SYNTHESIS of NOVEL 6,7-DIHYDRO-*5H*-OXEPIN-2-ONE DERIVATIVES

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ABSTRACT

SYNTHESIS OF NOVEL 6,7-DIHYDRO-*5H*-OXEPIN-2-ONE DERIVATIVES

In last decades, biologically active natural compound (*R*)-goniothalamin and its derivatives received great attention from researchers. The reason for this interest is the wide range of biological properties of goniothalamin; including anti-microbial, anti-protozoan, anti-inflammatory, cytotoxic and anti-proliferative activities.

The present study sets out the asymmetric large scale synthesis of α,β-unsaturated lactone derivative (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one. In recent studies, this linker modified analog of goniothalamin was shown to be cytotoxic against PC-3 (prostate cancer) and MCF-7 (human breast cancer) cell lines with half maximal inhibitory concentration values of 0.13 μM and 2.6 μM, respectively. The preparation of the target compound consists of three steps. First, asymmetric synthesis of homoallylic alcohol using (*R*)-Tol-BINAP•AgF catalyst complex was performed with allyltrimethoysilane. After that, treating the chiral homoallylic alcohol with acryloylchloride in the presence of triethylamine followed by ring closing metathesis of acrylate ester using 1st generation Grubbs' catalyst finally yielded the lead compound. The large scale preparation of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one was achieved in order to evaluate its in-vivo anti-cancer activity in mice, and to study its mechanism of action in the cell.

Additionally, synthesis of three new 7-membered β-γ unsaturated lactone derivatives was carried out. Allylation reaction of corresponding aldehydes with allyltrimethoxysilane using CuCl-TBAT gave the racemic homoallylic alcohols. Coupling reactions of this homoallylic alcohol with 3-butenoic acid in the presence of DCC/DMAP yilded the esters. Ring closing metathesis of the related esters was studied by using 2nd generation Grubbs' catalyst.

ÖZET

YENİ 6,7-DİHİDRO-*5H*-OKSEPİN-2-ON TÜREVLERİNİN SENTEZİ

Biyolojik olarak aktif (*R*)-goniothalamin molekülü ve türevleri, son yıllarda araştırmacıların büyük ilgisini çekmektedir. Bu ilginin başlıca nedeni goniothalaminin antimikrobiyal, antiprotozoan, sitotoksik ve antiproliferatif özellikler gibi geniş bir spektrumda biyolojik aktiviteye sahip olmasından ileri gelmektedir.

Bu çalışma bir α,β-doymamış lakton türevi olan (*R*)-(+)-6-(2-Metilnaftalen-1-il)-5,6-dihidro-*2H*-piran-2-on'un asimetrik olarak büyük ölçekli sentezini açıklamaktadır. Bu bağlaç türevlendirilmiş goniothalamin türevinin, PC-3 (prostat kanseri) ve MCF-7 (meme kanseri) hücrelerinde sitotoksik etkiye sahip olduğu daha once yapılan çalışmalarda bulunmuş ve. IC_{50} (hücre çoğalmasını %50 inhibe eden konsantrasyon) değeri prostat ve meme kanseri hücreleri için sırayla 0.13 μM and 2.6 μM olarak belirtilmiştir. Sentezi amaçlanan lakton türevi üç basamakta sentezlenmiştir. Başlangıç olarak hedef homoallilik alkol, (*R*)-Tol-BINAP, AgF katalizör kompleksi yardımıyla, alliltrimetoksisilan ile asimetrik olarak sentezlenmiştir. Ardından bu kiral homoallilik alkol akriloyil klorür ile trietilamin bazı varlığında muamele edilerek ilgili akrilat esteri elde edilmiştir. Son basamakta ise bu esterin 1. Nesil Grubbs katalizörü ile halka kapanma reaksiyonu gerçekleştirilerek hedef (*R*)-(+)-6-(2-Metilnaftalen-1-il)-5,6-dihidro-*2H*-piran-2-on molekülü elde edilmiştir. Molekülün büyük ölçekli sentezi farelerde in vivo anti-kanser çalışmalarda kullanılmak üzeredir. Bu doğrultuda, sentezlenen molekül hayvan deneylerinde ve çalışma mekanizmalarının incelenmesi deneylerinde uygulanacaktır.

Çalışmanın bir diğer amacı, üç yeni 7 üyeli α,β-doymamış lakton türevlerinin sentezidir. 1-naftaldehit, 2-naftaldehit ve *trans*-sinamaldehit moleküllerinden yola çıkılarak önce bu aldehitlerin CuCl-TBAT varlığında alliltrimetoksisilan ile allilenme tepkimeleri gerçekleştirilmiş ve rasemik homoallilik alkoller elde edilmiştir. Elde edilen alkoller DCC/DMAP kullanılarak 3-butenoik asit ile esterleştirildikten sonra bu esterlerin 2. nesil Grubbs katalizörü varlığında halka kapanma reaksiyonları üzerinde çalışılmıştır.

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CHAPTER 1

INTRODUCTION

1.1. Cancer and Chemotherapy

Cancer is simply defined as uncontrolled growth of abnormal cells and their spreading of other healthy tissues. Cancer is a general name for a group of diseases those are possible to occur in 60 different tissues of the body. World Health Organization (WHO) announced that; cancer is the reason for 13% of all the deaths in the worldwide which means 7.6 million deaths in 2008. In 2030, the number of death caused by cancer is expected to be rise to around 3.1 million (GLOBOCAN-2008-IARC-Section of Cancer Information-10/10/2012). About 30% of the global cancer death is caused by tobacco use, high body mass index, low fruit and vegetable intake, lack of physical activity and alcohol use.

Cells that have similar structure and function constitute tissues in our body. There are four main groups of tissues: Epithelial, Connective, Muscle, and Nervous Tissue. Epithelial tissue, both inside and outside, covers most parts of the body. It provides physical protection, controls permeability, provides sensation by creating our "skin". Connective tissue protects and supports the body and the organs. Muscle tissue is responsible for not only skeletal movement, but also movement of food, blood and secretions. Main duty of nervous tissue is conducting the electrical impulses between some parts of the body. All of these structures and functions of the tissues are managed by particular cell types, so the number of the cells should be controlled during this constitution deliberately.

Cell loss and cell regeneration capacities differ from tissue to tissue. Some regions in our body for example; the skin, intestine and the haematopoietic system, possess rapidly self-renewing system. It means that the fast loss of these cells-by ageing or damaging- are being recovered rapidly by proliferation (Sarraf 2005). In conditionally renewing tissues, like liver, breast, prostate, proliferation is moderate. It occurs only when significant changes are present in the structure of the tissue. At least, some tissues like female germ line or central nervous systems, are essentially non-

renewing tissues that have a little or no cell replacement in older ages. When a cell is damaged; either DNA can be repaired or apoptosis can be triggered. Apoptosis is the suicide of the cell in a programmed manner. Tissue homeostasis depends on the balance between proliferation and apoptosis of the cells. The case of "cancer" steps in at this point; if proliferation becomes more "favored", cancer may occur then.

The term chemotherapy is used to express killing cancer cells or preventing them from proliferating by using cytotoxic or cytostatic drugs respectively (King and Robins 2006). It is the treatment of cancer which is often includes both surgery and radiation (Hanson 2006). Proliferation of tumor cells is faster than that of healthy cells and the evolution of chemotherapeutic agents depends on this investigation (Johnstone, Ruefli et al. 2002). These agents can prevent tumor cell proliferation and survival by inducing some cellular responses (Lowe and Lin 2000). Nowadays it is considered that apoptosis is the foremost inducing response and these pathways assist the cytotoxic action of cancer drugs (Lowe and Lin 2000).

Natural compound goniothalamin (**1**) was first extracted from the bark of *Cryptocarya caloneura* (Hlubucek and Robertson 1967) and then synthesized with different routes by various research groups (Ramachandran, Reddy et al. 2000), (Sundby, Perk et al. 2004), (de Fátima and Pilli 2003). Goniothalamin (**1**) is a 6-membered α,β-unsaturated styryl lactone and a potential anti-tumor agent by inducing apoptosis in Jurkat T-cells (Inayat-Hussain, Osman et al. 1999). Also *Goniothalamus sp.* showed cytotoxic activity on human breast cancer cell lines and trigger apoptosis (Chien and Pihie 2003). Goniothalamin (**1**) showed similar apoptotic activity in vascular smooth muscle cells (Chan, Rajab et al. 2006).

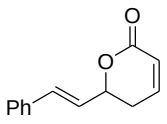

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Figure 1. Structure of goniothalamin (**1**).

A set of bicycloaryl substituted and conformationally constrained analogues of compound (**1**) derivatives were synthesized and tested for the cytotoxic activity (Kasaplar, Yilmazer et al. 2009). It is found out that goniothalamin (**1**) analogues; 1-

naphthyl substituted *(R)*-5,6-dihydro-*2H*-pyran-2-ones shows high cytotoxic activity against PC-3 and MCF-7 cancer cell lines. Especially two analogues, containing methyl substituent in 1-naphthyl at positions 2 and 4, exhibited superior toxicity.

1.2. Biological Activities of α,β-unsaturated Lactones

1.2.1. 7-membered Lactones

Regard to our knowledge, there are not any reported biological activities for 7-membered α,β-unsaturated lactones. Biological activity of these compounds, and especially their behaviour in plasma with regard to 6-membered rings are in our interest.

1.2.2. 6-membered Lactones

A well known pharmacophore, α,β-unsaturated carbonyl compounds constitute an important part of biologically active molecules which are used in pharmaceutical industry. As long as there are naturally occurring examples of α,β-unsaturated lactones; most of these compounds can be produced synthetically. One of the members of this class of compounds is 6-membered α,β-unsaturated lactones having broad range of biological properties including antioxidant, antibacterial, antifungal, antimicrobial, anticancer, anti-inflammatory and immunosuppressive effects (Lee, Lee et al. 2011).

Biological activity of α,β-unsaturated lactones results from their "Michael Acceptor property". Michael acceptor is a conjugated π-bond system to an electron withdrawing group such as carbonyl, nitrile, imino, immonium, sulfonyl and nitro (Ahn and Sok 1996). These electron withdrawing groups make the β-carbon of the double bond more electropositive; so it becomes more suitable for nucleophilic attacks (Figure 2).

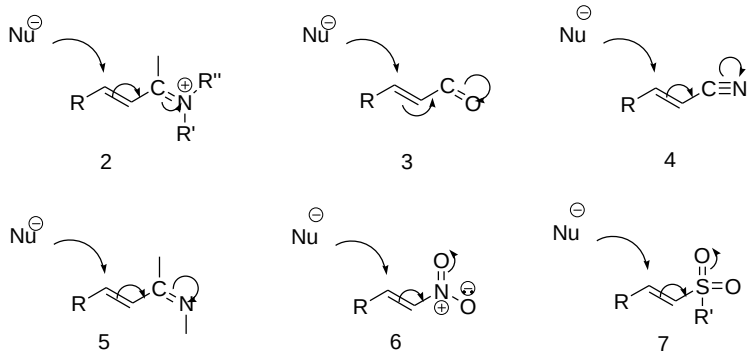


Figure 2. Nucleophilic attacks to the electropositive β-carbon of the various types of Michael acceptor.

Macromolecules of the cells have some nucleophilic sides like nucleophilic amino acid side chains (cysteine, lysine, serine, threonine). As a target, the nucleophile can attack to the electropositive β-carbon of the Michael acceptor (Figure 3). So a covalent bonding will occur between macromolecule and β-carbon of the conjugated double bond. This covalent bonding is thought to be the reason for irreversible inhibition of enzymes (Kasaplar, Cakmak et al. 2010).

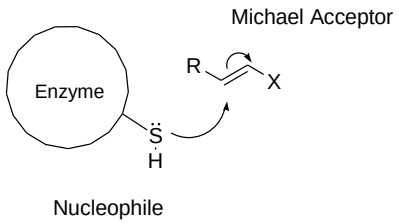
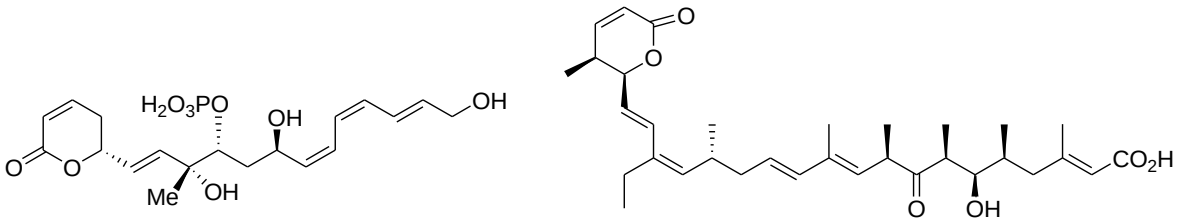


Figure 3. The attack of nucleophilic side of an enzyme to the electrophilic β-carbon of a conjugated alkene.

Fostriecin (**8**) is known for its cytotoxic activity in leukemia, lung cancer, breast cancer and ovarian cancer cells. The Topoisomerase II enzyme inhibition of compound (**8**) is reported as IC_{50}= 40 μM (Boritzki, Wolfard et al. 1988). In a study, saturated lactone analogue of (**8**) was synthesized (Buck, Hardouin et al. 2003) and it was determined that the cytotoxic activity is almost lost with 200-fold decrease in protein phosphatase 2A inhibition with respect to fostriecin (**8**).



8 9

Figure 4. Structures of fostriecin (**8**) and leptomycin B (**9**).

Leptomycin B (**9**) is an another anti-cancer agent which is reported as an inhibitor of CRM-1 mediated nuclear export of proteins. CRM-1 is an export receptor for leucine-rich nuclear export signals. Leptomycin B (**9**) makes covalent bonding to cysteine residue of proteins with Michael type addition to inactivate CRM-1 and inhibition of nuclear transport occurs in this way (Kudo, Matsumori et al. 1999).

There are many other naturally occurring examples of 6-membered α,β-unsaturated lactones; such as kazusamycin A (**10**), ratjadone (**11**), obolactone (**12**), kavain (**13**), argentilactone (**14**), parasorbic acid (**15**), massoialactone (**16**), goniodiol (**17**), goniotriol (**18**), anamarine (**19**), spicigerolide (**20**), strictifolione (**21**), asperlin (**22**), cryptocarya diacetate (**23**), tarchonanthuslactone (**24**), isoaltholactone (**25**), callystatin A (**26**), phomopsolide C (**27**), boronolide and pironetin.

Kazusamycin A (**10**) was first isolated from *Streptomyces* sp (Umezawa, Komiyama et al. 1984) and it has antitumor activity against leukemia. Although kazusamycin (**10**) has hepatic and gastrointestinal toxicity, it is discovered that it has antitumor activity against P388 leukemia, HeLa cells and sarcoma 180. It also has antimicrobial activity (Komiyama, Okada et al. 1985), and it showed potential anti-HIV activity (Wang, Ponelle et al. 1997). The anti-tumor activity of compound (**10**) is also depends on the irreversible Michael type addition in order to inhibit the CRM1 dependent nucleocytoplasmic transport (Kudo, Matsumori et al. 1999).

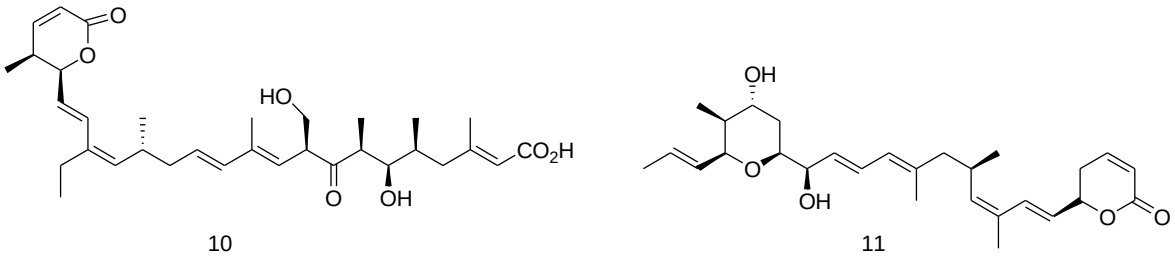


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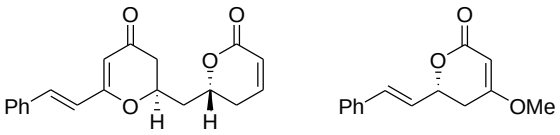
Figure 5. Structures of kazusamycin A (**10**) and ratjadone (**11**).

One of the biologically active α,β-unsaturated compound ratjadone (**11**) was first isolated from *Sorangium cellulosum* (Schummer, Gerth et al. 1995). Ratjadone (**11**) is structurally similar to leptomycin B (**9**) and kazusamycin A (**10**) and it shows high cytotoxic activity (IC_{50}: 50 pg/mL) in cultured mouse cell lines (L929). In addition, it inhibits the growth of the HeLa cell line (KB3.1) at significantly low concentrations (40 pg/mL) (Kalesse, Christmann et al. 2001).



12 13

Figure 6. Structures of obolactone (**12**), and kavain (**13**) compounds.

Alpha-pyrone obolactone (**12**) was first isolated from the fruits and trunk bark of *Cryptocarya obovata* which is a tropical tree of the cinnamon family. Obolactone (**12**) exhibits medium cytotoxic acitivity on human nasopharyngeal carcinoma KB cells (56% and 23% inhibition at 10 μg/mL for ethanolic extracts of the fruit and trunk bark, respectively). Inhibitory activity on the growth of KB cells for (**12**) was reported 3 μM as the half maximal inhibitory concentration (IC_{50} value) (Dumontet, Van Hung et al. 2004).

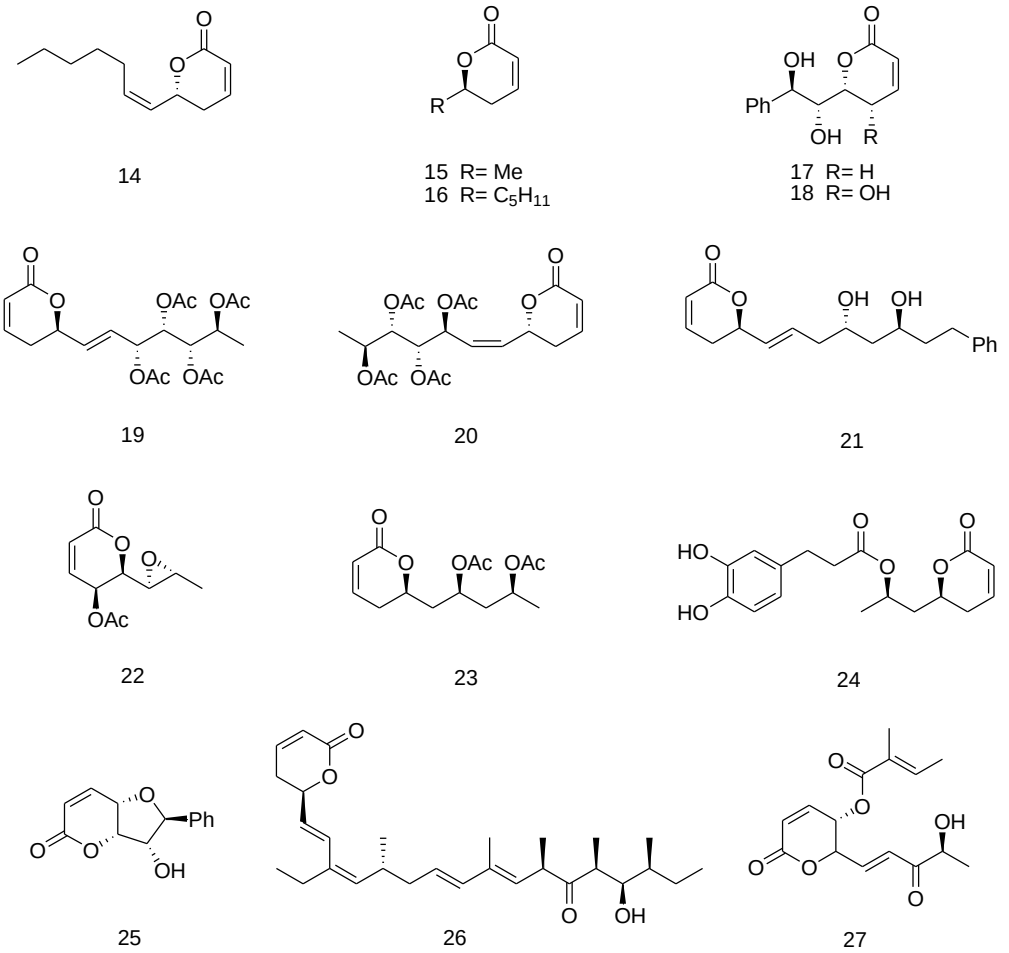


Figure 7. Structure of argentilactone (**14**), parasorbic acid (**15**), massoialactone (**16**), goniodiol (**17**), goniotriol (**18**), anamarine (**19**), spicigerolide (**20**), strictifolione (**21**), asperlin (**22**), cryptocarya diacetate (**23**), tarchonanthuslactone (**24**), isoaltholactone (**25**), callystatin A (**26**), phomopsolide C (**27**).

1.2.3. Goniothalamin

In last decades, the styryl pyrone derivative goniothalamin (**1**) have been of great interest by researchers. Recent reports expose that goniothalamin (**1**) possess a wide range of biological properties including anti-proliferative, anti-tumor, anti-microbial, anti-protozoan, anti-fungal, larvicidal, insecticidal and anti-inflammatory activities.

Secondary metabolite goniothalamin (**1**) can be isolated from the plant *Goniothalamus sp*, and the richest source of compound (**1**) was found to be *G.*

andersonii with highest concentration in fruits and lowest in young stems and leaves (Jewers, Davis et al. 1972).

Caspases are a family of cysteine proteases and these molecules play role in apoptosis by activating other crucial enzymes in biochemical processes. Poly (ADP-ribose) polymerase (PARP) is a nuclear DNA repair enzyme which is activated by caspases after DNA damage. PARP is proposed to be a biochemical marker of apoptosis (Kaufmann, Desnoyers et al. 1993). In recent studies, compound (**1**) was shown to be apoptosis inducer in leukemic T-Cell Jurkats; reffering to caspase-3 and caspase-7 activation proved by PARP cleveage (Inayat-Hussain, Osman et al. 1999). In addition, Goniothalamin (**1**) treated HL-60 cells show a significant loss of mitochondrial transmembrane potential over control cells (77.7 ± 5.8% and 13.4 ± 0.9%, respectively). Caspase-9 activation was also observed in compound (**1**) treated leukemic cells (Inayat-Hussain, Annuar et al. 2003). Lately it was demonstrated that Goniothalamin (**1**) induces apoptosis by DNA damaging and oxidative stress without any dependence on neither caspase-2 nor Bcl-2 (Inayat-Hussain, Chan et al. 2010).

Anti-microbial activity studies of compound (**1**) were also accomplished. Goniothalamin (**1**) isolated from *Bryonopsis laciniosa* showed weak anti-bacterial activity at 200 µg/disc in comparison with standard kanamycin (30 µg/disc). Also it showed significant anti-bacterial activity against both gram-positive and gram-negative bacteria. Additionally, cytotoxic activity of compound (**1**) was tested against brine shrimp (*Artemia salina*) and it showed potent cytotoxicity with LC_{50} values 5.03 µg/mL) (Mosaddik and Haque 2003).

Bax is a protein which is a member of Bcl-2 family and it is related with apoptosis induced cell death. The control mechanism of apoptosis is regulated by Bcl-2 protein family means of increase and decrease in levels of Bcl-2 protein family (Reed, Miyashita et al. 1996). Pihie and Chien was studied the correlation between goniothalamin induced apoptosis and Bcl-2 protein levels and they discovered that compound (**1**) induces apoptosis by regulating Bcl-2 protein levels. In goniothalamin (**1**) treated breast cancer cells (MCF-7), significant increase in pro-apoptotic Bax levels were determined; on the other hand anti-apoptotic Bcl-2 levels did not increase. An increase in Bax levels accompanied by apoptosis (Chien and Pihie 2003).

A. de Fatima et al. have synthesized (*R*)-goniothalamin (**28**) and its derivatives and evaluated their cytotoxic activities in eight different cell lines including; MCF-7 (breast), NCR-ADR (breast expressing the multidrug resistance phenotype), NCI 460

(lung, non-small cells), UACC62 (melanoma), 786-0 (kidney), OVCAR03 (ovarian), PCO 3 (prostate), and HT-29 (colon) cell lines. The results show that compound (**28**) exhibits cytotoxic activity in all cell lines, especially at low doses in NCR-ADR, NCI 460 and 786-0 cell lines. Besides, compound (**28**) displays higher antiproliferative activity than that of positive control doxorubicin in NCR-ADR and 786-0 cell lines (de Fátima, Kohn et al. 2005).

