SYNTHESES OF NOVEL 4'-ALKYL SUBSTITUTED KLAVUZON DERIVATIVES

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Tuğçe KANBUR

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ABSTRACT

SYNTHESES OF NOVEL 4'-ALKYL SUBSTITUTED KLAVUZON DERIVATIVES

Styryl lactones, which are compounds isolated from natural sources, are known for their cytotoxic property against variety cancer cell lines. Goniothalamin is a well known member of stryl lactones, include α,β-unsaturated δ-lactone in its structure. Being a α,β-unsaturated δ-lactone subunit is an important structural feature. Since, Goniothalamin has a selective cytotoxic property for cancer cell lines with no significant cytotoxic activity toward non-malignant cells. Recent studies show that naphthalen-1-yl substituted α,β-unsaturated δ-lactone derivative has slightly better cytotoxic activity than (*R*)-goniothalamin. As a result of that naphthalen-1-yl substituted α,β-unsaturated δ-lactones derivative was named as klavuzon by Çağır Research group.

In this study it is aimed to synthesize 4'-alkyl substituted klavuzon derivatives. Syntheses were started with the Cu catalayzed addition of Grignard reagents to ethyl 4-(bromomethyl)-1-naphthoate to achieve alkyl substitution. For lactone synthesis a well-known three steps synthesis was used starting from aldehyde. Thus 1-naphthoate esters first reduced to alcohol then oxidized to aldehyde by using $LiAlH_4$ and PCC. These aldehydes were reacted with allymagnesium bromide then formed alcohols were acrylated with acryloyl chloride to yield the corresponding esters. Finally, target molecules were synthesised by ring closing metathesis by using 2^{nd} generation Grubbs' catalyst.

ÖZET

YENİ 4’-ALKİL SÜBSTİTÜELİ KLAVUZON TÜREVLERİNİN SENTEZLERİ

Sitiril laktonlar doğal kaynaklardan izole edilen ve çeşitli canserli hücre hatlarına karşı sahip oldukları sitotoksik etkisi ile bilinen yapılardır. Goniothalamin en bilinen sitiril laktonlardan biri olup yapsında α,β-doymamış-δ-lakton bulundurması sebebiyle değişik kanser hücrelerine karşı yüksek sitotoksiteye sahip olduğu gözlemlenmiştir. Bunun yanında goniothalamin sağlıklı hücreler üzerinde de test edilmiş ve minimal etki gözlemlenmiştir. Son zamanlarda yapılan çalışmalarda 5-aril sübstütientli-α,β-doymamış δ-laktonların (*R*)-goniothalamin yapısından daha sitotoksik olduğu gözlemlenmiştir. Bunun sonucunda naftalen-1-il sübstitüentli α,β-doymamış-δ-laktonlar Çağır araştırma grubu tarafından klavuzon olarak adlandırılmıştır.

Bu çalışmada 4’-alkil substitüeli klavuzon türevlerinin sentezi çalışılmıştır. Sentezler Cu katalizörlüğünde etil 4-(bromometil)-1-naftoata Grignard reaktifi ile benzilik alkilasyon gerçekleştirilerek başlanmıştır. Lakton sentezinde literatürde iyi bilinen ve aldehit ile başlayan üç basamaklı sentez yöntemi kullanılmıştır. Bu sebeple daha önce alkil eklenmiş olan 1-naftoat esterleri $LiAlH_4$ kullanılarak önce alkole indirgenmiş ardından PCC kullanılarak aldehite yükseltgenmiştir. Bu aldehitlere allilmagnezyum bromür ile muamele edilmiş ve elde edilen alkoller akriloil klorür ile akrilat estere dönüştürülmüştür. Son olarak 2. Nasil Grubbs katalizörü yardımıyla sentezlenmesi planlanan α,β-doymamış-δ-laktonlar elde edilmiştir.

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LIST OF ABBREVIATIONS

µL	Microliter
CdC	Carbon-carbon double bond
CtC	Carbon-carbon triple bond
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublet
ddd	Doublet of doublet of doublet
DNA	Deoxyribonucleic acid
dt	Doublet of triplet
HBV	Hepatitis B virus
HCV	Hepatitis C virus
HPV	Human papillomavirus
m	Multiplet
mg	Milligram
mL	Millilitre
nNOS	Neuronal nitric oxide synthase
eNOS	Endothelial nitric oxide synthase
PCC	Pyridinium Chlorochromate
q	Quartet
s	Singlet
t	Triplet
UV	Ultraviolet
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine

CHAPTER 1

INTRODUCTION

Cancer is likely to become the most common fatal disease all around the world. An important characteristic of cancer cells is their uncontrolled proliferation. They don't respond to the normal signals from adjacent cells that indicate that cell division should stop.

Cancer cells don't grow any faster than normal cells but they continue to divide when normal cells would not. For this reason, a cancer can grow rapidly and its demands for nutrients can literally starve the host. Cancer tends to weaken the immune system, making the host more susceptible to infections. In addition, cancers often interfere directly with the functioning of various organs and may cause death in this way.

The science of statistics shows us cancer is becoming the leading causes of mortality worldwide. World Health Organisation announced that approximately 14 million new cases and 8.2 million cancer related deaths were seen in 2012. It is expected that the number of new cases will increase about 70% over the next 2 decades.

Among men, the 5 most common sites of cancer diagnosed in 2012 were lung, prostate, colorectum, stomach, and liver cancer. Among women the 5 most common sites diagnosed were breast, colorectum, lung, cervix, and stomach cancer.

Cancer can be triggered by many reason, and people having genetic predisposition and characteristic chromosomal aberrations are usually associated with cancer. Regrettably, in daily life human can take carcinogenic chemical compounds from their eatings, drugs, parfumes and many other daily use goods. Certain viruses can also be the reason of cancer disease. Additionally there is no doubt about radiation leading cancer by demaging the DNA. There is a distinct relation between skin cancer and the UV rays in sunlight. As a result of spending too much time in the sun, people get skin cancer.

The risk of cancer increases explicitly with age. In adults, diabetes, hypertension, low fruit and vegetable intake, lack of physical activity, and being overweight or obese increase the risk of several types of cancer. In addition to that the most important risk

factors of cancer is tobacco smoking and alcoholism. For example 20% of global cancer deaths and around 70% of global lung cancer deaths are caused by tobacco use.

Up to 20% of cancer deaths are caused by cancer resulting from viral infections such as HBV/HCV and HPV in low and middle income countries which are especially in Africa, Asia and Central and South America where more than 60% of world's total new annual cases occur in. Additionally, these regions correspond %70 of the World cancer deaths. It is anticipated that sessional cancer cases within the next 2 decades will increase from 14 million to 22 million. ("World Health Organization Report 2014,")

Household surveys are significant source of data on risk factors and health-related behaviours. It is an undeniable fact that, quality of the sampling frames and methods used on interviewer training, data-quality assurance procedures directly affect the reliability of these estimations. For this reason, during curing cancer period, the most important thing is being removed or destroy all the malignant cells from the patient's body.

American Cancer Society categorize cancer treatment such as surgery, chemotherapy, radiation therapy, immunotherapy, targeted therapy, hyperthermia and many others. Chemotherapy plays a central role in curing the disease or considerably prolonging and improving the patient's quality of life. National Cancer Institute define chemotherapy is a type of cancer treatment that uses small compounds to destroy cancer cells. Sometimes, chemotherapy can be used alone to treat patients but more often, it is used along with surgery, radiation therapy, or biological therapy. ("American Cancer Society,")

Chemotherapy can be used before surgery or radiation therapy to make the tumor smaller. After surgery or radiation therapy it is used to destroy cancer cells that may remain. This is called adjuvant chemotherapy. Chemotherapy also can help radiation therapy and biological therapy work better. It prevent cancer cells that have come back (recurrent cancer) or spread to other parts of your body (metastatic cancer).

We know that plants and plant products are used for treatment of many diseases instead of drugs or medicines in traditional medicine. *Cassia auriculata* (Family; *Caesalpinaceae*) is used medicine to treat diseases namely, helminthes infection, eye diseases, diabetes and skin problems in Asia. For example diabetic patients use this plant to cure diabet by drinking their dried flovers as tea or consuming their seeds because this parts of *Cassia auriculata* have anti-diabetic activity and emollient effect. (Esakkirajan et al., 2014)

In this regard, natural products are great source for the discovery and the development of new compounds for cancer treatment. (Barcelos et al., 2012) Today there are at least 120 known chemical substances extracted from plants that are accepted as important drugs and active ingredients. (Esakkirajan et al., 2014).

Goniothalamin **(1)** is natural compound which has styryl lactone in its structure, was first isolated in 1967 by Hlubucek from *Cryptocarya caloneura* (Hlubucek and Robertson 1967). In many countries of the world, its species have been used in traditional medicine to treat illnesses. (Choo, Abdullah, & Diederich, 2014).

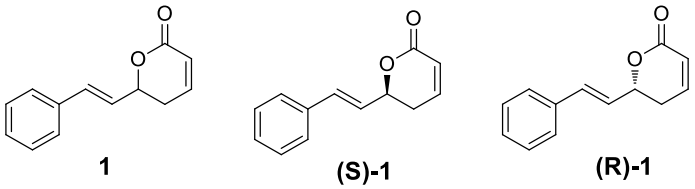


Figure 1.1. Structure of goniothalamin derivatives and its sterioisomers

Goniothalamin is a derivative member of styrly lactone. Goniothalamin derivatives were sythesised by many research groups as well as our group. Naphthalen-1-yl substituted α,β-unsaturated δ-lactone derivative **(2)** has slightly better cytotoxic activity than (R)-goniothalamin. As a result of that naphthalen-1-yl substituted α,β-unsaturated δ-lactone derivative was named as klavuzon **(2)** by Çağır research group.

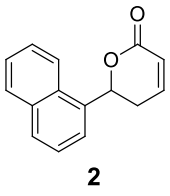


Figure 1.2. Structure of klavuzon

In this study we aimed to synthesize novel 4'-alkyl substituted klavuzon derivatives and their anti-proliferative activities over the cancer cell lines will be investigated in near future.

1.1. Biological Activities of α,β-Unsaturated δ-Lactones

Nearly %40 of the all drugs that have been approved over the last years are the derivatives of natural products so it is surely beyond doubt that nature is an important resource for natural drugs. Therefore, when it is compared the number of all plant types on earth and the number of plants which are thoroughly used for their potential value as a source of drug. It can be clearly seen that the number of plants used for this purpose is too restricted, but all of these challenges can be ignored because nature is essential source for mankind to develop new drugs. Additionally, lots of drug are synthesized to be inspired by natural products.

A well-known pharmacophore, α,β-unsaturated δ-lactones are a common structural unit found in a large number of natural products that have a wide range of biological activities. The α,β-unsaturated δ-lactone functionality is assumed to be responsible for the biological activities because of its Michael acceptor property, enabling these molecules to bind covalently to a target enzyme. (Enders & Steinbusch, 2003)

Michael acceptors, possess a wide range of reactivity. Carbon-carbon double (CdC) or triple (CtC) bonds next to an electron-withdrawing substituent are characterizated by Michael acceptors. As a result of that a polarizable electron density at the π-bond occur, where the β-carbon atom is positively polarized which makes molecule the preferred site of an attack for soft nucleophiles. (Schwöbel et al., 2010)

Michael acceptors can also form covalent bonds to nucleophilic sites of proteins and DNA in biological organisms, resulting in diseases such as carcinogenicity, allergic contact dermatitis, and excess toxicity (as compared to the unspecific narcosis or baseline toxicity) toward aquatic organisms. (Mulliner, Wondrousch, & Schuurmann, 2011)

1.1.1. Goniothalamin

Goniothalamin **(1)** is natural styryl lactone was first isolated in 1967 by Hlubucek from *Cryptocarya caloneura* (Hlubucek and Robertson 1967). Goniothalamin **(1)** (5,6-dihydro-6-styryl-2-pyranone, GN; Fig. 1) is also derived from the skin, bark, roots and

leafs of *Goniothalamus spp*. It is commonly found in Malaysia and traditionally it is used to treat various ailments such as cold, fever, malaria and cholera. In addition to that it has been used as arbortifacient to stop pregnancy in Malaysia. (Chan et al., 2006).

Goniothalamin shows variety of biological activities, such as antitumor, antibacterial, antifungal or immunosuppressive properties. Being α,β-unsaturated δ-lactone family is an important structural feature. (Enders & Steinbusch, 2003)

Compounds **(*R*)-1** and **(*S*)-1** were cytotoxic to cultured 786-0 kidney cancer cells, inhibited the activity of constitutive NOS and decreased the expression of nNOS and eNOS. Compound **(*R*)-1** caused cell death primarily by apoptosis whereas **(*S*)-1** caused cell death primarily by autophagy. **(*S*)-1** was generally more potent in producing these alterations than **(*R*)-1**. These findings highlight the importance of using enantiomers to study the biological activities of agents with potential therapeutic applications. (de Fátima et al., 2008)

In the context of antiproliferative activity, Xiao and co-workers reported selectivity of goniothalamin **(1)** on both drug-resistant and transformed hepatocytes when compared to a primary cell line. (de Fátima, Marquissolo, de Albuquerque, Carraro-Abrahão, & Pilli, 2006) Pilli and co-workers prepared new analogs of goniothalamin and evaluated them in a panel of eight cancer cell lines leading to potent derivatives against kidney cancer cells and adriamycin resistant breast cancer cells. Goniothalamin has been reported to selectively trigger caspase induced apoptosis in cancer cells, with minimal activity on normal cell lines. Interestingly, up-regulation of p53 has been observed in goniothalamin treated rats. (de Fátima et al., 2006) In all these studies, the exact mechanism of action and the target of goniothalamin **(1)** remained unclear. (Wach, Guttinger, Kutay, & Gademann, 2010)

The crucial point is that goniothalamin has no significant cytotoxic activity toward non-malignant cells (Wach et al., 2010) additionally it acts mainly on malignant cells (HL-60 and CEM-SS cells) (Rajab et al. 2005).

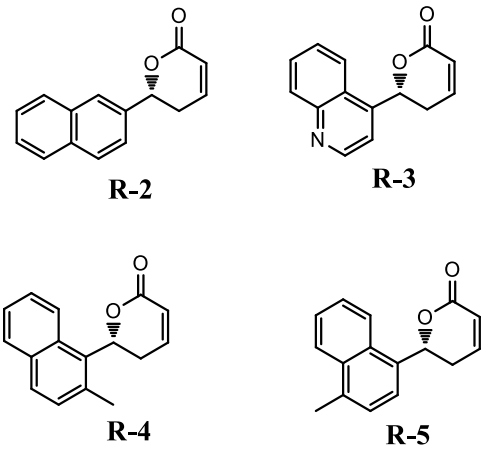


Figure 1.3. Structures of the previously synthesized 6-bicycloaryl substituted 5,6-dihydro-*2H*-pyran-2-ones **(2-5)**

Çağır and co-workers prepared and evaluated a series of naphthalene-1-yl and naphthalene-2-yl derived unsaturated lactones **(2-5)** in order to better understand the role of the exo double bond of goniothalamin in the antiproliferative activity. It was observed that compound ***R*-2** and ***R*-3** had slightly better and compounds ***R*-4** and ***R*-5** had much higher antiproliferative activities against prostate (PC-3) and breast (MCF-7) cancer cell lines compared to *R*-goniothalamin **(*R*)-1**, which may be related to higher conformational restriction or steric hindrance due to the naphthalene-1-yl and naphthalene-2-yl substituents. Interestingly, 1-naphthyl substitution in the lactone ring dramatically enhanced the cytotoxic activity, especially when it posses a methyl group in the 2'- or 4'- positions. For example, analogue ***R*-5** was 80- and 40-fold more potent against PC-3 and MCF-7 cells respectively, in comparison with *R*-goniothalamin **(*R*)-1**. (Kasaplar, Yilmazer, & Cagir, 2009)

1.2. Synthesis of α,β-Unsaturated δ-Lactones

As summarized above α,β-unsaturated δ-lactone derivatives are valuable compounds because of their potential biological activities. Since their discover many derivatives of that were synthesized. In this part of the thesis a short summary of racemic and asymmetric synthesis of α,β-unsaturated δ-lactone derivatives will be discussed.

1.2.1. A Three Step Synthetic Method for α,β-Unsaturated Lactones

The most well known three step procedure for the synthesis of α,β-unsaturated δ-lactones is shown in figure 1.4. Different aldehydes **6** was treated with allyl magnesium bromide or allyl zinc bromide to obtain an allyl alcohol **7**. The R groups included naphthalene, quinoline, benzene, substituted benzene (methyl and methoxy groups at the ortho-, meta-, and para-positions), benzofuran, benzothiophene, furan, thiophene, benzyloxy, styryl, diphenyl, and adamantine. Acrylic acid was introduced to form an acrylate ester under basic conditions. Finally the formation of the α,β-unsaturated lactone **9** was achieved with the help of second-generation Grubb's catalyst via a ring-closing metathesis. (Lee, Lee, Kim, & Ko, 2011) (Figure 1.4.)

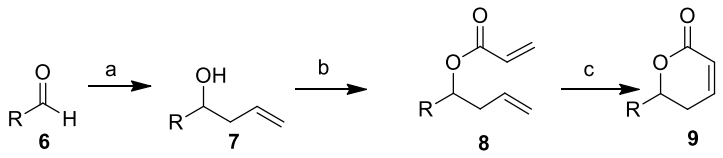


Figure 1.4. The synthesis of racemic α,β-unsaturated lactones by a well known three steps procedure

Reagents and conditions: (a) AllylMgBr or allylZnBr, (THF), 0 ^{o}C, rt; (b) TEA, EDC, acrylic acid, DCM, rt 12 h; (c) Grubb's catalyst 2nd generation, DCM, rt 8 h.

1.2.2. Asymmetric Allylboration

In this study Reddy, et al. reported the synthesis of a pyranone containing molecules via an asymmetric allylboration-ring-closing metathesis strategy. Allylboration of trans cinnamaldehyde (**10**) was performed with (-)-*B*-allyldiisopinocampheylborane in Et_2O–pentane mixture at -100 °C for 1 h with 76% yield of compound **11** in 96% ee. This product was used in the following steps without purification because the additional product of oxidation (isopinocampheol) did not disrupt other reactions that it was not separated until after the ring-closing metathesis reaction. Compound **11** was treated with with acryloyl chloride and base to provide an 80% yield of the corresponding acryloyl ester **12**, along with isopinocampheyl acrylate.

Mixture was treated with 10% of Grubbs' catalyst **20** in refluxing DCM for 12 h with 84% isolated yield. The enantiomeric excess of **(*S*)-1** was not affected during these processes. (Ram Reddy, Brown, & Ramachandran, 2001)

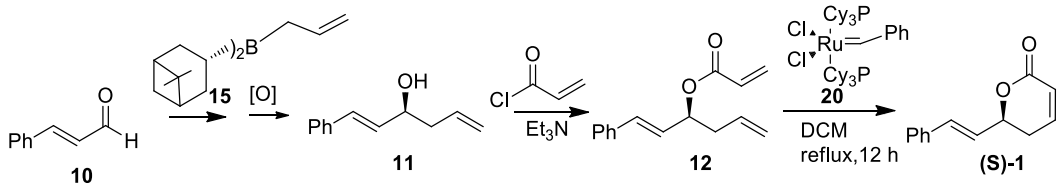
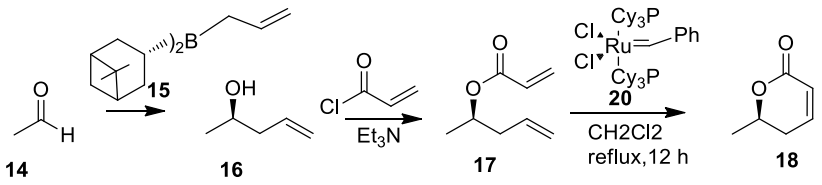


Figure 1.5. Asymmetric synthesis of (S)-goniothalamin **(S)-1** starting with allylboration with (+)-*B*-allyldiisopinocampheylborane

1.2.3. Asymmetric Synthesis

Ramachandran and coworkers were reported the synthesis of optically active lactones inter- and intra-molecular asymmetric reduction with *B*-chlorodiisopinocampheylborane (DIP-Chloride™) in high enantiomeric excess (ee). Optically active homoallylic alcohols were formed via allylboration of aldehydes with *B*-allyldiisopinocampheylborane (**15**). Before the ring-closing metathesis reaction to form lactone, acrylation of asymetric homoallylic alcohol was required. (Figure 1.6.)

