ASYMMETRIC SYNTHESIS OF 5,6-DIHYDRO-2*H*-PYRAN-2-ONE DERIVATIVES

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ABSTRACT

ASYMMETRIC SYNTHESIS OF 5,6-DIHYDRO-2*H*-PYRAN-2-ONE DERIVATIVES

α,β-unsaturated lactone derivatives are very important structural core which are isolated from nature and shown as source for several biological activities. Biologically active styryl δ-lactones are well known α,β-unsaturated-δ-lactones. Up to date, many α,β-unsaturated-δ-lactones and their analogues have been isolated and synthesized, exhibiting promising anti-proliferative properties against different cancer cell lines.

In this thesis, large scale asymmetric syntheses of (*R*)-4'-methylklavuzon and (*R*)-2'-methylklavuzon were completed successfully. Also, syntheses of heteroatom functionalized naphthyl substituted novel α,β-unsaturated-δ-lactone (5,6-dihydro-2*H*-pyran-2-one) derivatives, α,β-unsaturated-γ-lactone (furan-2(5*H*)-one) derivatives and 7-membered α,β-unsaturated lactone (6,7-dihydro-5*H*-oxepin-2-one) derivatives were accomplished.

Development of a method for one-pot synthesis of 6-membered α,β-unsaturated-δ-lactone was also studied, and a new vinylogous aldol addition method was developed. By this method, new α,β-unsaturated methyl esters were prepared via dienolate formation starting with methyl buten-3-oate.

ÖZET

5,6-DİHİDRO-2*H*-PİRAN-2-ON TÜREVLERİNİN ASİMETRİK SENTEZİ

α,β-doymamış lakton türevleri doğadan izole edilen ve çeşitli biyolojik aktivitelerinin kaynağı olarak gösterilen önemli yapı taşlarıdır. Biyolojikçe aktif stiril δ-laktonlar α,β-doymamış δ-laktonlar içinde en iyi bilinenleridir. Birçok çeşitli doğal ürün yapısında α,β-doymamış δ-lakton yapısını içerir. Günümüze kadar kanser hücreleri üzerinde anti-proliferatif özelliğe sahip ve gelecek vaat eden birçok α,β-doymamış-δ-laktonlar ile analogları doğadan izole edilmiş ve sentezlenmiştir.

Bu tez çalışmasında, (*R*)-4'-metilklavuzon ve (*R*)-2'-metilklavuzon'un büyük ölçekli asimetrik sentezleri başarıyla tamamlanmıştır. Ayrıca heteroatom fonksiyonuna sahip naftalenil sübsititüyeli yeni α,β-doymamış-δ-lakton (5,6-dihidro-2*H*-piran-2-on) türevlerinin, α,β-doymamış-γ-lakton (furan-2(5*H*)-on) türevlerinin ve 7 üyeli α,β-doymamış lakton (6,7-dihidro--5*H*-oksepin-2-on) türevlerinin sentezleri başarılmıştır.

Altı üyeli α,β-doymamış-δ-laktonların tek kap yöntemiyle sentezine yönelik yeni bir metot geliştirme çalışmaları yapılmış ve yeni bir vinilogous eklenme yöntemi geliştirilmiştir. Bu metot ile metil büten-3-oat ile başlanarak yeni α,β-doymamış metil esterleri dienolat oluşumu aracılığıyla hazırlanmıştır.

TABLE OF CONTENT

LIST OF FIGURES

Figure **Page**

LIST OF TABLES

Table **Page**

LIST OF ABBREVIATIONS

mL	Millilitre
mg	Milligram
g	Gram
μM	Micromolar
M	Molar
GTN	Goniothalamin
RT	Room temperature
mmol	Millimol
min	Minute
h	Hour
DMF	*N*,*N*-dimethylformamide
GSH	Glutathione
TBAT	Tetrabutylammonium difluorotriphenylsilicate
IC_{50}	Half maximal inhibitory concentration
ee%	Percent enantiomeric excess
Hz	Hertz
MHz	Megahertz
δ	Chemical shift
s	Singlet
t	Triplet
d	Doublet
dd	Doublet of doublets
m	Multiplet
ddd	Doublet of doublets of doublets
td	Triplet of doublets

CHAPTER 1

INTRODUCTION

Cancer is general name of more than 100 diseases which cells begin to divide abnormally and grow out of control.[1] Cancer cells can invade and metastasize from origin of cell to other part of the body. There are many kinds of cancer, and if they untreated they can cause death.

A normal cell in human or animal body grows normally, divide and die. This is the normal progression of healthy body cells. In early ages of human, normal cells grow and divide faster than the other periods of human life and this situation let a person to grow. However, a cancerous cell continues dividing and growing and apoptosis (programmed cell death) does not take place in cancerous cells.

There are many factors leading to cancer formation. Genetic factors, smoking, diet and lack of physical activity, UV exposure and even medical tests (radiation, menopausal hormone replacement therapy, e.g.) can cause a cancer.

Chemotherapy is one of the treatments of cancer by drugs. These drugs might be taken before or after surgery. Chemotherapy might take place with other type of therapies (e.g. radiotherapy) or alone. Patient may get chemotherapy once a day, once a week, or even once a month, depending on the type of cancer and the medicine. The length of the chemotherapy depends on the type of cancer, and patient's response to the drugs.

There are many therapeutic agents for the treatment of cancer, and the origin of them is mainly nature. In traditional medicine, many plants are used as medication since they contain many active components. Synthetic analogues of natural products can be prepared to improve the potency of active natural product. Natural products provide a huge biologically active structural diversity one could say that natural products are starting points of drug discovery.[2] Plants sometimes do not include sufficient amount of active molecule. In that case natural products can be prepared by total synthesis; therefore they play a central role in organic chemistry.[3]

One of the most famous building block in biologically active lactones is α,β-unsaturated-δ-lactone. Wide variety of natural products contain α,β-unsaturated-δ-lactone core in their structures. Compounds containing α,β-unsaturated carbonyl group can react

with biological nucleophiles such as cysteine by Michael type addition reaction.[4] Up to date, many α,β-unsaturated lactone analogues were isolated and synthesized to investigate their antiproliferative properties against cancer cell lines.[5]

Styryl lactones are a group of secondary metabolites ubiquitous in the genus *Goniothalamus* that have demonstrated interesting biological properties. There are three main classes of compounds found in *Goniothalamus* species including alkaloids, annonaceous acetogenins and styryl lactones.[6]

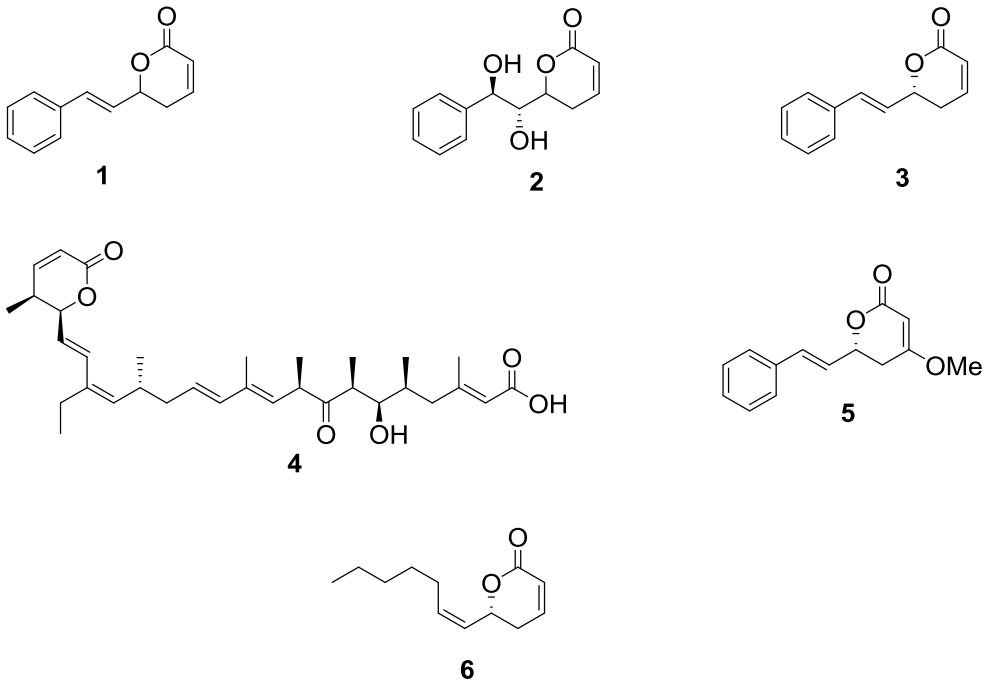

Figure 1.1. Structures of goniothalamin (1) and selected examples of naturally occurring α,β-unsaturated-δ-lactones product include goniodiol (2), (*R*)-goniothalamin (3), leptomycin B (4), kavain (5), argentilactone (6)

In next part, biological activities and synthesis methods of 6-membered, 5-membered and 7-membered α,β-unsaturated lactones are presented in details.

1.1. Six-Membered α,β-Unsaturated Lactones

1.1.1. Properties of Naturally Occurring Goniothalamin and Synthetic Six-Membered α,β-Unsaturated-δ-Lactones

Goniothalamin (**1**), a styryl lactone, was isolated from the skin, bark, roots and leafs of *Goniothalamus* sp.[7] It induces apoptosis in vascular smooth muscle cell lines.[8] (*R*)-Goniothalamin **(3)** is cytotoxic towards different cell lines including cervical, gastric, breast, leukemia, prostate and colon carcinomas.[9] It also induces apoptosis in MCF-7 and Jurkat T cells by activating the caspase 3 and caspase 7.[10]

Many groups have been focused on the synthesis of new goniothalamin derivatives and α,β-unsaturated lactones because of the significant cytotoxic and antiproliferative activities of goniothalamin **(1)** against many cancer cell lines such as kidney, breast, prostate, lung and liver.

Mosaddik and Haque isolated goniothalamin from *Bryonopsis laciniosa* and investigated its antimicrobial activity. Goniothaiamin showed weak antibacterial activity against *Bacillus cereus* and *Shigella shiga* with 64 μg/mL minimum inhibitory concentration. Goniothalamin also showed cytotoxic activity against *Artemia salina* with LC_{50} values of 5.03 μg/mL when compared to standard molecule gallic acid (4.53 μg/mL).[11]

Chien-Chih Chiu et al., investigated the possible anticancer activity of goniothalamin **(1)** against the human non-small cell lung cancer (NSCLC) line, H1299. They found that cellular proliferation was significantly inhibited by goniothalamin. Also a significant increase in the tail DNA was observed. Wound healing and zymography assays studies showed that goniothalamin attenuated cell migration and caused a reduction in the activity level of two major migration-associated matrix metalloproteinases, MMP-2 and MMP-9. They concluded that the DNA-damaging effect of goniothalamin against lung cancer cells led to growth inhibition as well as a depression in migration ability.[12]

The antifungal activity of *(R)*-goniothalamin (**3**) and *(S)*-goniothalamin **(7)** was evaluated against six *Candida* species by de Fatima and co-workers. They also investigated compounds' in *vitro* effects on yeast adhesion to human buccal epithelial cells (BEC), *Candida albicans* and *C. dubliniensis* biofilm progression. (*S*)-

Goniothalamin exhibited higher potency than (*R*)-goniothalamin against all fungi. (*R*)-Goniothalamin and (*S*)-goniothalamin were found to be as effective as fluconazole (positive control) in the inhibition of the adhesion of *C. albicans* and *C. dubliniensis* to BEC. XTT assay and scanning electron microscopy revealed that both enantiomers had shown two fold more activity than fluconazole in the inhibiton of yeast biofilm progressions when compared to fluconazole.[13]

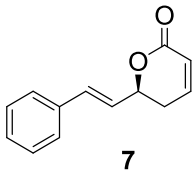

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Figure 1.2. Structure of (*S*)-goniothalamin (7)

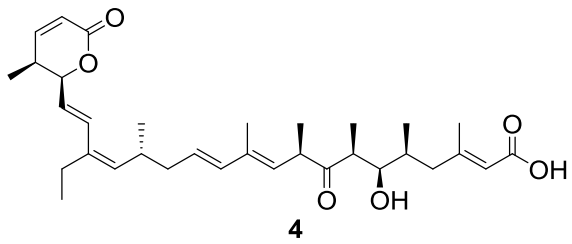
Goniothalamin induces apoptosis in a variety of cancer cell lines including Jurkat T lymphoblastic leukemia cells. Inayat-Hussain et al., revealed that goniothalamin caused a decrease in GSH with an elevation of reactive oxygen species as early as 30 min and DNA damage as assessed by Comet assay. Analysis using topoisomerase II processing of supercoiled pBR 322 DNA showed that GTN caused DNA damage via a topoisomerase II-independent pathway suggesting that cellular oxidative stress may contribute to genotoxicity. They observed a 12-fold increase of caspase-2 activity in goniothalamin-treated Jurkat cells after 4 h treatment. Although the caspase-2 inhibitor Z-VDVAD-FMK inhibited the proteolytic activity of caspase-2, apoptosis ensued, confirming that caspase-2 activity was not crucial for goniothalamin-induced apoptosis. However, goniothalamin-induced apoptosis was completely abrogated by N-acetylcysteine further confirming the role of oxidative stress. Since cytochrome C release was observed as early as 1 h without any appreciable change in Bcl-2 protein expression, they further investigated whether overexpression of Bcl-2 confers resistance in goniothalamin-induced cytotoxicity. Using a panel of Jurkat Bcl-2 transfectants, goniothalamin cytotoxicity was not abrogated in these cells. Finally they concluded that goniothalamin induces DNA damage and oxidative stress resulting in apoptosis, independent of both caspase-2 and Bcl-2.[14]

Moharam et al., investigated the platelet-activating receptor binding of styryl lactones which were isolated from *Goniothalamus tapis* Miq. and *G. uvaroides* King. Among the isolated compounds (*S*)-goniothalamin (**7**) exhibited a significant and

concentration-dependent inhibitory effect on PAF receptor binding with inhibitory with IC_{50} value of 19.7 μM.[15]

Development of experimental model contributes to the study of understanding mechanism of action of antineoplastic compounds. There are many *in vivo* experimental models based on laboratory animals. De Carvalho and co-workers studied the effect of goniothalamin (**1**) on the development of Ehrlich solid tumor in mice. Ehrlich solid tumor is derived from the mouse breast adenocarcinoma which is an aggressive and fast growing carcinoma. No toxic effect was observed on animals after single and repeated doses. The antiedematogenic activity was displayed by racemic mixture in the carrageenan edema model in mice together with the reduction of Ehrlich solid tumor. The results suggested a correlation between anticancer and anti-inflammatory activities.[16]

Another study to understand the mechanism of action of Goniothalamin was performed by Gademann and coworkers.[17] The group demonstrated that (*R*)-goniothalamin (**3**) is an inhibitor of nucleocytoplasmic transport above 500 nM. They use an *in vivo* nuclear export assay (immunostaining of Rio2 in HeLa cells). The results showed that the target of goniothalamin was the exportin CRM1, and its antiproliferative activity might be due to blockage of CRM1-mediated nuclear export. Based on the results, the simple unsaturated lactones other than leptomycin B (LMB) (**4**) were suggested to inhibit cell growth via similar mechanism targeting the CRM1 nuclear transport. Before Gademann's work on CRM1, Kudo et al., had provided evidence that LMB covalently bonded to a single cysteine residue and inactivated CRM1.[18]



4

Figure 1.3. Structure of leptomycin B (4)

Recently, Orlikova et al., studied on the goniothalamin modulated TNF-α-induced NF-κB activation.[19] Goniothalamin (**1**) showed low cytotoxic effects in K562 chronic myelogenous leukemia and Jurkat T cells even at 20 μM. Importantly, up to 20 μM concentrations, no cytotoxicity was observed in healthy peripheral blood mononuclear cells. Results indicated that goniothalamin inhibited tumor necrosis factor-α (TNF-α)-

induced NF-κB activation in Jurkat and K562 leukemia cells at concentrations as low as 5 μM as shown by reporter gene assays and western blots.

De Fatima et al., synthesized and evaluated the cytotoxic effects of *(R)*-goniothalamin (**3**), *(S)*-Goniothalamin **(7)** and *(S)*-Goniothalamin analogues towards eight different cancer cell lines such as kidney, breast carcinoma, prostate cancer cell lines. They showed that, among the synthesized molecules, **7** and **8** showed the strongest activity towards kidney cancer cell lines (IC_{50}: 4 nM and 5 nM, respectively). Compound **9** also showed much more cytotoxic effect towards breast cancer cells with resistance phenotype adriamycin (NCI.ADR) (IC_{50}: 4 nM).[20]

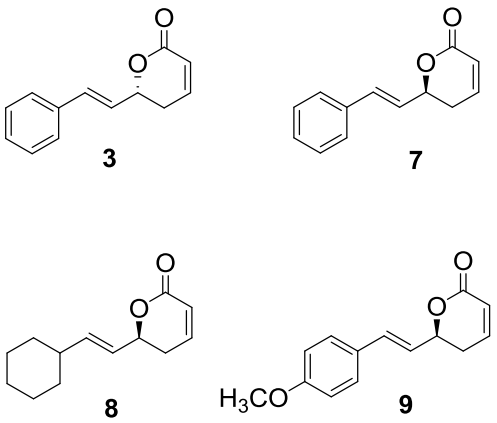
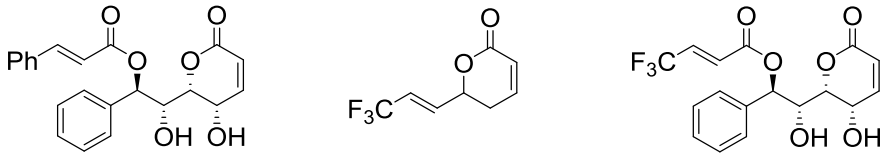


Figure 1.4. Structures of (*R*)-gonithalamin (3), (*S*)-goniothalamin (7) and other synthetic biologically active goniothalamin derivatives (8 and 9)

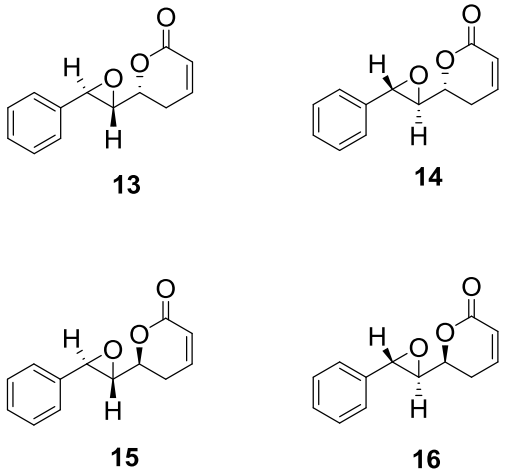
Fluorine incorporation into a molecule improves the pharmacological profile of the bioactive compounds, especially by increasing the metabolic stability. Bonnet-Delpon and co-workers synthesized fluorinated analogues of (*R*)-goniothalamin (**3**) and howiinol A (**10**) to evaluate their cytotoxic activities against KB (human oral epidermoid carcinoma), MCF-7 (breast cancer cells), HT 29 (human colon cancer cells), HepG2, A549 (human lung carcinoma). Trifluoro goniothalamin (**11**) showed slightly lower activity than (*R*)-goniothalamin (**3**), however trifluoromethyl howiinol A (**12**) exhibited similar activities compared to howiinol A. Trifluoromethyl derived compounds remained unchanged when submitted to biomimetic oxidative systems. It means that all sites of the molecules were protected from the oxidation.[21]



10 **11** **12**

Figure 1.5. Structures of howiinol A (10), trifluoro goniothalamin (11), trifluoromethyl howiinol A (12)

Goniothalamin oxide **(13)** is also a styryl lactone and this natural product shows larvicidal and trypanocidal activities. Marquissolo et al., synthesized goniothalamin oxide and its isomers to determine their antiproliferative effects. In addition to goniothalamin oxide, they also synthesized isogoniothalamin oxide (**14**), enantiomer of goniothalamin oxide (**15**) and enantiomer of isogoniothalamin oxide (**16**). These compounds were treated to MCF-7 (breast), NCI-ADR/RES (ovarian expressing the resistance phenotype for adriamycin), NCI-H460 (lung, non-small cells), UACC-62 (melanoma), 786-0 (kidney), OVCAR-03 (ovarian), PC-3 (prostate), and HT-29 (colon). Among the synthesized isomers, antiproliferative activity of the enantiomer of isogoniothalamin oxide (**15**) was the highest against all cancer cell lines. It was also indicated that 6*S*, 7*R* and 8*R* absolute configurations were beneficial for the activity.[22]



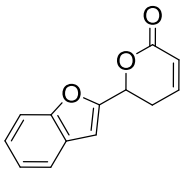
13 **14**

15 **16**

Figure 1.6. Structures of goniothalamin oxide isomers (13-16)

Lee et al., synthesized 6-membered α,β-unsaturated lactones with various substituents at the δ-position to investigate their immunosuppressive effects by measuring inhibition of interleukin-2 (IL-2) production. Benzofuran-substituted analogue of 6-membered α,β-unsaturated lactones (**17**) showed the best inhibition properties towards

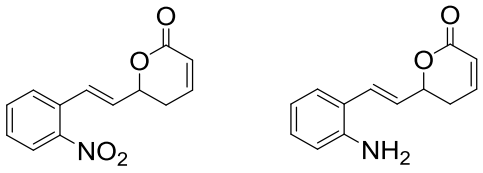
IL-2 production in Jurkat e6-1 T lymphocytes with 66.9 nM IC_{50} value. Another important result was that, compound **17** showed no cytotoxic effect at 10 μM concentration implying high therapeutic index.[23]



17

Figure 1.7. Benzofuran substituted goniothalamin (17)

Zhou et al., reported the derivatives of goniothalamin prepared by chemical modification and semi-synthetic methods. They evaluated *in vitro* antitumor activities of these derivatives against different human tumor cell lines, and most of them showed inhibitory effect against HL-60 cancer cell lines. The derivatives 10-nitrogoniothalamin (**18**) and 10-aminogoniothalamin (**19**) showed inhibitory concentration at 1.10 and 1.14 μg/mL respectively, against human stomach cancer cell lines (SGC-7901) while the positive control (etoposide, vp-16) was active at 6.07 μg/mL. The results indicated that IC_{50} values of the acylamino compounds were high for A549 and SGC-7901. It was proposed that free amino group at C-10 was important for antitumor activity, and activity was lost when the lone pairs of electrons on nitrogen were used for resonance with carbonyl group.[24]

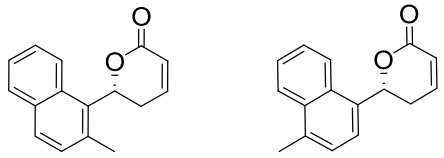


18 **19**

Figure 1.8. Structures of 10-nitro-goniothalamin (18) and 10-amino-goniothalamin (19)

Çağır and coworkers synthesized constrained analogues of 6-aryl substituted (*R*)-5,6-dihydro-2*H*-pyran-2-ones. Cytotoxic activities of the synthesized compounds showed that, restriction of the rotation around the single bond between the phenyl ring and double bond resulted in an enhancement in the cytotoxicity. They also indicated that size of the substituent and the stereochemistry in the lactone ring was also important; (*R*) enantiomer

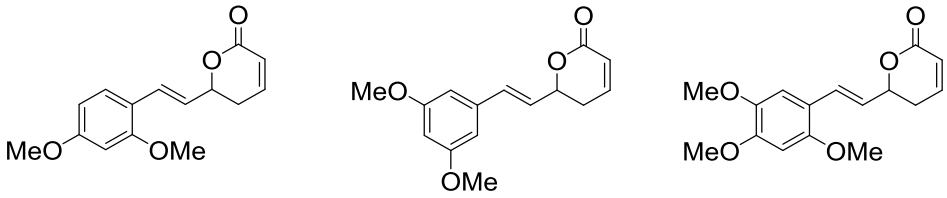
had lower IC_{50} value for 2-naphthyl substituted analogues. 1-Naphthyl substitution in the lactone ring dramatically enhanced the activity among the synthesized compounds. Methyl substitution in the naphthalene ring at position 2 (**20**) and position 4 (**21**) produce highly cytotoxic compounds especially against PC-3 cell line[5c] (IC_{50} values: 0.13 μM and 0.04 μM, respectively).



20 **21**

Figure 1.9. 2-methylnaphthalen-1-yl (20) and 4-methylnaphthalen-1-yl (21) substituted klavuzon derivatives

Recently, Barcelos et al., prepared library of 29 novel goniothalamin analogues and evaluated their activities against seven human cancer cell lines. The γ-pyrones and the azagoniothalamin analogues showed less cytotoxic effect than the lead compound goniothalamin. 2,4-Dimethoxy analogue (**22**) was found to be more potent in vitro than goniothalamin against all cancer cell lines. Furthermore, compound **22** was more potent than doxorubicin against NCI-ADR/RES, OVCAR-03 and HT-29 while being less toxic to human keratinocytes (HaCat). Also 3,5-dimethoxy analogue (**23**) and 2,4,5-trimethoxy analogue (**24**) also displayed promising antiproliferative activities compared to starting compound (**1**).[25]



22 **23** **24**

Figure 1.10. Structures of methoxy substituted goniothalamin analogues (22-24)

1.1.2. Synthesis Strategies of (*R*)-Goniothalamin and Other Synthetic Six-Membered α,β-Unsaturated-δ-Lactones

With the development of highly enantioselective allylation procedures, conversion of homoallylic alcohols to corresponding asymmetric α,β-unsaturated-δ-lactone has become most popular approach to yield such molecules.[26] The strategy starts with the asymmetric synthesis of corresponding homoallylic alcohols. Then synthesized alcohols are converted to their acrylate esters, and the last step to yield α,β-unsaturated lactones is ring closing metathesis (RCM) reactions of acrylate esters. This strategy was firstly described by Gosh[27], has been used in many total syntheses of natural products ing α,β-unsaturated-δ-lactone moiety.

Ramachandran and coworkers synthesized (*R*)-goniothalamin via sequential allylboration-esterification-cyclization strategy in 2000.[28] Allylboration of *trans*-cinnamaldehyde (**25**) with (+)-*B*-allyldiisopinocampheylborane (**28**) in an Et_2O-pentane mixture at -100 °C yielded (*R,E*)-1-phenylhexa-1,5-dien-3-ol (**26**) with 72% yield and 92% ee. Esterification of **26** was performed with acryloyl chloride (**29**) and provided (*R,E*)-1-phenylhexa-1,5-dien-3-yl acrylate (**27**). Acrylate ester was treated with 1st generation Grubbs' catalyst, and finally *R*-goniothalamin (**3**) was obtained with 76% yield.

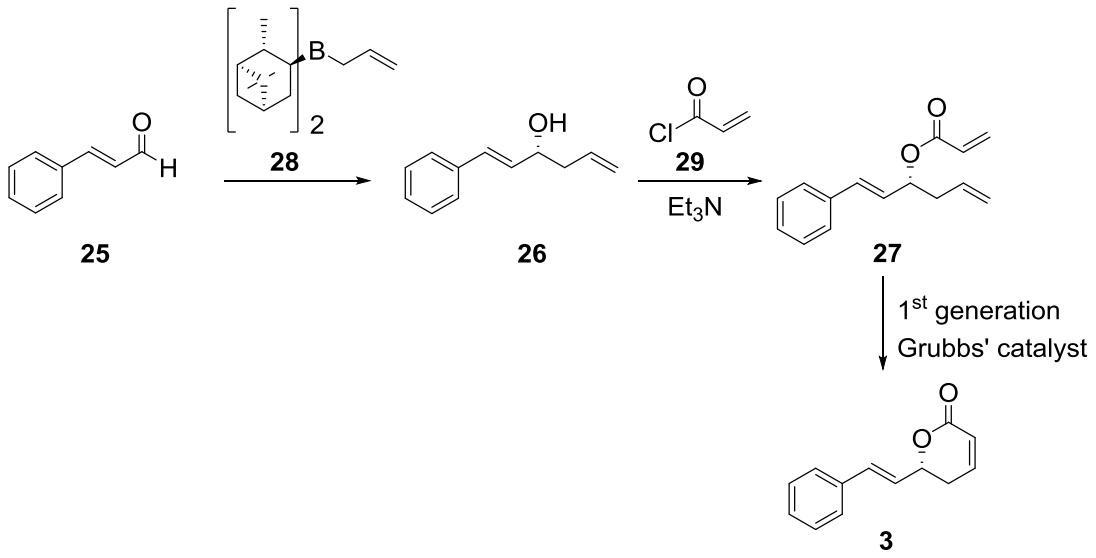


Figure 1.11. Asymmetric synthesis of *(R)*-goniothalamin (3) via sequential allylboration -esterification-cyclization reactions

De Fatima and Pilli have performed the total synthesis of (*R*)-goniothalamin (**3**). Catalytic enantioselective allylation of *trans*-cinnamaldehyde with allyltributyltin, under the effect of the (*R,R*) μ-oxo bis(binaphthoxy)(isopropoxy)titanium complex (developed by Maruoka and coworkers before)[29] yielded the homoallylic alcohol **26** with 78% yield and 96% ee. Homoallylic alcohol **26** was treated with acryloyl chloride (**29**) and triethyl amine to afford acrylate ester **27** with 80% yield. Ring-closing metathesis of acrylate ester **27** with 1st generation Grubbs' catalyst furnished (*R*)-goniothalamin in 61% yield from *trans*-cinnamaldehyde in three steps.[30]

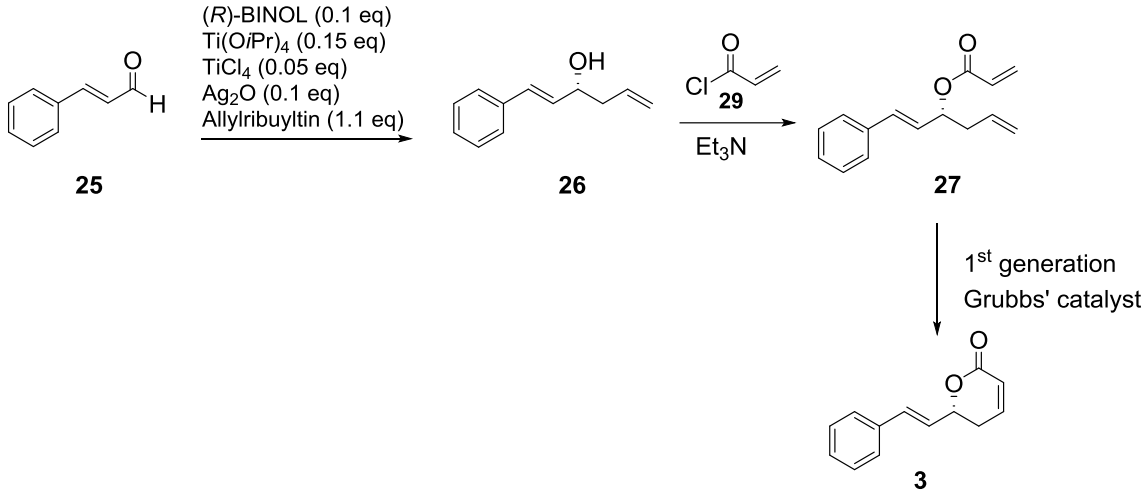


Figure 1.12. Total synthesis of (*R*)-goniothalamin (3)

In 2004, Sundby et al., reported the synthesis of (*R*)-goniothalamin by combination of lipase catalyzed resolution and alkene metathesis.[31] Racemic alcohol (rac-**26**) was prepared by Grignard reaction between allylmagnesium bromide (**30**) and *trans*-cinnamaldehyde (**25**). Prepared alcohol was kinetically resolved by transesterification reaction using vinyl acrylate (**31**) and *Candida antarctica* lipase B (CALB). In this conditions, compound **27** ((*R)*-acrylate ester) and compound **32** (*S*)-homoallylic alcohol) were obtained. After separation, compound **27** was treated with 1st generation Grubbs' catalyst and (*R*)-goniothalamin (**3**) was obtained with 99% ee. *S*-homoallylic alcohol **32** was treated with acryloyl chloride and Et_3N to yield acrylate ester **33**, and then treated with 1st generation Grubbs' catalyst to afford (*S*)-goniothalamin (**7**).