28 29

Figure 8. Structures of (*R*)-goniothalamin (**28**) and (*S*)-goniothalamin (**29**).

Table 1. IC_{50} Values (μM) for anti-proliferative activities of (*R*)-goniothalamin (**28**) against cancer cell lines.

Cell line / **Compound**	**Breast (MCF-7)**	**Breast expressing the multidrug resistance phenotype (NCI-ADR)**	**Lung (NCI 460)**	**Kidney (786-0)**	**Colon (HT-29)**
(28)	10.5	2.3	6.4	6.4	11.2
Doxorubicin	3.3	48.7	1.8	>100	5.3

A. de Fatima et al have also synthesized the non-natural enantiomer (*S*)-goniothalamin (**29**) and its analogues and evaluated their cytotoxic acitivity against the same eight cancer cell lines. The results show that both goniothalamin enantiomers (**28** and **29)** displays high cytotoxicity against 786-0 kidney cancer cell line and especially compound (**29**) shows remarkable high activity and selectivity with IC_{50} 4 nM. Also both two enantiomers (**28** and **29)** show higher acitivity against NCR-ADR and 786-0 cancer cell lines than that of positive control doxorubicin.

Comparing (*R*)- and (*S*)-enantiomers of goniothalamin (**28** and **29)**, while (*R*)-enantiomer is more cytotoxic against NCI.ADR, NCI.460, UACC.62, and HT-29, (*S*)-

enantiomer have higher cytotoxic activity against MCF-7, 786-0, OVCAR03, and PCO.3 cancer cell lines. Additionally (*R*)-goniothalamin (**28)** exhibits no cytotoxic activity against PCO.3 cancer cell lines (de Fátima, Kohn et al. 2006).

Table 2. IC_{50} values (μM) for (*R*)- and (*S)*-goniothalamin (**28** and **29)** and doxorubicin necessary for inhibiting tumor cell proliferation.

Cell line / **Compound**	**Breast (MCF-7)**	**Breast expressing the multidrug resistance phenotype (NCI-ADR)**	**Lung (NCI 460)**	**Kidney (786-0)**	**Colon (HT-29)**
(28)	10.5	2.3	6.4	6.4	11.2
(29)	9.4	23.5	14.6	0.004	22.5
Doxorubicin	3.3	48.7	1.8	>100	5.3

Structure activity relationship studies of goniothalamin (**1**) derivatives indicates that, hydrophobic groups like aromatic ring or cyclohexyl group ensure compound to bind the hydrophobic domains of the target biomolecule which is crucial for this compound to be cytotoxic. Also α,β-unsaturated groups provides Michael acceptor property, which is also essential for activity. Additionally chirality and double bond on the linker part of the molecule are important factors for high anti-proliferative activity (de Fátima, Kohn et al. 2006).

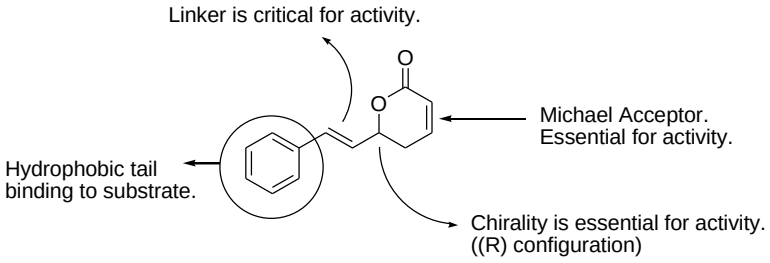


Figure 9. Pharmacophoric groups of goniothalamin (**1**).

Goniothalamin (**1**) also induces apoptosis in vascular smooth muscle cells those are abnormally proliferates in order to cause restenosis. MTT results show that Goniothalamin (**1**) [IC_{50} 4.4 μg/mL (22μM)] possesses higher cytotoxic activity than

clinically used rapamycin [IC_{50} of 25μg/mL (27.346μM)] and induces DNA damage that triggers apoptosis in vascular smooth muscle cells (Chan, Rajab et al. 2006).

In eukaryotic cells, a transport proceeds between nucleus and cytoplasm and this mechanism called "nucleocytoplasmic transport". It is mediated by soluble receptors those are responsible for specific cargoes to carry them through the nuclear pore complex (Cook, Bono et al. 2007). Goniothalamin (**1**) was discovered to be a strong inhibitor of CRM-1 (an export receptor for leucine-rich nuclear export signals) dependent nuclear export of Rio2 protein in HeLa cells.

Recently published X-Ray crystal study indicates that leptomycin B (**9**) is also inhibitor of CRM-1, and covalently binds on a cysteine residue of CRM-1 (Kudo, Matsumori et al. 1999). Superposition of goniothalamin (**1**) to leptomycin B (**9**) depending on recently published X-Ray crystal structure exhibits a high compliance. Compound (**1**) fit the hydrophobic binding sites of compound (**9**) so, goniothalamin (**1**) is expected to be covalently bound to CRM-1 and styryl group of (**1**) mimics the hydrophobic diene part of leptomycin B (**9**).

The effect of compound **1** on solid tumors in laboratory animals was also studied for racemic goniothalamin (**1**). A relationship between anti-cancer and anti-inflammatory activities was found, and it is thought that the anti-inflammatory activity favors the anti-proliferative activity itself (Vendramini-Costa, Castro et al. 2010).

Goniothalamin (**1**) was also found to be a potential anti-tumor agent against lung cancer with IC_{50} value of 0.83 μM at 48 h. Additionally, DNA damage was detected in H1299 lung cancer cells after treatment with **1** and this leads to dose dependent growth inhibition as well as a depression in migration ability (Chiu, Liu et al. 2011).

Moreover, the chemotherapeutic effect of compound (**1**) was determined in oral cancer cells, with an IC_{50} value of 13.5 μM in Ca9-22 oral cancer cells. Besides, compound (**1**) induced growth inhibition and apoptosis induced by increased level of ROS (Reactive Oxygen Species), DNA damaging and mitochondria membrane depolarization (Yen, Chiu et al. 2012).

1.3. Synthesis of α,β-unsaturated Lactones

1.3.1. Synthesis of 7-membered Rings

Despite the presence of numbers of 6-membered α,β-unsaturated lactone synthesis in literature; there are not many examples for the synthesis of 7-membered α,β-unsaturated lactones. Therefore, only few synthesis of examples for substituted or fused α,β-unsaturated 7-membered lactones will be given for a general consideration.

Grubbs' et al. achieved ring closing metathesis reaction (Figure 10) starting from a suitable diene (**30**) and using 2nd generation Grubbs' catalyst (**31**) to synthesize α,β-unsaturated 7-membered lactone **32** with 97% yield (Chatterjee, Morgan et al. 2000).

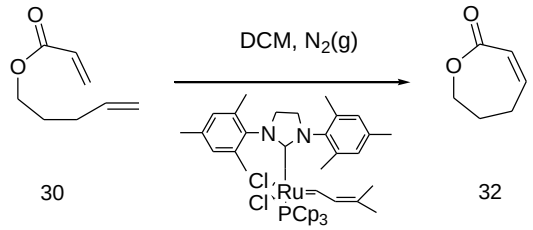


Figure 10. Synthesis of 7-membered α,β-unsaturated lactone **32** by ring closing metathesis.

Cyclocarbonylation of allenyl alcohols **33** in the presence of triethylamine and ruthenium catalyst leads to α,β-unsaturated 7-membered lactone **34** (Figure 11) (Yoneda, Zhang et al. 2001).

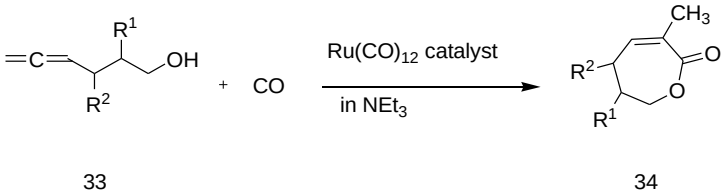


Figure 11. Synthesis of 7-membered α,β-unsaturated lactone **34** by cyclocarbonylation method.

A fused ring α,β-unsaturated 7-membered lactone **37** was synthesized via cyclization reaction of iodobenzyl alcohol **35** and alkyl propiolate **36** in presence of nickel and zinc catalysts (Figure 12) (Rayabarapu and Cheng 2002).

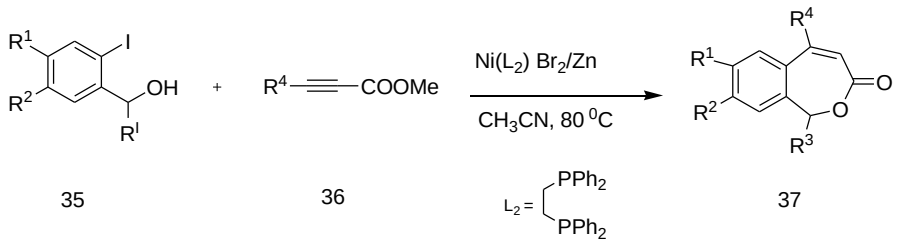


Figure 12. Synthesis of 7-membered α,β-unsaturated lactone **37** by cyclization reaction.

1.3.2. Synthesis of Goniothalamin

Along with the biological activity studies of goniothalamin (**1**), there are many reports for the synthesis of (**1**) in the literature. Allylboration reaction of *trans*-cinnamaldehyde (**42**) was performed with chiral catalyst *B*-allyldiisopinocampheylborane (DIP-Chloride ™) reagent (**43**) (Figure 13). Asymmetric induction yielded homoallylic alcohol (**44**) in 92% ee. Esterification reaction with acryloyl chloride in the presence of triethylamine in dichloromethane followed by ring closing metathesis of corresponding acryloyl ester (**45**) with 10 mol% of 1st generation Grubbs' catalyst yields *(R)*-goniothalamin (**28**) (Ramachandran, Reddy et al. 2000).

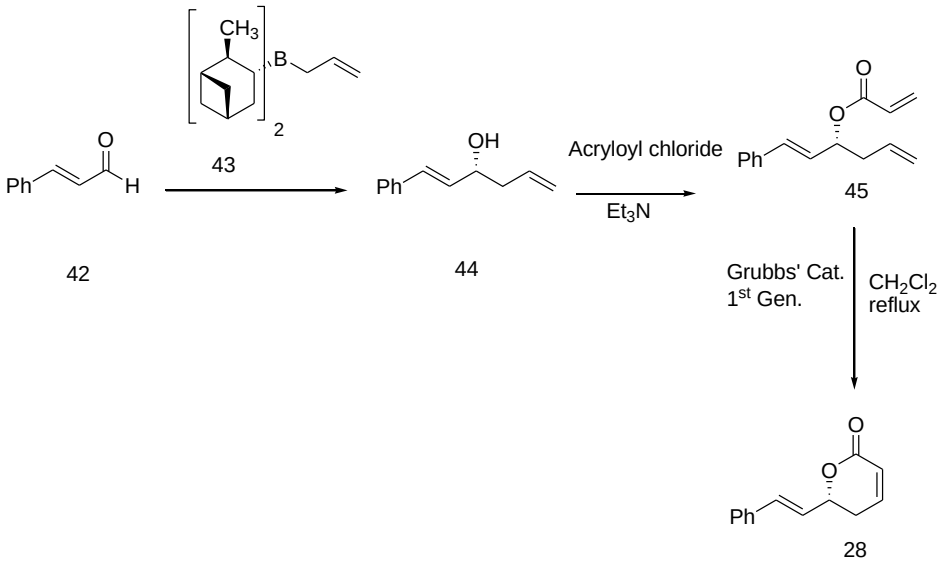
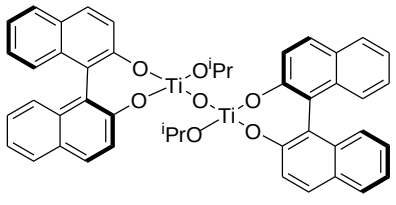


Figure 13. Asymmetric synthesis of (*R*)-goniothalamin (**28**) starting by allylboration reaction with chiral catalyst *B*-allyldiisopinocampheylborane (**43**).

Another study represents the total asymmetric synthesis of *(R)*-goniothalamin (**28**) again is achieved by A. de Fatima and co-workers (Figure 15). Asymmetric allylation of *trans*-cinnamaldehyde (**42**) was performed with allyltributyltin using (R)-BINOL derived chiral catalyst (**46**) (Figure 14). This titanium complex was developed as a catalyst for highly selective allylation of aldehydes. The coordination capacity and double activation ability of bidentate Ti (IV) are the key reasons for the efficiency of chiral catalyst (**46**). Allylation was performed at -20 ^{o}C in dichloromethane to afford 78% yield and 96% ee (Hanawa, Hashimoto et al. 2003).



46

Figure 14. Structure of chiral catalyst bis(((*S*)-binaphthoxy)(isopropoxy)titanium) Oxide (**46**).

The resulting homoallylic alcohol (**44**) was converted to related acrylate ester (**45**) with acryloyl chloride and triethylamine with 80% yield. Last step was ring closing metathesis of the synthesized ester (**45**) with 10 mol% of 1st generation Grubbs' catalyst

under reflux at dichloromethane medium. The desired product (**28**) was afforded with 61% overall yield (de Fátima and Pilli 2003).

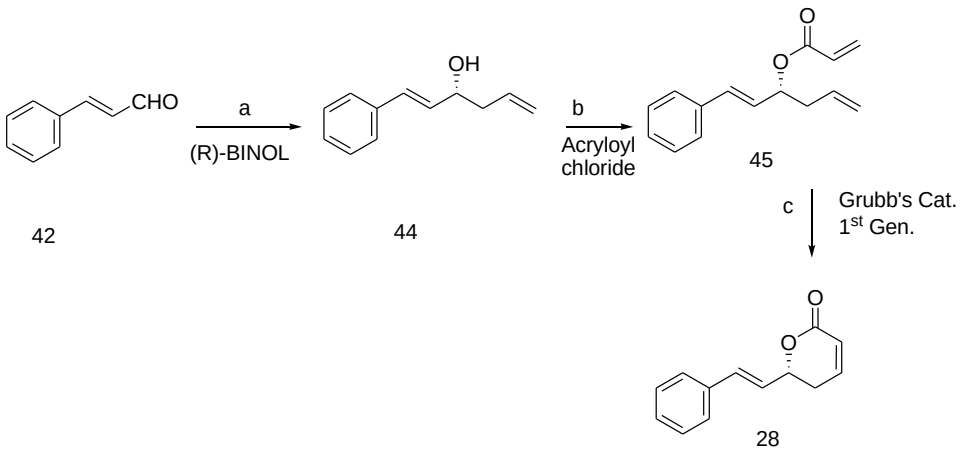


Figure 15. Asymmetric synthesis of (*R*)-goniothalamin (**28**) via allylation reaction by chiral Lewis acid catalyst (**46**) (a) (*R*)-BINOL, $Ti(OiPr)_4$, $TiCl_4$, Ag_2O, allyltributyltin, CH_2Cl_2, −20°C, 24 h, (b) acryloyl chloride, Et_3N, CH_2Cl_2, 0°C; (c) Grubbs' catalyst [$(Pcy_3)_2Cl_2Ru$=CHPh], CH_2Cl_2.

The other asymmetric synthesis of (*R*)-goniothalamin (**28**) was carried out starting from benzyl alcohol (**47**) (Figure 16). Deprotonation of alcohol **47** with sodium hydride and nucleophilic substitution with allylbromide, followed by oxidative cleveage produce benzyloxyacetaldehyde (**49**). Then it was treated with allyltributyltin using chiral catalyst (*R*-BINOL-Ti(O^iPr))$_2$-O complex, generated in situ and molecular sieves at –20 ^oC, to produce homoallylic alcohol (**50**) with 78% yield and 94% ee.

The next step was conversion of homoallylic alcohol **50** to acrylate ester **51** with acryloyl chloride in the presence of Et_3N, and catalytic amount of DMAP in $CHCl_2$ at -23 ^oC. In last step ring closing metathesis of acrylate ester **51** with 10 mol% of 1st generation Grubbs' catalyst furnished related α,β-unsaturated lactone **52** (de Fátima and Pilli 2003).

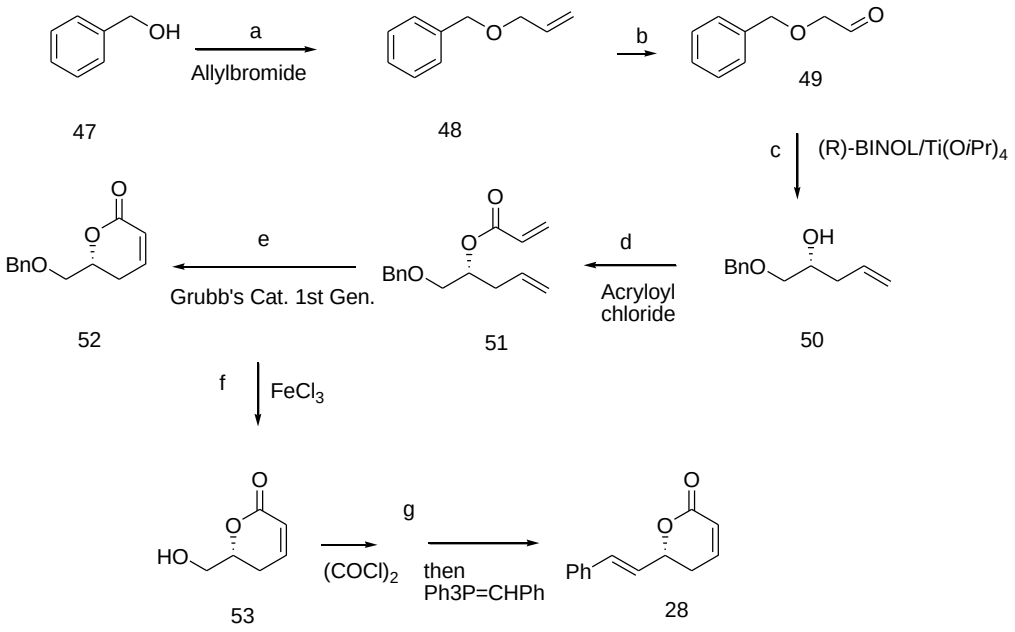


Figure 16. Asymmetric synthesis of (*R*)-goniothalamin (**28**) starting from benzyl alcohol (**47**) a) NaH, KI, DMF, allyl bromide; b) OsO_4, Et_2O/H_2O, $NaIO_4$; c) (*R*)-BINOL, $Ti(O^iPr)_4$, molecular sieves, allyltributyltin, -20 ^oC, 60 h; d) Acryloyl chloride, Et_3N, CH_2Cl_2, 0 ^oC; e) Grubbs' catalyst $[(Pcy_3)_2Cl_2Ru=CHPh]$, CH_2Cl_2; f) $FeCl_3$, CH_2Cl_2; g) $(COCl)_2$, CH_2Cl_2, DMSO, Et_3N, -65 ^oC; then $Ph_3P=CHPh$, THF.

After metathesis reaction, debenzylation reaction of the synthesized lactone (**52**) was performed with ferric chloride in $CHCl_2$. The final step includes the following two steps; Swern oxidation of alcohol (**53**) to yield corresponding aldehyde and then Wittig Olefination of resulted aldehyde with a solution of benzylidenetriphenylphosphorane (prepared by treatment of the corresponding triphenyl phosphonium chloride with n-BuLi in THF) yields the desired product; (*R*)-goniothalamin (**28**) (de Fátima and Pilli 2003).

Alternatively (+) and (-) goniothalamin compounds were synthesized through lipase catalyzed kinetic resolution of (*R*)-(*1E*)-1-phenylhexa-1,5-dien-3-ol (±-**44**) and non-enzymatic transesterification of (*S*)-alcohol (**(*S*)-44**) separated from resolution step (Figure 17).

Firstly, homoallylic alcohol (±-**44**) was prepared from allylmagnesium bromide and *trans*-cinnamaldehyde (**42**). Kinetic resolution of resulted alcohol (±-**44**) is carried out by transesterification reaction in hexane using vinylacrylate as acyl donor and *Candida antarctica* lipase B (CALB) as catalyst. The stereopreference of CALB is over (*R*)-enantiomer, optical rotation value of the product showed that (*R*)-enantiomer reacts

faster. After 45% conversion, the transesterification reaction was stopped. The (*R*)-ester (**45**) is yielded with 93% ee and (*S*)-enantiomer of starting alcohol (**(*S*)-44**) was yielded with 74% ee after purification. The (*S*)-alcohol (**(*S*)-44**) was converted to acrylate ester (**(*S*)-45**) with acryloyl chloride and Et_3N.

Both acrylate esters were treated with 8 mol% of 1st generation Grubbs' catalyst. (*R*)-goniothalamin (**28**) was furnished with 92% yield and >99% ee. (*S*)-goniothalamin (**29**) was furnished with 81% yield with 85% ee (Sundby, Perk et al. 2004).

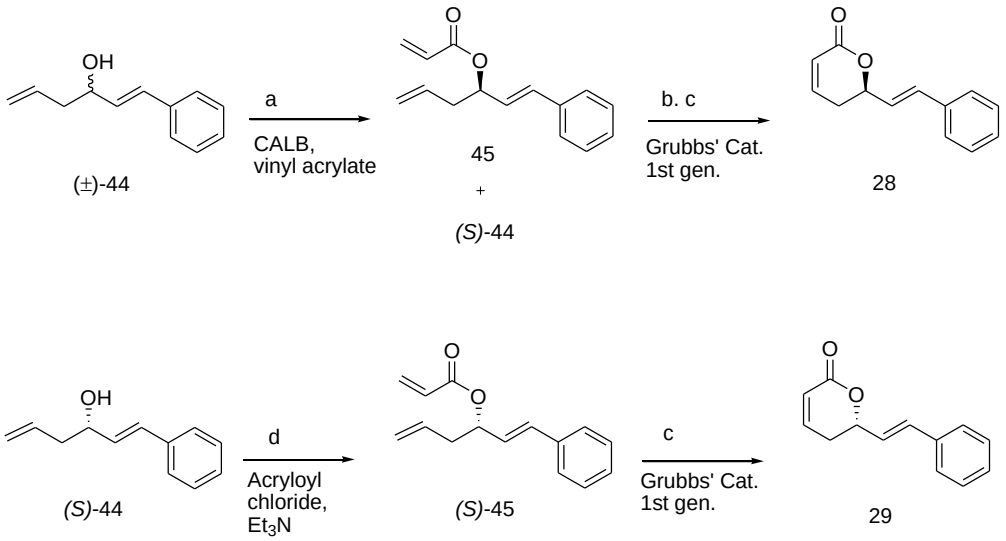


Figure 17. Synthesis of (*R*)- and (*S*)-goniothalamin with lipase catalyst resolution and ring closing metathesis (a) CALB, vinyl acrylate, hexane. (b) Separation by chromatography, (c) Grubbs'cat., CH_2Cl_2, (d) Acryloyl chloride, Et_3N, THF.

CHAPTER 2

RESULTS AND DISCUSSION

Due to the interesting biological activities of (*R*)- and (*S*)-goniothalamin (**28** and **29**), several structure activity relationship and asymmetric synthesis studies were reported in the literature. In 2009, Kasaplar et al. have synthesized a number of conformationally constrained and bicycloaryl substituted goniothalamin (**1**) derivatives (**54-61**) in three steps; first asymmetric allylation reaction with allyltrimethyltin and l-oxobis(*R*-binaphthoxy)(isopropoxy)titanium complex, then acrylation with acryloyl chloride followed by ring closing metathesis with Grubbs' catalyst (Kasaplar, Yilmazer et al. 2009).

