SYNTHESES OF NOVEL 3,6-DIHYDRO-2*H*-PYRAN-2-ONE AND KLAVUZON DERIVATIVES

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ABSTRACT

SYNTHESES OF NOVEL 3,6-DIHYDRO-2*H*-PYRAN-2-ONE AND KLAVUZON DERIVATIVES

The styryl-lactones are a group of secondary metabolites which have α,β–unsaturated δ–lactone moiety in their structures. One of the most important member of this group of compound is goniothalamin. Goniothalamin and its analogs having a common α,β-unsaturated δ–lactone moiety. Investigations on these species have been increased in the last decade because of their interesting biological activities.

Present study aims the synthesis of novel 4'-alkyl substituted klavuzon and naphthalen-1-yl substituted 3,6-dihydro-2*H*-pyran-2-one derivatives. Syntheses were started with the preparation of ethyl 4-(bromomethyl)-1-naphthoate. Copper-catalyzed cross coupling reactions between ethyl 4-bromoethyl-1-naphthoate and Grignard reagents gave alkyl substituted esters. Next, alkylated ester derivatives were converted to alklylated-naphthaldehyde derivatives via reduction with $LiAlH_4$ and then oxidation with PCC. Allylation reaction of corresponding aldehydes with allylmagnesium bromide gave homoallylic alcohols. Finally, homoallylic alcohols were reacted with acryloyl chloride in the presence of a base to produce acrylate esters, then ring closing metathesis by second generation Grubbs' catalyst yielded the final klavuzon derivatives.

Additionally, synthesis of new five β,γ-unsaturated δ–lactone derivatives was also completed. Vinylation reaction of corresponding aldehydes with vinylmagnesium bromide gave the allylic alcohols. Coupling reactions of these alcohols with 3-butenoic acid in the presence of DCC/DMAP yielded the ester. Ring closing metathesis of the related ester was studied by using 2^{nd} generation Grubbs' catalyst.

ÖZET

YENİ 3,6-DİHİDRO-2*H*-PİRAN-2-ON VE KLAVUZON TÜREVLERİNİN SENTEZİ

Sitiril laktonlar, yapılarında α,β doymamış yapıya sahip bir grup ikincil metabolitlerdir. Bu grubun en önemli üyelerinden birisi goniothalamindir. Goniothalamin ve onun türevleri α,β–doymamış yapıya sahiptir. Bu yapıya sahip moleküller üzerindeki araştırmalar bunların önemli miktarda biyolojik aktivite göstermelerinden dolayı son on yılda artmıştır.

Bu çalışma 4'-alkil sübstitüentli klavuzon ve naftalin-1-il türevlendirilmiş 3,6-dihidro-2*H*-piran-2-on türevlerinin sentezlerini amaçlamaktadır. Sentezler etil 4-brommetil-1-naftoatın hazırlanmasıyla başlamıştır. Etil 4-bromometil-1-naftoat ve Grignard reaktiflerinin bakır katalizörlüğünde reaksiyonları sonucu alkil sübstitüentli esterler elde edilmiştir. Ardından alkillenmiş esterler $LiAlH_4$ ile indirgenip, PCC ile yükseltgenerek alkillenmis naftaldehit türevleri elde edilmiştir. Alkillenmiş naftaldehitler allilmagnezyum bromür ile reaksiyona sokularak homoallilik alkoller elde edilmiştir. Son olarak homoallilik alkoller akriloyil klorür ile baz varlığında reaksiyona sokulup akrilat esterler elde edilmiş ve 2. nesil Grubbs' katalizörü varlığında halka kapanması reaksiyonu ile klavuzon türevleri elde edilmiştir.

Ek olarak, yeni beş β,γ-doymamış lakton türevleri de sentezlenmiştir. Aldehitlerin vinilmagnezyum bromür ile reaksiyonları sonucu allilik alkoller elde edilmiştir. Alkoller vinil asetik asit ve DCC/DMAP katalizör varlığında estere dönüştürüldükten sonra 2. nesil Grubbs' katalizörü ile halka kapanma reaksiyonları çalışılmıştır.

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LIST OF ABBREVIATIONS

d	Doublet
dd	Doublet of doublet
dt	Doublet of triplet
DBU	1,8-Diazabicycloundec-7-ene
DCC	N,N'-Dicyclohexylcarbodiimide
ddd	Doublet of doublet of doublet
DDQ	2,3-Dichloro-5,6-Dicyanobenzoquinone
ddt	Doublet of doublet of triplet
DIBAH	Diisobutylaluminium hydride
DMAP	4-(Dimethylamino)pyridine
IBX	2-Iodoxybenzoic acid
m	Multiplet
mg	Milligram
mL	Millilitre
PMB	4-Methoxybenzyl ether
PCC	Pyridinium Chlorochromate
PPTS	Pyridinium p-toluenesulfonate
s	Singlet
q	Quartet
t	Triplet
TBAT	Tetrabutylammonium difluorotriphenylsilicate
TBDMS	tert-Butyldimethylsilyl ether
TBDMSCl	tert-Butyldimethylsilyl chloride
TES	Triethylsilane
TMEDA	Tetramethylethylenediamine
µL	Microliter

CHAPTER 1

INTRODUCTION

Cancer is one of the major reason of death and one of the most scared of illnesses. There are over 100 different types of cancer, and each type of cancer is usually named by the organs or tissues where the cancers form.

According to the International Agency for Research on Cancer (IARC) in 2012, there were 14 million new cancer cases and 8.2 million cancer related deaths. According to the predictions for 2030, these numbers will rise to 21.7 million new cases and 13 million cancer deaths. Part of the reason for this is globalization of unhealthy lifestyles, especially cigarette smoking and heavy use of alcohol ("Global Cancer Facts & Figures 3rd Edition," 2007).

Cancer can start anywhere in the human body, which is made up about 30 trillion of cells. Usually, most of the cells grow and divide to make a new cells to keep the body healthy. When cells grow old or become damaged, they die, and new cells get their place. In the case of cancer, damaged cells survive instead of dying, cancer cells continue to grow and form new, abnormal cells. Cancer is a disease where cells start to grow out of control. Cancer cells can also invade other tissues.

Cancers are a broad group of diseases and have a wide range of causes. Not all the causes of cancer is known yet. However, these can be classified under two main factors. One of them is external factors. There are lots of chemical, physical and biological agents that have been shown to trigger the mutagenesis in the cell. These are called carcinogens and include tobacco, reactive chemicals, ultraviolet and other radiations. In addition, infectious organisms like viruses can cause the cancer. Pollution and malnutrition can also trigger the formation of cancer. The other factor is the internal factors such as hormones, immune conditions and genetic mutations. External and internal factors may lead up together to cause cancer ("American Cancer Society," 2015).

Nowadays, there have been many different treatments against cancer and it depends on the type of cancer, age and health status. Cancer treatments categorizes surgery, radiation, chemotherapy, immunotherapy, and hormone therapy ("American Cancer Society," 2015).

Cancer treatment includes many strategies and chemotherapy plays a dominant role to cure diseases. Chemotherapy (also called chemo) is a type of cancer treatment that uses chemical ingredients to kill cancer cells. Chemotherapy drugs can be given in different ways. It can be given intravenously (as an injection) or orally (taken by mouth). Chemo drugs travel to all parts of the body. The target of treatment with chemotherapy depends on the type of cancer, how much it has spread and how she/he responds to the drugs ("American Cancer Society," 2015).

According to World Health Organization, 80% of the world populations depend on traditional medicine for primary health care needs and 85% of traditional medicine includes the use of plant extracts (Bhanot, Sharma, & Noolvi, 2011). More than 80000 of the 250000 known species of plants use for health care purposes and 60% of the effective anticancer drugs come from natural sources. Researches on this area shows that plants are good source for anticancer agents. The differrent kind of biologically active natural compounds and their structural derivatives might be useful as chemotherapeutic agents (Cragg, Grothaus, & Newman, 2009).

Plants such as vegetables or fruits, have been used to cure many diseases since ancient time. The *Genus Goniothalamus* (*Annonaceace*) are an important plants and consists of 160 species and some species used in the folk medicine for treatment of different illnesses (Lan et al., 2003).

Only 22 species out of the 160 species of the *Genus Goniothalamus* have been investigated (Wiart, 2007). Four main groups of secondary metabolites are discovered in the Goniothalamus species, which are acetogenins, alkaloids, flavanoids and styryl lactones (Tantithanaporn, Wattanapiromsakul, Itharat, & Keawpradub, 2011).

Investigations on Goniothalamus species have been increased in the last decade because these styryl lactones have notable cytotoxic properties. Styryl lactones are secondary metabolites, with either 5- or 6-membered lactones (de Fátima, Kohn, de Carvalho, & Pilli, 2006). These show significant biological activities including antitumour and antifungal properties. So far, more than twenty styryl lactones have been isolated from plants (Chen, Lin, & Liu, 2004).

1.1. Biological Activities of Stryl Lactones

Many of today's important drugs are derived from natural products mostly from plants. Interest in this area has increased dramatically in recent years due to the diverse structures and the complex carbon skeletons of natural products (Cragg et al., 2009). It is noteworthy that new compounds from natural products with a wide variety of structural arrangements and possessing distinct biological activities directed the chemists to look for the isolation of new compounds (Brahmachari, 2006).

Interestingly, 5,6-dihydro-2*H*-pyran-2-one (α,β–unsaturated δ-lactone) moiety is structural subunits of many natural products (Figure 1.1) (Boucard, Broustal, & Campagne, 2007). The α,β–unsaturated δ–lactone structure plays an important role for the biological activity including antifungal, antibacterial and antitumaral properties. These pharmacologial effects can be explained by the presence of conjugate carbon carbon double bond that can act as a Michael acceptor (Warner, Shevchenko, Jouda, Bogár, & Bäckvall, 2013).

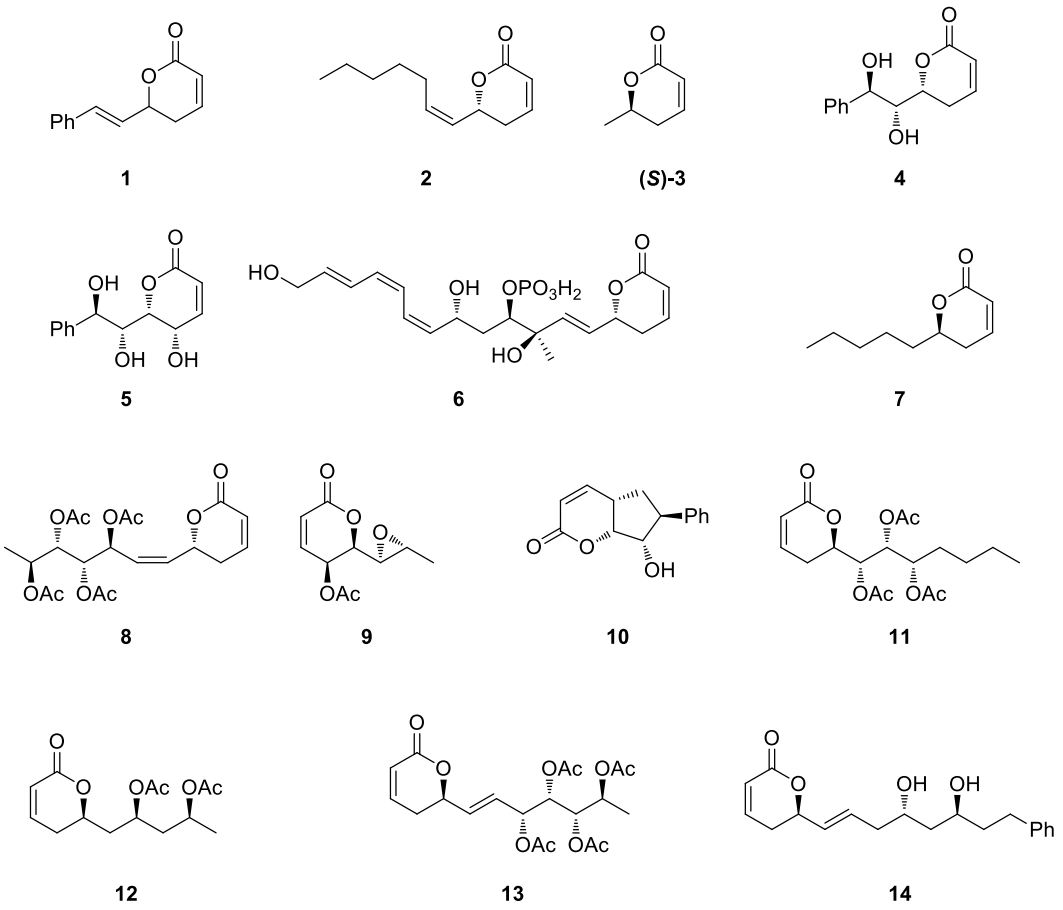


Figure 1.1. Selected examples of naturally occuring α,β-unsaturated δ-lactones.

Stryl lactones are secondary metabolites with either 5 or 6 membered lactones (de Fátima et al., 2006) displaying important biologic activity. Stryl lactones can be classified into two main groups according to size of lactone ring (γ- or -δ lactones) (Favre, Carreaux, Deligny, & Carboni, 2008). Because of their unique structures and their biologic properties these natural products become the targets of several synthesis.

Many natural products containing styryl lactone moiety, isolated from *Goniothalamus* plant species. Goniothalamin (GTN) **1** or 6-styrl-5,6-dihydro-2*H*-pyran-2-one was first isolated in 1967 from the dried bark of *Cryptocarya caloneura*. Later it was obtained from *Cryptocarya moschata*, *Broyonopsis laciniosa* and different *Goniothalamus* species (Blázquez, Bermejo, Zafra-Polo, & Cortes, 1999).

Recent studies have shown that Goniothalamin (***R*)-1** displayed cytotoxic effect by inducing apoptosis on different cancer cell lines such as cervical carcinoma (Hela), gastric carcinoma (HGC-27), breast carcinoma (MCF-7, T47D, and MDA-MB-231),

leukemia carcinoma (HL-60), and ovarian carcinoma (Caov-3)] (Ali et al., 1997), (Salmaan H. Inayat-Hussain et al., 1999), (S. H. Inayat-Hussain, Annuar, Din, Ali, & Ross, 2003), (Pihie, Stanslas, & Din, 1998). In addition, (*R*)-goniothalamin (Figure 1.2) have tumoridical and tumoristatic activity on the Sprague-Dawley rats (Meenakshii, Lee, Azimahtol, & Hasidah, 2000).

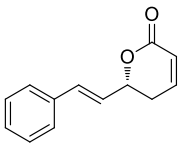


Figure 1.2. Structure of goniothalamin (*R*)-**1**.

It has been suggest that the biological activity of α,β−unsaturated δ-lactone ring is related to act as a Michael receptor, permitting them to bind target enzymes via nucleophilic residues of amino acids (lysine, serine and cysteine). In Michael addition reaction, the nucleophile attacks to C=C double bond, in order to bind itself to the β position affording Michael adduct as shown in figure 1.3 (Cardona, Guerra, & Restrepo, 2013).

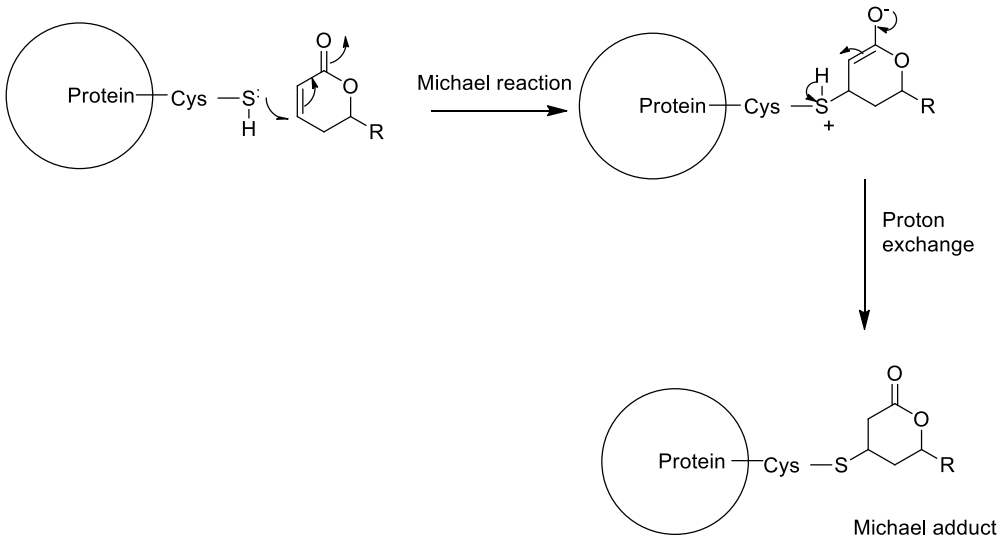
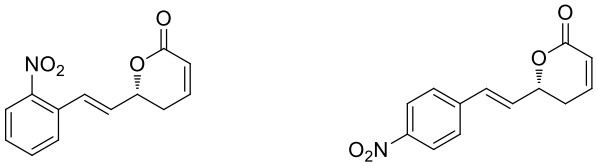


Figure 1.3. Suggested mechanism for the binding of α,β−unsaturated δ-lactones to enzymes.

1.2. Structure Activity Relationship (SAR) of Goniothalamin Derivatives

Synthesis of goniothalamin (***R***)-**1** and its derivatives getting importance in the last decade. So far, there is limited information about the structure activity relationship (SAR) of goniothalamin anologues.

Mu et.al, described the semi-synthesis of (*R*)-goniothalamin derivatives and they found that 2- and 4-nitro analogues of (*R*)-goniothalamin derivatives (**15, 16**) were the most active against promyelotic leukemia (HL-50) and human lung carcinoma (A549) cells (Figure 1.4).



15 (***R***)-**16**

Figure 1.4. Structures of 2- and 4-nitro analogues of (*R*)-goniothalamin derivatives.

Pilli and coworkers prepared (*R*)- and (*S*)- goniothalamin derivatives and they found that goniothalamin (***R***)-**1** was 1600 times less potent than goniothalamin (***S***)-**1** against kidney cancer cells (786-0). They also showed that, synthesis of anologues (**17-21**) allowed to understand pharmacophoric groups responsible for high antiproliferative activity and selectivity (Figure 1.5).

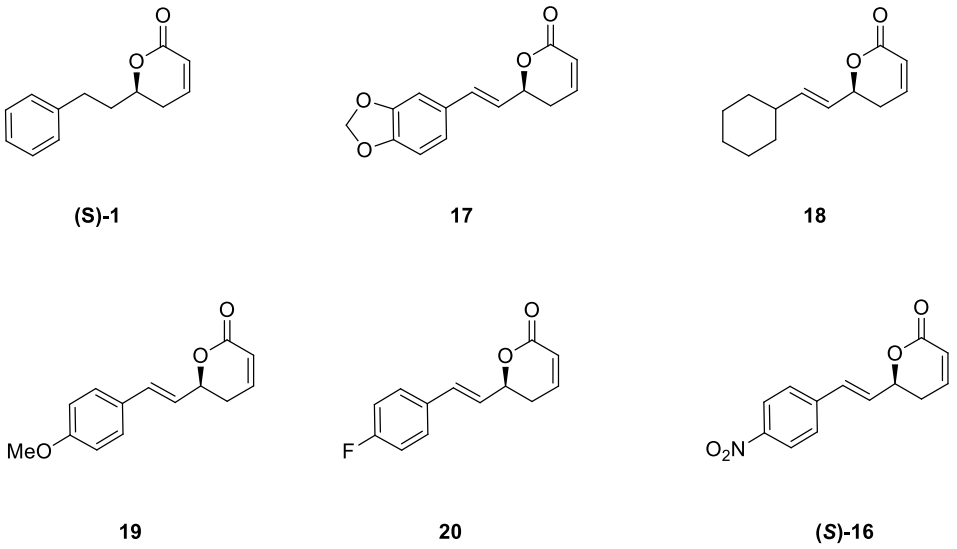


Figure 1.5. Structures of goniothalamin (*S*)-1 and its analogues **17-20**.

Analogues (**21-22**) displayed that the endo and exo double bonds related to the pyrone ring are also important for the activity (Figure 1.6). They also recognized that, the α,β-unsaturated δ-lactone moiety is crucial for activity due to its act as a Michael acceptor.

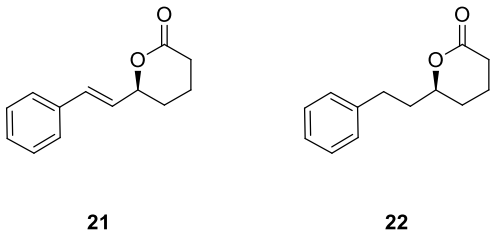


Figure 1.6. Structures of (*S*)-goniothalamin analogues having saturated lactone rings (**21** and **22**).

Barcelos and co-workers prepared the racemic mixture of the trifluoromethylated and methoxylated analogues of goniothalamin (compounds **23-30**). They found that, 2,4-dimethoxy goniothalamin **26** was shown to be more potent than goniothalamin **1**. Also, when they compared 4-methoxy analogue **25** to 2,4-dimethoxy anologue **26,** they show that compound **26** displayed higher potency against human cancer cell lines. Among trimethoxylated series of compounds (**29** and **30**) analogue **30** was more potent than the monosubstituted derivative **25** and displayed higher antiproliferative activity than the 3,4,5-trimethoxy analogue **29**. The 3,5-dimethoxy and

the 2,4,5-trimethoxy analogues (**28** and **30**) showed good antiproliferative activity when compared to goniothalamin **1** (Figure 1.7).

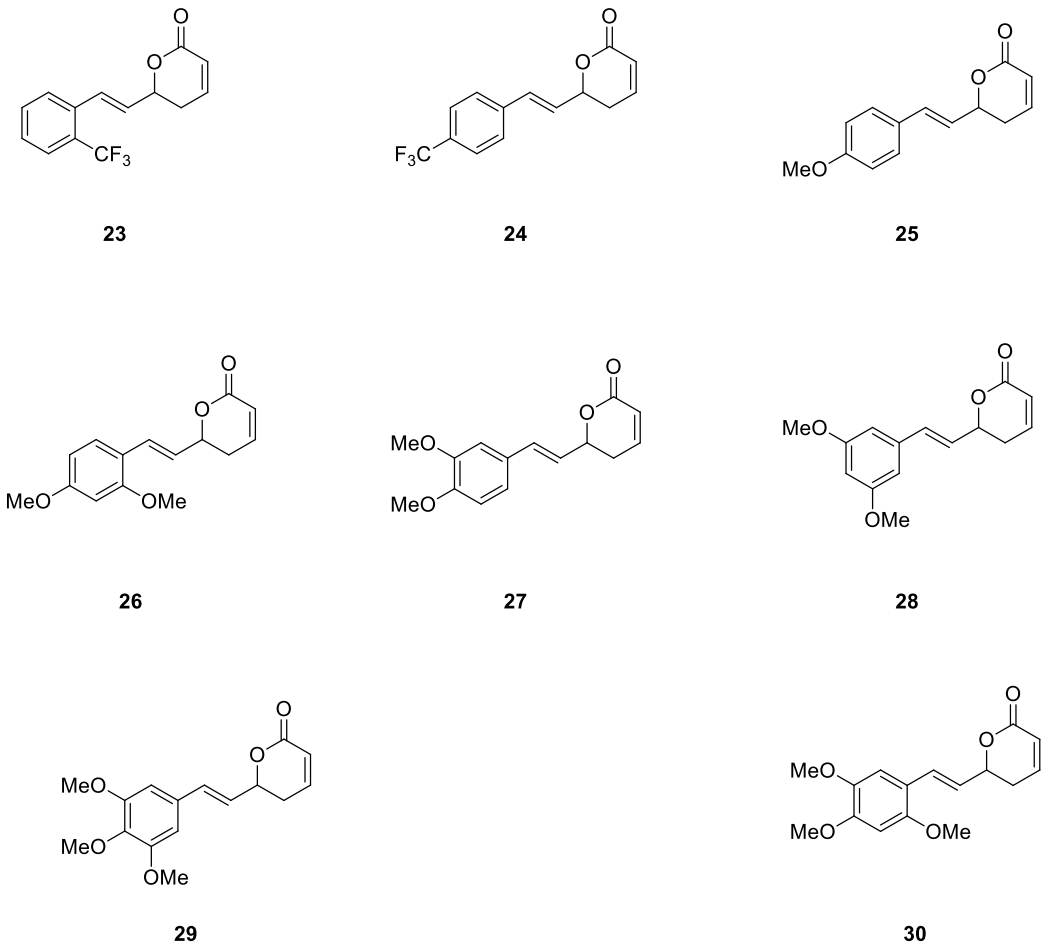
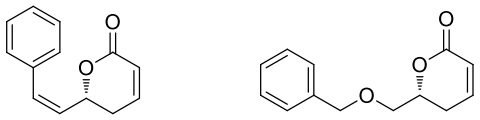


Figure 1.7. Structures of methoxylated and trifluoromethylated derivatives of goniothalamin (**23-30**).

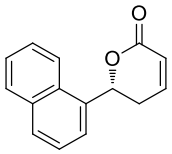
De Fatıma et al., displayed that goniothalamin (***R***)-**1** was two times more cytotoxic compared to (*R*)-goniothalamin analogue (**31**) possesing cis double bond between the carbons in the linker part (**31**) and (*R*)-goniothalamin analogue, possesing ether funcionality in the linker part (**32**) was 2-6 times lower cytotoxic than goniothalamin (***R***)-**1** (Figure 1.8). It is considered that, the trans oriented double bond in the linker part and Michael acceptor properties are very important for biological activity (de Fátima, Kohn, Antônio, de Carvalho, & Pilli, 2005).



31 32

Figure 1.8. (*R*)-goniothalamin analogues having cis C=C (**31**) and ether (**32**) functionality at linker domain.

Kasaplar et al., synthesized 6-bicycloaryl substituted 5,6-dihydro-2*H*-pyran-2-one derivatives including klavuzon (**33**) which was named by the same group (Figure 1.9). According to de Fatima's results, they changed linker part with napthhalen-1-yl, napthhalen-2-yl and quinolin-3-yl derivatives to understand the role of the linker part for biologic activity (Kasaplar, Yılmazer, & Çağır, 2009).



33

Figure 1.9. Chemical structure of (*R*)-klavuzon **33**.

They observed that, analogues **34** and **35** have slightly better anti-proliferative properties than goniothalamin (***R***)-**1**. On the other hand compound **34** is four and two times more cytotoxic activity in PC-3 and MCF-7 cells, compared to its enantiomer **36**. They also observed that, 1-naphthyl substituted (*R*)-5,6-dihydro-2*H*-pyran-2-ones (**33**, **37**, and (***R***)-**38** gave good results. In particular goniothalamin (***R***)-**1** is 80 times less potent compared to compound (***R***)-**38** in PC-3 cells (IC_{50} = 50 nM) and compound (***R)*-38** 40 times more potent compared to goniothalamin (***R***)-**1** in MCF-7 cells (IC_{50} = 440 nM).

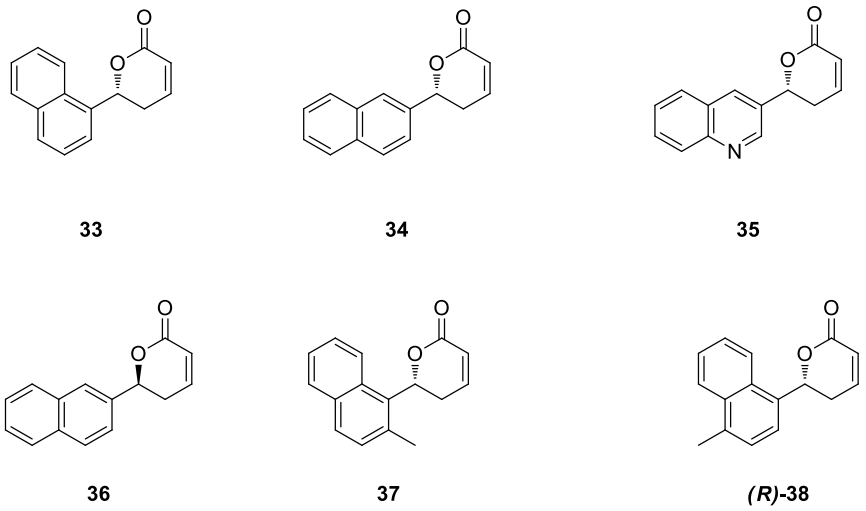


Figure 1.10. Structures of bicycloaryl substituted 5,6-dihydro-2*H*-pyran-2-ones derivatives (**33-38**).

They reported that, cytotoxic activities of these compounds stemmed from, restriction of the rotation around the single bond between the phenyl ring and double bond. In addition to this, size of the substituent and the stereochemistry in the lactone ring are also important. Especially, naphthalen-1-yl substitution in the lactone ring enhanced the activity and additional methyl substitution in the naphthalene ring at position 2 and 4 produce highly cytotoxic compounds.

In this thesis, we interested in the synthesis of novel 4'-alkyl substituted klavuzon derivatives due to its promising anti-proliferative over cancer cells activities and naphthalen-1-yl substituted 3,6-dihydro-2*H*-pyran-2-one derivatives.

1.3. Synthetic Routes for the Preparation of α,β–Unsaturated δ-Lactones

In literature, many different synthetic methods for the building of 5,6-dihydropyran-2-one rings have been reported and some of them will be displayed as a short summary.

1.3.1. Asymmetric Allylboration

Chiral unsaturated lactones are commonly found in a series of natural products. Several approaches to prepare chiral lactones have been made in the literature. Ramachandran et.al., synthesized 6-substituted-5,6-dihydro-2*H*-pyran-2-one derivatives via sequential asymmetric allyboration, esterification and ring closing metathesis.

In this synthesis method, (*R*)-homoallylic alcohol (***R***)-**41** was prepared by allylboration of cinnamaldehyde (**39**) with (+)-*B*-allyldiisopinocampheylborane **40** in an Et_2O pentane mixture at –100 °C. Then esterification of homoallylic alcohol (***R***)-**41** with acryloyl chloride **42** gave acryloyl ester (***R***)-**43** which was treated with Grubbs' catalyst to provide goniothalamin (***R***)-**1** (Ramachandran, Reddy, & Brown, 2000) (Figure 1.11).

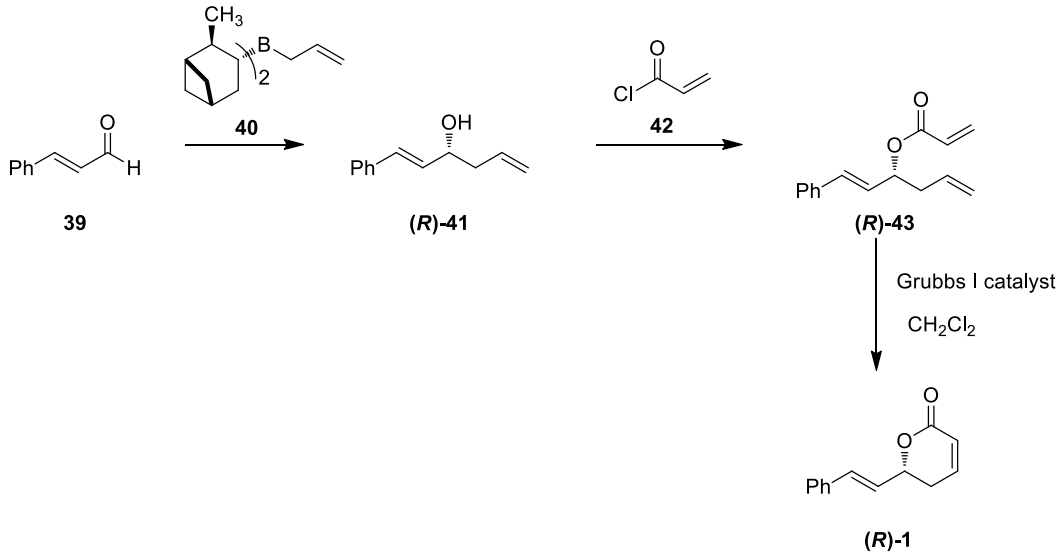


Figure 1.11. Asymmetric synthesis of (*R*)-goniothalamin (***R***)-**1** via allylboration with (+)-B-allyldiisopinocampheylborane **40**.

