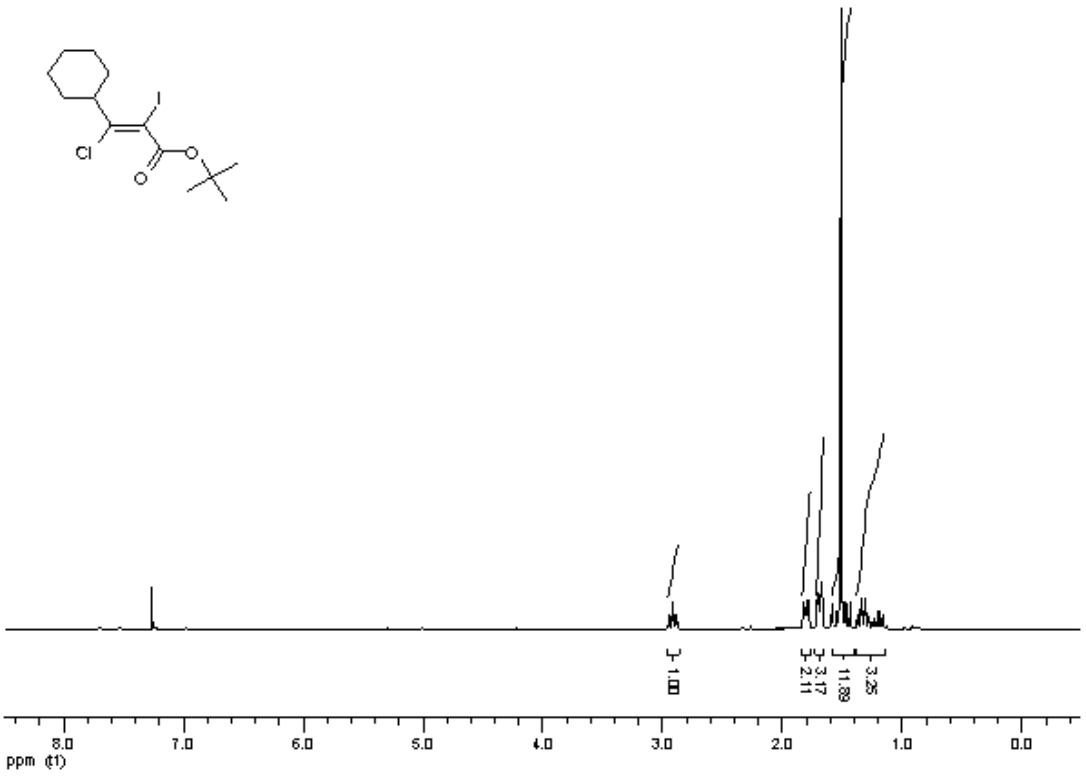
26.999
26.246
14.310
150
100
50
ppm (t1)

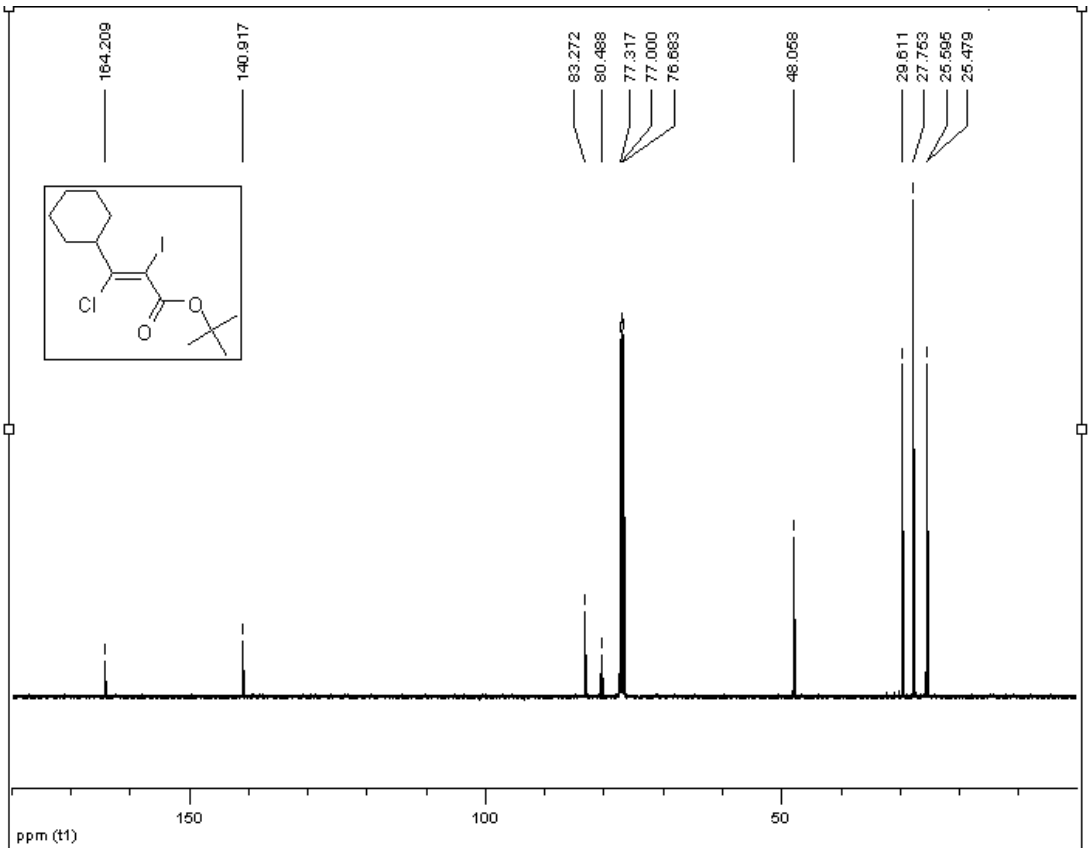
33


1.00
2.11
2.04
12.22
3.11
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

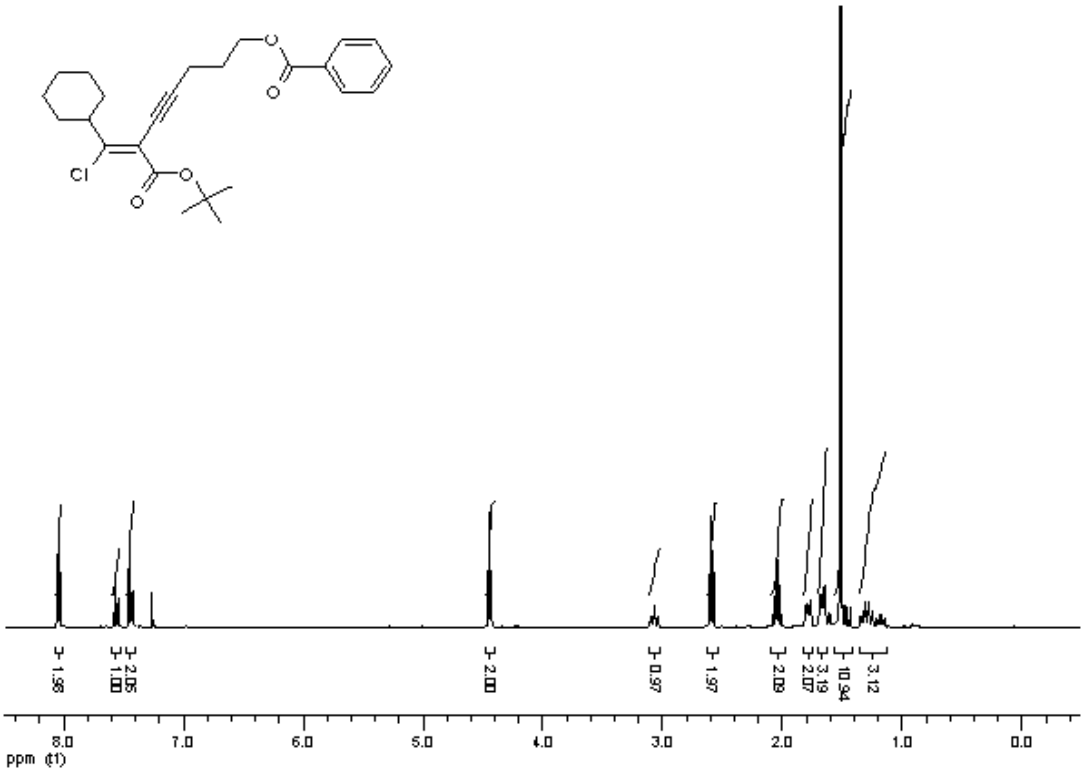

153.164
90.362
82.758
77.317
77.000
76.682
74.347
31.510
28.836
27.988
25.595
24.698
150
100
50
ppm (t1)

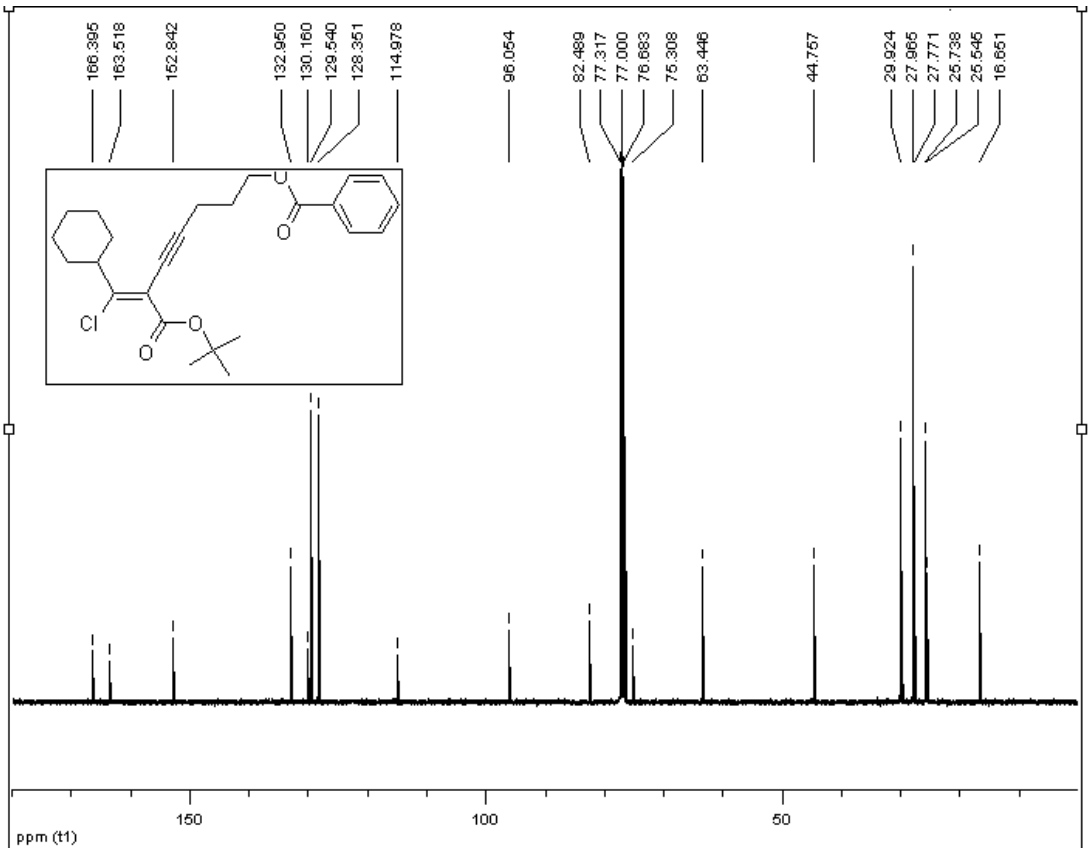
34


Cl
I
O
O
1.00
2.11
3.17
11.89
3.25
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

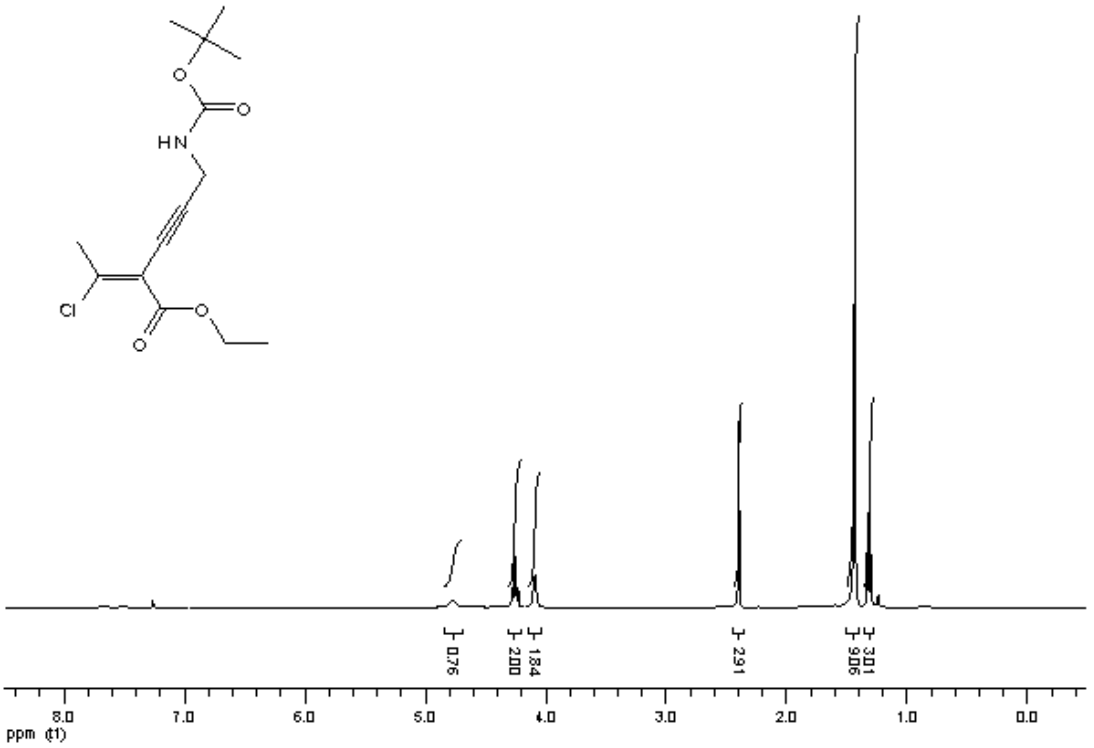

164.209
140.917
83.272
80.488
77.317
77.000
76.683
48.058
29.611
27.763
25.595
25.479
Cl
I
O
O
150
100
50
ppm (t1)

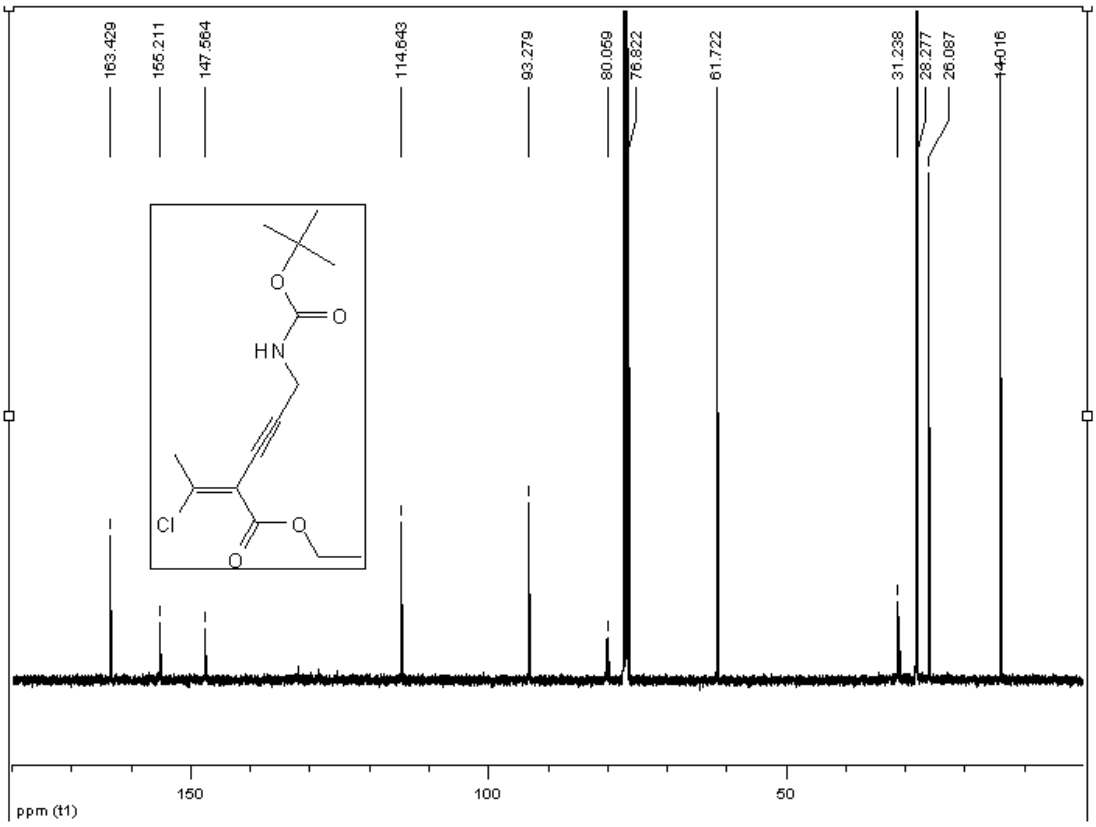
35


Cl
O
O
O
O
1.96
1.00
2.05
2.00
0.97
1.97
2.09
3.19
2.07
10.94
3.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

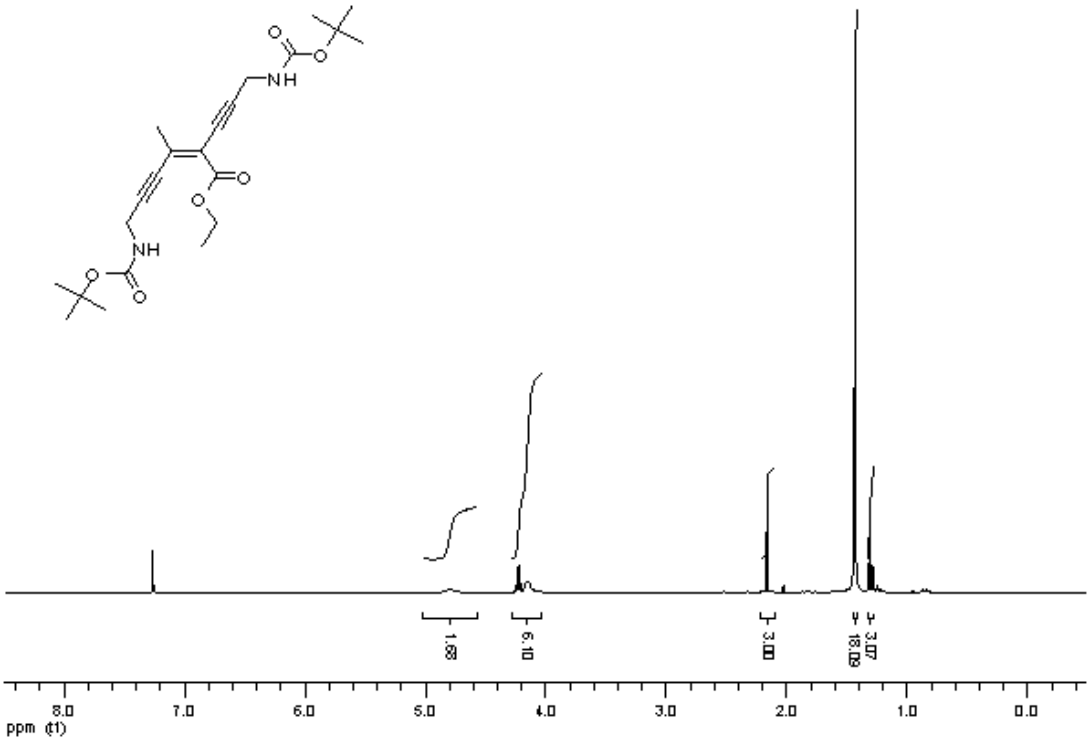

166.395
163.518
152.842
132.950
130.160
129.540
128.351
114.978
96.054
82.489
77.317
77.000
76.683
75.308
63.446
44.757
29.924
27.965
27.771
25.738
25.545
16.661
Cl
O
O
O
O
150
100
50
ppm (t1)

46

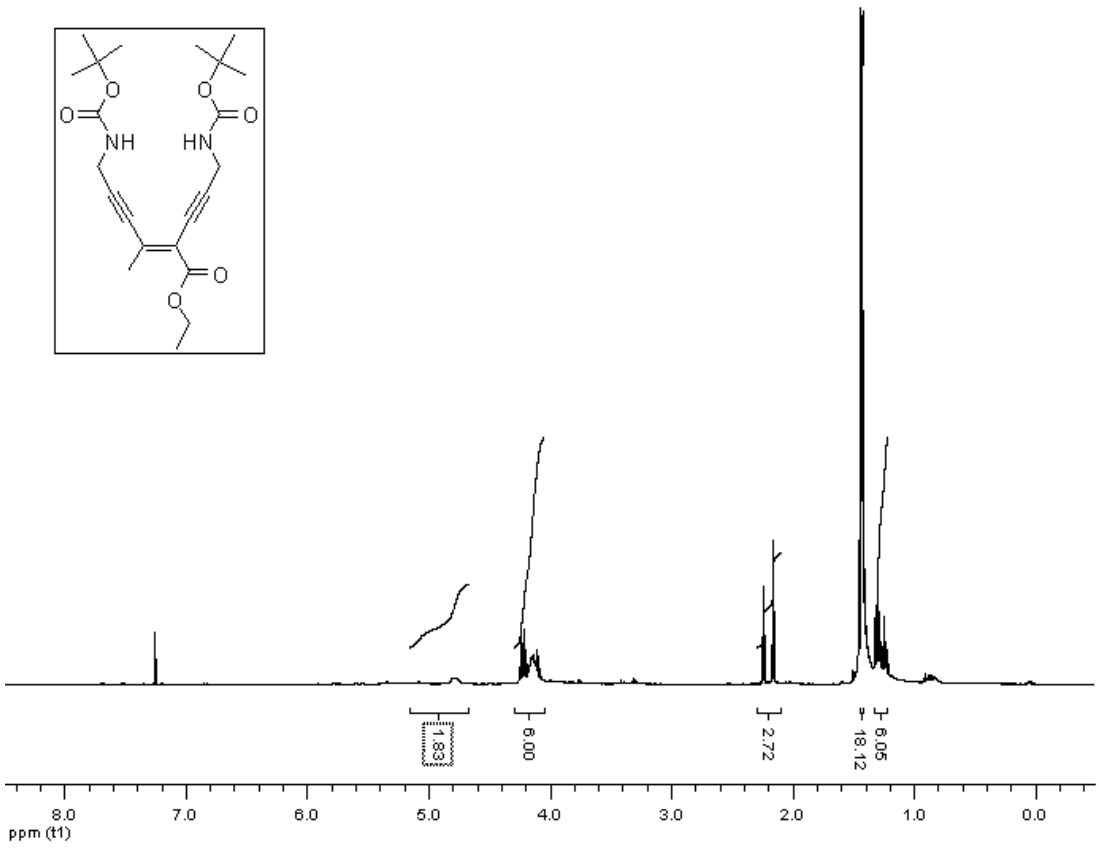

HN
Cl
O
O
O
O
0.76
2.00
1.84
1.91
9.06
2.01
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


163.429
155.211
147.564
114.843
93.279
80.059
76.822
61.722
31.238
28.277
26.087
14.016
HN
Cl
O
O
O
O
150
100
50
ppm (t1)