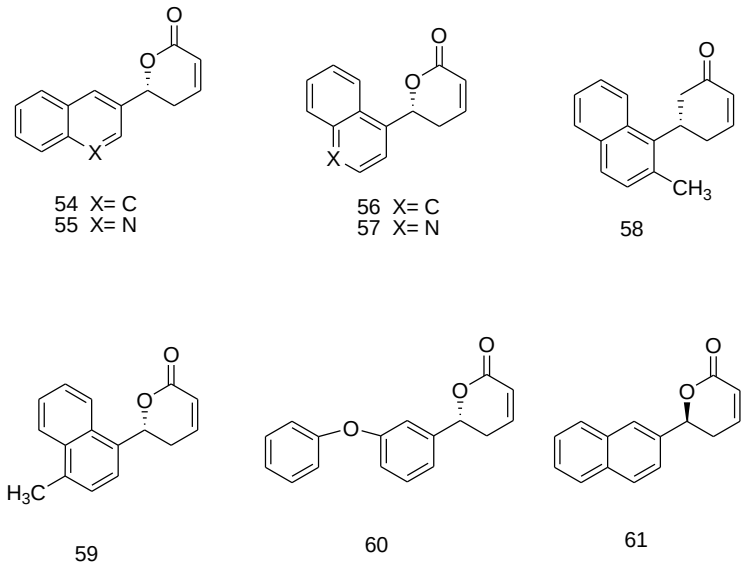


Figure 18. Synthesized (*R*)- and (*S*)-goniothalamin derivatives (**54-61**) starting by asymmetric allylation

Anti-proliferative effect of synthesized bicycloaryl substituted α,β-unsaturated δ-lactone derivatives (**54-61**) were also studied by the same group. MTT assay was applied for four different cancer cell lines PC-3 (prostate cancer) and MCF-7 (human breast adenocarcinoma), DU-145 (metastatic human prostate adenocarcinomas), and

LNCAP (lymph node metastasis of human prostate adenocarcinoma). According to MTT cell viability test, compounds **58** and **59** have enhanced cytotoxic activity which encourage us to study large scale synthesis and in-vivo anti-cancer properties. Compound **58** showed anti-proliferative activity with IC_{50} value of 0.13 μM in prostate cancer cells and IC_{50} value of 2.6 μM in breast cancer cells. Compound **59** showed anti-proliferative activity with IC_{50} value of 0.05 μM in prostate cancer cells and IC_{50} value of 0.44 μM in breast cancer cells. Both compounds exhibited higher cytotoxicity than (*R*)-goniothalamin (**28**) against these cell lines.

In addition, compounds **54** and **56** also displayed high cytotoxic activity against prostate cancer cell lines, with IC_{50} values of 3.0 μM and 0.8 μM for compounds **54** and **56**, respectively. Against breast cancer cell line, IC_{50} values are 12.0 μM and 2.6 μM for compounds **54** and **56**, respectively. This IC_{50} values was lower than that of (*R*)-goniothalamin (**28**).

In this study, due to the enhanced cytotoxic activity, large scale synthesis of compound **58** ((*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one) was performed in order to evaluate its anti-cancer activities in vivo. Additionally, synthesis of three new 7-membered β,γ-unsaturated lactones were studied.

2.1. Large Scale Preparation of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one

Asymmetric large scale synthesis of compound (**58**) ((*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one) was carried out according to the slightly modified procedure reported by Kasaplar, Yilmazer et al. (2009). Synthesis route is made up of three steps to reach the target compound **58**; asymmetric synthesis of homoallylic alcohol **63** starting from aldehyde **62**, followed by esterification reaction. In the last step, formed acrylate ester **64** was converted to desired compound **58** by ring closing metathesis reaction.

Asymmetric synthesis of homoallylic alcohol **63** was performed via the route reported by (Yanagisawa, Kageyama et al. 1999) (Figure 19). (*R*)-Tol-BINAP (**66**) was used with AgF to form a catalyst complex in order to use in allylation reaction of aldehydes with allylic trimethoxysilanes. Also same research group reported that yield and enantioselectivity of allylation reaction are still remain satisfactory at -20 ^{o}C.

So, allylation reaction was performed using (*R*)-Tol-BINAP-AgF (**66**-AgF) catalyst complex in methanol at -20 ^{o}C with allyltrimethoxysilane as allylation reagent. As starting material, 2-methly-1-naphthaldehyde (**62**) was used and converted to homoallylic alcohol (*R*)-1-(2-Methylnaphthalen-1-yl)-but-3-en-1-ol (**63**) in 48-50 hours as optimum reaction time for maximum yield and enantiomeric excess. The results are shown in Table 3.

Hata! Başvuru kaynağı bulunamadı.

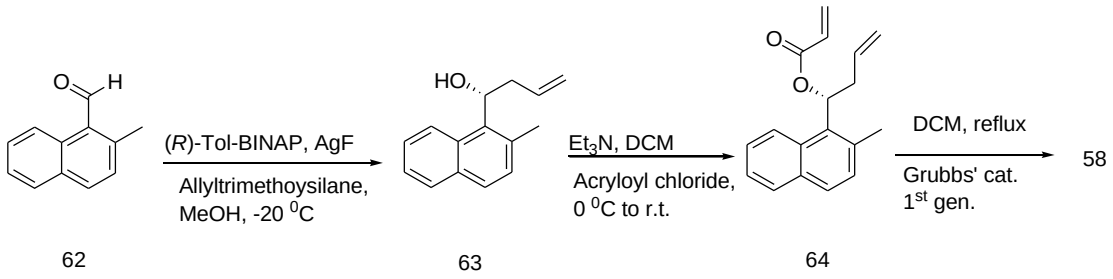


Figure 19. Synthesis route for the asymmetric synthesis of target compound (**58**).

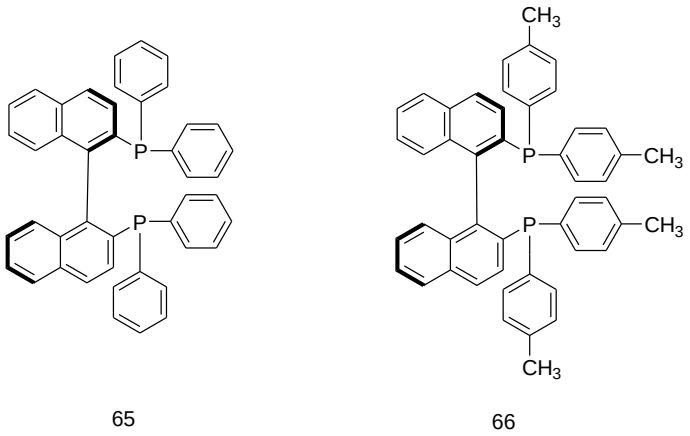
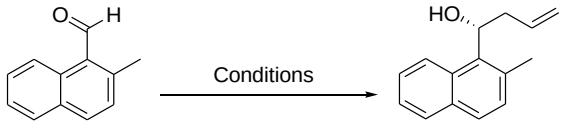


Figure 20. Structures of (*R*)-BINAP (**65**) and (*R*)-Tol-BINAP (**66**).

Asymmetric allylation of 2-methyl-1-naphthaldehyde (**62**) (1 eq) was performed using 0.06 equivalent of (*R*)-Tol-BINAP as chiral auxiliary and 0.1 equivalent of AgF as fluoride ion source. Excess amount of allyltrimethoxsilane (1.05 equivalent) was used as allylation reagent to be sure the consumption of all starting aldehyde **62**. Increasing the amount of silane reagent to 1.20 equivalent did not increase the yield of reaction significantly. Also excess amount of AgF with regard to (*R*)-Tol-BINAP was used to gain higher enantioselectivity as reported in Yamamoto's report.

As summarized in Table 3, asymmetric synthesis of homoallylic alcohol **63** was first tried at small scale (80-170 mg) of starting aldehyde **62**. At room temperature yield and enantioselectivity of the reaction were quite low and it is decided to repeat the reaction at -20 ^{o}C. After 48 hours of reaction time, at low temperature both the yield and enantioselectivity of the reaction increased up to 54% and 50% respectively.

Table 3. Asymmetric allylation reactions of 2-methyl-1-naphthaldehyde (**62**).



62 63

Ex.	Aldehyde	*R*-Tol-BINAP	AgF	Ally-trimethoxy-silane	Solvent (mL)	Temp. (^{o}C)	Time (h)	% Yield	Yield (mg)	% ee	Specific Rotation; Conc.; Solvent
	Eq. (Amount, mg)			Eq. (Amount, µL)							
1	1.00 (88)	0.06 (20)	0.1 (6)	1.05 (90)	MeOH (16)	R.T.	50	9	95	29	$[\alpha]_D^{31}$ = -6.00; c: 0.10, $CHCl_3$
2	1.00 (170)	0.06 (41)	0.10 (13)	1.20 (253)	MeOH (8)	-20	48	54	112	50	$[\alpha]_D^{24}$ = +29.27; c: 0.82, $CHCl_3$
3	1.00 (1030)	0.06 (238)	0.10 (74)	1.20 (1090)	MeOH (16)	-20	52	36	281	47	$[\alpha]_D^{23}$ = +45.24; c: 0.84, $CHCl_3$
4	1.00 (614)	0.06 (115)	0.10 (44)	1.05 (720)	MeOH (16)	-20	52	60	448	51	$[\alpha]_D^{31}$ = +40.80; c: 0.20, $CHCl_3$
5	1.00 (2250)	0.06 (481)	0.10 (162)	1.05 (2310)	MeOH (16)	-20	90	53	1445	62	$[\alpha]_D^{26}$ = +35.90; c: 0.78, $CHCl_3$
6	1.00 (2750)	0.06 (652)	0.10 (202)	1.05 (2890)	MeOH (16)	-20	48	44	1054	46	$[\alpha]_D^{25}$ = +26.20; c: 0.69, $CHCl_3$
7	1.00 (2750)	0.06 (652)	0.10 (202)	1.05 (2890)	MeOH (16)	-20	49	30	1000	32	$[\alpha]_D^{25}$ = +18.00; c: 0.67, $CHCl_3$
8	1.00 (2750)	0.06 (652)	0.10 (202)	1.05 (2890)	MeOH (16)	-20	48	53	1811	40	$[\alpha]_D^{27}$ = +18.00; c: 0.67, $CHCl_3$

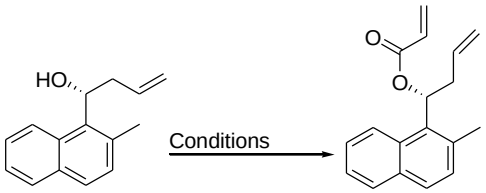
All of the enantiomeric excess values of the allylation products were determined by HPLC studies by using a chiral column OJ-H and hexane: *i*-propanol elution system.

After these preliminary results it was decided to scale up the reaction to grams levels, entry 3-8 in Table 3. Prolonged reaction time (90h) improved the enantioselectivity of the reaction while the yield was still moderate. Otherwise all of the reactions gave moderate yields (35-53%) and enantioselectivities (32-51%).

Homoallylic alcohol **63** was converted to acrylate ester **64** with esterification reaction using 1.5 equivalent of acryloyl chloride in the presence of 3 equivalent of triethylamine base (Table 4). The reaction was started at 0 ^{o}C (exothermal reaction) and continued at room temperature for 16-17 hours.

Acrylate ester **64** was obtained with approximately 83-85% yields after purification with SiO_2 flash column chromatography. Enantiomeric excess values of the reactions were monitored by Chiral HPLC studies and it is observed that enantiomeric excess values for ester were similar to those of homoallylic alcohol.

Table 4. Esterification reactions of homoallylic alcohol **63**.



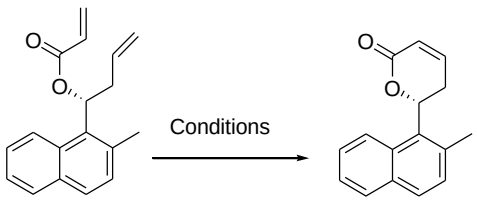
63 64

Ex.	Homoallylic alcohol	Acryloyl chloride	Triethyl-amine	Solvent (mL)	Temp. (^{o}C)	Time (h)	% Yield	Yield (mg)	% ee	Specific Rotation; Conc.; Solvent
	Eq. (Amount, mg)									
1	1.00 (1500)	1.5 (1000)	3.0 (2155)	DCM (14)	0 to 25	15	88	1891	48	$[\alpha]_D^{26}$ = +51.90; c: 0.77, $CHCl_3$
2	1.00 (1800)	1.5 (1119)	3.0 (2574)	DCM (17)	0 to 25	17	83	1887	40	$[\alpha]_D^{21}$ = +48.00; c: 0.83, $CHCl_3$
3	1.00 (1000)	1.5 (666)	3.0 (1430)	DCM (10)	0 to 25	17	84	1054	32	$[\alpha]_D^{21}$ = +36.52; c: 0.77, $CHCl_3$

At last step, ring closing metathesis reaction of acrylate ester (**64**) was achieved to yield the final product pyran-2-one (**58**). Metathesis reaction was performed with using 10% mol of 1st generation Grubbs' catalyst (Figure 21) at nitrogen atmosphere

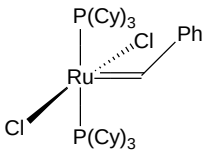
and under reflux. Dry dichloromethane was used as solvent. Optimum reaction time was 8 hours for higher yield in order to eliminate olefinic side products occuring distinctively after this reaction time. Enantiomeric excess values for the products of the reactions did not change during the reactions. The yields of the reactions were in the range of 42-75% and except one case repeatedly it gave 72% yield. Asymmetric synthesis of total 5 grams of target molecule was completed.

Table 5. Ring closing metathesis reactions of acrylate ester **64**.



64 58

Ex.	Acrylate ester	1st gener. Grubbs' cat.	Solvent (mL)	Temp. (°C)	Time (h)	% Yield	Yield (mg)	% ee	Specific Rotation; Conc.; Solvent
	Eq. (Amount, mg)	Eq. (Amount, mg)							
1	1.00 (1887)	0.10 (583)	DCM (770)	60	8.0	42	712	44	$[\alpha]_D^{21}$ = +225.00; c: 0.72, $CHCl_3$
2	1.00 (1053)	0.10 (325)	DCM (430)	60	8.5	72	684	50	$[\alpha]_D^{21}$ = +243.00; c: 0.75, $CHCl_3$
3	1.00 (1657)	0.10 (512)	DCM (680)	60	8.0	71	1054	43	$[\alpha]_D^{24}$ = +178.00; c: 0.63, $CHCl_3$
4	1.00 (858)	0.10 (265)	DCM (350)	60	8.5	72	554	43	$[\alpha]_D^{24}$ = +218.00; c: 0.67, $CHCl_3$
5	1.00 (684)	0.10 (200)	DCM (243)	60	8.0	75	434	35	$[\alpha]_D^{23}$ = +267.00; c: 0.71, $CHCl_3$



67

Figure 21. Structure of 1st generation Grubbs' catalyst (**67**).

2.2. Preparation of Novel Oxepin-2-ones

2.2.1. Retrosynthetic Analysis of Synthesis of Novel Oxepin-2-ones

Racemic synthesis of novel bicycloaryl substituted 6,7-dihydro-*5H*-oxepin-2-one derivatives (**80-82**) were planned (Figure 22) starting from corresponding aldehydes (**68-70**). As last step of the synthesis, isomerization of β,γ-unsaturated lactones into α,β-unsaturated system can be applied. Lactones **68-70** can be prepared from the ring closing metathesis (RCM) of precursor esters **74-76** which can be prepared from homoallylic alcohols **71-73** simply by Mitsunobu reaction, transesterification, or Steglich esterification with corresponding butenoic acids or esters. Homoallylic alcohols **71-73** can be prepared from aldehydes **68-70** by using well established allylation reaction in the presence of allyltrimethoxysilane catalayzed by CuCl-TBAT (Yamasaki, Fujii et al. 2002).

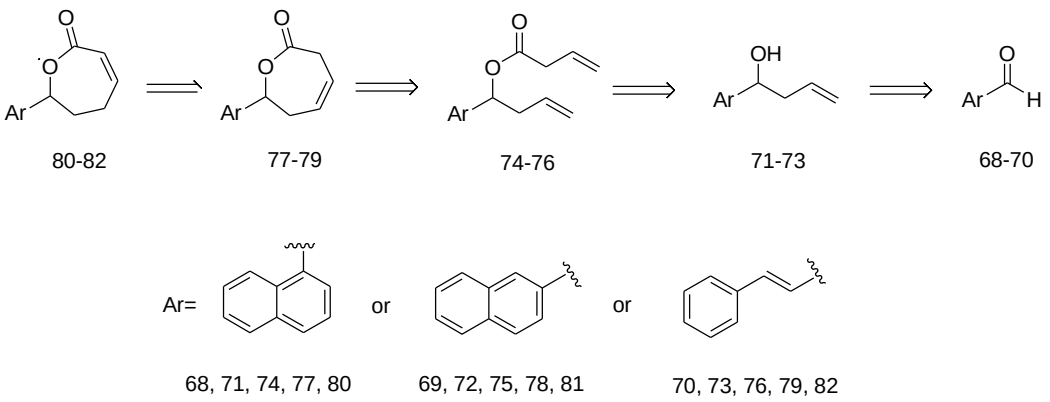
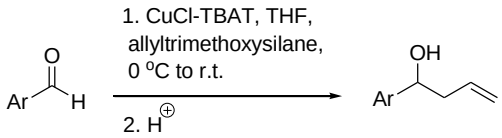


Figure 22. Retrosynthetic analysis of Novel oxepin-2-ones (**80-82**).

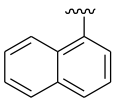
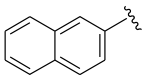
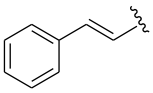
2.2.2. Preparation of Alcohols

In order to prepare homoallylic alcohols (**71-73**)**,** as shown in Table 6, starting 1-naphthaldehyde (**68**), 2-naphthaldehyde (**69**), and *trans*-cinnamaldehyde (**70**) were converted to corresponding racemic alcohols with allyltrimethoxysilane in the presence of CuCl-TBAT with 89%, 90% and 86% yields respectively in THF.

Table 6. Synthesis of racemic homoallylic alcohols starting from aldehydes (**68-70**).



68-70 71-73

Ex.	Aldehyde		CuCl	TBAT	Ally-trimethoxy-silane	Solvent (mL)	Temp. (°C)	Time (h)	% Yield	Yield (mg)
	Ar	Eq. (Amount)	Eq. (Amount, mg)		Eq. (Amount, µL)					
1	 68	1.00 (72 µL)	0.10 (5)	0.10 (28)	1.50 (126)	THF (3)	0 to R.T.	24	89	88
2		1.00 (715 µL)	0.10 (51)	0.10 (278)	1.50 (1330)	THF (10)	0 to R.T.	3	89	870
3	 69	1.00 (83 mg)	0.10 (5)	0.10 (28)	1.50 (126)	THF (3)	0 to R.T.	24	90	89
4		1.00 (781 mg)	0.10 (51)	0.10 (278)	1.50 (1263)	THF (10)	0 to R.T.	3	58	577
5		1.00 (781 mg)	0.10 (51)	0.10 (278)	1.50 (1330)	THF (10)	0 to R.T.	3	78	776
6		1.00 (781 mg)	0.10 (51)	0.10 (278)	1.50 (1330)	THF (10)	0 to R.T.	3	75	750
7	 70	1.00 (251 µL)	0.10 (20)	0.10 (111)	1.50 (505)	THF (5)	0 to R.T.	24	40	70
8		1.00 (629 µL)	0.10 (51)	0.10 (278)	1.50 (1264)	THF (10)	0 to R.T.	24	38	332
9		1.00 (629 µL)	0.10 (51)	0.10 (278)	1.50 (1330)	THF (10)	0 to R.T.	3	86	748

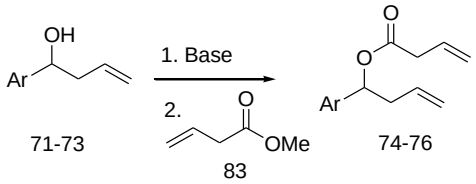
The catalyst complex was prepared at 0 °C and the reaction was carried out at room temperature. Reaction was completed in 3 hours in THF. When DCM was used as solvent, reaction either did not yield any product formation or yielded product at low yields. Somewhat the yields of the reactions were higher in larger scale reactions compared to lower scales.

2.2.3. Preparation of Corresponding Esters

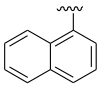
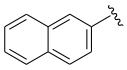
2.2.3.1. Transesterification

Transesterification reactions of methyl-3-butenoate with synthesized homoallylic alcohols **71-73** were studied under acidic or basic conditions. Variety of solvents, acids or bases were tried. All of the attempts for transesterification reaction were failed as summarized in Table 7.

Table 7. Transesterification reactions of 3-butenoate with secondary alcohols (**71-73**).



71-73 83 74-76

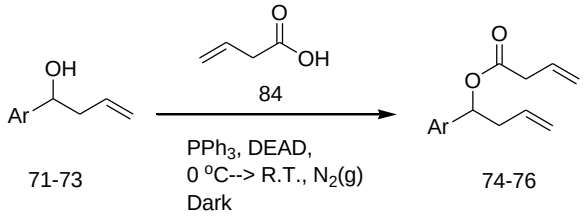
Ex.	Ar	Base	Solvent	Temp. (^oC)	Time (h)	Ester
1		-	- (Molecular Sieves)	R.T.	24	N.R.
2		Et_3N	DMF (Molecular Sieves)	70		
3	71	NaH	THF	R.T.		
4		Et_3N	DMF (Molecular Sieves)	70		
5		Et_3N	Toluene	Reflux		
6		NaH	DMF (Molecular Sieves)	70		
7		NaH	THF-DMF (Molecular Siev.)	R.T.		
8		Imidazolium Salt, KO*t*-Bu	THF (Molecular Sieves)	R.T.		
9	72	Imidazolium Salt, DBU	CH_2Cl_2 (Molecular Sieves)	R.T.		
10		Imidazolium Salt, NaH	DMF (Molecular Sieves)	R.T.		
11		KO*t*-Bu	DMF (Molecular Sieves)	R.T.		
12		TFA	CH_2Cl_2	Reflux		

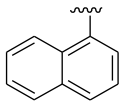
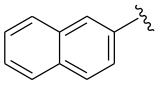
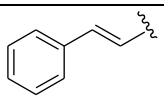
2.2.3.2. Mitsunobu Reaction

As a second alternative, Mitsunobu reactions of homoallylic alcohols **71-73** with vinylacetic acid were studied, as summarized in Table 8. All attempts for Mitsunobu reaction were failed when THF and DCM were used as solvents. Under the same conditions reaction proceeded smoothly in toluene. Although product formations were observed, all attempts to purify the final product from PPh_3 was failed in our hands and

all obtained esters had triphenylphosphine impurities. Formed esters will be used in next step for ring closing metathesis reaction in the presence of triphenylphosphine impurity. If the reaction yields the target esters then it might be easily purified from triphenylphosphine impurity.

Table 8. Esterification reactions of homoallylic alcohols (**71-73**) via Mitsunobu reaction.

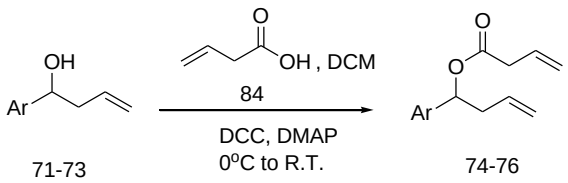


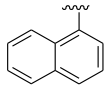
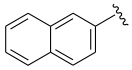
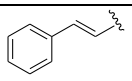
Ex.	Alcohol		Vinylacetic acid	PPh_3	DEAD	Solvent (mL)	Temp. (°C)	Time (h)	Yield (mg)
	Ar	Eq. (Amount, mg)	Eq. (Amount, µL)	Eq. (Amount, mg)	Eq. (Amount, mg)				
1	 71	1.00 (25.0)	1.00 (11)	1.00 (34)	1.00 (60)	THF (4)	0 → R.T.	Over night	N.R.
2		1.00 (25)	1.00 (11)	1.5 (51)	1.5 (84)	THF (4)			N.R.
3		1.00 (25)	1.00 (11)	1.5 (51)	1.5 (84)	DCM (4)			N.R.
4		1.00 (25)	1.00 (11)	1.5 (51)	1.5 (84)	Toluene (4)			Mixed With PPh_3 (34.8 mg)
5		1.00 (300)	1.00 (131)	1.00 (393)	1.00 (683)	Toluene (35)			Mixed With PPh_3 (229 mg)
6	 72	1.00 (776)	1.00 (342)	1.00 (1022)	1.00 (1780)	Toluene (55)	0 → R.T.	Over night	Mixed With PPh_3
7	 73	1.00 (330)	1.00 (166)	1.00 (498)	1.00 (856)	Toluene (35)	0 → R.T.	Over night	Mixed With PPh_3 (253 mg)

2.2.3.3. Steglich Esterification

Alternatively, Steglich esterification reaction of homoallylic alcohols (**71-73**) with vinylacetic acid was studied to form target esters (**74-76**). The coupling reaction was performed in the presence of DCC and DMAP in dichloromethane and ester products were obtained in high (89% and 90%) yields.

Table 9. Esterification reactions of homoallylic alcohols (**71-73**) in the presence of vinylacetic acid (**84**) via Steglich esterification.