1.3.2. Lipase Catalyzed Resolution and Alkene Metathesis

Sundby et al., were reported the synthesis of goniothalamin by an lipase catalyzed resolution in the presence of vinyl acrylate followed by ring closing metathesis. In this study, racemic alcohol **44** was prepared via grignard reaction between allylmagnesium bromide and trans cinnamaldehyde **39**. The racemic alcohol **44** was kinetically resolved by a transesterification reaction using vinyl acrylate and as catalyst *Candida antarctica* lipase B (CALB) to obtain compounds (***R***)-**43** and (***S***)-**41**. After separation of the products, alcohol (***S***)-**41** was reacted with acryloyl chloride **42** to give compound (***S***)-**43**. Finally, acrylate esters (***R***)**-43** and **(*S*)-43** treated with Grubbs' catalyst to give (***R)*** and (***S)*** goniothalamin as shown in figure 1.12 (Sundby, Perk, Anthonsen, Jørgen Aasen, & Vidar Hansen, 2004).

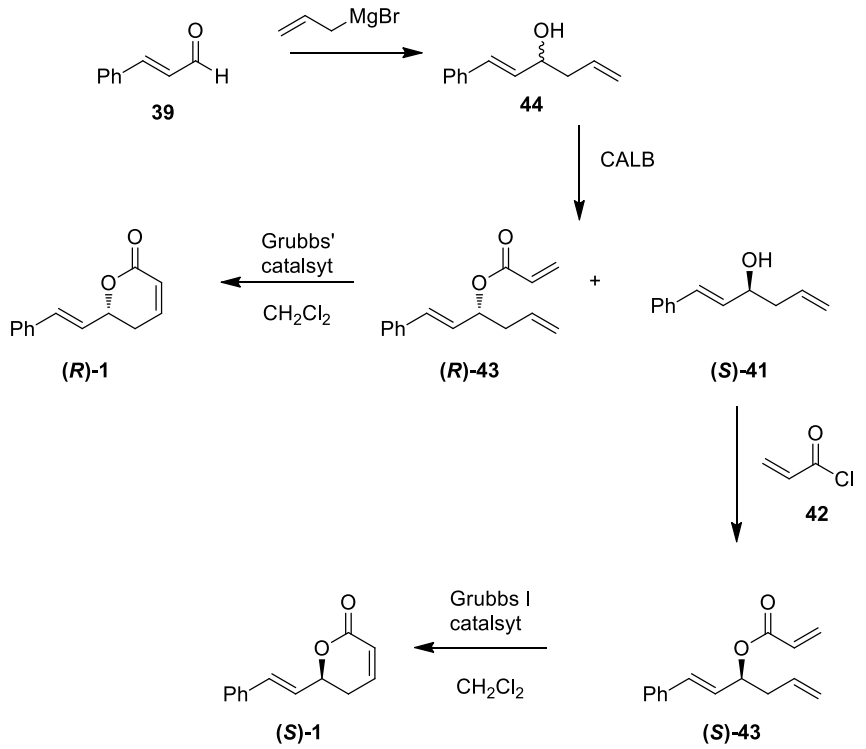


Figure 1.12. Lipase catalyzed synthesis of (*S*)- and (*R*)-goniothalamin **1**.

1.3.3. Catalytic Enantioselective Allylation of Aldehydes with *R*-BINOL-Ti Complex

De Fatima et al., synthesized goniothalamin (***R***)-**1** in three steps. The first step was catalytic asimetric allylation of *trans*-cinnamaldehyde **39** with allyltributyltin in the presence of chiral (*R*,*R*)-**A** complex (**46**) which was prepared from (*R*)-BINOL (**45**) according to Maruoka and co-workers method (Hanawa, Hashimoto, & Maruoka, 2003) (Figure 1.13).

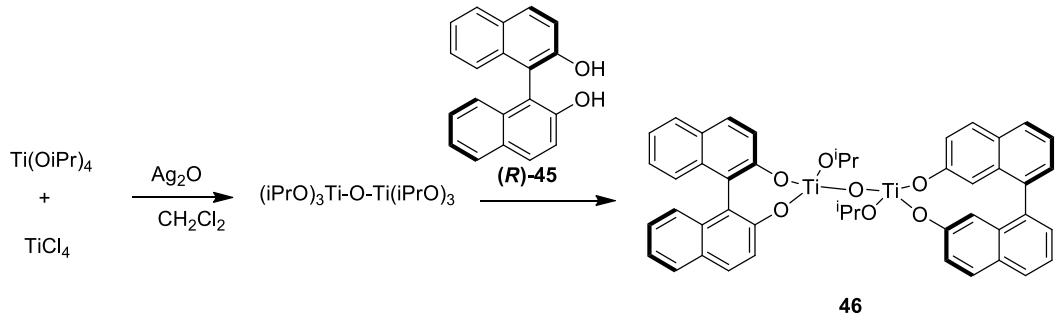


Figure 1.13. Preparation of chiral auxiliary **46** from (*R*)-BINOL **45**.

Homoallyl alcohol (***R***)-**41** was obtained in high yield and good enantioselectivity from the reaction between *trans*-cinnamaldehyde (**39**) and allyltributyltin in the presence of catalyst **46**. In the next step homoallylic alcohol (***R***)-**41** was treated with acryloyl chloride (**42**) to produce acryloyl ester (***R***)-**43**. Finally, ring closing metathesis was used to produce compound (***R***)-**1** (de Fátima & Pilli, 2003) (Figure 1.14).

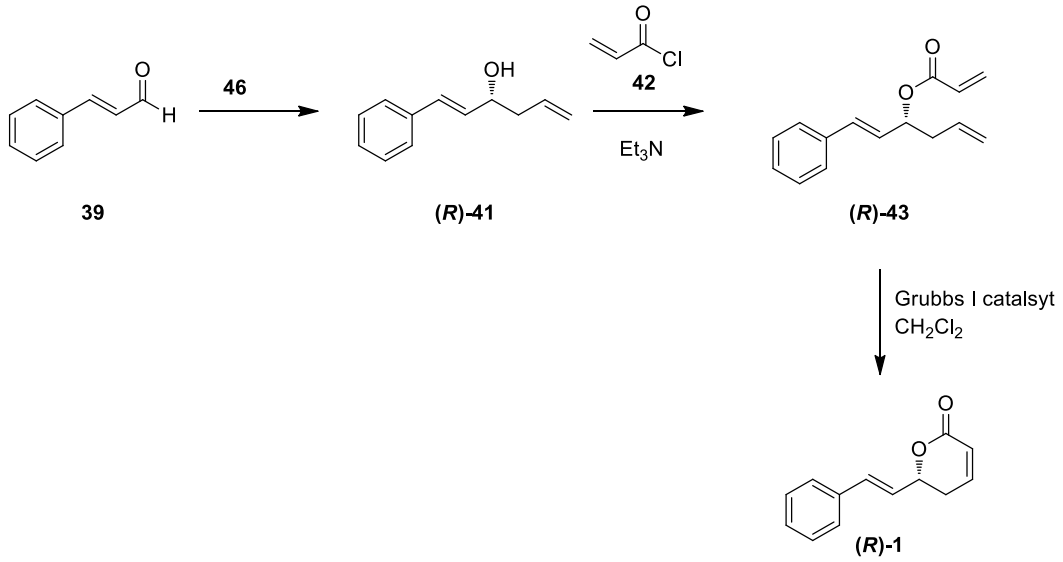


Figure 1.14. Asymmetric synthesis of (*R*)-goniothalamin (***R***)-**1**.

1.3.4. Asymmetric Total Synthesis Starting from Chiral Epoxide

Sabitha et al., developed the asymetric route for the total synthesis of (*R*)-(-)-tuberolactone (***R***)-**55** in eight steps. In this synthesis method, they started with epoxide (***S***)-**47**, it was prepared according to Jacobsen's hydrolytic kinetic resolution method (Schaus et al., 2002). Homopropargylic alcohol (***R***)-**48** was obtained from the reaction between lithium acetylide and enantiomerically pure epoxide (***S***)-**47**. Then, alcohol was subjected to alkylation with ethyl bromide to give compound (***R***)-**49**. Sillylation of secondary alcohol by using TBDMSCl and imidazole affords compound (***R***)-**50**. After removal of PMB group with DDQ, alcohol (***R***)-**51** was oxidized and then formed aldehyde (***R***)-**52** was converted to *Z*-unsaturated ester (***R***)-**53** via Still-Gennari modification of the Horner-Emmons reaction in good yield (82%) (Still & Gennari, 1983). The ester (***R***)-**53** treated with p-TSA in methanol to afford compound (***S***)-**54** via in situ deprotection of TBDMS group. Finally, partial hydrogenation of the triple bond with Lindlar's catalsyt gave chiral α,β–unsaturated δ-lactone derivative which named as tuberolactone (***R***)-**55** (Sabitha, Bhaskar, & Yadav, 2006) (Figure 1.15).

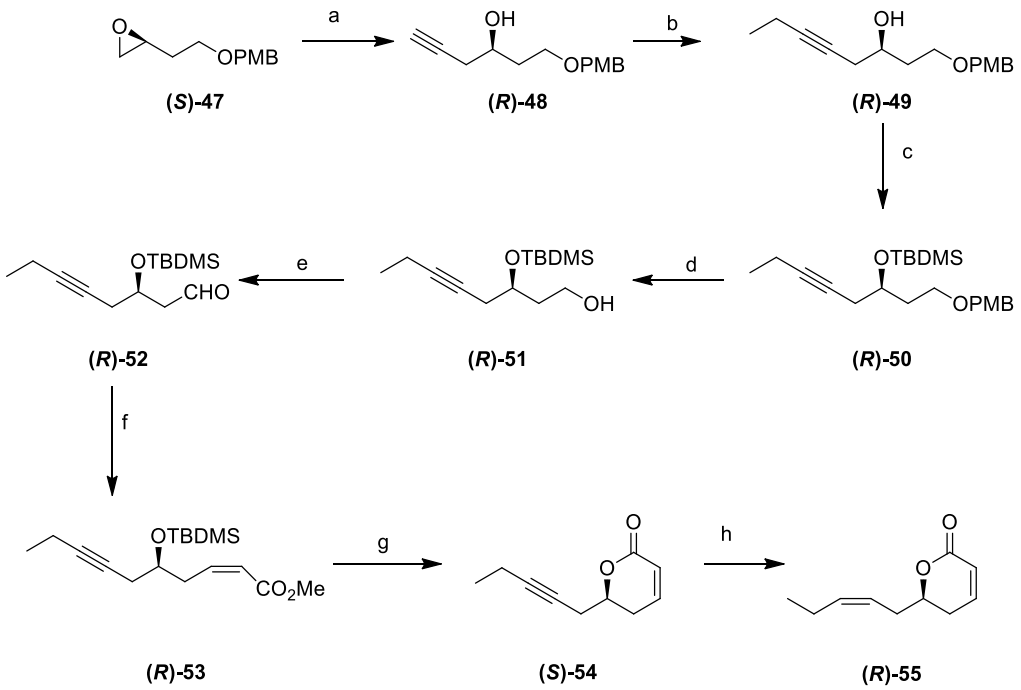


Figure 1.15. Asymmetric total synthesis of (*R*)-(-)-tuberolactone. Reagents and conditions: (a) lithium acetylide, ethylenediamine complex, DMSO, 6 h, rt, (b) (*i*) Li/liq NH_3, dry THF, -78 ^oC, (*ii*) EtBr, THF, 3–4 h (c) TBDMSCl, imidazole, DCM, rt, 1–1.5 h, (d) DDQ, DCM/H_2O (9:1), rt, 30 min, (e) IBX, DMSO, 0 ^oC to rt, 1–2 h, (f) (*i*) NaH/THF, -78 ^oC, 30 min, (*ii*) $(CF_3CH_2O)_2P(O)CH_2COOCH_3$, THF, 30–45 min, (g) p-TSA/MeOH, rt, 3–4 h, (h) H_2, Lindlar's cat., EtOAc, quinoline, 2 h.

1.3.5. Stereoselective Hetero Diels-Alder Reaction

In this study, Wach et.al., reported a new synthetic route to goniothalamin (***R***)-**1** based on stereoselective hetero Diels-Alder and cross coupling reactions. The key intermediate compound **58** was synthesized in three steps via Cr(III) catalyzed asymmetric hetero Diels-Alder reaction according to Jacobsen and co-workers method (Dossetter, Jamison, & Jacobsen, 1999). Compound **58** obtained by the reaction of methoxybutadiene **56** with propargylic aldehyde **57** which is TES protected followed by transacetalization and deprotection. Then the key intermediate converted to the gonitholamin lactol eter **59** by hydrozirconation, transmetallation and Negishi cross coupling (Huang & Negishi, 2006). Finally, deprotection and oxidation gave goniothalamin (***R***)-**1** (Figure 1.16) (Wach, Güttinger, Kutay, & Gademann, 2010).

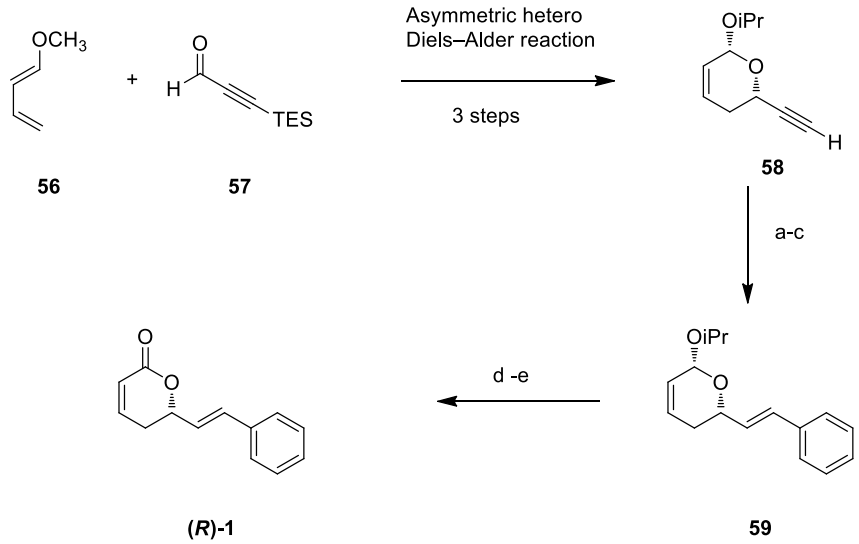
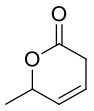


Figure 1.16. Synthesis of (*R*)-goniothalamin (*R*)-1 via asymmetric Hetero Diels–Alder reaction. Reagents and conditions: (a) Cp_2ZrHCl, 0 ^oC to rt, THF, 1 h, (b) $ZnCl_2$, THF, rt, 30 min, (c) iodobenzene, $Pd(PPh_3)_4$ (5 mol %), DIBAH (1.0 M in hexane), rt to 40 ^oC, 12 h, (d) PPTS, acetone/water (3:1), rt, 22 h, (e) PCC, 4 Å MS, AcOH, CH_2Cl_2, rt, 3 h.

1.4. β,γ-Unsaturated δ-Lactones

Beside α,β–unsaturated δ–lactone derivatives, the synthesis of β,γ-unsaturated δ-lactones known as 3,6-dihydro-2*H*-pyran-2-ones, is the subject of this thesis.



60

Figure 1.17. Structure of 3,6-dihydro-2*H*-pyran-2-one **60**.

The δ-lactone moiety comprises structural subunits in a number of natural products. During the synthesis of these biologically active natural products β,γ-unsaturated δ-lactones are key intermediates. For example, reaction of meta-chloroperoxybenzoic acid with compound **60** gives 3,7-dioxabicyclo[4.1.0]heptan-4-one **61** derivative. Compound **60** can be converted to 5,6-dihydro-2*H*-pyran-2-one **3** derivatives in the presence of DBU (1, 8-Diazabicyclo[5.4.0]undec-7-ene). Treatment of

compound **60** with ethanol in the presence of hydrocloric acid and potassium hidroxide affords the dienoicacid derivatives **62**. Catalytic hydrogenations of compound **60** give the saturated lactone derivatives **63** (Figure 1.18).

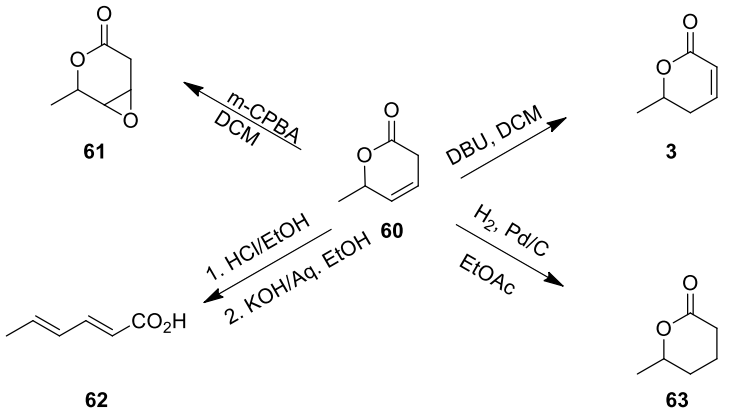


Figure 1.18. Conversion 3,6-dihydro-2*H*-pyran-2-one to biologically active compounds.

So far, there is no information about the biologic activity of 3,6-dihydro-2*H*-pyran-2-one derivatives in literature. However, we know that 3,6-dihydro-2*H*-pyran-2-one derivatives can be easily transform into 5,6-dihydro-2*H*-pyran-2-one derivatives in the presence of bases such as DBU, or ^{t}BuOK (Takii, Kanbayashi, & Onitsuka, 2012).

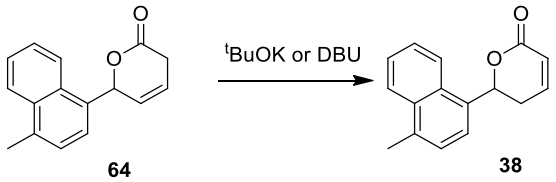


Figure 1.19. Proposed conversion 3,6-dihydro-2*H*-pyran-2-one to 5,6-dihydro-2*H*-pyran-2-one structure.

Various types basic compounds can also be found in cells including proteins and peptides. Amino acids side chains are responsible for the activity of proteins. One of the property is their basic characters. Especially, amino acids such as (*L*)-histidine **65**, (*L*)-arginine **66** and (*L*)-lysine **67** contain basic residues. These amino acids may accept protons from other molecules similar to DBU (Figure 1.20).

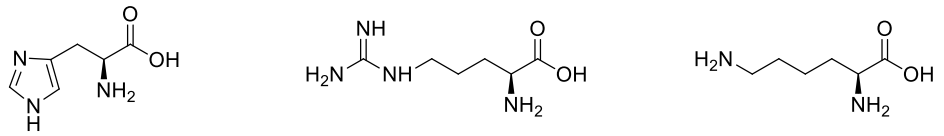


Figure 1.20. Chemical structure of basic amino acids (*L*)-histidine **65**, (*L*)-arginine **66** and (*L*)-lysine **67**.

In this thesis, novel 3,6-dihydro-2*H*-pyran-2-one derivatives were synthesized and it is expected that they may be isomerized by basic amino acids in peptides or proteins. Due to the lack of a Michael acceptor these organic molecules may bind to such proteins with weak interactions. Such interactions may lead molecules give protons to proteins side chains and change their bonding profile. In that case, double bond between β,γ–carbons may isomerize to between α,β–carbons to produce corresponding klavuzon derivatives (Figure 1.21).

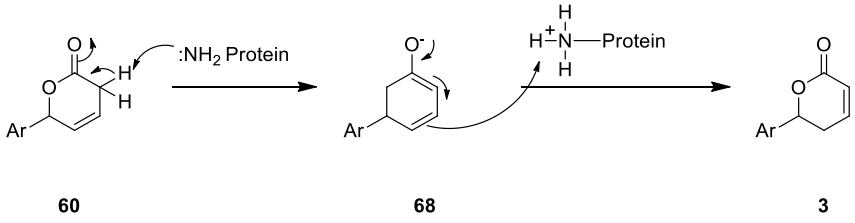


Figure 1.21. Proposed mechanism for the conversion of 3,6-dihydro-2*H*-pyran-2-one to 5,6-dihydro-2*H*-pyran-2-one in the cell with basic side chains of proteins.

1.5. Synthesis of β,γ-Unsaturated δ-Lactones

In literature different synthetic methods for the preparation of 3,6-dihydro-pyran-2-one rings have been reported. Just some of them will be described as a short summary in here.

1.5.1. Gold Catalyzed Cyclization of Allene-Substituted Malonate Esters

In this study, Piera et.al., developed a new route to β,γ–unsaturated δ–lactones by means of gold-catalzyed intramolecular nucleophilic attack of a carboxy ester to an allene. The starting material **72** was obtained from Pd (0)-catalyzed allylic substition of the acetate **69** with dimethyl malonate to afford compound **70** followed by bromoallene **71** addition reaction. Treatment of compound **72** with $AuCl_3$ in the presence of silver salt additives which is used to form cationic gold species and it leds to increase of yield to furnish compound **73** (Figure 1.22) (Piera, Krumlinde, Strübing, & Bäckvall, 2007).

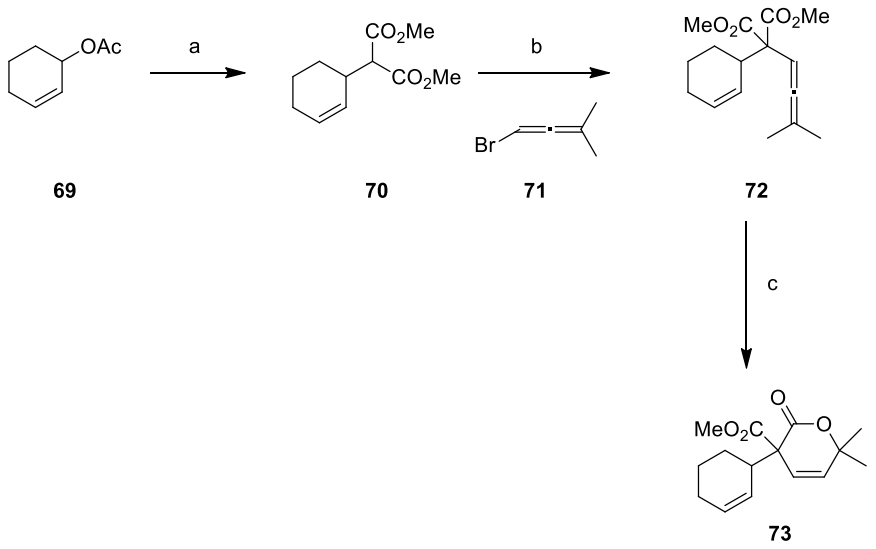


Figure 1.22. Synthesis of 3,6-dihydro pyran-2-one derivatives via gold catalyzed cyclization of allene-substituted malonate esters. Reagents and conditions: (a) NaH, $(MeO_2C)_2CH_2$, $Pd(OAc)_2$, PPh_3, THF, reflux, (b) NaH, **71**, THF, reflux, (c) $AuCl_3/AgSbF_6$, AcOH.

1.5.2. Ru-Catalyzed Asymmetric Allylic Carboxylation

Takii et al., developed a new synthetic route to optically active δ-lactones via asymmetric allylic carboxylation with a planar-chiral *Cp'-Ru* catalyst **74** followed by RCM. First, treatment of cinnamyl chloride **75** with (*E*)-pent-3-enoic acid **76** in the presence of Cp'-Ru catalyst produced allylic ester **77** in good yield. Then, allylic ester was converted to β,γ–unsaturated δ–lactones **78** via ring closing metathesis by using Grubbs' II catalyst (Figure 1.23) (Takii et al., 2012).

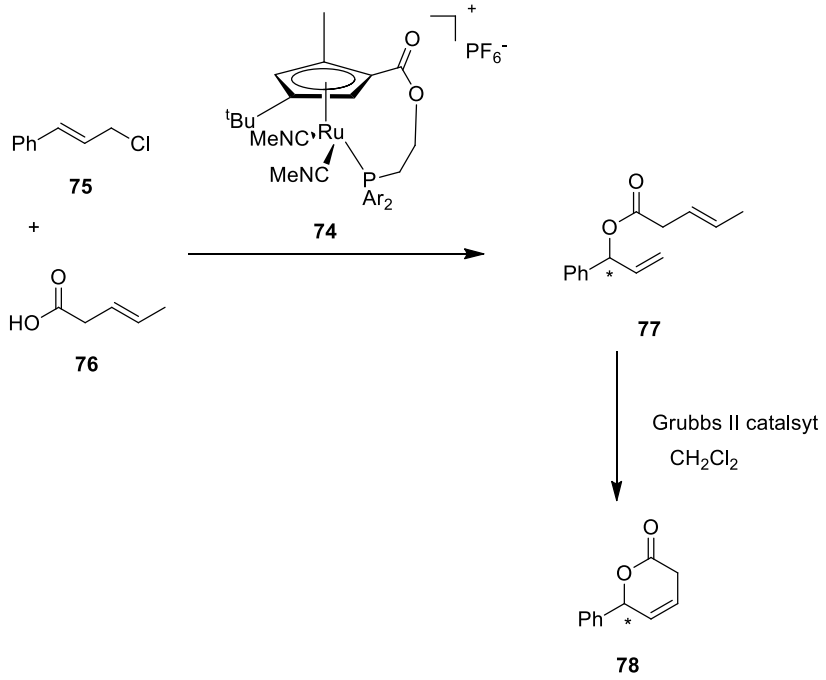


Figure 1.23. Synthesis of compound **78** with a planar-chiral *Cp'-Ru* catalyst **74**.

1.5.3. NHC-Catalyzed Cascade Epoxide-Opening and Lactonization

N-Heterocyclic carbenes are important organocatalysts and they provide a wide range of useful synthetic transformations. In this study, Qi et al., reported NHC-catalyzed intramolecular redox reaction of γ-epoxy-α,β–enals to give dihydropyrone ring via a cascade epoxide-opening and lactonization pathway. Key intermediates in the mechanism for the formation of compound **84** is shown in figure 1.24. In the first step, N-heterocyclic carbene **80** was generated from thiazolium salt, and added to the

aldehyde **79** to form Breslow İntermediate **81**. Then, homoenolate **82** underwent the epoxide ring-opening and generated the intermediate **83**. Finally, intramolecular attack of alkoxide moiety afforded the product **84** (Qi et al., 2011).

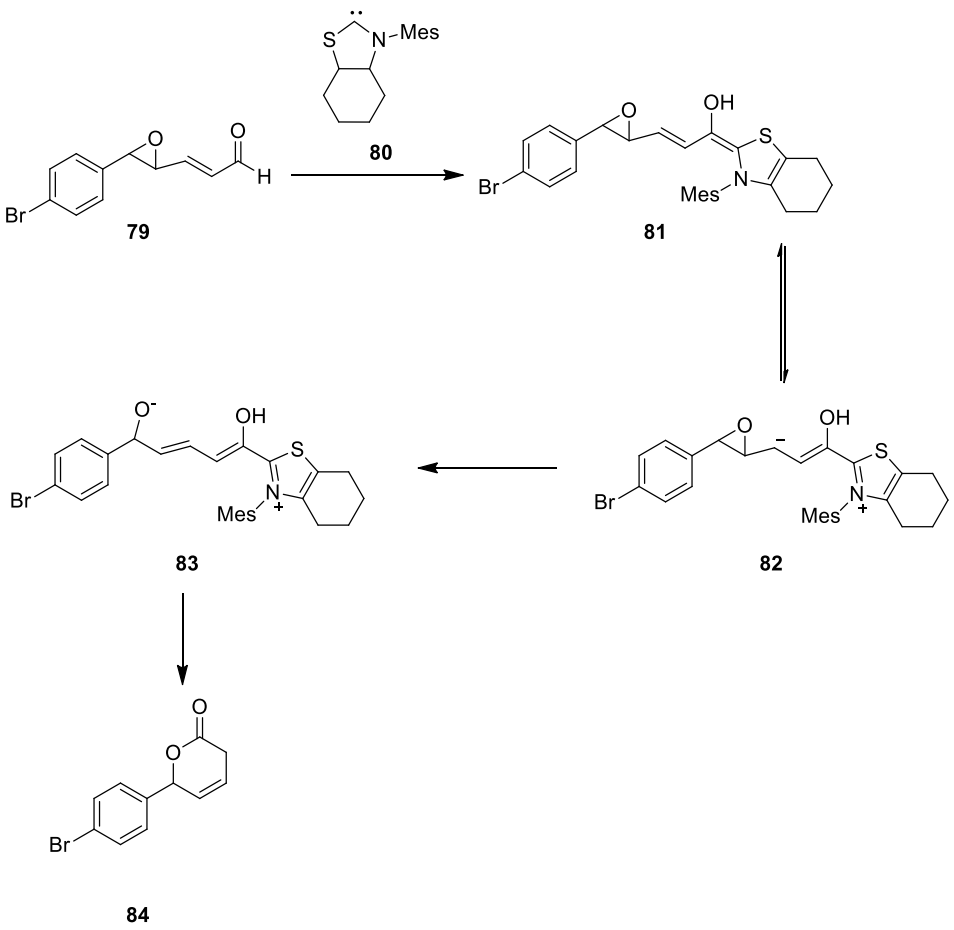


Figure 1.24. Key intermediates in the formation of compound **84** by NHC-catalyzed cascade epoxide opening.

1.5.4. Nucleophilic 1,2-Addition of (*Z*)-γ-Silyloxyvinylzinc and Cyclization

Dieter et al., was reported to synthesis of 3,6-dihydro-3-hydroxypyran-2-one derivatives via nucleophilic 1,2-addition of (*Z*)-γ-silyloxyvinylzinc reagents to ethyl glyoxylate followed by desilylation and cyclization reactions. The compound **86** was prepared from the reaction between compound **85** and NaI by using small amount of AcOH (Piers, Harrison, & Zetina-Rocha, 2001). Metalation of compound **86** with *t*-

BuLi and addition of $ZnBr_2$ afforded vinylzinc species **87**. Then, 1,2–addition to ethyl glyoxylate **88** to vinylzinc species gave α-hydroxy esters **89**. Finally, utilization of homogenous methanol solution of H_2SiF_6 gave the δ–lactones **90** in high yield (Figure 1.25) (Dieter & Guo, 2006).

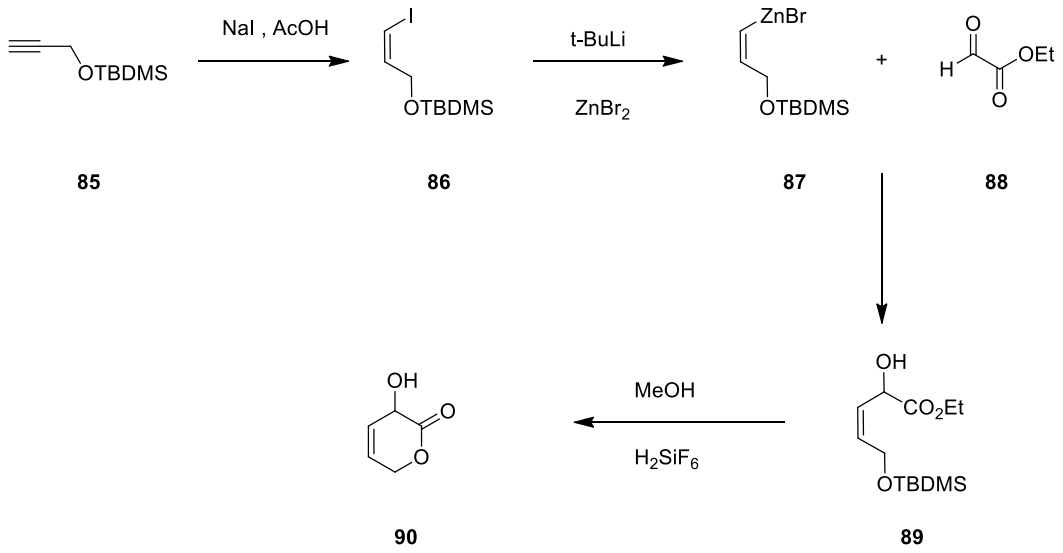


Figure 1.25. Synthesis of compound **90** via nucleophilic 1,2-addition of (*Z*)-γ-silyloxyvinylzinc and cyclization.