For the allylboration of acetaldehyde (**14**) (+)-*B*-allyldiisopinocampheylborane ((+)-**15**), was used, in an Et_2O pentane mixture at –100 °C to afford (*S*)-(+)-4-penten-2-ol (**16**) in 94% ee. Compound **16** was treated with acryloyl chloride for esterification and it provide an 80% yield of the corresponding acryloyl ester **17**. Then 10% of **14** was in refluxing DCM for 6 h provided compound **18** in 81% yield. (Mohideen et al., 2013)



Figue 1.6. Asymmetric synthesis of compound **18**

1.2.4. Hydrozirconation–Carbonylation

Sabitha and coworkers reported the asymmetric synthesis (R)-tuberolactone (**19)** (Figure 1.7.). The syntheses of tuberolactone, jasmine lactone and decalactone began with the known epoxide **20**, prepared by Jacobsen's hydrolytic kinetic resolution method. Enantiomerically pure epoxide (**20)** was treated with lithium acetylide therefore opening of epoxide was oberved and homopropargylic alcohol (**21)** was formed. Alkylation of homopropargylic alcohol (**21)** was performed with ethylbromide to produce alkylated compound (**22)** in 68% yield. The secondary alcohol in compound (**22)** was silylated by using TBDMSCl and imidazole in DCM to afford compound **23**. With the help of DDQ, PMB was removed and compond **24** was obtained and then oxidized to corresponding aldehyde (**25). (Dupont & Donato, 1998)**

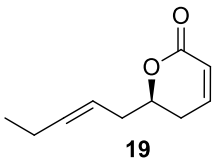


Figure 1.7. Structure of (R)-tuberolactone

Aldehyde (**25)** was exposed to Still–Gennari modification (Still & Gennari, 1983) of the Horner–Emmons reaction (Wadsworth, 2004) to form Z-unsaturated carboxylic ester **(26)**. Treatment with p-TSA (in methanol) catalayzed the cyclization of ester to afford lactone **(27)** in situ by deprotection of TBDMS group.

This key intermediate was utilized for the synthesis of (R)-tuberolactone **(19)**. Thus, partial hydrogenation of the triple bond in compound **27** over Lindlar's catalyst afforded compound **19** in 88% yield.

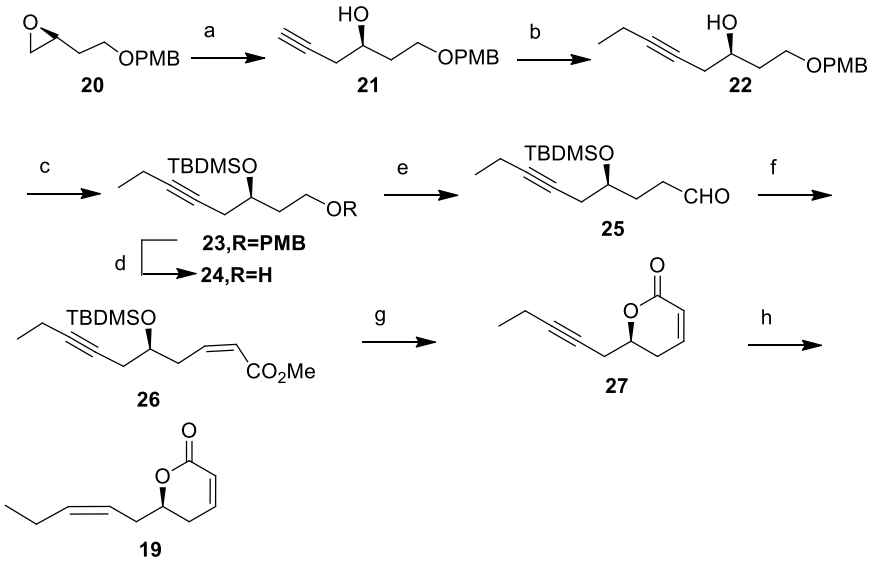


Figure 1.8. Asymmetric total synthesis of (R)-tuberolactone

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, ^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 cat., EtOAc, quinoline, 2 h.

1.2.5. Total Syntheses via Catalytic Enantioselective Allylation of Aldehydes

Catalytic enantioselective allylation of aldehydes which is one of the fundamental and powerful C-C bond forming reactions, attracted considerable attention in asymmetric synthesis. Specifically, Maruoka and co-workers have developed a new class of highly selective titanium complexes for the allylation of aldehydes. The μ-oxo bis(binaphthoxy)(isopropoxy)-titanium complex (*S*,*S*)-**A 28** (Figure 1.9.), which display excellent enantioselectivity for the addition of allyltributyltin to aldehydes, including cinnamaldehyde. The efficiency of this catalyst is proposed to be due to simultaneous coordination and double activation ability of the bidentate Ti(IV) catalyst (*S*,*S*)-**A 28**.

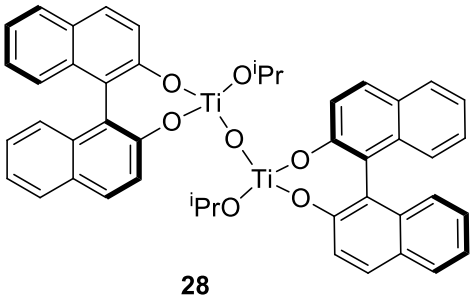


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Figure 1.9. The μ-oxo bis(binaphthoxy)(isopropoxy)titaniumcomplexes **(S,S)-A 28** developed by Maruoka and co-workers

In this study, the total synthesis of argentilactone (**29**) and goniothamin **(R)-1** (Figure 1.10.) from 1-heptyne and *trans*-cinnamaldehyde was described respectively, featuring enantioselective Maruoka allylation and ring-closing metathesis as the key steps.

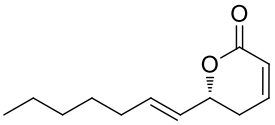

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Figure1.10. Structures of (R)-argentilactone (**29**)

Propargylic aldehyde **31** was prepared from 1-heptyne **(30)** by treating with *n*-BuLi, followed by addition of DMF. Despite the recent developments in the catalytic asymmetric allylation catalyzed by chiral Lewis acids, no successful example with propargylic aldehydes has yet been reported. In this case, the enantioselective addition of allyltributyltin to propargylic aldehyde **31** was performed with in situ generated chiral (*R*,*R*)-**A 28** complex in dichloremethane, −20 °C for 24 h, to afford compound **32** with 86% ee. After conversion of propargylic alcohol **32** to (*Z*)-allylic alcohol **33** with the help of Lindlar's catalyst and quinoline in EtOAc:1-octene (1:1, v/v) with 74% yield, ring-closing metathesis of ester (**34)** was performed with 10 mol% of Grubbs' catalyst in refluxing DCM for 6 h provided argentilactone (**29**) in 25% overall yield from compound **30** (Figure 1.11.). Total synthesis of goniothalamin was also proved with the same methodology. (Mohideen et al., 2013)

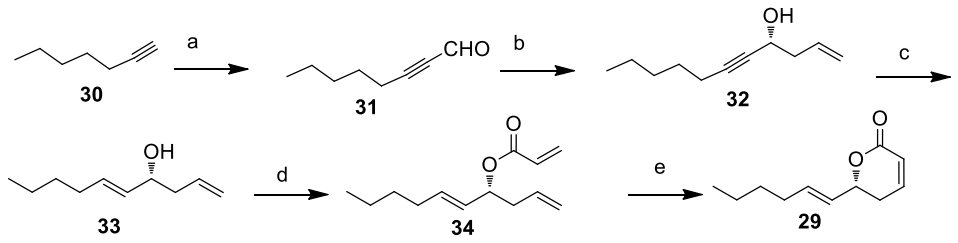


Figure 1.11. Total synthesis of (R)-argentilactone (**29**)

Reagents and conditions: (a) *n*-BuLi, Me_2NCHO, THF −78 to 0 °C; (b) (*R*)-BINOL, $Ti(O_iPr)_4$ (15 mol%), $TiCl_4$ (5 mol%), Ag_2O (10 mol%), allyltributyltin (1.1. equiv.), DCM, −20°C, 24 h; (c) Lindlar's catalyst, quinoline, EtOAc:1-octene (1:1); (d) acryloyl chloride, Et_3N (3.6 equiv.), DCM, 0 °C; (e) Grubbs' catalyst, DCM.

Catalytic asymmetric allylation of *trans*-cinnamaldehyde (**35**) with allyltributyltin was performed in the prescence of catalytic amount of chiral (*R*,*R*)-**A 28** complex, prepared in situ (DCM, −20°C, 24 h). As a result of that compound **36** was synthezied with 78% yield and 96% ee. After conversion of allylic alcohol **36** to acrylate ester **37** with acryloyl chloride, Et_3N, cat. DMAP in dichloromethane at −23 °C in 80% yield. When compared to other catalytic asymmetric allylation methodology, the one developed by Maruoka and co-workers preseted higher level of enantioselection in the addition of allyltributyltin to *trans*-cinnamaldehyde.

Ring-closing metathesis of **37** was performed with 10 mol% of Grubbs' catalyst in refluxing DCM for 12 h (98% yield) to provide goniothalamin **(*R*)-1** in 61% overall yield from cinnamaldehyde (Figure 1.12.).

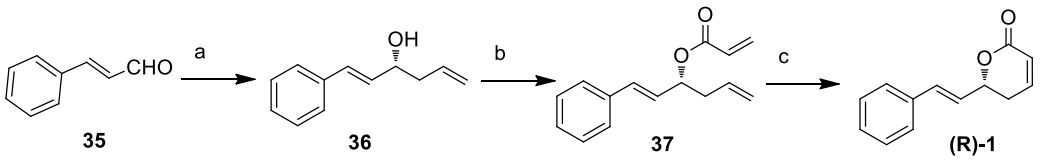


Figure 1.12. Asymmetric synthesis of (*R*)-goniothalamin **(R)-1** with R-BINOL-Ti complex

Reagents and conditions: (a) (*R*)-BINOL (10 mol%), $Ti(O_iPr)_4$ (15 mol%), $TiCl_4$ (5 mol%), Ag_2O (10 mol%), allyltributyltin (1.1. equiv.), DCM, −20 °C, 24 h; (b) acryloyl chloride (1.8 equiv.), Et_3N, DCM, 0 °C; (c) Grubbs' catalyst, DCM.

1.2.6. Chemoenzymatic Synthesis of Goniothalamin

Lipases are the most widely existing enzymes because of being cheap and readily available from many different sources, additionally, they show high enantioselectivity for a broad range of substrates and high stability in organic solvents. (Gruttadauria, Lo Meo, & Noto, 2004)

Gruttadauria, et al. improved the three step synthesis of goniothalamin by ring closing metathesis after enzymatic kinetic resolution in the presence of vinyl acrylate. In this study, the racemic allylic alcohol **38** was used as starting material and the resolution of that was carried out with PS-C Amano II lipase to form the ester of (*S*)-enantiomer. After purification, the pure ester **12** was treated with the 1st generation Grubbs' catalyst. In this study to improve the yield, alcohol **(*R*)-38** were converted back to racemic **38**. The starting racemate was achieved in one pot synthesis while treating with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in diethyl ether and then adding methanol and $NaBH_4$ (Figure 1.13.).

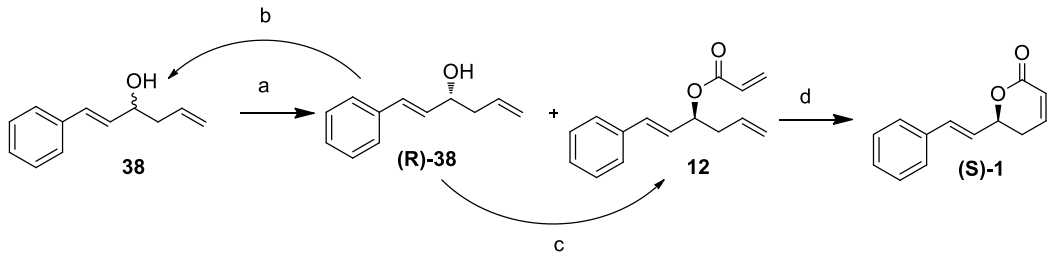


Figure 1.13. Asymmetric synthesis of (*S*)-goniothalamin **(*S*)-1** with chemoenzymatic synthesis

Reagents and conditions: (a) PS-C Amano II, solvent, vinyl acrylate, 25 ^{o}C, 24 h; (b) 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ), diethyl ether, then CH_3OH, $NaBH_4$, rt; (c) PPh_3, DEAD, acrylic acid, toluene, 0 ^{o}C – rt, 20 % ee; (d) $(PCy_3)_2Cl_2Ru$=CHPh, $Ti(OiPr)_4$, DCM, 18 h, reflux.

1.2.7. Lipase Catalyzed Resolution and Alkene Metathesis

In this study combination of enzymatic trans esterification and alkene metathesis was performed in two steps (Sundby, et al. 2004). First of all, racemic alcohol **38** was prepared with allylmagnesium bromide addition to cinnamaldehyde. The racemic alcohol **(38)** was kinetically resolved by a transesterification reaction using vinyl acrylate as acyl donor and Candida antarctica lipase B (CALB) as catalyst in hexane. After separation of the products, preparation of the unsaturated lactone, goniothalamin **(S)-1** was prepared with the help of 8 mol% of 1st generation Grubbs' catalyst via a ring closing metathesis reaction in 92% yield. (Sundby, Perk, Anthonsen, Jorgen Aasen, & Vidar Hansen, 2004)

Unreacted homoallylic alcohol **(*R*)-38** was treated with acryloyl chloride and Et_3N in THF to afford acrylate ester **37**. Goniothalamin **(*R*)-1** was prepared from compound **37**, with 8 mol% of 1st generation Grubbs' catalyst via a ring closing metathesis reaction in 92% yield.

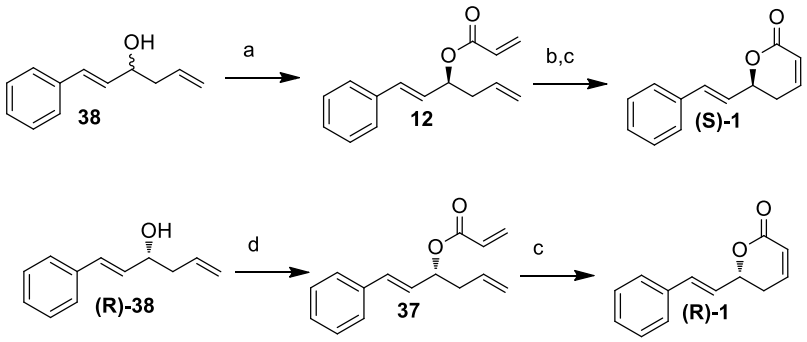


Figure 1.14. Synthesis of **(*S*)**- and **(*R*)**-1 goniothalamin with lipase catalyzed resolution and alkene metathesis

Reagents and conditions: (a) CALB, vinyl acrylate, hexane. (b) Separation by chromatography, (c) Grubbs' cat., DCM, d, (d) acryloyl chloride, Et_3N, THF.

1.2.8. Diels Alder Reaction

Jacobsen and co-workers used Cr(III) catalyzed asymmetric hetero Diels–Alder reaction which provides a rapid and high-yielding synthetic entry into α,β-unsaturated lactones. In addition, the resulting intermediates can be rapidly functionalized by cross-coupling to provide a range of derivatives. For this reason in this sutdy Cr(III) catalyzed asymmetric hetero Diels–Alder reaction methodolgy was performed for the preparation of goniothalamin **(1)** and its analogs. (Wach et al., 2010)

Methoxybutadiene (**39**) was reacted with TES protected propargylic aldehyde (**40**) to form the key intermediate **41** after that transacetalization and deprotection. Then goniothalamin lactol ether was formed by converting the dihydropyran with hydrozirconation, transmetallation and Negishi cross-coupling. (King, Okukado, & Negishi, 1977) (Figure 1.14)

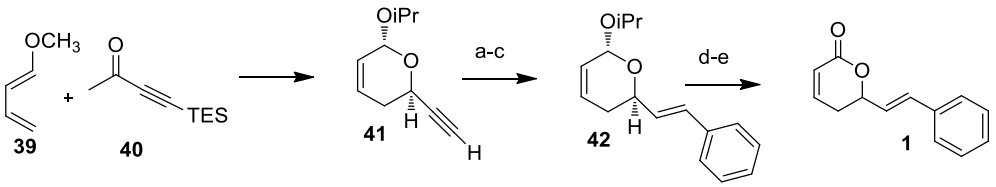


Figure 1.15. Synthesis of goniothalamin (**1**) by Diels-Alder reaction.

Reagents and conditions: (a) Cp_2ZrHCl, 0 ^oC to rt, THF, 1 h; (b) $ZnCl_2$, THF, rt, 30 min; (c) iodobenzene, $Pd(PPh_3)_4$, DIBAH, rt to 40 ^oC, 12 h; (d) PPTS, acetone/water (3:1), room temperature, 22 h; (e) PCC, 4 Å MS, AcOH, DCM, rt, 3 h.

1.2.9. Hydrozirconation–Carbonylation

A solution of (*S*)-(−)-propylene oxide was treated with the lithium acetylide ethylene diamine complex and afforded (*S*)-(−)-4-pentyn-2-ol that has been transformed without isolation into compound **44** by reaction with benzylbromide. Compound **44** was treated with the suspension of the Schwartz reagent $Cp_2Zr(H)Cl$ in benzene at room temperature. Crude compound of hydrozirconated alkynes was carbonylated under 1.1 atm of carbon monoxide affords an orange solution, which was treated with iodine for

2–3 h. Column chromatography of the reaction mixture gave the lactone **45** as product**.** (Dupont & Donato, 1998) (Figure 1.15.)

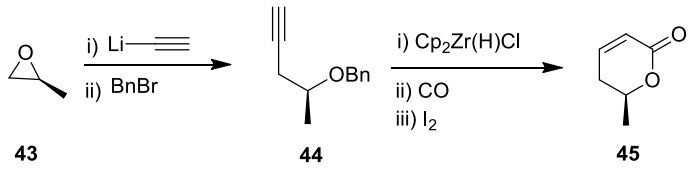


Figure 1.16. Lactone synthesis with hydrozirconation–carbonylation

1.2.10. Sulfoxide-Modified Julia Olefination in Total Synthesis

In literature, Fatima, et al. and Pospisil-Marco's research groups represented different sulfoxide modified olefination methods for the enantioselective synthesis of *R*-goniothalamin Pospisil-Marco's research groups start with commercially available (*R*)-glycidol **46**, which was protected with protected-groups, (a=Bn, b=PMB, c =TBS, d=TBPDS) to afford the corresponding epoxy ethers **47a-d**. For synthesis of optically active homoallylic alcohol, copper-catalyzed vinyl magnesium bromide addition furnished selective opening of epoxides in excellent yields and purities. acryloyl chloride or acrylic acid was used for acylation of alcohol **48a–d**, to afford smoothly the metathesis precursors **49a–d** . (Pospíšil & Markó, 2006)

Finally, It was reported that the nature of the protecting group in substrate **47** had a significant influence on the reaction rate in ring closing metathesis. When the benzyl protected ester **49a** was treated with the 1st generation Grubbs' catalyst (GC-1) poor conversion yield was observed. To overcome this problem, $Ti(OPr^i)_4$ was added as an additive. In the event, treatment of substrate **49a** with GC-1/ $Ti(OPr^i)_4$ resulted in the smooth formation of the desired lactone **50a** in 92% yield.

A similar situation was observed with the PMB-protected derivative, the usage of GC-1/$Ti(OPr^i)_4$ did not lead to complete conversion of **49b** to **50b**. So that, the more reactive 2nd generation Grubbs' catalyst (GC-2)/$Ti(OPr^i)_4$ were used to complete the synthesis.

Finally, TBS and TBPDS-containing substrates **49c** and **d**, there is no need the addition of $Ti(OPr^i)_4$ because the steric bulk of these protecting groups effectively inhibits any undesired interaction between the ether and Grubbs' catalyst.

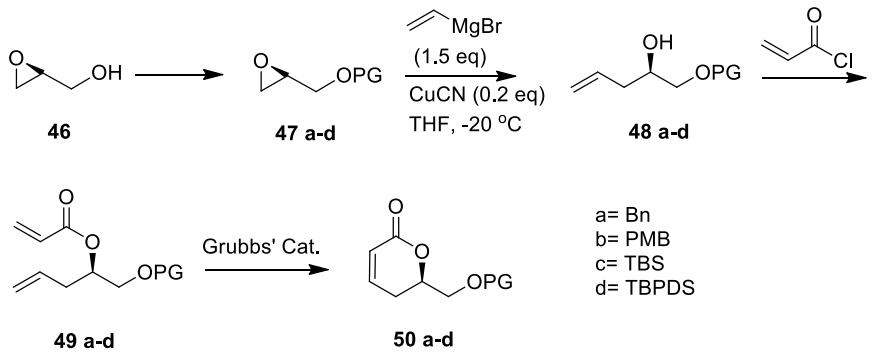


Figure 1.17. Lactone synthesis with sulfoxide-modified Julia olefination

CHAPTER 2

RESULT AND DISCUSSION

Since 4'-methyl substituted klavuzon is the most cytotoxic compound reported by Kasaplar et. al. In here it is aimed to synthesize 4'-alkyl substituted klavuzon deriatives. In this thesis larger R groups will be installed at 4' position of klavuzon. For this purpose, it is propsed that benzylic alylation of acetal **(52)** in the prescence of a strong base would be a key step to prepare 4'-alkyl substituted 1-naphtaldehydes (**54a-c**). (Figure 2.1.).