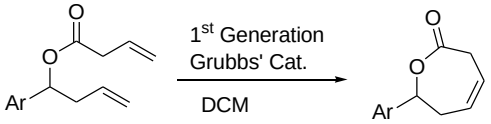
Ex.	Alcohol		Vinyl-aceticacid	DCC	DMAP	Solvent (mL)	Temp. (°C)	Time (h)	% Yield (mg)
	Ar	Eq. (Amount, mg)	Eq. (Amount, µL)	Eq. (Amount, mg)					
1	 71	1.00 (888)	2.00 (785)	2.10 (1942)	1.10 (602)	DCM (20)	0 →R.T.	5	89 (1067)
2	 72	1.00 (689)	2.00 (609)	2.10 (1502)	1.10 (467)	DCM (20)	0→ R.T.	5	90 (831)
3	 73	1.00 (748)	2.00 (753)	2.10 (1859)	1.10 (577)	DCM (20)	0→ R.T.	5	90 (942)

2.2.4. Preparation of β,γ-unsaturated Lactones

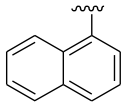
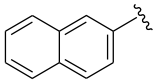
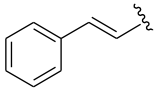
2.2.4.1. Lactone Formation of Mitsunobu Products

In this step, the esters which were synthesized with Mitsunobu reaction, mixed with PPh_3, were treated with 1st generation Grubbs' catalyst to perform ring closing metathesis. Also in some of the trials, Lewis acid additives were also used to prevent the interactions between Grubbs' catalyst and carbonyl group of the ester.

Table 10. Ring closing metathesis of the esters synthesized with Mitsunobu Reaction (mixed with PPh_3) to obtain 7-membered lactones (**77-79**).



74-76 77-79

Ex.	Ester		1st Gen. Grubbs' Cat.	Solvent (mL)	Temp. (°C)	Acid Catalyst		Time (h)	% Yield (mg)
	Ar	Eq. (Amount, mg)	Eq. (Amount, µL)			Acid	Eq. (Amount, µL)		
1	 74	1.00 (159.0 mg)	0.10 (49.4 mg)	DCM (60)	50	-	-	6	20 29 mg
2		1.00 (20.0 mg)	0.10 (6.0 mg)	DCM (8)	45	Ti(O-*i*Pr)$_4$	1.05 (23.0 µL)	Over night	Mixture of products.
3		1.00 (34.0 mg)	0.05 (6.0 mg)	DCM (15)	R.T.	-	-	Over night	N.R.
4	 75	1.00 (50.0 mg)	0.10 (16 mg)	DCM (20)	45	Ti(O-*i*Pr)$_4$	0.50 (27.0 µL)	Over night	Mixture of products.
5		1.00 (60.0 mg)	0.10* (18.5 mg)	DCM (25)	45	-	-	6	Mixture of products.
6		1.00 (60.0 mg)	0.10* (18.5 mg)	Toluene (24)	40	-	-	Over night	N.R.
7		1.00 (60.0 mg)	0.10 (18.5 mg)	DCM (25)	R.T.	-	-	Over night	N.R.
8		1.00 (60.0 mg)	0.10 (18.5 mg)	DCM (25)	45	$AlCl_3$	3.00 (92 mg)	Over night	N.R.
9	 76	1.00 (253 mg)	0.10 (87 mg)	DCM (100)	45	-	-	8	Could not be purified.

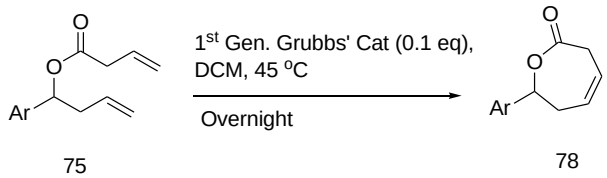
*Grubbs' catalyst was added in pieces.

When ring closing metathesis reactions of 1-naphthyl substituted ester (**74**) were performed, formation of many products were observed on T.L.C. and only one of them was isolated with 20% yield. The ^{1}H-NMR spectrum of this compound was very similar to the expected ^{1}H-NMR spectrum of the desired lactone; however, it contains one more proton than that of target lactone. Same product formations were also observed in the presence of Ti(O- *i*Pr)$_4$. Lowering the reaction temperature did not give a selective product formation, as well.

Similar experiments were carried out for 2-naphthyl and styryl substituted esters (**75** and **76**) and it was observed that the reaction did not occur at room temperature, or in toluene or in the presence of Lewis acid $AlCl_3$. Formation of new products was observed only in dichloromethane and at 45 ^{o}C for styrene substituted ester. The purification attempts for lactone (**79**) were failed. To understand if there is any effect of PPh_3 impurities on the results of these experiments, the synthesis of these lactones were also studied starting from the esters synthesized by Steglich esterification.

2.2.4.2. Lactone Formation of Steglich Products

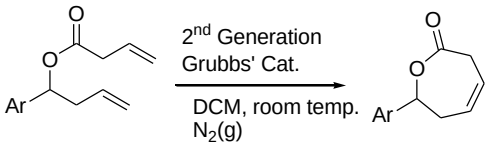
The ester (**75**), which was synthesized by Steglich coupling reaction, was treated with 1st generation Grubbs' catalyst to yield the corresponding lactone **78** with ring closing metathesis which also failed to form target lactone selectively.



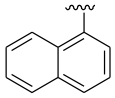
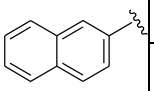
75 78

Figure 23. Ring closing metathesis reaction of the ester (**75**) synthesized with Steglich esterification to obtain 7-membered lactone with 1st generation Grubbs' catalyst **67**.

Table 11. Ring closing metathesis reaction of the esters (**74-75**) synthesized with Steglich esterification to obtain 7-membered lactones (**77-78**) by using 2nd generation Grubbs' catalyst.



74-75 77-78

Ex.	Ester		2nd Gen. Grubbs' Cat.	Solvent (mL)	Temp. (°C)	Time (h)	Acid Catalyst		% Yield (mg)
	Ar	Eq. (Amount, mg)	Eq. (Amount, µL)				Acid	Eq. (Amount, µL)	
1	 74	1.00 (50)	0.05 (8)	DCM (30)	45	5	-	-	Many spots on T.L.C.
2		1.00 (50)	0.05 (8)	DCM (30)	R.T.	Over night	-	-	18 (8)
3		1.00 (25)	0.05 (4)	DCM (15)	R.T.	Over night	$AlCl_3$	3.00 (38)	N.R.
4		1.00 (25)	0.05 (4)	DCM (15)	R.T.	Over night	BF_3-O $(Et)_2$	3.00 (34)	N.R.
5		1.00 (25)	0.05 (4.0)*	DCM (16)	R.T.	Over night	Ti(O-*i*Pr)$_4$	0.50 (14)	Many spots on T.L.C.
6		1.00 (892)	0.05 (144)	DCM (500)	R.T.	Over night	-	-	Could not be purified. (114 mg)
7	 75	1.00 (25)	0.05 (4)	DCM (15)	45	Over night	Ti(O-*i* Pr)$_4$	0.50 (14)	No change on T.L.C.
8		1.00 (25)	0.05 (4)	DCM (15)	R.T.	Over night	Ti(O-*i* Pr)$_4$	0.50 (14)	No change on T.L.C.
9		1.00 (896)	0.05 (143)	DCM (500)	R.T.	Over night	-	-	Could not be purified. (109 mg)

*Grubbs' catalyst was added in pieces.

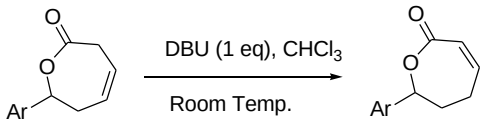
Hence, 2nd generation Grubbs' catalyst used for conversion of the synthesized esters **74-76** to 6,7-dihydro-3*H*-oxepin-2-one derivatives (**77-79**). According to the results shown in

Table 11, while many product formations were being observed at 45 °C; the number of these product formations decreased to 3 at room temperature. After purification, one of these three products was determined to be the desired lactone product by ^{1}H-NMR experiments. For ester **74,** the desired lactone was obtained with 18% yield. On the other hand, the same procedure was applied for the large scale production of esters **75** and **76**. Although the formation of esters were seen in NMR

studies, they could not be purified from impurities. Lewis acids $AlCl_3$, Ti(O-*i*Pr)$_4$, and BF_3 were tried out to increase the yield of the reaction; however, no positive or negative effect of Ti(O-*i*Pr)$_4$ was observed while the other acids were failed the reaction.

2.2.5. Isomerization Reactions of β,γ-unsaturated Lactones to Form α,β-unsaturated Lactones

To synthesize the target α,β-unsaturated 7-membered lactone **80**, the β,γ-unsaturated 7-membered lactone **77** was treated with DBU base (Figure 24), but it was failed to produce the final product.



77 80

Figure 24. Isomerization reaction of β,γ-unsaturated lactone (**77**) to form α,β-unsaturated lactone (**80**).

2.2.6. Direct Synthesis of Lactone from Homoallylic Alcohol

As an alternative route, silica-gel was treated with base to form negative charged oxygen ions on the surface. Then, transesterification reaction of methyl-3-butenoate (**83**) with negatively charged silica was studied, to increase the amount of cross olefin metathesis reactions. Finally, olefin cross metathesis reaction between the produced ester modified silica-gel and homoallylic alcohol was tried; but no product formation was observed.

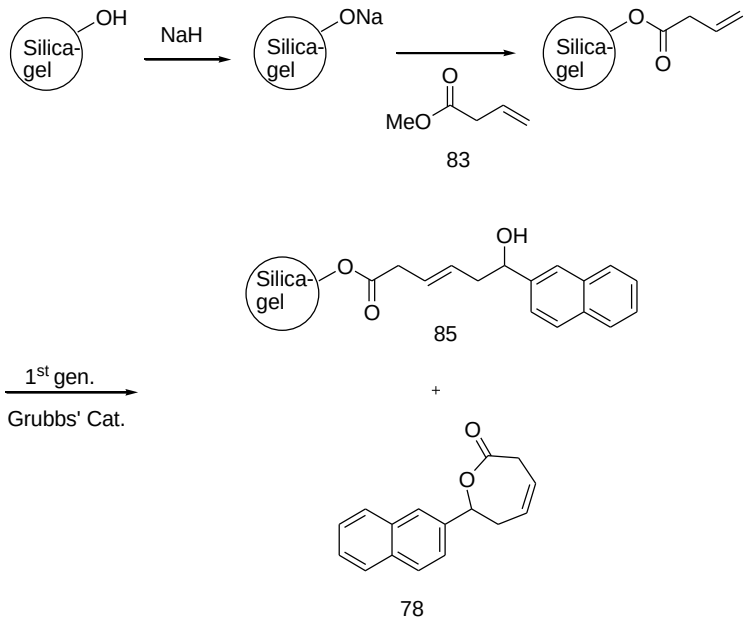


Figure 25. Synthesis of 7-membered lactone (**78**) from homoallylic alcohol (**72**) on silica-gel surface.

CHAPTER 3

EXPERIMENTAL

3.1. General Methods

Dichloromethane and tetrahydrofuran were dried by MBraun-SPS-Solvent Purification System, and dichloromethane was distilled over Calcium hydride. Merck TLC Silica-Gel 60 F_{254} glass plates were used while performing Thin Layer Chromatography. 60Å, 40-63 μm, high purity silica-gel was used in column chromatography experiments. Solvents used for column chromatography and extraction were commercially grade. Solvents for HPLC experiments were used ultra pure grade. HPLC experiments were performed with HPLC Agilent Tech. 1200 Series and Chiral OJ-H Column Chiralcel 0.46 cmΦ x 15 cm DAIC 17324. ^{1}H NMR and ^{13}C NMR experiments were performed with Varian 400-NMR (400 MHz) Spectrometer. Chemical shifts were reported in δ (ppm). $CDCl_3$ was used as solvent in NMR acquisition and MestReNova NMR Processing Software is used for processing of NMR spectra. Optical Rotation measurements were studied with Bellingham Stanley Ltd. ADP410 Polarimeter. FTIR experiments were performed by Perkin Elmer Spectrum 100 FT-IR Spectrometer using KBr pellets.

3.2. Large Scale Preparation of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (58)

3.2.1. Preparation of (*R*)-1-(2-Methylnaphthalen-1-yl)-but-3-en-1-ol (63)

Into a two neckled flask, 12.6 mg of AgF and 40.7 mg of (R)-Tol-BINAP were weighed and dissolved in 8 mL of dried methanol. The mixture was stirred at room temperature for 20 minutes. After cooling the mixture to -20 ^{o}C, 170.5 mg (1 mmol, 1 eq) of 2-methyl-1-naphthaldehyde and 253 μL (1.2 mmol, 1 eq) of allyltrimethoxysilane were added. The reaction mixture was stirred at -20 ^{o}C under nitrogen atmosphere.

After 7 hours, the resulting mixture was filtered through celite and silica gel and washed with mL of EtOAc. After removal of the solvent 43 mg of (*R*)-1-(2-Methylnaphthalen-1-yl)-but-3-en-1-ol was purified as a yellow oil by silica-gel column, (EtOAc/Hex; 1:10) with 20% yield. Rf 0.3 (EtOAc: Hex, 1:6). $[\alpha]_D^{32}$ = +0, 25 (c 1,12 $CHCl_3$). Enantiomeric excess was found as 50% with HPLC-Chiracel OJ-H column (i-propanol/hexane 5:95, 1 mL/min t_1 = 7.09 min 'major enantiomer', t_2 = 11,06 min 'minor enantiomer'). ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.66 (d, *J* = 8.6 Hz, 1H), 7.80 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.67 (d, *J* = 8.4 Hz, 1H), 7.47 (ddd, *J* = 8.6, 6.8, 1.6 Hz, 1H), 7.41 (ddd, *J* = 8.0, 6.8, 1.3 Hz, 1H), 7.26 (d, *J* = 8.4 Hz, 1H), 5.95–5.84 (m, 1H), 5.64–5.58 (m, 1H), 5.24–5.11 (m, 2H), 3.05–2.96 (m, 1H), 2.74–2.66 (m, 1H), 2.55 (s, 3H), 2.15 (d, *J* = 2.3 Hz, 1H). FTIR: 3538, 3390, 3051, 2953, 2852, 1640, 1599, 1510, 1441, 1361, 1178, 1041, 993, 915, 867, 811, 785, 744 cm^{-1}.

3.2.2. Preparation of (*R*)-(+)-1-(2-Methylnaphthalen-1-yl)-but-3-enyl acrylate (64)

Into a two necked flask, 1500 mg (7,1 mmol, 1 eq) of (*R*)-1-(2-Methylnaphthalen-1-yl)-but-3-en-1-ol was weighed and dissolved in dried dichloromethane. The reaction medium was cooled to 0 ^oC with ice bath and then 964 mg (10,65 mmol, 1,5 eq) of acryloyl chloride and ,35 mg (21,3 mmol, 3 eq) of triethylamine was added to the reaction medium slowly. Then the ice bath was removed and reaction was stirred under N_2 atmosphere for 15 hours. When the reaction was completed, the mixture was filtered through celite with ethyl acetate. The filtrate was divided into two fragments and both of the fragments poured into pure water. Then both of them was extracted with dichloromethane. The organic layer was dried with $MgSO_4$ and concentrated under vacuum, then flash column chromatography was performed with 1: 10 (EtOAc: Hex) as a mobile phase; silica-gel as stationary phase. 1894.9 mg of (*R*)-(+)-1-(2-Methylnaphthalen-1-yl)-but-3-enyl acrylate was purified with 88% yield. R_f 0.3 (EtOAc: Hex, 1:6). $[\alpha]_D^{26}$= +0,051 (c 7,73; $CHCl_3$) Enantiomeric excess 48% with (HPLC-Chiracel OJ-H Column) (*i*-propanol: Hex, 5:95, 1 mL/min t_1 = 3.39 min. 'major enantiomer', t_2 = 4.08 min. 'minor enantiomer').; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.50–8.45 (m, 1H), 7.82–7.78 (m, 1H), 7.70–7.66 (m, 1H), 7.52–7.44 (m, 1H), 7.44–7.38 (m, 1H), 7.28 (s, 1H), 6.70–6.60 (m, 1H), 6.43–6.35 (m, 1H), 6.19–6.11 (m, 1H),

5.82–5.77 (m, 1H), 5.77–5.69 (m, 1H), 5.14–5.02 (m, 2H), 3.16–3.04 (m, 1H), 2.90–2.80 (m, 1H), 2.65 (s, 3H).

3.2.3. Preparation of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (58)

Into a two necked flask, 325 mg (0.4 mmol, 0.1 eq.) of 1st Generation Grubbs' catalyst was dissolved in 40 mL of dried dichloromethane and heated to 60 ^{o}C. Then 1053 mg (3.95 mmol, 1 eq.) of (*R*)-(+)-1-(2-Methylnaphthalen-1-yl)-but-3-enyl acrylate was dissolved in 400 mL of dried dichloromethane and added into the catalyst solution. The reaction was stirred under N_2 atmosphere for 8 hours under reflux. When all the starting material consumed, the reaction mixture was cooled down to room temperature and the solvent of the reaction mixture was evaporated under vacuum. Flash column chromatography eluted with 1:8 (EtOAc: Hex) was performed with silica-gel column for two times. 684 mg of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one was purified as a white-grey solid with 72% yield. R_f 0.30 (1:4 EtOAc-Hex).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.83 (dd, *J* = 8.4, 0.6 Hz, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.50–7.40 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.11–7.04 (m, 1H), 6.31 (dd, *J* = 13.3, 4.4 Hz, 1H), 6.24 (ddt, *J* = 9.8, 2.8, 0.9 Hz, 1H), 3.29–3.17 (m, 1H), 2.57 (s, 3H), 2.54–2.44 (m, 1H). FTIR: 3056, 3045, 2951, 2940, 1715, 1621, 1598, 1509, 1447, 1429, 1381, 1251, 1186, 1147, 1050, 1017, 979, 957, 912, 871, 815, 752 cm^{-1}.

3.3. Preparation of 7-substituted 6,7-dihydro-*3H*-oxepin-2-ones (77-79)

3.3.1. Preparation of Alcohols (71-73)

3.3.1.1. Preparation of 1-(Naphthalen-1-yl)-but-3-en-1-ol (71)

Into a two necked flask, 51.0 mg (0.5 mmol, 0.1 eq) of copper (I) chloride and 278.3 mg (0.5 mmol, 0.1 eq) of TBAT were placed and dissolved in 10 mL THF and

stirred for an hour at room temperature. After cooling the reaction medium to 0 ^{o}C with an ice bath, 715 µL (5.0 mmol, 1.0 eq) of 1-naphthaldehyde and 1330.0 µL (7.5 mmol, 1.5 eq) allyltrimethoxysilane were added. Then the ice bath was removed and the reaction mixture was stirred at room temperature under N_2 atmosphere for 3 hours. Reaction was monitored by thin layer chromatography. After the starting material was consumed in TLC, 2 N HCl aq. in MeOH (1:1) was added for desilylation and quenching was performed. After extraction with 2x50 mL of EtOAc; the organic layer was dried with $MgSO_4$ and concentrated under vacuum. Purification was performed by SiO_2 flash column chromatography, eluted with 1:10 (EtOAc: Hex) and 888 mg of 1-(Naphthalen-1-yl)-but-3-en-1-ol was purified as a colorless oil in 89% yield. R_f 0.30 (1:6 EtOAc-Hex); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.09 (d, *J* = 8.2 Hz, 1H), 7.91–7.76 (m, 2H), 7.68 (d, *J* = 7.1 Hz, 1H), 7.56–7.46 (m, 3H), 6.00–5.89 (m, 1H), 5.55 (dd, *J* = 8.1, 3.1 Hz, 1H), 5.27–5.16 (m, 2H), 2.78 (dddt, *J* = 14.3, 6.6, 4.1, 1.3 Hz, 1H), 2.67–2.57 (m, 1H), 2.17 (d, *J* = 1.9 Hz, 1H). ^{13}C-NMR data is in the same trend as reported in the literature (Kasaplar, Yilmazer et al. 2009).

3.3.1.2. Preparation of 1-(Naphthalen-2-yl)-but-3-en-1-ol (72)

Into a two necked flask, 51.0 mg (0.5 mmol, 0.1 eq) of copper (I) chloride and 278 mg (0.5 mmol, 0.1 eq) of TBAT were placed and dissolved in 10 mL THF and stirred for an hour at room temperature. After cooling the reaction medium to 0 ^{o}C with ice bath; 780.9.mg (5 mmol, 1 eq) of 2-naphthaldehyde and 1330.0 µL (7.5 mmol, 1.5 eq) of allyltrimethoxysilane were added respectively. Then the ice bath was removed and the reaction mixture was stirred at room temperature under N_2 atmosphere for 3 hours. Reaction was controlled by thin layer chromatography. After the starting material was disappeared in TLC, 2 N HCl aq. in MeOH (1:1) was added for desilylation and quenching was performed. After extraction with 2x50 mL of EtOAc; the organic layer was dried with $MgSO_4$ and concentrated under vacuum. Purification was performed by SiO_2 flash column chromatography, eluted with 1:10 (EtOAc: Hex) and 689.0 mg of 1-(Naphthalen-2-yl)-but-3-en-1-ol was purified with 78% yield as a colorless oil. R_f 0,30 (1:6 EtOAc-Hex).; ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87–7.79 (m, 4H), 7.52–7.44 (m, 3H), 5.90–5.78 (m, 1H), 5.24–5.13 (m, 2H), 4.95–4.89 (m, 1H), 2.68–2.54 (m, 2H),

2.17 (d, *J* = 2.5 Hz, 1H). ^{13}C-NMR data is the same as reported in the literature (Kasaplar, Yilmazer et al. 2009).

3.3.1.3. Preparation of (*E*)-1-phenylhexa-1,5-diene-3-ol (73)

Into a two necked flask, 51.0 mg (0.5 mmol, 0.1 eq) of copper (I) chloride and 278.mg (0.5 mmol, 0.1 eq) of TBAT were weighed and dissolved in 10 mL of THF and stirred for an hour at room temperature. After cooling the reaction medium to 0 ^{o}C with ice bath; 629 µL (5 mmol, 1.0 eq) of *trans*-cinnamaldehyde and 1330 µL (7.5 mmol, 1.5 eq) of allyltrimethoxysilane were added. Then the ice bath was removed and the reaction mixture was stirred at room temperature under N_2 atmosphere for 3 hours. Reaction was controlled by thin layer chromatography. After the starting material was disappeared in TLC, 2 N HCl aq. in MeOH (1:1) was added for desilylation and quenching was performed. After extraction with 2x50 mL of EtOAc; the organic layer was dried with $MgSO_4$ and concentrated under vacuum. Purification was performed by SiO_2 flash column chromatography, eluted with 1:10 (EtOAc: Hex) and 748.0 mg of (*E*)-1-phenylhexa-1,5-dien-3-ol was purified with 86 % yield. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42–7.22 (m, 5H), 6.61 (dd, *J* = 15.9, 0.5 Hz, 1H), 6.25 (dd, *J* = 15.9, 6.3 Hz, 1H), 5.93–5.81 (m, 1H), 5.24–5.15 (m, 2H), 4.41–4.33 (m, 1H), 2.51–2.33 (m, 2H), 1.93 (s, 1H). ^{13}C NMR (100 MHz, $cdcl_3$) δ 136.75, 134.15, 131.66, 130.46, 128.68, 127.77, 126.59, 118.62, 71.83, 42.12. FTIR: 3366, 3079, 3027, 2979, 2905, 1641, 1599, 1578, 1494, 1449, 1311, 1069, 1029, 966, 916, 869, 750, 693 cm^{-1}.

3.3.2. Preparation of Esters (74-76)

3.3.2.1. Preparation of 1-(Naphthalen-1-yl)-but-3-enyl-but-3-enoate (74)

Into a two necked flask, 888 mg (4.48 mmol, 1 eq.) of 1-(Naphthalen-1-yl)-but-3-en-1-ol and 785.0 µL (8.96 mmol, 2 eq.) of vinylacetic acid were placed and dissolved in 20 mL of dried DCM. After the reaction mixture was cooled with ice bath 1942 mg (9.41 mmol, 2.1 eq.) of DCC and 602 mg (4.93 mmol, 1.1 eq.) of DMAP was added to the reaction medium respectively. Then the ice bath was removed and the

reaction was stirred for 5 hours at room temperature under N_2 atmosphere. When the reaction was completed, the final mixture was concentrated under vacuum. The product was purified by flash column chromatography in silica gel column and 1:10 (EtOAc: Hex) was used as eluent. 1067 mg of 1-(Naphthalen-1-yl)-but-3-enyl-but-3-enoate was purified with 89% yield as a colorless oil. R_f 0.53 (1:6; EtOAc: Hex); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.13 (d, *J* = 8.6 Hz, 1H), 7.88–7.76 (m, 2H), 7.58 – 7.42 (m, 4H), 6.61 (t, *J* = 6.6 Hz, 1H), 6.00–5.88 (m, 1H), 5.78 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.18 (ddt, *J* = 6.4, 2.8, 1.4 Hz, 1H), 5.15 (q, *J* = 1.4 Hz, 1H), 5.12 (dd, *J* = 3.1, 1.5 Hz, 1H), 5.09–5.03 (m, 1H), 3.16 (ddd, *J* = 6.9, 3.5, 1.5 Hz, 2H), 2.81-2.75 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.86, 136.08, 134.04, 133.69, 130.54, 130.38, 129.13, 128.72, 126.51, 125.87, 125.42, 124.13, 123.40, 118.84, 118.21, 72.72, 40.61, 39.56. 3075, 3010, 2985, 2854, 1738, 1643, 1598, 1512, 1429, 1399, 1293, 1249, 1171, 1101, 1047, 977, 919, 800, 777 cm^{-1}.