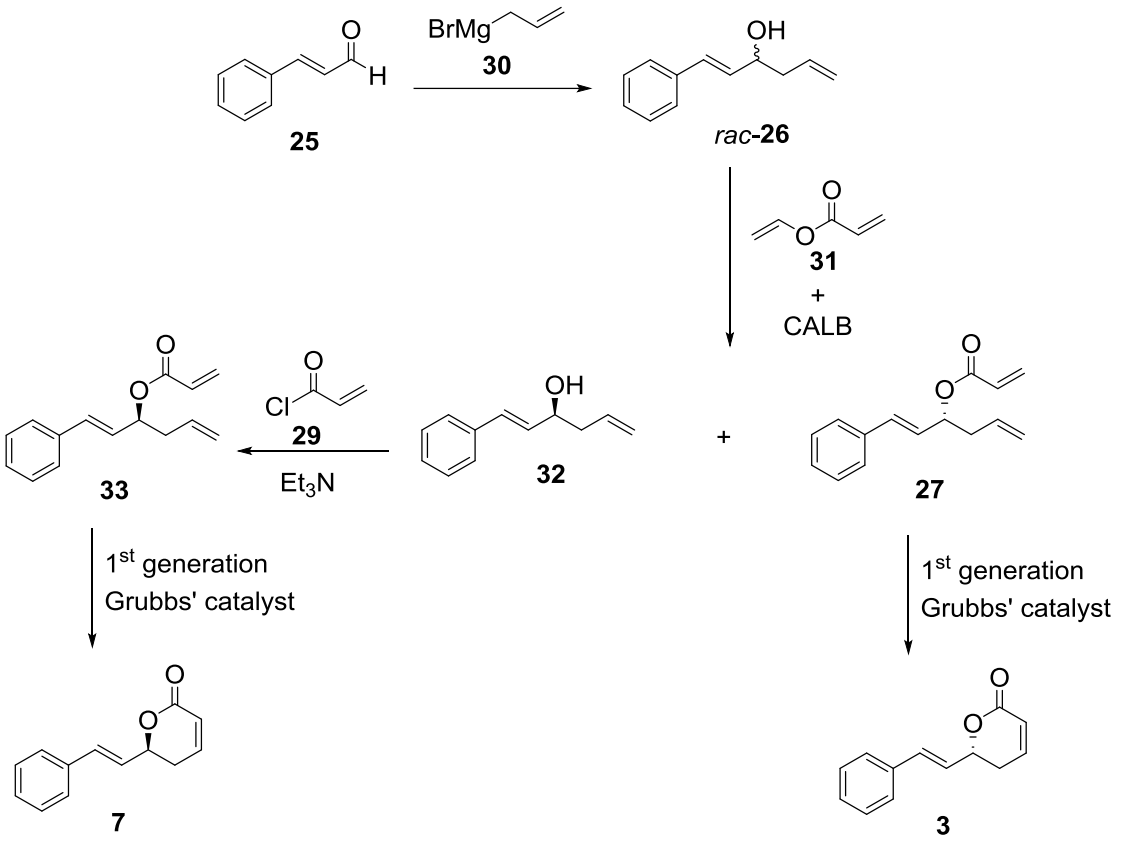


Figure 1.13. Synthesis of (*R*)-goniothalamin (3) and (*S*)-goniothalamin (7) by combination of lipase catalyzed resolution and alkene metathesis

In 2004, almost the same time, Gruttadauria and coworkers published an article about the synthesis of goniothalamin involving enzymatic resolution in the presence of vinyl acrylate followed by ring-closing metathesis. The main difference between these two works was the enzyme used in the experiment. The resolution was carried out with PS-C Amano II enzyme. With an excess vinyl acrylate (5 eq. of **31**), the reaction gave almost quantitative yields and very high ee% especially with CH_2Cl_2 solvent (>99% ee with **32** and 98% ee with **27**). With the same manner like other alcohol starting strategies, **27** was treated with 1st generation Grubbs' catalyst and Ti(O*i*Pr)$_4$ after separation process to obtain (*R*)-goniothalamin **(3)**. (*S*)-homoallylic alcohol **32** was treated with acryloyl chloride **(29)**, Et_3N and DMAP to yield acrylate ester **33**, and then treated with 1st generation Grubbs' catalyst to afford (*S*)-goniothalamin **(7)**.[32]

In previous strategy, the key point was to obtain homoallylic alcohols in good yields with high enantioselectivity. In literature, numerous allylation reactions exist. Besides this synthetic route, there are many strategies to yield α,β-unsaturated-δ-lactone moieties. Unfortunately it is impossible to mention all the reactions in the literature. Instead, some fascinating reactions are given below in detail.

Jean Marc Campagne and coworkers described a direct route to α,β-unsaturated-δ-lactones through the use of catalytic asymmetric vinylogous Mukaiyama (CAVM) reaction in the presence of Carreira's catalyst.[26] By using this method, α,β-unsaturated-δ-lactones were obtained as major products. In the reactions, the linear vinylogous aldol products were collected as minor products. Although the α,β-unsaturated-δ-lactone products were obtained up to 85% ee, the linear products had no selectivity (ee%< 10%).[33] This methodology has also been applied to the aliphatic ketones, and α,β-unsaturated-δ-lactone product was furnished with 72% yield and up to 88% ee .[34]

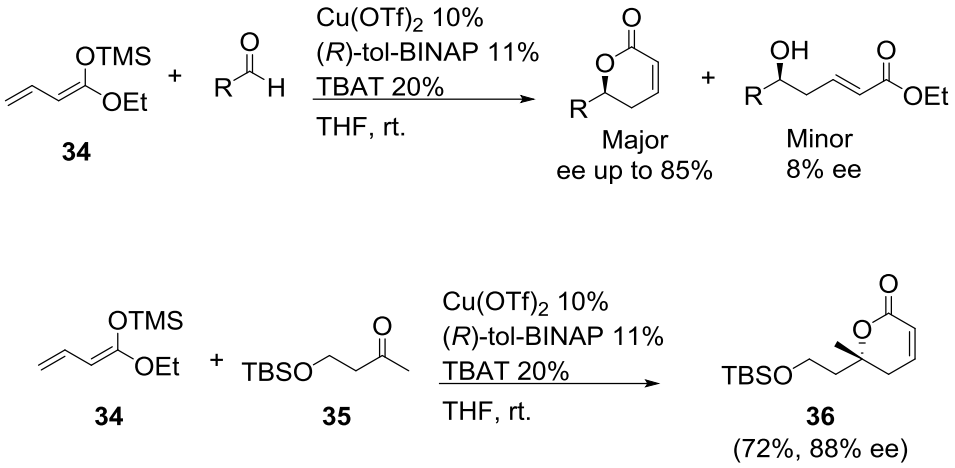


Figure 1.14. Synthesis of α,β-unsaturated-δ-lactones via catalytic and asymmetric vinylogous Mukaiyama reactions

Keck described the direct conversion of β-acetoxy aldehydes into the corresponding α,β-unsaturated-δ-lactones.[35] In the reaction, lithium enolate of methyl acetate was treated with β-acetoxy aldehyde. This transformation proceeds through an aldol reaction, followed by an acyl migration, a cyclization and irreversible β-elimination to yield the α,β-unsaturated-δ-lactone (Figure 1.15).

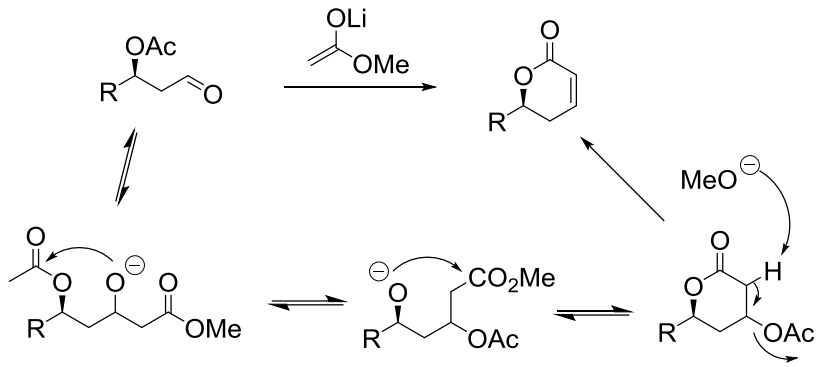


Figure 1.15.Synthesis of α,β-unsaturated-δ-lactones by "Keck's Annulation"

Tiseni and Peters developed a tertiary-amine-catalyzed enantioselective [4+2] cycloaddition of α,β-unsaturated acid chlorides (**37**) and electron-poor aldehyde chloral **(38)** to obtain α,β-unsaturated-δ-lactone building block.[36] In this method, vinylketenes was formed in situ by dehydrogenation of α,β-unsaturated acid chlorides **(37)**. Vinylketenes are unstable species, but they are trapped and activated as a diene component of Diels –Alder reaction at the same time by an enantiopure tertiary amine to form a zwitterionic dienolate. The method provides up to 80% yield and 97% ee (Figure 1.16).

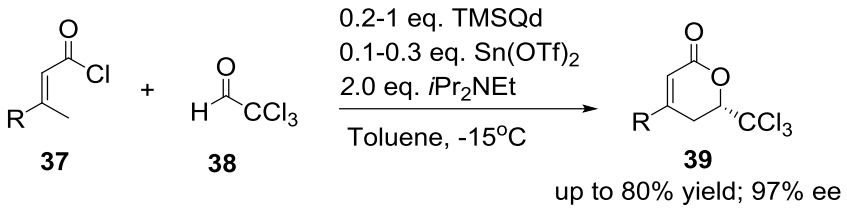


Figure 1.16. Synthesis of α,β-unsaturated lactones by tertiary-amine-catalyzed enantioselective [4+2] cycloaddition

In another study of Tiseni and Peters, a complex was formed in situ from $Er(OTf)_3$ and commercially available norephedrine ligand **(41)** promoting [4+2] cycloaddition of α,β-unsaturated acid chlorides with different aldehydes.[37] δ-Lactone building block was obtained by the cooperative bifunctional Lewis acid-Lewis base catalytic mode of action in this reaction (Figure 1.17).

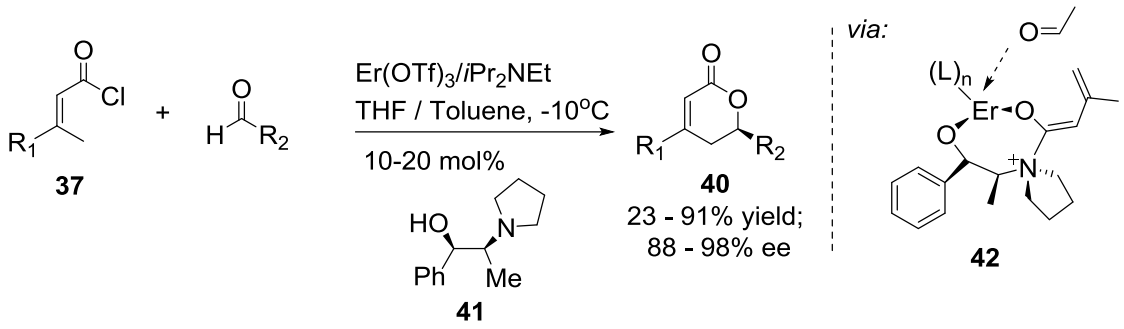


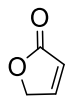
Figure 1.17. Synthesis of α,β-unsaturated lactones by [4+2] cycloaddition of α,β-unsaturated acid chlorides with different aldehydes

1.2. Five and Seven-Membered α,β-Unsatrated Lactones

1.2.1. Biological Properties of Naturally Occurring and Synthesized Five-Membered α,β-Unsatrated Lactones

One of the other naturally occurring α,β-unsaturated lactone moieties are γ-lactones. Natural products containing γ-lactones show varied biological activities and these activities will be mentioned in this part.

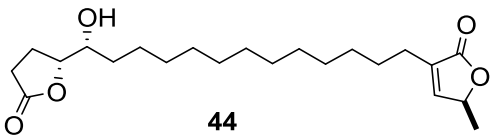
Butenolides (γ-lactones) are class of lactones being the simplest member of furan-2-one **(43)** and one of the components of bigger natural products. They are found in sesquiterpenes, and steroidal glycosides. They are also found in some animal species such as sponges, butterflies and insects.[38] Most of the butenolides containing natural products exhibit antifungal, antibacterial, anti-inflamatory, antibiotic and potential anticancer activity.[39]



43

Figure 1.18. Structure of the simplest butenolide (43)

Rollicosin, squamostolide and muricatacin are structurally related members of the Annonaceus acetogenin family of natural products. Annonaceus acetogenins display biological activities such as antitumor, antimalarial, antibiotic and antifungal activities.[40] More than 400 acetogenins have been isolated from Annonaceae plants.[41]

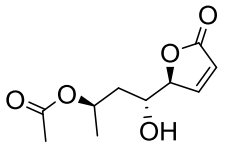


44

Figure 1.19. Naturally isolated acetogenin squamostolide (44)

Csuk et al., synthesized several γ-lactones and butenolides starting from the substituted betulinic aldehydes. Antitumor activities of these compounds evaluated against 15 different cancer cell lines and compounds with α,β-unsaturated γ-lactone part showed significant activities in all cancer cell lines.[42]

Reddy et al., synthesized the botryolide-E (**45**) stereoselectively and evaluated its biological behaviour against a panel of bacteria and fungi. Botryolide-E exhibited significant activity against *Staphylococcus aureus* (MTCC 96) with 6.25 μg/mL minimum inhibitory concentration (MIC) value, good activity against *Escherichia coli* (MTCC 443) with 12.5 μg/mL MIC values, *Bacillus subtilis* (MTCC 441) with 25 μg/mL value. Compound **45** exhibited good to moderate antifungal activity.[43]



45

Figure 1.20. Structure of botryolide-E (45)

Tantithanaporn et al., investigated the chemical constituents of dichloromethane extracts of *Goniothalamus undulatus* root. They isolated 3 known styryl lactones and 4 known annonaceous acetogenins **(46-49)**. The isolated compounds were subjected to a sulphorhodamine B cytotoxicity assay against human large cell lung carcinoma (COR-L23) and normal human fetal fibroblast (MRC-5) cell lines. The acetogenins showed higher cytotoxicity against COR-L23 compared to the styryl lactones, and similar pattern was observed for the other cell line MRC-5.[44]

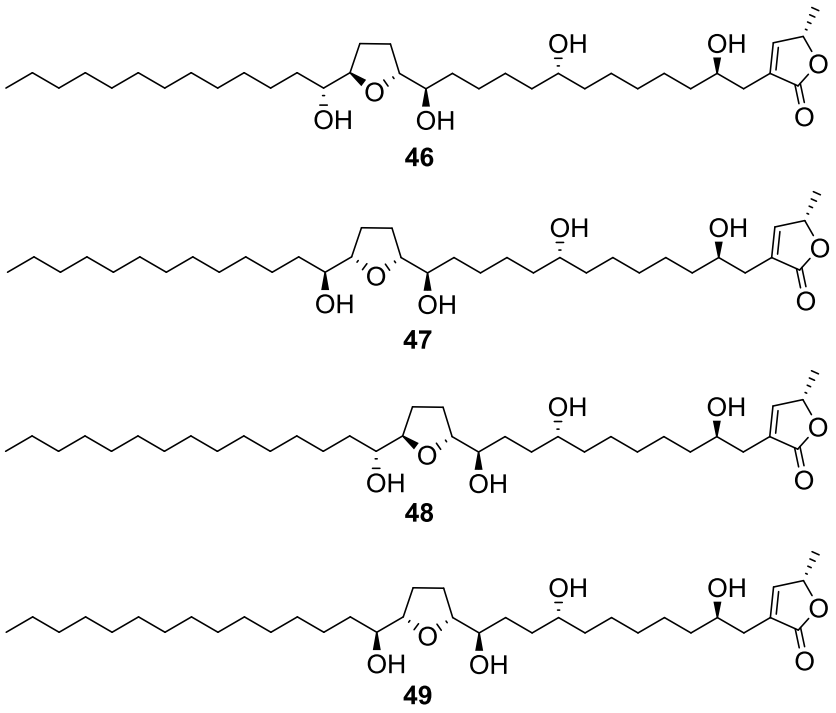


Figure 1.21. Structures of isolated acetogenins; annonacin (46), cis-annonacin (47), goniothalamicin (48), cis-goniothalamicin (49)

Annonaceae family compounds possess a terminal α,β-unsaturate-γ-lactone ring, this could be a pharmacophore to react with the new target proteins. Thus butenolide compounds and their derivatives with α,β-unsaturated-γ-lactone ring could be a good drug candidate for cancer treatment.

Sugar linked butenolides **(50)** demonstrated efficacy as potent insecticides against *Drosophila melanogaster* Meig, and were more activite than imidacloprid a commercial product.[45]

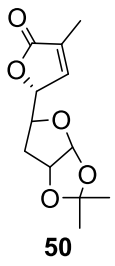


Figure 1.22. Structure of the sugar-linked butenolide (50)

De Hai Li et al., isolated four known butenolides from the marine derived bacterium, *Streptoverticillium luteoverticillatum.* Compounds **51-53** showed *in vitro* cytotoxicity against the murine lymphoma p388 and human leukaemia K562 cell lines.[46]

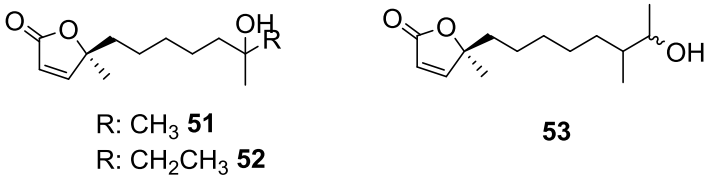


Figure 1.23. Structures of the butenolides from *Streptoverticillium luteoverticillatum*

Şardan et al., synthesized heteroaryl substituted γ-lactone derivatives **(54-55)** and evaluated their antimicrobial and antioxidant activities of both enantiomers. Among synthesized compounds, rac-54 and (S)-54 showed significant radical scavenging activities (93.30% and 50.65% respectively) compared to alpha tocopherol (66.21%). Compounds rac-55 and (S)-55 exhibited the highest activity in TBA assay (54.7% and 58.8%, respectively). Rac-54 and rac-55 also exhibited antifungal activity.[47]

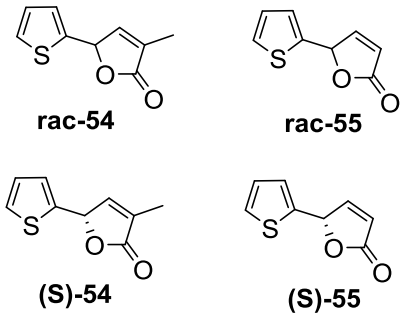
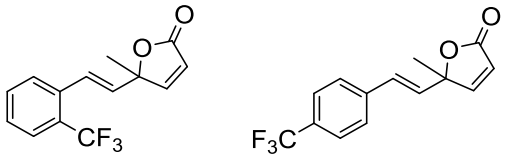


Figure 1.24. Structures of antifungal heteroaryl substituted butenolides

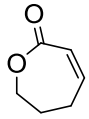
Bruder et al., synthesized 17 new goniothalamin derivatives possessing 5-methyl-2,5-dihydrofuran-2-one structure, and their cytotoxicities evaluated against nine different cancer cell lines. The compounds **56** and **57** (ortho and para-trifluoromethyl analogues, respectively) exhibited similar cytotoxic effects compared to goniothalamin (**1**) against most cancer cell lines evaluated.[48]



56 **57**

Figure 1.25. Structures of the ortho and para-trifluoromethyl analogues of 5-methyl-2,5-dihydrofuran-2-one

In literature, other known α,β-unsaturated lactone moieties are 7-membered lactones. These compounds have 6,7-dihydro-(5*H*)oxepin-2-one structured core. Generally, they are found as a part of biologically active large molecules.[49] There are also limited synthetic derivatives[50], but according to our knowledge these simple derivatives were not tested against cancer cell lines.



58

Figure 1.26. Structure of the 6,7-dihydro-*5H*-oxepin-2-one

CHAPTER 2

RESULTS AND DISCUSSIONS

2.1. Large Scale Asymmetric Synthesis of (*R*)-4'-methylklavuzon and (*R*)-2'-methylklavuzon

As indicated before, α,β-unsaturated lactones are important molecules because of their potent anti-cancer activity and other biological activities. In our laboratory, conformational constrained analogues of goniothalamin were synthesized previously, and two of the compounds (20 and 21) showed very strong cytotoxic activities against MCF-7 and PC-3 cell lines. Such impressive antiproliferative activities encouraged us to investigate *in vivo* anticancer activities of compounds **20** and **21**. For this purpose large scale synthesis of these compounds should be accessed. In previous studies, compounds **20** and **21** were successfully prepared from corresponding aldehydes in a three step route in small amounts.

In the previous synthesis, asymmetric homoallylic alcohols were prepared with low yields.[5c] To achieve an applicable big scale synthesis of the target compounds, the problem in the synthesis of asymmetric homoallylic alcohol should have been overcome. Because of that, the most challenging part of the synthesis was producing the target compounds with high ee % and yield %. This difficulty was figured out in this work. Then prepared chiral homoallylic alcohols were converted to acrylate esters by acryloyl chloride in the presence of triethyl amine. Targeted α,β-unsaturated lactones were achieved by the RCM reactions of acrylate esters by 1st generation Grubbs' catalyst.

Previously in our group, catalytic enantioselective allylation reactions of 2-methyl-1-naphthaldehyde and 4-methyl-1-naphthaldehyde were performed with allyltributyltin, in the presence of the (*R,R*) μ-oxo bis(binaphthoxy)(isopropoxy) titanium complex.[29] However, very low reaction yields were achieved (19% for 2-methyl-1-naphthaldehyde and 14% for 4-methyl-1-naphthaldehyde).[5c] Hence this method was not applicable for large asymmetric synthesis of methyl substituted klavuzon derivatives.

As mentioned before, many different methods were developed for the asymmetric synthesis of homoallylic alcohols previously. One of the options is metal catalyzed

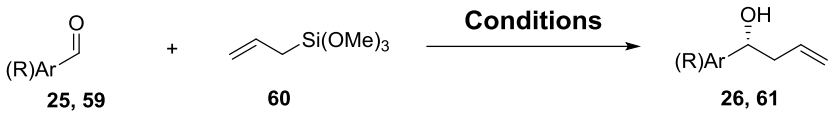
asymmetric allylation of the aldehyde. Allyltrimethoxysilane or allyltrimethylsilane can generally be used as allylating reagent for aldehydes and/or ketones in these trasformation. The method developed by Yamamoto and coworkers is very efficient for the synthesis of homoallylic alcohols.[51] Method includes the formation of AgF.(*R*)-Tol-BINAP catalyst, adding aldehyde and then allyltrimethoxysilane as allylating reagent at -20 ºC. By this method synthesis of homoallylic alcohol is achieved in higher yield and enantioselectivity.

The main aim of this study was to synthesize asymmetric homoallylic alcohol by using 4-methyl-1-naphthaldehyde and 2-methyl-1-naphthaldehyde. However, optimization reactions were started with *trans*-cinnamaldehyde and 1 naphthaldehyde (Table 2.1).

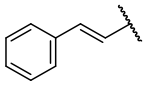
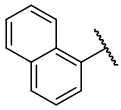
In the first reaction, 0.05 eq. of *R*-Tol-BINAP, 0.05 eq. of AgF and 1.2 eq. of allyltrimethoxysilane were used compared to *trans*-cinnamaldehyde. Methanol was used as solvent. The yield of the reaction depended on the dryness of the methanol. When commercial available methanol was used directly, very low product formation was achieved, while molecular sieve treated methanol afforded higher yields up to 19%.

The final product had a 4-methyl-1-naphthyl substituent, so to resemble such fragment, a similar aldehyde (1-naphthaldehyde) was used as starting compound in the model reaction (Table 2.1). At first attempt, lower yield was observed, and R-Tol-BINAP and AgF amount were increased to 10% at second attempt, which related in lower yield than the previous reaction. At this point, water content in the reaction solvent was considered as a reason for lower yields, and dried methanol was used in the next reaction. After 16 hours of reaction, the yield was 79%.

Table 2.1. Asymmetric allylation reactions of *trans*-cinnamaldehyde (25) and 1-naphthaldehyde (59)



25, 59 **60** **26, 61**

Entry	Aldehyde		*R*-Tol-BINAP	AgF	Allyltrimethoxysilane	Solvent (mL)	Temp. (°C)	Time (h)	Yield (%)	ee (%)
	(R)Ar	Eq.	Eq.	Eq.	Eq.					
1	 **25**	1	0.05	0.05	1.2	*MeOH (10)	-20	5.5	19	--
2	 **59**	1	0.05	0.05	1.2	*MeOH (10)	-20 to -5	7	22	67
3		1	0.1	0.1	1.2	*MeOH (10)	-20	5	16	88
4		1	0.1	0.1	1.2	**MeOH (7)	-20	16	79	85

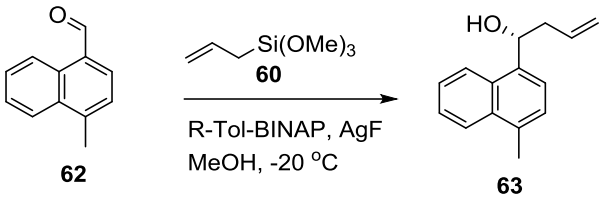
* Molecular sieves treated methanol was used.
** Methanol was used after drying procedure.

At this point, optimization of asymmetric preparation of homoallylic alcohols (**63** and **65**) were studied in dry methanol as summarized in table 2.2 and table 2.3.

Shortly, temperature of the reaction was crucial for the yield of the reaction. When the reaction started at -20 °C, the yield of the reaction was 68%, while the reaction started at room temperature the yield dropped down to 42% (Table 2.2, entries 1 and 2). Additionally when the amount of *R*-Tol-BINAP decreased down to 0.06 eq., the reaction gave higher yields (80-95%) repeatedly for prolonged reaction times (46-51 hours). On the other hand, the ee% of the reaction was not clear, because the product gave a single signal in both Chiralpak AD-H and Chiralcel OJ-H columns. It is possible that this signal can arise from poor separation of enantiomers in column, so the enantiomeric excesses of this product was determined in the ester form. In entry 7 and 8, the enantiomers were separated in Chiralcel OJ-H column by long optimization studies.

The reaction also gave alcohol **65** somehow in moderate yield and selectivity. This might be due to the steric interaction of methyl group at position 2 in 1-naphthaldehyde in formed transition state complex.

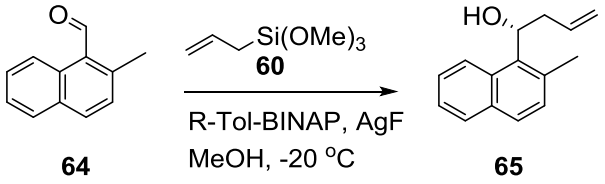
Table 2.2. Asymmetric allylation reactions of 4-methyl-1-naphthaldehyde (62)



Entry	Aldehyde	*R*-Tol-BINAP	AgF	Allyltrimethoxysilane	Solvent* (mL)	Temp. (°C)	Time (h)	Yield (%)	ee (%)
	Eq (Amount, mg)	Eq. (Amount, mg)	Eq. (Amount, mg)	Eq. (Amount, mg)					
1	1 (165)	0.10 (68)	0.10 (13)	1.2 (213)	MeOH (7)	-20 to RT	36	68	100
2	1 (85)	0.10 (34)	0.10 (6,4)	1.2 (107)	MeOH (10)	RT	36	42	100
3	1 (2000)	0.06 (464)	0.10 (145)	1.05 (2060)	MeOH (20)	-20	46	84	100
4	1 (2035)	0.06 (468)	0.10 (151)	1.05 (2060)	MeOH (20)	-20	51	88	100
5	1 (2076)	0.06 (461)	0.10 (145)	1.05 (2060)	MeOH (20)	-20	48	80	100
6	1 (3000)	0.06 (700)	0.10 (219)	1.05 (3090)	MeOH (20)	-20	48	84	100
7	1 (3000)	0.06 (697)	0.10 (219)	1.05 (3090)	MeOH (20)	-20	51	85	86
8	1 (2053)	0.06 (490)	0.10 (153)	1.05 (2180)	MeOH (20)	-20	51	95	92

* Commercial available dry methanol was used in the reactions

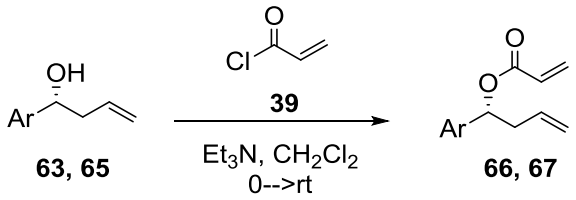
Table 2.3. Asymmetric allylation reactions of 2-methyl-1-naphthaldehyde (64)

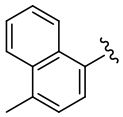
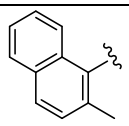


Entry	Aldehyde	*R*-Tol-BINAP	AgF	Allyltrimethoxysilane	Solvent (mL)	Temp. (°C)	Time (h)	Yield (%)	ee %
	Eq (Amount, mg)	Eq. (Amount, mg)	Eq. (Amount, mg)	Eq. (Amount, mg)					
1	1 (85)	0.10 (34)	0.10 (6,4)	1.2 (107)	MeOH (10)	-20 to RT	48	31	40
2	1 (2000)	0.06 (464)	0.10 (145)	1.05 (2060)	MeOH (20)	-20	68	66	50

After the syntheses of alcohols, esterification reactions ((*R*)-1-(4-methylnaphthalen-1-yl)but-3-en-1-ol) and (*R*)-1-(2-methylnaphthalen-1-yl)but-3-en-1-ol)) were performed. For this purpose, asymmetric alcohols were treated with acryloyl chloride in the presence of triethyl amine. Reactions were relatively completed in high yields as expected (Table 2.4).