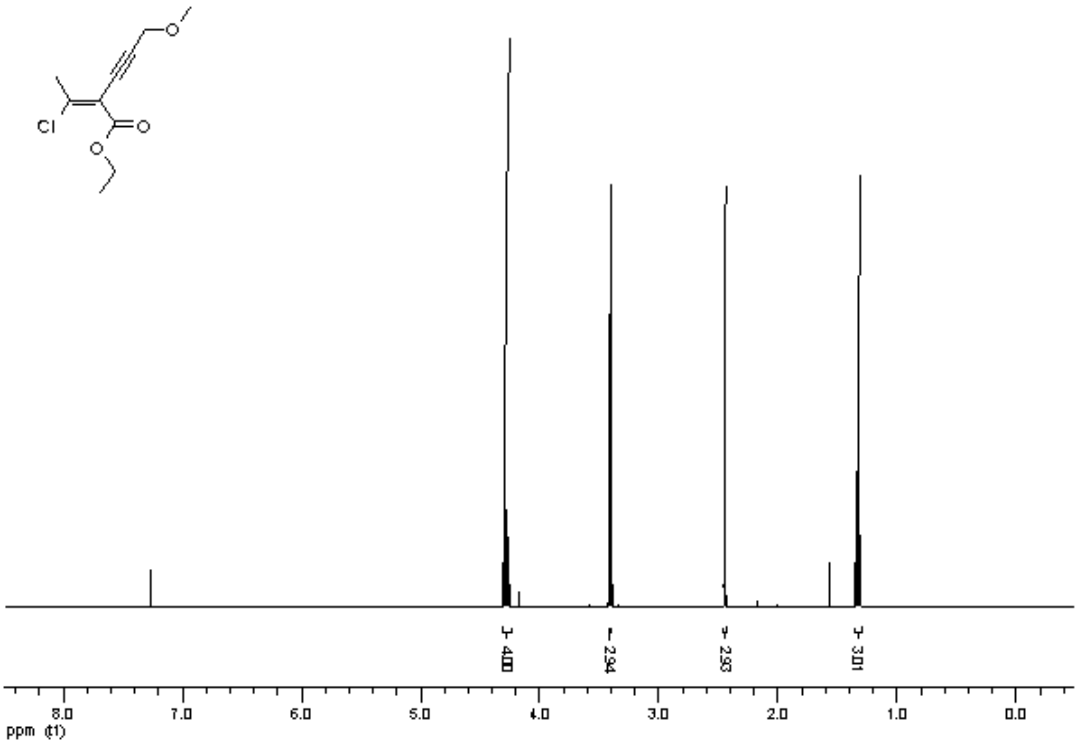
47 trans

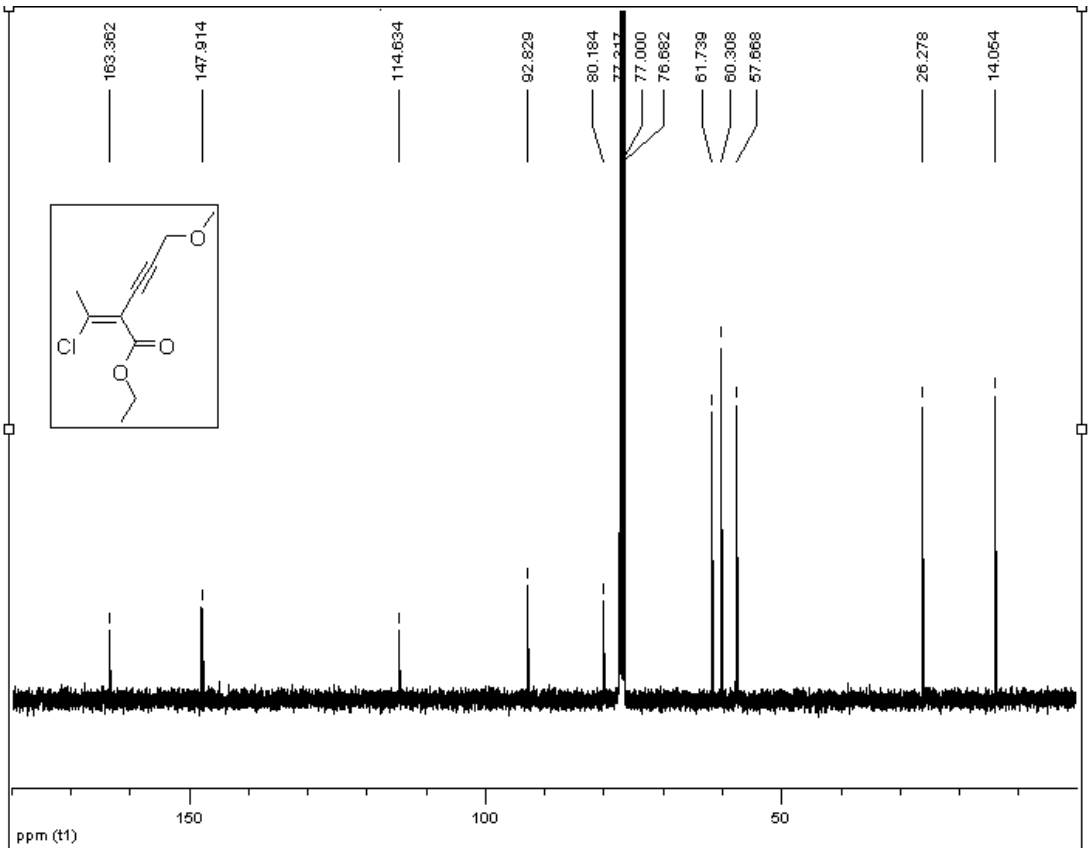


47 cis

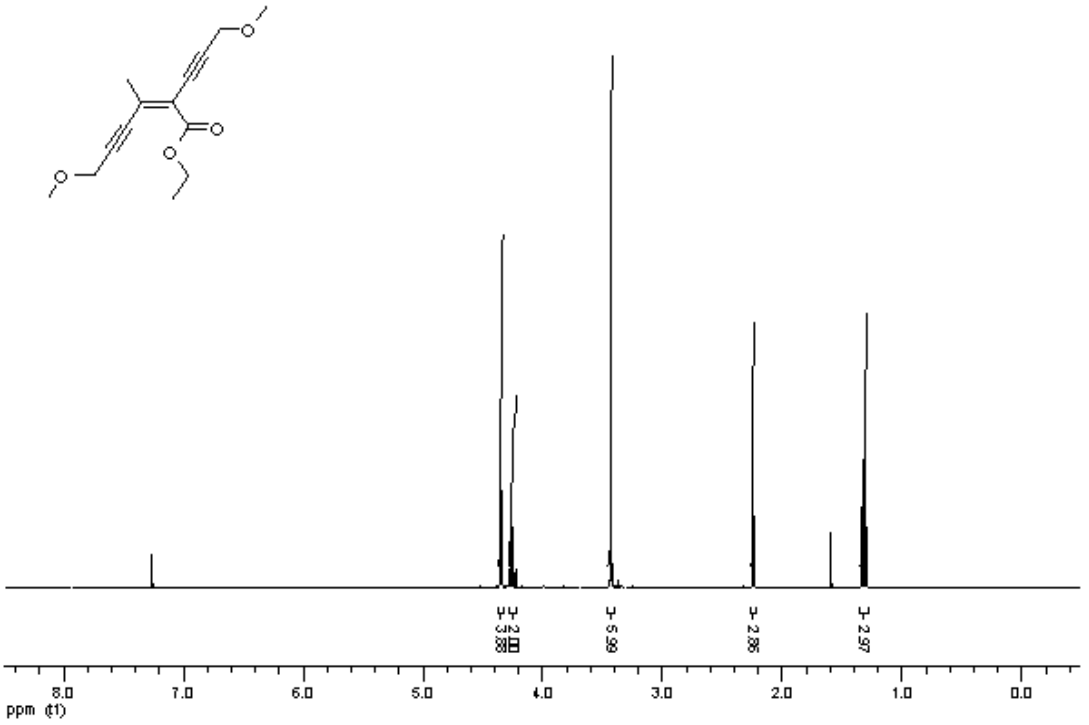


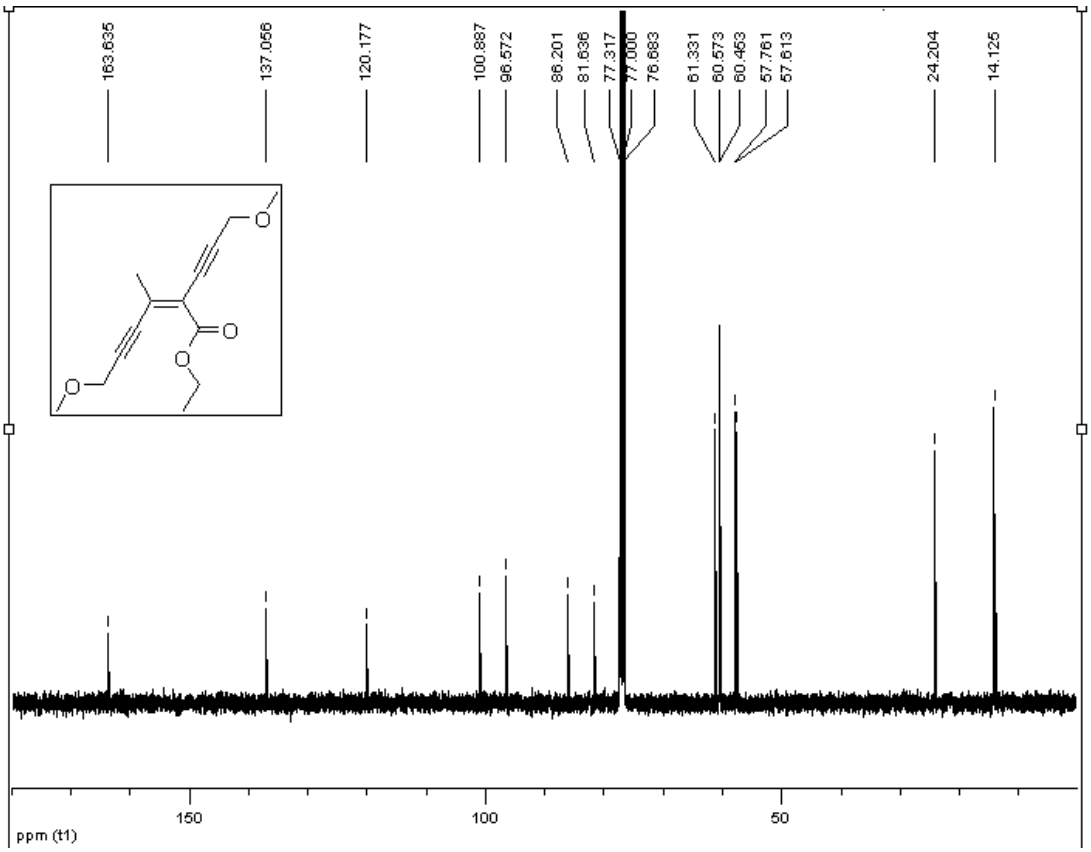
54


Cl
O
O
O
4.00
2.94
2.93
3.01
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

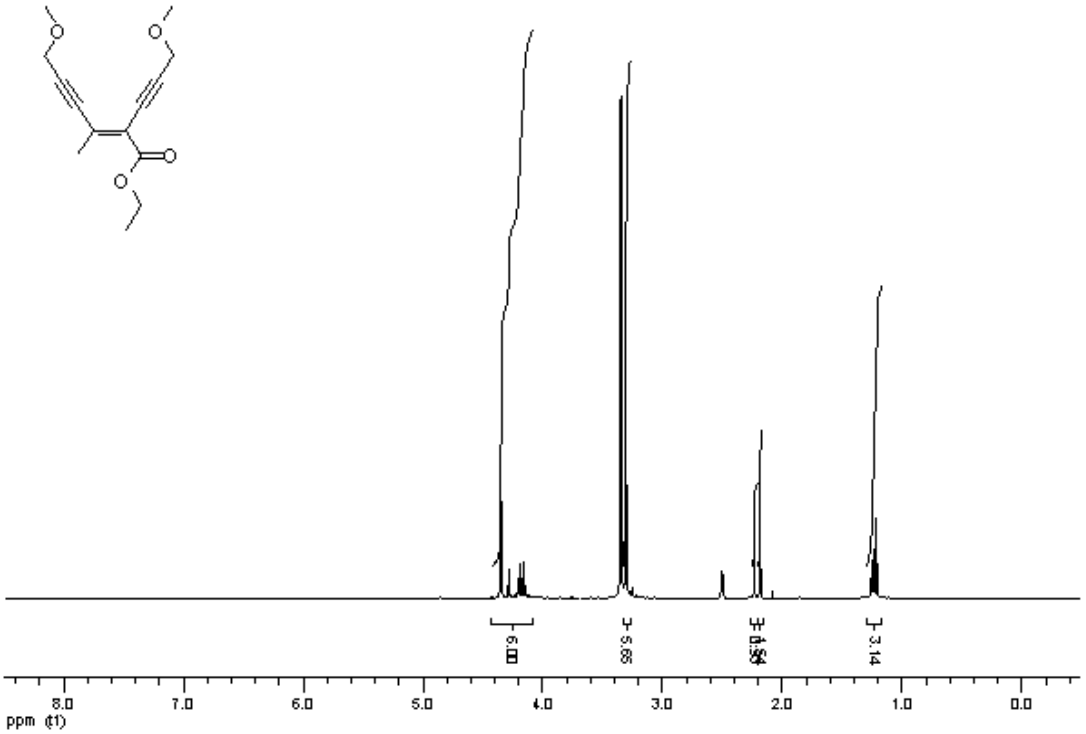

163.362
147.914
114.634
92.829
80.184
77.317
77.000
76.682
61.739
60.308
57.668
26.278
14.054
Cl
O
O
O
150
100
50
ppm (t1)

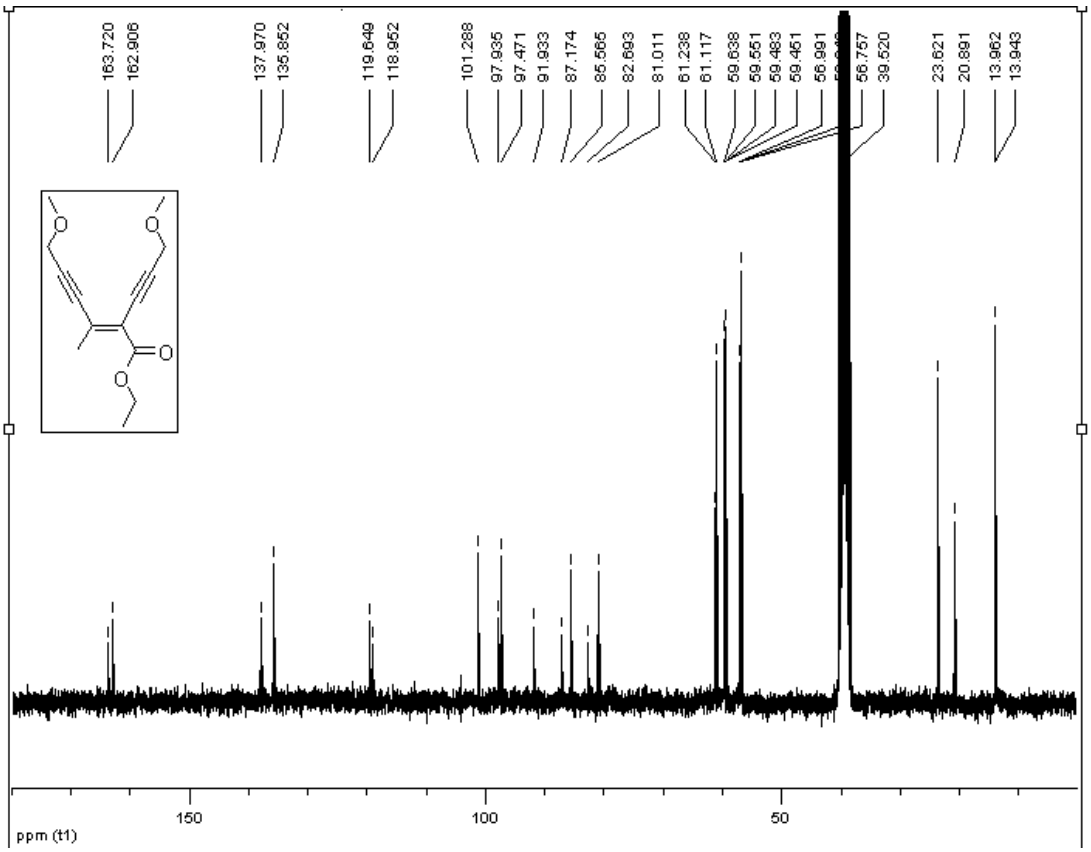
55 *trans*


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

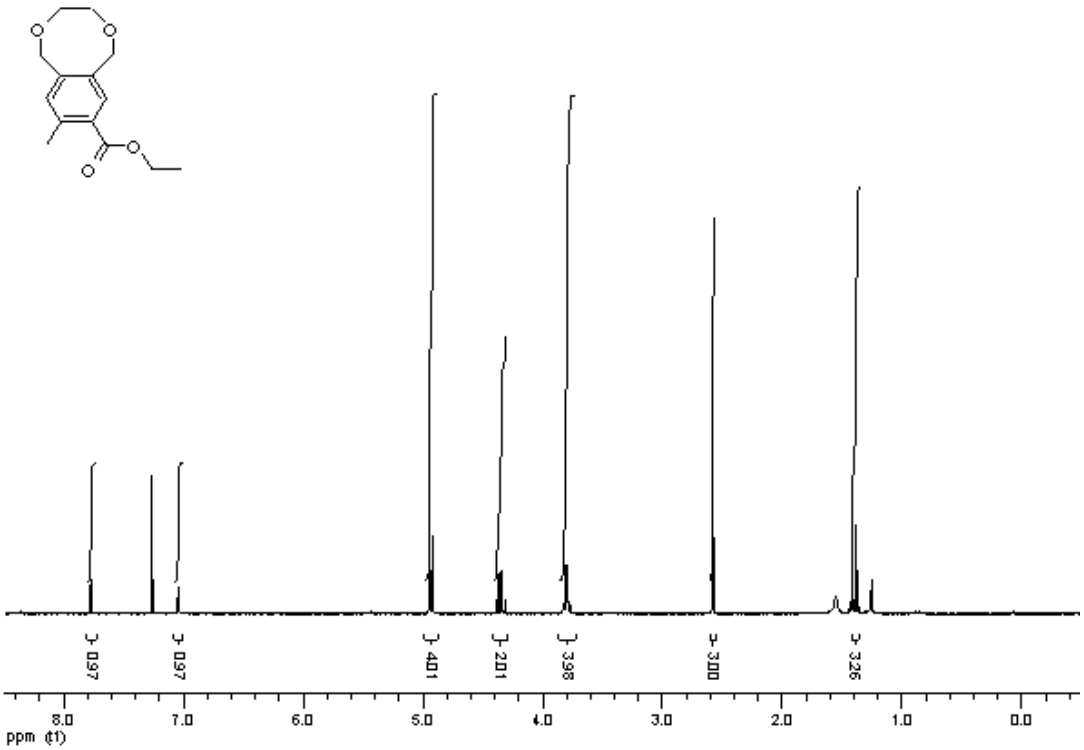

163.635
137.056
120.177
100.887
96.572
86.201
81.636
77.317
77.000
76.683
61.331
60.573
60.463
57.761
57.613
24.204
14.125
150
100
50
ppm (t1)

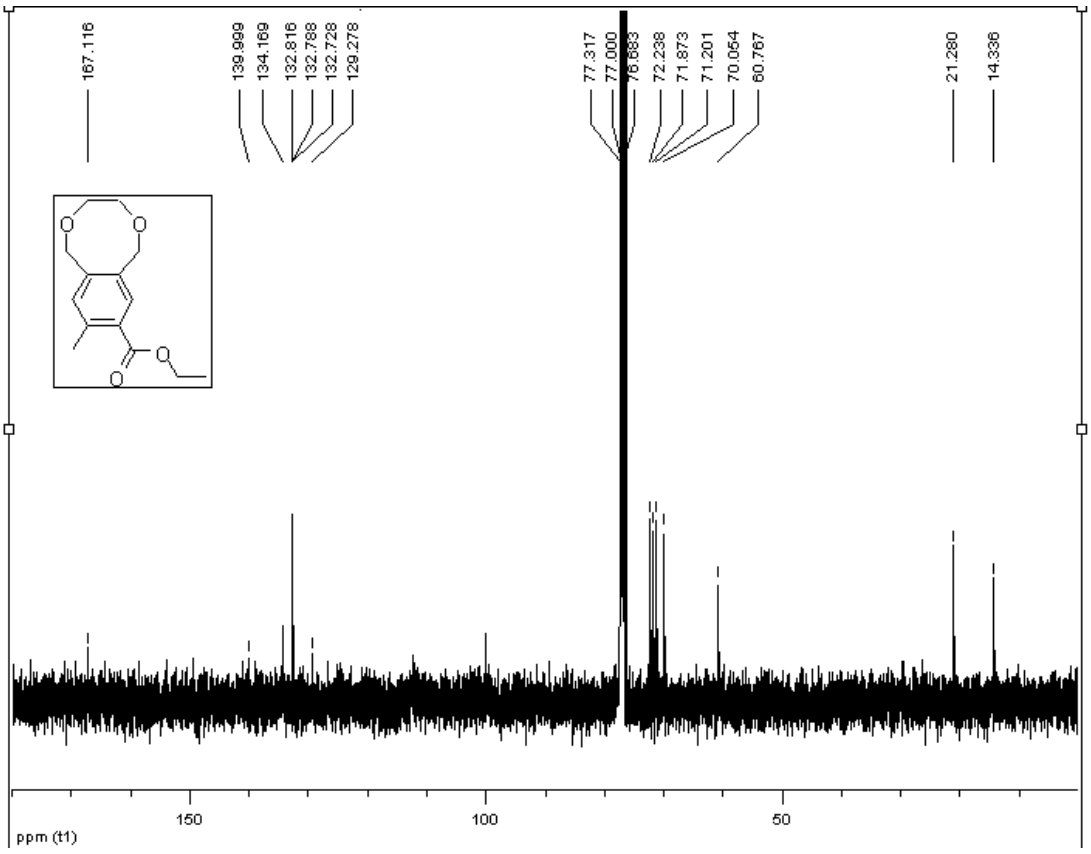
55 *cis*


6.00
5.66
4.00
3.14
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

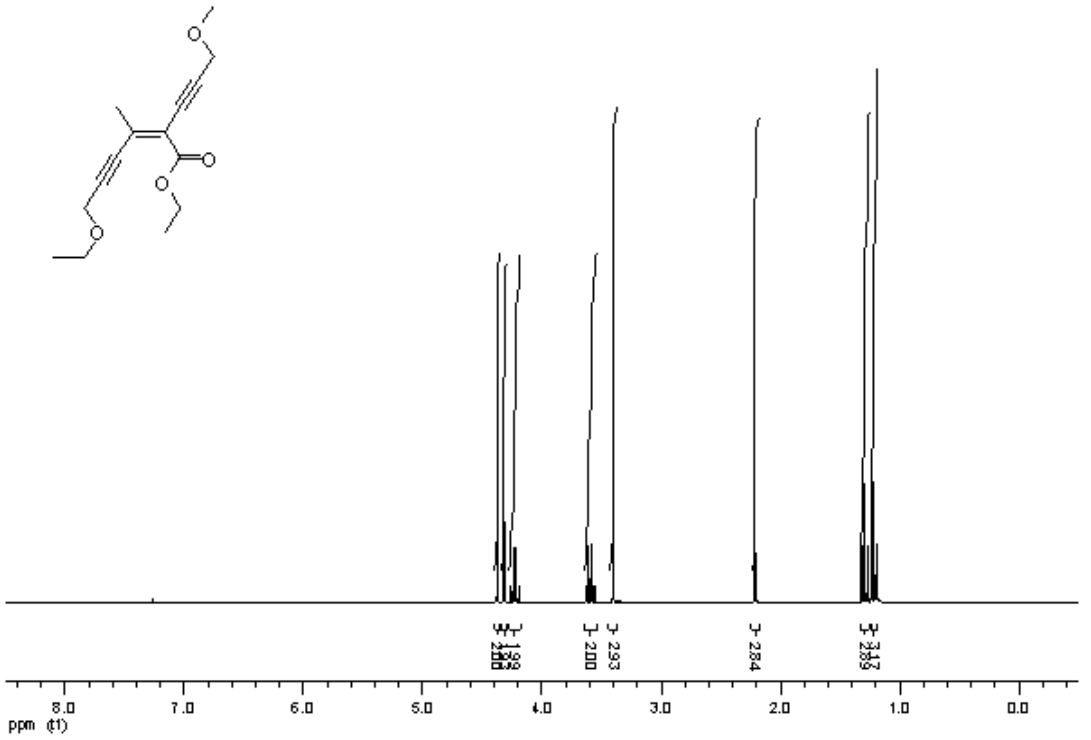

163.720
162.906
137.970
135.852
119.649
118.952
101.288
97.935
97.471
91.933
87.174
85.565
82.893
81.011
61.238
61.117
59.638
59.551
59.483
59.461
56.991
56.757
39.520
23.621
20.891
13.962
13.943
150
100
50
ppm (t1)