1.5.5. Cationic Palladium (II) Complex-Catalyzed Tandem [2+2] Cycloadditon-Allylic Rearrangement of Ketene

Cationic palladium (II) complexes are a class of transition metal-based on Lewis acids. In this synthesis Hattori et al., used palladium complex **91** as a catalyst for the [2+2] cycloaddition reactions between ketene and aldehydes to form 3,6-dihydro-2*H*-pyran-2-one derivatives. Reaction between ketene **93** and crotonaldehyde **92** in the presence of palladium (II) complexes afforded to 3,6-dihydro-6-methyl-2*H*-pyran-2-one (isoparasorbic acid) **60**.

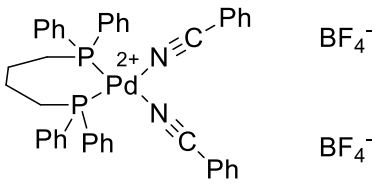


Figure 1.26. Structure of palladium(II) [1,3-bis(diphenylphosphino)butane]-bis(benzonitrile)-bis-tetrafluoroborate **91**.

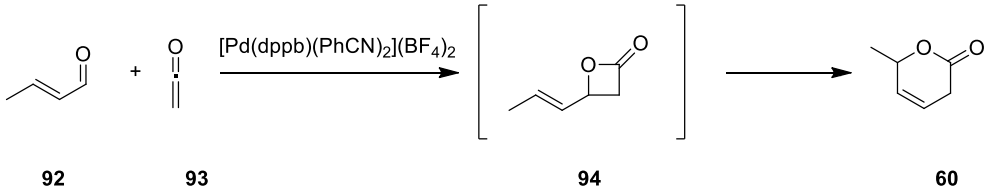


Figure 1.27. Synthesis of isoparasorbic acid **60** via Pd(II) complex.

After synthesized of compound **60**, it is treated with ethanol in the presence of HCl followed by saponification reaction to obtain dienoic acids. This method is useful for the sythesis of biological active other dienoic acid derivatives (Figure 1.28) (Hattori, Suzuki, Ito, Hotta, & Miyano, 2002).

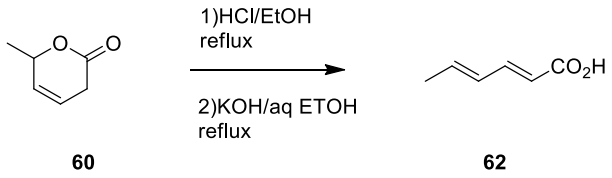


Figure 1.28. Conversion of 3,6-dihydro-6-methyl-2*H*-pyran-2-one to hexa-2,4-dienoic acid **62**.

1.5.6. Ring-Closing/Cross Coupling Metathesis

The ring closing metathesis (RCM) have become a helpful synthetic tool in organic chemistry and it is useful in the preparation of carbo- and heterocycles having different ring size. In this study, Virolleaud et al., synthesized (*E*)-δ–alkenyl-β,γ–unsaturated δ–lactones via ring closing metathesis with Grubbs' II catalsyt. Compound **98** (pentadienyl ester) was prepared from the reaction between vinyl acetic

acid **95** and 1,4-pentadien-3-ol **96** under DCC **97** activation (Neises & Steglich, 1978). Then, ester **98** was converted to intermediate vinyl lactone **99**. Finally, addition of alkene **100** and Grubbs' catalsyt final product **101** was obtained (Figure 1.29) (Virolleaud, Bressy, & Piva, 2003).

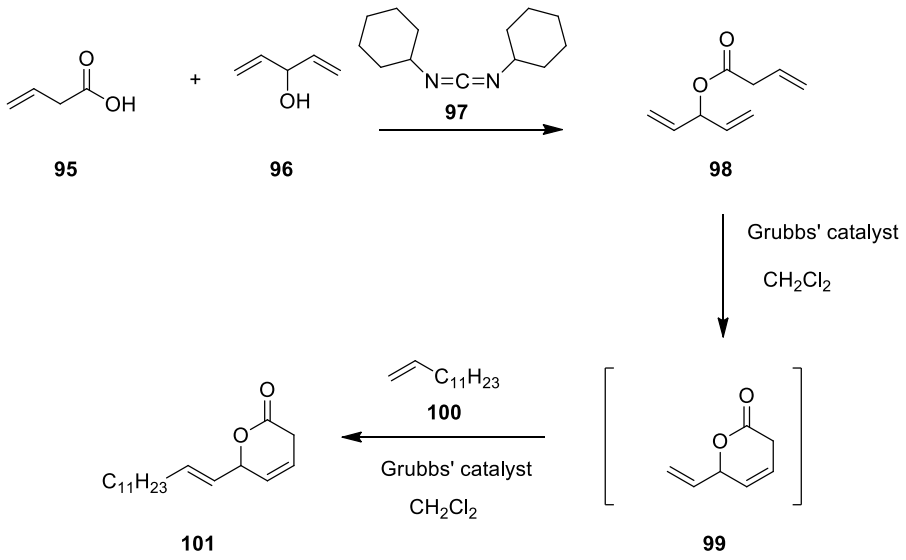


Figure 1.29. Synthesis of compound **101** via ring-closing/cross coupling metathesis.

CHAPTER 2

RESULTS AND DISCUSSIONS

Compound **38** (4'-methyl substituted klavuzon) shows significant cytotoxic activity against PC-3 and MCF-7 cells. So in this work, 4-methyl napthaldehyde **110** was chosen as the starting material to synthesize target molecules which are 4'-alkyl substituted klavuzon (**38**, **102**-**105**) and 3,6-dihydro-2*H*-pyran-2-one (**64**,**106**-**109**) derivatives.

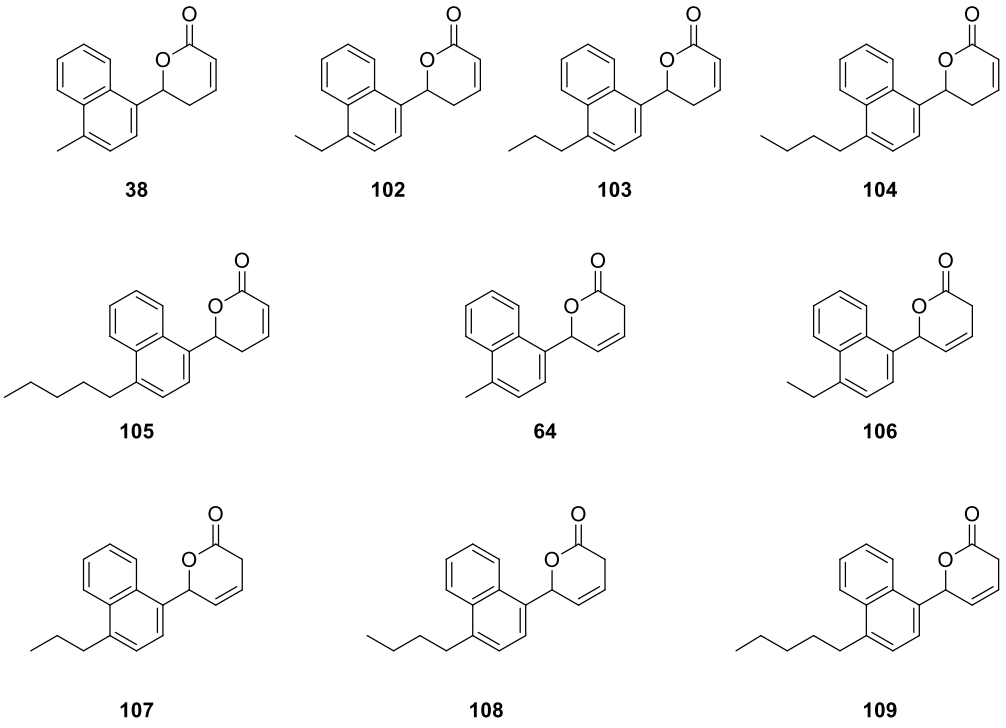


Figure 2.1. Structure of proposed 4'-alkyl substituted klavuzon and 3,6-dihydro-2*H*-pyran-2-one derivatives.

2.1. Synthesis of 4'-Alkyl Klavuzon Derivatives

Toward the synthesis of novel 4'-alkyl klavuzon derivatives commercially available 4-methyl-1-napthaldehyde **110** was chosen as starting material. Synthesis plan for the conversion of **110** to the final products involves seven steps. As shown in figure 2.2 protection of aldehyde followed by benzylic carbanion formation and alkyl halide substitution is the key steps for these transformations. Then, deprotection of aldehyde and conversion of that to the final products is well known procedures in literature (Daignault & Eliel, 1967).

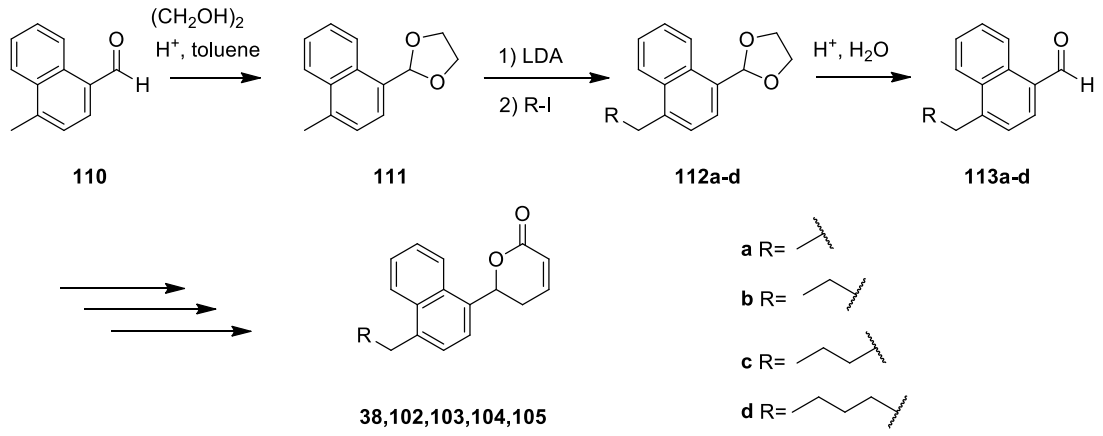


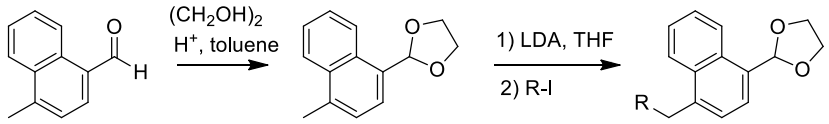
Figure 2.2. Synthetic route to 4'-alkyl substituted klavuzon derivatives.

2.1.1. Toward to Synthesis of 4-Alkyl Napthalen-1-yl Substituted Acetal Derivatives Using LDA or n-BuLi

In the first step of synthesis, aldehyde **110** was protected as an acetal to prevent from reaction between aldehyde and formed benzylic carbanion. For this purpose, aldehyde **110** was converted to acetal **111** in the presence of ethylene glycol and PTSA (p-toluene sulfonic acid) in high yields 63%. Next, formation of a benzylic carbanion with a strong base and nucleophilic substitution reactions of these carbanions to primary alkyl halides were studied to form C-C sigma bonds. LDA base is strong enough to abstract acidic proton of benzylic carbon of compound **111**, so various equivalents of LDA was mixed with compound **111**. After 1 hour of stirring, alkyl halides were added

to form C-C bond formations. As summarized in table 2.1 all attempts were failed and no product formation was observed. Since there was no C-C bond formation, it is concluded there was no significant carbanion formations with the usage of LDA, so in the next trials n-BuLi was used as a strong base.

Table 2.1. Benzylic alkylation attempts of acetal **111** with LDA.

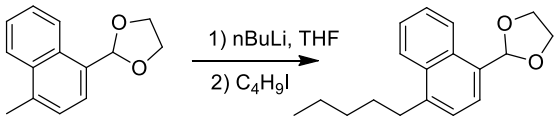


110 **111** **112a-d**

		Alkyl halide		
entry	LDA	R	Eq	Yield%
1	1.5	**a**	1.5	N.R
2	1.5	**b**	2.0	N.R
3	1.5	**c**	2.0	N.R
4	2.0	**d**	3.0	N.R

At this stage compound **111** was treated with various equivalents of n-BuLi and then butyl iodide was added over it after 1 hour stirring. Reaction was tried both in THF and hexane as solvent but no product formation was observed. It is known that n-BuLi can form agglomerates which inversely reflect the reactivity of n-BuLi. To distrub the possible agglomeration reaction TMEDA was added to the reaction medium. By help of TMEDA cage like structure can be formed which enhances the reactivity of n-BuLi or formed benzylic carbanion. But all trials were failed in our hands (Table 2.2).

Table 2.2. Benzylic alkylation attempts of compound **111** by using nBuLi.



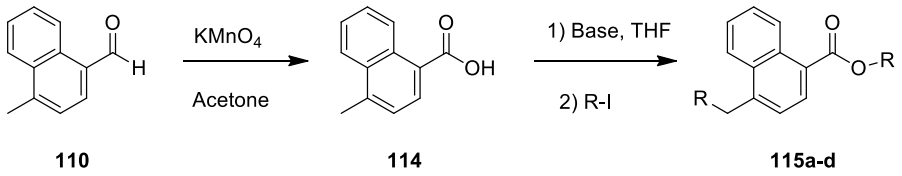
111 **112d**

entry	nBuLi (eq)	TMEDA (eq)	Alkyl halide (eq)	Solvent	Yield %
1	1.0	-	3.0	THF	N.R
2	1.5	-	1.5	THF	N.R
3	3.5	-	2.0	Hexane	N.R
4	1.0	1.0	1.8	THF	N.R

2.1.2. Toward to Synthesis of 4-Alkyl Substituted Carboxylic Acid Derivatives Using nBuLi

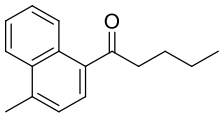
Carboxylic acids can be considered as the precursors of aldehyde so an alternative approach, 1-naphthaldehyde **110** first oxidized to carboxylic acid **114** by $KMnO_4$ in 38% yield (Fruttero, 2009). Then, it was treated with 2.0–4.5 eq of n-BuLi to form carboxylate ion, deprotonated at benzylic position too. Afterwards, varying amount of alkyl halides were added. All experiment were carried out in THF, but none of them yielded the target product instead one product of entry 3 was isolated and characterized as the ketone product. It seems that carboxylate side of the compound **114** first reacts with alkyl halide to form an ester then nucleophilic addition of unreacted n-BuLi gave compound **116** in 9% yield.

Table 2.3. Synthesis 4-methyl-1-naphtoic acid and benzylic alkylation by using nBuLi as base.



110 **114** **115a-d**

		Alkyl halide		
entry	n-BuLi (eq)	R	Eq	Yield%
1	2.0	**a**	1.3	N.R
2	2.0	**b**	1.3	N.R
3	2.5	**c**	1.3	N.R
4	4.5	**d**	1.5	N.R



116

Figure 2.3. Structure of undesired side product **116**.

2.1.3. Toward to Synthesis of 4-Alkyl Naphthalen-1-yl Substituted Benzothiazole Derivatives Using nBuLi as Base

All experiments toward the preparation of a benzylic carbanion are failed as shown above. To control the applicability of the proposed system benzothiazole derivative **118** was prepared from 4-methyl-1-naphthoic acid **114** and o-mercapto aniline **117** in the presence of CCl_4 and PPh_3 in toluene (Lenstra, Rutjes, & Mecinovic, 2014).

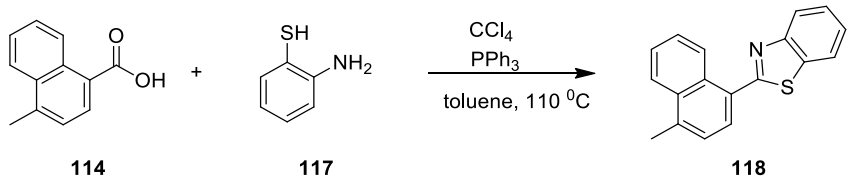


Figure 2.4. Preparation of benzothiazole derivative **118**.

Unreactive nature of the newly formed aromatic ring may direct the n-BuLi to benzylic methy group. But all trials for the alkylation of benzylic carbon failed. For the deprotonation of benzylic carbon n-BuLi is used alone or in the presence of TMEDA. All reactions were monitored by TLC but no product formation was observed in figure 2.5.

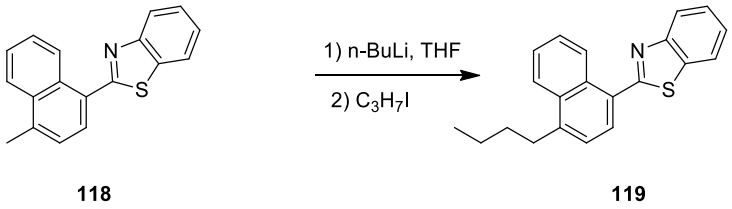


Figure 2.5. Benzylic alkylation of benzothiazole **118** by using n-BuLi as a base.

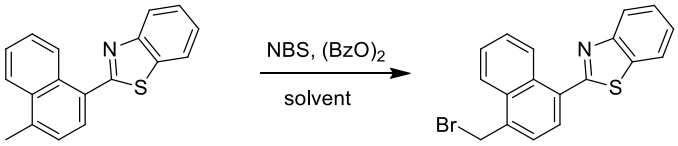
Because all of the attempts toward the preparation of a benzylic carbanion, having acetal, carboxylic acid or benzothiazole functionality, was failed. At this point, it is aimed to generate an electrophilic carbon at benzylic positions by radicalic brominations.

2.1.4. Synthesis of 4-Alkyl Naphthalen-1-yl Substituted Benzothiazole Derivatives Via Copper-Catalyzed Cross Coupling Reaction

Another methodology for the formation of C-C bond is metal catayzed cross coupling reactions. Ren et al., developed an efficient method for the cross coupling of alkyl halides and tosylates with Grignard reagents. CuCl was used as a catalyst to achieve cross coupling reactions in this work (Ren, Stern, & Hu, 2012).

To use a similar approach, benzylic bromination of previously prepared 4-methylnaphthalen-1-yl substituted benzothiazole **118** was performed by using NBS and benzoyl peroxide in different solvents. As summarized in table 2.4 benzylic bromination gave highest yield in CCl_4 while it also gives 34% product in CH_3CN, there was no product formation in CH_2Cl_2.

Table 2.4. Benzylic bromination of compound **118** with NBS and $(BzO)_2$ in different solvents.



118 **120**

entry	Solvent	Temperature,^oC	Yield %
1	CH_2Cl_2	50	-
2	CCl_4	40	56
3	CH_3CN	87	34

Then copper-catalyzed cross coupling reactions between compound **120** and Grignard reagents were studied. In the absense of Cu catalsyt, no coupling product was formed between compound **120** and vinyl magnesium bromide. In the presence of a copper salt, such as CuCl, C-C bond formation cross coupling reaction was succesful between compound **120** and butylmagnesium bromide to gave compound **122** in 15% yield (Figure 2.6).

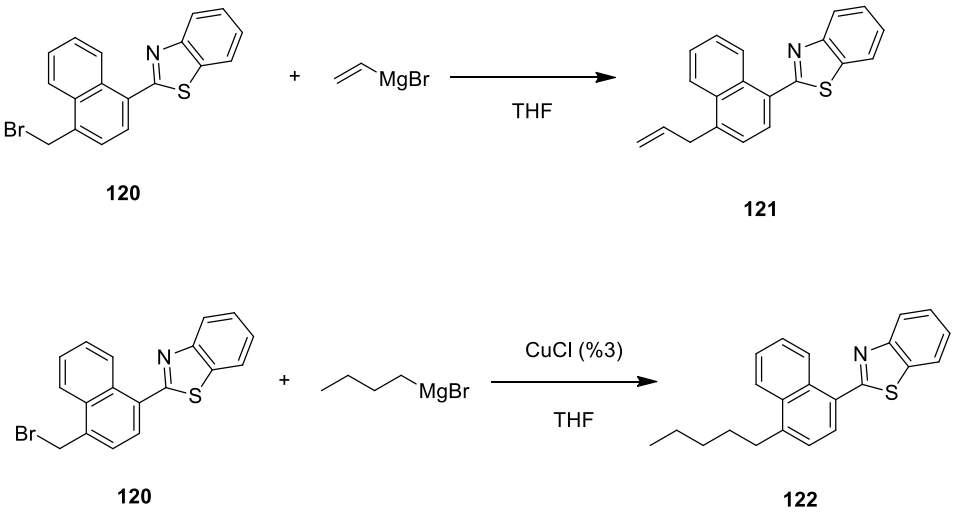


Figure 2.6. Coupling reactions between compound **120** and grignard reagents.

2.1.5. Synthesis of 4-Alkyl Substituted Ethyl 1-Naphthoate Derivatives (136a-d) Via Copper-Catalyzed Cross Coupling Reactions

Although Cu (I) catalyzed benzylic C-C bond formation was succesful for benzothiazole, conversion of benzothiazole to carboxylic acid was found troublesome. Because of that a similar cupper (I) catalyzed cross coupling reaction was performed between ethyl 4-methyl 1-naphthoate, prepared from corresponding carboxylic acid and alcohol in the presence of an acid catalyst, and grignard reagents. Conversion of carboxylic acid **114** to ester **123** gave 92% yield, and then it is subjected to benzylic bromination in the presence of NBS and benzoyl peroxide to produce compound **124** with 92% yield (Figure 2.7).

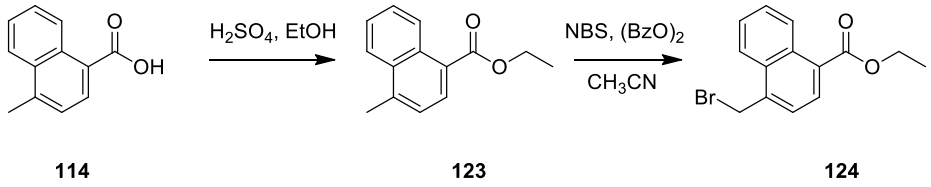
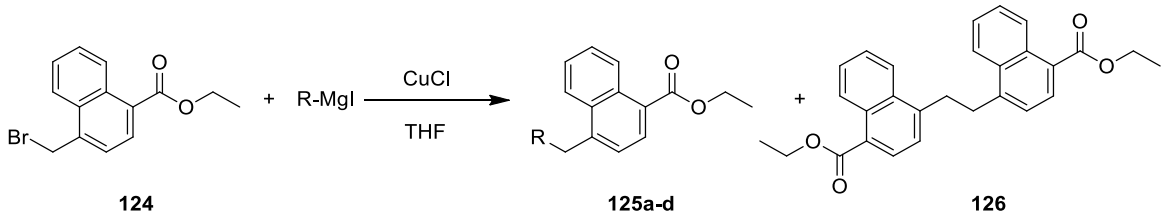


Figure 2.7. Benzylic bromination of ethyl naphthoate derivative **124**.

Cupper (I) catalyzed Cross-coupling reactions of freshly prepared Grignard reagents and benzylic alkyl halide **124** were also studied as summarized in table 2.5. Although all attempts gave product formation, the yields were quite low when only 2.0-2.5 equivalents of Grignard reagents are prepared and used. When the amount of the Grignard reagent is increased to 3.0-4.0 equivalent, target products were obtained in moderate yields (41-58%). A dimerization products of benzylic alkyl halide **126** was also obtained during the reaction (Table 2.5).

Table 2.5. Reaction between brominated ester and Grignard reagents in the presence of CuCl.



124 **125a-d** **126**

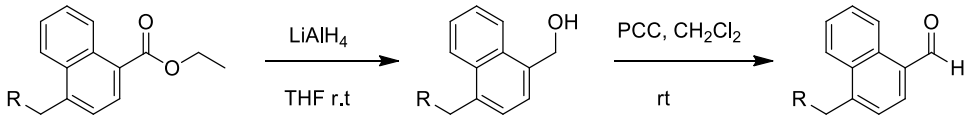
		Grignard					
entry	Grignard (R)	R (eq)	Mg (eq)	CuCl (eq)	Time (hours)	Yield% **136a-d**	Yield% **137**
1	**a**	2.5	2.5	0.4	2	22	32
2	**a**	2.5	2.5	0.6	2	25	56
3	**a**	2.0	2.0	0.6	2	22	30
4	**b**	3.0	3.0	0.6	2	58	42
5	**b**	4.0	4.0	0.2	2	51	34
6	**c**	3.0	3.0	0.2	2	29	32
7	**c**	4.0	4.0	0.2	2	44	40
8	**c**	3.5	3.5	0.6	2	29	34
9	**d**	3.0	3.0	0.6	2	41	44
10	**d**	3.0	3.0	0.6	4	42	38

As shown in entries 1-10, it was found that 3 or 4 eq of grignard reagent and 6 mol% CuCl are sufficient to promote C-C coupling reaction. It should be note that the coupling product (entry 4) was obtained in 58% yield at 25 ^{o}C for 2h. Prolonged reaction time did not improve the yield (entry 10, 42% for 4h).

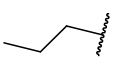
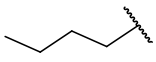
2.1.6.Synthesis of 4'-Alkyl Derived Klavuzons (38, 102-105)

Alkylated 1-naphthoate derivatives (**125a-d**) was converted to 4'-alkyl substituted klavuzon derivatives in five steps. Firstly, alkylated ester derivatives (**125a-d**) was converted to alklylated-naphthaldehyde derivatives (**113a-d**). As shown in table 2.7 simply reduction of esters (**125a-d**) with $LiAlH_4$ gave compounds (**127a-d**) then they were oxidized to the corresponding aldehydes (**113a-d**) by PCC. For both steps the yields of the reactions were high (75-90%).

Table 2.6. Conversion of ester derivatives to aldehyde derivatives.

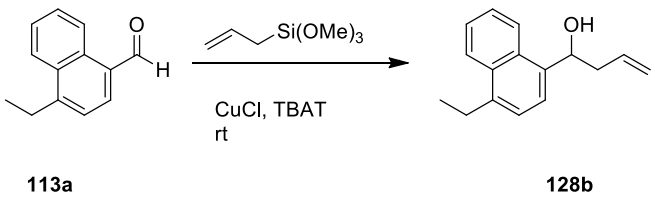


125a-d **127a-d** **113a-d**

entry	R	Yield% **127a-d**	Yield% **113a-d**
1	**a** 	87	90
2	**b** 	80	80
3	**c** 	75	89
4	**d** 	82	86

The next step is the conversion of aldehydes (**113a-d**) to homoallylic alcohols. First attempts in the allylation of aldehydes is addition of allyltrimethoxysilane in the presence of catalytic amount of CuCl and TBAT.

As a model reaction, compound **113a** was converted to homoallylic alcohol **128b** in the presence of allyltrimethoxy silane and CuCl-TBAT in very good yield (96%) (Figure 2.8). ^{1}H-NMR analysis indicates the presence of an impurity ranged from 7.00-8.00 ppm but the purification of this compound are quite challenging because of the unseen impurity on the TLC studies.

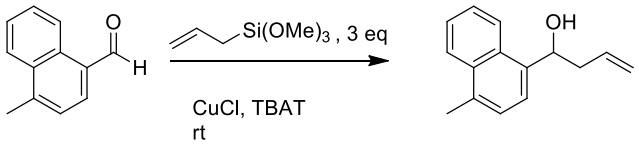


113a **128b**

Figure 2.8. Allylation of aldehyde in the presence of allytrimethoxy silane and CuCl-TBAT.

Previously it was reported that TBAT is not stable in acidic conditions and its decomposition products ^{1}H-NMR has similarities with the observed peaks for impurity (Handy, Lam, & DeShong, 2000). In order to minimize or eliminate the formation of this impurity, different amounts of HCl solutions was used in the work-up procedure. Also acidification time was changed but in all experiments formation of impurity was observed.

Table 2.7. Allylation of aldehyde **110** with allyltrimethoxy silane.

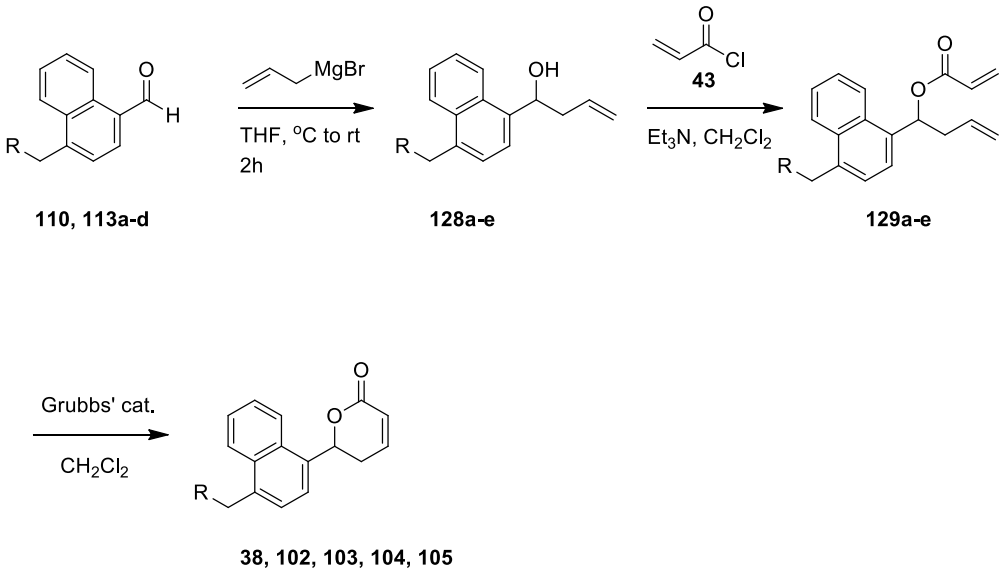


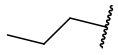
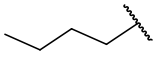
110 **128a**

entry	CuCl (mmol %)	TBAT (mmol %)	Reaction time (h)	1M HCl(mL) ; Time (min)
1	40	30	16	0.5;5
2	40	30	16	0.5;4
3	20	20	3	0.5;6
4	10	10	3	0.05;5
5	10	10	18	0.5;10
6	10	10	16	0.5;10

Due to the difficulties in purification of homoallylic alcohols this route was also abandoned. Addition of allylmagnesium bromide to aldehyde is one of the well-known methodology to produce the homoallylic alcohols. Hence allyl bromide was treated with metalic magnesium to obtain fresh allylmagnesium bromide then it is reacted with 1-naphthaldehyde derivatives to produce corresponding homoallylic alcohols (**128a-e**). Finally, purified homoallylic alcohols were reacted with acryloyl chloride in the presence of a base to produce acrylate esters (**129a-e**), then ring closing metathesis by second generation Grubbs' catalyst yielded the final klavuzon derivatives (**38**, **102**-**105**) in good yields (70-94%) as shown in table 2.8.