3.3.2.2. Preparation of 1-(Naphthalen-2-yl)-but-3-enyl-but-3-enoate (75)

In a two necked flask, 689 mg (4.29 mmol, 1 eq.) of 1-(Naphthalen-2-yl)-but-3-en-1-ol and 609 μL (8.59 mmol, 2 eq.) of vinylacetic acid were placed and dissolved in 20 mL of dried DCM. After the reaction mixture was cooled with ice bath and 1502 mg (9.01 mmol, 2.1 eq.) of DCC and 467 mg (4.72 mmol, 1.1 eq.) of DMAP was added to the reaction medium. Then the ice bath was removed and the reaction was stirred for 5 hours at room temperature under N_2 atmosphere. When the reaction was completed, the final mixture was concentrated under vacuum. The product was purified by flash column chromatography in silica gel column and 1:10 (EtOAc: Hex) was used as eluent. 831 mg of 1-(Naphthalen-2-yl)-but-3-enyl-but-3-enoate was purified with 90% yield as a colorless oil. R_f 0.56 (1:6; EtOAc: Hex); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.85–7.76 (m, 4H), 7.50–7.42 (m, 3H), 6.02-5.87 (m, 2H), 5.72 (ddt, *J* = 17.1, 10.2, 7.0 Hz, 1H), 5.20–5.02 (m, 4H), 3.14 (ddd, *J* = 7.0, 3.1, 1.5 Hz, 2H), 2.80–2.61 (m, 2H).; ^{13}C-NMR (100 MHz, $CDCl_3$) δ 170.56, 137.19, 133.06, 133.01, 132.98, 130.08, 128.18, 127.94, 127.56, 126.11, 126.00, 125.65, 124.16, 118.48, 118.08, 75.39, 40.55, 39.24. 3079, 3058, 3021, 2981, 2937, 2854, 1732, 1643, 1602, 1509, 1428, 1342, 1319, 1293, 1249, 1170, 1120, 1043, 991, 919, 857, 818, 748 cm^{-1}.

3.3.2.3. Preparation of (*E*)-1-phenylhexa-1,5-diene-3-yl-but-3-enoate (76)

Into a two necked flask, 748.0 mg (4.29 mmol, 1 eq.) of (*E*)-1-phenylhexa-1,5-dien-3-ol and 753.0 µL (8.59 mmol, 2 eq.) of vinylacetic acid were dissolved in 20 mL of dried DCM. After the reaction mixture was cooled with ice bath 1859.0 mg (9.01 mmol, 2.1 eq.) DCC and 577.0 mg (4.72 mmol, 1.1 eq.) DMAP was added to the reaction medium. Then the ice bath was removed and the reaction was stirred for 5 hours at room temperature under N_2 atmosphere. When the reaction was completed, the final mixture was concentrated under vacuum. The product was purified by flash column chromatography in silica gel column and 1:10 (EtOAc: Hex) was used as eluent. 942.0 mg of (*E*)-1-phenylhexa-1,5-dien-3-yl but-3-enoate was purified with 90% yield as a colorless oil. R_f 0.62 (1:6 EtOAc-Hex); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.49–7.09 (m, 5H), 6.74–6.49 (m, 1H), 6.25–6.05 (m, 1H), 5.99–5.86 (m, 1H), 5.85–5.70 (m, 1H), 5.56–5.44 (m, 1H), 5.24–5.00 (m, 4H), 3.15–3.06 (m, 2H), 2.55–2.41 (m, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.20, 136.80, 133.54, 133.29, 130.82, 129.08, 128.49, 127.48, 127.13, 119.05, 118.69, 74.48, 39.91, 39.62.

3.3.3. Preparation of Lactones (77-79)

3.3.3.1. Preparation of (*Z*)-7-(Naphthalen-1-yl)-6,7-dihydro-*3H*-oxepin-2-one (77)

Into a two necked flask, 5 mg (0.009 mmol, 0.05 eq) of 2nd generation Grubbs' catalyst was placed and dissolved in 2 mL of dried dichloromethane. Then 50 mg (0.19 mmol, 1 eq) of 1-(Naphthalen-1-yl)-but-3-enyl-but-3-enoate was dissolved in 25 mL of dried dichloromethane and added into the catalyst solution. The reaction was stirred under N_2 atmosphere at room temperature. After 24 hours, the solvent of the reaction mixture was evaporated under vacuum. The product was purified by SiO_2 flash column chromatography eluted with 1:10 (EtOAc: Hex) to yield 8.3 mg of (*Z*)-7-(Naphthalen-1-yl)-6,7-dihydro-*3H*-oxepin-2-one as a white-grey solid with 18% yield. R_f 0.30 (1:10 EtOAc-Hex); ^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.75 (d, *J* = 8.1 Hz, 1H), 7.55–7.40 (m, 4H), 6.68 (dd, *J* = 8.2, 4.0 Hz, 1H),

5.81–5.72 (m, 1H), 5.63–5.54 (m, 1H), 3.11 (dd, *J* = 14.1, 7.6 Hz, 1H), 2.95 (dd, *J* = 13.8, 6.3 Hz, 1H), 2.71 (dd, *J* = 13.0, 6.1 Hz, 2H); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 171.31, 136.28, 134.38, 130.55, 129.57, 129.45, 129.01, 126.95, 126.79, 126.26, 125.89, 124.26, 123.48, 71.83, 40.16, 39.75.

3.3.3.2. Preparation of (*Z*)-7-(Naphthalen-2-yl)-6,7-dihydro-*3H*-oxepin-2-one (78)

Into a two necked flask, 4.2 mg (0.005 mmol, 0.05 eq.) of 2nd generation Grubbs' catalyst was placed and dissolved in 2 mL of dried dichloromethane. Then 30 mg (0.10 mmol, 1 eq.) of 1-(Naphthalen-2-yl)-but-3-enyl-but-3-enoate was dissolved in 25 mL of dried dichloromethane and added into the catalyst solution. The reaction was stirred under N_2 atmosphere at room temperature. After 24 hours, the solvent of the reaction mixture was evaporated under vacuum. All attempts were failed for purification of (*Z*)-7-(Naphthalen-2-yl)-6,7-dihydro-*3H*-oxepin-2-one from impurities.

3.3.3.3. Preparation of (*4Z*)-(7-styryl)-6,7-dihydro-*3H*-oxepin-2-one (79)

Into a two necked flask, 5 mg (0.006 mmol, 0.05 eq.) of 2nd generation Grubbs' catalyst was weighed and dissolved in 2 mL of dried dichloromethane. Then 30 mg (0.12 mmol, 1 eq.) of 1 (*E*)-1-phenylhexa-1,5-dien-3-yl but-3-enoate was dissolved in 25 mL of dried dichloromethane and added into the catalyst solution. The reaction was stirred under N_2 atmosphere at room temperature. After 24 hours, the solvent of the reaction mixture was evaporated under vacuum. All attempts were failed for purification of (*4Z*)-(7-styryl)-6,7-dihydro-*3H*-oxepin-2-one from impurities.

CHAPTER 4

CONCLUSIONS

In this study large scale asymmetric preparation of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (**58**) and racemic synthesis of three new β,γ-unsaturated seven membered lactone derivatives (**77, 78, 79**) were performed.

Large scale preparation of (**58)** was accomplished in order to evaluate its anti-cancer potentive in vivo studies in animal testing. Asymmetric induction was performed at allylation step of aldehydes and final product 6-membered α,β-unsaturated lactone was obtained enantioselectively from esterification of the chiral alcohol followed by ring closing metathesis.

Racemic synthesis of seven membered lactones was achieved in three steps, starting with well established allylation of aldehydes with allyltrimethoxysilane. The yield of this step was quite high, up to 90%. At second step esterification of racemic alcohols were tried by three different procedures. Transesterification of methyl but-3-enoate with asymmetric alcohols was failed, and Mitsunobu reactions between secondary alcohol and 3-butenoic acid gave an unseperable mixtures of product and triphenyl phosphine. Alternatively Steglich esterification in the presence of DCC and DMAP yielded the target esters up to 90% yields. Ring closing reactions of synthesized esters with 1st generation Grubbs' catalyst did not give any satisfactory product formation. Finally, ring closing metathesis reactions with 2nd generation Grubbs' catalyst were performed and only the β,γ-unsaturated seven membered lactone (**77)** was obtained**.** The other two β,γ-unsaturated seven membered lactone (**78, 79**) could not be purified from impurities. The designed α,β-unsaturated seven membered lactones could not be synthesized from β,γ-unsaturated lactones by isomerization with DBU.

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APPENDIX A

^{1}H- and ^{13}C-NMR, FTIR and HPLC SPECTRA OF COMPOUNDS

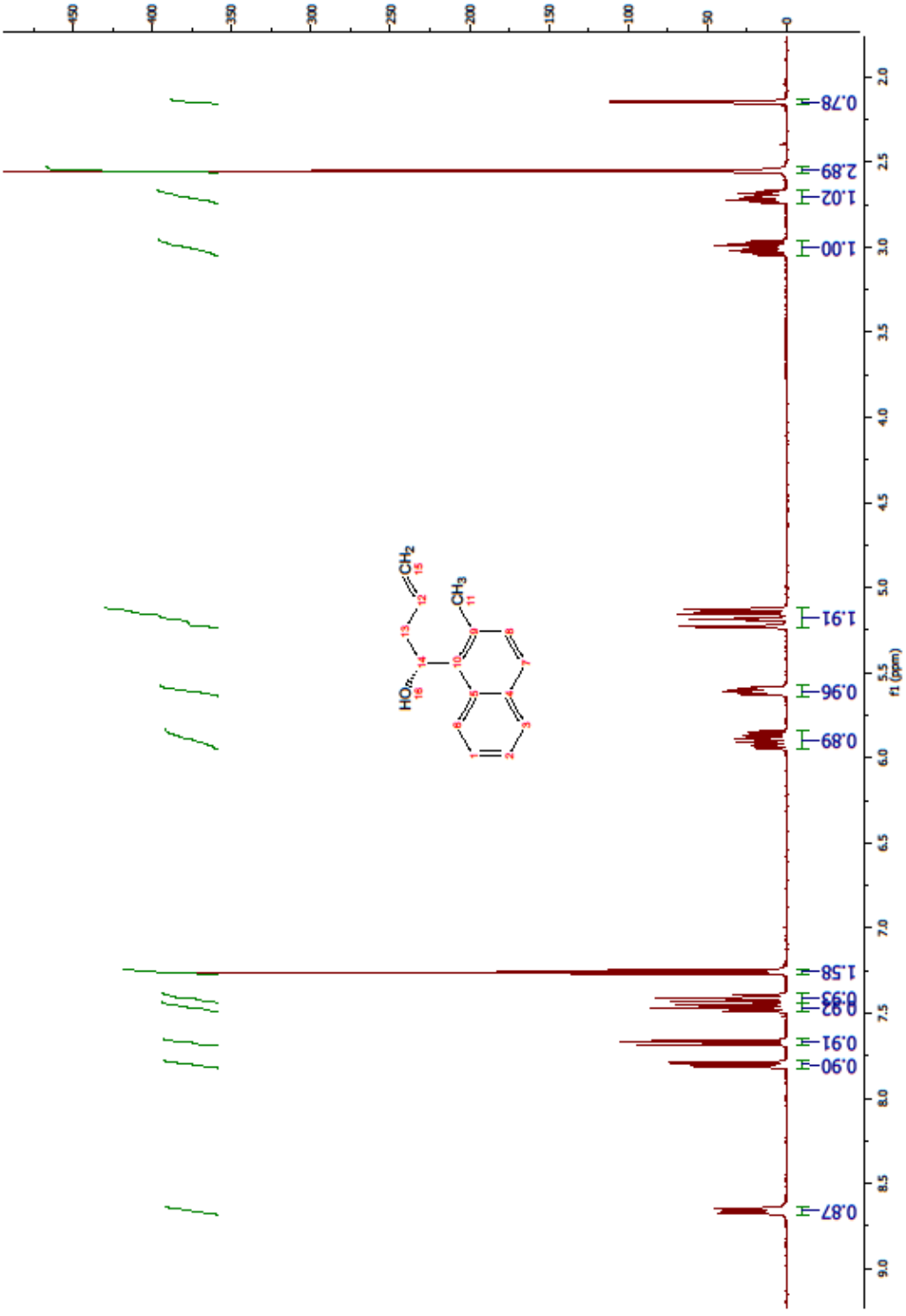

Figure A.1. ^{1}H NMR spectrum of (*R*)-1-(2-Methylnaphthalen-1-yl)-but-3-en-1-ol (**63**).

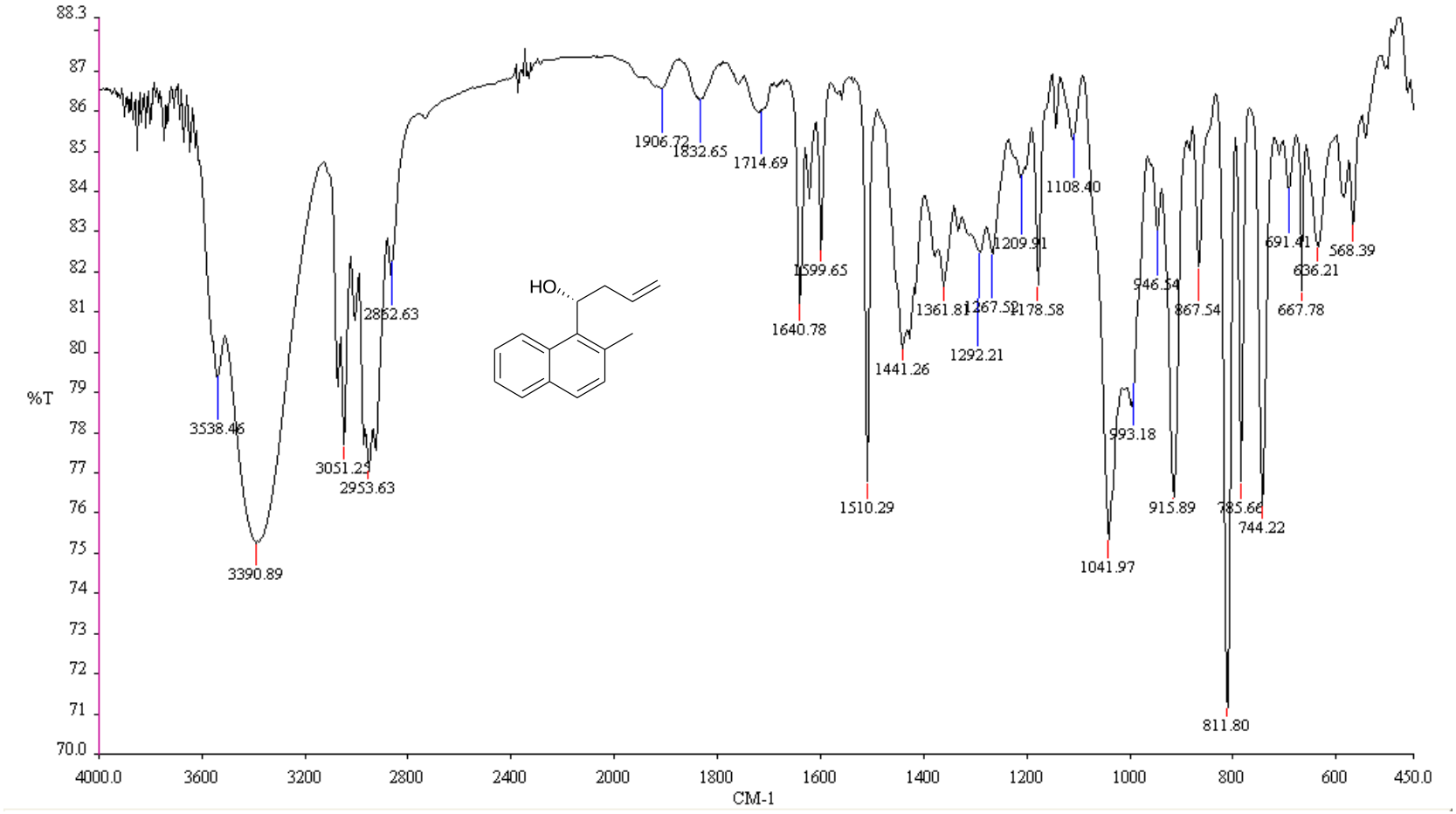

Figure A.2. Infrared spectrum of (*R*)-1-(2-Methylnaphthalen-1-yl)-but-3-en-1-ol (**63**).

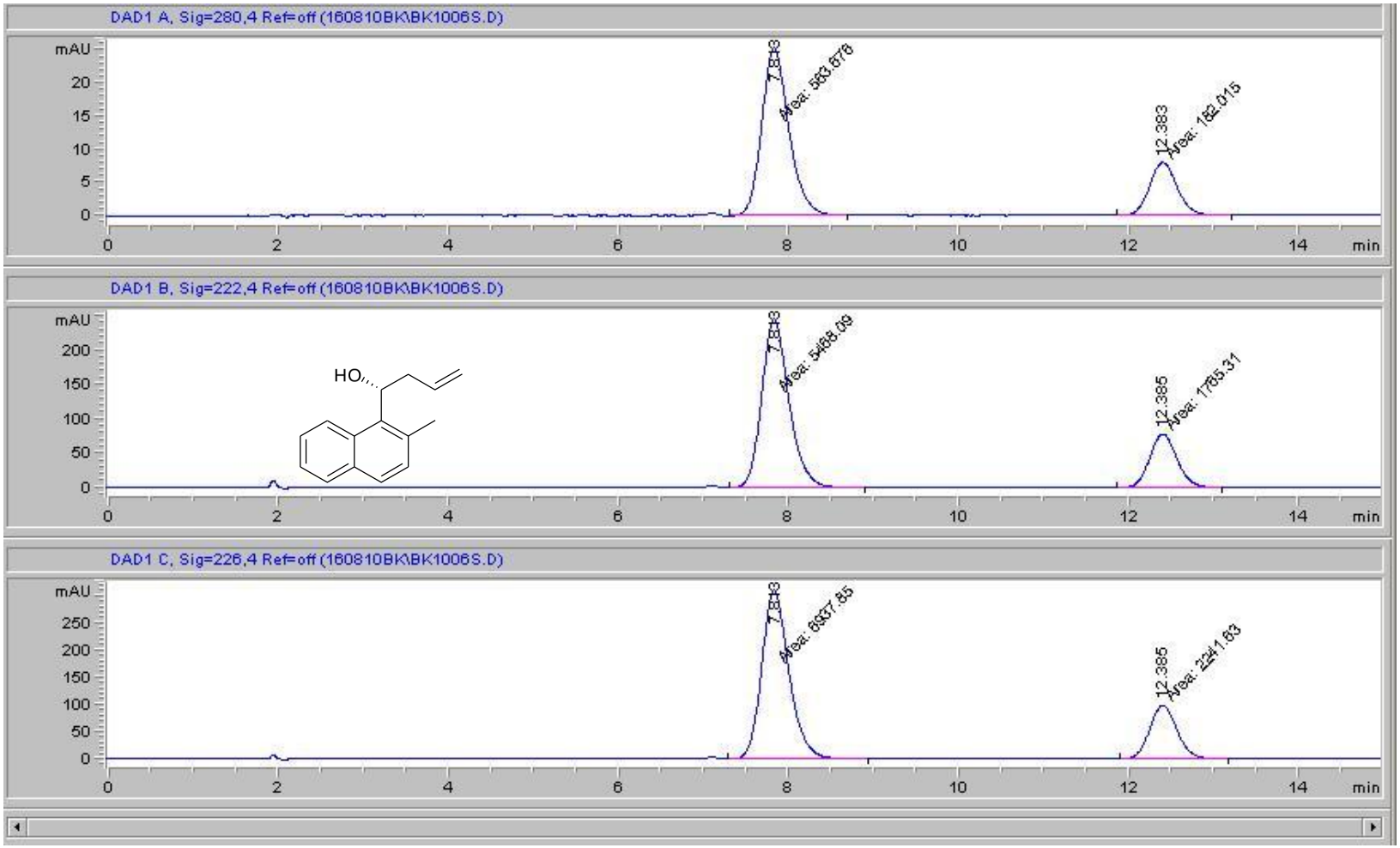

Figure A.3. Chiral HPLC chromatogram of compound **63** (DAD, Sig=280, 222, 226 nm)

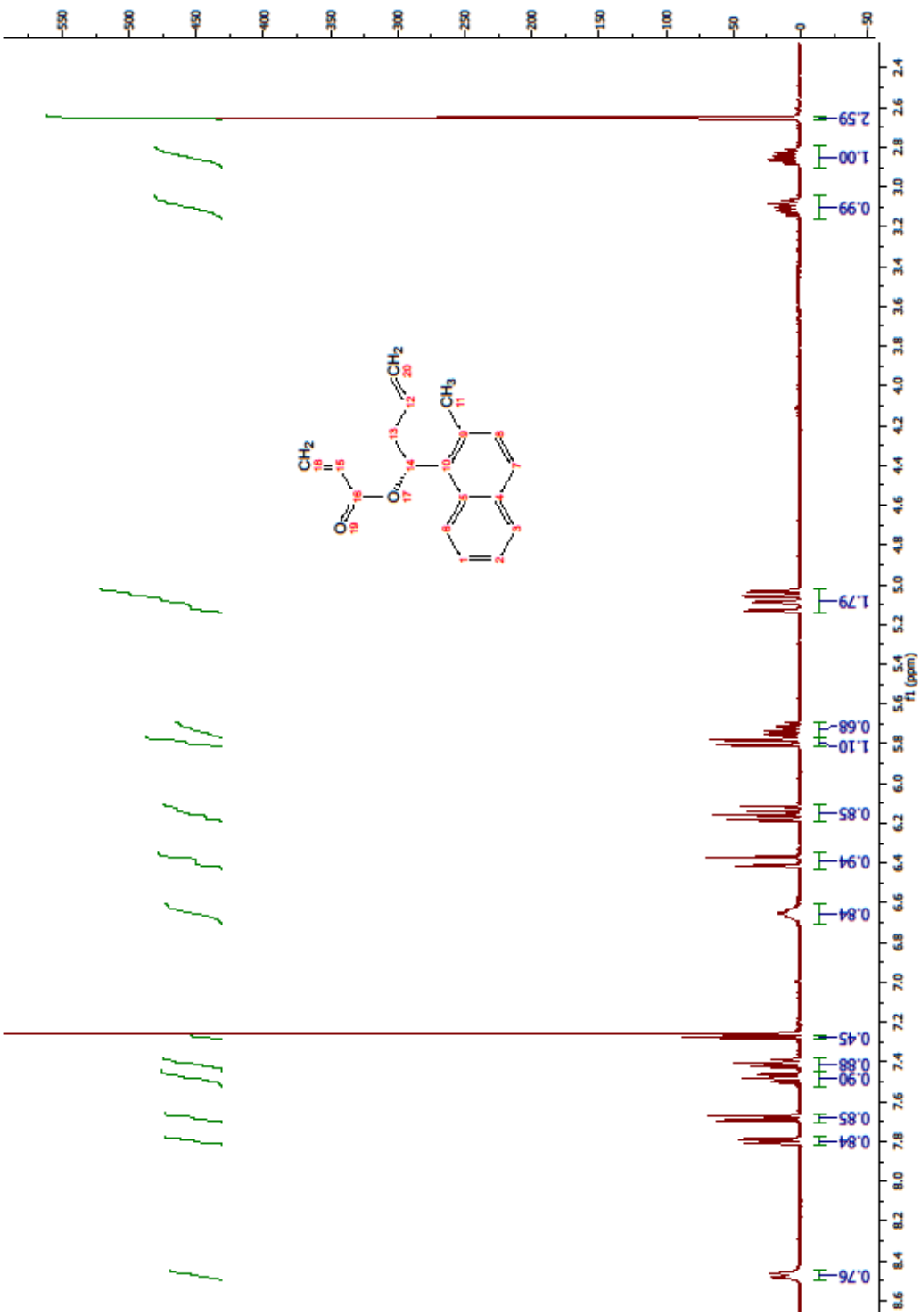

Figure A.4. ^{1}H NMR spectrum of (*R*)-(+)-1-(2-Methylnaphthalen-1-yl)-but-3-enyl acrylate (**64**).