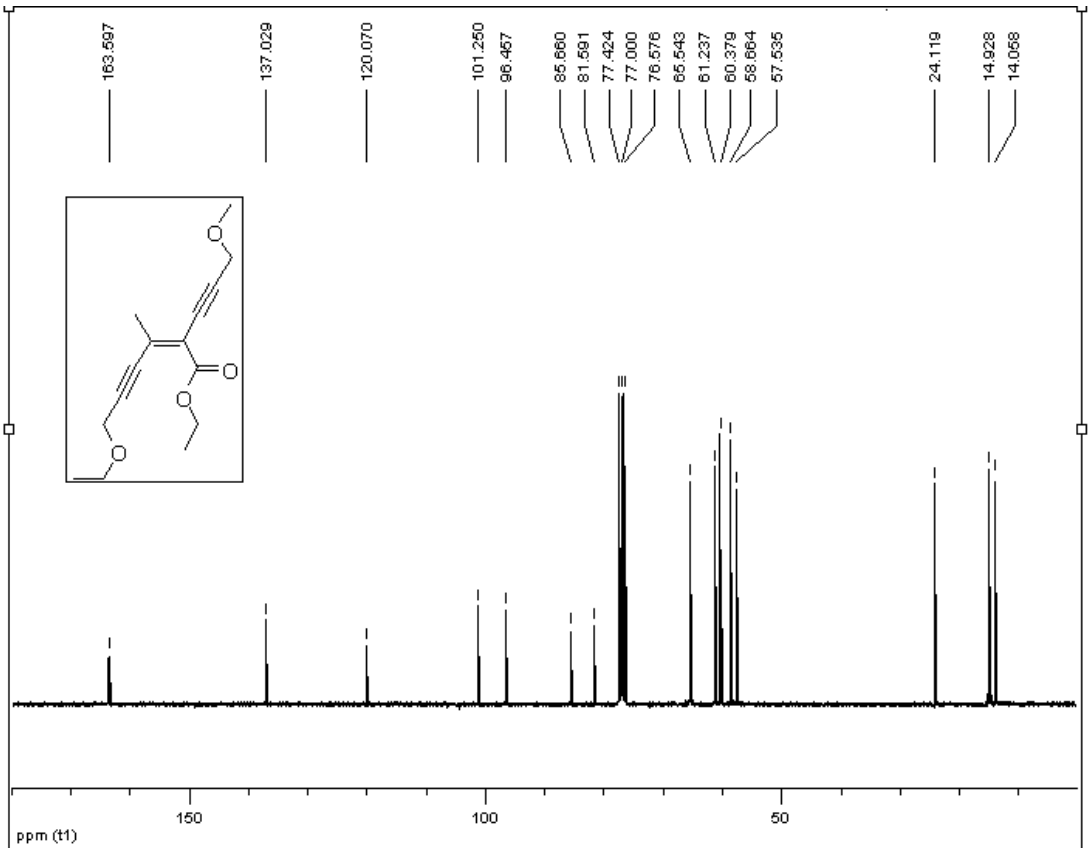
57


0.937
0.937
1.000
2.011
3.398
3.000
3.326
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

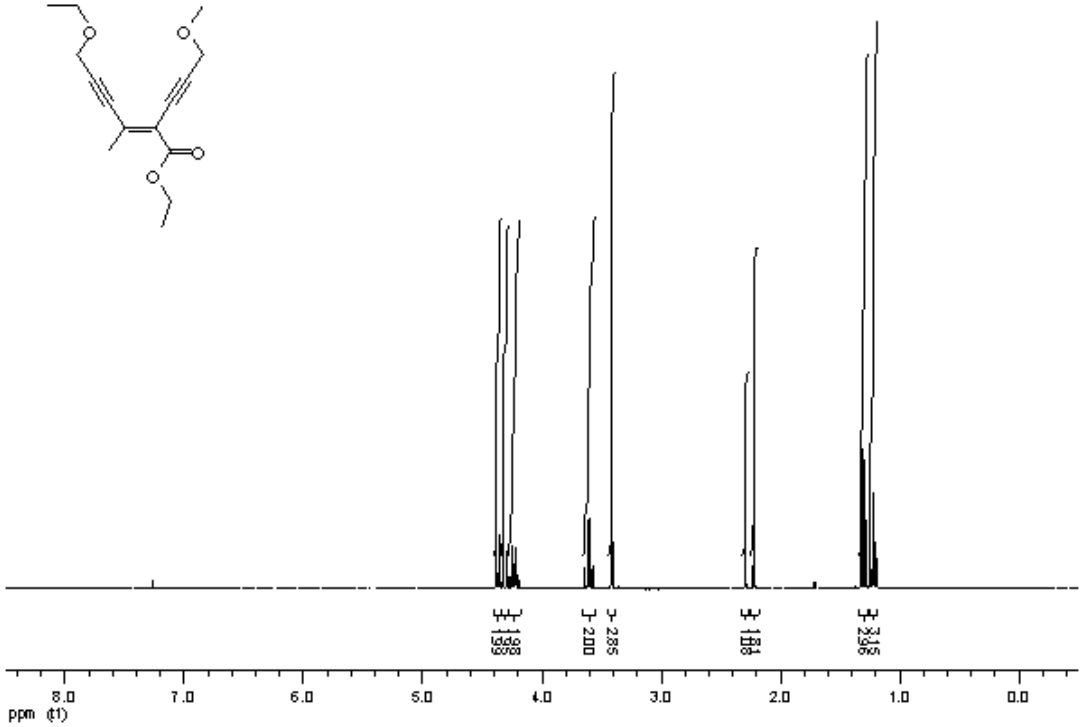

167.116
139.999
134.169
132.816
132.788
132.728
129.278
77.317
77.000
76.683
72.238
71.873
71.201
70.054
60.767
21.280
14.336
150
100
50
ppm (t1)

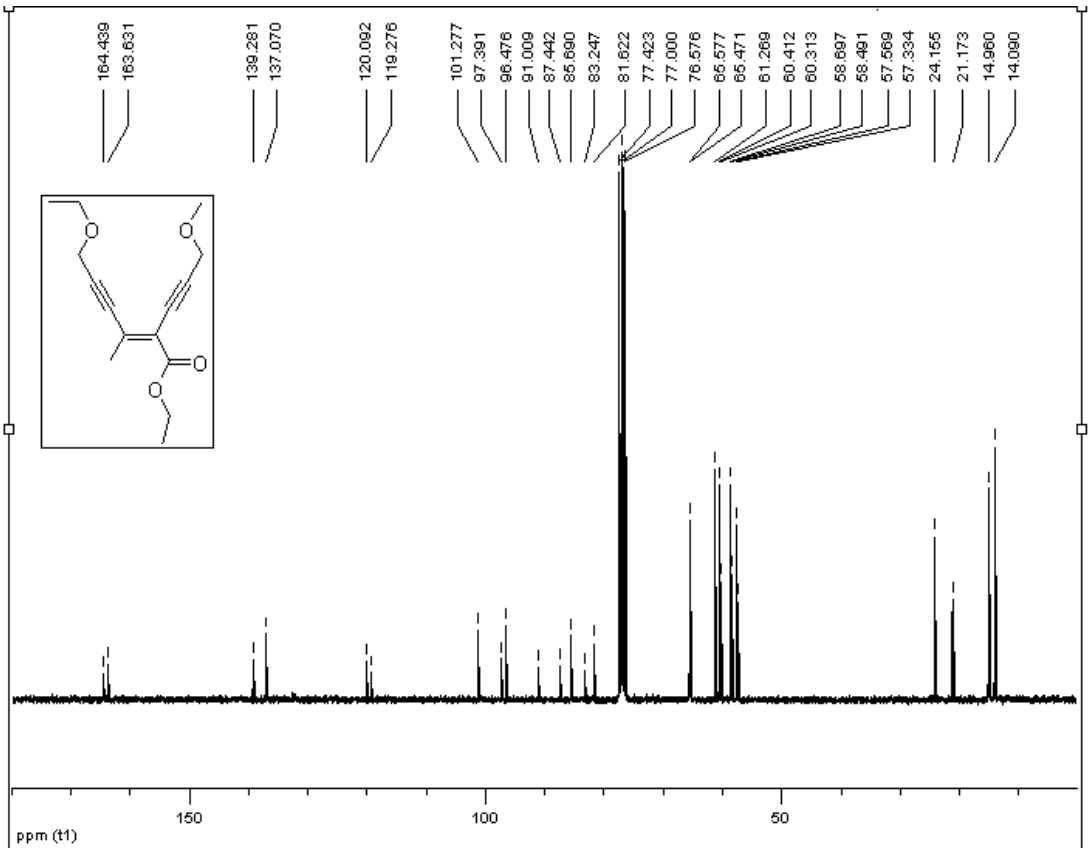
59a *trans*


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

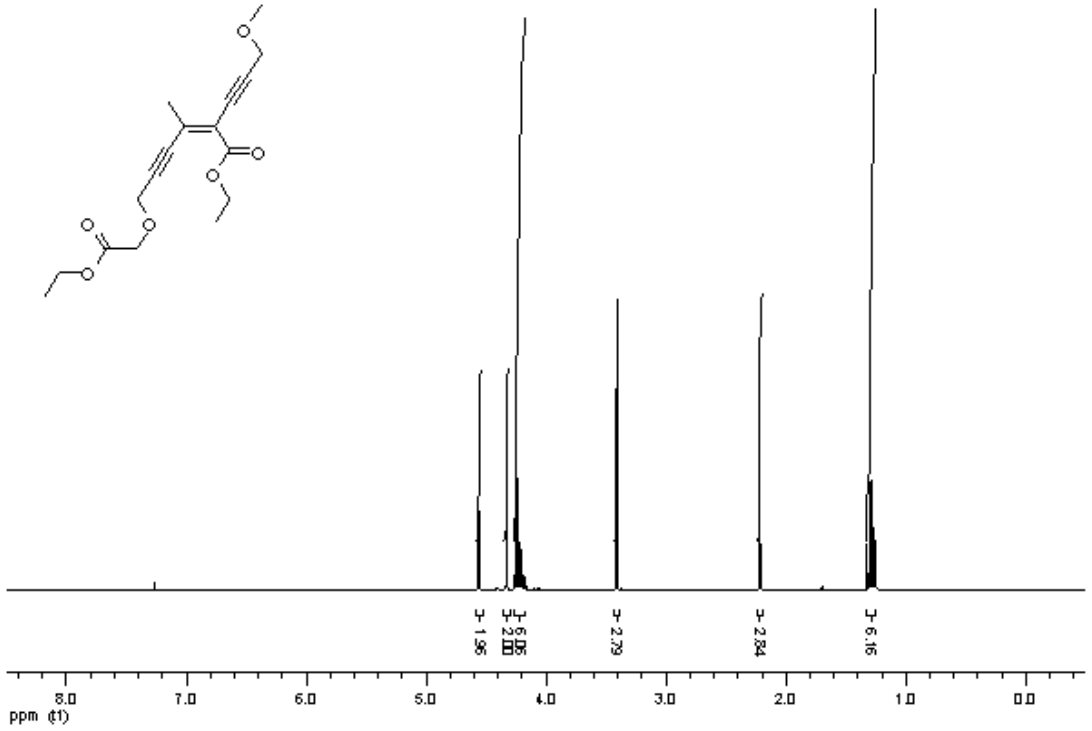

163.597
137.029
120.070
101.250
96.467
85.660
81.591
77.424
77.000
76.576
65.543
61.237
60.379
58.664
57.535
24.119
14.928
14.058
150
100
50
ppm (t1)

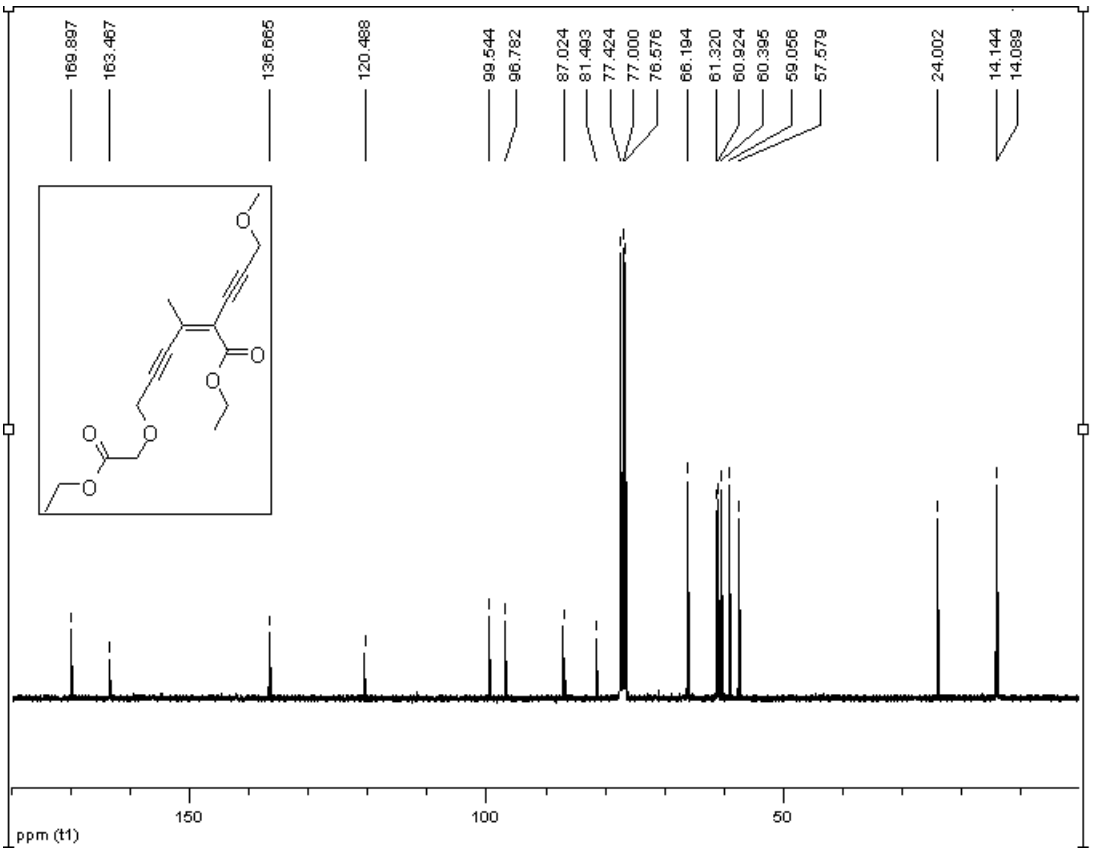
59a *cis*


1.993
1.983
2.000
2.285
1.881
2.595
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

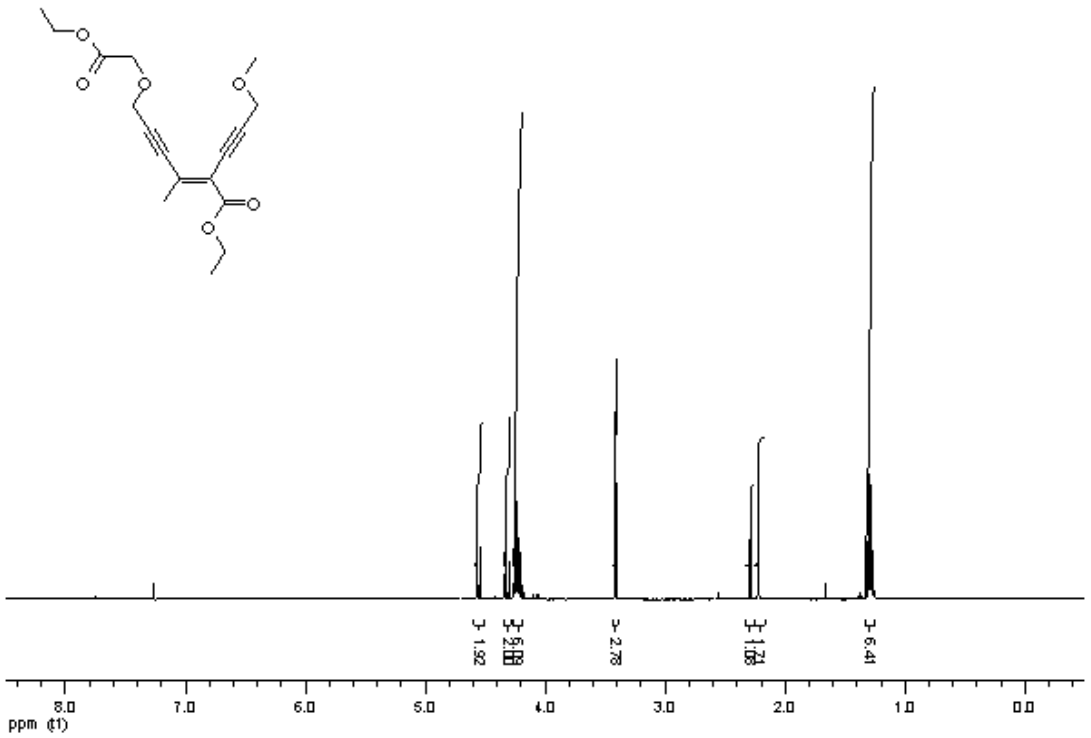

164.439
163.631
139.281
137.070
120.092
119.276
101.277
97.391
96.476
91.009
87.442
85.690
83.247
81.622
77.423
77.000
76.576
65.577
65.471
61.269
60.412
60.313
58.697
58.491
57.569
57.334
24.155
21.173
14.960
14.090
150
100
50
ppm (t1)

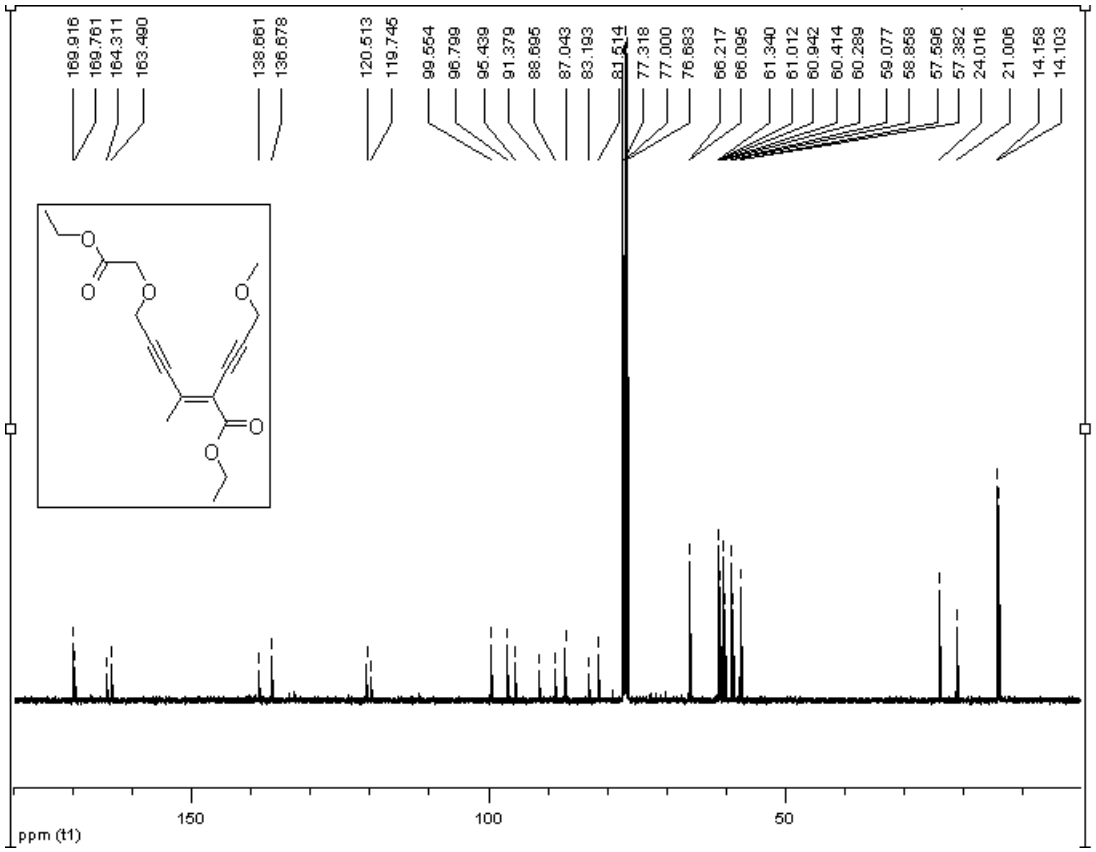
59b *trans*


4.16
2.84
2.79
2.00
1.96
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

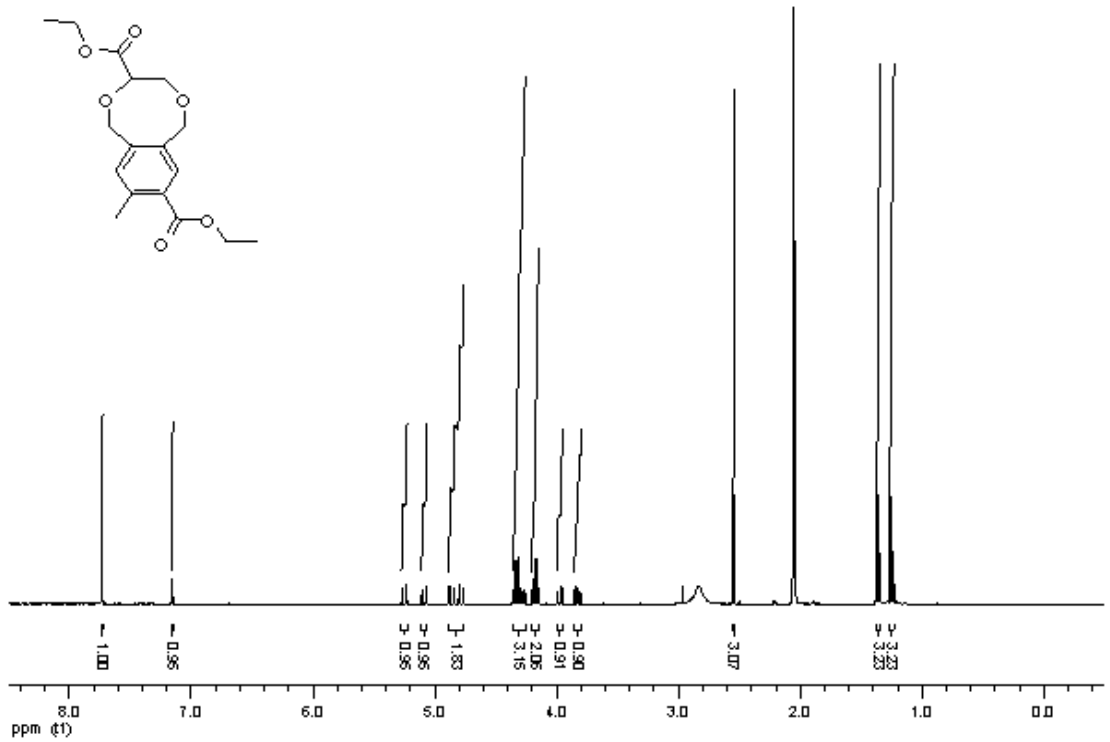

169.897
163.467
136.865
120.488
99.544
96.782
87.024
81.493
77.424
77.000
76.576
66.194
61.320
60.924
60.395
59.056
57.579
24.002
14.144
14.089
150
100
50
ppm (t1)

