CYCLIC ENEDIYNES AND ENYNE-ALLENES CONTAINING ADDITIONAL FUNCTIONALITIES: ACHIEVING CONTROL OF THE MECHANISM AND REACTIVITY

by

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(Under the Direction of Vladimir V. Popik)

ABSTRACT

Natural enediyne antibiotics are perhaps the most potent natural anticancer agents. Their extreme cytotoxicity is attributed to the ability of either (*Z*)-3-ene-1,5-diyne or (*Z*)-1,2,4-heptatrien-6-yne fragment to undergo cyclization producing a reactive 1,4-biradical. Enediynes undergo Bergman cyclization, while enyne-allenes undergo Myers-Saito cycloaromatization. These reactions cause simultaneous cleavage of both strands of duplex DNA. Unfortunately, low selectivity, poor thermal stability, and high general toxicity of naturally occurring enediynes, as well as designed compounds, prevent their wide use in clinical practice thus far.

The goal of this work was to investigate the mechanism, the kinetics, and the triggering mode of the Bergman and Myers-Saito cyclizations in order to achieve control over the enediyne and enyne-allene activity. We have developed and synthesized 10- (**3.1a**, **4.1**–**4.6**) and 11- (**3.1b**) membered cyclic enediynes with conjugated exo-double bond at the acetylenic termini of the (*Z*)-3-ene-1,5-diyne fragment. Kinetic studies and deuterium-labeling experiments confirmed our hypothesis that keto-endiynes (**3.1a** and **b**) undergo Bergman cycloaromatization *via* rate determining enolization, followed by cyclization of enol into 1,4-biradical. It was also found that electron-donating substituents at the β-position, with respect to the one of acetylenic termini of

enediynes, increase the rate of cyclization, while electron-withdrawing groups have an opposite effect. The cyclization step is the rate determining step in these reactions.

In order to achieve spatial and temporal control over the action of enediynes, we also developed compounds that are thermally stable, but their action can be triggered photochemically. The reactive allenes (**5.3** and **6.4**) and enyne-allene (**6.10**) compounds were proposed. The allene **5.3** was generated by UV irradiation of a thermally stable precursor (**5.1**) in which an aldehyde group was protected with a photoremovable protecting group as an acetal moiety. Reactive allene **6.4** and cyclic enyne-allene **6.10** were generated from acyclic 2-diazo-1,3- dicarbonyl compounds by the photochemical Wolff reaction. Allene **6.4** and enyne-allene **6.10** readily add nucleophiles to the electron-poor double bond; **6.10** presumably undergoes fast Myers-Saito cyclization in non-nucleophilic solutions.

INDEX WORDS: Enediynes, Enyne-allenes, Wolff rearrangement, Bergman cyclization, Myers-Saito cyclization, Diazo-compounds

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M.S., Saint-Petersburg State University, Russia, 2004

A Dissertation Submitted to the Graduate Faculty of The University of Georgia in Partial Fulfillment of the Requirements for the Degree

DOCTOR OF PHILOSOPHY

ATHENS, GEORGIA

2011

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May 2011

ACKNOWLEDGEMENTS

I am heartily thankful to those who made this dissertation possible. First of all I would like to say thanks to my Mother who gave me the moral support I required. I owe my deepest gratitude to my advisor, Dr. Vladimir Popik, whose encouragement, supervision and support from the preliminary to the concluding level enabled me to develop an understanding of the subject. I am also thankful to my committee members for their valuable advices and members of Dr. Popik's research group for fruitful discussions and helpful suggestions. I also would like to make a special reference to Dr. Gregori Karpov who shared his professional experience with me during my first years as a graduate student. Lastly, I offer my regards to all of my friends who supported me in any respect during the completion of my dissertation.

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CHAPTER 1

LITERATURE REVIEW

1.1 Introduction

The chemistry of (*Z*)-3-ene-1,5-diyns (henceforth called "enediynes") have attracted considerable attention from organic chemists and biochemists since their discovery. Naturally occurring DNA-damaging enediyne antibiotics such as maduropeptin,[1] calicheamicins,[2] esperamicins,[3] dynemicins,[4] and C-1027[5] are among the most potent antitumor agents ever discovered. Their suggested mechanism of action involves a cyclization reaction which was reported by Robert Bergman[6] in 1972. Upon activation, the enediyne fragment undergoes cycloaromatization leading to the formation of the highly reactive 1,4-benzenoid biradical capable of efficient double hydrogen abstraction.[7] Application of these enediyne anticancer antibiotics is quite limited due to their inadequate selectivity. Therefore, a safe antitumor drug with high cyctotoxic activity toward tumor cells and low toxicity in normal cells has yet to be developed. To address this problem, cycloaromatization of the enediyne fragment should be effectively controlled with an efficient triggering mechanism. Also, structural complexity issues of natural enediynes require synthetically more accessible analogs. The number of studies dedicated to the synthesis and factors controlling cycloaromatization of designed enediynes grew exponentially for the last thirty years.

1.2 Enediyne Anticancer Antibiotics. Mechanism of Action

Naturally occurring enediyne antibiotics, a relatively new class of anticancer agents, are related by containing a common structural motif–the enediyne functionality captured within 9- or

10-membered rings, with varying degree of chemical complexity in the remainder of the molecules.[8]

Nine-membered natural enediynes are noncovalently associated complexes between unstable chromophores and stabilizing proteins. They possess DNA-cleaving properties (both single and double stranded) associated with the chromophore, and they are potent cytotoxic agents.[9] The first compound discovered and reported by Ishida *et al.* in 1965[10] was neocarzinostatin (NCS). In 1979, a non-protein chromophore was discovered and isolated from an antitumor polypeptide antibiotic NCS,[11] which contained 1:1 mixture of noncovalently associated mixture of NCS chromophore and a protein component. The structure of the chromophoric component **1.1** was not elucidated until 1985.[12] The role of the apoprotein is to protect the NCS chromophore molecule, unstable in its free form.

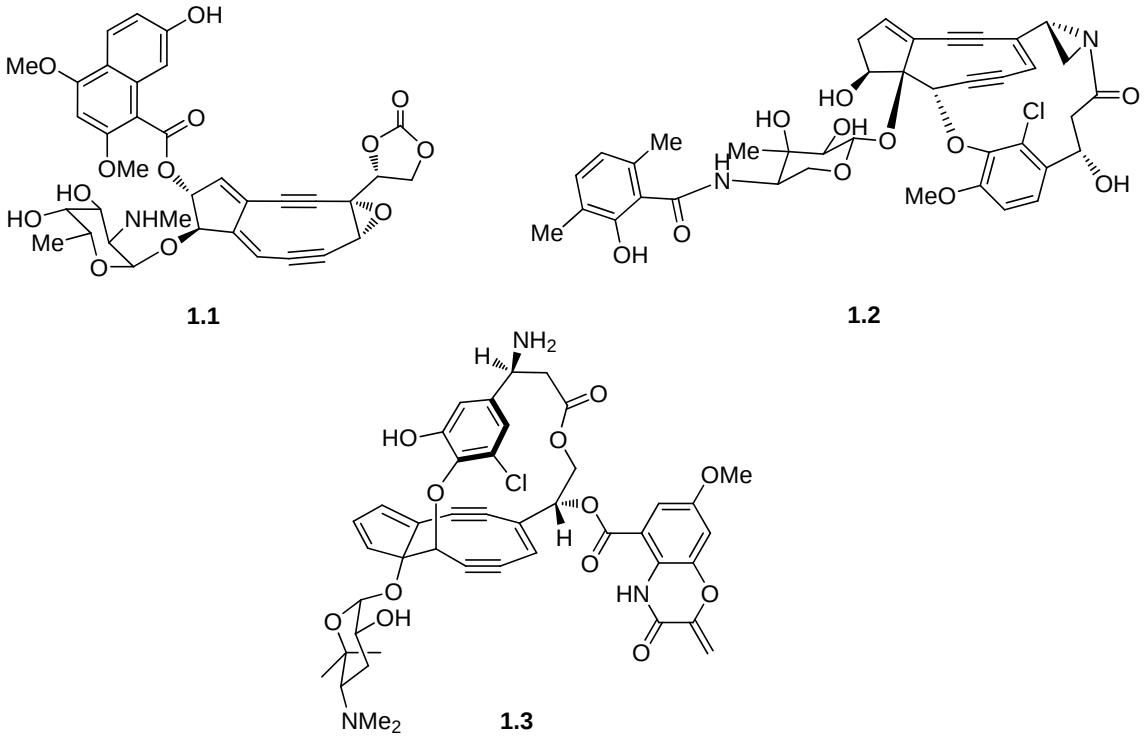


Figure 1.2.1 Neocarzinostatin, Maduropeptin, and C-1027.

Other examples of 9-membered ring natural enediynes are maduropeptin (**1.2**) and C-1027 (**1.3**). Maduropeptin **1.2** was isolated from fermentation broth in 1990[13] and its highly labile chromophoric core was structurally characterized by 1995.[14] The total synthesis of maduropeptin chromophore was reported in 2007.[15] Maduropeptin antibiotic consists of a 1:1 complex of an acidic, water soluble carrier protein and a nine-membered ring enediyne chromophore. C-1027 (**1.3**) was isolated in 1988[16] and synthesized twenty years later.[17] Similar to NCS and maduropeptin, C-1027 exists as a highly biologically active unstable chromophoric molecule non-covalently associated with an apoprotein.

The potent antitumor and antibacterial activity of NCS is exposed through DNA cleavage. Neocarzinostatin does not possess a conjugated (*Z*)-1,5-diyn-3-ene fragment in contrast to other enediyne antibiotics. The active part of the chromophore, the unsaturated bicyclic core, exhibits a mechanism of action slightly different from that of other enediynes. The mechanism by which NCS chromophore destroys DNA was first proposed in 1987 (Figure 1.2.2).[9]

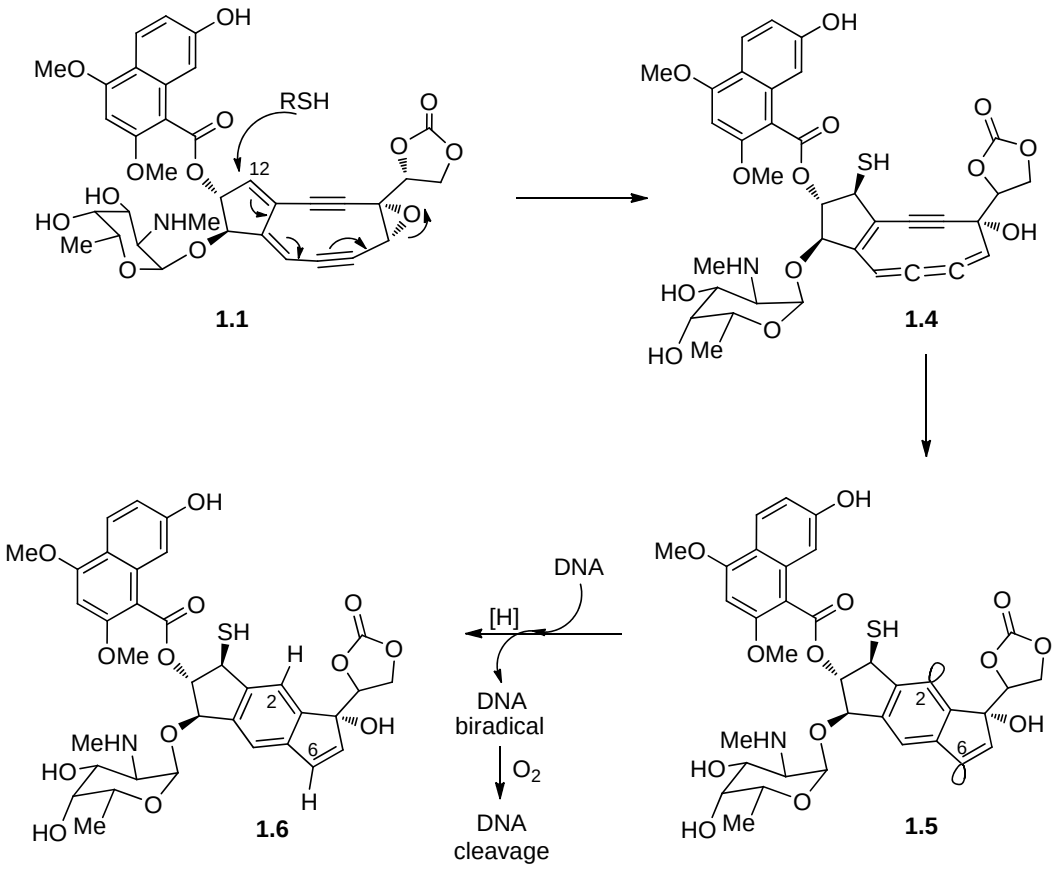


Figure 1.2.2 Triggering pathway and mechanism of action for the NCS chromophore.

The cleaving ability of the NCS chromophore is enhanced by thiols and UV irradiation.[18] The cascade reaction leading to the DNA cleavage begins with the stereospecific attack by nucleophile at the electrophilic C12 position of NCS chromophore, followed by the double bond's movement in the polyunsaturated bicyclic core, and opening of the epoxide ring. This process leads to the formation of the cumulene intermediate **1.4**. Its structure was confirmed by NMR at low temperatures.[19] This highly strained reactive intermediate undergoes immediate cycloaromatization to form biradical **1.5** which further attacks DNA with abstraction of two hydrogen atoms from the minor grove of DNA, resulting in **1.6**. Neocarzinostatin conjugated

with poly (styrene-co-maleic acid) (SMANCS) was approved in Japan[20] as a treatment for liver and lung cancer.

Maduropeptin (**1.2**) and C-1027 (**1.3**) exhibit potent inhibitory activity against bacteria and tumor cells as well as strong *in vivo* antitumor activity in P388 leukemia and B16 melanoma implanted mice.[9,21] Unlike NCS, maduropeptin and C-1027 possess a fully conjugated enediyne system restrained within a nine-membered ring. The geometry of the polycyclic cores of these compounds in the complex form with apoprotein is such that the Bergman cyclization is impossible at room temperature since the chromophoric units are extremely unstable in their free form.

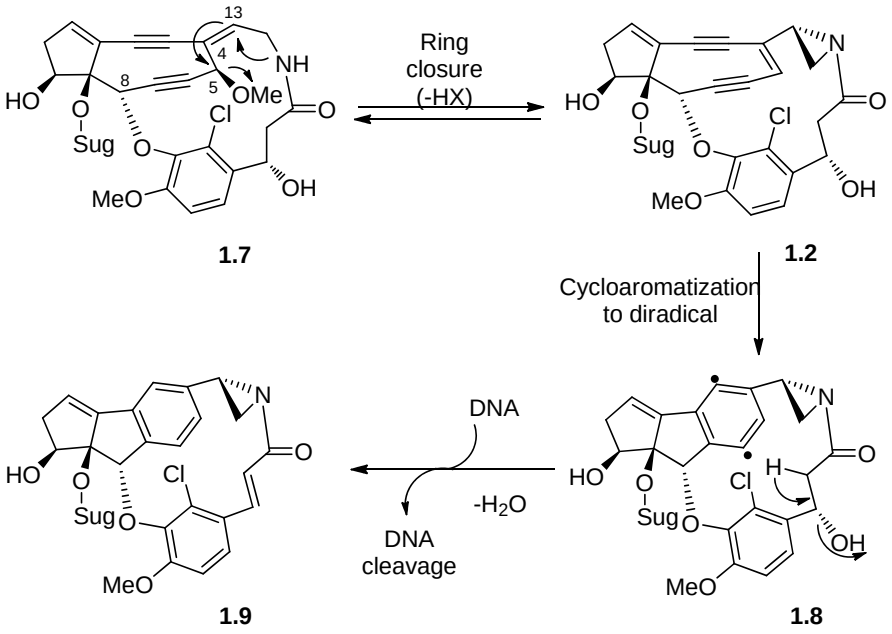
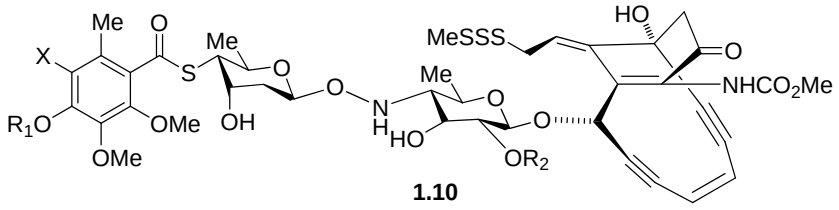


Figure 1.2.3 Proposed mechanism of action for maduropeptin chromophore.

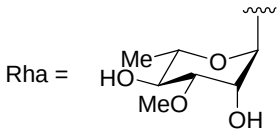
The maduropeptin chromophore exists in an equilibrium with methanol adduct in methanol solutions (Figure 1.2.3) and as chlorine adduct in some cases. The nitrogen in the amide group attacks the electrophilic C13 position, causing migration of the double bond and anti-elimination of the group that was initially attached to C5. Upon formation of **1.2**, there are no more constrains to inhibit cycloaromatization of enediyne to a highly reactive biradical **1.8,**

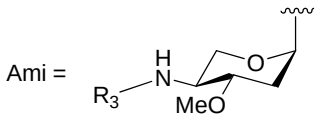
which is capable of hydrogen abstraction and DNA double-strand cleavage. It was found that C-1027 behaves similarly. The chromophore exists as an equilibrium mixture of enediyne and its biradical.[22] Recently, C-1027 has entered phase II clinical trial in China as an anti-tumor agent.[21]

Calicheamicins **1.10** (Figure 1.2.4) and esperamicins **1.11** (Figure 1.2.5) are two families of 10-membered cyclic enediynes with similar structures and mechanism of action toward DNA. Calicheamicins were identified in 1986[2] and the whole family was fully characterized by 1989.[23] Their total structure, including absolute configuration, was confirmed by total synthesis of calicheamicin γ_1^I by Nicolaou *et al.* and Danishefsky *et al.* in 1992-1993.[24]



1.10

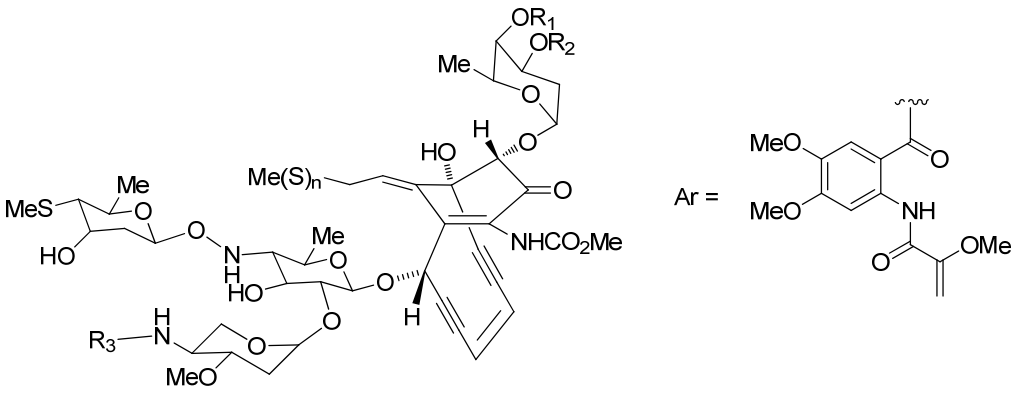




Calicheamicin	X	R_1	R_2	R_3
calicheamicin β_1^{Br}	Br	Rha	Ami	$CHMe_2$
calicheamicin γ_1^{Br}	Br	Rha	Ami	Et
calicheamicin α_1^I	I	H	Ami	Et
calicheamicin α_3^I	I	Rha	H	H
calicheamicin β_1^I	I	Rha	Ami	$CHMe_2$
calicheamicin γ_1^I	I	Rha	Ami	Et
calicheamicin δ_1^I	I	Rha	Ami	Me

Figure 1.2.4 Calicheamicin family.

Esperamicins were isolated in 1985[25] and their structure was determined[2] simultaneously with the calicheamicins, to which they are closely related. Structural assignment, including absolute configuration, of the esperamicin family was complete in 1992.[26]



1.11

Esperamicin	n	R_1	R_2	R_3
esperamicin A_1	3	H	Ar	$CHMe_2$
esperamicin A_{1b}	3	H	Ar	Et
esperamicin A_{1c}	3	H	Ar	Me
esperamicin P	4	H	Ar	$CHMe_2$
esperamicin A_2	3	Ar	H	$CHMe_2$
esperamicin A_{2b}	3	Ar	H	Et
esperamicin A_{2c}	3	Ar	H	Me

Figure 1.2.5 Esperamicin family.

The structure of calicheamicins and esperamicins are almost identical, esperamicins differ from calicheamicins only in an additional hydroxyl group in the bicyclic core and rather unusual structural motifs in sugar appendages. Therefore it's not surprising that they also have similarity in biological activities and the mechanism of their action. Both families exert their

biological activity by damaging the DNA. The mechanism of DNA cleavage by esperamicin A_1, identical to one by calicheamicin γ_1^I, is shown in Figure 1.2.6.[27]

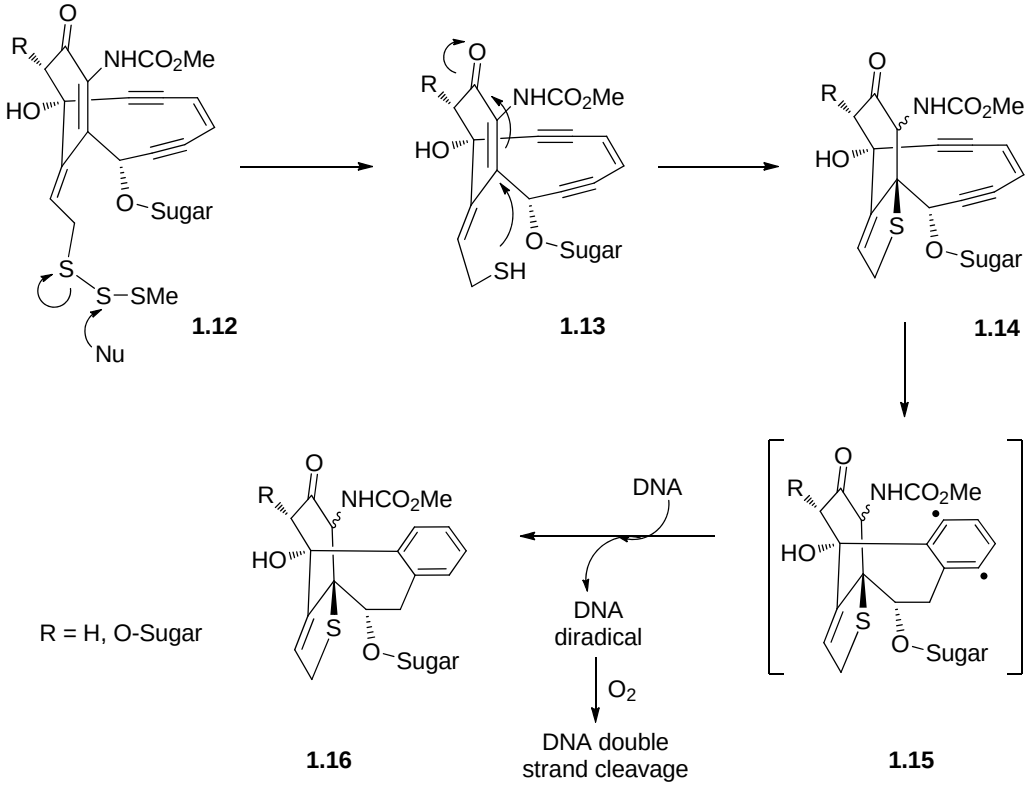


Figure 1.2.6 Calicheamicin/Esperamicin mechanism of action.

The aglycone of **1.12** is a rigid bicyclic core containing an enediyne moiety and allylic trisulfide as well, which serves as a trigger. A nucleophile attacks the central atom in the allylic trisulfide leading to the formation of thiol **1.13**, which undergoes intramolecular Michael addition to the α,β-unsaturated ketone moiety incorporated into the bicyclic core. Thus, reduction of the bridgehead double bond relieves ring strain and changes the structural geometry of an agylcone leading to a great deal of strain of the 10-membered enediyne ring. At this point a Bergman cyclization becomes possible thereby triggering the DNA-damaging mechanism. The sugar appendages assist the drug binding into minor groove of the DNA.

When conjugated to a humanized anti-CD33 antibody specific for tumour-associated antigens, calicheamicin exerts strong antigen-specific anti-tumour effects against human tumours. Antibody-targeted chemotherapy with immunoconjugates of calicheamicin, exemplified by gemtuzumab ozogamicin (Mylotarg®), was a clinically validated therapeutic strategy for the treatment of acute myeloid leukemia in elderly patients.[28] In June 2010, Mylotarg was withdrawn from U.S. market due to the concerns about the drug's safety and its failure to demonstrate clinical benefit to patients enrolled in trials.

Dynemicines are also 10-membered cyclic enediyne antibiotic. The member of the dynemicin family of enediyne antibiotics that was first discovered is dynemicin A (**1.17**). Its molecular structure was fully determined in 1989[3] and its absolute configuration was confirmed in 1995 by total synthesis by Myers et al.[29] Dynemicin A exhibit high efficiency against a variety of cancer cells and antibacterial activity *in vivo* with low toxicity. Deoxydynemicin A (**1.18**) has a similar biological profile as dynemicin A.[9]

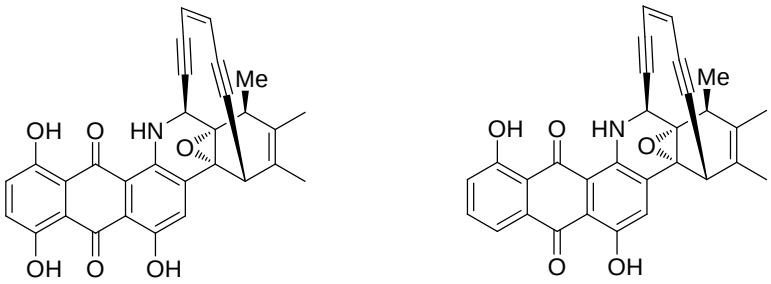
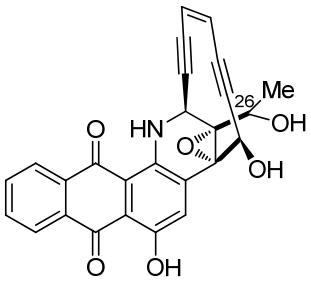


Figure 1.2.7 The dynamicin family.

The dynemicins possess a 10-membered ring with an enediyne moiety embedded within an anthraquinone chromophore. It is believed that the cascade reaction, leading to the DNA cleavage, begins with positioning of the aminopolyhydroxyanthraquinone moiety of dynemicin A into the minor groove of the DNA. The dynemicin molecule recognizes conformationally

flexible regions of the DNA and acts as a "molecular wedge". Biological reduction of the anthraquinone moiety leads to the formation of electron-rich anthraquinol which is able to open the epoxide ring. This process is accompanied with Bergman cycloaromatization of the 3-ene-1,5-diyne moiety.[9,30]

Uncialamycin (**1.19**) is another 10-membered ring enediyne antibiotic and its structure was elucidated in 2005 by analysis of spectroscopic data but assigning the absolute configuration of C26 was not possible.[31] The initial biological evaluations showed that **1.19** possesses potent *in vitro* antibacterial activity against *Staphylococcus aurens*, *Escheridia coli*, and *Burkholderia apia*.



1.19

Figure 1.2.8 Uncialamycin.

The total synthesis of racemic uncialamycin and chiral uncialamycin has been reported by Nicolaou and coworkers[32] in 2008. They work proved without ambiguity the complete structure of uncialamycin and determined the absolute stereochemistry at C26 being 26R epimer. They also studied biological properties of **1.19** in DNA-cleavage, antibacterial, and cytotoxic activities. These investigations discovered highly potent antitumor activities and broad-spectrum antibacterial properties. Another synthetic pathway towards synthesis of uncialamycin involving intramolecular imino Diels-Alder reaction was reported by van de Weghe in 2009.[33]

It is assumed that uncialamycin damages DNA through a mechanism that involves a cascade sequence initiated by biological reduction in a similar manner as dynemicin A.

1.3 Factors Affecting the Rate of Bergman Cyclization

The Bergman cyclization is responsible for the DNA cleavage by enediyne antibiotics. Therefore, it is important to determine the factors that affect reactivity of *Z*-enediynes in order to be able to control the rate of Bergman cycloaromatization reaction. These factors can be classified as follows:

- Distance between two triple bonds in the enediyne fragment,
- Effects of strain in the chromophore of cyclic enediynes,
- Effects of electronic factors or substituent effect,
- Concentration of the trapping agent–hydrogen donor.

1.3.1 Distance between Triple Bonds of Enediyne Fragment

Nicolaou et al.[34] proposed the hypothesis that critical distances (*cd*) between two triple bonds in the enediyne fragment must be between 3.20 and 3.31 Å for cyclization to proceed spontaneously at room temperature (Figure 1.3.1). If the *cd* distance is larger than ~3.31 Å, the molecule is relatively stable, however if this distance is less than 3.2 Å, such compounds should undergo spontaneous cyclization even at lower temperatures. A DFT-based calculation[35] suggests a correlation between the spontaneity of Bergman cyclization and the *cd* distance. Mitra at al. have developed a theoretical model to predict the rate of cyclization of the enediyne anticancer antibiotics based on the *cd* distance.[36]

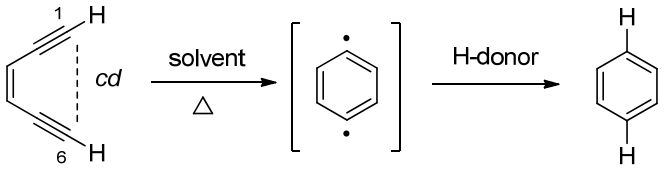


Figure 1.3.1 *cd* Distance between C1–C6 carbon atoms.

Indeed, acyclic enediynes undergo the Bergman reaction at much higher temperature than cyclic ones (Figure 1.3.2). It was shown that acyclic enediynes **1.20** and **1.21** have high

activation barrier, while the energy of activation for cyclic enediynes like **1.22** is lower, so they undergo Bergman cyclization at lower temperature.

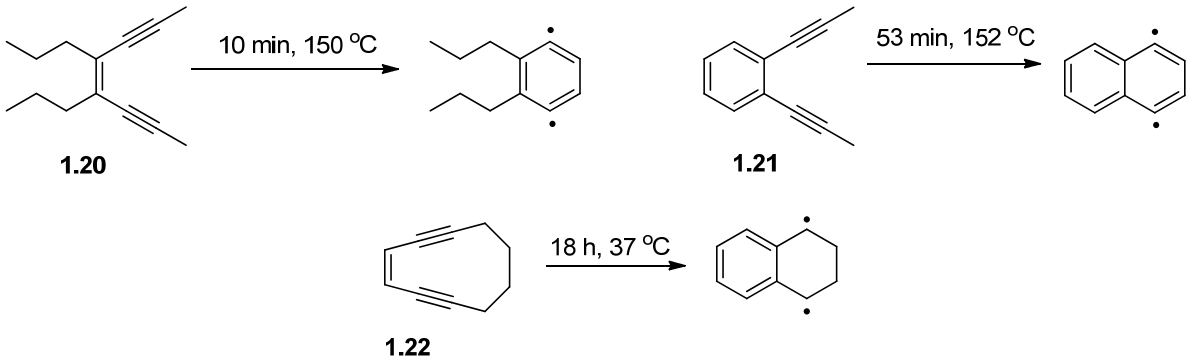


Figure 1.3.2 Rates of cyclization.

The rate of Bergman cyclization decreases by increasing the number of members in enediyne ring. For example, nine-membered ring enediynes undergo spontaneous cycloaromatization even at lowered temperatures, 10-membered ring enediynes are less reactive, and 11- and 12-membered ring enediynes are stable at room temperature.

An example of quite different reactivity of 10- and 12-membered ring enediynes can be found in the work of Reitz et al.[37]. They incorporated the enediyne group into 10- and 12-membered ring cyclic amino acids and dipeptides, respectively (Figure 1.3.3), and explored their reactivity toward cyclization. Half-lives for cyclization of 10-membered ring amino acids (**1.23**–**1.28**) in DMF/1,4-cyclohexadiene at 55 °C were found to be from 4 to 55 hours depending on substituents on the nitrogen atom in the ring. As expected, the 12-membered ring enediyne amino acid **1.29** was thermally stable. The distance between two relevant alkynyl carbons of this enediyne in the solid state is 3.86 Å, which is much higher than required 3.31 Å. Thus, enlarging of the ring size, indeed, decelerates the cycloaromatization reaction.

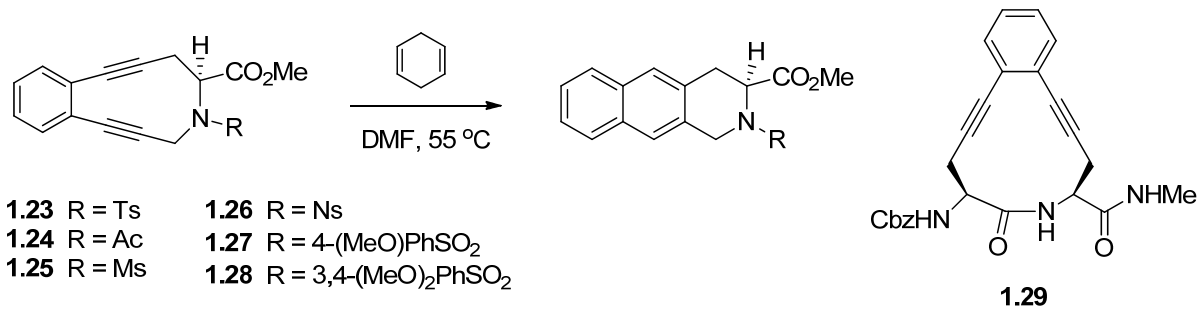


Figure 1.3.3 10- and 12-membered ring enediyne amino acids

Therefore, reducing the *cd* distance value is a way to overcome the energy value which is necessary for cyclization. Control over the *cd* value can be achieved either by decreasing the size of the ring, in case of cyclic enediynes, or by complexation with transition metals.

An example of decreasing ring size of enediynes and, therefore, *cd* distance is shown in the work of Popik et al.[38]

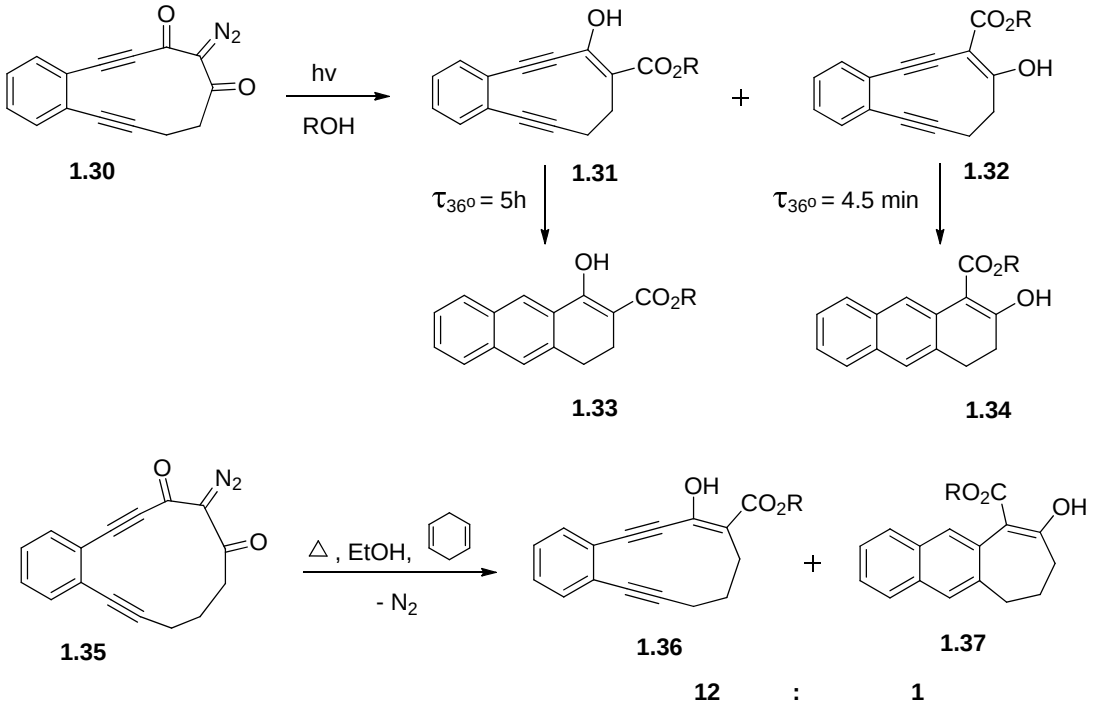


Figure 1.3.4 Wolff rearrangement of enediyne α-diazo-β-diketones.

Eleven- and twelve-membered enediynes **1.30** and **1.35**, which incorporate an α-diazo-*β*-diketone moiety, were designed and synthesized. Both enediynes are stable at temperatures

below 80 °C. Upon irradiation or thermolysis, these diazo-diketones undergo Wolff rearrangement to produce reactive 10- and 11-membered enediynes **1.31**, **1.32**, and **1.36** respectively. While 10-membered ring enediynes undergo spontaneous Bergman cyclization, 11-membered ring enediyne **1.36** is less reactive.

Complexation of the enediynes with transition metals can be used to reduce the value of the *cd* distance, which increases rate of the cycloaromatization reaction. The enediynes having ligating systems in the two acetylenic arms can chelate a metal ion forming a metallocycle. This chelation is expected to lower the activation barrier for Bergman cyclization.

The first example of use the metal ions to control the rate of cycloaromatization was demonstrated by Kerwin et al. in 1994.[39] They designed a crown ether-based enediyne in which crown ether ring was directly incorporated onto the enediyne chromophore. This compound effectively coupled molecular recognition by the crown to the decreasing of the critical distance in the enediyne moiety to facilitate the Bergman cyclization.

Incorporation of a tetra-aza-crown ether into the *bis*-enediyne core was reported by Basak et al.[40] 24-Membered tetra-azaenediyne **1.38** and its copper(II) complex **1.39** have been synthesized and differential scanning calorimetry (DSC) measurements revealed a lowering of onset temperature for Bergman cyclization upon complexation (Figure 1.3.5). In the tetraaza system **1.38**, the inner cavity size is sufficient to accommodate Cu(II) ion and, thus, to form an 11-membered ring. As a result, the distance between acetylenic carbons is lowered and hence Bergman cyclization is facilitated at a lower temperature.

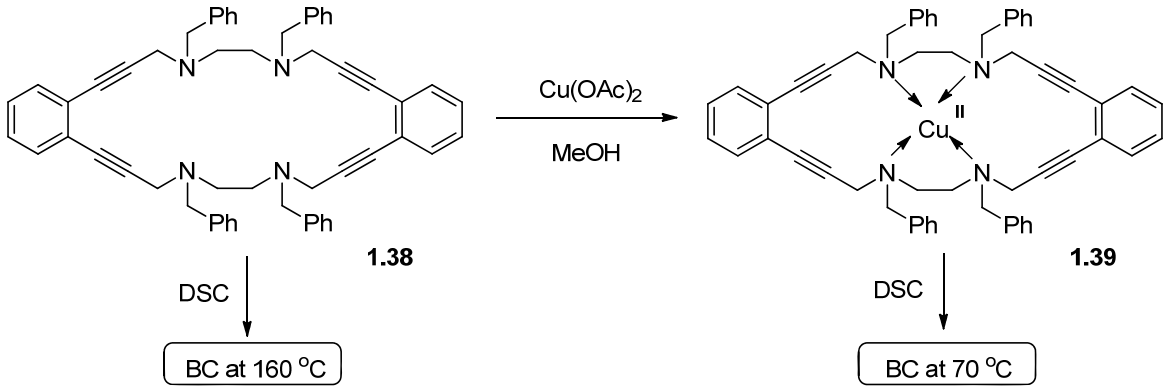


Figure 1.3.5 BC of tetra-azaenediyne.

Cyclam-based enediynes **1.40**, **1.41**, and **1.42** were synthesized in 2005 by Basak et al. (Figure 1.3.6).[41] Enediyne **1.40** readily forms a complex with Ni(II), which lowered the onset temperature for Bergman cyclization of the metal-free enediyne by 60 °C.

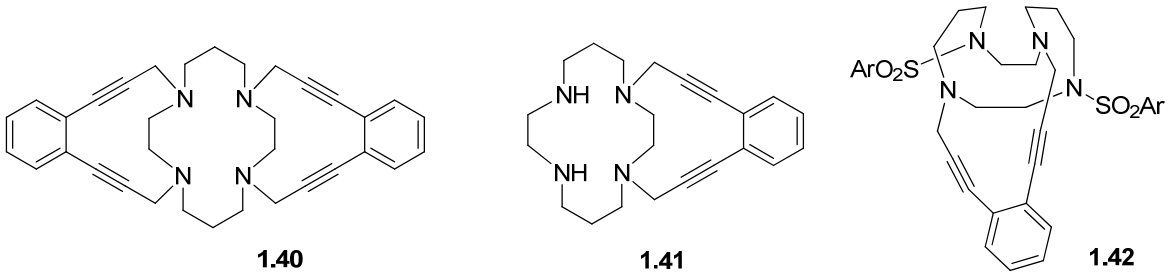


Figure 1.3.6 Cyclam-based enediynes.

Dramatic changes of the Bergman cyclization kinetics were observed upon metal-ion chelation to an acyclic enediyne were reported by Buchwald et al.[42] The enediyne **1.43** (Figure 1.3.7) was found to be stable in air and shows no signs of decomposition upon heating at 95 °C for 20 days. Free ligand **1.43** as well as its metal complexes derived from coordination of enediyne with $PdCl_2$ (**1.43a**), $PtCl_2$ (**1.43b**), and $HgCl_2$ (**1.43c**) were modeled and *cd* distances were found to be 4.1Å, 3.3Å, 3.3Å, and 3.4Å respectively. These distances suggested that **1.43a** and **b** should undergo Bergman cyclization at room temperature while **1.43c** should not cyclize.

These three complexes were prepared and their properties were investigated by both NMR and DSC analyzes.

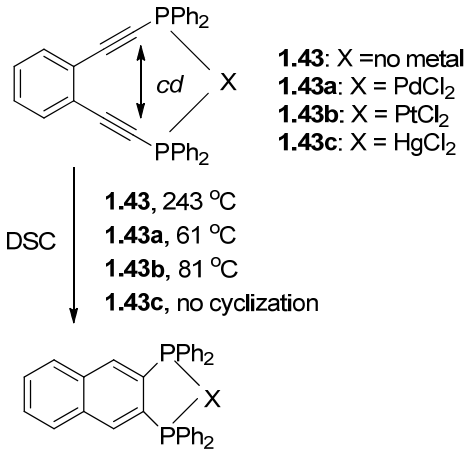


Figure 1.3.7 Temperatures of BC by DSC.

Based on the DSC data, palladium and platinum 1:1 complexes of enediyne **1.43** showed similar behavior. Chelated enediyne **1.43a** cyclizes at 61 °C and **1.43b** –at 81 °C, which is more than 150 °C lower than for the parent free ligand enediyne **1.43**. This difference shows that the rate of the Bergman cyclization can be enormously increased by coordination of **1.43** to palladium or platinum dichloride. In contrast, mercury dichloride complex **1.43c** (*cd* = 3.4Å) displayed no evidences for cyclization at temperatures up to 450 °C. Therefore, complexation to $HgCl_2$ inhibits the Bergman cyclization of **1.43**. This example shows that choice of the metal is critical for the acceleration or the inhibition of cycloaromatization. It should be noted that the DSC-monitored reaction was run in the solid state with no radical trapping agent.

The NMR kinetic studies of **1.43a** and **1.43b** in deuterated dichloromethane in the presence of 1,4-CHD as a trapping agent showed that the rate of cyclization of the platinum complex (**1.43b**) was 2.7 times that of the palladium complex (**1.43a**), although **1.43a** underwent cyclization at a lower temperature than **1.43b** as monitored by DSC. The authors proposed that the mixture of parent enediyne **1.43** and $PdCl_2$ forms a dimeric species **1.44a** that further

disproportionates to a monomeric species **1.43a** which finally undergoes cyclization to the biradical in a rate-limiting step (Figure 1.3.8).

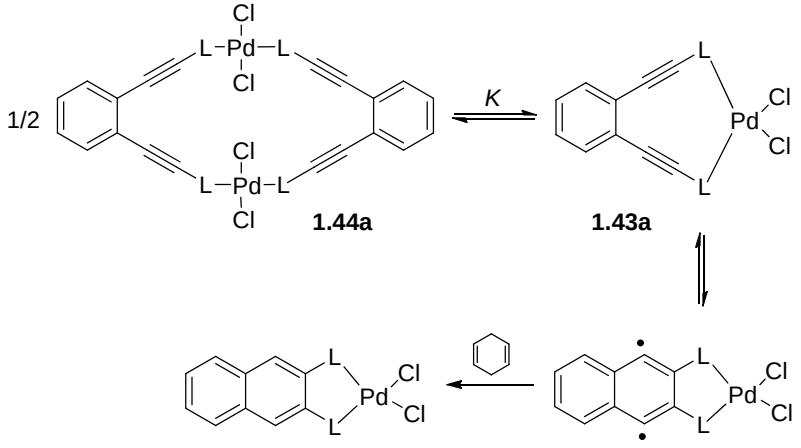


Figure 1.3.8 Equilibrium between dimeric and monomeric complexes.

The lowering of the *cd* distance can be achieved not only by formation of a cyclic network upon complexation but by a change in conformation of the enediyne. Konig et al.[43] showed that conformational changes can play major role in decreasing the activation barrier of the Bergman cyclization. They synthesized a bipyridyl-based macrocyclic enediyne **1.45** (Figure 1.3.9) and showed that without metal-ion complexation the bipyridyl core exists in the transoid conformation forcing the terminal acetylenic carbons to be far apart. Upon Hg^{2+} binding, the bipyridyl unit preferss a cisoid conformation which allows the ligand to coordinate to the metal ion. Thus the *cd* distance decreases and thermal reactivity of the enediyne increases. Temperatures for Bergman cyclization were found using DSC. The cyclization temperature was found to drop by 92 °C.

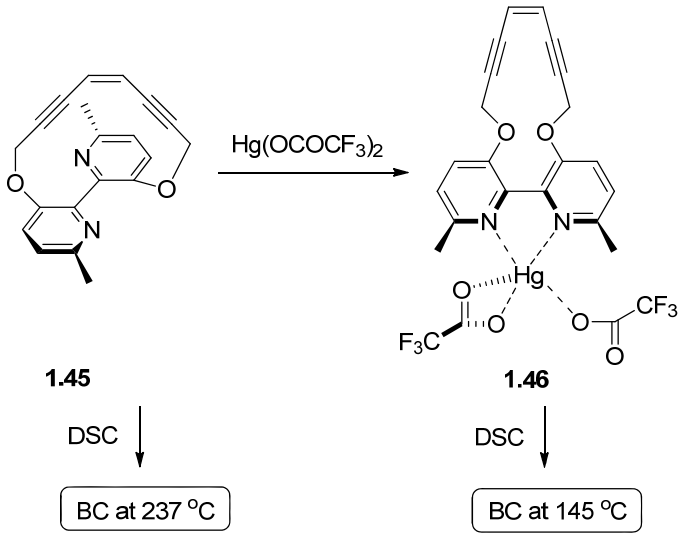


Figure 1.3.9 Conformational changes.

Amino and sulfonamido enediynes were also expected to lower the activation barrier of the Bergman cyclization upon metal ion coordination because of their rigid structure. Two macrocyclic enediynes possessing two N-atoms **1.47** ad **1.48** (Figure 1.3.10) were synthesized and their properties were investigated by Basak et al.[44] The onset temperature for the Bergman cyclization of *bis*-sulfonamido enediyne **1.47** was determined to be 130 °C. However, the Ag (I) ion chelate cyclizes at 110 °C representing a 20 °C decrease in the cyclization temperature. This complexation leads to the absence of transannular repulsion between lone pairs of electrons on the nitrogen atoms, bringing them closer to each other and, therefore, causing the decrease in the distance between the reacting acetylenic carbons. The onset temperature of Bergman cyclization for *bis*-N-substituted enediyne **1.48** lowers by 130 °C upon complexation to Cu(II) when treated with copper acetate in methanol.

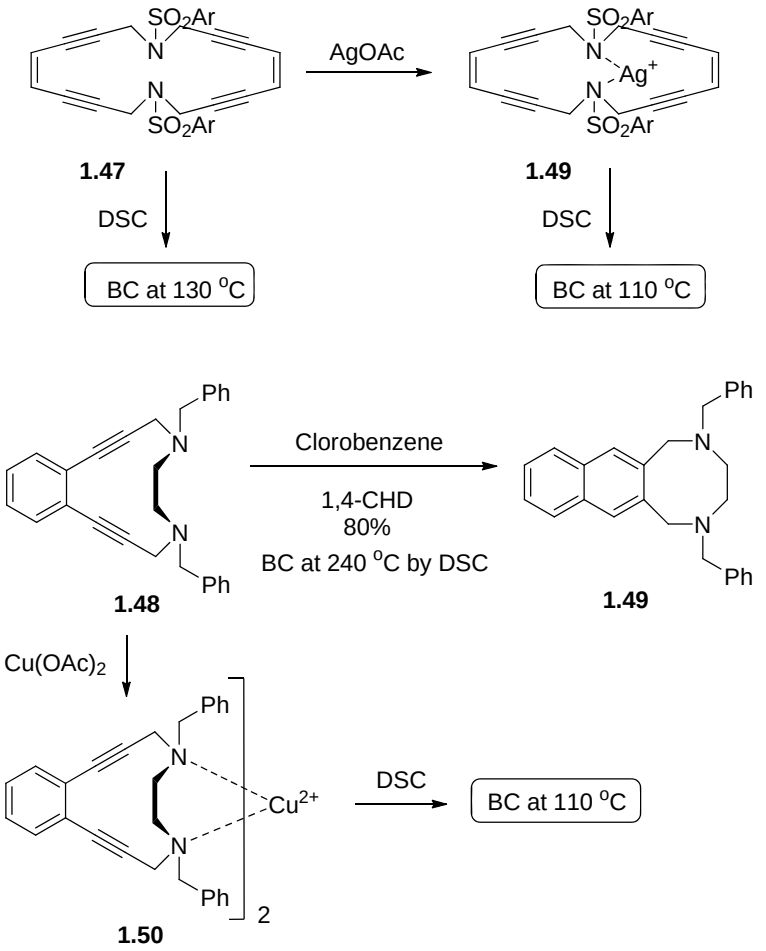


Figure 1.3.10 BC of amino and sulfonamido enediynes.

Aromatic enediynes are thermally stable and their cyclization temperature is higher than ambient conditions even in case of metal-ion complexation of these enediynes. In contrast, the cyclization temperatures of aliphatic enediynes are lower. Such an example is reported in the work of Zaleski et al.,[45] who synthesized pyridine-based nonaromatic fused enediyne **1.51** (Figure 1.3.11). While unchelated **1.51** cyclizes at 100 °C as established by DSC, its complex with Mg^{2+} undergoes cyclization spontaneously at room temperature. This result is the first remarkable example of ability of a nontoxic biorelevant magnesium(II) ion to lower the activation energy barrier of an acyclic enediyne in such way that the reaction takes place at room temperature.

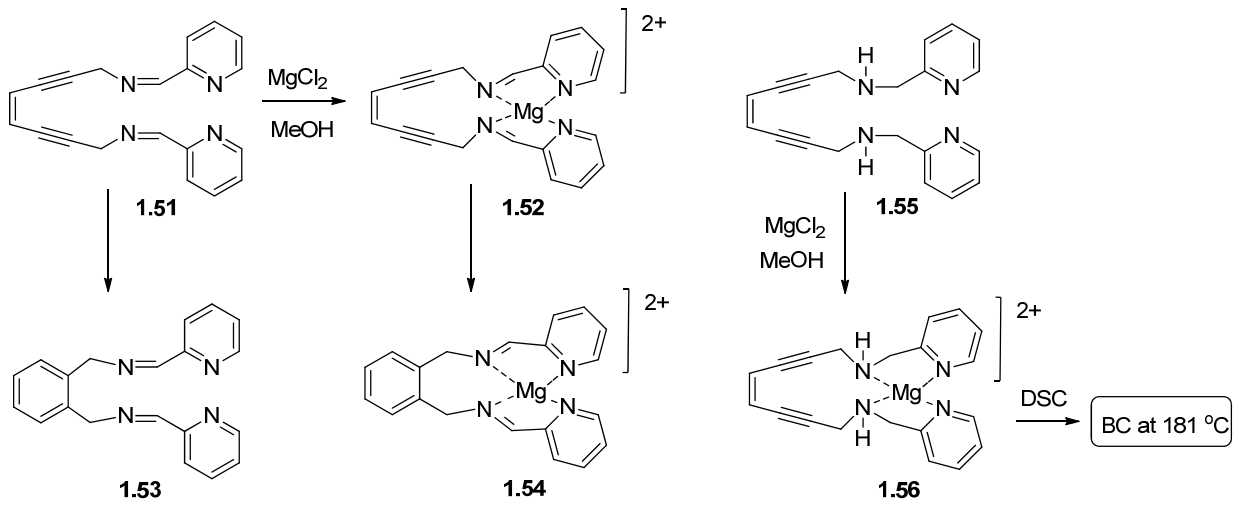


Figure 1.3.11 Pyridine-based non-aromatic fused enediynes.

In contrast to enediyne **1.51**, Mg^{2+} complex **1.56** of amino enediyne **1.55** undergoes Bergman cyclization at the temperature as high as 181 °C. The authors explained such a tremendous disparity in reactivity upon metal complexation by the basicity of the coordinating amino and imino nitrogens. Imine nitrogens are less basic than the corresponding amine, and consequently Mg^{2+} needs to adopt additional ligands possibly by solvent or counterion to satisfy the Lewis acidity of the metal center. Computational studies have shown that the increase in coordination number can reduce the alkyne termini separation (*cd* distance) and lower the barrier to thermal Bergman cyclization.[45]

The aromatic fused bis-salicylaldimino enediynes with different spacers separating the ligand and enediyne core show different reactivity (Figure 1.3.12).[46] Based on evaluation of the cyclization temperatures, the reaction rate of the enediyne **1.57** decreases upon complexation with the metals such as Cu^{2+} and Ni^{2+}. On the contrary, the other enediyne **1.59** with two methylenes separating the ligands and the enediyne core shows an opposite effect. The reason for such different behavior is not clear.

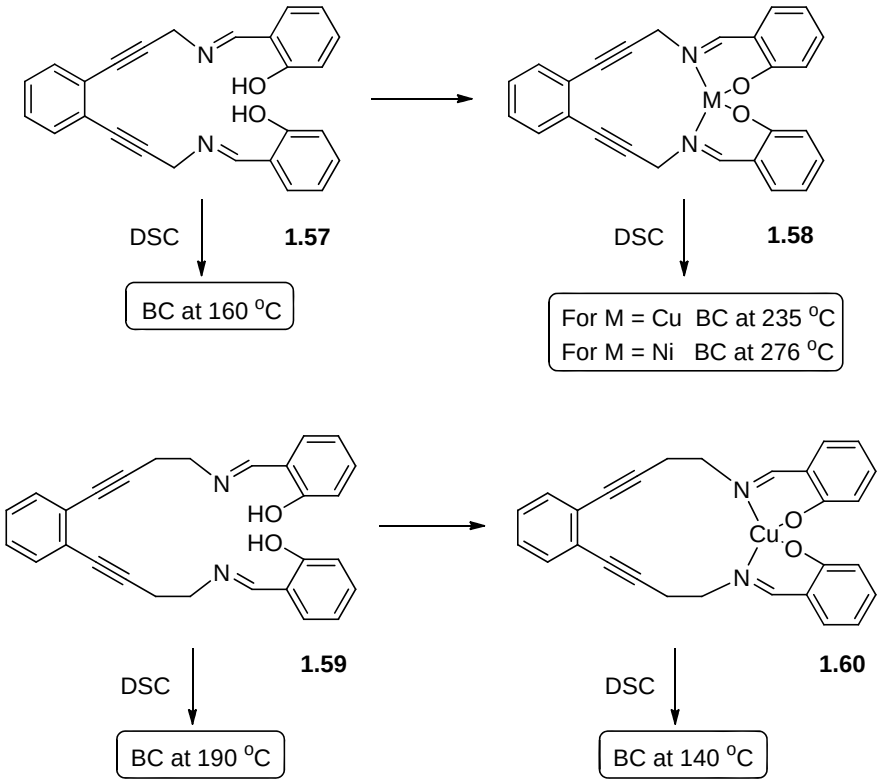


Figure 1.3.12 BC of bis-salicylaldimino enediynes and their metal complexes.

The critical distance can also be decreased by introducing donor-donor and donor-acceptor substituents into the enediyne's side chains.[47] Several 1,2-dialkynyl benzenes incorporating various combinations of donor and acceptor units in the two arms of the endiynes were designed and synthesized and effect of charge-transfer (CT) and π-stacking interactions between the two arms on a Bergman cyclization was investigated. The thermal reactivity, as studied by DSC, increases for the donor/acceptor (D/A) or donor/donor (D/D) combinations of the substituents compared to the acceptor/acceptor (A/A).

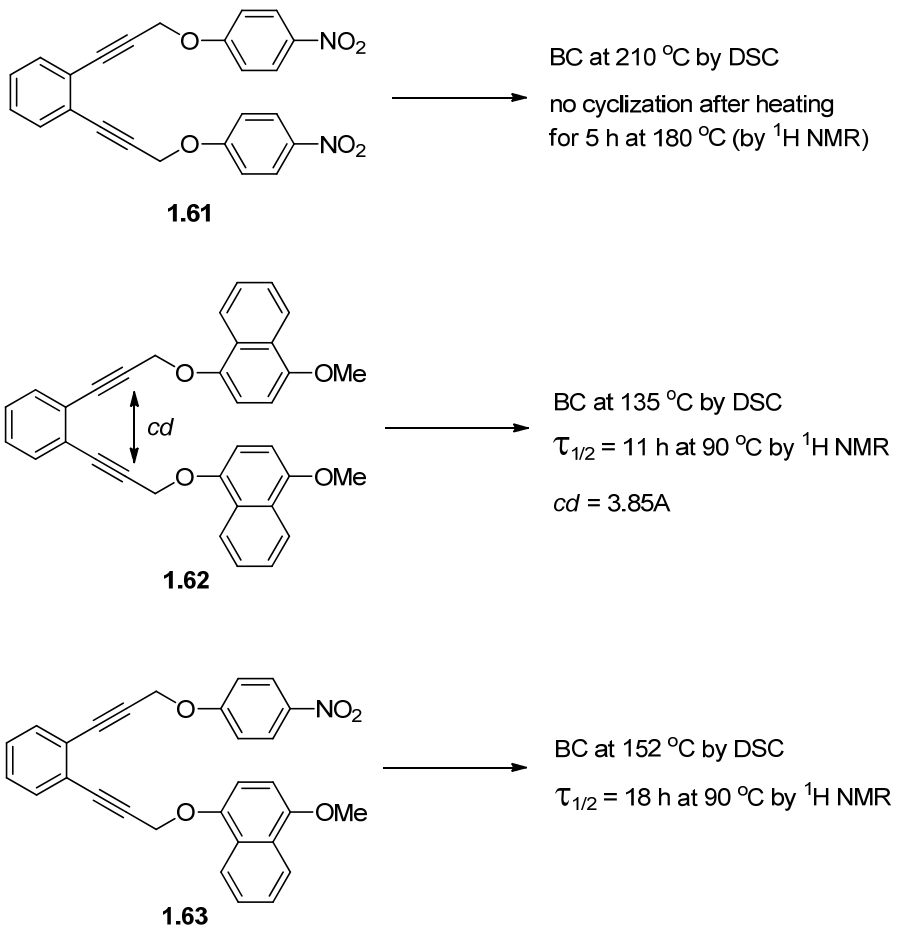


Figure 1.3.13 Cycloaromatization of A/A, D/D, and D/A containing 1,2-dialkynylbenzenes.

Examples of A/A, D/D, and D/A containing 1,2-dialkynylbenzenes, their onset temperatures and kinetic data of Bergman cyclization are shown in Figure 1.3.13. The onset temperatures for the Bergman cyclization for D/A (**1.63**) and D/D (**1.62**) combinations were found to be lower than for the A/A (**1.61**) pair. This reactivity can be explained on the grounds of the proximity theory.[34b] In D/A compounds CT complex forms, therefore electrons' flow from the donor in one arm to the acceptor in another arm of the enediyne occurs through space. As this happens, two acetylenic arms come closer together and, as a result, the cyclization temperature becomes lower. For the D/D compounds such as **1.62** CT is not possible but there is a possibility of π-stacking interactions between the aromatic units in the two arms of enediynes, which also

can lower the *cd* distance. On the contrary, A/A enediynes have high electron densities of their aromatic rings in the two arms and remain far apart from each other due to the coulombic repulsion. Thus, the *cd* distance increases as well as thermal cyclization barrier for the A/A enediynes.

The solution-phase kinetic data by ^{1}H NMR in presence of 1,4-CHD demonstrated some interesting results. The A/A enediyne **1.61** failed to cyclize at 180 °C even after heating for 5 h. In solution D/D enediyne **1.62** reacts about 1.6 times faster than the D/A enediyne **1.63** meaning that the π-stacking interaction in the solution phase is more distinct than the CT interaction. Also, single-crystal X-ray analysis revealed the *cd* distance in **1.62** is being 3.85 Å, which is significantly lower than expected for an acyclic enediyne (ca. 4.12 Å).[34b]

1.3.2 Effects of Strain in the Chromophore of Cyclic Enediynes

Alternatively to the *cd* distance theory, there is an assumption that the overall change in the molecular strain energy, when an enediyne undergoes cycloaromatization, determines the cycloaromatization rates rather than does acetylenic bond proximity theory.[48] Basak et al.[49] demonstrated how a remote double bond in a pyridazine system incorporated into the enediyne ring can affect the kinetic of Bergman cyclization. For this purpose, the authors synthesized pyridazinedione-based dihydro enediyne **1.64** and tetrahydro enediyne **1.65** (Figure 1.3.14). Their single-crystal X-ray structures revealed similar *cd* distances.

The reactivity of **1.64** and **1.65** towards the Bergman cyclization was studied in both solid-phase by DSC and solution-phase by ^{1}H NMR spectroscopy. The onset temperatures for the Bergman cyclization were found to be 228 °C for **1.64** and 196 °C for **1.65**. Although these temperatures are different, the compounds have similar structures. The only difference is that enediyne **1.65** has a double bond between C4 and C5 atoms of the heterocyclic ring. The *cd*

distance in both molecules was found to be equal to 3.79 Å. Therefore, saturation of the C4-C5 bond changes the activation barrier of Bergman cyclization.

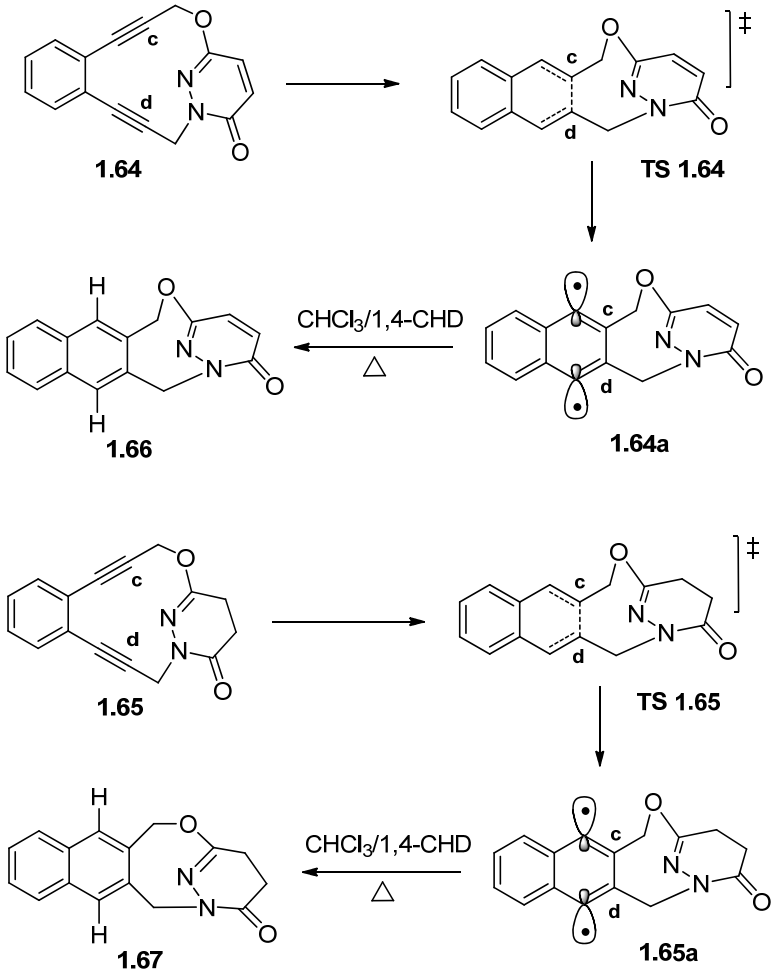


Figure 1.3.14 Formation of cyclized products and TS.

Kinetics measured by ^{1}H NMR in deuterated chloroform containing an excess of 1,4-cycloxehadiene indicated that the half-life for tetrahydropyridazine **1.65** was 120 h at 130 °C but **1.64** failed to cyclize at 130 °C even after heating for 168 h. Its half-life was determined at 150 °C to be 200 h. These data demonstrated that the enediyne **1.65** is much more reactive than the corresponding unsaturated compound **1.64**. Inspection of the X-ray structure showed that there is less strain in the ground state of **1.65** because of the presence flexible methylene chain, which gives the molecule a possibility to assume a more puckered structure, releasing the strain. On the

other hand, the lone pair of electrons on the nitrogen atom of **1.64** participates in delocalization with the carbonyl more than **1.65** because of attainment of aromaticity. The C-O bond in **1.64** is longer compared to **1.65**. Thus, a greater delocalization in the unsaturated system **1.64** exists.

Computational analysis of the transition states of the calicheamicin/esperamicin framework, represented by **1.68**, evaluated the reactivity of chair and boat conformations (**1.68a** and **1.68b** respectively, Figure 1.3.15).[50] Semmelhack et al. that the enediyne containing chair conformation has lower transition state energy and is more reactive toward cycloaromatization. The experimental half-life of, presumably, the chair conformer is 10 min at 21 °C. Therefore, the idea was to restrict the boat conformation in the molecule and experimentally measure the kinetics of cyclization for both conformers.

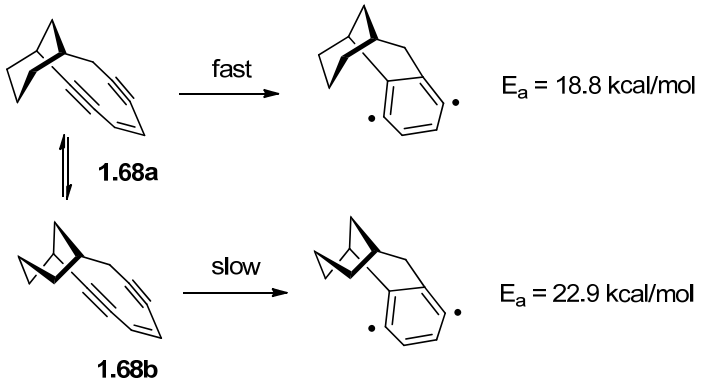


Figure 1.3.15 The reactivity of chair and boat conformations.

For these purposes, test compounds **1.69** and **1.70** were synthesized (Figure 1.3.16). According to their calculations, compound **1.69** should be stable at room temperature. Experimental data showed decomposition of the boat conformer **1.69** with a half-life of 110 h at 74 °C. It should be noted that no expected products of typical cycloaromatization were found. In order to evaluate the conformational effect on cycloaromatization reactivity, chair conformer **1.70** was prepared from **1.69** and its kinetics of cyclization was studied. With this goal in mind, **1.69** was treated with diisobutylaluminum hydride and cycloaromatization process–

disappearance of the absorption for the enediyne unit–was followed by UV spectroscopy. The half-life for the chair intermediate **1.70** was 43.5 min at 24.5 °C. The observed half-life times for the boat conformer **1.69** and the chair intermediate **1.70** correspond to the energies of activation for the cyclization of 29 and 22 kcal/mol, respectively. Consequently, the calculations underestimated the barriers but correctly predicted the difference in the activation energies.

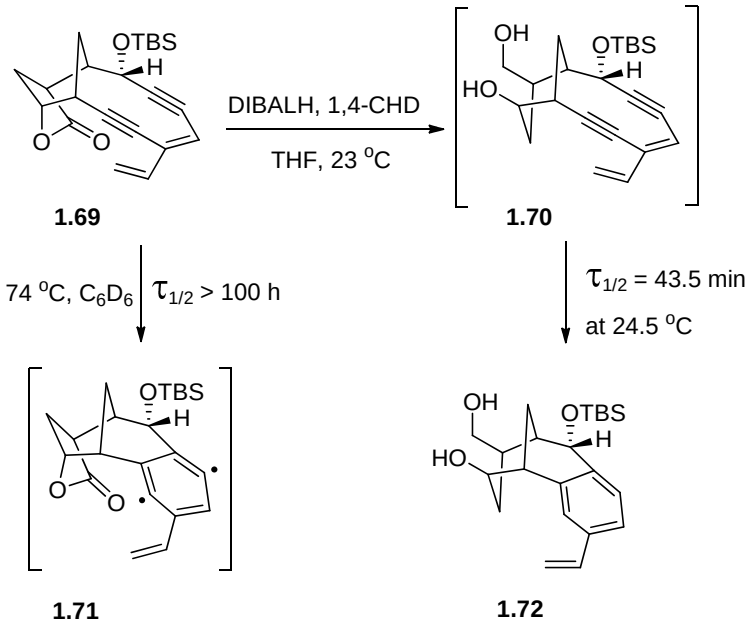


Figure 1.3.16 Kinetic experiments of **1.69** and **1.70**.

The rate of the Bergman cyclization can be significantly affected by the steric bulk of the functional groups at the termini of acyclic enediynes. Simple nitrogen donor enediyne chelates were designed and synthesized.[51] Four of them are symmetric and two are asymmetric compounds as shown in Figure 1.3.17. The Bergman cyclization temperatures of enediynes **1.73a-f** were measured in solid-phase (neat conditions) by DSC (Table 1.1). Compound **1.73a**, containing dimethylamino groups in both 1 and 8 position of the enediyne framework, is a thermally stable compound which cyclizes at 186 °C. When one of the dimethylamino groups is substituted with 3-hydroxypyridine (**1.73b**), the Bergman cyclization temperature reduces

dramatically to 149 °C. The reasons for such dropping in the temperatures are: first of all, the pyridine ring is able to rotate out of the enediyne plane, hence relieving steric hindrance. Secondly, addition of the sp^3-hybridized oxygen between the triple bond and pyridine ring distances the substituents from one another. The same effect plays a role in compound **1.73e** where both substituents are 3-hydroxypyridine (BC at 136 °C). It is interestingly to note that removal of the oxygen and ethylene group from **1.73e** to form fully conjugated **1.73f** restores the high Bergman cyclization temperature (195 °C).

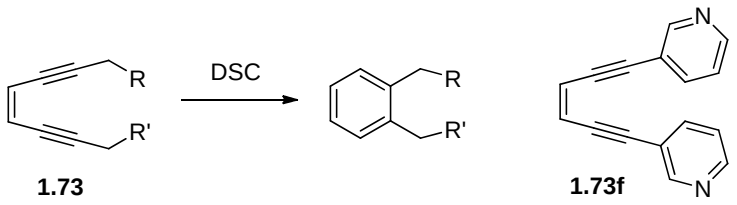


Figure 1.3.17 Bergman cyclization of symmetric and asymmetric acyclic enediynes.

Compound	R	R'	Cyclization temperature (°C)
1.73a	NMe_2	NMe_2	186
1.73b	NMe_2		149
1.73c	NMe_2	NH_2	139
1.73d	NH_2	NH_2	106
1.73e			136
1.73f	-	-	195

Table 1.1 Temperature of Bergman cyclization.

A more distinct trend of dependency of the cyclization temperature on nitrogen-containing substituents is observed between three compounds: **1.73a**, **1.73c**, and **1.73d**. Monosubstitution of the amino group for the bulky dimethylamino (**1.73c**) leads to a dramatic

decrease in the Bergman cyclization temperature by 47 °C. Further substitution to form the even less sterically hindered diamino compound **1.73d** yields an additional decrease in the cyclization temperature by 33 °C. Compound **1.73d** has one of the highest thermal reactivity of an acyclic enediyne reported.