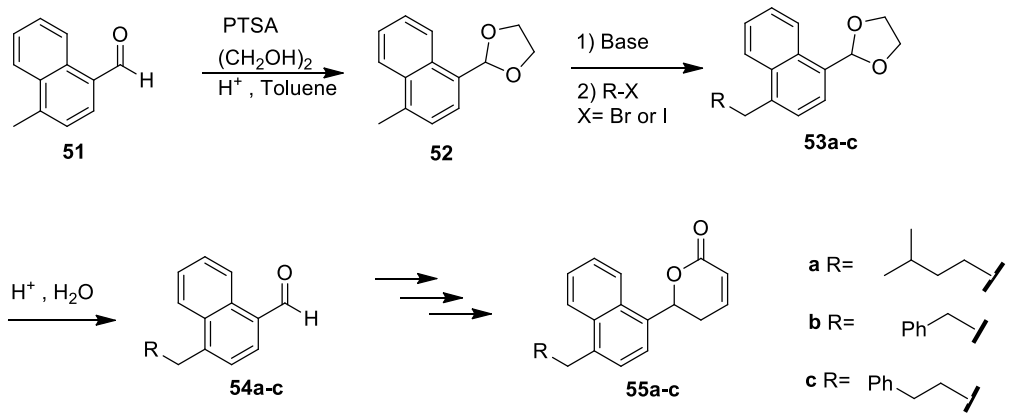


Figure 2.1. Proposed route for the synthesis of 4'-alkyl substituted klavuzon derivatives **55a-c**

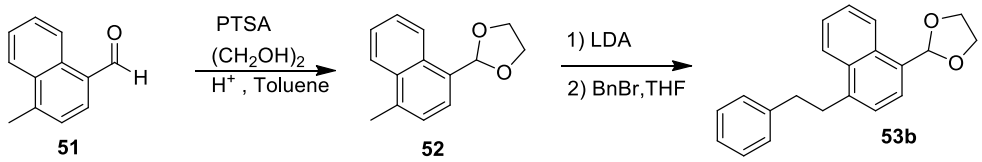
2.1. Studies Toward the Benzylic Alkylation of Acetal (52) by Using LDA or n-BuLi

At the beginning of synthesis, compound **51** was treated with *p-t*oluenesulfonic acid (PTSA) and ethylene glycol in toluene and converted to compound **52** in 68% yield. In the second step LDA was used as strong base to react with benzylic proton to form a relatively stable benzylic carbanion. Addition of benzyl bromide over this benzylic carbanion would give compound **53b**. (Table 2.1.)

Altough acetal formation was quite effective, benzylic substitution attempts were failed in all cases. Three parameters were evaluated in these attempts; relative amounts of base and benzyl bromide and reaction time.

As summarized in table 2.1 up to 2.0 equivalent of base 3.0 equivalent of benzyl bromide and prolonged reaction times were not enough to accomplish this reaction. Because of that in the next trials a much more stronger base, n-BuLi, was used.

Table 2.1. Attempts for the preparation of 4' -alkyl substituted acetal with LDA

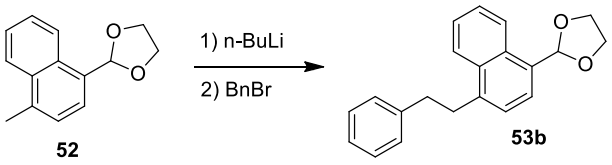


51 52 53b

Entry	LDA (Eq.)	BnBr (Eq)	Time	Result
1	1.0	2.0	2 hour	No Rxn
2	1.0	2.0	Overnight	No Rxn
3	1.0	3.0	2 hour	No Rxn
4	1.5	3.0	Overnight	No Rxn
5	2.0	3.0	Overnight	No Rxn

Treatment of acetal **(52)** with differant equivalents (1.0-3.5) of nBu-Li followed by benzyl bromide in THF or hexane were inconclusive (Table 2.2, entries 1-3). Crude products of the reactions were analyzed by ^{1}H-NMR but no product formation was observed. It is known that agglomeration of n-BuLi might be a problem in these reactions. To prevent the agglomeration of n-BuLi varying amounts of TMEDA or KO*t*-Bu were added to the reaction medium to form a cage-like structure which increase the reactivity of benzylic carbanion (also n-BuLi). Unfortunately, these additives also were not helpful. (Table2.2, entries 4-5).

Table 2.2. Attempts for the preparation of 4’ -alkyl substituted acetal with n-BuLi

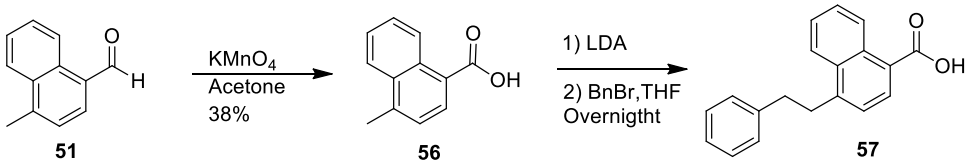


Entry	BuLi(Eq)	TMEDA (Eq)	KO*t*-Bu (Eq)	BnBr(Eq)	Conditions	Result
1	1.0	-	-	2.0	THF, 4 h.	No Rxn
2	1.8	-	-	2.0	Hexane, 24 h.	No Rxn
3	3.5	-	-	1.5	THF, 4 h.	No Rxn
4	1.1	1.1	-	1.0	Hexane, 16 h.	No Rxn
5	2.4	2.4	2.4	1.8	THF, 4 h.	No Rxn

2.2. Benzylic Alkylation of 4-methyl-1-naphtoic Acid

After failure of the attempts for the alkylation of acetal, benzylic alkylation of carboxylic acid **(56)** can be a good alternative. Thus 4-methyl-1-naphtaldehyde **(51)** was oxidized to 4-methyl-1-naphtoic acid **(56)** while treating with $KMnO_4$ in 38% yield. Then compound **(56)** was reacted first with LDA (2 eq.) and then benzyl bromide (2 eq.) in THF was added. A similar reaction was also performed by using n-BuLi instead of LDA. Both reaction was monitored by TLC and crude products were analyzed with ^{1}H-NMR, but no product formation was observed in these trials too. (Table 2.3).

Table2.3. Attempts for the synthesis of 4'-alkyl substituted carboxylic acid with n-BuLi and LDA



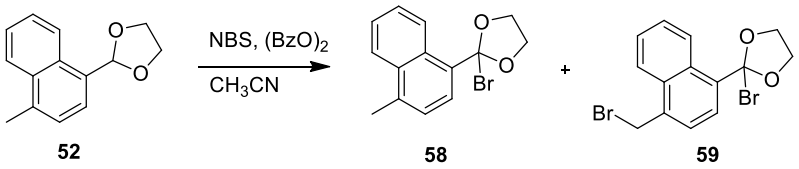
51 56 57

Entry	Base	BnBr (Eq)	Result
1	LDA (2,0 Eq.)	2,0	No Rxn
2	n-BuLi (3.5 Eq.)	1,5	No Rxn

2.3. Benzylic Bromination as a Key Step

As summarized above all attempts to generate a nucleophilic benzylic carbon failed. In this part of the thesis generation of an electrophilic benzylic carbon on naphthalene was studied. A well-known benzylic bromination procedure with NBS was used for the benzylic bromination of acetal **(52)** as shown in figure 2.2.

Reaction of compound **(52)** with NBS and peroxide gave the products as shown in figure 2.2. It seems that reaction is somehow selective for benzylic acetal proton, probably due to the stabilization of the electron deficient benzylic radical intermediate by oxygens.



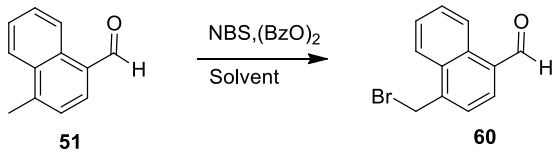
52 58 59

Figure 2.2. Benzylic bromination of acetal **52**

The same benzylic bromination procedure was also used for the bromination of 4-methyl-1-naphtaldehyde **(51).** Compared to the previous attempts this time reaction was successful but the yield of the reaction was too low. These reactions could work better in CCl_4 but because of the environmental pollution concerns it is forbidden to

import it to Turkey. Instead, this reaction was tried in DCM, $CHCl_3$ and CH_3CN. Best yield was 8% which was formed in the case of $CHCl_3$ and DCM was used as solvent.

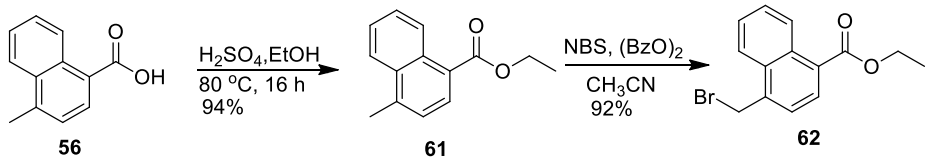
Table 2.4. Preparation of 4-bromomethyl 1-naphthaldehyde **(60)**



51 60

Entry	Solvet	Temperature, ^oC	Yield, %
1	DCM	reflux	8
2	$CHCl_3$	reflux	8
3	CH_3CN	reflux	5

Benzylic bromination of ester **61**, prepared from 1-naphthoic acid **(56)** in 94% yield, was much more promising. Repetitively, this reaction gave brominated ester **(62)** with 92% yield in CH_3CN. (Figure 2.3)



56 61 62

Figure 2.3. Benzylic bromination of ester **61**

2.4. Benzylic Alkylation of Methyl 4-bromoethyl-1-naphthoate (62)

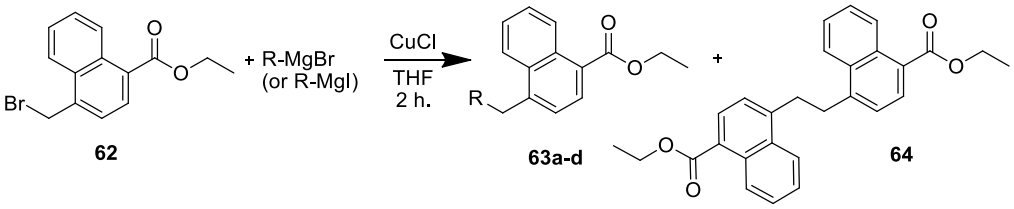
In the next step of synthesis, prepared brominated-1-naphthoate **(62)** was treated with magnesium based dialkyl cuprates to form alkyl substituted esters **63a-d**. For each reaction grignard reagents were prepared freshly, and then added to the 0.6 equivalent of CuCl to form alkyl magnesium cuprate. Then these cuprates were added on the compound **62** to achieve carbon carbon bond formation. Grignard reagents were prepared 3.0 equivalent to obtain maximum yield. As it can be seen from table 2.5, the experiment which was performed with benzyl bromide was successful but it was quite

difficult to separate from unreacted ester **(62)** in column chromatography. Thus this product was used directly in the step without any further purifications.

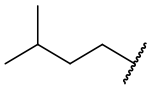
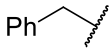
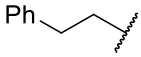
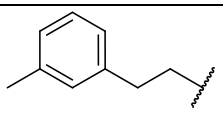
Interestingly, in these reactions, dimerization product of ester was also produced. It seems that somehow magnesium cuprate activates one of the benzylic carbon of compound **62** as nucleophile to react with a second equivalent of ester **(62)**.

Among these alkylation reactions, addition of dibenzylmagnesium cuprate to the ester was quite challenging. More than 10 times it was repeated but all tries gave either low yields of product formation or unseperable mixtures. In these trials also the formation of 1,2-diphenylethane **(65)** was also observed. (Figure 2.4)

Table 2.5. Benzylic alkylation of ethyl 4-bromomethyl-1-naphthoate **(62)**



62 **63a-d** **64**

Entry	Compound	Grignard (R, 3.0 Eq.)	CuCl (Eq)	Yiels, % 63a-c	Verim, % 64
1	**63a**		0.6	28	45
2	**63b**		0.6	*	47
3	**63c**		0.5	65	34
4	**63d**		0.6	39	48

*****Product could not be purified from starting material.

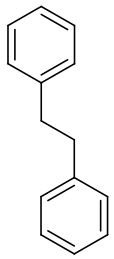


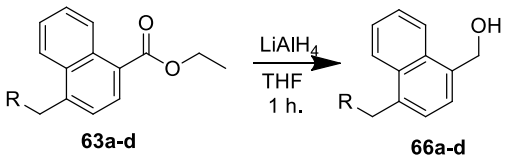
Figure 2.4. Structure of 1,2-diphenylethane **(65)**

2.5. Reduction of Ethyl 4-alkyl-1-naphthoate (63a-d) to 4-alkylnaphthalene-1-yl methanol (66a-d) with $LiAlH_4$

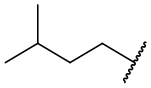
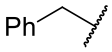
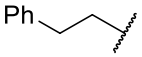
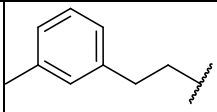
To convert the ester functional group to aldehyde, the formed ester derivatives **(63a-d)** were reduced to 4-alkylnaphthalene-1-yl methanol derivatives by using 1.5 equivalent of $LiAlH_4$ as reducing agent in THF. The yield of the product formed starting from benzyl bromide **66b** was calculated as 8% for two steps, and it is successfully isolated from impurity which was coming from previous alkyl substitution step. (Table 2.6)

Unexpectedly the yield for the reaction of compound **66c** was quite low. Probably the solvent was contaminated with a small amount of moisture, which can cause a dramatic effect for the reactions carried out in low amount of starting material.

Table 2.6. Reduction of ethyl 4-alkyl-1-naphthoate derivatives (**63a-d)** to 4-alkylnaphthalene-1-yl methanol derivatives **(66a-d)** with $LiAlH_4$



63a-d 66a-d

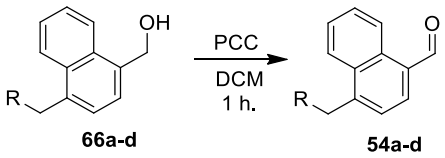
Entry	Compound	R	Yield, %
1	**66a**		78
2	**66b**		8*
3	**66c**		19
4	**66d**		78

*Calculated for two steps.

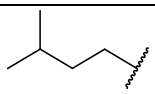
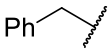
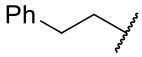
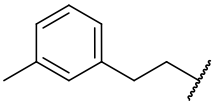
2.6. Oxidation of 4-alkyl naphthalene-1-yl methanol Derivatives (66a-d) to 4-alkyl-1-naphtaldehydes (54a-d) with PCC

Aldehyde is the key functional group for the synthesis of klavuzon derivatives. In this respect 4-alkyl naphthalene-1-yl methanol derivatives **(66a-d)** were oxidized to 4-alkyl-1-naphtaldehydes **(54a-d)**. For oxidation of alcohols PCC, an efficient oxidizing agent to oxidize primary alcohols, was used. These reactions were performed in DCM to get aldehydes **(54a-d)** in 67, 91 and 90% yields respectively. (Table 2.7) The relative amount of PCC was fixed as 1.1 equivalent compared to the alcohols **(54a-d)**. If more PCC is used oxidation of benzylic methylene carbon can also occur.

Table 2.7. Oxidation of 4-alkyl-1-naphthalene1-yl methanol **(66a-d)** to 4-alkyl-1-naphtaldehyde (**54a-d)** with PCC



66a-d 54a-d

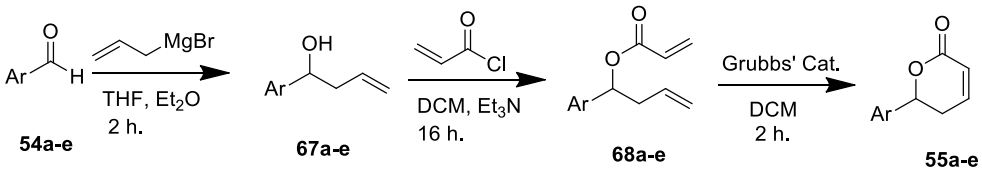
Entry	Compound	R	Yield, %
1	**54a**		67
2	**54a**		91
3	**54c**		90
4	**54d**		58

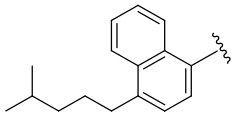
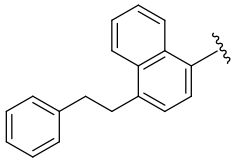
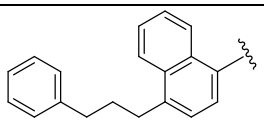
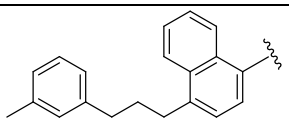
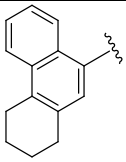
2.7. Synthesis of Klavuzon Derivatives (55a-d)

In the last part of the synthesis a well-known three steps procedure was applied. For this purpose obtained aldehydes **(54a-e)** was treated with 4.0 equivalent of freshly prepared ally magnesium bromide solution in THF. The yields of these reactions vary from moderate 54% to high 85%. Although it seems that 4.0 equivalent of Grignard reagent is quite excess for such reaction the real concentrations of the Grignard reagents might be lower compared to the starting ally bromide amounts due to the possible dimerization reactions during the preparation of Grignard reaction. (Ren, Stern, & Hu, 2012)

In the next step homoallylic alcohols **67a-e** was reacted with acryloyl chloride in the presence of triethylamine to form esters **(68a-e**) generally in high yields (40-89%). At last, formed acrylate esters were transferred into klavuzon derivatives **(55a-e)** via alkene metathesis reactions by using 2nd generation Grubbs' catalayst in moderate yields (62-85%). (Table 2.8)

Table 2.8. Synthesis of klavuzon derivatives **(55a-e)**



Entry	**Ar**	**Yield, % 67a-d**	**Yield, % 68a-d**	**Yield, % 55a-d**
1	 **54a, 67a, 68a, 55a**	60	75	62
2	 **54b, 67b, 68b, 55b**	54	40	83
3	 **54c, 67c, 68c, 55c**	71	73	73
4	 **54d, 67d, 68d, 55d**	59	70	68
5	 **54e, 67e, 68e, 55e**	85	89	85

CHAPTER 3

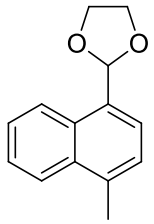
EXPERIMENTAL

3.1. General Methods

Reagents were used as supplied and purchased from Sigma-Aldrich and Riedel (Extra pure grade). Reactions were monitored by thin layer chromatography by using Merck TLC plates (Silica gel 60 F254). Chromatographic separations and isolations of compounds were performed by column chromatography. 70-230 mesh silica gel was used for column chromatography. Solvents were also commercial grade and were used as supplied. ^{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.

3.1.1. 2-(4-Methylnaphthalen-1-yl)-1,3-dioxolane (52)

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 1.47 mL ethylene glycol (26.10 mmol, 2.5 eq.) and 56.00 mg PTSA (0.33 mmol, 0.05 eq.) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 16 hours, mixture was cooled down to room temperature to room temperature and 10 mL saturated $NaHCO_3$ was added to end up the reaction. This crude product was extracted with ethyl acetate (3x25 mL) and then washed with 15 mL saturated brine solution. The organic phase was dried over anhydrous $MgSO_4$ and filtered. After removal of solvent of the crude product, purification was performed by column chromatography (EtOAc/Hex; 1:100) to obtain 950.7 mg desired product with 68% yield.



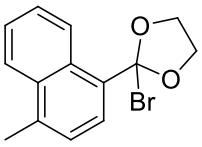
R_f: 0.37 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 - 8.17 (m, 1H), 8.10 - 8.00 (m, 1H), 7.66 (d, *J* = 7.4 Hz, 1H), 7.62 - 7.44 (m, 2H), 7.44 - 7.29 (m, 1H), 6.47 (s, 1H), 4.31 - 4.10 (m, 4H), 2.71 (d, *J* = 0.8 Hz, 3H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 133.1, 131.5, 131.2, 126.1, 126.0, 125.9, 125.7, 125.6, 124.8, 124.7, 123.5, 102.5, 65.4, 19.8.

3.1.2. Bromination of 2-(4-methylnaphthalen-1-yl)-1,3-dioxolane (52)

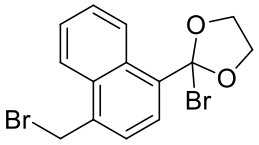
In a two necked flask 50.0 mg of 2-(4-methylnaphthalen-1-yl)-1,3-dioxolane (0.23 mmol, 1.0 eq.) was placed and dissolved in 6 mL of DCM. Then 45.0 mg NBS (0.25 mmol, 1.1 eq.) and 2.0 mg benzoyl peroxide (0.01 mmol, 0.043 eq.) were directly added into mixture. Mixture was stirred under reflux and after 16 hours reflux, reaction mixture was cooled down to room temperature to room temperature and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and and solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:15) resulted desired 33 mg of compound **58** with 50% yield and 17 mg of compound **59** with 20% yield.