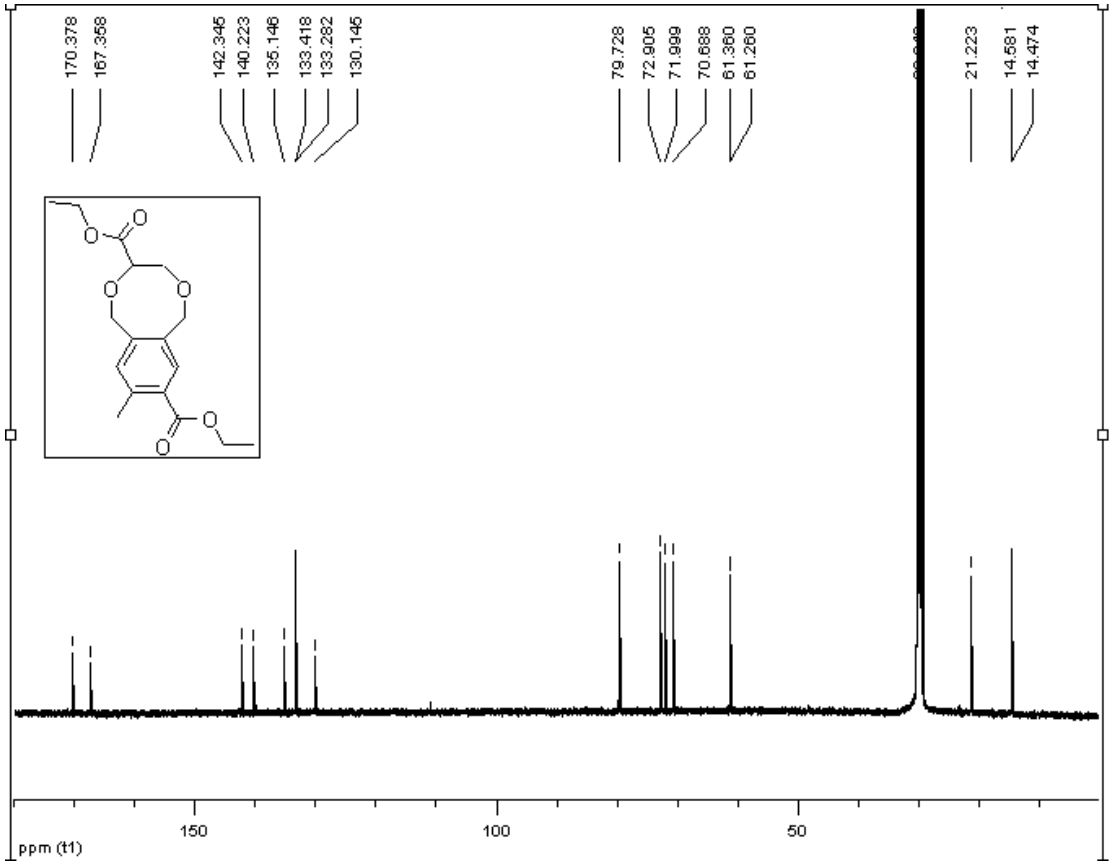
59b *cis*


4.32
2.78
6.41
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

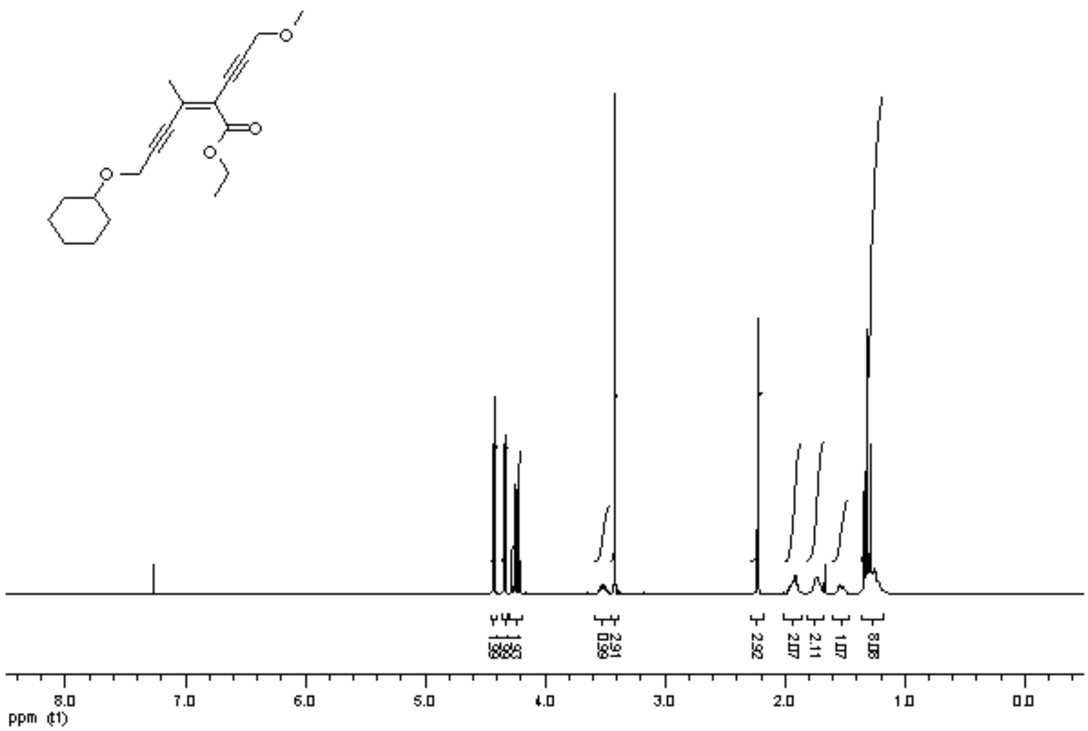

169.916
169.761
164.311
163.490
138.861
136.678
120.513
119.745
99.554
96.799
95.439
91.379
88.695
87.043
83.193
81.514
77.318
77.000
76.683
66.217
66.095
61.340
61.012
60.942
60.414
60.289
59.077
58.858
57.596
57.382
24.016
21.006
14.158
14.103
150
100
50
ppm (t1)

63

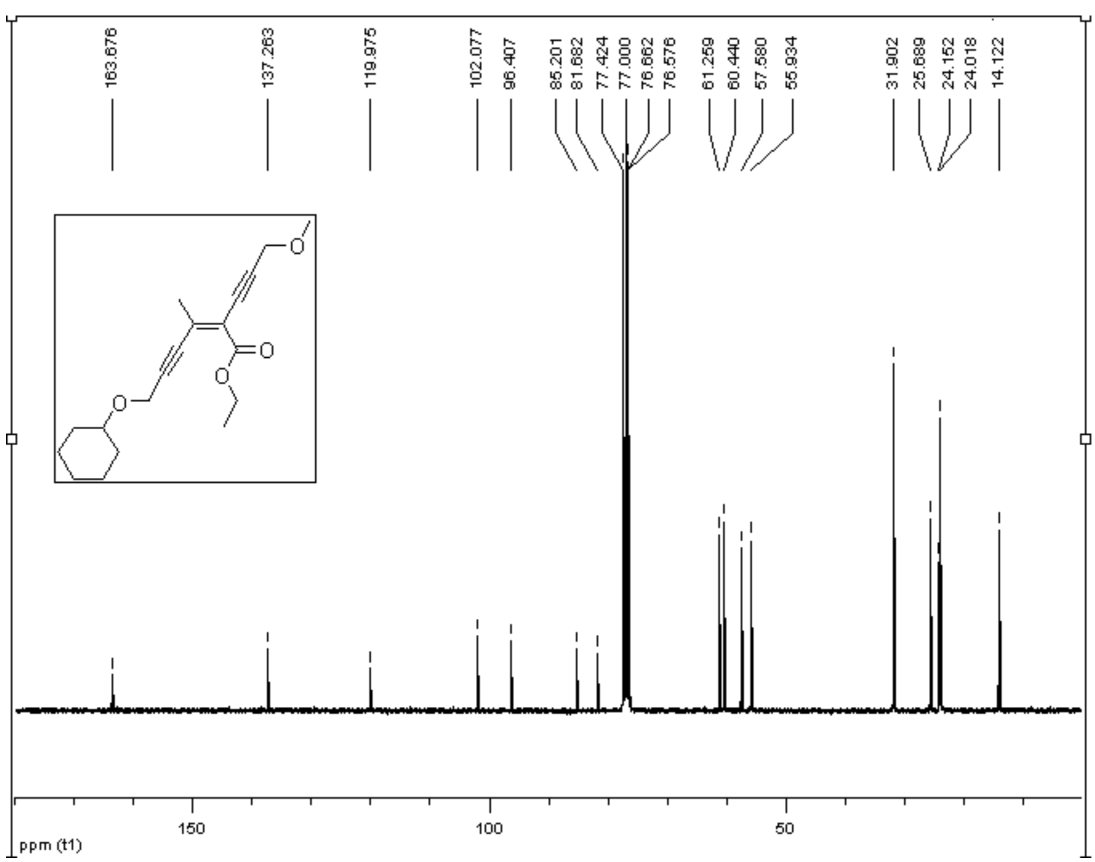

1.00
0.96
0.96
0.96
1.83
3.15
2.06
0.91
0.90
3.07
3.33
3.33
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


170.378
167.368
142.345
140.223
135.146
133.418
133.282
130.145
79.728
72.905
71.999
70.688
61.360
61.260
21.223
14.581
14.474
150
100
50
ppm (t1)

59e *trans*

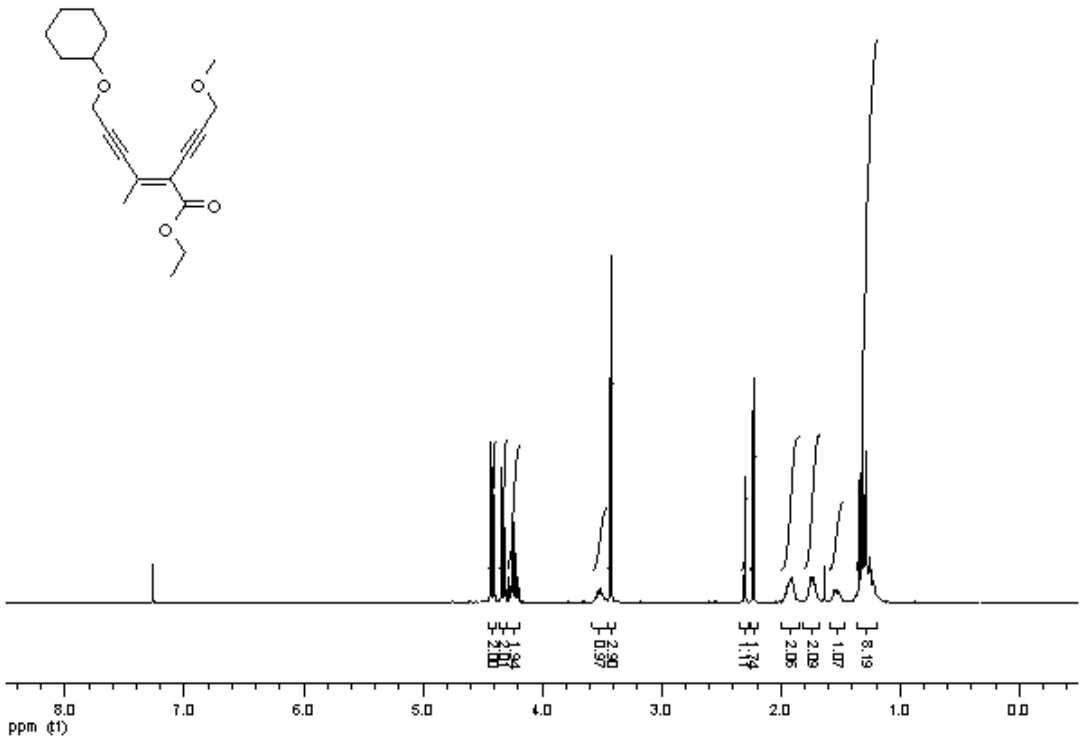


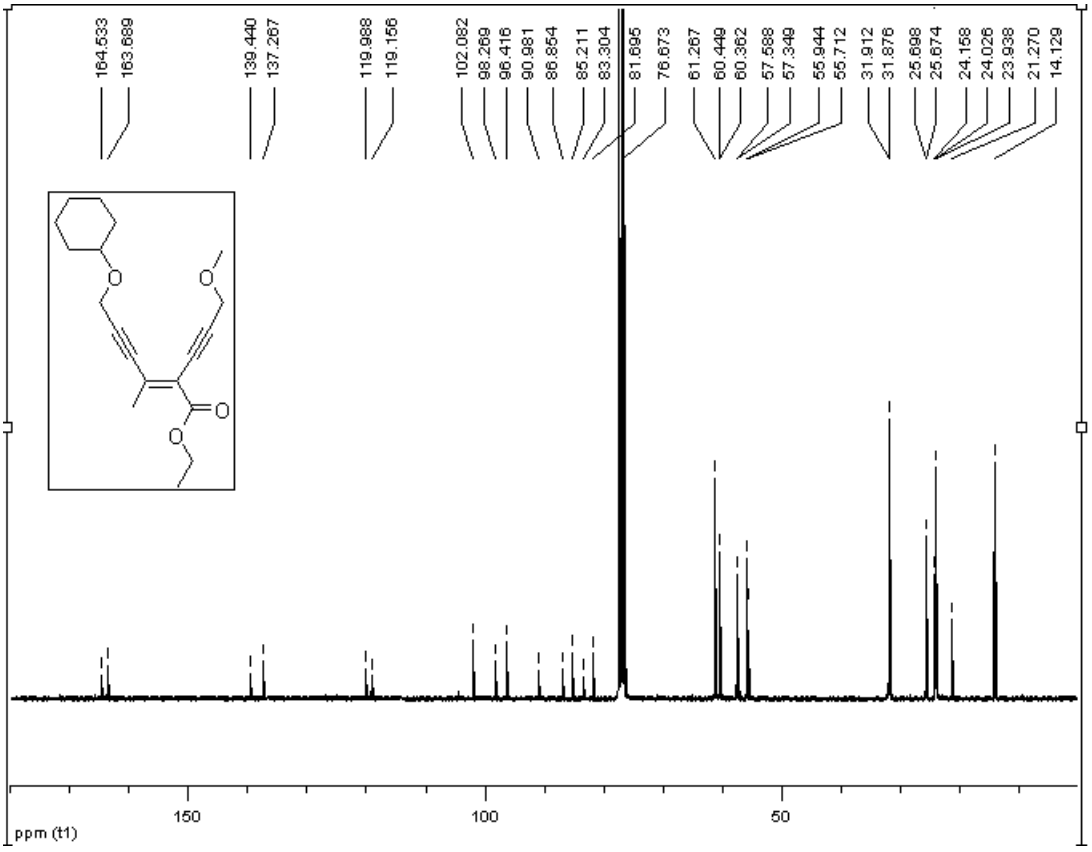
2.92
2.07
2.11
1.07
8.08
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)



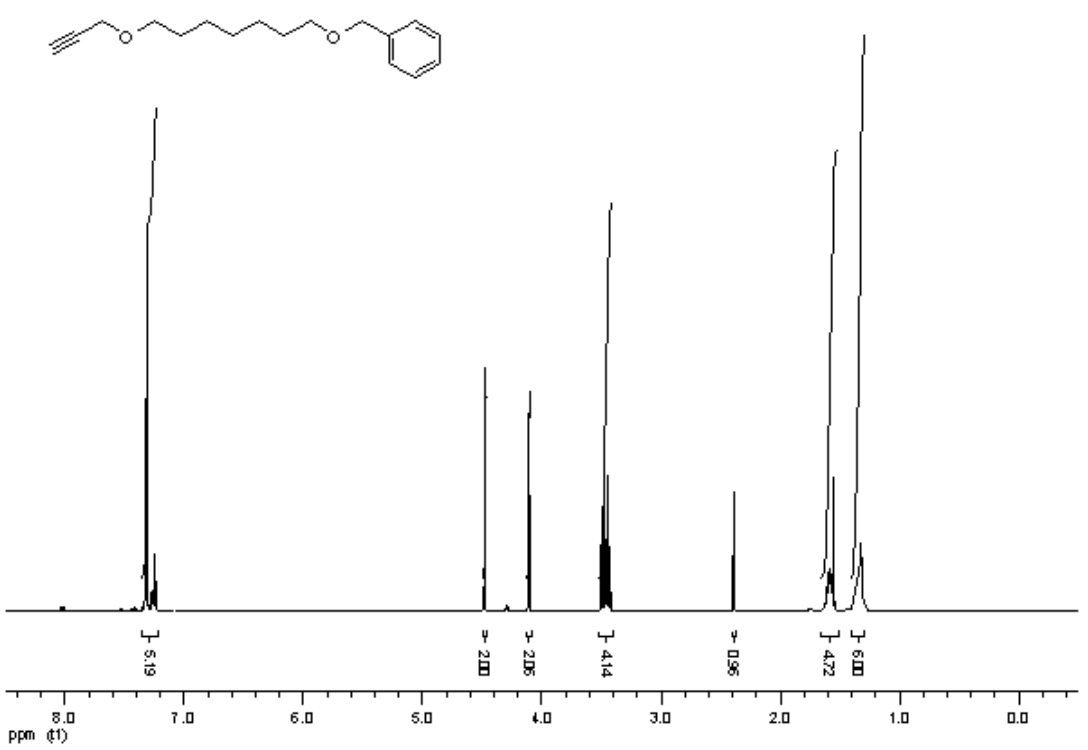
163.676
137.263
119.975
102.077
96.407
85.201
81.682
77.424
77.000
76.662
76.576
61.259
60.440
57.580
55.934
31.902
25.689
24.152
24.018
14.122
150
100
50
ppm (t1)

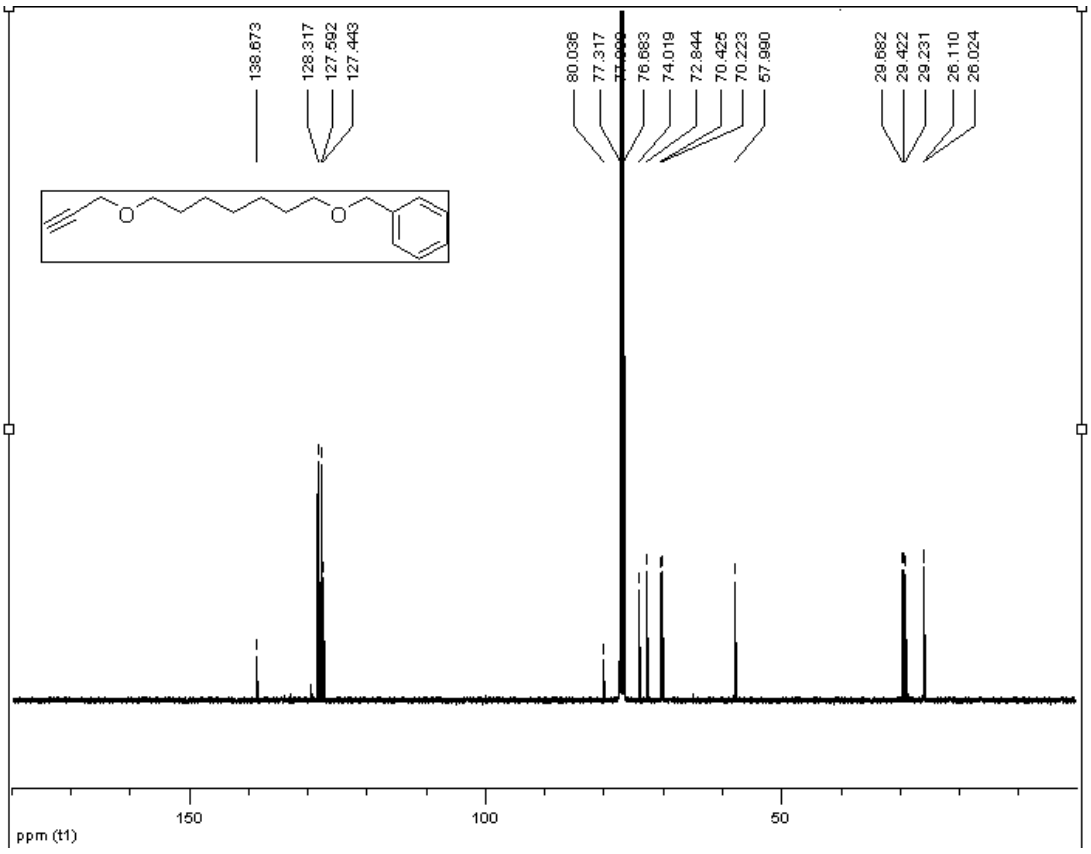
59e *cis*


8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

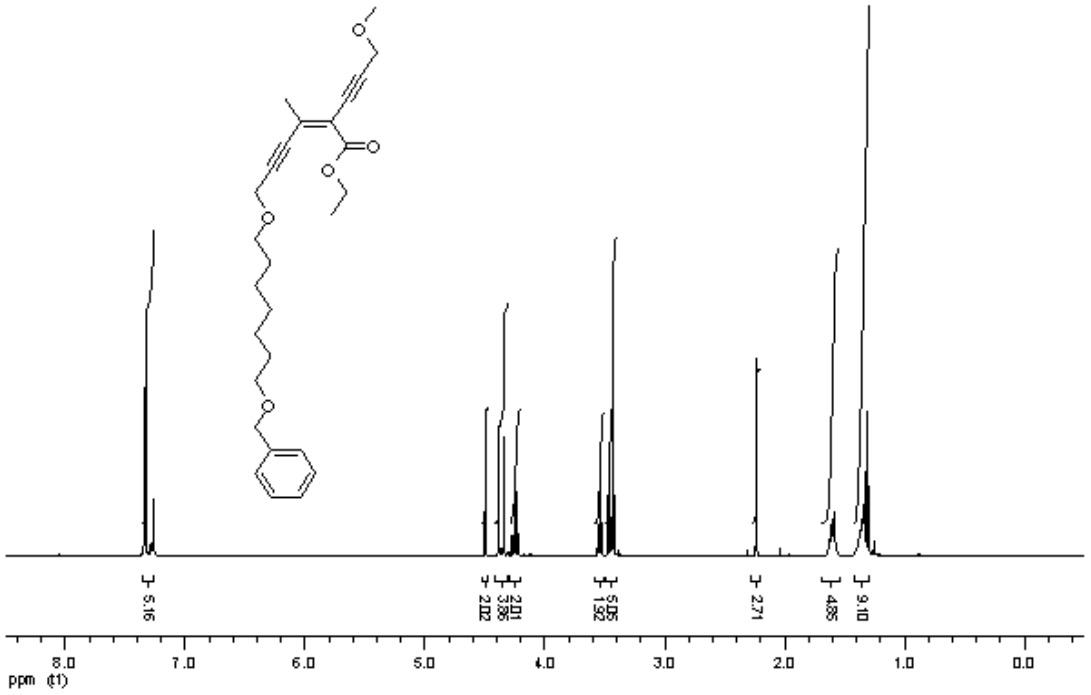

164.533
163.689
139.440
137.267
119.988
119.156
102.082
98.269
96.416
90.981
86.854
85.211
83.304
81.695
76.673
61.267
60.449
60.382
57.588
57.349
55.944
55.712
31.912
31.876
25.698
25.674
24.158
24.026
23.938
21.270
14.129
150
100
50
ppm (t1)

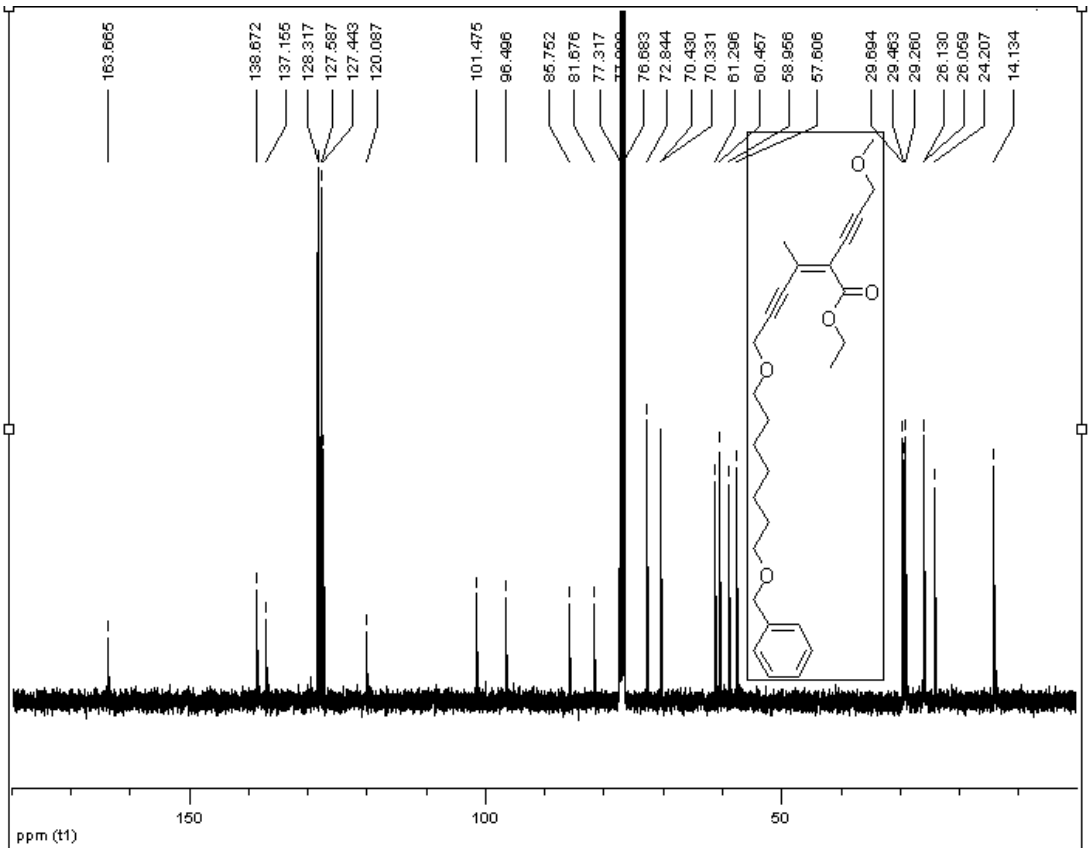
58d


5.19
2.00
2.05
4.14
0.96
4.72
6.00
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