This thermal reactivity of described enediynes systematically illustrates the importance of intraligand steric hindrance in influencing Bergman cyclization temperatures.

Another example of strain affecting the rate of Bergman cyclization in the enediyne's cyclic chromophore is demonstrated in a series of enediyne-containing amino acids with ring size varying from 10 to 12 atoms.[52] Compounds **1.74a** through **1.74f** shown in Figure 1.3.18 were synthesized and their half-life times were determined by ^{1}H NMR in deuterated DMSO in presence of 1,4-cyclohexadiene (CHD) and internal standard in sealed under argon NMR tubes. *cd* Distances of the compounds **1.74b** and **1.74d**-**f** were determined based on their crystal structures. As can be seen, the *cd* distance in the 11-membered ring benzo-fused enediyne **1.74d** is almost equal to the *cd* distance in the 12-membered ring benzo-fused enediyne **1.74f**, although these compounds undergo Bergman cyclization with quite different rates. Compound **1.74d** is stable at 80 °C, while increasing the temperature to 90 °C causes only slight increase in the rate of Bergman cyclization–a small amount of cycloaromatization product was observed after 24 hours. At 120 °C, a half-life of 175 h was measured. 12-Membered ring enediyne **1.74f** appeared to be unchanged at 120 °C. Therefore it is evident that ring strain plays a major role–increase in ring size goes along with the distinct decrease of the rate of Bergman cyclization while the *cd* distance remains unchanged. This fact can be explained by the higher strain in the smaller ring.

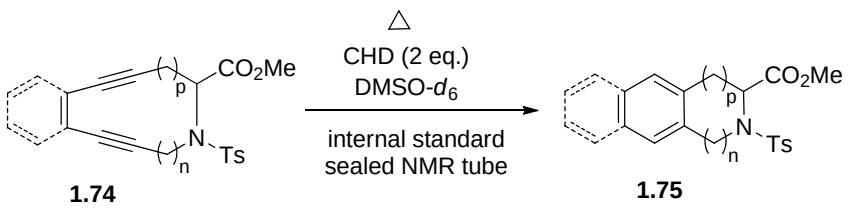


Figure 1.3.18 Cyclization of **1.74**.

Enediyne	Benzo-fused	n, p	Ring size	*cd* (Å)	T (°C)	$\tau_{1/2}$
1.74a	No	1, 1	10	N/A	rt-30	< 30 min
1.74b	Yes	–	–	3.23	80	59 min
1.74c	No	1, 2	11	N/A	80	Trace[a]
–	–	–	–	–	90	26 h
1.74d	Yes	–	–	3.76	80	Stable[b]
–	–	–	–	–	90	Trace[a]
–	–	–	–	–	120	175 h
1.74e	No	3, 1	12	3.88	90	Stable[b]
–	–	–	–	–	120	Trace[a]
1.74f	Yes	–	–	3.77	120	Stable[b]

[a]A small amount of the aromatization product was observed by ^{1}H NMR after 24h at the indicated temperature. [b]No product was observed by ^{1}H NMR after 24h at the indicated temperature.

Table 1.2 Half-life determination of cyclic enediynes.

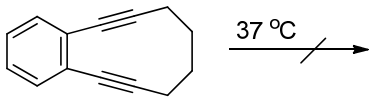
Although the above examples showed that molecular strain played the major role in the cyclization rate, the theory of distances is widely used due to its simplicity and adequate correlation between spontaneous Bergman cyclization and the distance between acetylenic carbon atoms.

1.3.3 Effects of Electronic Factors or Substituent's Effect

1.3.3.1 Enediynes with Unsubstituted Olefinic Portion vs. Benzene-fused Enediynes.

Although the electronic influences on the BC are perhaps the least studied, it is known that benzannulation of the olefinic portion of cyclic enediynes slows down the cyclization process. Annelation of aryl systems such as benzene and naphthalene on the enediyne moiety has an impeding effect on the cycloaromatization rate of the designed enediynes. An example for this

can be found in work of Semmelhack et. al.[53] Unsubstituted enediyne **1.22** has half-life time of 18 hours at 37 °C in benzene with 1,4-CHD as a trapping agent. The benzofused analog of **1.22** enediyne **1.76** is stable under the same conditions for more than one week.



1.76

Figure 1.3.19 Benzo-fused enediyne.

Benzannulated enediyne-containing amino acids with ring size varying from 10 to 12 atoms react faster than their unsubstituted analogs of same sizes (Figure 1.3.18).[52] The 10-membered enediyne **1.74a** underwent cycloaromatization spontaneously while its benzofused analog **1.74b** had half-life of 59 min at 80 °C in solution of DMSO-d_6 and 2 equivalents of 1,4-CHD. As can be seen from the table, the same tendency was observed for 11- and 12-membered ring enediynes.

Kinetic studies of azoenediynes were performed by Kar et al.[54] Stable *E*-izomers of azoenediynes **1.77** and **1.78** were successfully synthesized and it was found that photochemical isomerization into *Z*-isomers **1.77b** and **1.78b** occurs under UV irradiation for 7 hours (Figure 1.3.20). Enediynes **1.77b** and **1.78b** have similar *cd* distances calculated using MM2 calculations. The reactivity toward the BC was studied by DSC. The onset temperature of the BC of benzofused **1.77b** was more than twice as high as the one for unsubstituted azoenediyne **1.78b**.

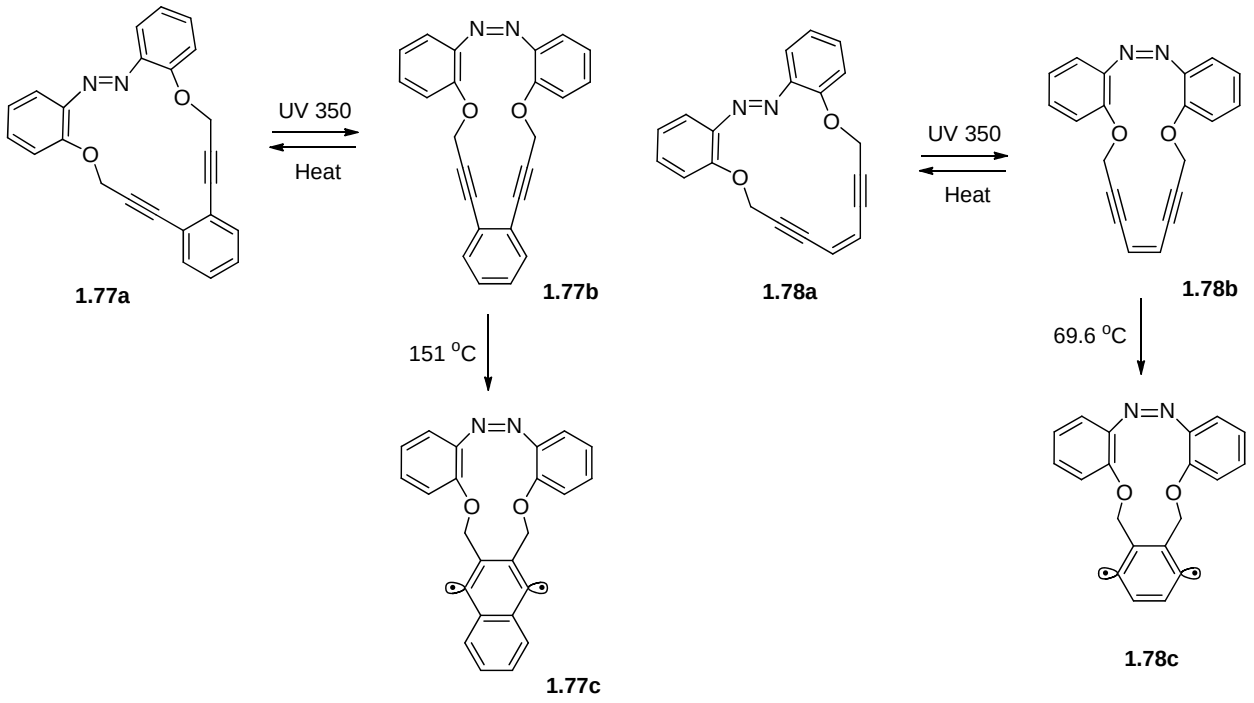


Figure 1.3.20 *E-Z* photoisomerization of enediynes and their thermal reactivity.

p-Quinone-substituted enediyne **1.79** has a higher half-life time of Bergman cyclization[55] than its unsubsituted analog **1.22** (Figure 1.3.21). The *p*-quinoid substituent influences the rate of Bergman cyclization making the enediyne more stable and, therefore, less reactive.

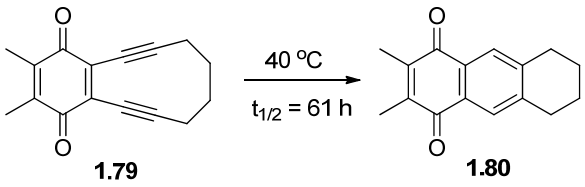


Figure 1.3.21 Cyclization of enediyne **1.79**.

1.3.3.2 Electronic Effects of the Substituents on the Acetylenic Carbon, Vinyl Carbon of Enediynes, and Enediyne Core.

Theoretical and experimental results suggest that σ-acceptor and π-donor substituents at the acetylenic terminal carbon increase the rate of Bergman cyclization. Benefits from both rate-enhancing effects can be seen when, for example, the carbon atom in the enediyne next to the

acetylenic one is replaced with nitrogen. The rate of cycloaromatization of aza-enediyne **1.81**, measured by both ^{1}H NMR and UV-spectroscopy in isopropanol, was more than two orders of magnitude higher than its carbocyclic analog (Figure 1.3.22).[56]

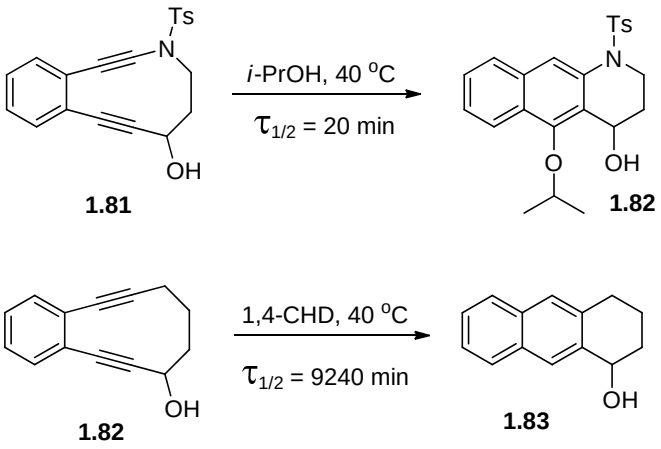


Figure 1.3.22 Cycloaromatization of aza-enediyne and its carbocyclic analog.

It should be noted that the expected product of a Bergman cyclization was not found after thermal experiments in various solvents. Overnight heating of **1.81** at 40 °C in benzene led to the formation of formal C–H insertion product **1.84** with benzene as a major product which is inconsistent with the reactivity of *p*-benzyne biradical (Figure 1.3.23).

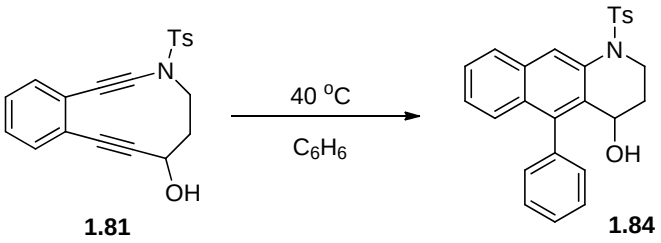


Figure 1.3.23 Cycloaromatization of aza-enediyne in benzene.

The reaction mechanism involves formation of a ketenimmonium cation intermediate with following intramolecular nucleophilic attack by the second acetylenic moiety and formation of a phenyl cation, which undergoes a Friedel-Crafts-type reaction with the solvent–benzene (Figure 1.3.24).

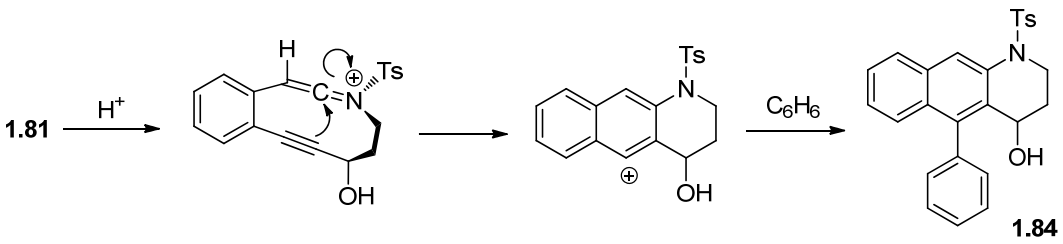


Figure 1.3.24 Polar mechanism of the cycloaromatization of aza-enediyne **1.81**.

Example of the influence of the π-acceptor substituents at the acetylenic termini of the enediynes on the rate of Bergman cyclization can be found in work of König et al.[57]

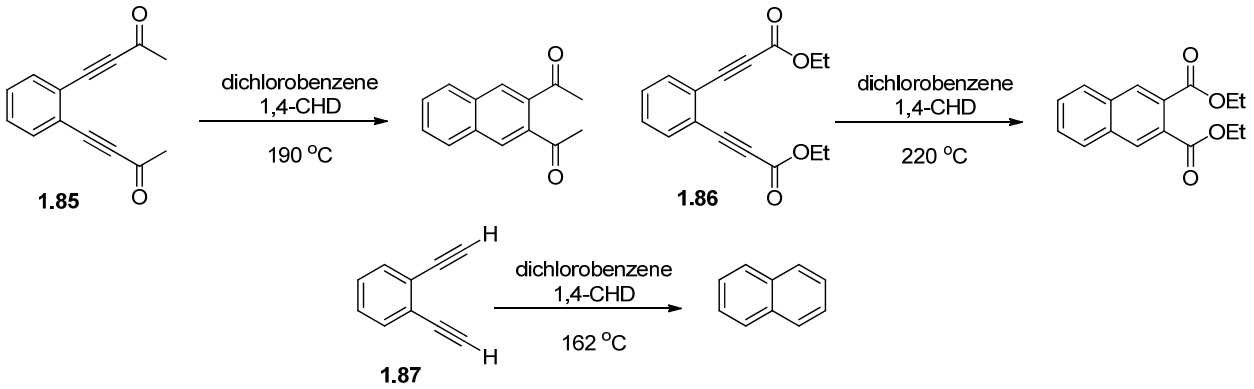


Figure 1.3.25 Cycloaromatization of the acyclic enediynes with electron-withdrawing groups.

Carbonyl (**1.85**) and carboxyl (**1.86**) substituted enediynes (Figure 1.3.25) were heated in the presence of dichlorobenzene and 1,4-CHD at 200 °C and kinetic measurements were performed by HPLC assay. The half-lives for compounds **1.85** and **1.86** under identical conditions were found to be $t_{1/2}$ = 481 min and $t_{1/2}$ = 660 min, respectively, which is longer than half-life time of the parent enediyne **1.87** (162 °C, $t_{1/2}$ = 29 min). These results support theoretical findings that electron withdrawing groups at the alkyne termini do not increase the thermal reactivity of the enediyne systems.

Graham Jones and co-workers[58] examined the effect of heteroatoms directly attached to the vinyl position of the enediynes. They expected that both inductive and electronegativity effects would influence cycloaromatization either by destabilizing the ground state or by

stabilizing the transition state of the reaction. But their studies proved just the opposite, i.e. the halogen atoms had a retardative effect on the rate of Bergman cycloaromatization.

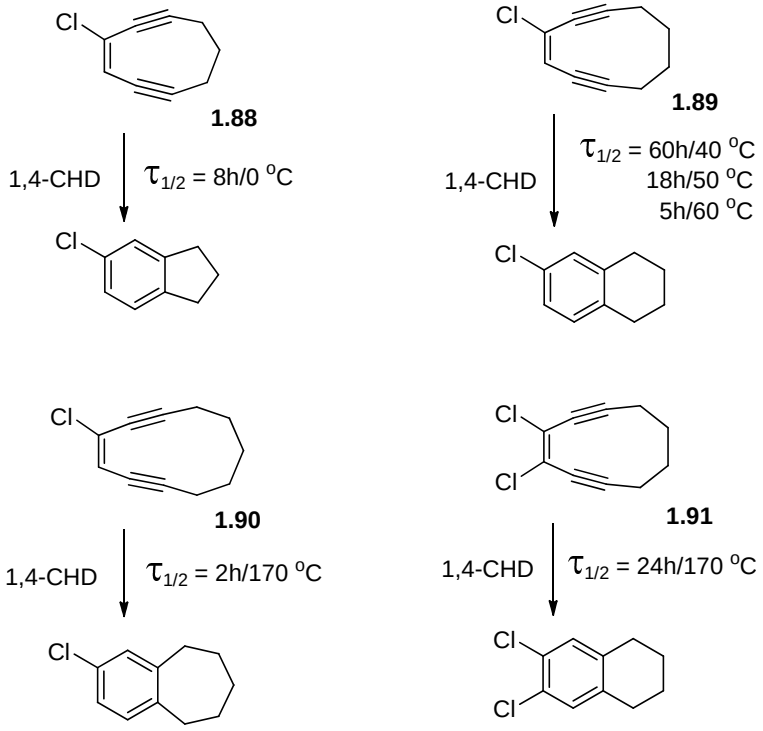


Figure 1.3.26 Bergman cyclization of cyclic halovinyl enediynes.

Monochloro substituted 9-membered ring enediyne **1.88** (Figure 1.3.26) was isolated and half-life was measured in 1,4-CHD at 0 °C, while unsubstituted "parent" enediyne analog is extremely unstable and its half-life cannot be measured. The half-life times of **1.89** and **1.90** are also higher compare to their unsubstituted analogs. Addition of the second chlorine (**1.91**) tremendously retards cycloaromatization in comparison to monochlorinated 10-membered ring enediyne **1.89**. Presumably, electronic effect is responsible for such stabilization, since there is no difference in the *cd* distances of **1.89**, **1.91**, and their unsubstituted enediyne analog.

In addition, DFT calculations showed that σ-electron withdrawing substituents in the vinyl position of the enediynes inhibit Bergman cycloaromatization.[59]

Enediynes that possess a carbonyl group in α position to the acetylenic termini undergo Bergman cyclization at higher rates than their unsubstituted analogs. An example can be found in the work of Popik et al.[60]

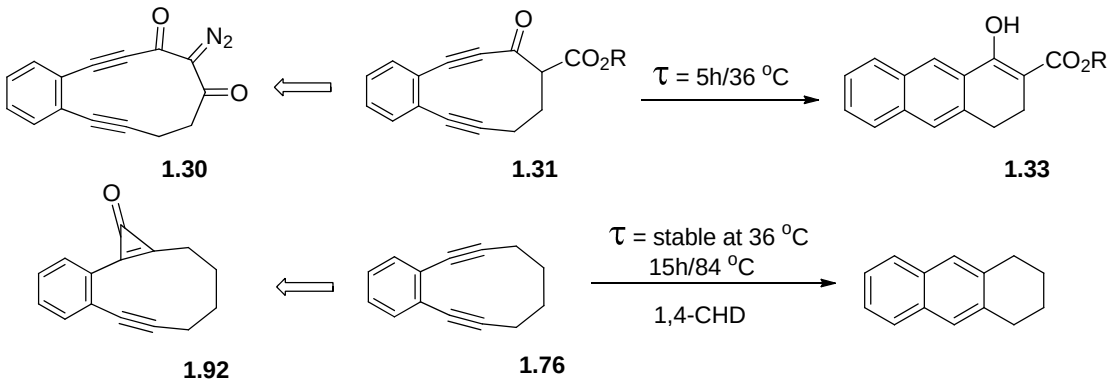


Figure 1.3.27 Cyclization of the carbonyl-containing enediyne vs. unsubstituted one.

UV irradiation of diazo-enediyne **1.30** leads to the formation of carbonyl-containing enediyne **1.31** as one of the products, which rapidly cyclizes to naphthalene derivative **1.33** (Figure 1.3.27). Such an efficient Bergman cyclization is rather unusual compared to the cycloaromatization of parent enediyne **1.76,** which is stable at room temperature. The authors suggested that the observed higher reactivity can be explained by formation of an endocyclic double bond due to enolization which reduces the barrier for the Bergman cyclization.

1.3.3.3 Electronic Effects of the Substituents in the Aromatic Portion of the Benzo-fused Enediynes.

The activation barrier of the Bergman cyclization can be lowered by incorporation of the electron withdrawing groups into the aromatic ring, which is the part of the enediyne system. Basak A. et al.[61] incorporated nitro-groups into aromatic part of *N*-substituted cyclic enediynes (Figure 1.3.28) and studied the onset temperature for BC and kinetics.

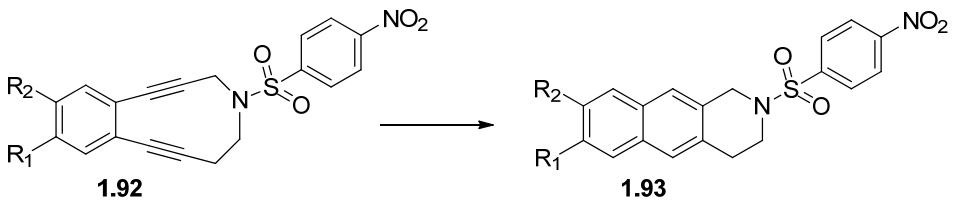


Figure 1.3.28 Bergman cyclization of N-substituted cyclic enediynes.

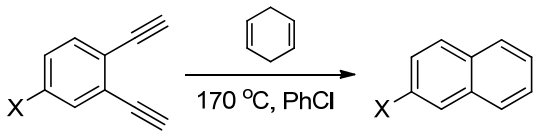
Compound	R_1	R_2	Onset temperature for BC (°C)	Half-life time at 70 °C in DMSO-d_6, h
1.92a	H	H	240	48
1.92b	NO_2	H	166	12
1.92c	NO_2	NO_2	128	9.5

Table 1.3 BC and results of DSC and kinetic studies.

First, the effect on the electron withdrawing nitro group(s) on the onset temperature for BC was shown. DSC method was employed to record the exothermic peaks that can be regarded as the onset temperature for BC. Enediyne **1.92b**, containing just one nitro group, had the onset temperature of 166 °C, while for non-nitrobenzene fused enediyne **1.92a** the onset temperature was found to be 240 °C (Table 1.3). Therefore significant lowering of onset temperature for BC in case of the nitro-enediyne is shown. Further lowering of the onset temperature for BC to 128 °C is found in case of dinitrobenzene fused enediyne **1.92c**. Kinetic studies were carried out in the DMSO-d_6 solution at 70 °C using ^{1}H NMR spectroscopy. Half-lives for all three enediynes are shown in Figure 1.3.28. The reactivity trend obtained from DSC measurements agrees with that obtained from solution phase kinetic studies. Therefore, it has been shown that electron withdrawing groups, indeed, enhance the reactivity towards Bergman cyclization.

Discussed results strongly support the notion that when aromatic ring is electron-deficient, Bergman cyclization is accelerated. Russell K.C. et al.[62] determined that a linear free

energy relationship exists for the Bergman cyclization of 4-substituted-1,2-diethynyl benzenes (Figure 1.3.29). They synthesized six enediynes with electron-donating and electron withdrawing groups in fourth position of the aromatic ring and kinetics were measured at 170 °C using chlorobenzene as a solvent and 100 equiv. of 1,4-CHD. In each case the kinetic data gave an excellent linear correlation. As expected, the **1.94f**, containing the strongest electron-withdrawing group, had the shortest half-life time (4.3 min) and **1.94a**, containing electron-donating dimethylamino group had the longest half-life time of 15.6 min (Table 1.4).



1.94 **1.95**

Figure 1.3.29 Bergman cyclization of 4-substituted-1,2-diethynyl benzenes.

Compound	X	Half-life, min	σ_m	Corr
1.94a	$N(CH_3)_2$	15.6	-0.1600	0.9977
1.94b	H	11.8	0.0000	0.9900
1.94c	CO_2CH_3	5.9	0.3700	0.9949
1.94d	$COCH_3$	6.5	0.3800	0.9986
1.94e	CN	5.2	0.5600	0.9915
1.94f	NO_2	4.3	0.7100	0.9987

	σ_m	F	R
Corr	0.992	0.994	0.994
ρ	0.654	0.662	0.227
intercept	0.002		

Table 1.4 Kinetic data and Hammett-type parameters.

Individual Hammett plots were constructed for the different σ parameters. The coefficients for the field and resonance parameters were determined. The best correlation was achieved using the Hammett σ_m value. This gave a Hammett constant of 0.654. Authors showed that none of the other parameters gave nearly the same correlation. As a result from this Hammett study, it was established that linear free energy relationship between the rate of Bergman cyclization and the Hammett σ_m value exist. Also, an appropriate contribution from the field and resonance effects was indicated. Russell K.C. et all. showed that ρ value from σ_m (0.654) is reasonable because the reactions proceed through uncharged transition states and intermediates. The larger field parameter (0.662) versus the resonance parameter (0.227) from is

also reasonable since the developing in BC 1,4-biradical is orthogonal to the p-system of benzene ring.

An importance of the *ortho* effect in the Bergman cyclization was discussed in the work of Alabugin I. et al.[63] They claimed that the Bergman cyclization is highly sensitive to *ortho* substitution. As it was shown above, in general electron-withdrawing groups accelerate the BC and electron-donating groups retard cyclization. In *ortho* position, quite the contrary, electron-donating methoxy group has an enhancing effect. Authors found that the cyclization step is highly sensitive to the nature of *ortho* substitution as a result of a combination of electronic, steric, and electrostatic effects, and evaluated specific mechanisms accounting for this phenomenon.

Computational and experimental studies support the mechanism of cyclization of 2,3-diethynyl-1-methoxybenzene shown in Figure 1.3.30. Intramolecular abstraction of the hydrogen atom from *ortho*-methoxy group effectively prevents external hydrogen-abstraction or retro-Bergman ring opening.

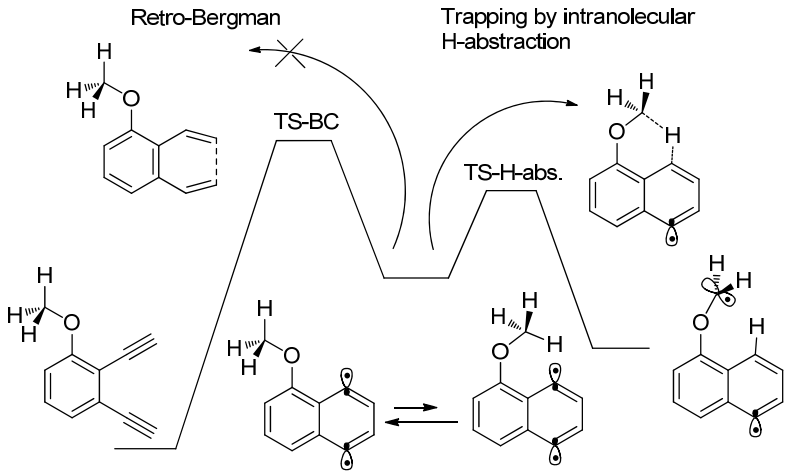


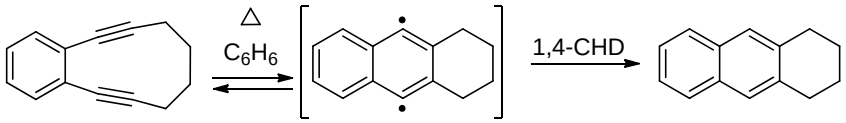
Figure 1.3.30 Alternative mechanisms of the cyclization of 2,3-diethynyl-1-methoxybenzene.

This process leads to the producing a new biradical with a different topology and lifetime and makes the cyclization step irreversible. Studies showed that this new biradical is likely longer

living compare to the *p*-benzyne. Further computational and experimental results[63] confirmed that both *ortho*-NO_2 and *ortho*-CHO groups substantially accelerate the Bergman cyclization.

1.3.4 Effect of the Concentration and the Nature of the Trapping Agent–Hydrogen Donor

The availability of trapping agent has a profound impact on the cycloaromatization profile at low concentration.[53] Cycloaromatization of enediyne **1.76** showed unexpected dependence on the concentration of the trapping agent, 1,4-CHD (Figure 1.3.31, Table 1.5).



1.76

Figure 1.3.31 Cyclization of **1.76**.

Entry	Conc. of 1,4-CHD (M)	$\tau_{1/2}$ (h)
1	0.00	129
2	0.25	39
3	0.50	24
4	10.50 (neat)	10.5

Table 1.5 Dependence of the cyclization rate on concentration of the trapping agent.

Semmelhack et al. suggest that careful concentration measurements are necessary in order to compare data among kinetic experiments. Factors, such as a change in solvation or the importance of the bimolecular trapping step in the kinetic expression for the rate of disappearance **1.76**, were proposed to explain these observations.

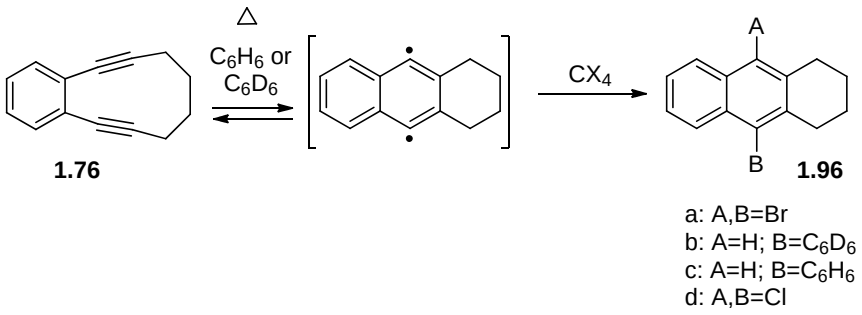


Figure 1.3.32 Cyclization of **1.76** in presence of CBr_4 and CCl_4.

Preparative and kinetic experiments with **1.76** in presence of CBr_4 and CCl_4 as trapping agents showed that at low temperatures (40 °C) reaction produces only product of the solvent, C_6D_6, insertion **1.96b**. At higher temperature (84 °C) a mixture of **1.96b** and the simple arene-1,4-diyl trapping product, **1.96a** were formed. At 150 °C the only major product was **1.96a**. Similar results were observed with CCl_4 as trapping agent. Slow reaction at 84 °C produced a mixture of **1.96c** and **1.96d**, while at 150 °C the only product detected was simple 9,10-dichloride, **1.96d**. These results suggest that more than one mechanism exists for the disappearance of **1.76**.

1.4 Conclusions and Goals of the Project

Natural enediyne antibiotics are extremely efficient DNA-cleaving agents, however, they posses no anti-tumor selectivity. This results in extreme general toxicity, which is the major stumbling block for the clinical applications of natural enediynes. Another serious problem is low thermal stability of these compounds. In order to address these issues, synthetic enediynes, where the Bergman cyclization can be effectively controlled, should be designed. Therefore, further investigation of factors that affect cycloaromatization and mechanisms by which enediynes cyclize is important for the development of novel enediyne-based anti-tumor drugs.

Development of a compound that is inactive and, therefore, has low toxicity but can be activated by, for instance, irradiation with light can help to solve the problem. The idea is to

develop compounds that are stable in the dark, but their action can be triggered photochemically. This approach will allow for achieving a certain degree of spatial and temporal control over the action of enediynes. Stable in the dark and, thus, less toxic compounds will act as a warhead to attack the DNA molecules when irradiated. Since simultaneous presence of both light and photoactivatable drug is required the damage to the healthy cells will be minimized.

When designing enediynes, three major requirements should be met: (1) synthetic enediynes should be chemically stable under neutral conditions but undergo cycloaromatization upon activation; (2) they should be more synthetically accessible compared to the natural enediynes; and (3) they should be easy to conjugate to an appropriate delivery and DNA-targeting systems.

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CHAPTER 2

NON-CONJUGATED TEN-MEMBERED ENEDIYNE PRECURSORS: ATTEMPTED SYNTHESIS

2.1 Attempted Synthesis of 8-Diazo-12-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10]annulene-7,9-dione

It has previously been shown in our laboratory that a photochemical Wolff rearrangement can be used for the activation of enediynes.[1] Irradiation of thermally stable cyclic enediynes containing α-diazo-β-diketone moiety causes a ring contraction to produce the reactive enediynes. β-Oxoesters that are formed *in situ* in this reaction exist in a fully enolized form. In this project we decided to employ photo-Wolff reaction to achieve two goals simultaneously: ring contraction of a ten-membered ring enediyne precursor and generation of the central enediyne double bond. Irradiation of diazo-diketone **2.1** will result in the loss of nitrogen, ring contraction from a ten- to a nine-membered cycle, and the formation of enolized β-oxoester **2.2**, thus completing the (*Z*)-3-ene-1,5-diyne fragment (Figure 2.1). It is known that nine-membered ring enediynes are usually very unstable and cyclize rapidly; that is why generation simplified benzo-fused core **2.2** *in situ* from diacetylenic diazodiketone **2.1** is expected to be an excellent tool for photochemical triggering of the reactive enediyne. This approach gives the possibility of spatial and temporal control of the biological activity of the enediyne pro-drugs. Design of the enediyne **2.2** was inspired by the structure of the extremely potent natural enediyne antibiotic C-1027 with a nine-membered active core.

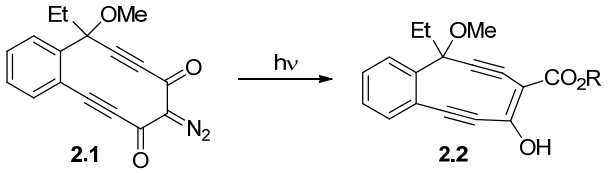


Figure 2.1 Photochemical generation of the active core of model compound **2.2**.

Introduction of the second substituent–ethyl group–at C-12 position was necessary in order to eliminate acidic hydrogen, which interacting with any bases could lead to acetylene-allene isomerization. Such systems, containing triple bond, an aromatic system and an allene moiety in conjugation–eneyne-allenes, can easily undergo thermal Myers-Saito cyclization[2] on an early stage before photochemical activation of **2.1**. The potential Myers-Saito cyclization should be prevented in the model compound **2.1** since there is no acidic hydrogen present at C12 position, therefore formation of the necessary allene fragment is impossible.

Retro-synthetic scheme for diazodiketone **2.1** is shown in Figure **2.2**. We intended to obtain diazodiketone **2.1** by means of a Regitz diazo transfer reaction to 1,3-diketone **2.3**. For the preparation of cyclic diketone **2.3,** we decided to use Nozaki-Hiyama-Kishi reaction of iodo-aldehyde **2.4** or **2.5**, followed by oxidation of secondary hydroxyl group. This reaction is a useful tool for the coupling of allylic[3], vinylic[4], and acetylenic[5] halides with activated carbonyl compounds under mild conditions.

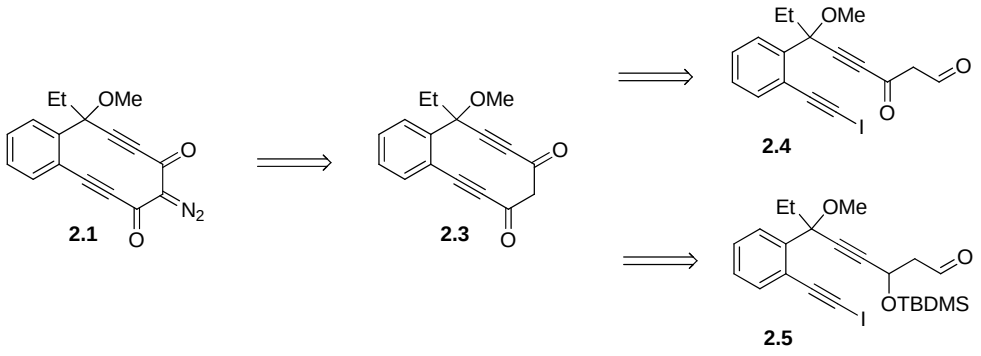
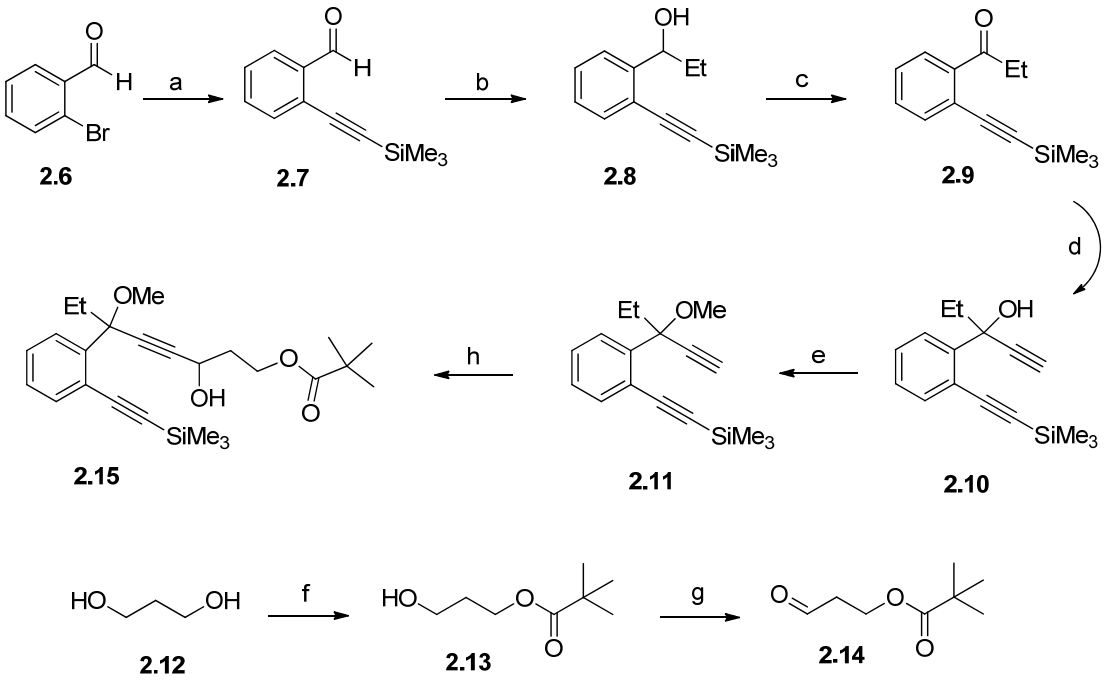


Figure 2.2 Proposed retro-synthetic scheme of the cyclic diazo-diketone **2.2** and cyclic diketone **2.3**.

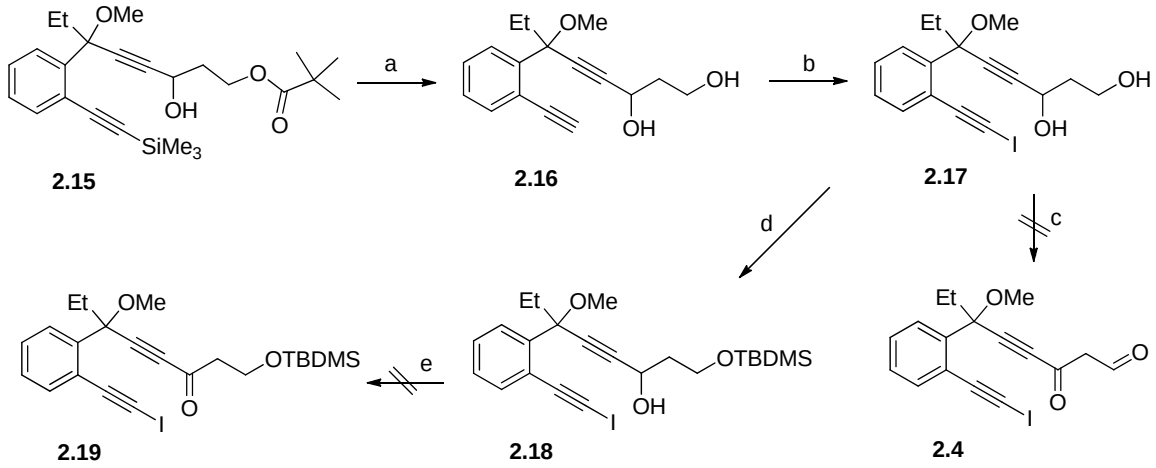
Our synthesis started with a Sonogashira cross coupling[6] of 2-bromobenzaldehyde (**2.6**) with trimithylsilylacetylene to obtain acetylenic aldehyde **2.7**, which was then converted into secondary alcohol **2.8** by means of the Grignard reaction conditions with ethylmagnesium bromide in dry THF (Figure 2.3). The hydroxyl group of **2.8** was oxidized into ketone **2.9** using Dess-Martin periodinane[7] as the oxidizing agent with an excellent yield. A Brandsma reaction of this ketone with ethynylmagnesium bromide afforded tertiary alcohol **2.10**, which was further methylated with methyl iodide and *n*-butyllithium as a base. The resulting methyl ether **2.11** was converted into the ester **1.12** via addition of acetylide to 3-oxopropyl pivalate **2.14**, which was synthesized from 1,3-propanediol in two straightforward steps.



(a) HC≡CSiMe$_3$, Pd(II), CuI, Et$_3$N/THF, rt, 72 hours, 86%; (b) EtMgBr, THF, 90%; (c) Dess-Martin periodinane, CH_2Cl_2, 2 hours, 98%; (d) HC≡CMgBr, THF, rt, 4 hours, 62%; (e) i. n-BuLi, THF, ii. CH_3I, DMSO, 94%; (f) pivaloyl chloride, Et_3N, CH_2Cl_2, 82%; (g) PCC, CH_2Cl_2, 80%; (h) i. *n*-BuLi, ii **2.14**, 69%.

Figure 2.3 Synthesis of 3-hydroxy-6-methoxy-6-(2-((trimethylsilyl)ethynyl)phenyl)oct-4-ynyl pivalate **2.12.**

The trimethylsilyl and pivaloyl protecting groups were removed in one step by the action of potassium carbonate in methanol[8] and the terminal acetylenic moiety was iodinated by an iodine-morpholine donor-acceptor complex in benzene[9] to give iodo-diol **2.27**. However, attempts to oxidize diol **2.27** with either PCC or Dess-Martin periodinane failed to provide targeted keto-aldehyde **2.4** perhaps due to its instability. Therefore, we decided to protect the primary hydroxyl group as *tert*-butyldimethylsilyl ether.[10] Unfortunately, oxidation of the secondary hydroxyl group in the presence of iodinated acetylene failed to provide ketone **2.19**.

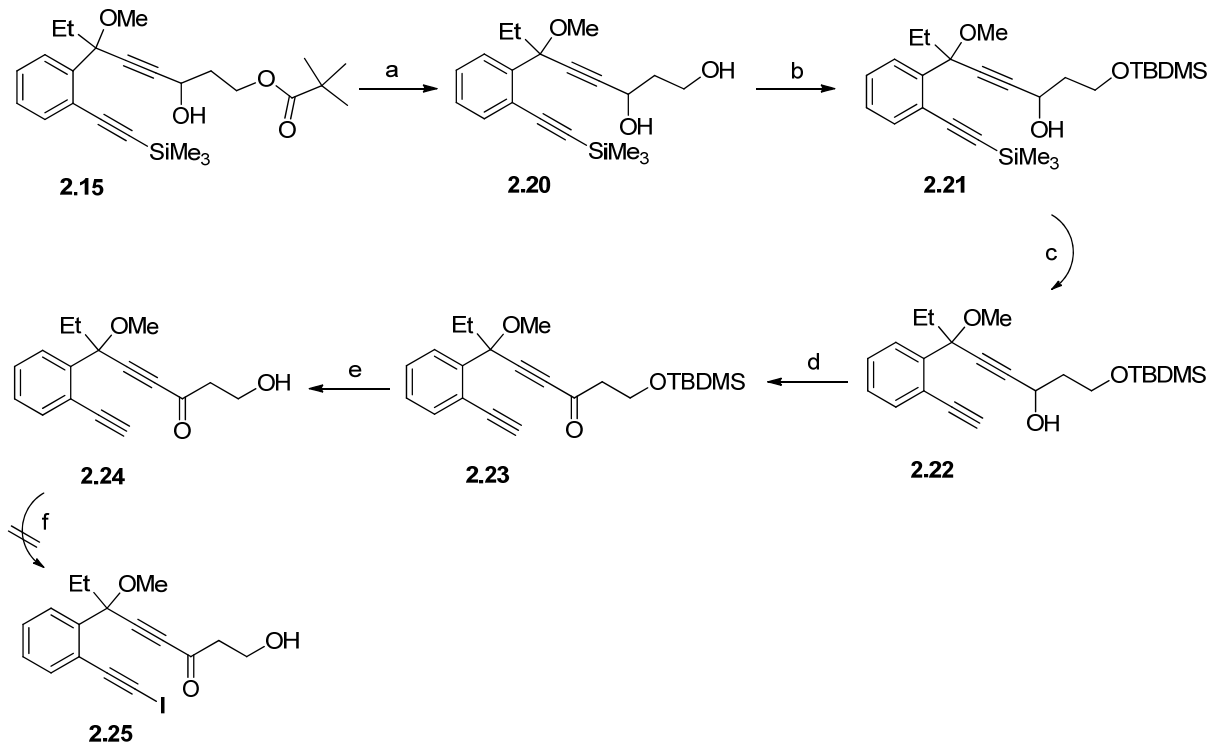


(a) K_2CO_3, MeOH, 86%; (b) I_2/Morpholine, C_6H_6, 45 °C, 67%; (c) Dess-Martin periodinane or PCC, CH_2Cl_2; (d) TBDMSCl, DAP, Et_3N, CH_2Cl_2, 65%; (e) Dess-Martin periodinane, CH_2Cl_2.

Figure 2.4 Attempted synthesis of 1-((*tert*-butyldimethylsilyl)-oxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-yn-3-one **2.19**.

Another attempt to synthesize keto-aldehyde **2.4** was made starting from secondary alcohol **2.15**. DIBAL reduction of the ester functionality afforded diol **2.20** with following protection of the primary hydroxyl group as *tert*-butyldimethylsilyl ether (Figure 2.5). The trimethylsilyl protecting group was removed from **2.21** and the secondary hydroxyl group was oxidized with PCC. The TBDMS-protecting group was then removed[11] yielding keto-alcohol **2.24**. Attempts to iodinate terminal acetylenic moiety with either the iodine-morpholine complex

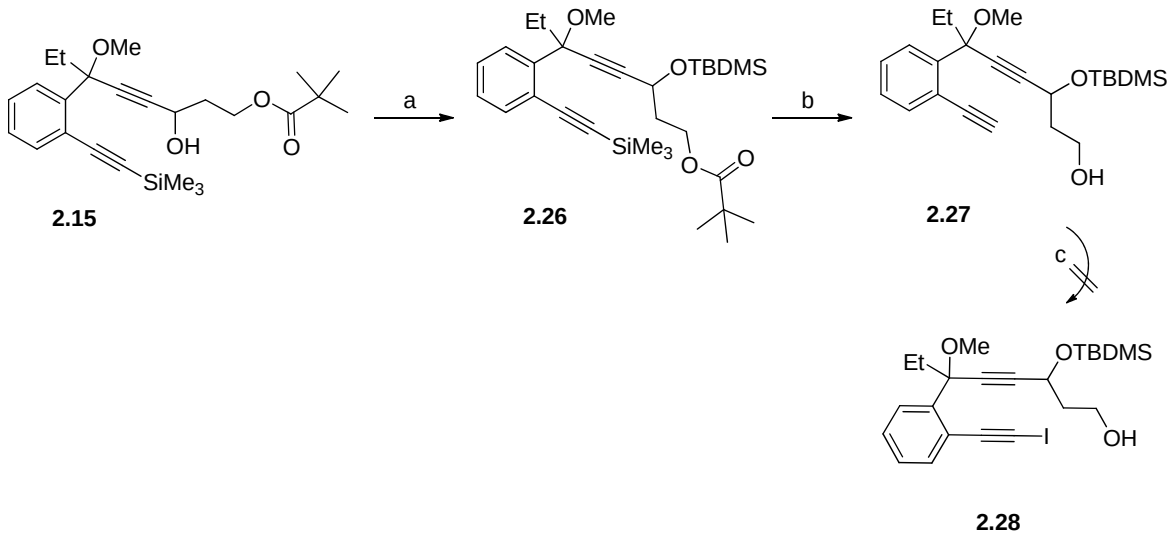
or with *N*-iodosuccinimide and silver nitrate in acetone led to the decomposition of the starting material.



(a) DIBAL, CH_2Cl_2, 81%; (b) TBDMSCl, DAP, Et_3N, CH_2Cl_2, 65%; (c) K_2CO_3, MeOH, 89%; (d) PCC, CH_2Cl_2, 93%; (e) HF, CH_3CN, 97%; (f) NIS, $AgNO_3$, acetone; or I_2/morpholine, C_6H_6, 45 °C.

Figure 2.5 Attempted synthesis of 1-hydroxy-6-(2-(2-iodoethynyl)phenyl)-6-methoxyoct-4-yn-3-one **2.25**.

A slightly modified synthetic scheme was employed (Figure 2.6). The secondary alcohol **2.15** was converted into a TBDMS derivative **2.26** utilizing the standard procedure.[10] Then **2.26** was treated with potassium carbonate to remove both protective groups from an alcohol and a terminal acetylene affording **2.27**. But, as in the previous case, iodination of the acetylenic moiety with the iodine-morpholine complex did not produce **2.28** proving that iodination of the terminal acetylene is impossible in the presence of a primary hydroxyl group.



(a) TBDMSCl, Imidazole, DMAP, CH_2Cl_2, 52%; (b) K_2CO_3, MeOH, 55%; (c) I_2/Morpholine, C_6H_6, 45 °C.

Figure 2.6 Attempted synthesis of 3-(*tert*-butyldimethylsilyloxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-yn-1-ol **2.28.**

We changed the synthetic scheme for the preparation of the targeted diazodiketone **2.1** as shown in Figure 2.7. We planned to obtain diketone **2.3** by means of the Nozaki-Hiyama-Kishi reaction conditions with iodo-aldehyde **2.5** with the protected secondary hydroxyl group. This synthetic scheme should eliminate complications due to iodination of the terminal acetylene in the presence of the hydroxyl groups.

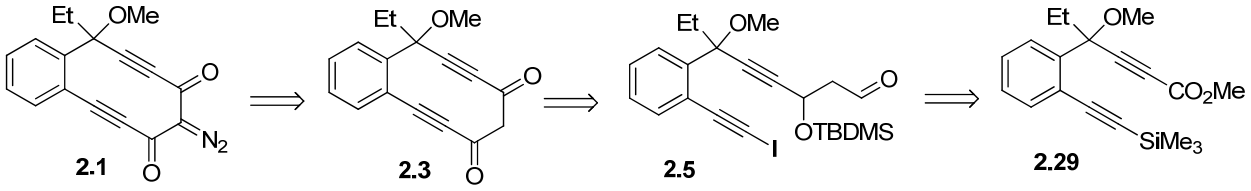
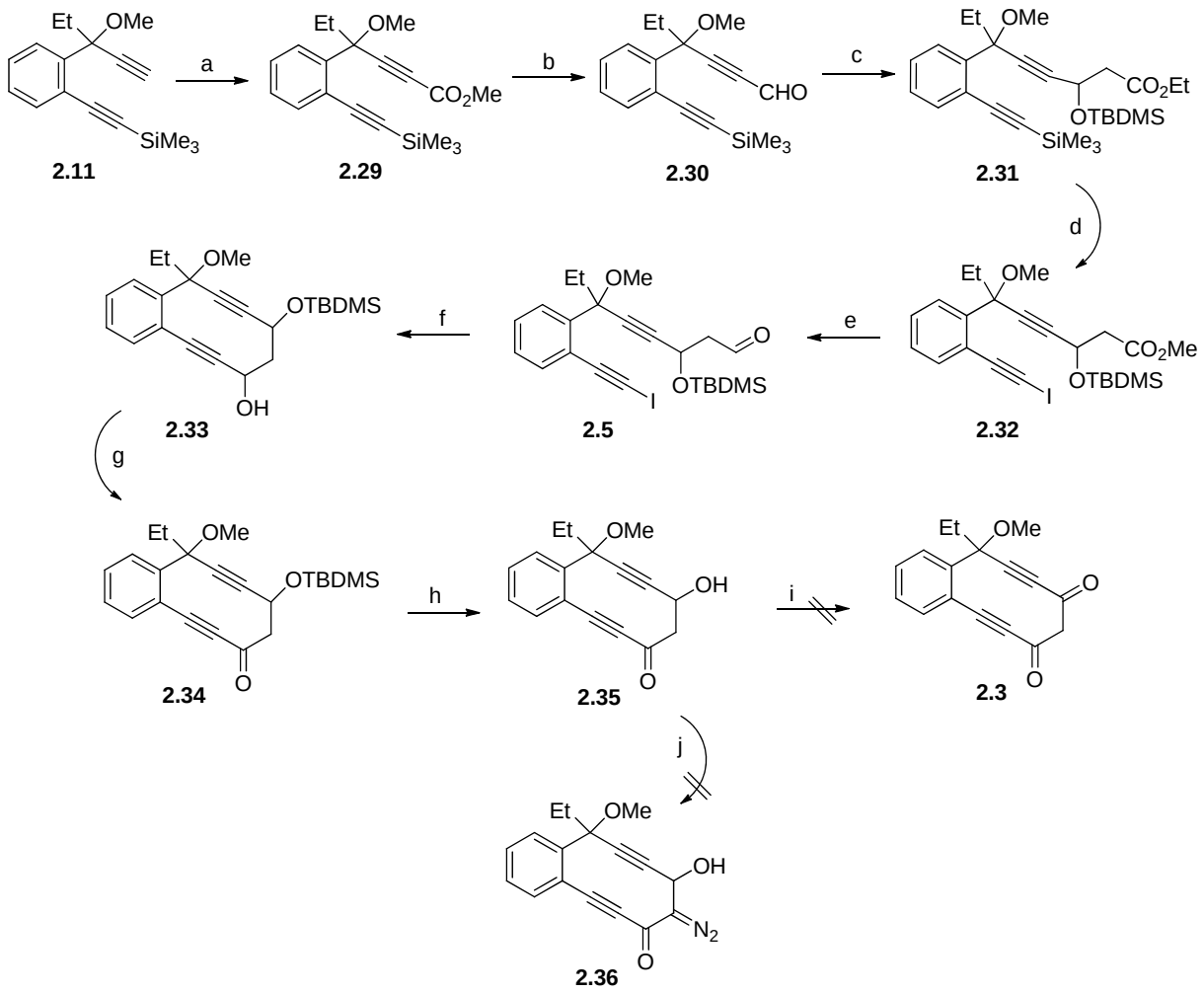


Figure 2.7 Proposed retro-synthetic scheme of the key intermediates.

We started this synthesis with diacetylenic ether **2.11** (described above). Conversion of this ether into the ester **2.29** was performed *via* acetylide addition-elimination reaction with methyl chloroformate. The following reduction of the ester functionality with DIBAL[12] provided aldehyde **2.30,** which was highly unstable thermally and sensitive to light. This aldehyde was

immediately introduced into an aldol reaction with ethyl acetate and freshly prepared LDA as a base[13] (Figure 2.8). The secondary hydroxyl group was protected as a *tert*-butyldimethylsilyl ether[9] to give **2.31** as an inseparable mixture of two diastereomers. The trimethylsilyl protecting group was selectively removed from the acetylene moiety using potassium carbonate in methanol.[8] This reaction was accompanied with trans-esterification of the ethyl ester functionality. Terminal acetylene was then iodinated yielding **2.32** in a good yield.



(a) i. n-BuLi, ii. $ClCO_2Me$, 76%; (b) DIBAL, CH_2Cl_2, 80%; (c) 1) i. LDA, ii. EtOAc, 76%; 2) TBDMSCl, Imidazole, DMAP, CH_2Cl_2, 83%; (d) i. K_2CO_3, MeOH, 88%, ii. I_2/morpholine, C_6H_6, 45 °C, 89%; (e) DIBAL, CH_2Cl_2, 81%; (f) $CrCl_2/NiCl_2$, THF, 91%; (g) Dess-Martin periodinane, CH_2Cl_2, 62%; (h) HF, CH_3CN, 65%; (i) Dess-Martin periodinane, CH_2Cl_2; (j) i. *t*BuOK, TsN_3, DMPU, THF, ii. AcOH.

Figure 2.8 Attempted synthesis of 12-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10]annulene-7,9-dione (**2.3**).

Following DIBAL reduction of ester **2.32** led to the formation of the aldehyde **2.5** which was found to be an inseparable mixture of two diastereomers. The iodo-aldehyde is thermally unstable and should be introduced into the following reaction immediately after purification. The ring was closed by means of the Nozaki-Hiyama-Kishi reaction conditions. Cyclic alcohol **2.33** was obtained in a good yield as a mixture of inseparable diastereomers. The secondary hydroxyl

group was oxidized by Dess-Martin periodinane[7] in a moderate yield utilizing the standard reaction procedure. The TBDMS-protective group was removed according to the literature procedure[11] to afford **2.35** as a mixture of diastereomers. The reaction yields of the cyclic compounds were around 60% for both steps due to low stability of these cyclic enediynes. Attempts to oxidize the secondary hydroxyl group in **2.35** with a variety of oxidizing agents, such as PCC, CAN, and Dess-Martin periodinane, failed, presumably, because the targeted diketo-enediyne **2.3** decomposes upon formation.

The attempts to introduce the diazo group into the keto-alcohol **2.35** was performed as described in the only reference found,[14] but no expected product was found in either test reactions with 4-hydroxy-4-methylpentane-2-one and 3-hydroxy-3-methyl-1-phenylbutan-1-one or the reaction with **2.35**.

2.2 Conclusions

Although the targeted 8-diazo-12-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10]annulene-7,9-dione **2.1** was not obtained, valuable theoretical and practical synthetic experience in the design and the preparation of the potential enediyne pro-drugs were gained. A few different synthetic approaches towards synthesis of **2.1** were used but the key cyclic precursors of **2.2** were found to be highly unstable, therefore the required cyclic framework with a diazo diketone moiety was synthetically inaccessible. The high probability of the targeted molecule being extremely unstable limits the applicability of the project. Thus, further work on this project was not performed.

2.3 Experimental Section

2.2.1 Materials and Instruments

All oxygen- and moisture-sensitive reactions were carried out under an inert atmosphere in the oven-dried glassware. Solvents for the moisture-sensitive reactions were dried by distillation prior to usage. Dry inhibitor-free THF (≥99.9%, Sigma-Aldrich) was used for palladium-catalyzed cross-coupling reactions. All commercially available materials were used without purification unless otherwise stated. Dess-Martin periodinane was prepared according to the literature procedure.[7a] TLC analyses were performed using aluminum-backed silica gel TLC plates. Chromatographical separation and purification of the reaction products were performed using standard grade flash chromatography silica gel (40-63 μm particle size) or premium grade flash chromatography silica gel (40-75 μm particle size). All NMR spectra were recorded in deuterochloroform on Bruker Avance 300 MHz or Varian 400 MHz or 500 MHz spectrometers with tetramethylsilane (TMS) as an internal standard. ^{1}H-NMR chemical shifts (δ) are reported in ppm versus the TMS reference, ^{13}C-NMR chemical shifts (δ) are reported in ppm versus the residual solvent peak reference. GC/MS data were collected using a Shimadzu GC-2010 equipped with a SHR5XLB column. High resolution mass spectra analyses were performed by the Mass Spectrometry Laboratory, University of Georgia at Athens, GA.

2.2.2 Experimental Procedures

2-((Trimethylsilyl)ethynyl)benzaldehyde (2.7).

Bis(triphenylphosphine)palladium dichloride (3.26 g, 4.82 mmol) was added to a stirred solution of 2-bromobenzaldehyde (89.6 g, 482 mmol) in degassed THF (200 mL) under argon atmosphere. The solution was degassed with a strong flux of argon for 20 min, and powdered copper (I) iodide (5.58 g, 28.9 mmol) was added to the mixture. After 5 minutes of stirring,

trimethylsilyl acetylene (61.44 g, 0.627 mmol, 88mL) was added to a mixture, followed by addition of triethylamine (174 mL) and triphenylphosphine (3.6 g). The reaction vessel was purged with argon, sealed, and left with stirring for 2 days at room temperature. According to the GC/MS analysis, approximately 95% of the starting material was converted into the desired product. The reaction mixture was filtered through 5 cm layer of the silica gel (5% ethyl acetate in hexanes); fractions containing the desired product were combined, washed with water, and dried over magnesium sulfate. The solvents were evaporated under reduced pressure. Crude product was purified by distillation (pump, bath 100–130 ºC, cooling water 50 ºC) yielding 84.08 g (86%) of pure product as a yellowish crystalline solid, m.p. ~ 30 ºC. NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 0. 29 (s, 9H), 7.40-7.46 (m, 1H), 7.51-7.59 (m, 2H), 7.89-7.92 (m, 1H), 10.56 (d, 1H); ^{13}C NMR ($CDCl_3$, 300 MHz): δ -0.29, 100.05, 102.36, 126.72, 126.82, 128.76, 133.45, 133.58, 136.16, 191.70. GC/MS *m/z*: 202(4) [M^+], 201(18), 187(100), 161(19), 143(6), 129(9), 128(28), 105(9), 93(8), 73(13).

1-(2-Trimethylsilanylethynyl-phenyl)-propan-1-ol (2.8).

To a stirred solution of **2.7** (25.35 g, 125 mmol) in absolute THF (150 mL) a solution of ethylmagnesium bromide in THF (3.13M in THF, 150 mmol, 48 mL) was added dropwise under argon atmosphere at 0 °C. The reaction mixture was left with stirring for 30 min at the temperature and then for 3 hours at room temperature. Saturated solution of the ammonium chloride (50 mL) and diethyl ether (50 mL) were added. The organic layer was separated and the aqueous solution was extracted with ether (2 x 40 mL). The combined organic phases were washed with water, brine, dried over anhydrous magnesium sulfate, and concentrated in vacuo. The residual material was subjected to the column chromatography on silica gel (hexanes–20% EtOAc in hexanes) yielding 26.25 g (90%) of pure 1-(2-trimethylsilanylethynyl-phenyl)-

propane-1-ol (**2.8**). NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 7.50-7.48 (m, 1H), 7.36-7.33 (m, 3H), 5.15-5.40 (m, 1H), 2.40 (br. s, 1H), 1.50 (p, 2H), 0.9 (t, 3H), 0.3 (s, 9H). High res. MS.: 232.1281 (found), 232.1283 (calc.).

1-(2-Trimethylsilanylethynyl-phenyl)-propanone (2.9).

The Dess-Martin reagent (72g, 170 mmol) was added to a solution of **2.8** (26.25g, 113 mmol) in CH_2Cl_2 (150 mL). The reaction mixture was stirred for 30 min. Progress of the reaction was followed by TLC analysis. Diethyl ether (300 mL) was added to the reaction mixture, mixture was washed with 2M solution of sodium hydroxide, water, and combined organic phases were dried with magnesium sulfate. Mixture was filtered and solvents were evaporated under reduced pressure. The residual material was purified by column chromatography on silica gel (hexanes–20% EtOAc in hexanes) yielding 25.247 g (97%) of pure 1-(2-trimethylsilanylethynyl-phenyl)-propanone (**2.9**). NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 7.33-7.32 (d, J = 6 Hz, 1H), 7.28-7.27 (d, J = 6 Hz, 1H), 7.14-7.05 (m, 2H), 2.91-2.86 (q, J = 6 Hz, 2H), 0.97-0.94 (t, J = 6 Hz, 3H), 0.00 (s, 9H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 202.21, 142.47, 134.23, 130.90, 129.56, 128.92, 128.19, 121.08, 103.59, 100.71, 35.77, 8.65, 0.15. High res. MS, M^{+}-CH_3 (15): 215.0892 (found), 215.0892 (calc.).

3-(2-Trimethylsilanylethynyl-phenyl)-pent-1-yn-3-ol (2.10).

To a stirred solution of **2.9** (25.247 g, 98 mmol) in dry THF ethynylmagnesium bromide (0.5M in THF, 120 mmol, 242 mL) was added dropwise under an inert atmosphere. After 8 hours of stirring, small amount of the starting material was still presented in the mixture, according to the TLC analysis. Reaction mixture was quenched with saturated solution of the ammonium chloride (10 mL) and diluted with diethyl ether (50 mL). The organic layer was separated; aqueous phase was extracted with diethyl ether (2 x 30 mL). The combined organic phases were washed with

water, brine, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (3% EtOAc in hexanes) yielding 17.39 g (62%) of pure 3-(2-trimethylsilanylethynyl-phenyl)-pent-4-yn-3-ol (**2.10**). NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 7.77-7.75 (d, *J* = 8 Hz, 1H), 7.51-7.49 (d, *J* = 8 Hz, 1H), 7.33-7.31 (t, *J* = 6.8 Hz, 1H), 7.26-7.23 (t, *J* = 6.8 Hz, 1H), 3.91 (s, 1H), 2.67 (s, 1H), 2.28-2.24 (quin, *J* = 7.2 Hz, 2H), 1.04-1.00 (t, *J* = 7.6 Hz, 3H), 0.26 (s, 9H). High res. MS, M^+: 256.1276 (found), 256.1283 (calc.).

(2-(1-Methoxy-1-ethyl-prop-2-ynyl)-phenylethynyl)-trimethylsilane (2.11).

n-Butyllitium (2.56 M in hexane, 68 mmol, 26.6 mL) was added dropwise to a solution of **2.10** (17.39 g, 68 mmol) in absolute THF (100 mL) cooled to -78 °C over 5 min under argon atmosphere. The mixture was stirred for 10 min, and then iodomethane (77.248 g, 38 mL, 544 mmol) was added. After the temperature was raised to -25 °C, the distilled DMSO (10 ml) was added to the resulting mixture. The mixture was stirred for 1 hour at the temperature and then cooling bath was removed. Reaction mixture was left with stirring overnight. After that reaction mixture was poured into a saturated ammonium chloride solution, extracted with ether (2 x 40 mL). The organic extracts were combined and washed with water and brine, dried over anhydrous magnesium sulfate. The product was purified by column chromatography on silica gel (1% of EtOAc in hexanes) yielding 17.32g (94%) of pure (2-(1-methoxy-1-ethyl-prop-2-ynyl)-phenylethynyl)-trimethyl-silane (**2.11**). NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 7.72-7.70 (d, *J* = 8 Hz, 1H), 7.63-7.61 (d, *J* = 8 Hz, 1H), 7.43-7.30 (m, 2H), 3.28 (s, 3H), 2.46-2.29 (m, 2H), 1.00-0.95 (t, *J* = 7.2 Hz, 3H), 0.34 (s, 3H). High res. MS, M^+: 270.1454 (found), 270.1440 (calc.).

3-Hydroxypropyl pivalate (2.13).

To a stirred solution of triethylamine (19.9 g, 197.36 mmol) in dichloromethane (250 mL) pivaloyl chloride (15.79 g, 131.6 mmol, 16 mL) was added. 1,3-Propanediol **(2.12)** (10 g, 131.6 mmol, 9.49 mL) was added to the mixture dropwise at 0 °C. The reaction mixture was left with stirring overnight. Then reaction mixture was washed with water to remove remained 1,3-propanediol, aqueous layer was extracted with dichloromethane (3 x 40 mL), combined organic phases were dried over magnesium sulfate, and solvent was evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (5–60% EtOAc in hexanes) yielding 17.26 g (82%) of pure 3-hydroxypropyl pivalate (**2.13**) as colorless oil. NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 4.23-4.19 (t, 2H), 3.69-3.66 (t, 2H), 3.05 (br. s, 1H), 1.91-1.85 (p, 2H), 1.11 (s, 9H). ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 179.35, 61.39, 59.40, 39.03, 32.08, 27.43. IR spectrum: 3456.44, 2962.66, 1726.29, 1710.86, 1481.33.

3-Oxopropyl pivalate (2.14).

To a stirred solution of **2.13** (14.13 g, 88.3 mmol) in dichloromethane (250 mL) PCC (24.8 g, 114.8 mmol) was added. Reaction mixture was left with stirring overnight. After that period TLC analysis indicated on the complete conversion of the starting material. Reaction mixture was filtered through the layer of the silica gel (40% of EtOAc in Hexanes as eluent), solvents were evaporated under reduced pressure, and the residue was purified by column chromatography on silica gel (5% of EtOAc in hexanes) yielding 11.18 g (80%) of 3-oxopropyl pivalate (**2.14**) as colorless oil. NMR ^{1}H spectrum: solvent is $CDCl_3$, (δ, ppm) 9.80 (s, 1H), 4.41 (t, 2H), 2.76 (t, 2H), 1.18 (s, 9H). Lit.[15]

3-Hydroxy-6-methoxy-6-(2-((trimethylsilyl)ethynyl)phenyl)oct-4-ynyl pivalate (2.15).

To a stirred solution of **2.11** in dry THF (100 mL) n-buthyllithium (2.86 M in hexanes, 15.81 mmol, 5.53 mL) was added dropwise at -78 °C and the reaction mixture was left with stirring for 30 min at the temperature. After that period 3-oxopropyl pivalate (**2.14**) (3.41 g, 21.56 mmol) in small amount of THF was added to the mixture and stirring was continued for one more hour at the temperature, and for another 4 hours at the room temperature. Reaction mixture was quenched by ammonium chloride (10 mL), diluted with diethyl ether, washed with water and brine, aqueous layer was extracted with diethyl ether (2 x 40 mL), combined organic solutions were dried over magnesium sulfate and solvents were evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (eluent–20% EtOAc/Hexanes) affording 4.2602 g (69%) of pure 3-hydroxy-6-methoxy-6-(2-((trimethylsilyl)ethynyl)phenyl)oct-4-ynyl pivalate (**2.15**) as colorless oil and 1.28 g of unconverted staring material . NMR ^{1}H solvent is $CDCl_3$, (δ, ppm) 7.66-7.64 (d, J = 8 Hz, 1H), 7.53-7.50 (d splitted further, 1H), 7.31-7.27 (m, 1H), 7.25-7.21 (td, J_1 = 5.6 Hz, J_2 = 1.6 Hz, 1H), 4.67-4.63 (m, 1H), 4.40-4.33 (br.m, 1H), 4.26-4.21 (m, 1H), 3.26 (2s, 3H), 2.32-2.22 (br.m, 2H), 2.14-2.10 (q, J = 6.4 Hz, 2H), 1.21 (s, 9H), 0.86-0.82 (t, J = 7.6 Hz, 3H), 0.24 (s, 9H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm) 178.81, 142.53, 135.41, 128.60, 128.23, 127.63, 120.76, 104.64, 100.30, 88.24, 84.82, 81.32, 73.67, 61.12, 59.94, 52.54, 38.98, 37.16, 33.90, 27.40, 9.19. High res. MS, MNa^+: 451.2268 (found), 451.2275 (calc.).

6-(2-Ethynylphenyl)-6-methoxyoct-4-yne-1,3-diol (2.16).

To a stirred solution of **2.15** (4.9984 g, 11.68 mmol) in methanol (70 mL) potassium carbonate (3.2237 g, 23.36 mmol) was added and the reaction mixture was left with stirring for 15 hours. The mixture was diluted with ethyl acetate and washed with ammonium chloride, water and

brine. Aqueous layer was extracted with ethyl acetate (5 x 30 mL), dried over magnesium sulfate, and solvents were evaporated under reduced pressure. Column chromatography was performed on silica gel (20–70% EtOAc in hexanes) yielding 2.727 g (86%) of pure 6-(2-ethynylphenyl)-6-methoxyoct-4-yne-1,3-diol (**2.16**). NMR ^{1}H spectrum**,** solvent is $CDCl_3$, (δ, ppm): 7.70-7.69 (d, J = 8 Hz, 1H), 7.58-7.56 (dd, J_1 = 6.4 Hz, J_2 = 1.2 Hz, 1H), 7.33 (td, 1H), 7.26 (td, 1H), 4.86-4.82 (m, 1H), 4.03-4.10 (m, 1H), 3.88-3.95 (m, 1H), 3.38 (s, 1H), 3.27 (d, 3H), 2.81 (t, 1H), 2.17 (m, 5H), 0.86 (t, J = 7.2 Hz, 3H). NMR ^{13}C spectrum**,** solvent is $CDCl_3$, (δ, ppm): 142.33, 135.97, 128.68, 128.36, 127.59, 119.54, 88.70, 84.33, 82.93, 82.79, 81.32, 61.98, 60.57, 52.47, 38.97, 34.21, 9.06. High res. MS: MNa^+: 295.1315 (found), 295.1305 (calc.).