Table 2.4. Transformations of homoallylic alcohols (63-65) to acrylate esters (66-67)



Entry	Homoallylic alcohol		Acryloyl chloride (96%)	Triethyl amine	Solvent (mL)	Time (h)	Yield (%)	ee (%)
	Ar	Eq. (Amount, mg)	Eq. (Amount, mg)	Eq. (Amount, mg)				
1	 **63**	1 (2026)	1.5 (1349)	3 (2465)	CH_2Cl_2 (25)	20	89	84
2		1 (2150)	1.5 (1374)	3 (3072)	CH_2Cl_2 (25)	14,5	87	88
3		1 (1995)	1.5 (1329)	3 (2853)	CH_2Cl_2 (25)	22	91	88
4		1 (3030)	1.5 (1940)	3 (4336)	CH_2Cl_2 (25)	22	87	84
5		1 (3060)	1.5 (2038)	3 (4374)	CH_2Cl_2 (25)	18	82	84
6		1 (2410)	1.5 (1697)	3 (3643)	CH_2Cl_2 (25)	18	93	88
7	 **65**	1 (1570)	1.5 (1005)	3 (2246)	CH_2Cl_2 (25)	15	81	50

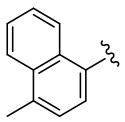
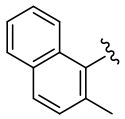
As a last step of the syntheses, ring closing metathesis reactions were performed. Acrylate esters were treated with 1st generation Grubbs' catalyst in order to get α,β-unsaturated lactones.[52] Reaction conditions and results are summarized in the table 2.5.

During the reactions of entry 1, entry 2 and entry 3 (Table 2.5), totally 100 mL of CH_2Cl_2 was used for each reaction. However, in the ring closing metathesis reactions of

acrylate esters, the concentration of the starting material must be around 0.01 M. For this reason in the entries 1, 2 and 3 relatively lower yields (34% to 45%) were achieved due to high concentration of the starting material. In RCM reactions, higher concentration reaction medium causes the formation of unwanted oligomeric or polymeric side products. In entries 4 and 5, reaction concentration were set to 0.01 M and higher reaction yields were achieved.

Table 2.5. Transformations of acrylate esters (66, 67) to (*R*)-5,6-dihydro-2*H*-pyran-2-ones (21, 20)

66, 67 **21, 20**

Entry	**Acrylate esters**		**1st generation Grubbs' catalyst**	**Solvent (mL)**	**Temp. (°C)**	**Time (h)**	**Yield (%)**	**ee (%)**
	Ar	**Eq. (Amount, mg)**	**% (Amount, mg)**					
1	 **66**	1 (2236)	10 (692)	CH_2Cl_2 (100)	60	18	45	84
2		1 (2321)	10 (718)	CH_2Cl_2 (100)	60	11.5	45	90
3		1 (2270)	10 (702)	CH_2Cl_2 (100)	60	9	34	84
4		1 (3272)	10 (1011)	CH_2Cl_2 (1000)	60	8	68	90
5		1 (2771)	10 (856)	CH_2Cl_2 (1000)	40-43	17.5	69	90
6	 **67**	1 (1572)	10 (486)	CH_2Cl_2 (600)	60	9	69	50

2.2 Studies Towards the Asymmetric Synthesis of New (*R*)-Klavuzon Derivatives

Previously, it was shown that dimethoxy substituted goniothalamin had shown much stronger activity compared to goniothalamin.[25, 53] Because of this reason, we aimed to synthesize new heteroatom substituted 5,6-dihydro-2*H*-pyran-2-one derivatives.

It was discussed before that the first step of the α,β-unsaturated lactone synthesis was formation of asymmetric homoallylic alcohols. For this purpose the method which was developed by Yamamoto and co-workers was used.[51] In the method AgF·*R*-Tol-BINAP is used as the catalyst system. The preparation and usage of the catalyst is very convenient since the preparation is carried out at mild conditions. One hour mixing of AgF and R-Tol-BINAP in room temperature in methanol under N_2 atmosphere is enough to obtain the catalyst. Aldehyde and allyltrimethoxy silane addition takes place at -20 ºC. This method was used in our group previously and it worked well especially with the 4-methyl-1-naphthaldehyde with up to 95% yield and 92% ee.

Synthesis attempts were started with 4-dimethylamino substituted derivative of α,β-unsaturated-δ-lactone. In the first step, asymmetric allylation of 4-dimethylamino-1-naphthaldehyde was achieved by AgF.(*R*)-Tol-BINAP catalyst system and asymmetric alcohol **(*R*)-69** was obtained with 69% isolated yield. In the next step, esterification of synthesized homoallylic alcohol **(*R*)-69** was tried in the presence of triethyl amine and acryloyl chloride. This step was repeated 3 times but synthesis of acrylate ester could not be achieved. Reaction was monitored with TLC, and conversion of the alcohol into a single spot was observed. In purification step of the crude material with SiO_2 column, the synthesized compound converted to the elimination product **71**. Structure of this elimination product was confirmed by NMR study (Figure 2.1).

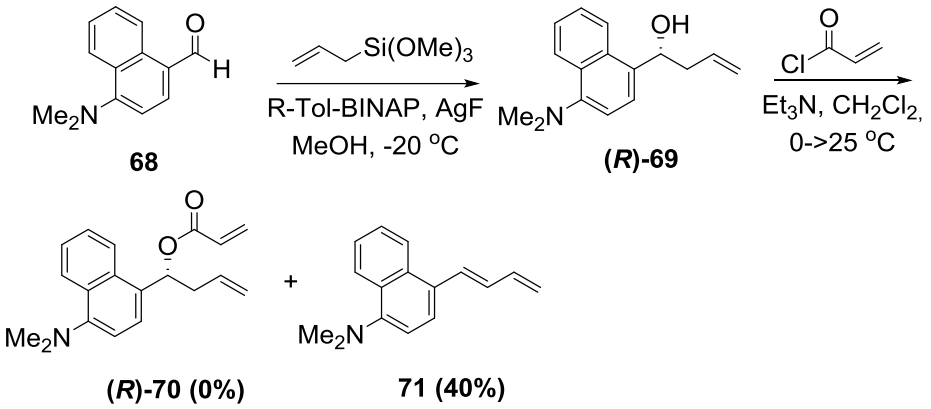
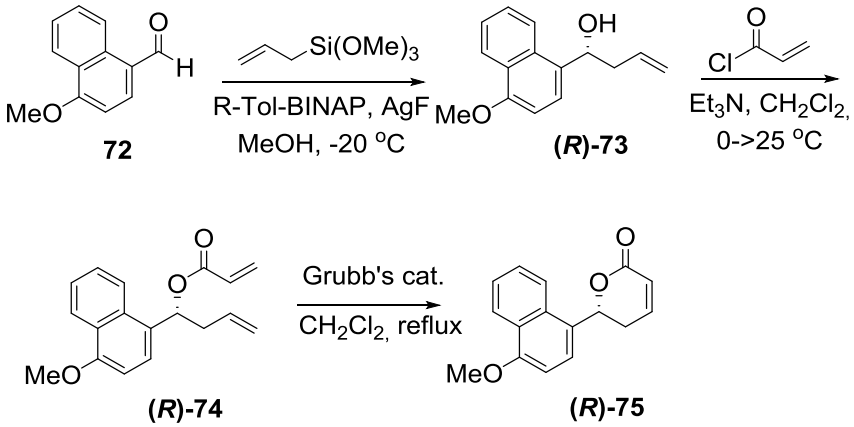


Figure 2.1. Structures of 4-dimethylaminonaphthalen-1-yl substituted acrylate ester ((*R)*-70) and elimination product (71)

In the next attempt, allylation reaction of 4-methoxy-1-naphthaldehyde with allyltrimethoxysilane and AgF.(*R*)-Tol-BINAP catalyst was performed. As a result of the allylation reaction, alcohol **(*R*)-73** was achieved with 50% yield and 91% ee. This reaction

was also performed at room temperature with similar reaction time. At this temperature alcohol **(*R*)-73** was produced with lower yield but almost same ee%. Alcohol **(*R*)-73** was converted to acrylate ester **(*R*)-74**, and then used in the next ring closing metathesis reaction without purification because of the possible formation of elimination product as observed in 4-dimethylamino substituted ester. At the end of the RCM reactions, the target molecule **(*R*)-75** was obtained with 27% overall yield starting from alcohol. (Table 2.6)

Table 2.6. Synthesis of (*R*)-6-(4-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (*(R)*-75)



Entry	Conditions	Alcohol (*R*)-73		Acrylate Ester (*R*)-74	Lactone (*R*)-75 Yield (%)
		Yield (%)	%ee (HPLC)		
1	*R*-Tol-BINAP, AgF, MeOH,-20 °C, 72 h	50	91	Not performed	Not performed
2	*R*-Tol-BINAP, AgF, MeOH, RT, 75 h	29	90	It was used without purification in next step.	27 (From alcohol)

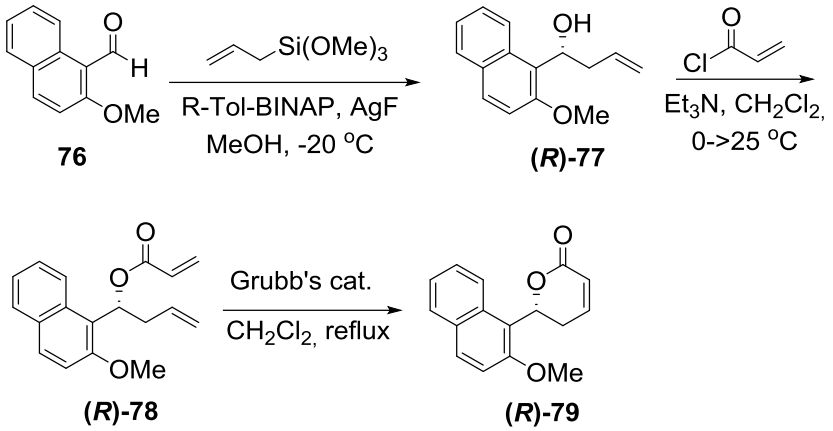
**Yields are reported based on the isolated products and ee% values are determined by Chiralcel OJ-H HPLC column.*

Allylation reaction of 2-methoxy-1-naphthaldehyde was performed in the same reaction condition as 4-methoxy-1-naphthaldehyde. Alcohol **(*R*)-77** was obtained with 22% yield and 55 ee%. At room temperature, reaction was achieved with 30% yield and 50 ee%. Then it was converted to acrylate ester **(*R*)-78** and then used in the next ring closing metathesis reaction without purification for RCM reactions gave target molecule **(*R*)-79** with 25% overall yield starting from alcohol (Table 2.7).

Similar synthesis strategy was performedfor the preparation of another target lactone **(*R*)-10** which had 4,7-dimethoxynaphthalen-1-yl substituent. In previous examples, it was noted that, presence of only one methoxy substituent on

naphthaldehydes caused lower yield in allylation reactions. In this case, the presence of two methoxy substituent on the naphthaldehyde caused much lower yield (9% yield at -20 °C and 12% yield at RT), but higher enantioselectivity was observed (87 ee% ee at -20 °C and 84 ee% ee at RT) (Table 2.8).

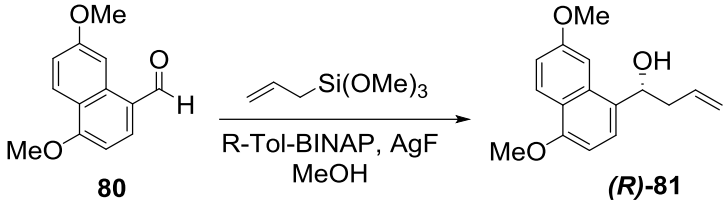
Table 2.7. Synthesis of (*R*)-6-(2-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (**(*R*)-79**)



Entry	Conditions	Alcohol (*R*)-77		Acrylate Ester (*R*)-78	Lactone (*R*)-79 Yield (%)
		Yield (%)	%ee (HPLC)		
1	*R*-Tol-BINAP, AgF, MeOH,-20 °C, 72 h	22	55	Not performed.	Not performed.
2	*R*-Tol-BINAP, AgF, MeOH, RT, 75 h	30	50	It was used without purification in next step.	25 (From alcohol)

**Yields are reported based on the isolated products, and ee% values are determined by Chiralcel OJ-H HPLC column.*

Table 2.8. Synthesis of (*R*)-1-(4,7-dimethoxynaphthalen-1-yl)-but-3-en-1-ol **((*R*)-81)**



Entry	Conditions	Alcohol (*R*)-81	
		Yield (%)	%ee (HPLC)
1	R-Tol-BINAP, AgF, MeOH,-20 °C, 73 h	9	87
2	R-Tol-BINAP, AgF, MeOH, RT, 90 h	12	84

**Yields are reported based on the isolated products, and %ee values are determined by Chiralcel OJ-H HPLC column.*

2.3. Racemic Syntheses of New Heteroatom Substituted α,β-Unsaturated-δ-Lactone Derivatives

Because asymmetric allylation of heteroatom substituted 1-naphthaldehydes gave lower yields than expected in prolonged reaction times, our interest changed from asymmetric synthesisof lactones to racemic ones. For this purpose, the method, developed by Shibasaki and co-workers was chosen.[54] In this method CuCl is used as a metal source, allytrimethoxysilane as an allylating agent and TBAT is used as a fluoride source. In this reaction, the dual activation concept was the initial idea. It means that if a catalyst activates both allylsilane and carbonyl compound simultaneously, high catalyst activity could be achieved. Allyltrimethoxysilane was used because of its ability to form pentacoordinate silicate much easier than allyltrimethylsilane. Besides this, it is well known from the literature that a fluoride anion activates the silylated nucleophiles.

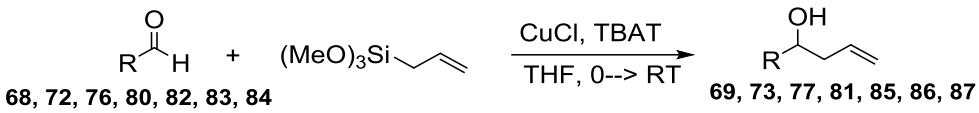
As summarized in table 2.9, racemic allylation reactions of selected naphthaldehydes were performed with 10% CuCl, 10% TBAT and 1,5 eq. of allyltrimethoxysilane as stated in the literature. Isolated yields of these reactions were high. only the allylation reaction of 4,7-dimethoxy-1-naphthaldehyde occurred with lower yield (11%). Reaction was repeated with the changing amount of CuCl and TBAT as 2%, but the yield of the reaction could not be improved. In allylation reaction of 4-dimethylamino-1-naphthaldehyde, moderate isolated yield was achieved with 54% (Table 2.9).

Acrylate esters are very important precursors for the synthesis of unsaturated lactone moieties. For this reason, synthesized homoallylic alcohols (**69**, **73**, **77**, **81**, **85-87**) were transformed to acrylate esters (**70**, **74**, **78**, **88-91**). It is a widely utilized reaction in the literature to synthesize acrylate esters from alcohols. Alcohols and acryloyl chloride were dissolved in dichloromethane (CH_2Cl_2) and cooled to 0 ^oC, and then triethyl amine was added dropwise. Then reactions were stirred and carried out at RT. Reactions afforded up to 97% isolated yield. Results are summarized in table 2.10.

In entry 1 (Table 2.10), the 4-dimethylamino-1-naphthalen-1-yl acrylate ester derivative could not be isolated, because its decomposition to compound **71** during in SiO_2 column chromatography. Reaction was repeated, and the synthesized crude compound was used in the next step without purification.

To get target molecules as α,β-unsaturated lactones, acrylate esters were treated with 1st generation Grubbs' catalyst. Reactions were carried out in CH_2Cl_2 in 0.01 M solution at 45-50 °C. Isolated yields were over 80% mostly, except the case of the 4-dimethylamino-1-naphthyl moiety (45% isolated yield for two step). Since this crude mixture was used without purification in this step, starting material was not consumed completely even after 21 h. This lower yield could be caused by the interferences of the impurities from the crude material of acrylate ester (Table 2.11).

Table 2.9. Allylation reactions of selected aldehydes



68, 72, 76, 80, 82, 83, 84 **69, 73, 77, 81, 85, 86, 87**

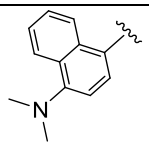
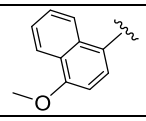
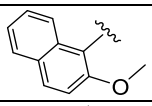
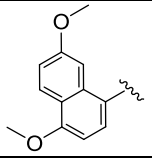
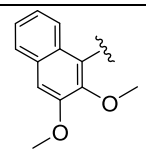
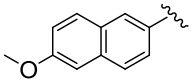
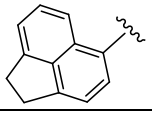
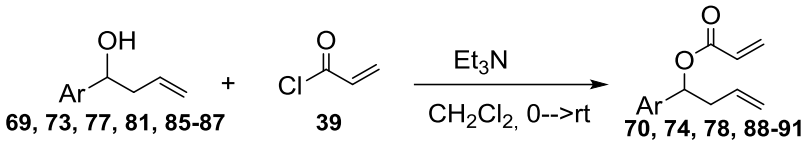
Entry	Aldehyde		CuCl	TBAT	Allyltrimethoxysilane	Time	Yield
	(R) Ar	Eq.	Eq.	Eq.	Eq.	(h)	(%)
1		1	0.1	0.1	1.5	14	54
2		1	0.1	0.1	1.5	7	88
3		1	0.1	0.1	1.5	5	87
4		1	0.1	0.1	1.54	4	11
5		1	0.02	0.02	1.2	18	9
6		1	0.1	0.1	1.5	8	95
7		1	0.1	0.1	1.5	3	98
8		1	0.1	0.1	1.5	12	86

Table 2.10. Transformations of homoallylic alcohols (69, 73, 77, 81, 85-87) to acrylate esters (70, 74, 78, 88-91)



69, 73, 77, 81, 85-87 **39** **70, 74, 78, 88-91**

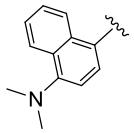
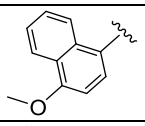
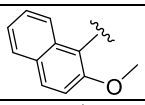
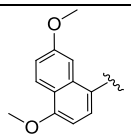
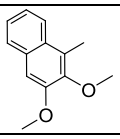
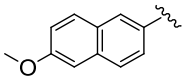
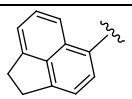
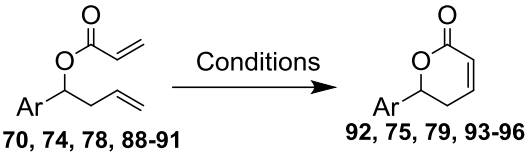
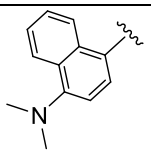
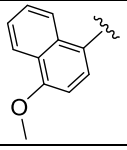
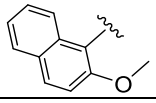
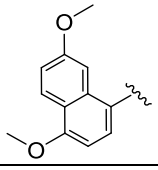
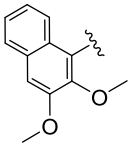
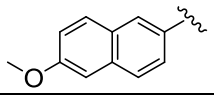
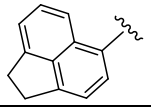
Entry	**Homoallylic alcohol**		**Acryloyl chloride (96%)**	**Triethyl amine**	**Time (h)**	**Yield (%)**
	Ar	**Eq.**	**Eq.**	**Eq.**		
1		1	2	4	16	It was used without purification in next step.
2		1	2	4	18	73
3		1	2	4	18	90
4		1	2	4	15	82
5		1	2	4	24	97
6		1	2	4	15	84
7		1	2	4	0.5	80

Table 2.11. Ring closing metathesis reactions of acrylate esters (70, 74, 78, 88-91) to yield 5,6-dihydro-2*H*-pyran-one derivatives (92, 75, 79, 93-96)

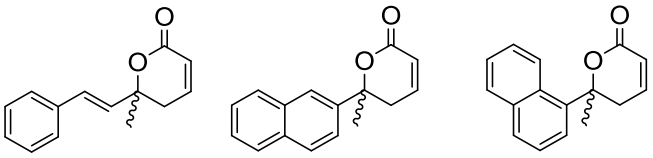


70, 74, 78, 88-91 **92, 75, 79, 93-96**

Entry	**Acrylate ester**		**1st Generation Grubbs' Catalyst**	**Solvent**	**Temp. (ºC)**	**Time (h)**	**Yield (%)**
	Ar	**Eq.**	**Amount %**				
1		1 (Crude material)	10	CH_2Cl_2	45	21	45
2		1	10	CH_2Cl_2	50	8	86
3		1	10	CH_2Cl_2	50	8	81
4		1	10	CH_2Cl_2	50	8	77
5		1	10	CH_2Cl_2	45	8	82
6		1	10	CH_2Cl_2	50	8	85
7		1	10	CH_2Cl_2	45	8	80

2.4. Asymmetric Syntheses of 6-methyl substituted 5,6-dihydro-2*H*-pyran-2-one Derivatives

This part of the thesis includes the syntheses of three compounds based on the 6-methyl substituted 5,6-dihydro-2*H*-pyran-2-one (**97**-**99**). These compounds may help us to understand the effect of the benzylic protons on the antiproliferative effect of the bicycloaryl substituted α,β-unsaturated-δ-lactones.



97 **98** **99**

Figure 2.2. Structures of α,β-unsaturated-δ-lactones (97-99) synthesized from ketones

To create an asymmetric alcohol, the method which used in the asymmetric allylation reactions of aldehydes was applied to the selected ketones.[51] However, no change was observed in the starting material. We did not observe any new product formation by TLC, and crude NMR spectrum. Thus, another asymmetric allylation method should have been used to generate corresponding homoallylic alcohols.

In the literature, there is another work with the same catalyst system, but with different catalyst formation procedure developed by Yamamoto.[55] Catalytic amount of AgF and *(R)*-Tol-BINAP are dissolved in MeOH and excess MeOH is removed under vacuum. Finally a solid catalyst complex is prepared. This complex is soluble in THF, although AgF is not soluble in THF alone. The origin of the alcoholic proton originated from the small amount of MeOH is used for the catalyst preparation. Also an additional equivalent of MeOH improves the yield of the product.

By using this method, target tertiary alcohols were synthesized with very high yields. However desired ee% could not be achieved. Percent enantiomeric excesses (ee%) were determined with Chiralcel OJ-H column. Enantiomeric excesses 2-acetonaphthone and 1-acetonaphthone derivatives of tertiary alcohols were determined with this chiral column, whereas enantiomeric separation of *trans*-4-phenyl-3-buten-one derivative (**97**) could not be accomplished.

Because of the formation of homoallylic alcohols with low ee%, another method was used for the asymmetric allylation of selected ketones.[54] In this case, R-Tol-BINAP,

TBAT and CuCl were used at RT. However in this method, asymmetric allylation reactions of selected ketones provided with lower yields but the similar ee% values compared to the previous method.

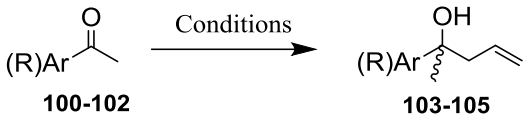
Transformations of the tertiary alcohols to acrylate esters were performed with acryloyl chloride and triethyl amine. Compared to secondary alcohols, transformation of the tertiary alcohols to acrylate esters was challenging. Side product formation was observed in long reaction times, and yields were much lower compared to secondary alcohols (17-60% isolated yields).

RCM reactions, in the last step, were performed with 2nd generation Grubbs' catalyst with high isolated yields. (26-94%)

During the synthesis, all ee% are monitored by chiral HPLC column, and no racemisation or enantiomeric enrichment were observed. Among the formed products, only the ee% of the alcohol derived from (*E*)-4-phenyl-3-buten-2-one could not be separated in chiral column.The ee% of this alcohol was determined in lactone form (**97**).

To confirm the equality of ee% of alcohol and lactone forms, HPLC analysis of the 2-acetonaphthone derivative of lactones also were performed, and ee% values were compared with each other. We observe the same ee% values (60%) for the 2-acetonaphthone derivative for alcohol and lactone forms. Therefore, there is not any racemisation or enantiomeric enrichment during the synthesis.

Table 2.12. Asymmetric allylation reactions of selected ketones (100-102)



100-102 103-105

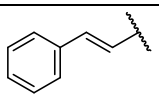
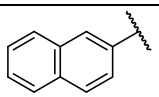
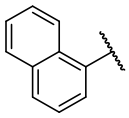
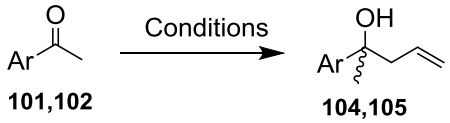
Entry	Ketone		*R*-Tol-BINAP	AgF	Allyltrimethoxy silane	MeOH (Eq.)	Solvent	Temp. (°C)	Time (h)	Yield (%)	ee (%)
	(R)Ar	Eq.	Eq.	Eq.	Eq.						
1	 **100**	1	0.05	0.05	2	1	THF	-50	18	89	100
2	 **101**	1	0.05	0.05	2	1	THF	-70	42	91	60
3	 **102**	1	0.05	0.05	2	1	THF	-50	18	97	60

Table 2.13. Asymmetric allylation reactions of selected ketones (101, 102)



101,102 104,105

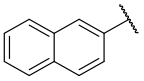
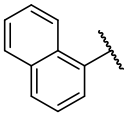
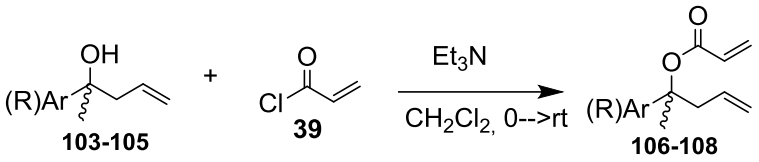
Entry	Ketone		R-Tol-BINAP	TBAT	CuCl	Allyltrimethoxy silane	Solvent	Temp. (°C)	Time (h)	Yield (%)	ee %
	(R)Ar	Eq.	Eq.	Eq.	Eq.	Eq.					
1	 **101**	1	0.15	0.15	0.15	1.0	THF	0 °C to RT	72	44	55
2	 **102**	1	0.15	0.15	0.15	1.2	THF	0 °C to RT	17	40	50

Table 2.14. Transformations of homoallylic alcohols (103-105) to acrylate esters (106-108)



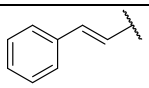
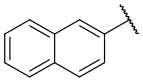
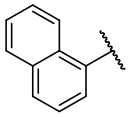
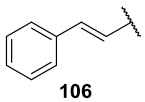
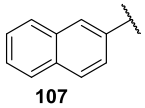
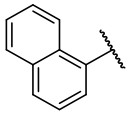
Entry	Homoallylic alcohol		Acryloyl chloride (96%)	Triethyl amine	Time (h)	Yield (%)
	Ar	Eq.	Eq.	Eq.		
1	 **103**	1	1.5	3	26	32
2	 **104**	1	2	4	14	58
3	 **105**	1	2	4	20	60

Table 2.15. Ring closing metathesis reactions of acrylate esters (106-108)

Entry	Acrylate ester		1st or 2nd Generation Grubbs' Catalyst	Solvent	Temp. (ºC)	Time (h)	Yield (%)	ee (%)
	Ar	Eq.	Amount %					
1	 **106**	1	2nd gen. Grubbs' cat. 5%	CH_2Cl_2	45	68	No Reaction	--
2		1	1st gen. Grubbs' cat. 10%	CH_2Cl_2	45	24	26	20
3	 **107**	1	1st gen. Grubbs' cat. 10%	CH_2Cl_2	45	15	90	60
4	 **108**	1	1st gen. Grubbs' cat. 10%	CH_2Cl_2	45	5	94	--

2.5. Racemic syntheses of α,β-Unsaturated-γ-Lactones

Similar to 6-membered α,β-unsaturated-δ-lactones, 5-membered α,β-unsaturated-γ-lactones can also possess biological activities as indicated in introduction part. To discuss the effect of the ring size in biological activities, syntheses of bicycloaryl substituted α,β-unsaturated-γ-lactones were aimed.

In the beginning of the study, two pathways were designated to get desired products. 5-Membered α,β-unsaturated lactones can be synthesized starting from either selected ketones or aldehydes. In the first route, methyl ketones can be converted to α,β-unsaturated ketones, which can easily be reduced to alcohols by Luche reduction. Acrylate esters can be synthesized from obtained alcohols, and then 5-membered α,β-unsaturated lactones can be obtained by RCM reaction (Figure 2.3).