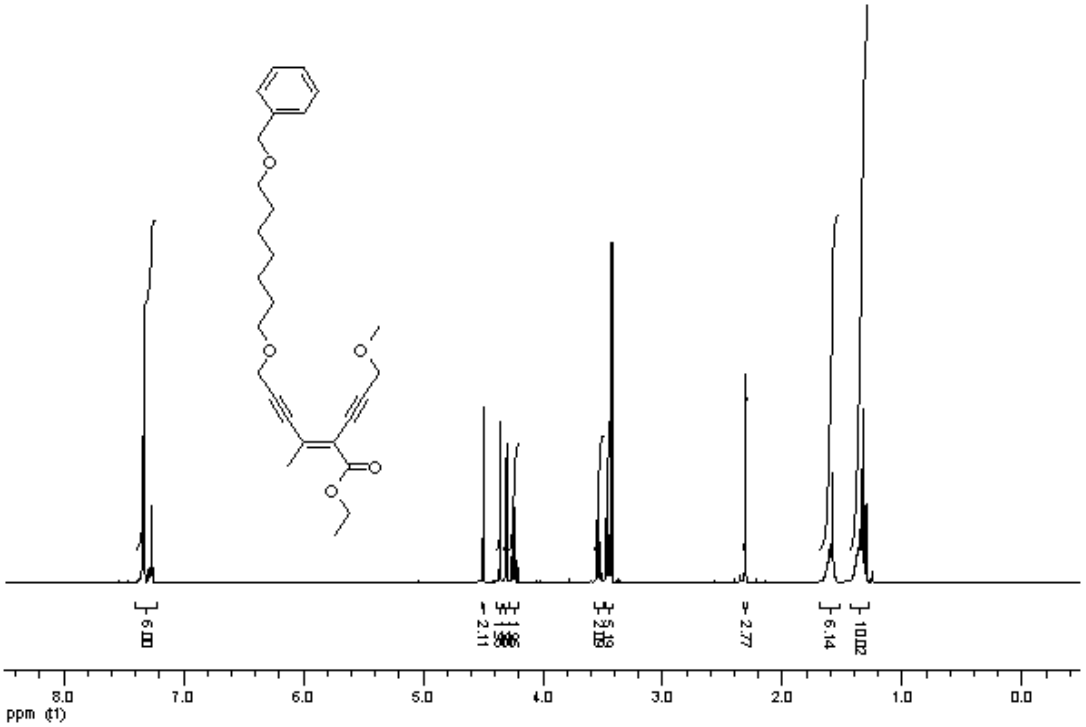

138.673
128.317
127.592
127.443
80.036
77.317
76.683
74.019
72.844
70.425
70.223
57.990
29.682
29.422
29.231
26.110
26.024
150
100
50
ppm (t1)

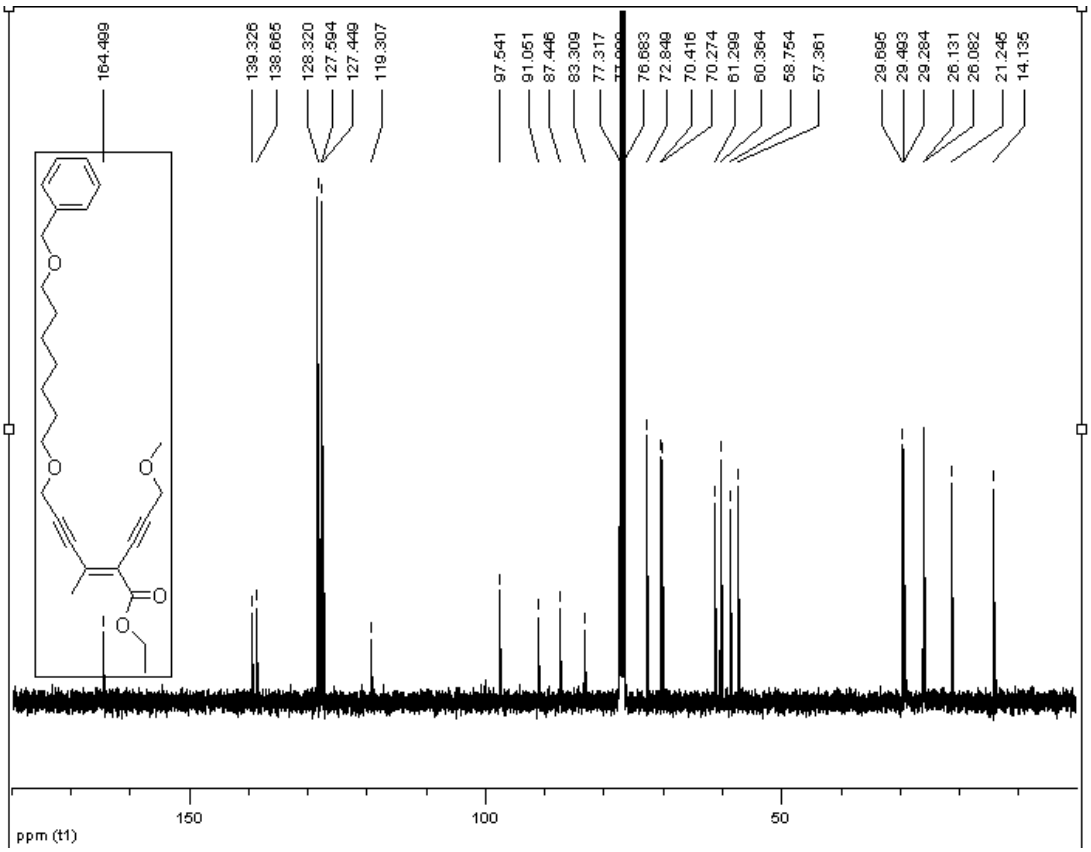
59d *trans*


5.16
2.02
3.86
2.01
1.92
5.05
2.71
4.85
9.10
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

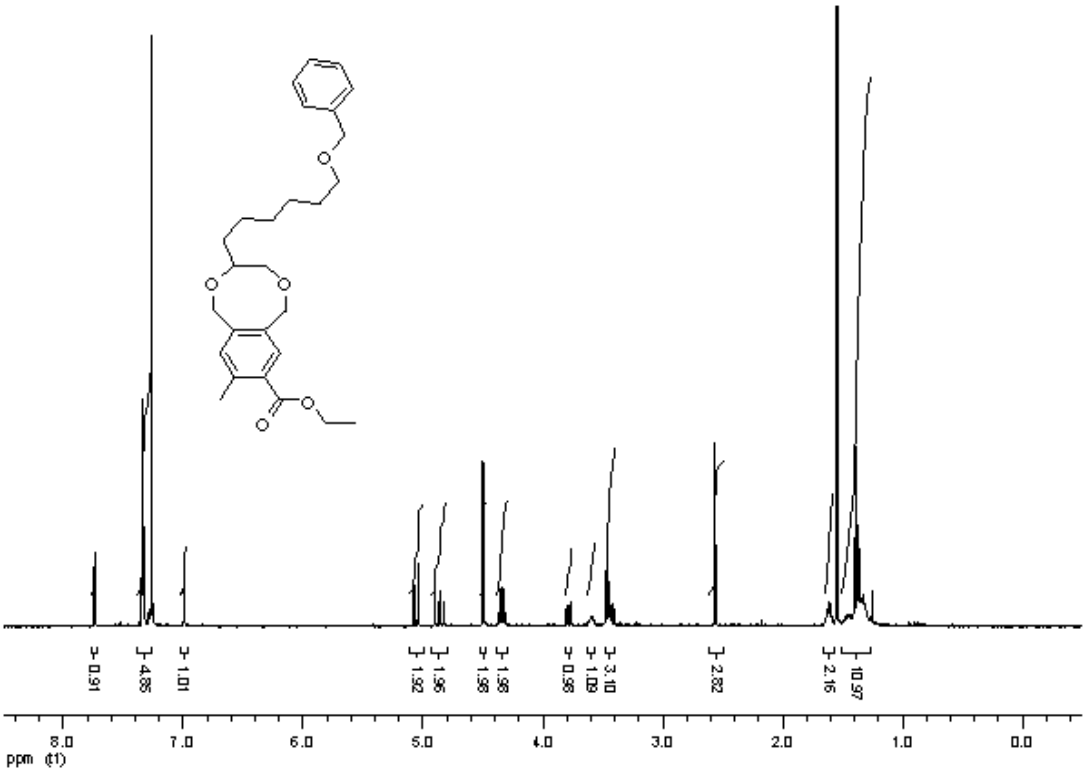

163.665
138.672
137.155
128.317
127.587
127.443
120.087
101.475
96.496
85.752
81.676
77.317
76.683
72.844
70.430
70.331
61.296
60.457
58.956
57.606
29.694
29.463
29.260
26.130
26.059
24.207
14.134
150
100
50
ppm (t1)

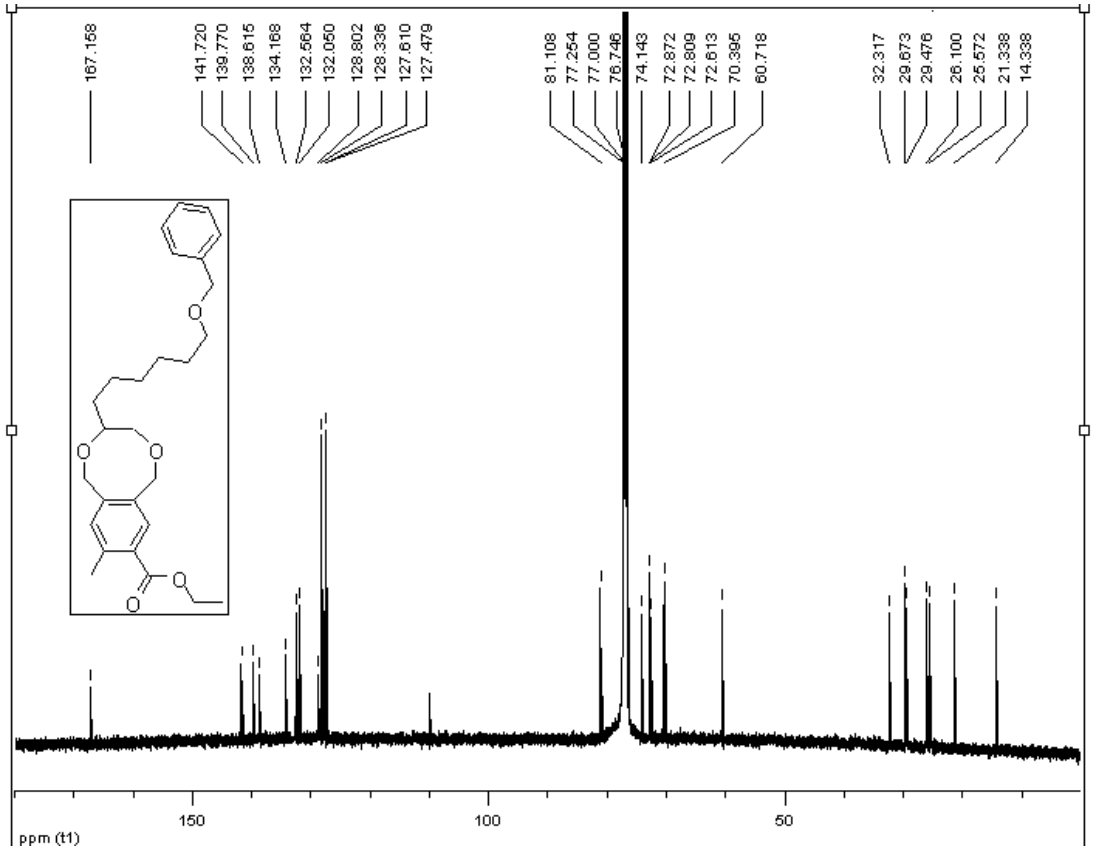
59d *cis*


6.00
2.11
2.77
9.14
10.02
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

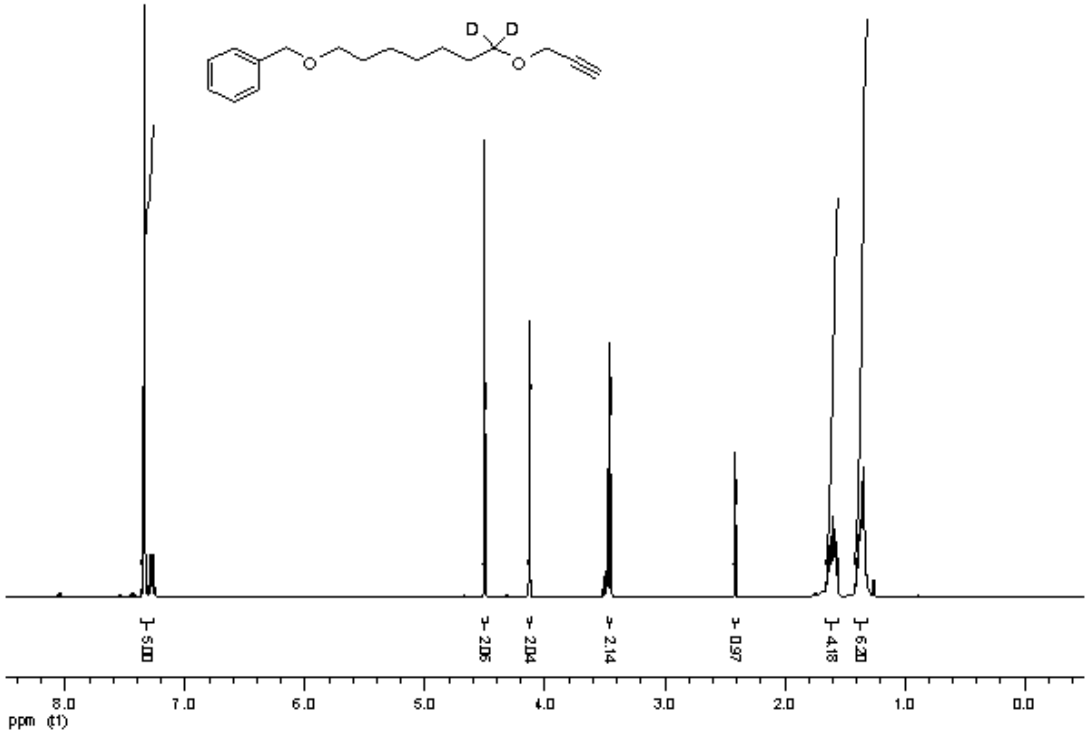

164.499
139.326
138.665
128.320
127.594
127.449
119.307
97.541
91.051
87.446
83.309
77.317
76.683
72.849
70.416
70.274
61.299
60.364
58.754
57.361
29.695
29.493
29.284
26.131
26.082
21.245
14.135
150
100
50
ppm (t1)

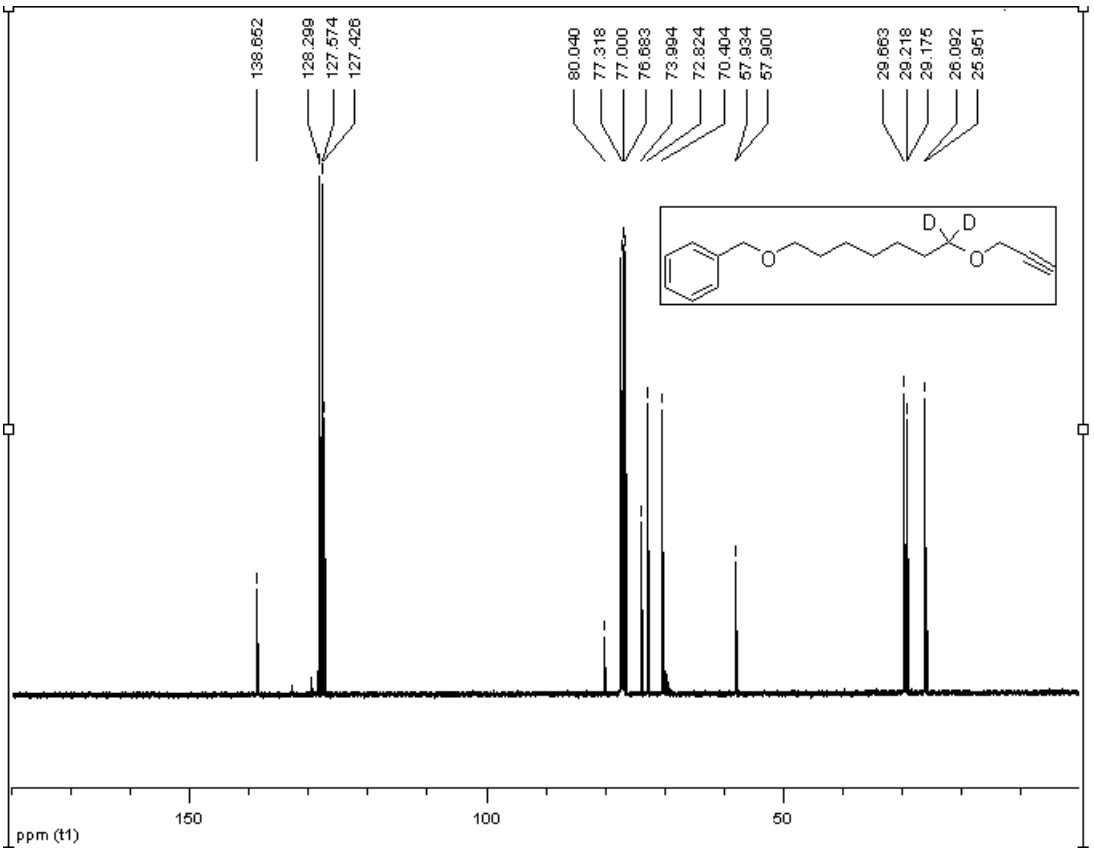
65


0.91
4.85
1.01
1.92
1.96
1.98
1.98
0.96
1.09
3.10
2.82
2.16
10.97
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

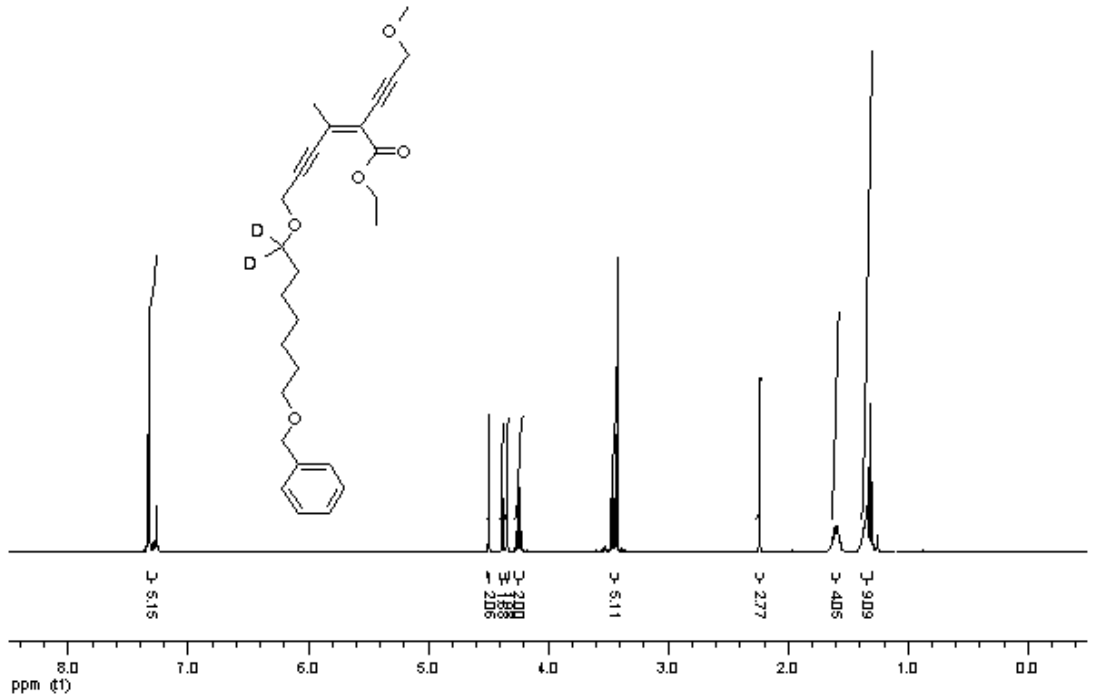

167.158
141.720
139.770
138.615
134.168
132.564
132.050
128.802
128.336
127.610
127.479
81.108
77.254
77.000
76.746
74.143
72.872
72.809
72.613
70.395
60.718
32.317
29.673
29.476
26.100
25.572
21.338
14.338
150
100
50
ppm (t1)

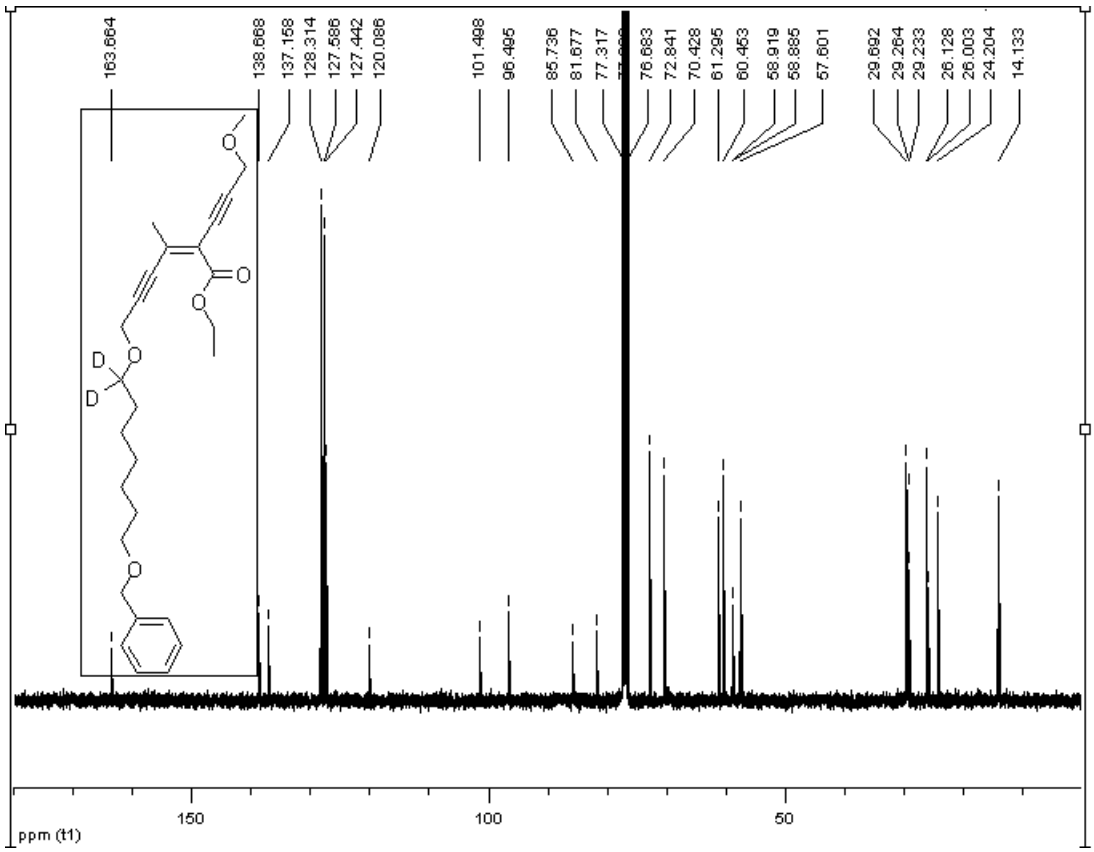
73


D
D
O
O
5.00
2.05
2.04
2.14
0.97
4.18
6.20
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

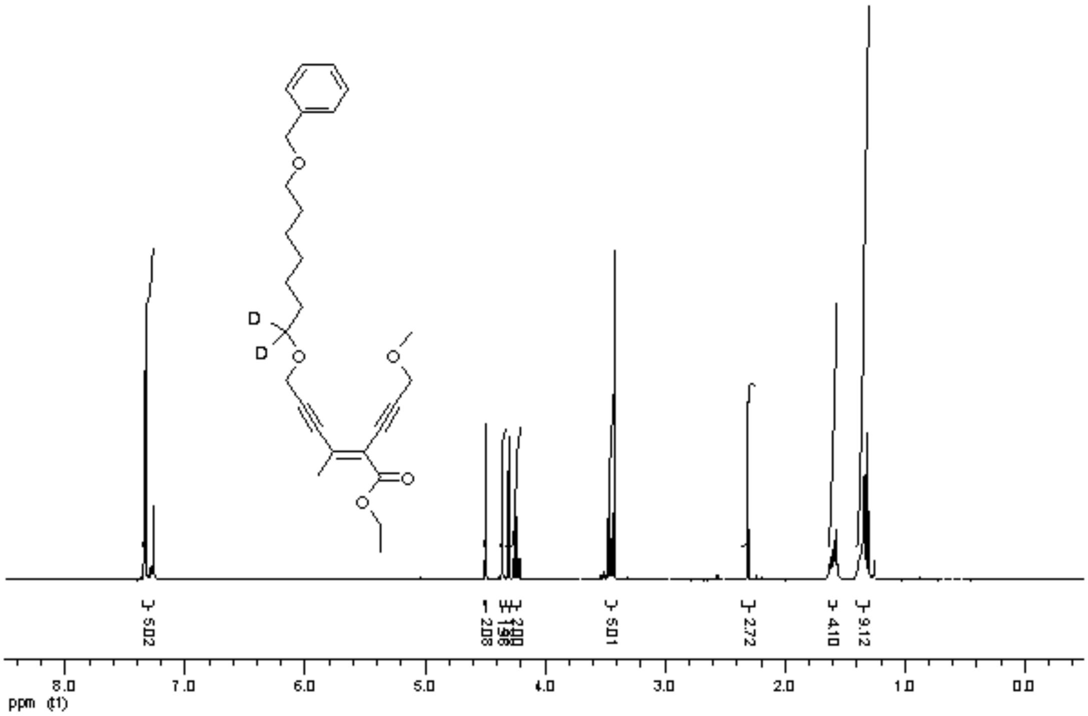

138.652
128.299
127.574
127.426
80.040
77.318
77.000
76.683
73.994
72.824
70.404
57.934
57.900
29.663
29.218
29.175
26.092
25.951
D
D
O
O
150
100
50
ppm (t1)