R_f: 0.34 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.05 – 9.0 (m, 1H), 8.18 (d, *J* = 7.4 Hz, 1H) 8.08 - 8.04 (m, 1H), 7.67 - 7.56 (m, 2H) 7.36 (dd, *J* = 7.4 Hz and 0.8 Hz, 1H), 4.71 (dd, *J* = 6.8 Hz and 5.3 Hz, 2H), 3.71 (dd, *J* = 6.7 Hz and 5.4 Hz, 2H), 2.75 (s, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.68, 138.83, 131.96, 131.45, 129.99, 128.16, 127.96, 127.05, 126.67, 126.51, 124.21, 64.61, 30.67, 29.04.



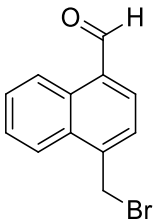
R_f: 0.30 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.0 – 9.84 (m, 1H), 8.22 - 8.19 (m, 1H), 8.16 (d, *J* = 7.5 Hz, 1H), 7.70 - 7.64 (m, 2H), 7.60 - 7.56 (m, 1H), 4.94 (s, 2H), 4.73 (t, *J* = 6.0 Hz, 2H), 3.71 (t, *J* = 6.0 Hz, 2H)

^{13}C-NMR (100 MHz, $CDCl_3$) δ 166.68, 138.83, 131.96, 131.45, 129.99, 128.16, 127.96, 127.05, 126.67, 126.51, 124.21, 64.61, 30.67, 29.04.

3.1.3. 4-(Bromomethyl)-1-naphthaldehyde (60)

In a two necked flask 104.0 mg of 4-Methyl-1-naphaldehyde (0.61 mmol, 1.0 eq.) was placed and dissolved in 6 mL of DCM. Then 119.0 mg NBS (0.67 mmol, 1.1 eq.) and 2.18 mg benzoyl peroxide (0.01 mmol, 0.016 eq.) were directly added into mixture. Mixture was stirred under reflux and after 16 hours reflux, reaction mixture was cooled down to room temperature to room temperature and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and and solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:15) resulted desired 102 mg of product with 68% yield.



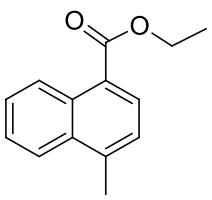
R_f: 0.35 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.23 - 10.12 (m, 1H), 9.19 - 9.05 (m, 1H), 8.13 - 7.95 (m, 1H), 7.76 - 7.66 (m, 1H), 7.58 - 7.42 (m, 3H), 4.80 - 4.72 (m, 2H)**.**

^{13}C-NMR (100 MHz, $CDCl_3$) δ. 193.3, 140.7, 136.0, 132.3, 131.5, 131.4, 129.4, 127.7, 126.9, 125.8, 124.3, 30.5.

3.1.4. Ethyl 4-methyl-1-naphthoate (61)

In a two necked flask 186 mg of 4-methyl-1-naphthoic acid (1.0 mmol, 1.0 eq.) was placed and dissolved in 5 mL of ethanol and was stirred under reflux. Then 5-6 drops of sulfuric acid was directly added into mixture. After 16 hours, mixture was cooled down to room temperature and extracted with ethyl acetate (3x25 mL) and the organic phase was dried over anhydrous $MgSO_4$ and filtered. After removal of solvent of the crude product, purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 201 mg of product with 94% yield.



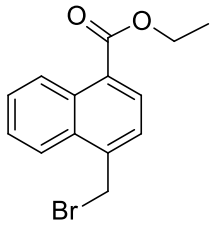
R_f: 0.50 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.03 (d, *J* = 8.6 Hz, 1H), 8.11 (d, *J* = 7.4 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.67 - 7.54 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 4.49 (q, *J* = 7.2 Hz, 2H), 2.73 (s, 3H), 1.48 (t, *J* = 7.0 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.

3.1.5. Ethyl 4-(bromomethyl)-1-naphthoate (62)

In a two necked flask 569 mg of ethyl 4-methyl-1-naphthoate (2.66 mmol, 1.0 eq.) was placed and dissolved in 5 mL of acetonitrile. Then 506 mg NBS (2.9 mmol, 1.1 eq.) and 14 mg benzoyl peroxide (0.077 mmol, 0.03 eq.) were directly added into mixture. Mixture was stirred under reflux and after 16 hours reflux, reaction mixture was cooled down to room temperature and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and organic solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted 717 mg of desired product with 92% yield.



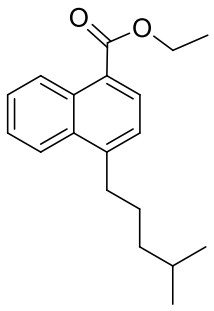
R_f: 0.45 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99 - 8.92 (m, 1H), 8.24 - 8.18 (m, 1H), 8.07 (d, *J* = 7.4 Hz, 1H), 7.71 - 7.61 (m, 2H), 7.54 (d, *J* = 7.4 Hz, 1H), 4.92 (s, 2H), 4.54 - 4.44 (m, 2H), 1.51 - 1.42 (m, 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.

3.1.6. Ethyl 4-(4-methylpentyl)-1-naphthoate (63a)

Into a two necked flask 121.5 mg of magnesium turnings (5.11 mmol, 3.0 eq.) were placed and solved in 3 mL of dry ether under nitrogen atmosphere. Then 771.8 mg of 1-bromo-3-methylbutane (5.11 mmol, 3.0 eq.) was added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 101.0 mg of CuCl (1.02 mmol, 0.6 eq.) and 500 mg of ethyl 4-(bromomethyl)-1-naphthoate (1.7 mmol, 1.0 eq.) were dissolved in 2 mL THF and Grignard reagent was added into these mixture drop wise at room temperature. After 2 hour reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 81 mg product with 28% yield.

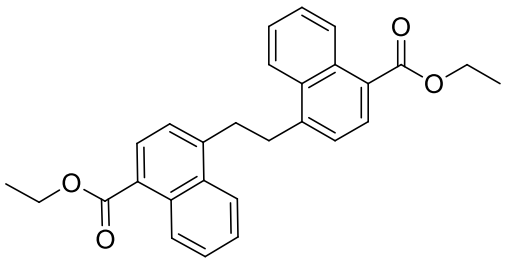


R_f: 0.39 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.99 (ddd, *J* = 8.6, 1.6 and 0.7 Hz, 1H), 8.24 – 8.04 (m, 2H), 7.76 – 7.49 (m, 2H), 7.36 (d, *J* = 7.5 Hz, 1H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.28 – 2.95 (m, 2H), 1.85 – 1.70 (m, 2H), 1.67 – 1.55 (m, 1H), 1.46 (t, *J* = 7.1 Hz, 3H), 1.38 – 1.29 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.90, 144.85,

132.27, 131.84, 129.94, 127.19, 126.59, 126.03, 125.88, 124.87, 124.29, 61.01, 39.16, 33.96, 28.66, 28.03, 22.74, 22.74, 14.54.



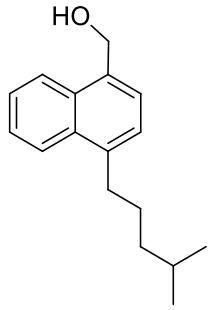
R_f: 0.23 (1:8 EtOAc-Hex)

^{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.

3.1.7. (4-(4-Methylpentyl)naphthalen-1-yl)methanol (66a)

Into a two necked flask 136.4 mg of ethyl 4-(4-methylpentyl)-1-naphthoate (0.45 mmol 1.0 eq) was placed and solved in 3 mL of dry THF under nitogen and stirred under reflux. Afterwards a solution of 25.5 mg of $LiAlH_4$ (0.67 mmol, 1.5 eq.) in 2 mL dry THF was added drop-wise into mixture which was cooled down to 0 ^oC. Then the reaction was stirred at room temperature for 2 hours. Then reaction mixture was cooled again 0 ^oC and acidified with 1 N HCl. Crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10 to 1:2) resulted desired 85 mg product with 78% yield.



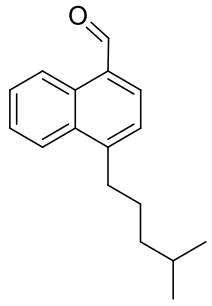
R_f: 0.31 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.17 (ddd, *J* = 6.4, 3.3 and 0.7 Hz, 1H), 8.10 (ddd, *J* = 6.5, 3.3 and 0.7 Hz, 1H), 7.57-7.53 (m, 2H), 7.42 (dd, *J* = 7.2 and 0.8 Hz, 1H), 7.30 (d, *J* = 7.1 Hz, 1H), 5.11 (d, *J* = 0.7 Hz, 2H), 3.09 – 3.01 (m, 2H), 1.84 (s, 1H), 1.81 – 1.70 (m, 2H), 1.66-1.57 (m, 1H), 1.39 – 1.32 (m, 2H), 0.91 (d, *J* = 6.7 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 139.82, 134.50, 132.36, 131.78, 125.97, 125.77, 125.49, 125.44, 124.68, 124.54, 63.99, 39.26, 33.59, 28.86, 28.07, 22.77.

3.1.8. 4-(4-Methylpentyl)-1-naphthaldehyde (54a)

Into a two necked flask 29.8 mg of PCC (0.138 mmol, 1.1 eq.) was placed and solved in 4 mL of dry DCM under nitrogen atmosphere, and then 74.0 mg of (4-(4-methylpentyl)naphthalen-1-yl)methanol (0.3 mmol, 1.0 eq.) was dissolved in 3 mL dry DCM. Afterwards alcohol solution was added into PCC solution drop-wise. The reaction mixture was stirred 2 hours under nitrogen atmosphere and then the solid part of the mixture was filtered with the help of filter paper. The organic phase (filtrate) was washed with 1 M NaOH (20 mL) and then 1 M HCl (20 mL). Organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 48 mg product with 67 % yield.



R_f: 0.47(1:8 EtOAc-Hex)

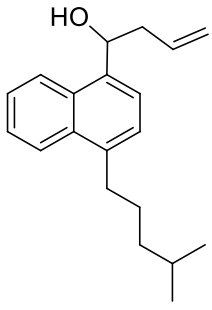
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.34 (s, 1H), 9.34 (ddd, *J* = 8.5, 1.4 and 0.7 Hz, 1H), 8.23 – 7.85 (m, 2H), 7.71 – 7.59 (m, 2H), 7.49 (d, *J* = 7.3 Hz, 1H), 3.23 – 2.98 (m, 2H), 1.89 – 1.69 (m, 2H), 1.65 – 1.58 (m, 1H), 1.42 – 1.30 (m, 2H), 0.91 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.77, 160.22,

147.98, 137.30, 132.51, 131.47, 130.38, 128.95, 127.20, 126.02, 125.57, 124.63, 39.53, 34.55, 29.00, 28.36, 23.04.

3.1.9. 1-(4-(4-Methylpentyl)naphthalen-1-yl)but-3-en-1-ol (67a)

Into a two necked flask 12.0 mg of magnesium turnings (0.50 mmol, 4.0 eq.) were placed and solved in 3 mL of dry ether under nitrogen atmosphere. Then 60.5 mg of allybromide (0.50 mmol, 4.0 eq.) were added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 30.0 mg of 4-(4-methylpentyl)-1-naphthaldehyde (0.125 mmol, 1.0 eq.) were dissolved in 2 mL THF and Grignard reagent was added into this mixture drop-wise at room temperature. After 2 hour reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 21 mg product with 60% yield.



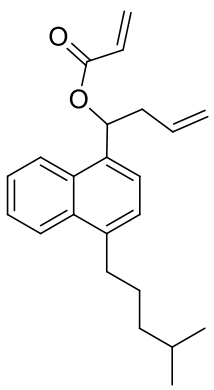
R_f: 0.25 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.05 (m, 2H), 7.58 (dd, *J* = 7.3 and 0.7 Hz, 1H), 7.58 – 7.47 (m, 2H), 7.34 (d, *J* = 7.4 Hz, 1H), 6.03 – 5.87 (m, 1H), 5.51 (dd, *J* = 7.9 and 3.8 Hz, 1H), 5.29 – 5.15 (m, 2H), 3.13 – 2.95 (m, 2H), 2.83 – 2.55 (m, 2H), 2.14 (d, *J* = 3.0 Hz, 1H), 1.80 – 1.57 (m, 3H), 1.40 – 1.29 (m, 2H), 0.91 (d, *J* = 0.9 Hz, 3H), 0.89 (d, *J* = 0.9 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 138.96, 137.55, 135.10, 132.28, 130.80, 125.67, 125.62, 125.43, 124.91, 123.76, 122.69, 118.40, 70.10, 42.96, 39.30, 33.65, 28.86, 28.09, 22.80, 22.79.

3.1.10. 1-(4-(4-Methylpentyl)naphthalen-1-yl)but-3-en-1-yl acrylate (68a)

Into a two necked flask 41.8 mg of 1-(4-(4-methylpentyl)naphthalen-1-yl)but-3-en-1-ol (0.134 mmol 1.0 eq) was placed and solved in 5 mL of dry DCM under nitogen. Afterwards 21.8 mg of acryloyl chloride (0.24 mmol, 1.8 eq.) was added into mixture which was cooled 0 ^{o}C before adding 48.6 mg trimethylamine (0.48 mmol, 3.6 eq.) drop-wise. Reaction was stirred at room temperature for 16 hours. Then reaction mixture was filtered with celite and poured into water. Crude product was extracted with DCM (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 33.8 mg product with 75% yield.



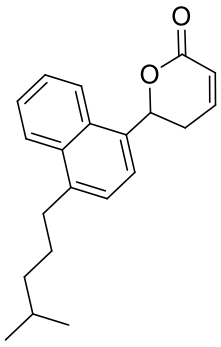
R_f: 0.59 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.16 (m, 1H), 8.08 (ddd, *J* = 9.3, 5.6 and 2.5 Hz, 1H), 7.56 – 7.52 (m, 1H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.32 (d, *J* = 7.4 Hz, 1H), 6.67 (t, *J* = 6.6 Hz, 1H), 6.48 (d, *J* = 1.5 Hz, 1H), 6.44 (d, *J* = 1.5 Hz, 1H), 6.24 – 6.16 (m, 1H), 5.86 (d, *J* = 1.5 Hz, 1H), 5.85 – 5.83 (m, 1H), 5.16 – 5.04 (m, 2H), 3.07 – 2.98 (m, 2H), 2.86 – 2.79 (m, 2H), 1.79 – 1.70 (m, 2H), 1.65 – 1.59 (m, 1H), 1.38 – 1.32 (m, 2H), 0.90 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.71, 139.69, 134.12, 133.92, 132.44, 131.23, 130.96, 128.87, 126.07, 125.70, 125.53, 124.99, 124.07, 123.93, 118.18, 72.79, 40.64, 39.46, 33.81, 28.94, 28.22, 22.92.

3.1.11. 6-(4-(4-Methylpentyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (55a)

Into a two necked flask 36.2 mg of 1-(4-(4-methylpentyl)naphthalen-1-yl)but-3-en-1-yl acrylate (0.098 mmol, 1.0 eq.) was dissolved in 10 mL dry DCM and into another two neckled flask 8.3 mg of 2nd generation Grubbs' catalyst (0.0098 mmol, 0.1 eq.) was placed and solved in 1 mL of dry DCM under nitrogen atmosphere and then added on the ester solution. This mixture was stirred under nitrogen atmosphere at reflux during 2 hours. Organic solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:2) resulted desired 18 mg product with 62% yield.



R_f: 0.10(1:8 EtOAc-Hex)

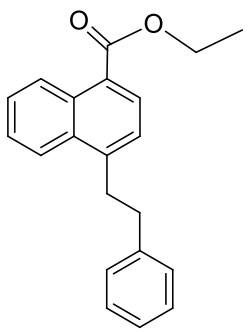
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 1H), 8.03 – 7.97 (m, 1H), 7.62 (dd, *J* = 7.4 and 0.7 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.09 – 7.01 (m, 1H), 6.28 – 6.16 (m, 2H), 3.05 (dd, *J* = 8.8 and 6.9 Hz, 2H), 2.89 – 2.78 (m, 2H), 1.82 – 1.69 (m, 2H), 1.68 – 1.58 (m, 1H), 1.38 – 1.29 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.91, 145.79, 140.68, 132.60, 132.29, 130.81, 126.53, 126.04, 125.85, 125.41, 124.38, 123.62, 122.11, 110.44, 39.56, 33.96, 31.53, 29.11, 28.38, 23.10, 23.09.

3.1.12. Ethyl 4-phenethyl-1-naphthoate (63b)

Into a two necked flask 99.6 mg of magnesium turnings (4.08 mmol, 3.0 eq.) were placed and solved in 4 mL of dry ether under nitrogen atmosphere then 498 µL of benzyl bromide (4.08 mmol, 3.0 eq.) was added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room

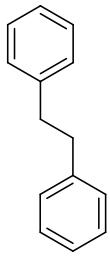
temperature. Then into another two necked flask 81 mg of CuCl (0.816 mmol, 0.6 eq.) and 400 mg of ethyl 4-(bromomethyl)-1-naphthoate (1.36 mmol, 1.0 eq.) were dissolved in 2 mL THF and Grignard reagent was added into this mixture drop-wise at room temperature. After 2 hours reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired product with ethyl 4-(bromomethyl)-1-naphthoate and 1,2-diphenylethane as side product.



R_f: 0.46 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 9.03 – 8.97 (m, 1H), 8.19 – 8.15 (m, 1H), 8.09 (d, *J* = 7.4 Hz, 1H), 7.67 – 7.56 (m, 2H), 7.33-7.29 (m, 3H), 7.26 – 7.22 (m, 3H), 4.48 (q, *J* = 7.1 Hz, 2H), 3.47 – 3.40 (m, 2H), 3.12 – 3.04 (m, 2H), 1.47 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.73, 143.31, 141.45, 132.03, 131.73, 129.75, 128.47, 128.40, 127.17, 126.59, 126.15, 124.96, 123.93, 60.96, 36.82, 35.52, 14.41.



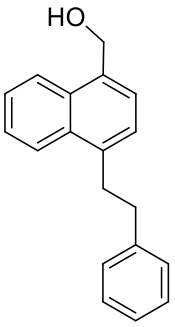
R_f: 0.81(1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$ δ 7.31 (q, *J* = 1.6 Hz, 1H), 7.30 (q, *J* = 1.1 Hz, 2H), 7.29 – 7.27 (m, 2H), 7.22 (d, *J* = 1.2 Hz, 1H), 7.22 – 7.18 (m, 4H), 2.94 (s, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ (101 MHz, $cdcl_3$) δ 141.60, 128.30, 128.27, 128.23, 128.15, 125.73, 37.77.

3.1.13. (4-Phenethylnaphthalen-1-yl)methanol (66b)

Into a two neckled flask 176.3 mg of ethyl 4-phenethyl-1-naphthoate (0.58 mmol 1.0 eq) was placed and solved in 3 mL of dry THF under nitrogen atmosphere and stirred under reflux. Afterwards a solution of 33 mg of $LiAlH_4$ (0.869 mmol, 1.5 eq.) in 2 mL dry THF was added drop wise into mixture which was cooled down to 0 ^oC. Then the reaction was stirred at room temperature for 2 hours. Then reaction mixture was cooled again 0 ^oC and acidified with 1 N HCl. Crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10 to 1:2) resulted desired 30 mg product with 8% yield for two steps.



R_f: 0.13 (1:8 EtOAc-Hex)

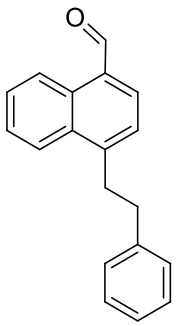
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.23 – 8.15 (m, 2H), 7.62 – 7.55 (m, 2H), 7.43 (d, *J* = 7.1, 1H), 7.37 – 7.20 (m, 6H), 5.13 (s, 2H), 3.39 (dd, *J* = 9.6 and 6.8, 2H), 3.07 (dd, *J* = 9.6 and 6.8, 2H), 1.92 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.99, 138.50, 134.91, 132.23, 131.81, 128.56, 128.52, 126.17, 126.07, 126.00, 125.64, 125.40, 124.65, 124.43, 63.93, 37.19, 35.29.

3.1.14. 4-Phenethyl-1-naphthaldehyde (54b)

Into a two necked flask 27.14 mg of PCC (0.126 mmol, 1.1 eq.) was placed and solved in 4 mL of dry DCM under nitrogen atmosphere, and then 30 mg of (4-phenethylnaphthalen-1-yl)methanol (0.114 mmol, 1.0 eq.) was dissolved in 3 mL dry DCM. Afterwards alcohol solution was added into PCC solution drop-wise. The reaction mixture was stirred 2 hours under nitrogen atmosphere and then the solid part of the mixture was filtered with the help of filter paper. The organic phase (filtrate) was washed with 1 M NaOH (20 mL) and then 1 M HCl (20 mL). Organic phase was dried

over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted 27 mg desired product with 91 % yield.