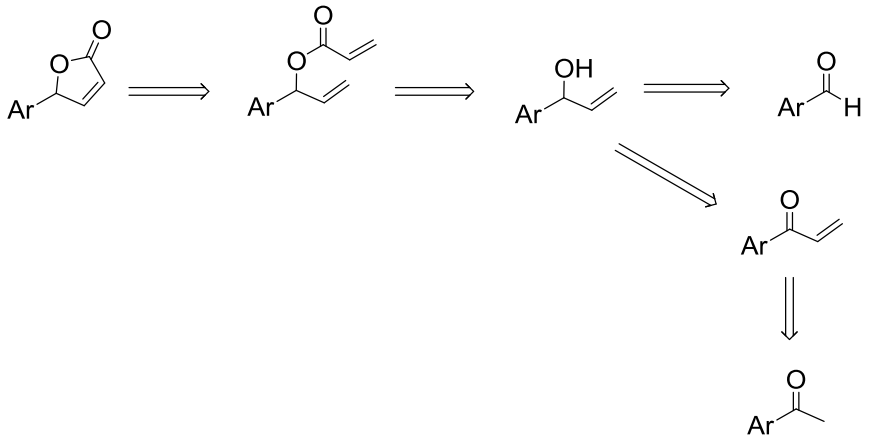
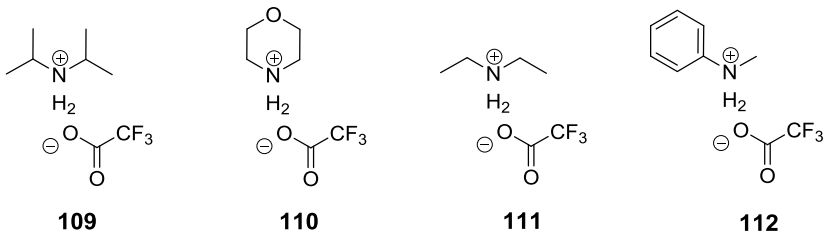


Figure 2.3. Retro-synthetic analysis of α,β-unsaturated-γ-lactones

Second alternative for the synthesis of 5-membered α,β-unsaturated lactones is to start the synthesis with vinylation of the corresponding aldehydes, to form allylic alcohols, and then synthesized alcohols could be transformed to acrylate esters. Finally 5-membered α,β-unsaturated lactones could be achieved via RCM reactions.

Synthesis attempts were started with route 1. α-methylenation of ketones is a well known reaction in the literature.[56] It is Mannich type reaction between ketone and paraformaldehyde in the presence of catalyst, an ammonium salt (Figure 2.4). Catalyst **110** was prepared by the reaction of morpholine and trifluoroacetic acid. Our first attempts were performed starting by *trans*-4-phenyl-3-buten-2-one (**100**) to get α,β-unsaturated ketone derivative (**113**). Unfortunately, no change was observed in the

starting material. Although varying amounts of TFA and amine were used in catalytic system no product formation was observed in TLC on crude NMR studies (Table 2.16, entries 1-4).

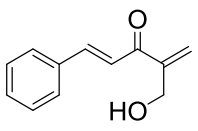


109 **110** **111** **112**

Figure 2.4. Structures of ammonium salts (109-112)

Then two alternative secondary amines were used to form catalyst **111** and catalyst **112**. These catalysts were seemed to work, but desired α,β-unsaturated ketone (**113**) was collected with low yield. Besides many side product peaks were observed in the crude NMR spectrum (Table 2.16, entries 5 and 6). Amount of the added TFA was changed to 0.5 eq. and maximum 15% isolated yield was observed with the 4 eq. of paraformaldehyde (Table 2.16, entry 8). In same conditions with longer reaction time it was observed much more side product peaks in crude NMR (Table 2.16, entry 7).

In the presence of 0.1 eq. of TFA and 18 h reaction time, the yield of the desired product was 2%. Two side products were also collected from silica gel column chromatography. One of the side products was collected with 45% isolated yield, and the structure of the side product was characterized by NMR spectroscopy. One of the side products (**114**) was characterized as the Baylis-Hillman adduct of the α,β-unsaturated ketone and paraformaldehyde. Baylis-Hillman reaction is catalyzed by a tertiary amine like DABCO. Although there is no DABCO in our reaction, N-methyl aniline salt works like DABCO to give allylic alcohol **114** (Figure 2.5).

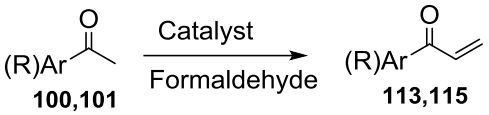


114

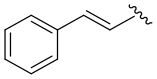
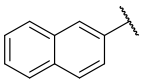
Figure 2.5. Structure of the side product (**114**)

To prevent the formation of the side product (**114**), the further reactions were carried out in a more dilute system (0.04 M). In this condition, the yield was raised up to 40% (Table 2.16, entry 10). Catalyst **111** was also used for 2-acetonaphthone, after 48 h reaction time just 3% yield was achieved for desired α,β-unsaturated ketone (**115**).

Table 2.16. Direct α-methylenation reactions of selected ketones (100, 101)



100,101 113,115

Entry	R (Ar)	Catalyst (Eq.)	Formaldehyde (Eq.)	TFA (Eq.)	Amine (Eq.)	Solvent	Temp. (Time)	Yield (%)
1	 100	**110** (1)	4	0.1	--	THF (2 mL)	Reflux (24 h)	No Reaction
2		**110** (1)	4	0.1	0.15	THF (2 mL)	Reflux (24 h)	No Reaction
3		**110** (1)	2	0.1	--	THF (2 mL)	Reflux (24 h)	No Reaction
4		**110** (1)	2	0.1	--	DMF (2 mL)	125 °C (24 h)	No Reaction
5		**112** (1)	6	0.5	--	THF (5 mL)	Reflux (46 h)	Side Product
6		**112** (1)	6	1.0	--	THF (7 mL)	Reflux (65 h)	Side Product
7		**112** (1)	4	0.5	--	THF (1 mL)	Reflux (24 h)	Side Product
8		**112** (1)	4	0.5	--	THF (1 mL)	Reflux (7 h)	15
9		**112** (1)	4	0.1	--	THF (3 mL)	Reflux (18 h)	2
10		**112** (1)	4	05	--	THF (50 mL)	Reflux (72 h)	40
11	 101	**111** (1)	4	0.5	--	THF (1 mL)	Reflux (48 h)	3
12		**112** (1)	4	0.3	--	THF (10 mL)	Reflux (95 h)	Side Product

Synthesized α,β-unsaturated ketone was treated with $Ce(NO_3)_3.6H_2O$ and $NaBH_4$ to get desired alcohol by Luche reduction.[57] This reaction gave allylic alcohol (**116**) in very good yield (90% yield) in 40 minutes.

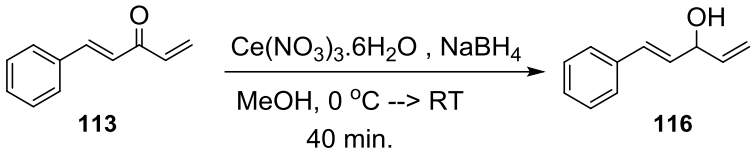
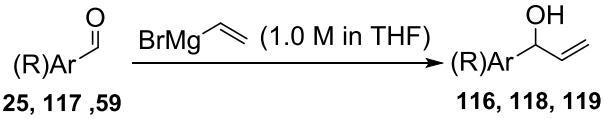


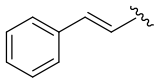
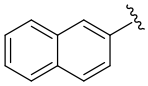
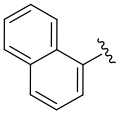
Figure 2.6. Luche reduction reaction for α,β-unsaturated ketone (113)

Route 1 was abandoned, since getting the product low yield, side product formations and low reproducibility in the first step. Therefore it was decided to use 2nd route in which alcohol could be formed by Grignard reagent.[58]

In order to produce the desired allyllic alcohols, aldehydes were treated with vinylmagnesium bromide solution (1.0 M in THF). Alcohols were produced with very high yield for all aldehydes (89% to 98% isolated yields) (Table 2.17).

Table 2.17. Synthesis of allylic alcohols (116, 118, 119) from selected aldehydes (25, 117, 59)



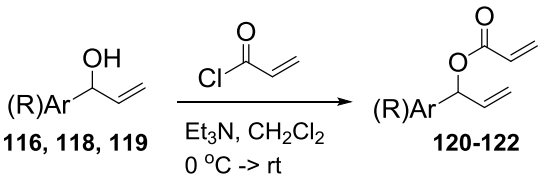
Entry	Ar (R), Eq.		Vinylmagnesium bromide (1.0 M in THF) (Eq.)	Solvent	Temp. (Time)	Yield (%)
1	 **25**	1	1 (1)	THF	-20 -> RT (2 h)	98
2	 **117**	1	1.1 (1.1)	THF	-20 -> RT (2,5 h)	89
3	 **59**	1	1.1 (1.1)	THF	-20 -> RT (2 h)	91

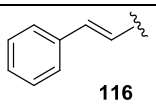
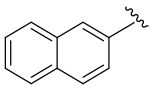
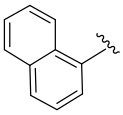
Transformations of alcohols to acrylate esters were performed with the method which was used previously on the synthesis of 6-membered lactones. Reactions were monitored by TLC and crude NMR, and conversions were highly efficient. Both 1-naphthyl and 2-naphthyl derivatives were isolated in high yields. (80-93%) However, the isolation of *trans*-cinnamaldehyde derivative could not be accomplished on SiO_2 column

chromatography. Formed acrylate ester (**120**) was decomposed during the purification process. For this reason, crude product of ester starting from *trans*-cinnamaldehyde was used without purification.

Ring closing metathesis reactions of esters were started with rude product (**120**) which was formed from *trans*-cinnamaldehyde. 1st generation Grubbs' catalyst was used in the reaction and the reaction was controlled by TLC. Reaction was performed many times but starting material was never consumed completely and formations of many product peaks were observed in TLC. Because of this reason, Ti(O*i*Pr)$_4$ was used to prevent possible complexation of Grubbs' catalyst with carbonyl at 1-naphthaldehyde and 2-naphthaldehyde derivatives. However there could not be seen any improvement in the reaction.

Table 2.18. Transformations of allylic alcohols (116, 118, 119) to acrylate esters (120-122)



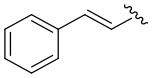
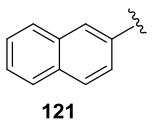
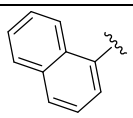
Entry	Alcohol	Acryloyl chloride (Eq.)	Triethyl amine (Eq.)	Time (h)	Yield (%)
1	 **116**	2	4	7	Used without purification in next step
2	 **118**	2	4	16	86
3	 **119**	2	4	16	93

For 2-naphthaldehyde and 1-naphthaldehyde derivatives of acrylate esters, 1st generation Grubbs' catalyst solution were prepared (10% compared to ester, 0.01 M in CH_2Cl_2). This solution was added to the 0.01 M acrylate ester solution at 45 °C slowly. TLC showed that all starting materials were consumed after 7 hours, but purification of the products was found quite problematic in SiO_2 column. During purification in SiO_2 column, TLC showed the formation of another isomerisation product which had similar

R_f value with our product and it was quite difficult to separate the side product from our target product. Although NMR studies of the crude product shows the formation of target compound solely, only 11% 2-naphthyl derived lactone and 38% 1-naphthyl derived lactone could be purified from isomerisation product (Table 2.19). During the purification process of 2-naphthyl derived product isomerisation product was also obtained in pure form and characterized by ^{1}H- and ^{13}C-NMR. The structure of the isomerisation product may elucidated as β,γ-unsaturated-γ-lactone structure and it is proposed that our α,β-unsaturated lactone produces 2-hydroxy furan under acidic conditions. Then 2-hydroxy furan can produce β,γ-unsaturated isomerisation product (**126**) (Figure 2.7).

Table 2.19. Ring closing metathesis reactions of acrylate esters (120-122)

120-122 **123-125**

Entry	**Acrylate Ester**	**1st generation Grubbs' catalyst (Eq.)**	**Ti(O*i*Pr)$_4$ (Eq.)**	**Solvent**	**Temp. (Time)**	**Yield (%)**
1	 **120**	0.1	-	CH_2Cl_2	43-45 °C (21 h)	No Reaction
2	 **121**	0.1	1	CH_2Cl_2	45 °C (17 h)	No Reaction
3		0.1	-	CH_2Cl_2	50 °C (5 h) RT (12 h)	Could not be separated from isomerisation product.
4		0.1	-	CH_2Cl_2	42 °C (7 h)	11
5	 **122**	0.1	1	CH_2Cl_2	27-30 °C (24 h)	No Reaction
6		0.1	-	CH_2Cl_2	45 °C (6 h)	38

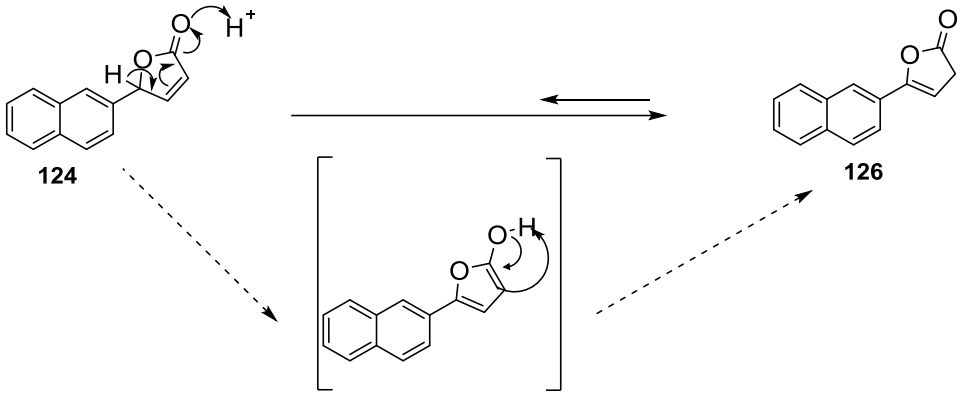


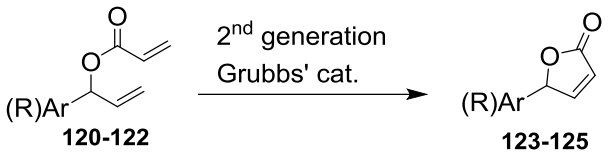
Figure 2.7. Plausible mechanism for the formation of isomerisation product

Alternatively, the same RCM reactions were performed with 2nd generation Grubbs' catalyst as summarized in table 2.20. Although no reaction was seen for styryl derived ester (**120**), 2-naphthyl and 1-naphthyl esters (**121** and **122**) were consumed completely after 2 hours. Further purifications of the crude products yielded isomerisation as indicated above. To prevent the isomerisation following purification alternatives were used;

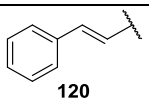
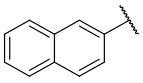
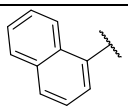
- Aluminum oxide (Al_2O_3) column chromatography (Grade I)
- Aluminum oxide (Al_2O_3) column chromatography (Grade V)
- Celite filtration
- Et_3N treated SiO_2 column chromatography
- 1% Et_3N treated SiO_2 column chromatography
- Short and quickly performed SiO_2 column chromatography.

Among these attempts, only 55% of 2-naphthyl substituted furan-2-one (**124**) could be isolated.

Table 2.20. Ring closing metathesis reactions of acrylate esters (120-122)



120-122 123-125

Entry	Acrylate Ester	2nd generation Grubbs' cat.(Eq.)	Solvent (mL)	Temperature (Time)	Yield (%)
1	 **120**	0.1	CH_2Cl_2	45 °C (22 h)	No Reaction
2	 **121**	0.05	CH_2Cl_2	45 °C (2 h)	Could not be separated from isomerisation product.
3		0.05	CH_2Cl_2	45 °C (2 h)	55 + Isomerisation product
4	 **122**	0.05	CH_2Cl_2	45 °C (2 h)	Decomposed in alumina

2.6. Syntheses of Seven-Membered α,β-Unsaturated Lactone Derivatives

In this part of the thesis study, syntheses of s 7-membered α,β-unsaturated lactone derivatives were aimed. As described in previous sections, syntheses of 7-membered α,β-unsaturated lactone derivatives were designed as the formation of corresponding alcohols, acrylate esters and α,β-unsaturated lactones respectively. Four different aldehydes were selected as starting material. *Trans*-cinnamaldehyde was selected to synthesize the 7-membered lactone derivative of goniothalamin. Other aldehydes were 2-naphthaldehyde, 1-naphthaldehyde and 4-methyl-1-naphhthaldehyde. These aldehydes were selected because their 6-membered α,β-unsaturated lactones were quite cytotoxic against cancer cell lines Synthesizing these derivatives provides information about the effects of the ring size on cytotoxic activity of the α,β-unsaturated lactone family compounds.

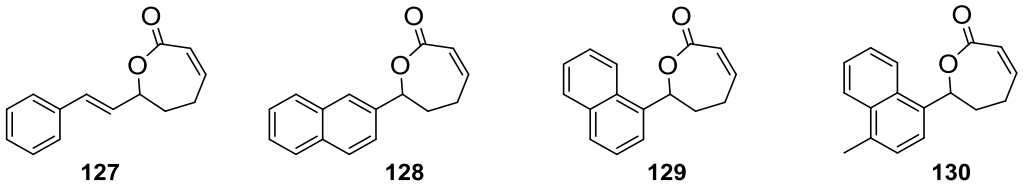
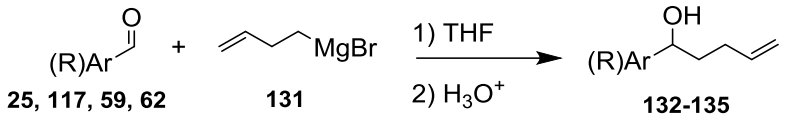


Figure 2.8. Structures of 7-membered α,β-unsaturated lactones (**127-130**)

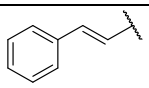
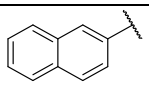
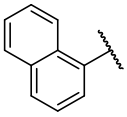
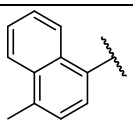
To produce the 7-membered α,β-unsaturated lactone derivatives, 1-buten-4-yl magnesium bromide (**131**), prepared from 4-bromo-1-butene, was added over the starting aldehydes (**25**, **117**, **59**, **62**) to produce racemic alcohols (**132-135**) with moderate to good yields (41-89%). A similar product formation was reported in the literature with for similar Grignard reagents (Table 2.21).[59]

Transformations of alcohols (**132-135**) to acrylate ester (**136-138**) were performed in presence of acryloyl chloride and triethyl amine. This well known reaction yielded acrylate esters with high yields (up to 88%) (Table 2.22).

Table 2.21. Synthesis of alcohols from selected aldehydes (25, 59, 122, 62) via Grignard reagent (131)



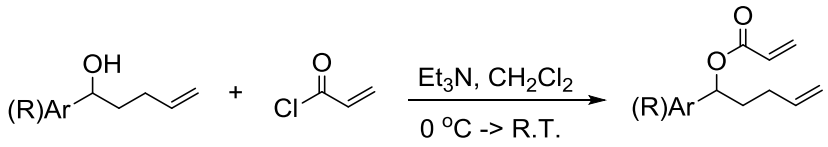
25, 117, 59, 62 **131** **132-135**

Entry	Aldehyde		131	Solvent	Temp. (ºC)	Time (h)	Yield (%)
	(R)Ar	Eq.	Eq. (Amount, mmol)				
1	 **25**	1	2 (4 mmol in 10 mL Et_2O)	THF	-10 to RT	12	41
2	 **117**	1	2 (2 mmol in 5 mL Et_2O)	THF	-10 to RT	3	89
3	 **59**	1	2 (4 mmol in 10 mL Et_2O)	THF	-10 to RT	12	62
4	 **62**	1	2 (4 mmol in 10 mL Et_2O)	THF	-10 to RT	12	56

Ring closing metathesis (RCM) reactions of acrylate esters were performed in the presence of the 2nd generation Grubbs' catalyst. Compared to other RCM reactions performed in our laboratory, yields of these reactions were relatively lower than previous works (five and six membered of α,β-unsaturated lactones). In all reactions starting material were not consumed completely and some unexpected spot formation were observed beside the formation of target molecules. Because these spots were not separable, they could not be identified. Most probably these unknown mixtures included oligomeric compounds. (Table 2.23)

In the reactions of naphthalen-1-yl and 4-methyl-naphthalen-1-yl derivatives only desired final products were collected as 39% and 33% yield. In the reaction of *trans*-cinnamaldehyde very small amount of target molecule were detected by NMR spectroscopy (3%), and formation of stilbene as a side product with 24% yield was observed. These compounds were characterized by NMR studies and unexpectedly the coupling constants between α- and β- protons of lactone ring was observed as 16 Hz which indicates the formation of *E* isomer for a 7-membered ring system

Table 2.22. Transformations of alcohols (132-135) to acrylate esters (136-139)



132-135 **39** **136-139**

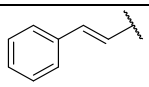
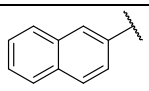
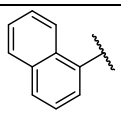
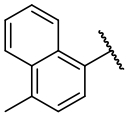
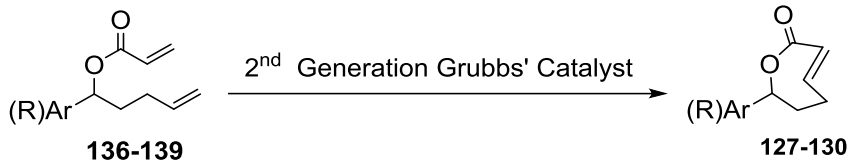
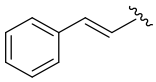
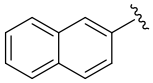
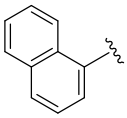
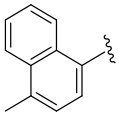
Entry	Alcohol		Acryloyl chloride (Eq.)	Et3N (Eq.)	Time (h)	Yield (%)
	R(Ar)	Eq.				
1	 **132**	1	2	4	12	76
2	 **133**	1	2	4	14	89
3	 **134**	1	2	4	14	69
4	 **135**	1	2	4	13	88

Table 2.23. Transformation of acrylate esters (136-139) to 6,7-dihydro-5*H*-oxepin-2-one (127-130) derivatives



136-139 **127-130**

Entry	**Acrylate Ester**		**2nd Generation Grubbs' Catalyst**	**Solvent**	**Temp. (°C)**	**Time (h)**	**Yield (%)**
	Ar	**Eq.**	**mmol %**				
1	 **136**	1	5	CH_2Cl_2	45	4	<3 + 24% S.P.
2	 **137**	1	5	CH_2Cl_2	45	24	60 + 21% S.P
4	 **138**	1	5	CH_2Cl_2	50	18	39
5	 **139**	1	5	CH_2Cl_2	50	18	33

* S.P. : Side product

RCM reaction of naphthalene-2-yl derivative, gave the formation of two products after the purification by column chromatography. ^{1}H and ^{13}C NMR analyses of the products indicated that these two compounds gave almost similar chemical shifts. COSY spectrum of these compounds implied that both molecules are unsaturated lactones and they are isomers of each other (Figure 2.9 and 2.10).

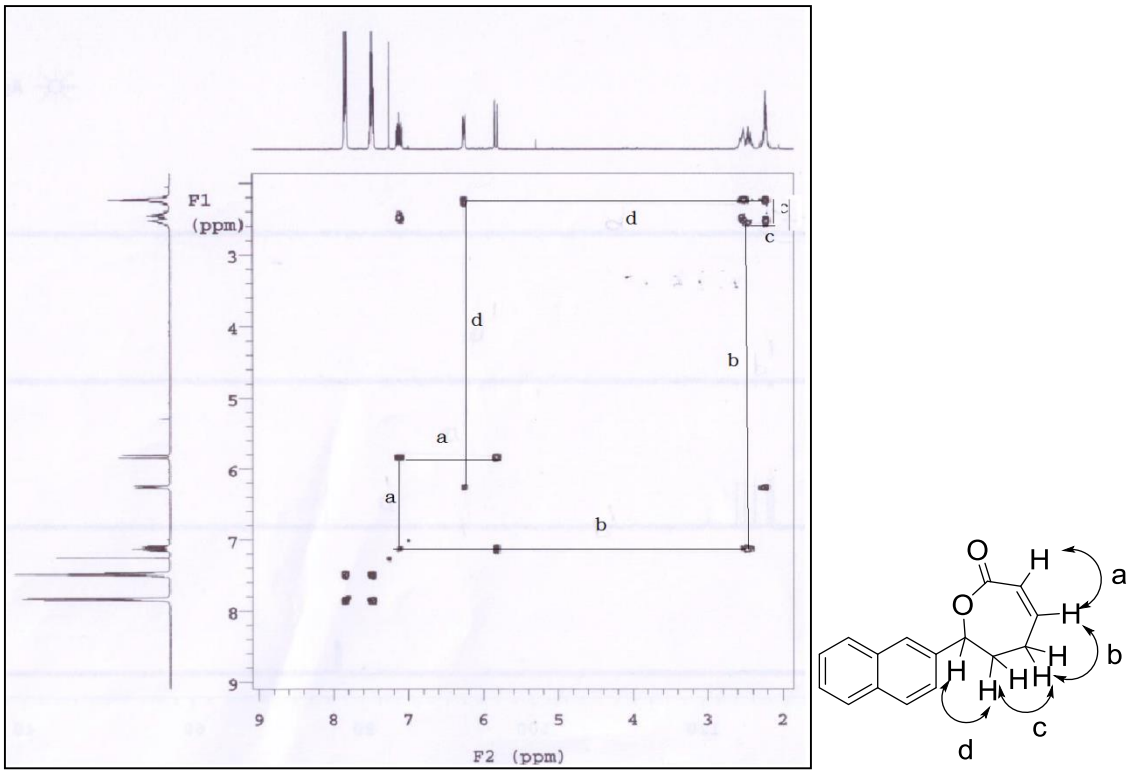


Figure 2.9. COSY spectra of compound 128

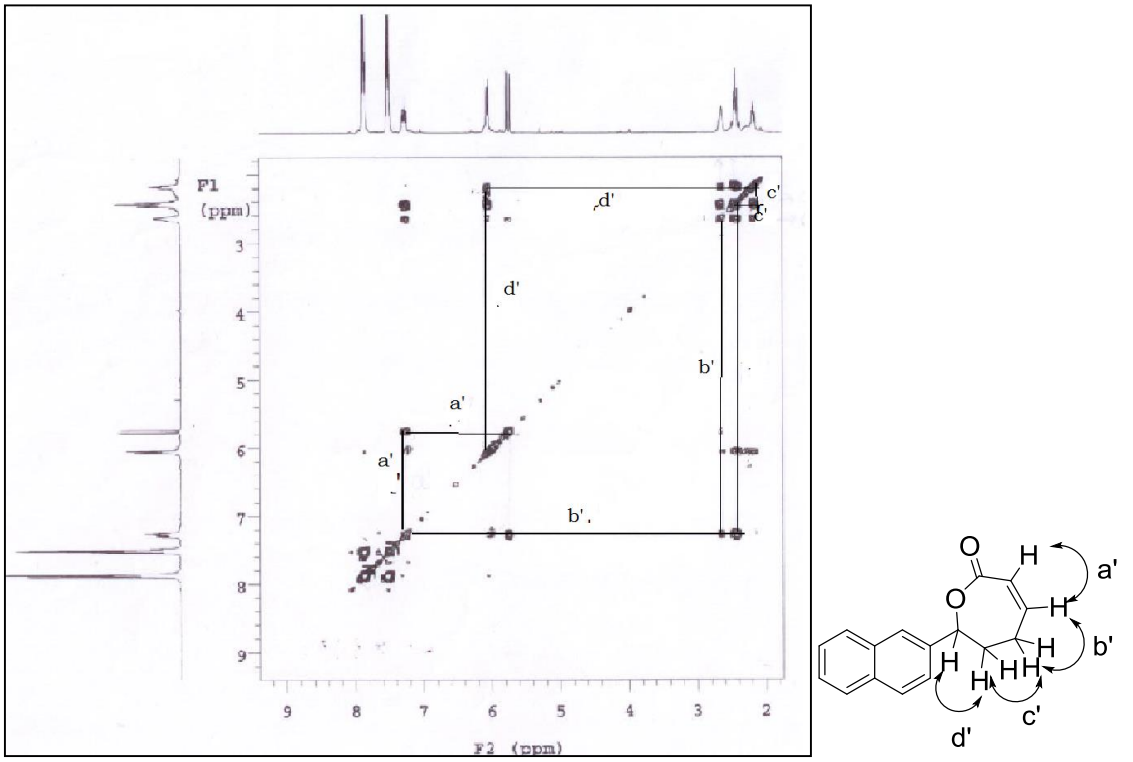


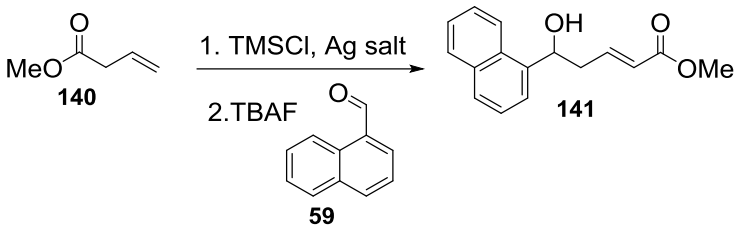
Figure 2.10. COSY spectra of the isomer of compound 128

2.7. A Method Development Studies for the Synthesis of α,β-Unsaturated-δ-Lactone

The last object of this thesis study was conversion of methyl-3-butenoate to unsaturated pyran-2-one structures in the presence of a silver salts and trimethylsillyl chloride (TMSCl). In literature there is not any similar enolization study, therefore optimization of reaction conditions were made by trial and error.

As a starting point, different silver salts and solvents were used for enolization of methyl-3-butenoate. As summarized in the table 2.24, AgOTf alone or in the presence of triethyl amine has not shown any effect, when used in admixture with sodium carbonate in DMF yielded compound **141** with 6% yield. From other tested silver salts Ag_2CO_3, Ag_2O, and $AgNO_3$ could catalyze this transformation successfully. Ag_2CO_3 gave the highest yield, and it was chosen silver salt for further optimization studies (Table 2.24). Besides, it was found that DMF was relatively convenient solvent compared to other tested solvents like NMP, THF and toluene (Table 2.25).