6-(2-(Iodoethynyl)phenyl)-6-methoxyoct-4-yne-1,3-diol (2.17).

To a stirred solution of iodine (5.095 g, 20.06 mmol) in absolute benzene (70 mL) morpholine (5.43 mL, ca. 5.43 g, 60.18 mmol) was added. The mixture was stirred at 45 °C for 20 min. A solution of **2.16** (2.727g, 10.03 mmol) in absolute benzene (5 mL) was added to the stirred suspension of the iodination reagent, and the reaction mixture was stirred at 45 °C for 4 hours. Then the reaction mixture was diluted with ethyl acetate and washed with aqueous sodium tiosulfate solution (2 x 30 mL) and brine (70 mL). Aqueous layer was extracted with ethyl acetate (4 x 30 mL), combined organic layers were dried over magnesium sulfate, filtered, and the solvents were evaporated under reduced pressure. Product was purified by column chromatography on silica gel (50–70% EtOAc in hexanes) yielding 2.66 g (67%) of pure 6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-yne-1,3-diol (**2.17**) as yellowish oil. NMR ^{1}H solvent is $CDCl_3$, (δ, ppm): 7.65-7.63 (dd, J_1 = 6.4 Hz, J_2 = 1.2 Hz, 1H), 7.51-7.49 (d, J_1 = 5.6 Hz, J_2 = 1.6 Hz, 1H), 7.34-7.29 (td, J_1 = 6.4 Hz, J_2 = 1.2 Hz, 1H), 7.26-7.22 (td, J_1 = 6.4 Hz, J_2 = 1.2 Hz, 1H),

4.86-4.82 (m, 1H), 4.03-4.09 (m, 1H), 3.88-3.93 (m, 1H), 3.29 (s, 3H), 2.65 (s, 1H), 2.30-2.00 (m, 5H), 0.83 (t splitted further, 3H). High res. MS: MNa^+: 421.0278 (found), 421.0271 (calc.).

Attempted synthesis of 6-(2-(iodoethynyl)phenyl)-6-methoxy-3-oxooct-4-ynal (2.4).

The Dess-Martin reagent (470 mg, 1.11 mmol) was added to the stirred solution of **2.17** (184 mg, 0.462 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for one hour. Progress of the reaction was followed by TLC analysis, which indicated formation of new compound in the reaction mixture. Diethyl ether (40 mL) and hexanes (20 mL) were added and the reaction mixture was filtered through a layer of silica gel, the solvents were evaporated under reduced pressure. The residual material was purified by column chromatography (10–90% EtOAc in Hexane) yielding small amount of unidentified compound. NMR H^1 spectrum showed no formation of any distinct product. Probably, targeted keto-aldehyde is thermally unstable.

To a stirred solution of **2.17** (268 mg, 0.673 mmol) in dichloromethane (10 mL) PCC (385 mg, 1.751 mmol) was added. After overnight stirring at room temperature, TLC analysis showed complete decomposition of the starting material without formation of any distinct compound.

6-(2-(Iodoethynyl)phenyl)-1-(*tert*-butyldimethylsilyloxy)-6-methoxyoct-4-yne-3-ol (2.18).

To a stirred solution of TBDMSCl (1.27 g, 8.465 mmol), dimethylaminopyridine (38 mg, 0.308 mmol), and triethyamine (855 mg, 8.465 mmol, 1.18 mL) in dichloromethane (60 mL) **2.17** (3.063 g, 7.695 mmol) in small amount of dichloromethane was added. After overnight stirring at room temperature, starting material was completely converted into product according to the TLC analysis. The reaction mixture was washed with ammonium chloride solution, water; aqueous layer was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over magnesium sulfate, and the solvents were evaporated under reduced pressure. Residual material was purified by column chromatography on silica gel (5–20% of EtOAc in hexanes) yielding

2.55 g (65%) of pure 6-(2-(iodoethynyl)phenyl)-1-(*tert*-butyldimethylsilyloxy)-6-methoxyoct-4-yne-3-ol (**2.18**) as a mixture of two diastereomers in 1:1 ratio. NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.70-7.68 (d, J = 8 Hz, 1H), 7.50-7.48 (d splitted further, 1H), 7.32-2.28 (td, J_1 = 6 Hz, J_2 = 1.2 Hz, 1H), 7.26-7.21 (td, 1H), 4.84-4.79 (m, 1H), 4.13-4.65 (m, 1H), 3.90-3.84 (m, 1H), 3.48 (dd, J_1 = 6 Hz, J_2 = 12.8 Hz, 1H), 3.28 (s, 3H), 2.30-2.06 (br.m, 4H), 2.00-1.92 (m, 1H), 0.90 (2s, 9H), 0.83 (td, J_1 = 6.4 Hz, J_2 = 0.8 Hz, 3H), 0.10-0.07 (m, 6H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 148.74, 141.46, 133.94, 133.82, 132.90, 126.38, 98.79, 94.51, 89.17, 86.38, 67.67, 66.80, 57.97, 44.41, 39.96, 36.49, 31.41, 23.70, 14.56, 5.57, 1.99. IR spectrum: 3392.79, 2953.02, 2929.87, 2881.65, 2856.58, 1469.76. High res. MS, MH^+: 513.1340 (found), 513.1316(calc.).

Attempted synthesis of 6-(2-(iodoethyl)phemyl)-1-(*tert*-butyldimethylsilyloxy)-6-methoxyoct-4-yn-3-one (2.19).

The Dess-Martin reagent (4.22 g, 9.96 mmol) was added to the stirred solution of **2.18** (2.5 g, 4.98 mmol) in CH_2Cl_2 (50 mL). The reaction mixture was stirred for two hours and process was followed by TLC analysis, which showed formation of a few new compounds in the reaction mixture. Diethyl ether (50 mL) and hexanes (20 mL) were added and the reaction mixture was filtered through a layer of silica gel. The solvents were evaporated under reduced pressure. After the work-up, TLC analysis showed presence of five different compounds in the reaction mixture. This mixture was separate by column chromatography (5–40% of EtOAc in hexane) yielding three fractions with small amounts of unidentified compounds, forth fraction contained mixture of at least two compounds. None of them represented a ketone **2.19**.

6-Methoxy-6-(2-(2-(trimethylsilyl)ethynyl)phenyl)oct-4-yne-1,3-diol (2.20).

To a stirred solution of **2.15** (6.64 g, 15.59 mmol) in absolute dichloromethane (100 mL) DIBAL (34.29 mmol, 28.34 mmol) was added at -78 °C under argon atmosphere. Reaction mixture was left with stirring for 6 hours at the temperature. After that period reaction mixture was quenched with ammonium chloride (10 mL). The reaction mixture was diluted with dichloromethane and washed with water and brine. Aqueous solution was extracted with dichloromethane (5 x 20 mL), combined organic solutions were dried over magnesium sulfate, filtered, and solvent was evaporated under reduced pressure. Residue was purified by column chromatography on silica gel (20–40% EtOAc/Hexanes) yielding 4.35 g (80%) of pure 6-methoxy-6-(2-(2-(trimethylsilyl)ethynyl)phenyl)oct-4-yne-1,3-diol (**2.20**) and 172.7 mg of unconverted starting diol **2.15**.

6-Methoxy-6-(2-(2-(trimethylsilyl)ethynyl)phenyl)oct-4-yne-1-(*tert*-butyldimethylsilyloxy)-3-ol (2.21).

To a stirred solution of TBDMSCl (0.833 g, 5.555 mmol), dimethylaminopyridine (24.6 mg, 0.202 mmol), and triethyamine (510 mg, 5.555 mmol, 0.7 mL) in dichloromethane (50 mL) **2.20** (1.738 g, 5.05 mmol) in small amount of dichloromethane was added. Reaction mixture was left for overnight stirring at room temperature. After that all starting material was completely converted into the product, according to the TLC analysis. The reaction mixture was washed with ammonium chloride solution and water. Aqueous phase was extracted with dichloromethane (3 x 30 mL), combined organic layers were dried over magnesium sulfate, filtered, and the solvents were evaporated under reduced pressure. Residue was purified by column chromatography on silica gel (5– 10% EtOAc in hexanes) yielding 1.496 g (65%) of 6-methoxy-6-(2-(2-(trimethylsilyl)ethynyl)phenyl)oct-4-yne-1-(*tert*-butyldimethylsilyloxy)-3-ol

(**2.21**). NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.73-7.71 (d splitted further, 1H), 7.52-7.50 (d splitted further, 1H), 7.30-7.26 (t splitted further, 1H), 7.24-7.20 (t splitted further, 1H), 4.81-4.78 (m, 1H), 4.11-4.06 (m, 1H), 3.89-3.83 (m, 1H), 3.55-3.46 (m, 1H), 3.25 (s, 3H), 2.36-2.19 (m, 2H), 2.12-2.05 (m, 1H), 1.99-1.90 (m, 1H), 0.90 (s, 9H), 0.86 (t, J = 7.2 Hz, 3H), 0.24 (s, 9H), 0.08 (s, 6H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 148.14, 140.69, 134.41, 133.51, 132.90, 126,15, 110.07, 105.41, 94.29, 89.45, 86.98, 67.58, 66.73, 57.86, 44.38, 39.41, 31.41, 23.71, 14.67, 5.36. High resolution MS, M^+: 458.2656 (found), 458.2672 (calc.).

6-Methoxy-6-(2-(2-ethynyl)phenyl)oct-4-yne-1-(*tert*-butyldimethylsilyloxy)-3-ol (2.22).

To a stirred solution of **2.21** (1.469 g, 3.27 mmol) in methanol (70 mL) potassium carbonate (483 mg, 3.5 mmol) was added. After two hours of stirring reaction mixture was diluted with diethyl ether, washed with ammonium chloride solution, water, and brine. Aqueous layer was extracted with diethyl ether twice. Combined organic solutions were dried over magnesium sulfate, filtered, and solvent was evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (10% of EtOAc in hexanes) affording 1.108 g (89%) of pure 6-methoxy-6-(2-(2-ethynyl)phenyl)oct-4-yne-1-(*tert*-butyldimethylsilyloxy)-3-ol (**2.22**). NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.76-7.74 (d, J = 7.6 Hz, 1H), 7.58-7.55 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H), 7.34-7.7.30 (t splitted further, 1H), 7.27-7.24 (t splitted further, 1H), 4.83-4.79 (q splitted further, 1H), 4.14-4.09 (m, 1H), 3.91-3.86 (m, 1H), 3.60-3.56 (dd, J_1 = 6 Hz, J_2 = 4 Hz, 1H), 3.36 (s, 1H), 3.26 (s, 3H), 2.36-2.19 (m, 2H), 2.14-2.07 (m, 1H), 1.92-1.99 (m, 1H), 0.91 (s, 9H), 0.87 (t, J = 7.2 Hz, 3H), 0.09 (s, 6H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 148.03, 141.48, 134.71, 133.82, 133.10, 125.07, 94.68, 89.20, 88.52, 88.10, 87.22, 67.78, 66.85, 58.02, 44.21, 39.90, 31.21, 23.69, 14.76, 5.57. High resolution MS, M^+: 386.2261 (found), 386.2277 (calc.).

6-Methoxy-6-(2-(2-ethynyl)phenyl)oct-4-yne-1-(*tert*-butyldimethylsilyloxy)-3-one (2.23).

To a stirred solution of **2.22** (1.108 g, 2.87 mmol) in dichloromethane (50 mL) PCC (874 m g, 4.046 mmol) was added. The reaction mixture was left with stirring overnight. After that period TLC analysis showed complete conversion of the starting material. Reaction mixture was filtered through a layer of silica gel, solvent was evaporated under reduced pressure, and residue was purified by column chromatography on silica gel (10% of EtOAc in hexanes) affording 1.03 g (93%) of pure 6-methoxy-6-(2-(2-ethynyl)phenyl)oct-4-yne-1-(*tert*-butyldimethylsilyloxy)-3-one (**2.23**). NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.65-7.63 (d splitted further, 1H), 7.60-7.57 (d splitted further, 1H), 7.37-7.33 (t splitted further, 1H), 7.31-7.26 (t splitted further, 1H), 4.04-4.01 (t, J = 5.6 Hz, 2H), 3.40 (s, 1H), 3.31 (s, 3H), 2.88-2.85 (t, J = 6.4 Hz, 2H), 2.40-2.26 (m, 2H), 0.87 (m, 12H), 0.06 (s, 6H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 191.25, 146.35, 133.97, 133.38, 125.03, 110.21, 96.16, 92.49, 88.71, 87.80, 86.93, 63.86, 58.40, 54.15, 39.44, 31.25, 23.67, 14.30, 5.43. High res. MS, M^+: 384.2111 (found), 384.2121 (calc.).

6-(2-Ethynylphenyl)-1-hydroxy-6-methoxyoct-4-yn-3-one (2.24).

To a stirred solution of **2.23** (1.03 g, 2.68 mmol) in acetonitrile (60 mL) hydrofluoric acid (52%, 1 mL) was added. After one hour of stirring, TLC showed complete conversion of the starting material. Reaction mixture was diluted with ethyl acetate, washed with sodium bicarbonate solution, water, and brine. Aqueous layer was extracted with ethyl acetate twice. Combined organic solutions were dried over magnesium sulfate, filtered, and solvents were evaporated under reduced pressure. Residue was purified by column chromatography on silica gel (15% of EtOAc in hexanes) yielding 707 mg (97%) of pure 6-(2-ethynylphenyl)-1-hydroxy-6-methoxyoct-4-yn-3-one (**2.24**). NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.63-7.58 (t splitted further, 2H), 7.38-7.34 (t splitted further, 1H), 7.31-7.27 (t splitted further, 1H), 3.99-

3.95 (m, 2H), 3.41 (s, 1H), 3.32 (s, 3H), 2.97-2.94 (t, J = 5.6 Hz, 2H), 2.40-2.26 (m, 2H), 2.15-2.19 (t, 1H), 0.90-0.87 (t, J = 7.2 Hz, 3H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 186.71, 140.80, 136.04, 128.63, 128.13, 128.01, 119.60, 91.75, 86.70, 83.45, 82.33, 81.25, 57.53, 52.99, 47.89, 33.89, 8.77. High res. MS, M^+: 270.1250 (found), 270.1256 (calc.).

Attempted synthesis of 1-hydroxy-6-(2-(2-iodoethynyl)phenyl)-6-methoxyoct-4-yn-3-one (2.25).

A solution of **2.24** (706 mg, 2.61 mmol), NIS (1.027 g, 3.132 mmol), and $AgNO_3$ (44 mg, 0.261 mmol) in acetone (20 mL) was stirred for 3 hours at ambient temperature. After that period TLC analysis showed that few minor and one major compounds were presented in the mixture. The volatiles were evaporated under reduced pressure, residue was diluted with dichloromethane, washed with sodium thiosulfate solution, water; aqueous layer was extracted with dichloromethane (5 x 30 mL), combined organic layers were dried over magnesium sulfate, filtered, and solvent was evaporated under reduced pressure. Residual material was subjected to column chromatography (10–30% EtOAc in hexanes) yielding 400 mg of unidentified compound as a major fraction.

3-(*tert*-Butyldimethylsilyloxy)-6-methoxy-6-(2-trimethylsilylethynylphenyl)oct-4-ynyl-pivalate (2.26).

This reaction was carried out utilizing regular procedure described for **2.21** using **2.15** (4.15 g, 9.69 mmol), *tert*-butyldimethylsilyl chloride (2.18 g, 14.54 mmol), dimethylamino pyridine (275 mg, 2.26 mmol), imidazole (2.45 g, 36 mmol), and dichloromethane (100 mL). Column chromatography was performed (2 – 10% EtOAc in hexanes) yielding **2.724 g (52%)** of pure 3-(*tert*-butyldimethylsilyloxy)-6-methoxy-6-(2-trimethylsilylethynylphenyl)oct-4-ynyl pivalate **2.26** as a mixture of two diastereomers. NMR ^1H: solvent is $CDCl_3$, (δ, ppm): 7.69 (t, 1H), 7.49

(d, 1H), 7.29-7.22 (m , 2H), 4.64 (m, 1H), 4.22 (q, 2H), 3.22 (d, 3H), 2.33-2.23 (m, 2H), 2.10 (q, 2H), 1.21 (d, 9H), 0.91 (d, 9H), 0.84 (t splited further, 3H), 0.24 (s, 9H), 0.13 (d, 6H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 183.6, 147.5, 140.4, 134.3, 134.2, 133.1, 132.7, 132.6, 125.8, 109.7, 94.4, 88.7, 87.1, 86.8, 65.9, 65.0, 57.5, 44.0, 43.2, 39.1, 38.9, 32.4, 30.9, 30.8, 23.4, 14.4, 14.3, 5.2, 5.0, 0.7.

3-(*tert*-Buthyldimethylsilyloxy)-6-(2-ethynylphenyl)-6-methoxyoct-4-yn-1-ol (2.27).

To a stirred solution of **2.26** (2.72 g, 5.03 mmol) in methanol (50 mL) potassium carbonate (1.387 g, 10.05 mmol) was added. Reaction mixture was left overnight with stirring, monitored by TLC. After that period TLC analysis indicated on the complete conversion of the starting material. Diethyl ether was added to the mixture and washed with saturated ammonium chloride solution. Aqueous layer was extracted with ether (3 x 30 mL), combined organic phases were washed with water and brine, dried over magnesium sulfate, and solvents were evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (5–20% EtOAc/Hexanes as eluent) yielding 1.069 g (55%) of pure 3-(*tert*-buthyldimethylsilyloxy)-6-(2-ethynylphenyl)-6-methoxyoct-4-yn-1-ol **(2.27)**. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.73-7.70 (dt, 1H), 7.56 (dd, J_1 = 6 Hz, J_2 = 1.6 Hz, 1H), 7.34-7.24 (m, 2H), 4.85-4.82 (t splitted further, 1H), 4.08-4.01 (m, 1H), 3.86-3.81 (m, 1H), 3.36 (s, 1H), 3.25 (s, 3H), 2.36-2.20 (m, 2H), 2.14-1.96 (m, 2H), 0.93 (s, 9H), 0.87-0.83 (t, J = 7.4 Hz, 3H), 0.18 (2s splitted further, 6H).

Attempted synthesis of 3-(*tert*-butyldimethylsilyloxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-yn-1-ol (2.28).

To a stirred solution of iodine (1.402 g, 5.52 mmol) in absolute benzene (50 mL) morpholine (1.49 mL, ca. 1.49 g, 16.56 mmol) was added. The mixture was heated at 45 °C for 20 min. with stirring. A solution of **2.7** (1.069 g, 2.76 mmol) in absolute benzene (5 mL) was added to the

stirred suspension of the iodination reagent, and the reaction mixture was stirred at 45 °C. Reaction was monitored by TLC analysis. After 2 hours, TLC indicated on the formation of two new compounds. Reaction mixture was left with stirring for another 5 hours at the temperature. Compound with retention time of the starting material and another two new compounds were detected in the mixture by that time. The reaction mixture was then washed with aqueous sodium tiosulphate solution (3 x 70 mL) and brine (100 mL), dried with magnesium sulfate, solids were filtered, and the solvents were evaporated under reduced pressure. Residue was subjected to the separation by column chromatography on silica gel (5–25 % EtOAc in hexanes) producing 300 mg of the first compound, 170 mg of the second compound, and 300 mg of the third compound. None of these compounds represented the targeted 3-(*tert*-butyldimethylsilyloxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-yn-1-ol (**2.28**).

Methyl 4-methoxy-4-(2-(trimethylsilylethynyl)phenyl)-hex-2-ynoate (2.29).

A solution of (2-(1-Methoxy-1-ethyl-prop-2-ynyl)-phenylethynyl)-trimethyl-silane (**2.11**) (2.3641 g, 8.76 mmol) in absolute THF (60 mL) under argon atmosphere was cooled to -78 °C. A solution of *n*-BuLi (2.56 M in hexanes, 3.76 mL, 9.636 mmol) was added and the reaction mixture was stirred for 30 min at the temperature. Methyl chloroformate (3.35 mL, 43.8 mmol) was then added and the reaction mixture was stirred at -78 °C for 30 min. Cooling bath was removed and the reaction mixture was left with stirring overnight at ambient temperature. Then reaction mixture was diluted with diethyl ether (80 mL), and the mixture was washed with saturated aqueous ammonium chloride (40 mL) and sodium chloride (40 mL) solutions. Aqueous phases were extracted with diethyl ether twice. Combined organic phases were dried over magnesium sulfate and solvents were evaporated under reduced pressure. Crude product was purified by column chromatography (3% of Et_2O in hexanes) yielding 2.17g (76%) of pure

methyl 4-methoxy-4-(2-(trimethylsilylethynyl)phenyl)-hex-2-ynoate (**2.29**) as colorless oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.61-7.59 (d, *J* = 8 Hz, 1H), 7.54-7.52 (d, *J* = 8 Hz, 1H), 7.34-7.30 (t, *J* = 7.2 Hz, 1H), 7.29-7.23 (t, *J* = 7.2 Hz, 1H), 3.81 (s, 3H), 3.33 (s, 3H), 2.37-2.25 (m, 2H), 0.90-0.87 (t, *J* = 7.6 Hz, 3H), 0.24 (s, 9H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 154.2, 141.3, 135.6, 128.5, 128.2, 121.0, 103.9, 101.5, 86.8, 81.2, 79.8, 53.2, 53.0, 33.8, 9.0, 0.02. High res. MS, M^+: 328.1496 (found), 328.1495 (calc.).

4-Methoxy-4-[2-(trimethylsilylethynyl)phenyl]-hex-2-ynal (2.30).

A solution of diisobutylaluminum hydride (1.21 M, 10 mL, 11.03 mmol) was added to a solution of **2.29** (3.0143 g, 9.19 mmol) in absolute dichloromethane (40 mL) at -78 °C under argon atmosphere. The reaction mixture was stirred for 4 hours at the temperature, the cooling bath was removed, and the reaction was quenched by addition of saturated aqueous ammonium chloride solution (5 mL) before it reached ca 0 °C. After 10 min of stirring reaction mixture was diluted with diethyl ether (100 mL), organic layer was separated, washed with water, and brine. Aqueous layer was extracted with diethyl ether (4 x 30 mL). Combined organic layers were dried over magnesium sulfate, filtered, and the solvents were evaporated under reduced pressure. Crude product was purified by column chromatography on silica gel (10% of Et_2O in hexanes) yielding **2.19 (80%)** of pure 4-methoxy-4-[2-(trimethylsilylethynyl)phenyl]-hex-2-ynal (**2.30**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 9.3 (s, 1H), 7.60-7.58 (d, *J* = 8 Hz, 1H), 7.55-7.54 (d, *J* = 7.5 Hz, 1H), 7.35-7.32 (m, 1H), 7.28-7.26 (m, 1H), 3.35 (s, 3H), 2.40-2.30 (m, 2H), 0.90-0.87 (m, 3H), 0.25 (s, 9H). High res. MS, M^+: 298.1382 (found), 298.1389 (calc.).

Ethyl 3-(*tret*-butyldimethylsilyloxy)-6-methoxy-6-(2-((trimethylsilyl)ethynyl)phenyl)oct-4-ynoate (2.31).

A solution of diisopropylamine (1.1 mL, 0.801 g, 8.1 mmol) in freshly distilled THF (50 mL), cooled to -5 °C, was treated with *n*-BuLi (2.56M in THF, 3.16 mL, 8.1 mmol) and stirred for 1 hour. The resulting LDA solution was cooled to -78 °C and ethyl acetate (0.72 mL, 0.71 g, 8.1 mmol) was added. Resulting mixture was stirred for 1 hour at the same temperature. A solution of **2.30** (2.19 g, 7.36 mmol) in THF (10 mL) was added to the mixture so as to keep the temperature of the reaction mixture below -70 °C. After stirring for 1 hour, the cooling bath was removed; reaction mixture was quenched with saturated solution of the ammonium chloride (5 mL) and placed in a water bath. As soon as the reaction mixture reached room temperature, it was diluted with diethyl ether (60 mL) and poured into saturated solution of the sodium chloride (50 mL). Organic phase was separated, and the aqueous phase was extracted with ether (3 x 40 mL). Combined organic phases were dried over magnesium sulfate, filtered, and solvents were evaporated under reduced pressure. Crude compound was purified by column chromatography on silica gel (10–25% EtOAc in hexanes) yielding 2.079 g (76%) of pure ethyl 3-hydroxy-6-methoxy-6-(2-((trimethylsilyl)ethynyl)phenyl)oct-4-ynoate. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.66-7.64 (m, 1H), 7.50-7.49 (m, 1H), 7.29-7.26 (m, 1H), 7.23-7.20 (td, J_1 = 6.5 Hz, J_2 = 1 Hz, 1H), 4.91-4.80 (m, 1H), 4.20-4.16 (qd, J_1 = 5.5 Hz, J_2 = 1.5 Hz, 2H), 3.23-3.21 (m, 3H), 2.82-2.80 (m, 2H), 2.33-2.17 (m, 2H), 1.28-1.24 (m, 3H), 0.85-0.82 (t, J = 7.5 Hz, 3H), 0.24-0.21 (m, 9H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 171.5, 142.5, 135.4, 128.8, 128.2, 127.6, 120.8, 104.6, 100.2, 87.5, 84.5, 81.5, 61.3, 59.2, 52.5, 42.3, 33.9, 14.4, 9.20. High res. MS, M^+-*tert*-Butyl (57): 386.1895 (found), 386.1913 (calc.).

A solution of ethyl 3-hydroxy-6-methoxy-6-(2-((trimethylsilyl)ethynyl)phenyl)oct-4-ynoate (2.079 g, 5.58 mmol) in dry dichloromethane (20 mL) was added to a stirred solution of TBDMSCl (1.685 g, 11.16 mmol), imidazole (1.518 g, 22.32 mmol) and DMAP (142 mg, 1.17 mmol) in dry dichloromethane (40 mL). The reaction mixture was stirred at the room temperature for 15 hours. The mixture was diluted with diethyl ether (100 mL) and poured into a mixture of water (25 mL), saturated aqueous ammonium chloride solution (25 mL) and brine (25 mL). Organic phase was separated; aqueous phase was extracted with diethyl ether (2 x 40 mL). Combined organic phases were washed with brine, dried over magnesium sulfate, and solvents were evaporated under reduced pressure. Crude product was purified by column chromatography on silica gel (10% of EtOAc in hexanes) yielding 2.262 g (83%) of pure ethyl 3-(*tret*-butyldimethylsilyloxy)-6-methoxy-6-(2-((trimethylsilyl)ethynyl)phenyl)oct-4-ynoate **(2.31**) as a mixture of two diastereomers in 1:1 ratio. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.70-7.67 (m, 1H), 7.51-7.49 (d, J = 7.5 Hz, 1H), 7.27-7.24 (m, 1H), 7.23-7.20 (t, J = 7.5Hz, 1H), 5.02-4.98 (m, 1H), 4.20-4.09 (m, 2H), 3.22-3.21 (2s, 3H), 2.85-2.80 (m, 1H), 2.77-2.66 (m, 1H), 2.35-2.19 (m, 2H), 1.27-1.24 (t, J = 7 Hz, 3H), 0.90-0.88 (m, 3H),0.85-0.82 (td, J_1 = 4.5 Hz, J_2 = 3 Hz, 3H), 0.25-0.23 (m, 9H), 0.17-0.13 (m, 6H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 175.4, 147.6, 140.5, 134.5, 134.3, 133.1, 132.7, 125.9, 109.7, 105.1, 93.7, 88.9, 87.0, 86.8, 65.9, 65.3, 57.6, 49.7, 39.1, 38.9, 30.9, 23.3, 19.5, 14.4, 5.09, 0.71, 0.66, 0.02. High res. MS, M^+-*tert*-Butyl (57): 443.2095 (found), 443.2074 (calc.).

Methyl 3-(*tert*-butyldimethylsilyloxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-ynoate (2.32).

A solution of **2.31** (1.4373 g, 2.87 mmol) in methanol (7 mL) was added to a stirred suspension of potassium carbonate (386 mg, 2.88 mmol) in methanol (30 mL). The reaction mixture was

stirred at room temperature for 2 hours and poured into a mixture of saturated sodium chloride solution (40 mL) and water (180 mL). Layers were separated, aqueous phase was extracted with mixture of diethyl ether/hexanes (4/1) (5 x 40 mL). Combined organic phases were washed with brine, dried with magnesium sulfate, and solvents were evaporated under reduced pressure. Product was purified by column chromatography on silica gel (10% of EtOAc in hexanes) yielding 1.01 g (88%) of pure ethyl 3-(*tert*-butyldimethylsilyloxy)-6-(2-ethynylphenyl)-6-methoxyoct-4-ynoat as a mixture of two diastereomers in 1:1 ratio. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.71-7.69 (m, 1H), 7.56-7.54 (m, 1H), 7.32-7.29 (m, 1H), 7.27-7.24 (m, 1H), 5.01-4.99 (m, 1H), 3.69 (s, 3H), 3.35 (s, 1H), 3.23 (s, 3H), 2.87-2.83 (m, 1H), 2.80-2.75 (m, 1H), 2.37-2.29 (m, 1H), 2.25-2.18 (m, 1H), 0.90 (s, 9H), 0.85-0.82 (t, J = 7.5 Hz, 3H), 0.17 (s, 3H), 0.14 (s, 3H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 175.8, 147.5, 144.2, 134.5, 133.5, 132.9, 124.8, 93.9, 88.7, 88.1, 87.9, 87.0, 65.2, 57.7, 57.0, 49.4, 39.5, 30.9, 23.3, 14.4, 0.65. High res. MS, M^+-*tert*-Butyl (57): 357.1524 (found), 357.1522 (calc.).

To a stirred solution of iodine (1.283 g, 5.05 mmol) in absolute benzene (50 mL) morpholine (1.37 mL, ca. 1.37 g, 15.18 mmol) was added. The mixture was heated at 45 °C for 20 min. with stirring. A solution of pure ethyl 3-(*tert*-butyldimethylsilyloxy)-6-(2-ethynylphenyl)-6-methoxyoct-4-ynoat (1.01 g, 2.53 mmol) in absolute benzene (5 mL) was added to the stirred suspension of the iodination reagent, and the reaction mixture was stirred at 45 °C for 5 hours. The reaction mixture was then washed with aqueous sodium tiosulfate solution (2 x 100 mL) and brine (100 mL), dried over magnesium sulfate, filtered, and solvents were evaporated under reduced pressure. Product was purified by column chromatography on silica gel (7% of EtOAc in hexanes) yielding 1.181 g (89%) of a pure mixture of 1:1 diastereomers of methyl 3-(*tert*-butyldimethylsilyloxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-ynoate (**2.32**) which is

sensitive to the light and high temperature. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.66-7.64 (m, 1H), 7.49-7.47 (dt, J = 1.5 Hz, 1H), 7.30-7.27 (td, J_1 = 6 Hz, J_2 = 1.5 Hz, 1H), 7.25-7.21 (td, J_1 = 6 Hz, J_2 = 1.5 Hz, 1H), 5.03-4.99 (m, 1H), 3.68 (2s, 3H), 3.23 (2s, 3H), 2.89-2.83 (m, 1H), 2.80-2.74 (m, 1H), 2.28-2.22 (m, 1H), 2.19-2.11 (m, 1H), 0.89 (2s, 9H), 0.83-0.80 (td, J_1 = 5 Hz, J_2 = 2.5 Hz, 3H), 0.16-0.13 (m, 6H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 175.8, 148.0, 141.2, 133.9, 133.4, 132.7, 126.1, 98.3, 93.8, 88.7, 86.3, 65.2, 57.7, 57.0, 49.5, 39.6, 36.9, 30.9, 28.0, 23.3, 19.4, 16.7, 14.3, 0.72. High res. MS, M^+-*tert*-Butyl (57): 483.0471 (found), 483.0489 (calc.).

3-(*tert*-Butyldimethylsilyloxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-ynal (2.5).

A solution of **2.32** (1.78 g, 3.49 mmol) in dichloromethane (50 mL) was cooled to -78 °C and DIBAL (1.21 M in toluene, 3.66 mmol, 3 mL) was added to this stirred solution. The reaction mixture was stirred for 4 hours at the temperature, the cooling bath was removed, and the reaction was quenched by addition of saturated aqueous ammonium chloride solution (2 mL) before it reached ca 0 °C. After 10 min of stirring anhydrous magnesium chloride was added to the reaction mixture. After 3 hours reaction mixture was filtered and solvents were evaporated under reduced pressure. Crude product was purified by column chromatography on silica gel (10–15% EtOAc in hexanes) yielding 1.447 g (81%) of pure 3-(*tert*-butyldimethylsilyloxy)-6-(2-(iodoethynyl)phenyl)-6-methoxyoct-4-ynal (**2.5**) as a mixture of diastereomers. NMR ^{1}H spectrum: solvent is $CDCl_3$, (δ, ppm): 9.88-9.87 (m, J_1 = 1.6 Hz, J_2 = 2 Hz, 1H), 7.63-7.62 (d, J = 6.4 Hz, 1H), 7.49-7.48 (d, J = 6 Hz, 1H), 7.30-7.27 (td, J_1 = 4.8 Hz, J_2 = 1.2 Hz, 1H), 7.24-7.21(td, J_1 = 5.2 Hz, J_2 = 0.8 Hz, 1H), 5.08-5.04 (m, 1H), 3.25 (2s, 3H), 2.93-2.86 (m, 1H), 2.81-2.74 (m, 1H), 2.30-2.22 (m, 1H), 2.20-2.12 (m, 1H), 0.90-0.88 (m, 9H), 0.82-0.80 (td, J_1 = 3.2 Hz, J_2 = 2.8 Hz, 3H), 0.176-0.149 (m, 6H). NMR ^{13}C spectrum: solvent is $CDCl_3$, (δ, ppm):

200.4, 142.9, 136.2, 128.6, 128.5, 127.7, 121.0, 93.3, 88.3, 84.6, 81.1, 58.6, 52.7, 51.9, 34.5, 34.3, 31.8, 25.9, 25.5, 22.9, 18.3, 14.4, 11.8, 9.19, 9.14, -4.29, -4.34, -4.94, -4.97. High res. MS, M^+: 510.1110 (found), 510.1087 (calc.).

9-(*tert*-Butyldimethylsilyloxy)-12-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10]annulene-7-ol (2.33).

To the solution of **2.5** (421 mg, 0.825 mmol) in thoroughly deaerated with a strong flux of argon, freshly distilled absolute THF (200 mL) a chromium dichloride (604 mg, 4.95 mmol) and nickel dichloride (cat. amount) were added with vigorous stirring under argon atmosphere at room temperature. The color of the reaction mixture turned into dark green-brownish. The reaction mixture was stirred at room temperature for 2 hours. After that period TLC analysis indicated on the complete conversion of the starting material. Reaction mixture was diluted with diethyl ether (300 mL), washed with ammonium chloride (50 mL) and brine (50 mL), dried over magnesium sulfate, and solvents were evaporated under reduced pressure. Purification was carried out by column chromatography on silica gel (10–30% EtOAc in hexanes) yielding 285 mg (90%) of pure 9-(*tert*-butyldimethylsilyloxy)-11-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo [10]annulene-7-ol (**2.33**) as yellowish oil (mixture of diastereomers in 1:3 ratio). NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.55-7.51 (m, 1H), 7.39-7.30 (m, 2H), 7.25-7.20 (m, 1H), 4.99-4.90 (m, 1H), 4.85-4.72 (m, 1H), 3.30 (s, 0.7H), 3.27 (m, 2H), 2.22-2.10 (m, 2H), 1.99-1.85 (m, 2H), 0.93-0.89 (m, 9H), 0.18-0.13 (m, 6H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 142.9, 142.4, 141.8, 133.5, 133.2, 132.8, 129.1, 129.0, 127.5, 126.6, 126.3, 122.0, 121.7, 95.3, 94.8, 91.6, 90.9, 90.3, 87.8, 87.2, 86.8, 86.0, 85.3, 85.2, 79.9, 79.8, 79.7, 63.6, 62.5, 60.0, 59.7, 59.6, 53.4, 53.2, 53.0, 44.3, 42.8, 40.5, 39.5, 39.3, 26.0, 25.9, 18.4, 18.3, 9.09, 9.00, 8.96, -4.32, -4.38, -4.45, -4.78, -4.83, -4.11.

9-(*tert*-Butyldimethylsilyloxy)-12-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10]annulene-7-one (2.34).

Dess-Martin periodinane (472 mg, 1.11 mmol) was added to a stirred solution of **2.33** (285 mg, 0.742 mmol) in CH_2Cl_2 (20 mL). The reaction mixture was stirred for 3 hours and 150 mL of diethyl ether was added. A mixture was filtered through the layer of silica gel twice and solvents were evaporated under reduced pressure. The residue was purified by the column chromatography on silica gel (7% of EtOAc in hexanes) yielding of the product is 176 mg (62%) of pure 9-(*tert*-butyldimethylsilyloxy)-11-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10]annulene-7-one (**2.34**) as a mixture of two diastereomers. NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.53-7.51 (m, 1H), 7.47-7.40 (m, 2H), 7.23-7.20 (m, 1H), 4.7-4.65 (m, 1H), 3.21-3.19 (2s, 3H), 2.86-2.77 (m, 2H), 1.95-1.78 (m, 2H), 0.86-0.75 (m, 9H), 0.08-0.05 (2s, 3H), 0.01-0.00 (2s, 3H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm):184.7, 184.4, 145.3, 144.9, 135.2, 135.0, 131.8, 128.0, 127.0, 126.9, 119.3, 119.1, 99.4, 98.1, 94.3, 93.6, 91.2, 90.6, 86.4, 85.8, 79.9, 79.8, 60.2, 60.1, 53.7, 53.4, 53.2, 52.8, 39.5, 34.9, 31.8, 25.8, 22.9, 18.3, 14.4, 9.0, -4.4, -4.5, -4.8, -4.9.

12-Ethyl-9-hydroxy-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10] annulene-7-one (2.35).

Hydrofluoric acid (55%, 1 mL) was added to a stirred solution of **2.34** (277 mg, 0.73 mmol) in acetonitrile (25 mL) at room temperature. TLC analysis indicated on the complete conversion of the starting material after 1.5 hours of stirring. Diethyl ether (40 mL) was added to the reaction mixture, mixture washed with water/brine (20 mL, 2/1), $NaHCO_3$ (3 x 15 mL), and brine (2 x 15 mL), dried over magnesium sulfate, solids were filtered, and solvents were evaporated under reduced pressure. Crude compound was purified by column chromatography on silica gel (30–

40% EtOAc in hexanes) affording 127.6 mg (65%) of pure 11-ethyl-9-hydroxy-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10] annulene-7-one (**2.35**) as a mixture of two diastereomers. **A**fter 2 days of staying in the refrigerator ratio of the diastereomers has changed. NMR ^{1}H spectrum, solvent is $CDCl_3$, (δ, ppm): 7.63-7.61 (d, *J* = 6.8 Hz, 1H), 7.58-7.52 (m, 2H), 7.35-7.32 (t, *J* = 6 Hz, 1H), 4.86-4.80 (m, 1H), 3.32-3.29 (m, 3H), 3.05-2.92 (m, 2H), 2.46 (br s, 1H), 2.04-1.90 (m, 2H), 0.97-0.92 (m, 3H). NMR ^{13}C spectrum, solvent is $CDCl_3$, (δ, ppm): 183.8, 144.8, 135.2, 134.7, 131.9, 127.9, 126.9, 126.8, 118.8, 99.8, 98.6, 93.3, 90.1, 89.7, 87.4, 86.8, 79.7, 59.4, 59.3, 53.2, 53.1, 52.4, 51.2, 39.3, 39.1, 8.82, 8.76. High resolution MS, M^+ -CH_3 (15)+FC-40 (40): 293.0893 (found), 293.0865 (calc.).

Attempted synthesis of 12-ethyl-12-methoxy-5,6,10,11-tetradehydro-7,8,9,12-tetrahydrobenzo[10]annulene-7,9-dione (2.3).

Dess-Martin periodinane (159 mg, 0.376 mmol) was added to a stirred solution of **2.35** (84 mg, 0.313 mmol) in dichloromethane (20 mL). The reaction mixture was stirred for 30 min followed by TLC analysis. After that period all starting material was completely converted. TLC showed big spot with tale close to the starting line in 50% EtOAc in hexanes phase. Diethyl ether (30 mL) was added to the reaction mixture, and reaction mixture was filtered through 2 cm layer of silica gel. Solvent was evaporated under reduced pressure. After the work-up procedure, TLC of the residue looked the same as directly after the reaction was completed. Base on the NMR data, no distinct compound was obtained.

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CHAPTER 3

CONJUGATED TEN-MEMBERED CARBOCYCLIC MODEL ENEDIYNES WITH AN EXO-CARBONYL GROUP IN THEIR CORE: SYNTHESIS, THERMOCHEMISTRY AND KINETICS

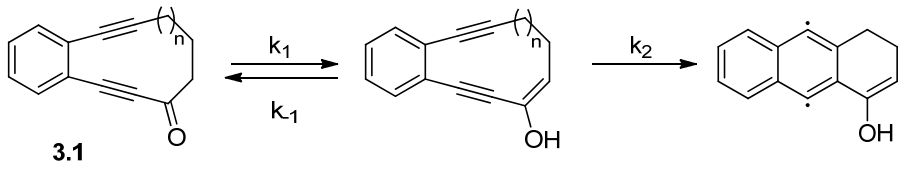
3.1 Synthesis and Cyclization of 5,6,11,12-Tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene-7-one and 5,6,12,13-Tetradehydro-8,9,10,11-tetrahydro-7*H*-benzo[11]annulene-7-one

In order to effectively control and trigger the Bergman cyclization of synthetic enediynes it is important to know the factors that affect the rate of the reaction and understand the mechanism of cycloaromatization.

As it is described in the literature, enediynes with a conjugated carbon-oxygen double bond undergo cycloaromatization with higher rates than enediynes without a carbonyl group.[1] This effect is usually attributed to the inductive electronic effect of the keto-group, but we hypothesized that the increase in the reaction rate might be due to a change in the cyclization mechanism. Based on our previous results with cyclic enediynes containing 2-diazo-1,3-diketo moiety, we proposed that an enol form of keto-enediyne might be more reactive. The fast cyclization of cyclic keto-enediynes in this case is due to a presence of the enol form of these compounds. Keto-enediynes **3.1a** and **3.1b** might undergo enolization on the first step of the reaction and then, upon formation of the enol form, cycloaromatize into the products. Rate enhancement of Bergman cyclization of keto-enediynes **3.1a** and **3.1b** might be explained by the kinetic scheme shown in Figure 1.3. In the case when enolization is the rate determining step, reactive enol slowly forms on the first step and then it rapidly cyclizes into 1,4-benzenoid

biradical. In this case k_{-1}[base] is much smaller than k_2, therefore, the rate of the reaction is determined by the rate of the first enolization step and should be catalyzed by base. The enolization reaction is usually strongly catalyzed by base; also, a weaker acid catalysis might be seen. In an alternative kinetic scheme, the rate of keto-enol equilibration is much faster than the cyclization, so hydrogen abstraction from **3.1** happens quickly on the fast pre-equilibrium step. In this case k_2 is much smaller than k_{-1}[base] and k_{obs} does not depend on the concentration of base. Cyclization of the enol is the rate determining step.

To explore the feasibility of Bergman cyclization *via* enolization, we have studied the reactions of 10- and 11-membered ring keto-enediynes.



3.1

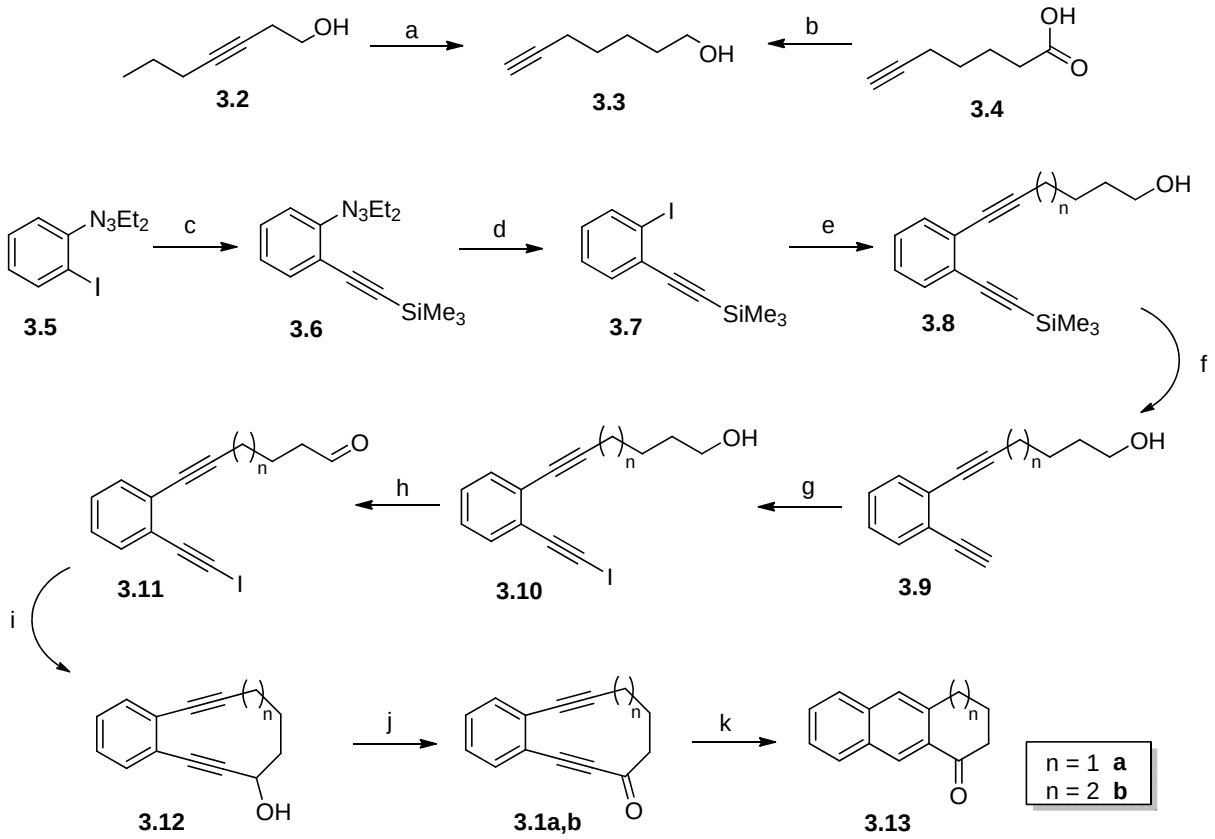
$$k_{obs} = \frac{k_1 \times [base] \times k_2}{k_{-1} \times [base] + k_2}$$

Figure 3.1 Possible mechanism of cycloaromatization for **3.1a** and **3.1b**.

Ten- and eleven-membered ring enediynes (**3.1a** and **3.1b**) were synthesized in nine steps, as shown in Figure **3.2**. Again, we used Sonogashira cross-coupling reactions to introduce the acetylenic moieties into the molecules and utilized a chromium(II)/nickel(II)-mediated Nozaki-Hiyama-Kishi reaction to close the enediyne ring.

A straightforward synthetic route began with synthesis of ((2-diethyltriazenylphenyl)ethynyl)trimethylsilane **3.6** from iodotriazene **3.5** which is known and had been synthesized in our laboratory.[2] Iodotriazene **3.5** was introduced into Sonogashira coupling[3] with trimethylsilyl acetylene. The diethyltriazeno group of the resultant diethyltrazeno-

acetylene **3.6** was then exchanged for iodine using a high temperature and high pressure reaction with iodomethane[4] affording iodo-acetylene **3.7** (Figure 3.2).



(a) NaH, $NH_2CH_2CH_2NH_2$, THF, 60 °C; (b) $LiAlH_4$, THF, 98%; (c) $HC{\equiv}CSiMe_3$, Pd(II), CuI, Et_3N, THF, 95-98%; (d) CH_3I, 135 °C, 80-97%; (e) hex-5-yn-1-ol or **3.3**, Pd(II), CuI, Et_3N, THF, 65-67%; (f) K_2CO_3, MeOH, 83-95%; (g) I_2/morpholine, C_6H_6, 85-90%; (h) PCC, CH_2Cl_2, 86-90%; (i) $CrCl_2$, $NiCl_2$, 70-93%; (j) Dess-Martin periodinane, CH_2Cl_2, 90-92%; (k) Δ, *i*-PrOH or 1,4-CHD, C_6H_6, 61%.

Figure 3.2 Synthesis of keto-enediynes **3.1a** and **3.1b**.

The Sonogashira coupling[3] of **3.7** with commercially available hex-5-yn-1-ol produced a primary diacetylenic alcohol **3.8a** in 85% yield. Hept-6-yn-1-ol **3.3** was synthesized using a "zipper reaction"[5] of less expensive hept-3-yn-1-ol. Unfortunately, this reaction and formation of amide, particularly, were extremely sensitive to moisture. Sodium hydride found was to be the best base for this reaction as no desired product was obtained when potassium *tert*-butoxide or lithium were used. The amount of solvent (THF) used also greatly influenced the result of the

reaction. For instance, a four-fold decrease of the concentration of the reaction mixture produced no hept-6-yn-1-ol. Formation of the amide in the reaction mixture was detected based on its color change from gray into violet and hydrogen gas evolution. Analysis of the product was performed using GC/MS, NMR ^{1}H, and by the ability of the product to react in the Sonogashira cross-coupling with iodobenzene. Reaction time and temperature played a major role when preparing hept-6-yn-1-ol **3.3**. A variety of reaction conditions were employed but, unfortunately, only two trials gave positive results and were not repeatable. It was decided to reduce hept-6-ynoic acid **3.4** to the targeted hept-6-yn-1-ol **3.3**. The reduction reaction successfully yielded the alcohol and was used for synthesis of **3.3** in the future. The Sonogashira coupling of alcohol **3.3** with **3.7** afforded **3.8b** in good yield.

The trimethylsilyl protecting group was removed from **3.8a** and **b**, as discussed in chapter 2, and both compounds were subjected to iodination with an iodine-morpholine complex in benzene[6] to produce **3.10a** and **b**. In both cases, mixtures of **3.10** (**a** and **b**) and the byproducts from iodination reaction into the alkyl chain of **3.10** were obtained. Yield of the iodo-alcohols **3.10** was increased by decreasing the reaction time and temperature, but a small amount of by-products was still observed based on GC/MS and NMR analyses. The identical R_f of the product and its by-product made it impossible to separate compounds on the silica gel, so the mixture was introduced into the oxidation reaction and then aldehydes were separated.

The Nozaki-Hiyama-Kishi reaction,[7] discussed in the chapter 2, was utilized to cyclize pure iodo-aldehydes **3.11a** and **b**. This reaction required a high dilution and slow addition of iodoaldehyde to provide the best yield and minimize the formation of the dimer. Secondary alcohols **3.12a** and **b** were submitted to the Dess-Martin oxidation reaction[8] to give **3.1a** and **b** as single products.

We prepared products from the cycloaromatization reactions of **3.1a** and **b** in order to measure yields and confirm the structures of the cyclized products **3.13a** and **b**. Ten-membered ring keto-enediyne **3.1a** was subjected to the thermolysis 75 °C in neat isopropanol, which also served as a hydrogen donor. The tetrahydroanthracene derivative **3.13a** was isolated and its structure was confirmed by spectroscopic methods and compared to the tetra-dehydro-anthracenone described in the literature.[9] 11-Membered ring keto-enediyne **3.1b** was much more stable, as expected. No sign of the Bergman cyclization was observed when **3.1b** was heated for two days in isopropanol at 75 °C. Increasing the reaction temperature to 150 °C and switching to the benzene with 1,4-CHD, a better hydrogen donor, produced cyclized ketone **3.13b**.

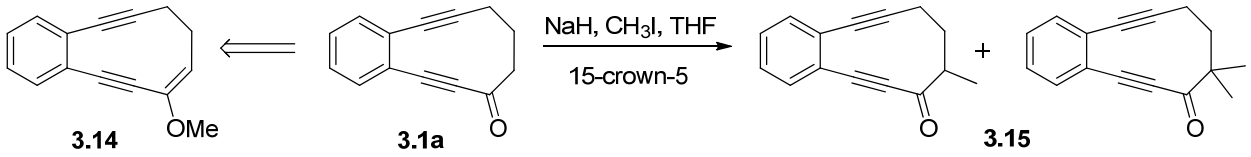


Figure 3.3 Attempted synthesis of **3.14**.

We attempted to synthesize the methyl ether of the enol-enediyne **3.14** for kinetic studies using sodium hydride and methyl iodide. Unfortunately, the only product of the reaction was an inseparable mixture of the methylation products of **3.1a** to the α-position of the alkyl chain **3.15** (Figure 3.3).

3.2 Kinetic Studies of the Cycloaromatization Reaction of Enediynes 3.1a and 3.1b

We believe that the conjugated carbonyl group in the enediyne core increases the rate of Bergman cyclization because of the mechanistic change of the cycloaromatization reaction when compared to enediynes without a carbonyl (rf. **3.12**). In order to establish the mechanism of cycloaromatization of 10- and 11-membered ring keto-enediynes **3.1a** and **3.1b,** we studied the kinetics of their cyclization.

UV spectroscopy was found to be the most efficient method for the kinetic analysis of keto-enediynes. The accurate rate measurements of the cyclization of 10-membered ring keto-enediyne **3.1a** in 2-propanol were conducted following the growth of the characteristic 252 nm band of 3,4-dihydroanthracen-1(2*H*)-one **3.13a** (Figure 3.4). The experimental data fits well to a single exponential equation (*i.e.*, the reaction followed the first-order equation, Figure 3.4). The rate of the cycloaromatization of **3.1a** in 2-propanol at 60 ± 0.1 °C was k = (2.91±0.06) x 10^{-5} sec^{-1}.

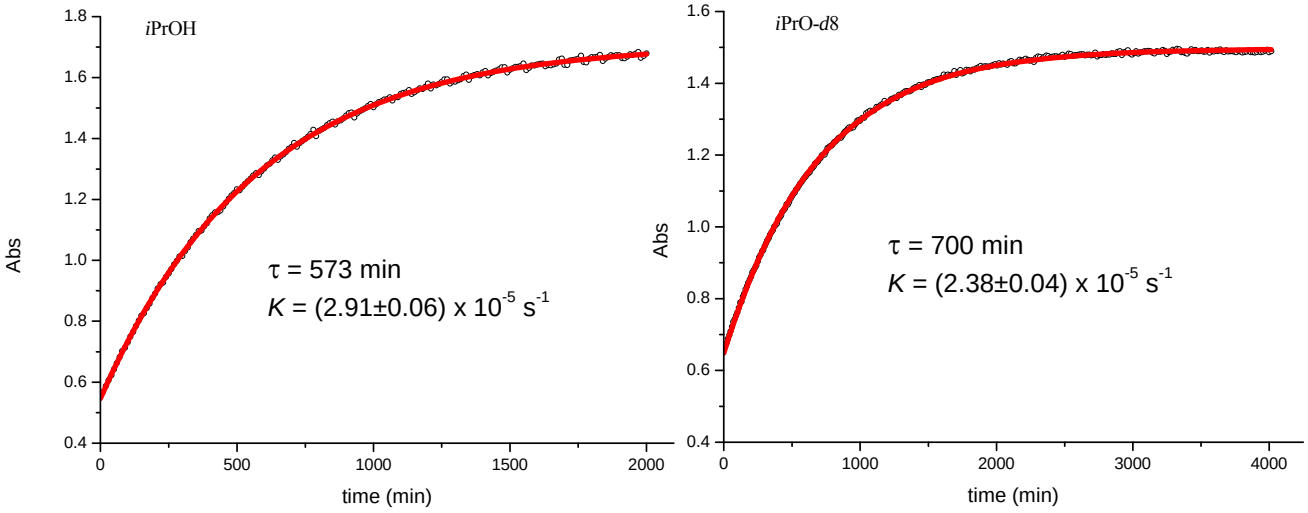


Figure 3.4 Kinetic traces of enediyne **3.1a** observed at 252nm, 60 °C in neat 2-propanol and 2-propanol-d_8.

The observed rate of cycloaromatization of **3.13a** in deuterated isopropanol at 60 °C was similar to the rate in conventional isopropanol (k_D = (2.38±0.064) x 10^{-5} sec^{-1} vs. k_H = (2.91±0.06) x 10^{-5} sec^{-1}). The observed kinetic isotope effect (KIE = k_H/k_D = 1.22) indicates that the hydrogen abstraction step by 1,4-biradical is not rate limiting. There is a secondary kinetic isotope effect due to involvement of the deuterated solvent as a reactant on the rate limiting step. 2-Propanol-d_8 acts as a base, abstracting hydrogen from the α-position of keto-enediyne on the

rate limiting step. Since O-H bond is weaker than O-D bond, deuterated isopropanol is a weaker base than conventional isopropanol when it abstracts hydrogen leading to the enolization.

Similar kinetic experiments were performed with the hydroxyl-enediyne **3.12a** in order to compare the rates and determine if there are any differences in the mechanism of cycloaromatization.

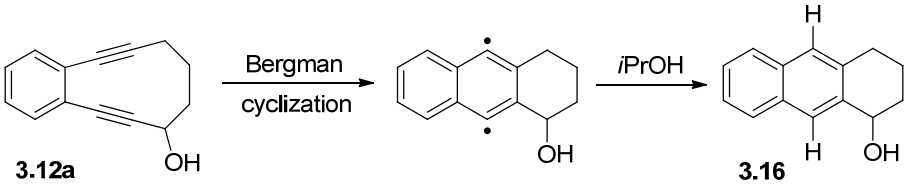


Figure 3.5 Cycloaromatization of the hydroxyl analog **3.12a**.

The rate of the cycloaromatization of the hydroxyl-enediyne **3.12a** under the same conditions was found to be (1.98±0.16) x 10^{-6} s^{-1} which is ca. 15 times lower than for **3.1a**. Kinetic studies in the deuterated isopropanol revealed the presence of the significant kinetic isotope effect. The rate of Bergman cyclization in 2-propanol-d_8 was 2.50 x 10^{-7} s^{-1} giving k_H/k_D = 7. This high value of the KIE clearly indicates that the hydrogen abstraction happens during the rate limiting step. Both reactions followed the pseudo-first order kinetics and data fits well into the single exponential function. The reactions were followed either at the decreasing band of **3.12a** at 260 nm or growth of the 286 nm band of the 1,2,3,4-tetrahydroanthracene-1-ol **3.16**. These observations confirm that not only electronic effects influence the rate of cycloaromatization of keto-enediyne **3.1a** but also there is a different mechanism of cyclization where hydrogen abstraction is no longer the rate limiting step.

If the cycloaromatization proceeds through enolization as the rate limiting step, the reaction is supposed to be strongly catalyzed by a base. The base would pull the proton from α-position of methyl group creating a carboanion that would be in resonance with enolate.

Protonation of this enolate then would lead to the enol form of ketone **3.1a**. At first, sodium hydroxide was chosen as a base for catalytic experiments because standardized solutions can be purchased or easily prepared. The preparative experiment of cyclization of keto-enediyne **3.1a** in isopropanol with 2.6 eq of sodium hydroxide produced rather unexpected results (Figure 3.6).

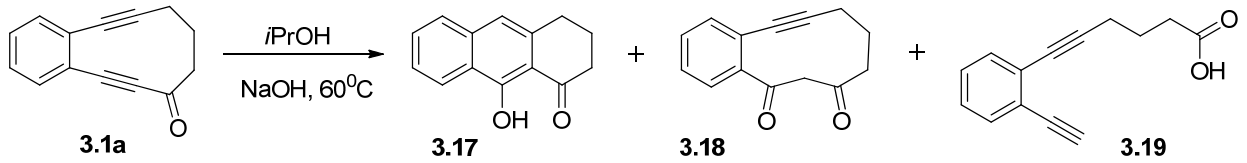


Figure 3.6 Thermal reaction of **3.1a** with addition of NaOH in 2-propanol.

Instead of formation of 3,4-dihydroanthracen-1(2*H*)-one **3.13a**, the reaction yielded 9-hydroxy-3,4-dihydroanthracen-1(2*H*)-one **3.17** as a minor product, the product of the hydration of the triple bond **3.18** as a major fraction, and the acid **3.19**. Hydroxide anion acted as a nucleophile in this reaction producing products of the nucleophilic addition. It was decided to choose a base which was less nucleophilic but still strong and soluble in 2-propanol. 1,8-Diazabicyclo[5.4.0]undec-7-ene (DBU) became our base of choice when the preparative experiment confirmed formation of the expected cycloaromatization product **3.13a**.

The rates of Bergman cyclization of **3.1a** (ca. 3.5 x 10^{-5} M in 2-propanol) at 60 °C in the presence of different concentrations of DBU were measured following the growth of the 252 or 295 nm band of **3.13a** with at least three measurements for each concentration of DBU. The dependence of the rate of Bergman cyclization on the concentration of DBU is shown in Figure 3.7.

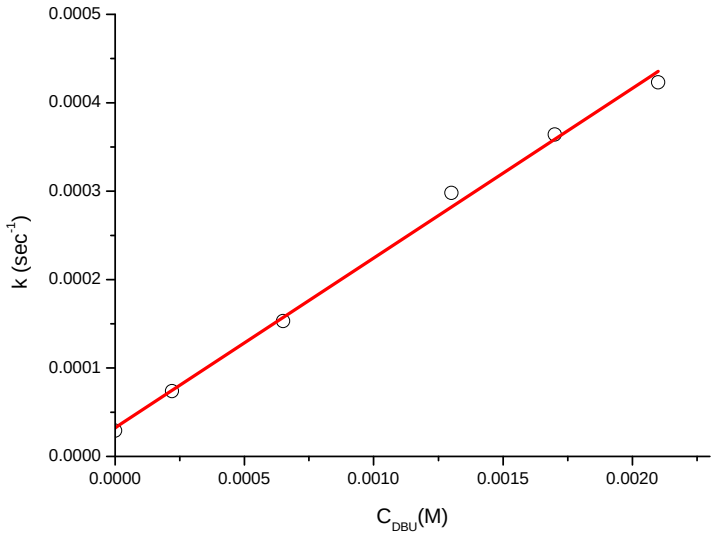


Figure 3.7 Cyclization of 3.5 x 10^{-5} M solution of 5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene-7-one (**3.1a**) in isopropanol at 60 °C in the presence of various concentrations of DBU.

The graph shown in Figure 3.7 clearly shows that the reaction is catalyzed by the base because the rate of the cycloaromatization linearly depends on the concentration of DBU. Similar experiments were performed with hydroxyl analog **3.12a**. Enediyne **3.12a** in the presence of 2.1 x 10^{-3} M DBU, or in the absence of the base in 2-propanol, at 60 °C undergoes conversion to **3.16** with the same rate. This observation, again, confirms the different mechanism for the cyclization of keto-enediyne **3.1a**.

If enolization is the rate limiting step, it is also expected to be catalyzed by acid, while conventional Bergman cyclization shows no acid catalysis.[10] The rates were measured in the same manner as for basic catalysis with variable concentration of perchloric acid.

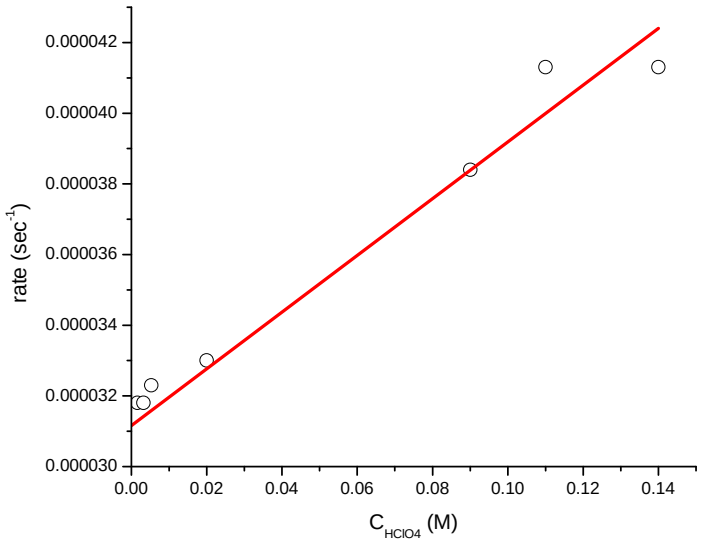


Figure 3.8 Cyclization of 3.5 x 10^{-5} M solution of 5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene-7-one (**3.1a**) in isopropanol at 60 °C in the presence of various concentrations of $HClO_4$.

The data demonstrates the presence of weak acid catalysis of the cycloaromatization of **3.1a** supporting that enolization is indeed the rate limiting step of the reaction.

We also made attempts to measure the rate of enolization directly using a variety of methods but the best results were produced utilizing DIP-MS analysis of the cycloaromatization of **3.1a** in deuterated 2-propanol at 60±0.1 °C. We followed the decay of the peak's intensity corresponding to **3.1a** (M^+) (Figure 3.9) and the rate of the conversion was found to be 3.14 x 10^{-5} s^{-1}. We also followed the formation of the peak, which corresponded to the **3.1a-d** (M^{+1}) as it formed and decayed, producing a cyclized product with molecular mass M^{+3}. Kinetic of **3.1a-d** is rather complicated since there is a growth and decay of its peak in DIP-MS but it forms from **3.1a** and the rate of its formation was found to be 7.6 x 10^{-6} s^{-1}.

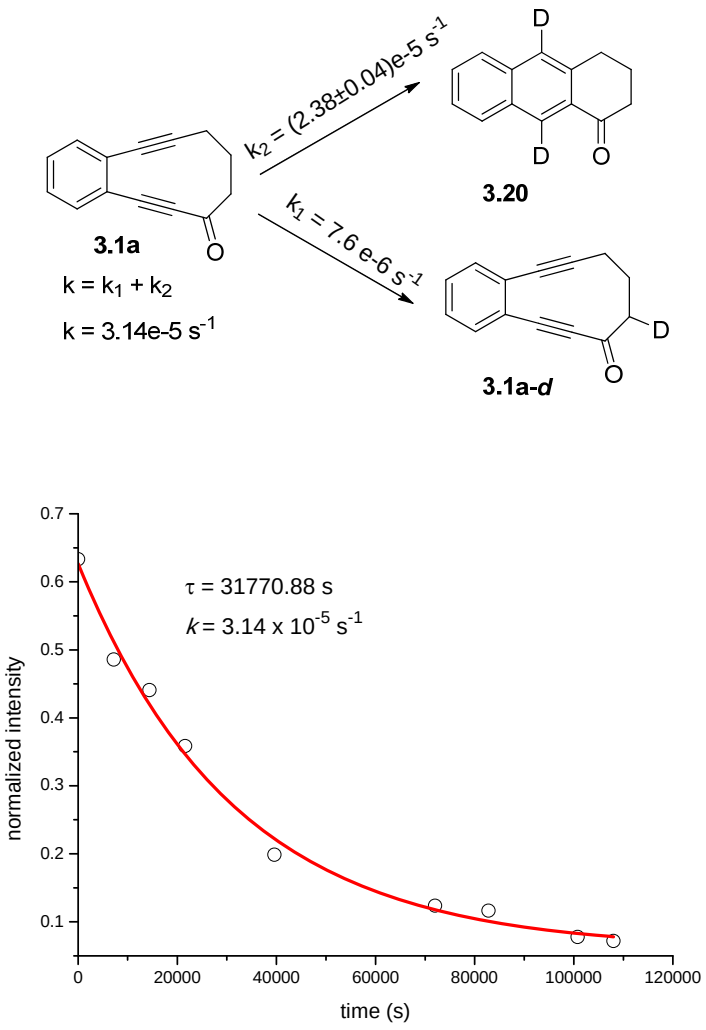


Figure 3.9 Enolization of keto-enediyne **3.1a** in isopropanol-d_8 at 60 °C by DIP/MS analysis.

Since formation of **3.20** has the reaction rate of 2.38 x 10^{-5} s^{-1} the enolization rate should be equal to 7.6 x 10^{-6} s^{-1}. Both rates are comparable in value, meaning that enolization is a slow process.

As we expected, enlarging of the enediyne ring size to 11-membered cycle as in **3.1b** greatly decelerated the cycloaromatization reaction. The rate of cyclization of keto-enediyne **3.1b** was measured using HPLC analysis. Decay of **3.1b** (8.2 x 10^{-4} M) was followed at 150 °C in isopropanol for three days and samples for HPLC analysis were taken every few hours. The obtained data allowed us to calculate the rate of the reaction as 9.04 x 10^{-4} s^{-1} with a lifetime of

ca. 18 hours. This reaction was found to be catalyzed by the base (Figure 3.10). The rate of the cyclization of **3.1b** to **3.13b** in 2-propanol was linearly proportional to the concentration of DBU up to 0.1M. In contrast to the cyclization reaction of **3.1a**, cyclization of **3.1b** is not catalyzed by acid. It can be concluded that the Bergman cyclization proceeds through the enolization step but this step is most likely not rate determining.

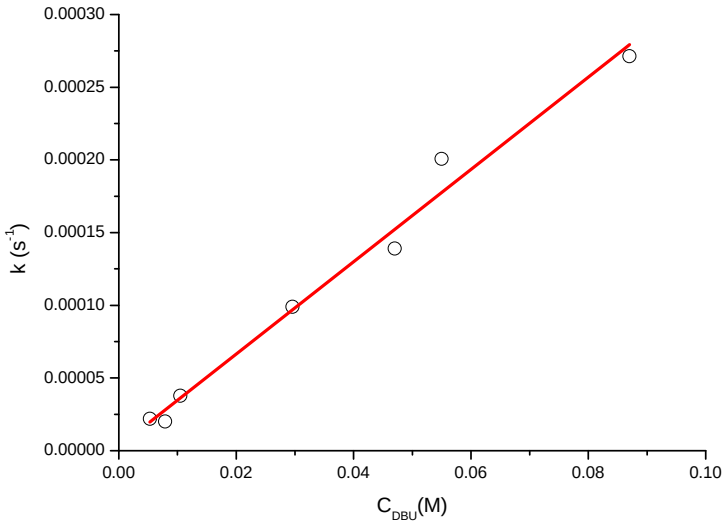


Figure 3.10 Cyclization of 8.2 x 10^{-4} M solution 5,6,12,13-tetradehydro-8,9,10,11-tetrahydro-7*H*-benzo[11]annulene-7-one (**3.1b**) in isopropanol at 60 °C in the presence of DBU.

The rate of enolization of keto-enediyne **3.1b** was measured by NMR spectroscopy in deuterated methanol (MeO-d_4) at 60 °C (Figure 3.11). We followed the decay of the signal from the α-methylene group with respect to the carbonyl as it decays in H^1 NMR, exchanging with deuterium. Deuterated methanol acts as a base pulling α-protium from keto-enediyne, re-protonating it back with deuterium. As it is shown in Figure 3.11, the rate of enolization was found to be 1.99 x 10^{-6} s^{-1}. In this case, enolization is a faster process than cycloaromatization (k = 9.04 x 10^{-4} s^{-1} at 150 ºC). Since enolization of **3.1b** is faster but comparable to the cycloaromatization process and the reaction is catalyzed by the base, it can be concluded that

enolization is not the rate limiting step for the reaction of the 11-membered ring keto-enediyne **3.1b**. In this case cyclization is decelerated because of the larger ring size so relatively fast enolization was observed for **3.1b**.

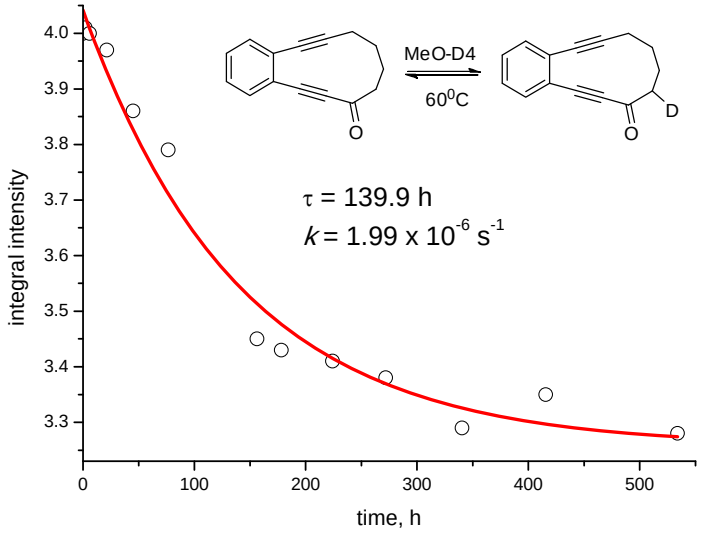


Figure 3.11 Enolization of keto-enediyne **3.1b** in methanol-d_4 at 60 °C by H^1 NMR analysis.