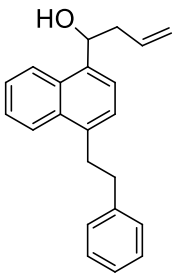
R_f: 0.39 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ10.35 (s, 1H), 9.36 (ddd, *J* = 8.6, 1.5 and 0.7 Hz, 1H), 8.39 – 8.05 (m, 1H), 7.88 (d, *J* = 7.3 Hz, 1H), 7.79 – 7.57 (m, 2H), 7.49 – 7.10 (m, 6H), 3.62 – 3.36 (m, 2H), 3.20 – 2.99 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.49, 193.41, 146.14, 141.29, 136.84, 132.10, 131.17, 130.33, 128.74, 128.66, 128.52, 128.52, 127.10, 126.41, 125.83, 125.52, 124.10, 36.89, 35.88.

3.1.15. 1-(4-phenethylnaphthalen-1-yl)but-3-en-1-ol (67b)

Into a two neckled flask 9.98 mg of magnesium turnings (0.416 mmol, 4.0 eq.) was placed and solved in 3 mL of dry ether under nitrogen atmosphere. Then 35.87 μL of allybromide (0.416 mmol, 4.0 eq.) were added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 27 mg of 4-phenethyl-1-naphthaldehyde (0.104 mmol, 1 eq.) were dissolved in 2 mL THF and Grignard reagent was added into this mixture drop-wise at room temperature. After 2 hour reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:8) resulted desired 17 mg product with 54% yield.



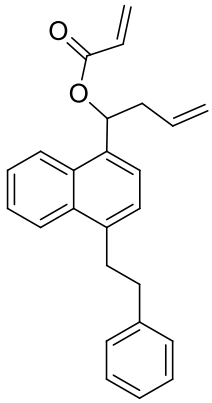
R_f: 0.25 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.22 – 8.10 (m, 2H), 7.61 – 7.49 (m, 3H), 7.37 – 7.30 (m, 3H), 7.29 – 7.20 (m, 3H), 6.01 – 5.95 (m, 1H), 5.95 – 5.88 (m, 1H), 5.57 – 5.47 (m, 1H), 5.29 – 5.15 (m, 1H), 3.45 – 3.32 (m, 2H), 3.10 – 3.01 (m, 2H), 2.82 – 2.74 (m, 1H), 2.68 – 2.55 (m, 1H), 2.17 (d, *J* = 3.2 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ142.07, 137.97, 137.70, 135.00, 132.16, 130.84, 128.57, 128.53, 126.17, 125.78, 125.66, 124.66, 123.89, 122.72, 118.44, 70.10, 42.98, 37.22, 35.37, 29.84

3.1.16. 1-(4-Phenethylnaphthalen-1-yl)but-3-en-1-yl acrylate (68b)

Into a two necked flask 17.1 mg of 1-(4-phenethylnaphthalen-1-yl)but-3-en-1-ol (0.057 mmol 1.0 eq) was placed and solved in 5 mL of dry DCM under nitrogen atmosphere. Afterwards 8.02 µL of acryloyl chloride (0.102 mmol, 1.8 eq.) was added into mixture which was cooled 0 ^oC before adding 17.4 mg trimethylamine (0.204 mmol, 3.6 eq) drop wise. Reaction was stirred at room temperature for 16 hours. Then reaction mixture was filtered with celite and poured into water. Crude product was extracted with DCM (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 8 mg product with 40% yield.



R_f: 0.53 (1:4 EtOAc-Hex)

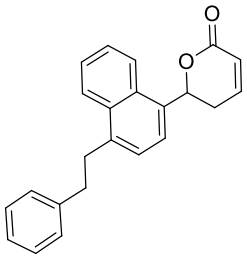
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.27 – 8.08 (m, 2H), 7.59 – 7.52 (m, 2H), 7.49 (d, *J* = 7.4 Hz, 1H), 7.43 – 7.16 (m, 6H), 6.67 (t, *J* = 6.6 Hz, 1H), 6.46 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.25 – 6.14 (m, 1H), 5.90 – 5.74 (m, 2H), 5.17 – 5.03 (m, 2H), 3.36 (dd, *J* = 9.8 and 6.8 Hz, 2H), 3.05 (dd, *J* = 9.8 and 6.8 Hz, 2H), 2.86 – 2.80 (m,

2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.40, 141.89, 138.14, 136.47, 134.85, 134.53, 134.21, 133.54, 130.94, 128.56, 128.42, 128.36, 126.03, 125.90, 125.66, 125.41, 124.46, 123.91, 123.65, 117.93, 72.49, 40.35, 36.98, 35.24, 29.69.

3.1.17. 6-(4-Phenethylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (55b)

Into a two necked flask 8.1 mg of 1-(4-phenethylnaphthalen-1-yl)but-3-en-1-yl acrylate (0.022 mmol, 1.0 eq.) was dissolved in 6 mL dry DCM and into another two necked flask 2 mg of 2nd generation Grubbs' catalyst (0.0022 mmol, 0.1 eq.) was placed and solved in 1 mL of dry DCM under nitrogen atmosphere and then added into the ester solution. This mixture was stirred under nitrogen atmosphere at reflux during 2 hours. Organic solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:2) resulted desired 6 mg product with 83% yield.



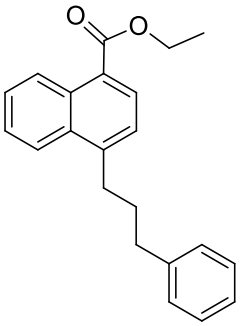
R_f: 0.10 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.07 (m, 1H), 8.03 – 7.97 (m, 1H), 7.62 (dd, *J* = 7.4 and 0.7 Hz, 1H), 7.57 – 7.51 (m, 2H), 7.36 (d, *J* = 7.4 Hz, 1H), 7.09 – 7.01 (m, 1H), 6.28 – 6.16 (m, 2H), 3.05 (dd, *J* = 8.8 and 6.9 Hz, 2H), 2.89 – 2.78 (m, 2H), 1.82 – 1.69 (m, 2H), 1.68 – 1.58 (m, 1H), 1.38 – 1.29 (m, 2H), 0.89 (d, *J* = 6.6 Hz, 6H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.91, 145.79, 140.68, 132.60, 132.29, 130.81, 126.53, 126.04, 125.85, 125.41, 124.38, 123.62, 122.11, 110.44, 39.56, 33.96, 31.53, 29.11, 28.38, 23.10, 23.09.

3.1.18. Ethyl 4-(3-phenylpropyl)-1-naphthoate (63c)

Into a two necked flask 123.9 mg of magnesium turnings (5.1 mmol, 3.0 eq.) was placed and solved in 5 mL of dry ether under nitrogen atmosphere. Then 512 mg of (2-Bromoethyl)benzene (5.1 mmol, 3.0 eq.) was added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 84.2 mg of CuCl (0.85 mmol, 0.5 eq.) and 500 mg of ethyl 4-(bromomethyl)-1-naphthoate (1.7 mmol, 1.0 eq.) were dissolved in 3 mL THF and Grignard reagent was added into these mixture drop-wise at room temperature. After 2 hours, reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 337 mg product with 65% yield.



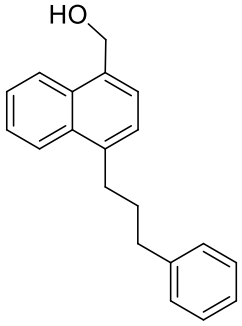
R_f: 0.54 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.96 (ddd, *J* = 8.7, 1.4 and 0.7 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.01 (ddd, *J* = 8.4, 1.5 and 0.7 Hz, 1H), 7.60 (ddd, *J* = 8.5, 6.8 and 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.3, 6.8 and 1.4 Hz, 1H), 7.38 – 7.27 (m, 3H), 7.25 – 7.18 (m, 3H), 4.47 (q, *J* = 7.1 Hz, 2H), 3.26 – 3.00 (m, 2H), 2.76 (t, *J* = 7.6 Hz, 2H), 2.11 (t, *J* = 7.7 Hz, 2H), 1.46 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.54, 143.89, 141.66, 131.96, 131.58, 129.55, 128.28, 128.28, 128.20, 128.20, 126.92, 126.34, 125.86, 125.79, 125.74, 124.63, 123.89, 60.72, 35.62, 32.79, 31.89, 14.23.

3.1.19. (4-(3-Phenylpropyl)naphthalen-1-yl)methanol (66c)

Into a two necked flask 337 mg of ethyl 4-(3-phenylpropyl)-1-naphthoate (1.06 mmol 1.0 eq.) was placed and solved in 3 mL of dry THF under nitrogen atmosphere and stirred under reflux. Afterwards a solution of 60.2 mg of $LiAlH_4$ (1.59 mmol, 1.5 eq.) in 2 mL dry THF was added drop wise into mixture which was cooled down to 0 ^oC. Then the reaction was stirred at room temperature for 2 hours. Then reaction mixture was cooled again 0 ^oC and acidified with 1 N HCl. Crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10 to 1:2) resulted desired 55 mg product with 19% yield.



R_f: 0.20 (1:8 EtOAc-Hex)

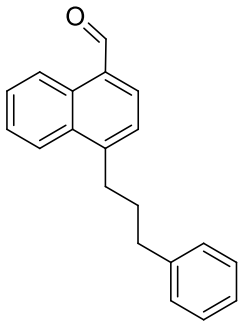
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.14 (m, 1H), 8.04 – 7.98 (m, 1H), 7.58 – 7.50 (m, 2H), 7.43 (dd, *J* = 7.2, 2.1 Hz, 1H), 7.34 – 7.28 (m, 3H), 7.27 – 7.20 (m, 3H), 5.11 (d, *J* = 2.1 Hz, 2H), 3.11 (td, *J* = 7.8 and 2.1 Hz, 2H), 2.77 (td, *J* = 7.7 and 2.1 Hz, 2H), 2.15 – 2.07 (m, 2H), 1.79 (s, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.89, 138.84, 134.36, 131.99, 131.47, 128.28, , 128.28, 128.15, 128.15, 125.70, 125.64, 125.52, 125.24, 125.11, 124.27, 124.23, 63.65, 35.65, 32.44, 32.04.

3.1.20. 4-(3-Phenylpropyl)-1-naphthaldehyde (54c)

Into a two necked flask 47.2 mg of PCC (0.219 mmol, 1.1 eq.) was placed and solved in 4 mL of dry DCM under nitrogen atmosphere, and then 55 mg of (4-(3-phenylpropyl)naphthalen-1-yl)methanol (0.199 mmol, 1 eq.) was dissolved in 3 mL dry DCM. Afterwards alcohol solution was added into PCC solution drop-wise. The reaction mixture was stirred 2 hours under nitrogen atmosphere and then the solid part

of the mixture was filtered with the help of filter paper. The organic phase (filtrate) was washed with 1 M NaOH (20 mL) and then 1 M HCl (20 mL). Organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 51 mg product with 90% yield.



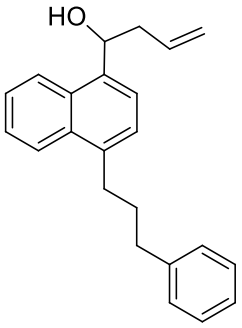
R_f: 0.19 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 9.40 – 9.32 (m, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.70 (ddd, *J* = 8.4, 6.8 and 1.3 Hz, 1H), 7.60 (ddd, *J* = 8.3, 6.8 and 1.4 Hz, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.37 – 7.31 (m, 2H), 7.27 – 7.22 (m, 3H), 3.21 – 3.13 (m, 2H), 2.80 (t, *J* = 7.6 Hz, 2H), 2.18 – 2.07 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.42, 146.98, 141.75, 136.91, 132.09, 131.08, 130.12, 128.65, 128.56, 128.56,128.53, 128.53, 126.91, 126.11, 125.68, 125.28, 124.19, 35.91, 33.30, 32.17.

3.1.21. 1-(4-(3-Phenylpropyl)naphthalen-1-yl)but-3-en-1-ol (67c)

Into a two necked flask 17.9 mg of magnesium turnings (0.747 mmol, 4.0 eq.) were placed and solved in 3 mL of dry ether under nitrogen atmosphere.Then 64.6 μL of allybromide (0.747 mmol, 4.0 eq.) were added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 51 mg of 4-(3-phenylpropyl)-1-naphthaldehyde (0.187 mmol, 1.0 eq.) was dissolved in 2 mL THF and Grignard reagent was added into this mixture drop-wise at room temperature. After 2 hours reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:8) resulted desired 41.8 mg product with 71% yield.



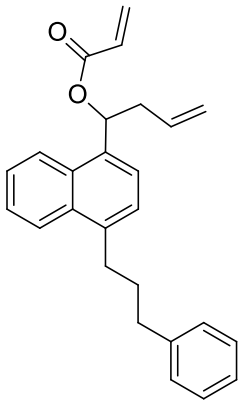
R_f: 0.19 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.09 (m, 1H), 8.07 – 8.00 (m, 1H), 7.59 (d, *J* = 6.7 Hz, 1H), 7.54 – 7.50 (m, 2H), 7.36 – 7.29 (m, 3H), 7.26 – 7.21 (m, 3H), 6.02 – 5.90 (m, 1H), 5.52 (dd, *J* = 8.4 and 4.0 Hz, 1H), 5.27 – 5.14 (m, 2H), 3.12 (td, *J* = 7.4 and 2.6 Hz, 2H), 2.82 – 2.72 (m, 3H), 2.68 – 2.56 (m, 1H), 2.19 – 2.05 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 141.82, 137.84, 137.31, 134.62, 131.80, 130.39, 128.17, , 128.17, 128.03, 128.03, 125.52, 125.28, 125.27, 125.05, 124.38, 123.34, 122.22, 117.97, 69.63, 42.53, 35.57, 32.36, 31.92.

3.1.22. 1-(4-(3-Phenylpropyl)naphthalen-1-yl)but-3-en-1-yl acrylate (68c)

Into a two necked flask 41.8 mg of 1-(4-(3-phenylpropyl)naphthalen-1-yl)but-3-en-1-ol (0.134 mmol 1 eq.) was placed and solved in 5 mL of dry DCM under nitrogen atmosphere. Afterwards 21.8 mg of acryloyl chloride (0.241 mmol, 1.8 eq.) was added into mixture which was cooled 0 ^oC before adding 48.6 mg trimethylamine (0.48 mmol, 3.6 eq.) drop wise. Reaction was stirred at room temperature for 16 hours. Then reaction mixture was filtered with celite and poured into water. Crude product was extracted with DCM (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 36 mg product with 73% yield.



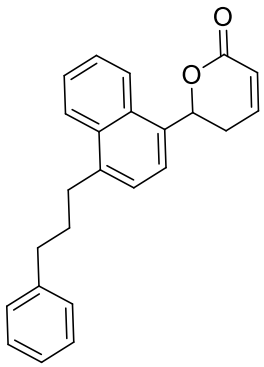
R_f: 0.45 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.20 – 8.17 (m, 1H), 8.03 – 8.00 (m, 1H), 7.57 – 7.48 (m, 3H), 7.34 – 7.29 (m, 3H), 7.25 – 7.19 (m, 3H), 6.67 (t, *J* = 6.6 Hz, 1H), 6.47 (dd, *J* = 17.4 and 1.5 Hz, 1H), 6.21 (dd, *J* = 17.3 and 10.4 Hz, 1H), 5.89 – 5.75 (m, 2H), 5.16 – 5.03 (m, 2H), 3.14 – 3.07 (m, 2H), 2.85 – 2.75 (m, 4H), 2.15 – 2.05 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.88, 142.53, 139.20, 134.50, 134.06, 132.57, 131.43, 131.15, 129.02, 128.91, 128.91, 128.78, 128.78, 126.29, 126.28, 125.95, 125.82, 125.08, 124.26, 124.06, 118.38, 72.95, 40.81, 36.33, 33.12, 32.59.

3.1.23. 6-(4-(3-Phenylpropyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (55c)

Into a two necked flask 36.2 mg of 1-(4-(3-phenylpropyl)naphthalen-1-yl)but-3-en-1-yl acrylate (0.098 mmol, 1.0 eq.) were dissolved in 5 mL dry DCM and into another two necked flask 8.29 mg of 2nd generation Grubbs' catalyst (0.0098 mmol, 0.1 eq.) was placed and solved in 1 mL of dry DCM under nitrogen atmosphere and then added into the ester solution. This mixture was stirred under nitrogen atmosphere at reflux during 2 hours. Organic solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:2) resulted desired 25 mg product with 73% yield.



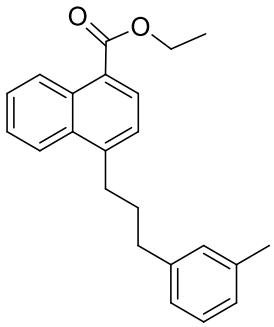
R_f: 0.06 (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.05 – 8.02 (m, 1H), 8.00 – 7.97 (m, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.33 – 7.28 (m, 2H), 7.24 – 7.20 (m, 3H), 7.07 – 7.02 (m, 1H), 6.24 – 6.16 (m, 2H), 3.14 – 3.09 (m, 2H), 2.84 – 2.74 (m, 4H), 2.13 – 2.07 (m, *J* = 7.9, 6.6, 1.5 Hz, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.55, 145.44, 142.11, 139.72, 132.25, 132.18, 130.51, 128.59, 128.49, 126.25, 126.00, 125.79, 125.63, 125.00, 124.03, 123.32, 121.79, 76.94, 35.95, 32.78, 32.29, 31.21.

3.1.24. Ethyl 4-(3-(m-tolyl)propyl)-1-naphthoate (63d)

Into a two necked flask 98.16 mg of magnesium turnings (4.09 mmol, 3.0 eq.) was placed and solved in 5 mL of dry ether under nitrogen atmosphere. Then 815.38 mg of 3-methylphenethyl bromide (4.09 mmol, 3.0 eq.) was added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 81.4 mg of CuCl (0.82 mmol, 0.6 eq.) and 400 mg of ethyl 4-(bromomethyl)-1-naphthoate (1.4 mmol, 1.0 eq.) were dissolved in 3 mL THF and Grignard reagent was added into these mixture drop-wise at room temperature. After 2 hours, reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 172 mg product with 39% yield.



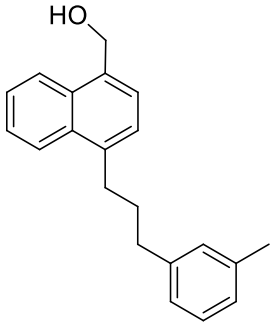
R_f: 0.57(1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) 9.04 (d, *J* = 8.5 Hz, 1H), 8.16 (d, *J* = 7.5 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.68 – 7.61 (m, *J* = 8.5, 4.8 and 1.3 Hz, 1H), 7.61 – 7.54 (m, 1H), 7.39 (d, *J* = 7.4 Hz, 1H), 7.28 – 7.21 (m, 1H), 7.07 (d, *J* = 6.8 Hz, 3H), 4.57 – 4.47 (m, 2H), 3.20 – 3.14 (m, 2H), 2.77 (t, *J* = 7.6 Hz, 2H), 2.39 (s, 3H), 2.19 – 2.09 (m, 2H), 1.51 (t, *J* = 7.1 Hz, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 167.82, 144.25, 141.88, 137.99, 132.24, 131.86, 129.87, 129.37, 128.38, 127.21, 126.75, 126.61, 126.06, 125.57, 124.90, 124.22, 61.00, 35.82, 33.11, 32.18, 21.52, 14.52.

3.1.25. (4-(3-(m-tolyl)propyl)naphthalen-1-yl)methanol (66d)

Into a two necked flask 172.0 mg of ethyl ethyl 4-(3-(m-tolyl)propyl)-1-naphthoate (0.52 mmol 1.0 eq.) was placed and solved in 3 mL of dry THF under nitrogen atmosphere and stirred under reflux. Afterwards a solution of 29.5 mg of $LiAlH_4$ (0.78 mmol, 1.5 eq.) in 2 mL dry THF was added drop wise into mixture which was cooled down to 0 ^oC. Then the reaction was stirred at room temperature for 2 hours. Then reaction mixture was cooled again 0 ^oC and acidified with 1 N HCl. Crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10 to 1:2) resulted desired 117.0 mg product with 78% yield.



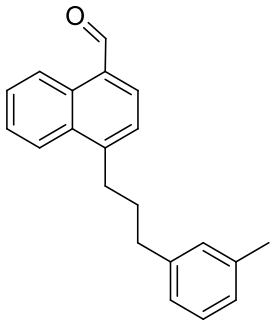
R_f: 0.13(1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.25 – 8.14 (m, 1H), 8.11 – 8.04 (m, 1H), 7.60 – 7.55 (m, 2H), 7.44 (d, *J* = 7.2 Hz, 1H), 7.33 (d, *J* = 7.2 Hz, 1H), 7.29 – 7.24 (m, 1H), 7.10 (d, *J* = 7.6 Hz, 2H), 5.10 (s, 2H), 3.19 – 3.12 (m, 2H), 2.85 – 2.68 (m, 2H), 2.41 (s, 3H), 2.22 – 2.05 (m, 3H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ142.28, 139.21, 138.09, 134.80, 132.42, 131.89, 129.52, 128.49, 126.82, 126.07, 125.90, 125.73, 125.64, 125.45, 124.71, 124.65, 63.89, 36.03, 32.90, 32.48, 21.67.