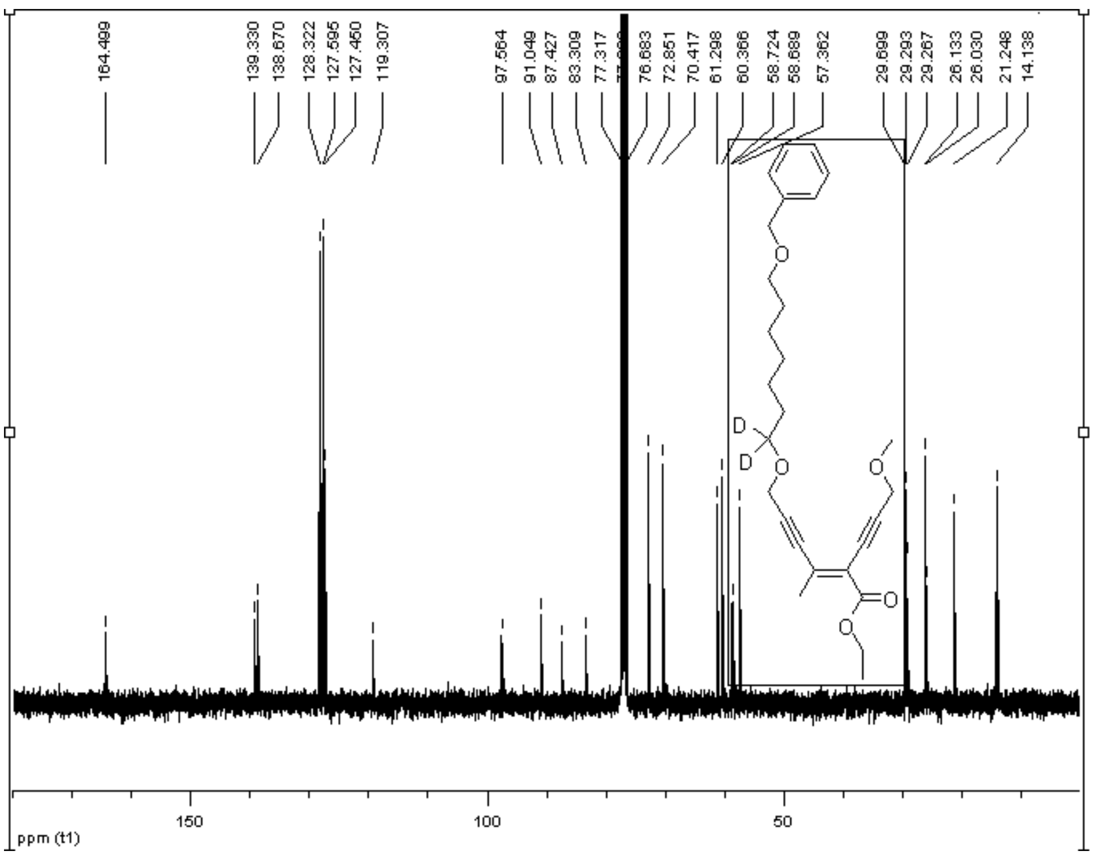
76 *trans*


D
D
5.15
2.06
5.11
2.77
4.05
9.09
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

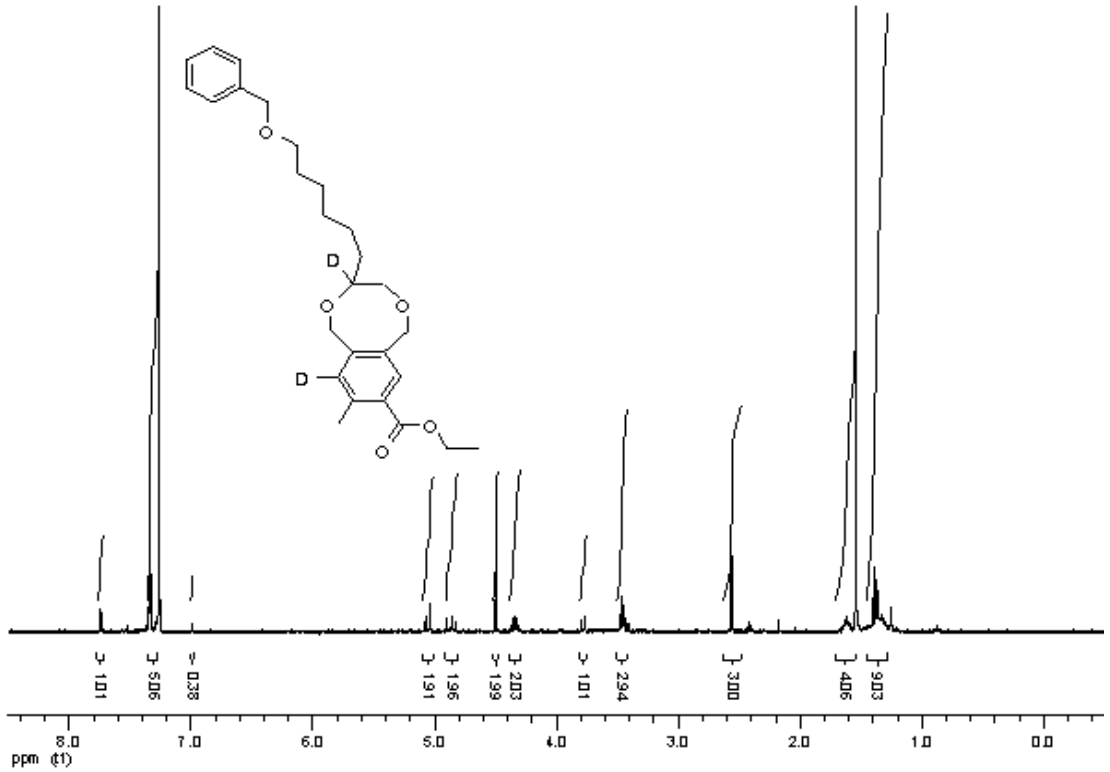

163.664
138.668
137.158
128.314
127.586
127.442
120.086
101.498
96.495
85.736
81.677
77.317
76.683
72.841
70.428
61.295
60.453
58.919
58.886
57.601
29.692
29.264
29.233
26.128
26.003
24.204
14.133
D
D
150
100
50
ppm (t1)

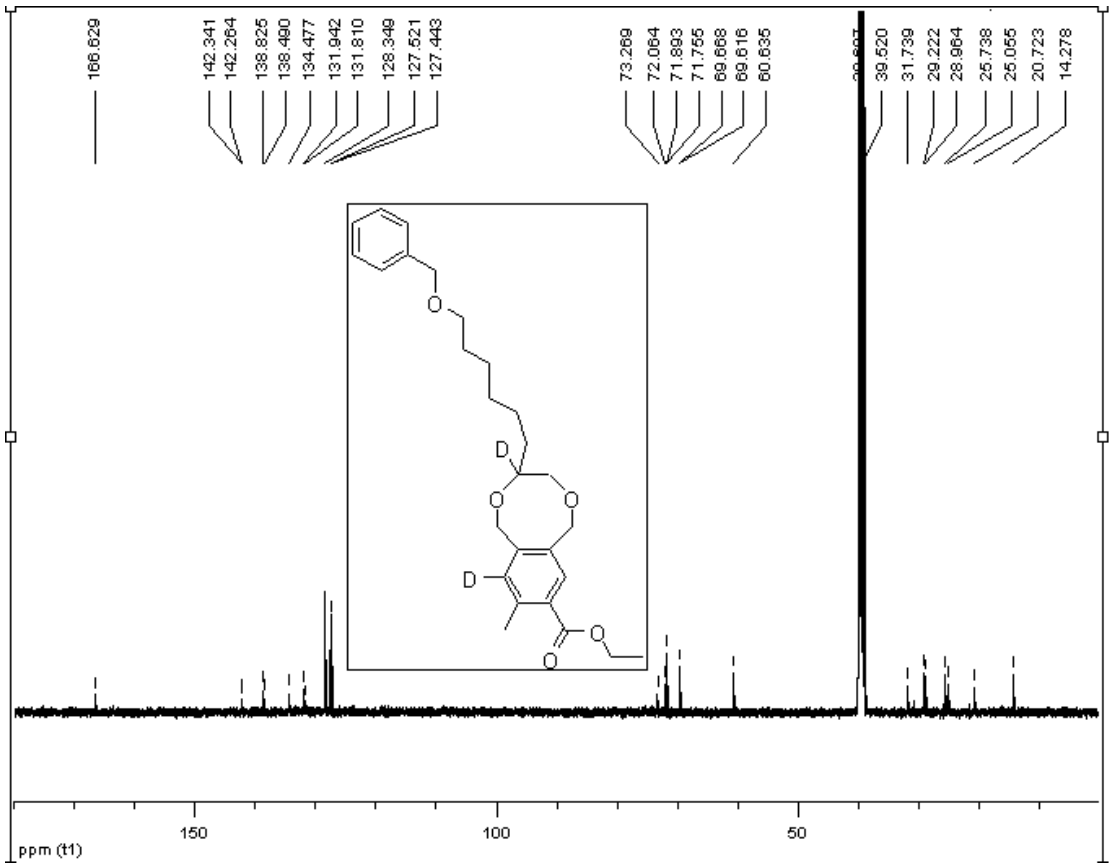
76 *cis*

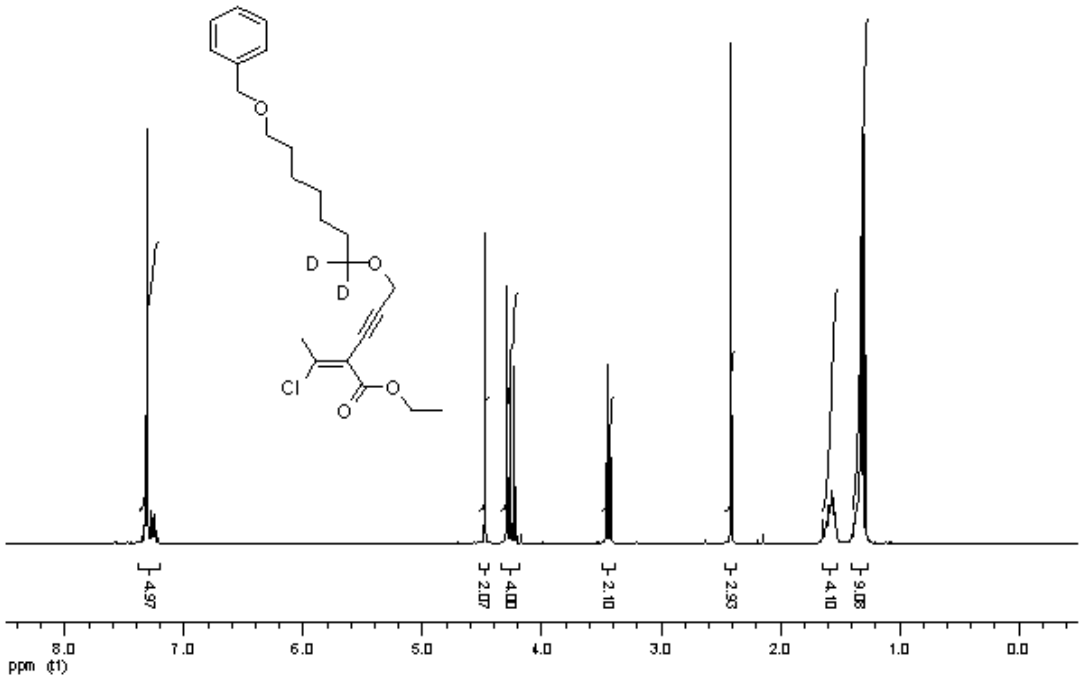

D
D
O
O
O
O
O
5.02
2.08
2.00
1.96
5.01
2.72
4.10
9.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

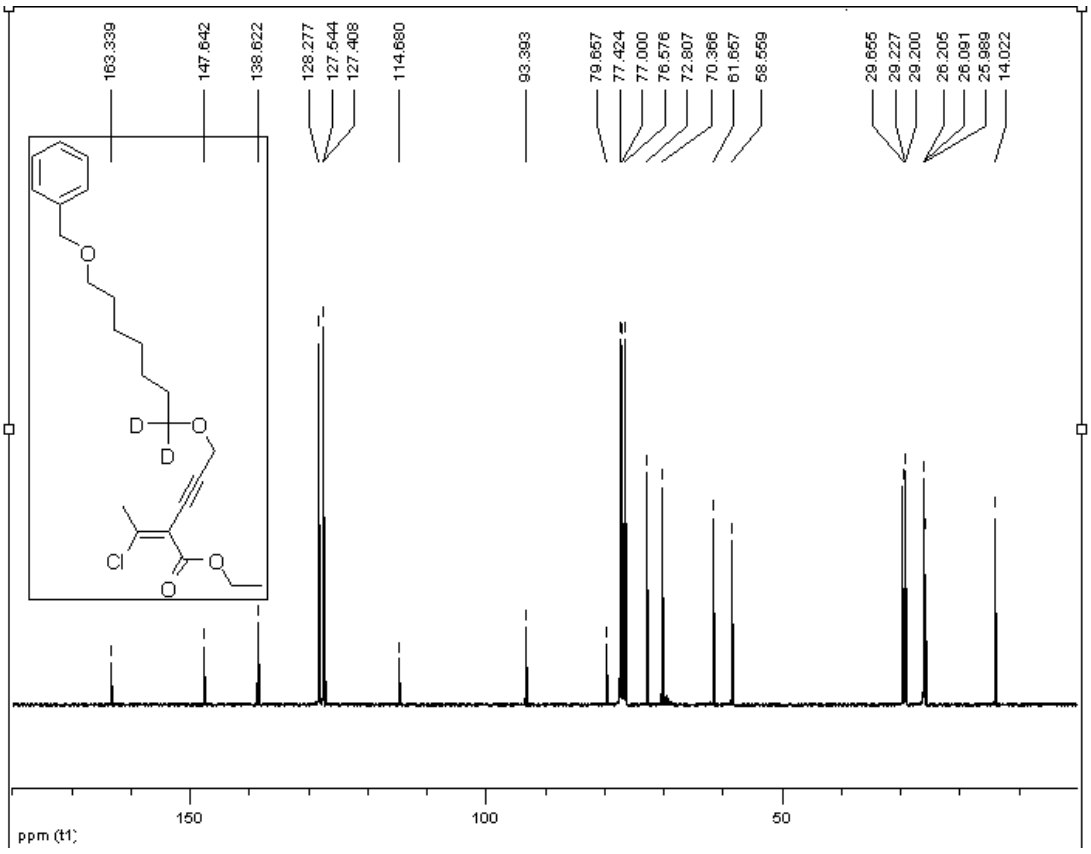

164.499
139.330
138.670
128.322
127.595
127.450
119.307
97.564
91.049
87.427
83.309
77.317
76.683
72.851
70.417
61.298
60.366
58.724
58.689
57.362
29.699
29.293
29.267
26.133
26.030
21.248
14.138
D
D
O
O
O
O
O
150
100
50
ppm (t1)

78

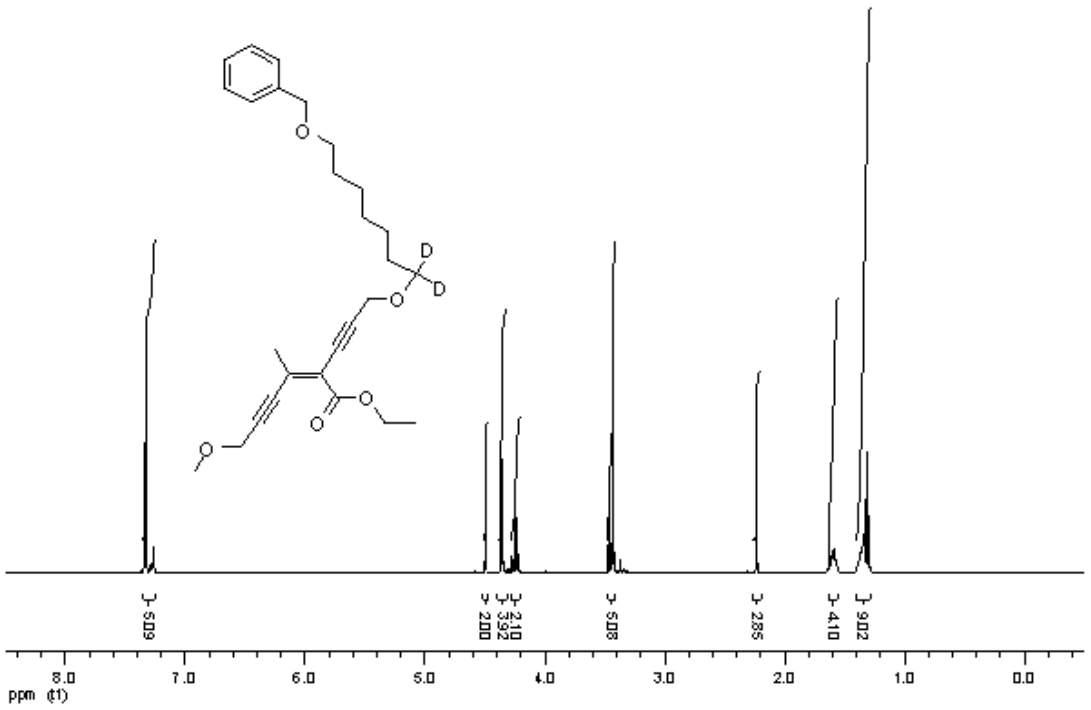

D
D
O
O
O
O
1.01
5.06
0.38
1.91
1.96
1.99
2.03
1.01
2.94
3.00
4.06
9.03
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

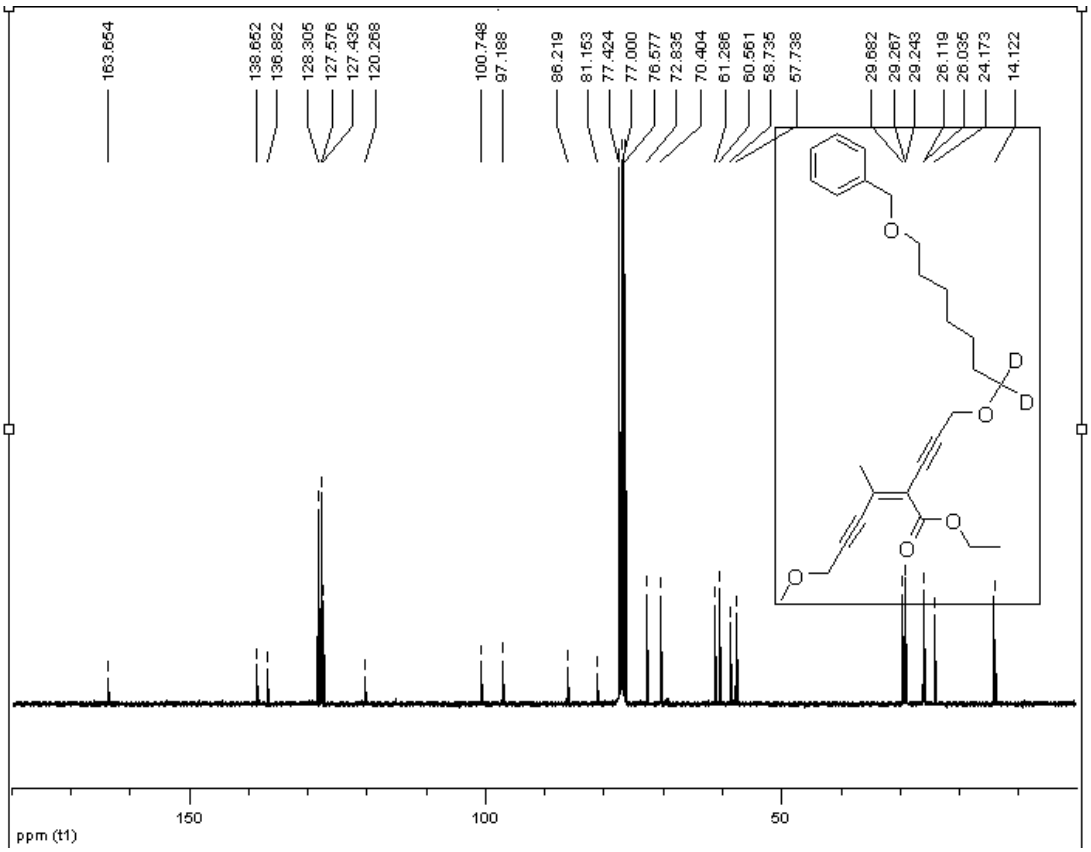

166.629
142.341
142.264
138.825
138.490
134.477
131.942
131.810
128.349
127.521
127.443
73.269
72.064
71.893
71.755
69.668
69.616
60.635
39.520
31.739
29.222
28.964
25.738
25.055
20.723
14.278
D
D
O
O
O
O
150
100
50
ppm (t1)


4.97
2.07
4.00
2.10
2.93
4.10
9.08
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

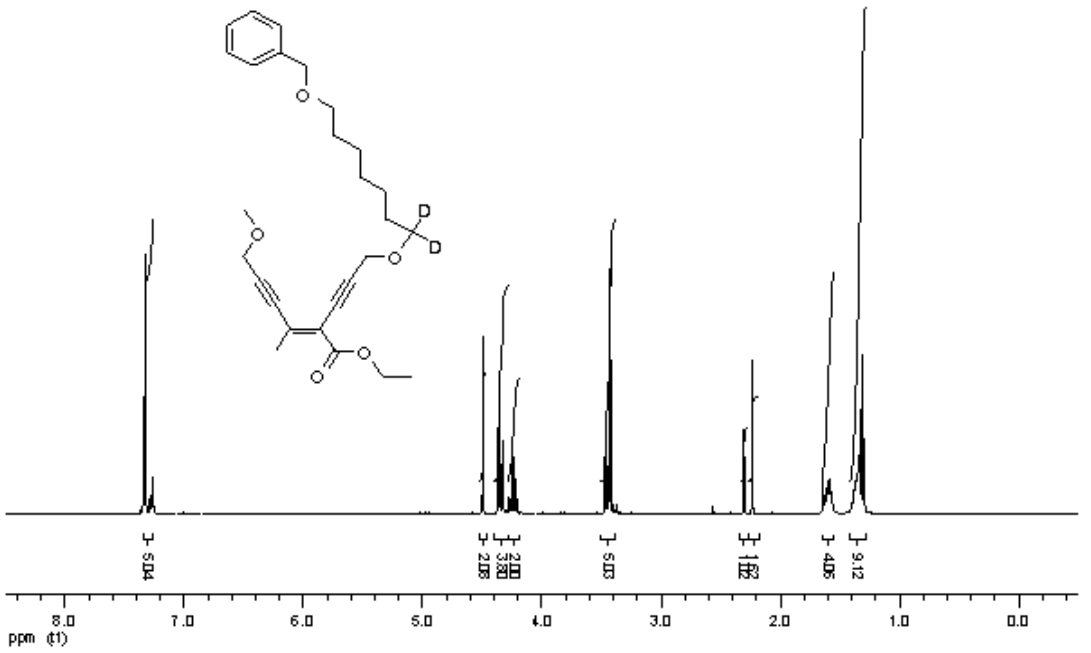

163.339
147.642
138.622
128.277
127.544
127.408
114.680
93.393
79.657
77.424
77.000
76.576
72.807
70.366
61.667
58.569
29.655
29.227
29.200
26.205
26.041
25.989
14.022
150
100
50
ppm (t1)