3.3 Conclusions

Ten- and eleven-membered ring enediynes **3.1a** and **b** were synthesized and their cycloaromatization products **3.13a** and **b** were characterized. The experimental data allows us to conclude that the introduction of the conjugated carbonyl group next to the acetylenic carbon of enediyne core increases the rate of the Bergman cyclization. This increase is caused not only by inductive electronic effect but also by a mechanistic change. Keto-enediyne **3.1a** undergoes a Bergman cyclization 15 times faster than its hydroxyl analog **3.12a** and involves enolization on the rate limiting step. Increasing the ring size of keto-enediynes leads to a great decrease of the reaction rate. Cycloaromatization of 11-membered ring keto-endiyne **3.1b** is catalyzed by bases. No signs of acid catalysis were seen. It undergoes enolization with comparable to the cyclization rate.

3.4 Experimental Section

3.4.1 Materials and Instruments

All oxygen- and moisture-sensitive reactions were carried out under an inert atmosphere in the oven-dried glassware. Solvents for moisture-sensitive reactions were dried by distillation prior to usage. Dry inhibitor-free THF (Sigma-Aldrich) was used for palladium-catalyzed cross-coupling reactions. All commercially available materials were used without purification unless otherwise stated. Dess-Martin periodinane was prepared according to the literature procedure.[11] TLC analyses were performed using aluminum-backed silica gel TLC plates. Chromatographical separation and purification of the reaction products were performed using standard grade flash chromatography silica gel (40-63 μm particle size) or premium grade flash chromatography silica gel (40-75 μm particle size). All NMR spectra were recorded in deuterochloroform on Varian Mercury 400 MHz or 500 MHz spectrometers with tetramethylsilane (TMS) as an internal standard. ^{1}H-NMR chemical shifts (δ) are reported in parts per million (ppm) versus TMS reference, ^{13}C-NMR chemical shifts (δ) are reported in ppm versus residual solvent peak reference. IR spectra were recorded on Shimadzu IRPrestige-21 FTIR instrument. GC-MS data were collected using Shimadzu GC-2010 equipped with SHR5XLB column. High resolution mass spectra analyses were performed by the Mass Spectrometry Laboratory, University of Georgia at Athens, GA. HPLC data were collected on HP series 1100.

3.4.2 Experimental Synthetic Procedures

Hept-6-yn-1-ol (3.3) from hept-3-yn-1-ol (3.2).

To a suspension of sodium hydride washed with distilled hexanes (0.72 g, 17.9 mmol, 60% of NaH in oil) in anhydrous THF (2 mL) freshly distilled ethylene diamine (2.16 g, 35.7 mmol, 2.4 mL) was added under argon at room temperature. The reaction mixture was left with stirring at

room temperature and carefully monitored for the color change from gray into a violet as a sign of amide's formation. Evolution of hydrogen gas was observed during this period. 3-Heptyn-1-ol (0.5 g, 4.46 mmol, 0.57 mL) was added in one portion and the reaction mixture was heated at 45 °C for one hour (not longer than that!). GC/MS analysis showed presence of only one peak with retention time of 5.96 min and m/z = 111. Reaction mixture was poured into ice, extracted with diethyl ether (2 x 30 mL), washed with water, diluted solution of hydrochloric acid, water again, and then with brine. Combined organic solution was dried over magnesium sulfate, filtered and the solvents were evaporated under reduced pressure. NMR analysis showed possible formation of the desired alcohol along with other isomer.

Hept-6-yn-1-ol (3.3) from hept-6-ynoic acid (3.4).

$LiAlH_4$ (500 mg, 13.2 mmol) was added to an anhydrous THF (20 mL) under nitrogen atmosphere at 0 °C. A solution of 6-heptynoic acid (828 mg, 6.5 mmol) in dry THF (5 ml) was added dropwise to the mixture with vigorous stirring. The mixture was then allowed to warm to room temperature and stirred for an additional hour. 1M solution of hydrochloric acid (20 ml) was added dropwise and the reaction mixture stirred for 30 min before being diluted with Et_2O (20 mL). Layers were separated and aqueous layer extracted with Et_2O (3 x 20 m). The organic layers were combined, dried over $MgSO_4$, and then filtered. Solvent was removed under reduced pressure and the crude residue was purified by column chromatography on silica gel affording 720 mg (98%) of pure hept-6-yn-1-ol (**3.3**) as clear colorless oil. NMR ^1H: solvent is $CDCl_3$, (δ, ppm): 3.67-3.63 (t, J = 6.4Hz, 2H), 2.23-2.19 (td, J_1 = 6.4Hz, J_2 = 2.4Hz, 2H), 2.03 (br. s, 1H), 1.97-1.95 (t, J = 2.4Hz, 1H), 1.61-1.54 (m, 4H), 1.51-1.45 (m, 2H).

((2-Diethyltriazenylphenyl)ethynyl)trimethylsilane (3.6).[2]

Palladium(II) complex (1.3 g, 1.85 mmol, 2% mol) and copper(I) iodide (1.06 g, 5.54 mmol, ca. 6 mol. %) were added to a stirred degassed with argon solution of the 3.5 (28 g, 92.4 mmol) in THF (250 mL) under an inert atmosphere. After 10 min of stirring, trimethylsilyl acetylene (11.77 g, 120.12 mmol, 16.8 mL) was added followed by triethylamine (50 mL). The reaction vessel was purged with argon, sealed and left with stirring overnight. TLC indicated on complete conversion of the starting material. Reaction mixture was filtered through 1 cm layer of the silica gel, solvent was evaporated and residue was subjected to the column chromatography on silica gel (5% of EtOAc in hexanes). Yield of the ((2-diethyltriazenylphenyl)ethynyl)trimethylsilane (**3.6**) was 24.7 g (98%). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.45-7.48 (m, 1H), 7.36-7.39 (m, 1H), 7.21-7.26 (m, 1H), 7.00-7.05 (td, J_1 = 7.5 Hz, J_2 = 1.2 Hz, 1H), 3.75-3.79 (q, J = 7.2 Hz, 4H), 1.30 (t, J = 7.2 Hz, 6H), 0.24 (s, 9H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 152.83, 133.25, 129.07, 124.54, 118.59, 116.80, 103.59, 97.82, 49.05, 41.83, 14.45, 11.32, 0.11.

((2-Iodophenyl)ethynyl)trimethylsilane (3.7).[4]

A solution of **3.6** (24.7 g, 90.6 mmol) in methyl iodide (80 mL) was placed into the steel pressure vessel, sealed, and subjected to heating at 135 °C overnight. After cooling, then reaction mixture was diluted with hexane to precipitate byproduct and filtered. Solvents were evaporated under reduced pressure and residue was subjected to the column chromatography on silica gel (hexanes–5% of EtOAc in hexanes) to give 19.1 g (70%) of pure ((2-iodophenyl)ethynyl)trimethylsilane (**3.7**) as yellowish oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.84-7.82 (d, J = 8Hz, 1H), 7.48-7.46 (d, J = 7.6Hz, 1H), 7.29-7.26 (t, J = 7.6Hz, 1H), 7.01-6.97 (t, J = 8Hz, 1H), 0.29 (s, 9H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 138.7, 132.7, 129.6, 129.5, 127.6, 106.5, 101.2, 98.8, -0.19.

6-(2-(Trimethylsilyl)ethynyl)phenyl)hex-5-yn-1-ol (3.8a).[12]

Bis(triphenylphosphine)palladium dichloride (597 mg, 0.85 mmol, ca. 2 mol. %) was added to a stirred solution of **3.7** (12.8 g, 42.5 mmol) in absolute THF (150 mL) under inert atmosphere. The solution was degassed with a strong flux of argon, and powdered copper (I) iodide (0.491 g, 2.56 mmol, ca. 6mol. %) was added to the mixture. After 5 minutes of stirring, 5-hexyn-1-ol (5 g, 51 mmol) was added, followed by triethylamine (30 mL). The reaction vessel was purged with argon, sealed and left with stirring for 24 hours. GC/MS analysis showed complete conversion of the starting material. Then the reaction mixture was filtered through 1 cm layer of the silica gel with 50% of EtOAc in hexanes as eluent. Solvents were evaporated under reduced pressure. Crude mixture was purified by column chromatography on silica gel (5–50% of EtOAc in hexanes) yielding 9.7g (85%) of the pure 6-(2-(trimethylsilyl)ethynyl)phenyl)hex-5-yn-1-ol (**3.8a**) product as slightly yellowish oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.45-7.43 (d splitted further, 1H), 7.39-7.37 (d splitted further, 1H), 7.24-7.17 (m, 2H), 3.72-3.69 (t, J = 6.2 Hz, 2H), 2.53-2.50 (t, J = 6.2 Hz, 2H), 1.78-1.70 (m, 5H), 0.27 (s, 9H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 132.41, 132.02, 128.37, 127.46, 126.91, 125.58, 104.05, 98.10, 94.53, 79.79, 62.57, 32.14, 25.23, 19.61, 0.25. MS: 270 (M+, 27), 255 (20), 227 (13), 209 (15), 197 (27), 179 (34), 165 (54), 153 (35), 129 (12), 73 (100).

7-(2-((Trimethylsilyl)ethynyl)-phenyl)hept-6-yn-1-ol (3.8b).

3.8b was prepared using the same procedure in 50% yield as colorless oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.435-7.43 (d splitted firther, 1H), 7.39-7.37 (d splitted further, 1H), 7.25-7.18 (m, 2H), 3.69-3.66 (t, 2H), 2.50-2.47 (t, 2H), 1.71-1.54 (m, 6H), 0.27 (s, 9H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 132.1, 131.8, 128.1, 127.1, 126.8, 125.4, 103.8, 97.8, 94.5, 79.3, 62.8, 32.3, 28.6, 25.1, 19.6, 0.03. High res. MS: $MH^+ - H_2O$ (18): 267.1568 (found), 267.1564 (calc.).

6-(2-Ethynylphenyl)hex-5-yn-1-ol (3.9a).

To a stirred solution of **3.8a** (5.815 g, 21.54 mmol) in methanol (50 mL) potassium carbonate (3.262 g, 23.64 mmol) was added and reaction mixture was left with stirring for 30 min. Then the reaction mixture was poured into mixture of ammonium chloride and water and extracted with diethyl ether (20 mL). Organic layer was separated; aqueous solution was extracted with diethyl ether (3 x 15 mL). Combined organic solution was washed with water twice, dried over magnesium sulfate, filtered, and solvents were evaporated under reduced pressure. Residue was purified by column chromatography on silica gel (20–50% of EtOAc in hexanes) yielding 3.554 g (83%) of pure 6-(2-ethynylphenyl)hex-5-yn-1-ol (**3.9a**) as a colorless oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.49-7.47 (dd, J_1 = 1Hz, J_2 = 7.4 Hz, 1H), 7.41-7.39 (dd, J_1 = 1Hz, J_2 = 7.4 Hz, 1H), 7.29-7.20 (m, 2H), 3.73-3.70 (t, J = 6.4 Hz, 2H), 3.31 (s, 1H), 2.54-2.51 (t, J = 6.4 Hz, 2H), 1.84-1.77 (m, 2H), 1.75-1.68 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 132.77, 132.13, 128.70, 127.54, 127.13, 124.58, 94.70, 82.74, 80.81, 79.68, 62.66, 32.00, 25.09, 19.58. MS: 198 (M+, 3), 197 (5), 183 (7), 178 (20), 170 (52), 165 (59), 152 (67), 141 (100), 139 (96), 128 (29), 115 (43), 102 (5), 89 (22).

7-(2-Ethynylphenyl)hept-6-yn-1-ol (3.9b).

Compound **3.9b** was prepared using the same procedure in 95% yield as yellowish oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.48-7.46 (d, J = 7.6Hz, 1H), 7.40-7.38 (d, J = 7.6Hz, 1H), 7.27-7.19 (m, 2H), 3.68-3.65 (t, J = 5.6 Hz, 2H), 2.50-2.47 (m, 2H), 1.68-1.55 (m, 7H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 132.5, 131.9, 128.4, 127.2, 127, 124.4, 94.7, 82.5, 80.6, 79.3, 62.8, 32.3, 28.4, 25, 19.5. High res. MS: MH^+: 213.1273 (found), 213.1274 (calc.).

6-(2-(Iodoethynyl)phenyl)hex-5-yn-1-ol (3.10a).

To a stirred solution of iodine (9.119 g, 35.9 mmol) in absolute benzene (90 mL) morpholine (6.462 mL, ca. 6.462 g, 71.8 mmol) was added. The mixture was heated at 45 °C for 30 min with stirring. A solution of 6-(2-trimethylsilanylethynyl-phenyl)-hex-5-yn-1-ol (3.5539 g, 17.95 mmol) in absolute benzene (10 mL) was added to the stirred suspension of the iodine-morpholine complex, and the reaction mixture was stirred at 45 °C for 2.5 hours. After cooling to room temperature, the reaction mixture was diluted with ethyl acetate and washed with aqueous sodium tiosulfate solution (2 x 30 mL) and brine (70 mL), aqueous layer was extracted with ethyl acetate (4 x 30 mL), combined organic layer was dried over magnesium sulfate, filtered and solvents were evaporated under reduced pressure. The residue was subjected to column chromatography on silica gel (10–30% of EtOAc in hexanes) affording one main fraction (one spot on the TLC plate) which contained 6-(2-(iodoethynyl)phenyl)hex-5-yn-1-ol (**3.10a**) 5.22 g (90%) and by-product of iodinated into alkyl chain as yellowish oil. This mixture was introduced into the following reaction without further separation due to the identical R_f of both compounds.

7-(2-(Iodoethynyl)phenyl)hept-6-yn-1-ol (3.10b).

3.10b was prepared using the same procedure as a mixture of **3.10b** and by-product of iodination into the alkyl chain as yellowish oil.

6-(2-(Iodoethynyl)phenyl)hex-5-ynal (3.11a).

To a stirred solution of **3.10a** (5.22 g, 16.11 mmol) in dichloromethane (200 mL) powdered PCC (4.52 g, 20.94 mmol) was added. The reaction mixture was left for overnight stirring and then filtered through 5 cm layer of the silica gel using dichloromethane or EtOAc in hexanes as eluent. Solvents were evaporated under reduced pressure; residue was subjected to the column chromatography on silica gel (20–50% of Et_2O in hexanes). Two major fractions were obtained:

pure 6-(2-(iodoethynyl)phenyl)hex-5-ynal (**3.11a**) 3.04 g (59% over two steps) as slightly yellowish oil and product of iodination into α-position of alkyl chain 1.03g. The yield was increased up to 72% over two steps by decreasing of the reaction time to 30 min. NMR ^{1}H spectra of **3.11a**: solvent is $CDCl_3$, (δ, ppm): 9.90 (s, 1H), 7.43-7.41 (d splitted further, 1H), 7.39-7.37 (m, 1H), 7.26-7.20 (m, 2H), 2.80-2.76 (td, J_1 = 7.2Hz, J_2 = 1.2Hz, 2H), 2.59-2.56 (t, J = 6.8 Hz, 2H), 2.00-1.93 (quin, J_1 = 7.2 Hz, J_2 = 6.8Hz, 2H). NMR ^{1}H of by-product: solvent is $CDCl_3$, (δ, ppm): 9.45 (d, 1H), 7.42 (m, 1H), 7.40 (m, 1H), 7.25 (m, 2H), 4.98 (t spl. further, 1H), 2.8-2.61 (dm, 2H), 2.35-2.17 (dm, 2H).

7-(2-(Iodoethynyl)phenyl)hept-6-ynal (3.11b).

3.11b was prepared using the same procedure in 48% over two steps as slightly yellowish oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 9.83-9.82 (t, 1H), 7.42-7.37 (m, 2H), 7.25-7.21 (m, 2H), 2.56-2.51 (m, 4H), 1.94-1.86 (quin, 2H), 1.73-1.66 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 202.7, 132.8, 131.8, 128.7, 127.5, 126.0, 94.3, 93.4, 79.8, 43.7, 28.3, 21.6, 19.6.

5,6,11,12-Tetradehydro-7,8,9,10-tetrahydro-benzo-[10]annulene-7-ol (3.12a).

To the thoroughly degassed with a strong flux of argon freshly distilled absolute THF (600 mL) a chromium dichloride (1.34 g, 10.98 mmol) and nickel dichloride (cat. amount) were added with vigorous stirring under argon atmosphere at room temperature. A solution of **3.11a** (589 mg, 1.83 mmol) in absolute THF was added dropwise to the suspension. The reaction mixture was stirred at room temperature for 2 hours. After that period TLC indicated on the complete conversion of the starting material. The reaction mixture was diluted with diethyl ether (200 mL) and hexane (50 mL), washed with ammonium chloride (100 mL) and brine (80 mL), aqueous solution was extracted with diethyl ether (2 x 40 mL), combined organic solution was dried over magnesium sulfate, and solvents were evaporated under reduced pressure. Purification was

performed by column chromatography on silica gel (20–50% of EtOAc in hexanes) yielding 319 mg (89%) of pure 5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo-[10]annulene-7-ol (**3.12a**) as colorless oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.39-7.37 (d splitted further, 1H), 7.33-7.31 (d splitted further, 1H), 7.28-7.21 (m, 2H), 4.67-4.63 (m, 1H), 2.51-2.48 (m, 2H), 2.24-2.09 (m, 3H), 1.97-1.95 (d, J = 6Hz, 1H), 1.86-1.77 (m, 1H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 129.8, 128.5, 128.3, 128.1, 128.08, 127.3, 63.4, 38.0, 23.7, 21.3. DIP/MS: 196 (M+, 32), 195 (24), 178 (70), 165 (31), 152 (53), 139 (100).

5,6,12,13-tetradehydro-8,9,10,11-tetrahydro-7*H*-benzo[11]annulene-7-ol (3.12b).

3.12b was prepared using the same procedure in 70% yield as white crystals. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.39-7.37 (d splitted further, 1H), 7.35-7.33 (d, J = 6.4Hz, 1H), 7.27-7.19 (m, 2H), 4.77-4.74 (m, 1H), 2.56-2.52 (m, 2H), 2.21 (br s, 1H), 2.15-2.08 (m, 1H), 2.04-1.97 (m, 1H), 1.92-1.80 (br m, 2H), 1.70-1.60 (m, 2H). MS: 210 (M+, 20), 192 (100), 181 (38), 165 (92), 153 (61), 152 (70), 139 (68), 128 (15), 115 (39), 102 (4), 89 (18), 77 (14).

5,6,11,12-Tetradehydro-7,8,9,10-tetrahydro-benzo-[10]annulene-7-one (3.1a). To a stirred solution of **3.12a** (319 mg, 1.63 mmol) in dichloromethane (25 mL) Dess-Martin periodinane (1.38 g, 3.26 mmol) was added. The reaction mixture was left with stirring for 3 hours and then was diluted with diethyl ether and filtered through 0.5 cm layer of the silica gel. Solvents were evaporated under reduced pressure and rest was subjected to the column chromatography on silica gel (toluene) yielding 202.8 mg (64%) 5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo-[10]annulene-7-one (**3.1a**) as slightly yellowish oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.52-7.50 (d, *J* = 7.2Hz, 1H), 7.43-7.38 (m, 2H), 7.32-7.27 (m, 1H), 2.92-2.89 (m, 2H), 2.63-2.60 (m, 2H), 2.22-2.16 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 187.90, 131.48, 130.93, 130.83,

128.42, 127.67, 125.36, 100.58, 95.44, 96.21, 81.88, 46.43, 25.43, 22.02. DIP/MS: 194 (M+, 9), 165 (40), 138 (42), 88 (19), 70 (40), 61 (47), 45 (100).

5,6,12,13-Tetradehydro-8,9,10,11-tetrahydro-7*H*-benzo[11]annulene-7-one (3.1b).

3.1b was obtained using the same procedure in 90% as white crystals. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.55-7.53 (d, *J* = 7.2Hz, 1H), 7.40-7.36 (m, 2H), 7.31-7.27 (m, 1H), 2.55-2.52 (m, 2H), 2.49-2.47 (m, 2H), 2.35-2.28 (m, 2H), 1.79-1.72 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 189.88, 132.41, 130.86, 129.61, 129.46, 127.79, 124.99, 98.66, 93.68, 90.49, 81.43, 43.64, 28.49, 23.07, 19.91. High res. MS: MH^+: 209.0960 (found), 209.0961(calc.).

3,4-Dihydroanthracen-1(2*H*)-one (3.13a).

A solution of **3.1a** (33 mg, 0.17 mmol) in isopropanol (10 mL) was heated at 75 °C in the sealed pressure vessel for two days. Then isopropanol was evaporated under reduced pressure and residue was subjected to the column chromatography on silica gel (10–50% of EtOAc in hexanes) affording 18.3 mg (55%) of white crystals of 3,4-dihydroanthracen-1(2*H*)-one (**3.13a**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 8.61 (s, 1H), 7.95-7.93 (d, *J* = 8.4 Hz, 1H), 7.79-7.77 (d, *J* = 8.4Hz, 1H), 7.67 (s, 1H), 7.57-7.53 (t splitted further, 1H), 7.48-7.44 (t splitted further, 1H), 3.14-3.11 (t, *J* = 6.4Hz, 2H), 2.77-2.73 (t, *J* = 6.4Hz, 2H), 2.22-2.16 (quin, *J* = 6,4Hz, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 199.02, 139.50, 136.10, 131.92, 130.94, 130.17, 129.03, 128.80, 127.29, 126.93, 126.17, 39.91, 30.25, 23.55. High res. MS: MH^+: 197.0960 (found), 197.0961 (calc.) M.P. 92 °C.

7,8,9,10-Tetrahydro-6*H*-cyclohepta[*b*]naphthalene-6-one (3.13b).

Enediyne **3.1b** (12 mg, 0.057 mmol) was dissolved in the mixture of benzene and 1,4-cyclohexadiene (5/1) and heated in the steel pressure vessel for 12 days at 150 °C. After that the solvents were removed under reduced pressure and residue was subjected to the column

chromatography on silica gel (10–30% of diethyl ether in petroleum ether). The purification afforded 7.4 mg (61%) of **7**,8,9,10-tetrahydro-6*H*-cyclohepta[*b*]naphthalene-6-one (**3.13b**) as yellowish solid. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 8.21 (s, 1H), 7.92-7.90 (d, J = 8Hz, 1H), 7.81-7.79 (d, J = 8Hz, 1H), 7.63 (s, 1H), 7.56-7.52 (t splitted further, 1H), 7.49-7.45 (t splitted further, 1H), 3.08-3.05 (t, J = 6.4 Hz, 2H), 2.81-2.78 (m, 2H), 1.98-1.92 (m, 2H), 1.86-1.80 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 206.75, 137.75, 136.74, 135.23, 131.70, 129.31, 129.23, 127.96, 127.65, 127.05, 126.00, 40.82, 32.43, 25.94, 20.99. High res. MS: MH^+: 211.1122 (found), 211.1117 (calc.).

Attempted synthesis of 7-methoxy-5,6,11,12-tetradehydro-9,10-dihydro-benzo-[10]annulene (3.14).

To a stirred solution of sodium hydride (27.6 mg, 1.149 mmol) in absolute THF (40 mL) solution of **3.1a** (202.8 mg, 1.045 mmol) in small amount of absolute THF and few drops of 15-crown-5 were added under argon atmosphere at -78 °C. Reaction mixture was left for 30 min with stirring at the temperature and then methyl iodide (890 mg, 6.27 mmol, 0.39 mL) was added, temperature was raised to ~ -30 °C and was left with stirring for one hour, then cold bath was removed and reaction mixture was stirred for another hour. After that period TLC analysis showed complete conversion of the starting material. Reaction mixture was quenched with saturated ammonium chloride solution (3 mL), extracted with ethyl acetate (3 x 20 mL), washed with water and brine solution, combined organic solution was dried over magnesium sulfate, filtered, and solvents were evaporated under reduced pressure. Column chromatography was performed on the silica gel (toluene) affording one major fraction of 92 mg of the mixture **3.15**.

Preparative thermal cycloaromatization of 3.1a with addition of NaOH.

The concentration of **3.1a** was 5 x 10^{-2} M (136 mg in 14 mL of isopropanol and aqueous sodium hydroxide), the concentration of sodium hydroxide was 1.3 x 10^{-1} M. After addition of sodium hydroxide to the solution of **3.1a** in isopropanol the color changed to the brown instantly. Reaction was heated at 60 °C with stirring for one hour. After cooling to the room temperature, mixture was diluted with ethyl acetate and washed with saturated solution of ammonium chloride till pH 7 and then with water and brine. Combined organic solution was dried over magnesium sulfate and solvents were evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (10–50% of ethyl acetate in hexanes). Three major fractions were obtained: 9-hydroxy-3,4-dihydroanthracen-1(2*H*)-one (**3.17**) 7.2 mg (4.9%), 86 mg (58%) of 5,6-didehydro-7,8,9,10,11,12-hexahydro-benzo-[10]annulene-10,12-dione (**3.18**), 29 mg (19.6%) of 6-(2-ethynylphenyl)hex-5-ynoic acid (**3.19**). 9-Hydroxy-3,4-dihydroanthracen-1(2*H*)-one (**3.17**) NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 8.39-8.37 (d, *J* = 8 Hz, 1H), 7.67-7.64 (d, *J* = 8Hz, 1H), 7.61-7.57 (t splitted further, 1H), 7.46-7.43 (t, *J* = 8.4Hz, 1H), 7.06 (s, 1H), 3.05-3.02 (m, 2H), 2.78-2.73 (m, 2H), 2.18-2.11 (m, 2H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 205.15, 163.26, 138.29, 137.41, 132.46, 130.36, 126.84, 124.99, 124.40, 123.80, 116.26, 39.04, 30.21, 23.02. High resolution MS: calculated M^+ = 212.0837, found M^+ = 212.0827. 5,6-didehydro-7,8,9,10,11,12-hexahydro-benzo-[10]annulene-10,12-dione (**3.18**): NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 8.04-8.02 (d splitted further, 1H), 7.49-7.46 (m, 1H), 7.42-7.38 (m, 2H), 4.35 (s, 2H), 2.60-2.57 (m, 4H), 2.32-2.27 (m, 2H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 203.71, 193.82, 138.44, 132.63, 130.09, 128.49, 128.01, 122.87, 99.87, 84.93, 58.03, 42.91, 26.90, 20.35. High resolution MS: calculated M^+= 212.0837, found M^+ = 212.0830. 6-(2-Ethynylphenyl)hex-5-ynoic acid (**3.19**) NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 7.49-7.47 (d, *J* = 7.2 Hz, 1H), 7.41-

7.39 (d, *J* = 7.2Hz, 1H), 7.29-7.21 (m, 2H), 3.32 (s, 1H), 2.69-2.65 (m, 2H), 2.60-2.56 (t, *J* = 6.8Hz, 2H), 1.99-1.92 (m, 2H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 179.32, 132.48, 131.80, 128.46, 127.43, 126.71, 124.52, 93.11, 82.46, 80.71, 80.19, 32.65, 23.46, 18.93. High resolution MS: calculated M^+= 212.0837, found M^+ = 212.0841.

3.4.3 Kinetic Studies

Rate measurements were performed using either Varian Carry 300 UV-Vis spectrometer equipped with a thermostatable cell holder or HPLC HP series 1100. Enolization rates were measured using GC/MS equipped with DIP on Shimadzu GC-2010 or NMR spectroscopy using Varian Mercury 500 MHz spectrometer. Each measurement was repeated not less than three times. The temperature was controlled with 0.1°C of accuracy. Integral intensities of the signals were normalized when DIP analysis was used. Observed first-order rate constants were calculated by least-squares fitting of the data to a single exponential function. The nonlinear least square fitting calculations were conducted using OriginPro 8 by OriginLab. The consumption of the starting material and formation of product was followed by TLC or HPLC (Shimadzu SCL-10A VP, equipped with HibarR RT250-4, RP-18).

3.5 References

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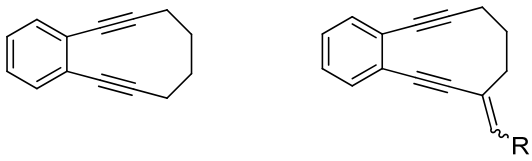
CHAPTER 4

INFLUENCE OF SUBSTITUENTS' ELECTRONIC EFFECTS ON THE RATE OF BERGMAN CYCLIZATION IN SERIES OF METHYLIDENE DERIVATIVES OF 10-MEMBERED CYCLIC ENEDIYNES

4.1 Synthesis, Thermo-Chemistry and Kinetic Studies of Methylidene-Derivatives of 10-Membered Cyclic Enediynes

As it was shown in Chapter 1, the electronic effects of the substituents have great influence on the rate of the Bergman cyclization.[1,2] Although there are some reports regarding the electronic effects of the substituents in the enediyne core,[3,4] the electronic effects of the substituents at the exo-cyclic double bond connected to the acetylenic carbon of the enediynes were not well studied. This project was designed to investigate how the presence of a conjugated exo-cyclic double bond with electron-withdrawing and electron-donating groups affects the rate of cycloaromatization. As we described in Chapter 3, the endo-cyclic double bond enhances the rate of Bergman cyclization of enediynes producing more ring strain and lowering the *cd* distance between acetylenic termini. In the case of a conjugated exo-cyclic double bond, we expected an increase of the cycloaromatization rate because of either ring strain due to the out of plain π-system or electron density of the extended π-conjugation. The introduction of the electron-donating and electron-withdrawing groups through the exo-cyclic double bond of the enediynes and measuring the rates of their cyclization would help us to distinguish between the effect of the ring strain and the electronic effects of the substituents. For these purposes, compounds **4.1** through **4.6** were envisioned, and we attempted to synthesize them. The ten-

membered cyclic enediyne **4.1** represents a "parent" enediyne lacking a conjugated exo-double bond. Enediynes **4.2** and **4.3** possesses electron-withdrawing groups, while **4.4**, **4.5**, and **4.6** contain electron-donating groups attached to the exo-cyclic double bond (Figure 4.1).



4.1

R = CN, **4.2** R = CH_2 **4.5**
R = CO_2Et, **4.3** R = CH_2OMe **4.6**
R = nBu, **4.4**

Figure 4.1 Target compounds.

Enediynes containing electron withdrawing groups (**4.2** and **4.3**) have been synthesized from keto-enediyne **3.1a** utilizing the Horner-Wadsworth-Emmons olefination (HWE olefination).[5] If the conventional Wittig reaction was used in these cases, then "stabilized" ylides, where the electron-withdrawing groups stabilize a negative charge on the carbon atom, would form, requiring higher reaction temperatures. Thus, phosphonates with the appropriate electron-withdrawing groups were used to produce **4.2** and **4.3**. The HWE olefination[6] has three advantages over a Wittig reaction: (1) phosphonate carbanions are more nucleophilic than the corresponding phosphorous ylides, so milder conditions are needed to react with ketones; (2) hindered ketones, unreactive in Wittig reaction, react readily in HWE olefination; and (3) the byproduct, dialkyl phosphonate, is water-soluble, making it easier to separate on work-up.

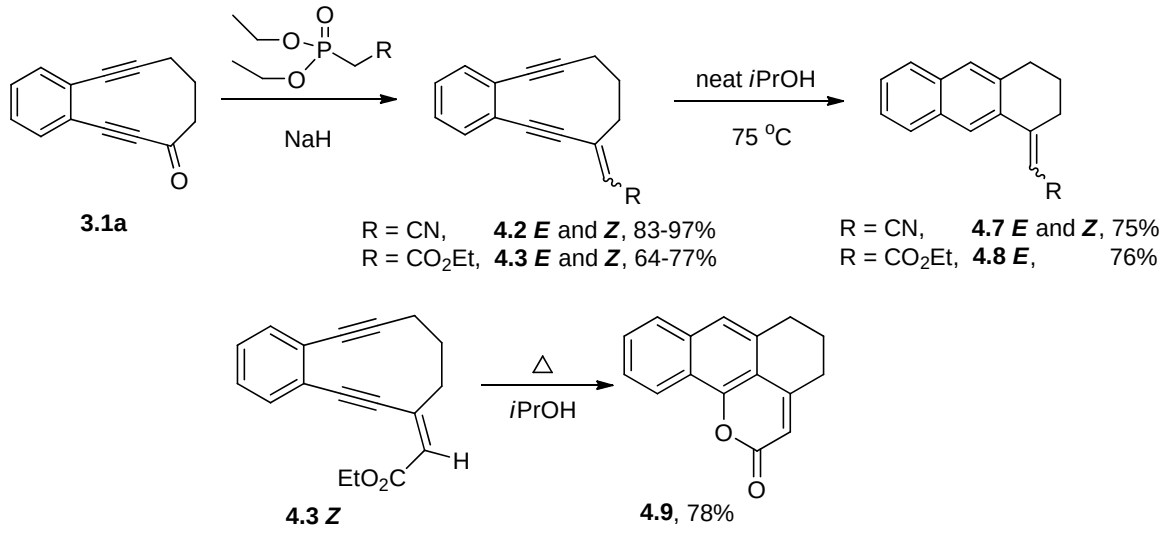


Figure 4.2 Synthesis and cycloaromatization of *E* and *Z* isomers of **4.2** and **4.3**.

Both cyano- and carboethoxy-derivatives were obtained as separable *E* and *Z* isomers. In case of **4.2**, more of the *E* isomer was formed as expected. Surprisingly, the reaction of **3.1a** with ethyl 2-(diethoxyphosphoryl)acetate produced predominantly the *Z* isomer (**4***Z*). The synthesis of keto-enediyne **3.1a** is described in Chapter 4. The cycloaromatization products were isolated from preparative thermolysis and fully characterized. The cyanomethylidene-derivative **4.2** produced cycloaromatized product **4.7** when heated in neat isopropanol as a hydrogen donor. A similar result was obtained in the case of **4.3***E*. When **4.3***Z* was heated in isopropanol, surprisingly, no formation of the expected product was detected, but tetra-cyclic compound **4.9** was produced (Figure 4.2). Its structure was confirmed by NMR, HRMS, and X-Ray spectroscopy.

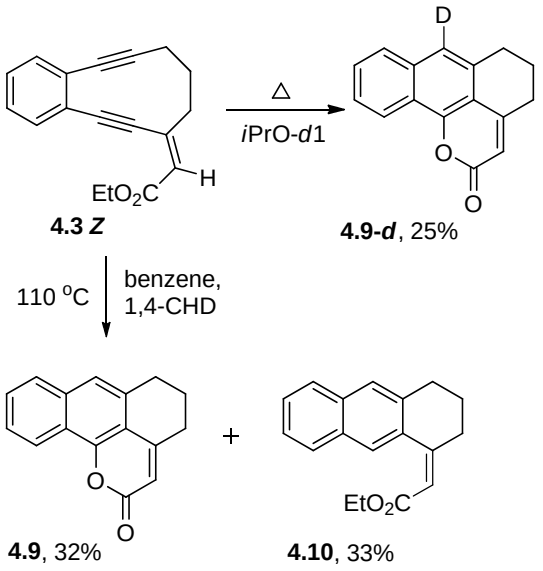


Figure 4.3 Cyclization of **4.3***Z* under various conditions.

In order to determine if the mechanism of cyclization is radical or polar, reactions were carried out in different solvents (Figure 4.3). The cyclization experiment in mono-deuterated isopropanol (2-propanol-d_1) as a hydrogen/deuterium donor provides a good method for distinguishing between radical and polar pathways. If this cyclization goes through a Bergman radical mechanism, *p*-benzyne diradical is expected to preferentially abstract protium from the secondary carbon of 2-propanol-d_1, because the C-H bond of a methine group is much weaker than the O-D bond. Since only the deuterium insertion product (**4.9-*d***) was formed, the mechanism has to be polar and involve a deuteron transfer from a more acidic OD group. The reaction in 2-propanol-d_1 proceeded much slower than in conventional isopropanol, and by the time reaction was stopped, unconverted starting material was still presented in the mixture. The experiment in dry benzene with addition of 1,4-CHD produced tetracyclic compound **4.9** along with a typical product of cycloaromatization **4.10** in a 1:1 ratio, suggesting that the mechanism varies based on the solvents. The mechanism is polar in neat isopropanol, and partially radical in non-polar aprotic benzene/1,4-CHD.

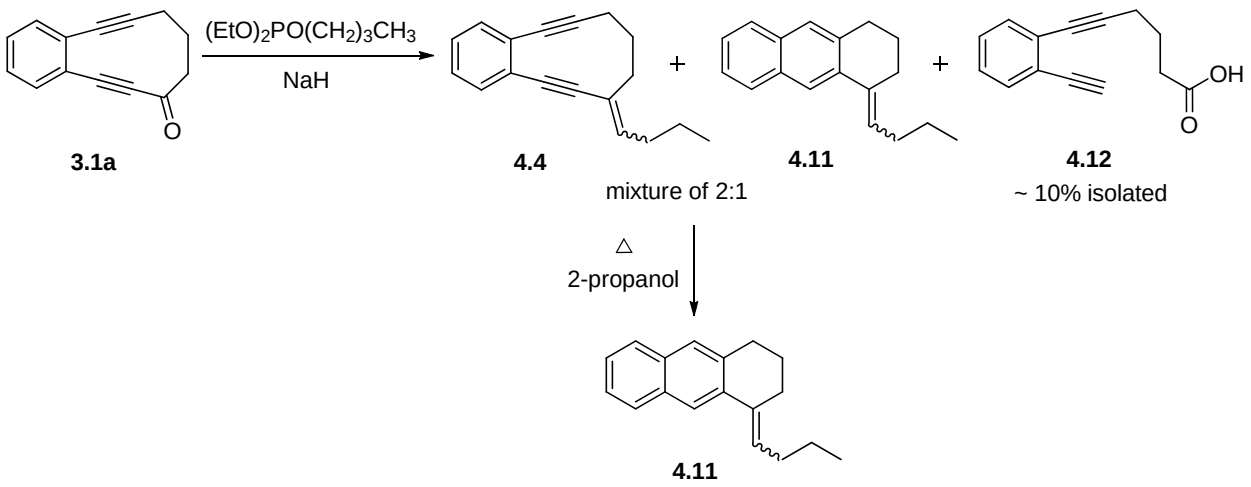


Figure 4.4 Synthesis and cycloaromatization of butylidene-derivative **4.4**.

The Wittig reaction was used to synthesize enediynes with electron-donating groups (**4.4** and **4.6**) and the methylidene derivative **4.5**. When attempting to introduce a butylidene group onto **3.1a**, three major products were obtained. A 2:1 inseparable mixture of targeted enediyne **4.4** and its cyclization product **4.11** was isolated along with 10% of 6-(2-ethynylphenyl)hex-5-ynoic acid (**4.12**) (Figure 4.4). The mixture of uncyclized enediyne and cyclized product was heated in isopropanol and expected Bergman cyclization product **4.11** was produced.

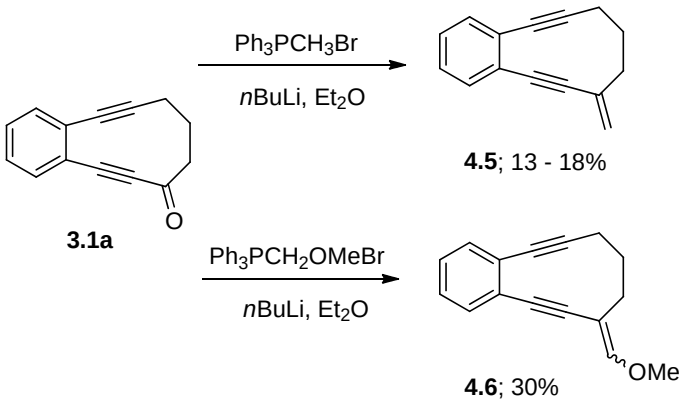


Figure 4.5 Attempted synthesis of methylidene- and methoxymethylidene-derivatives (**4.5** and **4.6**).

The reaction of keto-enediyne **3.1a** with methyltriphenylphosphonium bromide yielded a methylidene derivative **4.5**, which appeared to be unstable even at low temperatures. The reaction was scaled-up, column chromatography was used to purify the enediyne **4.5**. As soon as the solvents were evaporated under reduced pressure at room temperature, a brown colored polymer film was formed in the flask which partially dissolved in deuterated chloroform but precipitated after a few minutes in the NMR tube. The resulting polymer was not soluble in THF or in DMSO.

The methoxymethylidene-derivative **4.6** appeared to be more stable, but after isolation it still cyclized overnight at a low temperature.

We were curious how introducing an aromatic group to investigate how it would affect the rate of the Bergman cyclization. Compounds **4.15** and **4.17** were proposed for this purpose (Figure 4.6).

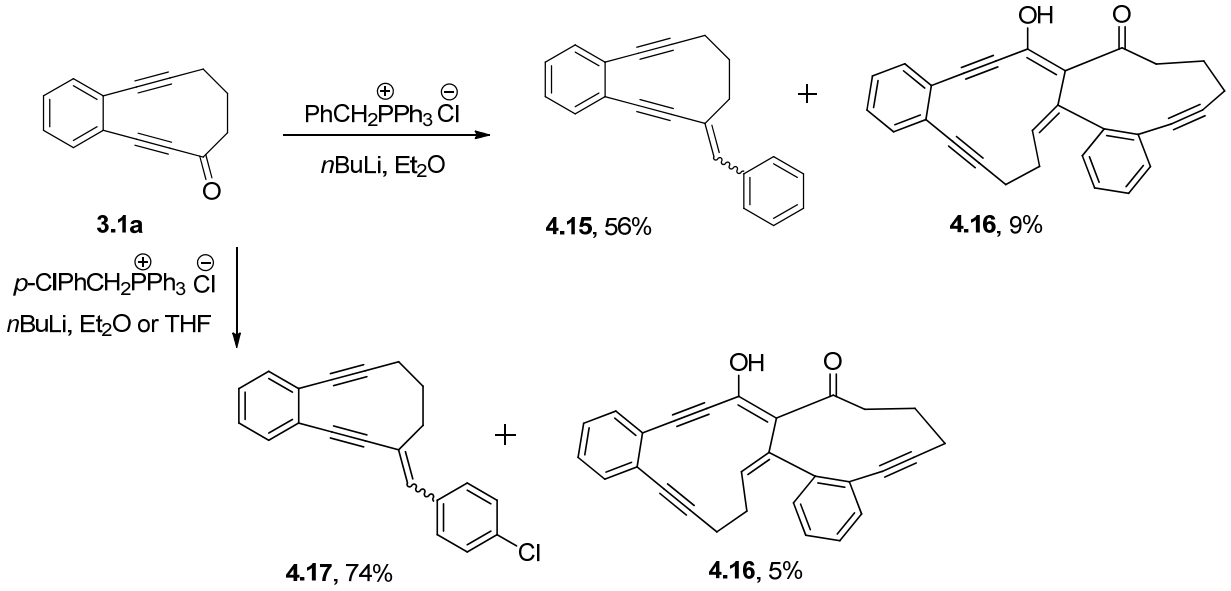


Figure 4.6 Synthesis of benzylidene- and *p*-chlorobenzylidene-derivatives **4.15** and **4.17**.

The Wittig reaction of keto-enediyne **3.1a** with benzyltriphenylphosphonium chloride most likely produced **4.15** as an inseparable mixture of two isomers (*E* and *Z*) in moderate yield.

This finding was confirmed by NMR, HPLC and HRMS; the ^{13}C NMR spectrum looks rather complicated due to the presence of two isomers. The byproduct of this reaction was found to be polycyclic compound **4.16** as it was confirmed by NMR, HRMS, and X-Ray analysis. Since **4.16** was obtained as a minor product, the mechanism of its formation was not studied. A similar result was obtained in the case of **4.17**. The Wittig reaction produced the major product as a mixture of *E* and *Z* isomers (**4.17**) and a minor byproduct **4.16** (Figure 4.7).

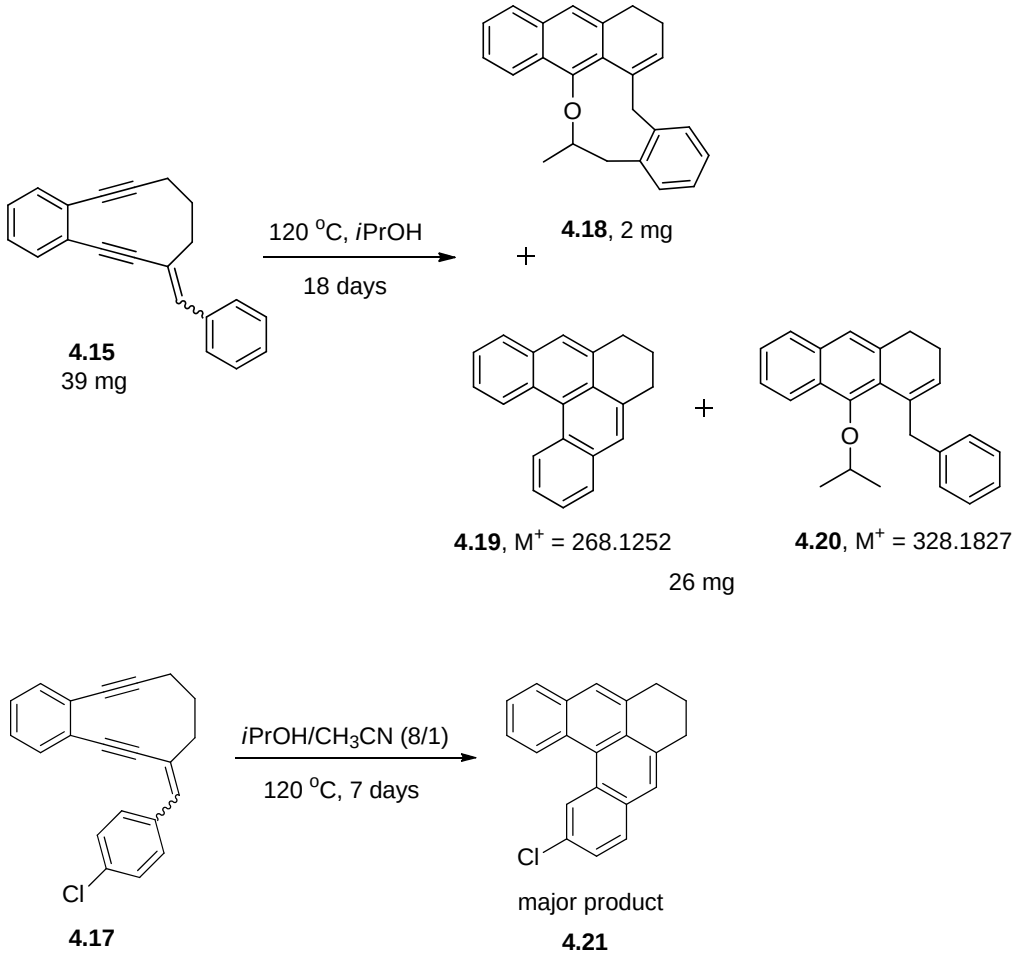


Figure 4.7 Thermo-chemistry of **4.15** and **4.16**.

After heating the benzylidene-derivative **4.15** in isopropanol at 75 °C for two days, the only traces of new compounds were observed according to the NMR spectroscopy. So, **4.15** was heated for 18 days at 120 °C, while the reaction was monitored by TLC and GC/MS. This

reaction produced a complicated mixture which was separated. One of the separated products was a compound with the proposed structure of **4.18**. It was confirmed by NMR ^{1}H, ^{13}C, and DEPT, but HRMS analysis showed no peak with the molecular weight of the proposed compound but rather M^{+2} peak. The major fraction contained a mixture of three inseparable compounds. According to the GC/MS, HPLC and NMR H^{1} analysis, it might contain 7,8-dihydro-6*H*-naphtho[3,2,1-*de*]anthracene (**4.19**), 4-benzyl-10-isopropoxy-1,2-dihydroanthracene (**4.20**), and another unidentified compound (Figure 4.7). No expected product of Bergman cyclization was found in the reaction mixture.

The *p*-chlorobenzylidene derivative was heated at 120 °C for 7 days. The reaction produced an inseparable mixture of two compounds as a major product. One of these compounds has been identified as 2-chloro-7,8-dihydro-6H-naphtho[3,2,1-de]anthracene (**4.21**).

Since thermal reactions of **4.15** and **4.17** have not produced expected products of Bergman cyclization, they were not considered for further studies.

We decided to obtain 10-membered cyclic benzo-fused enediyne **4.1** in order to compare its reactivity to the methhylidene derivatives. Enediyne **4.1** does not have an exo-double bond in its core and is considered as a parent enediyne without substitution.

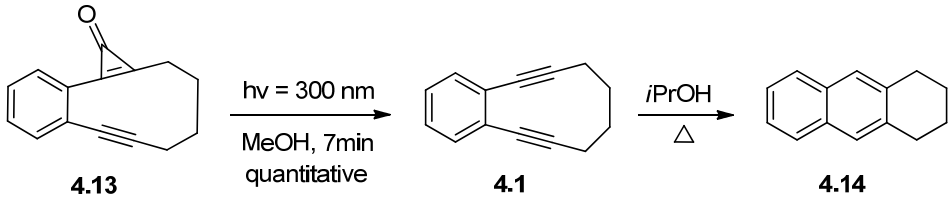


Figure 4.8 Synthesis and cyclization of parent enediyne **4.1**.

Enediyne **4.1** was obtained by photolysis of the cyclopropenone-containing compound **4.13** (Figure 4.8). Irradiation at 300 nm in methanol produced **4.1** with good yield. We have chosen this approach since compound **4.13** was already available in our laboratory.[7] Masked

enediyne **4.13** was previously obtained by the low temperature selective mono-addition of the dichlorocarbene to **4.1**. Parent enediyne **4.1** was heated in isopropanol in order to isolate the cyclization product.

The UV spectroscopy and HPLC methods were found to be the most efficient for the kinetic studies of the obtained enediynes. The accurate rate measurements of the cyclization of the *E* isomer of **4.2** in neat 2-propanol at 75 °C were conducted using UV spectroscopy, following the decay of the characteristic 310 nm band of **4.2***E* (Figure 4.9). The represented data fits well to a single exponential equation (the reaction followed the first-order equation). The data obtained from this exponential function shows that the rate of the cycloaromatization at 75±0.1 °C was k = (1.19±0.046) x 10^{-5} sec^{-1}. Thus, the enediyne **4.2***E* underwent Bergman cyclization reaction with a lifetime of ca. 23 h at 75 °C in isopropanol (Figure 4.10). The rate of the Bergman cyclization for a *Z* isomer of **4.2** was found to be similar to **4.2***E* ((1.60±0.085) x 10^{-5} s^{-1}) under the same conditions. All measurements were performed at least three times and conditions were kept constant.

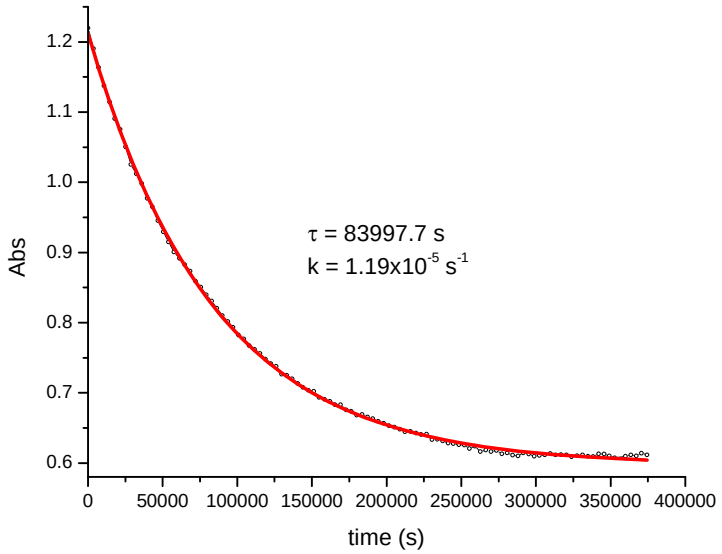


Figure 4.9 Kinetic traces of enediyne **4.2***E* observed at 310 nm, 75 °C in neat 2-propanol.

A kinetic experiment with **4.2***Z* in deuterated isopropanol-d_8 was performed to determine whether there is a kinetic isotope effect (KIE) of this reaction. The rate of cyclization of **4.2***Z* was found to be 1.57 x 10^{-5} s^{-1}, which is similar to the cyclization rate in conventional isopropanol. This result demonstrates the absence of any kinetic isotope effects (KIE = $k_H/k_D \sim 1$), proving that hydrogen abstraction is not the rate limiting step while Bergman cyclization is.

HPLC and UV spectroscopy methods were employed to find rates of cyclization for both isomers of **4.3**. The rate of cycloaromatization for **4.3***E* was found to be (6.0±0.268) x 10^{-6} s^{-1} in neat isopropanol at 75 °C. The rate of cyclization of *Z*-carboethoxy-derivative **4.3***Z* into tetra-cycle **4.9** was studied using NMR spectroscopy, HPLC, and UV spectroscopy methods. *Z* isomer of **4.3** reacts slower than *E* isomer, but the reason for that fact remains unclear, as does a mechanism of cyclization. Summary of the kinetic data is shown in Table 4.1.

Derivative	λ, nm	Average k, s^{-1}	k, s^{-1}	Conditions	C of derivative, M
E-carboethoxy **4.3** *E*	310	$(6.0\pm0.268)\times10^{-6}$	6.03×10^{-6}	2-propanol, 75 °C	$C = 7.2\times10^{-5}$
			5.72×10^{-6}		
			6.26×10^{-6}		
Z-carboethoxy **4.3** *Z*	309	1.60×10^{-6}		2-propanol, 75 °C	$C = 4.19\times10^{-4}$
E-cyano **4.2** *E*	310 and 270	$(1.19\pm0.046)\times10^{-5}$	1.19×10^{-5}	2-propanol, 75 °C	$C = 7.19\times10^{-5}$
			1.15×10^{-5}		
			1.24×10^{-5}		
Z-cyano **4.2** *Z*	310	$(1.60\pm0.085)\times10^{-5}$	1.614×10^{-5}	2-propanol, 75 °C	$C = 7.16\times10^{-5}$
			1.5128×10^{-5}		
			1.6814×10^{-5}		
Z-cyano **4.2** *Z*	309	1.57×10^{-5}		2-propanol-d_8, 75 °C	$C = 7.16\times10^{-5}$

Table 4.1 Summary of the kinetic data of methylidene-derivatives.

The cyclization rate of the parent enediyne **4.1** was followed using gas chromatography; the experiment was performed at 75 °C in neat isopropanol. The curve fits well to a single exponential equation (the reaction followed the first-order equation). The rate of cyclization was found to be $k = (2.829\pm0.377) \times 10^{-6}$ s^{-1}. The comparison of this rate to the enediynes with electron-withdrawing groups reveals that the reaction is slower for parent enediyne **4.1**, therefore

methylidene-derivatives cyclizes faster than enediyne with no substitution at the acetylenic carbon atom. Thus, we showed that the presence of conjugated exo-cyclic double bond in the enediyne core increases the rate of Berman cyclization.

Kinetic studies were not performed for the compounds with electron-donating substituents (**4.4** and **4.6**) and the methylidene derivative **4.5** due to their thermal instability. The methylidene-derivative **4.5** polymerized without a solvent at room temperature during a work-up procedure. The buthylidene-derivative **4.4** got partially cyclized in the reaction mixture upon formation.

4.2 Conclusions

It was found that when a conjugated exo-cyclic double bond was introduced into the enediyne core the Bergman cyclization proceeded faster. The electronic effects of the extended π-system play a major role in this enhancement in the rate. Kinetics of the enediynes with electron-donating substituents connected to the enediyne core through the conjugated exo-double bond were not studied due to their thermal instability. These compounds underwent Bergman cyclization quickly, therefore their isolation was impossible. Enediynes with electron-withdrawing groups cyclized slower than those with electron-donating groups. The absence of any kinetic isotope effects indicates that hydrogen abstraction is not a rate limiting step.

Cyclization of the *Z* isomer of the carboethoxymethylidene derivative **4.3** produced unexpected product tetra-cycle **4.9**. Its cyclization rate was lower than the cyclization rate of the parent enediyne without an exo-double bond **4.1**. Mechanism of the formation of **4.9** remains unclear at this time, but our results suggest that this reaction in 2-propanol proceeds via a polar mechanism.

Benzylidene-derivatives **4.15** and **4.17** have not produced the expected products of the conventional Bergman cyclization, and therefore, they were not further studied.

4.3 Experimental Section

4.3.1 Materials and Instruments

All oxygen- and moisture-sensitive reactions were carried out under an inert atmosphere in the oven-dried glassware. Solvents for moisture-sensitive reactions were distilled prior to usage. All commercially available materials were used without purification unless otherwise stated. TLC analyses were performed using aluminum-backed silica gel TLC plates. Chromatographical separation and purification of the reaction products were performed using standard grade flash chromatography silica gel (40-63 μm particle size) or premium grade flash chromatography silica gel (40-75 μm particle size). All NMR spectra were recorded in deuterated chloroform on Varian Mercury 400 MHz or 500 MHz spectrometers with tetramethylsilane (TMS) as an internal standard. ^{1}H-NMR chemical shifts (δ) are reported in parts per million (ppm) versus the TMS reference, ^{13}C-NMR chemical shifts (δ) are reported in ppm versus the residual solvent peak reference. The IR spectra were recorded on a Shimadzu IRPrestige-21 FTIR instrument. GC/MS data were collected using Shimadzu GC-2010 equipped with a SHR5XLB column. High resolution mass spectra analyses were performed by the Mass Spectrometry Laboratory, University of Georgia at Athens, GA. HPLC data were collected on a HP series 1100; X-Ray analysis was performed by the X-Ray Laboratory, University of Georgia at Athens, GA.

4.3.2 Experimental Synthetic Procedures

7-Cyanomethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.2).

To a suspension of sodium hydride (0.0371 g, 60% dispersion in mineral oil, 0.928 mmol), washed with distilled hexane, in an anhydrous THF (10 mL) cooled to 0 °C diethyl cyanomethylphosphonate (137 mg, 0.773 mmol, 0.12 mL) was added under an argon atmosphere and a mixture was stirred for 15 min at the temperature. 5,6,11,12-Tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene-7-one (**3.1a**) (100 mg, 0.52 mmol) was added to the mixture at 0 °C and stirred for one hour at the temperature. Then reaction was warmed up to room temperature and left with stirring for another five hours. Reaction was monitored by TLC, which showed presence of two compounds, one of which had the same R_f as R_f of the starting material **3.1a**. The reaction mixture was then diluted with diethyl ether (20 mL) and treated with brine (2 x 10 mL). The aqueous layer was further extracted with diethyl ether (2 x 10 mL). Combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered, and the solvents were evaporated under reduced pressure. Residue was subjected to the purification by column chromatography on silica gel (5–10% of EtOAc in hexanes). Separation of *E* and *Z* isomers yielded 60 mg (53%) of pure (*E*)-7-cyanomethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.2** *E*) as white crystals and 50 mg (44%) of pure (Z)-7-cyanomethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.2** *Z*) as yellowish oil, making it total amount of 110 mg (97%).

(*E*)-7-Cyanomethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.41-7.39 (d splitted further, 1H), 7.37-7.31 (m, 2H), 7.29-7.25 (m, 1H), 5.42 (s, 1H), 2.93-2.91 (m, 2H), 2.56-2.53 (m, 2H), 2.13-2.07 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 147.46, 130.31, 129.67, 129.16, 128.47, 127.62, 126.96, 116.35,

101.37, 100.38, 100.18, 95.97, 81.97, 35.91, 28.22, 21.61. (*Z*)-7-Cyanomethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.52-7.50 (d splitted further, 1H), 7.36-7.27 (m, 3H), 5.41 (s, 1H), 2.70-2.67 (m, 2H), 2.53-2.50 (m, 2H), 2.09-2.03 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 147.46, 130.20, 129.68, 129.65, 128.30, 127.67, 127.01, 116.70, 102.90, 100.09, 99.95, 94.24, 82.08, 38.21, 28.39, 21.54. High res. MS calculated 217.0891, found 217.0886.

2-(3,4-Dihydroanthracen-1(2*H*)-ylidene)acetonitrile (4.7).

A solution of 7-cyanomethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.2**) (20 mg) in isopropanol (8 mL) was heated at 85 °C for 48 hours. The reaction was monitored by TLC. The retention factor of the product was the same as the retention factor of the starting material, but spot on the TLC plate became fluorescent. Mixture was cooled to the room temperature and isopropanol was evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (5–10% of EtOAc in hexanes) yielding 15 mg (75%) of pure 2-(3,4-dihydroanthracen-1(2*H*)-ylidene)acetonitrile (**4.7**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 8.09 (s, 1H), 7.83-7.81 (d, J = 8.4 Hz, 1H), 7.75-7.73 (d, J = 8.4 Hz, 1H), 7.63 (s, 1H), 7.51-7.42 (m, 2H), 5.92 (s, 1H), 3.05-2.97 (2t, 4H), 2.00 (qu, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 159.60, 136.07, 134.50, 131.88, 130.62, 128.47, 127.57, 127.23, 127.00, 125.98, 124.21, 117.95, 91.60, 31.13, 30.36, 22.87. High res. MS calculated 219.1048, found 219.1042.

7-Carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.3).

To a suspension of sodium hydride (85 mg, 60% dispersion in mineral oil, 1.438 mmol), washed with distilled hexanes, in an anhydrous THF (15 mL) cooled to 0 °C ethyl 2-

(diethoxyphosphoryl)acetate (248 mg, 1.106 mmol, 0.2 mL) was added under argon atmosphere and mixture was stirred for 15 min at the temperature. 5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene-7-one (**3.1a**) (143 mg, 0.737 mmol) was added to the mixture at 0 °C and stirred for one hour at the temperature. Then reaction was warmed up to room temperature and left for stirring for another four hours. The reaction mixture was then diluted with diethyl ether (25 mL) and washed with brine (15 mL) twice. The aqueous layer was further extracted with diethyl ether (2 x 15 mL). Combined organic extracts were washed with water (10 mL) and brine (10 mL), and dried over magnesium sulfate. Drying agent was filtered out and solvents were evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (3–10% of EtOAc in hexanes) yielding 20 mg (20%) of pure (*E*)-7-carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.3** *E*) as yellow oil and 130 mg (67%) of (*Z*)-7-carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.3** *Z*) as white crystals. Total yield of the product was 150 mg (77%). (*E*)-7-Carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene NMR ^{1}H: $CDCl_3$ (δ, ppm): 7.39-7.33 (m, 2H), 7.30-7.22 (m, 2H), 5.99 (s, 1H), 4.21-4.16 (q, *J* = 7.2 Hz, 2H), 3.18-3.16 (m, 2H), 2.53-2.50 (t, 2H), 2.092.05 (m, 2H), 1.32-1.28 (t, *J* = 7.2 Hz, 3H). NMR ^{13}C: $CDCl_3$ (δ, ppm): 166.27, 143.31, 130.37, 129.14, 129.07, 128.69, 127.83, 127.66, 121.41, 100.46, 99.01, 97.80, 82.03, 60.41, 32.64, 29.06, 21.92, 14.48. MS: 264 (100, M+), 249 (25), 236 (13), 223 (19), 178 (15), 165 (18), 152 (12), 128 (14). (*Z*)-7-Carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene NMR ^{1}H: $CDCl_3$ (δ, ppm): 7.52-7.50 (d splitted further, 1H), 7.34-7.31 (t splitted further, 1H), 7.29-7.23 (m, 2H), 5.97 (s, 1H), 4.28-4.23 (q, *J* = 7.2 Hz, 2H), 2.71-2.68 (m, 2H), 2.51-2.48 (m, 2H), 2.11-2.05 (m, 2H), 1.36-1.33 (t, *J* = 7.2 Hz, 3H). NMR ^{13}C: $CDCl_3$ (δ, ppm) 165.28, 140.20,

129.98, 129.84, 129.09, 128.29, 128.08, 127.48, 122.05, 102.68, 99.73, 95.67, 82.21, 60.35, 39.06, 29.00, 21.64, 14.29.

5,6-Dihydrodibenzo[*de,h*]chromen-2(4H)-one (4.9). Cyclization of (*Z*)-7-carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.3 *Z*).

A solution of (*Z*)-7-carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.3** *Z*) (25.4 mg, 0.096 mmol) in 2-propanol (7 mL) was heated at 100 °C for six days and the reaction mixture was monitored by TLC and GC/MS. Upon completion, mixture was cooled to room temperature and isopropanol was evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel (3–20% of EtOAc in hexanes) affording 17.7 mg (78%) of 5,6-dihydrodibenzo[*de,h*]chromen-2(4*H*)-one (**4.9**) as yellowish crystals. NMR ^{1}H: $CDCl_3$ (δ, ppm): 8.50-8.48 (d, J = 8.4 Hz, 1H), 7.76 (d, J = 7.6 Hz, 1H), 7.61-7.52 (m, 2H), 7.43 (s, 1H), 6.27 (s, 1H), 3.09-3.06 (t, J = 6 Hz, 2H), 2.91-2.88 (t splitted further, 2H), 2.08-2.02 (q, J = 6 Hz, 2H). NMR ^{13}C: $CDCl_3$ (δ, ppm): 161.40, 155.33, 151.19, 134.90, 133.40, 128.94, 127.34, 126.35, 122.76, 122.18, 122.00, 113.24, 111.47, 30.71, 30.05, 22.60. Refer to appendix for X-ray data.

(*E*)-Ethyl 2-(3,4-dihydroanthracen-1(2*H*)-ylidene)acetate (4.8). Cyclization of (*E*)-7-carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.3 *E*).

(*E*)-7-Carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.3** *E*) (15 mg, 0.057 mmol) was heated in isopropanol at 100 °C for four days. After that, solvent was evaporated under reduced pressure and residue was subjected to the column chromatography on silica gel (3–60% of EtOAc in hexanes) affording 11.5 mg (76%) of (*E*)-

ethyl 2-(3,4-dihydroanthracen-1(2*H*)-ylidene)acetate (**4.8**). NMR ^{1}H: $CDCl_3$ (δ, ppm): 8.16 (s, 1H), 7.83-7.81 (d, *J* = 8.2 Hz, 1H), 7.75-7.73 (d, *J* = 8.2 Hz, 1H), 7.60 (s, 1H), 7.48-7.40 (m, 2H), 6.51-6.50 (t, *J* = 2 Hz, 1H), 4.27-4.21 (q, *J* = 7.2 Hz, 2H), 3.29-3.26 (t splitted further, 2H), 2.96-2.93 (t, *J* = 6.4 Hz, 2H), 1.92-1.89 (q, *J* = 6.4 Hz, 2H), 1.37-1.33 (t, *J* = 7.2 Hz, 3H). NMR ^{13}C: $CDCl_3$ (δ, ppm):166.96, 155.31, 137.58, 133.94, 133.45. 132.16, 128.44, 126.93, 126.90, 126.39, 125.54, 124.57, 113.56, 106.00, 59.78, 30.56, 28.63, 22.78, 14.42. MS: 266 (93, M+), 237 (15), 220 (100), 192 (41), 178 (52), 165 (28), 152 (10).

Cyclization of *Z*-7-carboethoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.3 *Z*) in 2-propanol-d_1.

Carboethoxy-derivative **4.3** *Z* (28 mg, 0.106 mmol) was dissolved in 5 mL of isopropanol-d_1, solution was degassed, sealed, and heated at 75 °C for 5 days. After that period TLC and GC/MS analyses indicated formation of new compound with M^+ = 237, corresponding to the deuterated tetra-cyclic compound **4.9**. Some amount of the starting material still was remained in the reaction mixture. The mixture was concentrated and subjected to the column chromatography on silica gel with 10–20% of EtOAc in hexanes affording two major compounds: 8 mg of the starting **4.3** *Z* and 6.2 mg (25%) of deuterated tetra-cycle (**4.9**). **4.9**: NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 8.52-8.50 (d, *J* = 8.2 Hz, 1H), 7.78 (d, *J* = 8.2 Hz, 1H), 7.62-7.54 (m, 2H), 6.29 (s, 1H), 3.11-3.08 (t, *J* = 6 Hz, 2H), 2.91 (t, *J* = 6 Hz, 1.36H), 2.07-2.03 (m, 2H).

7-Propylmethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.4).

To a suspension of sodium hydride (17 mg, 60% dispersion in mineral oil, 0.42 mmol) in an anhydrous THF (15 mL) cooled to 0 °C diethyl *n*-butylphosphonate (68 mg, 0.35 mmol, 0.69 mL) was added under an inert atmosphere and mixture was stirred for 15 min at the temperature. **3.1a** (40 mg, 0.206 mmol) was added to the mixture at 0 °C and stirred for one hour at the

temperature. Reaction mixture was warmed up to room temperature and left for stirring for another 3 hours. Reaction was monitored by TLC, which indicated two spots with quite different retention times. One of them had the same retention time as a starting material. The reaction mixture was then diluted with diethyl ether (25 mL) and treated with ammonium chloride solution and brine (2 x 15 mL). The aqueous layer was further extracted with diethyl ether (2 x 15 mL). The combined organic extracts were washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and the solvents were evaporated under reduced pressure. Residue was subjected to column chromatography on silica gel (5 – 50% of EtOAc in hexanes). Two major fractions were obtained. First fraction (6.4 mg) mixture of desired diyne product, 7-propylmethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.4**), and 1-butylidene-1,2,3,4-tetrahydroantracene. Second fraction (80 mg) contained a mixture of diethyl *n*-butylphosphonate and 6-(2-ethynylphenyl)hex-5-ynoic acid (3:1 respectively). NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): for 6-(2-ethynylphenyl)hex-5-ynoic acid 7.49-7.47 (d, splitted further, 1H), 7.41-7.39 (m, 1H), 7.29-7.21 (m, 2H), 3.32 (s, 1H), 2.65-2.61 (t, J = 7 Hz, 2H), 2.59-2.56 (t, J = 7 Hz, 2H), 1.98-1.92 (q, J = 7 Hz, 2H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 176.57, 132.67, 132.03, 128.65, 127.58, 127.04, 124.75, 93.64, 82.67, 80.94, 80.23, 32.80, 23.89, 19.23. NMR ^{31}P, solvent is $CDCl_3$, (δ, ppm): 33.85.

1-Butylidene-1,2,3,4-tetrahydroantracene (4.11). Cyclization of 4.4.

Mixture of two compounds from previous experiment (**4.1** and **4.11**) (6.4 mg) was heated at 120 °C in isopropanol for 24 hours. After that the solvent was evaporated under reduced pressure and residue material was purified by column chromatography on silica gel (15% of EtOAc in hexanes). Yield of pure 1-butylidene-1,2,3,4-tetrahydroanthracene (**4.11**) is 5.3 mg (82%). NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 8.71 (s, 1H), 7.98-7.96 (d, J = 7.6 Hz, 1H), 7.81-7.79 (d, J = 8.4

Hz, 1H), 7.71 (s, 1H), 7.61-7.57 (dt, J_1 = 1.2 Hz, J_2 = 7.2 Hz, 1H), 7.52-7.48 (t splitted further, 1H), 4.75-4.72 (m, 1H), 3.51-3.43 (m, 1H), 3.20-3.13 (m, 1H), 2.69-2.62 (m, 1H), 2.57-2.48 (m, 1H), 1.20-1.28 (m, 4H), 0.89-0.82 (m, 4H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 137.8, 136.0, 130.7, 130.0, 129.2, 127.2, 126.9, 126.3, 60.1, 32.5, 29.7, 29.6, 26.3, 22.7.

7-**Methoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.6).**

To a stirred solution of methoxymethyltriphenylphosphonium bromide (80.9 mg, 0.236 mmol) in absolute diethyl ether (10 mL) *n*-butyllithium (2.58 M solution in hexanes, 0.236 mmol, 0.09 mL) was added dropwise under inert atmosphere. The mixture was stirred for 30 min and then **3.1a** (45.7 mg, 0.236 mmol) in small amount of diethyl ether was added. Reaction mixture was left with stirring for 6 hours, and then for 12 hours with reflux in diethyl ether. After that period TLC indicated presence of starting material and two new compounds in the reaction mixture. Reaction mixture was diluted with ether/hexanes (3/1), washed with water and brine, aqueous layer was extracted with diethyl ether/hexanes (3/1) twice, combined organic solution was dried over magnesium sulfate, filtered and solvents were evaporated under reduced pressure. Crude mixture was separated and purified by column chromatography on silica gel (5–10% of EtOAc in hexanes). Three major fractions were isolated: 12.1 mg as the mixture of unknown compound and 7-methoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.6**); 13.3 mg (26%) of 7-methoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.6**); and 11.2 mg of the mixture of three compounds, probably, products of cyclization.