3.1.26. 4-(3-(m-tolyl)propyl)-1-naphthaldehyde (54d)

Into a two necked flask 96.0 mg of PCC (0.44 mmol, 1.1 eq.) was placed and solved in 4 mL of dry DCM under nitrogen atmosphere, and then 117.0 mg of (4-(3-(m-tolyl)propyl)naphthalen-1-yl)methanol (0.4 mmol, 1.0 eq.) was dissolved in 3 mL dry DCM. Afterwards alcohol solution was added into PCC solution drop-wise. The reaction mixture was stirred 2 hours under nitrogen atmosphere and then the solid part of the mixture was filtered with the help of filter paper. The organic phase (filtrate) was washed with 1 M NaOH (20 mL) and then 1 M HCl (20 mL). Organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 67.3 mg product with 58% yield.



R_f: 0.50(1:8 EtOAc-Hex)

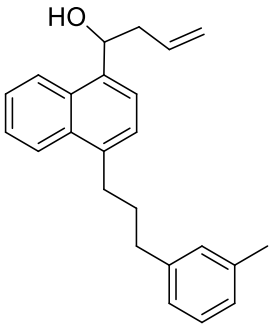
^{1}H-NMR (400 MHz, $CDCl_3$) 10.35 (s, 1H), 9.40 – 9.33 (m, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.90 (d, *J* = 7.3 Hz, 1H), 7.70 (ddd, *J* = 6.9, 4.1, 0.9 Hz, 1H), 7.65 – 7.57 (m, 1H), 7.49 (d, *J* = 7.3 Hz, 1H), 7.27 – 7.19 (m, 1H), 7.10 – 7.02 (m, 3H), 3.22 – 3.15 (m, 2H), 2.81 – 2.71 (m, 2H), 2.37 (s, 3H), 2.18 – 2.08 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.26, 146.93, 141.57, 137.94, 136.74, 132.00, 130.98, 130.01, 129.24, 128.51, 128.30, 126.77, 126.72, 125.55, 125.45, 125.15, 124.11, 35.72, 33.22, 32.05, 21.40.

3.1.27. 1-(4-(3-(m-tolyl)propyl)naphthalen-1-yl)but-3-en-1-ol (67d)

Into a two necked flask 22.4 mg of magnesium turnings (0.936 mmol, 4.0 eq.) were placed and solved in 3 mL of dry ether under nitrogen atmosphere. Then 113.2 mg of allybromide (0.936 mmol, 4.0 eq.) were added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 67.3 mg of 4-(3-(m-tolyl)propyl)-1-naphthaldehyde (0.234 mmol, 1.0 eq.) was dissolved in 2 mL THF and Grignard reagent was added into this mixture drop-wise at room temperature. After 2 hours reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:8) resulted desired 45.8 mg product with 59% yield.

R_f: 0.26(1:8 EtOAc-Hex)

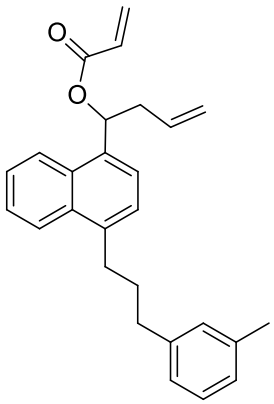


^{1}H-NMR (400 MHz, $CDCl_3$) 8.16 – 8.11 (m, 1H), 8.07 – 8.03 (m, 1H), 7.60 (d, *J* = 7.3 Hz, 1H), 7.56 – 7.50 (m, 2H), 7.39 – 7.34 (m, 1H), 7.27 – 7.16 (m, 1H), 7.09 – 7.02 (m, 3H), 6.02 – 5.89 (m, 1H), 5.53 (dd, *J* = 8.3, 4.0 Hz, 1H), 5.30 – 5.15 (m, 2H), 3.19 – 3.07 (m, 2H), 2.81 – 2.70 (m, 3H), 2.68 – 2.56 (m, 1H), 2.37 (s, 3H), 2.16 – 2.06 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 142.19, 138.33, 137.97, 137.73, 135.05, 132.25, 130.83, 129.39, 128.35, 126.67, 125.69, 125.67, 125.60, 125.45, 124.83, 123.77, 122.66, 118.33, 70.09, 42.94, 35.92, 32.82, 32.34, 21.54.

3.1.28. 1-(4-(3-(m-tolyl)propyl)naphthalen-1-yl)but-3-en-1-yl acrylate (68d)

Into a two necked flask 45.8 mg of 1-(4-(3-(m-tolyl)propyl)naphthalen-1-yl)but-3-en-1-ol (0.139 mmol 1.0 eq.) was placed and solved in 5 mL of dry DCM under nitrogen atmosphere. Afterwards 22.6 mg of acryloyl chloride (0.250 mmol, 1.8 eq.) was added into mixture which was cooled 0 ^{o}C before adding 50.6 mg trimethylamine (0.50 mmol, 3.6 eq.) drop wise. Reaction was stirred at room temperature for 16 hours. Then reaction mixture was filtered with celite and poured into water. Crude product was extracted with DCM (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 37 mg product with 70% yield.



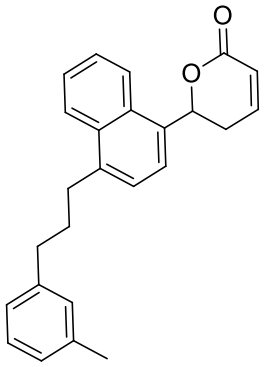
R_f: 0.32(1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.21 – 8.12 (m, 1H), 8.01 (dd, *J* = 14.8 and 6.6 Hz, 1H), 7.71 (dd, *J* = 5.7 and 3.4 Hz, 1H), 7.55 – 7.47 (m, 3H), 7.35 – 7.29 (m, 1H), 7.18 (t, *J* = 7.3 Hz, 1H), 7.03 (d, *J* = 3.5 Hz, 2H), 6.66 (t, *J* = 6.6 Hz, 1H), 6.47 (d, *J* = 1.5 Hz, 1H), 6.43 (d, *J* = 1.5 Hz, 1H), 6.25 – 6.15 (m, 1H), 5.87 – 5.82 (m, 1H), 5.16 – 5.01 (m, 2H), 3.16 – 3.02 (m, 2H), 2.93 – 2.79 (m, 2H), 2.76 – 2.70 (m, 2H), 2.33 (s, 3H), 2.13 – 2.03 (m, 2H).

3.1.29. 6-(4-(3-(m-tolyl)propyl)naphthalen-1-yl)-5,6-dihydro-2H-pyran-2-one (55d)

Into a two necked flask 7 mg of 1-(4-(3-(m-tolyl)propyl)naphthalen-1-yl)but-3-en-1-yl acrylate (0.018 mmol, 1.0 eq.) were dissolved in 5 mL dry DCM and into another two necked flask 1.6 mg of 2nd generation Grubbs' catalyst (0.0018 mmol, 0.1 eq.) was placed and solved in 1 mL of dry DCM under nitrogen atmosphere and then added into the ester solution. This mixture was stirred under nitrogen atmosphere at

reflux during 2 hours. Organic solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:2) resulted desired 5 mg product with 70% yield.

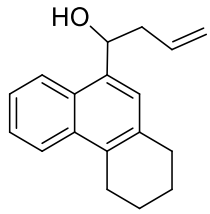


R_f: (1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ ^{1}H NMR (400 MHz, cdcl$_3$) δ 8.07 – 8.01 (m, 1H), 8.01 – 7.95 (m, 1H), 7.73 – 7.69 (m, 1H), 7.62 (d, *J* = 7.4 Hz, 1H), 7.54 – 7.51 (m, *J* = 5.9, 3.2, 1.3 Hz, 2H), 7.37 (d, *J* = 7.4 Hz, 1H), 7.26 (s, 1H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.04 – 7.01 (m, 2H), 6.24 – 6.20 (m, *J* = 3.7, 2.9, 1.7 Hz, 1H), 4.21 (dd, *J* = 11.0, 4.9 Hz, 1H), 3.14 – 3.07 (m, 2H), 2.84 – 2.79 (m, 2H), 2.76 – 2.69 (m, 2H), 2.34 (s, 3H), 2.13 – 2.03 (m, 2H).

3.1.30. 1-(1,2,3,4-Tetrahydrophenanthren-9-yl)but-3-en-1-ol (67e)

Into a two necked flask 34.25 mg of magnesium turnings (1.427 mmol, 4.0 eq.) were placed and solved in 3 mL of dry ether under nitrogen atmosphere. Then 172.6 mg of allybromide (1.427 mmol, 4.0 eq.) were added and this mixture was stirred under reflux. When the turbidity was observed the solution was continued to stir at room temperature. Then into another two necked flask 75 mg of 1,2,3,4-tetrahydrophenanthrene-9-carbaldehyde (0.357 mmol, 1.0 eq.) was dissolved in 2 mL THF and Grignard reagent was added into this mixture drop-wise at room temperature. After 2 hours reaction was quenched with 10 mL saturated NH_4Cl and crude product was extracted with ethyl acetate (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:8) resulted desired 76 mg product with 85% yield.



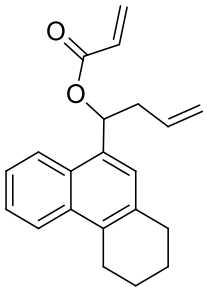
R_f: 0.40(1:8 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) 8.06 – 8.02 (m, 2H), 7.57 – 7.46 (m, 2H), 7.41 (s, 1H), 6.03 – 5.92 (m, 1H), 5.48 (dd, *J* = 8.5 and 3.9 Hz, 1H), 5.29 – 5.19 (m, 2H), 3.12 (t, *J* = 6.3 Hz, 2H), 2.94 (t, *J* = 6.1 Hz, 2H), 2.82 – 2.73 (m, 1H), 2.65 – 2.56 (m, 1H), 2.27 (s, 1H), 2.03 – 1.95 (m, 2H), 1.94 – 1.86 (m, 2H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.00, 135.38, 134.24, 133.22, 131.55, 129.20, 125.77, 125.41, 125.12, 123.91, 123.58, 118.45, 70.13, 43.28, 30.85, 26.03, 23.59, 23.22.

3.1.31. 1-(1,2,3,4-Tetrahydrophenanthren-9-yl)but-3-en-1-yl acrylate (68e)

Into a two necked flask 76 mg of 1-(1,2,3,4-tetrahydrophenanthren-9-yl)but-3-en-1-ol (0.302 mmol 1 eq.) was placed and solved in 5 mL of dry DCM under nitrogen atmosphere. Afterwards 49.23 mg of acryloyl chloride (0.544 mmol, 1.8 eq.) was added into mixture which was cooled 0 ^oC before adding 110.1 mg trimethylamine (1.088 mmol, 3.6 eq.) drop wise. Reaction was stirred at room temperature for 16 hours. Then reaction mixture was filtered with celite and poured into water. Crude product was extracted with DCM (3x25 mL) and then the combined organic phase was dried over anhydrous $MgSO_4$. Organic layer was filtered, and concentrated under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:10) resulted desired 82 mg product with 89% yield.



R_f: 0.61 (1:8 EtOAc-Hex)

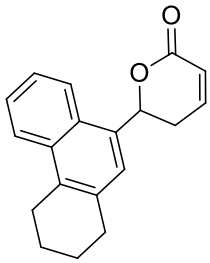
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.18 – 8.13 (m, 1H), 8.05 – 8.00 (m, 1H), 7.56 – 7.48 (m, 2H), 7.31 (s, 1H), 6.65 (dd, *J* = 7.4 and 5.9 Hz, 1H), 6.48 (ddd, *J* = 17.3, 1.5 and 0.5 Hz, 1H), 6.22 (ddd, *J* = 17.3, 10.4 and 0.5 Hz, 1H), 5.90 – 5.79 (m, 2H), 5.20 – 5.06 (m, 2H), 3.11 (t, *J* = 6.2 Hz, 2H), 2.95 – 2.82 (m, 4H), 2.04 – 1.82 (m,

4H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.42, 133.74, 133.71, 133.09, 132.94, 131.98, 130.84, 128.96, 128.60, 126.36, 125.58, 125.05, 123.56, 123.54, 117.80, 72.66, 40.38, 30.48, 25.74, 23.18, 22.81.

3.1.32. 6-(1,2,3,4-tetrahydrophenanthren-9-yl)-5,6-dihydro-*2H*-pyran-2-one (55e)

Into a two necked flask 82 mg of 1-(1,2,3,4-tetrahydrophenanthren-9-yl)but-3-en-1-yl acrylate (0.267 mmol, 1.0 eq.) were dissolved in 5 mL dry DCM and into another two necked flask 22.67 mg of 2nd generation Grubbs' catalyst (0.0267 mmol, 0.1 eq.) was placed and solved in 2 mL of dry DCM under nitrogen atmosphere and then added into the ester solution. This mixture was stirred under nitrogen atmosphere at reflux during 2 hours. Organic solvent was removed under reduced pressure to yield crude product. Purification by column chromatography (EtOAc/Hex; 1:2) resulted desired 63 mg product with 85% yield.



R_f: 0.31(1:4 EtOAc-Hex)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 – 8.02 (m, 1H), 7.91 – 7.88 (m, 1H), 7.55 – 7.44 (m, 3H), 7.07 – 7.00 (m, 1H), 6.24 – 6.14 (m, 2H), 3.12 (t, *J* = 6.3 Hz, 2H), 2.92 (t, *J* = 7.0 Hz, 2H), 2.82 – 2.75 (m, 2H), 2.01 – 1.84 (m, 4H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.82, 145.62, 134.33, 133.19, 132.90, 131.51, 128.73, 126.75, 126.02, 125.58, 124.10, 123.02, 121.91, 77.01, 31.68, 30.73, 26.06, 23.42, 23.07.

CHAPTER 4

CONCLUSION

Derivatives of α,β-unsaturated δ-lactones are valuable, biologically active compounds. In this thesis, novel 4'-alkyl substituted klavuzon derivatives were synthesised in order to evaluate for their cytotoxic activity against cancer cell lines in near future. Design of the structure has been done on the basis of the knowledge about the structure activity relationship (SAR) studies of naphthalen-1-yl substituted α,β-unsaturated δ-lactone derivatives.

First attempts toward the synthesis of target compounds were started with alkyl substitution at benzylic carbons of naphthalene 1-yl derived acetal and carboxylic acids with base (LDA and n-BuLi) to form klavuzon derivatives however this route was not succesful. Thus alkyl substituted esters were synthesised from ethyl 4-bromoethyl-1-naphthoate **(62)** via cupper (I) catalayzed addition of Grignard reagents. For the synthesis of klavuzon derivatives a well-known three steps was used and aldehyde was the key functutional group of these method. Thus, the formed ester derivatives **(63a-d)** were reduced to 4-alkylnaphthalene-1-yl methanol derivatives and these products were oxidized to 4-alkyl-1-naphtaldehydes **(54a-d)**. In the last part of the synthesis obtained aldehydes **(54a-e)** was treated with ally magnesium bromide solution to obtain homoallylic alcohols via Grignard reaction. In the next step homoallylic alcohols converted to esters **(68a-e**) with the help of acryloyl chloride in the presence of trimethylamine. Finally formed acrylate esters were transferred into klavuzon derivatives **(55a-e)** via alkene metathesis reactions by using 2nd generation Grubbs' catalayst.

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APPENDIX A

1H NMR AND 13C NMR SPECTRUM OF COMPOUNDS 63a, 66a, 54a, 67a, 68a AND 55a

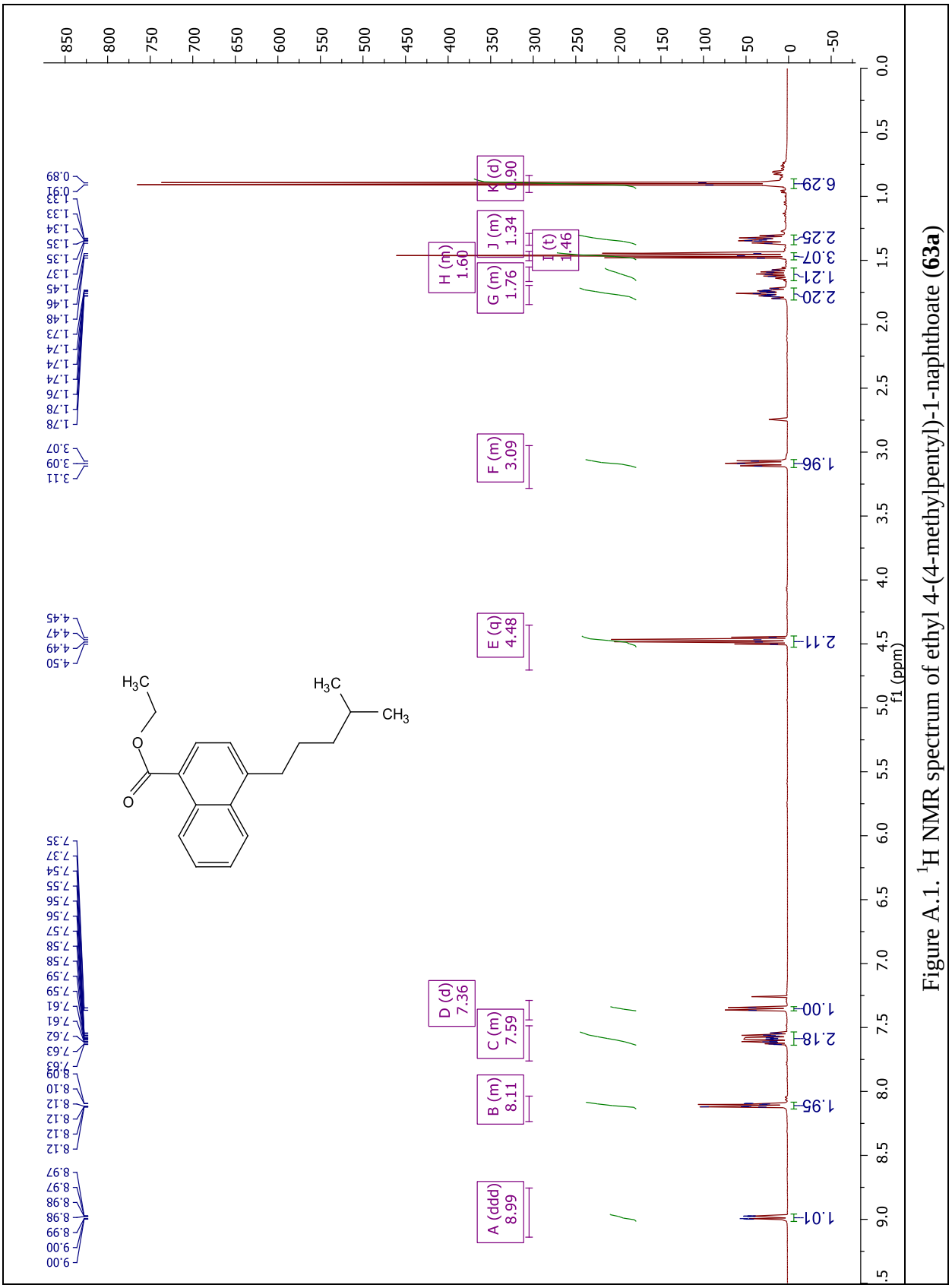

Figure A.1. ^{1}H NMR spectrum of ethyl 4-(4-methylpentyl)-1-naphthoate (**63a**)