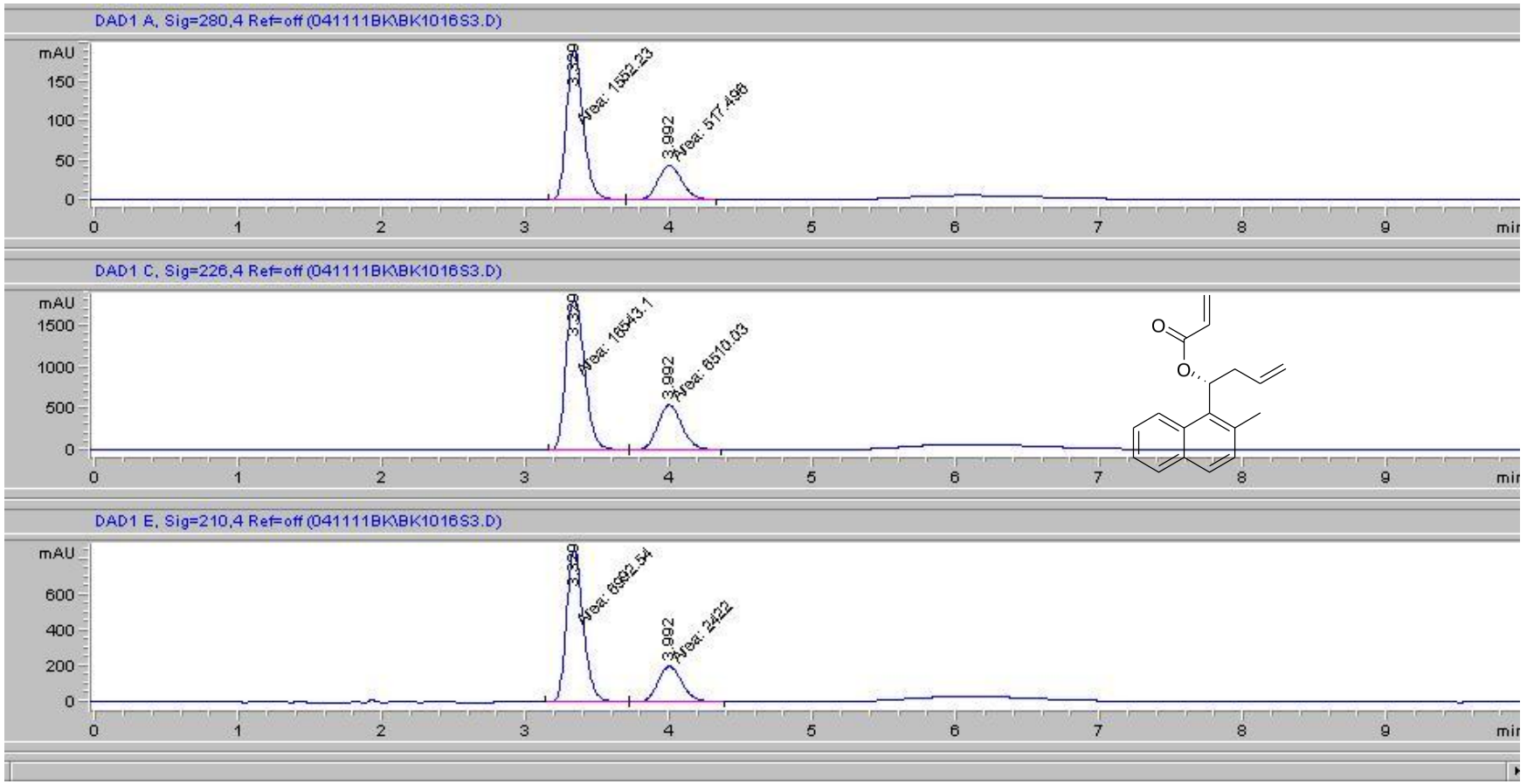

Figure A.5. Chiral HPLC chromatogram of compound (**64**) (DAD, Sig=280, 222, 226 nm).

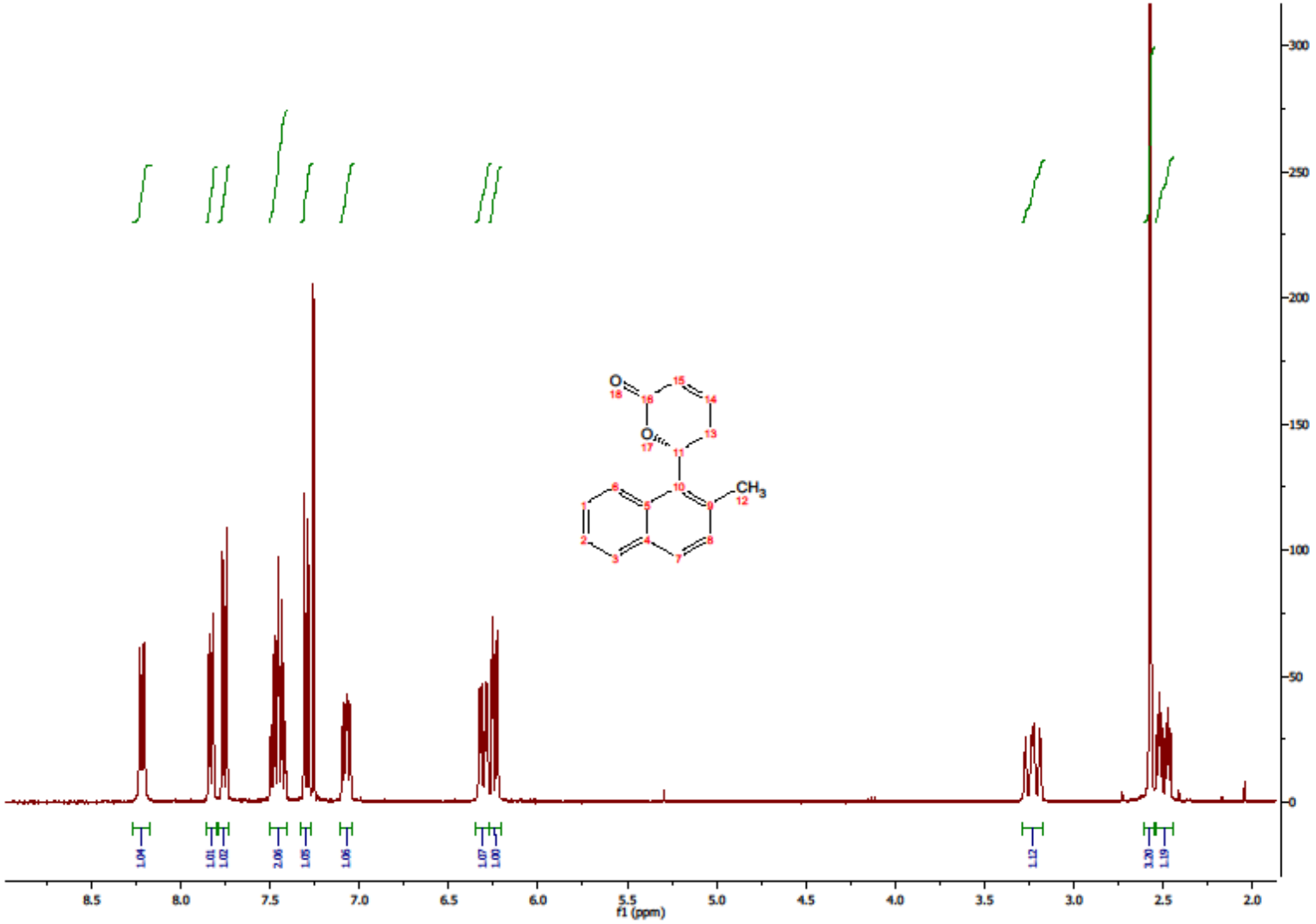

Figure A.6. ^{1}H NMR Spectrum of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (**58**).

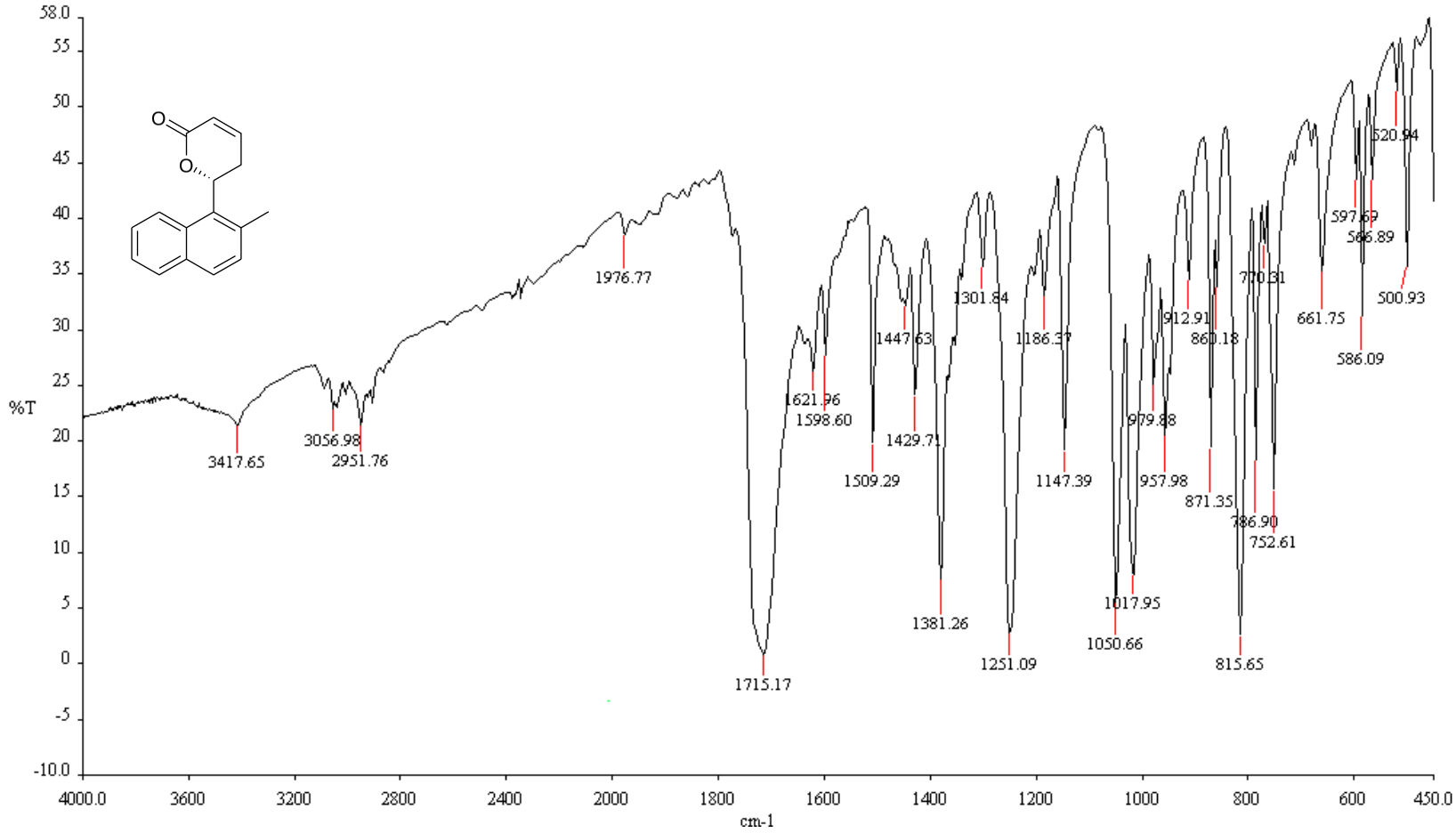

Figure A.7. Infrared spectrum of (*R*)-(+)-6-(2-Methylnaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (**58**).

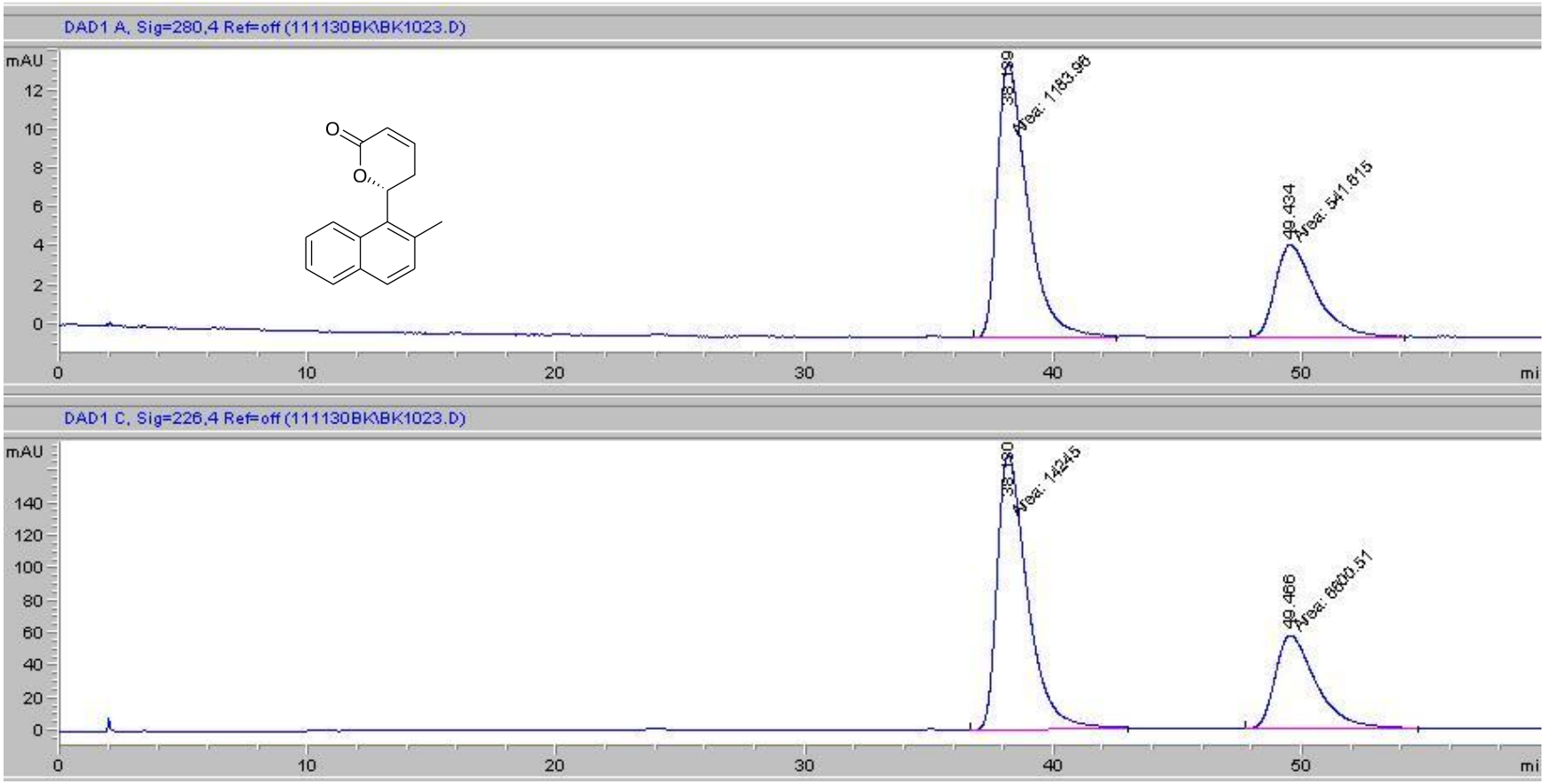

Figure A.8. Chiral HPLC chromatogram of compound **58** (DAD, Sig=280, 226 nm).

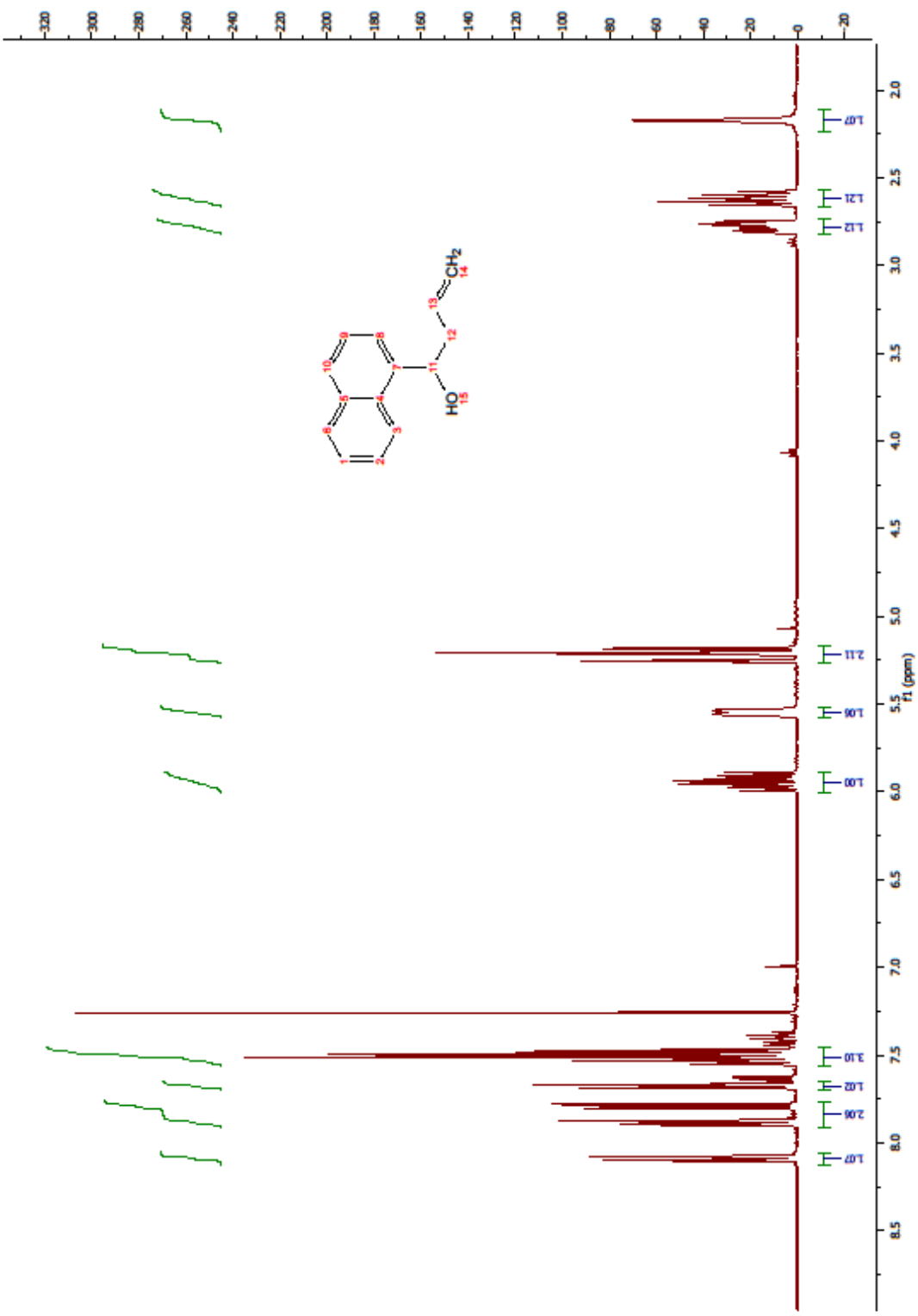

Figure A.9. ^{1}H NMR Spectrum of 1-(Naphthalen-1-yl)-but-3-en-1-ol (**71**).

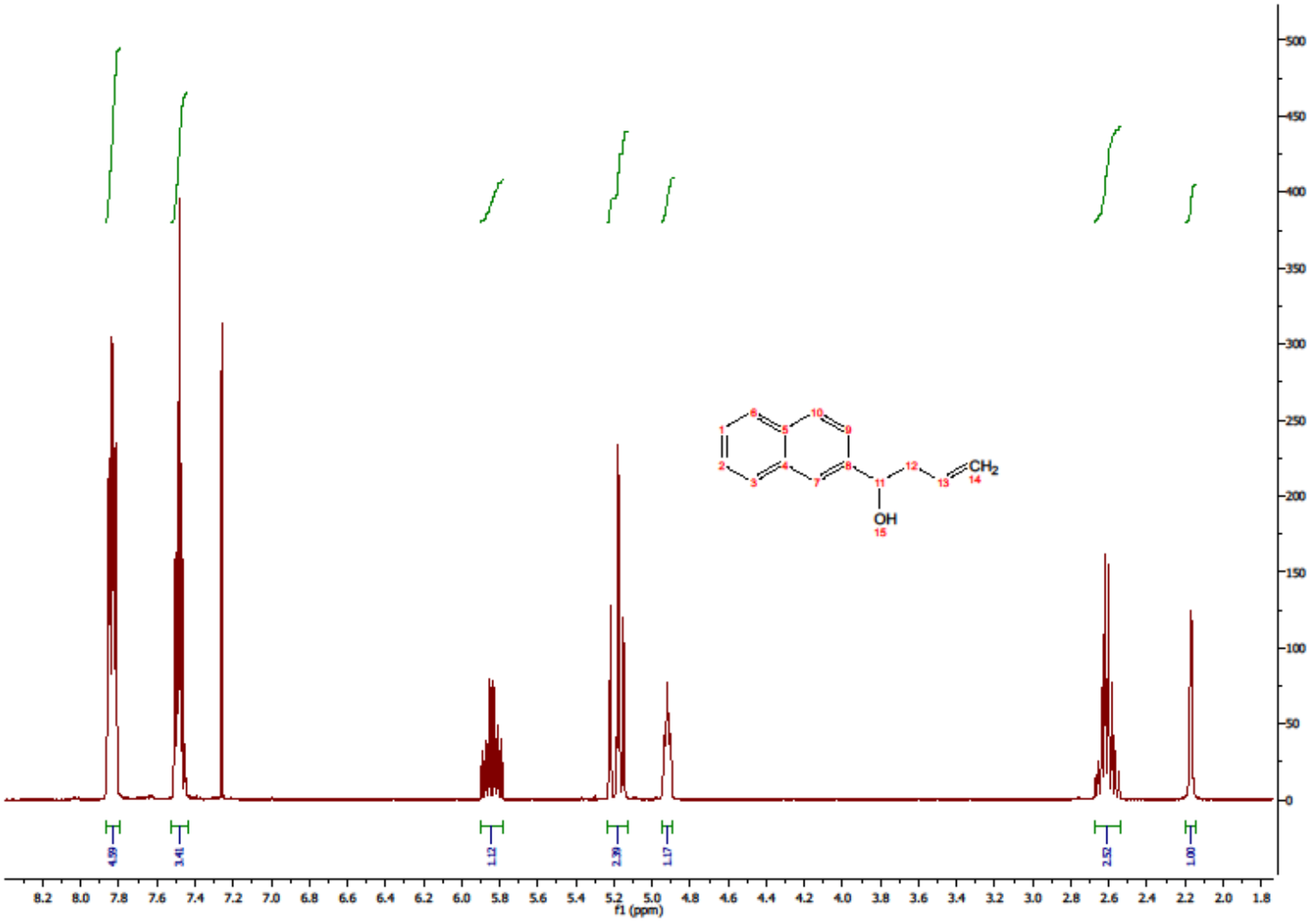

Figure A.10. ^{1}H NMR Spectrum of 1-(Naphthalen-2-yl)-but-3-en-1-ol (**72**)

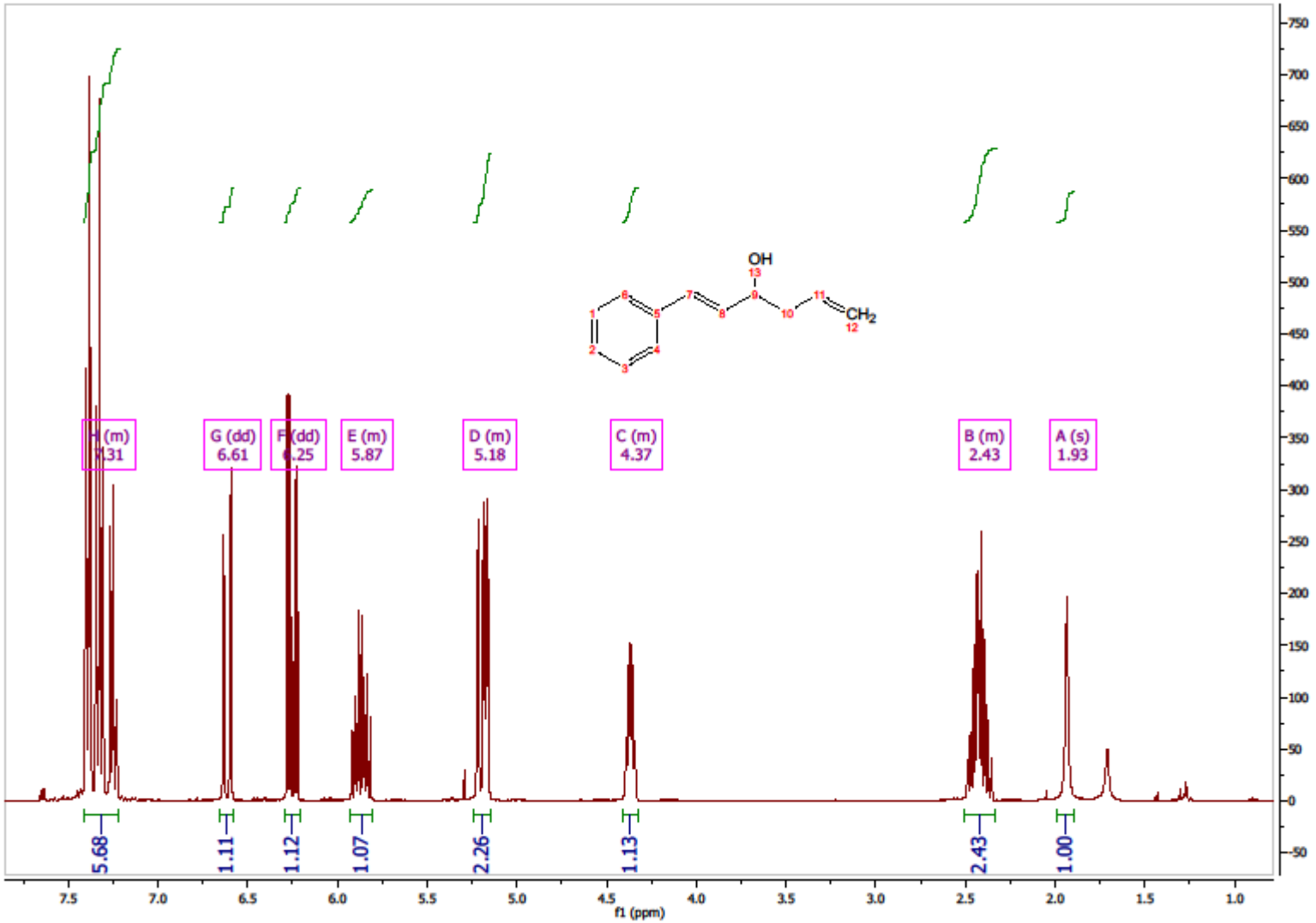

Figure A.11. ^{1}H NMR Spectrum of (*E*)-1-phenylhexa-1,5-diene-3-ol (**73**).