Table 2.8. Synthesis of 4’-alkyl substitued klavuzon derivatives.



entry		R	Yield% **128a-e**	Yield% **129a-e**	Yield% **38, 102-105**
1	**a**	H	77	73	88
2	**b**		91	84	94
3	**c**		85	73	89
4	**d**		84	90	70
5	**e**		59	85	81

2.2. Synthesis of Naphthalen-1-yl Substituted 3,6-Dihydro-2*H*-Pyran-2-one Derivatives

In the second part of this thesis, synthesis of 4-alkylnaphthalen-1-yl substituted 3,6-dihydro-2*H*-pyran-2-one derivatives (**64, 106, 107, 108, 109**) were studied. As it was mentioned above, 3,6-dihydro-2*H*-pyran-2-one derivatives converted to 5,6 dihydro-2*H*-pyran-2-one derivatives in basic medium. To prove this conversion and also to check the antiproliferative activities of these, substituents present at C-4 of

naphthalene were same with those of corresponding α,β−unsaturated lactone derivatives. The synthetic strategy toward the synthesis of 3,6-dihydro-2*H*-pyran-2-one is outlined in figure 2.9.

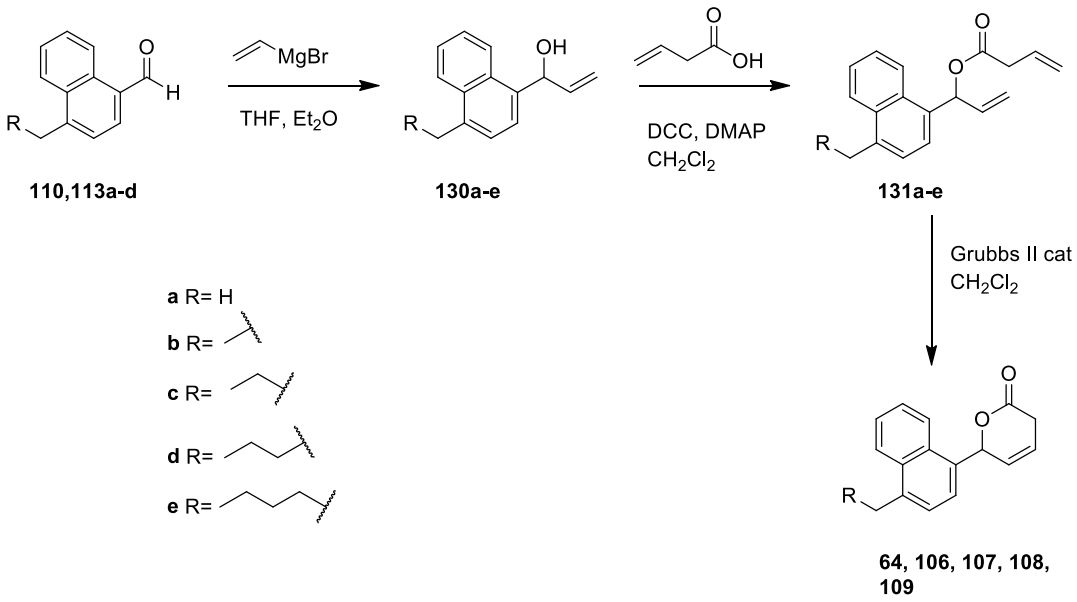
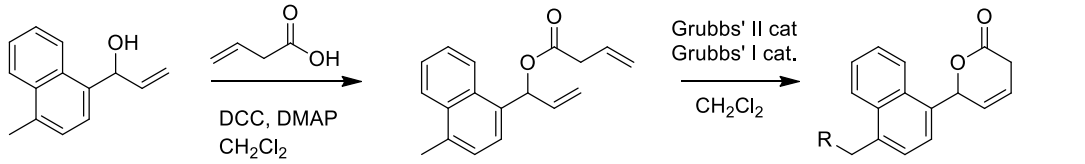


Figure 2.9. Synthetic route for the preparation of 4-alkylnaphthalen-1-yl substituted 3,6-dihydro-2*H*-pyran-2-one derivatives.

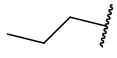
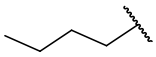
The starting aldehydes (**110, 113a-d**) were prepared as described in table 2.6. The alcohols (**130a-e**) were prepared from the Grignard reaction between vinylmagnesium bromide and aldehydes (**110, 113a-d**). Then esters **131a-e** was prepared from allylic alcohol by steglich esterification of vinylacetic acid, DCC and DMAP in high yield (Neises & Steglich, 1978). The final step is ring closing metathesis reaction by using Grubbs' catalsyt.

Table 2.9. Synthesis of 4-alkylnaphthalen-1-yl substituted 3,6-dihydro-2*H*-pyran 2-ones.

.



130a-e **131a-e** **64, 106, 107, 108, 109**

entry	R	Yield% **130a-e**	Yield% **131a-e**	Yield% **64, 106-109**
1	**a** H	82	88	84
2	**b** 	67	80	68
3	**c** 	87	81	69
4	**d** 	73	95	86
5	**e** 	76	85	61

Compounds **131a-e** were converted to compounds **64, 106-109** in the presence of Grubbs' II catalsyt in moderate yields. After column chromotagraphy, compound **64** was obtained in very pure form with 84% yield. It is noticed that the colour of the compound began to change when time passes. Because of this, ^{1}H-NMR of the compound **64** was acquired after 1 and 3 months. According to NMR results, compound **64** is not stable and it completely decompose in 3 months. It might be possible that, this decomposition may stem from the Grubbs' II catalsyt. So, it was also synthesized with Grubbs' I catalsyt in low yield (52%).

After 1 weeks again a colour change was observed in the compound as an indicator of decomposition. Although, there was no information about the instability of this compound in literature. So, it would be pointless to look therapeutic effects these compound since their half life would be less than 3-months!

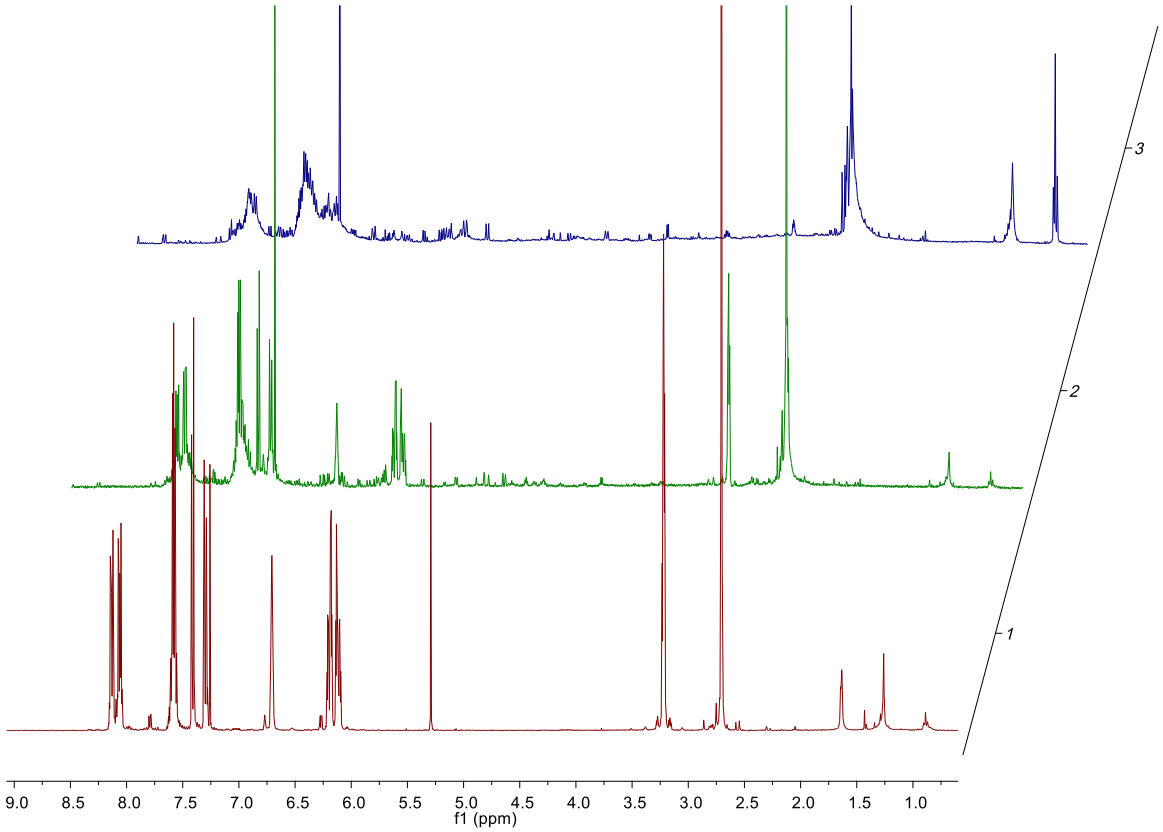
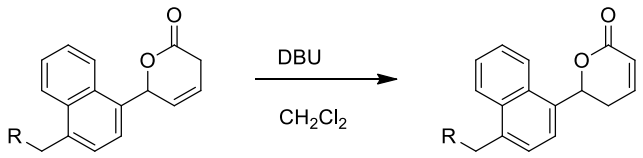


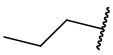
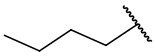
Figure 2.10. ^{1}H-NMR spectrum of compound **64** (Red just after column chromatography, Green: after 1 month; Blue: after 3 months).

The β,γ-unsaturated lactones **64, 106-109** were efficiently reconjugated into klavuzon derivatives **38, 102-105** by treatment with a catalytic amount of DBU (0.1 equivalent) at room temperature as shown in table 2.10.

Table 2.10. Conversion of 4 alkylsubstituted 3,6-dihydro-2*H*-pyran 2-one to 4 alkyl substituted klavuzon derivatives



106, 107, 108, 109 **102, 103, 104, 105**

entry	R	Yield%
1		43
2		45
3		61
4		58

CHAPTER 3

EXPERIMENTAL

3.1. General methods

Reagents and solvents were commercial grade and were used as supplied. All experiments were conducted under N_2 atmosphere. Reactions were monitored by TLC chromatography using Merck TLC plates (Silicagel 60 F254). Chromatographic purification of the products were performed by flash column using 70-230 mesh sized silica gel. ^{1}H-NMR and ^{13}C-NMR data were recorded on Varian 400-MR (400 MHz) spectrometer. Chemical shifts for ^{1}H-NMR and ^{13}C-NMR are reported in δ (ppm). $CDCl_3$ peaks were used as reference in ^{1}H-NMR (7.26 ppm), and ^{13}C-NMR (77.36 ppm) respectively. All NMR spectrum were analyzed in Mestrenova 6.02.

3.1.1. Synthesis of klavuzon derivatives (38, 102-105)

3.1.1.1. 2-(4-methylnaphthalen-1-yl)-1,3-dioxolane (111)

In a two necked flask, 1.11 g of 4-methyl-1-naphaldehyde (6.53 mmol, 1.0 eq) was placed and dissolved in 20 mL of dry toluene then 1.62 mg ethylene glycol (1.47 mL, 26.10 mmol, 4.0 eq.) and 56 mg p-TSA (0.33 mmol, 0.05 eq.) were added to a refluxing solution of aldehyde. The mixture was heated under reflux in N_2 atmosphere for 16 h. The resulting solution was quenced with 10 mL saturated $NaHCO_3$ and extracted with ethyl acetate (3x15 mL) then washed with 15 mL brine solution. The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:100 EtOAc/Hexanes) to give 951 mg 2-(4-methylnaphthalen-1-yl)-1,3-dioxolane (4.43 mmol) as yellow oil with 68% yield. R_f = 0.73 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.18 (m, 1H), 8.05 – 7.98 (m, 1H), 7.63 (d, *J* = 7.3 Hz, 1H),

7.57 – 7.47 (m, 2H), 7.30 (dd, *J* = 7.2 and 0.7 Hz, 1H), 6.44 (s, 1H), 4.22 – 4.09 (m, 4H), 2.68 (d, *J* = 0.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.83, 132.91, 131.31, 131.08, 125.92, 125.81, 125.58, 124.64, 124.54, 123.34, 102.30, 65.21, 19.66.

3.1.1.2. 4-methyl-1-naphthoic acid (114)

A solution of 85 mg 4-methyl 1-napthaldehyde (0.5 mmol, 1.0 eq) in 3.0 mL acetone was cooled down to 0 ^{o}C then 118 mg $KMnO_4$ (0.75 mmol, 1.5 eq) was added. The reaction mixture was stirred at rt under N_2 atmosphere for 1 h, while stirring 2 mL AcOH was added. The resulting mixture was filtered through a short pad of celite and extracted with 10 mL water dried with $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:25:0.01 EtOAc/Hexanes/AcOH) to give 35 mg 4-methyl-1-naphthoic acid (0.19 mmol) with 38% yield. R_f = 0.13 (ethyl acetate/hexanes/AcOH, 1:8:0,01); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.33 – 9.26 (m, 1H), 8.47 – 8.40 (m, 2H), 7.97 – 7.87 (m, 2H), 7.71 (dd, *J* = 7.4 and 0.8 Hz, 1H), 3.05 (d, *J* = 0.7 Hz, 3H).

3.1.1.3. 1-(4-methylnaphthalen-1-yl)pentan-1-one (116)

In a two necked flask, 65 mg 4-methyl-1-naphthoic acid (0.35 mmol, 1.0 eq) was dissolved in 5 mL THF at -78 ^{o}C. Then 350 µL n-BuLi (0.87 mmol, 2.5 eq) was added dropwise. After 1 hour stirring at -78 ^{o}C, 78 mg iodo propane (45 µL ,0.46 mmol, 1.3 eq) was added and the mixture was warmed rt and stirred 16 h under N_2 atmosphere .The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (3x10 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:15 EtOAc/Hexanes) to give 7 mg 1-(4-methylnaphthalen-1-yl)pentan-1-one (0.03 mmol) with 9% yield. R_f = 0.73 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, *J* = 6.9 and 3.0 Hz, 1H), 8.05 – 7.99 (m, 1H), 7.74 (d, *J* = 7.3 Hz, 1H), 7.60 – 7.52 (m, 2H), 7.32 (dd, *J* = 7.3 and 0.9 Hz, 1H), 3.06 – 2.97 (m, 2H), 2.72 (d, *J* = 0.8 Hz, 3H), 1.80 – 1.68 (m, 2H), 1.46 –

1.36 (m, 2H), 0.93 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 204.80, 139.10, 134.67, 132.84, 130.11, 127.19, 127.04, 126.23, 126.06, 125.04, 124.11, 41.72, 26.86, 22.35, 19.87, 13.79.

3.1.1.4. 2-(4-methylnaphthalen-1-yl)benzo[d]thiazole (118)

In two necked flask, 372 mg 4-methyl-1-naphthoic acid (2.0 mmol, 2.0 eq) was placed and dissolved in 8 mL toluene then 1573 mg triphenyl phosphine (6.0 mmol, 3.0 eq), 923 mg CCl_4 (582 µL, 6.0 mmol, 3.0 eq) and 325 mg o-aminothio phenol (278 µL, 2.6 mmol, 1.3 eq) were sequentially added to refluxing solution of carboxylic acid. The mixture was heated under reflux in N_2 atmoshere for 5 h. When the reaction was completed the solvent was removed under vacuum and the mixture was redissolved in 10 mL EtOAc and 10 mL saturated $NaHCO_3$ solution. Organic layer was seperated, dried with $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:25 EtOAc/Hexanes) to give 472 mg 2-(4-methylnaphthalen-1-yl)benzo[d]thiazole (1.71 mmol) with 86% yield. R_f = 0.48 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.00 – 8.91 (m, 1H), 8.19 – 8.14 (m, 1H), 8.10 – 8.04 (m, 1H), 7.97 – 7.92 (m, 1H), 7.81 (d, *J* = 7.3 Hz, 1H), 7.64 – 7.56 (m, 2H), 7.55 – 7.49 (m, 1H), 7.45 – 7.38 (m, 2H), 2.76 (d, *J* = 0.6 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.02, 154.27, 137.87, 135.47, 133.10, 130.70, 129.28, 127.30, 126.55, 126.43, 126.27, 126.00, 125.22, 124.47, 123.52, 121.41, 20.02.

3.1.1.5. 2-(4-(bromomethyl)naphthalen-1-yl)benzo[d]thiazole (120)

In two necked flask, 176 mg 2-(4-methylnaphthalen-1-yl)benzo[d]thiazole (0.64 mmol, 1.0 eq) was placed and dissolved in 6 mL CCl_4. Then 125 mg NBS (0.7 mmol, 1.1 eq) and 2.3 mg benzoyl peroxide (0.01 mmol, 0.02 eq) were directly added into the mixture. It was heated under reflux under N_2 atmosphere for 16 h. The resulting solution was quenced with 10 mL water and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:30

EtOAc/Hexanes) with 56% yield. R_f = 0.33 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.97 (d, *J* = 8.3 Hz, 1H), 8.25 (d, *J* = 8.4 Hz, 1H), 8.21 (dd, *J* = 8.1 and 0.6 Hz, 1H), 7.98 (d, *J* = 8.0 Hz, 1H), 7.84 (d, *J* = 7.4 Hz, 1H), 7.75 – 7.61 (m, 3H), 7.60 – 7.53 (m, 1H), 7.50 – 7.43 (m, 1H), 5.00 (s, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.13, 154.22, 136.22, 135.63, 132.44, 131.65, 131.40, 128.92, 127.91, 127.28, 126.98, 126.97, 126.53, 125.61, 124.16, 123.80, 121.57, 31.21.

3.1.1.6. 2-(4-pentylnaphthalen-1-yl)benzo[d]thiazole (122)

In two necked flask, 25 mg Mg turnings (1.01 mmol, 4.0 eq) were suspended in 3 mL dry ether. Then, 187 mg iodo butane (116 µL, 1.01 mmol, 4.0 eq) in 2 mL dry ether was added to Mg solution. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This grignard reagent was then added slowly to 8 mL of THF solution containing 60 mg CuCl (0.01 mmol, 0.03 eq) and 90 mg (4-(bromomethyl)naphthalen-1-yl)benzo[d]thiazole (0.25 mmol, 1.0 eq). The reaction mixture was stirred at rt under N_2 atmosphere for 2 h. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:15 EtOAc/Hexanes) to give 13 mg ethyl 4-pentyl-1-naphthoate (0.04 mmol) as yellow oil with 15% yield. R_f = 0.40 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.00 – 8.94 (m, 1H), 8.23 – 8.13 (m, 2H), 7.97 (d, *J* = 7.9 Hz, 1H), 7.84 (dd, *J* = 7.3 and 3.9 Hz, 1H), 7.66 – 7.51 (m, 3H), 7.48 – 7.40 (m, 2H), 3.18 – 3.09 (m, 2H), 1.81 (dt, *J* = 15.4 and 7.5 Hz, 2H), 1.49 – 1.25 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H).

3.1.1.7. Ethyl 4-methyl-1-naphthoate (123)

In two necked flask, 558 mg 4-methyl-1-naphthoic acid (3.0 mmol, 1.0 eq) was dissolved in 7 mL ethanol then 0.5 mL H_2SO_4 was added to dropwise to a refluxing solution of carboxylic acid. The mixture was heated under reflux within N_2 atmosphere for 16 h. The resulting solution was quenced with 15 mL water and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:12 EtOAc/Hexanes) to give 589 mg ethyl 4-methyl-1-naphthoate (2.74 mmol) as yellow oil with 92% yield. R_f = 0.50 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.97 (dd, *J* = 8.4 and 1.0 Hz, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 8.07 – 8.03 (m, 1H), 7.62 (ddd, *J* = 8.5, 6.8 and 1.6 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.8 and 1.5 Hz, 1H), 7.35 (dd, *J* = 7.4 and 0.9 Hz, 1H), 4.46 (q, *J* = 7.2 Hz, 2H), 2.75 (d, *J* = 0.8 Hz, 3H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.88, 140.25, 133.01, 131.55, 130.05, 127.38, 126.51, 126.13, 125.99, 125.65, 124.55, 61.04, 20.27, 14.57.

3.1.1.8. Ethyl 4-(bromomethyl)-1-naphthoate (124)

In a two necked flask, 569 mg of ethyl 4-methyl-1-naphthoate (2.66 mmol, 1.0 eq.) was placed and dissolved in 7 mL of CH_3CN. Then 506 mg NBS (2.9 mmol, 1.1 eq) and 14 mg benzoyl peroxide (0.07 mmol, 0.03 eq) were directly added into the mixture. It was heated under reflux with N_2 atmosphere for 16 h. The resulting solution was quenced with 15 mL water and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 717 mg ethyl 4-(bromomethyl)-1-naphthoate (2.44 mmol) with 92% yield. R_f = 0.45 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.95 – 8.91 (m, 1H), 8.21 – 8.18 (m, 1H), 8.07 (d, *J* = 7.4 Hz, 1H), 7.69 – 7.62 (m, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 4.95 (s, 2H), 4.48 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.43, 138.18, 131.92, 131.46, 129.34, 129.21, 127.91, 126.93, 126.77, 126.52, 124.15, 61.41, 30.83, 14.51.

3.1.1.9. Ethyl 4-ethyl-1-naphthoate (125a)

In two necked flask, 83 mg Mg turnings (3.41 mmol, 2.5 eq) were suspended in 3 mL dry ether. Then 484 mg methyl iodide (213 μL, 3.41 mmol, 2.5 eq) in 2 mL dry ether was added to Mg solution. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added slowly to 8 mL of THF solution containing 81 mg CuCl (0.82 mmol, 0.6 eq) and 400 mg ethyl 4-(bromomethyl)-1-naphthoate (1.36 mmol, 1.0 eq). The reaction mixture was stirred at rt under N_2 atmosphere for 2 h. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:15 EtOAc/Hexanes) to give 78 mg ethyl 4-ethyl-1-naphthoate (0.34 mmol) as yellow oil with 25% yield and to give 163 mg diethyl 4,4'-(ethane-1,2-diyl)bis(1-naphthoate) (0.38 mmol) as white solid with 56% yield. R_f = 0.54 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.05 – 9.01 (m, 1H), 8.16 – 8.10 (m, 2H), 7.66 – 7.60 (m, 1H), 7.60 – 7.55 (m, 1H), 7.37 (d, *J* = 7.5 Hz, 1H), 4.49 (q, *J* = 7.1 Hz, 2H), 3.15 (q, *J* = 7.6 Hz, 2H), 1.48 (t, *J* = 7.1 Hz, 3H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.82, 145.97, 132.09, 131.73, 130.07, 127.16, 126.57, 126.02, 125.83, 124.07, 123.80, 60.95, 26.46, 14.89, 14.48.

3.1.1.10. Diethyl 4,4'-(ethane-1,2-diyl)bis(1-naphthoate) (126)

Compound **126** was obtained as side product from Cu (I) catalyzed coupling reactions as white solid with 56% yield. R_f = 0.23 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 8.6 and 1.1 Hz, 1H), 8.13 (d, *J* = 8.1 Hz, 1H), 8.04 (d, *J* = 7.5 Hz, 1H), 7.62 (ddd, *J* = 8.5, 6.8 and 1.5 Hz, 1H), 7.57 (ddd, *J* = 8.2, 6.8 and 1.5 Hz, 1H), 7.25 – 7.23 (m, 1H), 4.46 (q, *J* = 7.1 Hz, 2H), 3.54 (s, 2H), 1.44 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.83, 143.10, 132.16, 131.93, 129.87, 127.42, 126.85, 126.57, 126.45, 125.13, 123.95, 61.16, 34.35, 14.56.

3.1.1.11. Ethyl 4-propyl-1-naphthoate (125b)

In two necked flask, 99 mg Mg turnings (4.08 mmol, 3.0 eq) were suspended in 3 mL dry ether. Then 636 mg ethyl iodide (328 μL, 4.08 mmol, 3.0 eq) in 2 mL dry ether was added to Mg solution. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added slowly to 8 mL of THF solution containing 81 mg CuCl (0.82 mmol, 0.6 eq) and 400 mg ethyl 4-(bromomethyl)-1-naphthoate (1.36 mmol, 1.0 eq). The reaction mixture was stirred at rt under N_2 atmosphere for 2 h. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:15 EtOAc/Hexanes) to give 190 mg ethyl 4-propyl-1-naphthoate (0.78 mmol) as yellow oil with 58% yield. R_f = 0.43 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.02 – 8.95 (m, 1H), 8.14 – 8.08 (m, 2H), 7.61 (ddd, *J* = 8.6, 6.8 and 1.5 Hz, 1H), 7.55 (ddd, *J* = 8.2, 6.8 and 1.5 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.13 – 3.05 (m, 2H), 1.86 – 1.74 (m, 2H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.90, 144.53, 132.32, 131.85, 129.88, 127.17, 126.60, 126.58, 126.00, 124.96, 124.32, 61.00, 35.73, 23.89, 14.54, 14.34.

3.1.1.12. Ethyl 4-butyl-1-naphthoate (125c)

In two necked flask, 65.5 mg Mg turnings (2.73 mmol, 4.0 eq) were suspended in 3 mL dry ether. Then 464 mg propyl iodide (266 μL, 2.73 mmol, 4.0 eq) in 2 mL dry ether was added to Mg solution. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added slowly to 8 mL of THF solution containing 13.5 mg CuCl (0.14 mmol, 0.2 eq) and 200 mg ethyl 4-(bromomethyl)-1-naphthoate (0.68 mmol, 1.0 eq). The reaction mixture was stirred at rt under N_2 atmosphere for 2 h. The reaction mixture was

quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:15 EtOAc/Hexanes) to give 76.3 mg ethyl 4-butyl-1-naphthoate (0.3 mmol) as yellow oil with 44% yield. R_f = 0.68 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.98 (dd, *J* = 8.4, and 0.9 Hz, 1H), 8.13 – 8.09 (m, 2H), 7.61 (ddd, *J* = 8.5, 6.8 and 1.6 Hz, 1H), 7.56 (ddd, *J* = 8.2, 6.8 and 1.5 Hz, 1H), 7.35 (d, *J* = 7.5 Hz, 1H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.14 – 3.09 (m, 2H), 1.79 – 1.70 (m, 2H), 1.50 – 1.43 (m, 5H), 0.98 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.89, 144.82, 132.30, 131.87, 129.92, 127.18, 126.61, 126.01, 125.92, 124.88, 124.32, 61.00, 33.44, 32.94, 22.96, 14.54, 14.08.

3.1.1.13. Ethyl 4-pentyl-1-naphthoate (125d)

In two necked flask, 73 mg Mg turnings (3 mmol, 3.0 eq) were suspended in 3 mL dry ether. Then 552 mg iodobutane (342 µL, 3 mmol, 3.0 eq) in 2 mL dry ether was added to Mg solution. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added slowly to 8 mL of THF solution containing 60 mg CuCl (0.6 mmol, 0.6 eq) and 293 mg ethyl 4-(bromomethyl)-1-naphthoate (1 mmol, 1.0 eq). The reaction mixture was stirred at rt under N_2 atmosphere for 2 h. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:15 EtOAc/Hexanes) to give 114 mg ethyl 4-pentyl-1-naphthoate (0.42 mmol) as yellow oil with 42% yield. R_f = 0.62 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.07 – 8.97 (m, 1H), 8.15 – 8.10 (m, 2H), 7.66 – 7.54 (m, 2H), 7.36 (d, J = 7.5 Hz, 1H), 4.49 (q, J = 7.1 Hz, 2H), 3.14 – 3.08 (m, 2H), 1.83 – 1.72 (m, 2H), 1.52 – 1.36 (m, 7H), 0.94 (t, J = 7.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.83, 144.81, 132.24, 131.83, 129.91, 127.14, 126.56, 125.97, 125.83, 124.83, 124.27, 60.95, 33.65, 32.04, 30.45, 22.65, 14.50, 14.15.

3.1.1.14. (4-ethylnaphthalen-1-yl)methanol (127a)

In a two necked flask, 180 mg ethyl 4-ethyl-1-naphthoate (0.79 mmol, 1.0 eq) was dissoved in 5 mL THF under N_2 atmosphere and it was cooled down to 0 ^oC then 48 mg (1.34 mmol, 1.7 eq) $LiAlH_4$ in 2 mL THF was added. The mixture was warmed to rt and stirred for 2 h under N_2 atmosphere. The resulting solution was quenced at 0 ^oC with diluted HCl (5 mL) and was extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:20 EtOAc/Hexanes) to give 128 mg (4-ethylnaphthalen-1-yl)methanol (0,69 mmol) with 87% yield. R_f = 0.52 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.09 (m, 2H), 7.59 – 7.53 (m, 2H), 7.42 (d, *J* = 7.2 Hz, 1H), 7.31 (d, *J* = 7.2 Hz, 1H), 5.08 (d, *J* = 1.7 Hz, 2H), 3.13 (q, *J* = 7.5 Hz, 2H), 2.02 (s, 1H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, CDCl3) δ 140.95, 134.50, 132.20, 131.69, 125.96, 125.78, 125.54, 124.53, 124.48, 124.44, 63.87, 26.09, 15.14.

3.1.1.15. (4-propylnaphthalen-1-yl)methanol (127b)

In a two necked flask, 190 mg ethyl 4-propyl-1-naphthoate (0.78 mmol, 1.0 eq) was dissoved in 5 mL THF under N_2 atmosphere and it was cooled down to 0 ^oC then 40 mg (1.10 mmol, 1.4 eq) $LiAlH_4$ in 2 mL THF was added. The mixture was warmed to rt and stirred for 2 h under N_2 atmosphere. The resulting solution was quenced at 0 ^oC with diluted HCl (5 mL) and was extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:20 EtOAc/Hexanes) to give 126 mg (4-propylnaphthalen-1-yl)methanol (0,63 mmol) of with 80% yield. R_f = 0.31 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.14 (m, 1H), 8.13 – 8.08 (m, 1H), 7.58 – 7.52 (m, 2H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 1H), 5.10 (s, 2H), 3.09 – 3.02 (m, 2H), 1.91 (s, 1H), 1.85 – 1.73 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.49, 134.52, 132.37, 131.76, 125.96, 125.73, 125.55, 125.43, 124.70, 124.52, 63.97, 35.39, 24.04, 14.41.

3.1.1.16. (4-butylnaphthalen-1-yl)methanol (127c)

In a two necked flask, 100 mg ethyl 4-butyl-1-naphthoate (0.39 mmol, 1.0 eq) was dissoved in 5 mL THF under N_2 atmosphere and it was cooled down to 0 ^oC then 24 mg (0.66 mmol, 1.7 eq) $LiAlH_4$ in 2 mL THF was added. The mixture was warmed to rt and stirred for 2 h under N_2 atmosphere. The resulting solution was quenced at 0 ^oC with diluted HCl (5 mL) and was extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:20 EtOAc/Hexanes) to give 63 mg (4-butylnaphthalen-1-yl)methanol (0,29 mmol) with 75% yield. R_f = 0.60 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.16 (m, 1H), 8.12 – 8.08 (m, 1H), 7.57 – 7.52 (m, 2H), 7.42 (d, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 1H), 5.12 (s, 2H), 3.11 – 3.04 (m, 2H), 1.79 – 1.69 (m, 2H), 1.66 (s, 1H), 1.51 – 1.42 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.67, 134.37, 132.25, 131.66, 125.83, 125.61, 125.37, 125.34, 124.58, 124.40, 109.99, 63.91, 32.99, 22.85, 13.98.

3.1.1.17. (4-pentylnaphthalen-1-yl)methanol (127d)

In a two necked flask, 126 mg ethyl 4-pentyl-1-naphthoate (0.47 mmol, 1.0 eq) was dissoved in 5 mL THF under N_2 atmosphere and it was cooled down to 0 ^oC then 23.5 mg (0.65 mmol, 1.7 eq) $LiAlH_4$ in 2 mL THF was added. The mixture was warmed to rt and stirred for 2 h under N_2 atmosphere. The resulting solution was quenced at 0 ^oC with diluted HCl (5 mL) and was extracted with EtOAc (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:20 EtOAc/Hexanes) to give 87 mg (4-pentylnaphthalen-1-yl)methanol (0,38 mmol) with 82% yield. R_f = 0.6 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.08 (m, 2H), 7.58 – 7.52 (m, 2H), 7.41 (d, *J* = 7.1 Hz, 1H), 7.29 (d, *J* = 7.1 Hz, 1H), 5.09 (s, 2H), 3.11 – 3.03 (m, 2H), 1.92 (s, 1H), 1.77 (dt, *J* = 9.6 and 7.6 Hz, 2H), 1.50 – 1.35 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.84, 134.51,

132.38, 131.80, 125.98, 125.76, 125.50, 125.47, 124.71, 124.54, 64.03, 33.32, 32.15, 30.69, 22.73, 14.22.