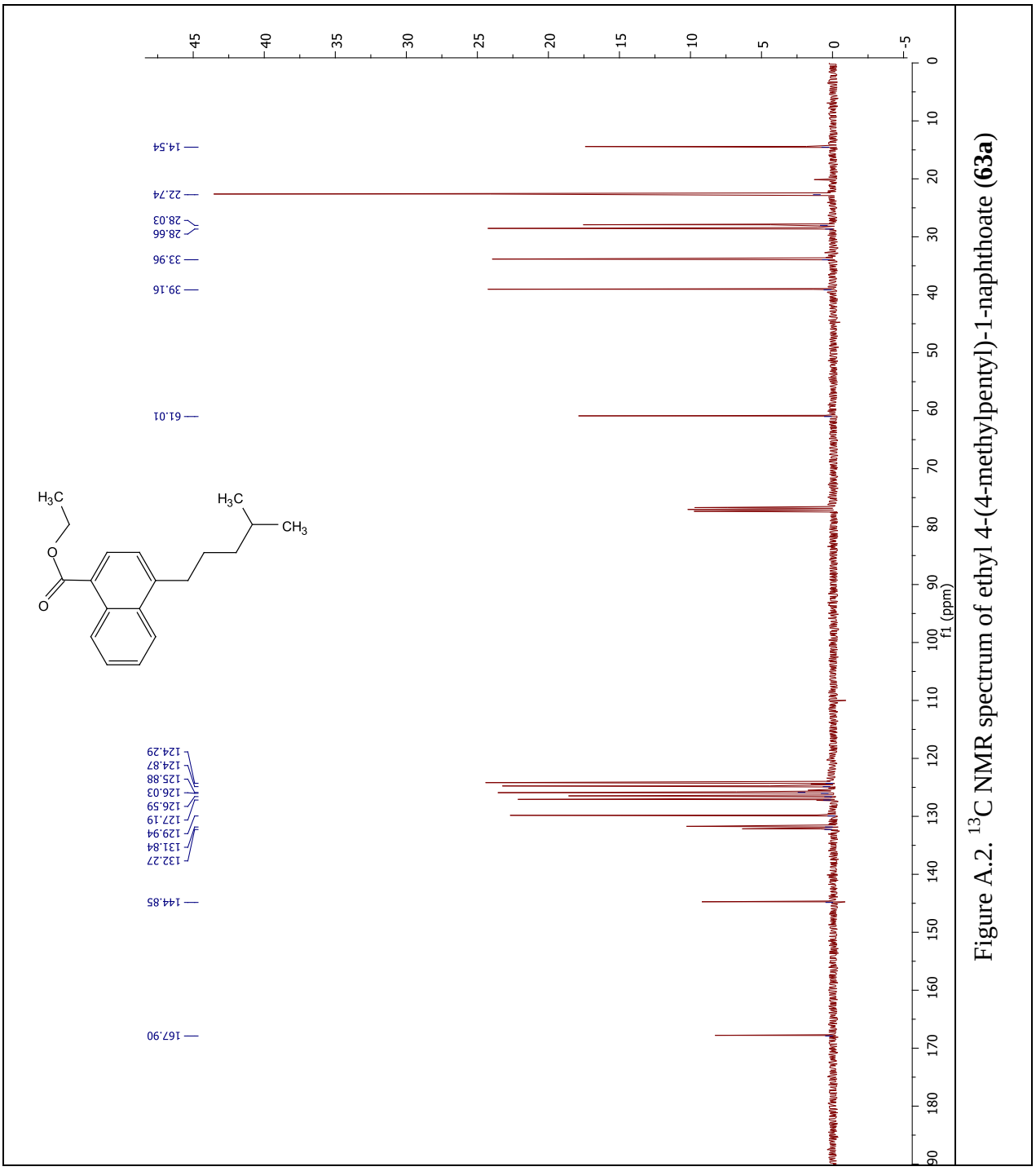

Figure A.2. ^{13}C NMR spectrum of ethyl 4-(4-methylpentyl)-1-naphthoate (**63a**)

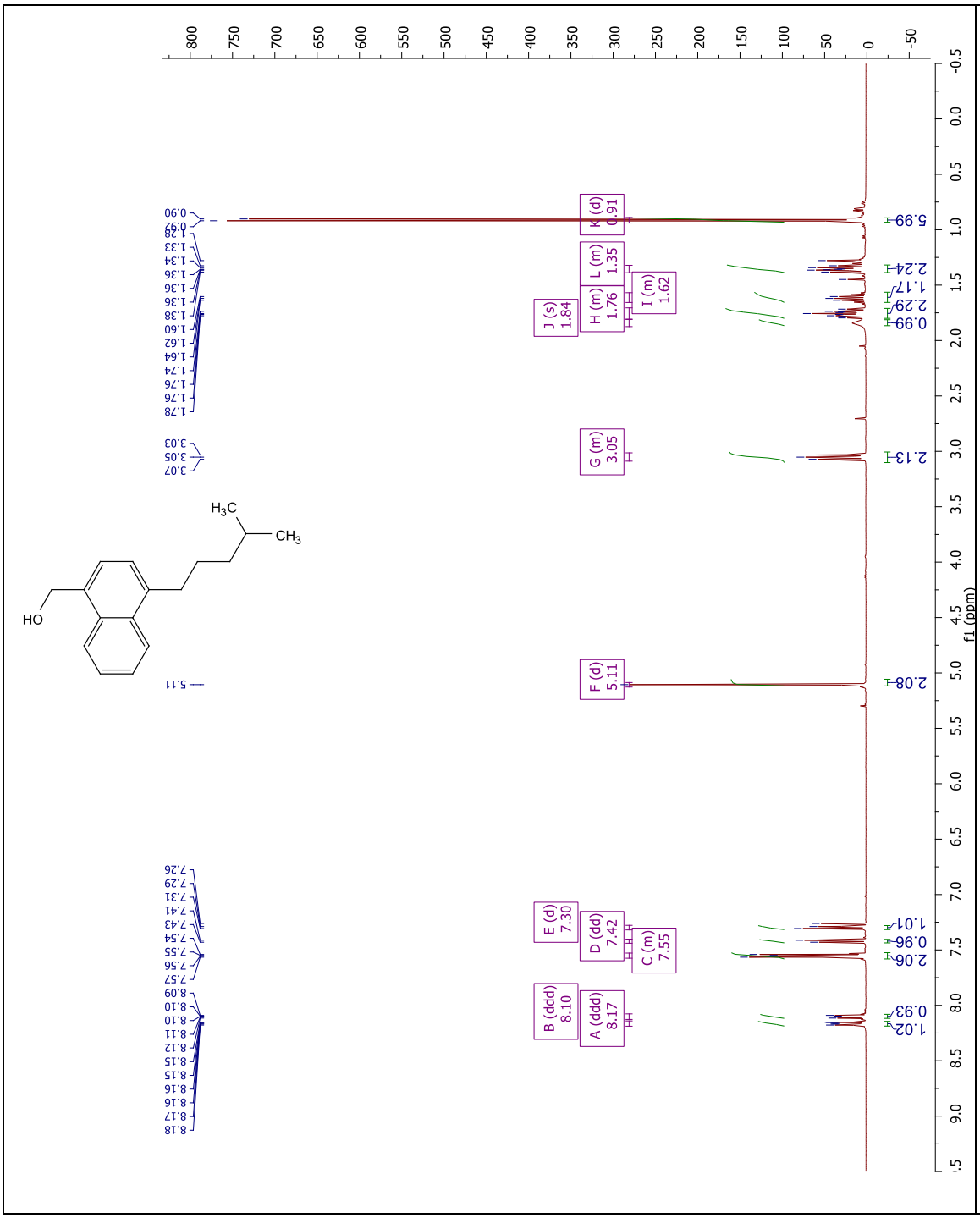

Figure A.3. ^{1}H NMR spectrum of (4-(4-methylpentyl)naphthalen-1-yl)methanol (**66a**)

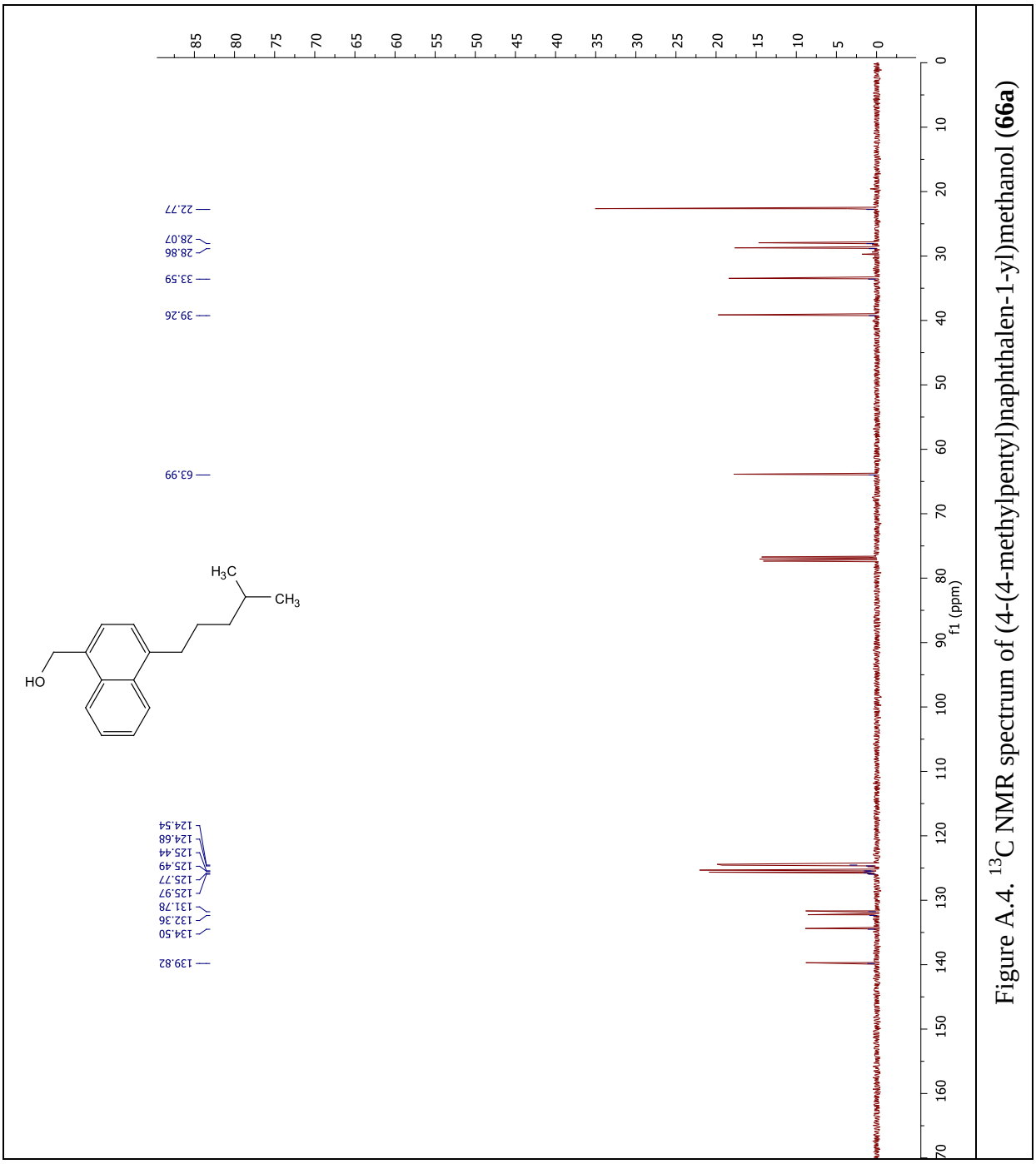

Figure A.4. ^{13}C NMR spectrum of (4-(4-methylpentyl)naphthalen-1-yl)methanol (**66a**)

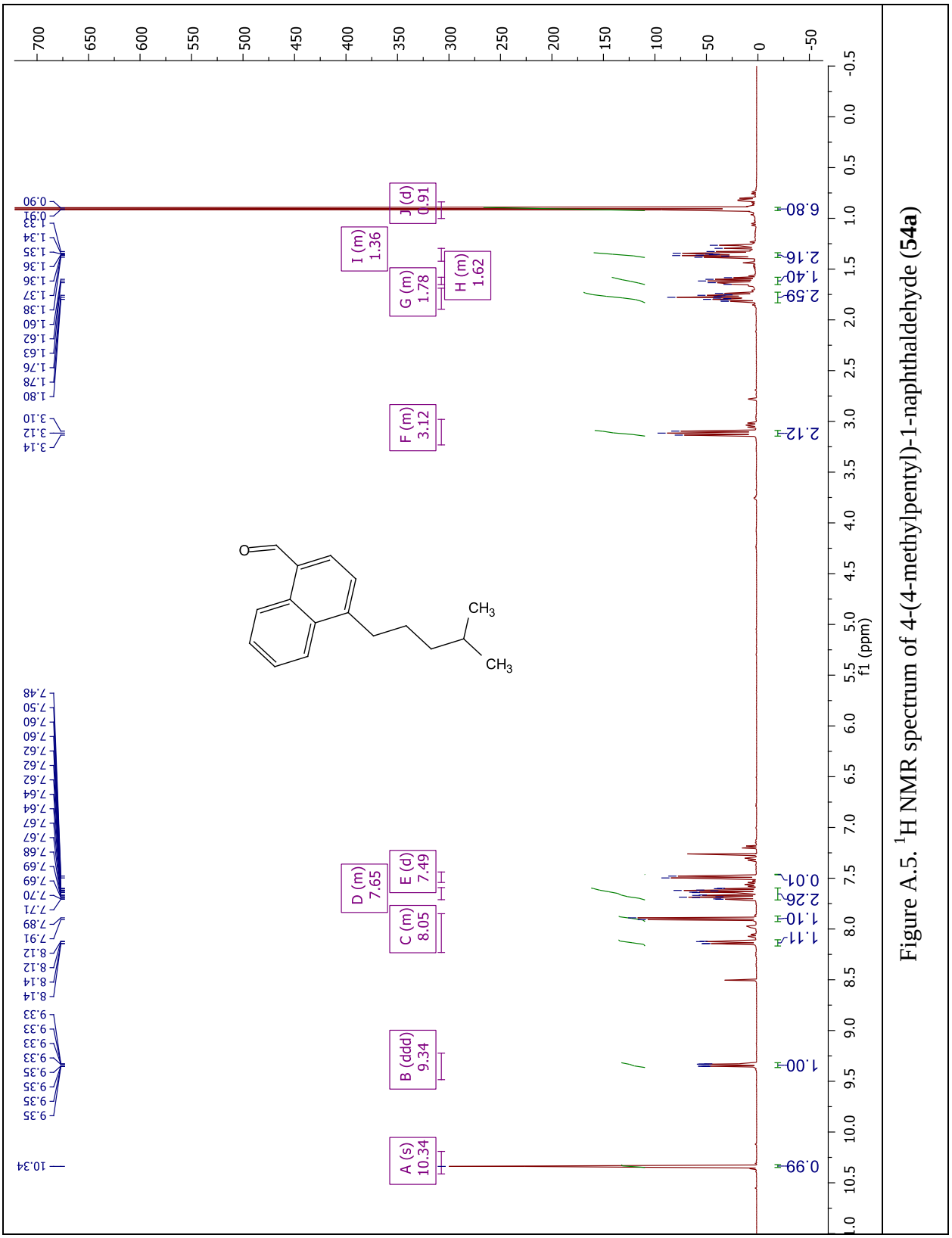

Figure A.5. ^{1}H NMR spectrum of 4-(4-methylpentyl)-1-naphthaldehyde (**54a**)

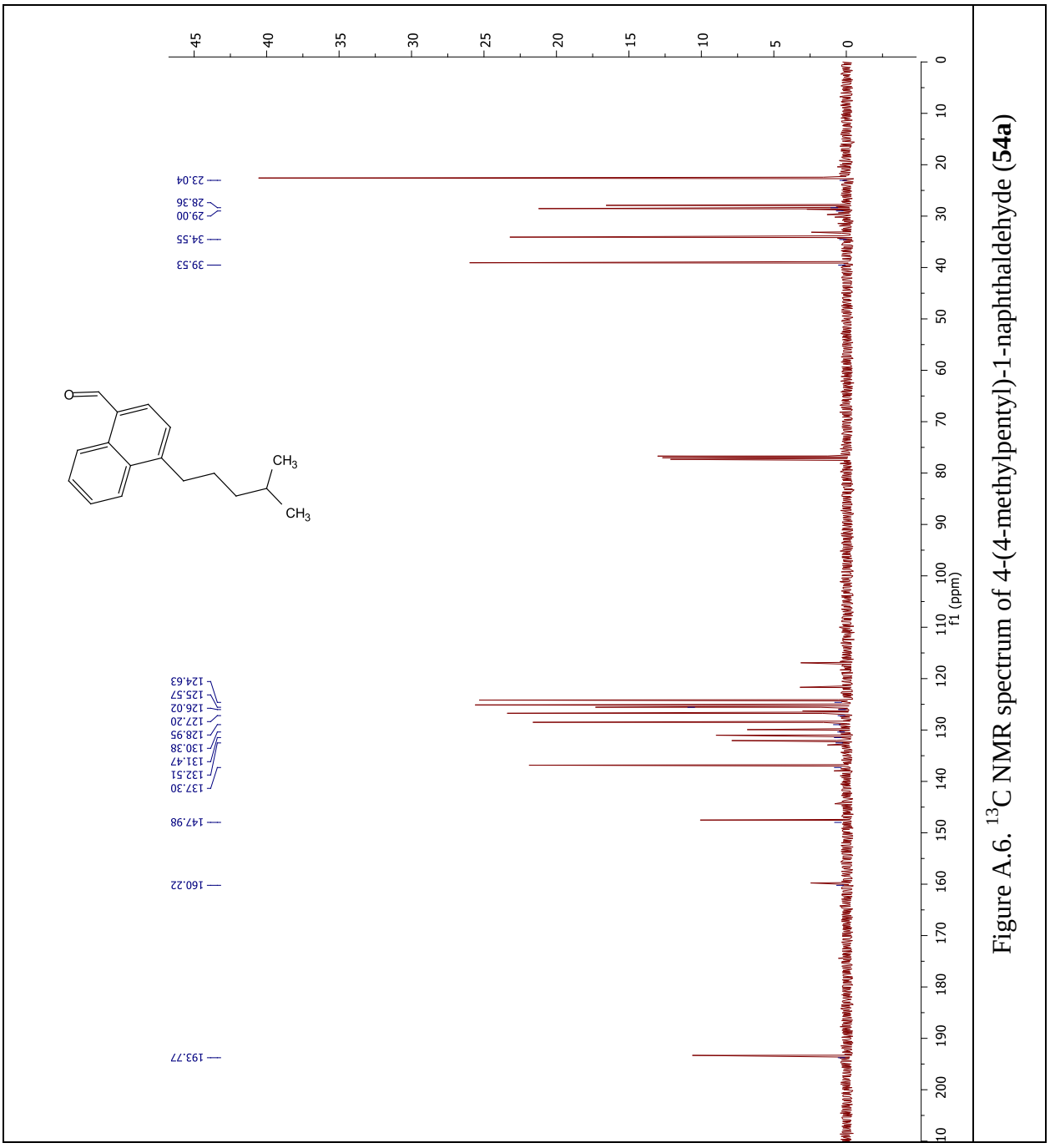

Figure A.6. ^{13}C NMR spectrum of 4-(4-methylpentyl)-1-naphthaldehyde (**54a**)

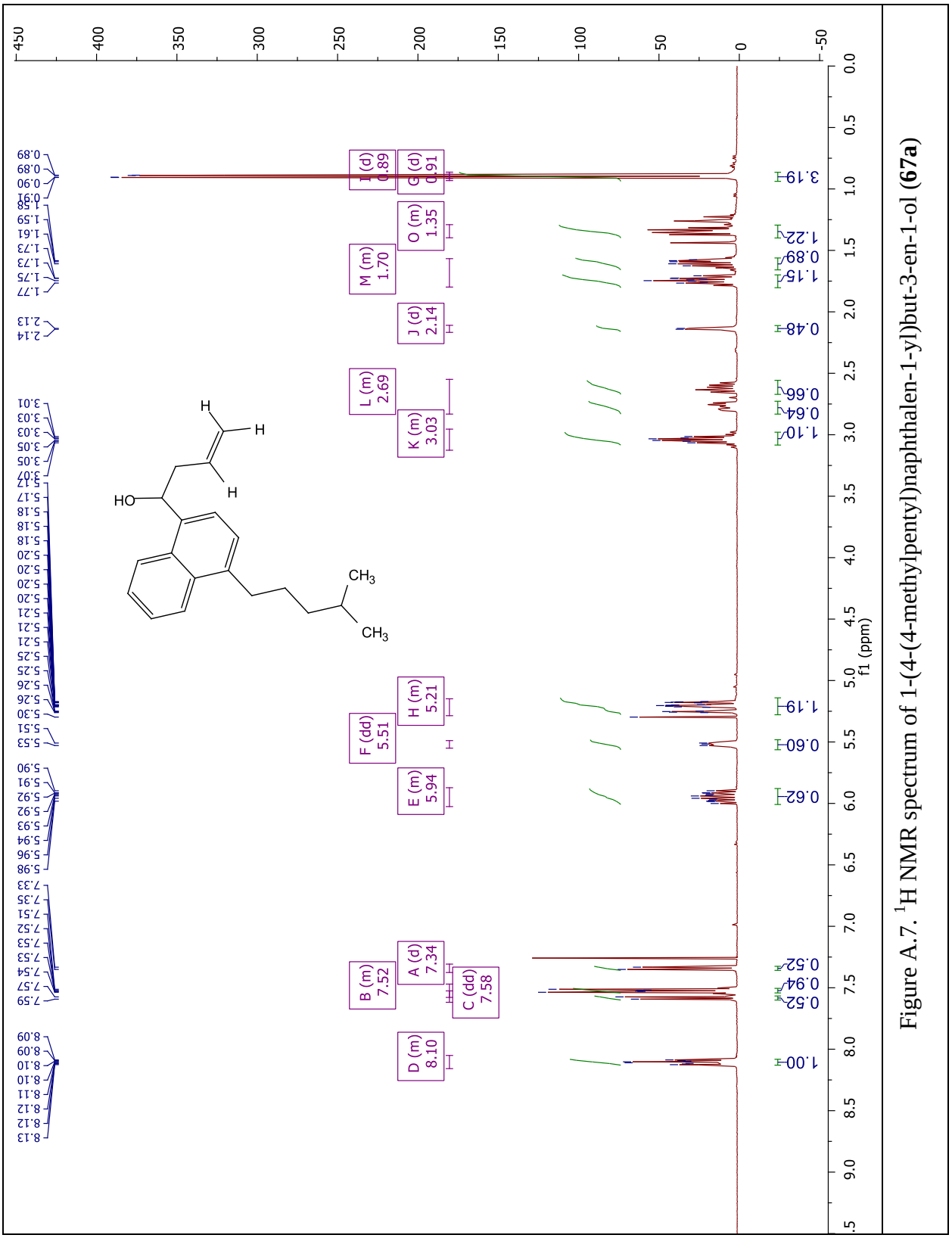

Figure A.7. ^{1}H NMR spectrum of 1-(4-(4-methylpentyl)naphthalen-1-yl)but-3-en-1-ol (**67a**)