7-Methoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.6**): NMR ^{1}H spectrum: solvent is $CDCl_3$, (δ, ppm): 7.31 (m, 1H), 7.18 (m, 3H), 6.43 (s, 1H), 3.71 (s,

3H), 2.54 (m, 2H), 2.49 (m, 2H), 1.96 (m, 2H). 7-Methoxymethylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene decomposed during overnight at low temperature.

7-Methylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.5).

To a solution of methyltriphenylphosphonium bromide (145.3 mg, 0.407 mmol) in absolute diethyl ether (20 mL) *n*-butyllithium (2.85M, 0.407 mmol, 0.143 mL) was added dropwise at room temperature under inert atmosphere. The mixture was stirred for 30 min and then **3.1a** (78.9 mg, 0.407 mmol) in small amount of diethyl ether was added. The reaction mixture was left with stirring for 4 hours, after that period TLC analysis showed presence of starting material in the reaction mixture. Mixture was left with stirring for overnight, but after that time still not all starting material was converted. Reaction mixture was diluted with ether/hexanes mixture (3/1), washed with water and brine, aqueous layer was extracted with diethyl ether/hexanes mixture (3/1, 2 x 15 mL), combined organic solution was dried over magnesium sulfate, filtered, and solvents were evaporated under reduced pressure. Crude mixture was separated by column chromatography on silica gel (5–20% of EtOAc in hexanes) affording 45.7 mg of starting **3.1a** and 10 mg (13%) of 7-methylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**4.5**). NMR ^{1}H spectrum: solvent is $CDCl_3$, (δ, ppm): 7.37 (m, 1H), 7.33 (m, 1H), 7.23 (m, 2H), 7.25 (dd, 2H), 2.57 (m, 2H), 2.49 (m, 2H), 2.04 (m, 2H).

This reaction was repeated on the larger scale with 3 eq of the phosphonium ylide. The reaction time was 3 hours at ambient temperature. After that only one new compound was found in the reaction mixture which was purified by column chromatography on silica gel with 5–10% of EtOAc in hexanes. As soon as solvents were evaporated under reduced pressure at room temperature, brown colored polymer film was formed in the flask which partially dissolved in

deuterated chloroform but precipitated after a few minutes in NMR tube. This solid was not soluble in either THF or DMSO.

5,6,11,12-Tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (1.14).

Cyclopropenone 2,3-benzobicyclo[8.1.0]undec-1(10)-en-4-yn-11-one (**4.13**) (27 mg, 0.13 mmol) was dissolved in 75 mL of methanol and irradiated with 300 nm light for seven minutes. Then solvent was evaporated under reduced pressure, residue was subjected to the column chromatography on silica gel with 5% EtOAc in hexanes yielding 19.7 g (84%) of pure white crystalline solid 5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (**1.14**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.30 (m, 2H), 7.19 (m, 2H), 2.44 (m, 4H), 1.91 (m, 4H).[8]

7-Benzylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.15).

To a suspension of benzyltriphenylphosphonium chloride (204 mg, 0.526 mmol) in an anhydrous diethyl ether (10 mL) *n*-butyllithium (2.5M, 0.526 mmol, 0.2 mL) was added at room temperature under argon atmosphere and mixture was stirred for 30 min. **3.1a** (85 mg, 0.44 mmol) was added to the mixture and stirred for 3 hours. Reaction was monitored by TLC, which indicated on presence of the compound with the same R_f as for starting material and second compound with different retention factor R_f. The reaction mixture was then diluted with diethyl ether (20 mL) and washed with brine (2 x 10 mL). The aqueous layer was further extracted with ether (2 x 10 mL). The combined organic extract was washed with water (10 mL) and brine (10 mL), dried over magnesium sulfate, filtered and solvent was evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel with 10-30% of EtOAc in hexanes affording two major fractions: first fraction 66.1 mg (56%) contained two different compounds according to the HPLC, *E* and *Z* isomers (**4.15**). Second fraction 7.3 mg (9%) was tetracyclic keto-enol **4.16**. **4.15**: NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.91-7.89 (d, J = 7.6 Hz,

1H), 7.70-7.64 (m, 0.5H), 7.56-7.44 (m, 1.5H), 7.40-7.33 (m, 3H), 7.30-7.23 (m, 3H), 6.85 (s, 0.35H), 6.54 (s, 0.65H), 2.78-2.72 (m, 2H), 2.57-2.54 (m, 0.85H), 2.52-2.49 (m, 1.15H), 2.19-2.09 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 136.71, 136.45, 133.6, 132.66, 132.15, 132.05, 131.96 (d), 129.34 (d), 128.85, 128.74, 128.67, 128.57, 128.45, 128.36 (m), 128.27, 128.19, 128.09, 127.84, 127.77, 127.42 (d), 127.33, 123.31, 100.87, 100.18, 99.58, 98.02, 97.68, 92.24, 82.19, 82.12, 39.95, 31.89, 29.70, 29.56, 29.43, 21.80, 21.66. **4.16**: ^{1}NMR H: solvent is $CDCl_3$, (δ, ppm): 7.94-7.92 (dd, J_1 = 0.8 Hz, J_2 = 8 Hz, 1H), 7.54-7.50 (t splitted further, 2H), 7.42-7.38 (dt, J_1 = 0.8 Hz, J_2 = 8 Hz, 1H), 7.32-7.27 (m, 2H), 7.15-7.05 (m, 2H), 5.87-5.83 (dd, J_1 = 3.6 Hz, J_2 = 12 Hz, 1H), 3.65-3.57 (m, 1H), 2.83-2.68 (m, 3H), 2.66-2.52 (m, 3H), 2.51-2.40 (m, 1H), 2.37-2.31 (m, 1H), 2.29-2.23 (m, 1H), 2.00-1.91 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 197.73, 165.36, 141.83, 137.50, 137.13, 133.19, 132.38, 131.63, 130.66, 130.00, 127.75, 127.59, 126.88, 126.77, 123.67, 122.87, 121.23, 115.30, 96.95, 95.48, 94.97, 89.00, 85.24, 81.56, 33.79, 25.51, 25.35, 21.58, 19.79, 17.03. High res. MS calculated 268.1252, found 268.1254.

Cyclization of 4.15.

Enediyne **4.15** (39 mg, 0.146 mmol) was heated at 120 °C in isopropanol for 18 day (after 2 days of heating at the temperature no significant changes were observed). After that period solvent was evaporated and residue was subjected to the column chromatography on silica gel with 10–20% of EtOAc in hexane. Two major fractions were obtained: first fraction 26 mg represented three compounds according to the GC/MS and HPLC, and might contain 7,8-dihydro-6*H*-naphtho[3,2,1-*de*]anthracence (**4.19**), 4-benzyl-10-isopropoxy-1,2-dihydroanthracene (**4.20**) and some other unknown compound. Second fraction 2 mg contained just one compound, possibly compound with the structure of **4.18**. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 8.01-7.99 (d, J = 8

Hz, 1H), 7.72-7.70 (d, *J* = 8 Hz, 1H), 7.63 (s, 1H), 7.45-7.41 (m, 3H), 7.32-7.28 (m, 2H), 7.21-7.17 (m, 1H), 5.96-5.94 (t, *J* = 4.8 Hz, 1H), 4.23-4.19 (sx, *J* = 6.4 Hz, 1H), 3.92 (s, 2H), 3.38-3.26 (m, 2H), 3.15-3.08 (m, 1H), 3.02-2.95 (m, 1H), 2.39-2.34 (q, *J* = 6.4 Hz, 2H), 1.37-1.36 (d, *J* = 6.4 Hz, 3H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 140.29, 136.01, 134.83, 133.48, 132.73, 132.27, 130.44, 129.42, 129.20, 129.07, 128.59, 126.26, 126.05, 125.21, 124.16, 123.22, 122.83, 121.89, 69.01, 39.64, 37.81, 26.11, 23.87, 23.45. HSQC NMR spectrum supports that this compound is 15-methyl-7,8,15,16-tetrahydro-5*H*-anthra[9,1-*bc*]benzo[*f*]oxonine (**4.18**).

7-(*p*-Chloro)benzylidene-5,6,11,12-tetradehydro-7,8,9,10-tetrahydro-benzo[10]annulene (4.17).

This reaction was performed according to the procedure described above with the following quantities of the reagents: **3.1a** 55.3 mg, 0.285 mmol; *p*-benzyltriphenylphosphonium chloride 145 mg, 0.34 mmol; *n*BuLi 2.5M, 0.136 mL, 0.34 mmol; THF 10 mL. Reaction time was 2 hours after addition of ketone. TLC indicated presence of two major compounds in the reaction mixture. Column chromatography was performed on silica gel with 5–10% of EtOAc in hexanes. First fraction of 63.5 mg, 74% contained two compounds according to the HPLC, possibly E and Z isomers (**4.17**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.83-7.81 (d, J = 8.8 Hz, 1H), 7.44-7.42 (m, 0.5H), 7.38-7.36 (m, 0.5H), 7.34-7.30 (m, 3H), 7.27-7.22 (m, 2H), 7.18-7.15 (m, 1H), 6.76 (s, 0.4H), 6.46 (m, 0.6H), 2.73-2.69 (m, 2H), 2.56-2.52 (m, 0.9H), 2.51-2.48 (m, 1.1H), 2.15-2.06 (m, 2H). Second fraction of 5 mg represented **4.16**.

Cyclization of 4.17.

Enediyne **4.17** was heated at 120 °C in the mixture of isopropanol (8 mL) and acetonitrile (1 mL) for 7 days. Mixture was cooled down and solvents were evaporated under reduced pressure. Residue was subjected to the column chromatography on silica gel with 5–50% of EtOAc in

hexane. Major fraction of 13 mg represents at least two compounds, one of which might be a 2-chloro-7,8-dihydro-6*H*-naphtho[3,2,1-*de*]anthracence (**4.21**).

4.3.4 Kinetic Studies

Rate measurements were performed using either Varian Carry 300 UV-Vis spectrometer equipped with a thermostatable cell holder or by HPLC. Each measurement was repeated not less than three times. The temperature was controlled with 0.1°C of accuracy. Observed first-order rate constants were calculated by least-squares fitting of the data to a single exponential function. The nonlinear least square fitting calculations were conducted using OriginPro 8 by OriginLab. The consumption of the starting material and formation of product was followed by TLC or HPLC (Shimadzu SCL-10A VP, equipped with HibarR RT250-4, RP-18).

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CHAPTER 5

PHOTOCHEMICAL GENERATION OF ALLENES:

4-PHENYLBUTA-2,3-DIENAL

5.1 Synthesis and Photolysis of Allene-Aldehyde Precursor 2-(2-(3-Phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)cyclohexa-2,5-diene-1,4-dione

The mode of action of some families of enediyne natural products, such as the neocarzinostatin family, is somewhat different from the Bergman cyclization reaction. Upon activation, neocarzinostatin forms cyclic cumulene-enyne fragment followed by subsequent cycloaromatization (Chapter 1). C1–C6 cycloaromatization of eneyne-allene fragment calls Myers-Saito cyclization[1] (Figure 5.1). The cyclization preferentially proceeds in an exo-cyclic fashion on one side of the ring system and leads to the formation of a new C1-C6 bond along with a highly reactive 1,4-biradical. This biradical (Figure 5.1) is also capable of hydrogen abstraction from the sugar phosphate backbone of adjacent strands of DNA, causing scission of the DNA double helix. The major advantage of the Myers-Saito cyclization is that it usually requires lower temperature to proceed than the Bergman reaction, therefore allowing temporal control of the reactivity of enyne-allenes in biological media.

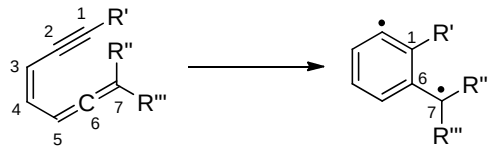

Figure 5.1 Myers-Saito cyclization.

We decided to look into possible modes of generation of the allene fragment necessary for the Myers-Saito reaction with future incorporation of allenes into the enyne core of the

molecule. This project focuses on photochemical generation of allene-containing compound. One of the ways to photochemicaly generate allenes is to mask the acetylenic fragment of alkyne-aldehyde with a photoremovable protective group (PPG) first and then upon irradiation with light recover an aldehyde moiety which is supposed to quickly rearrange into allene-aldehyde (Figure 5.2).[2]

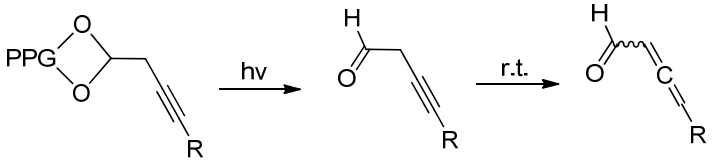

Figure 5.2 Generation of allenes.

We have chosen (2,5-dihydroxyphenyl)ethylene glycol acetal as a photolabile protecting group for the aldehyde moiety. It has been proven that this group can be efficiently cleaved and an aldehyde regenerated in good chemical yield upon irradiation with 300 nm light.[3] Figure 5.3 demonstrates model acetylenic compound **5.1** which was designed to test feasibility of generation of allene-aldehyde **5.3** from a stable precursor. The phenyl group has been chosen to simulate an aromatic part of benzofused enyne-allene that might be used in the future.

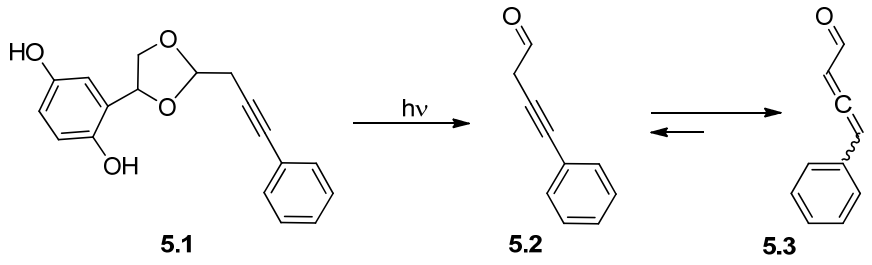

Figure 5.3 Proposed pathway to **5.3**.

Phenylacetylene derivative **5.1** was independently synthesized starting from 2,5-dimethoxybenzaldehyde **5.4** (Figure 5.4). Aldehyde **5.4** was converted into 2,5-dimethoxystyrene (**5.5**) under standard Wittig reaction conditions.[4] A double bond of **5.5** was hydroxylated with

sodium periodate in acetic acid under reflux, followed by hydrolysis of the resulting mixture of acetates with potassium carbonate in methanol.[5]

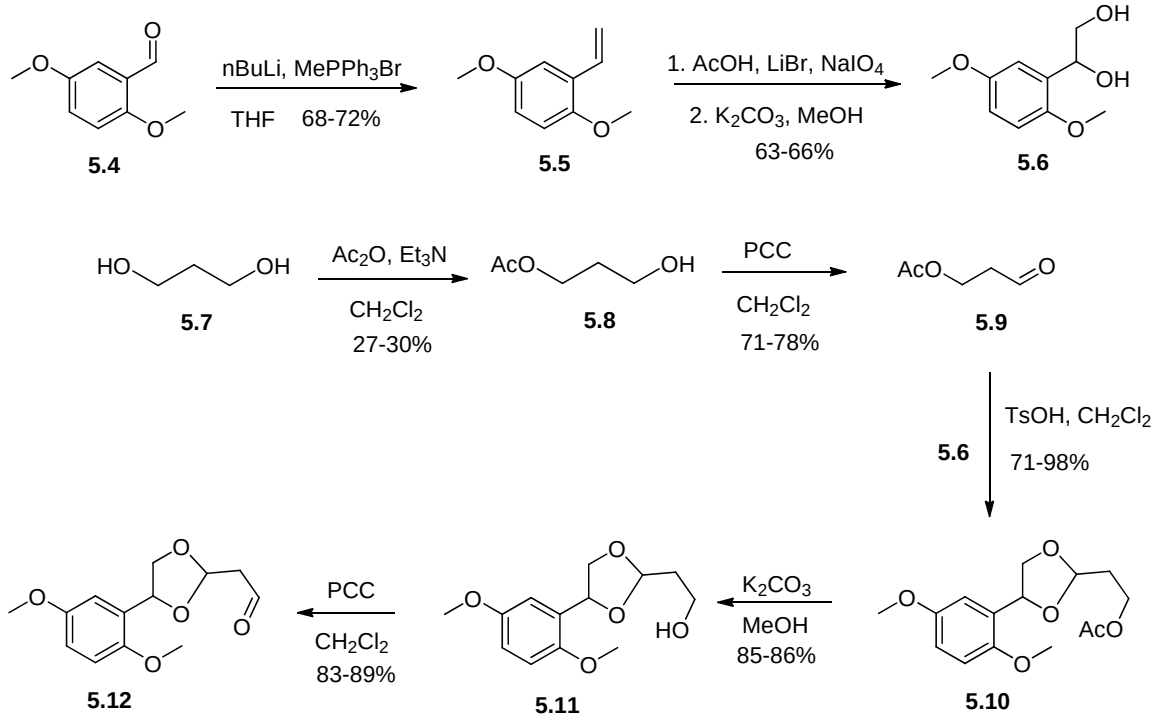

Figure 5.4 Synthesis of aldehyde **5.12**.

The synthesis of target compound **5.3** was carried out starting with 1,2-diol **5.6** (Figures 5.4). While other synthetic approaches were tested, it was found that the pathway shown in Figure 5.4 and 5.5 is the most successful one. Aldehyde **5.9**, which was necessary for the further functionalization, was obtained in two-steps. In the first step, one of the hydroxyl groups in 1,3-propanediol (**5.7**) was protected as an acetate. Then, the remaining hydroxyl group was oxidized into aldehyde **5.12** with PCC in dichloromethane.

Although the standard procedure of acid-catalyzed acetalization of aldehydes and ketones with glycol **5.6** often requires use of triethyl orthoformate,[3] the reaction between glycol **5.6** and aldehyde **5.9** gave acetal **5.10** without the triethyl orthoformate in excellent yield. Moreover, this reaction failed to produce **5.10** when either triethyl or trimethyl orthoformates were added. As

found by NMR analysis, 2-(4-(2,5-dimethoxyphenyl)-1,3-dioxolan-2-yl)ethyl acetate (**5.10**) was obtained as an inseparable mixture of two diastereomers. Next, an acetyl protective group was removed using potassium carbonate in methanol. Primary alcohol **5.11** was oxidized by PCC in dichloromethane gave aldehyde **5.12** in a good yield but as an inseparable mixture of two diastereomers in 1:2 ratio based on NMR and GC/MS analyses.

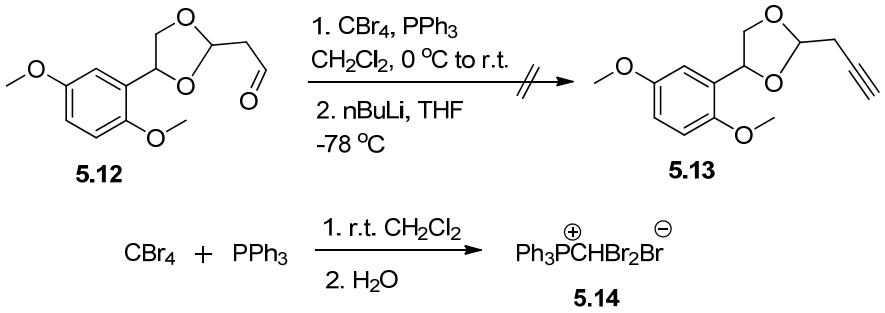

Figure 5.5 Synthesis of terminal acetylene derivative **5.13** and dibromomethyl-triphenylphosphonium bromide.

We attempted to convert the carbonyl group of **5.12** into a terminal acetylene by a Wittig–type reaction with carbon tetrabromide and triphenyl phosphine *via* the corresponding dibromo olefin, followed by elimination,[6] which is known to produce acetylene **5.13** (Figure 5.5). Unfortunately, the first reaction yielded a complicated mixture of at least three compounds. Perhaps, it was a mixture of products where at least partial loss of the acetal protective group occurred and the product of decomposition of initial aldehyde **5.12** were formed in the reaction. Thus, we decided to use a dibromomethyl-triphenylphosphonium bromide (**5.14**) reagent for the purpose of synthesis of **5.13**. It was obtained according to the literature procedure[7] (Figure 5.5).

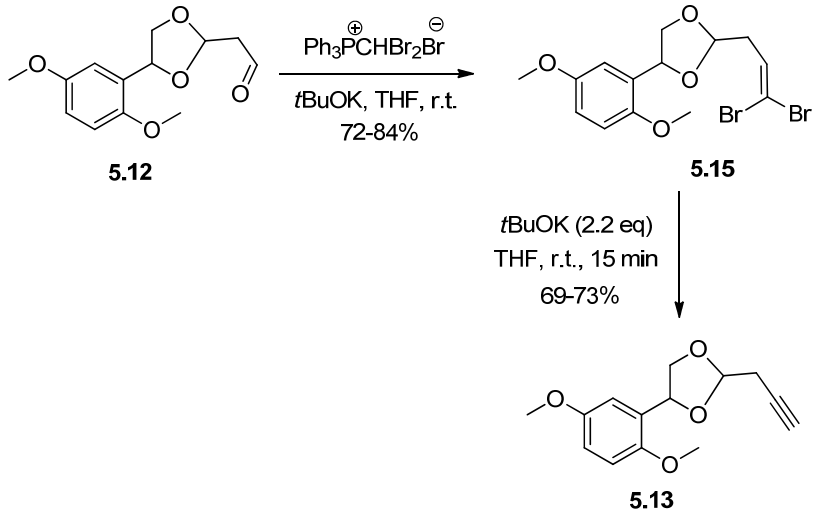

Figure 5.6 Synthesis of 5.13 employing dibromomethyl-triphenylphosphonium bromide.

The one-pot procedure[7] described in the literature was found to be less efficient for synthesis of **5.13** than a stepwise route. Isolation of dibromo olefine **5.15** and introduction into the reaction with potassium *tert*-butoxide led to the clean and rapid conversion. *n*-Butyl lithium could also be used in the second elimination reaction but better yields were obtained using potassium *tert*-butoxide.

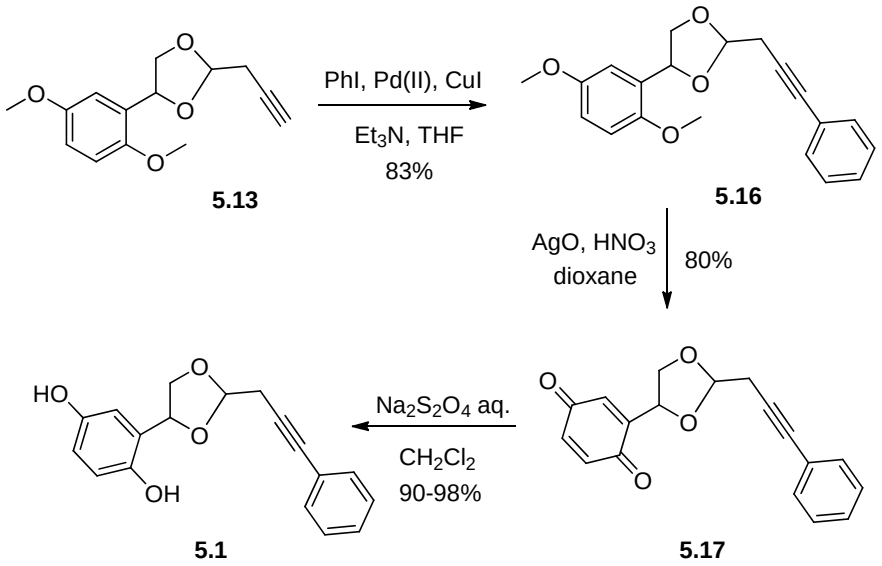

Figure 5.7 Synthesis of allene's precursor **5.1**.

The Sonogashira coupling[8] of acetylene **5.13** with phenyl iodide was used to introduce a phenyl group onto the molecule. Next, oxidative demethylation of the acetal **5.16** with silver oxide/nitric acid[9] produced 2-(2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)cyclohexa-2,5-diene-1,4-dione (**5.17**). Benzoquinone derivative **5.17** was then subjected to a mild reduction by sodium dithionite in a water–methylene chloride biphasic system[10] affording the target 2-(2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)benzene-1,4-diol (**5.1**).

Acetal **5.1** is stable in the dark in the solid state, as well as in the acetonitrile/water and methanol solutions. UV spectrum of this compound contains the characteristic band of 2,5-dihydroxybenzyl group at λ_{max} = 295 nm. The expected products of the uncaging reaction have virtually no absorption at this wavelength. Irradiation of 2.1 x 10^{-4} M solutions of **5.1** in various solvent systems, *viz*., MeOH-water (30:70), MeCN-water, water, and MeCN-water containing ca. 0.1M of ethyl vinyl ether, was performed. We used 300 nm light to irradiate **5.1** for 5 to 15 min. Irradiation resulted in the rapid bleaching of the 297 nm band and the formation of a new band at 265 nm (Figure 5.8). The release of photochemical products was monitored by HPLC or GC/MS. HPLC analysis of the reaction mixture indicated the presence of numerous by-products mostly from the chromophoric part of the molecule. When **5.1** was irradiated in 100% water, the photoproduct precipitated after 1 min resulting in a complicated mixture.

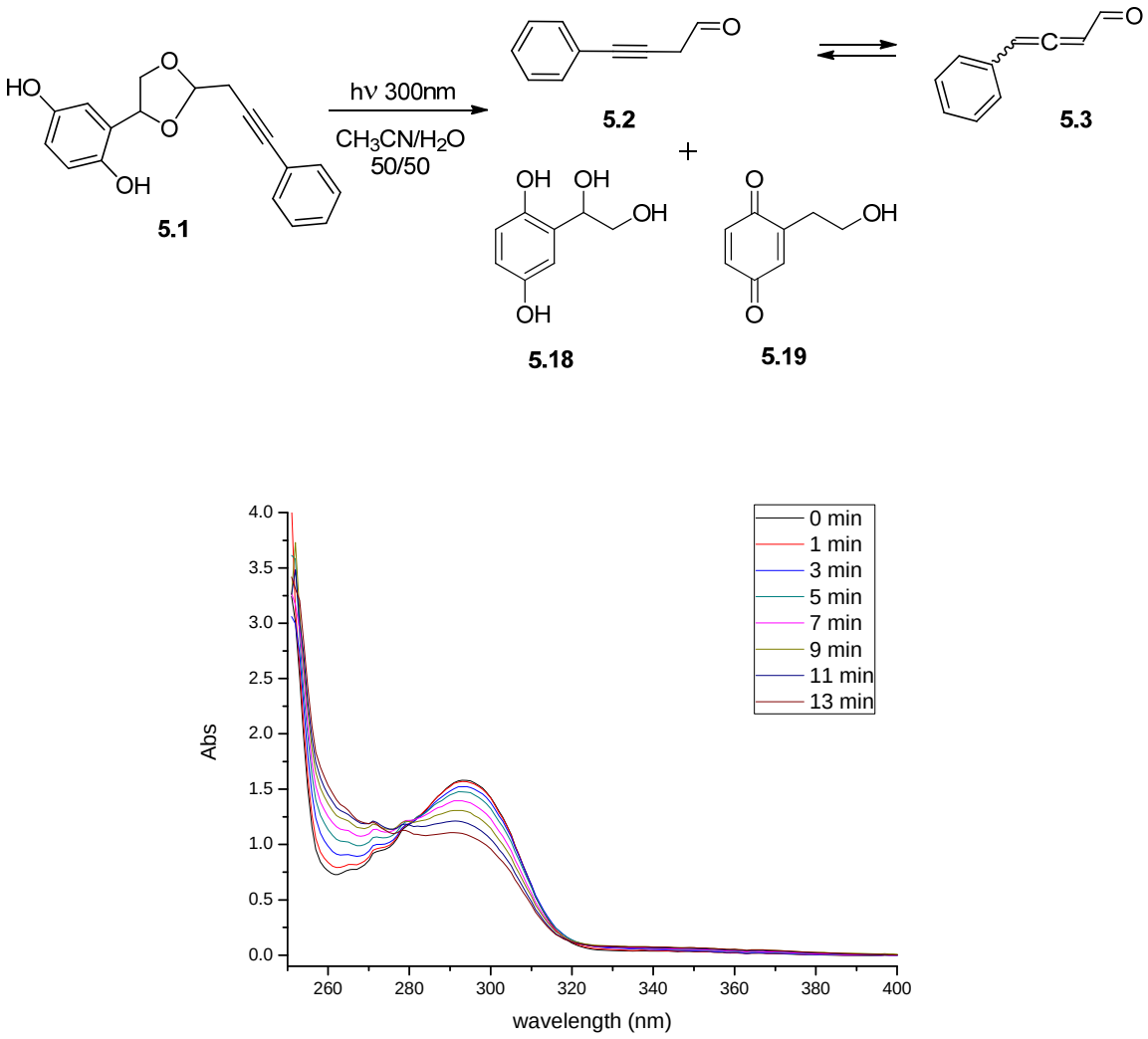

Figure 5.8 Irradiation of 2-(2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)benzene-1,4-diol in acetonitrile/water mixture.

It was found that the reaction in an acetonitrile/water (50:50) mixture (Figure 5.8) produces the cleanest result. At low conversions, there were two main products from the chromophore part: the rearranged *p*-quinone derivative **5.19** and the product of hydration **5.18**. Both products were identified by HPLC analysis. We had previously obtained similar compounds, so their UV spectra were compared to the UV spectra of **5.18** and **5.19**. Neither alkyne-aldehyde **5.2** nor allene-aldehyde **5.3** was identified using the HPLC method due to the complexity of the reaction mixture. GC/MS analysis of the mixture after photolysis indicates the

presence of both alkyne-aldehyde **5.2** and allene-aldehyde **5.3**, presumably formed from **5.2**. These conclusions were made based on the comparison of the GC/MS data for these compounds to the chromatograms of **5.2** and **5.3** recently synthesized in our laboratory. Alkyne-aldehyde **5.2** quickly isomerizes into allene-aldehyde **5.3** as found by GC/MS analysis. In addition, allene **5.3** has a poor thermal stability. Preparative photo-irradiation at 20 mg scale produced target aldehyde products but all attempts to isolate either **5.2** or **5.3** failed due to their instability.

5.2 Conclusions and Future Directions

We have shown that allene-aldehyde **5.3** can be generated upon irradiation of the precursor **5.1** and isomerization of resulting alkyne-aldehyde **5.2**. Although **5.3** was not thermally stable enough for isolation, this finding still presents possibilities for future investigations. For example, if a second conjugated triple bond is introduced into the phenyl group, a Myers-Saito cyclization may proceed faster than decomposition of the allene, therefore leading to the formation of 1,4-biradical and further hydrogen abstraction. Such a possibility gives immense spatial control of the reaction in biological media.

Another great application of our discovery is that it can be useful for click reactions in a cell's imaging technique. Preliminary results show that allenes with electron-withdrawing groups react with azide-derivatives quite effectively forming triazole rings. Thus, allene **5.2** can possibly be trapped by azides and then isolated as a stable adduct (Figure 5.9).

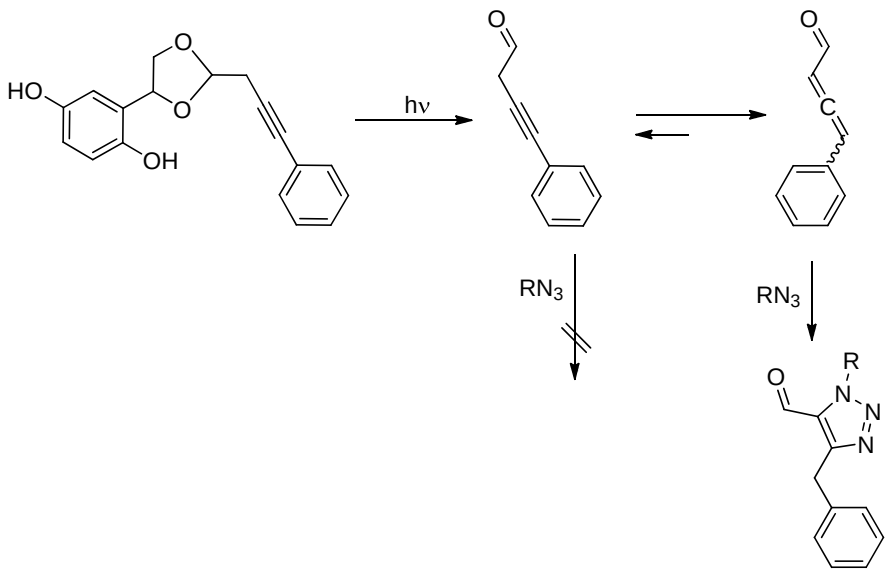

Figure 5.9 Trapping allene-aldehyde with azide.

5.3 Experimental Section

5.3.1 Materials and Instruments

All oxygen- and moisture-sensitive reactions were carried out under an inert atmosphere in the oven-dried glassware. Solvents for moisture-sensitive reactions were distilled prior to usage. All commercially available materials were used without purification unless otherwise stated. TLC analyses were performed using aluminum-backed silica gel TLC plates. Chromatographical separation and purification of the reaction products were performed using standard grade flash chromatography silica gel (40-63 μm particle size) or premium grade flash chromatography silica gel (40-75 μm particle size). All NMR spectra were recorded in deuterated chloroform on Varian Mercury 400 MHz or 500 MHz spectrometers with tetramethylsilane (TMS) as an internal standard. ^{1}H-NMR chemical shifts (δ) are reported in parts per million (ppm) versus the TMS reference, ^{13}C-NMR chemical shifts (δ) are reported in ppm versus the residual solvent peak reference. UV spectra were recorded on Cary-300 or Cary-50 instrument. GC/MS data were collected using Shimadzu GC-2010 equipped with SHR5XLB

column. High resolution mass spectra analyses were performed by the Mass Spectrometry Laboratory, University of Georgia at Athens, GA. HPLC data were collected on HP series 1100. Photolyses of 2.1 x 10^{-4} M (HPLC/GCMS analyses) solutions of compound **5.1** were conducted using Rayonet photochemical reactor equipped with 8 fluorescent UV lamps (4W, 300 nm, at ambient temperatures). Reaction mixtures after photolysis were analyzed by HPLC and GC/MS using pure substrates as references.

5.3.2 Experimental Synthetic Procedures

2,5-Dimethoxystyrene (5.5).

Methyltriphenyl phosphonium bromide (30.7 g, 86 mmol) was suspended in THF (250 mL) and *n*-butyllithium (33 mL, 95 mmol, 2.9M in hexane) was added dropwise under nitrogen atmosphere. The resulting yellowish solution was stirred for 2 h at room temperature, and then 2,5-dimethoxybenzaldehyde (**5.4**) (14.6 g, 86 mmol) in THF (50 mL) was added dropwise. The reaction mixture was refluxed overnight, then cooled to room temperature, filtered, and washed consequently with aqueous ammonium chloride (10%, 3 x 100 mL) and brine (100 mL). The organic phase was dried over anhydrous sodium sulfate, filtered, and all solvents were removed *in vacuo*. Column chromatography on silica gel with 3–20% of ethyl acetate in hexanes afforded 10.2 g (72%) of 2,5-dimethoxystyrene (**5.5**) as colorless oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.06-6.99 (m, 2H), 6.77-6.79 (m, 2H), 5.75-5.70 (dd, J_1 = 1.2 Hz, J_2 = 11.2 Hz, 1H), 5.29-5.26 (dd, J_1 = 1.2 Hz, J_2 = 11.2 Hz, 1H), 3.81 (s, 3H), 3.79 (s, 3H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 56.0, 56.5, 113.1, 112.5, 114.0, 114.9, 127.8, 131.7, 151.4, 153.9. MS: 164 (100, M^+), 149 (52), 121 (66), 91 (84), 78(34), 77 (39).

1-(2,5-Dimethoxyphenyl)ethylene glycol (5.6).

Glacial acetic acid (77 mL) was added to the mixture of 2,5-dimethoxystyrene (**5.5**) (10.2 g, 62.1 mmol), sodium periodate (4 g, 18.6 mmol), and dry lithium bromide (1.1 g, 12.4 mmol). The reaction mixture was stirred at 100 ºC overnight, then cooled to room temperature, partially concentrated *in vacuo* and poured in 100 mL of water. The product was extracted with ethyl acetate (3 x 30 mL). Combined organic layer was washed with aqueous sodium bicarbonate solution (2 x 30 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The resulting residue was re-dissolved in methanol (60 mL) and stirred with potassium carbonate (12.8 g, 93 mmol) at ambient temperature for 30 min. The resulting mixture was then diluted with ethyl acetate (100 mL), washed with brine (3 x 30 mL), dried over anhydrous sodium sulfate, filtered, and solvents evaporated under reduced pressure. The resulting crude product was purified by column chromatography on silica gel with 30–60% of ethyl acetate in hexanes to afford 8.17 g of pure diol **5.6** (66 %) as white solid.

NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 6.99-6.98 (d, J = 2.4 Hz, 1H), 6.82-6.76 (m, 2H), 5.03-5.00 (dd, J_1 = 3.6 Hz, J_2 = 8 Hz, 1H), 3.82-3.80 (m, 1H), 3.80 (s, 3H), 3.77 (s, 3H), 3.68-3.63 (m, 1H), 3.06 (br s, 1H), 2.34 (br s, 1H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 154.03, 150.82, 129.70, 113.51, 113.31, 111.66, 71.57, 66.77, 56.04, 55.90. DIP: 198 (4, M^+), 167 (15), 152 (5), 139 (9), 137 (7), 124 (6), 77 (19), 61 (65), 45 (100).

3-Hydroxypropyl acetate (5.8).

Acetic anhydride (12.7 g, 94.6 mmol, 11.7 mL) was added dropwise to the mixture of 1,3-propanediol (**5.7**) (7.19 g, 94.6 mmol) and triethylamine (14.4 g, 142.3 mmol) in dichloromethane (100 mL) at 0 ºC. Reaction mixture was left for overnight stirring, and then washed with water (3 x 30 mL), dried with sodium sulfate, filtered and solvents were evaporated

under reduced pressure. ^{1}H NMR analysis of the reaction mixture showed formation of the mixture of the mono- and di-protected diol (0.6:1). Mixture was separated by column chromatography on silica gel with 10–50% of ethyl acetate in hexanes affording 3.17 g (29%) of 3-hydroxypropyl acetate (**5.8**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 4.24-4.21 (t, J = 6.2 Hz, 2H), 3.72-3.68 (t, J = 6.2 Hz, 2H), 2.07 (s, 3H), 1.91-1.85 (qu, J = 6.2 Hz, 2H).

3-Oxopropyl acetate (5.9).

PCC (560 mg, 2.61 mmol) was added to a solution of 3-hydroxypropyl acetate (**5.8**) (181 mg, 1.54 mmol) in dichloromethane (7 mL). Reaction mixture was left with stirring for 3 hours. Then solids were filtered through silica gel (3 cm layer) using mixture ethyl acetate/hexanes as eluent. Solvents were evaporated under reduced pressure and residue was subjected to the flash column chromatography on silica gel affording 132 mg (75%) of 3-oxopropyl acetate (**5.9**). Aldehyde was immediately introduced into following reaction. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 9.79 (s, 1H), 4.42-4.40 (t, J = 6 Hz, 2H), 2.79-2.76 (dt, J_1 = 1 Hz, J_2 = 6 Hz, 2H), 2.05 (s, 3H).

2-(4-(2,5-Dimethoxyphenyl)-1,3-dioxolan-2-yl)ethyl acetate (5.10).

To a solution of 1-(2,5-dimethoxyphenyl)ethane-1,2-diol (**5.6**) (2.38 g, 12 mmol) and 3-oxopropyl acetate (**5.9**) (2.78 g, 24 mmol) in dichloromethane (50 mL) *p*-toluenesulfonic acid (cat. amount) was added. Reaction mixture was left with stirring overnight, then *p*-toluenesulfonic acid was filtered out, the filtrate was washed with water and brine (2 x 15 mL), dried over sodium sulfate, and dichloromethane was evaporated under reduced pressure. The residue was subjected to the column chromatography on silica gel with 10– 20% of ethyl acetate in hexanes yielding 3.47 g (98%) of 2-(4-(2,5-dimethoxyphenyl)-1,3-dioxolan-2-yl)ethyl acetate (**5.10**) as an inseparable mixture of two diastereomers. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.09-7.06 (m, 1H), 6.77 (s, 2H), 5.30-5.24 (m, 1H), 5.20-5.18 (t, J = 4.6 Hz, 1H), 4.33-4.26 (m,

3H), 3.79 (s, 3H), 3.77 (s, 1H), 3.68-3.62 (m, 1H), 2.19-2.14 (m, 2H), 2.07 (s, 3H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 170.98, 153.76, 150.29, 129.61, 112.70, 112.13, 110.93, 102.19, 73.49, 73.40, 71.98, 71.28, 55.74, 33.27, 20.98.

2-(4-(2,5-Dimethoxyphenyl)-1,3-dioxolan-2-yl)ethanol (5.11).

To a solution of 2-(4-(2,5-dimethoxyphenyl)-1,3-dioxolan-2-yl)ethyl acetate (**5.10**) (3.07 g, 10.4 mmol) in 60 mL of methanol potassium carbonate (~ 600 mg) was added. Reaction mixture was left with stirring for 30 min, then extracted with ethyl acetate (3 x 30 mL), washed with water (2 x 20 mL) and brine (20 mL), dried over sodium sulfate, and solvents were evaporated under reduced pressure. The residue was subjected to the column chromatography on silica gel with 20–50% of ethyl acetate in hexanes affording 2.2 g (85%) of 2-(4-(2,5-dimethoxyphenyl)-1,3-dioxolan-2-yl)ethanol (**5.11**) as an inseparable mixture of two diastereomers. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.08-7.05 (m, 1H), 6.78 (s, 2H), 5.32-5.28 (m, 1H), 5.23-5.21 (t, J = 4.4 Hz, 1H), 4.29-4.25 (t, J = 7.6 Hz, 1H), 3.98-3.85 (m, 2H), 3.78 (overlaped s, 6H), 3.72 (t, J = 6.4 Hz, 1H), 2.42 (br s, 1H), 2.13-2.11 (m, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 153.98, 150.58, 129.48, 113.24, 112.36, 111.29, 104.21, 73.64, 72.16, 71.40, 58.81, 56.01, 36.00.

2-(4-(2,5-Dimethoxyphenyl)-1,3-dioxolan-2-yl)acetaldehyde (5.12).

To a stirred solution of 2-(4-(2,5-dimethoxyphenyl)-1,3-dioxolan-2-yl)ethanol (**5.11**) (221 mg, 0.87 mmol) in dichloromethane (30 mL) PCC (422 mg, 1.97 mmol) was added. Reaction mixture was left with stirring for ~ 5 hours and then was filtered through a layer of silica gel with 50% of EtOAc in hexanes as eluent. Solvents were evaporated under reduced pressure; residue was subjected to the column chromatography on silica gel with 10–30% of ethyl acetate in hexanes yielding 27 mg (54%) of 2-(4-(2,5-dimethoxyphenyl)-1,3-dioxolan-2-yl)acetaldehyde (**5.12**) as an inseparable mixture of two diastereomers. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 9.90-9.88 (m,

1H), 7.06-7.03 (m, 1H), 6.78 (s, 1H), 5.55-5.53 (t, 0.3H), 5.48-5.46 (t, J = 4 Hz, 0.7H), 5.33-5.30 (m, 1H), 4.60-4.54 (t, 0.2H), 4.35-4.31 (t, J = 7.6 Hz, 0.8H), 3.79-3.77 (overlaped s, 6H), 3.73-3.69 (t, J = 7.2 Hz, 1H), 2.93-2.92 (m, 1.25H), 2.89-2.87 (m, 0.6H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 199.44, 153.98, 150.48, 129.16, 113.15, 112.14, 111.38, 100.60, 74.00, 72.33, 71.62, 55.96, 47.63. DIP: 252 (6), 164 (2), 149 (4), 121 (3), 88 (17), 77 (3), 70 (63), 61 (73), 49 (58), 45 (100).

Dibromomethyl-triphenylphosphonium bromide (5.14).[7]

Carbon tetrabromide (8.2 g, 24.7 mmol) was added to a solution of triphenylphosphine (13 g, 49.55 mmol) in methylene chloride (120 mL). The solution was stirred for 15 min at room temperature. Water (4 mL) was added to the resulting red reaction mixture. After 15 min of vigorous magnetic stirring, the aqueous layer was separated from CH_2Cl_2. The organic solution was dried over sodium sulfate, filtered, and methylene chloride was evaporated under reduced pressure to syrup. The salt was precipitated by addition of small amount of acetonitrile. The obtained yellow powder was filtered, dried, re-solubilized in dichloromethane (250 mL) and re-evaporated to syrup again. Then it was re-precipitated by addition of acetonitrile. The obtained white powder was filtered, dried *in vacuo*. Recrystallization step was not performed due to the purity of **5.14**. The resulting salt was stored at ~ -20^0C under an inert atmosphere.

2-(3,3-Dibromoallyl)-4-(2,5-dimathoxyphenyl)-1,3-dioxolane (5.15).

Potassium *tert*-butoxide (53.3 mg, 0.5 mmol) was mixed with dibromomethyl-triphenylphosphonium bromide (**5.14**) (258 mg, 0.5 mmol) in dry THF (7 mL) under an inert atmosphere. After 10 min 2-(4-(2,5-dimethoxyphenyl)-1,3-dioxolan-2-yl)acetaldehyde (**5.12**) (132 mg, 0.52 mmol) was added in small amount of THF. Reaction mixture was stirred for 10 min at room temperature. TLC showed complete formation of the new compound with all

starting aldehyde being converted. Reaction mixture was poured into water, brine, and extracted with diethyl ether (3 x 10 mL). Only one spot was observed on TLC plate after work-up procedure. Organic layer was dried over sodium sulfate, the solvents evaporated under reduced pressure, and residue was purified by column chromatography on silica gel with 15% of ethyl acetate in hexanes. The yield of 2-(3,3-dibromoallyl)-4-(2,5-dimathoxyphenyl)-1,3-dioxolane (**5.15**) was 153 mg (72%) as an inseparable mixture of two diastereomers (1:2 ratio). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.09 (s, 0.72H), 7.04 (s, 0.36H), 6.78 (s, 2H), 6.62-6.56 (m, 1H), 5.30-5.24 (m, 1.3H), 5.17 (t, *J* = 4.2 Hz, 0.7H), 4.55-4.52 (m, 0.36H), 4.31-4.27 (t, *J* = 7.4 Hz, 0.72H), 3.80-3.76 (m, 6H), 3.68-3.56 (2t, 1H), 2.66-2.63 (m, 1.25H), 2.60-2.57 (m, 0.6H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 154.02, 150.50, 132.86, 132.77, 129.32, 113.48, 112.85, 112.21, 111.90, 111.34, 111.28, 102.25, 102.19, 91.54, 74.05, 73.88, 72.22, 71.59, 56.06, 56.03, 38.20, 37.92. MS: 408 (14, M+), 209 (44), 181 (57), 149 (100), 121 (48), 91 (25), 77 (23).

4-(2,5-Dimethoxyphenyl)-2-(prop-2-yn-1-yl)-1,3-dioxolane (5.13).

To a solution of 2-(3,3-dibromoallyl)-4-(2,5-dimathoxyphenyl)-1,3-dioxolane (**5.15**) (63 mg, 0.15 mmol) in 7 mL of THF potassium *tert*-butoxide (38 mg, 0.34 mmol) was added at room temperature. After 5 min of stirring, TLC analysis showed almost complete conversion of the starting dibromide into acetylene. Reaction mixture was left with stirring for another 10 min and then quenched with water. Usual work-up was performed, and then crude mixture was purified on silica gel using 10–20% of ethyl acetate in hexanes affording 26 mg (69%) of 4-(2,5-dimethoxyphenyl)-2-(prop-2-yn-1-yl)-1,3-dioxolane (**5.13**) as an inseparable mixture of two diastereomers (2:1 ratio). NMR ^{1}H, solvent is $CDCl_3$, (δ, ppm): 7.17 (s, 0.72H), 7.06 (s, 0.36H), 6.77 (s, 2H), 5.36-5.31 (m, 1.4H), 5.26-5.24 (t, *J* = 4.6 Hz, 0.6H), 4.58-4.53 (m, 0.39H), 4.35-4.31 (t, *J* = 7.4 Hz, 0.72H), 3.76 (m, 6H), 3.73-3.69, 3.64-3.61 (2t, 1H), 2.73-2.70 (m, 1.25H),

2.68-2.64 (m, 0.6H), 2.10-2.08 (br t, 1H). NMR ^{13}C, solvent is $CDCl_3$, (δ, ppm): 154.01, 153.98, 150.59, 150.50, 129.54, 129.30, 113.25, 112.96, 112.30, 112.18, 111.31, 111.18, 102.51, 102.45, 79.11, 79.01, 74.19, 73.98, 72.26, 71.68, 70.86, 70.81, 56.0, 25.58, 25.39. MS: 248 (89, M+), 209 (24), 181 (66), 149 (100), 137 (33), 121 (61), 91 (42), 77 (37).

4-(2,5-Dimethoxyphenyl)-2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolane (5.16).

This reaction was performed according to the regular Sonogashira coupling procedure described in chapters 2,3, and 4. The amounts of the reagent used in this reaction were: 4-(2,5-dimethoxyphenyl)-2-(prop-2-yn-1-yl)-1,3-dioxolane (**5.13**) 470 mg, 1.90 mmol; phenyl iodide 388 mg, 1.9 mmol; Pd (II) 66.7 mg, 0.095 mmol; CuI 36 mg, 0.19 mmol; triethylamine 4 mL; THF 30 mL. Reaction time was four days at room temperature. GC/MS showed $M^+ = 324$ which corresponds to the product. After work up and column chromatography on silica gel (10–20% of ethyl acetate in hexanes) pure 4-(2,5-dimethoxyphenyl)-2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolane (**5.16**) as an inseparable mixture of two diastereomers (2:1 ratio) was obtained with 47% yield (289 mg). NMR ^1H: solvent is $CDCl_3$, (δ, ppm): 7.46-7.41 (m, 2H), 7.29-7.24 (m, 3.6H), 7.10 (s, 0.4H), 6.77 (s, 2H), 5.45-5.33 (m, 2H), 4.61-4.57 (m, 0.3H), 4.38-4.35 (t, J = 7.6 Hz, 0.75H), 3.80-3.74 (m, 6H), 3.71-3.63 (m, 1H), 2.96-2.94 (t, J = 4.2 Hz, 1.25H), 2.91-2.88 (m, 0.6H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 154.03, 150.63, 150.56, 131.99, 129.32, 128.37, 128.34, 128.09, 128.06, 123.69, 113.26, 113.04, 112.36, 112.14, 111.34, 111.20, 102.88, 102.77, 84.59, 82.83, 74.16, 74.00, 72.30, 71.74, 56.0, 31.15, 26.68, 26.44. MS: 342 (26, M+), 278 (5), 209 (55), 181 (49), 149 (100), 138 (27), 121 (50).

2-(2-(3-Phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)benzene-1,4-diol (5.1).

Silver oxide (29.8 mg, 0.24 mmol) was added to the solution of 4-(2,5-dimethoxyphenyl)-2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolane (**5.16**) (39 mg, 0.12 mmol) in dioxane (5 mL) followed by

0.1 mL of 6 M nitric acid. The resulting suspension was stirred for 50 min and then quenched with sodium bicarbonate (5 mL). The reaction mixture was extracted with dichloromethane (3 x 10 mL). Combined organic layers were washed with aqueous sodium bicarbonate (10% solution, 2 x 20 mL), dried over anhydrous sodium sulfate, and solvent was removed in *vacuum*. The column chromatography was not performed at this stage and crude 2-(2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)cyclohexa-2,5-diene-1,4-dione (**5.17**) was subjected to the following reaction.

Aqueous solution of sodium dithionite (69.9 mg, 0.4 mmol, 3 mL) was added to the solution of obtained 2-(2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)cyclohexa-2,5-diene-1,4-dione (**5.17**) in dichloromethane (3 mL). The resulting suspension was vigorously stirred for 30 min and the organic layer was separated. The aqueous layer was extracted with ether (3 x 10 mL) and the combined organic layers were washed with brine and dried over anhydrous sodium sulfate. Column chromatography on silica gel afforded 35 mg (98%) of pure 2-(2-(3-phenylprop-2-yn-1-yl)-1,3-dioxolan-4-yl)benzene-1,4-diol (**5.1**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.48-7.46 (t, J = 3.6 Hz, 1H), 7.44-7.42 (m, 0.5H), 7.29-7.26 (m, 2.5H), 6.75-6.58 (m, 4H), 5.48-5.46 (t, J = 4.2 Hz, 0.3H), 5.30-5.28 (m, 0.78H), 5.16-5.12 (t, *J* = 7.4 Hz, 0.7H), 5.05-4.95 (overlaped singlets, 1H), 4.53-4.94 (m, 0.32H), 4.28-4.25 (t, *J* = 7.4 Hz, 0.7H), 3.98-3.94 (t, *J* = 8 Hz, 0.6H), 3.84-3.80 (t, *J* = 8 Hz, 0.4H), 2.30-2.99 (d, *J* = 3.6 Hz, 1.25H), 2.89-2.88 (d, *J* = 4 Hz, 0.6H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 149.37, 149.14, 148.64, 148.20, 132.10, 131.98, 128.44, 128.42, 128.32, 128.25, 124.01, 123.45, 123.29, 122.99, 118.17, 117.79, 116.66, 116.16, 114.85, 113.69, 103.20, 102.77, 83.91, 83.83, 83.15, 78.58, 76.77, 71.62, 70.73, 26.68, 25.76. DIP: 296 (2, M^+), 250 (5), 181 (28), 152 (11), 135 (100), 123 (20), 115 (38), 107 (55), 89 (8), 77 (16), 57 (16). High res. MS, M^+: 296.1046 (found), 296.1049 (calc.).

5.4 References

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CHAPTER 6

PHOTOCHEMICAL GENERATION OF ALLENES AND ENYNE-ALLENES FROM DIAZO-DICARBONYL COMPOUNDS

6.1 Synthesis of Ethyl 2-Diazo-3-oxo-5-phenylpent-4-ynoate and Ethyl 2-Diazo-5-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-oxopent-4-ynoate

A photo-Wolff reaction of 2-diazo-1,3-diketones produces two isomeric β-ketoketenes that add alcohols which results in the corresponding β-ketoesters.[1] One of the acetylenic β-ketoesters rapidly tautomerizes into allene, while the other is stable. In this project, we used these reactions to achieve two goals: photochemical cyclization of enediyne and isomerization of the latter into a more reactive eneyne-allene. In order to achieve a selective formation of only tautomerizable isomer, we replaced 2-diazo-1,3-diketo functionality with a diazo-β-ketoester group to take advantage of the low migratory aptitude of oxygen in the Wolff rearrangement (Figure 6.1).

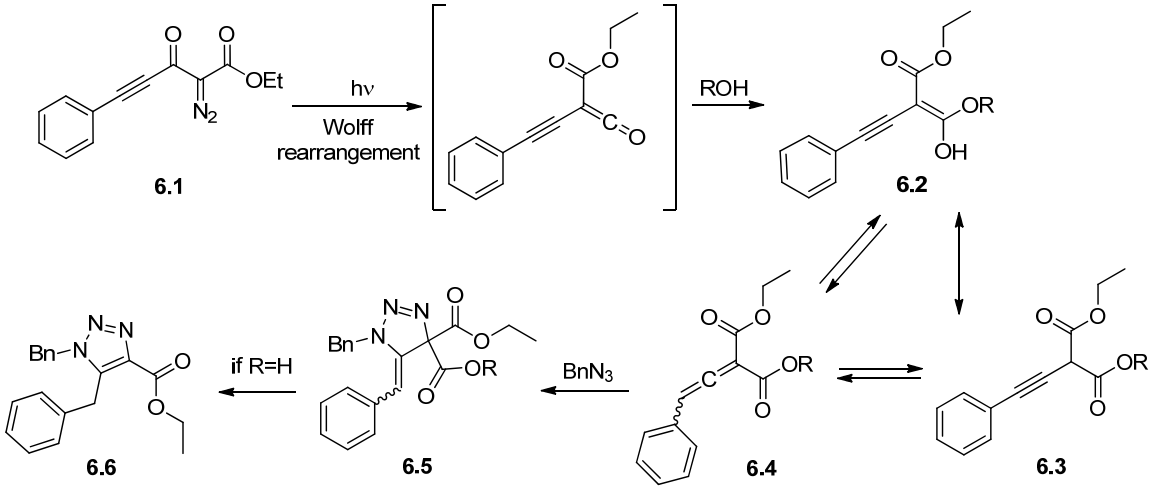

Figure 6.1 Proposed scheme of photochemical generation of allene **6.4**.

We proposed that photolysis of diazo-dicarbonyl compound **6.1** would produce enol **6.2** upon reaction of the ketene with either an alcohol or with water. Enol **6.2** can either tautomerize into dicarbonyl compound **6.3** or rearrange into allene-dicarbonyl compound **6.4**. The latter can also be produced from alkyne **6.3**. Allenes with electron-withdrawing groups, such as **6.4**, react with azides without the addition of copper at room temperature. Therefore, allene **6.4** can be trapped by a click reaction with benzyl azide. This copper-free click chemistry is potentially useful for cell imaging.

Diazo-dicarbonyl compound **6.7** possesses an acyclic enediyne fragment and it is expected to be stable for cycloaromatization at room temperature. According to the proposed photoreactivity scheme (Figure 6.2), diazo-dicarbonyl enediyne compound **6.7** is expected to lose nitrogen upon irradiation with UV light and rearrange into oxoketenes either *via* potential intermediacy of a carbene, or directly from the diazo compound **6.7** *via* the concerted mechanism. Unlike simple ketenes, α-oxoketenes are so reactive that they cannot be isolated. These α-oxoketenes can undergo an intramolecular reaction with the electron-rich oxygen in hydroxyl group instead of an intermolecular reaction with nucleophiles (Figure 6.2). Oxygen-containing diene-diyne **6.8** can further tautomerize into macro-lactone **6.9** or isomerize into enyne-allene **6.10**. Cyclic enyne-allene **6.10** is expected to undergo quick Myers-Saito cycloaromatization with a subsequent hydrogen abstraction.

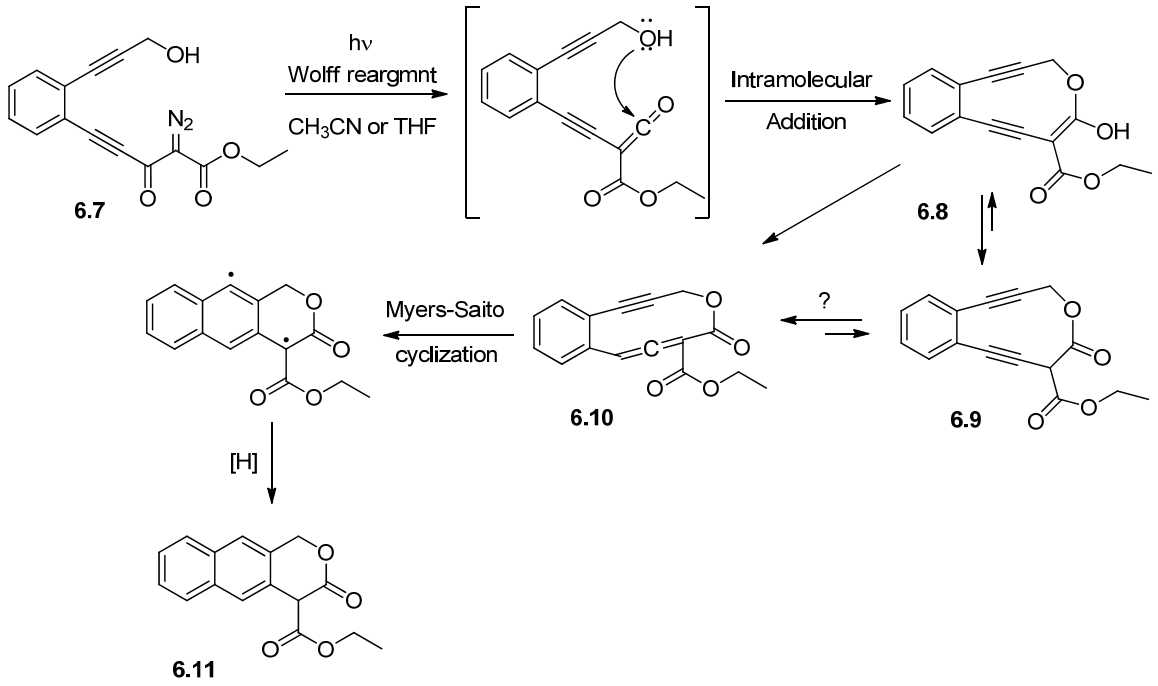

Figure 6.2 Proposed scheme of photochemical generation of enyne-allene **6.10.**

We intended to synthesize diazo-diketones **6.1** and **6.7** and study their photochemistry by irradiating these compounds with light of an appropriate wave-length. The synthesis of target diazodicarbonyl compound **6.1** began with a nucleophilic substitution reaction of ethynylbenzene with *N*,*N*-dimethylformamide in the presence of *n*-butyllithium (Figure 6.3). Purification of the resulting 3-phenylpropiolaldehyde (**6.13**) by column chromatography on a silica gel was not performed due to its instability. Aldehyde **6.13** was immediately introduced into the next reaction.

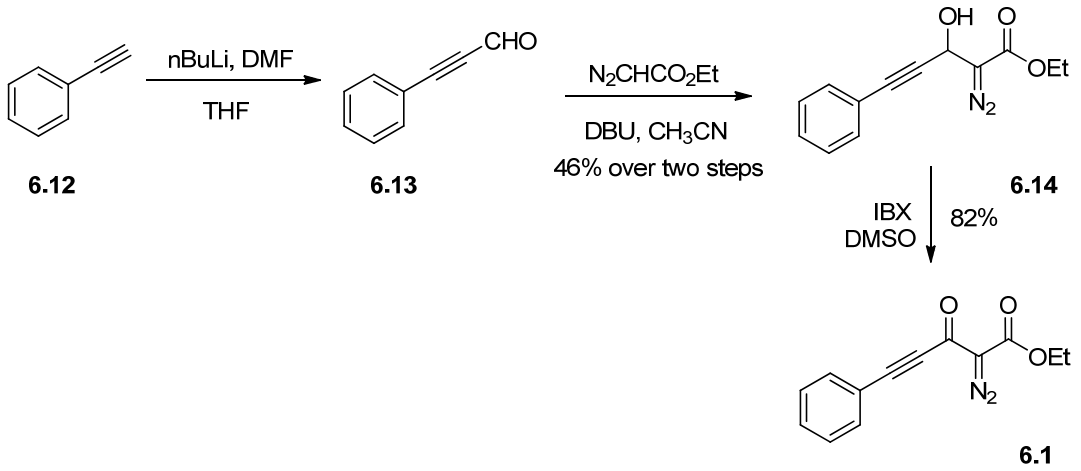

Figure 6.3 Synthesis of ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (**6.10**).

Aldehyde **6.13** was further introduced into the reaction with ethyl diazoacetate in the presence of catalytic amount of DBU affording diazo hydroxycarbonyl compound **6.14** in moderate yields over two steps. Yield of this reaction strongly depends on the purity of 3-phenylpropioaldehyde **6.3** and the reaction time. Stirring the reaction mixture for too long led to a yield decrease. DBU was a better base for the reaction than sodium hydride, as recommended in the literature.[2] The hydroxyl group in **6.14** was oxidized with 2-iodoxybenzoic acid (IBX) in DMSO. IBX has been chosen as an oxidizing agent because it is easier to prepare than Dess-Martin periodinane (DMP), where IBX is a precursor of DMP. Attempts to oxidize **6.14** with PCC in dichloromethane led to decomposition of the product and failed to produce a targeted compound. Pre-dissolving the IBX in DMSO before addition of alcohol helps to increase the yield of the reaction.

Acyclic diazo-enediyne **6.7** was obtained in a six-step synthesis starting with 1,2-diiodobenzene **6.15** (Figure 6.4). The Sonogashira cross-coupling of **6.15** with propargyl alcohol gave diol **6.16** in excellent yield. One of the hydroxyl groups in **6.16** was protected as an acetate using 4-dimethylaminopyridine as the base. A diacetate has also been isolated as a minor product. The remaining hydroxyl group in **6.17** was oxidized into aldehyde **6.18** using PCC in

dichloromethane. Quick filtration of the reaction mixture through the layer of silica gel was performed after the reaction was over in order to remove all residuals from PCC. Aldehyde **6.18** was not purified further by column chromatography for the same reasons as for aldehyde **6.13**.

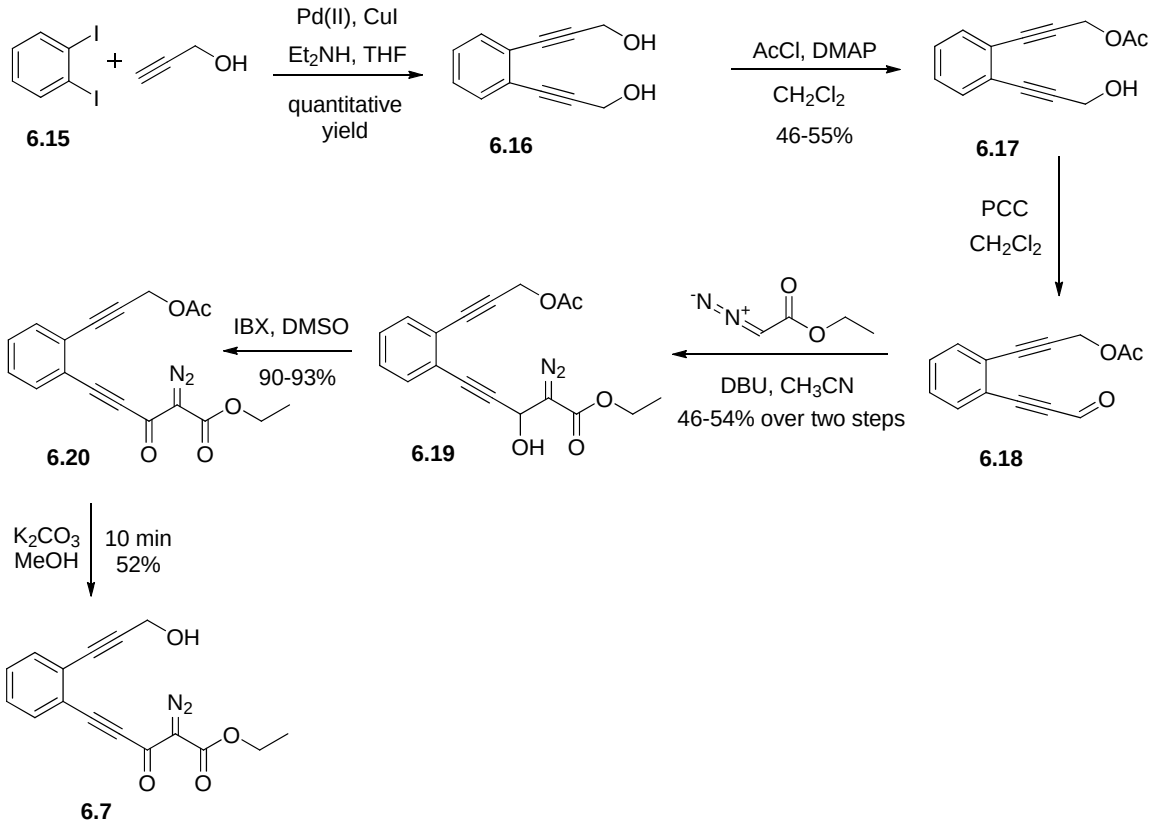

Figure 6.4 Synthesis of ethyl 2-diazo-5-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-oxopent-4-ynoate (**6.7**).

Compound **6.18** was introduced into the reaction with ethyl diazoacetate immediately after isolation to produce diazo hydroxycarbonyl acyclic enediyne **6.19** in 54% yield over two steps. The hydroxyl group in **6.19** was oxidized with IBX in DMSO as described above to produce diazo-dicarbonyl compound **6.20** in a good yield. The acetate protective group was then removed by treatment of **6.20** with potassium carbonate in aqueous methanol for a short period of time. In this case the other ester group in the molecule will not undergo hydrolysis, affording only one target product **6.7**.

6.2 Photochemical Studies of Ethyl 2-Diazo-3-oxo-5-phenylpent-4-ynoate and Ethyl 2-Diazo-5-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-oxopent-4-ynoate

Irradiation of ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (**6.1**) was performed in a variety of solvents and reaction conditions. Concentrations of irradiated solutions of **6.1** varied between 6 x 10^{-5} M and 4 x 10^{-4} M. Samples were irradiated in quartz cuvettes in a Rayonett photochemical reactor equipped with a carousel or a tubular flow-system placed in the Rayonett reactor. Analysis of the UV-visible spectrum of the reaction mixture (Figure 6.5) suggested employing a 300 nm irradiation wavelength.

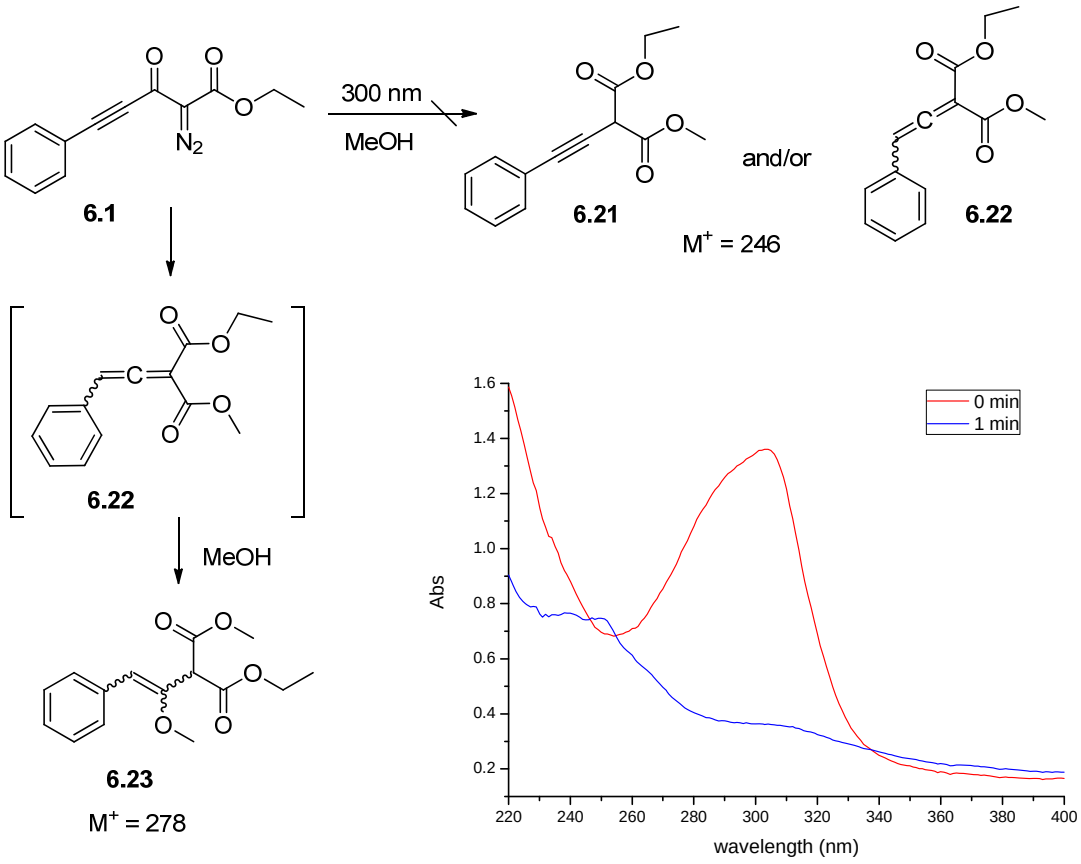

Figure 6.5 Irradiation of **6.1** by 300 nm light in neat methanol.

Photolysis of diazo-compound **6.1** in neat methanol was an efficient and fast reaction producing a single product. Based on the GC/MS analysis of the reaction mixture, this product

was neither the target alkyne **6.21** nor allene **6.22** but represented a compound with higher molecular mass. The proposed structure of the photochemical product – 1-ethyl 3-methyl 2-(1-methoxy-2-phenylvinyl)malonate (**6.23**) – was then confirmed by preparative photolysis with isolation of the product, which was characterized by NMR and HRMS. It has most likely been formed by the addition of the methanol to the electron-deficient double bond of the allene fragment of the **6.22** formed upon irradiation of the diazo-dicarbonyl compound **6.1**. When we irradiated **6.1** in methanol in the presence of approximately 10 eq. of benzyl azide, no traces of the triazol derivative were detected in the reaction mixture. Products of the addition of alcohols to one of the double bonds of allenes were also obtained upon irradiation of **6.1** in either ethanol or 2-propanol solutions (Figure 6.6).