3.1.1.18. 4-ethyl-1-naphthaldehyde (113a)

Solution of 151 mg (4-ethylnaphthalen-1-yl)methanol (0.81 mmol, 1.0 eq) in DCM (5 mL) was added to 343 mg PCC (1.62 mmol, 2.0 eq) in DCM (3 mL). The dark solution obtained and it was stirred for 2 h at rt under N_2 atmosphere. The dark solids were filtered from the reaction mixture and washed with DCM. The filtrate was washed with aq. NaOH (20 mL, 1 M) and HCl (20 mL, 1 M). The organic layer was separated, dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 135 mg 4-ethyl-1-naphthaldehyde (0.73 mmol) with 90% yield. R_f = 0.56 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.31 (s, 1H), 9.34 (dd, *J* = 8.4, and 0.8 Hz, 1H), 8.13 – 8.09 (m, 1H), 7.88 – 7.84 (m, 1H), 7.70 – 7.64 (m, 1H), 7.63 – 7.57 (m, 1H), 7.46 (d, *J* = 7.3 Hz, 1H), 3.14 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.34, 148.63, 137.08, 131.95, 130.93, 129.95, 128.53, 126.82, 125.62, 124.16, 124.04, 26.66, 14.75.

3.1.1.19. 4-propyl-1-naphthaldehyde (113b)

Solution of 130 mg (4-propylnaphthalen-1-yl)methanol (0.65 mmol, 1.0 eq) in DCM (5 mL) was added to 284 mg PCC (1.34 mmol, 2.07 eq) in DCM (3 mL). The dark solution obtained and it was stirred for 2 h at rt under N_2 atmosphere. The dark solids were filtered from the reaction mixture and washed with DCM. The filtrate was washed with aq. NaOH (20 mL, 1 M) and HCl (20 mL, 1 M). The organic layer was separated, dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 103 mg 4-propyl-1-naphthaldehyde (0.52 mmol) with 80% yield. R_f = 0.44 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 9.36 – 9.32 (m, 1H),

8.15 – 8.11 (m, 1H), 7.91 – 7.87 (m, 1H), 7.68 (ddd, *J* = 8.4, 6.8 and 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.3, 6.8 and 1.4 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 3.14 – 3.08 (m, 2H), 1.87 – 1.76 (m, 2H), 1.05 (t, *J* = 7.4 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.49, 147.32, 136.99, 132.17, 131.08, 130.03, 128.61, 126.83, 125.66, 125.33, 124.32, 35.95, 23.89, 14.37.

3.1.1.20. 4-butyl-1-naphthaldehyde (113c)

Solution of 70 mg (4-butylnaphthalen-1-yl)methanol (0.33 mmol, 1.0 eq) in DCM (4 mL) was added to 143 mg PCC (0,67 mmol, 2.07 eq) in DCM (3 mL). The dark solution obtained and it was stirred for 2 h at rt under N_2 atmosphere. The dark solids were filtered from the reaction mixture and washed with DCM. The filtrate was washed with aq. NaOH (20 mL, 1 M) and HCl (20 mL, 1 M). The organic layer was separated, dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 62,5 mg 4-butyl-1-naphthaldehyde (0.29 mmol) with 90% yield. R_f = 0.56 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.33 (s, 1H), 9.34 (dd, *J* = 8.5, and 0.8 Hz, 1H), 8.13 (d, *J* = 8.2 Hz, 1H), 7.89 (d, *J* = 7.3 Hz, 1H), 7.68 (ddd, *J* = 8.4, 6.8 and 1.4 Hz, 1H), 7.61 (ddd, *J* = 8.3, 6.8 and 1.4 Hz, 1H), 7.47 (d, *J* = 7.3 Hz, 1H), 3.16 – 3.10 (m, 2H), 1.82 – 1.69 (m, 2H), 1.54 – 1.41 (m, 2H), 0.99 (t, *J* = 8.6 and 6.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.50, 147.65, 137.04, 132.18, 131.13, 130.04, 128.64, 126.86, 125.70, 125.29, 124.35, 33.73, 32.93, 23.02, 14.10.

3.1.1.21. 4-pentyl-1-naphthaldehyde (114d)

Solution of 105 mg (4-pentylnaphthalen-1-yl)methanol (0.46 mmol, 1.0 eq) in DCM (5 mL) was added to 201 mg PCC (0.95 mmol, 2.07 eq) in DCM (3 mL). The dark solution obtained and it was stirred for 2 h at rt under N_2 atmosphere. The dark solids were filtered from the reaction mixture and washed with DCM. The filtrate was washed with aq. NaOH (20 mL, 1 M) and HCl (20 mL, 1 M). The organic layer was separated, dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude

product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 90 mg 4-pentyl-1-naphthaldehyde (0.4 mmol) with 86% yield. R_f = 0.58 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.32 (s, 1H), 9.35 (dd, *J* = 8.5 and 0.4 Hz, 1H), 8.12 (d, *J* = 8.4 Hz, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 7.71 – 7.57 (m, 2H), 7.46 (d, *J* = 7.3 Hz, 1H), 3.15 – 3.07 (m, 2H), 1.77 (dt, *J* = 15.5 and 7.5 Hz, 2H), 1.48 – 1.34 (m, 4H), 0.93 (t, *J* = 7.0 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.36, 147.56, 136.92, 132.12, 131.06, 129.98, 128.55, 126.79, 125.64, 125.18, 124.26, 33.88, 32.05, 30.43, 22.62, 14.12.

3.1.1.22. 1-(4-methylnaphthalen-1-yl)but-3-en-1-ol (128a)

In two necked flask, 21 mg Mg turnings (0.9 mmol, 3.0 eq) were suspended in 2 mL dry ether. Then 109 mg allylbromide (76 μL, 0.9 mmol, 3.0 eq) in 2 mL dry ether was added to Mg suspension. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added at slowly at 0 ^{o}C to a solution of 50 mg (0.29 mmol, 1.0 eq) 4-methyl-1-napthaldehyde in 4.0 mL THF. The mixture was warmed to rt and stirred for 1 h under N_2 atmosphere. The reaction mixture was quenched with 5 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 48 mg 1-(4-methylnaphthalen-1-yl)but-3-en-1-ol (0.23 mmol) with 77% yield. R_f = 0.5 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 – 8.05 (m, 2H), 7.59 – 7.53 (m, 3H), 7.34 (dd, *J* = 7.3 and 1.0 Hz, 1H), 6.02 – 5.87 (m, 1H), 5.50 (dd, *J* = 8.3 and 4.2 Hz, 1H), 5.27 – 5.16 (m, 2H), 2.80 – 2.73 (m, 1H), 2.71 (d, *J* = 0.9 Hz, 3H), 2.67 – 2.54 (m, 1H), 2.26 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.65, 135.02, 134.06, 132.93, 130.45, 126.31, 125.75, 125.44, 125.07, 123.59, 122.65, 118.22, 70.04, 42.92, 19.69.

3.1.1.23. 1-(4-ethylnaphthalen-1-yl)but-3-en-1-ol (128b)

In two necked flask, 19 mg Mg turnings (0.8 mmol, 3.0 eq) were suspended in 2 mL dry ether. Then 97 mg allyl bromide (70 μL, 0.8 mmol, 3.0 eq) in 2 mL dry ether was added to Mg suspension. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added at slowly at 0 ^{o}C to a solution of 50 mg (0.27 mmol, 1.0 eq) 4-ethyl-1-napthaldehyde in 4.0 mL THF. The mixture was warmed to rt and stirred for 1 h under N_2 atmosphere. The reaction mixture was quenched with 5 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 56 mg 1-(4-ethylnaphthalen-1-yl)but-3-en-1-ol (0.24 mmol) with 91% yield. R_f = 0.28 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.09 (m, 2H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 6.01 – 5.89 (m, 1H), 5.51 (dd, *J* = 8.2 and 3.7 Hz, 1H), 5.28 – 5.16 (m, 2H), 3.13 (q, *J* = 7.5 Hz, 2H), 2.83 – 2.55 (m, 2H), 2.23 (s, 1H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.10, 137.55, 135.08, 132.13, 130.72, 125.67, 125.45, 124.71, 124.60, 123.76, 122.79, 118.31, 70.07, 42.92, 26.11, 15.13.

3.1.1.24. 1-(4-propylnaphthalen-1-yl)but-3-en-1-ol (128c)

In two necked flask, 27 mg Mg turnings (1.13 mmol, 4.0 eq) were suspended in 2 mL dry ether. Then 137 mg allyl bromide (98 μL, 1.13 mmol, 4.0 eq) in 2 mL dry ether was added to Mg suspension. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added at slowly at 0 ^{o}C to a solution of 56 mg (0.28 mmol, 1.0 eq) 4-propyl-1-napthaldehyde in 4.0 mL THF. The mixture was warmed to rt and stirred for 1 h under N_2 atmosphere. The reaction mixture was quenched with 5 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x15 mL). The combined organic phase

was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 57 mg 1-(4-propylnaphthalen-1-yl)but-3-en-1-ol (0.24 mmol) with 85% yield. R_f = 0.44 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.09 (m, 2H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.55 – 7.50 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 5.95 (ddt, *J* = 17.5, 10.2 and 7.0 Hz, 1H), 5.51 (dd, *J* = 8.3 and 4.1 Hz, 1H), 5.26 – 5.16 (m, 2H), 3.12 – 3.00 (m, 2H), 2.81 – 2.73 (m, 1H), 2.67 – 2.58 (m, 1H), 2.07 (s, 1H), 1.86 – 1.74 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.62, 137.64, 135.11, 132.36, 130.86, 125.72, 125.64, 125.38, 124.92, 123.78, 122.68, 118.25, 70.16, 42.94, 35.42, 24.02, 14.41.

3.1.1.25. 1-(4-butylnaphthalen-1-yl)but-3-en-1-ol (128d)

In two necked flask, 7 mg Mg turnings (0.28 mmol, 3.0 eq) were suspended in 2 mL dry ether. Then 34 mg allyl bromide (25 μL, 0.28 mmol, 3.0 eq) in 2 mL dry ether was added to Mg suspension. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added at slowly at 0 ^{o}C to a solution of 20 mg (0.09 mmol, 1.0 eq) 4-butyl-1-napthaldehyde in 4.0 mL THF. The mixture was warmed to rt and stirred for 1 h under N_2 atmosphere. The reaction mixture was quenched with 5 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 20 mg 1-(4-butylnaphthalen-1-yl)but-3-en-1-ol (0.08 mmol) with 84% yield. R_f = 0.23 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.08 (m, 2H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.02 – 5.88 (m, 1H), 5.51 (dd, *J* = 8.4 and 4.0 Hz, 1H), 5.27 – 5.16 (m, 2H), 3.16 – 3.00 (m, 2H), 2.83 – 2.55 (m, 2H), 2.17 (s, 1H), 1.82 – 1.66 (m, 2H), 1.55 – 1.40 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.87, 137.55, 135.10, 132.27, 130.80, 125.65, 125.64, 125.39, 124.92, 123.75, 122.67, 118.35, 70.08, 42.94, 33.12, 33.08, 23.03, 14.16.

3.1.1.26. 1-(4-pentylnaphthalen-1-yl)but-3-en-1-ol (128e)

In two necked flask, 16 mg Mg turnings (0.66 mmol, 3.0 eq) was dissolved in 2 mL dry ether. Then 80 mg allyl bromide (57 μL, 0.66 mmol, 3.0 eq) in 2 mL dry ether was added to Mg suspension. The mixture was stirred at 35 ^{o}C and the mixture became blurry 2-3 mins later. When it began to boil, the mixture was warmed to rt and stirred until the magnesium turnings almost disappeared. This Grignard reagent was then added at slowly at 0 ^{o}C to a solution of 50 mg (0.22 mmol, 1.0 eq) 4-pentyl-1-napthaldehyde in 4.0 mL THF. The mixture was warmed to rt and stirred for 1 h under N_2 atmosphere. The reaction mixture was quenched with 5 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 35 mg 1-(4-pentylnaphthalen-1-yl)but-3-en-1-ol (0.13 mmol) with 59% yield. R_f = 0.26 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.09 (m, 2H), 7.58 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.02 – 5.89 (m, 1H), 5.51 (dd, *J* = 8.4 and 4.1 Hz, 1H), 5.27 – 5.16 (m, 2H), 3.14 – 3.00 (m, 2H), 2.82 – 2.57 (m, 2H), 2.07 (s, 1H), 1.81 – 1.72 (m, 2H), 1.49 – 1.35 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.91, 137.56, 135.10, 132.29, 130.82, 125.64, 125.61, 125.39, 124.91, 123.76, 122.68, 118.30, 70.11, 42.94, 33.34, 32.17, 30.67, 22.73, 14.22.

3.1.1.27. 1-(4-metylnaphthalen-1-yl)but-3-en-1-yl acrylate (129a)

To solution of 163 mg 1-(4-methylnaphthalen-1-yl)but-3-en-1-ol (0.76 mmol, 1.0 eq) in dry CH_2Cl_2 (7 mL) were added 112 μL (1.38 mmol, 1.8 eq) acryloyl chloride and 384 μL Et_3N (2.75 mmol, 3.6 eq) at 0 ^{o}C. The mixture was warmed to rt and stirred for 16 h. The resulting mixture was filtered through a short pad of celite, poured into water, and the product was extracted with CH_2Cl_2 (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 148 mg 1-(4-metylnaphthalen-1-yl)but-3-en-1-yl acrylate (0,55 mmol) with 73% yield. R_f = 0.78 (ethyl acetate/hexanes, 1:8) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.22

(m, 1H), 8.10 – 8.06 (m, 1H), 7.63 – 7.55 (m, 2H), 7.53 (d, *J* = 7.3 Hz, 1H), 7.35 (d, *J* = 7.3 Hz, 1H), 6.73 (t, *J* = 6.6 Hz, 1H), 6.51 (ddd, *J* = 17.3, 1.6 and 0.8 Hz, 1H), 6.25 (ddd, *J* = 17.3, 10.4 and 0.8 Hz, 1H), 5.93 – 5.79 (m, 2H), 5.22 – 5.08 (m, 2H), 2.93 – 2.82 (m, 2H), 2.72 (d, *J* = 0.8 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.48, 134.76, 134.08, 133.69, 132.96, 131.01, 130.51, 128.67, 126.16, 126.06, 125.62, 125.06, 123.76, 123.75, 118.02, 72.62, 40.46, 19.72.

3.1.1.28. 1-(4-etylnaphthalen-1-yl)but-3-en-1-yl acrylate (129b)

To solution of 54 mg 1-(4-ethylnaphthalen-1-yl)but-3-en-1-ol (0.24 mmol, 1.0 eq) in dry CH_2Cl_2 (5 mL) were added 34 μL (0.43 mmol, 1.8 eq) acryloyl chloride and 121 μL Et_3N (0.86 mmol, 3.6 eq) at 0 ^oC. The mixture was warmed to rt and stirred for 16 h. The resulting mixture was filtered through a short pad of celite, poured into water, and the product was extracted with CH_2Cl_2 (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 57 mg 1-(4-etylnaphthalen-1-yl)but-3-en-1-yl acrylate (0,20 mmol) with 84% yield. R_f = 0.54 (ethyl acetate/hexanes, 1:8) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 1H), 8.14 – 8.10 (m, 1H), 7.59 – 7.52 (m, 3H), 7.35 (d, *J* = 7.4 Hz, 1H), 6.69 (t, *J* = 6.6 Hz, 1H), 6.48 (dd, *J* = 17.3 and 1.5 Hz, 1H), 6.26 – 6.18 (m, 1H), 5.89 – 5.78 (m, 2H), 5.18 – 5.06 (m, 2H), 3.12 (q, *J* = 7.5 Hz, 2H), 2.88 – 2.82 (m, 2H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.55, 140.69, 134.00, 133.77, 132.18, 131.05, 130.76, 128.72, 125.96, 125.61, 124.69, 124.43, 123.94, 123.89, 118.03, 72.67, 40.49, 26.13, 15.03.

3.1.1.29. 1-(4-propylnaphthalen-1-yl)but-3-en-1-yl acrylate (129c)

To solution of 56 mg 1-(4-propylnaphthalen-1-yl)but-3-en-1-ol (0,23 mmol, 1.0 eq) in dry CH_2Cl_2 (6 mL) were added 33 μL (0.42 mmol, 1.8 eq) acryloyl chloride and 117 μL Et_3N (0.84 mmol, 3.6 eq) at 0 ^oC. The mixture was warmed to rt and stirred for

16 h. The resulting mixture was filtered through a short pad of celite, poured into water, and the product was extracted with CH_2Cl_2 (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 49 mg 1-(4-propylnaphthalen-1-yl)but-3-en-1-yl acrylate (0,17 mmol) with 73% yield. R_f = 0.52 (ethyl acetate/hexanes, 1:8) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.16 (m, 1H), 8.14 – 8.08 (m, 1H), 7.59 – 7.49 (m, 3H), 7.33 (d, *J* = 7.4 Hz, 1H), 6.69 (t, *J* = 6.6 Hz, 1H), 6.52 – 6.44 (m, 1H), 6.27 – 6.17 (m, 1H), 5.91 – 5.76 (m, 2H), 5.19 – 5.05 (m, 2H), 3.09 – 3.01 (m, 2H), 2.84 (t, *J* = 6.7 Hz, 2H), 1.85 – 1.73 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.55, 139.21, 134.01, 133.77, 132.32, 131.06, 130.82, 128.71, 125.91, 125.53, 125.51, 124.88, 123.91, 123.73, 118.03, 72.65, 40.49, 35.45, 23.96, 14.46.

3.1.1.30. 1-(4-butylnaphthalen-1-yl)but-3-en-1-yl acrylate (129d)

To solution of 34 mg 1-(4-butylnaphthalen-1-yl)but-3-en-1-ol (0,13 mmol, 1.0 eq) in dry CH_2Cl_2 (4 mL) were added 19 μL (0,24 mmol, 1.8 eq) acryloyl chloride and 67 μL Et_3N (0.48 mmol, 3.6 eq) at 0 ^oC. The mixture was warmed to rt and stirred for 16 h. The resulting mixture was filtered through a short pad of celite, poured into water, and the product was extracted with CH_2Cl_2 (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 37 mg 1-(4-butylnaphthalen-1-yl)but-3-en-1-yl acrylate (0,12 mmol) with 90% yield. R_f = 0.73 (ethyl acetate/hexanes, 1:8) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.15 (m, 1H), 8.12 – 8.07 (m, 1H), 7.58 – 7.52 (m, 2H), 7.50 (d, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.4 Hz, 1H), 6.67 (t, *J* = 6.6 Hz, 1H), 6.50 – 6.42 (m, 1H), 6.20 (dd, *J* = 17.3 and 10.4 Hz, 1H), 5.89 – 5.75 (m, 2H), 5.17 – 5.03 (m, 2H), 3.06 (dd, *J* = 8.9 and 6.7 Hz, 2H), 2.86 – 2.80 (m, 2H), 1.78 – 1.68 (m, 2H), 1.52 – 1.41 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.57, 139.47, 133.97, 133.79, 132.30, 131.09, 130.83, 128.72, 125.92, 125.54, 125.44, 124.88, 123.93, 123.77, 118.04, 72.65, 40.50, 33.11, 33.05, 23.05, 14.15.

3.1.1.31. 1-(4-pentylnaphthalen-1-yl)but-3-en-1-yl acrylate (129e)

To solution of 35 mg 1-(4-pentylnaphthalen-1-yl)but-3-en-1-ol (0,13 mmol, 1.0 eq) in dry CH_2Cl_2 (4 mL) were added 18 μL (0,23 mmol, 1.8 eq) acryloyl chloride and 65 μL Et_3N (0,47 mmol, 3.6 eq) at 0 ^oC. The mixture was warmed to rt and stirred for 16 h. The resulting mixture was filtered through a short pad of Celite, poured into water, and the product was extracted with CH_2Cl_2 (3x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 36 mg 1-(4-pentylnaphthalen-1-yl)but-3-en-1-yl acrylate (0,11 mmol) with 85% yield. R_f = 0.53 (ethyl acetate/hexanes, 1:8) ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.17 (m, 1H), 8.13 – 8.08 (m, 1H), 7.58 – 7.50 (m, 3H), 7.34 – 7.31 (m, 1H), 6.68 (t, *J* = 6.6 Hz, 1H), 6.47 (dd, *J* = 17.3 and 1.5 Hz, 1H), 6.26 – 6.16 (m, 1H), 5.88 – 5.76 (m, 2H), 5.17 – 5.05 (m, 2H), 3.06 (dd, *J* = 9.0 and 6.6 Hz, 2H), 2.87 – 2.82 (m, 2H), 1.81 – 1.71 (m, 2H), 1.50 – 1.35 (m, 4H), 0.93 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.55, 139.53, 133.99, 133.79, 132.33, 131.02, 130.86, 128.76, 125.92, 125.54, 125.42, 124.87, 123.94, 123.80, 118.02, 72.68, 40.51, 33.38, 32.19, 30.61, 22.73, 14.21.

3.1.1.32. 6-(4-metylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (38)

To a stirred solution of 47 mg second generation Grubbs' catalyst (10 mol%) in 5.5 mL dichloromethane at 45 ^oC was added a solution of 148 mg (0.56 mmol, 1 eq) 1-(4-metylnaphthalen-1-yl)but-3-en-1-yl acrylate in 55 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 116 mg 6-(4-metylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (0.49 mmol) with 88% yield. R_f = 0.31 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.10 – 8.03 (m, 1H), 8.01 – 7.95 (m, 1H), 7.61 – 7.51 (m, 3H), 7.35 (dd, *J* = 7.4 and 0.5 Hz, 1H), 7.06 – 6.99 (m, 1H), 6.22 – 6.14 (m, 2H), 2.81 – 2.76 (m, 2H), 2.70 (s, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.51, 145.46, 135.54, 132.93, 132.07, 130.14, 126.30, 126.20, 125.76, 125.23, 123.99, 123.15, 121.63, 76.89, 31.15, 19.72.

3.1.1.33. 6-(4-ethylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (102)

To a stirred solution of 17 mg second generation Grubbs' catalyst (10 mol%) in 2 mL dichloromethane at 45 ^{o}C was added a solution of 55 mg (0.20 mmol, 1 eq) 1-(4-etylnaphthalen-1-yl)but-3-en-1-yl acrylate in 20 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 46 mg 6-(4-etylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (0.18 mmol) with 94% yield. R_f = 0.27 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 1H), 8.03 – 7.96 (m, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.25 – 6.14 (m, 2H), 3.12 (q, *J* = 7.5 Hz, 2H), 2.84 – 2.77 (m, 2H), 1.39 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.53, 145.44, 141.53, 132.16, 131.98, 130.44, 126.21, 125.75, 124.89, 124.51, 124.17, 123.33, 121.73, 76.95, 31.16, 26.14, 15.05.

3.1.1.34. 6-(4-propylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (103)

To a stirred solution of 14 mg second generation Grubbs' catalyst (10 mol%) in 1.6 mL dichloromethane at 45 ^{o}C was added a solution of 48 mg (0.16 mmol, 1 eq) 1-(4-propylnaphthalen-1-yl)but-3-en-1-yl acrylate in 16 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The the crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 38 mg 6-(4-propylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (0.14 mmol) with 89% yield. R_f = 0.24 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 1H), 8.01 – 7.96 (m, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.23 – 6.15 (m, 2H), 3.08 – 3.03 (m, 2H), 2.88 – 2.73 (m, 2H), 1.85 – 1.73 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.55, 145.48, 140.01, 132.29, 131.99, 130.48, 126.17, 125.67, 125.60, 125.08, 123.99, 123.28, 121.71, 76.94, 35.39, 31.14, 23.95, 14.37.

3.1.1.35. 6-(4-butylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (104)

To a stirred solution of 10 mg second generation Grubbs' catalyst (10 mol%) in 2 mL dichloromethane at 45 ^{o}C was added a solution of 37 mg (0.12 mmol, 1 eq) 1-(4-butylnaphthalen-1-yl)but-3-en-1-yl acrylate in 20 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 24 mg 6-(4-butylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (0.08 mmol) with 70% yield. R_f = 0.47 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 1H), 8.01 – 7.97 (m, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.23 – 6.16 (m, 2H), 3.12 – 3.04 (m, 2H), 2.84 – 2.78 (m, 2H), 1.78 – 1.69 (m, 2H), 1.52 – 1.41 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.54, 145.42, 140.32, 132.32, 131.99, 130.53, 126.20, 125.70, 125.55, 125.11, 124.06, 123.32, 121.80, 76.97, 33.09, 33.06, 31.21, 22.99, 14.12.

3.1.1.36. 6-(4-pentylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (105)

To a stirred solution of 9 mg second generation Grubbs' catalyst (10 mol%) in 1 mL dichloromethane at 45 ^{o}C was added a solution of 34 mg (0.10 mmol, 1 eq) 1-(4-pentylnaphthalen-1-yl)but-3-en-1-yl acrylate in 10 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 25 mg 6-(4-pentylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (0.08 mmol) with 81% yield. R_f = 0.27 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.09 (m, 1H), 8.02 – 7.96 (m, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.24 – 6.16 (m, 2H), 3.11 – 3.04 (m, 2H), 2.85 – 2.78 (m, 2H), 1.81 – 1.70 (m, 2H), 1.48 – 1.33 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.54, 145.44, 140.34, 132.29, 131.97, 130.51, 126.19, 125.70, 125.53, 125.09, 124.06, 123.31, 121.78, 76.97, 33.36, 32.12, 31.20, 30.61, 22.70, 14.21.

3.1.2. Synthesis of 4'-alkyl substituted 3,6 dihydro-*2H*-pyran-2-one Derivatives (64, 106-109)

3.1.2.1. 1-(4-methylnaphthalen-1-yl)prop-2-en-1-ol (130a)

A solution of 190.2 mg (1.1 mmol, 1.0 eq) 4-methyl 1-napthaldehyde in 5.0 mL THF was cooled down to 0 ^{o}C then 2.2 mL (2.2 mmol, 2.0 eq) 1.0 M solution of vinylmagnesiumbromide was added. The mixture was warmed to rt and stirred for 1 h under nitrogen atmosphere. The reaction mixture was quenched with 15 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x15 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 178 mg 1-(4-methylnaphthalen-1-yl)prop-2-en-1-ol (0.90 mmol) with 82% yield. R_f = 0.43 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.18 (m, 1H), 8.09 – 8.04 (m, 1H), 7.60 – 7.53 (m, 2H), 7.51 – 7.48 (m, 1H), 7.32 (dd, *J* = 7.2 and 0.7 Hz, 1H), 6.24 (ddd, *J* = 17.2, 10.4 and 5.3 Hz, 1H), 5.88 (d, *J* = 5.2 Hz, 1H), 5.44 (dt, *J* = 17.2 and 1.5 Hz, 1H), 5.28 (dt, *J* = 10.4 and 1.5 Hz, 1H), 2.72 (d, *J* = 0.6 Hz, 3H), 2.43 (s, 1H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.82, 136.34, 134.69, 133.05, 130.82, 126.25, 125.80, 125.58, 124.90, 124.37, 123.79, 115.50, 72.22, 19.71.

3.1.2.2. 1-(4-ethylnaphthalen-1-yl)prop-2-en-1-ol (130b)

A solution of 57 mg (0.31 mmol, 1.0 eq) 4-ethyl 1-napthaldehyde in 4.0 mL THF was cooled down to 0 ^{o}C then 0.93 mL (0.93 mmol, 3.0 eq) 1.0 M solution of vinylmagnesiumbromide was added. The mixture was warmed to rt and stirred for 1 h under nitrogen atmosphere. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x10 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 44 mg 1-(4-ethylnaphthalen-1-yl)prop-2-en-1-ol (0.21 mmol) with 67% yield. R_f = 0.52 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.21 (m, 1H), 8.15 – 8.10 (m, 1H), 7.58 – 7.51 (m, 3H), 7.35 (d, *J* = 7.3 Hz, 1H), 6.31 – 6.20 (m, 1H),

5.91 (d, *J* = 4.3 Hz, 1H), 5.49 – 5.43 (m, 1H), 5.31 – 5.27 (m, 1H), 3.13 (q, *J* = 7.5 Hz, 2H), 2.21 (s, 1H), 1.40 (t, *J* = 7.5 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 140.81, 139.88, 136.29, 132.33, 131.17, 125.77, 125.63, 124.60, 124.58, 124.01, 115.58, 72.40, 26.15, 15.14.

3.1.2.3. 1-(4-propylnaphthalen-1-yl)prop-2-en-1-ol (130c)

A solution of 43.4 mg (0.22 mmol, 1.0 eq) 4-propyl 1-napthaldehyde in 4.0 mL THF was cooled down to 0 ^{o}C then 0.87 mL (0.87 mmol, 4.0 eq) 1.0 M solution of vinylmagnesiumbromide was added. The mixture was warmed to rt and stirred for 1 h under nitrogen atmosphere. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x10 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 43 mg 1-(4-propylnaphthalen-1-yl)prop-2-en-1-ol (0.19 mmol) with 87% yield. R_f = 0.22 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.19 (m, 1H), 8.15 – 8.06 (m, 1H), 7.56 – 7.50 (m, 3H), 7.32 (d, *J* = 7.3 Hz, 1H), 6.26 (ddd, *J* = 17.2, 10.4 and 5.3 Hz, 1H), 5.92 (d, *J* = 5.1 Hz, 1H), 5.46 (dt, *J* = 17.2 and 1.5 Hz, 1H), 5.29 (dt, *J* = 10.5 and 1.4 Hz, 1H), 3.08 – 3.03 (m, 2H), 2.09 (s, 1H), 1.85 – 1.74 (m, 2H), 1.05 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.93, 139.30, 136.36, 132.53, 131.28, 125.73, 125.69, 125.55, 124.80, 124.56, 123.86, 115.55, 72.43, 35.44, 24.03, 14.42.

3.1.2.4. 1-(4-butylnaphthalen-1-yl)prop-2-en-1-ol (130d)

A solution of 43 mg (0.20 mmol, 1.0 eq) 4-butyl 1-napthaldehyde in 4.0 mL THF was cooled down to 0 ^{o}C then 0.6 mL (0.61 mmol, 3.0 eq) 1.0 M solution of vinylmagnesiumbromide was added. The mixture was warmed to rt and stirred for 1 h under nitrogen atmosphere. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x10 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude

product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 35 mg 1-(4-butylnaphthalen-1-yl)prop-2-en-1-ol (0.14 mmol) with 73% yield. R_f = 0.45 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 1H), 8.14 – 8.08 (m, 1H), 7.57 – 7.50 (m, 3H), 7.32 (d, *J* = 7.3 Hz, 1H), 6.26 (ddd, *J* = 17.2, 10.4 and 5.3 Hz, 1H), 5.91 (s, 1H), 5.46 (dt, *J* = 17.2 and 1.5 Hz, 1H), 5.29 (dt, *J* = 10.4 and 1.5 Hz, 1H), 3.10 – 3.05 (m, 2H), 2.13 (d, *J* = 4.0 Hz, 1H), 1.79 – 1.69 (m, 2H), 1.54 – 1.42 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.84, 139.53, 136.24, 132.43, 131.21, 125.73, 125.59, 125.55, 124.78, 124.53, 123.86, 115.58, 72.37, 33.10, 33.09, 23.01, 14.15.