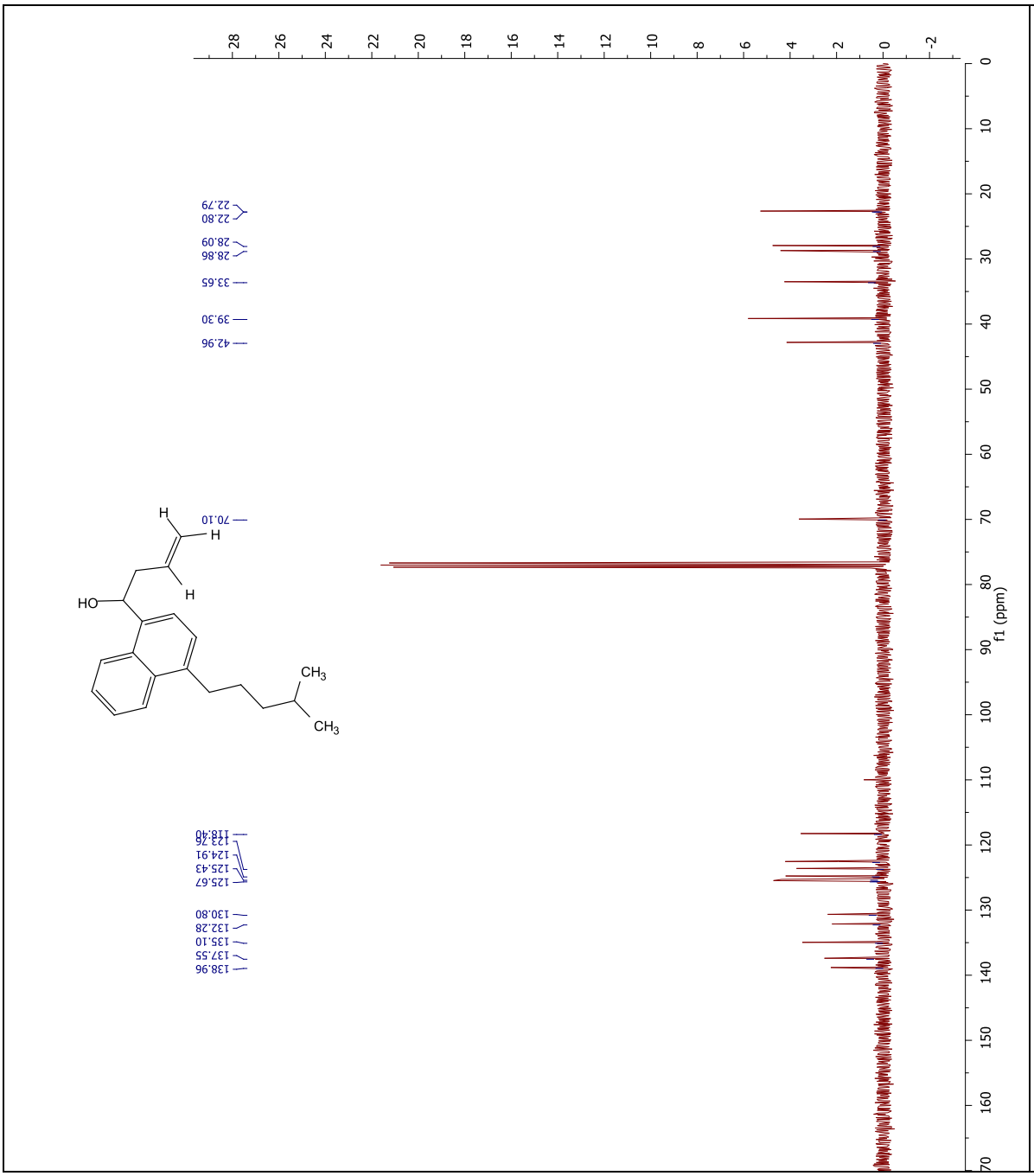

Figure A.8. ^{13}C NMR spectrum of 1-(4-(4-methylpentyl)naphthalen-1-yl)but-3-en-1-ol (**67a**)

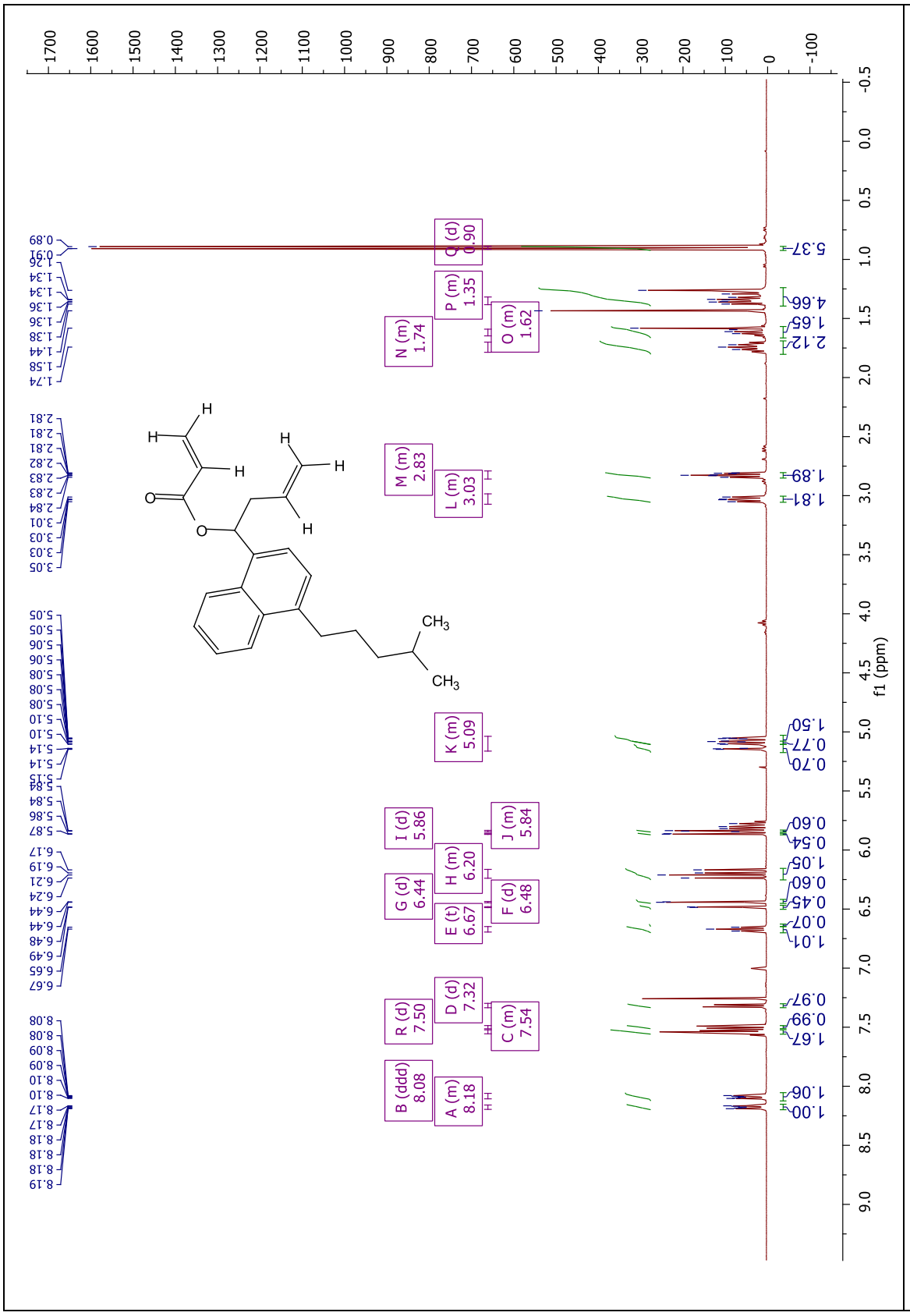

Figure A.9. ^{1}H NMR spectrum of 1-(4-(4-methylpentyl)naphthalen-1-yl)but-3-en-1-yl acrylate (**68a**)

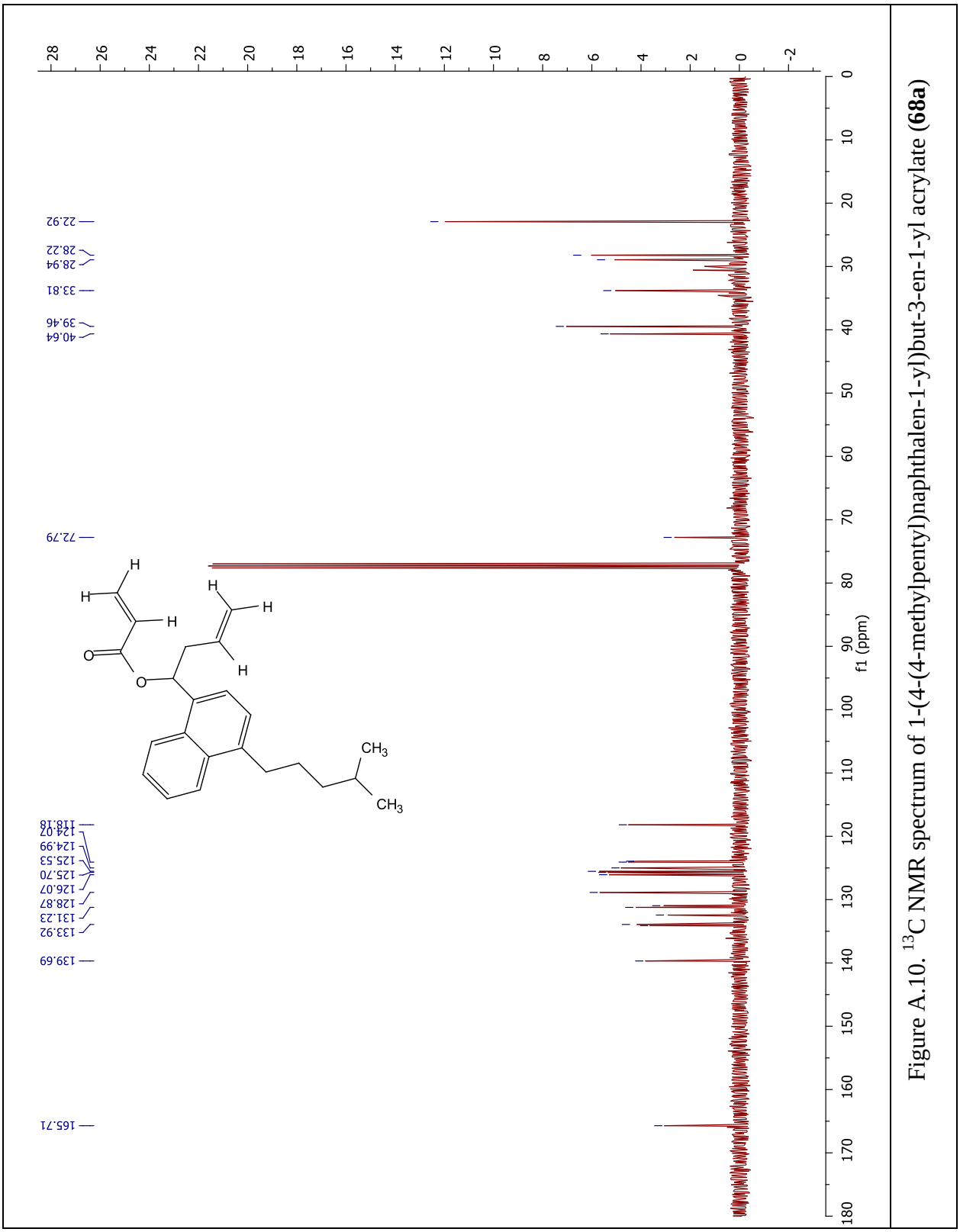

Figure A.10. ^{13}C NMR spectrum of 1-(4-(4-methylpentyl)naphthalen-1-yl)but-3-en-1-yl acrylate (**68a**)

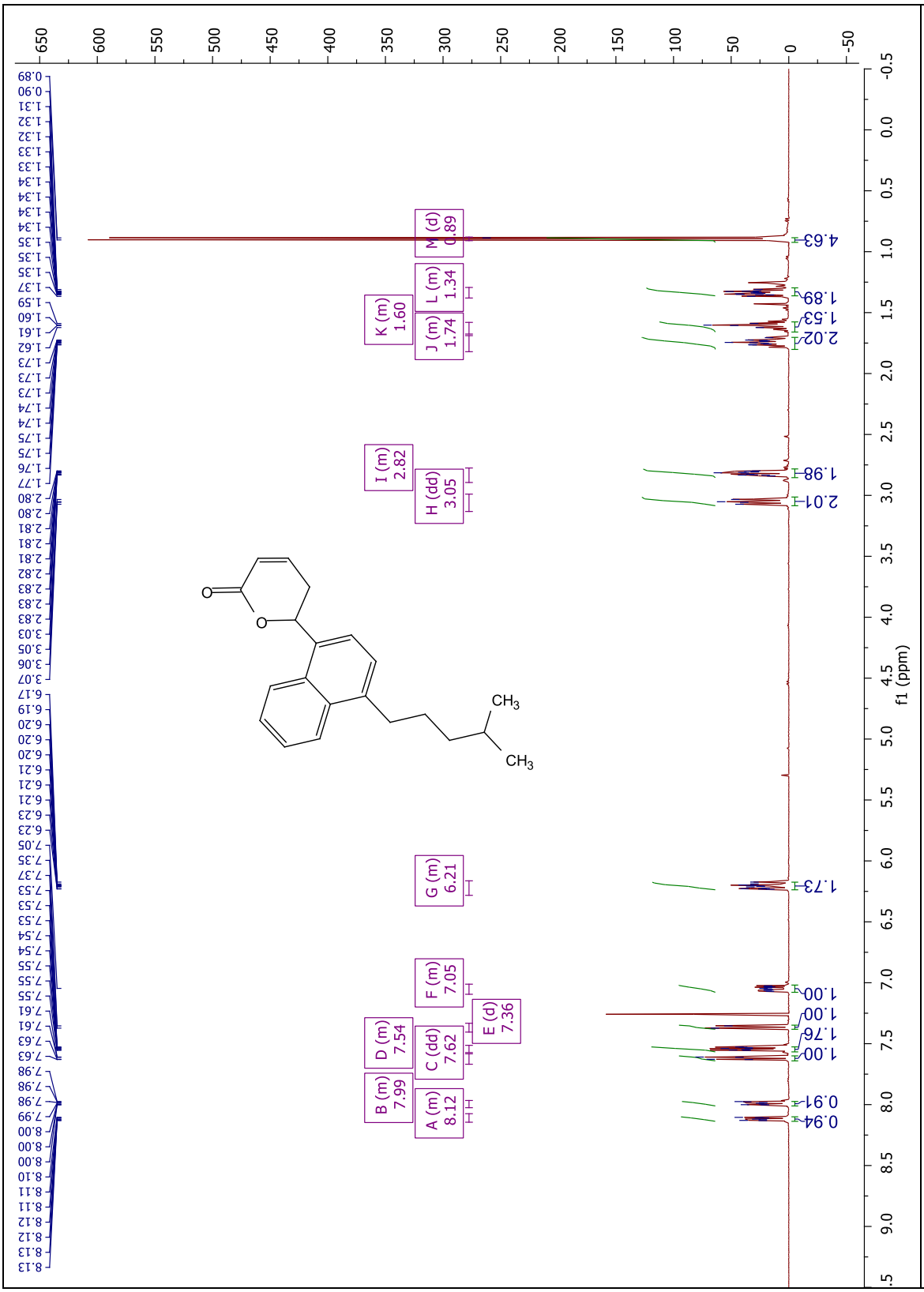

Figure A.11. ^{1}H NMR spectrum of 6-(4-(4-methylpentyl)naphthalen-1-yl)-5,6-dihydro-2H-pyran-2-one (**55a**)

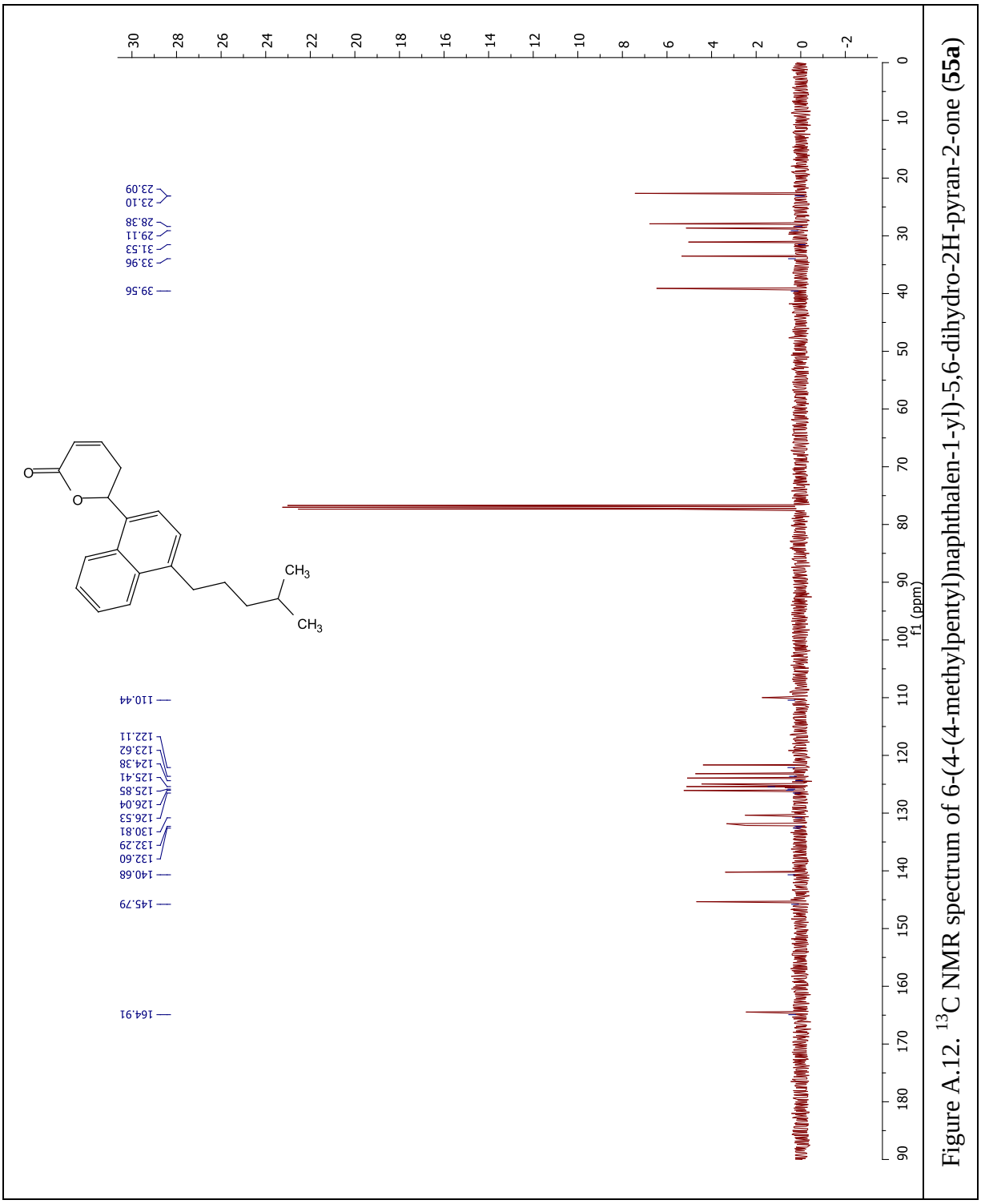

Figure A.12. ^{13}C NMR spectrum of 6-(4-(4-methylpentyl)naphthalen-1-yl)-5,6-dihydro-2H-pyran-2-one (**55a**)