Table 2.24. Addition of dienolate to 1-naphthaldehyde (59) in different silver salt and solvent



Entry	Ag salt (Eq.)	Solvent	T °C	1st step time (h)	2nd step time (h)	Yield (%)
1	AgOTf (1.0)	THF	0 to RT	0.1	66	No reaction
2	AgOTf (1.0)	NMP	0 to RT	1	72	No reaction
3	Ag_2CO_3 (1.0)	Toluene	0 to RT	1	24	30
4	Ag_2CO_3 (1.0)	THF	0 to RT	1	24	18
5	AgOTf+Na_2CO_3 (1.0)	DMF	0 to 80	4	24	6
6	AgOTf+Et_3N (1.0)	DMF	0 to RT	16	24	No reaction
7	Ag_2O	DMF	0 to RT	15	24	19
8	$AgNO_3$	DMF	0 to RT	16	24	2
9	Ag_2CO_3 (2.0)	DMF	0 to RT	1	24	44**

** 2 eq. of 1-naphthaldehyde was used.

Table 2.25. Solvent optimization for the addition of dienolate to 1-naphthaldehyde (59)

Entry	Ag_2CO_3 (Eq.)	Solvent	T °C	1st step time (h)	2nd step time (h)	Yield (%)
1	1	NMP	0 to RT	1	24	16
2	1	Toluene	0 to RT	1	24	16
3	1	DMF	0 to RT	1	24	39

With regard to the amount of the solvent (concentration of reactants) and the reaction time studies are summarized in table 2.26. Simply, it was observed that amount of the solvent (or concentration of the reactants) play a critical role. When amount of DMF was increased to 4 mL of DM, much more of the silver salt was dissolved and reaction has reached a higher yield. However, in 10 mL of DMF lower yield was observed due to the low concentration of reactants.

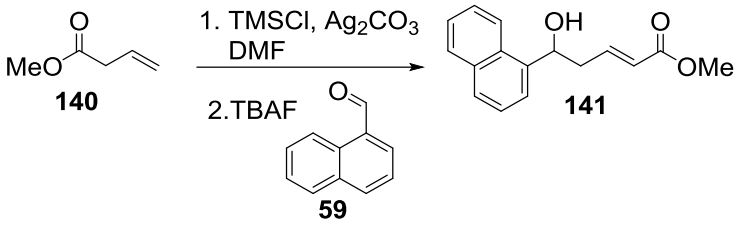
In table 2.26, if examined entry 3 and 5, when amount of silver salt halfed in 4 mL of solvent, the yield of the reaction increased slightly, and because of that 0.5 eq. of silver carbonate were used in further reactions. At this silver concentration, similar yields were observed in 4 and 10 mL of DMF. (55% and 52 % respectively)

The reaction was designed as two step procedure and the first step was dienolate formation. At the beginning of the optimization studies of the first step, the reaction mixture was stirred 16 hours to form dienolate intermediate. However, when the reaction time lowered to 1 hour, no change was observed in reaction yield. Because of this observation, 1 hour reaction time seemed enough for dienolate formation.

On the other hand, reactions in which 2 eq. of aldehyde were used in 4 mL DMF, the reaction yield was increased up to 75%. Finally TBDMSCl was used as sillyl source to test the effect of the sillyl source in the reaction. Lower reaction yield was observed compared to the reactions in where TMSCl used as sillyl source. So, the reaction conditions were optimized as 1 eq. of methyl-3-butenoate, 1 eq. of TMSCl, 0.5 eq. Ag_2CO_3, 1 eq. of TBAF, 2 eq. of aldehyde in 4 mL of DMF. Reaction times were optimized as 1 h for the first step and 24 hours for the second step.

Dienolate addition to different aldehydes (**25, 117, 142-145**) was also studied and 12-69% yields were obtained for their corresponding alcohols under optimized reaction conditions (Table 2.27).

Table 2.26. Amount of solvent and silver salt optimization for the addition of dienolate to 1-naphthaldehyde (59)



Entry	1-naphthaldehyde (Eq.)	Sillyl chloride source (Eq.)	Ag_2CO_3 (Eq.)	DMF (mL)	T°C	1st step time (h)	2nd step time (h)	Yield (%)
1	1.0	TMSCl (1.0)	1	1	0 to 80	4	90	19
2			1	1	0 to 80	15	7	16.
3			1	4	0 to RT	15	24	44
4			1	10	0 to RT	16	24	28
5			0.5	4	0 to RT	15	24	55
6			0.5	10	0 to RT	16	24	52
7			0.5	10	0 to RT	1	24	53
8	2.0		0.5	10	0 to RT	1	24	47
9			0.5	10	0 to RT	16	24	65
10			0.5	4	0 to RT	1	24	75
11		TBDMSCl (1)	0.5	4	0 to RT	1	24	51

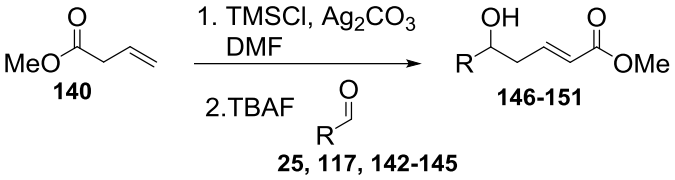
* Methyl-3-butenoate was used as 1 eq., and otherwise indicated other chemical equivalent values are given compared to methyl-3-butenoate. TBAF was used as 1 eq.

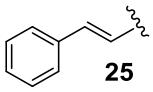
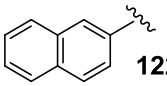
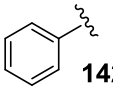
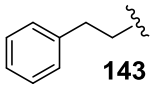
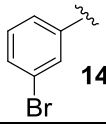
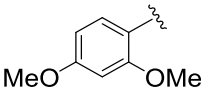
A similar reaction between dienolate and ketones were also studied and formed dienolate system was applied to selected ketones, but no any product formation was observed in all trials (Figure 2.11)

Under the optimized reaction conditions, additions of various esters without vinyl substituent at α-carbon to 1-naphthaldehyde were also studied. Unfortunately, ester without a vinyl group at α-carbon gave no product formation, while ester having vinyl group at α-carbon gave α,β-unsaturated ester (**163**) as product with 51% yield (Table 2.28).

These results indicate that reaction is only produces dienolate rather than the enolate and vinylogous aldol type addition occurs under specific pH values.

Table 2.27. Reactions of selected aldehydes (25, 117, 142-145**)** with dienolates



Entry	Aldehyde R	Yield (%)
1	 25	28
2	 122	69
3	 142	41
4	 143	No Reaction
5	 144 Br	67
6	 MeO OMe 145	12

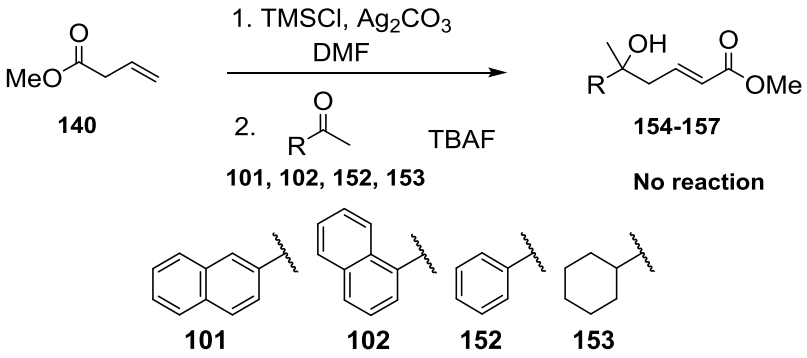
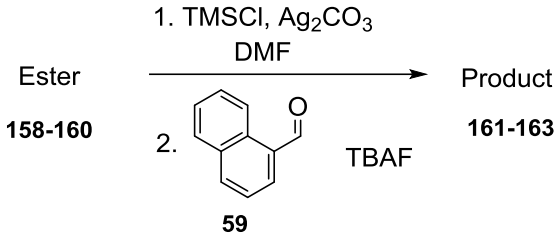
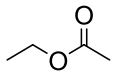
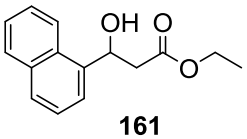
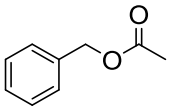
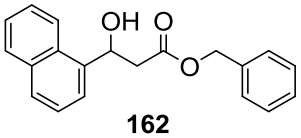
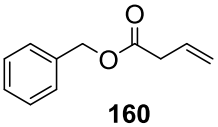
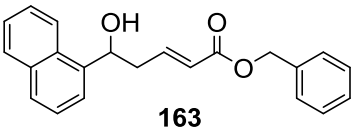


Figure 2.11.Reactions of selected ketones (101,102,152,153) with dienolates

Table 2.28. Dienolate formations of selected ester (158-160) andvinylogous aldol addition reactions with 1-naphthaldehyde (59)



Entry	Ester	Product	Sillyl chloride source (Eq.)	DMF (mL)	Yield (%)
1	 **158**	 **161**	TMSCl (1)	4	No reaction
2	 **159**	 **162**	TMSCl (1)	4	No reaction
3	 **160**	 **163**	TMSCl (1)	4	51
4			TBDMSCl (1)	15	23

CHAPTER 3

EXPERIMENTAL

3.1. General Methods

Reagents were commercial grade and were used as supplied. Dichloromethane (CH_2Cl_2) was distilled over calcium hydride. Tetrahydrofuran (THF) was dried by MBraun-SPS-Solvent Purification System. Reactions were monitored by TLC using Merck TLC plates (Silicagel 60 F 254). Chromatographic separations and isolations were performed using Fluka 70–230 mesh silica gel. Solvents, required for SiO_2 column chromatography, were commercial grade and were used as supplied. Solvents, required for HPLC, were HPLC grade and were used as supplied. ^{1}H NMR and ^{13}C NMR data were recorded on a Varian 400-NMR (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 (77.16 ppm), respectively. MestReNova NMR Processing Software was used for processing NMR spectra. Optical rotations were measured with ADP 410 Digital Polarimeter (Bellingham + Stanley Ltd.). HPLC studies were performed by employing Chiralpak AD-H column and Chiralcel OJ-H column (0.46cmΦ x 150cm) on Agilent 1100 Series HPLC and 1200 Series instrument.

3.2. Large Scale Asymmetric Synthesis of (*R*)-4'-Metilklavuzon and (*R*)-2'-Metilklavuzon

3.2.1. Procedure for Drying Methanol

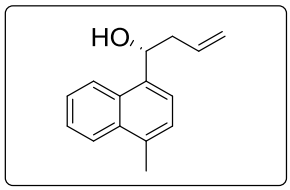
50 mL of methanol was treated with 3Å molecular sieve during 24 hours. Then 2.5 g of magnesium and 0.25 g of iodine were added to the methanol, and heated at reflux. After all magnesium had reacted (a colourless solution appears), 450 mL of methanol was added to the solution and heated at reflux about 3 hours. After that this

mixture was distilled under nitrogen atmosphere and stored in activated molecular sieve under nitrogen atmosphere.

3.2.2. General Procedure for Asymmetric Allylation Reactions of Aldehydes

In a two necked round bottom flask, R-Tol-BINAP (0.06 eq.) and AgF (0.1 eq.) were dissolved in 20 mL of anhydrous methanol. Solution was stirred about 20 minutes under nitrogen atmosphere at room temperature without expose of light. Then solution mixture was cooled down to –20 ºC and 4-methyl-1-naphthaldehyde (or 2-methyl-a-naphthaldehyde) (1 eq.) and allyltrimethoxysilane (1.05 eq.) were added to reaction mixture respectively. Final solution was allowed to stir about 48 hours at –20 ºC. Then resulting mixture was filtered through celite-silica gel mixture. Purification of crude product by column chromatography on silica gel (1:10 → 1:8 EtOAc:Hexane) furnished corresponding homoallylic alcohol.

3.2.2.1. (*R*)-1-(4-methylnaphthalen-1-yl)but-3-en-1-ol (63)



Purification of crude product by column chromatography on silica (1:10 → 1:8 EtOAc/Hexane) furnished 2432 mg of *(R)*-1-(4-methylnaphtalen-1-yl)but-3-en 1-ol as light yellow oil with 95% yield.

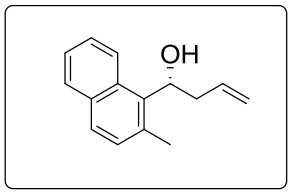
Rf: 0.25 (1:6, EtOAc:Hexane); $[\alpha]_D^{24}$ = +262 (c 1.47; CH_2Cl_2);

HPLC: Enantiomeric excess was found as 88% with Chiralcel OJ-H HPLC column (Hexane:Isopropanol, 99:1, 1 mL/min, 280 nm, R_{t1} = 15.217 min as minor peak, R_{t2} = 15.937 min as major peak);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 – 8.09 (m, 1H), 8.08 – 8.03 (m, 1H), 7.58 – 7.51 (m, 3H), 7.34 (d, *J* = 7.3 Hz, 1H), 6.01 – 5.88 (m, 1H), 5.55 – 5.49 (m, 1H), 5.26 – 5.16 (m, 2H), 2.81 – 2.73 (m, 1H), 2.70 (s, 3H), 2.67 – 2.57 (m, 1H), 2.12 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.59, 134.89, 133.47, 132.60, 130.22, 126.04, 125.34, 125.07, 124.70, 123.41, 122.46, 117.41, 69.76, 42.58, 19.38.

3.2.2.2. (*R*)-1-(2-methylnaphthalen-1-yl)but-3-en-1-ol (65)



Purification of crude product by column chromatography on silica gel (1:10 → 1:8 EtOAc/Hexane) furnished 1594 mg of *(R)*-1-(2-methylnaphtalen-1-yl)but-3-en 1-ol as light yellow oil with 66% yield.

Rf: 0.35 (1:6, EtOAc:Hexane); $[\alpha]_D^{24}$ = +26 (c: 1.33; $CHCl_3$);

HPLC: Enantiomeric excess was found as 50% with Chiralcel OJ-H HPLC column (Hexane:Isopropanol, 95:5, 1 mL/min, 280 nm, R_{t1} = 7.974 min as major peak, R_{t2} = 12.369 min as minor peak);

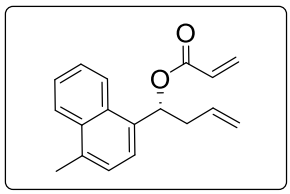
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67 (d, *J* = 8.5 Hz, 1H), 7.81 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.68 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.39 (m, 2H), 7.26 (d, *J* = 8.4 Hz, 1H), 5.96 – 5.83 (m, 1H), 5.64 – 5.56 (m, 1H), 5.24 – 5.17 (m, 1H), 5.17 – 5.12 (m, 1H), 3.06 – 2.94 (m, 1H), 2.76 – 2.66 (m, 1H), 2.55 (s, 3H), 2.21 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 135.43, 135.22, 133.51, 133.13, 131.40, 129.63, 128.84, 128.17, 125.78, 125.64, 124.78, 118.04, 71.34, 41.35, 21.14.

3.2.3. General Procedure for Conversion of Asymmetric Homoallylic Alcohols (63, 65) to Acrylate Esters (66, 67)

A solution of alcohol (1 eq.) in 25 mL of CH_2Cl_2 was cooled down to 0 °C, and then acryloyl chloride (1.58 eq.) and triethyl amine (3.16 eq.) were added sequentially. The mixture was allowed to warm to room temperature and stirred 18 h under nitrogen atmosphere. The final mixture was filtered through celite, poured into water and extracted with CH_2Cl_2. Combined organic phase concentrated under vacuum and purification of crude product by column chromatography on silica gel (1:10, EtOAc:Hexane) gave corresponding acrylate ester.

3.2.3.1. (*R*)-1-(4-methylnaphthalen-1-yl)but-3-en-1-yl acrylate (66)



Purification of crude product by column chromatography on silica gel (1:10, EtOAc:Hexane) gave 2792 mg of *(R)*-1-(4-methylnaphtalen-1-yl)but-3-enyl acrylate as colourless oil with 93% yield.

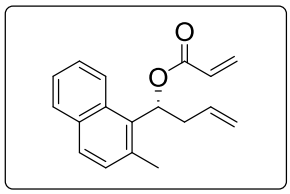
Rf: 0.45 (1:8, EtOAc:Hexane); $[\alpha]_D^{26}$ = +43 (c 1.08; CH_2Cl_2);

HPLC: Enantiomeric excess was found as 88% with Chiralcel OJ-H HPLC column (Hexane:Isopropanol 95:5, 1 mL/min, 280 nm, R_{t1} = 3.730 min as major peak, R_{t2} = 6.741 min as minor peak).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.6 Hz, 1H), 8.05 (d, *J* = 7.3 Hz, 1H), 7.61 – 7.51 (m, 2H), 7.48 (d, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 6.66 (t, *J* = 6.6 Hz, 1H), 6.45 (d, *J* = 17.3 Hz, 1H), 6.20 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.90 – 5.72 (m, 2H), 5.17 – 5.02 (m, 2H), 2.87 – 2.80 (m, 2H), 2.69 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.55, 134.83, 134.16, 133.75, 133.04, 131.00, 130.59, 128.77, 126.22, 126.11, 125.67, 125.11, 123.84, 118.04, 72.72, 40.51, 19.76.

3.2.3.2. (*R*)-1-(2-methylnaphthalen-1-yl)but-3-en-1-yl acrylate (67)



Purification of crude product by column chromatography on silica gel (1:10, EtOAc:Hexane) gave 1588 mg of *(R)*-1-(2-methylnaphtalen-1-yl)but-3-enyl acrylate as colourless oil with 81% yield and 50% ee.

Rf: 0.47 (1:6, EtOAc:Hexane); $[\alpha]_D^{25}$ = +75.5 (c 1.113; $CHCl_3$);

HPLC: Enantiomeric excess was found as 50% with Chiralcel OJ-H HPLC column (Hexane:Isopropanol 95:5, 1 mL/min, 280 nm, R_{t1} = 3.358 min as major peak, R_{t2} = 4.043 min as minor peak).

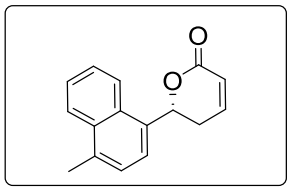
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.49 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.0 Hz, 1H), 7.69 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.46 (m, 1H), 7.45 – 7.39 (m, 1H), 7.28 (d, *J* = 8.4 Hz, 1H), 6.67 (s, 1H), 6.43 – 6.35 (m, 1H), 6.19 – 6.11 (m, 1H), 5.83 – 5.69 (m, 2H), 5.14 – 5.02 (m, 2H), 3.18 – 3.06 (m, 1H), 2.92 – 2.80 (m, 1H), 2.67 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.62, 134.47, 133.72, 133.45, 132.19, 131.25, 130.93, 129.52, 129.02, 128.71, 128.65, 125.88, 125.39, 124.72, 118.11, 73.05, 39.29, 21.11.

3.2.4. General Procedure for Ring Closing Metathesis Reactions of Acrylate Ester (66, 67)

To a solution of acrylate ester (1 eq.) in CH_2Cl_2 (0.01 M) was heated to 60 ^{o}C, and 1st Generation Grubbs' catalyst (0.1 eq.) in CH_2Cl_2 (0.01 M) was added. The resulting mixture was heated at reflux for 8 hours. At the end of the 8 hours, reaction mixture was cooled down to room temperature and concentrated under vacuum. Purification of crude product by column chromatography on silica gel (1:6 → 1:4 EtOAc/Hexane) furnished corresponding 5,6-dihydro-2*H*-pyran-2-one.

3.2.4.1. (*R*)-6-(4-methylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (21)



Purification of crude product by column chromatography on silica gel (1:6 → 1:4 EtOAc/Hexane) furnished 1998 mg (*R*)-6-(4-methylnaphtalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 68% yield.

Rf: 0.24 (1:2, EtOAc:Hexane); $[\alpha]_D^{25}$ = +485 (c 0.833; CH_2Cl_2);

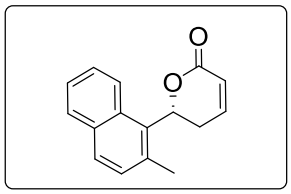
HPLC: Enantiomeric excess was found as 90% with Chiralpak AD-H HPLC column (Hexane:Isopropanol, 98:2, 0.8 mL/min, 280 nm, R_{t1} = 44.678 min as major peak, R_{t2} = 56.134 min as minor peak).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 – 8.04 (m, 1H), 8.02 – 7.96 (m, 1H), 7.60 (d, *J* = 7.4 Hz, 1H), 7.58 – 7.54 (m, 2H), 7.36 (d, *J* = 7.3 Hz, 1H), 7.08 – 7.00 (m, 1H), 6.26 – 6.15 (m, 2H), 2.85 – 2.78 (m, 2H), 2.72 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.59, 145.44, 135.64, 133.01, 132.14, 130.19, 126.38, 126.29, 125.83, 125.34, 124.07, 123.18, 121.82, 76.98, 31.31, 19.81.

HRMS: $[M+Na]^+$: $C_{16}H_{14}NaO_2$ found as: 261.0881 (Calculated for $[M+Na]^+$: 261.0891)

3.2.4.2. (*R*)-6-(2-methylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (20)



Purification of crude product by column chromatography on silica gel (1:6 → 1:4 EtOAc/Hexane) furnished 965 mg (*R*)-6-(2-methylnaphtalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as white colour with 69% yield.

Rf: 0.3 (1:3, EtOAc:Hexane); $[\alpha]_D^{24}$ = +362 (c 0.293, $CHCl_3$);

HPLC: Enantiomeric excess was found as 50% with Chiralcel OJ-H HPLC column (Hexane:Isopropanol 95:5, 1 mL/min, 280 nm, R_{t1} = 41.253 min as major peak, R_{t2} = 51.734 min as minor peak).

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 8.4 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.40 (m, 2H), 7.30 (d, *J* = 8.4 Hz, 1H), 7.11 – 7.03 (m, 1H), 6.31 (dd, *J* = 13.3, 4.4 Hz, 1H), 6.27 – 6.21 (m, 1H), 3.29 – 3.17 (m, 1H), 2.57 (s, 3H), 2.54 – 2.45 (m, 1H).

HRMS: $[M+H]^+$: $C_{16}H_{15}O_2$ found as: 239.1063 (Calculated for $[M+H]^+$: 239.1072)

3.3. Asymmetric Synthesis of New α,β-Unsaturated Lactone Derivatives

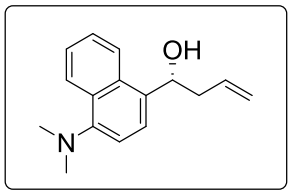
3.3.1. General Procedure for Synthesis of Asymmetric Homoallylic Alcohols at -20 ºC

Same procedure was applied with the allylation reaction of 4-methyl-1-naphthaldehyde and 2-methyl-1-naphthaldehyde. (Please see the section 3.2.2.)

3.3.2. General Procedure for Syntheses of Asymmetric Homoallylic Alcohols at room temperature

In a two necked round bottom flask, R-Tol-BINAP (0.06 eq.) and AgF (0.1 eq.) were dissolved in 20 mL of anhydrous methanol. Solution was stirred about 20 minutes under nitrogen atmosphere at room temperature without expose of light. Then 4-methyl-1-naphthaldehyde (1 eq.) and allyltrimethoxysilane (1.05 eq.) were added to reaction mixture respectively. Final solution was allowed to stir about 78 hours at room temperature. Then resulting mixture was filtered through celite-silica gel mixture. Purification of crude product by column chromatography on silica gel (1:10 → 1:8, EtOAc:Hexane) furnished corresponding homoallylic alcohol.

3.3.2.1. (*R*)-1-(4-(dimethylamino)naphthalen-1-yl)but-3-en-1-ol ((*R*)-69)



Purification of crude product by column chromatography on silica gel (1:6, EtOAc:Hexane) furnished 167 mg of (*R*)-1-(4-(dimethylamino)naphthalen-1-yl)but-3-en-1-ol as colourless oil, with 54% yield.

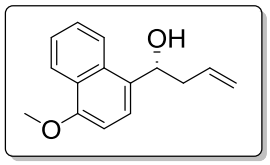
Rf: 0,29 (1:6, EtOAc:Hexane); $[\alpha]_D^{22}$ = +182 (c 1.67; CH_2Cl_2);

HPLC: Enantiomeric excess was found as 100% with Chiralcel OJ-H HPLC column (Hexane:Isopropanol, 95:5, 1 mL/min, 320 nm, R_t = 7.70 min as single peak)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.31 (m, 1H), 8.09 – 8.04 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.01 – 5.88 (m, 1H), 5.46 – 5.41 (m, 1H), 5.27 – 5.15 (m, 2H), 2.90 (s, 6H), 2.79 – 2.70 (m, 1H), 2.69 – 2.57 (m, 1H), 2.42 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.60, 135.20, 133.97, 131.66, 129.01, 125.94, 124.99, 124.85, 123.48, 123.03, 118.01, 113.54, 70.05, 45.34, 42.78.

3.3.2.2. (*R*)-1-(4-methoxynaphthalen-1-yl)but-3-en-1-ol ((*R*)-73)



Purification of crude product by column chromatography on silica gel (1:18, EtOAc:Hexane) furnished 113 mg of (*R*)-1-(4-methoxynaphthalen-1-yl)but-3-en-1-ol as white solid with 50% yield.

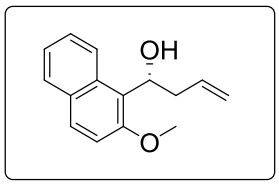
Rf: 0,23 (1:6, EtOAc:Hexane); $[\alpha]_D^{22}$ = +181 (c 0.45; CH_2Cl_2);

HPLC: Enantiomeric excess was found as 91% ee with Chiralcel OJ-H column (90:10 Hexane:Isopropanol, 1 mL/min; 280 nm, R_{t1}: 18.628 min as major peak, R_{t2}: 17.385 min as minor peak)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.38 - 8.32 (m, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.58 – 7.46 (m, 3H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.00 – 5.86 (m, 1H), 5.44 (dd, *J* = 8.1, 4.3 Hz, 1H), 5.26 – 5.14 (m, 2H), 4.01 (s, 3H), 2.80 – 2.71 (m, 1H), 2.68 – 2.58 (m, 1H), 2.11 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.21, 135.17, 131.48, 131.41, 126.72, 125.95, 125.04, 123.26, 122.98, 122.89, 118.25, 103.28, 70.15, 55.65, 42.88.

3.3.2.3. (*R*)-1-(2-methoxynaphthalen-1-yl)but-3-en-1-ol ((*R*)-77)



Purification of crude product by column chromatography on silica gel (1:18, EtOAc:Hexane) furnished 50 mg of (*R*)-1-(2-methoxynaphthalen-1-yl)but -3-en-1-ol as white solid, with 22% yield.

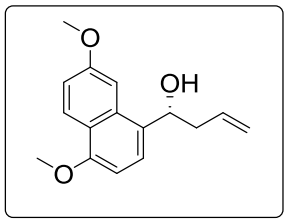
Rf: 0.26 (1:6, EtOAc:Hexane); . $[\alpha]_D^{25}$: +64 (c 0.50; CH_2Cl_2)

HPLC: 55% ee with Chiralcel OJ-H column (90:10 Hexane:Isopropanol, 1 mL/min; 280 nm, R_{t1}: 7.850 min as major peak, R_{t2}: 11.596 min as minor peak);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.52 – 7.46 (m, 1H), 7.39 – 7.33 (m, 1H), 7.29 (d, *J* = 9.1 Hz, 1H), 5.97 – 5.85 (m, 1H), 5.65 – 5.58 (m, 1H), 5.14 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.01 (s, 3H), 3.91 (s, 1H), 2.91 – 2.81 (m, 1H), 2.70 – 2.61 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.68, 135.63, 131.72, 129.51, 129.48, 128.75, 126.78, 124.11, 123.77, 123.16, 117.10, 113.37, 69.75, 56.49, 42.34.

3.3.2.4. (*R*)-1-(4,7-dimethoxynaphthalen-1-yl)but-3-en-1-ol ((*R*)-81)



Purification of crude product by column chromatography on silica gel furnished (*R*)-1-(4,7-dimethoxynaphthalen-1-yl)but-3-en-1-ol was collected as white solid with 9% yield.

Rf: 0,08 (1:8, EtOAc:Hexane); $[\alpha]_D^{25}$ = +163 (c 0.16; CH_2Cl_2).

HPLC: Enantiomeric excess was found as 87% ee with Chiralcel OJ-H column (90:10 Hexane:Isopropanol, 1 mL/min; 280 nm, R_{t1}: 10.189 min as major peak, R_{t2}: 12.268 min as minor peak)

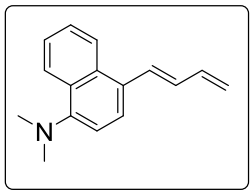
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.2 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 2.1 Hz, 1H), 7.17 - 7.11 (m, 1H), 6.66 (dd, *J* = 8.1, 3.0 Hz, 1H), 5.99 – 5.87 (m, 1H), 5.34 – 5.28 (m, 1H), 5.25 – 5.14 (m, 2H), 3.97 (s, 3H), 3.92 (s, 3H), 2.79 – 2.70 (m, 1H), 2.69 – 2.59 (m, 1H), 2.10 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.18, 155.34, 135.29, 132.90, 130.12, 124.51, 124.10, 120.99, 118.04, 116.74, 102.44, 101.36, 70.53, 55.53, 55.35, 42.37.

3.3.3. General Procedure for Syntheses of Asymmetric Acrylate Esters

Same procedure was applied with the acrylation reactions of asymmetric homoallylic alcohols. (Please see the section 3.2.3.)

3.3.3.1. *(E)*-4-(buta-1,3-dien-1-yl)-*N*,*N*-dimethylnaphthalen-1-amine (71)



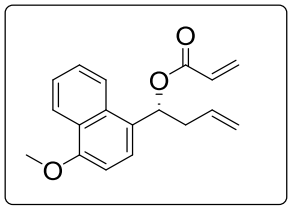
Purification of crude product by column chromatography on silica gel furnished 22 mg of *(E)*-4-(buta-1,3-dien-1-yl)-*N*,*N*-dimethylnaphthalen-1-amine as colourless oil with 40% yield as elimination product.

Rf: 0.75 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 – 8.25 (m, 1H), 8.18 – 8.12 (m, 1H), 7.61 (d, *J* = 7.9 Hz, 1H), 7.55 – 7.49 (m, 2H), 7.32 (d, *J* = 15.2 Hz, 1H), 7.07 (d, *J* = 7.9 Hz, 1H), 6.86 – 6.76 (m, 1H), 6.72 – 6.62 (m, 1H), 5.37 (d, *J* = 16.7 Hz, 1H), 5.21 (d, *J* = 9.9 Hz, 1H), 2.91 (s, 6H).