3.1.2.5. 1-(4-pentylnaphthalen-1-yl)prop-2-en-1-ol (130e)

A solution of 62 mg (0.27 mmol, 1.0 eq) 4-pentyl 1-napthaldehyde in 4.0 mL THF was cooled down to 0 ^{o}C then 0.82 mL (0.82 mmol, 3.0 eq) 1.0 M solution of vinylmagnesiumbromide was added. The mixture was warmed to rt and stirred for 1 h under nitrogen atmosphere. The reaction mixture was quenched with 10 mL of saturated NH_4Cl aqueous solution and extracted with EtOAc (2x10 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 53 mg 1-(4-pentylnaphthalen-1-yl)prop-2-en-1-ol (0.21 mmol) with 76% yield. R_f = 0.45 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.26 – 8.20 (m, 1H), 8.14 – 8.08 (m, 1H), 7.57 – 7.50 (m, 3H), 7.33 (d, *J* = 7.3 Hz, 1H), 6.26 (ddd, *J* = 17.2, 10.4 and 5.3 Hz, 1H), 5.91 (t, *J* = 4.5 Hz, 1H), 5.46 (dt, *J* = 17.2 and 1.5 Hz, 1H), 5.29 (dt, *J* = 10.4 and 1.5 Hz, 1H), 3.10 – 3.04 (m, 2H), 2.16 (d, *J* = 4.1 Hz, 1H), 1.83 – 1.71 (m, 2H), 1.51 – 1.33 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.83, 139.56, 136.23, 132.42, 131.20, 125.72, 125.58, 125.54, 124.77, 124.53, 123.86, 115.56, 72.35, 33.35, 32.15, 30.66, 22.73, 14.23.

3.1.2.6. 1-(4-methylnaphthalen-1-yl)allyl but-3-enoate (131a)

In a two necked flask, 50 mg (0.25 mmol, 1.0 eq) of 1-(4-methylnaphthalen-1-yl)prop-2-en-1-ol and 43 μL (0.50 mmol, 2.0 eq) of 3-butenoic acid were placed and dissolved in 10 mL of dried DCM. After the reaction mixture cooled down to 0 ^{o}C and 109 mg (0.53 mmol, 2.1 eq) of DCC and 34 mg (0.277 mmol, 1.1 eq) of DMAP were added to the reacion medium. The mixture was warmed to rt and stirred for 5 h under N_2 atmosphere. When the reaction was completed, the final mixture was concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 59 mg 1-(4-methylnaphthalen-1-yl)allyl but-3-enoate (0.22 mmol) as yellow oil with 88% yield. R_f = 0.58 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.15 (m, 1H), 8.09 – 8.04 (m, 1H), 7.59 – 7.54 (m, 2H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.34 (dd, *J* = 7.3 and 0.7 Hz, 1H), 7.03 (d, *J* = 5.2 Hz, 1H), 6.23 (ddd, *J* = 17.2, 10.5 and 5.3 Hz, 1H), 6.04 – 5.93 (m, 1H), 5.38 – 5.30 (m, 2H), 5.22 (m, 1H), 5.18 (t, *J* = 1.5 Hz, 1H), 3.27 – 3.15 (m, 2H), 2.72 (d, *J* = 0.7 Hz, 3H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.64, 136.08, 135.43, 133.11, 132.65, 130.87, 130.20, 126.19, 126.08, 125.74, 125.44, 124.98, 124.45, 118.84, 117.27, 74.04, 39.44, 19.75.

3.1.2.7. 1-(4-ethylnaphthalen-1-yl)allyl but-3-enoate (131b)

In a two necked flask, 42 mg (0.19 mmol, 1.0 eq) of 1-(4-ethylnaphthalen-1-yl)prop-2-en-1-ol and 34 μL (0.39 mmol, 2.0 eq) of 3-butenoic acid were placed and dissolved in 10 mL of dried DCM. After the reaction mixture cooled down to 0 ^{o}C and 86 mg (0.41 mmol, 2.1 eq) of DCC and 27 mg (0.21 mmol, 1.1 eq) of DMAP were added to the reacion medium. The mixture was warmed to rt and stirred for 5 h under N_2 atmosphere. When the reaction was completed, the final mixture was concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 44 mg 1-(4-ethylnaphthalen-1-yl)allyl but-3-enoate (0.16 mmol) as yellow oil with 80% yield. R_f = 0.57 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.07 (m, 2H), 7.59 – 7.51 (m, 3H), 7.35 (d, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 5.2 Hz, 1H), 6.35 – 6.15 (m, 1H), 6.07 – 5.89 (m, 1H), 5.39 – 5.28 (m, 2H),

5.27 – 5.15 (m, 2H), 3.22 – 3.17 (m, 2H), 3.13 (q, *J* = 7.5 Hz, 2H), 1.40 (t, *J* = 7.5 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.68, 141.36, 136.07, 132.54, 132.31, 131.13, 130.22, 125.96, 125.71, 125.57, 124.60, 124.47, 118.87, 117.27, 74.07, 39.46, 26.15, 15.04.

3.1.2.8. 1-(4-propylnaphthalen-1-yl)allyl but-3-enoate (131c)

In a two necked flask, 61 mg (0.27 mmol, 1.0 eq) of 1-(4-propylnaphthalen-1-yl)prop-2-en-1-ol and 45 μL (0.54 mmol, 2.0 eq) of 3-butenoic acid were placed and dissolved in 10 mL of dried DCM. After the reaction mixture cooled down to 0 ^{o}C and 117 mg (0.56 mmol, 2.1 eq) of DCC and 36 mg (0.3 mmol, 1.1 eq) of DMAP were added to the reacion medium. The mixture was warmed to rt and stirred for 5 h under N_2 atmosphere.When the reaction was completed, the final mixture was concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 64 mg 1-(4-propylnaphthalen-1-yl)allyl but-3-enoate (0.22 mmol) as yellow oil with 81% yield. R_f = 0.63 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.08 (m, 2H), 7.58 – 7.51 (m, 3H), 7.34 (d, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 5.2 Hz, 1H), 6.21 (ddd, *J* = 17.2, 10.5 and 5.3 Hz, 1H), 6.05 – 5.91 (m, 1H), 5.38 – 5.29 (m, 2H), 5.23 – 5.16 (m, 2H), 3.22 – 3.18 (m, 2H), 3.10 – 3.03 (m, 2H), 1.80 (m, 2H), 1.06 (t, *J* = 7.3 Hz, 3H)^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.68, 139.86, 136.07, 132.55, 132.46, 131.20, 130.22, 125.91, 125.63, 125.54, 125.41, 124.78, 124.56, 118.85, 117.25, 74.04, 39.45, 35.44, 23.96, 14.44.

3.1.2.9. 1-(4-butylnaphthalen-1-yl)allyl but-3-enoate (131d)

In a two necked flask, 34 mg (0.14 mmol, 1.0 eq) of 1-(4-butylnaphthalen-1-yl)prop-2-en-1-ol and 24 μL (0.28 mmol, 2.0 eq) of 3-butenoic acid were placed and dissolved in 10 mL of dried DCM. After the reaction mixture cooled down to 0 ^{o}C and 61 mg (0.3 mmol, 2.1 eq) of DCC and 19 mg (0.15 mmol, 1.1 eq) of DMAP were added to the reacion medium. The mixture was warmed to rt and stirred for 5 h under N_2 atmosphere. When the reaction was completed, the final mixture was concentrated

under vacuum. The crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 41 mg 1-(4-butylnaphthalen-1-yl)allyl but-3-enoate (0.13 mmol) as yellow oil with 95% yield. R_f = 0.57 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.06 (m, 2H), 7.57 – 7.50 (m, 3H), 7.33 (d, *J* = 7.3 Hz, 1H), 7.01 (d, *J* = 5.3 Hz, 1H), 6.25 – 6.15 (m, 1H), 6.03 – 5.90 (m, 1H), 5.37 – 5.28 (m, 2H), 5.22 – 5.16 (m, 2H), 3.28 – 3.13 (m, 2H), 3.12 – 3.04 (m, 2H), 1.80 – 1.69 (m, 2H), 1.54 – 1.42 (m, 2H), 0.99 (t, *J* = 7.3 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.68, 140.13, 136.08, 132.51, 132.44, 131.21, 130.23, 125.92, 125.64, 125.47, 125.45, 124.78, 124.58, 118.86, 117.26, 74.05, 39.46, 33.10, 33.05, 23.02, 14.12.

3.1.2.10. 1-(4-pentylnaphthalen-1-yl)allyl but-3-enoate (131e)

In a two necked flask, 52 mg (0.2 mmol, 1.0 eq) of 1-(4-pentylnaphthalen-1-yl)prop-2-en-1-ol and 35 μL (0.4 mmol, 2.0 eq) of 3-butenoic acid were placed and dissolved in 10 mL of dried DCM. After the reaction mixture cooled down to 0 ^{o}C and 88 mg (0.43 mmol, 2.1 eq) of DCC and 27 mg (0.22 mmol, 1.1 eq) of DMAP were added to the reacion medium. The mixture was warmed to rt and stirred for 5 h under N_2 atmosphere. When the reaction was completed, the final mixture was concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 EtOAc/Hexanes) to give 56 mg 1-(4-pentylnaphthalen-1-yl)allyl but-3-enoate (0.17 mmol) as yellow oil with 85% yield. R_f = 0.66 (ethyl acetate/hexanes, 1:8); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.19 – 8.06 (m, 2H), 7.58 – 7.50 (m, 3H), 7.33 (d, *J* = 7.4 Hz, 1H), 7.02 (d, *J* = 5.2 Hz, 1H), 6.34 – 6.16 (m, 1H), 6.05 – 5.91 (m, 1H), 5.38 – 5.26 (m, 2H), 5.27 – 5.15 (m, 2H), 3.29 – 3.13 (m, 2H), 3.12 – 3.04 (m, 2H), 1.84 – 1.70 (m, 2H), 1.51 – 1.35 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.67, 140.17, 136.07, 132.50, 132.44, 131.21, 130.23, 125.91, 125.64, 125.45, 125.44, 124.77, 124.58, 118.85, 117.25, 74.05, 39.45, 33.37, 32.16, 30.61, 22.71, 14.20.

3.1.2.11. 6-(4-methylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (64)

To a stirred solution of 16.5 mg second generation Grubbs' catalyst (10 mol%) in 2 mL dichloromethane at 45 ^{o}C was added a solution of 52 mg (0.19 mmol, 1 eq) 1-(4-methylnaphthalen-1-yl)allyl but-3-enoate in 20 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 39 mg 6-(4-methylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (0.16 mmol) with 84% yield. R_f = 0.3 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.11 (m, 1H), 8.08 – 8.04 (m, 1H), 7.62 – 7.54 (m, 2H), 7.41 (d, *J* = 7.3 Hz, 1H), 7.30 (dd, *J* = 7.3, and 0.7 Hz, 1H), 6.73 – 6.69 (m, 1H), 6.22 – 6.08 (m, 2H), 3.22 (ddd, *J* = 5.2, 3.5 and 1.8 Hz, 2H), 2.71 (d, *J* = 0.5 Hz, 3H);^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.91, 136.39, 133.28, 131.32, 130.95, 126.61, 126.45, 126.03, 125.97, 125.09, 124.66, 123.97, 122.80, 78.43, 30.34, 19.82.

3.1.2.12. 6-(4-ethylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (106)

To a stirred solution of 13 mg second generation Grubbs' catalyst (10 mol%) in 1.6 mL dichloromethane at 45 ^{o}C was added a solution of 44 mg (0.16 mmol,1 eq) 1-(4-ethylnaphthalen-1-yl)allyl but-3-enoate in 16 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 27 mg 6-(4-ethylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (0.11 mmol) with 68% yield. R_f = 0.36 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 2H), 7.60 – 7.54 (m, 2H), 7.45 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 6.74 – 6.68 (m, 1H), 6.24 – 6.08 (m, 2H), 3.22 (ddd, *J* = 4.9, 3.4 and 1.7 Hz, 2H), 3.16 – 3.09 (m, 2H), 1.38 (t, *J* = 7.5 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.87, 142.33, 132.49, 131.25, 126.48, 126.00, 124.81, 124.70, 124.27, 124.13, 122.80, 78.46, 30.36, 26.18, 15.07.

3.1.2.13. 6-(4-propylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (107)

To a stirred solution of 19 mg second generation Grubbs' catalyst (10 mol%) in 2.2 mL dichloromethane at 45 ^{o}C was added a solution of 64 mg (0.22 mmol, 1 eq) 1-(4-propylnaphthalen-1-yl)allyl but-3-enoate in 22 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 40 mg 6-(4-propylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (0.15 mmol) with 69% yield. R_f = 0.43 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.09 (m, 2H), 7.61 – 7.53 (m, 2H), 7.44 (d, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 6.74 – 6.69 (m, 1H), 6.24 – 6.17 (m, 1H), 6.15 – 6.09 (m, 1H), 3.25 – 3.20 (m, 2H), 3.09 – 3.02 (m, 2H), 1.78 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H)^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.88, 140.83, 132.66, 131.33, 131.27, 126.49, 126.46, 125.93, 125.36, 124.91, 124.66, 124.11, 122.80, 78.48, 35.45, 30.37, 23.99, 14.39.

3.1.2.14. 6-(4-butylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (108)

To a stirred solution of 11 mg second generation Grubbs' catalyst (10 mol%) in 1.4 mL dichloromethane at 45 ^{o}C was added a solution of 41 mg (0.13 mmol) 1-(4-butylnaphthalen-1-yl)allyl but-3-enoate in 14 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 32 mg 6-(4-butylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (0.11 mmol) with 86% yield. R_f = 0.44 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ8.17 – 8.08 (m, 2H), 7.62 – 7.52 (m, 2H), 7.43 (d, *J* = 7.4 Hz, 1H), 7.30 (d, *J* = 7.3 Hz, 1H), 6.73 – 6.69 (m, 1H), 6.23 – 6.08 (m, 2H), 3.24 – 3.20 (m, 2H), 3.11 – 3.05 (m, 2H), 1.78 – 1.68 (m, 2H), 1.52 – 1.40 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.87, 141.08, 132.63, 131.33, 131.23, 126.49, 126.45, 125.93, 125.27, 124.89, 124.68, 124.11, 122.79, 78.47, 33.10, 33.04, 30.36, 22.97, 14.10.

3.1.2.15. 6-(4-pentylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (109)

To a stirred solution of 14 mg second generation Grubbs' catalyst (10 mol%) in 1.7 mL dichloromethane at 45 ^{o}C was added a solution of 54 mg (0.16 mmol, 1 eq) 1-(4-pentylnaphthalen-1-yl)allyl but-3-enoate in 17 mL of dichloromethane. The resulting mixture was heated for 2 h under N_2 atmosphere. After this period, the mixture was cooled down to rt and concentrated under vacuum. The crude product was purified by column chromatography on silica gel (1:10 =>1:2 EtOAc/Hexanes) to give 30 mg 6-(4-pentylnaphthalen-1-yl)-3,6-dihydro-*2H*-pyran-2-one (0.10 mmol) with 61% yield. R_f = 0.54 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.08 (m, 2H), 7.61 – 7.52 (m, 2H), 7.43 (d, *J* = 7.3 Hz, 1H), 7.30 (d, *J* = 7.4 Hz, 1H), 6.73 – 6.69 (m, 1H), 6.23 – 6.17 (m, 1H), 6.15 – 6.09 (m, 1H), 3.22 (ddd, *J* = 4.8, 3.2 and 1.7 Hz, 2H), 3.11 – 3.03 (m, 2H), 1.81 – 1.70 (m, 2H), 1.48 – 1.32 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.86, 141.11, 132.61, 131.32, 131.21, 126.48, 126.44, 125.92, 125.25, 124.88, 124.68, 124.11, 122.78, 78.46, 33.36, 32.10, 30.60, 30.35, 22.69, 14.18.

General Procedure for Reconjugation:

To solution of the corresponding β,γ-unsaturated lactone **106** (22 mg, 0.09 mmol 1 eq) in CH_2Cl_2 (6 mL) 1.3 mg DBU (1.3 μL,0.009 mmol, 0.1 eq) was added at room temperature. The resulting mixture was stirred for 16 h and after this period the reaction mixture was quenched with 10 mL of saturated NH_4Cl solution and extracted with EtOAc (3x10 mL). The combined organic phase was dried over $MgSO_4$. After the removal of the solvent under vacuum, the crude product was purified by column chromatography on silica gel (1:15 EtOAc/Hexanes) to give 10 mg 6-(4-ethylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one 0.04 mmol with 43 yield%.

3.1.2.16.6-(4-etylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (102)

Eluent: EtOAc/Hexanes (1:10 =>1:2). Yield 43% R_f = 0.27 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 – 8.10 (m, 1H), 8.03 – 7.96 (m, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.59 – 7.50 (m, 2H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.08 – 6.98 (m, 1H), 6.25 – 6.14 (m, 2H), 3.12 (q, *J* = 7.5 Hz, 2H), 2.84 – 2.77 (m, 2H), 1.39 (t, *J* = 7.5 Hz, 3H).

3.1.2.17.6-(4-propylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (103)

Eluent: EtOAc/Hexanes (1:10 =>1:2). Yield 45% R_f = 0.24 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 1H), 8.01 – 7.96 (m, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.07 – 7.00 (m, 1H), 6.23 – 6.15 (m, 2H), 3.08 – 3.03 (m, 2H), 2.88 – 2.73 (m, 2H), 1.85 – 1.73 (m, 2H), 1.04 (t, *J* = 7.3 Hz, 3H).

3.1.2.18.6-(4-butylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (104)

Eluent: EtOAc/Hexanes (1:10 =>1:2). Yield 61% R_f = 0.47 (ethyl acetate/hexanes, 1:2); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.10 (m, 1H), 8.01 – 7.97 (m, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.07 – 7.01 (m, 1H), 6.23 – 6.16 (m, 2H), 3.12 – 3.04 (m, 2H), 2.84 – 2.78 (m, 2H), 1.78 – 1.69 (m, 2H), 1.52 – 1.41 (m, 2H), 0.98 (t, *J* = 7.3 Hz, 3H).

3.1.2.19.6-(4-pentylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (105)

Eluent: EtOAc/Hexanes (1:10 =>1:2). Yield 58% R_f = 0.27 (ethyl acetate/hexanes, 1:4); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.15 – 8.09 (m, 1H), 8.02 – 7.96 (m, 1H), 7.61 (d, *J* = 7.4 Hz, 1H), 7.57 – 7.50 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.07 –

7.01 (m, 1H), 6.24 – 6.16 (m, 2H), 3.11 – 3.04 (m, 2H), 2.85 – 2.78 (m, 2H), 1.81 – 1.70 (m, 2H), 1.48 – 1.33 (m, 4H), 0.92 (t, *J* = 7.1 Hz, 3H).

CHAPTER 4

CONCLUSION

In this study, 4'-alkyl substitued klavuzon and naphthalen-1-yl substituted 3,6-dihydro-2*H*-pyran-2-one derivatives were synthesized to evaluate for their cytotoxic activity against cancer cell lines in near future.

Syntheses were started with acetal to form alkylated acetal derivatives via alkyl substitution with base (LDA or n-BuLi). But these trials were unsuccesful. As an alternative preparation of a benzylic carbanion of carboxylic acid or benzothiazole derivatives were also studied and these trials were failed. Another methodology is to generate an electrophilic carbon at benzylic positions by radicalic brominations. For this purpose, benzothiazole substituted naphthalen derivative was brominated at benzylic position with NBS and benzoyl peroxide then cupper (I) catalyzed cross-coupling reactions was studied. At this trial, C-C bond formation was achieved but conversion of benzothiazole back to carboxylic acid was troublesome. Because of that similar approach was performed ethyl 4-methyl-1-naphthoate.

The preparation of the klavuzon derivatives was achieved in eight steps. Synthesis were started ethyl 4-methyl-1-naphthoate **123**, prepared from corresponding carboxylic acid **114** and alcohol in the presence of an acid catalyst followed by bromination with NBS and benzoyl peroxide yielded ethyl 4-bromoethyl-1-naphthoate **124**. Then copper (I)-catalyzed cross coupling reactions between ethyl 4-bromoethyl-1-naphthoate and Grignard reagents gave alkyl substituted esters (**125a-d**). Next alkylated ester derivatives, was converted to alklylated-naphthaldehyde derivatives (**113a-d)** by using $LiAlH_4$ and then with PCC.

Allylation reaction were done between alkylated naftaldehydes and allyltrimethoxy silane in the presence of CuCl-TBAT. But ^{1}H-NMR analysis indicates an impurity and realized that this impurity came from TBAT which is not stable in the acidic condition. Then another appoach was tried. Allylation reaction of corresponding aldehydes with allylmagnesium bromide gave homoallylic alcohols (**128a-e**). Finally, homoallylic alcohols were reacted with acryloyl chloride in the presence of a base to

produce acrylate esters (**129a-e**), then ring closing metathesis by second generation Grubbs' catalyst yielded the final klavuzon derivatives (**38**, **102, 103, 104, 105**).

Additionally, synthesis of new five β,γ-unsaturated δ–lactone derivatives was carried out. Vinylation reaction of corresponding aldehydes with vinylmagnesium bromide gave the alcohols (**130a-e**). Coupling reactions of these alcohols with 3-butenoic acid in the presence of DCC/DMAP yielded the ester (**131a-c)**. Finally, esters was converted to 3,6-dihydro-2*H*-pyran-2-one derivatives **64, 106, 107, 108** and **109** by using second generation Grubbs'' catalyst.

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APPENDIX A

^{1}H and ^{13}C NMR SPECTRUM OF COMPOUNDS

125b, 127b, 113b, 128c, 129c, 103 130c 128a 131c and 107

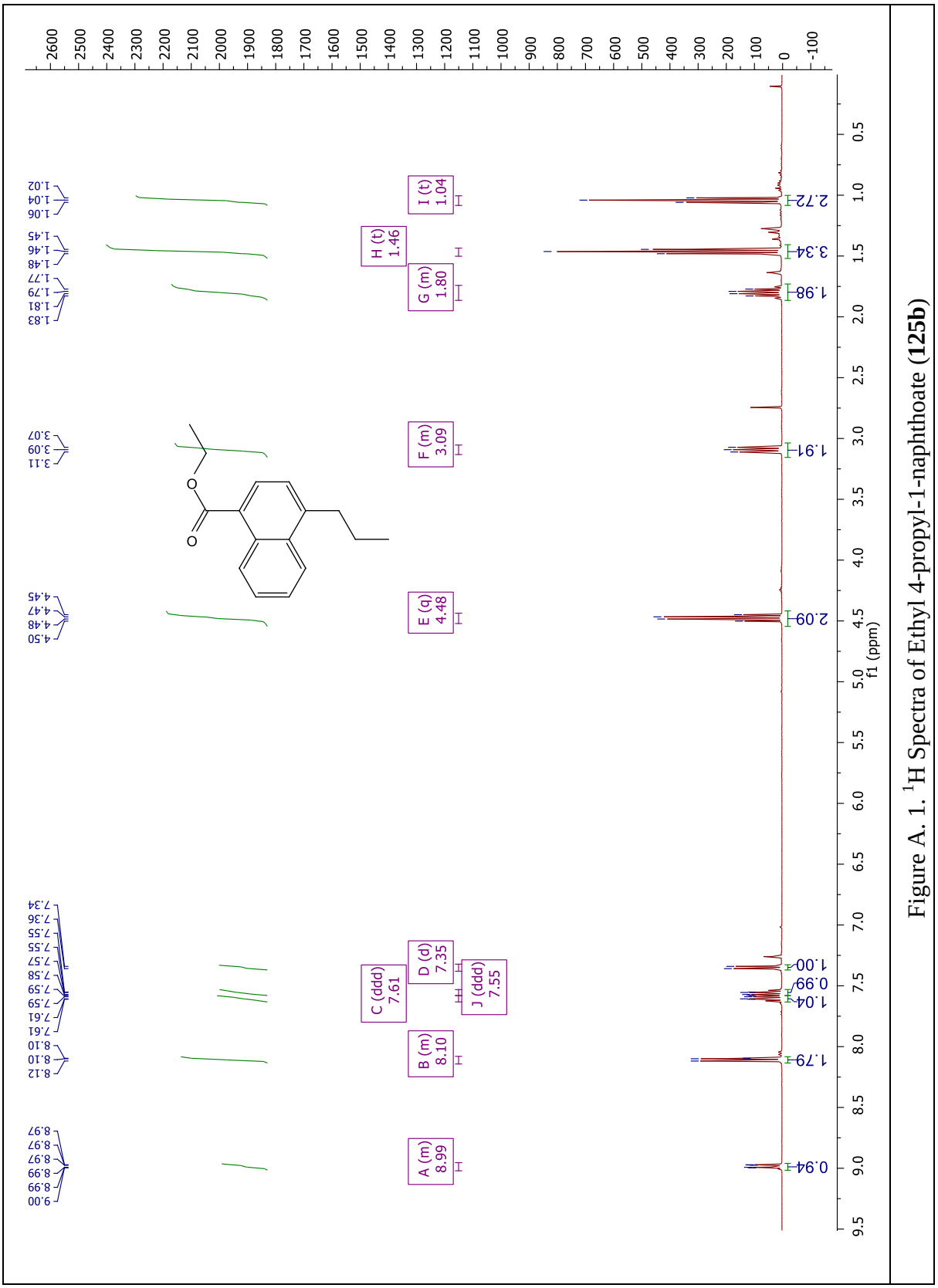

Figure A. 1. ^{1}H Spectra of Ethyl 4-propyl-1-naphthoate (**125b**)

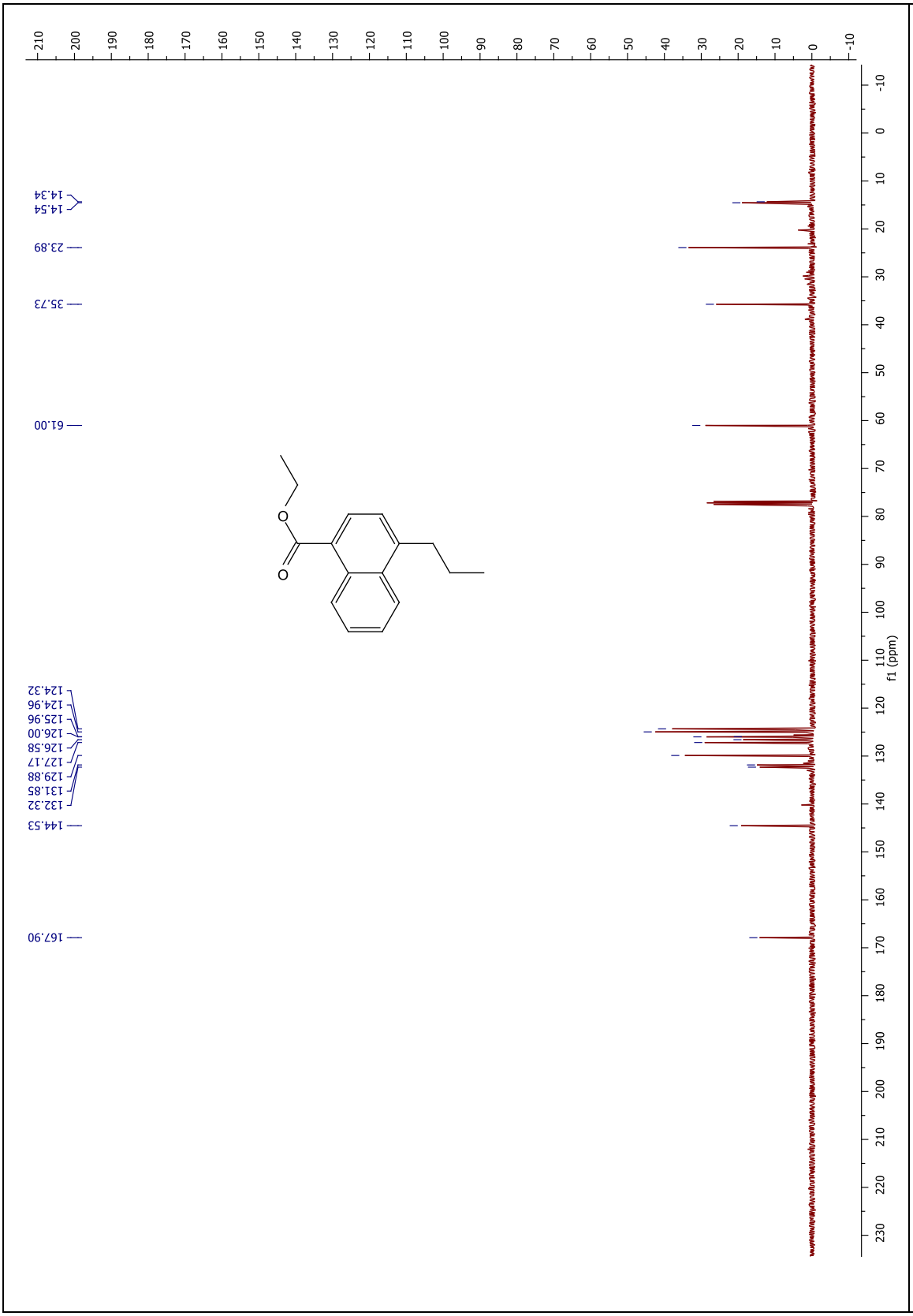

Figure A. 2. ^{13}C Spectra of Ethyl 4-propyl-1-naphthoate (**125b**)

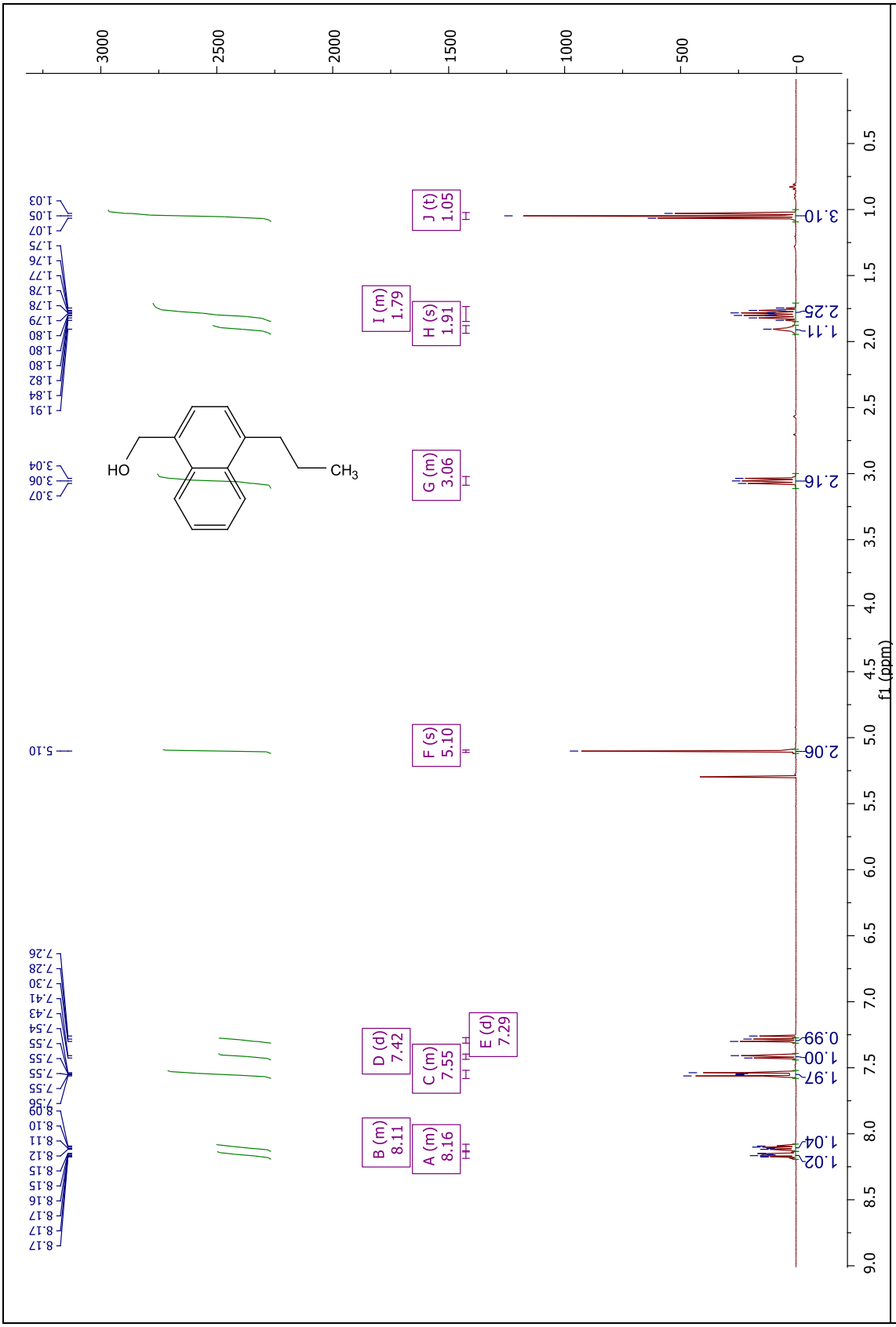

Figure A. 3. ^{1}H Spectra of (4-propylnaphthalen-1-yl)methanol (**127b**)