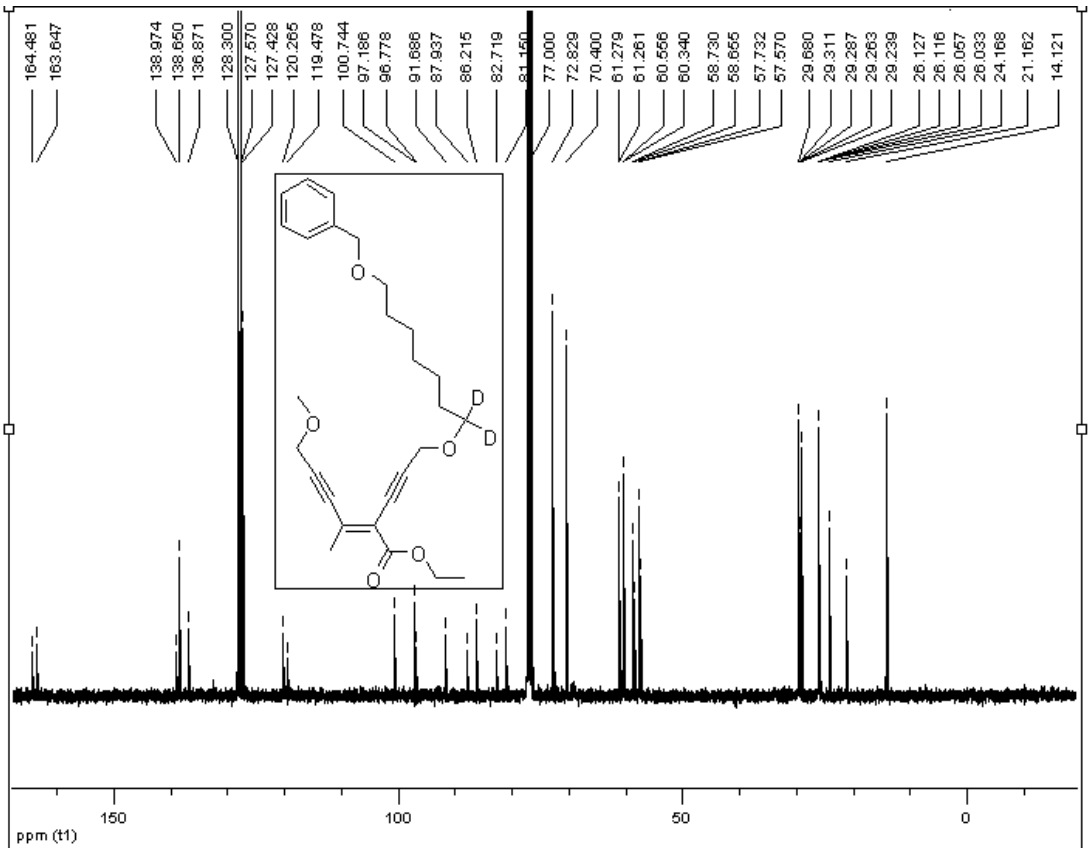
75 trans


1.509
2.000
3.325
3.310
4.508
2.285
4.410
9.202
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

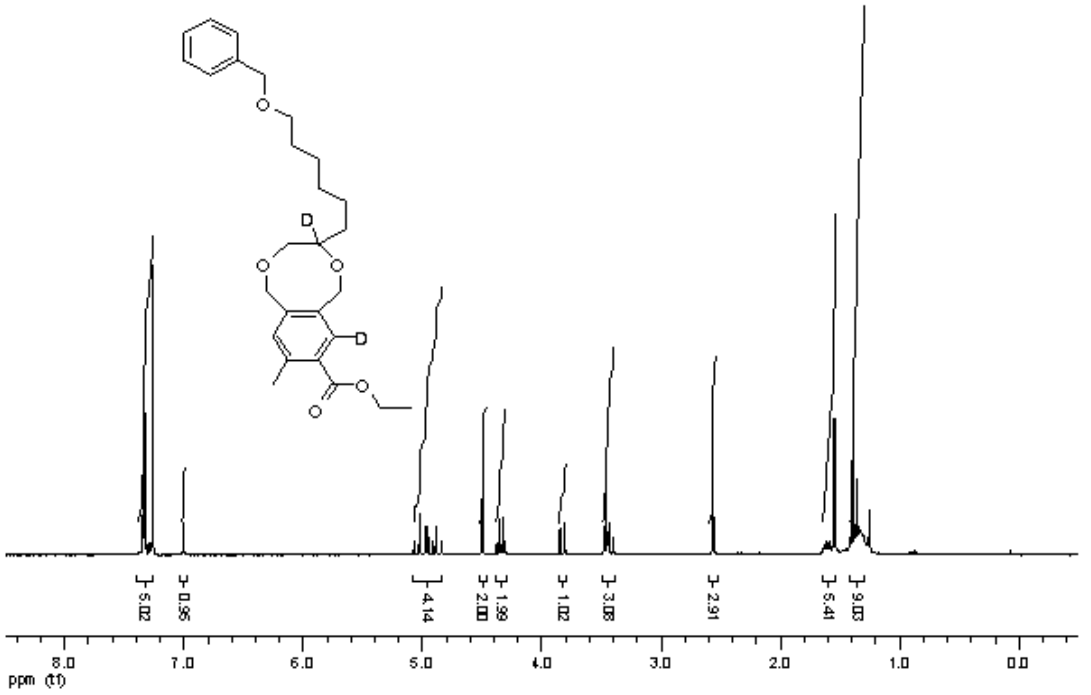

163.654
138.652
136.882
128.305
127.576
127.435
120.268
100.748
97.188
86.219
81.163
77.424
77.000
76.577
72.835
70.404
61.286
60.561
58.735
57.738
29.682
29.267
29.243
26.119
26.035
24.173
14.122
150
100
50
ppm (t1)

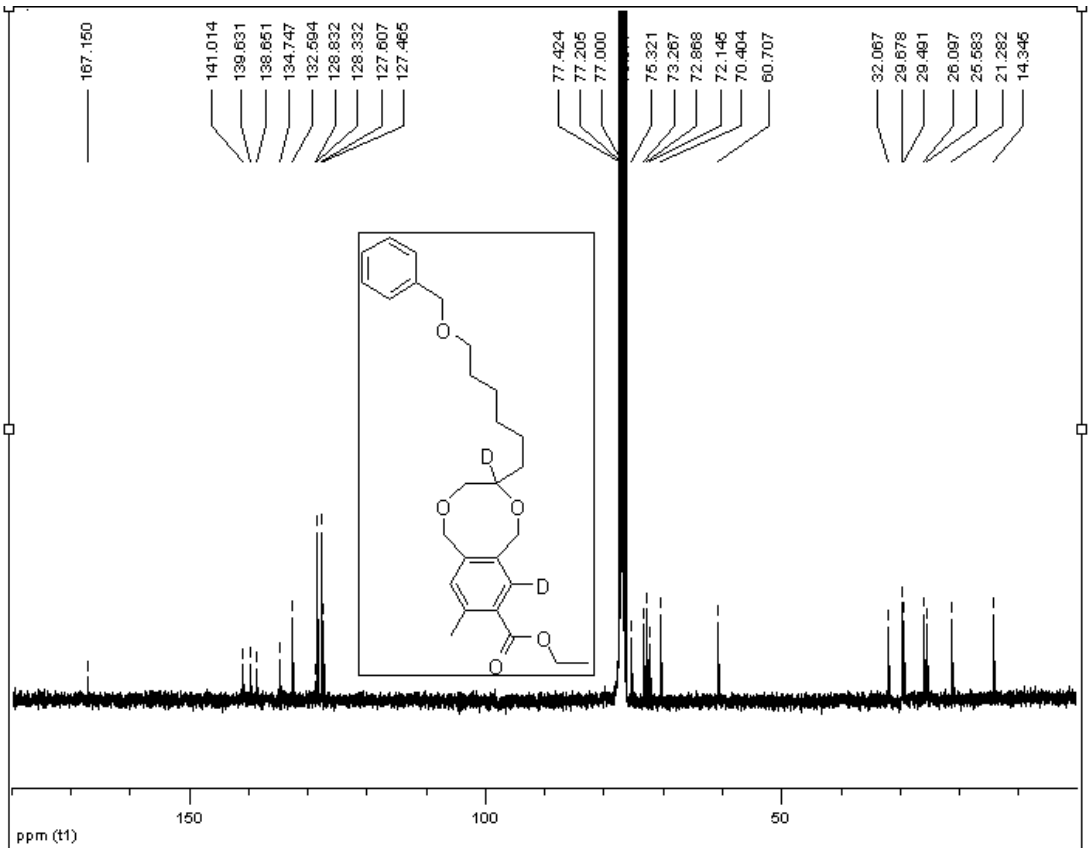
75 cis


5.04
2.05
2.00
2.33
5.03
1.93
4.06
9.12
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

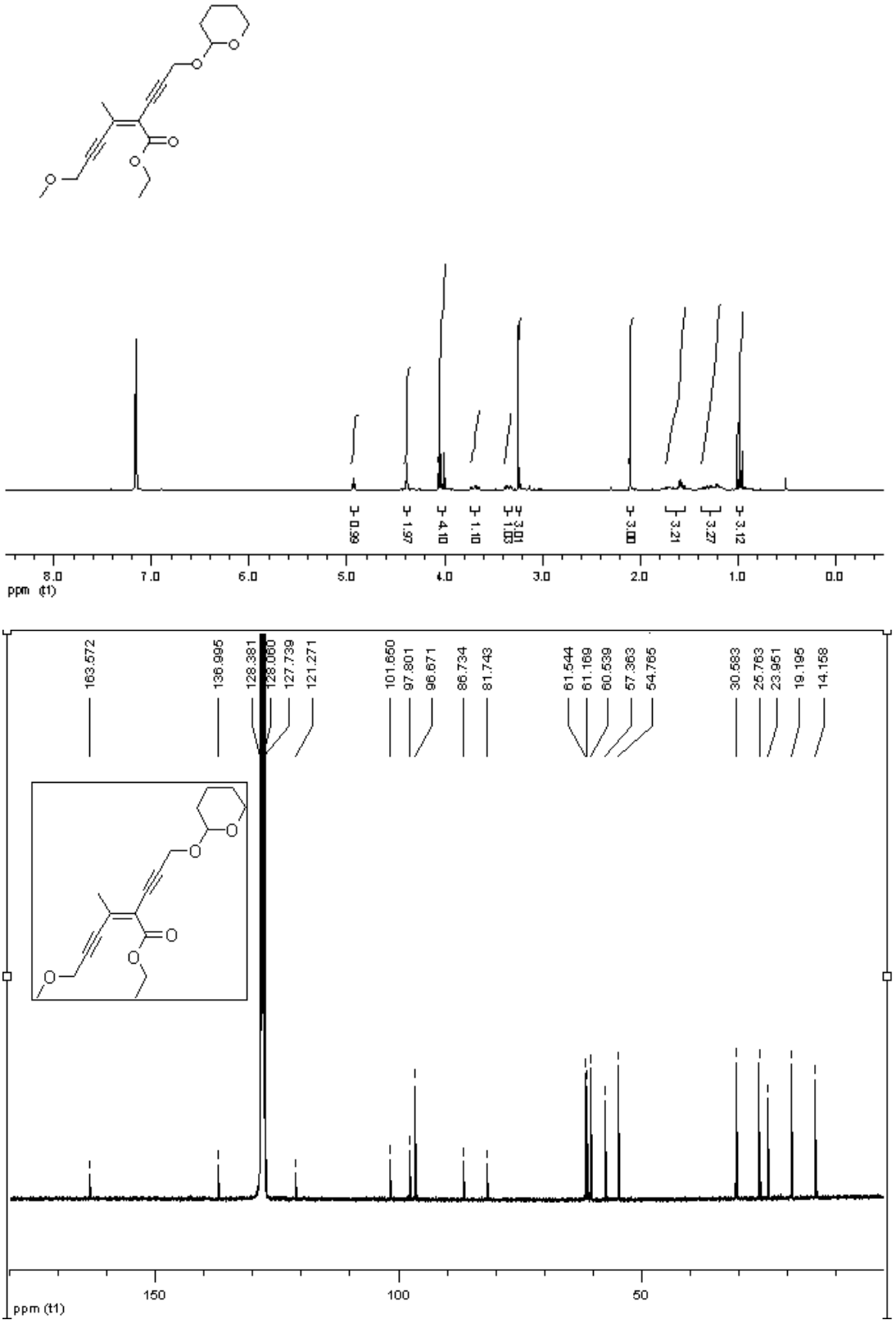

164.481
163.647
138.974
138.650
136.871
128.300
127.570
127.428
120.265
119.478
100.744
97.186
96.778
91.686
87.937
86.215
82.719
81.450
77.000
72.829
70.400
61.279
61.261
60.556
60.340
58.730
58.665
57.732
57.570
29.680
29.311
29.287
29.263
29.239
26.127
26.116
26.057
26.033
24.168
21.162
14.121
150
100
50
0
ppm (t1)

77

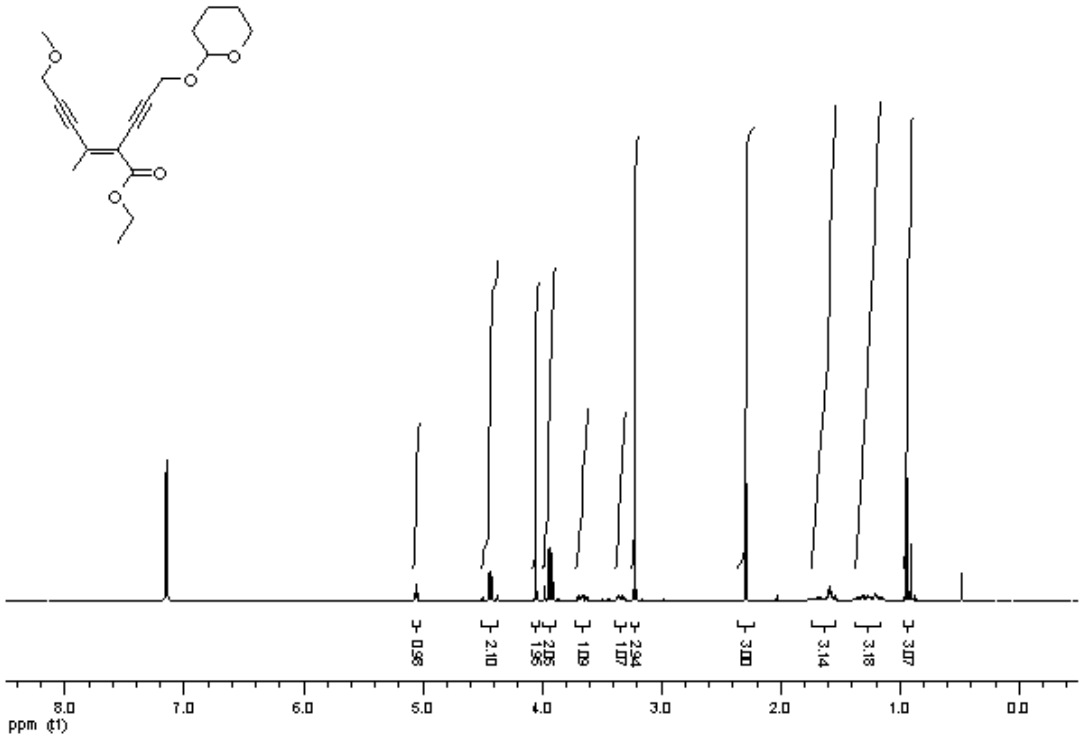

D
D
5.02
0.95
4.14
2.00
1.98
1.02
3.05
2.91
5.41
9.03
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

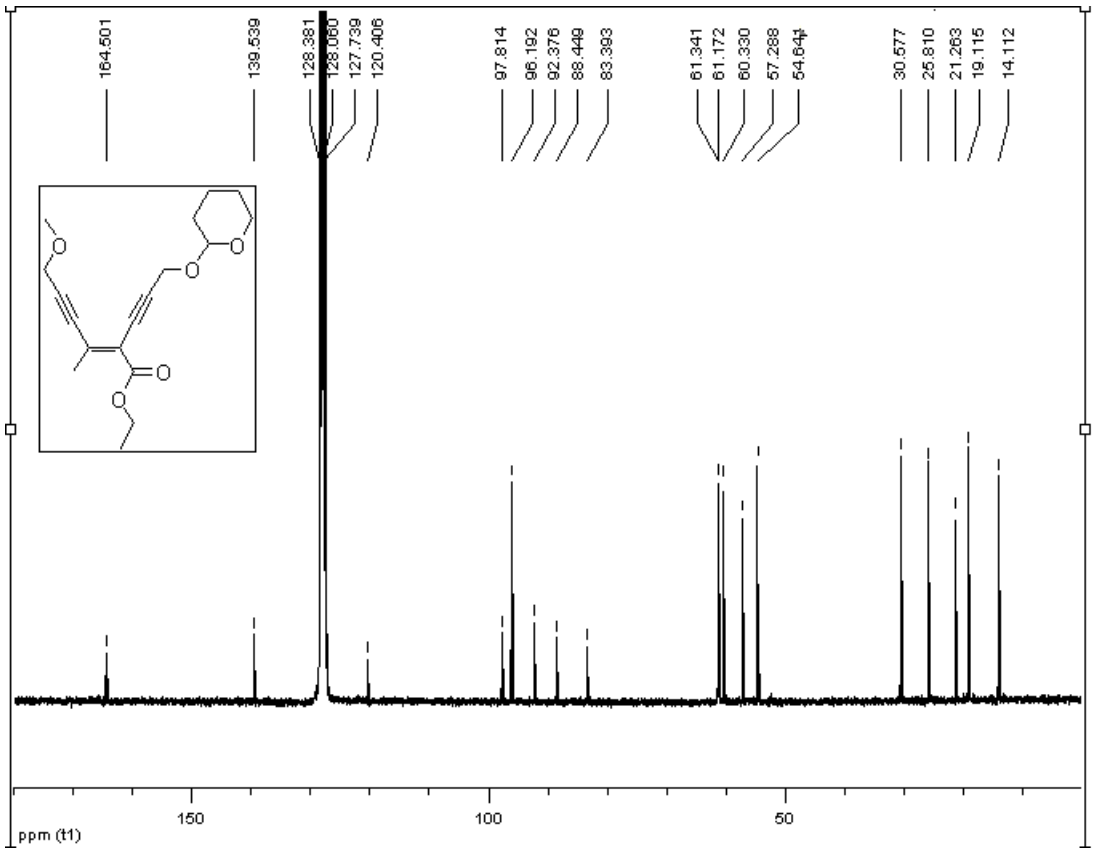

167.150
141.014
139.631
138.651
134.747
132.594
128.832
128.332
127.607
127.465
77.424
77.205
77.000
75.321
73.267
72.868
72.145
70.404
60.707
32.067
29.678
29.491
26.097
25.583
21.282
14.345
D
D
150
100
50
ppm (t1)

61 *trans*

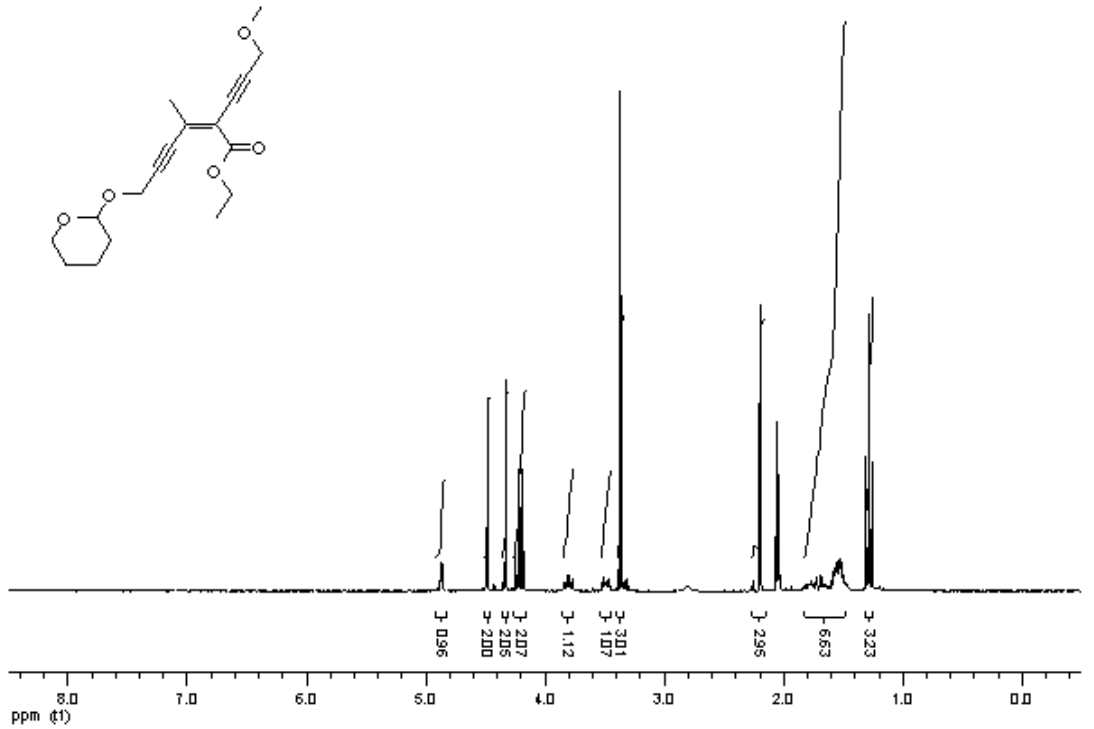

ppm (t1)
163.572
136.995
128.381
128.060
127.739
121.271
101.650
97.801
96.671
86.734
81.743
61.544
61.169
60.539
57.363
54.765
30.583
25.763
23.951
19.195
14.158
150
100
50
ppm (t1)

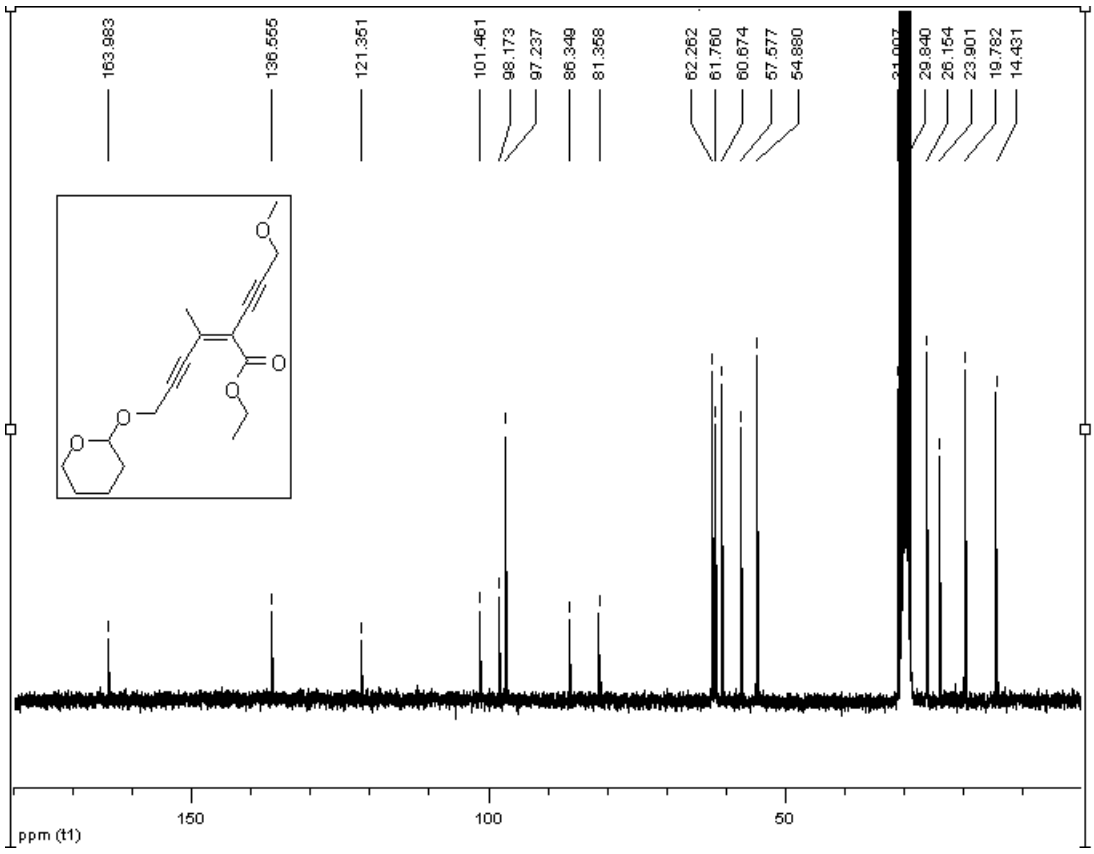
61 *cis*


0.96
2.10
2.05
1.00
2.54
3.00
3.14
3.18
3.07
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