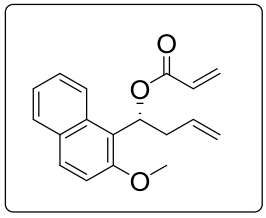
^{13}C NMR (100 MHz, $CDCl_3$) δ 151.03, 137.80, 132.49, 131.09, 129.96, 129.31, 128.80, 126.05, 125.14, 124.83, 124.15, 123.67, 117.07, 113.96, 45.30.

3.3.3.2. (*R*)-1-(4-methoxynaphthalen-1-yl)but-3-en-1-yl acrylate ((*R*)-74)



It was used without purification in next step.

3.3.3.3. (*R*)-1-(2-methoxynaphthalen-1-yl)but-3-en-1-yl acrylate ((*R*)-78)

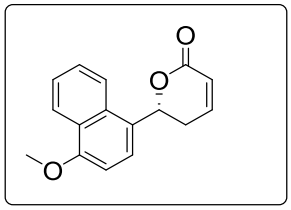


It was used without purification in next step.

3.3.4. General Procedure for Ring Closing Metathesis Reactions of Acrylate Esters

Same procedure was applied with the ring closing metathesis reactions of asymmetric acrylate esters. (Please see the section 3.2.4.)

3.3.4.1. (*R*)-6-(4-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((*R*)-75)

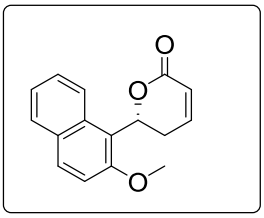


Purification of crude product by column chromatography on silica gel furnished 18 mg of (*R*)-6-(4-methoxynaphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one as beige solid, with 27% yield.

Rf: 0.25 (1:3, EtOAc:Hexane); . $[\alpha]_D^{25}$: +263 (c 0.32; CH_2Cl_2)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.32 (m, 1H), 7.94 (dd, *J* = 8.3, 1.2 Hz, 1H), 7.58 (d, *J* = 8.1 Hz, 1H), 7.57 – 7.46 (m, 2H), 7.08 – 6.98 (m, 1H), 6.82 (d, *J* = 8.1 Hz, 1H), 6.23 – 6.18 (m, 1H), 6.11 (dd, *J* = 11.8, 4.2 Hz, 1H), 4.02 (s, 3H), 2.90 – 2.80 (m, 1H), 2.79 – 2.71 (m, 1H).

3.3.4.2. (*R*)-6-(2-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one ((*R*)-79)



Purification of crude product by column chromatography on silica gel furnished 17 mg of (*R*)-6-(2-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as beige solid, with 25% yield.

Rf: 0.43 (1:3, EtOAc:Hexane);

Because of the non-removal Grubbs' catalyst contamination, NMR characterization was not given.

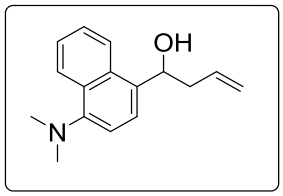
3.4. Racemic Synthesis of New α,β-Unsaturated Lactone Derivatives

3.4.1. General Procedure for Synthesis of Racemic Homoallylic Alcohols

A mixture of CuCl (0.1 eq.) and TBAT (0.1 eq.) in THF was stirred for 1 h at room temperature. After cooling the mixture in an ice bath, allyltrimethoxysilane (1.5 eq.) and aldehyde (1 eq.) were added and then the cooling bath was removed. After starting material disappeared on TLC, 2N HCl aq. in MeOH (1:1) was added for desilylation. Resulting mixture was extracted with ethyl acetate and collected organic phase washed with brine (2x40 mL) dried with $MgSO_4$. After removing excess solvent

under vacua, crude product was purified by column chromatography on silica gel (1:10 → 1:6, EtOAc/Hexane) to give desired alcohol

3.4.1.1. 1-(4-(dimethylamino)naphthalen-1-yl)but-3-en-1-ol (69)



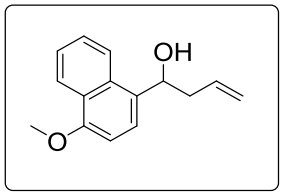
Purification of crude product by column chromatography yielded 129 mg of 1-(4-(dimethylamino)naphthalen-1-yl)but-3-en-1-ol as colourless oil, with 54% yield.

Rf: 0,29 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.31 (m, 1H), 8.09 – 8.04 (m, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.49 (m, 2H), 7.07 (d, *J* = 7.8 Hz, 1H), 6.01 – 5.88 (m, 1H), 5.46 – 5.41 (m, 1H), 5.27 – 5.15 (m, 2H), 2.90 (s, 6H), 2.79 – 2.70 (m, 1H), 2.69 – 2.57 (m, 1H), 2.42 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 150.60, 135.20, 133.97, 131.66, 129.01, 125.94, 124.99, 124.85, 123.48, 123.03, 118.01, 113.54, 70.05, 45.34, 42.78.

3.4.1.2. 1-(4-methoxynaphthalen-1-yl)but-3-en-1-ol (73)



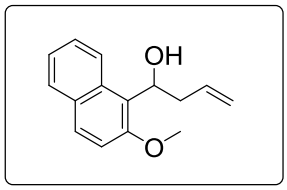
Purification of crude product by column chromatography yielded 400 mg of 1-(4-methoxynaphthalen-1-yl)but-3-en-1-ol as colourless oil, with 88% yield.

Rf: 0.23 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.30 (m, 1H), 8.06 (d, *J* = 8.7 Hz, 1H), 7.58 – 7.46 (m, 3H), 6.81 (d, *J* = 8.0 Hz, 1H), 6.00 – 5.86 (m, 1H), 5.44 (dd, *J* = 8.1 and 4.3 Hz, 1H), 5.26 – 5.14 (m, 2H), 4.01 (s, 3H), 2.80 – 2.71 (m, 1H), 2.68 – 2.58 (m, 1H), 2.11 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 155.21, 135.17, 131.48, 131.41, 126.72, 125.95, 125.04, 123.26, 122.98, 122.89, 118.25, 103.28, 70.15, 55.65, 42.88.

3.4.1.3. 1-(2-methoxynaphthalen-1-yl)but-3-en-1-ol (77)



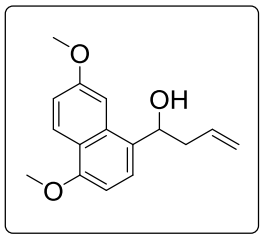
Purification of crude product by column chromatography yielded 398 mg of 1-(2-methoxynaphthalen-1-yl)but-3-en-1-ol as colorles oil, with 87% yield.

Rf: 0.26 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.7 Hz, 1H), 7.82 – 7.77 (m, 2H), 7.52 – 7.46 (m, 1H), 7.39 – 7.33 (m, 1H), 7.29 (d, *J* = 9.1 Hz, 1H), 5.97 – 5.85 (m, 1H), 5.65 – 5.58 (m, 1H), 5.14 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 4.01 (s, 3H), 3.91 (s, 1H), 2.91 – 2.81 (m, 1H), 2.70 – 2.61 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 154.68, 135.63, 131.72, 129.51, 129.48, 128.75, 126.78, 124.11, 123.77, 123.16, 117.10, 113.37, 69.75, 56.49, 42.34.

3.4.1.4. 1-(4,7-dimethoxynaphthalen-1-yl)but-3-en-1-ol (81)



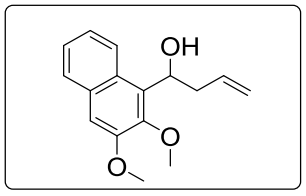
Purification of crude product by column chromatography yielded 57 mg of 1-(4,7-dimethoxynaphthalen-1-yl)but-3-en-1-ol as white solid, with 11% yield.

Rf: 0.09 (1:8, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 9.2 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.36 (s, 1H), 7.18 – 7.11 (m, 1H), 6.67 (d, *J* = 8.0 Hz, 1H), 5.99 - 5.87 (m, 1H), 5.36 – 5.28 (m, 1H), 5.25 – 5.13 (m, 2H), 3.98 (s, 3H), 3.93 (s, 3H), 2.80 – 2.70 (m, 1H), 2.70 – 2.60 (m, 1H), 2.11 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 158.26, 155.42, 135.31, 132.97, 130.16, 124.56, 124.15, 121.07, 118.06, 116.76, 102.54, 101.41, 70.60, 55.57, 55.39, 42.41.

3.4.1.5. 1-(2,3-dimethoxynaphthalen-1-yl)but-3-en-1-ol (85)



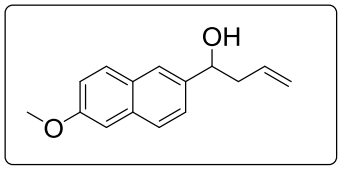
Purification of crude product by column chromatography yielded 245 mg of 1-(2,3-dimethoxynaphthalen-1-yl)but-3-en-1-ol as white solid, with 95% yield.

Rf: 0.23 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, *J* = 7.4 Hz, 1H), 7.76 – 7.66 (m, 1H), 7.45 – 7.32 (m, 2H), 7.13 (s, 1H), 6.01 – 5.86 (m, 1H), 5.67 – 5.56 (m, 1H), 5.22 – 5.07 (m, 2H), 3.99 (s, 3H), 3.98 (s, 3H), 3.62 (s (broad), 1H), 2.92 – 2.80 (m, 1H), 2.72 – 2.61 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 151.66, 147.21, 135.38, 131.69, 130.58, 127.43, 126.63, 125.32, 124.24, 124.06, 117.52, 107.50, 69.78, 61.74, 55.69, 43.13.

3.4.1.6. 1-(6-methoxynaphthalen-2-yl)but-3-en-1-ol (86)



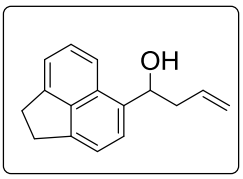
Purification of crude product by column chromatography yielded 449 mg of 1-(6-methoxynaphthalen-2-yl)but-3-en-1-ol as white solid, with 98% yield.

Rf: 0.22 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.68 (m, 3H), 7.45 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.18 – 7.11 (m, 2H), 5.90 – 5.77 (m, 1H), 5.23 – 5.11 (m, 2H), 4.91 – 4.83 (m, 1H), 3.92 (s, 3H), 2.65 – 2.55 (m, 2H), 2.11 (s (broad), 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 157.85, 139.16, 134.64, 134.26, 129.57, 128.88, 127.21, 124.71, 124.59, 119.08, 118.53, 105.89, 73.60, 55.46, 43.89.

3.4.1.7. 1-(1,2-dihydroacenaphthylen-5-yl)but-3-en-1-ol (87)



Purification of crude product by column chromatography yielded 193 mg of 1-(1,2-dihydroacenaphthylen-5-yl)but-3-en-1-ol as light yellow oil, with 86% yield.

Rf: 0.32 (1:6, EtOAc:Hexane);

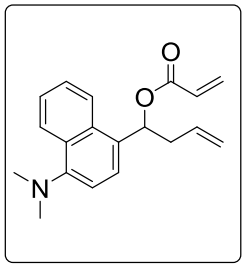
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, *J* = 8.4 Hz, 1H), 7.57 (d, *J* = 7.1 Hz, 1H), 7.48 (dd, *J* = 8.3, 7.0 Hz, 1H), 7.33 – 7.27 (m, 2H), 6.02 – 5.80 (m, 1H), 5.41 (s, 1H), 5.27 – 5.11 (m, 2H), 3.45 – 3.34 (m, 4H), 2.81 – 2.57 (m, 2H), 2.19 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 146.73, 145.91, 139.64, 135.47, 135.10, 135.08, 130.20, 128.92, 128.02, 127.92, 124.65, 119.33, 119.02, 118.98, 118.24, 70.55, 42.96, 30.66, 30.03.

3.4.2. General Procedure for Syntheses of Racemic Acrylate Esters

A solution of alcohol (1 eq.) in 7 ml of CH_2Cl_2 was cooled down to 0 ºC, then acryloyl chloride (1.5 eq.) and triethyl amine (3 eq.) were added sequentially. The mixture was allowed to warm to room temperature and stirred until alcohols were consumed under nitrogen atmosphere. The final mixture was poured into water and extracted with CH_2Cl_2. Combined organic phase concentrated under vacuum and purification of crude product by column chromatography on silica gel (EtOAc: Hexane, 1:10) gave the corresponding acrylate ester.

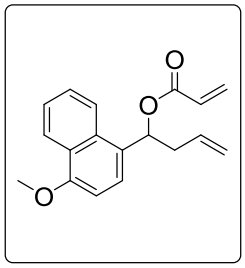
3.4.2.1. 1-(4-(dimethylamino)naphthalen-1-yl)but-3-en-1-yl acrylate (70)



1-(4-(dimethylamino)naphthalen-1-yl)but-3-en-1-yl acrylate. Purification was not performed. It was used without further purification in next step.

Rf: 0.52 (1:6, EtOAc:Hexane)

3.4.2.2. 1-(4-methoxynaphthalen-1-yl)but-3-en-1-yl acrylate (74)



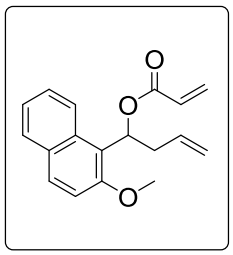
Purification of crude product by column chromatography yielded 348 mg of 1-(4-methoxynaphthalen-1-yl)but-3-en-1-yl acrylate as white solid with 73% yield.

Rf: 0.49 (1:8, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 8.4 Hz, 1H), 8.13 (d, *J* = 8.4 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8, 1.5 Hz, 1H), 7.52 – 7.47 (m, 2H), 6.80 (d, *J* = 8.0 Hz, 1H), 6.63 – 6.55 (m, 1H), 6.44 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.19 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.87 – 5.71 (m, 2H), 5.15 – 5.02 (m, 2H), 4.00 (s, 3H), 2.88 – 2.81 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.58, 155.64, 133.84, 131.63, 130.89, 128.83, 127.81, 126.97, 126.00, 125.16, 124.70, 123.20, 122.89, 117.97, 103.19, 72.89, 55.65, 40.34.

3.4.2.3. 1-(2-methoxynaphthalen-1-yl)but-3-en-1-yl acrylate (78)

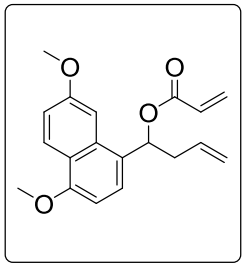


Purification of crude product by column chromatography yielded 420 mg of 1-(2-methoxynaphthalen-1-yl)but-3-en-1-yl acrylate as white solid, with 90% yield.
Rf: 0.43 (1:8, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.44 (d, *J* = 8.4 Hz, 1H), 7.82 – 7.76 (m, 2H), 7.52 – 7.45 (m, 1H), 7.38 – 7.32 (m, 1H), 7.27 (d, *J* = 8.8 Hz, 1H), 6.97 (dd, *J* = 8.3, 6.8 Hz, 1H), 6.39 (dd, *J* = 17.3, 1.3 Hz, 1H), 6.15 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.87 – 5.74 (m, 2H), 5.12 – 4.98 (m, 2H), 3.99 (s, 3H), 3.15 – 3.04 (m, 1H), 2.88 – 2.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.59, 155.04, 134.19, 132.14, 130.59, 130.43, 129.93, 128.95, 128.92, 126.41, 124.87, 123.51, 120.77, 117.49, 114.00, 69.97, 57.30, 39.16.

3.4.2.4. 1-(4,7-dimethoxynaphthalen-1-yl)but-3-en-1-yl acrylate (88)



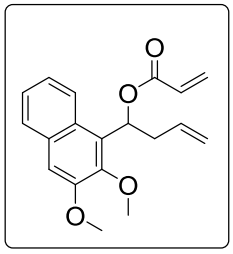
Purification of crude product by column chromatography yielded 56 mg of 1-(4,7-dimethoxynaphthalen-1-yl)but-3-en-1-yl acrylate as white solid with 82% yield.

Rf: 0.45 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, *J* = 9.2 Hz, 1H), 7.47 (d, *J* = 8.1 Hz, 1H), 7.41 (d, *J* = 2.5 Hz, 1H), 7.14 (dd, *J* = 9.2, 2.5 Hz, 1H), 6.67 (d, *J* = 8.1 Hz, 1H), 6.57 – 6.51 (m, 1H), 6.44 (dd, *J* = 17.3, 1.5 Hz, 1H), 6.17 (dd, *J* = 17.3, 10.4 Hz, 1H), 5.87 – 5.74 (m, 2H), 5.17 – 5.10 (m, 1H), 5.10 – 5.04 (m, 1H), 3.98 (s, 3H), 3.94 (s, 3H), 2.91 – 2.82 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.70, 158.49, 155.87, 133.93, 133.24, 130.97, 128.80, 126.35, 125.57, 124.56, 121.04, 118.00, 117.18, 102.43, 101.35, 72.82, 55.58, 55.42, 39.74.

3.4.2.5. 1-(2,3-dimethoxynaphthalen-1-yl)but-3-en-1-yl acrylate (89)



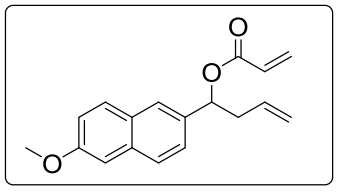
Purification of crude product by column chromatography yielded 270 mg of 1-(2,3-dimethoxynaphthalen-1-yl)but-3-en-1-yl acrylate as white solid 97% yield.

Rf: 0.41 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (dd, *J* = 5.4, 4.4 Hz, 1H), 7.74 – 7.69 (m, 1H), 7.41 – 7.34 (m, 2H), 7.14 (s, 1H), 6.89 (dd, *J* = 8.4, 6.8 Hz, 1H), 6.41 (d, *J* = 17.4 Hz, 1H), 6.16 (dd, *J* = 17.4, 10.3 Hz, 1H), 5.87 – 5.75 (m, 2H), 5.12 – 5.00 (m, 2H), 4.03 (s, 3H), 3.98 (s, 3H), 3.15 – 3.05 (m, 1H), 2.87 – 2.77 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.57, 151.72, 147.54, 133.93, 131.95, 130.85, 128.76, 127.62, 127.05, 126.64, 125.11, 125.08, 124.03, 117.84, 107.99, 70.62, 61.24, 55.69, 39.40.

3.4.2.6. 1-(6-methoxynaphthalen-2-yl)but-3-en-1-yl acrylate (90)



Purification of crude product by column chromatography yielded 455 mg of 1-(6-methoxynaphthalen-2-yl)but-3-en-1-yl acrylate as colourless oil with 84% yield.

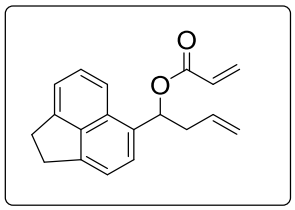
Rf: 0.52 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 – 7.70 (m, 3H), 7.46 (dd, *J* = 8.4, 1.7 Hz, 1H), 7.16 (dd, *J* = 8.9, 2.5 Hz, 1H), 7.13 (d, *J* = 2.4 Hz, 1H), 6.44 (dd, *J* = 17.3, 1.5 Hz,

1H), 6.18 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.07 – 6.00 (m, 1H), 5.83 (dd, *J* = 10.4, 1.5 Hz, 1H), 5.81 – 5.68 (m, 1H), 5.15 – 5.01 (m, 2H), 3.92 (s, 3H), 2.86 – 2.75 (m, 1H), 2.75 – 2.65 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.55, 158.05, 135.16, 134.44, 133.42, 130.91, 129.68, 128.81, 128.71, 127.25, 125.84, 125.05, 119.18, 118.23, 105.84, 75.70, 55.45, 40.76.

3.4.2.7. 1-(1,2-dihydroacenaphthylen-5-yl)but-3-en-1-yl acrylate (91)



Purification of crude product by column chromatography yielded 173 mg of 1-(1,2-dihydroacenaphthylen-5-yl)but-3-en-1-yl acrylate as light yellow oil with 80% yield.

Rf: 0.65 (1:6, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (d, *J* = 8.4 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.31 (d, *J* = 6.9 Hz, 1H), 7.27 (d, *J* = 7.7 Hz, 1H), 6.54 (t, *J* = 6.8 Hz, 1H), 6.45 (d, *J* = 17.3 Hz, 1H), 6.24 – 6.14 (m, 1H), 5.86 – 5.74 (m, 2H), 5.13 (d, *J* = 17.1 Hz, 1H), 5.06 (d, *J* = 10.2 Hz, 1H), 3.44 – 3.33 (m, 4H), 2.95 – 2.78 (m, 2H).

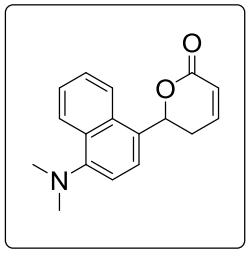
^{13}C NMR (100 MHz, $CDCl_3$) δ 165.57, 146.70, 146.60, 139.67, 133.78, 131.67, 130.92, 129.10, 128.77, 128.19, 126.06, 119.46, 119.29, 118.89, 118.01, 73.24, 40.29, 30.60, 30.10.

3.4.3. General Procedure for Ring Closing Metathesis Reactions of Racemic Acrylate Esters

To a solution of acrylate ester in CH_2Cl_2 (0.01 M) was heated to 45 ºC, and 1st Generation Grubbs' catalyst (10%) in CH_2Cl_2 (0.01 M) was added to the solution. The resulting mixture was heated at reflux until all starting material consumed. At the end of the reaction, solution was cooled down to room temperature and concentrated under

vacua. Purification of crude product by column chromatography on silica gel (EtOAc:Hexane, 1:5 →1:3) furnished the corresponding 5,6-dihydro-2*H*-pyran-2-one.

3.4.3.1. 6-(4-(dimethylamino)naphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (92)



Purification of crude product by column chromatography yielded 65 mg of 6-(4-(dimethylamino)naphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as yellow jelly compound with 45% yield (overall yield from alcohol).

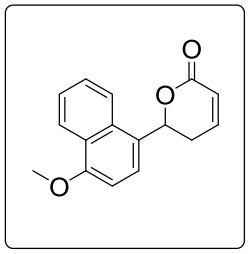
Rf: 0.31 (1:2, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.34 – 8.24 (m, 1H), 7.99 – 7.89 (m, 1H), 7.62 – 7.45 (m, 3H), 7.10 – 6.97 (m, 2H), 6.24 – 6.08 (m, 2H), 2.92 – 2.89 (m, 4H), 2.89 – 2.73.

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.66, 151.96, 145.49, 131.58, 129.11, 128.09, 126.57, 125.40, 125.16, 124.63, 123.14, 121.83, 113.39, 77.07, 45.31, 31.09.

HRMS : $C_{17}H_{17}NO_2Na$ found as $[M+Na]^+$: 290.1158 (Calculated for $[M+Na]^+$: 290.1157)

3.4.3.2. 6-(4-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (75)



Purification of crude product by column chromatography yielded 272 mg of 6-(4-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 86% yield.

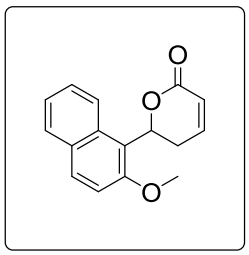
Rf: 0.29 (1:2, EtOAc:Hexane);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.37 – 8.32 (m, 1H), 7.94 (d, *J* = 8.4 Hz, 1H), 7.61 – 7.45 (m, 3H), 7.07 – 6.98 (m, 1H), 6.81 (d, *J* = 8.1 Hz, 1H), 6.22 – 6.17 (m, 1H), 6.10 (dd, *J* = 11.8, 4.2 Hz, 1H), 4.01 (s, 3H), 2.90 – 2.79 (m, 1H), 2.78 – 2.69 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.64, 156.11, 145.50, 131.28, 127.22, 125.98, 125.86, 125.30, 124.87, 123.09, 122.59, 121.76, 103.14, 77.04, 55.71, 31.08.

HRMS : $C_{16}H_{14}O_3Na$ found as $[M+Na]^+$: 277.0832 (Calculated for $[M+Na]^+$: 277.0841)

3.4.3.3. 6-(2-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (79)



Purification of crude product by column chromatography yielded 290 mg of 6-(2-methoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 81% yield.

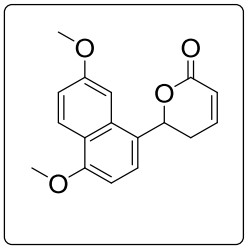
Rf: 0.26 (1:2, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, *J* = 8.7 Hz, 1H), 7.85 (d, *J* = 9.1 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.50 – 7.43 (m, 1H), 7.38 – 7.32 (m, 1H), 7.26 (d, *J* = 9.1 Hz, 1H), 7.05 (ddd, *J* = 9.9, 6.2, 2.0 Hz, 1H), 6.54 (dd, *J* = 13.2, 4.3 Hz, 1H), 6.20 (dd, *J* = 9.8, 2.8 Hz, 1H), 3.94 (s, 3H), 3.31 – 3.20 (m, 1H), 2.49 – 2.40 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.94, 154.92, 146.32, 132.15, 131.35, 129.75, 129.01, 126.88, 124.47, 123.75, 121.48, 118.04, 113.18, 73.62, 56.85, 29.53.

HRMS : $C_{16}H_{14}O_3Na$ found as $[M+Na]^+$: 277.0845 (Calculated for $[M+Na]^+$: 277.0841)

3.4.3.4. 6-(4,7-dimethoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (93)



Purification of crude product by column chromatography yielded 38 mg of 6-(4,7-dimethoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 97% yield.

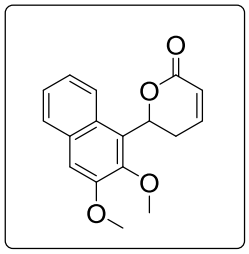
Rf: 0.22 (1:2, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 9.2 Hz, 1H), 7.53 (d, *J* = 8.1 Hz, 1H), 7.22 (d, *J* = 2.4 Hz, 1H), 7.16 (dd, *J* = 9.2, 2.5 Hz, 1H), 7.04 (ddd, *J* = 9.7, 6.0, 2.4 Hz, 1H), 6.69 (d, *J* = 8.1 Hz, 1H), 6.23 – 6.16 (m, 1H), 6.02 (dd, *J* = 11.9, 3.9 Hz, 1H), 3.99 (s, 3H), 3.92 (s, 3H), 2.94 – 2.82 (m, 1H), 2.78 – 2.67 (m, 1H);

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.65, 158.68, 156.36, 145.54, 132.91, 125.82, 124.86, 124.64, 121.80, 121.12, 116.77, 102.54, 101.36, 77.23, 55.66, 55.50, 30.64.

HRMS : $C_{17}H_{16}O_4$ found as 284.1061 (Calculated: 284.0849)

3.4.3.5. 6-(2,3-dimethoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (94)



Purification of crude product by column chromatography yielded 187 mg of 6-(2,3-dimethoxynaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 82% yield.

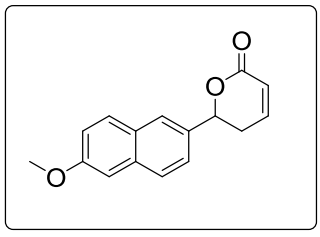
Rf: 0.28 (1:2, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, *J* = 8.2 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.43 – 7.33 (m, 2H), 7.20 (s, 1H), 7.06 (ddd, *J* = 9.8, 6.2, 1.9 Hz, 1H), 6.43 (dd, *J* = 13.2, 4.3 Hz, 1H), 6.22 (dd, *J* = 9.9, 2.8 Hz, 1H), 4.00 (s, 3H), 3.94 (s, 3H), 3.34 – 3.23 (m, 1H), 2.51 – 2.41 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.61, 151.53, 147.94, 146.17, 131.90, 127.72, 126.57, 125.46, 124.93, 124.61, 124.50, 121.43, 108.80, 74.23, 61.85, 55.80, 29.92.

HRMS : $C_{17}H_{17}O_4$ found as $[M+H]^+$: 285.1128 (Calculated for $[M+H]^+$: 285.1127)

3.4.3.6. 6-(6-methoxynaphthalen-2-yl)-5,6-dihydro-2*H*-pyran-2-one (95)



Purification of crude product by column chromatography yielded 332 mg of 6-(6-methoxynaphthalen-2-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 85% yield.

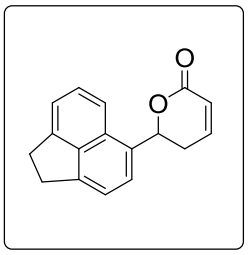
Rf: 0.25 (1:2, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 – 7.70 (m, 3H), 7.46 (dd, *J* = 8.5, 1.8 Hz, 1H), 7.20 – 7.10 (m, 2H), 6.98 (ddd, *J* = 9.8, 5.8, 2.6 Hz, 1H), 6.19 – 6.13 (m, 1H), 5.58 (dd, *J* = 11.4, 4.5 Hz, 1H), 3.92 (s, 3H), 2.79 – 2.60 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.28, 158.30, 145.03, 134.67, 133.64, 129.71, 128.64, 127.51, 125.28, 124.32, 121.87, 119.49, 105.87, 79.55, 55.47, 31.79.

HRMS : $C_{16}H_{14}O_3Na$ found as $[M+Na]^+$: 277.0849 (Calculated for $[M+Na]^+$: 277.0841)

3.4.3.7. 6-(1,2-dihydroacenaphthylen-5-yl)-5,6-dihydro-2*H*-pyran-2-one (96)



Purification of crude product by column chromatography yielded 109 mg of 6-(1,2-dihydroacenaphthylen-5-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 80%.

Rf: 0.33 (1:2, EtOAc:Hexane);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 – 7.65 (m, 1H), 7.63 – 7.57 (m, 1H), 7.52 – 7.45 (m, 1H), 7.36 – 7.27 (m, 2H), 7.07 – 6.99 (m, 1H), 6.24 – 6.17 (m, 1H), 6.12 – 6.04 (m, 1H), 3.41 (s, 4H), 2.93 – 2.67 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.62, 147.36, 146.96, 145.46, 139.60, 129.86, 128.49, 126.04, 121.79, 119.70, 118.99, 118.98, 118.61, 77.33, 31.26, 30.65, 30.15.