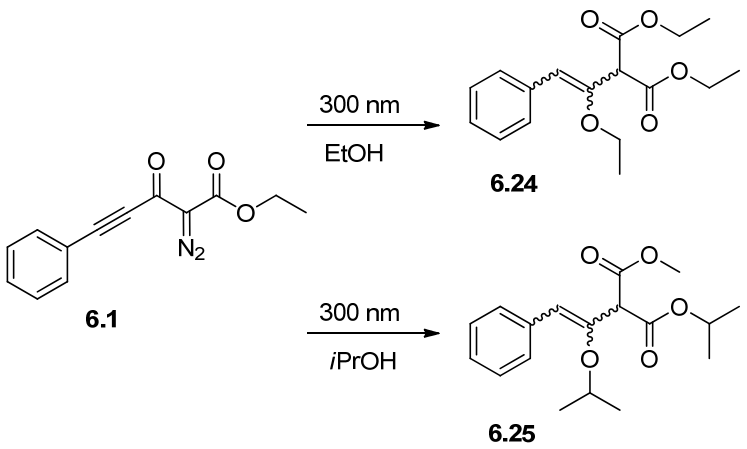

Figure 6.6 Irradiation of **6.1** by 300 nm light in ethanol and 2-propanol.

In order to determine whether this addition reaction is thermal or photochemical, photolysis of **6.1** was carried out in methanol by 350 nm light since allenyl-benzenes do not typically absorb light at 350 nm. Methanol adduct **6.23** was formed as a single product, indicating that the addition reaction is thermal and not photochemical.

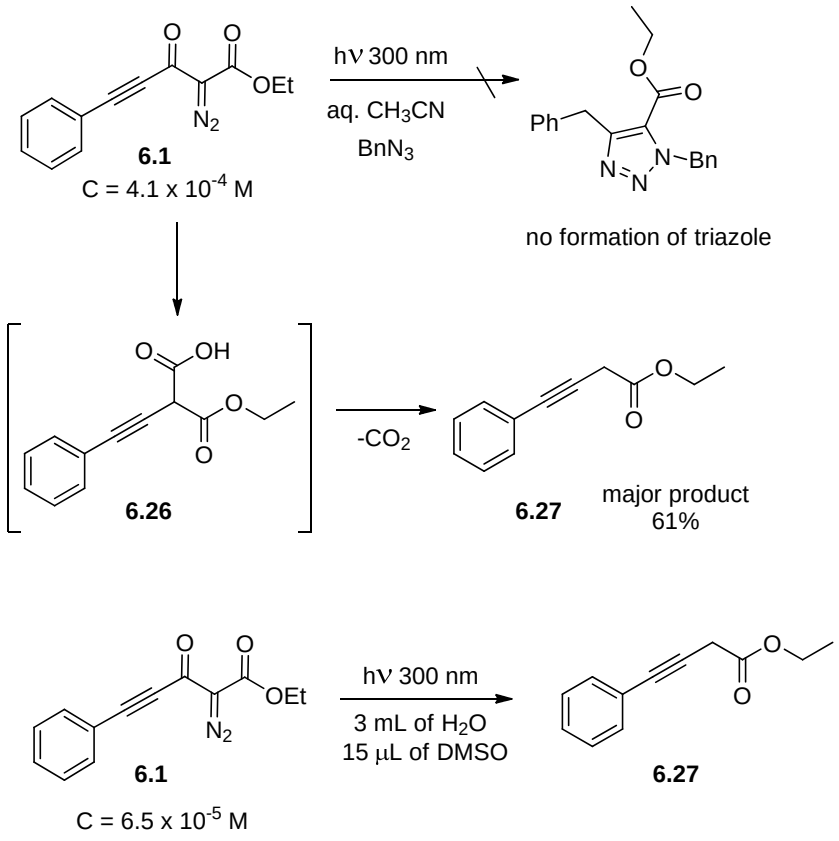

Figure 6.7 Irradiation of **6.1** by 300 nm light in acetonitrile and aqueous solutions.

Photoreaction of **6.1** in aqueous acetonitrile with addition of approximately 10 to 100 eq. of benzyl azide has not produced a product of click reaction with allene–ethyl 1,4-dibenzyl-1H-1,2,3-triazole-5-carboxylate. Instead, ethyl 4-phenylbut-3-ynoate (**6.27**) was formed as a single product. This observation was rationalized by the fast decarboxylation reaction of alkyne **6.2** formed by irradiation. The reaction did not proceed through isomerization of enol **6.2** into allene **6.4** but proceeded *via* tautomerization of **6.2** into acetylenic dicarbonyl compound **6.3** (Figure 6.1). Decarboxylation of the carboxyl group of **6.26** is faster than rearrangement into the allene-derivative.

The same result was obtained without addition of benzyl azide. Irradiation of **6.1** in aqueous solution also yielded decarboxylation product **6.27**.

We concluded that photoreaction of diazo-dicarbonyl compound **6.1** leads to the formation of alkyne **6.3**, which then rearranges into allene **6.4** if the nucleophile used in the reaction is an alcohol. In the case of aqueous solutions, alkyne-allene rearrangement does not take place due to the fast decarboxylation and formation of stable compound **6.27**. Allenes, such as **6.4**, are so reactive toward alcohols that they immediately form adducts with an alcohols.

We were interested to see if introducing a second triple bond in the molecule will trigger a Myers-Saito cyclization. If non-nucleophilic solvent is used, formed cyclic enyne-allene can undergo a Myers-Saito cyclization instead of an addition reaction (Figure 6.2).

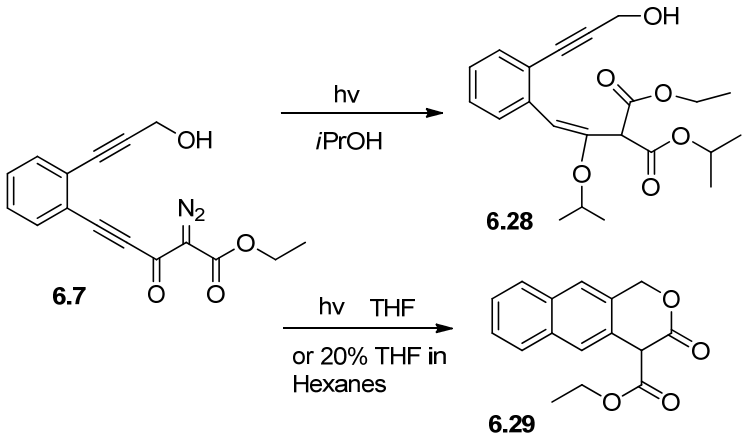

Figure 6.8 Irradiation of **6.7** by 300 nm light.

Acyclic diazo-dicarbonyl enediyne **6.7** was irradiated with 300 nm light in isopropanol to form the expected compound **6.28**. No products of intramolecular reaction of oxo-ketene with hydroxyl group were observed, and the allene reacted with 2-propanol in a similar manner to **6.1**.

When compound **6.7** was irradiated in absolute solvents such as THF and 20% THF in hexane, the major detected product was cyclic compound **6.29**, presumably formed *via* a Myers-Saito cyclization. Intramolecular reaction of ketene took place in the case of nucleophile-free solvents, leading to the formation of cyclic enyne-allene which cyclized.

6.3 Conclusions and Further Directions

Although photochemical generation of reactive species from stable without UV light compounds is an appealing and feasible idea, our findings limit the application of this chemistry to non-aqueous media. This obstacle can potentially be overcome by the replacment of the hydroxyl group with thiol (Figure 6.9). Thiols are better nucleophiles and can possibly make intramolecular addition reaction more competitive.

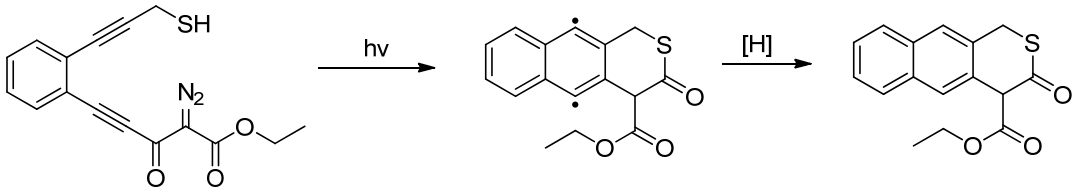

Figure 6.9 Future directions.

6.4 Experimental Section

6.4.1 Materials and Instruments

All oxygen- and moisture-sensitive reactions were carried out under an inert atmosphere in the oven-dried glassware. Solvents for moisture-sensitive reactions were distilled prior to usage. All commercially available materials were used without purification unless otherwise stated. TLC analyses were performed using aluminum-backed silica gel TLC plates. Chromatographical separation and purification of the reaction products were performed using standard grade flash chromatography silica gel (40-63 μm particle size) or premium grade flash chromatography silica gel (40-75 μm particle size). All NMR spectra were recorded in deuterated chloroform on Varian Mercury 400 MHz or 500 MHz spectrometers with tetramethylsilane (TMS) as an internal standard. ^{1}H-NMR chemical shifts (δ) are reported in parts per million (ppm) versus the TMS reference, ^{13}C-NMR chemical shifts (δ) are reported in ppm versus the residual solvent peak reference. UV spectra were recorded on Cary-300 or Cary-

50 instrument. GC/MS data were collected using Shimadzu GC-2010 equipped with SHR5XLB column. High resolution mass spectra analyses were performed by the Mass Spectrometry Laboratory, University of Georgia at Athens, GA. HPLC data were collected on HP series 1100. Photolyses of compounds **6.1** and **6.7** were conducted using Rayonet photochemical reactor equipped with 8 fluorescent UV lamps (4W, 300 or 350 nm, at ambient temperatures) in quartz cuvettes (HPLC/GCMS analyses) or tubular flow-system (preparative irradiation). Reaction mixtures after photolysis were analyzed by HPLC and GC/MS using pure substrates as references. In the case of preparative photolyses, reaxtion mixtures were separated on a silica gel; pure compounds were characterized by NMR, GC/MS, and HRMS analyses.

6.4.2 Experimental Synthetic Procedures

3-Phenylpropiolaldehyde (6.13).[2]

n-Butyllithium (1.13 mL, 1.8 mmol, 1.6 M in hexane) was added to a stirred solution of ethynylbenzene (**6.12**) (186 mg, 1.8 mmol) in 5 mL of THF that had been cooled to - 78 ºC under nitrogen atmosphere. *N*,*N*-dimethylformamide (263 mg, 3.6 mmol, 0.28 mL) was added dropwise over 10 min to the solution. The cooling bath was removed and the reaction mixture allowed warming to room temperature. Reaction was left with stirring for 30 min at the temperature and then the solution was added to a mixture of 5 mL of diethyl ether and 10 mL of 10% KH_2PO_4 solution which had been previously cooled to 0 ºC. The entire solution was stirred at 0 ºC for 30 min, warmed up to room temperature, and the aqueous and organic layers were separated. The organic layer was dried over magnesium sulfate, and solvents evaporated under reduced pressure to give clear oil. 3-Phenylpropiolaldehyde (**6.13**) was used in the next reaction without further purification due to its instability.

Ethyl 2-diazo-3-hydroxy-5-phenylpent-4-ynoate (6.14).[3]

To a solution of ethyl diazoacetate (246 mg, 2.16 mmol, 0.23 mL) in anhydrous CH_3CN (7 mL) 1,8-diazabicyclo[5.4.0]undec-7-ene (55 mg, 0.36 mmol, 54 μL) and 3-phenylpropioaldehyde (**6.13**) (234 g, 1.8 mmol) in anhydrous CH_3CN (3 mL) were added. The reaction mixture was stirred overnight at room temperature and then concentrated in *vacuo*. DIP/MS analysis showed formation of target diazo-compound (M^+ = 216 (244-N_2)). The residue was subjected to the column chromatography on a silica gel with 10– 30% of ethyl acetate in hexanes to give 200 mg (46% over two steps) of pure ethyl 2-diazo-3-hydroxy-5-phenylpent-4-ynoate (**6.14**) as yellow oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.46-7.44 (m, 2H), 7.33-7.31 (m, 3H), 5.76 (s, 1H), 4.32-4.26 (q, *J* = 7 Hz, 2H), 1.68 (br s, 1H), 1.33-1.30 (t, *J* = 7 Hz, 3H). IR spectrum: 3412, 2981, 2098, 1668, 1490. DIP/MS: 216 (M^+-N_2, 18), 200 (6), 188 (9), 171 (16), 151 (36), 137 (15), 129 (100), 114 (32), 102 (34).

Ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (6.1).

2-Iodoxybenzoic acid (344 mg, 1.23 mmol) was dissolved in DMSO (5 mL) over 20 min, ethyl 2-diazo-3-hydroxy-5-phenylpent-4-ynoate (**6.14**) (200 mg, 0.82 mmol) in DMSO (3 mL) was added, and the mixture was stirred for 3 h. TLC and DIP/MS (M^+ = 242) analyses showed complete formation of product as a single compound. The reaction mixture was poured into water (20 mL) and extracted with dichloromethane (2 x 20 mL). The combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The resulting crude oil was purified by flash chromatography on a silica gel with 15–20% of ethyl acetate in hexanes yielding 163 mg (82%) of pure ethyl 2-diazo-3-oxo-5-phenylpent-4-ynoate (**6.1**) as yellow crystals. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.65-7.64 (d, *J* = 7.2 Hz, 2H), 7.49-7.45 (m, 1H), 7.42-7.38 (t, *J* = 7.2 Hz, 2H), 4.40-4.34 (q, *J* = 7 Hz, 2H), 1.38-1.34 (t, *J* = 7 Hz, 3H). NMR ^{13}C:

solvent is $CDCl_3$, (δ, ppm): 180.7, 160.02, 133.07, 130.96, 128.64, 128.35, 120.00, 85.52, 76.72, 61.80, 14.41. DIP/MS: 242 (M+, 25), 214 (3), 142 (25), 129 (100), 114 (37), 101 (13). High res. MS, M^+: 242.0693 (found), 242.0691 (calc.).

3,3-(1,2-Phenylene)bis(prop-2-yn-1-ol) (6.16).[4]

Bis(triphenylphosphine)palladium dichloride (1 g, 1.4 mmol) was added to a stirred solution of 1,2-diiodobenzene (5 g, 15.2 mmol) in dry degassed THF (100 mL) under inert atmosphere. The solution was degassed with a strong flux of argon, and powdered copper(I) iodide (cat. amount) was added to the mixture. After 5 minutes of stirring, propargyl alcohol (3.4 g, 60.6 mmol, 3.5 mL) was added to a mixture, followed by diethyl amine (10 mL). The reaction vessel was purged with argon, sealed and left with overnight stirring at room temperature. By the end of this period GC/MS analysis indicated approximately 70% conversion into the desired product. Another two equivalents of propargyl alcohol and 5 mL of diethyl amine were added to the reaction mixture. After 2 more days of stirring TLC along with DIP/MS (M^+ = 186) showed complete conversion of the starting 1,2-diiodobenzene into the diol. The reaction mixture was filtered through 3 cm layer of a silica gel (5% ethyl acetate in hexanes); fractions containing the desired product were combined, solvents were evaporated under reduced pressure. Crude product was purified by column chromatography on a silica gel with 30–50% of ethyl acetate in hexanes and then 20–30% of ethyl acetate in dichloromethane as eluent yielding 3,3-(1,2-phenylene)bis(prop-2-yn-1-ol) (**6.16**) in quantitative yield. NMR ^1H: solvent is $CDCl_3$, (δ, ppm): 7.40-7.38 (dd, J_1 = 3.4 Hz, J_2 = 5.6 Hz, 2H), 7.25-7.23 (dd, J_1 = 3.4 Hz, J_2 = 5.6 Hz, 2H), 4.54 (s, 4H), 4.05 (br s, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 131.59, 128.28, 125.59, 92.01, 84.43, 51.65. DIP/MS: 186 (M+, 9), 168 (10), 139 (100), 128 (34), 115 (24), 102 (6), 89 (11).

3-(2-(3-Hydroxyprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl acetate (6.17).

A solution of 3,3-(1,2-phenylene)bis(prop-2-yn-1-ol) (**6.16**) (2.8 g, 15.1 mmol) in dichloromethane (100 mL) was treated with an equimolar amount of acetyl chloride (1.18 g, 15.1 mmol, 1.07 μL). DMAP (310 mg) was added, and the reaction mixture was left with stirring at room temperature overnight. GC/MS analysis showed that desired monoacetate ester was the major product in this reaction. There was some amount of diprotected compound (~ 37%) and starting material according to the TLC. The solvent was evaporated and residue was subjected to the column chromatography on a silica gel with 10–30% of ethyl acetate in hexanes to give 1.57 mg (46%) of pure 3-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl acetate (**6.17**) and 1.28 g of the diacetate by-product. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.45-7.41 (m, 2H), 7.31-7.25 (m, 2H), 4.93 (s, 2H), 4.54 (s, 2H), 2.96 (br s, 1H), 2.15 (s, 3H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 171.25, 132.22, 131.81, 128.84, 128.28, 126.19, 124.93, 92.32, 87.07, 85.01, 83.95, 53.29, 51.77, 21.15. MS: 228 (M+, 2), 210 (6), 195 (8), 168 (36), 139 (100), 127 (10), 115 (21), 91 (40).

3-(2-(3-Oxoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl acetate (6.18).

Celite was added to a stirred solution of 3-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl acetate (**6.17**) (1.1 g, 4.8 mmol) in dichloromethane (60 mL) and then PCC (1.6 g, 7.2 mmol) was added to the solution Reaction was left with stirring for 3 hours and filtered through 3 cm layer of a silica gel with 1:1 ethyl acetate/hexanes solvent's mixture. Solvents were evaporated under reduced pressure, crude 3-(2-(3-oxoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl acetate (**6.18**) was not further purified but immediately introduced into the next reaction.

Ethyl 5-(2-(3-acetoxyprop-1-yn-1-yl)phenyl)-2-diazo-3-hydoxypent-4-ynoate (6.19).

To a solution of ethyl diazoacetate (657 mg, 5.76 mmol, 0.608 mL) in anhydrous CH_3CN (40 mL) 1,8-diazabicyclo[5.4.0]undec-7-ene (146 mg, 0.96 mmol, 143 μL) and 3-(2-(3-oxoprop-1-yn-1-yl)phenyl)prop-2-yn-1-yl acetate (**6.18**) (1.08 g, 4.8 mmol) in anhydrous CH_3CN (10 mL) were added. The reaction mixture was stirred overnight at room temperature and then concentrated in *vacuo*. The residue was subjected to the column chromatography on a silica gel with 20–40% of ethyl acetate in hexanes as eluent affording 0.78 g (46% over two steps) of ethyl 5-(2-(3-acetoxyprop-1-yn-1-yl)phenyl)-2-diazo-3-hydoxypent-4-ynoate (**6.19**). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.47-7.43 (m, 2H), 7.32-7.27 (m, 2H), 5.76-5.74 (d, J = 6.4 Hz, 1H), 4.97-4.89 (m, 2H), 4.32-4.26 (q splitted further, 2H), 3.91 (br s, 1H), 2.14 (s, 3H), 1.33-1.30 (t, J = 7 Hz, 3H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 171.30, 165.41, 132.39, 132.20, 128.85, 125.14, 125.08, 88.72, 87.44, 85.18, 84.79, 61.55, 58.85, 53.34, 21.05, 14.68. DIP/MS: 312 (M^+-N_2, 13), 270 (22), 241 (35), 224 (32), 197 (16), 181 (45), 167 (23). 155 (37), 139 (47), 127 (58), 115 (37), 86 (40), 61 (69), 45 (100). IR (neat, cm^{-1}): 3447, 2984, 2359, 2342, 2099, 1744, 1689, 1558, 1481, 1442.

Ethyl 5-(2-(3-acetoxyprop-1-yn-1-yl)phenyl)-2-diazo-3-oxopent-4-ynoate (6.20).

Iodoxybenzoic acid (966 mg, 3.45 mmol) was dissolved in DMSO (7 mL) over 20 min, ethyl 2-diazo-3-hydroxy-5-phenylpent-4-ynoate (**6.19**) (0.78 g, 2.3 mmol) in DMSO (3 mL) was added, and the mixture was stirred for 5 h. TLC and DIP/MS (M^+ = 242) indicated complete formation of desired product (**6.20**). The reaction mixture was poured into water (20 mL) and extracted with dichloromethane (2 x 20 mL). Combined organic layers were dried over sodium sulfate and concentrated under reduced pressure. The residue was purified by column chromatography on a silica gel with 20% of ethyl acetate in hexanes to yield 718 mg (93%) of ethyl 5-(2-(3-

acetoxyprop-1-yn-1-yl)phenyl)-2-diazo-3-oxopent-4-ynoate (**6.20**) as yellowish oil. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.66-7.64 (d, *J* = 7.8, 1H), 7.53-7.51 (d, *J* = 7.8, 1H), 7.43-7.34 (m, 2H), 4.99 (s, 2H), 4.38-4.33 (q, *J* = 7.2 Hz, 2H), 2.14 (s, 3H), 1.37-1.33 (t, *J* = 7.2 Hz, 2H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 180.67, 170.50, 160.11, 133.88, 132.74, 130.70, 128.83, 126.25, 122.94, 88.80, 88.52, 84.11, 62.02, 53.08, 20.97, 14.56. DIP/MS: 338 (M+, 5), 281 (53), 240 (34), 222 (18), 211 (30), 194 (20), 183 (46), 150 (100), 139 (91), 127 (48), 115 (15). IR (neat, cm^{-1}):2984, 2207, 2133, 1724, 1669, 1600, 1481, 1442.

Ethyl 2-diazo-5-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-oxopent-4-ynoate (6.7).

To a stirred solution of 6.20 (37.7 mg, 0.11 mmol), in aqueous methanol (5 mL) potassium carbonate (1 eq., 15.2 mg, 0.11 mmol) was added in one portion. Solution was stirred for 5 min and then poured into the mixture of 10% of aqueous KH_2PO_4 and diethyl ether. After 15 min of vigorous stirring, layers were separated and organic phase was dried over sodium sulfate. Mixture was filtered; the solvents were removed under reduced pressure. Residue was subjected to the column chromatography on a silica gel (10-30 % of ethyl acetate in hexanes) yielding 17 mg (52%) of pure ethyl 2-diazo-5-(2-(3-hydroxyprop-1-yn-1-yl)phenyl)-3-oxopent-4-ynoate (**6.7**) and 12 mg (31%) of unconverted starting acetate **6.20**. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.67 (d, J = 7.2 Hz, 1H), 7.48-7.40 (m, 2H), 7.36-7.32 (m, 1H), 4.54 (s, 2H), 4.38-4.33 (q, *J* = 7.2 Hz, 2H), 1.76 (br s, 1H), 1.39-1.35 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR: 160.64, 154.92, 133.04, 131.95, 130.28, 128.36, 127.92, 122.76, 93.97, 89.09, 85.82, 83.51, 62.29, 53.17, 14.46. DIP/MS: 296 (M+, 1), 268 (1), 239 (12), 211 (16), 196 (10), 183 (23), 168 (21), 150 (30), 139 (100), 127 (67), 115 (20).

1-Ethyl 3-methyl 2-(1-methoxy-2-phenylvinyl)malonate (6.23). Preparative irradiation of 6.1 in methanol.

Diazo compound **6.1** (20 mg, 0.082 mmol) was irradiated in 200 mL of methanol with two lamps in the Rayonett for 18 min. Reaction was followed by UV spectroscopy. Solvent was removed under reduced pressure and residue was subjected to the column chromatography on a silica gel with 10–20% of acetone in hexanes. The yield of 1-ethyl 3-methyl 2-(1-methoxy-2-phenylvinyl)malonate (**6.23**) was 18 mg (82%). NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.34-7.30 (t, *J* = 7.6 Hz, 2H), 7.24-7.21 (m, 1H), 7.16-7.14 (d, *J* = 7.6 Hz, 1H), 5.93 (s, 1H), 4.62 (s, 1H), 4.26-4.21 (q, *J* = 7.2 Hz, 2H), 3.76 (s, 3H), 3.75 (s, 3H), 1.29-1.26 (t, *J* = 7.2 Hz, 3H). NMR ^{13}C: solvent is $CDCl_3$, (δ, ppm): 167.48, 166.92, 151.00, 135.78, 129.12, 128.87, 128.53, 127.53, 126.48, 104.30, 61.82, 55.64, 53.86, 52.79, 14.02. MS: 278 (M+, 53), 219 (7), 205 (9), 174 (37), 159 (12), 145 (100), 131 (39), 115 (34), 103 (45). High res. MS, ($M+H^+$): 279.1233 (found), 279.1227 (calc.).

Ethyl 4-phenylbut-3-ynoate (6.27).[5] Preparative irradiation of 6.1 in aqueous acetonitrile or water. General procedure.

Diazo-compound **6.1** (conc. from 1.49 x 10^{-4}M to 4.1 x 10^{-4}M) in solution of acetonitrile or water was irradiated using tubular flow-system placed in the Rayonett reactor. Solvents were evaporated under reduced pressure; the residue was subjected to the column chromatography on a silica gel with 10–30% of EtOAc in hexanes affording ethyl 4-phenylbut-3-ynoate (**6.27**) as a major product. NMR ^{1}H: solvent is $CDCl_3$, (δ, ppm): 7.46-7.43 (m, 2H), 7.31-7.29 (m, 3H), 4.25-4.21 (q, *J* = 7.2 Hz, 2H), 3.51 (s, 2H), 1.33-1.29 (t, *J* = 7.2 Hz, 3H). MS: 188 (M+, 21), 160 (7), 144 (5), 115 (100), 89 (12). High res. MS, M^+: 188.0833 (found), 188.0837 (calc.).

6.5 References

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APPENDICES

TABLE OF ABBREVIATIONS

BC–Bergman Cyclization

CAN–Ceric Ammonium Nitrate

1,4-CHD–1,4-Cyclohexadiene

CT–Charge Transfer

DBU–1,8-Diazabicyclo[5.4.0]undec-7-ene

DIBAL–Diisobutyl Lithium Hydride

DIP-MS–Direct Inlet Probe/Mass Spectrometry

DMP–Dess-Martin Periodinane

DMSO–Dimethyl Sulfoxide

DSC–Differential Scanning Calorimetry

GC/MS–Gas Chromatography/Mass Spectrometry

HPLC–High-performance Liquid Chromatography

HWE–Horner-Wadsworth-Emmons

IBX–2-Iodoxybenzoic Acid

IR–Inferred

KIE–Kinetic Isotope Effect

NCS–Neocarzinostatin

NMR–Nuclear Magnetic Resonance

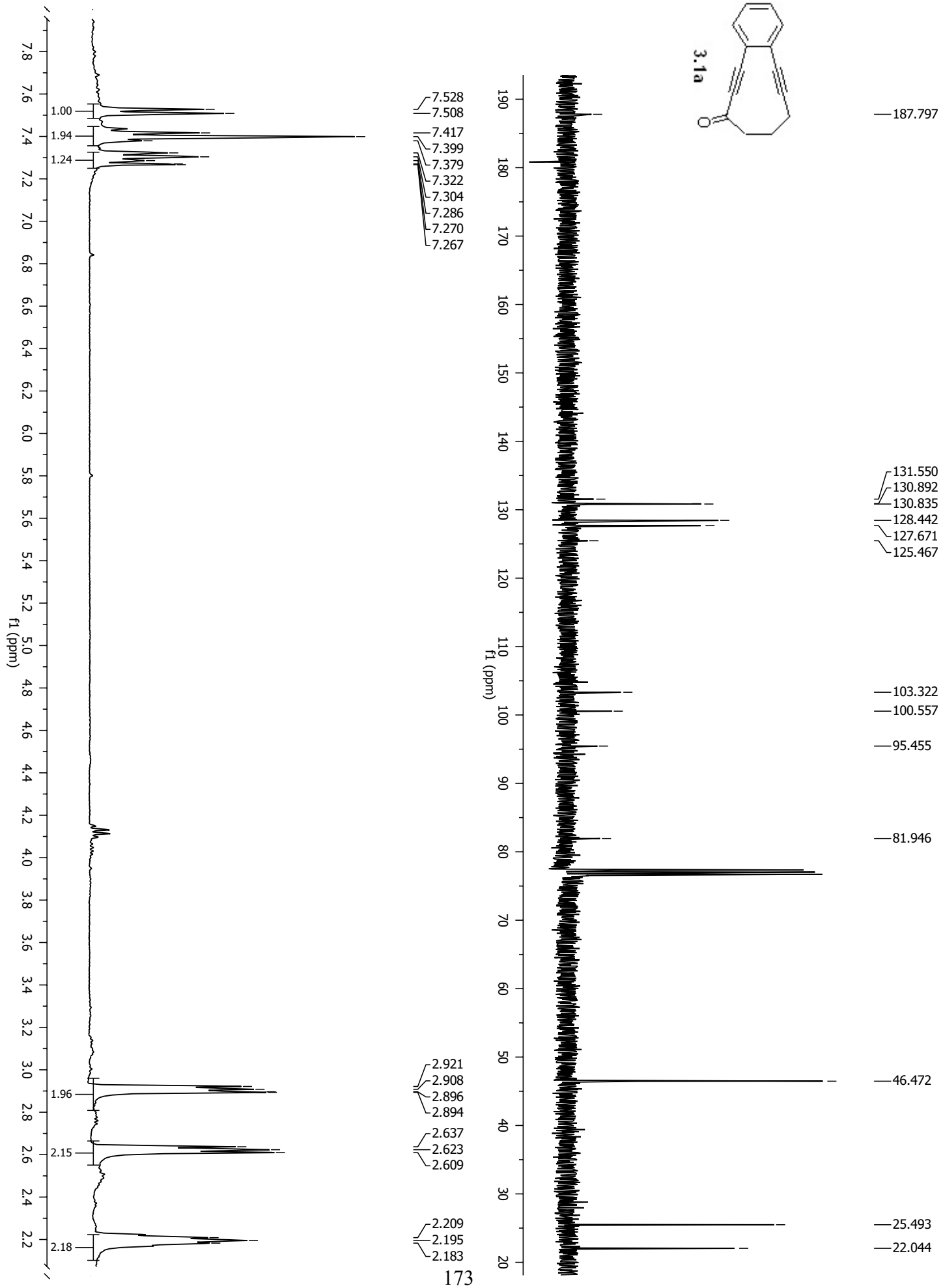
PCC–Pyridinium Chlorochromate

PPG – Photoremovable Protecting Groups

TS–Transition State

UV–Ultraviolet

^{1}H AND ^{13}C NMR SPECTRA OF COMPOUNDS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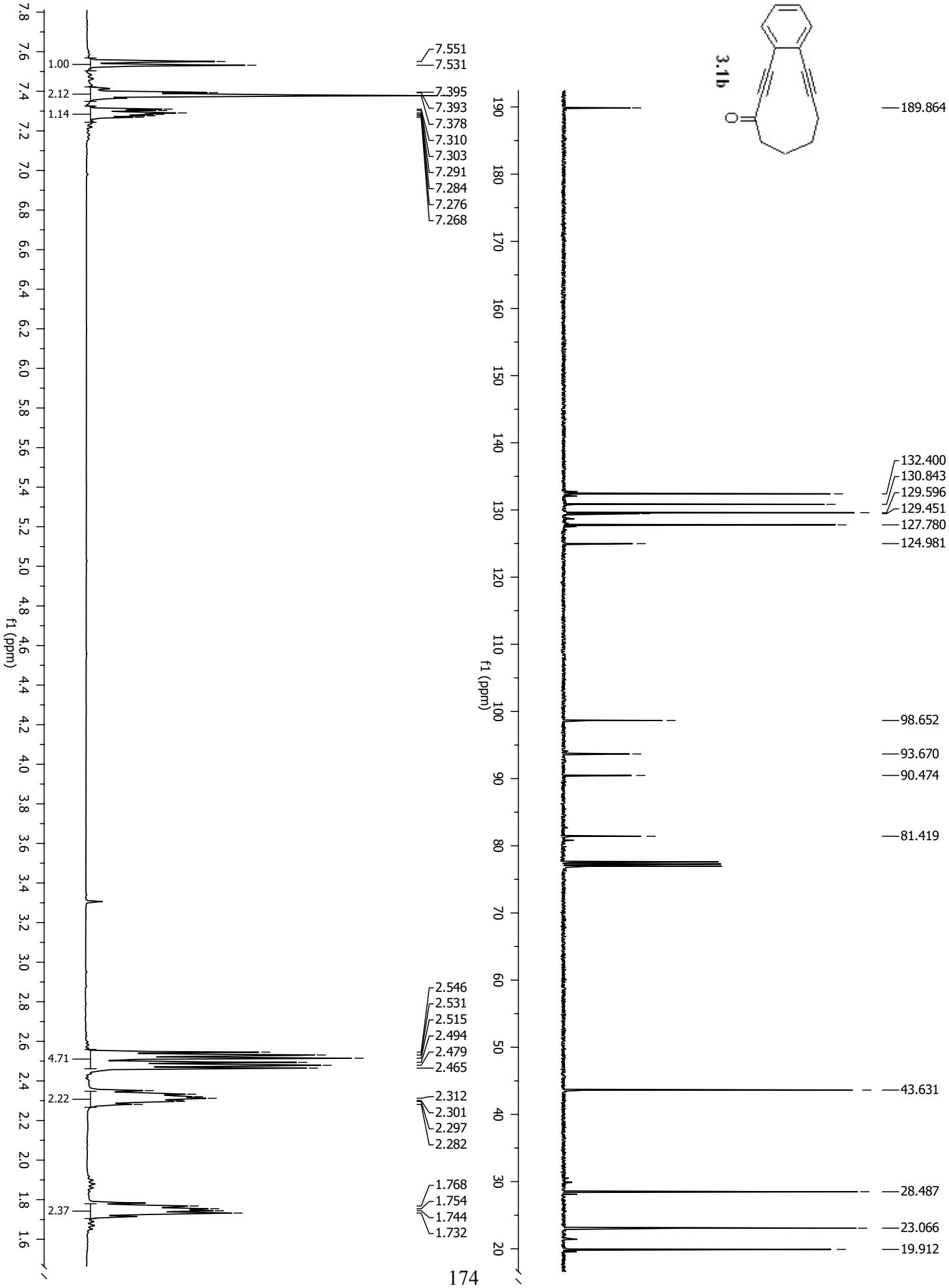
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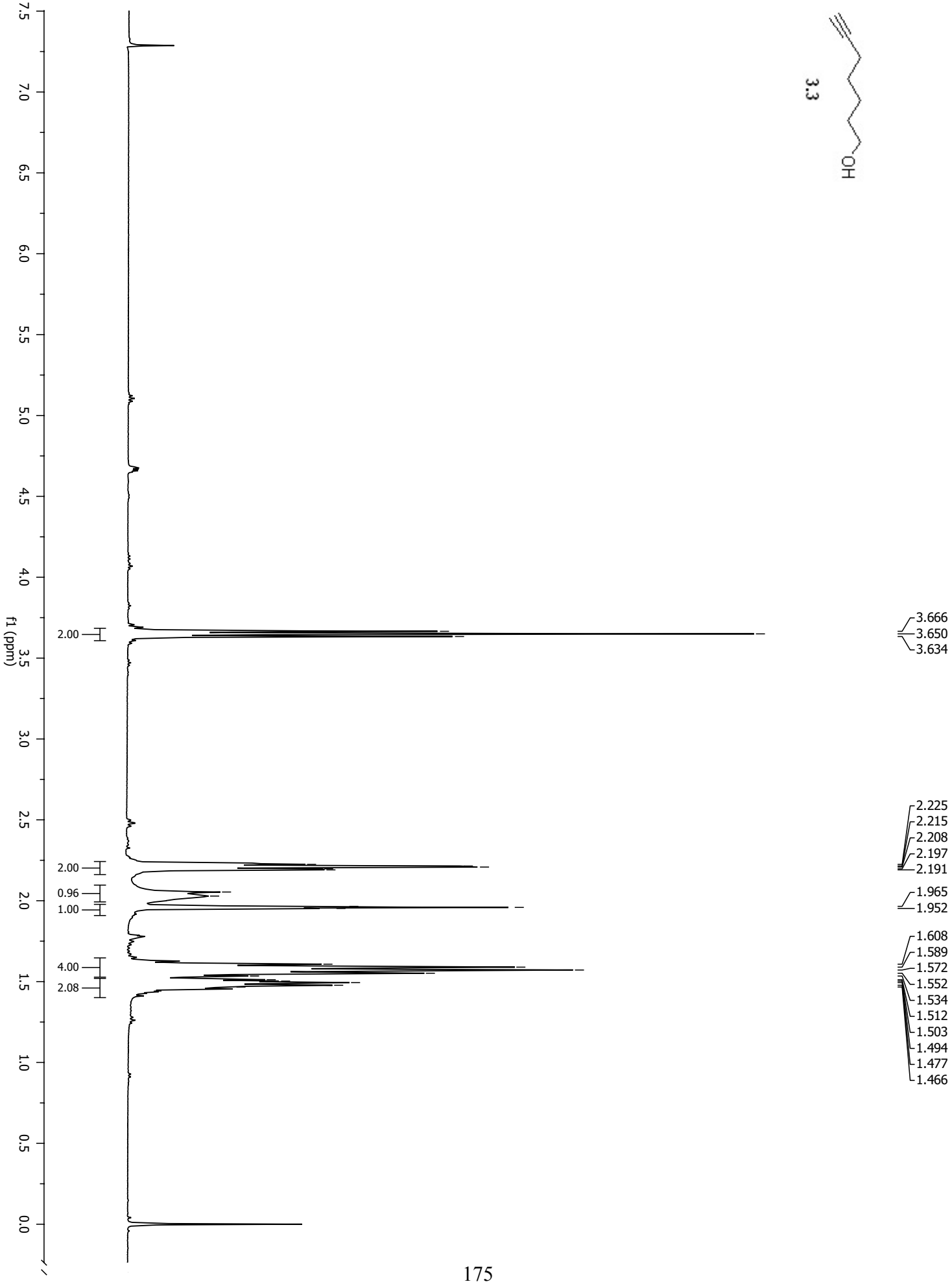
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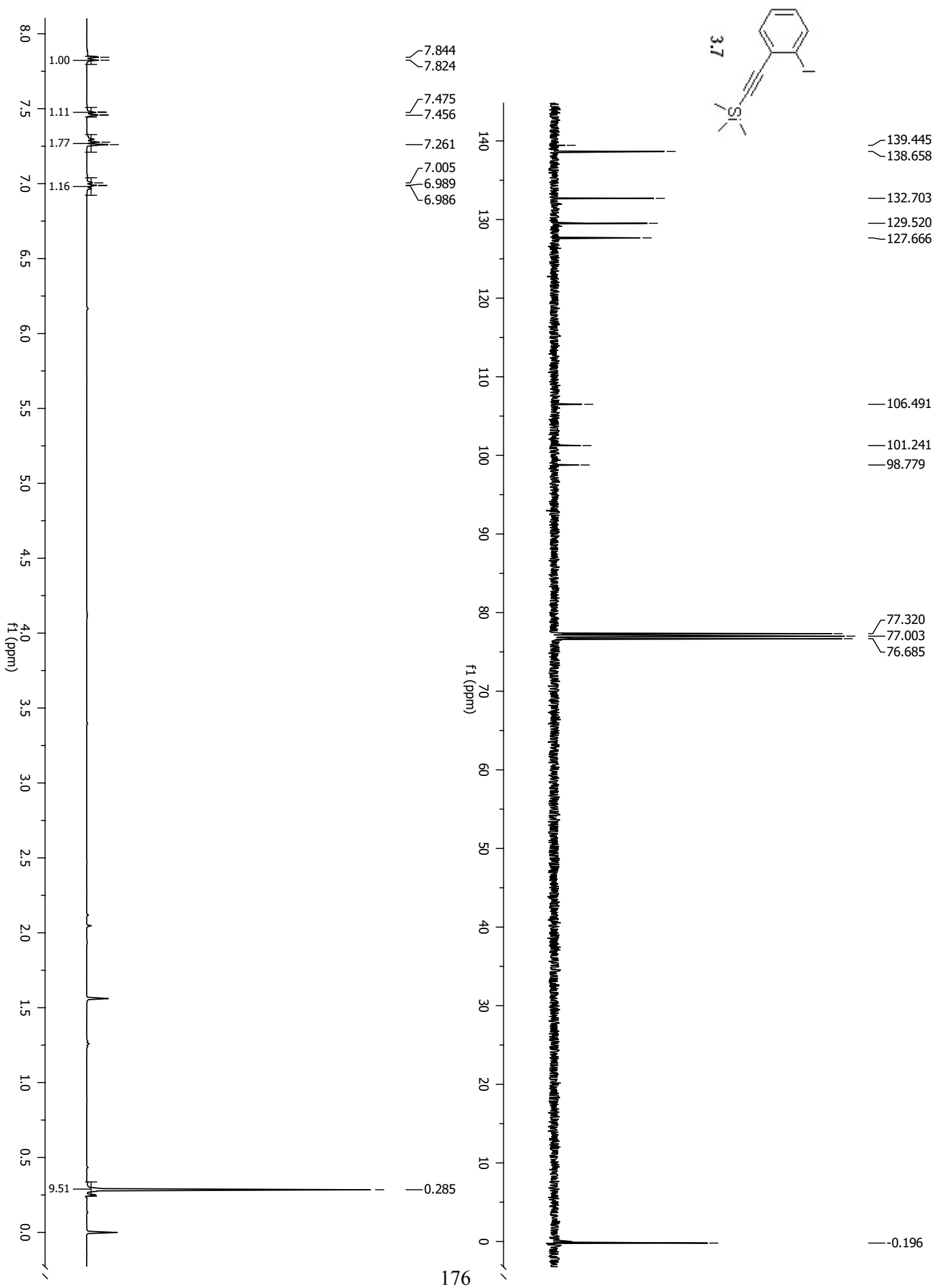
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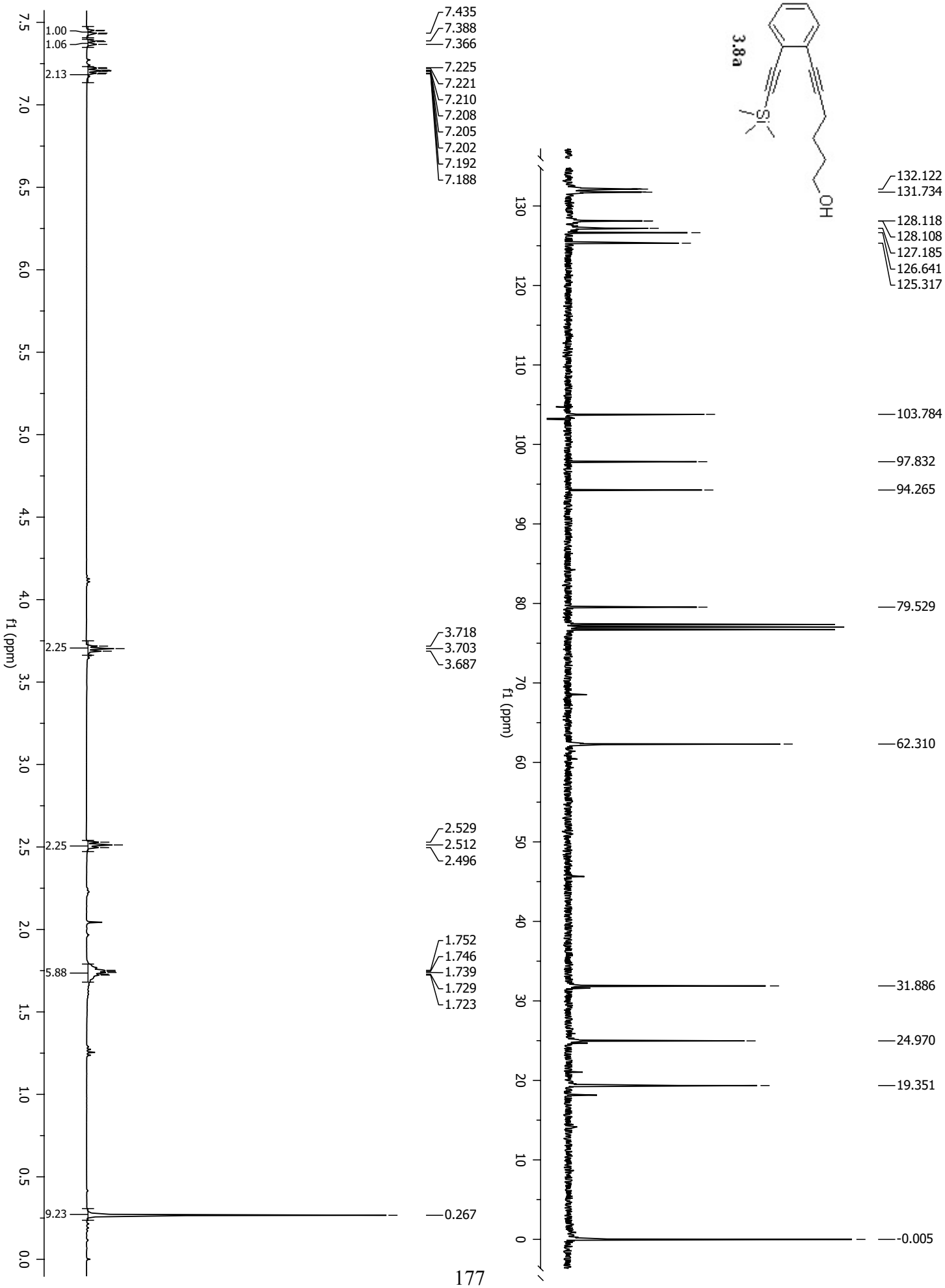
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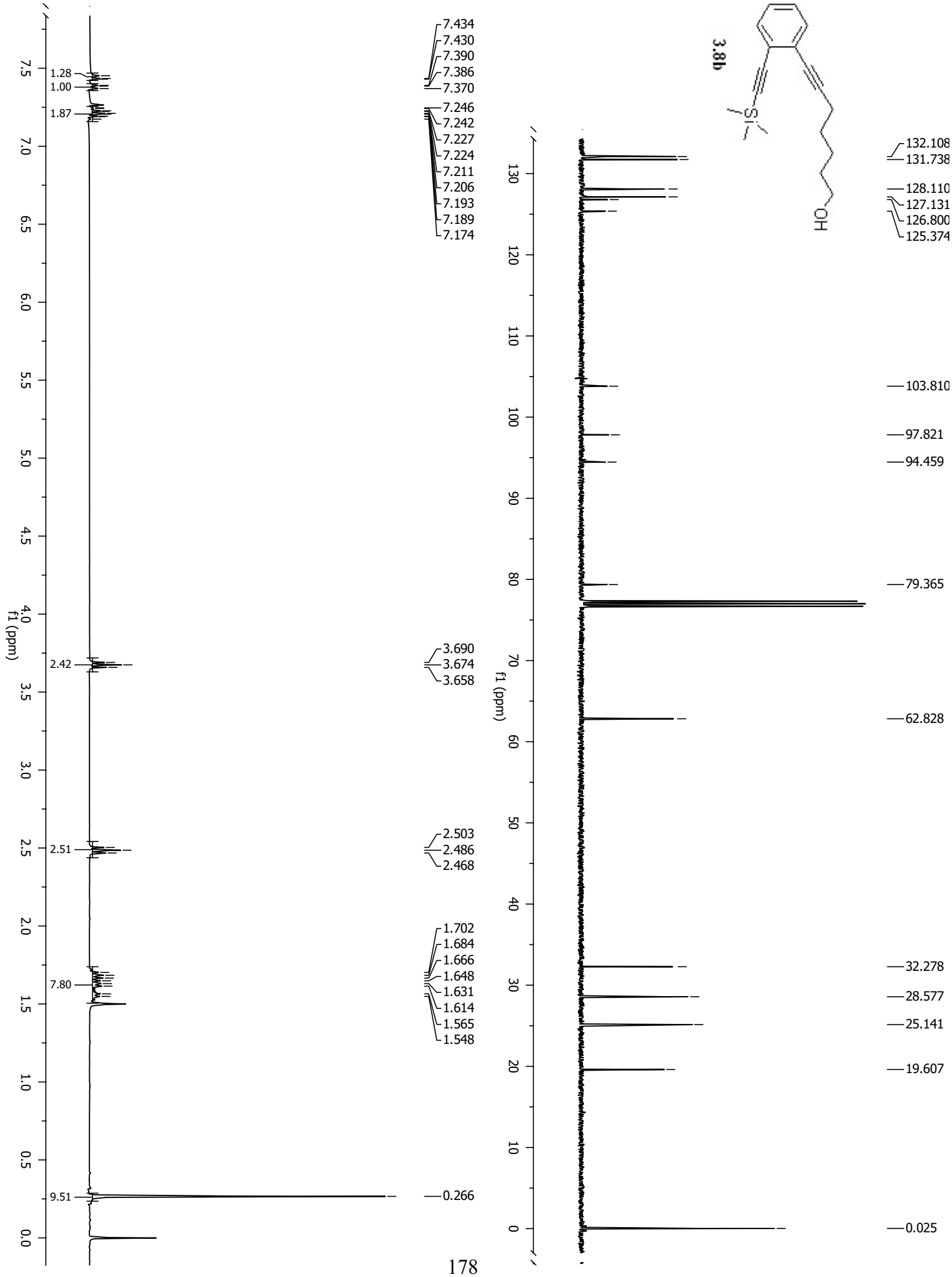
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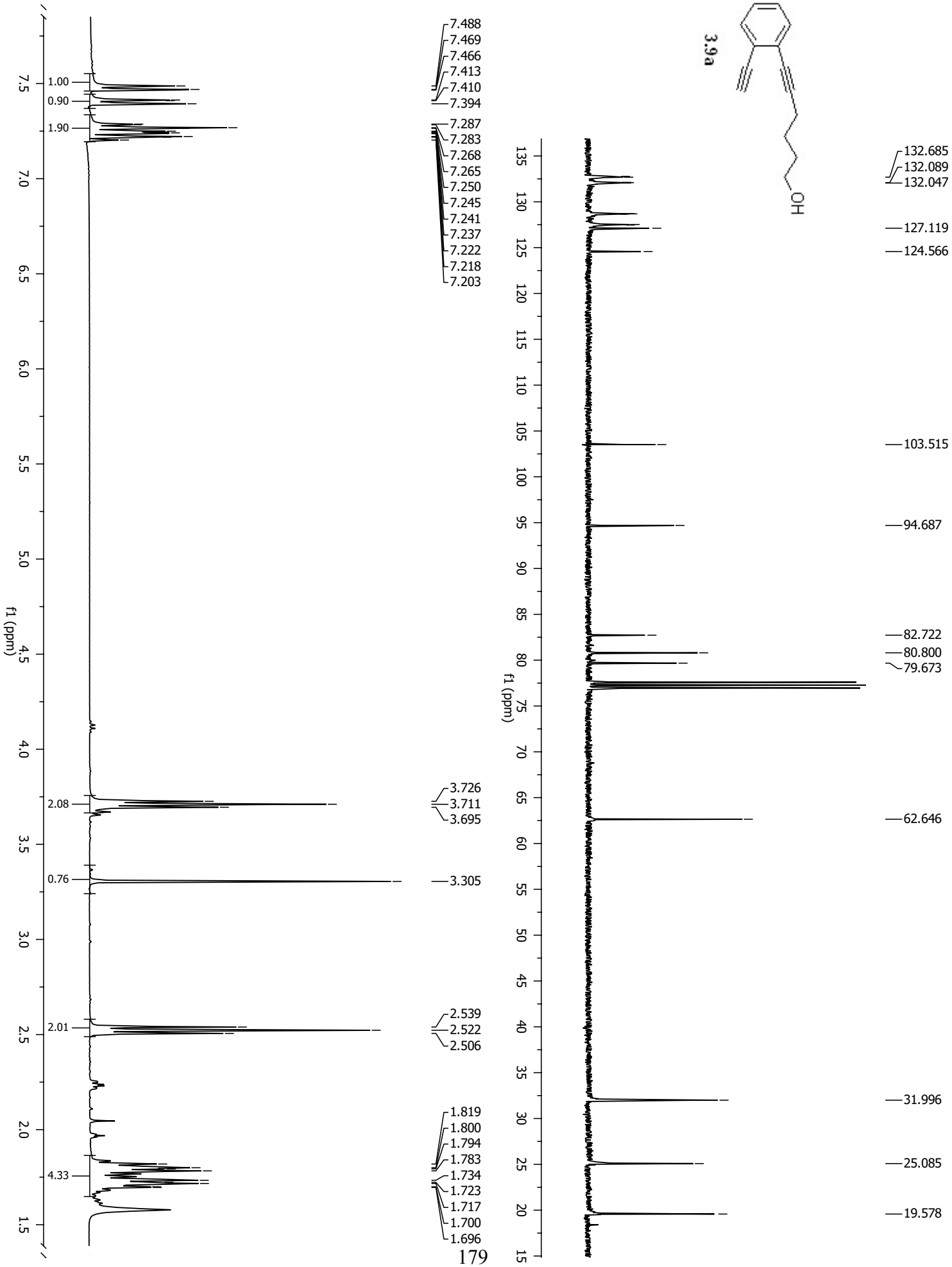
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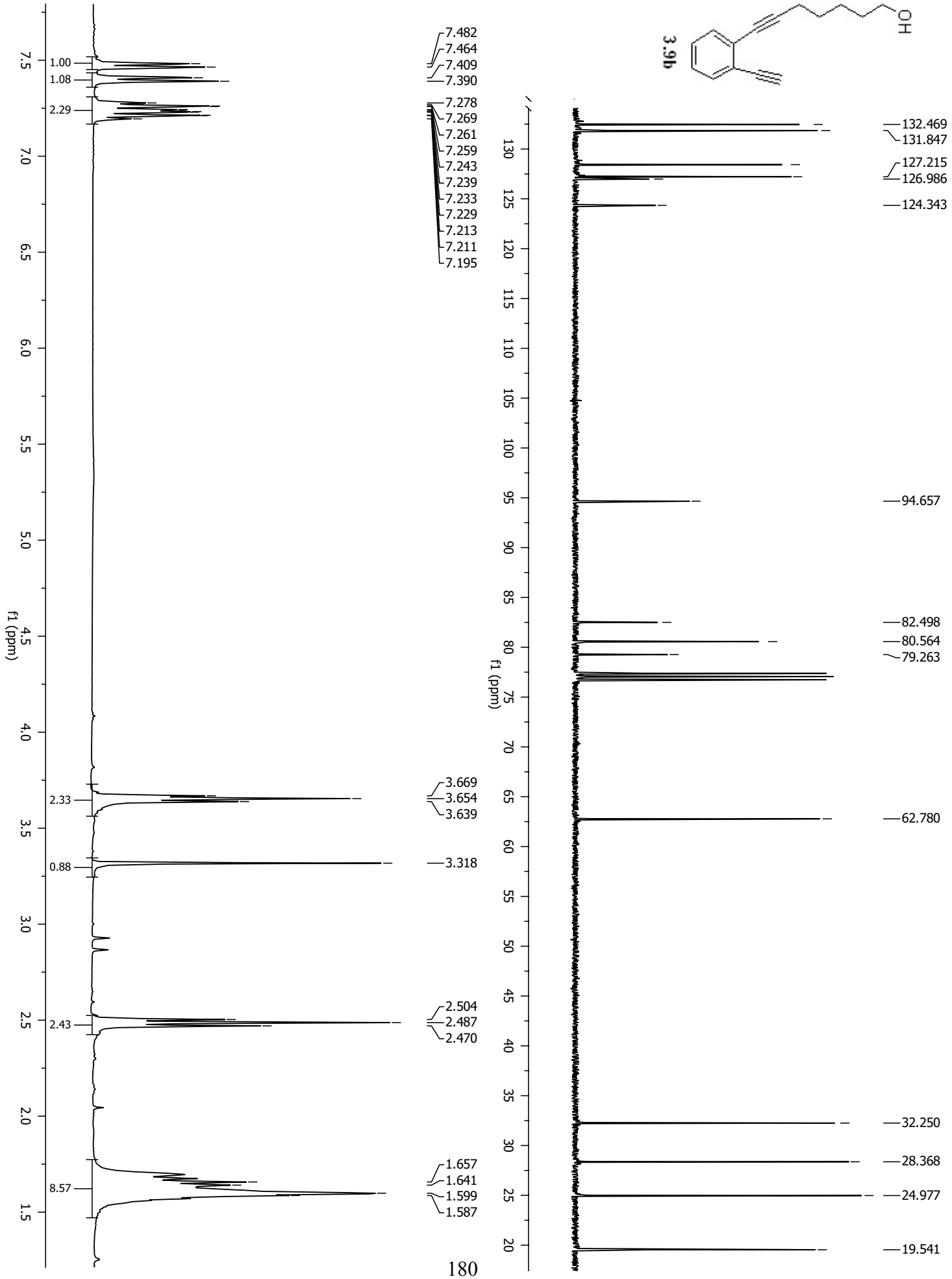
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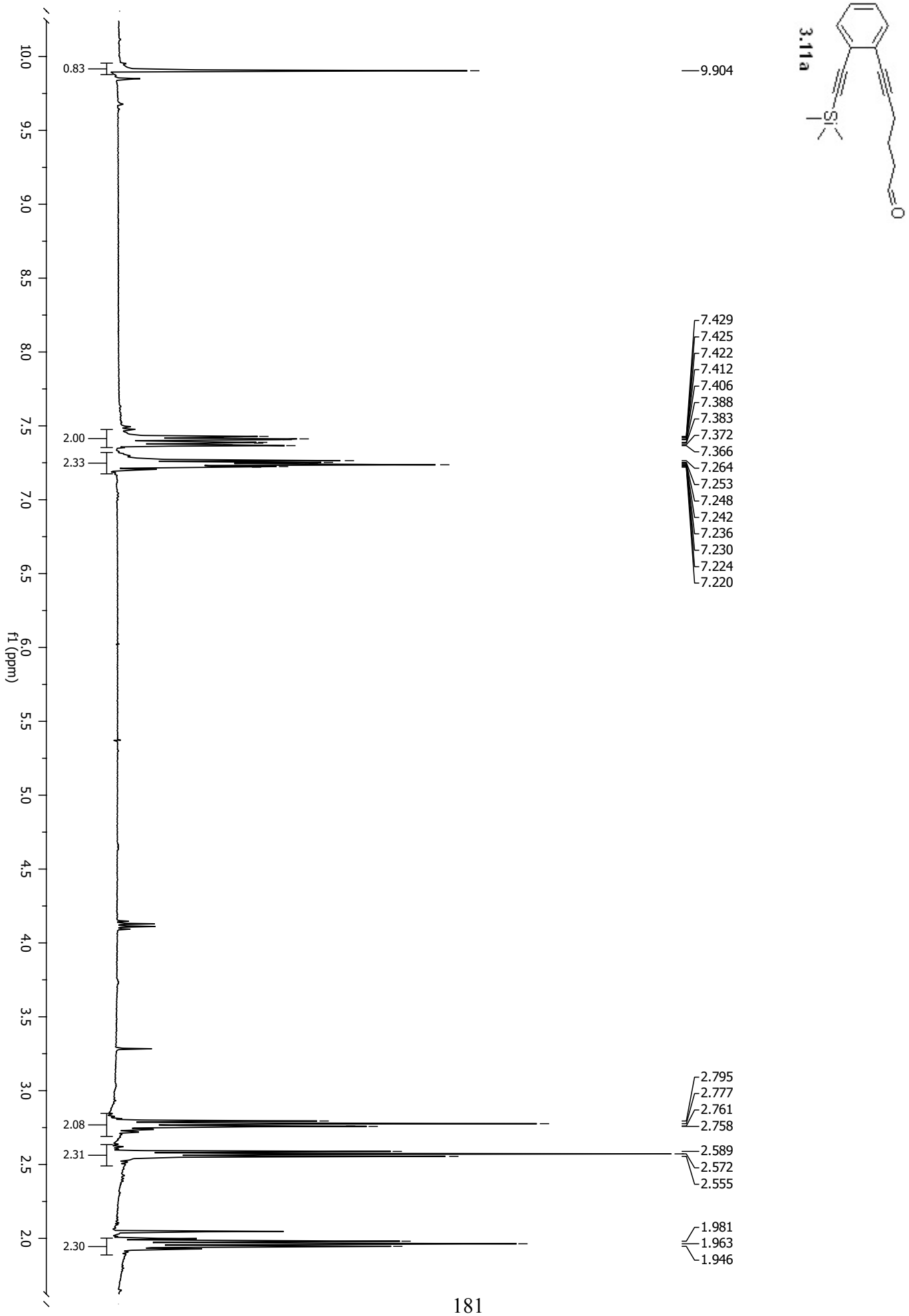
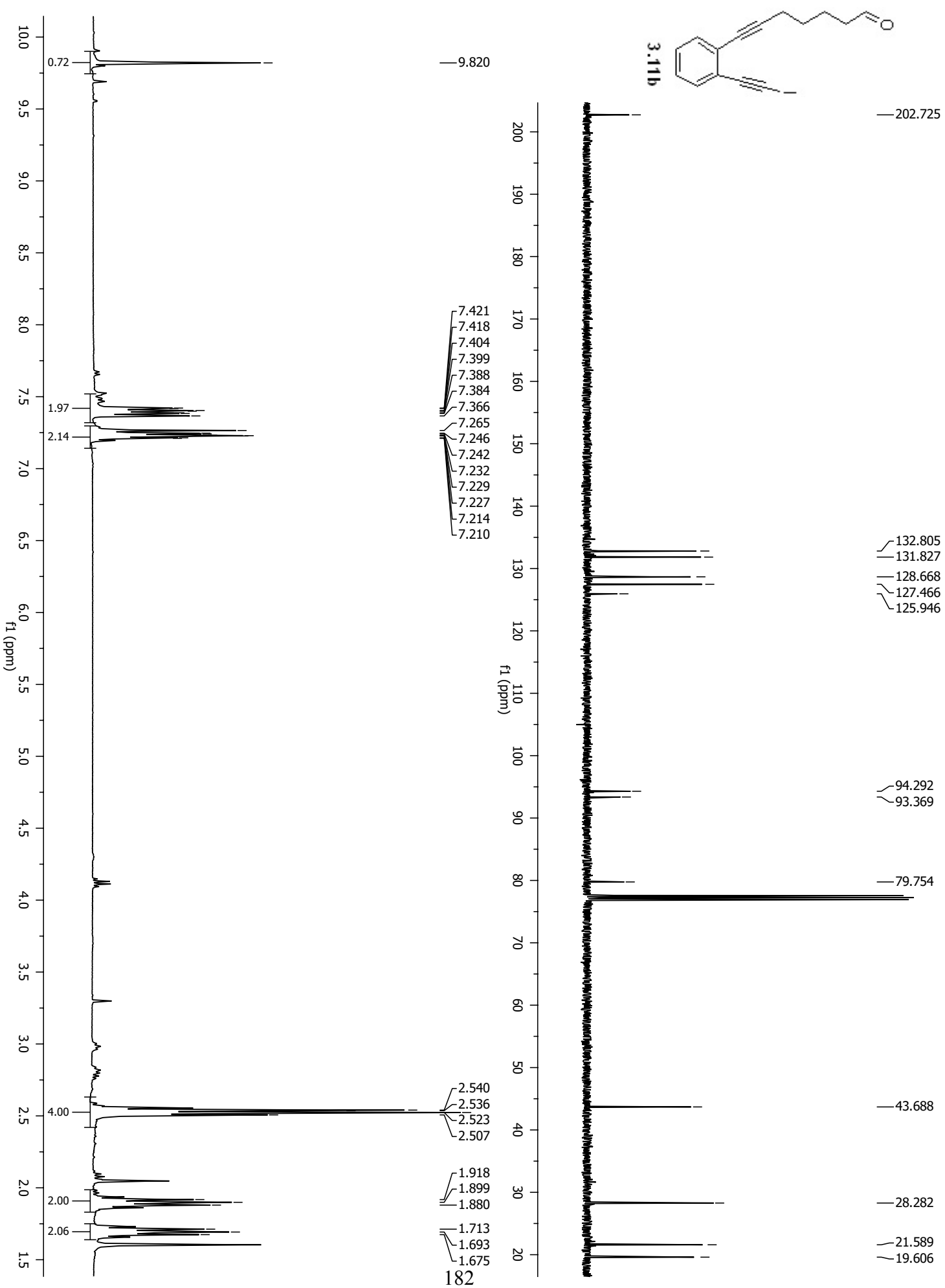
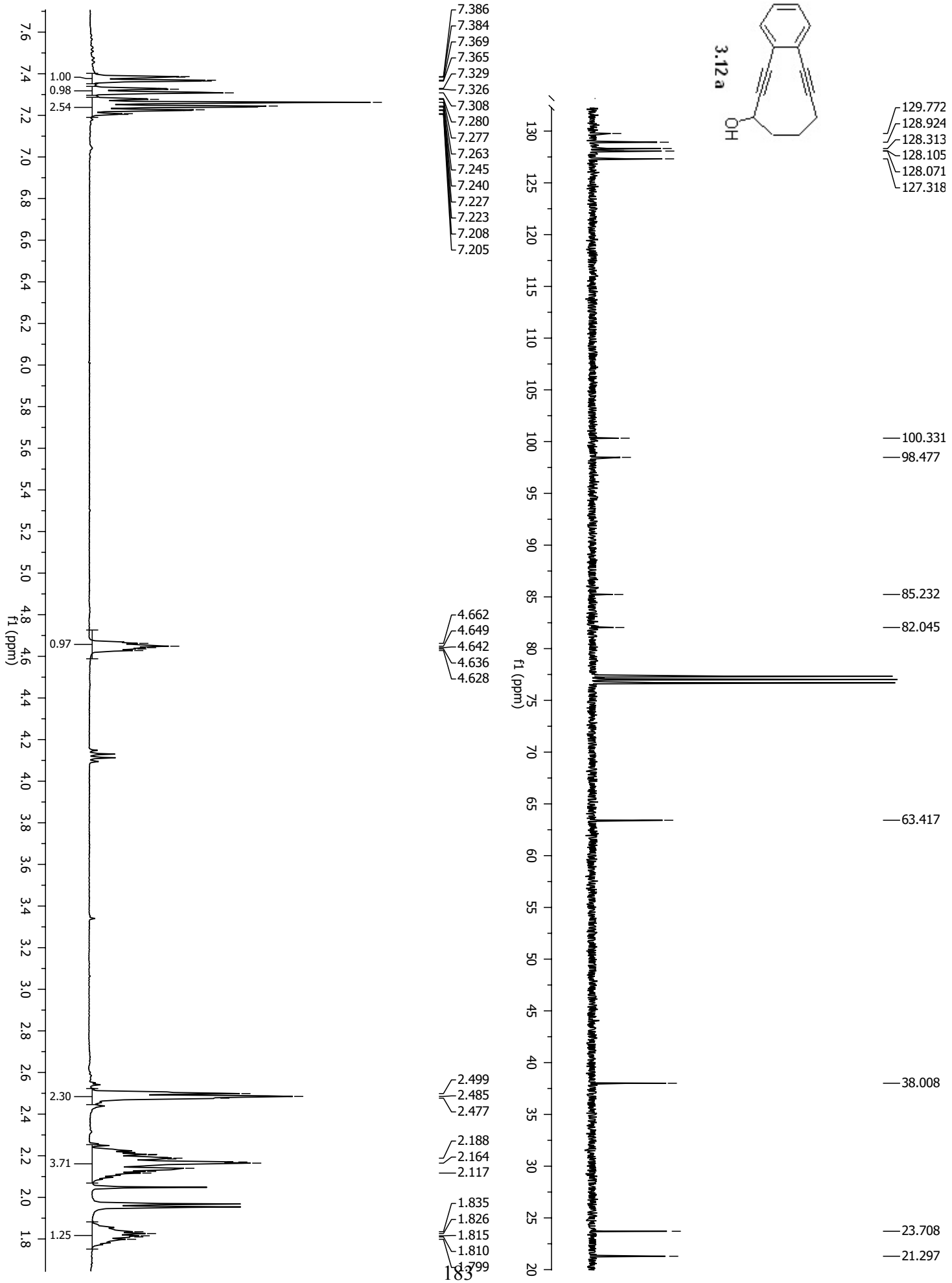
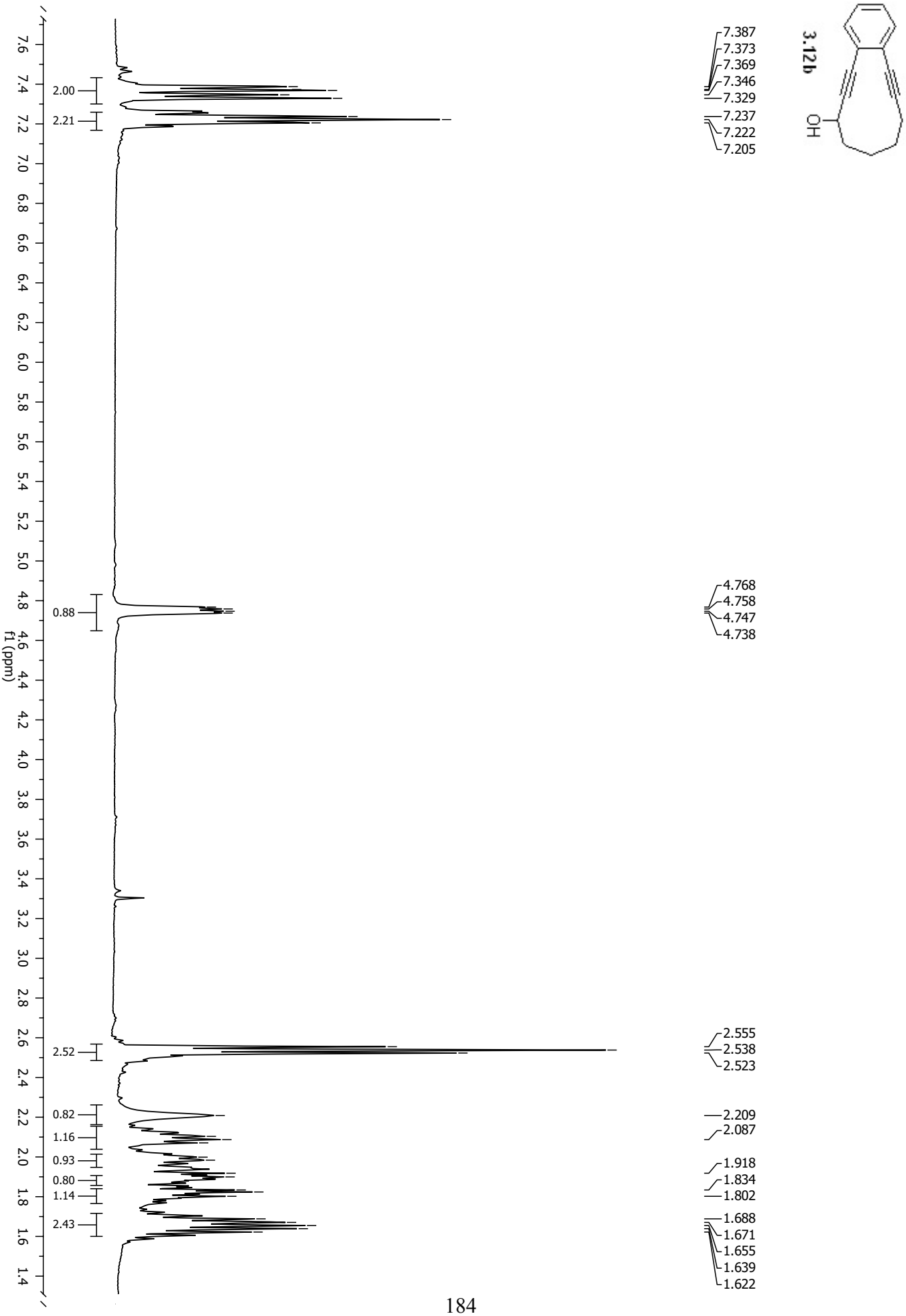
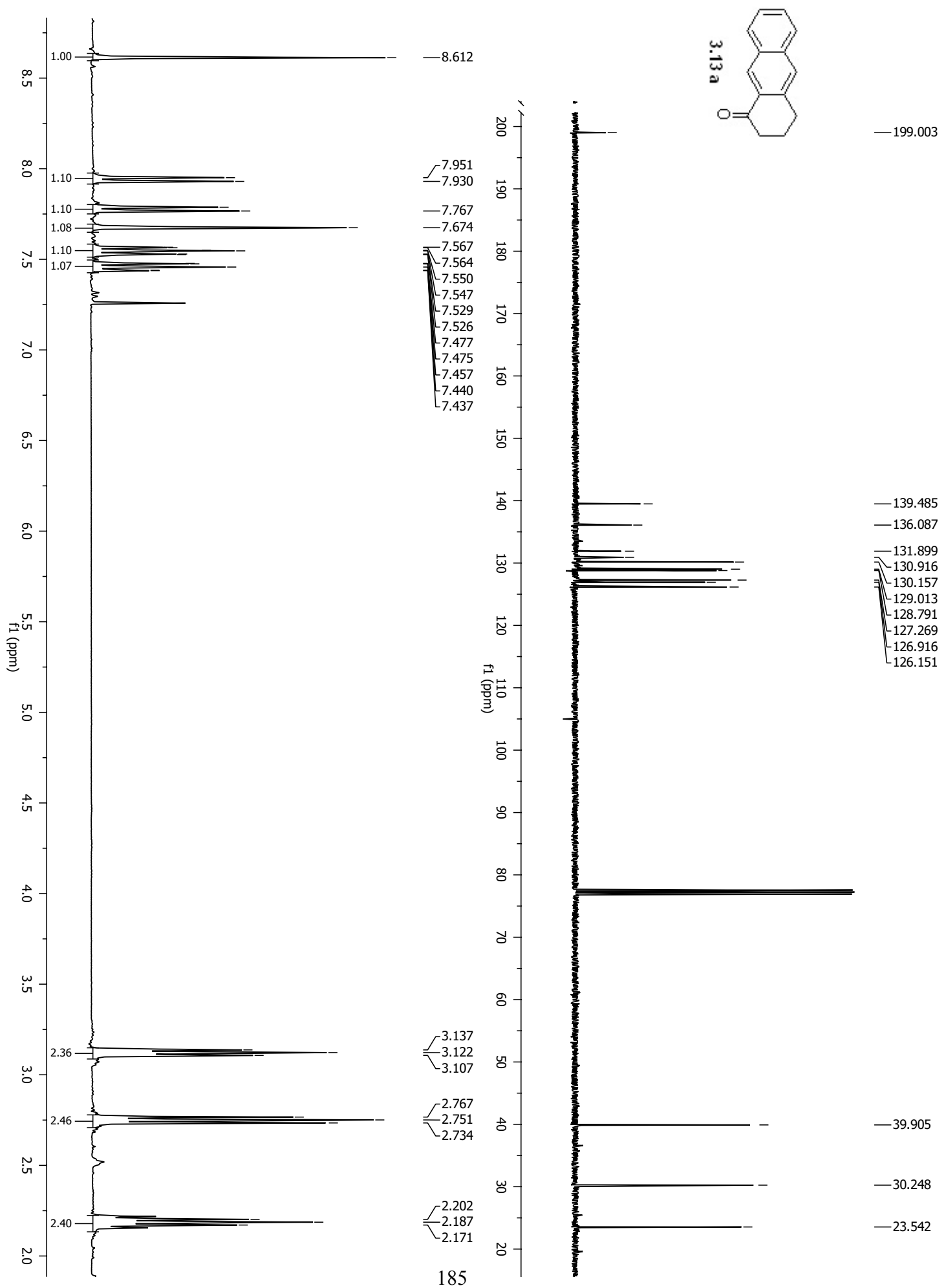
124.343
94.657
82.498
80.564
79.263
62.780
32.250
28.368
24.977
19.541