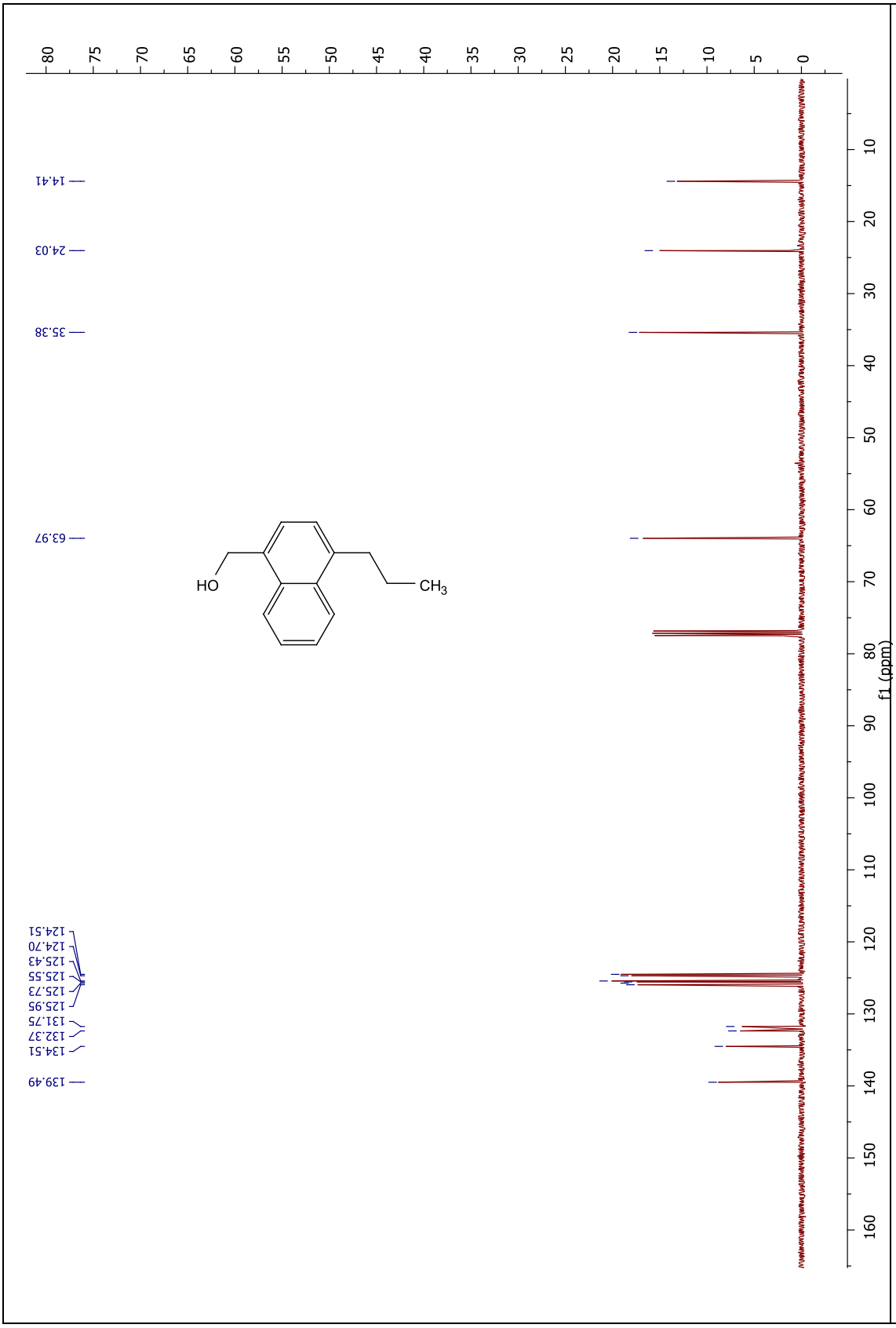

Figure A. 4. ^{13}C Spectra of (4-propylnaphthalen-1-yl)methanol (**127b**)

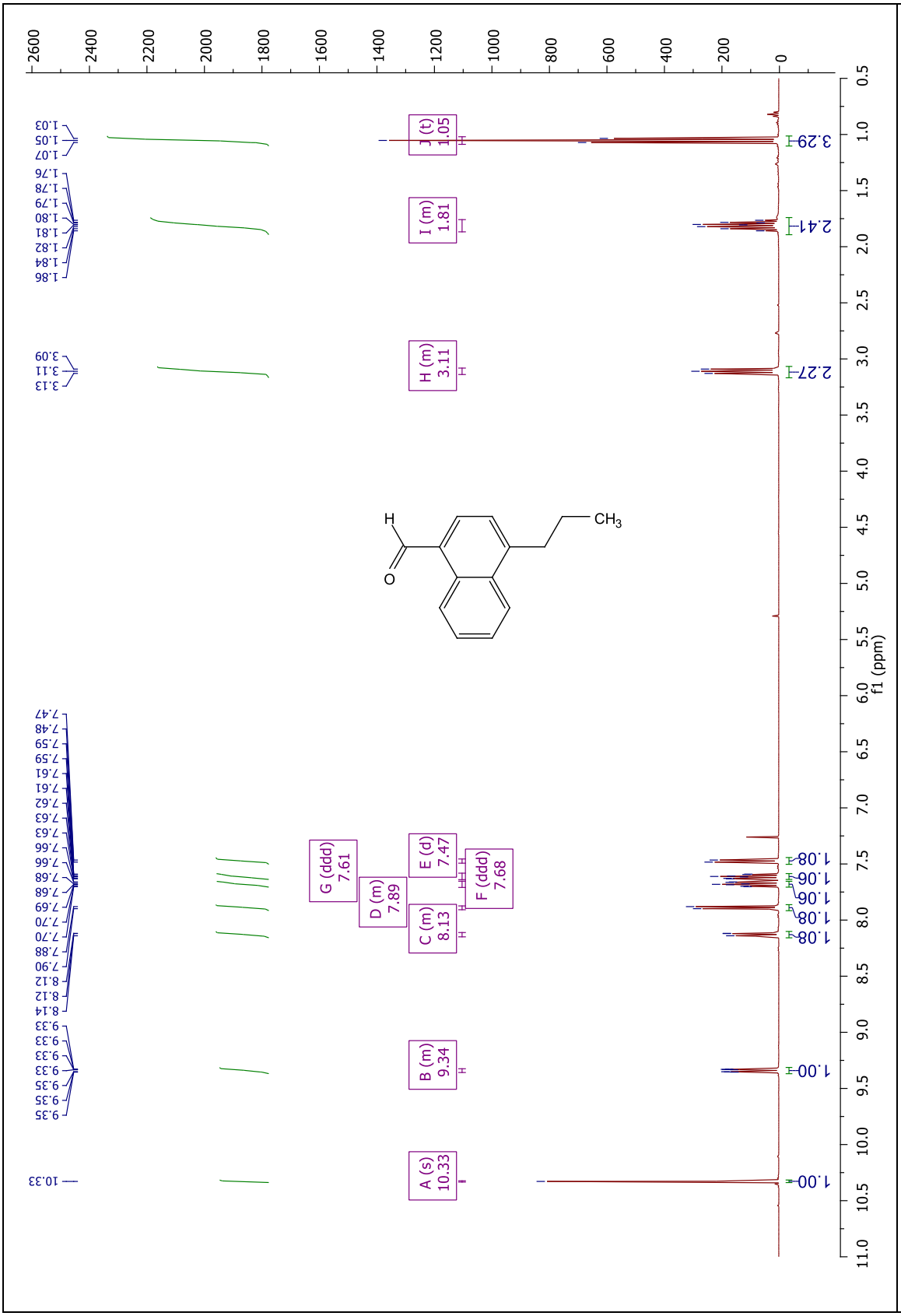

Figure A. 5. ^{1}H Spectra of 4-propyl-1-naphthaldehyde (**113b**)

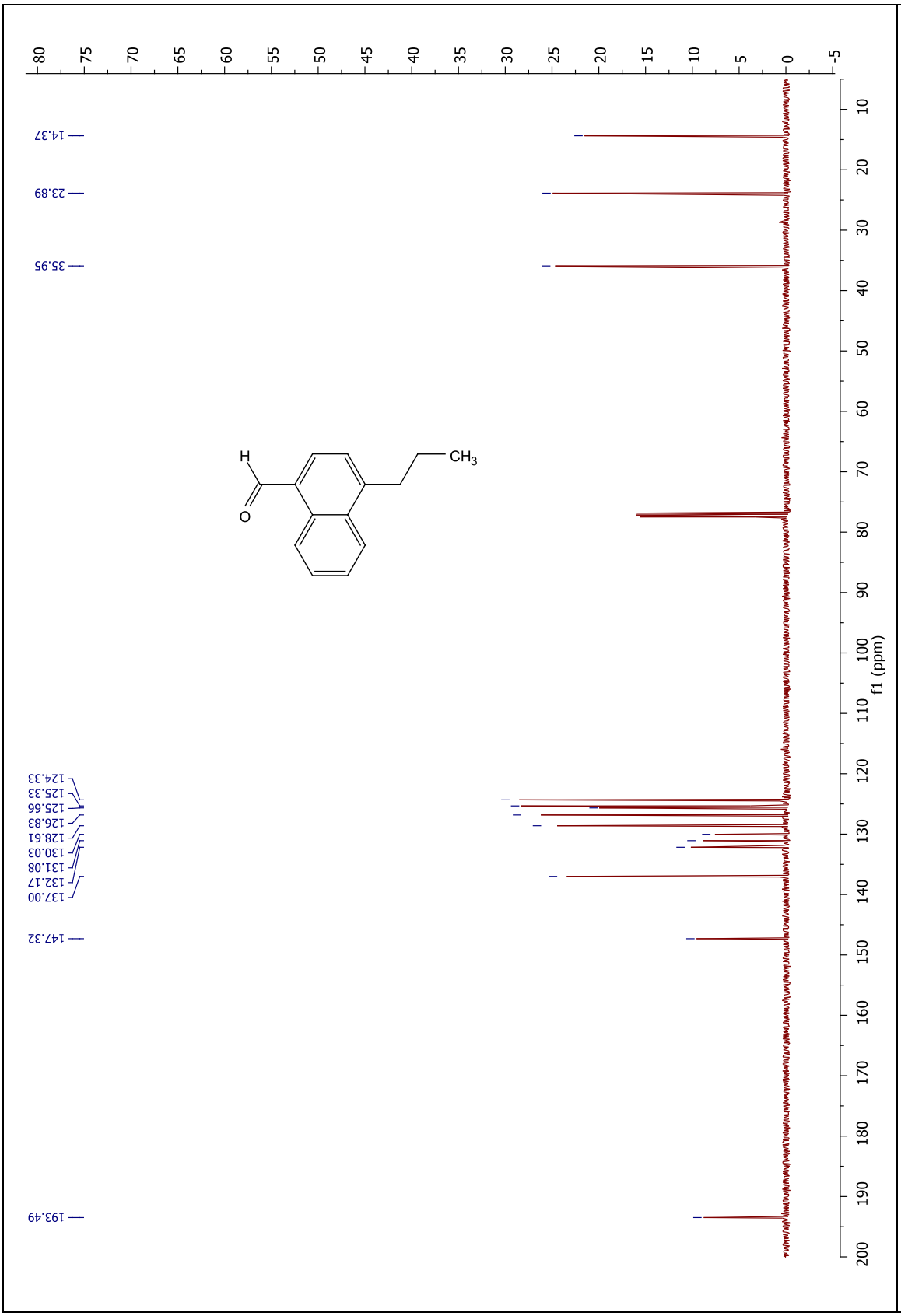

Figure A. 6. ^{13}C Spectra of 4-propyl-1-naphthaldehyde (**113b**)

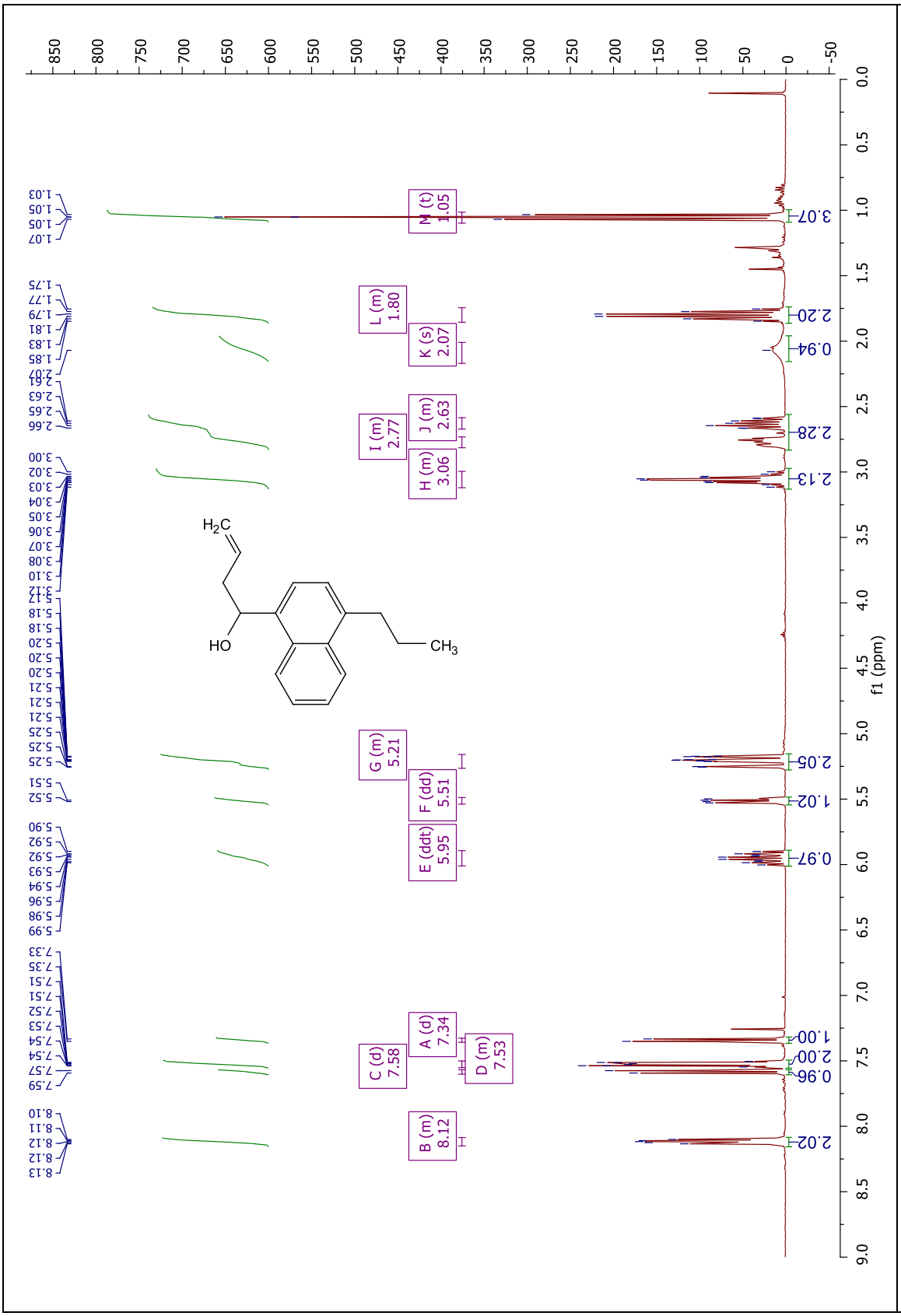

Figure A. 7. ^{1}H Spectra of 1-(4-propylnaphthalen-1-yl)but-3-en-1-ol (**128c**)

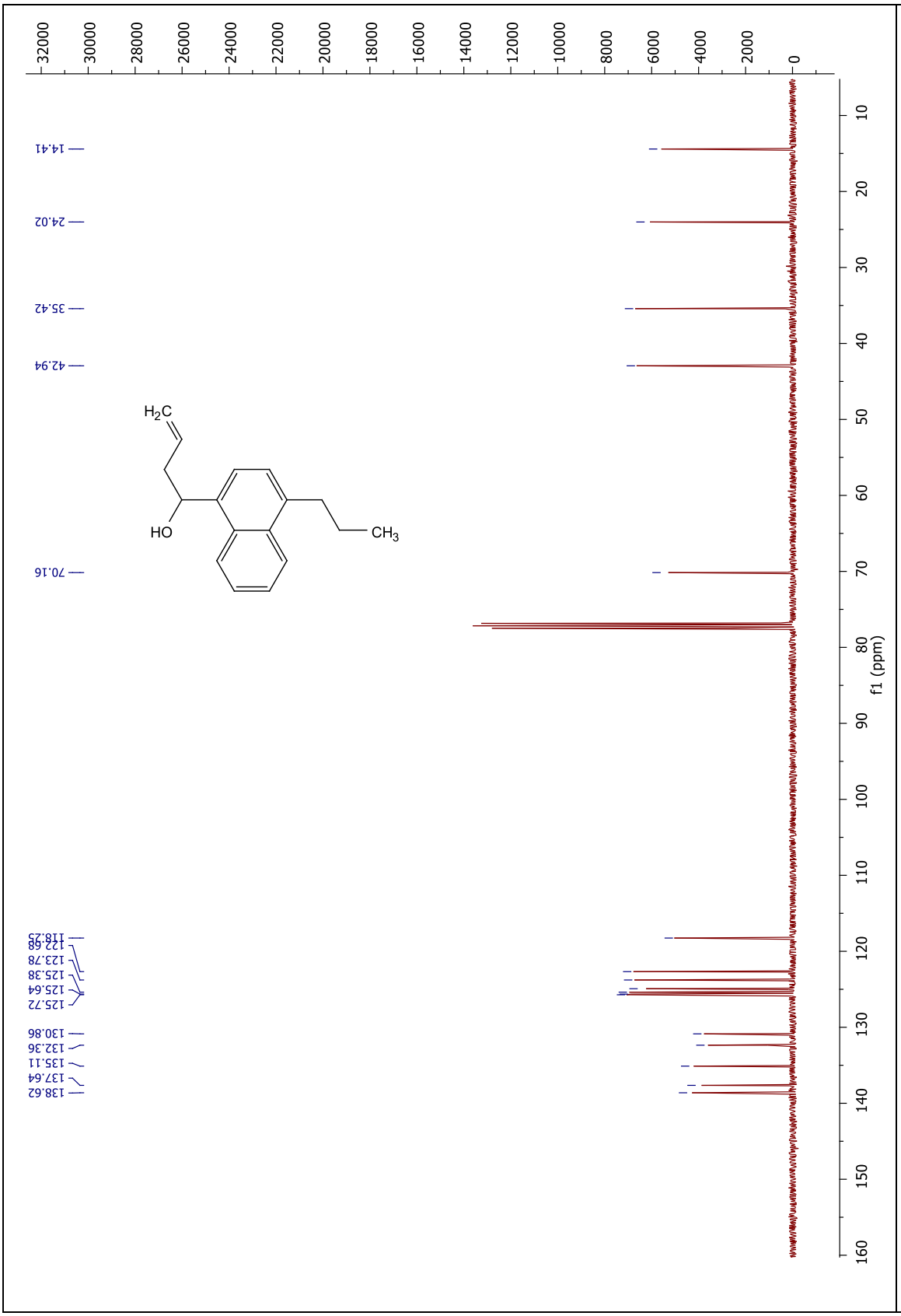

Figure A. 8. ^{13}C Spectra of 1-(4-propylnaphthalen-1-yl)but-3-en-1-ol (**128c**)

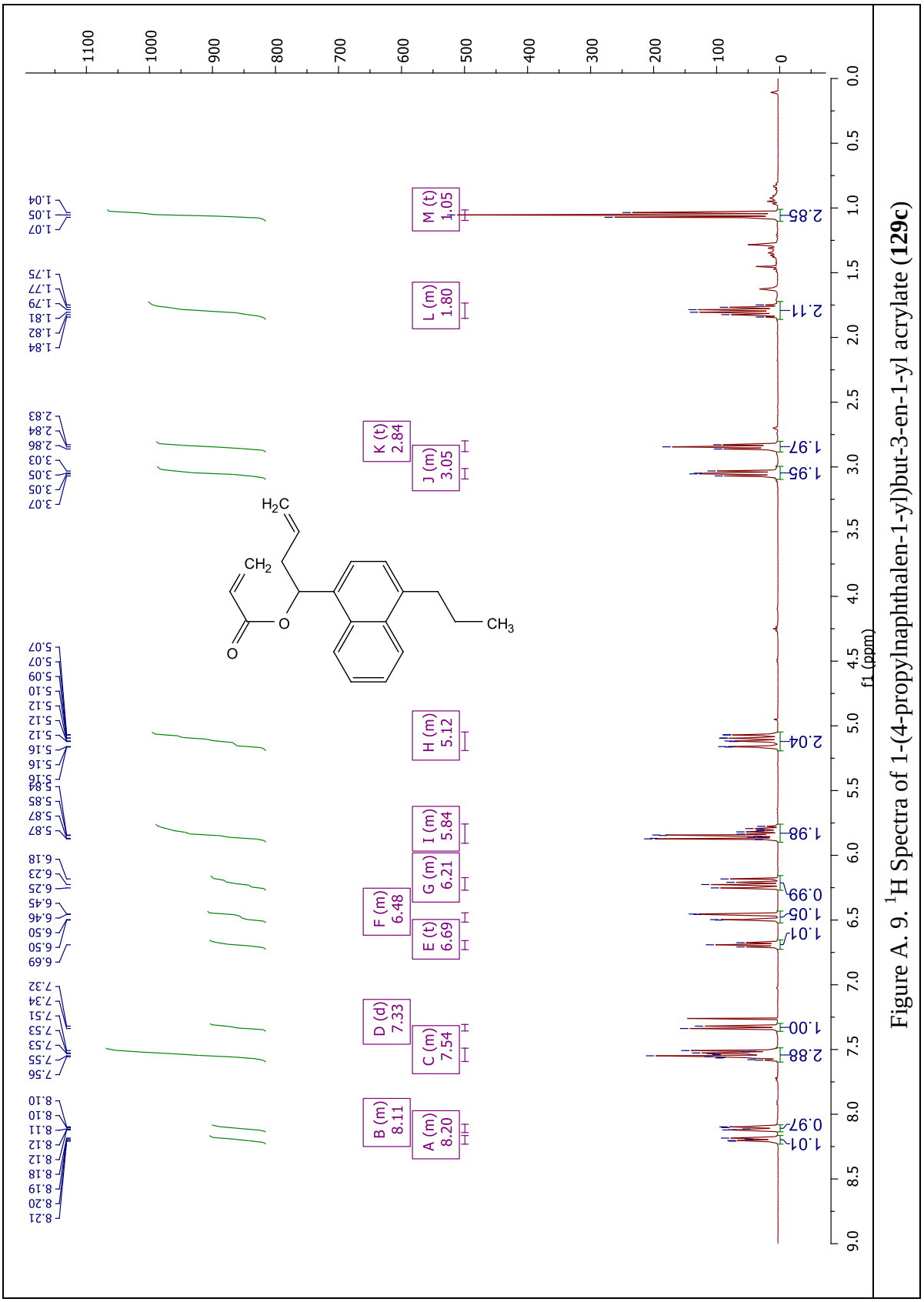

Figure A. 9. ^{1}H Spectra of 1-(4-propylnaphthalen-1-yl)but-3-en-1-yl acrylate (**129c**)

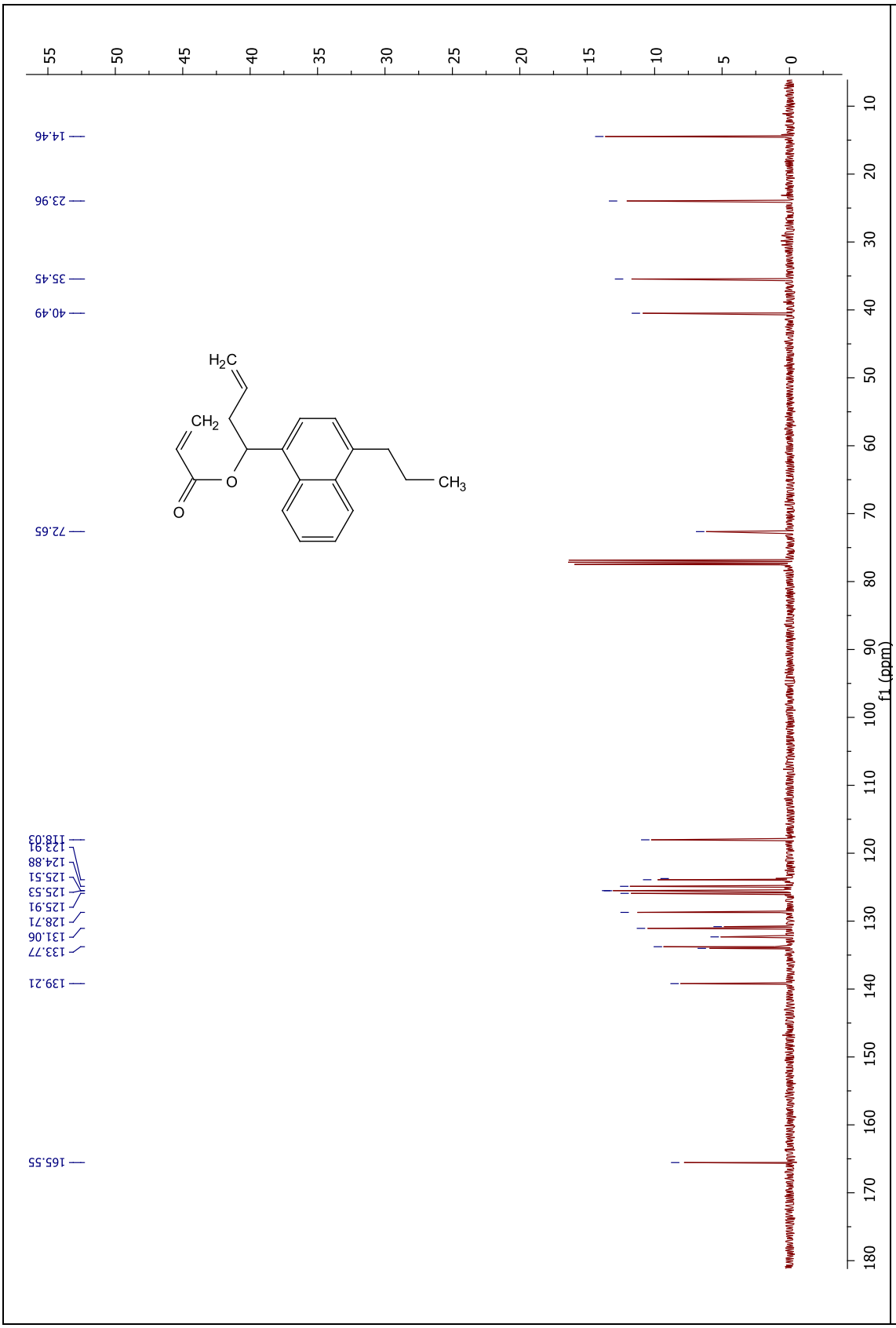

Figure A. 10. ^{13}C Spectra of 1-(4-propylnaphthalen-1-yl)but-3-en-1-yl acrylate (**129c**)

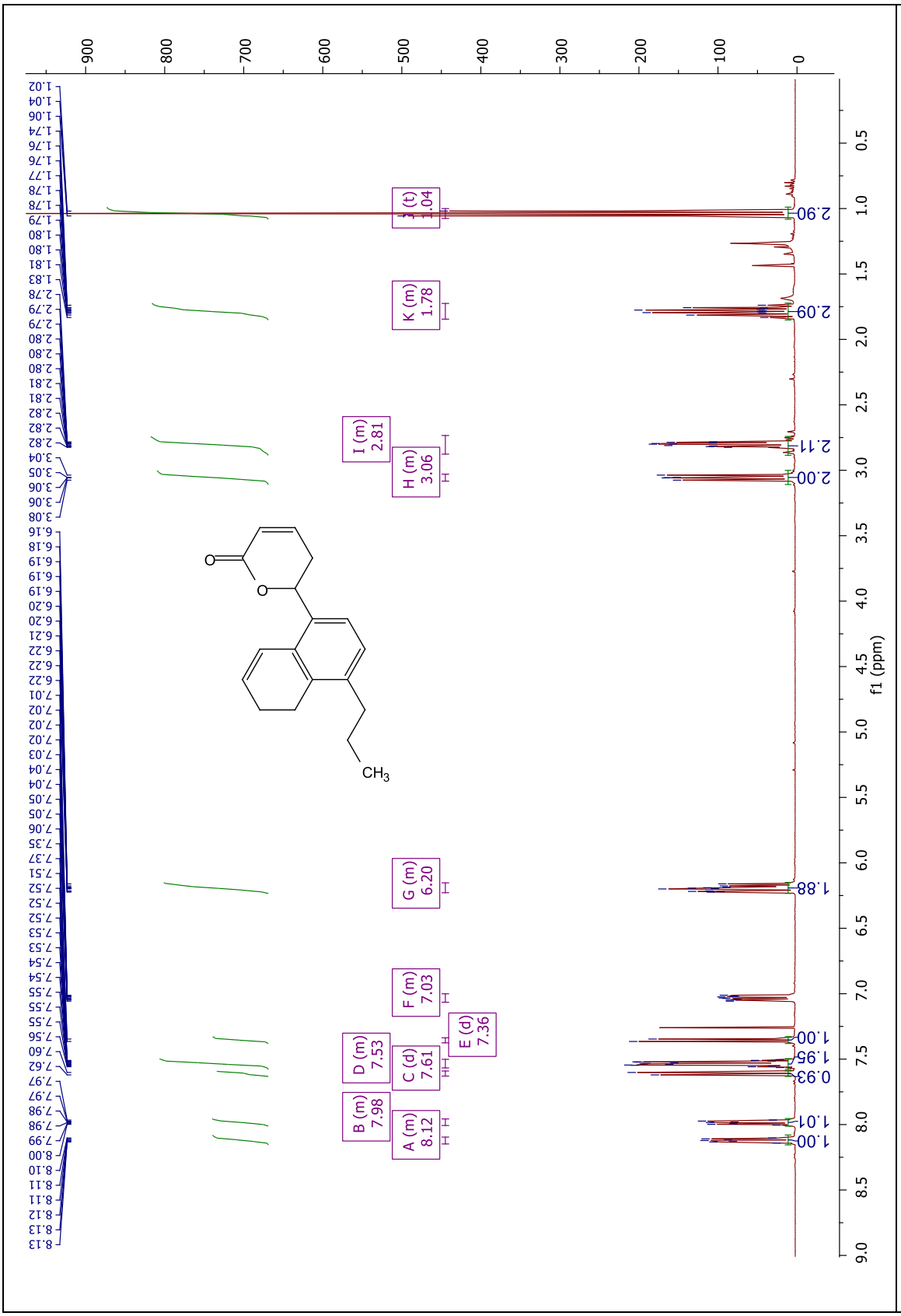

Figure A. 11. ^{1}H Spectra of 6-(4-propylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (**103**)