HRMS : $C_{17}H_{14}O_2Na$ found as $[M+Na]^+$: 273.0891 (Calculated for $[M+Na]^+$: 273.0891)

3.5. Asymmetric Synthesis of 6-methyl-5,6-dihydro-2*H*-pyran-one Derivatives

3.5.1. General Procedures for Synthesis of Asymmetric Homoallylic Alcohols Starting From Ketones

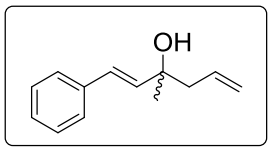
Method 1

In a two necked round bottom flask, R-Tol-BINAP (0.05 eq.) and AgF (0.05 eq.) were dissolved in 2 mL of anhydrous methanol. Solution was stirred about 10 minutes under nitrogen atmosphere at room temperature, and the solution was hold under vacuum without expose of light and excess solvent was removed. Then, formed crystals were cooled down to - 70 ^{o}C. After that, 1 eq. of methanol and 3 mL of THF was added, and stirred about 10 minutes. To reaction mixture, 2 eq. of allyltrimethoxysilane and 1 eq. of ketone were added. Reaction was stirred about 18 h at-70 ^{o}C. Then resulting mixture was filtered through celite-silica gel mixture to remove catalyst and washed with diethyl ether. After removing excess solvent, purification of crude product by column chromatography on silica gel (1:16, EtOAc:Hexane) furnished corresponding homoallylic alcohol.

Method 2:

A mixture of CuCl (0.15 eq.), *R*-Tol-BINAP (0.15 eq.) and TBAT (0.15 eq.) in THF (2 mL) was dissolved in THF and stirred under nitrogen atmosphere for 1 h at room temperature. After cooling in an ice bath, allyltrimethoxysilane (1.2 eq.) and ketone (1 eq.) were added and then the cooling bath was removed. After the starting material disappeared on TLC, 2 N HCl aq. in MeOH (1:1) was added for desilylation and extracted with ethyl acetate and washed with brine solution. Collected organic phase was dried over magnesium sulphate and excess solvent removed. Purification of crude product by column chromatography on silica gel (1:16, EtOAc:Hexane) furnished corresponding homoallylic alcohol.

3.5.1.1. (+,*E*)-3-methyl-1-phenylhexa-1,5-dien-3-ol (103) Method 1



Purification of crude product by column chromatography on silica gel furnished 168 mg (+,*E*)-3-methyl-1-phenylhexa-1,5-dien-3-ol as colourless oil with 89% yield.

Rf: 0.29 (1:6, EtOAc-Hexane); $[\alpha]_D^{25}$ = +54 (c 1.3, $CHCl_3$);

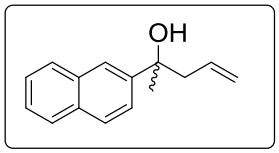
HPLC: Enantiomeric excess was found as 100% with Chiralcel OJ-H column (99:1 Hexane:Isopropanol, 0.75 mL/min, 280 nm, R_t = 16,940 min)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.46 – 7.41 (m, 2H), 7.40 – 7.33 (m, 2H), 7.31 – 7.27 (m, 1H), 6.65 (d, *J* = 16.1 Hz, 1H), 6.35 (dd, *J* = 16.1, 1.0 Hz, 1H), 5.95 – 5.83 (m, 1H), 5.24 (d, *J* = 0.8 Hz, 1H), 5.20 (dd, *J* = 6.6, 1.1 Hz, 1H), 2.50 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.41 (dd, *J* = 13.6, 8.2 Hz, 1H), 1.92 (s, 1H), 1.44 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 137.02, 136.32, 133.68, 128.69, 127.54, 127.54, 126.54, 119.48, 72.47, 47,46, 28.11.

IR: 3553, 3382, 3077, 3060, 3026, 2975, 2928, 1945, 1876, 1814, 1639, 1598, 1578, 1490, 1440, 1371, 1298, 1272, 1179, 1101, 968, 914, 746, 691 cm^{-1}.

3.5.1.2. (+)-2-(naphthalen-2-yl)pent-4-en-2-ol (104) Method 1



Purification of crude product by column chromatography on silica gel furnished 194 mg (+)-2-(naphthalen-2-yl)pent-4-en-2-ol as colourless oil with 91% yield.

Rf: 0.25 (1:12, EtOAc-Hexane); $[\alpha]_D^{25}$ = +122 (c 1.8, $CHCl_3$);

HPLC: Enantiomeric excess was found as 60% with Chiralcel OJ-H column (99:1 Hexane:Isopropanol, 0.75 mL/min, 280 nm, R_{t1} = 38.766 min as major peak, R_{t2} = 44.472 min as minor peak)

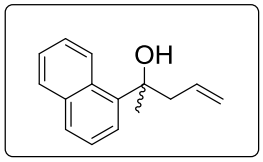
^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (s, 1H), 7.87 – 7.81 (m, 3H), 7.55 (dd, J = 8.6, 1.9 Hz, 1H), 7.52 – 7.43 (m, 2H), 5.70 – 5.57 (m, 1H), 5.17 (d, J = 17.1, 1H), 5.13

(d, J = 10.1 Hz, 1H), 2.81 (dd, J = 13.8, 6.3 Hz, 1H), 2.60 (dd, J = 13.8, 8.4 Hz, 1H), 2.21 (s, 1H), 1.65 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 145.13, 133.73, 133.32, 132.40, 128.28, 128.04, 127.61, 126.20, 125.85, 123.69, 123.34, 119.74, 73.95, 48.43, 30.09.

IR: 3407, 3056, 2976, 2929, 1638, 1600, 1505, 1429, 1375, 1272, 1188, 1118, 997, 917, 857, 818, 747 cm $^{-1}$.

3.5.1.3. (+)-2-(naphthalen-1-yl)pent-4-en-2-ol (105) Method 2



Purification of crude product by column chromatography on silica gel furnished 84 mg (+)-2-(naphthalen-1-yl)pent-4-en-2-ol as colourless oil with 40% yield.

Rf: 0.25 (1:12, EtOAc-Hexane); $[\alpha]_D^{25}$ = +27 (c 0.84, $CHCl_3$);

HPLC: Enantiomeric excess was found as 50% with Chiralcel OJ-H column (99:1 Hexane:Isopropanol, 0.75 mL/min, 280 nm, R_{t1} = 21.811 min as major peak, R_{t2} = 24.585 min as minor peak)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.77 (d, J = 8.3 Hz, 1H), 7.89 (d, J = 7.6 Hz, 1H), 7.79 (d, J = 8.2 Hz, 1H), 7.60 (dd, J = 7.4, 1.2, 1H), 7.55 – 7.46 (m, 2H), 7.46 – 7.39 (m, 1H), 5.75 – 5.61 (m, 1H), 5.20 – 5.09 (m, 2H), 3.13 (dd, J = 13.9, 6.8 Hz, 1H), 2.84 (dd, J = 13.9, 7.9 Hz, 1H), 2.37 (s, 1H), 1.84 (s, 3H).).

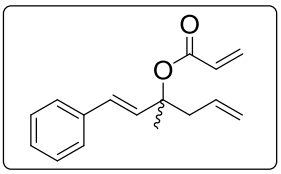
^{13}C NMR (100 MHz, $CDCl_3$) δ 142.27, 135.03, 134.03, 130.91, 128.28, 129.34, 128.73, 126.92, 125.45, 125.25, 124.91, 123.82, 119.42, 75.37, 47.37, 29.75.

IR**:** 3216, 3051, 2975, 2849, 1677, 1639, 1598, 1508, 1373, 1273, 1130, 1105, 1064, 925, 913, 804, 780 cm $^{-1}$.

3.5.2. General Procedure for Conversion of Homoallylic Alcohols (103-105) to Acrylate Esters (106-108)

A solution of alcohol (1 eq.) in 7 - 10 mL of CH_2Cl_2 was dissolved and cooled down to 0 ºC, and then acryloyl chloride (2 eq.) and triethyl amine (4 eq.) were added sequentially. The mixture was allowed to warm to room temperature and stirred up to 22 - 26 h under nitrogen atmosphere. The final mixture was poured into water and extracted with CH_2Cl_2. Combined organic phase concentrated under vacuum and purification of crude product by column chromatography on silica gel (1:10, EtOAc:Hexane) gave corresponding acrylate ester.

3.5.2.1. (+,*E*)-3-methyl-1-phenylhexa-1,5-dien-3-yl acrylate (106)



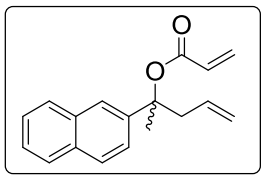
Purification of crude product by column chromatography on silica gel furnished 97 mg (+,*E*)-3-methyl-1-phenylhexa-1,5-dien-3-yl acrylate as colourless oil with 32% yield.

Rf: 0.65 (1:6, EtOAc-Hexane); $[\alpha]_D^{24}$ = +10 (c 0.97, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 – 7.37 (m, 2H), 7.34 – 7.28 (m, 2H), 7.27 – 7.20 (m, 1H), 6.56 (d, J = 16.3 Hz, 1H), 6.44 (d, J = 16.3 Hz, 1H), 6.35 (dd, J = 17.3, 1.6 Hz, 1H), 6.09 (dd, J = 17.3 Hz, 10.4 Hz, 1H), 5.87 – 5.74 (m, 2H), 5.18 – 5.07 (m, 2H), 2.79 – 2.71 (m, 2H), 1.68 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.05, 136.77, 132.92, 132.90, 130.08, 129.91, 129.11, 128.66, 127.80, 126.70, 118.87, 82.51, 44.55, 24.11.

3.5.2.2. (-)-2-(naphthalen-2-yl)pent-4-en-2-yl acrylate (107)



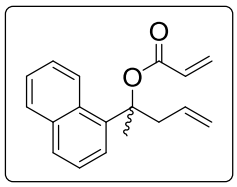
Purification of crude product by column chromatography on silica gel furnished 140 mg (-)-2-(naphthalen-2-yl)pent-4-en-2-yl acrylate as colourless oil with 58% yield.

Rf: 0.55 (1:6, EtOAc-Hexane); $[\alpha]_D^{24}$ = -22 (c 1.27, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.77 (m, 4H), 7.51 – 7.43 (m, 3H), 6.39 (dd, J = 17.3, 1.5 Hz, 1H), 6.18 (dd, J = 17.3, 10.3 Hz, 1H), 5.82 (dd, J = 10.3, 1.5 Hz, 1H), 5.73 – 5.60 (m, 1H), 5.10 (d, J = 10.6 Hz, 1H), 5.06 (d, J = 2.9 Hz, 1H), 2.99 (dd, J = 13.9, 7.1 Hz, 1H), 2.88 (dd, J = 13.9, 7.3 Hz, 1H), 1.97 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.86, 141.96, 133.19, 132.82, 132.59, 130.41, 129.78, 128.38, 128.21, 127.64, 126.22, 126.01, 123.62, 123.12, 118.97, 83.61, 46.71, 24.92.

3.5.2.3. (-)-2-(naphthalen-1-yl)pent-4-en-2-yl acrylate (108)



Purification of crude product by column chromatography on silica gel furnished 140 mg (-)-2-(naphthalen-1-yl)pent-4-en-2-yl acrylate as colourless oil with 60% yield.

Rf: 0.54 (1:6, EtOAc-Hexane); $[\alpha]_D^{24}$ = -70 (c 0.37, CH_2Cl_2);

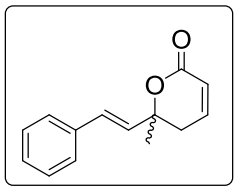
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.53 – 8.47 (m, 1H), 7.89 – 7.84 (m, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.54 (dd, *J* = 7.4, 1.2 Hz, 1H), 7.49 – 7.41 (m, 3H), 6.31 (dt, *J* = 17.3, 1.5 Hz, 1H), 6.13 (dd, *J* = 17.3, 10.3 Hz, 1H), 5.78 – 5.64 (m, 2H), 5.13 – 5.06 (m, 2H), 3.32 (dd, *J* = 13.8, 7.4 Hz, 1H), 2.98 (dd, *J* = 13.8, 7.0 Hz, 1H), .

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.38, 139.33, 134.84, 133.08, 130.45, 130.28, 129.70, 129.36, 129.03, 125.85, 125.50, 125.22, 124.98, 124.13, 118.84, 84.55, 45.59, 25.44.

3.5.3. General Procedure for Ring Closing Metathesis Reactions of Acrylate Ester

To a solution of acrylate ester (1 eq.) in CH_2Cl_2 (0.01 M) was heated to 45 ^oC, and 1st Generation Grubbs' catalyst (0.1 eq.) in CH_2Cl_2 (0.01 M) was added. The resulting mixture was heated at reflux for 5 - 24 hours. At the end of the reaction, mixture was cooled down to room temperature and concentrated under vacuum. Purification of crude product by column chromatography on silica gel (1:6 → 1:4 EtOAc/Hexane) furnished corresponding 5,6-dihydro-2*H*-pyran-2-one.

3.5.3.1. (+,*E*)-6-methyl-6-styryl-5,6-dihydro-2*H*-pyran-2-one (97)



Purification of crude product by column chromatography on silica gel furnished 22 mg (+,*E*)-6-methyl-6-styryl-5,6-dihydro-2*H*-pyran-2-one as white solid with 26% yield.

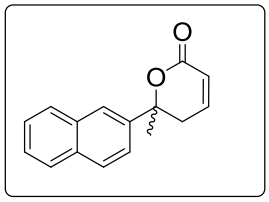
Rf: 0.16 (1:6, EtOAc-Hexane); $[\alpha]_D^{24}$ = +32 (c 0.44, CH_2Cl_2);

HPLC: Enantiomeric excess was found as 20% with Chiralcel OJ-H column (95:5 Hexane:Isopropanol, 0.75 mL/min, 280 nm, R_{t1} = 36.268 min as major peak ve R_{t2} = 40.270 min as minor peak)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38 – 7.29 (m, 4H), 7.28 – 7.22 (m, 1H), 6.78 (dt, J = 9.8, 4.3 Hz, 1H), 6.61 (d, J = 16.1 Hz, 1H), 6.21 (d, J = 16.1 Hz, 1H), 6.06 (dt, J = 9.8 Hz, 1.9 Hz, 1H), 2.66 – 2.62 (m, 2H), 1.62 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.01, 143.24, 135.99, 131.55, 129.86, 128.77, 128.18, 126.66, 121.67, 81.57, 34.90, 27.87.

3.5.3.2. (+)-6-methyl-6-(naphthalen-2-yl)-5,6-dihydro-2*H*-pyran-2-one (98)



Purification of crude product by column chromatography on silica gel furnished 103 mg (+)-6-methyl-6-(naphthalen-2-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 90% yield.

Rf: 0.13 (1:6, EtOAc-Hexane); $[\alpha]_D^{25}$ = +97 (c 0.44, CH_2Cl_2);

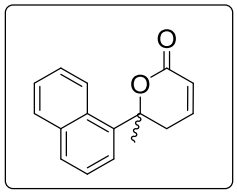
HPLC: Enantiomeric excess was found as 60% with Chiralcel OJ-H column (95:5 Hexane:Isopropanol, 0.75 mL/min, 280 nm, R_{t1} = 58.675 min as major peak ve R_{t2} = 69.842 min as minor peak)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.80 (m, 4H), 7.53 – 7.44 (m, 3H), 6.80 – 6.74 (m, 1H), 6.03 (dd, *J* = 9.8 Hz, 1.5, 1H), 3.12 - 3.01 (m, 1H), 2.93 – 2.84 (m, 1H), 1.81 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.07, 143.56, 141.24, 133.05, 132.63, 128.62, 128.34, 127.61, 126.65, 126.45, 123.58, 122.71, 121.98, 83.40, 35.47, 30.18.

HRMS : $C_{16}H_{14}NaO_2$ found as $[M+Na]^+$: 261.0883 (Calculated for $[M+Na]^+$: 261.0891)

3.5.3.3. (-)-6-methyl-6-(naphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one (99)



Purification of crude product by column chromatography on silica gel furnished 101 mg (-)-6-methyl-6-(naphthalen-2-yl)-5,6-dihydro-2*H*-pyran-2-one as white solid with 94% yield.

Rf: 0.13 (1:6, EtOAc-Hexane); $[\alpha]_D^{25}$ = -113 (c 1.01, CH_2Cl_2);

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.1, 1H), 7.74 - 7.54 (m, 2H), 7.37 – 7.15 (m, 4H), 6.66 (dd, *J* = 9.5, 4.1 Hz, 1H), 5.83 (d, *J* = 9.8 Hz, 1H), 3.18 (d, *J* = 18.7 Hz, 1H), 2.66 (d, *J* = 18.7, 1H), 1.85 (s, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 163.54, 144.26, 137.65, 135.02, 130.39, 129.75, 129.48, 126.21, 126.01, 125.52, 124.51, 123.99, 121.32, 84.97, 35.34, 28.54.

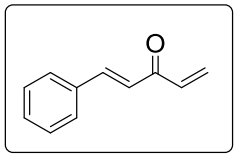
HRMS : $C_{16}H_{14}NaO_2$ found as $[M+Na]^+$: 261.0885 (Calculated for $[M+Na]^+$: 261.0891)

3.6. Racemic Syntheses of α,β-Unsaturated-γ-Lactones

3.6.1. General Procedure for Direct α-Methylenation Reaction of Ketones

Ketone (1 eq.) and paraformaldehyde (2 eq.) was dissolved in 50 mL of dry THF. To mixture, catalyst (1 eq.) and TFA (0.5 eq.) were added. Resulting mixture was heated at reflux 2 hours, and then cooled down to room temperature. At this stage paraformaldehyde (2 eq.) was added aditionally. Reaction mixture was heated at reflux about 72 hours. After cooling room tempetrature excess solvent was removed, and dissolved in diethyl ether. Final mixture was washed with 1 M HCl, 1 M NaOH and brine sequentially. Organic phase dried over with magnesium sulphate and excess solvent was removed. Purification of crude product by column chromatography on silica gel (EtOAc: Hexane, 1:12) gave the corresponding α,β-unsaturated ketone.

3.6.1.1. (*E*)-1-phenylpenta-1,4-dien-3-one (113)



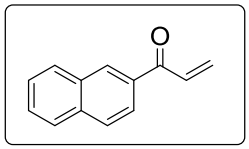
Purification of crude product by column chromatography on silica gel gave 60 mg of (*E*)-1-phenylpenta-1,4-dien-3-one with 40% yield.

Rf: 0.43 (1:6, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, *J* = 16.0 Hz, 1H), 7.56 (dd, *J* = 6.4, 3.1 Hz, 2H), 7.42 – 7.35 (m, 3H), 7.03 – 6.95 (m, 1H), 6.75 – 6.64 (m, 1H), 6.36 (d, *J* = 17.4 Hz, 1H), 5.86 (d, *J* = 10.7 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 189.47, 143.92, 135.42, 134.60, 130.55, 128.93, 128.54, 128.34, 124.11, 124.09.

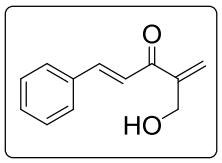
3.6.1.2. 1-(naphthalen-2-yl)prop-2-en-1-one (115)



Purification of crude product by column chromatography on silica gel gave 1.3 mg of 1-(naphthalen-2-yl)prop-2-en-1-one with 3% yield.

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.04 (d, *J* = 8.7 Hz, 1H), 7.98 (d, *J* = 7.5 Hz, 1H), 7.95 – 7.87 (m, 2H), 7.65 – 7.53 (m, 2H), 7.33 (dd, *J* = 16.9, 10.4 Hz, 1H), 6.51 (d, *J* = 17.1, 1H), 5.99 (d, *J* = 10.6 Hz, 1H).

3.6.1.3. (*E*)-4-(hydroxymethyl)-1-phenylpenta-1,4-dien-3-one (114)



Purification of crude product by column chromatography on silica gel furnished (*E*)-4-(hydroxymethyl)-1-phenylpenta-1,4-dien-3-one as side product with 44% yield.

Rf: 0.24 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 15.7, 4.1 Hz, 1H), 7.50 (q, *J* = 4.2 Hz, 2H), 7.31 (q, *J* = 4.6, 3.5 Hz, 3H), 7.25 – 7.17 (m, 1H), 6.14 (s, 1H), 6.05 (d, *J* = 1.7 Hz, 1H), 4.40 (s, 2H), 3.52 (s, 1H).

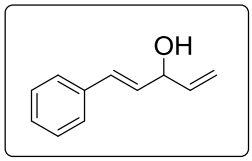
^{13}C NMR (100 MHz, $CDCl_3$) δ 191.49, 147.93, 144.22, 134.49, 130.48, 128.82, 128.34, 124.36, 121.11, 62.08, 62.04.

HRMS: $[M+Na]^+$: $C_{12}H_{12}NaO_2$ found as: 211.0719 (Calculated for $[M+Na]^+$: 211.0735)

3.6.2. General Procedure for Luche Reduction Reaction

α,β-unsaturated ketone (1 eq.) and $Ce(NO_3)_3.6H_2O$ (1.3 eq.) were added and stirred into 5 mL of methanol. Mixture was cooled down to 0 ^oC, $NaBH_4$ (3 eq.) was added, and stirred about 45 minutes. To the reaction mixture, 10 mL of saturated Na_2SO_4 was added and extracted with CH_2Cl_2. After removing excess solvent under vacuum, purification of crude product by column chromatography on silica gel (EtOAc: Hexane, 1:8) gave the corresponding alcohol.

3.6.2.1. (*E*)-1-phenylpenta-1,4-dien-3-ol (116)



Purification of crude product by column chromatography on silica gel gave 18 mg of (*E*)-1-phenylpenta-1,4-dien-3-ol as light yellow oil with 90% yield.

Rf: 0.21 (1:8, EtOAc:Hexane)

^1H NMR (400 MHz, $CDCl_3$) δ 7.45 – 7.39 (m, 2H), 7.38 – 7.32 (m, 2H), 7.31 – 7.25 (m, 1H), 6.64 (d, *J* = 16.0 Hz, 1H), 6.27 (dd, *J* = 16.0, 6.4 Hz, 1H), 6.07 – 5.94 (m, 1H), 5.37 (dd, *J* = 17.2, 1.3 Hz, 1H), 5.23 (dd, *J* = 10.4, 1.3 Hz, 1H), 4.88 – 4.77 (m, 1H), 2.41 (s, 1H).

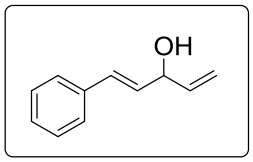
^{13}C NMR (100 MHz, $CDCl_3$) δ 139.34, 136.64, 130.80, 130.45, 128.63, 127.81, 126.61, 115.43, 73.81.

3.6.3. General Procedure for Syntheses of Allylic Alcohols

Aldehyde (1 eq.) was dissolved in 5 mL of dry THF and the olution was cooled down to -20 ^oC. After that, vinyl magnesium bromide (1.1 eq.; 1 M solution in THF) was added to the solution slowly. Reaction was controlled with TLC. After 2 hours reaction was quenched with 1 mL of water and 1 mL of 1 M HCl solution. Mixture was extracted with diethyl ether, and excess solvent was removed under vacuum.

Purification of crude product by column chromatography on silica gel (EtOAc: Hexane, 1:8) gave the corresponding allyllic alcohol.

3.6.3.1. *(E)*-1-phenylpenta-1,4-dien-3-ol (116)



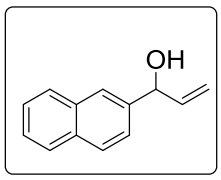
Purification of crude product by column chromatography on silica gel gave 157 mg of (*E*)-1-phenylpenta-1,4-dien-3-ol as light yellow oil with 98% yield.

Rf: 0.21 (1:8, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.44 - 7.39 (m, 2H), 7.39 - 7.32 (m, 2H), 7.26 (d, *J* = 6.8 Hz, 1H), 6.63 (d, *J* = 15.9 Hz, 1H), 6.25 (dd, *J* = 15.9, 6.4 Hz, 1H), 6.05 – 5.93 (m, 1H), 5.35 (d, *J* = 17.2 Hz, 1H), 5.21 (d, *J* = 10.4 Hz, 1H), 4.82 (t, *J* = 6.0 Hz, 1H), 1.93 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.34, 136.64, 130.80, 130.45, 128.63, 127.81, 126.61, 115.43, 73.81.

3.6.3.2. 1-(naphthalen-2-yl)prop-2-en-1-ol (118)



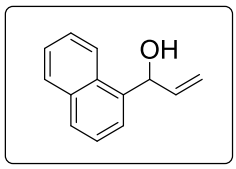
Purification of crude product by column chromatography on silica gel gave 164 mg of 1-(naphthalen-2-yl)prop-2-en-1-ol as colourless oil with 89% yield.

Rf: 0.32 (1:6, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.82 (m, 4H), 7.52 – 7.47 (m, 3H), 6.13 (ddd, *J* = 17.1, 10.3, 6.0 Hz, 1H), 5.42 (dt, *J* = 17.1, 1.4 Hz, 1H), 5.37 (d, *J* = 5.7 Hz, 1H), 5.25 (dt, *J* = 10.3, 1.3 Hz, 1H), 2.29 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 140.22, 140.03, 133.41, 133.10, 128.45, 128.12, 127.79, 126.28, 126.08, 125.04, 124.62, 115.52, 75.54.

3.6.3.3. 1-(naphthalen-1-yl)prop-2-en-1-ol (119)



Purification of crude product by column chromatography on silica gel gave 168 mg of 1-(naphthalen-1-yl)prop-2-en-1-ol as colourless oil with 91% yield.

Rf: 0.34 (1:6, EtOAc:Hexane)

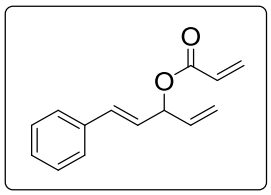
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.19 (d, *J* = 7.8 Hz, 1H), 7.91 – 7.86 (m, 1H), 7.82 (d, *J* = 8.1 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.57 – 7.44 (m, 3H), 6.26 (ddd, *J* = 16.8, 10.4, 5.4 Hz, 1H), 5.94 (d, *J* = 4.6 Hz, 1H), 5.48 – 5.42 (m, 1H), 5.31 – 5.26 (m, 1H), 2.17 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 139.79, 138.22, 134.10, 130.85, 128.94, 128.65, 126.23, 125.79, 125.56, 124.07, 123.89, 115.76, 72.43.

3.6.4. General Procedure for Syntheses of Acrylate Esters

A solution of alcohol (1 eq.) in 7 ml of CH_2Cl_2 was cooled down to 0 ºC, then acryloyl chloride (2 eq.) and triethyl amine (4 eq.) were added sequentially. The mixture was allowed to warm to room temperature and stirred until alcohols were consumed under nitrogen atmosphere. The final mixture was poured into water and extracted with CH_2Cl_2. Combined organic phase concentrated under vacuum and purification of crude product by column chromatography on silica gel (EtOAc:Hexane, 1:10) gave the corresponding acrylate ester.

3.6.4.1. (*E*)-1-phenylpenta-1,4-dien-3-yl acrylate (120)



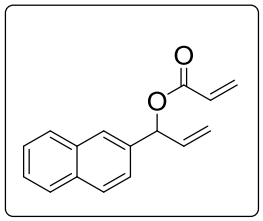
Since compound had decomposed in silica gel column, it was used without purification in next step. No % yield data is available. Crude NMR spectrum of the product is available.

Rf: 0.64 (1:6, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.43 - 7.36 (m, 2H), 7.35 – 7.28 (m, 2H), 7.28 – 7.20 (m, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.50 – 6.41 (m, 1H), 6.27 – 6.12 (m, 2H), 6.03 – 5.91 (m, 2H), 5.88 – 5.80 (m, 1H), 5.43 – 5.36 (m, 1H), 5.31 – 5.25 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.07, 136.15, 135.20, 133.24, 130.98, 128.58, 128.10, 126.67, 125.97, 117.50, 75.09.

3.6.4.2. 1-(naphthalen-2-yl)allyl acrylate (121)



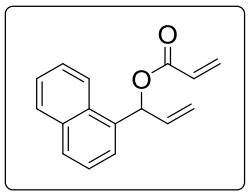
Purification of crude product by column chromatography on silica gel gave 125 mg of 1-(naphthalen-2-yl)allyl acrylate as colourless oil with 97% yield.

Rf: 0.65 (1:6, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.82 (m, 4H), 7.55 – 7.47 (m, 3H), 6.55 (d, *J* = 5.7 Hz, 1H), 6.51 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.24 (dd, *J* = 17.3, 10.4 Hz, 1H), 6.16 (ddd, *J* = 17.1, 10.5, 5.8 Hz, 1H), 5.88 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.45 – 5.29 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.24, 136.24, 133.31, 133.28, 131.25, 128.63, 128.54, 128.21, 127.80, 126.43, 126.39, 124.99, 117.36, 76.53.

3.6.4.3. 1-(naphthalen-1-yl)allyl acrylate (122)



Purification of crude product by column chromatography on silica gel gave 106 mg of 1-(naphthalen-1-yl)allyl acrylate as colourless oil with 88% yield.

Rf: 0.64 (1:6, EtAOc:Hexane)

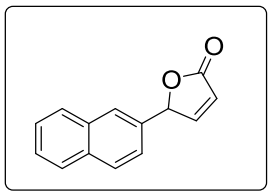
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.17 (d, *J* = 8.4 Hz, 1H), 7.87 (dd, *J* = 16.8, 8.0 Hz, 2H), 7.64 (d, *J* = 6.4 Hz, 1H), 7.58 – 7.45 (m, 3H), 7.10 (dd, *J* = 3.8, 1.5 Hz, 1H), 6.49 (dd, *J* = 17.3, 1.4 Hz, 1H), 6.30 – 6.19 (m, 2H), 5.87 (dd, *J* = 10.4, 1.4 Hz, 1H), 5.39 – 5.30 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.30, 135.96, 134.54, 134.09, 131.35, 130.89, 129.19, 128.96, 128.57, 126.47, 125.90, 125.61, 125.41, 123.95, 117.48, 73.94.

3.6.5. General Procedure for Syntheses of α,β-Unsaturated-γ-Lactones

In a two necked vessel, acrylate ester (1 eq.) was dissolved in dry CH_2Cl_2 (0.01 M final solution). Solution was heated at reflux, and first or second generation Grubbs' catalyst (0.1 eq. in CH_2Cl_2 (0.01 M final solution)) was added to the reaction mixture slowly. One piece of solution was added at the beginning of the reaction, another piece was added after one hour later. Reaction was heated at reflux until acrylate ester was consumed. At the end, reaction mixture cooled down to room temperature and solvent was removed under vacuum. Purification of crude product by column chromatography on silica gel gave the corresponding α,β-unsaturated-γ-lactone.