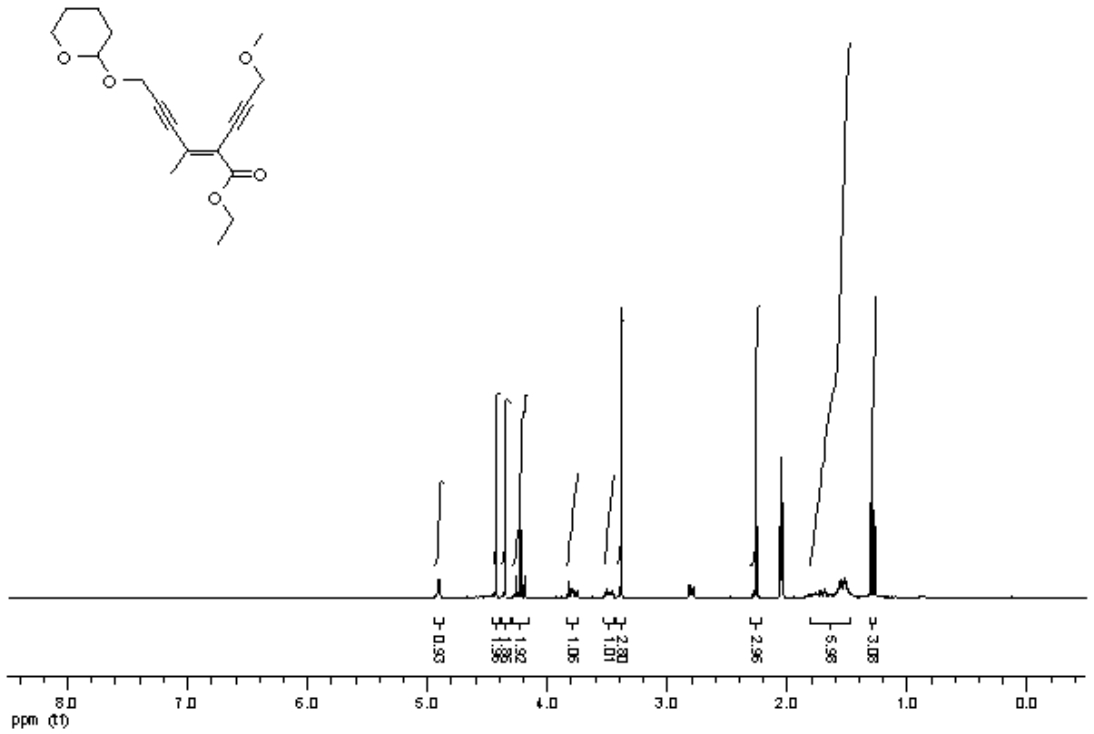

164.501
139.539
128.381
128.060
127.739
120.406
97.814
96.192
92.376
88.449
83.393
61.341
61.172
60.330
57.288
54.644
30.577
25.810
21.263
19.115
14.112
150
100
50
ppm (t1)

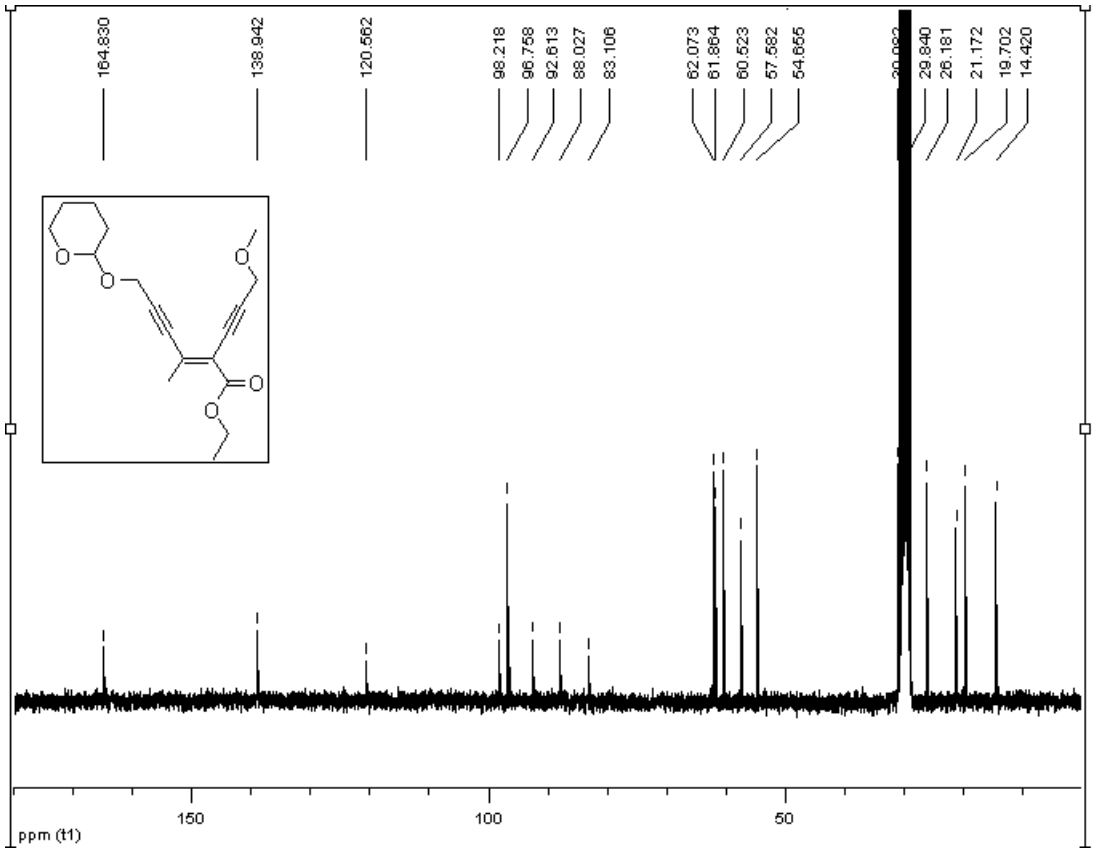
59f *trans*


0.96
2.00
5.05
2.07
1.12
3.07
3.01
2.96
6.63
3.23
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

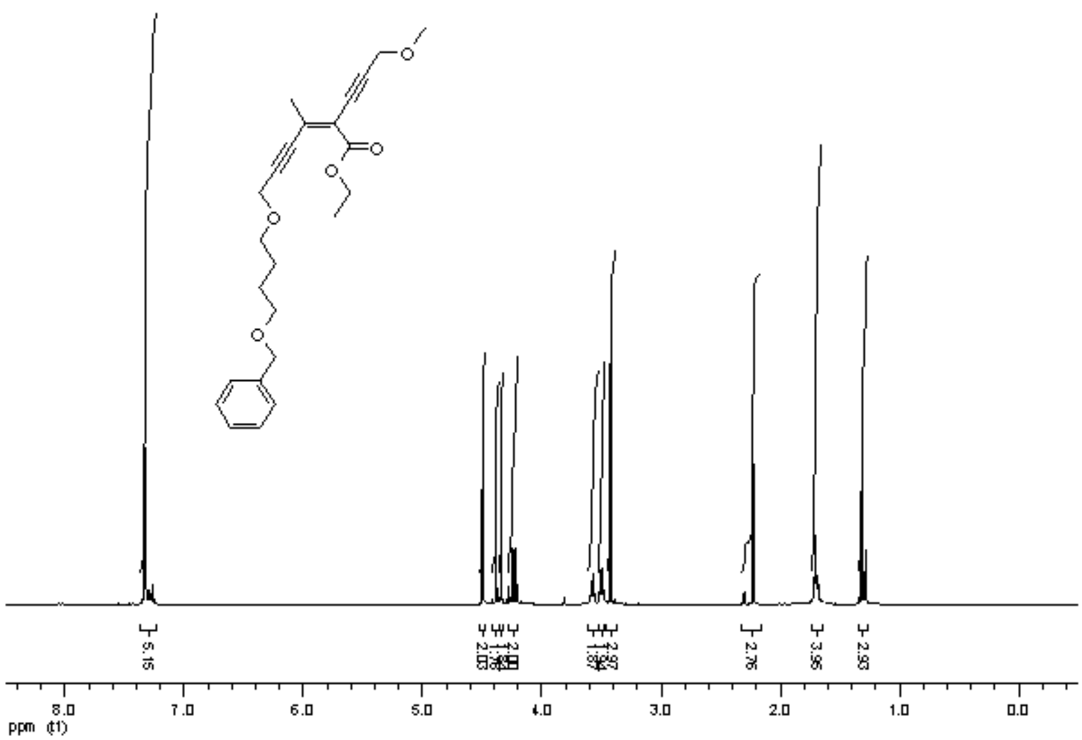

163.983
136.555
121.351
101.461
98.173
97.237
86.349
81.358
62.262
61.760
60.674
57.577
54.880
31.007
29.840
26.154
23.901
19.782
14.431
150
100
50
ppm (t1)

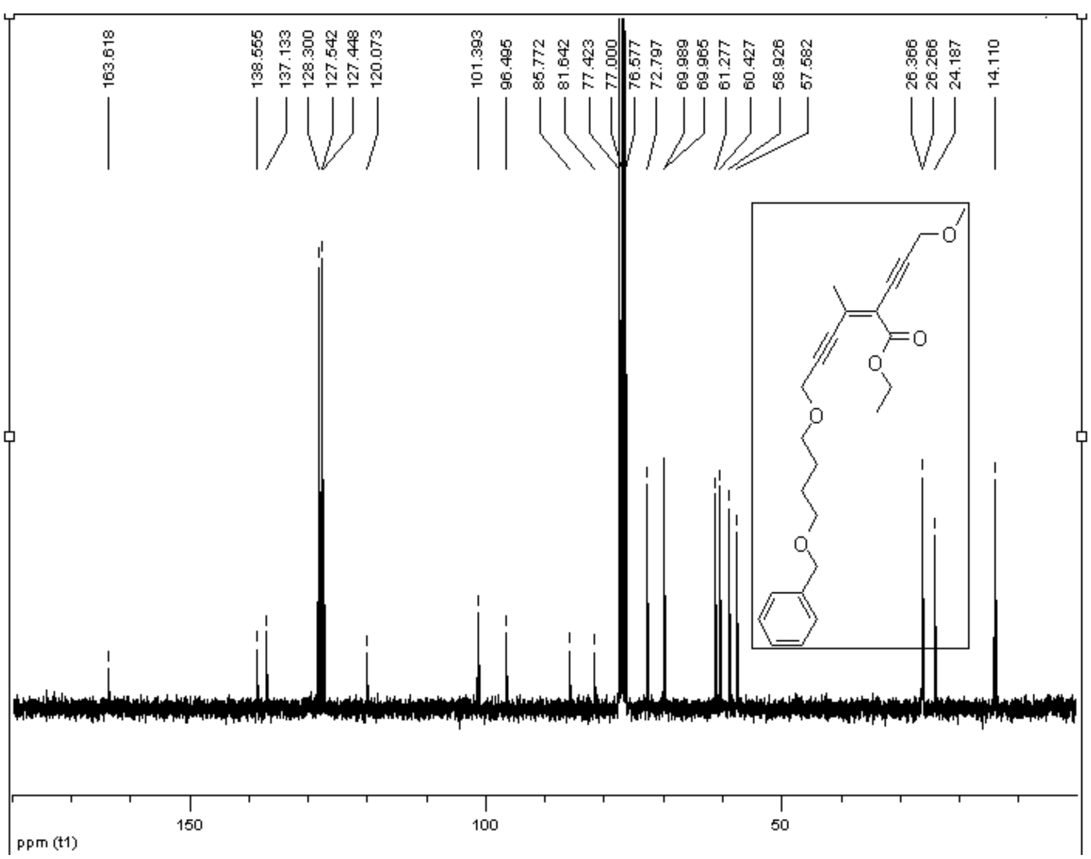
59f *cis*


0.93
1.92
1.06
2.96
5.98
3.08
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

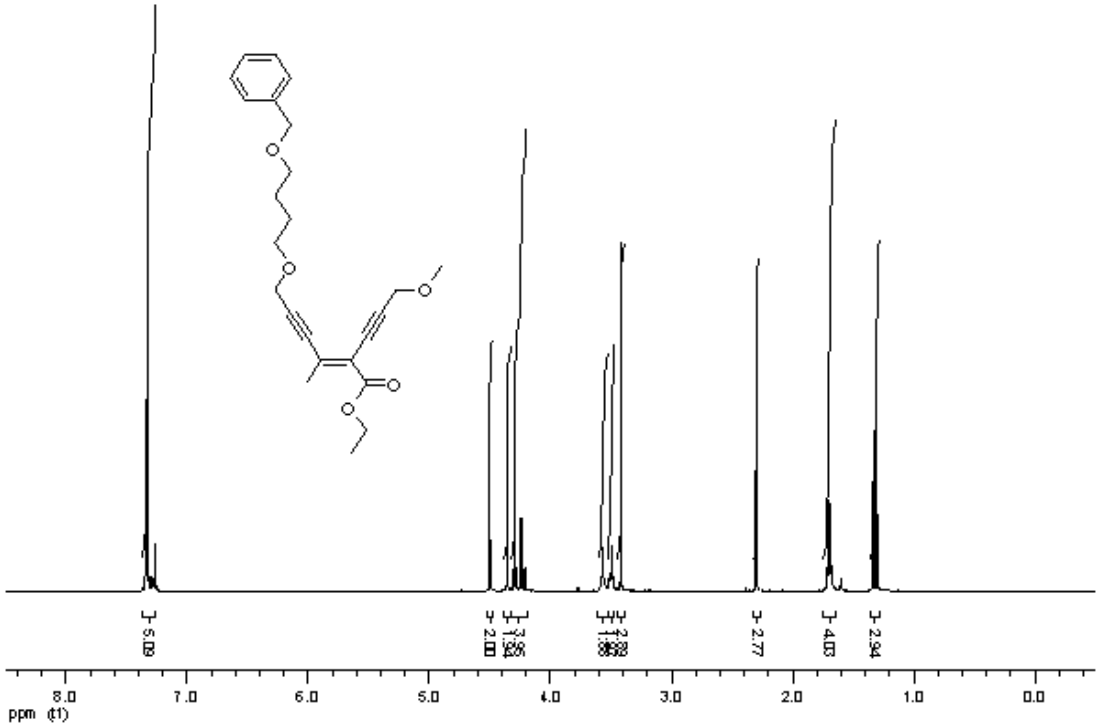

164.830
138.942
120.562
98.218
96.758
92.613
88.027
83.106
62.073
61.864
60.523
57.582
54.655
29.840
26.181
21.172
19.702
14.420
150
100
50
ppm (t1)

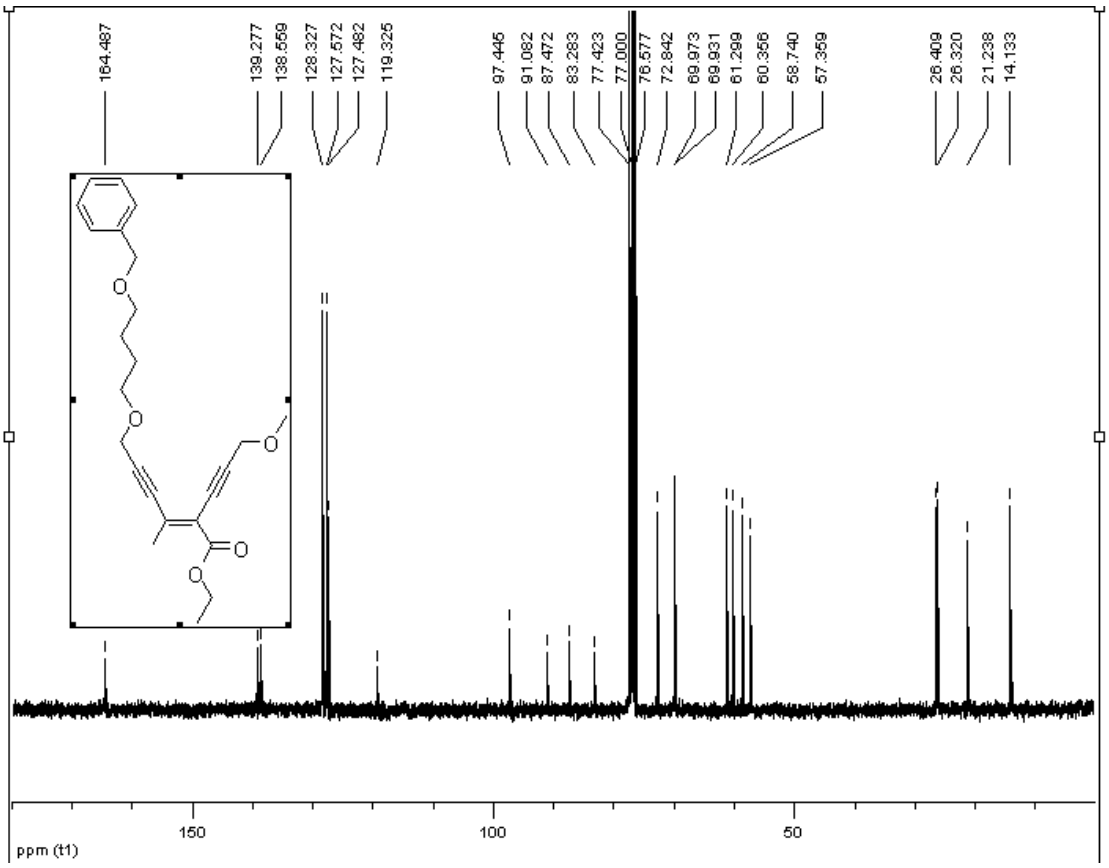
59c *trans*

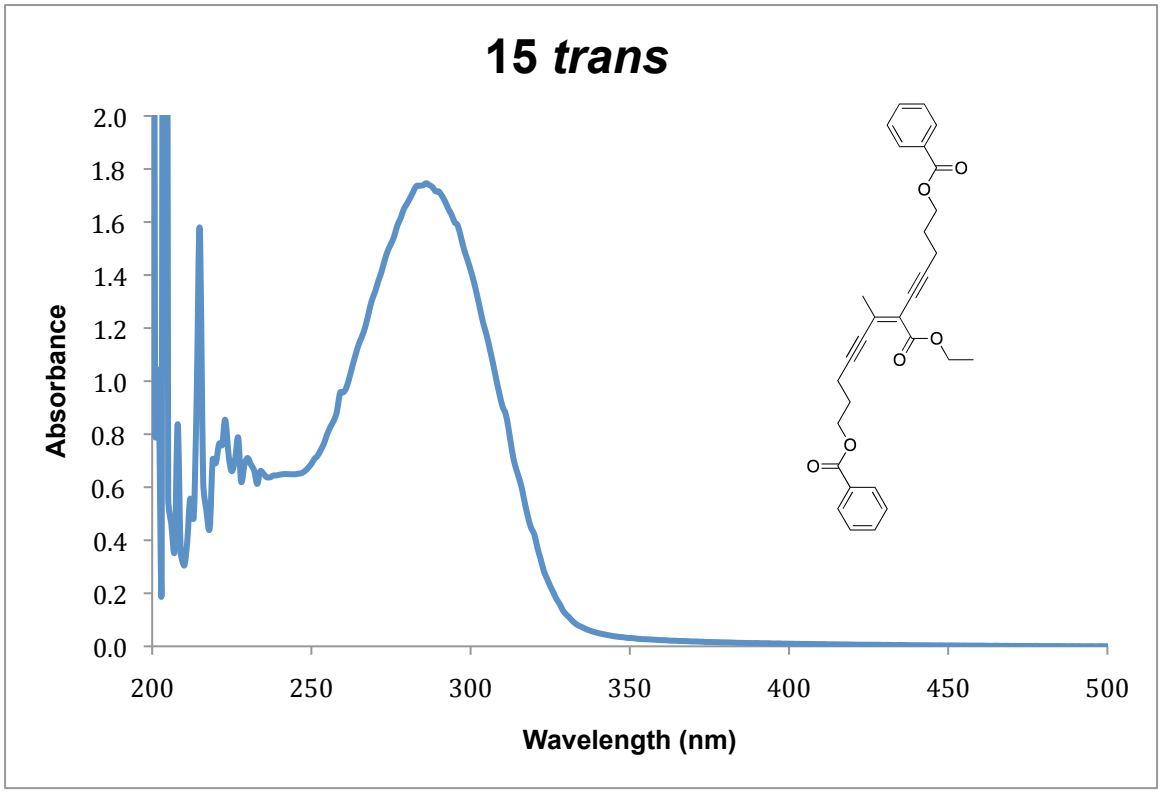

5.15
2.03
1.98
2.07
1.97
1.94
2.97
2.76
3.96
2.93
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

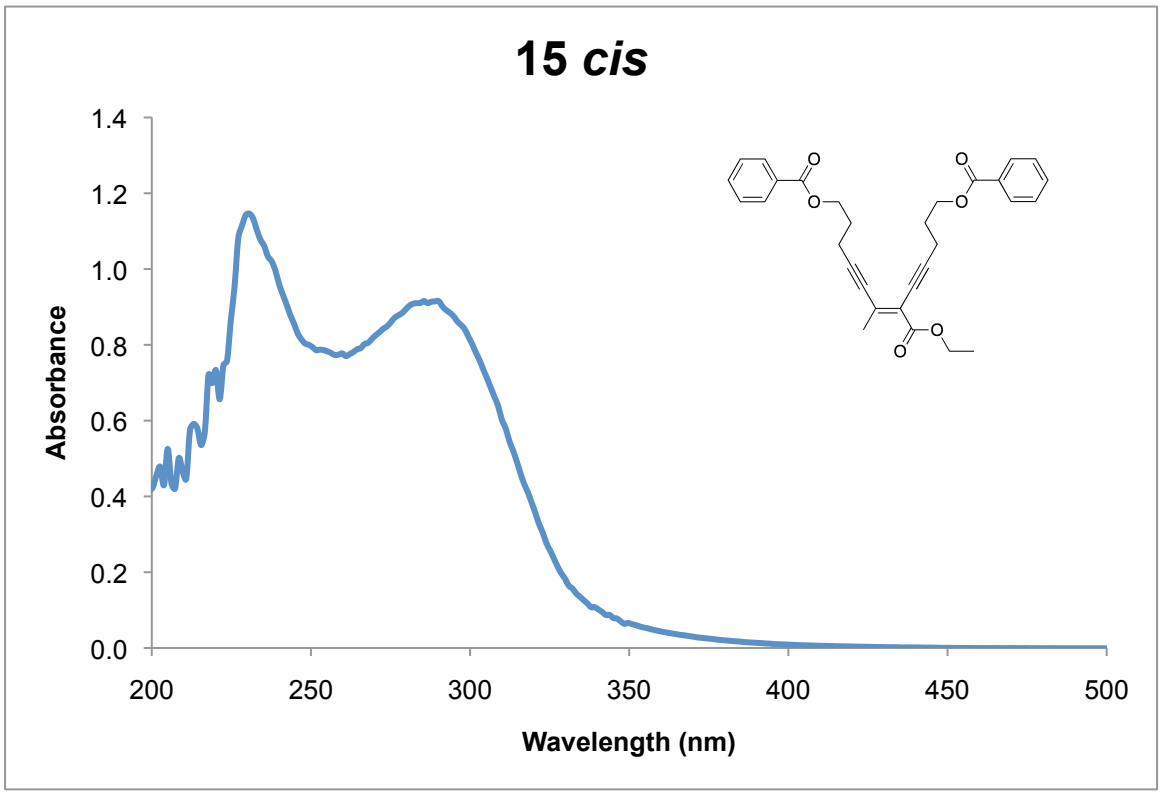

163.618
138.555
137.133
128.300
127.542
127.448
120.073
101.393
96.495
85.772
81.642
77.423
77.000
76.577
72.797
69.989
69.965
61.277
60.427
58.926
57.582
26.366
26.266
24.187
14.110
150
100
50
ppm (t1)

59c *cis*


5.00
2.00
1.93
1.88
2.77
4.00
2.34
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


164.487
139.277
138.559
128.327
127.572
127.482
119.325
97.445
91.082
87.472
83.283
77.423
77.000
76.577
72.842
69.973
69.931
61.299
60.356
58.740
57.359
26.409
26.320
21.238
14.133
150
100
50
ppm (t1)


15 trans
Absorbance
2.0
1.8
1.6
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
200
250
300
350
400
450
500
Wavelength (nm)


15 cis
Absorbance
1.4
1.2
1.0
0.8
0.6
0.4
0.2
0.0
200
250
300
350
400
450
500
Wavelength (nm)