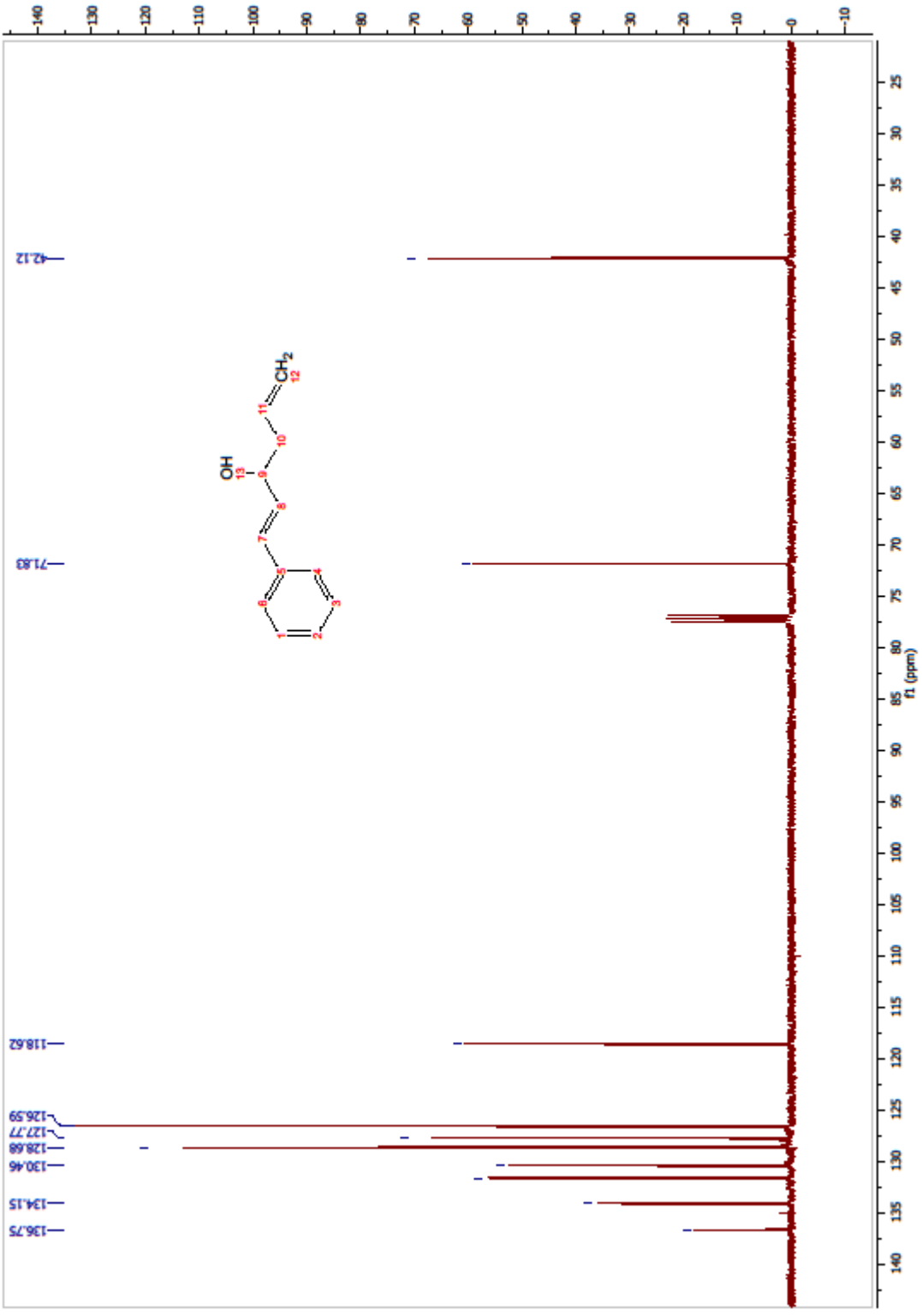

Figure A.12. ^{13}C NMR Spectrum of (*E*)-1-phenylhexa-1,5-diene-3-ol (**73**).

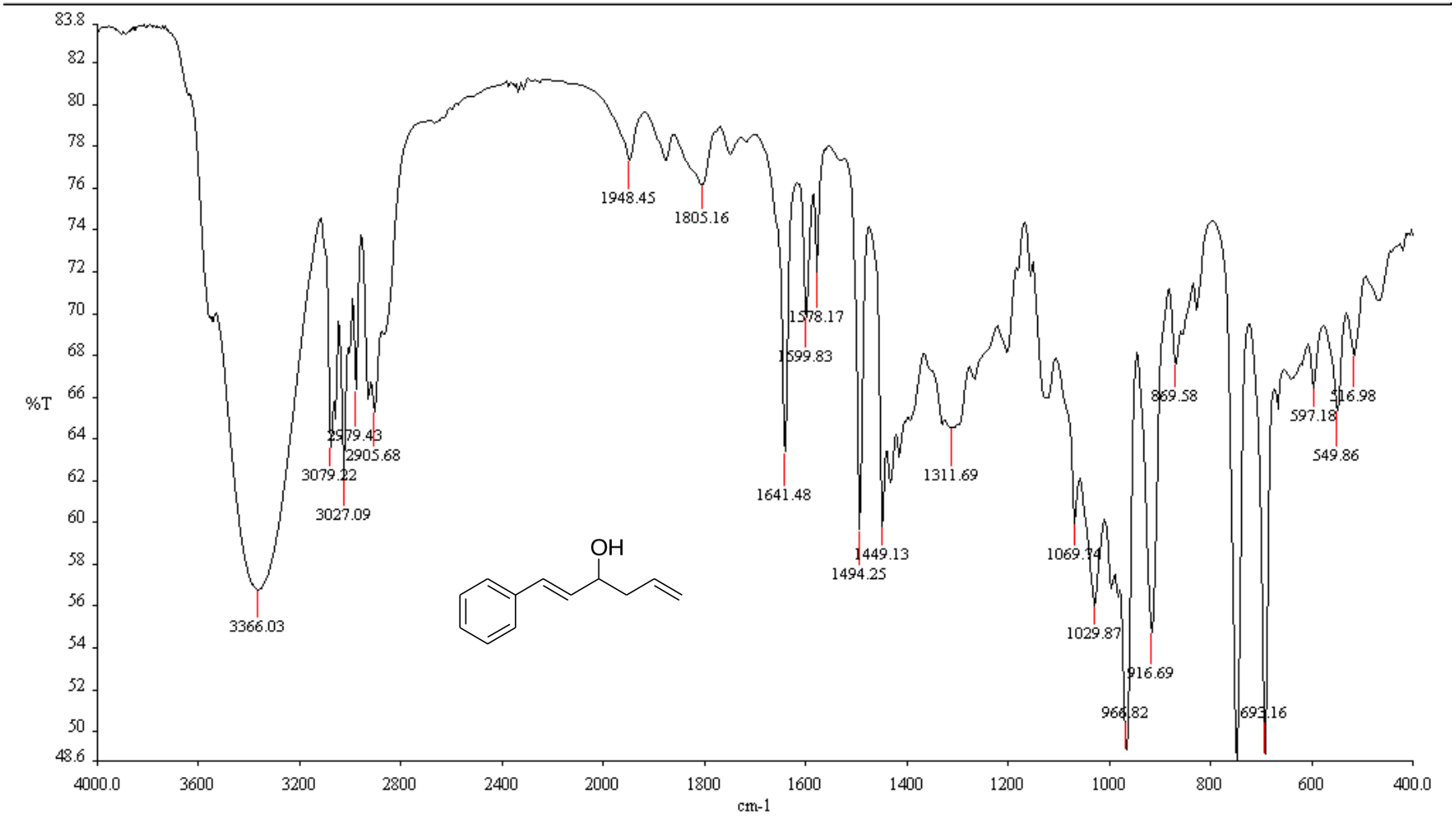

Figure A.13. Infrared spectrum of (*E*)-1-phenylhexa-1,5-diene-3-ol (**73**).

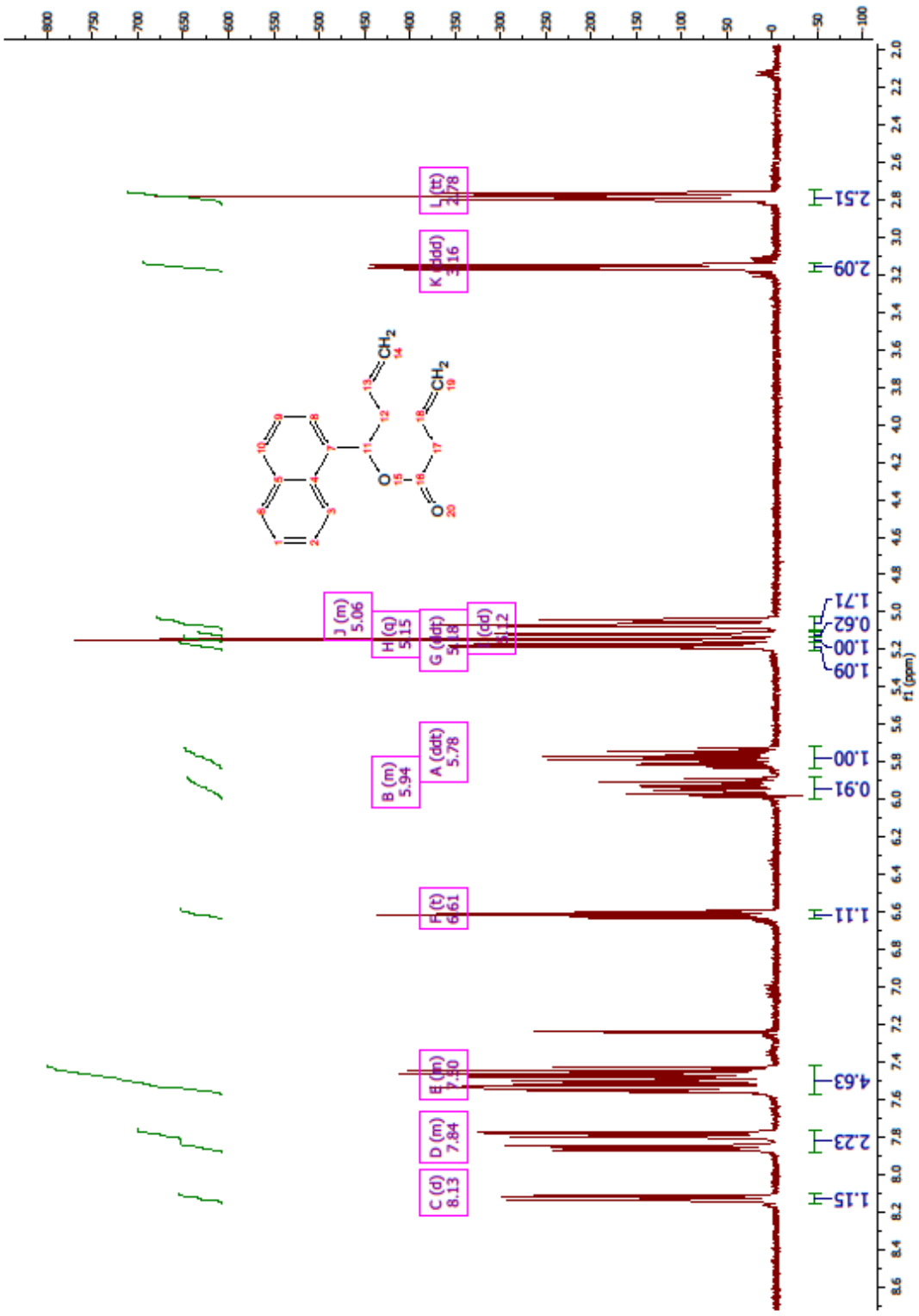

Figure A.14. ^{1}H NMR Spectrum of 1-(Naphthalen-1-yl)-but-3-enyl-but-3-enoate (**74**).

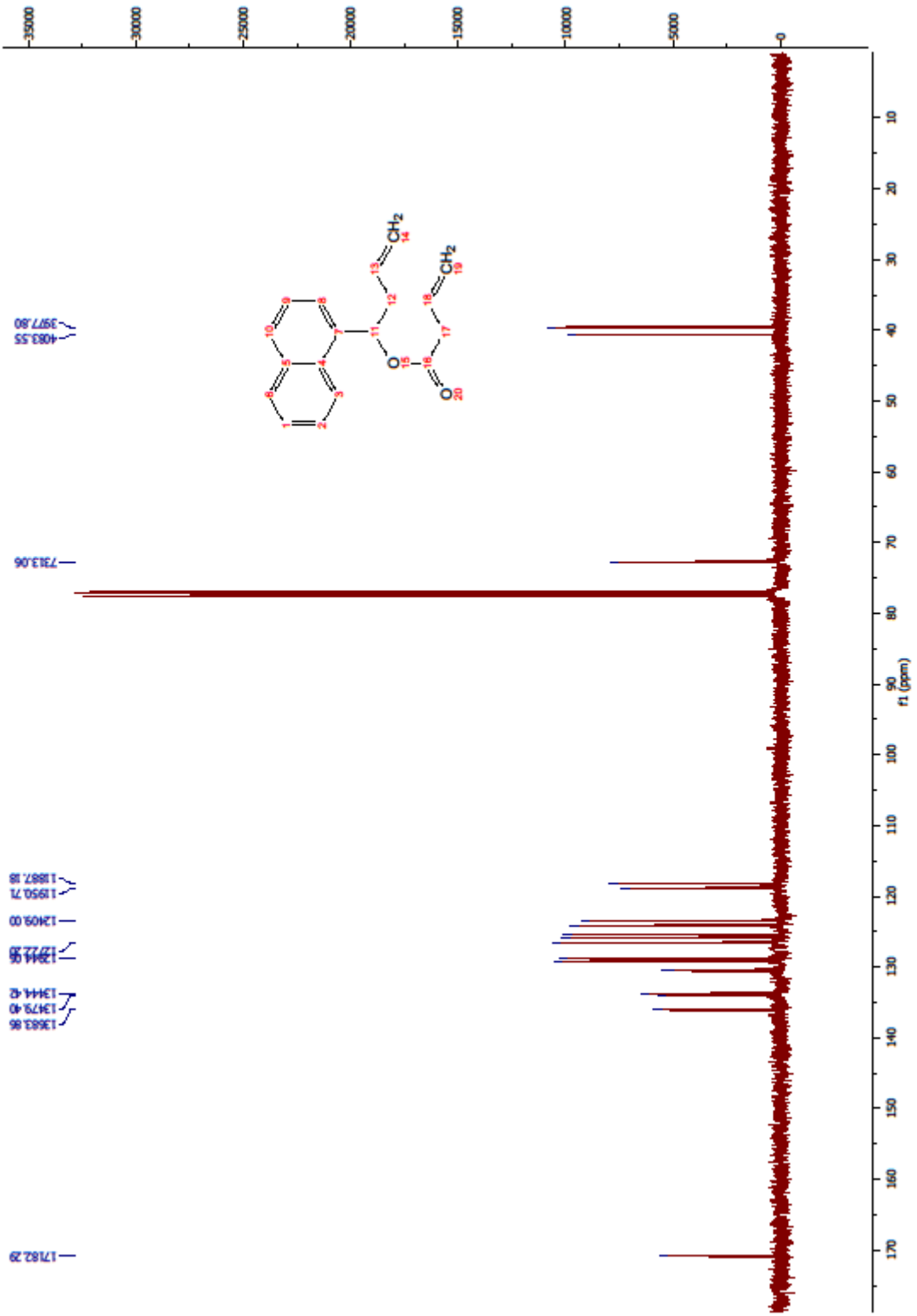

Figure A.15. ^{13}C NMR Spectrum of 1-(Naphthalen-1-yl)-but-3-enyl-but-3-enoate (**74**).

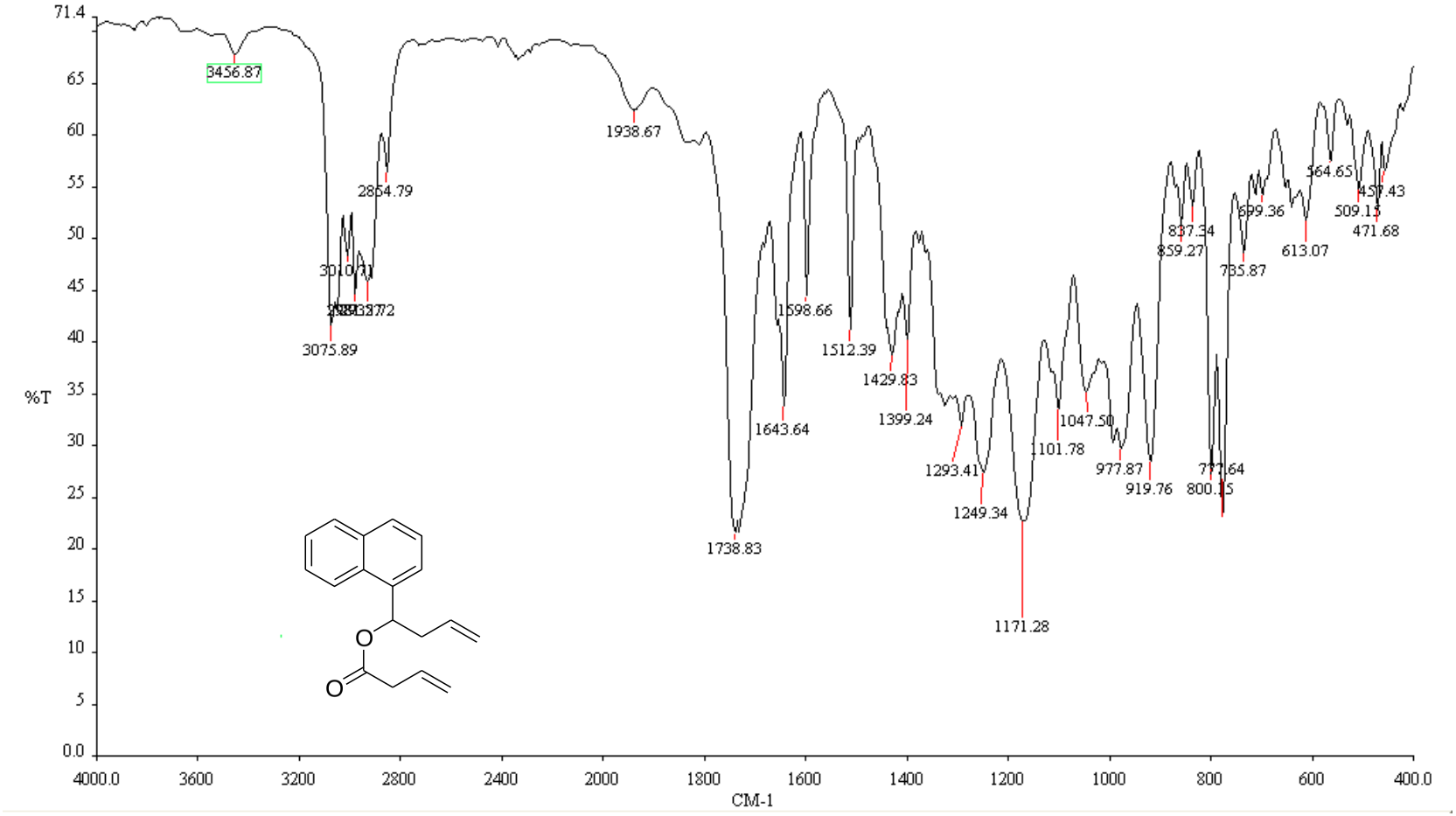

Figure A.16. FTIR Spectrum of 1-(Naphthalen-1-yl)-but-3-enyl-but-3-enoate (**74**).