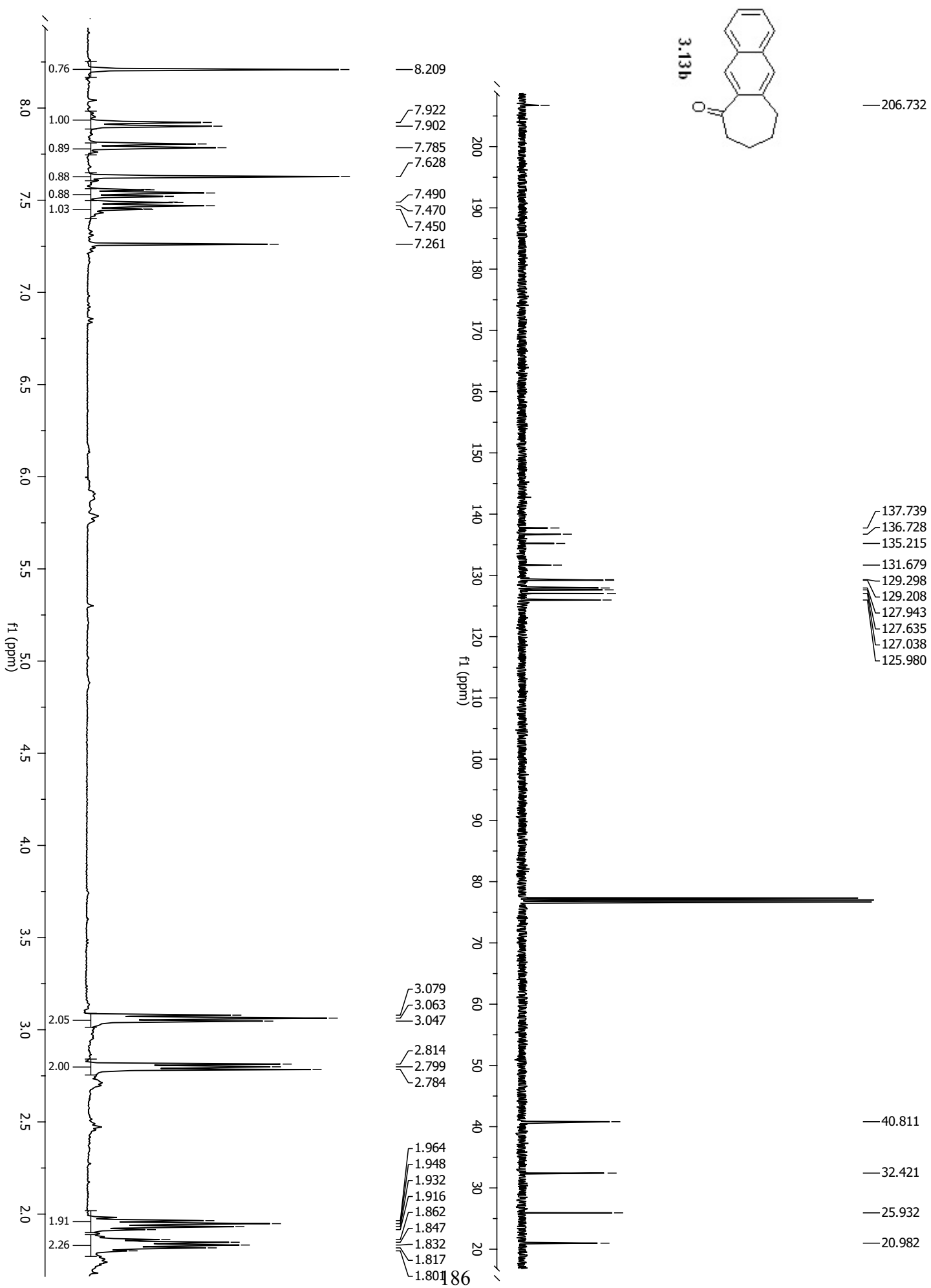

3.11a
Si
O
9.904
7.429
7.425
7.422
7.412
7.406
7.388
7.383
7.372
7.366
7.264
7.253
7.248
7.242
7.236
7.230
7.224
7.220
2.795
2.777
2.761
2.758
2.589
2.572
2.555
1.981
1.963
1.946
0.83
2.00
2.33
2.08
2.31
2.30
f1 (ppm)

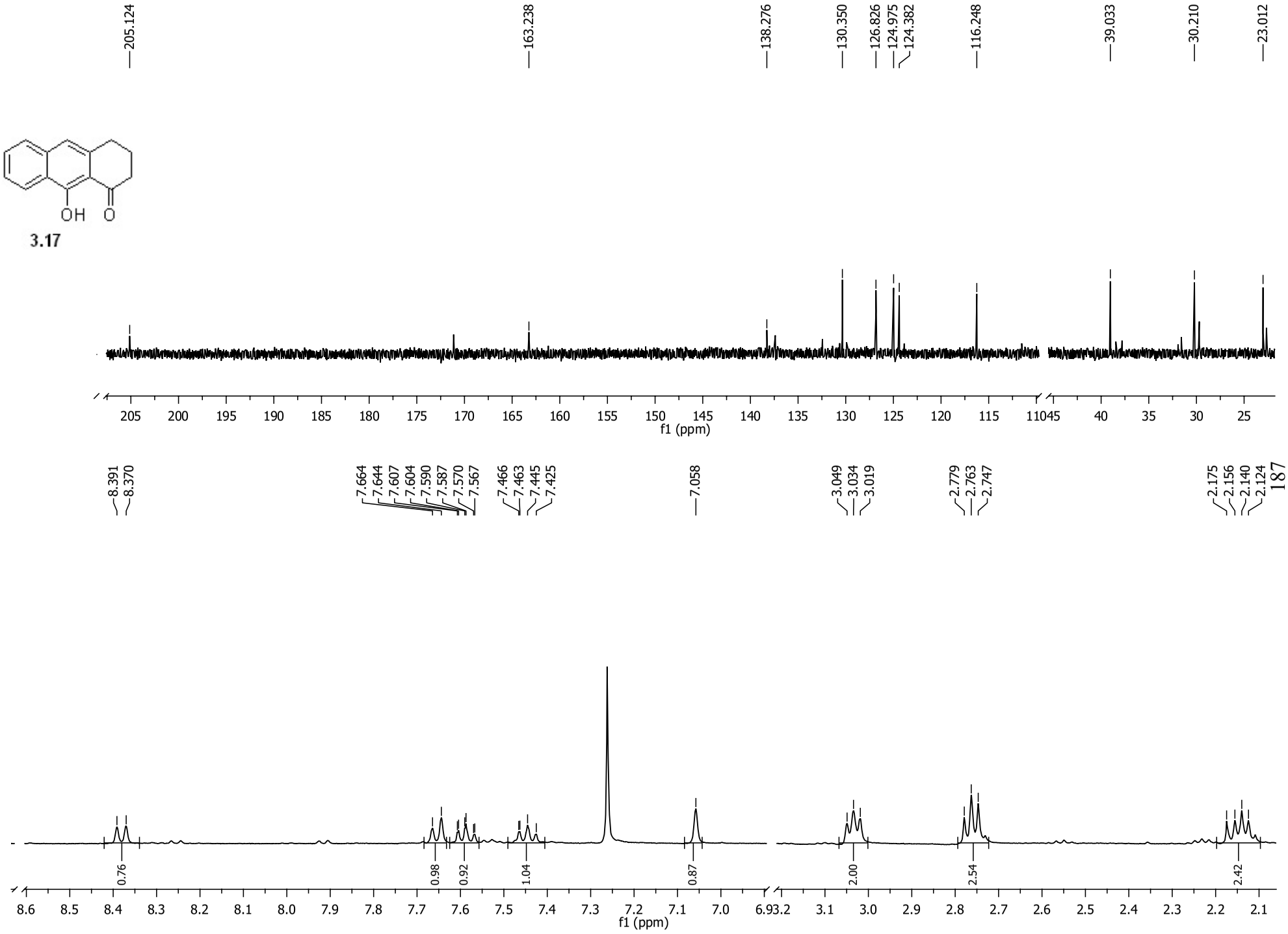

3.11b
O
9.820
7.421
7.418
7.404
7.399
7.388
7.384
7.366
7.265
7.246
7.242
7.232
7.229
7.227
7.214
7.210
2.540
2.536
2.523
2.507
1.918
1.899
1.880
1.713
1.693
1.675
0.72
1.97
2.14
4.00
2.00
2.06
f1 (ppm)
202.725
132.805
131.827
128.668
127.466
125.946
94.292
93.369
79.754
43.688
28.282
21.589
19.606
f1 (ppm)

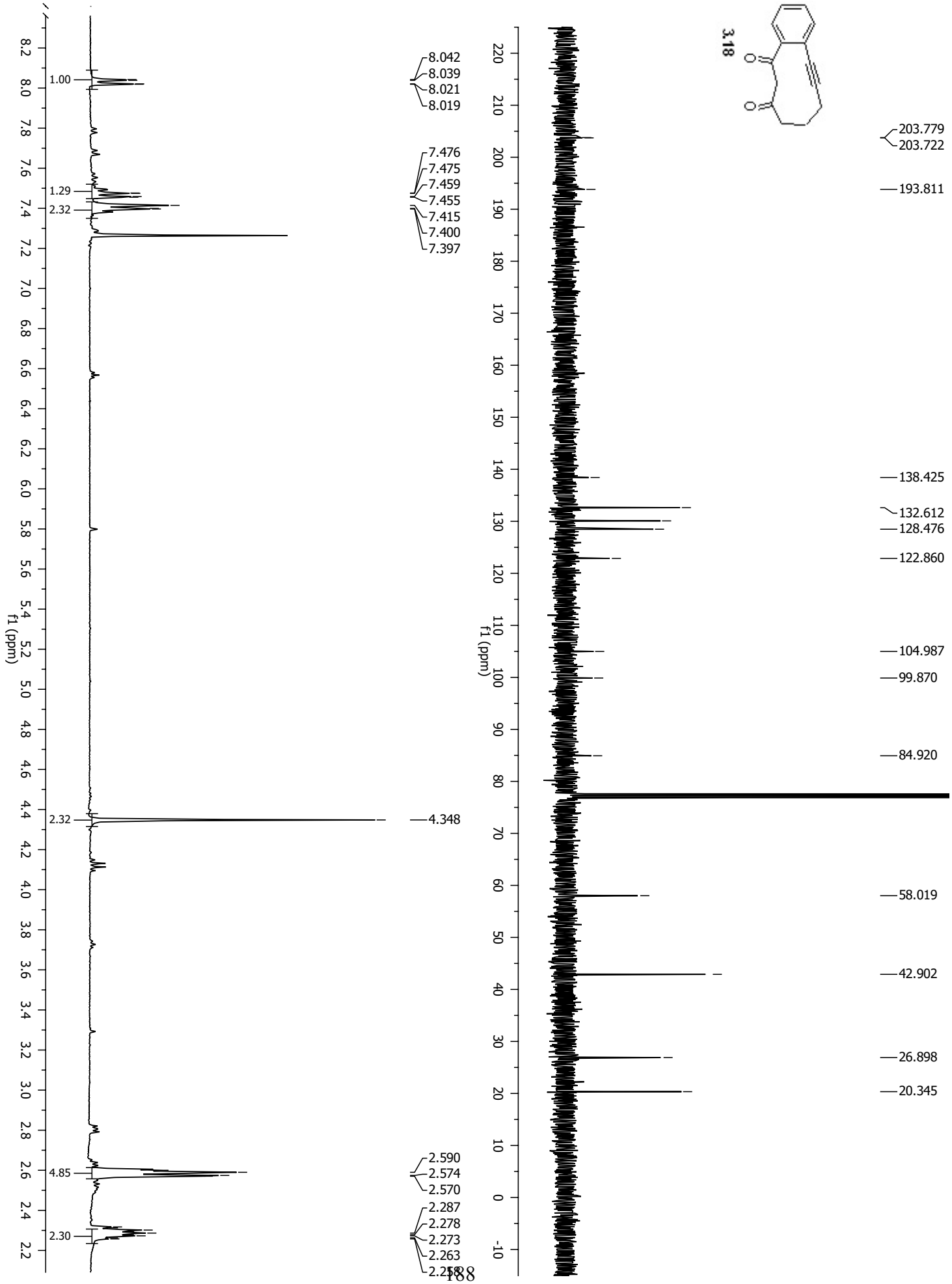

3.12a
OH
f1 (ppm)
1.00
0.98
2.54
0.97
2.30
3.71
1.25
7.386
7.384
7.369
7.365
7.329
7.326
7.308
7.280
7.277
7.263
7.245
7.240
7.227
7.223
7.208
7.205
4.662
4.649
4.642
4.636
4.628
2.499
2.485
2.477
2.188
2.164
2.117
1.835
1.826
1.815
1.810
1.799
129.772
128.924
128.313
128.105
128.071
127.318
100.331
98.477
85.232
82.045
63.417
38.008
23.708
21.297

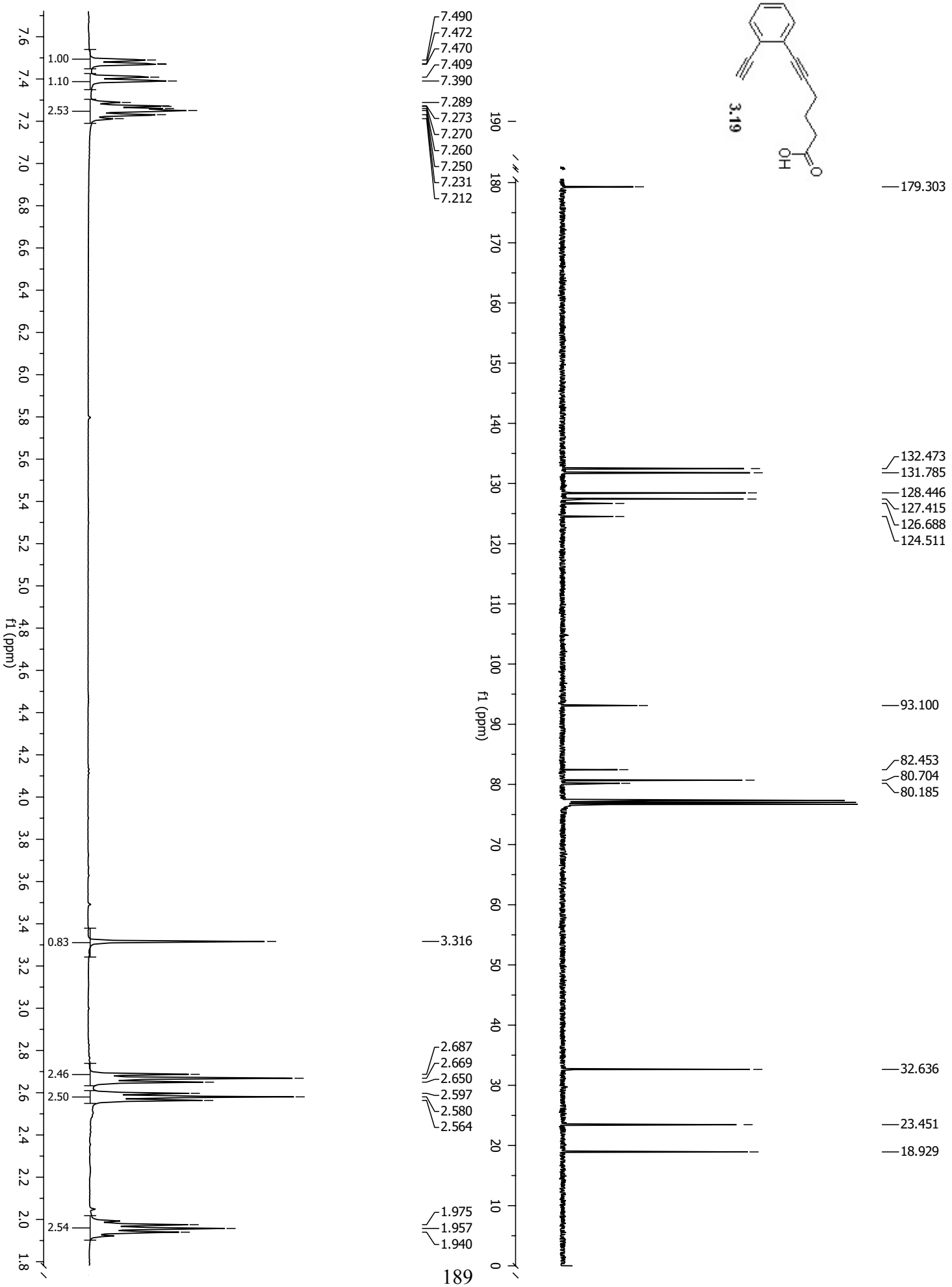

3.12b
OH
7.387
7.373
7.369
7.346
7.329
7.237
7.222
7.205
4.768
4.758
4.747
4.738
2.555
2.538
2.523
2.209
2.087
1.918
1.834
1.802
1.688
1.671
1.655
1.639
1.622
2.00
2.21
0.88
2.52
0.82
1.16
0.93
0.80
1.14
2.43
f1 (ppm)

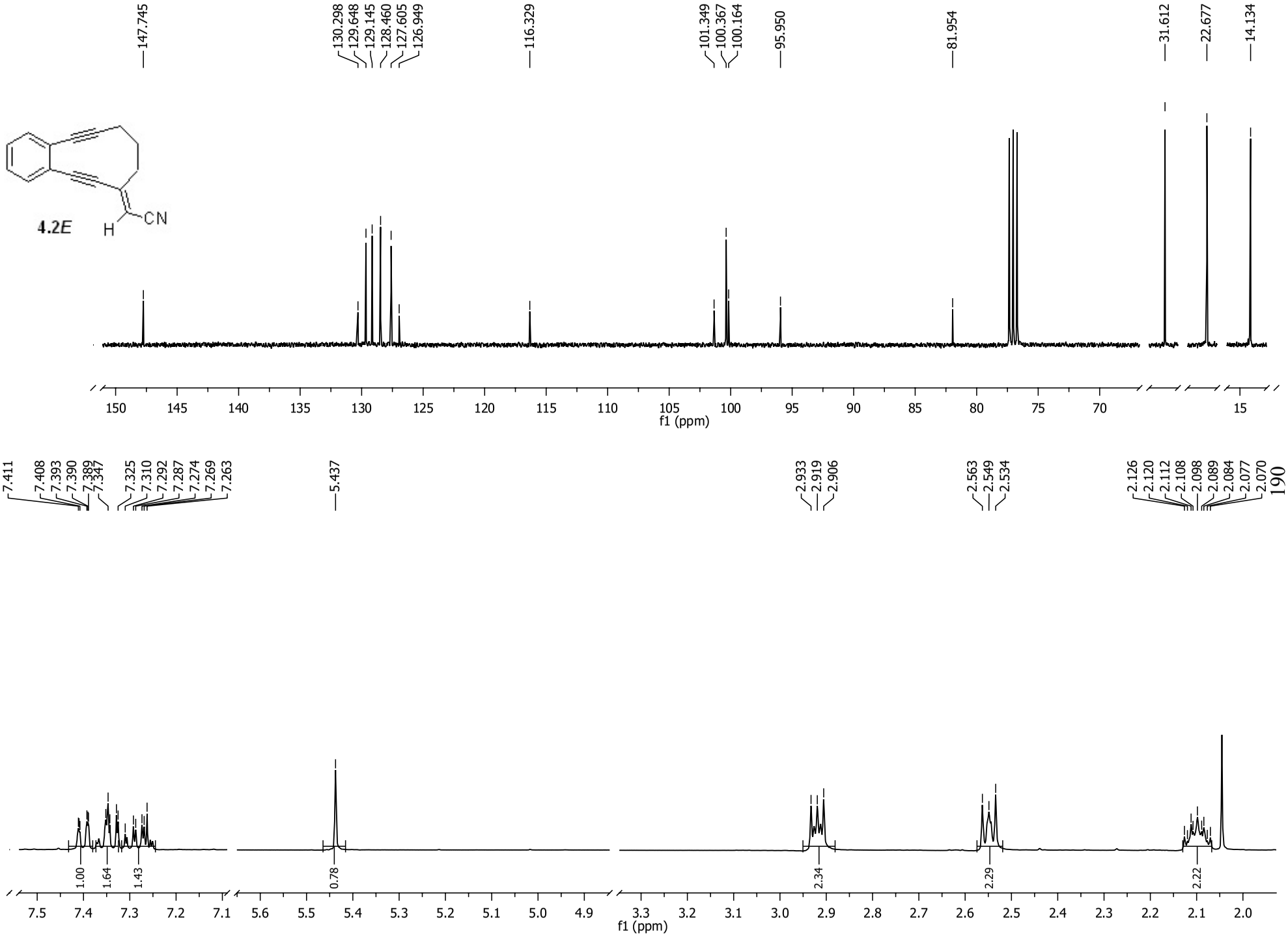

3.13 a
1.00
1.10
1.10
1.08
1.10
1.07
2.36
2.46
2.40
8.612
7.951
7.930
7.767
7.674
7.567
7.564
7.550
7.547
7.529
7.526
7.477
7.475
7.457
7.440
7.437
3.137
3.122
3.107
2.767
2.751
2.734
2.202
2.187
2.171
f1 (ppm)
199.003
139.485
136.087
131.899
130.916
130.157
129.013
128.791
127.269
126.916
126.151
39.905
30.248
23.542
f1 (ppm)

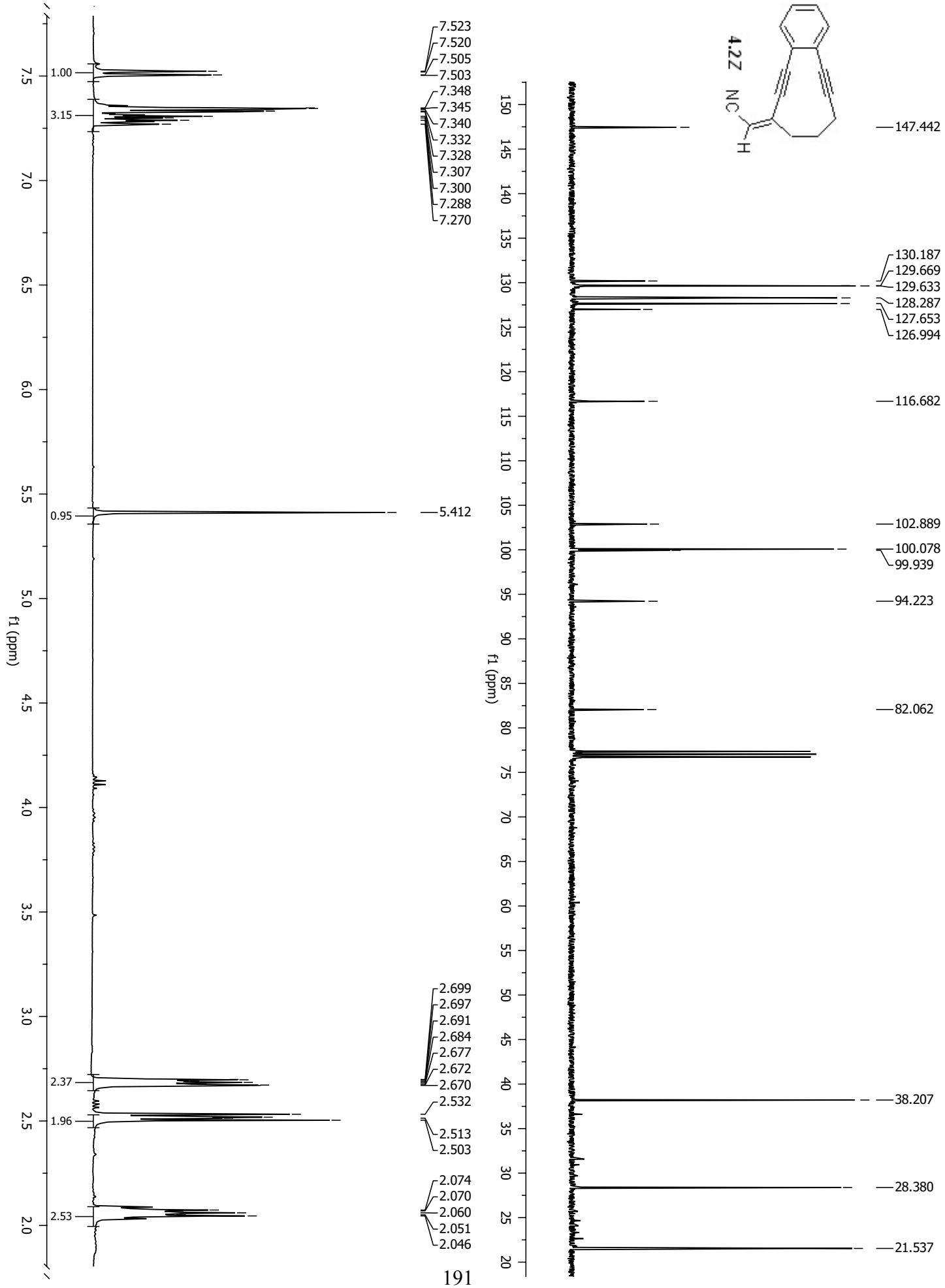

3.13b
O
f1 (ppm)
0.76
1.00
0.89
0.88
0.88
1.03
2.05
2.00
1.91
2.26
8.209
7.922
7.902
7.785
7.628
7.490
7.470
7.450
7.261
3.079
3.063
3.047
2.814
2.799
2.784
1.964
1.948
1.932
1.916
1.862
1.847
1.832
1.817
1.801
206.732
137.739
136.728
135.215
131.679
129.298
129.208
127.943
127.635
127.038
125.980
40.811
32.421
25.932
20.982

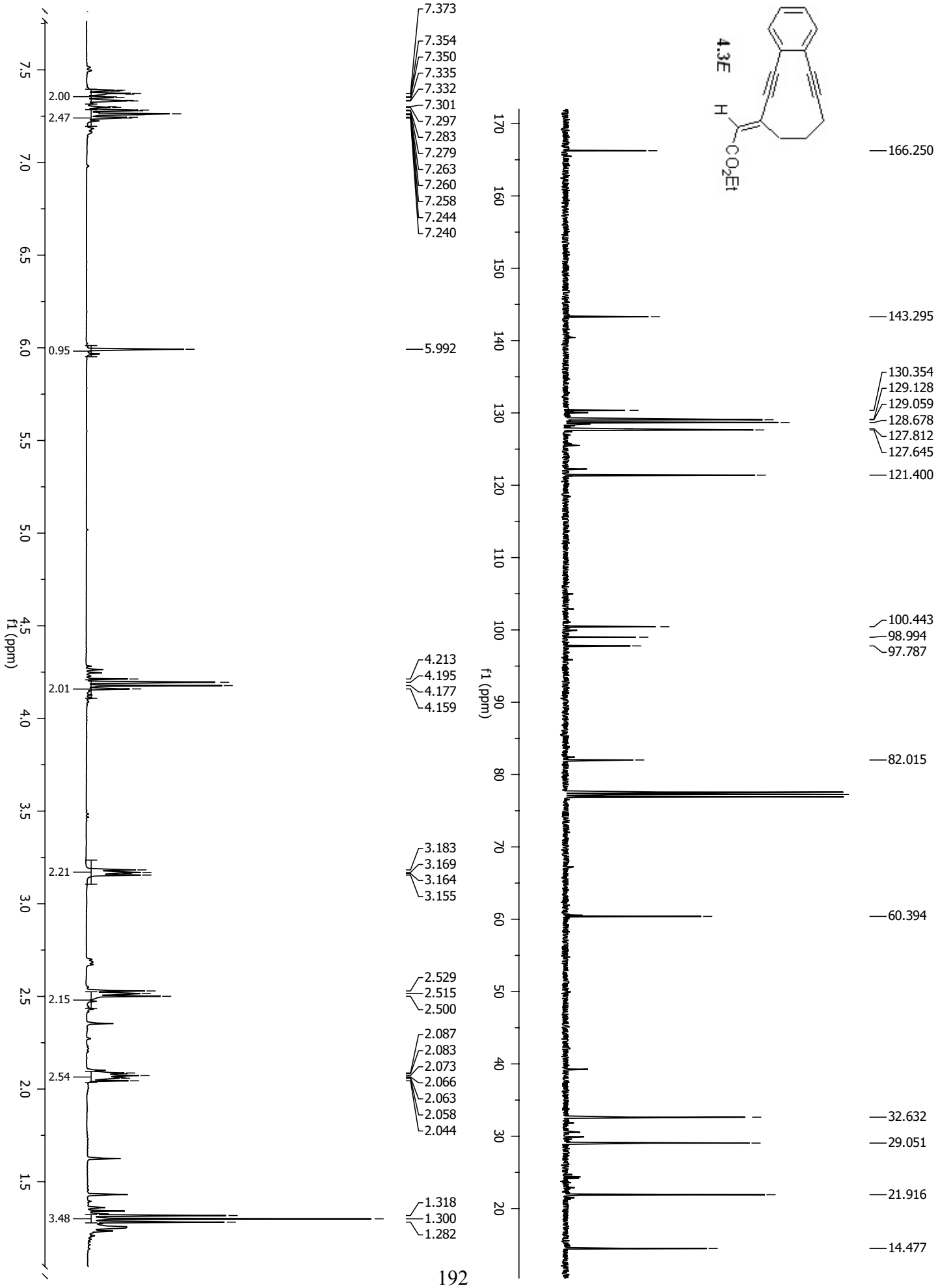

205.124
163.238
138.276
130.350
126.826
124.975
124.382
116.248
39.033
30.210
23.012
OH
O
3.17
f1 (ppm)
8.391
8.370
7.664
7.644
7.607
7.604
7.590
7.587
7.570
7.567
7.466
7.463
7.445
7.425
7.058
3.049
3.034
3.019
2.779
2.763
2.747
2.175
2.156
2.140
2.124
0.76
0.98
0.92
1.04
0.87
2.00
2.54
2.42
f1 (ppm)

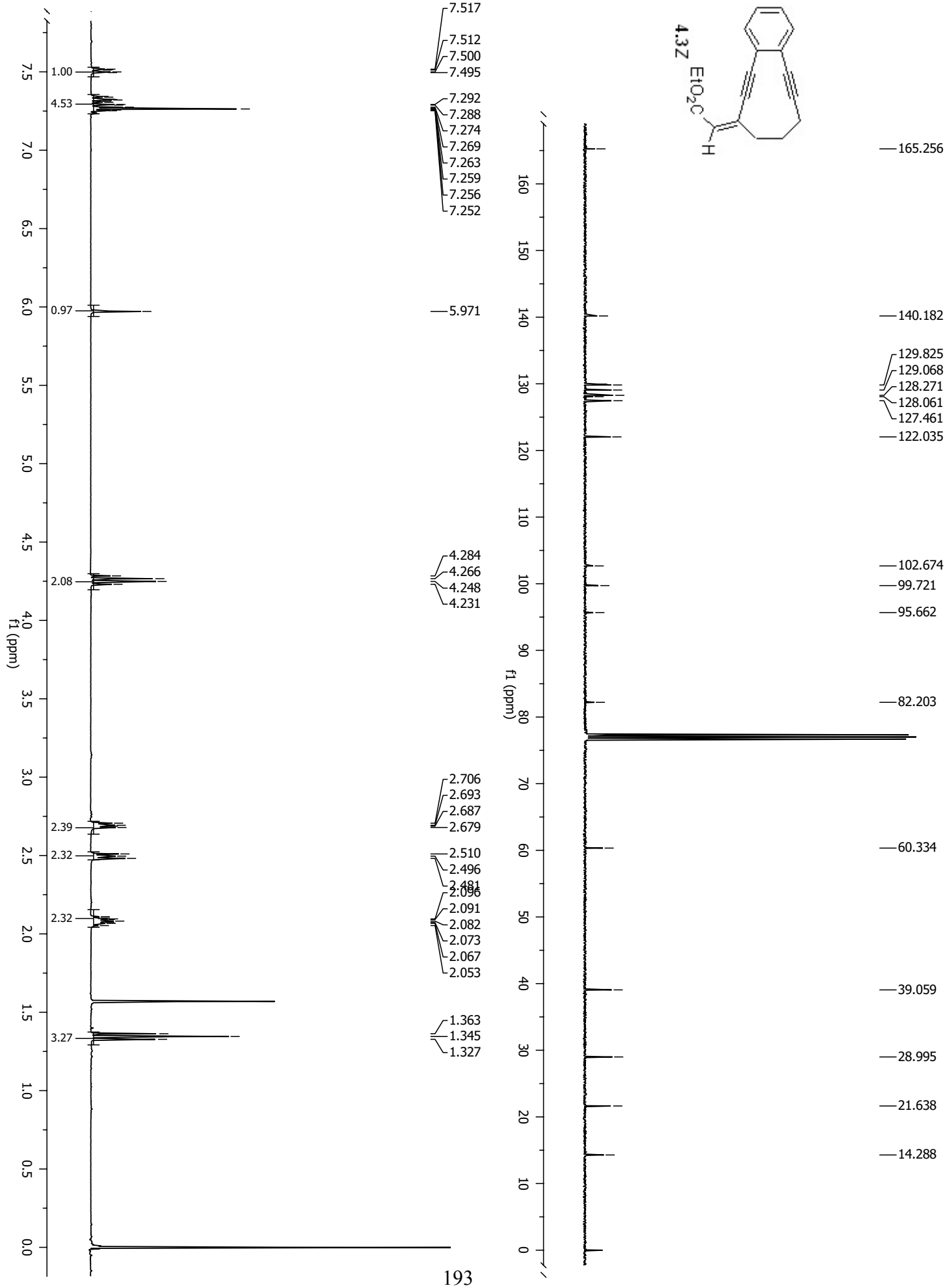

3.18
f1 (ppm)
1.00
1.29
2.32
2.32
4.85
2.30
8.042
8.039
8.021
8.019
7.476
7.475
7.459
7.455
7.415
7.400
7.397
4.348
2.590
2.574
2.570
2.287
2.278
2.273
2.263
2.258
203.779
203.722
193.811
138.425
132.612
128.476
122.860
104.987
99.870
84.920
58.019
42.902
26.898
20.345

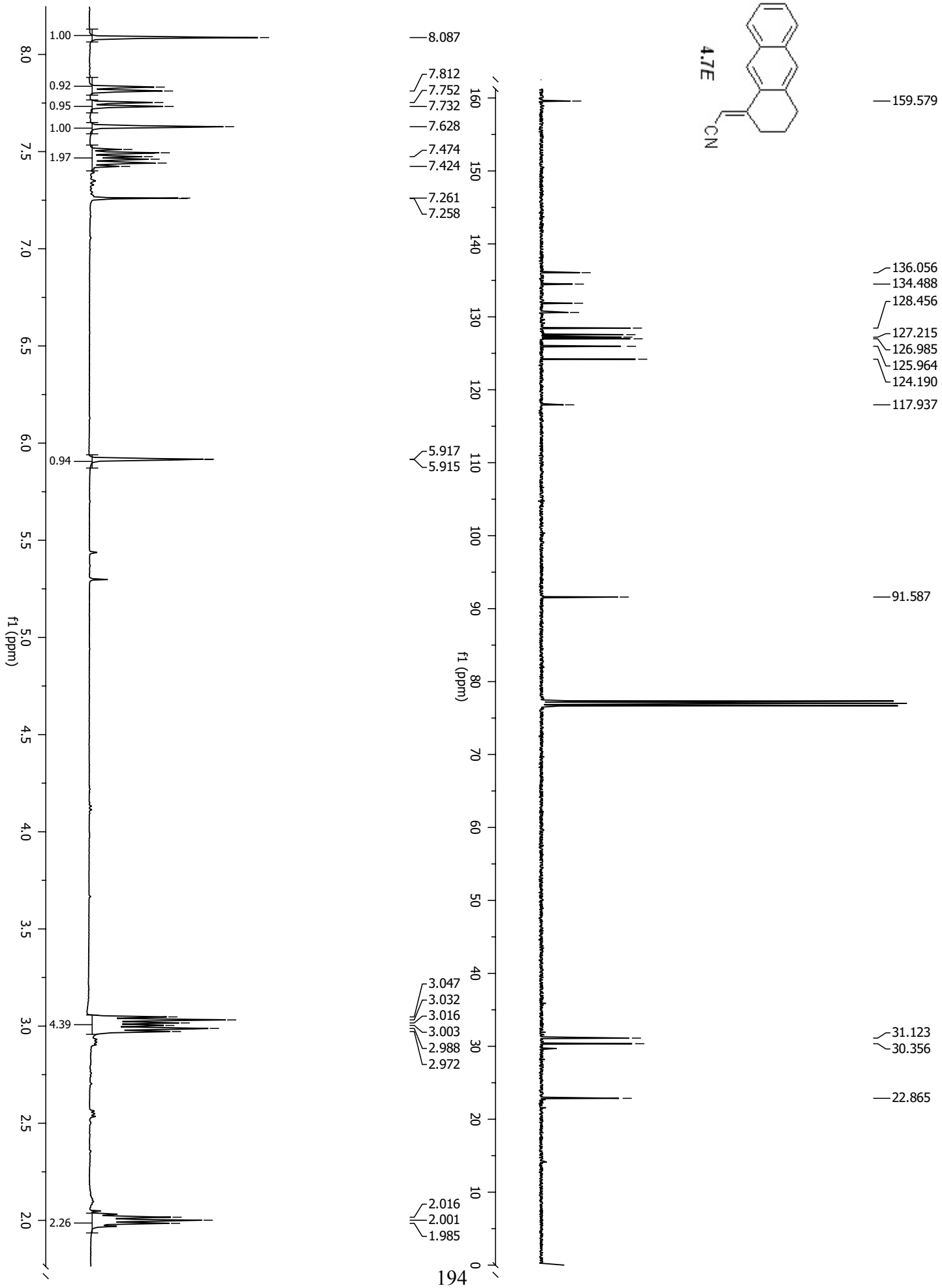

3.19
OH
O
7.490
7.472
7.470
7.409
7.390
7.289
7.273
7.270
7.260
7.250
7.231
7.212
1.00
1.10
2.53
0.83
2.46
2.50
2.54
3.316
2.687
2.669
2.650
2.597
2.580
2.564
1.975
1.957
1.940
179.303
132.473
131.785
128.446
127.415
126.688
124.511
93.100
82.453
80.704
80.185
32.636
23.451
18.929
f1 (ppm)
f1 (ppm)

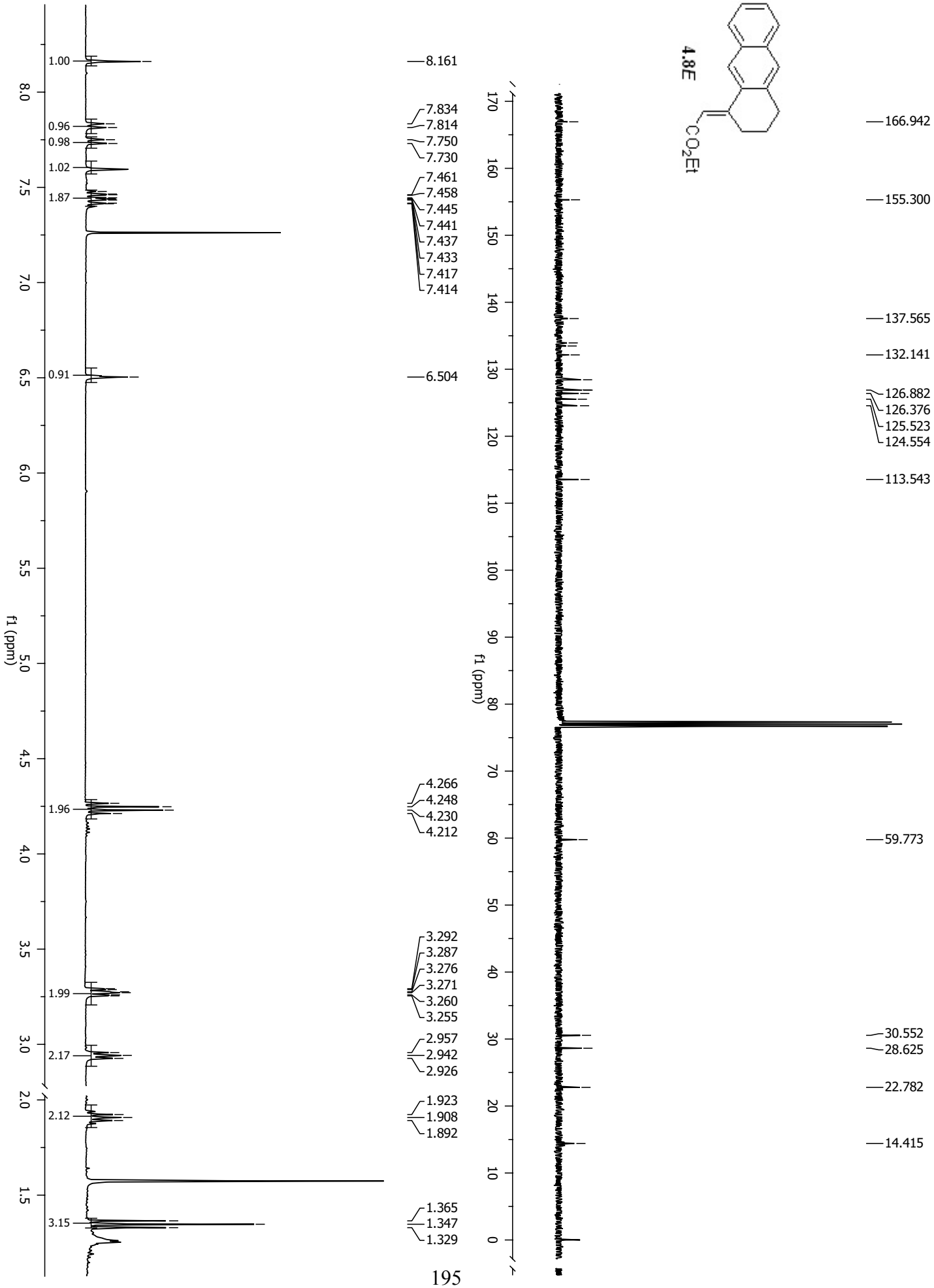

147.745
130.298
129.648
129.145
128.460
127.605
126.949
116.329
101.349
100.367
100.164
95.950
81.954
31.612
22.677
14.134
4.2E
CN
H
f1 (ppm)
7.411
7.408
7.393
7.390
7.389
7.347
7.325
7.310
7.292
7.287
7.274
7.269
7.263
5.437
2.933
2.919
2.906
2.563
2.549
2.534
2.126
2.120
2.112
2.108
2.098
2.089
2.084
2.077
2.070
1.00
1.64
1.43
0.78
2.34
2.29
2.22
f1 (ppm)

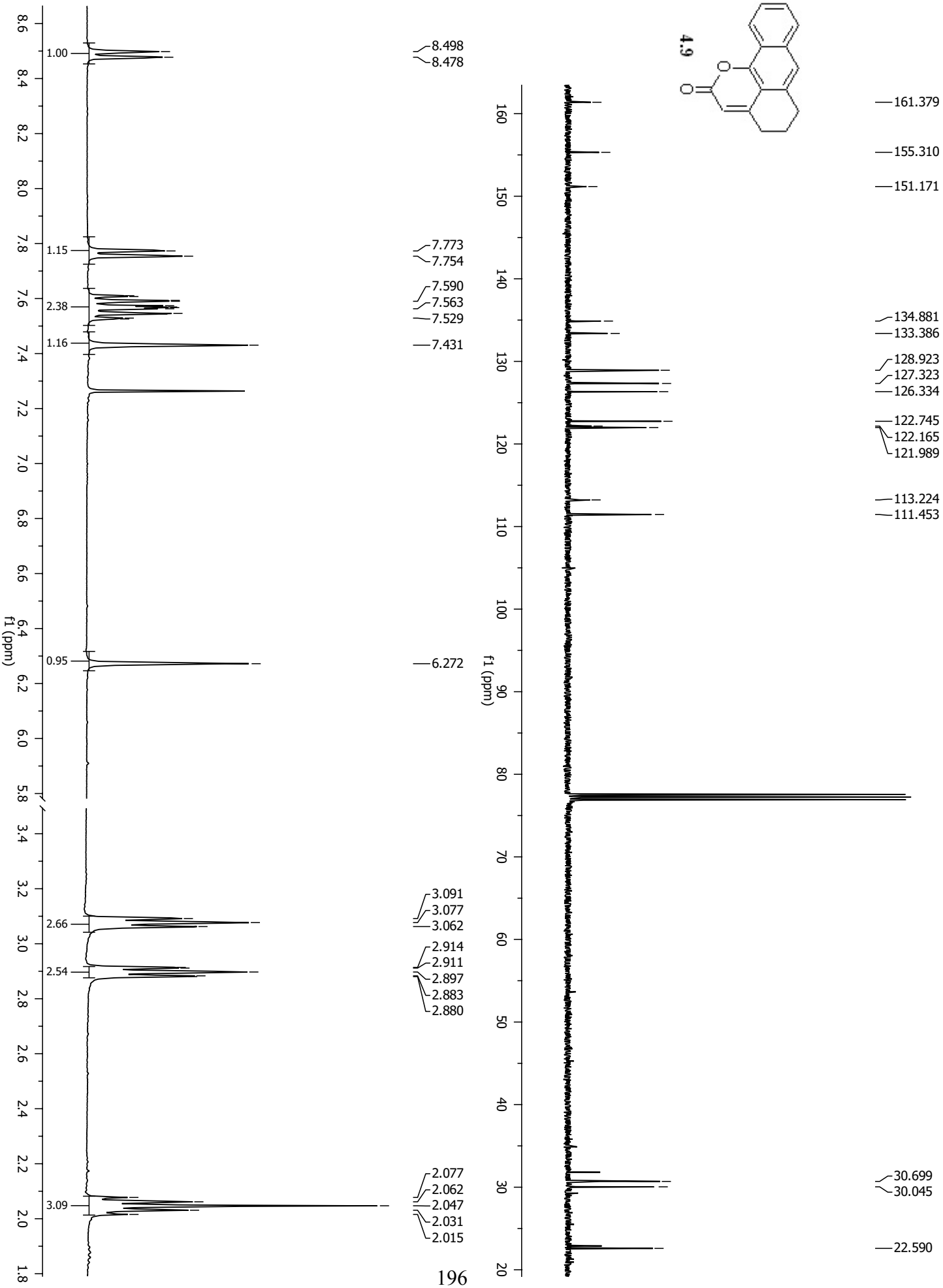

4.27
NC
H
1.00
3.15
0.95
2.37
1.96
2.53
7.523
7.520
7.505
7.503
7.348
7.345
7.340
7.332
7.328
7.307
7.300
7.288
7.270
5.412
2.699
2.697
2.691
2.684
2.677
2.672
2.670
2.532
2.513
2.503
2.074
2.070
2.060
2.051
2.046
f1 (ppm)
147.442
130.187
129.669
129.633
128.287
127.653
126.994
116.682
102.889
100.078
99.939
94.223
82.062
38.207
28.380
21.537
f1 (ppm)

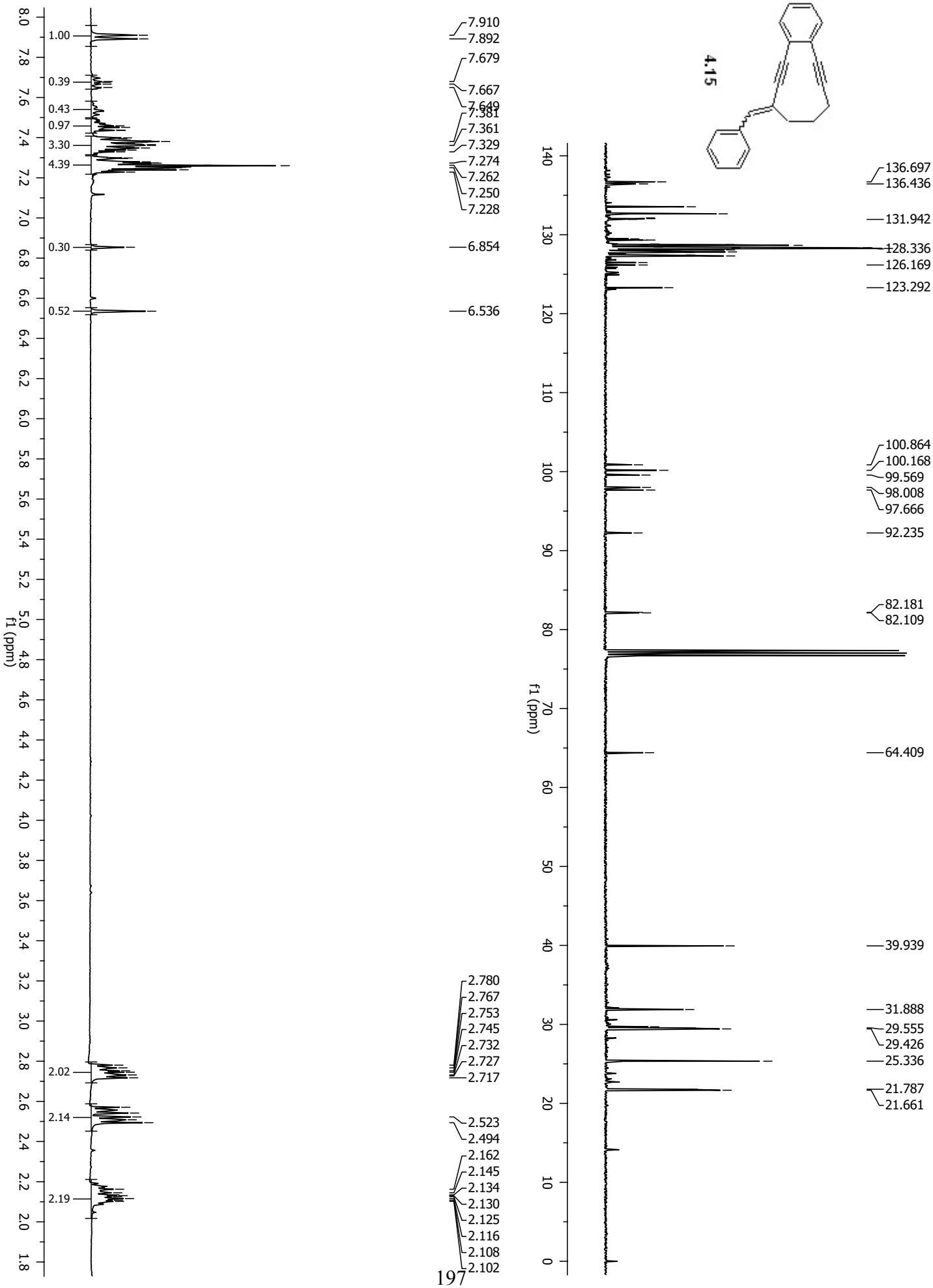

4.3E
H
CO2Et
f1 (ppm)
7.373
7.354
7.350
7.335
7.332
7.301
7.297
7.283
7.279
7.263
7.260
7.258
7.244
7.240
5.992
4.213
4.195
4.177
4.159
3.183
3.169
3.164
3.155
2.529
2.515
2.500
2.087
2.083
2.073
2.066
2.063
2.058
2.044
1.318
1.300
1.282
2.00
2.47
0.95
2.01
2.21
2.15
2.54
3.48
166.250
143.295
130.354
129.128
129.059
128.678
127.812
127.645
121.400
100.443
98.994
97.787
82.015
60.394
32.632
29.051
21.916
14.477

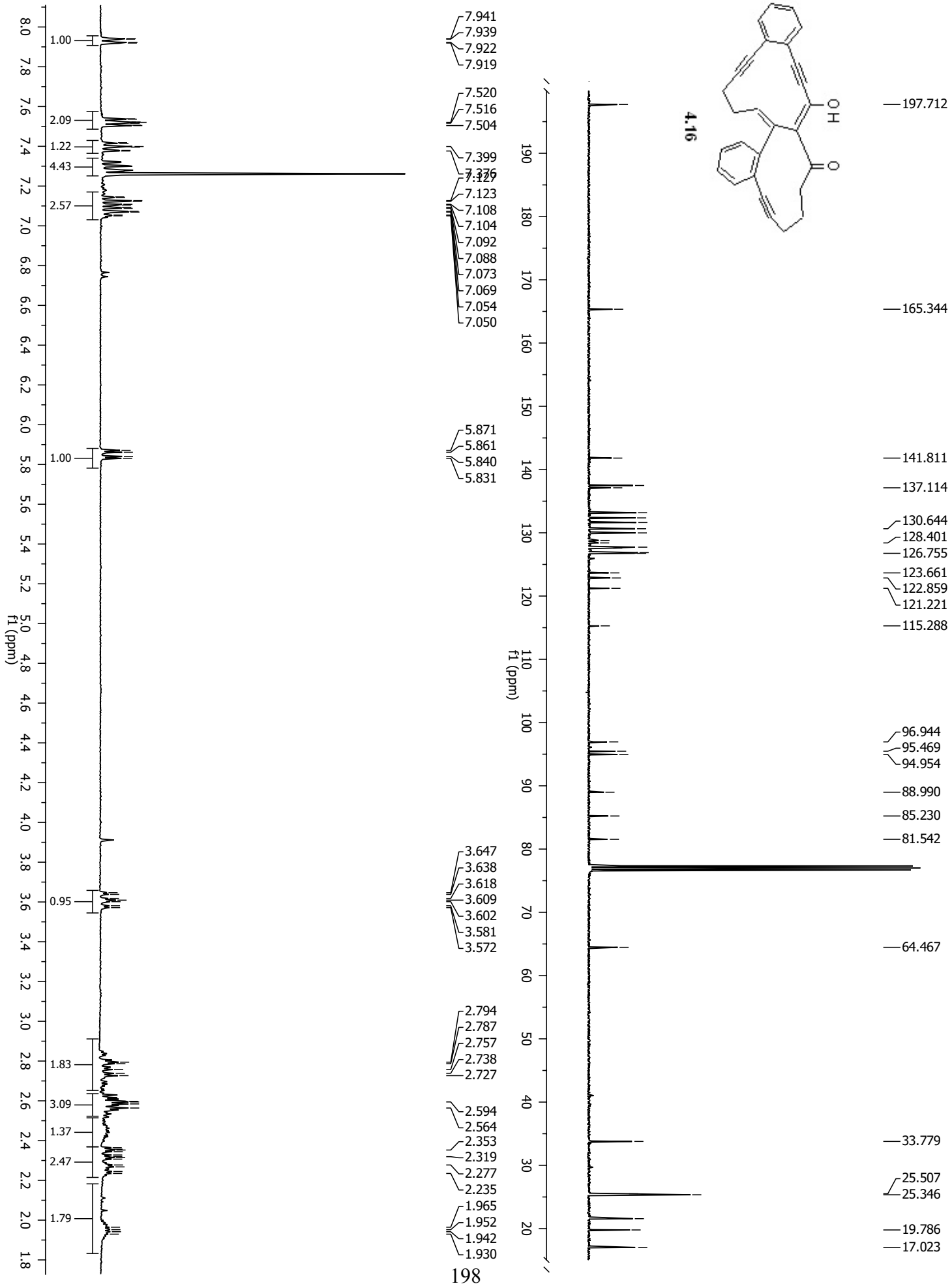

4.3Z
EtO2C
H
7.517
7.512
7.500
7.495
7.292
7.288
7.274
7.269
7.263
7.259
7.256
7.252
5.971
4.284
4.266
4.248
4.231
2.706
2.693
2.687
2.679
2.510
2.496
2.481
2.096
2.091
2.082
2.073
2.067
2.053
1.363
1.345
1.327
1.00
4.53
0.97
2.08
2.39
2.32
2.32
3.27
f1 (ppm)
165.256
140.182
129.825
129.068
128.271
128.061
127.461
122.035
102.674
99.721
95.662
82.203
60.334
39.059
28.995
21.638
14.288
f1 (ppm)

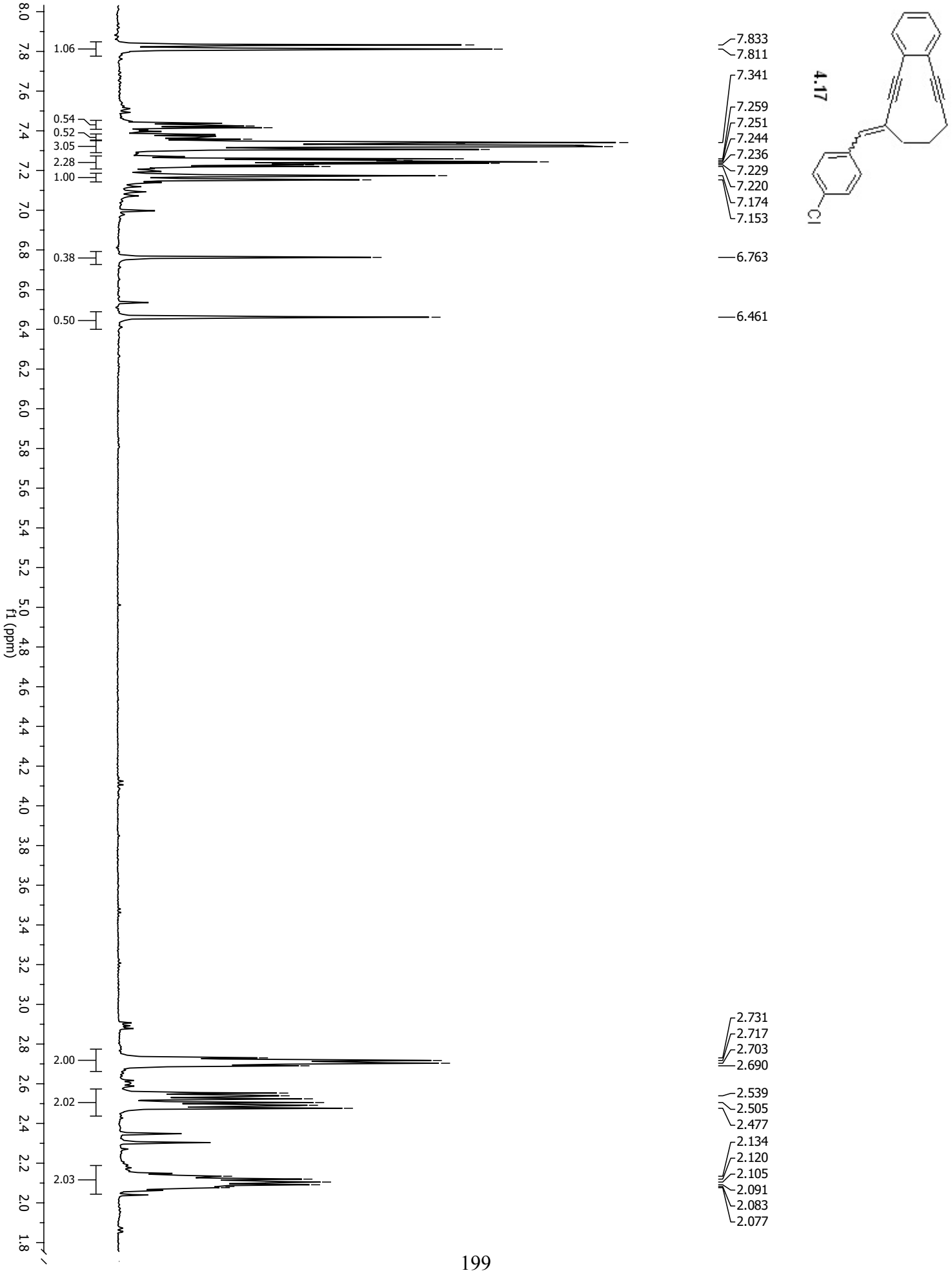

4.7E
CN
1.00
0.92
0.95
1.00
1.97
0.94
4.39
2.26
8.087
7.812
7.752
7.732
7.628
7.474
7.424
7.261
7.258
5.917
5.915
3.047
3.032
3.016
3.003
2.988
2.972
2.016
2.001
1.985
159.579
136.056
134.488
128.456
127.215
126.985
125.964
124.190
117.937
91.587
31.123
30.356
22.865
f1 (ppm)

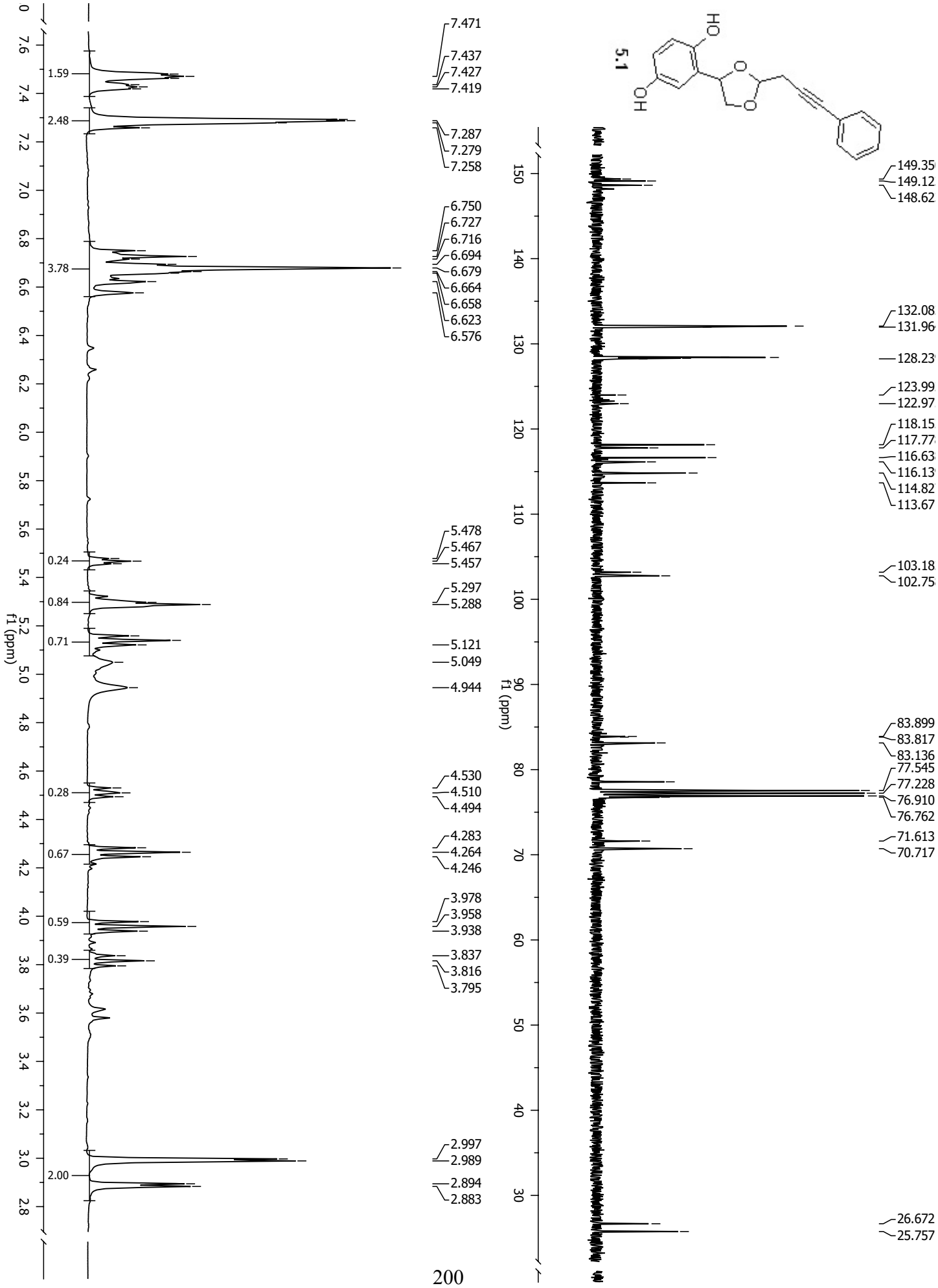

4.8E
CO2Et
f1 (ppm)
1.00
0.96
0.98
1.02
1.87
0.91
1.96
1.99
2.17
2.12
3.15
8.161
7.834
7.814
7.750
7.730
7.461
7.458
7.445
7.441
7.437
7.433
7.417
7.414
6.504
4.266
4.248
4.230
4.212
3.292
3.287
3.276
3.271
3.260
3.255
2.957
2.942
2.926
1.923
1.908
1.892
1.365
1.347
1.329
166.942
155.300
137.565
132.141
126.882
126.376
125.523
124.554
113.543
59.773
30.552
28.625
22.782
14.415

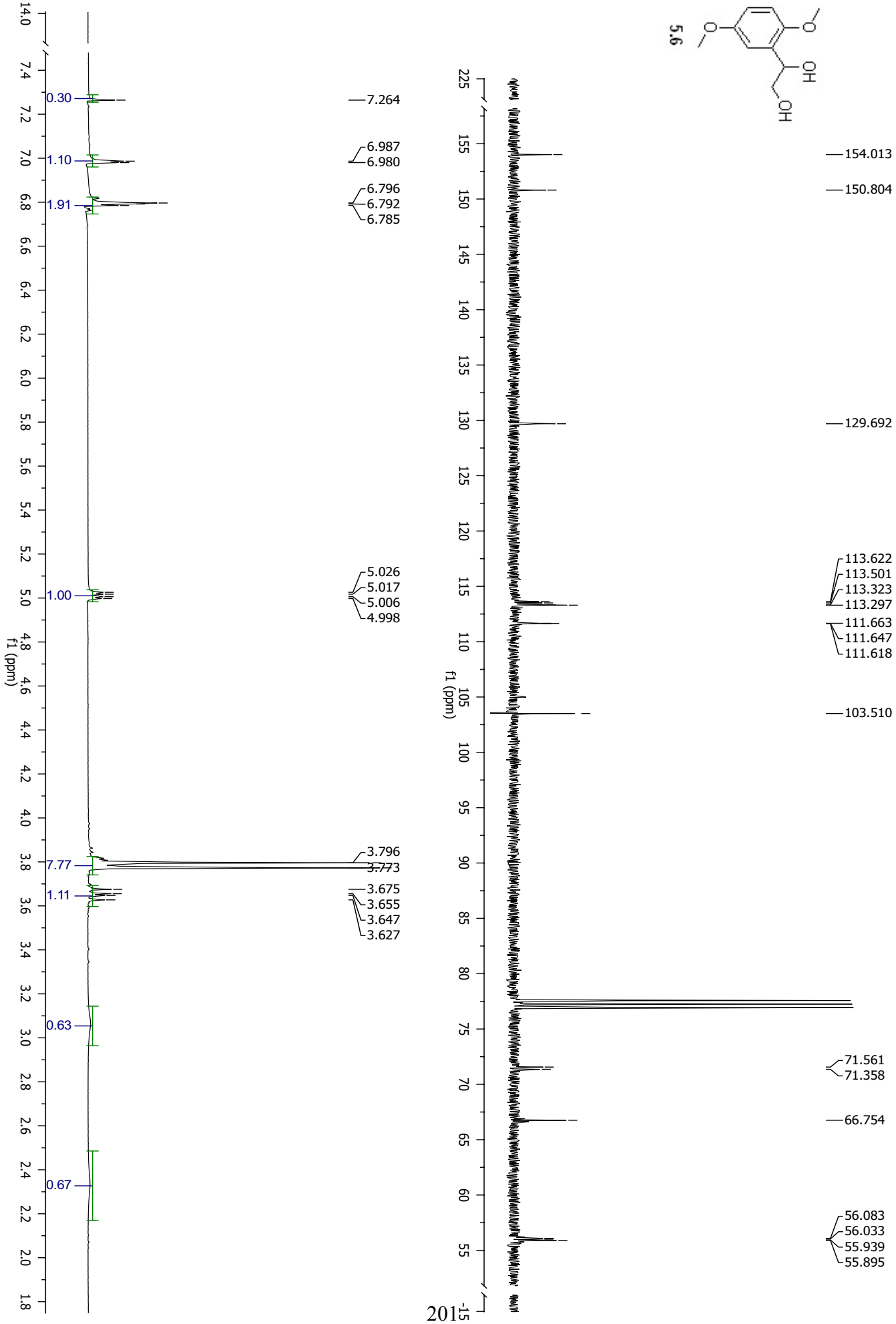

4.9
f1 (ppm)
1.00
1.15
2.38
1.16
0.95
2.66
2.54
3.09
8.498
8.478
7.773
7.754
7.590
7.563
7.529
7.431
6.272
3.091
3.077
3.062
2.914
2.911
2.897
2.883
2.880
2.077
2.062
2.047
2.031
2.015
161.379
155.310
151.171
134.881
133.386
128.923
127.323
126.334
122.745
122.165
121.989
113.224
111.453
30.699
30.045
22.590