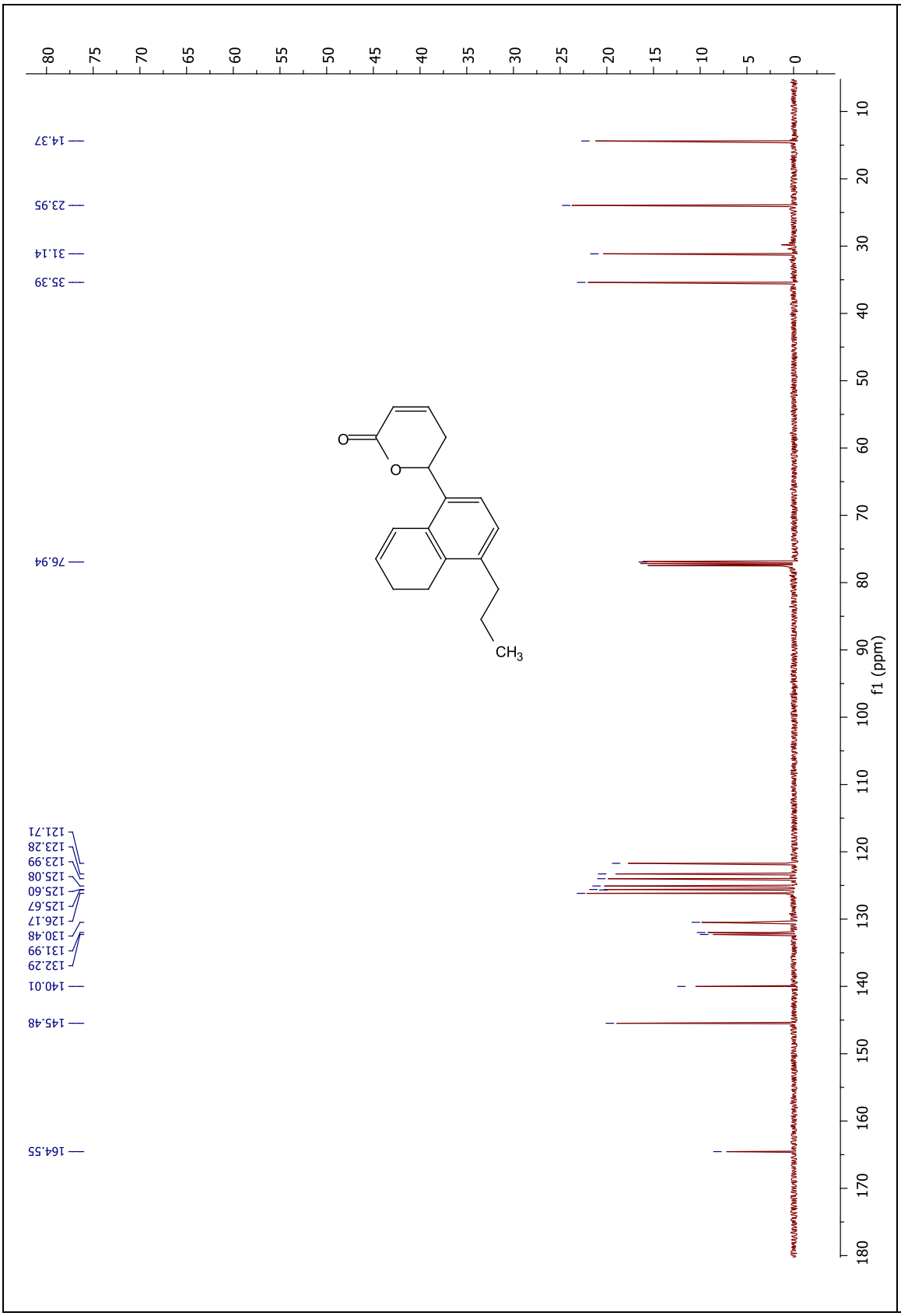

Figure A. 12. ^{13}C Spectra of 6-(4-propylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (**103**)

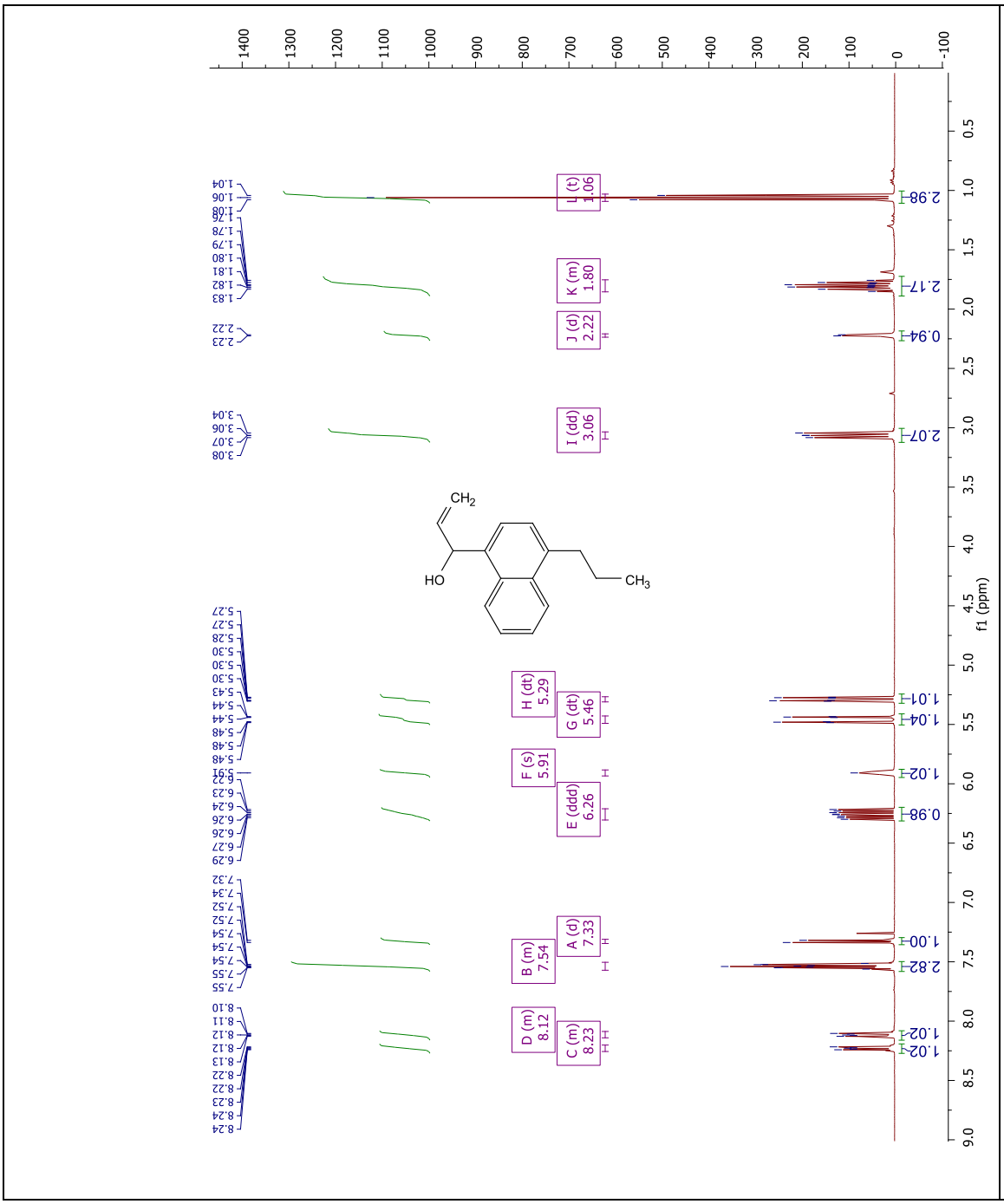

Figure A. 13. ^{1}H Spectra of 1-(4-propylnaphthalen-1-yl)prop-2-en-1-ol (**130c**)

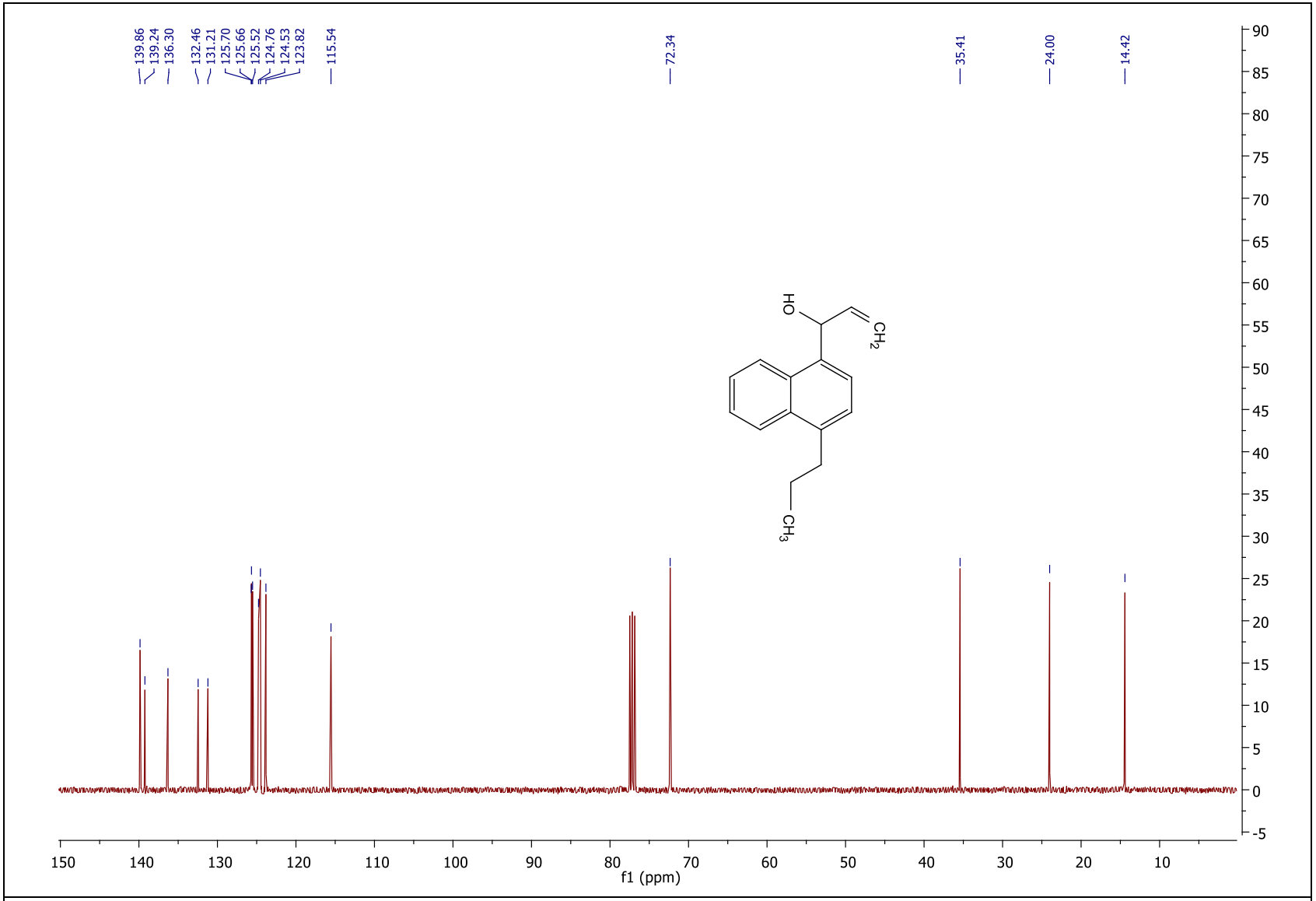

Figure A. 14. ^{13}C Spectra of 1-(4-propylnaphthalen-1-yl)prop-2-en-1-ol (**130c**)

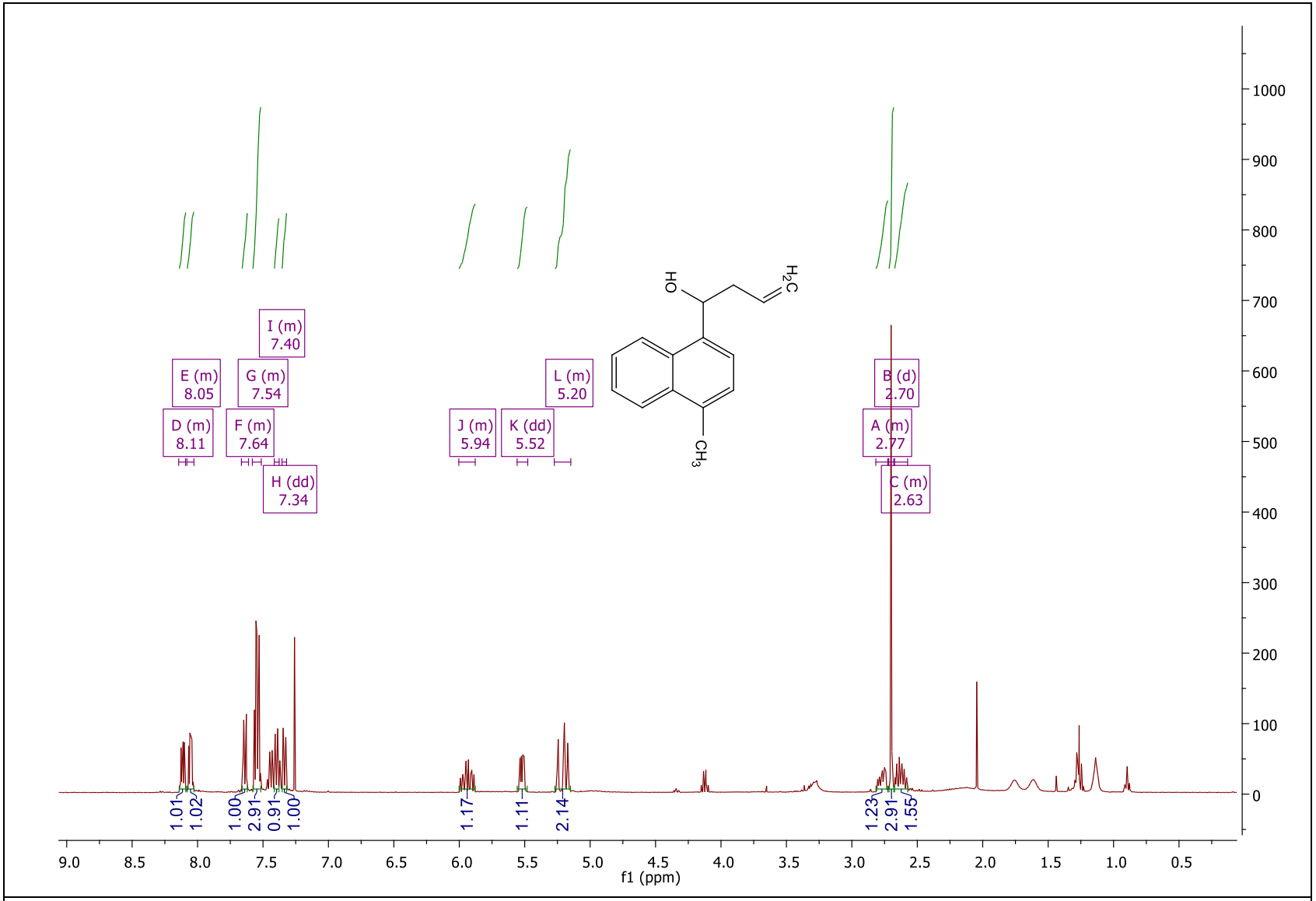

Figure A. 15. ^{1}H Spectra of 1-(4-methylnaphthalen-1-yl)but-3-en-1-ol (**128a**)

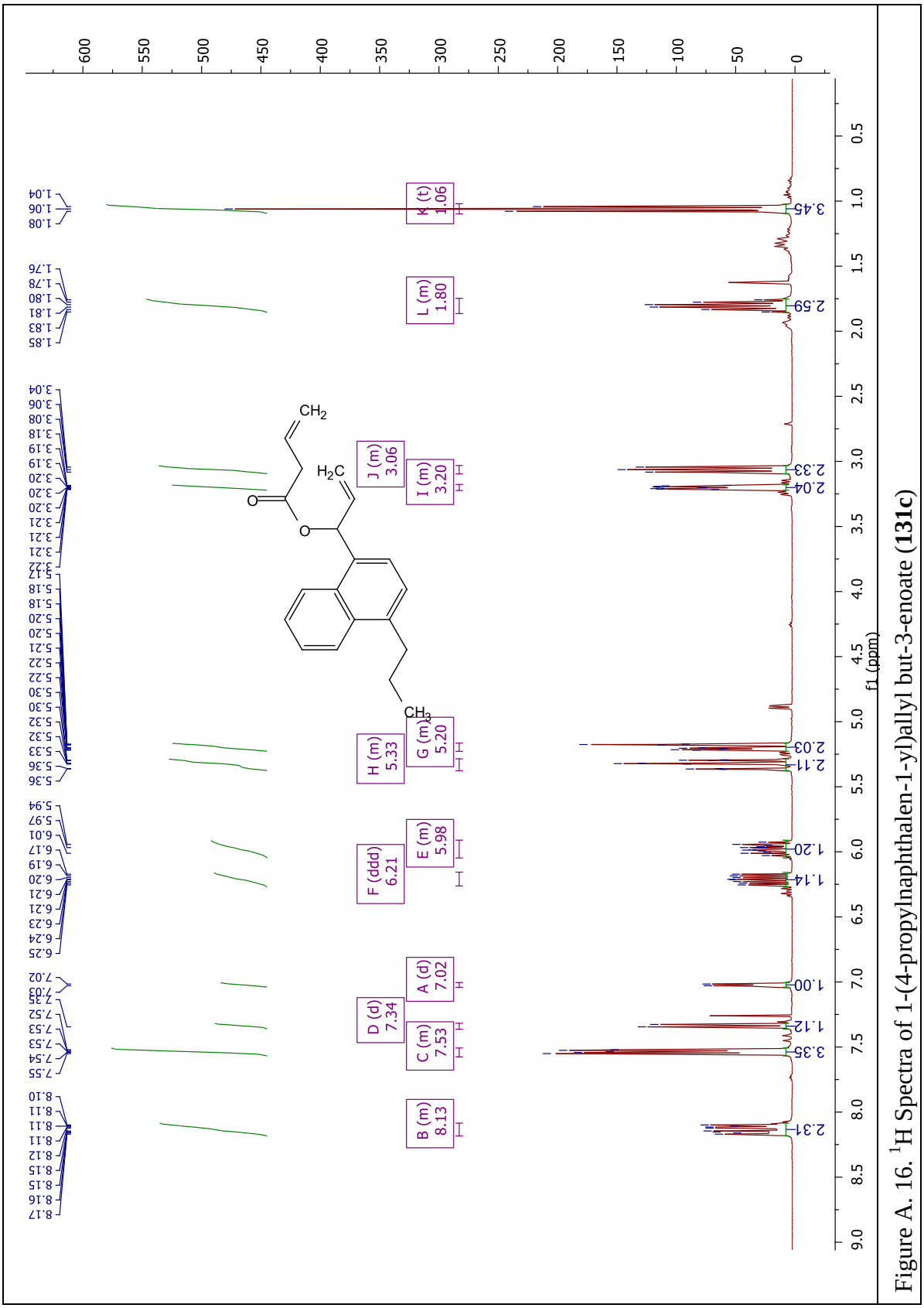

Figure A. 16. ^{1}H Spectra of 1-(4-propylnaphthalen-1-yl)allyl but-3-enoate (**131c**)

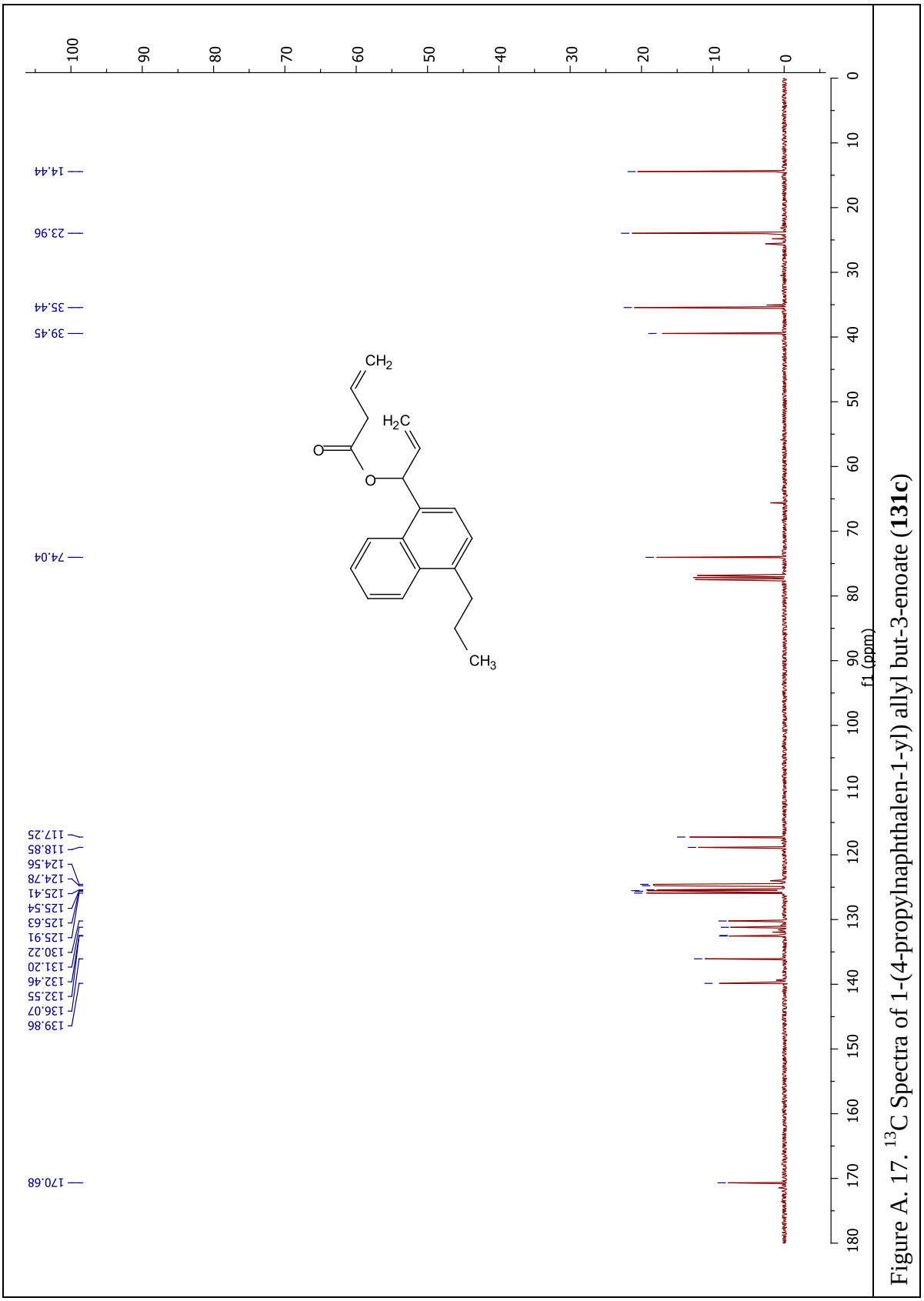

Figure A. 17. ^{13}C Spectra of 1-(4-propylnaphthalen-1-yl) allyl but-3-enoate (**131c**)

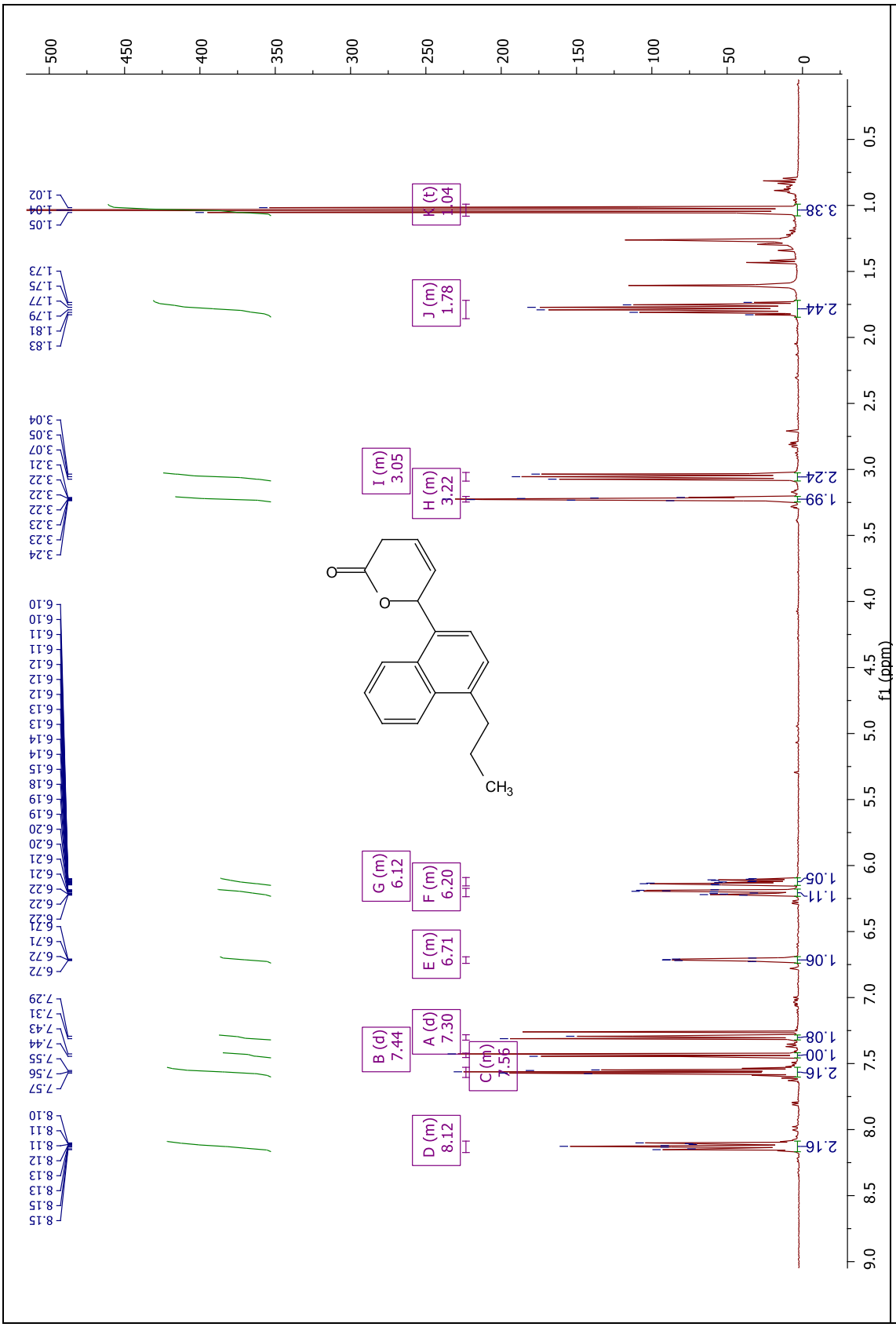

Figure A. 18. ^{1}H Spectra of 6-(4-propylnaphthalen-1-yl)-3,6-dihydro-2H-pyran-2-one (**107**)

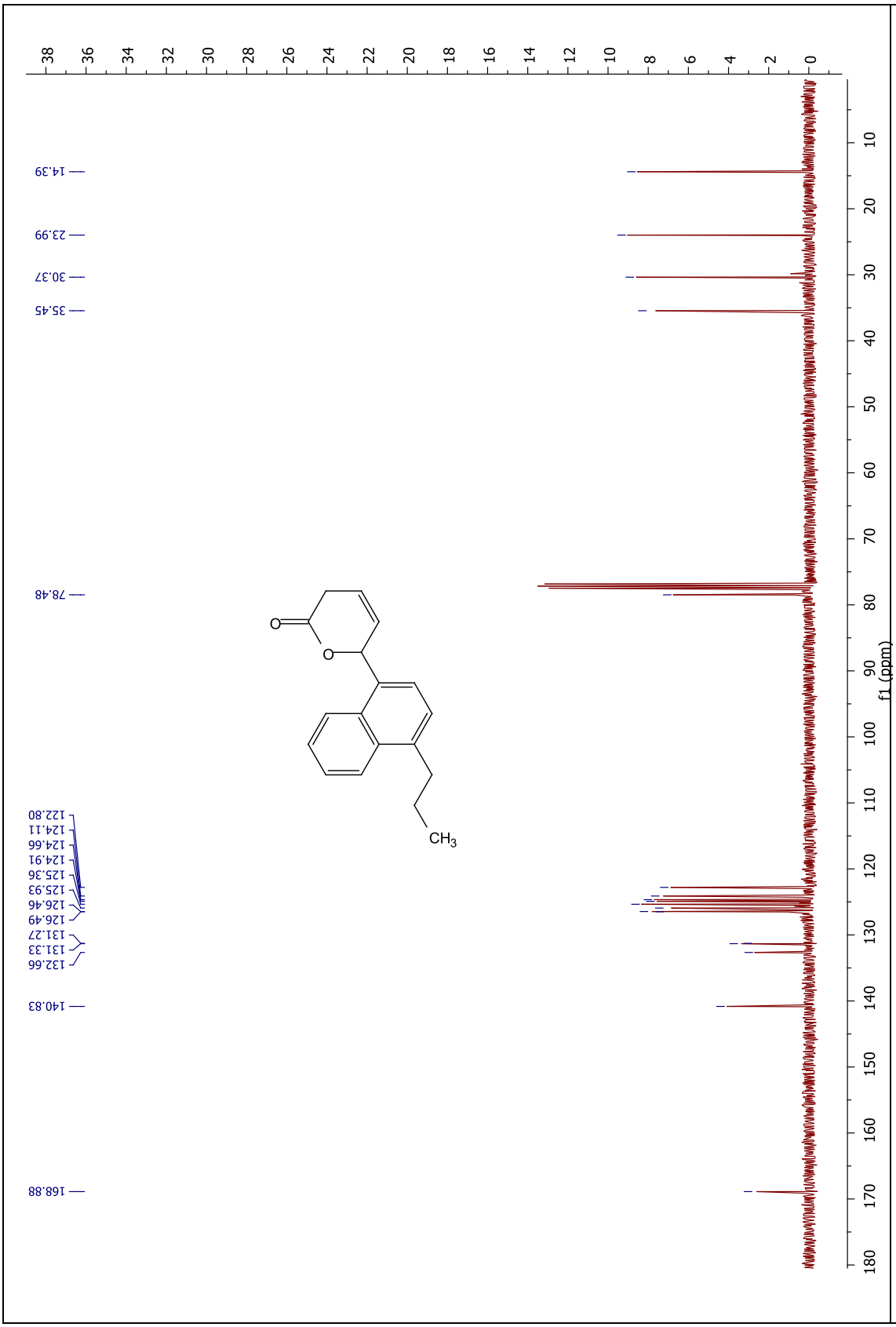

Figure A. 19. ^{13}C Spectra of 6-(4-propylnaphthalen-1-yl)-3,6-dihydro-2H-pyran-2-one (**107**)