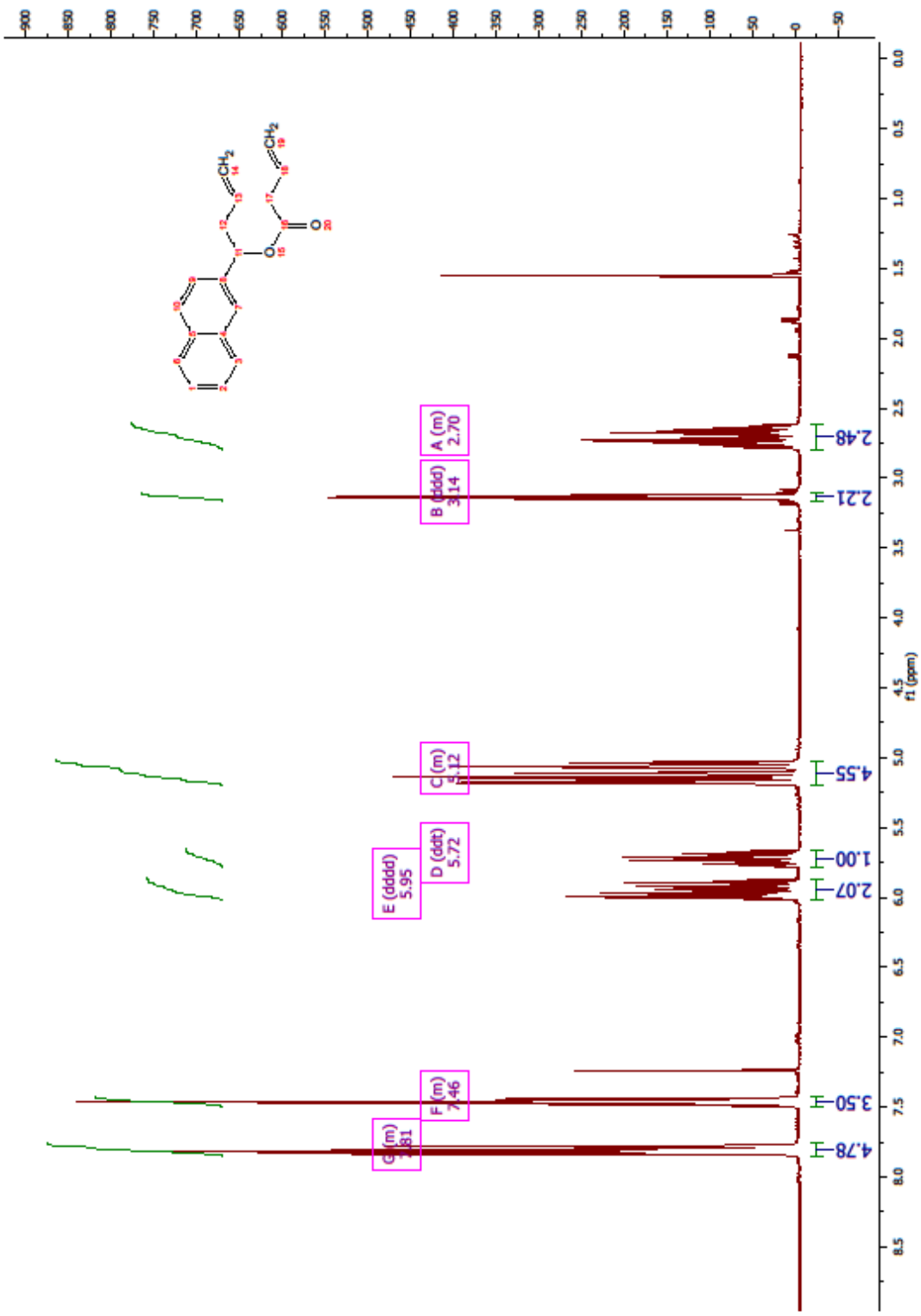

Figure A.17. ^{1}H NMR Spectrum of 1-(Naphthalen-2-yl)-but-3-enyl-but-3-enoate (**75**)

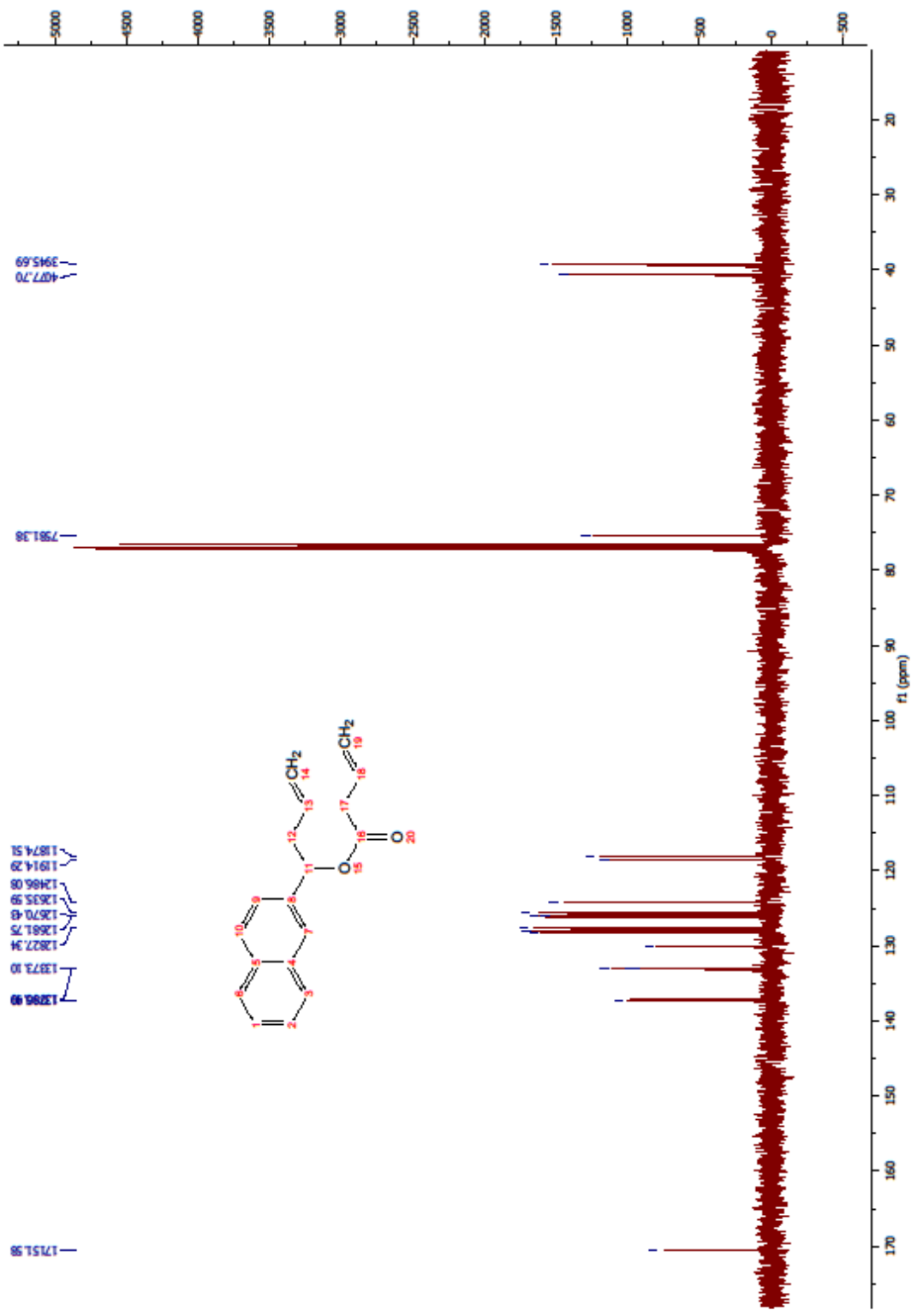

Figure A.18. ^{13}C NMR Spectrum of 1-(Naphthalen-2-yl)-but-3-enyl-but-3-enoate (75)

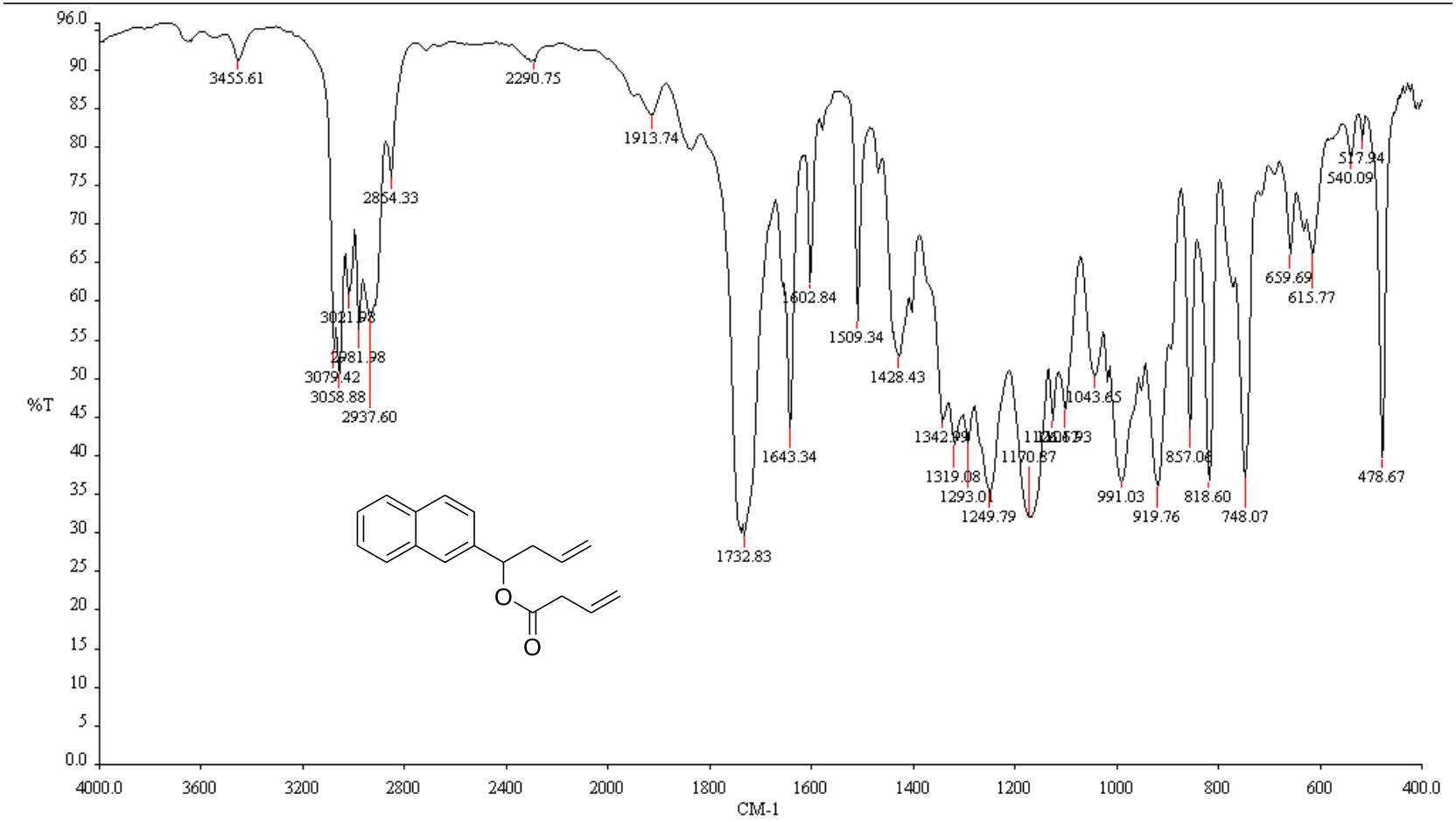

Figure A.19. FTIR Spectrum of 1-(Naphthalen-2-yl)-but-3-enyl-but-3-enoate (**75**)

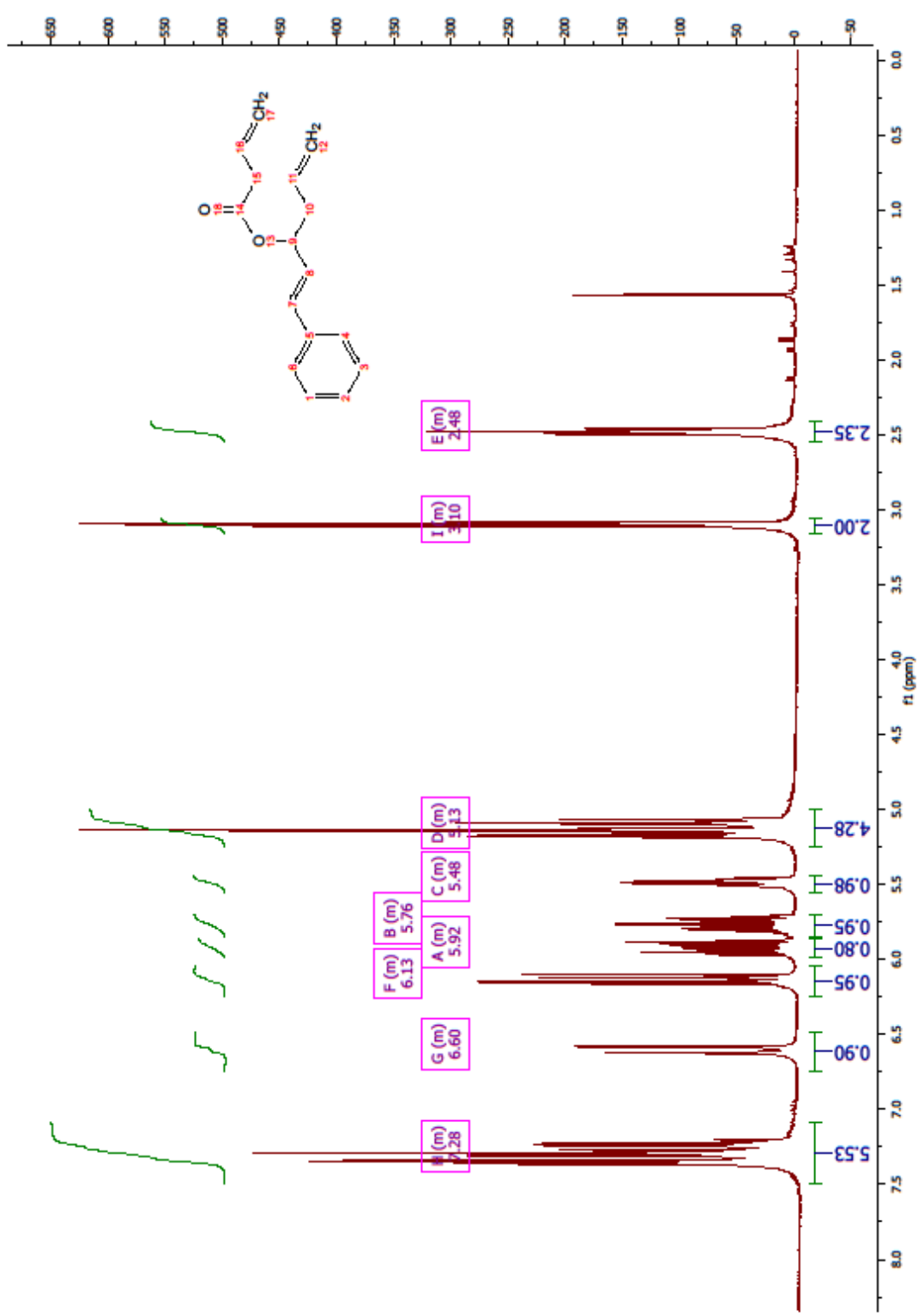

Figure A.20. ^{1}H NMR Spectrum of (*E*)-1-phenylhexa-1,5-diene-3-yl-but-3-enoate (**76**)

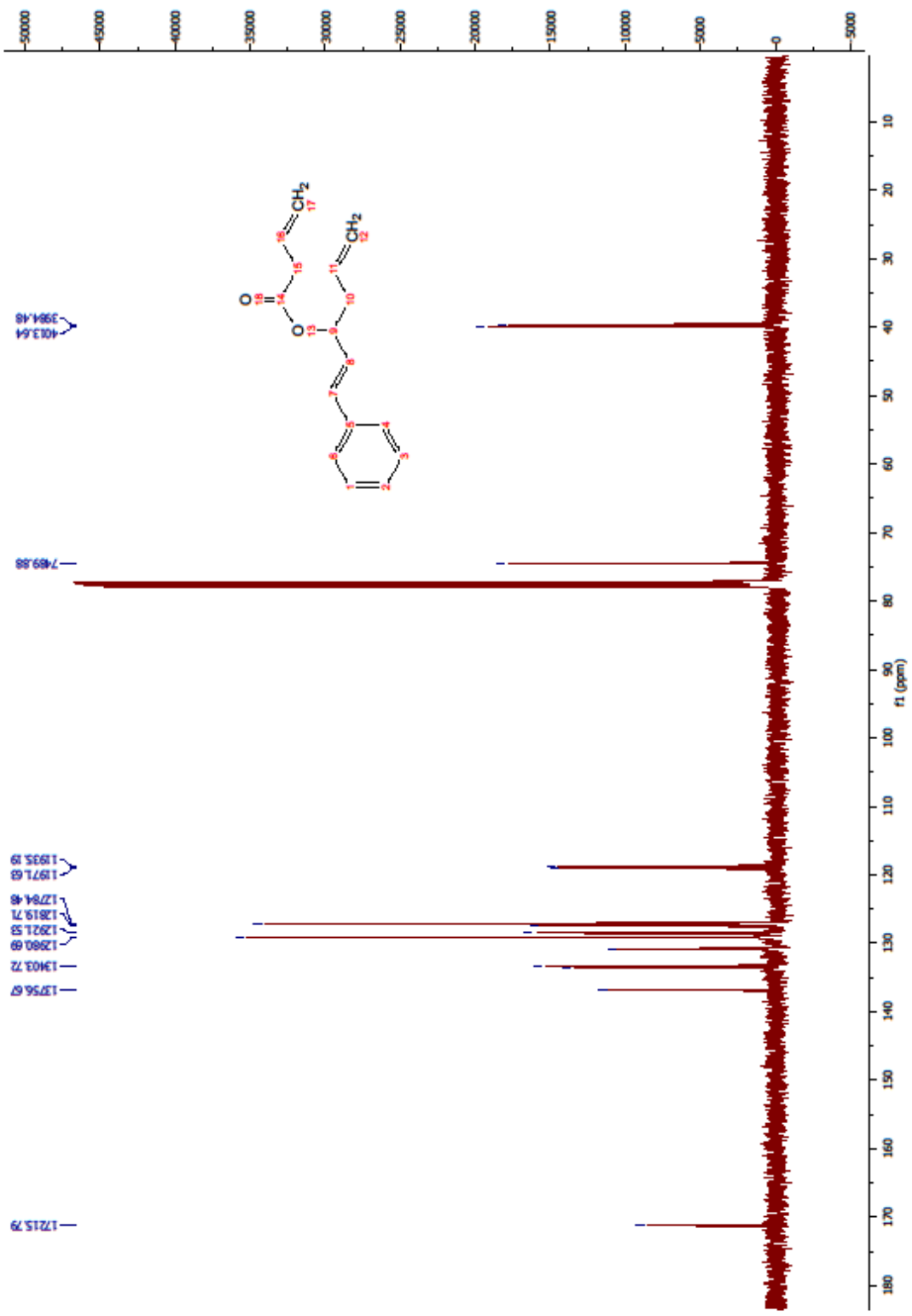

Figure A.21. ^{13}C NMR Spectrum of (*E*)-1-phenylhexa-1,5-diene-3-yl-but-3-enoate (**76**)

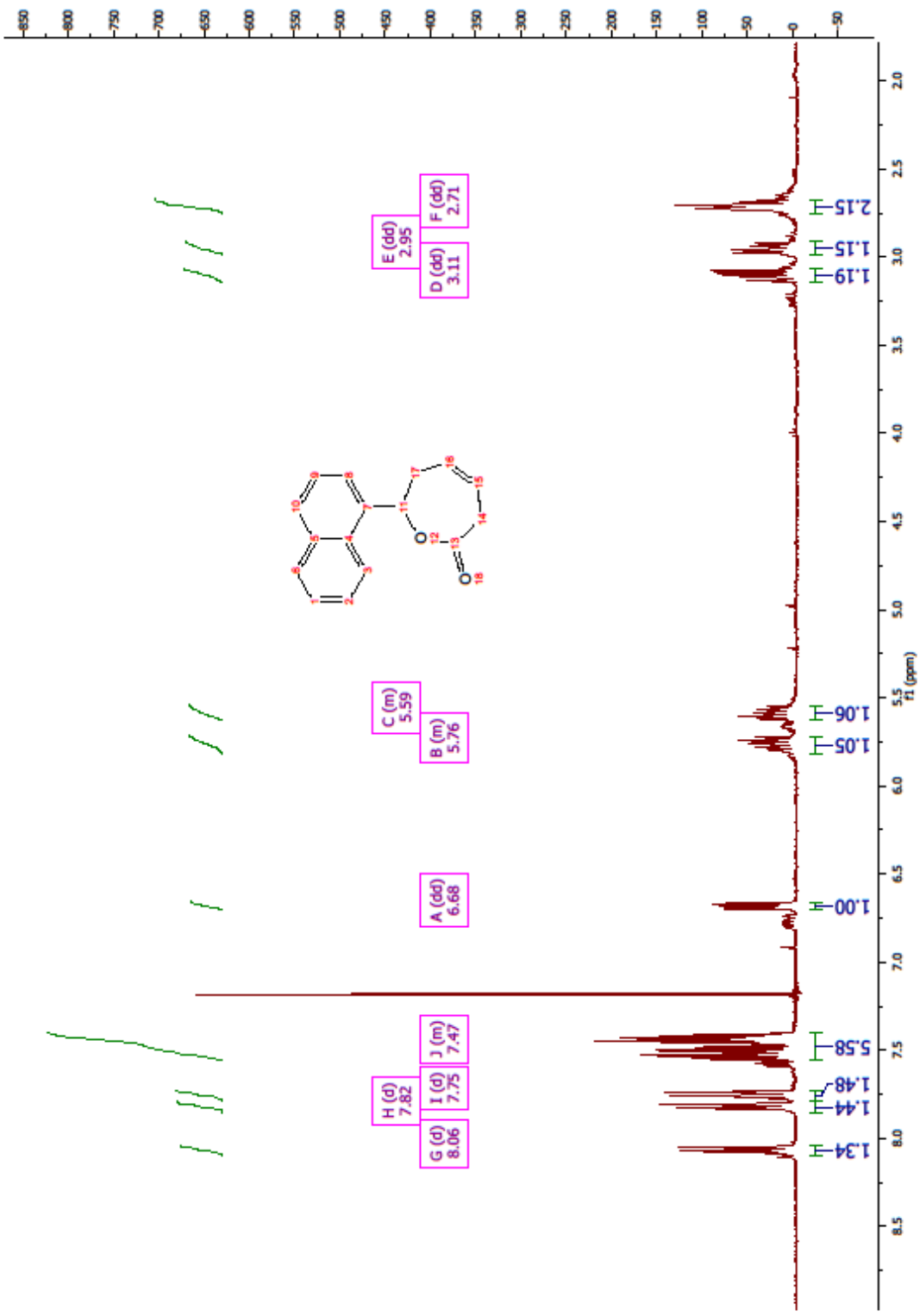

Figure A.22. ^{1}H NMR Spectrum of (*Z*)-7-(Naphthalen-1-yl)-6,7-dihydro-3*H*-oxepin-2-one (77)

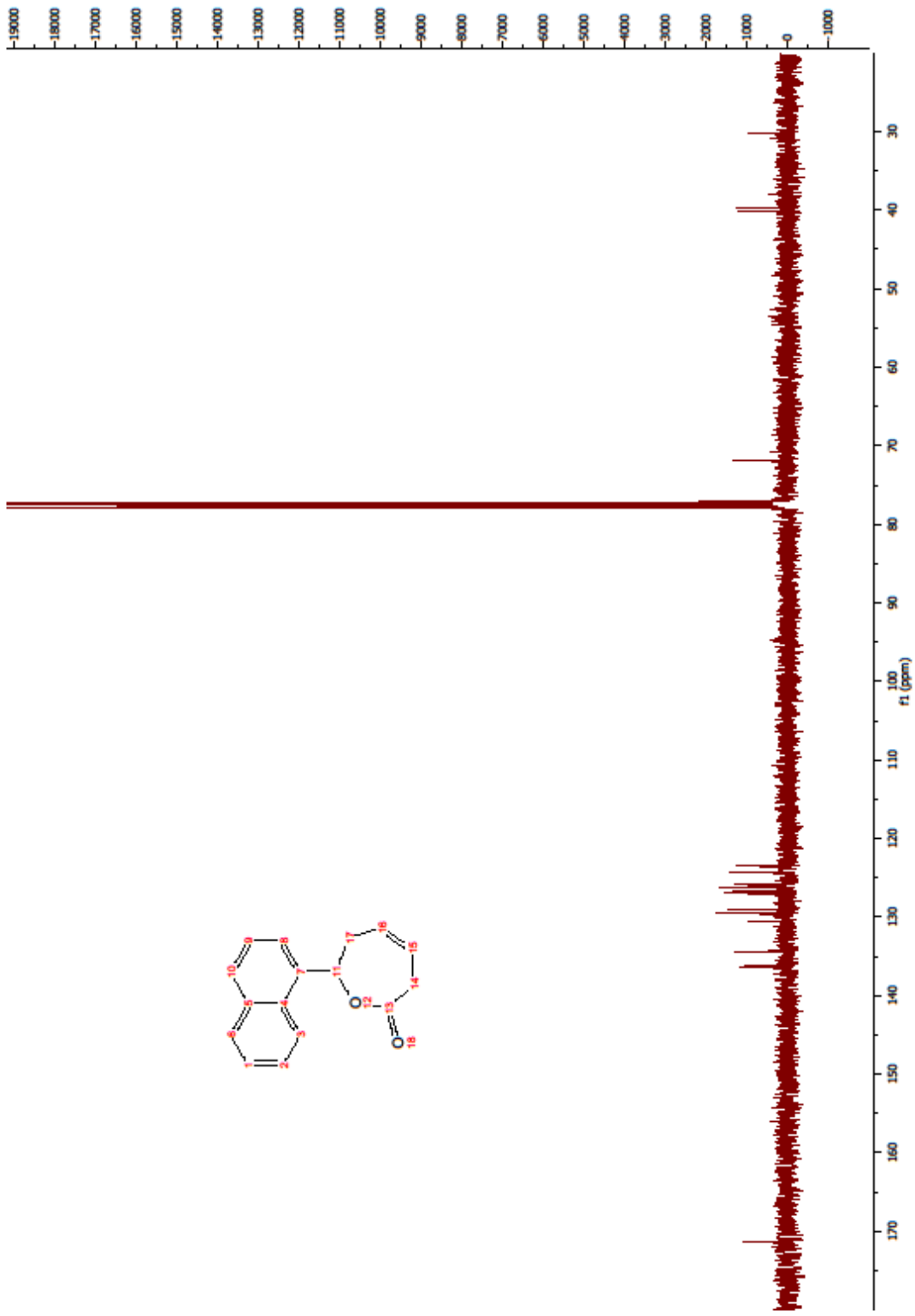

Figure A.23. ^{13}C NMR Spectrum of (*Z*)-7-(Naphthalen-1-yl)-6,7-dihydro-3*H*-oxepin-2-one (77)