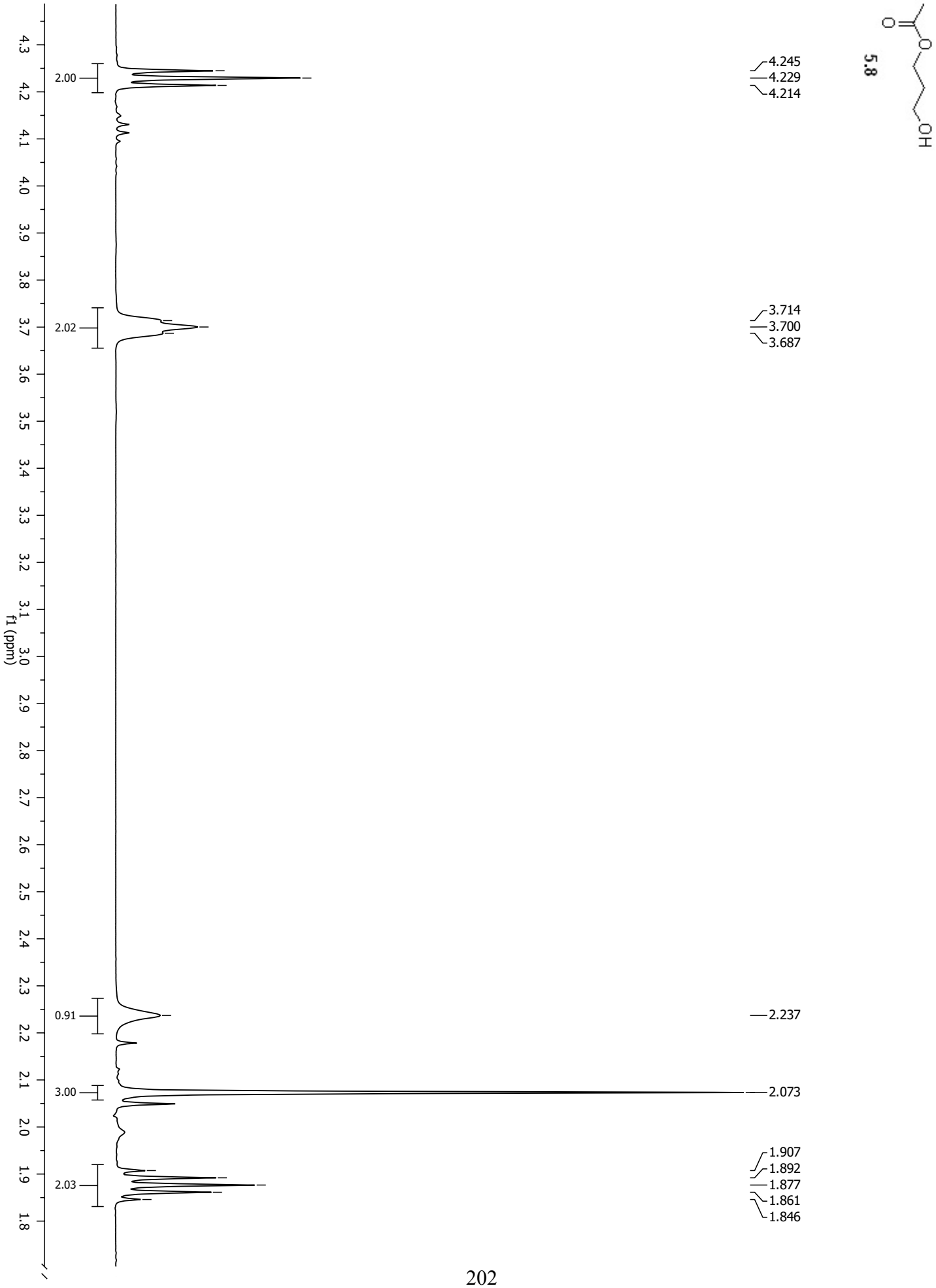

4.15
f1 (ppm)
1.00
0.39
0.43
0.97
3.30
4.39
0.30
0.52
2.02
2.14
2.19
7.910
7.892
7.679
7.667
7.649
7.381
7.361
7.329
7.274
7.262
7.250
7.228
6.854
6.536
2.780
2.767
2.753
2.745
2.732
2.727
2.717
2.523
2.494
2.162
2.145
2.134
2.130
2.125
2.116
2.108
2.102
136.697
136.436
131.942
128.336
126.169
123.292
100.864
100.168
99.569
98.008
97.666
92.235
82.181
82.109
64.409
39.939
31.888
29.555
29.426
25.336
21.787
21.661

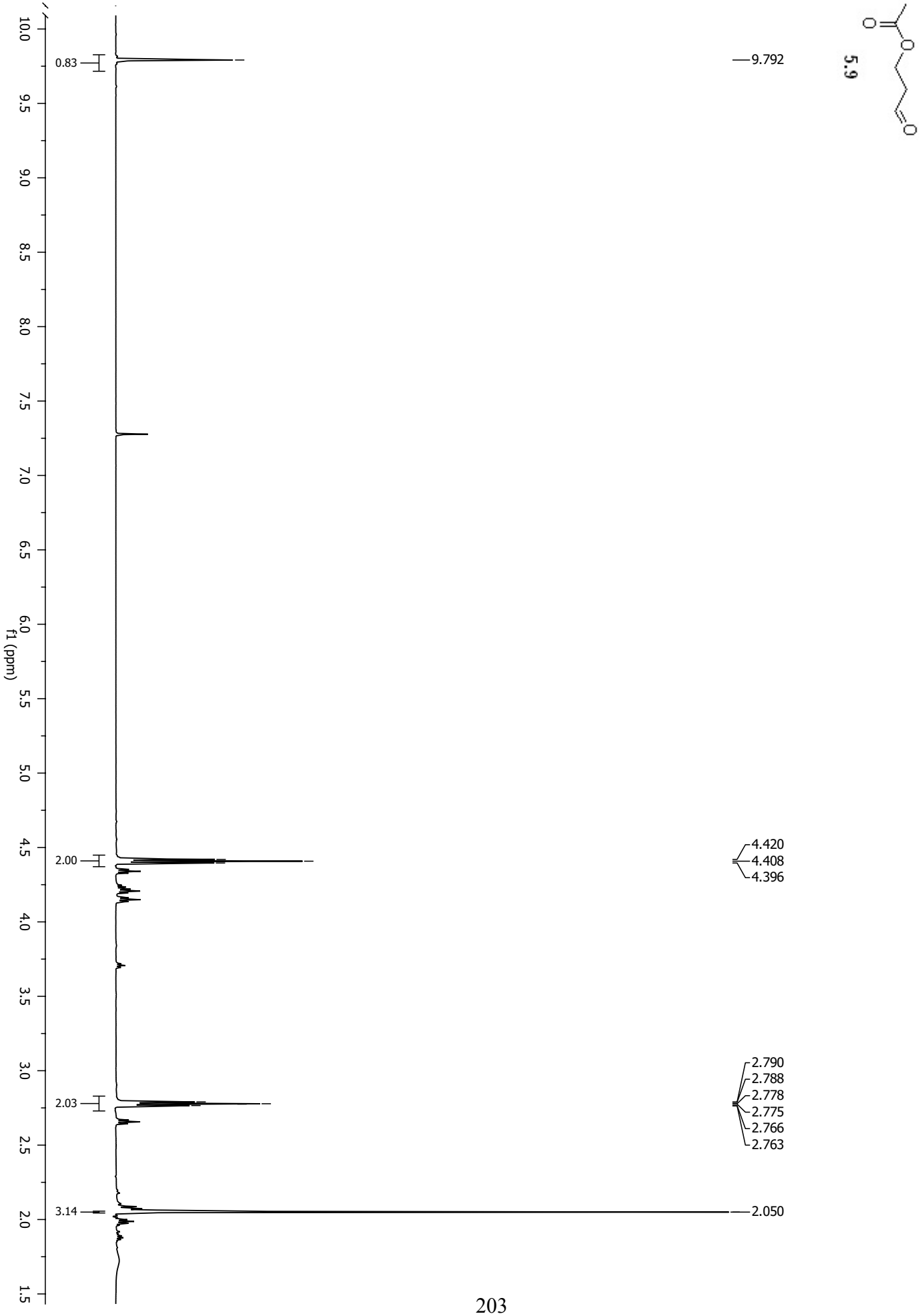

4.16
OH
O
197.712
165.344
141.811
137.114
130.644
128.401
126.755
123.661
122.859
121.221
115.288
96.944
95.469
94.954
88.990
85.230
81.542
64.467
33.779
25.507
25.346
19.786
17.023
7.941
7.939
7.922
7.919
7.520
7.516
7.504
7.399
7.376
7.127
7.123
7.108
7.104
7.092
7.088
7.073
7.069
7.054
7.050
5.871
5.861
5.840
5.831
3.647
3.638
3.618
3.609
3.602
3.581
3.572
2.794
2.787
2.757
2.738
2.727
2.594
2.564
2.353
2.319
2.277
2.235
1.965
1.952
1.942
1.930
1.00
2.09
1.22
4.43
2.57
1.00
0.95
1.83
3.09
1.37
2.47
1.79
f1 (ppm)
f1 (ppm)

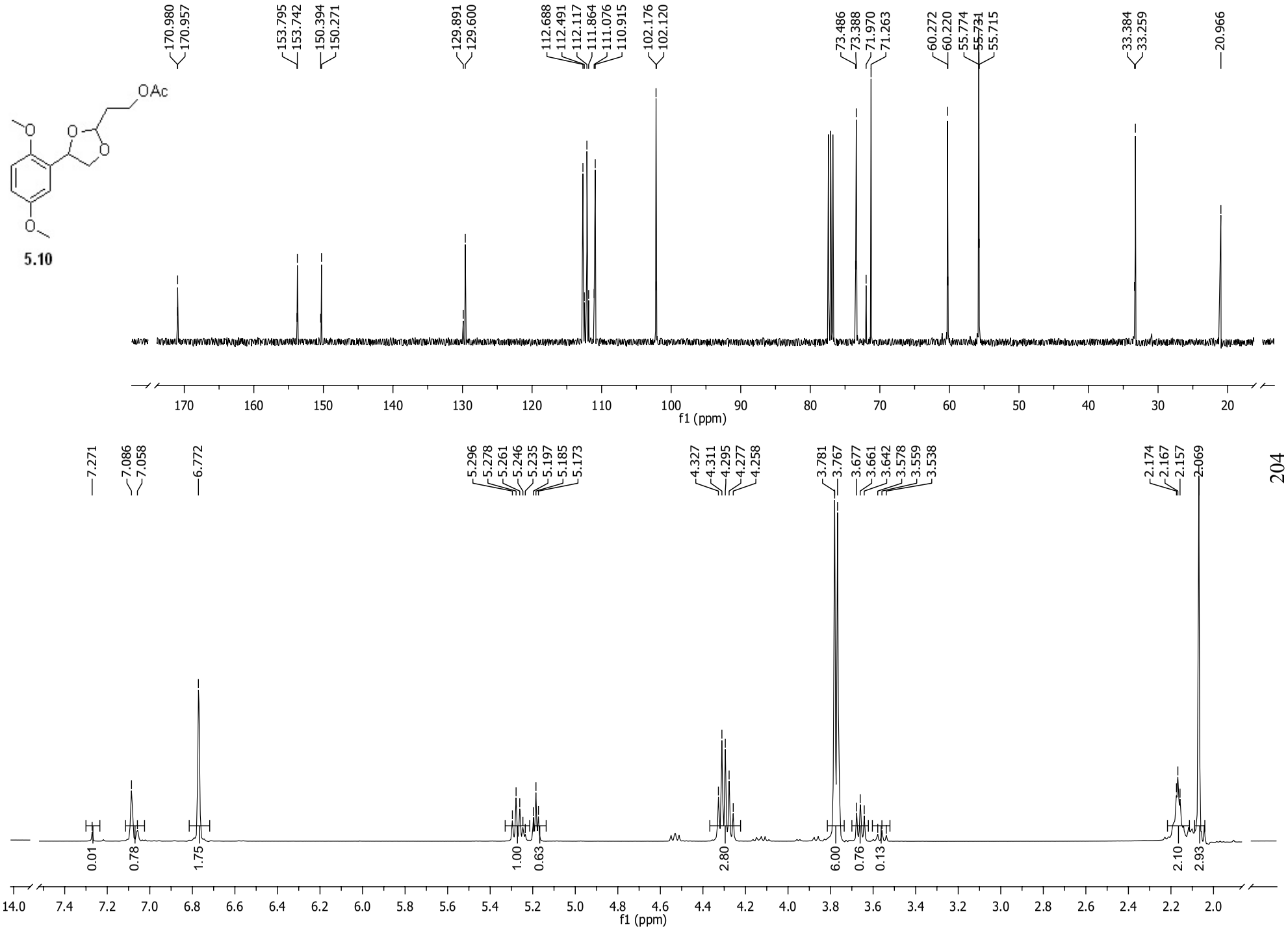

4.17
Cl
7.833
7.811
7.341
7.259
7.251
7.244
7.236
7.229
7.220
7.174
7.153
6.763
6.461
2.731
2.717
2.703
2.690
2.539
2.505
2.477
2.134
2.120
2.105
2.091
2.083
2.077
1.06
0.54
0.52
3.05
2.28
1.00
0.38
0.50
2.00
2.02
2.03
f1 (ppm)

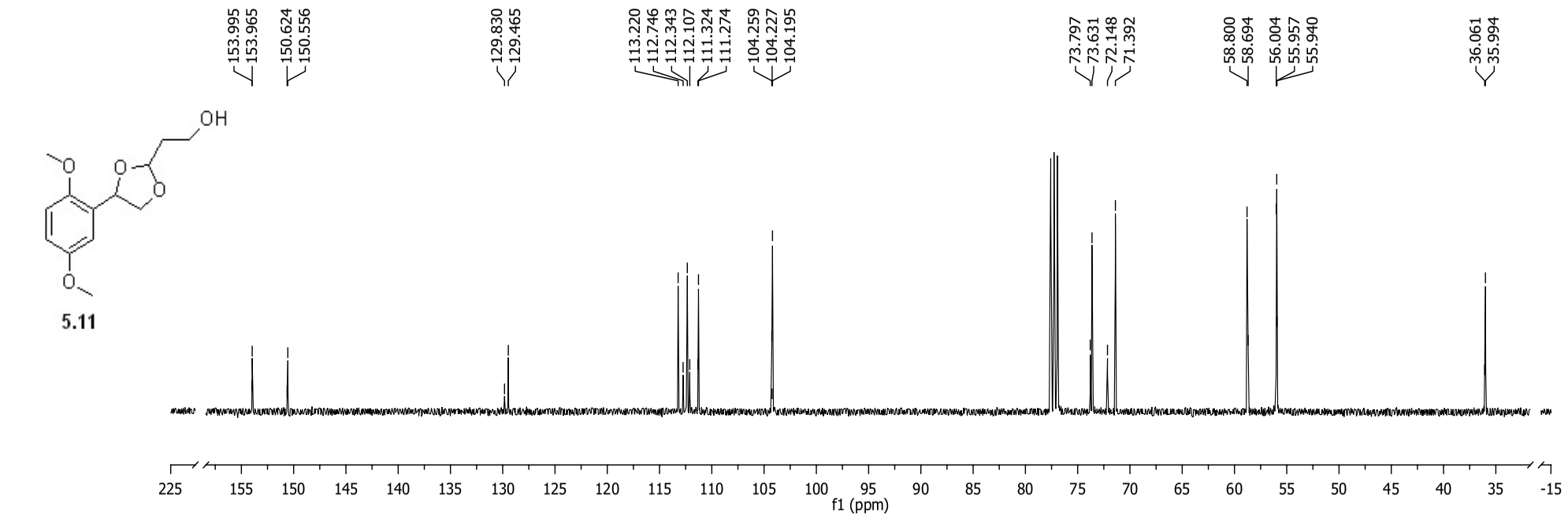

5.1
HO
OH
O
O
f1 (ppm)
1.59
2.48
3.78
0.24
0.84
0.71
0.28
0.67
0.59
0.39
2.00
7.471
7.437
7.427
7.419
7.287
7.279
7.258
6.750
6.727
6.716
6.694
6.679
6.664
6.658
6.623
6.576
5.478
5.467
5.457
5.297
5.288
5.121
5.049
4.944
4.530
4.510
4.494
4.283
4.264
4.246
3.978
3.958
3.938
3.837
3.816
3.795
2.997
2.989
2.894
2.883
149.35
149.12
148.62
132.08
131.96
128.23
123.99
122.97
118.15
117.77
116.63
116.13
114.82
113.67
103.18
102.75
83.899
83.817
83.136
77.545
77.228
76.910
76.762
71.613
70.717
26.672
25.757

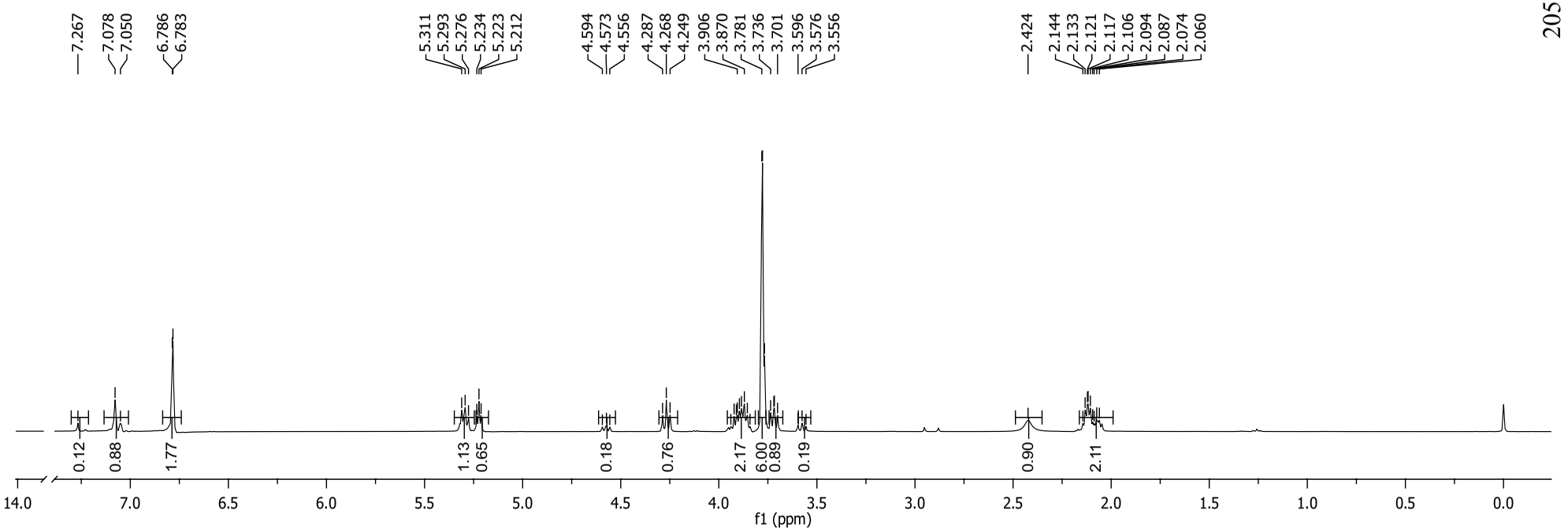

5.6
OH
OH
f1 (ppm)
7.264
6.987
6.980
6.796
6.792
6.785
5.026
5.017
5.006
4.998
3.796
3.773
3.675
3.655
3.647
3.627
0.30
1.10
1.91
1.00
7.77
1.11
0.63
0.67
154.013
150.804
129.692
113.622
113.501
113.323
113.297
111.663
111.647
111.618
103.510
71.561
71.358
66.754
56.083
56.033
55.939
55.895

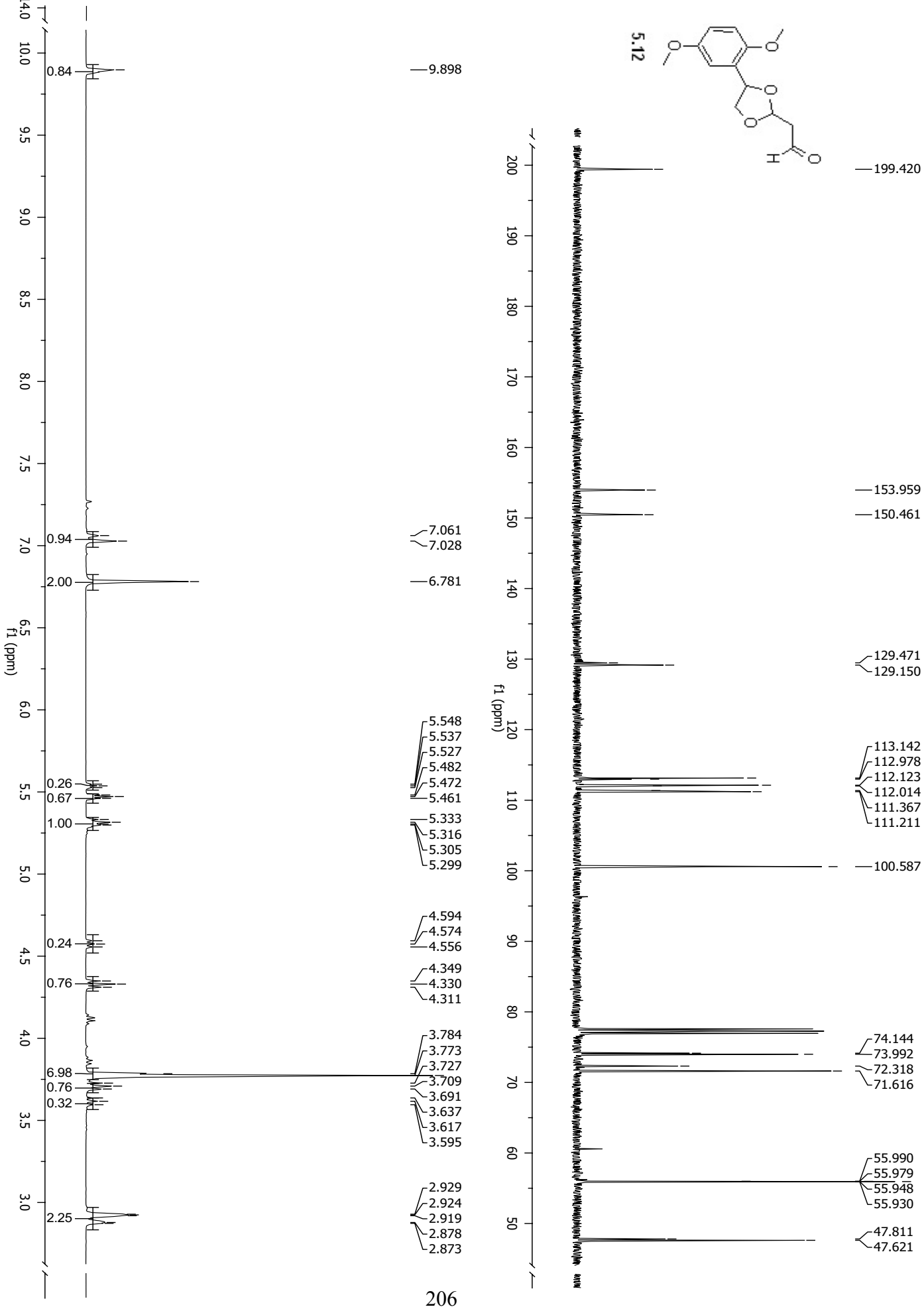

4.245
4.229
4.214
3.714
3.700
3.687
2.237
2.073
1.907
1.892
1.877
1.861
1.846
2.00
2.02
0.91
3.00
2.03
f1 (ppm)
5.8

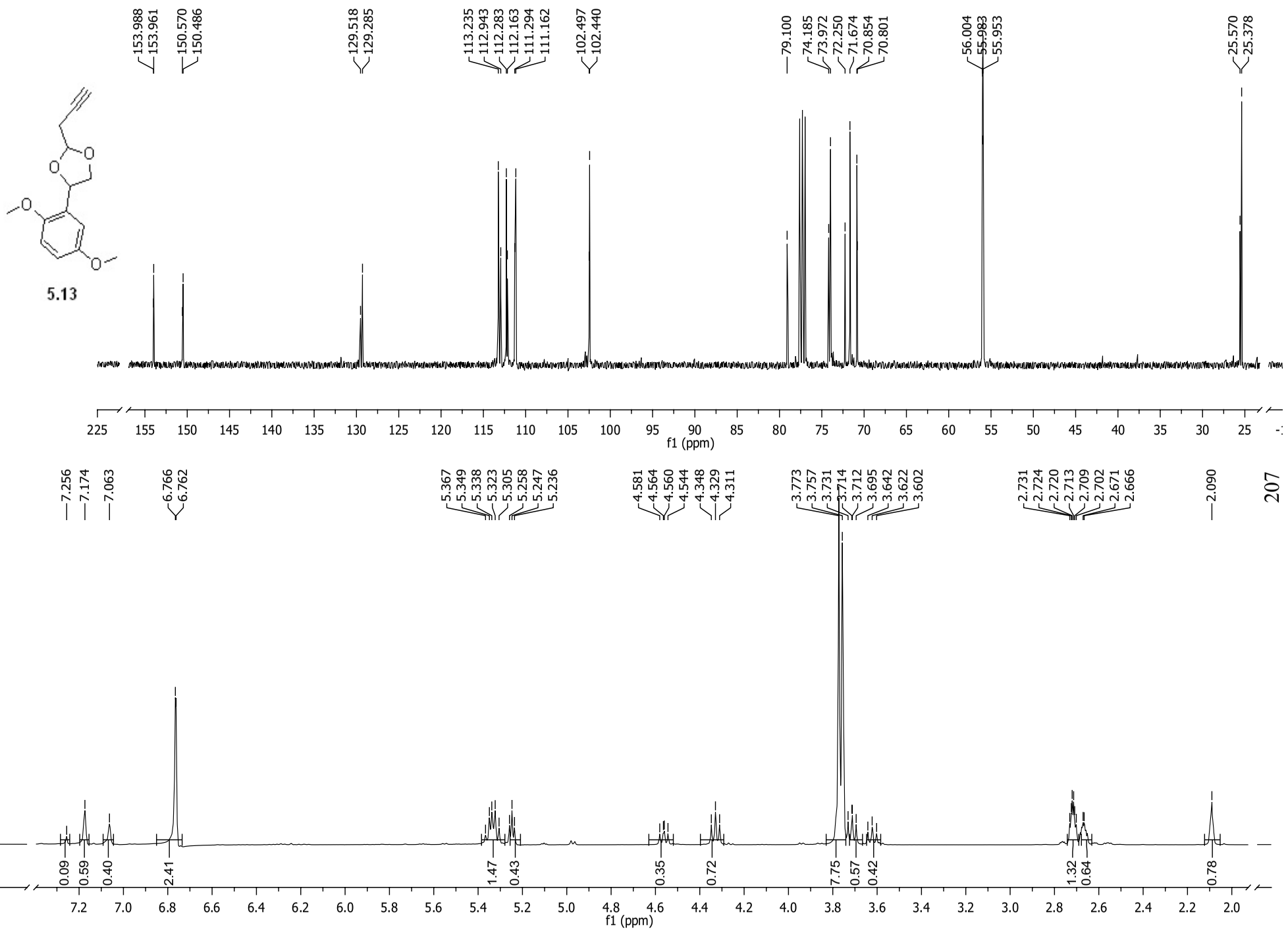

5.9
9.792
4.420
4.408
4.396
2.790
2.788
2.778
2.775
2.766
2.763
2.050
0.83
2.00
2.03
3.14
f1 (ppm)

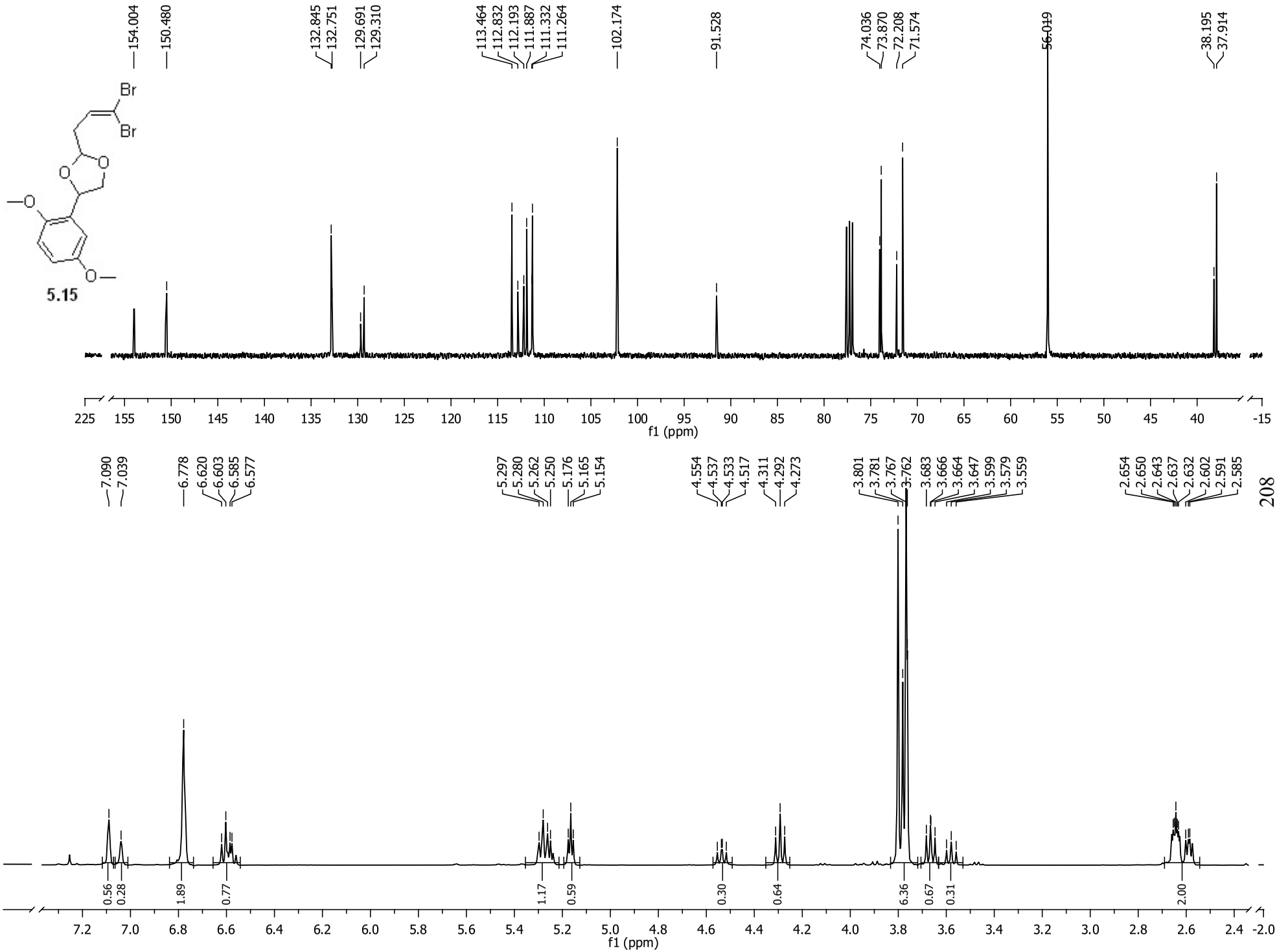

OAc
O
O
O
O
5.10
170.980
170.957
153.795
153.742
150.394
150.271
129.891
129.600
112.688
112.491
112.117
111.864
111.076
110.915
102.176
102.120
73.486
73.388
71.970
71.263
60.272
60.220
55.774
55.731
55.715
33.384
33.259
20.966
f1 (ppm)
7.271
7.086
7.058
6.772
5.296
5.278
5.261
5.246
5.235
5.197
5.185
5.173
4.327
4.311
4.295
4.277
4.258
3.781
3.767
3.677
3.661
3.642
3.578
3.559
3.538
2.174
2.167
2.157
2.069
0.01
0.78
1.75
1.00
0.63
2.80
6.00
0.76
0.13
2.10
2.93
f1 (ppm)

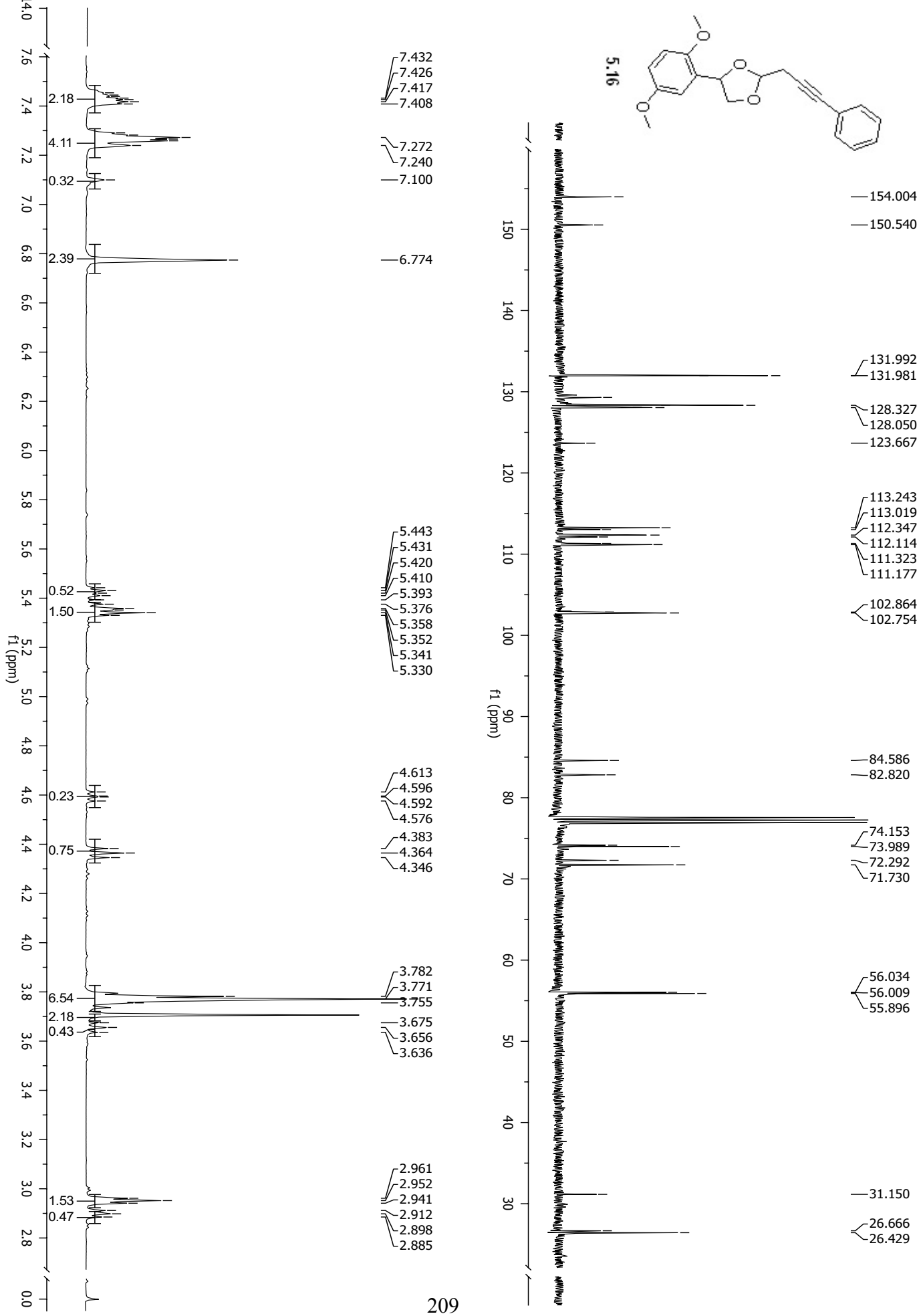

153.995
153.965
150.624
150.556
129.830
129.465
113.220
112.746
112.343
112.107
111.324
111.274
104.259
104.227
104.195
73.797
73.631
72.148
71.392
58.800
58.694
56.004
55.957
55.940
36.061
35.994
OH
O
O
O
O
5.11
225
155
150
145
140
135
130
125
120
115
110
105
100
95
90
85
80
75
70
65
60
55
50
45
40
35
-15
f1 (ppm)

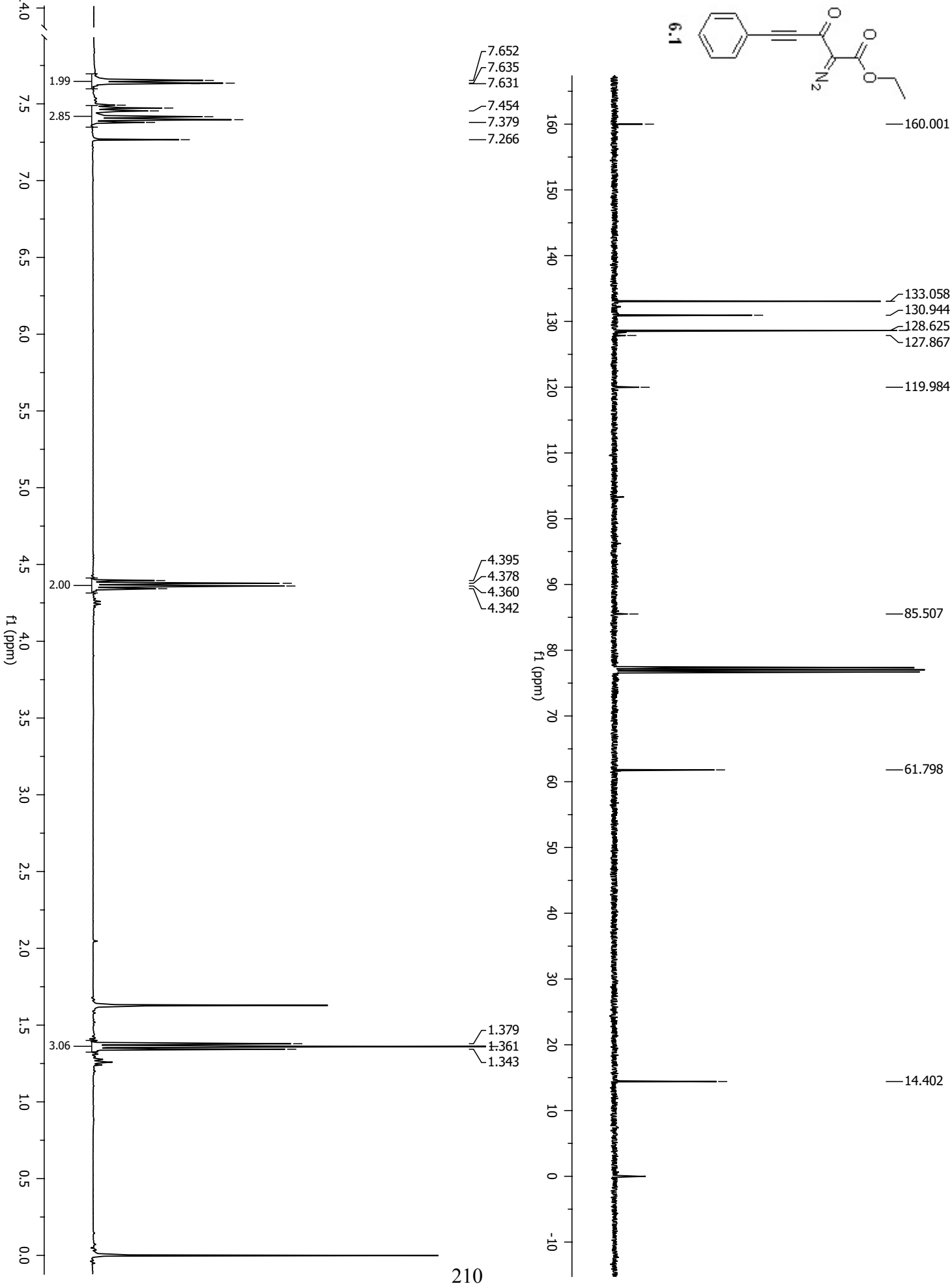

7.267
7.078
7.050
6.786
6.783
5.311
5.293
5.276
5.234
5.223
5.212
4.594
4.573
4.556
4.287
4.268
4.249
3.906
3.870
3.781
3.736
3.701
3.596
3.576
3.556
2.424
2.144
2.133
2.121
2.117
2.106
2.094
2.087
2.074
2.060
0.12
0.88
1.77
1.13
0.65
0.18
0.76
2.17
6.00
0.89
0.19
0.90
2.11
14.0
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

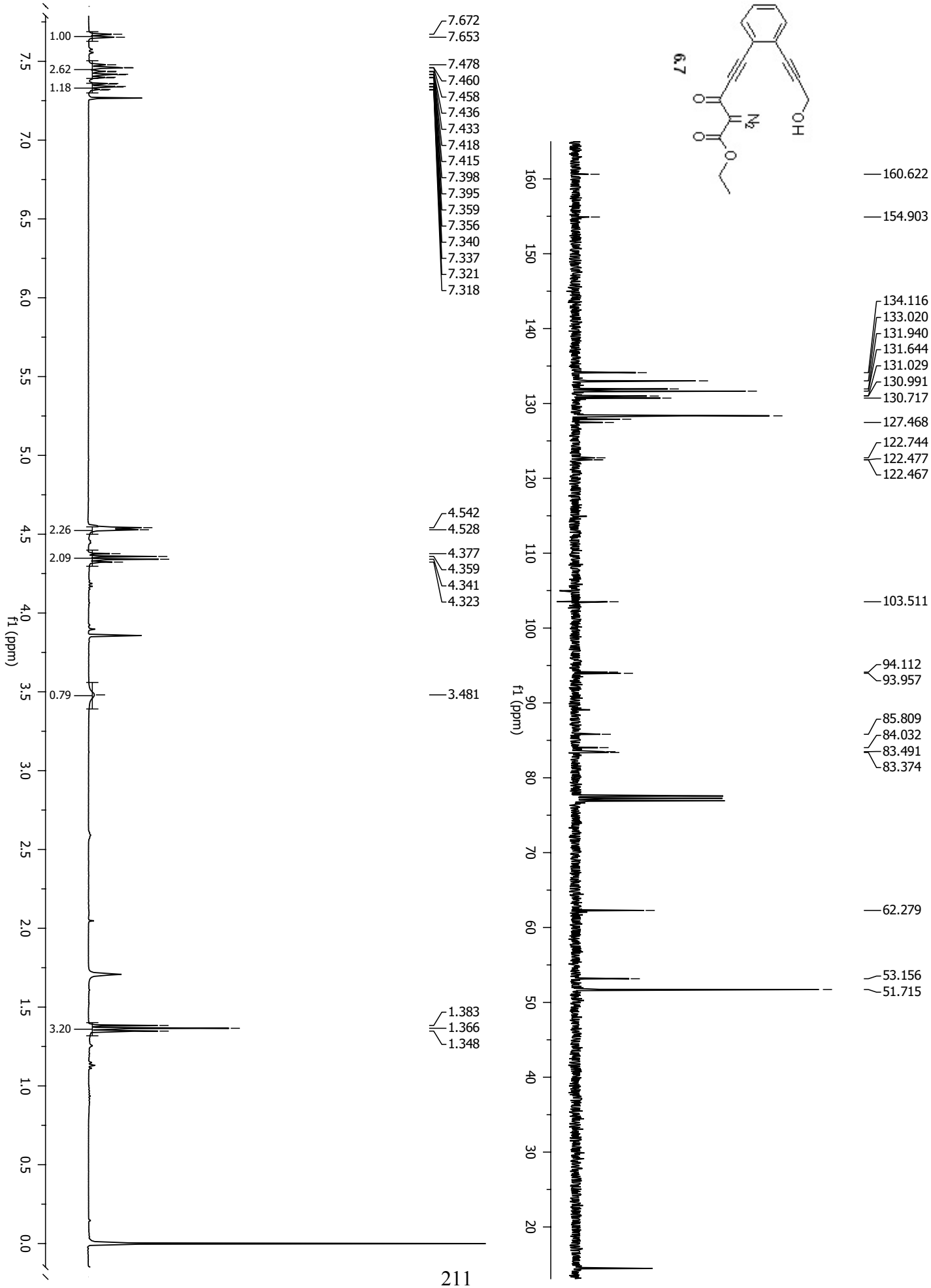

5.12
f1 (ppm)
0.84
0.94
2.00
0.26
0.67
1.00
0.24
0.76
6.98
0.76
0.32
2.25
9.898
7.061
7.028
6.781
5.548
5.537
5.527
5.482
5.472
5.461
5.333
5.316
5.305
5.299
4.594
4.574
4.556
4.349
4.330
4.311
3.784
3.773
3.727
3.709
3.691
3.637
3.617
3.595
2.929
2.924
2.919
2.878
2.873
199.420
153.959
150.461
129.471
129.150
113.142
112.978
112.123
112.014
111.367
111.211
100.587
74.144
73.992
72.318
71.616
55.990
55.979
55.948
55.930
47.811
47.621

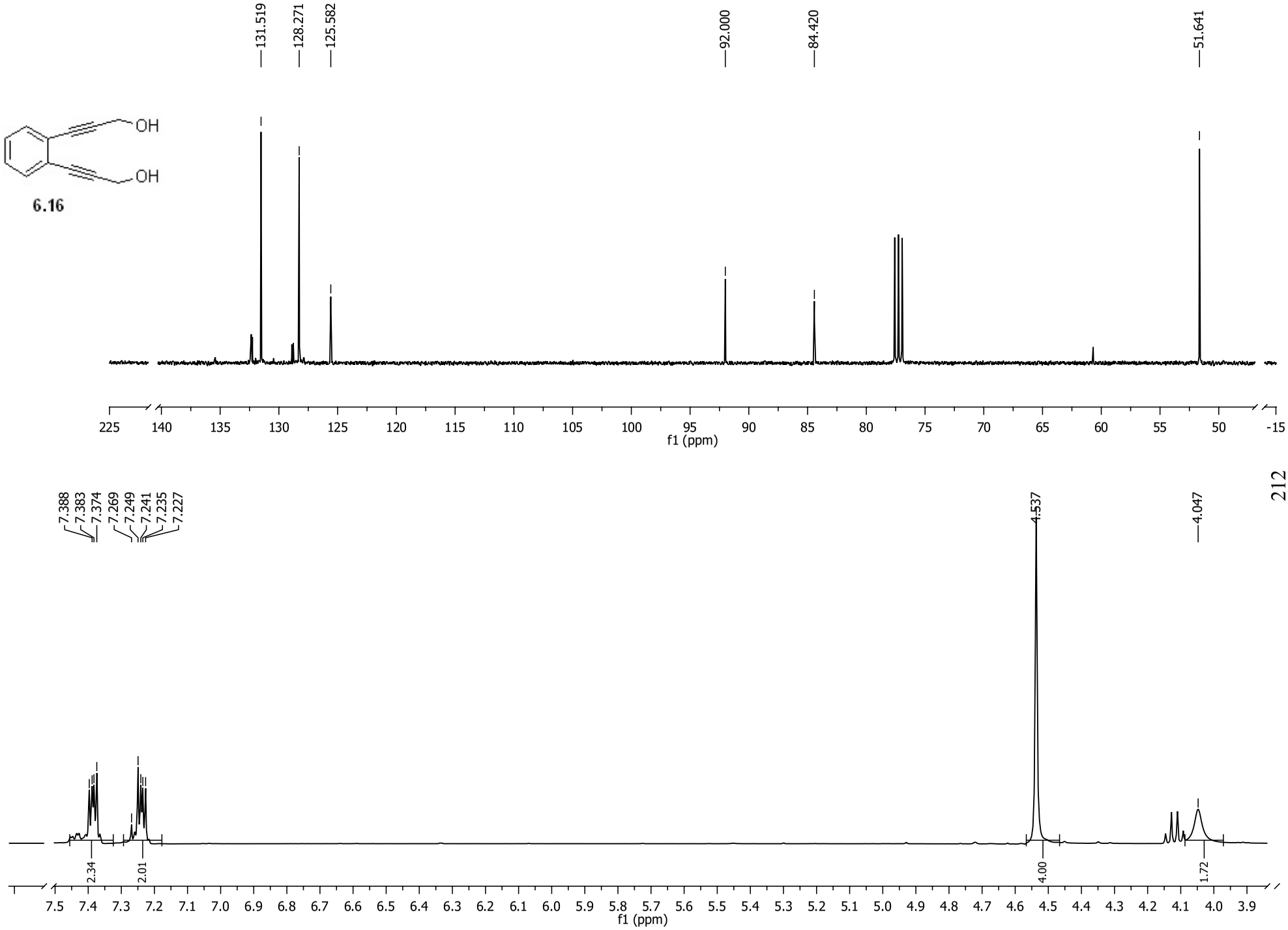

153.988
153.961
150.570
150.486
129.518
129.285
113.235
112.943
112.283
112.163
111.294
111.162
102.497
102.440
79.100
74.185
73.972
72.250
71.674
70.854
70.801
56.004
55.983
55.953
25.570
25.378
5.13
f1 (ppm)
7.256
7.174
7.063
6.766
6.762
5.367
5.349
5.338
5.323
5.305
5.258
5.247
5.236
4.581
4.564
4.560
4.544
4.348
4.329
4.311
3.773
3.757
3.731
3.714
3.712
3.695
3.642
3.622
3.602
2.731
2.724
2.720
2.713
2.709
2.702
2.671
2.666
2.090
0.09
0.59
0.40
2.41
1.47
0.43
0.35
0.72
7.75
0.57
0.42
1.32
0.64
0.78
f1 (ppm)

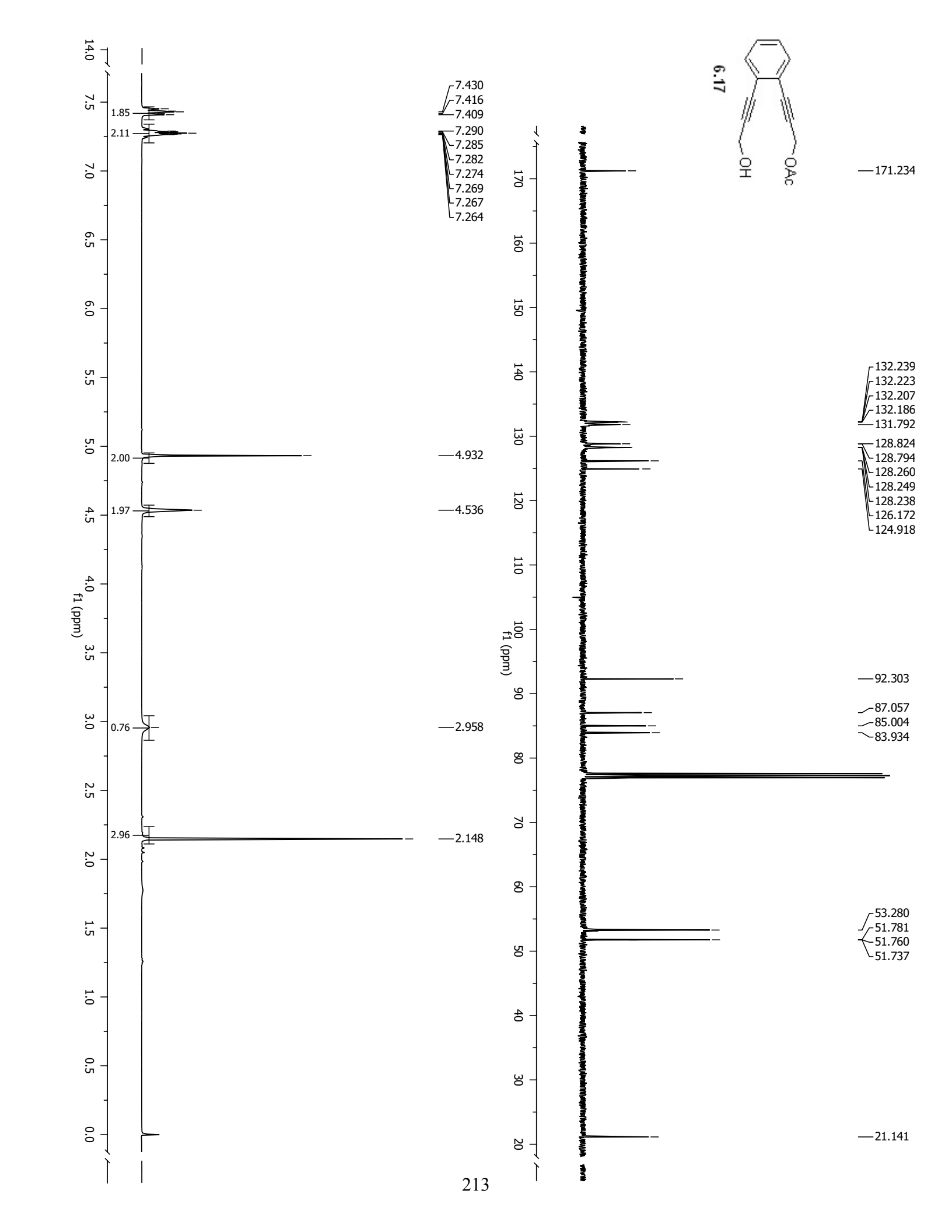

154.004
150.480
132.845
132.751
129.691
129.310
113.464
112.832
112.193
111.887
111.332
111.264
102.174
91.528
74.036
73.870
72.208
71.574
56.019
38.195
37.914
Br
Br
O
O
O
O
5.15
225 155 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 -15
f1 (ppm)
7.090
7.039
6.778
6.620
6.603
6.585
6.577
5.297
5.280
5.262
5.250
5.176
5.165
5.154
4.554
4.537
4.533
4.517
4.311
4.292
4.273
3.801
3.781
3.767
3.762
3.683
3.666
3.664
3.647
3.599
3.579
3.559
2.654
2.650
2.643
2.637
2.632
2.602
2.591
2.585
0.56
0.28
1.89
0.77
1.17
0.59
0.30
0.64
6.36
0.67
0.31
2.00
7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 -2.0
f1 (ppm)

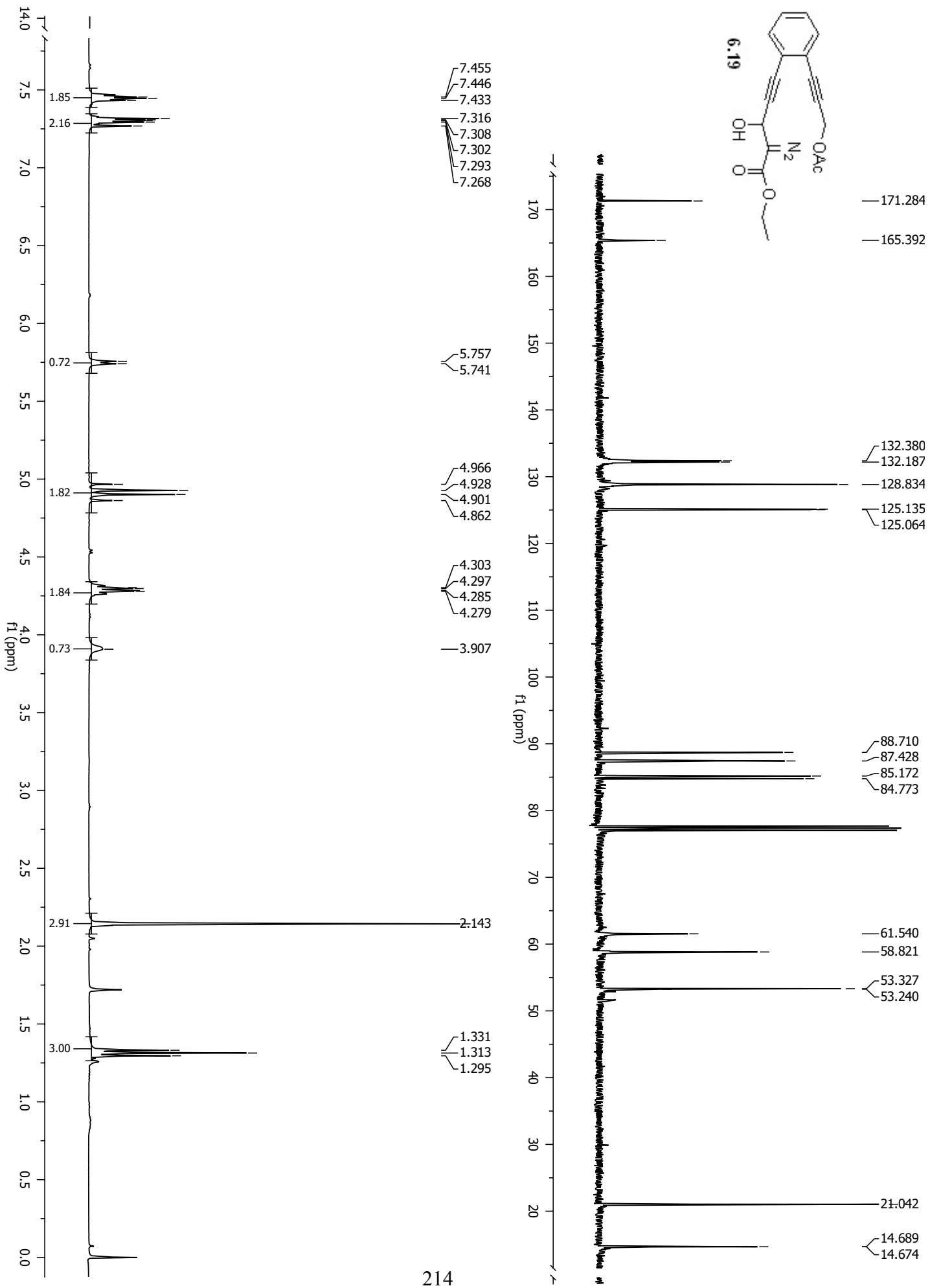

5.16
f1 (ppm)
7.432
7.426
7.417
7.408
7.272
7.240
7.100
6.774
5.443
5.431
5.420
5.410
5.393
5.376
5.358
5.352
5.341
5.330
4.613
4.596
4.592
4.576
4.383
4.364
4.346
3.782
3.771
3.755
3.675
3.656
3.636
2.961
2.952
2.941
2.912
2.898
2.885
2.18
4.11
0.32
2.39
0.52
1.50
0.23
0.75
6.54
2.18
0.43
1.53
0.47
154.004
150.540
131.992
131.981
128.327
128.050
123.667
113.243
113.019
112.347
112.114
111.323
111.177
102.864
102.754
84.586
82.820
74.153
73.989
72.292
71.730
56.034
56.009
55.896
31.150
26.666
26.429

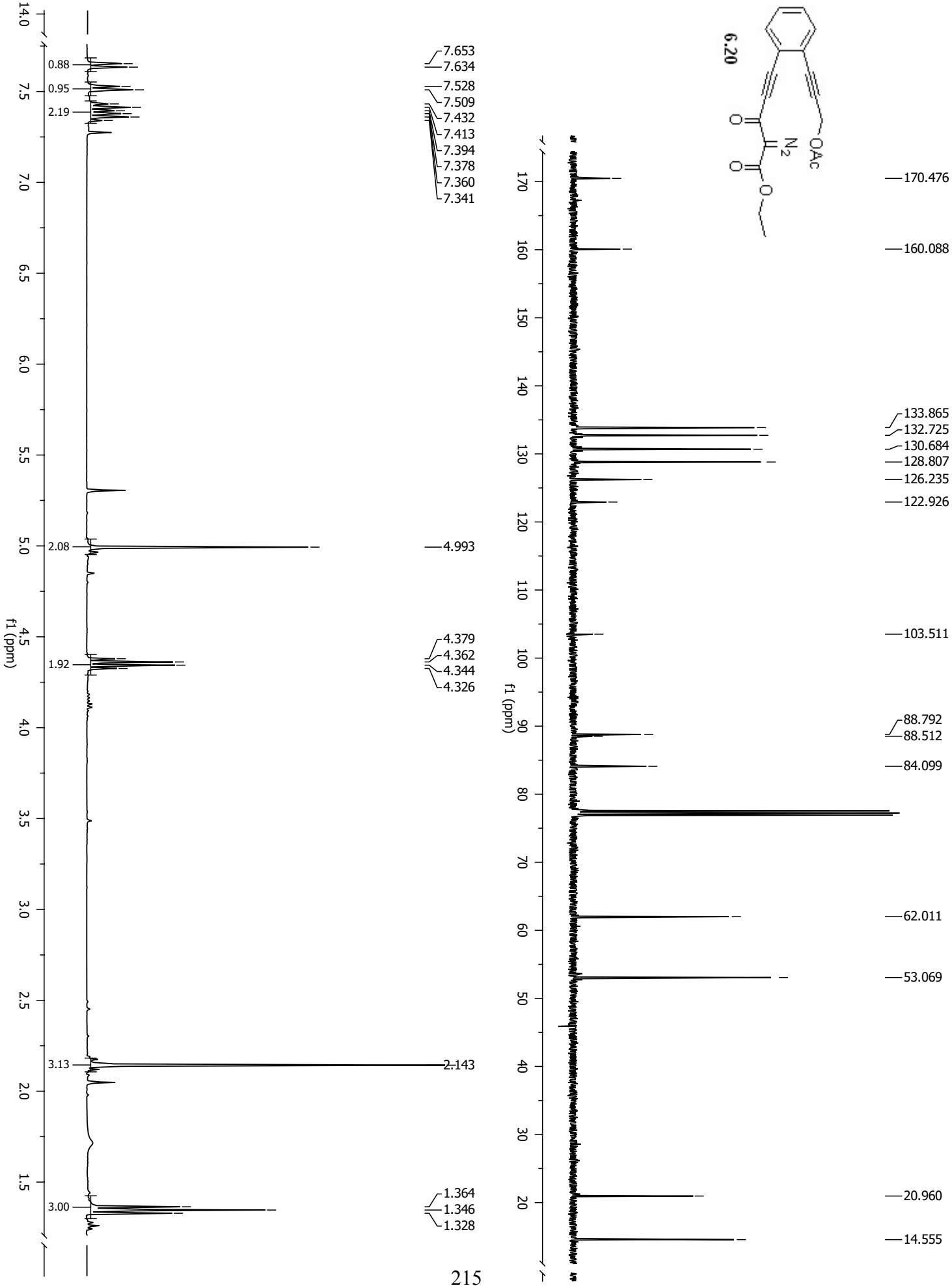

6.1
1.99
2.85
2.00
3.06
7.652
7.635
7.631
7.454
7.379
7.266
4.395
4.378
4.360
4.342
1.379
1.361
1.343
160.001
133.058
130.944
128.625
127.867
119.984
85.507
61.798
14.402
f1 (ppm)
f1 (ppm)

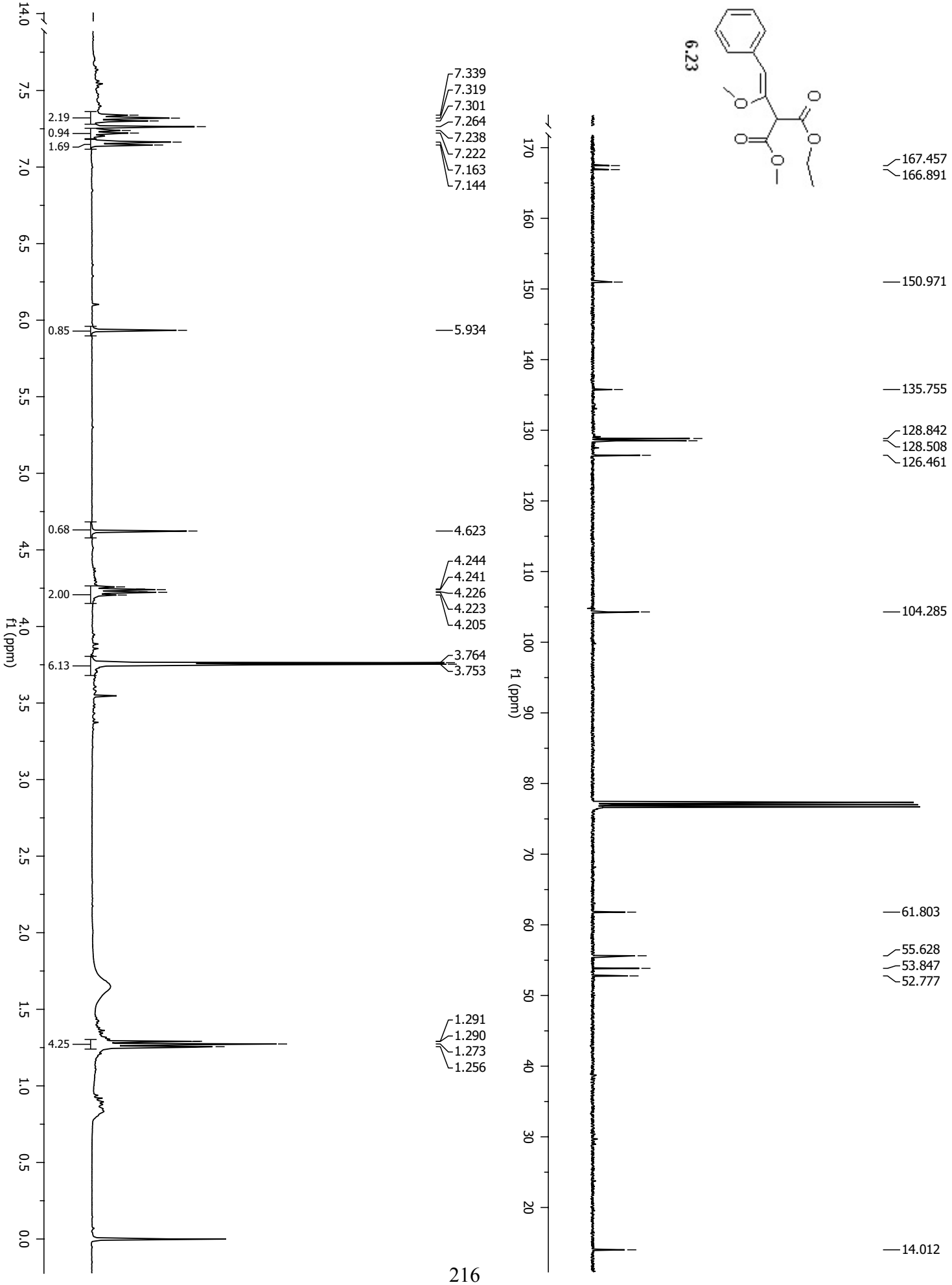

1.00
2.62
1.18
2.26
2.09
0.79
3.20
7.672
7.653
7.478
7.460
7.458
7.436
7.433
7.418
7.415
7.398
7.395
7.359
7.356
7.340
7.337
7.321
7.318
4.542
4.528
4.377
4.359
4.341
4.323
3.481
1.383
1.366
1.348
f1 (ppm)
6.7
N2
OH
160.622
154.903
134.116
133.020
131.940
131.644
131.029
130.991
130.717
127.468
122.744
122.477
122.467
103.511
94.112
93.957
85.809
84.032
83.491
83.374
62.279
53.156
51.715
f1 (ppm)

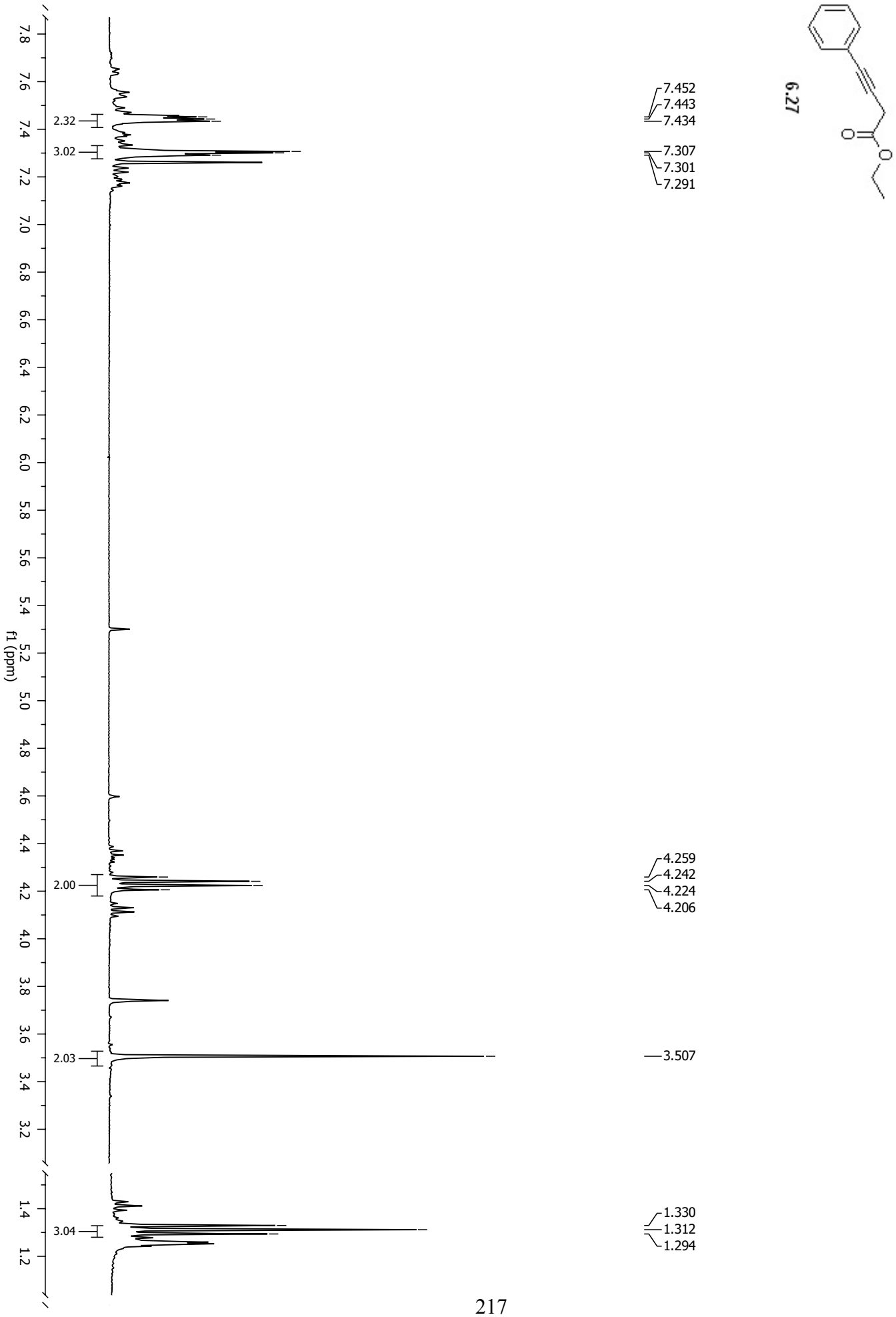

131.519
128.271
125.582
92.000
84.420
51.641
OH
OH
6.16
f1 (ppm)
7.388
7.383
7.374
7.269
7.249
7.241
7.235
7.227
4.537
4.047
2.34
2.01
4.00
1.72
f1 (ppm)


6.17
OH
OAc
f1 (ppm)
1.85
2.11
2.00
1.97
0.76
2.96
7.430
7.416
7.409
7.290
7.285
7.282
7.274
7.269
7.267
7.264
4.932
4.536
2.958
2.148
171.234
132.239
132.223
132.207
132.186
131.792
128.824
128.794
128.260
128.249
128.238
126.172
124.918
92.303
87.057
85.004
83.934
53.280
51.781
51.760
51.737
21.141


6.19
OAc
OH
N2
O
O
7.455
7.446
7.433
7.316
7.308
7.302
7.293
7.268
5.757
5.741
4.966
4.928
4.901
4.862
4.303
4.297
4.285
4.279
3.907
2.143
1.331
1.313
1.295
1.85
2.16
0.72
1.82
1.84
0.73
2.91
3.00
f1 (ppm)
171.284
165.392
132.380
132.187
128.834
125.135
125.064
88.710
87.428
85.172
84.773
61.540
58.821
53.327
53.240
21.042
14.689
14.674


6.20
OAc
N2
O
O
O
f1 (ppm)
0.88
0.95
2.19
2.08
1.92
3.13
3.00
7.653
7.634
7.528
7.509
7.432
7.413
7.394
7.378
7.360
7.341
4.993
4.379
4.362
4.344
4.326
2.143
1.364
1.346
1.328
170.476
160.088
133.865
132.725
130.684
128.807
126.235
122.926
103.511
88.792
88.512
84.099
62.011
53.069
20.960
14.555


6.23
f1 (ppm)
2.19
0.94
1.69
0.85
0.68
2.00
6.13
4.25
7.339
7.319
7.301
7.264
7.238
7.222
7.163
7.144
5.934
4.623
4.244
4.241
4.226
4.223
4.205
3.764
3.753
1.291
1.290
1.273
1.256
f1 (ppm)
167.457
166.891
150.971
135.755
128.842
128.508
126.461
104.285
61.803
55.628
53.847
52.777
14.012


9.27
7.452
7.443
7.434
7.307
7.301
7.291
4.259
4.242
4.224
4.206
3.507
1.330
1.312
1.294
2.32
3.02
2.00
2.03
3.04
f1 (ppm)