3.6.5.1. 5-(naphthalen-2-yl)furan-2(5*H*)-one (124)



Purification of crude product by column chromatography on silica gel furnished 5-(naphthalen-2-yl)furan-2(5*H*)-one as white solid with 55% yield.

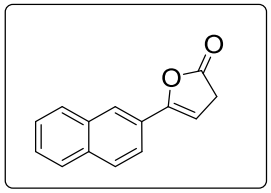
Rf: 0.17 (1:4 EtOAc-Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.81 (m, 3H), 7.79 (s, 1H), 7.60 (dd, *J* = 5.6, 1.6 Hz, 1H), 7.56 – 7.49 (m, 2H), 7.30 (dd, *J* = 8.5 ve 1.8 Hz, 1H), 6.28 (dd, *J* = 5.6, 2.1 Hz, 1H), 6.18 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.17, 155.90, 133.54, 133.13, 131.49, 129.05, 128.03, 127.80, 126.88, 126.76, 126.20, 123.26, 121.08, 84.55.

IR: 3108, 3053, 2927, 1947, 1735, 1600, 1508, 1309, 1167, 1091, 1035, 978, 912, 836, 822, 741, 697 cm $^{-1}$.

3.6.5.2. 5-(naphthalen-2-yl)furan-2(3*H*)-one (126)



Purification of crude product by column chromatography on silica gel furnished 5-(naphthalen-2-yl)furan-2(3*H*)-one as isomerisation product with 39% yield.

Rf: 0.35 (1:4 EtOAc-Hexane)

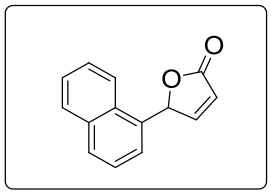
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (s, 1H), 7.92 – 7.78 (m, 3H), 7.63 (dd, *J* = 8.6, 1.7 Hz, 1H), 7.57 – 7.47 (m, 2H), 5.88 (t, *J* = 2.7 Hz, 1H), 3.46 (d, *J* = 2.7 Hz, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 175.91, 154.09, 133.75, 133.12, 128.71, 128.60, 127.84, 127.13, 126.90, 125.59, 124.66, 121.81, 98.40, 34.84.

IR: 3125, 3057, 2924, 1958, 1789, 1508, 1388, 1358, 1262, 1114, 1035, 992, 910, 842, 751 cm $^{-1}$.

HRMS: $[M+Na]^+$: $C_{14}H_{11}O_2$ found as: 211.0751 (Calculated for $[M+Na]^+$: 211.0759)

3.6.5.3. 5-(naphthalen-1-yl)furan-2(5*H*)-one (125)



Purification of crude product by column chromatography on silica gel furnished 5-(naphthalen-2-yl)furan-2(5*H*)-one as beige solid with 38% yield.

Rf: 0.18 (1:4 EtOAc-Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (d, *J* = 8.5 Hz, 1H), 7.92 (d, *J* = 8.6 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.81 (dd, *J* = 5.7, 1.6 Hz, 1H), 7.65 – 7.54 (m, 3H), 7.49 – 7.43 (m, 1H), 7.40 (d, *J* = 6.6 Hz, 1H), 6.80 (s, 1H), 6.29 (dd, *J* = 5.7, 2.2 Hz, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 173.19, 155.69, 133.91, 130.66, 130.47, 129.94, 129.29, 127.19, 126.37, 125.55, 123.82, 122.41, 121.55, 81.59.

IR: 3106, 3095, 3049, 2924, 1949, 1748, 1508, 1301, 1157, 1096, 1008, 808, 774 cm^{-1}.

3.7. Syntheses of Seven-Membered α,β-Unsaturated Lactones

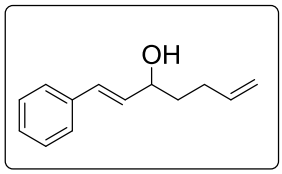
3.7.1. Preparation of But-1-en-4-yl Magnesium Bromide Reagent (131)

In a two necked round bottom flask 4-bromo-1-butene (1 eq.) was dissolved in dry diethyl ether, and magnesium turnings were added. Mixture was stirred at room temperature until magnesium turnings were disappeared (2 hours). Grignard reagent was ready when colourless solution turned to light yellow solution.

3.7.2. Syntheses of Alcohols by Using Grignard Reagent

In a two necked round bottom flask aldehyde (1 eq.) was dissolved in dry THF. After solution was cooled down to -10 ^{o}C, freshly prepared Grignard reagent (2 eq.) was added dropwise. Then reaction was stirred at room temperature. Reaction was controlled with TLC and after 12 h reaction was quenched with water and 1 M HCl. Mixture was extracted with EtOAc and washed with brine. Organic phase collected and dried over magnesium sulphate. Excess solvent was removed under vacuum. Purification of crude product by column chromatography on silica gel (1:10, EtOAc:Hexane) furnished corresponding alcohol.

3.7.2.1. (*E*)-1-phenylhepta-1,6-dien-3-ol (132)



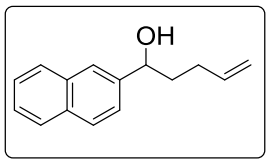
Purification of crude product by column chromatography on silica gel furnished 132 mg of (*E*)-1-phenylhepta-1,6-dien-3-ol as light yellow oil with 41% yield.

Rf**:** 0.26 (1:8, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 - 7.39 (m, 2H), 7.35 (t, *J* = 7.4 Hz, 2H), 7.31 – 7.27 (m, 1H), 6.61 (d, *J* = 15.9 Hz, 1H), 6.26 (dd, *J* = 15.9, 6.8 Hz, 1H), 5.89 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.10 (d, *J* = 17.1, 1.6 Hz, 1H), 5.03 (d, *J* = 10.2 Hz, 1H), 4.35 (d, *J* = 6.3 Hz, 1H), 2.30 – 2.16 (m, 2H), 1.85 – 1.70 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.33, 136.77, 132.34, 130.56, 128.72, 127.81, 126.59, 115.13, 72.67, 36.43, 29.87.

3.7.2.2. 1-(naphthalen-2-yl)pent-4-en-1-ol (133)



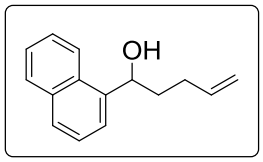
Purification of crude product by column chromatography on silica gel furnished 110 mg of 1-(naphthalen-2-yl)pent-4-en-1-ol as light yellow oil with 26% yield.

Rf**:** 0.25 (1:8, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 – 7.80 (m, 3H), 7.78 (s, 1H), 7.53 – 7.44 (m, 3H), 5.87 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.06 (ddd, *J* = 17.1, 3.6, 1.6 Hz, 1H), 5.01 (ddt, *J* = 10.2, 2.0, 1.3 Hz, 1H), 4.86 (dd, *J* = 7.3, 5.9 Hz, 1H), 2.25 – 2.12 (m, 2H), 2.11 (s, 1H), 2.04 – 1.84 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 142.03, 138.27, 133.36, 133.09, 128.44, 128.03, 127.80, 126.28, 125.95, 124.74, 124.16, 115.17, 74.25, 38.04, 30.20.

3.7.2.3. 1-(naphthalen-1-yl)pent-4-en-1-ol (134)



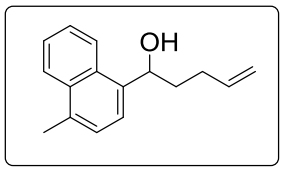
Purification of crude product by column chromatography on silica gel furnished 264 mg of 1-(naphthalen-1-yl)pent-4-en-1-ol as light yellow oil with 62% yield.

Rf**:** 0.25 (1:8, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, *J* = 8.1 Hz, 1H), 7.88 (d, *J* = 7.9 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.55 – 7.46 (m, 3H), 5.97 – 5.85 (m, 1H), 5.53 – 5.46 (m, 1H), 5.10 (d, *J* = 17.2 Hz, 1H), 5.03 (d, *J* = 10.1 Hz, 1H), 2.34 – 2.23 (m, 2H), 2.08 (s, 1H), 2.06 – 1.97 (m, 2H).

(NMR data matches with the literature study.[59])

3.7.2.4. 1-(4-methylnaphthalen-1-yl)pent-4-en-1-ol (135)



Purification of crude product by column chromatography on silica gel furnished 253 mg of 1-(4-methylnaphthalen-1-yl)pent-4-en-1-ol as light yellow oil with 56% yield.

Rf**:** 0.24 (1:8, EtOAc:Hexane)

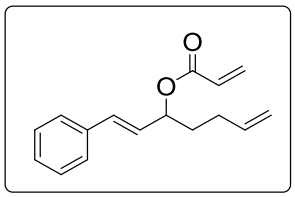
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 – 8.10 (m, 1H), 8.09 – 8.01 (m, 1H), 7.60 – 7.50 (m, 3H), 7.33 (d, *J* = 7.3 Hz, 1H), 5.91 (ddt, *J* = 16.9, 10.2, 6.6 Hz, 1H), 5.51 – 5.43 (m, 1H), 5.09 (ddd, *J* = 17.2, 3.4, 1.7 Hz, 1H), 5.05 – 5.00 (m, 1H), 2.70 (s, 3H), 2.35 – 2.20 (m, 2H), 2.10 – 1.94 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 138.56, 138.38, 134.14, 133.00, 130.56, 126.36, 125.78, 125.53, 125.09, 123.77, 122.70, 115.26, 70.72, 37.39, 30.60, 19.74.

3.7.3. General Procedure for Syntheses of Acrylate Esters

A solution of alcohol (1 eq.) in 7 ml of CH_2Cl_2 was cooled down to 0 ºC, then acryloyl chloride (2 eq.) and triethyl amine (4 eq.) were added sequentially. The mixture was allowed to warm to room temperature and stirred until alcohols were consumed under nitrogen atmosphere. The final mixture was poured into water and extracted with CH_2Cl_2. Combined organic phase concentrated under vacuum and purification of crude product by column chromatography on silica gel (EtOAc:Hexane, 1:10) gave the corresponding acrylate ester.

3.7.3.1. (*E*)-1-phenylhepta-1,6-dien-3-yl acrylate (136)



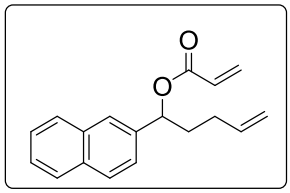
Purification of crude product by column chromatography on silica gel furnished 132 mg of (*E*)-1-phenylhepta-1,6-dien-3-yl acrylate as colourless oil with 82% yield.

Rf**:** 0.35 (1:8, EtOAc:Hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 2H), 7.38 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 6.67 (d, *J* = 15.9 Hz, 1H), 6.47 (dt, *J* = 17.3, 1.4 Hz, 1H), 6.23 – 6.13 (m, 2H), 5.92 – 5.80 (m, 2H), 5.55 (q, *J* = 7.1 Hz, 1H), 5.13 – 5.00 (m, 2H), 2.23 – 2.14 (m, 2H), 1.95 (td, *J* = 13.9, 7.2 Hz, 1H), 1.84 (td, *J* = 13.7, 6.7 Hz, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.62, 137.60, 136.39, 132.91, 130.88, 128.86, 128.69, 128.09, 127.44, 126.72, 115.41, 74.52, 33.85, 29.53.

3.7.3.2. 1-(naphthalen-2-yl)pent-4-en-1-yl acrylate (137)



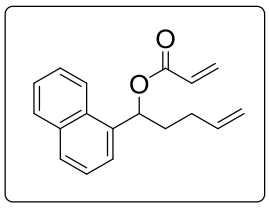
Purification of crude product by column chromatography on silica gel furnished 94 mg of 1-(naphthalen-2-yl)pent-4-en-1-yl acrylate as colourless oil with 75% yield.

Rf**:** 0.33 (1:8, EtOAc:Hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.87 – 7.79 (m, 4H), 7.52 – 7.45 (m, 3H), 6.48 – 6.42 (m, 1H), 6.25 – 6.14 (m, 1H), 6.01 (t, *J* = 6.5 Hz, 1H), 5.89 – 5.78 (m, 2H), 5.08 – 4.96 (m, 2H), 2.23 – 2.08 (m, 3H), 2.06 – 1.96 (m, 1H).

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.62, 137.82, 137.49, 133.23, 133.20, 131.08, 128.73, 128.50, 128.16, 127.79, 126.34, 126.21, 125.88, 124.35, 115.49, 75.93, 35.46, 29.85.

3.7.3.3. 1-(naphthalen-1-yl)pent-4-en-1-yl acrylate (138)



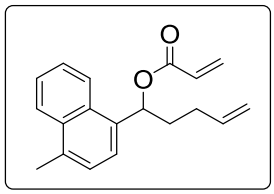
Purification of crude product by column chromatography on silica gel furnished 211 mg of 1-(naphthalen-1-yl)pent-4-en-1-yl acrylate as colourless oil with 69% yield.

Rf**:** 0.34 (1:8, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.18 (d, *J* = 8.4 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.1 Hz, 1H), 7.61 – 7.42 (m, 4H), 6.62 (t, *J* = 6.2 Hz, 1H), 6.52 – 6.41 (m, 1H), 6.22 (dd, *J* = 17.4, 10.4 Hz, 1H), 5.93 – 5.78 (m, 2H), 5.09 – 4.98 (m, 2H), 2.26 – 2.09 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.61, 137.48, 136.56, 133.98, 131.13, 130.47, 129.05, 128.70, 128.57, 126.39, 125.79, 125.41, 123.92, 123.39, 115.60, 73.03, 35.37, 30.16.

3.7.3.4. 1-(4-methylnaphthalen-1-yl)pent-4-en-1-yl acrylate (139)



Purification of crude product by column chromatography on silica gel furnished 255 mg of 1-(4-methylnaphthalen-1-yl)pent-4-en-1-yl acrylate as colourless oil with 88% yield.

Rf**:** 0.32 (1:8, EtOAc:Hexane)

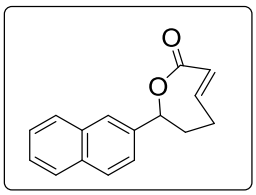
^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (dt, *J* = 3.8, 2.3 Hz, 1H), 8.09 – 8.01 (m, 1H), 7.60 – 7.51 (m, 2H), 7.47 (d, *J* = 7.3 Hz, 1H), 7.31 (d, *J* = 7.3 Hz, 1H), 6.61 (t, *J* = 6.2 Hz, 1H), 6.50 – 6.42 (m, 1H), 6.27 – 6.16 (m, 1H), 5.91 – 5.78 (m, 2H), 5.09 – 4.97 (m, 2H), 2.69 (s, 3H), 2.27 – 2.08 (m, 4H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 165.64, 137.54, 134.72, 134.69, 133.01, 131.04, 130.55, 128.76, 126.24, 126.03, 125.64, 125.08, 123.89, 123.71, 115.53, 73.11, 35.35, 30.19, 19.78.

3.7.4. General Procedure for Ring Closing Metahesis Reactions of Acrylate Esters

To a solution of acrylate ester (1 eq.) in CH_2Cl_2 (0.01 M) was heated to 45 ^oC. A solution of 2nd generation Grubbs' catalyst (0.05 eq.) was prepared in CH_2Cl_2 as 0.01 M, and added to acrylate ester solution dropwise. The resulting mixture was heated at reflux for 4 - 24 hours. At the end of the reaction, mixture was cooled down to room temperature and concentrated under vacuum. Purification of crude product by column chromatography on silica gel (1:8 → 1:3 EtOAc/Hexane) furnished corresponding 5,6-dihydro-2*H*-pyran-2-one as white solid.

3.7.4.1. 7-(naphthalen-2-yl)-6,7-dihydro-*5H*-oxepin-2-one (128)



Purification of crude product by column chromatography on silica gel furnished 17 mg of 7-(naphthalen-2-yl)-6,7-dihydro-5*H*-oxepin-2-one with 60% yield.

Rf**:** 0.34 (1:3, EtOAc:Hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.89 – 7.78 (m, 4H), 7.53 – 7.44 (m, 3H), 7.18 – 7.06 (m, 1H), 6.25 (dd, *J* = 8.6, 3.3 Hz, 1H), 5.82 (d, *J* = 15.5 Hz, 1H), 2.61 – 2.50 (m, 1H), 2.50 – 2.38 (m, 1H), 2.31 – 2.16 (m, 2H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.37, 150.96, 137.90, 133.31, 133.12, 128.50, 128.18, 127.81, 126.44, 126.26, 125.13, 124.23, 120.96, 75.84, 35.42, 30.80.

HRMS: $[M+H]^+$: $C_{16}H_{15}O_2$ found as: 239.1069 (Calculated for $[M+H]^+$: 239.1072)

Isomer:

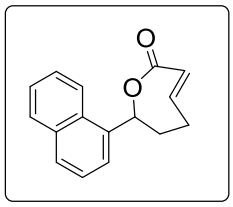
Rf: 0.3 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.90 – 7.79 (m, 4H), 7.54 – 7.45 (m, 3H), 7.30 – 7.19 (m, 1H), 6.06 – 6.00 (m, 1H), 5.73 (dd, J = 15.7, 2.1 Hz, 1H), 2.71 – 2.59 (m, 1H), 2.51 – 2.37 (m, 2H), 2.23 – 2.13 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.76, 150.70, 138.31, 133.33, 133.13, 128.54, 128.16, 127.81, 126.42, 126.23, 124.97, 124.07, 120.45, 76.24, 35.50, 31.24.

HRMS: $[M+H]^+$: $C_{16}H_{15}O_2$ found as: 239.1062 (Calculated for $[M+H]^+$: 239.1072)

3.7.4.2. 7-(naphthalen-1-yl)-6,7-dihydro-*5H*-oxepin-2-one (129)



Purification of crude product by column chromatography on silica gel furnished 70 mg of 7-(naphthalen-1-yl)-6,7-dihydro-5*H*-oxepin-2-one with 39% yield.

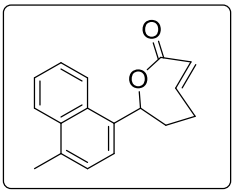
Rf**:** 0.33 (1:4, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, *J* = 8.4 Hz, 1H), 7.89 (d, *J* = 7.9 Hz, 1H), 7.81 (d, *J* = 8.2 Hz, 1H), 7.63 (d, *J* = 7.0 Hz, 1H), 7.61 – 7.55 (m, 1H), 7.55 – 7.46 (m, 2H), 7.41 – 7.30 (m, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 5.81 (dd, *J* = 15.7, 2.1 Hz, 1H), 2.72 – 2.61 (m, 1H), 2.61 – 2.35 (m, 2H), 2.34 – 2.24 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.63, 150.66, 136.98, 133.98, 129.93, 129.15, 128.46, 126.51, 125.87, 125.49, 123.02, 122.91, 120.68, 73.62, 35.48, 31.43.

HRMS: $[M+H]^+$: $C_{16}H_{15}O_2$ found as: 239.1063 (Calculated for $[M+H]^+$: 239.1072)

3.7.4.3. 7-(4-methylnaphthalen-1-yl)-6,7-dihydro-*5H*-oxepin-2-one (130)



Purification of crude product by column chromatography on silica gel furnished 70 mg of 7-(4-methylnaphthalen-1-yl)-6,7-dihydro-*5H*-oxepin-2-one with 33% yield.

Rf**:** 0.32 (1:4, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (dd, *J* = 7.4, 2.2 Hz, 1H), 8.09 – 8.04 (m, 1H), 7.62 – 7.54 (m, 2H), 7.52 (d, *J* = 7.3 Hz, 1H), 7.40 – 7.30 (m, 2H), 6.60 (d, *J* = 8.5 Hz, 1H), 5.80 (dd, *J* = 15.7, 1.8 Hz, 1H), 2.70 (s, 3H), 2.69 – 2.60 (m, 1H), 2.53 (dt, *J* = 17.2, 11.5 Hz, 1H), 2.46 – 2.35 (m, 1H), 2.33 – 2.23 (m, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.66, 150.63, 135.20, 134.57, 133.02, 129.99, 126.28, 126.13, 125.71, 125.19, 123.52, 122.64, 120.67, 73.65, 35.55, 31.41, 19.75.

HRMS: $[M+H]^+$: $C_{17}H_{17}O_2$ found as: 253.1221 (Calculated for $[M+H]^+$: 253.1229)

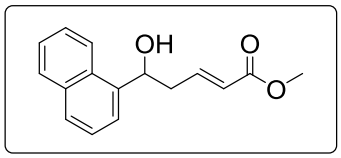
3.8. A Method Development Studies for the Synthesis of α,β-Unsaturated Lactone

3.8.1. General Procedure

In a two necked round bottom flask 34 mg of Ag_2CO_3 (0.125 mmol, 0.5 eq.) and 4 mL of anhydrous DMF were added. The mixture was stirred about 20 minutes at room temperature and cooled down to 0 ºC in ice bath. Then 31 µL of methyl 3-butenoate (0.25 mmol, 1 eq.) and 33 µL of TMSCl (0.25 mmol, 1 eq.) were added respectively. After solution had stirred 1 h at 0 ºC, 72 µL 1-naphthaldehyde (0.5 mmol, 2 eq.) and 0.25 mL TBAF (1.0 in M THF) (0.25 mmol, 1 eq.) were added reaction mixture respectively. Final mixture was allowed to warm to room temperature and stirred for 24 h. The mixture was poured into 30 mL of water and extracted with Et_2O (3x40 mL).

Collected organic phase were dried over $MgSO_4$ and excess solvent was removed under vacuum. Purification of crude product on SiO_2 column (1:6→1:4; EtOAc:Hexane) furnished 48 mg of *(E)*-methyl 5-hydroxy-5-(naphthalen-5-yl)pent-2-enoate as yellow oil with 75% yield.

3.8.1.1. Methyl (*E*)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (141)



Purification of crude product on silica gel column furnished (*E*)-methyl-5-hydroxy-5-(naphthalen-5-yl)pent-2-enoate as yellow oil with 75% yield.

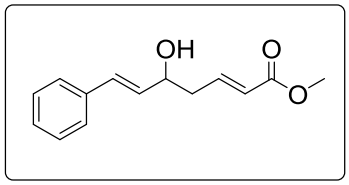
Rf: 0.46 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.03 (d, *J* = 9.2 Hz, 1H), 7.88 (d, *J* = 7.5 Hz, 1H), 7.79 (d, *J* = 8.2 Hz, 1H), 7.65 (d, *J* = 7.1 Hz, 1H), 7.56 – 7.44 (m, 3H), 7.10 (dt, *J* = 15.6, 7.2 Hz, 1H), 5.94 (dt, *J* = 15.7, 1.5, 1H), 5.58 (dd, *J* = 8.2, 4.1 Hz, 1H), 3.71 (s, 3H), 2.88 – 2.79 (m, 1H), 2.79 – 2.69 (m, 1H), 2.44 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.91, 145.58, 139.09, 133.91, 130.14, 129.15, 128.41, 126.37, 125.77, 125.56, 123.51, 122.97, 122.82, 69.89, 51.63, 40.98.

HRMS: $[M+Na]^+$: $C_{16}H_{16}O_3$ found as: 279.0986 (Calculated for $[M+Na]^+$: 279.0997)

3.8.1.2. Methyl (*2E,6E*)-5-hydroxy-7-phenylhepta-2,6-dienoate (146)



Purification of crude product on silica gel column furnished methyl (*2E,6E*)-5-hydroxy-7-phenylhepta-2,6-dienoate as light yellow oil with 28% yield.

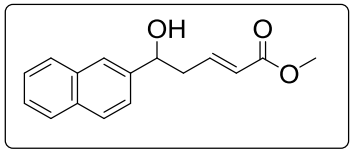
Rf: 0.53 (1:2, EtOAc:Hexane)

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.41 - 7.36 (m, 2H), 7.32 (t, *J* = 7.6 Hz, 2H), 7.28 – 7.26 (m, 1H), 7.01 (dt, *J* = 14.9, 7.3 Hz, 1H), 6.62 (d, *J* = 15.9 Hz, 1H), 6.23 (dd,

J = 15.9, 6.6 Hz, 1H), 5.95 (d, *J* = 15.7 Hz, 1H), 4.45 (q, *J* = 6.4 Hz, 1H), 3.73 (s, 3H), 2.55 (t, *J* = 6.9 Hz, 2H), 1.93 (s, 1H).

(NMR data matches with literature study.[60])

3.8.1.3. Methyl (*E*)-5-hydroxy-5-(naphthalen-2-yl)pent-2-enoate (147)



Purification of crude product on silica gel column furnished methyl (*E*)-5-hydroxy-5-(naphthalen-2-yl)pent-2-enoate as light yellow oil with 69% yield.

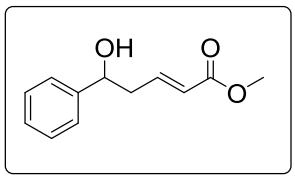
Rf: 0.43 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 – 7.79 (m, 3H), 7.76 (s, 1H), 7.48 (dt, *J* = 4.8, 3.3 Hz, 2H), 7.44 (dd, *J* = 8.6, 1.6 Hz, 1H), 7.03 – 6.93 (m, 1H), 5.89 (d, *J* = 15.7 Hz, 1H), 4.95 – 4.88 (m, 1H), 3.68 (s, 3H), 2.79 – 2.59 (m, 3H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.89, 145.20, 140.94, 133.30, 133.12, 128.51, 128.06, 127.77, 126.33, 126.08, 124.63, 123.84, 123.56, 73.15, 51.58, 41.79.

HRMS: $[M+Na]^+$: $C_{16}H_{16}NaO_3$ found as: 279.0971 (Calculated for $[M+Na]^+$: 279.0997)

3.8.1.4. Methyl (*E*)-5-hydroxy-5-phenylpent-2-enoate (148)



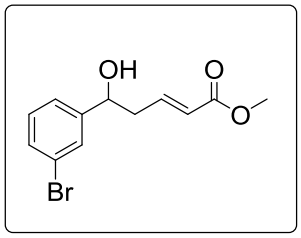
Purification of crude product on silica gel column furnished methyl (*E*)-5-hydroxy-5-phenylpent-2-enoate as light yellow oil with 41% yield.

Rf: 0.56 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 – 7.27 (m, 5H), 7.00 – 6.91 (m, 1H), 5.93 – 5.85 (m, 1H), 4.81 (s, 1H), 3.70 (s, 3H), 2.69 – 2.59 (m, 2H), 2.18 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.85, 145.11, 143.53, 128.76, 128.07, 125.85, 123.72, 73.22, 51.64, 41.96.

3.8.1.5. Methyl (*E*)-5-(3-bromophenyl)-5-hydroxypent-2-enoate (150)



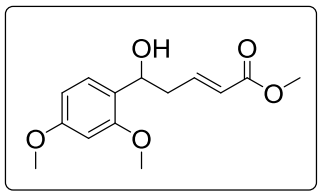
Purification of crude product on silica gel column furnished methyl (*E*)-5-(3-bromophenyl)-5-hydroxypent-2-enoate as light yellow oil with 67% yield.

Rf: 0.4 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (t, *J* = 1.5 Hz, 1H), 7.41 (dt, *J* = 7.5, 1.6 Hz, 1H), 7.28 – 7.18 (m, 2H), 6.99 – 6.89 (m, 1H), 5.89 (dt, *J* = 15.7, 1.3 Hz, 1H), 4.81 – 4.75 (m, 1H), 3.71 (s, 3H), 2.63 – 2.57 (m, 2H), 2.44 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 166.83, 145.89, 144.63, 131.02, 130.28, 128.95, 124.48, 123.96, 122.83, 72.40, 51.71, 41.92.

3.8.1.6. Methyl (*E*)-5-(2,4-dimethoxyphenyl)-5-hydroxypent-2-enoate (151)



Purification of crude product on silica gel column furnished methyl (*E*)-5-(2,4-dimethoxyphenyl)-5-hydroxypent-2-enoate as light yellow oil with 12% yield.

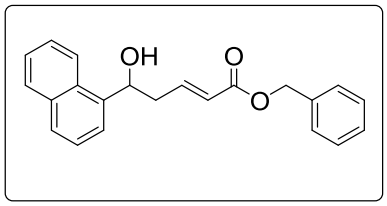
Rf: 0.3 (1:2, EtOAc:Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, *J* = 8.1 Hz, 1H), 7.05 – 6.94 (m, 1H), 6.50 – 6.44 (m, 2H), 5.89 (dd, *J* = 15.7, 0.9 Hz, 1H), 4.96 (s, 1H), 3.82 (s, 3H), 3.80 (s, 3H), 3.71 (s, 3H), 2.67 (t, *J* = 7.2 Hz, 2H), 2.53 (s, 1H).

^{13}C NMR (101 MHz $CDCl_3$) δ 166.99, 160.47, 157.60, 146.15, 127.53, 123.83, 123.06, 104.30, 98.86, 69.43, 55.53, 55.45, 51.57, 40.28.

HRMS: $[M+Na]^+$: $C_{14}H_{18}NaO_5$ found as: 289.1010 (Calculated for $[M+Na]^+$: 289.1052)

3.8.1.7. Benzyl (*E*)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate (163)



Purification of crude product on silica gel column furnished benzyl (*E*)-5-hydroxy-5-(naphthalen-1-yl)pent-2-enoate as light yellow oil with 51% yield.

Rf: 0.4 (1:2, EtOAc-Hexane)

^{1}H NMR (400 MHz, $CDCl_3$) δ 8.02 (d, *J* = 7.5 Hz, 1H), 7.89 (d, *J* = 7.2 Hz, 1H), 7.80 (d, *J* = 8.2 Hz, 1H), 7.66 (d, *J* = 7.0 Hz, 1H), 7.56 – 7.45 (m, 3H), 7.40 – 7.31 (m, 5H), 7.20 – 7.11 (m, 1H), 6.00 (dd, *J* = 15.7, 0.7 Hz, 1H), 5.58 (dd, *J* = 8.0, 3.8 Hz, 1H), 5.17 (s, 2H), 2.87 – 2.69 (m, 2H), 2.45 (s, 1H).

^{13}C NMR (100 MHz, $CDCl_3$) δ 164.76, 150.97, 150.70, 138.31, 137.89, 133.34, 133.14, 128.54, 128.17, 127.81, 126.42, 126.23, 125.12, 124.97, 124.22, 124.07, 120.94, 120.46, 110.13, 76.24, 35.50, 31.24.

CHAPTER 4

CONCLUSION

Many biologically active compounds have α,β-unsaturated lactone structural core in their structures. It is believed that the Michael acceptor properties of these functional group is the source of their wide range of biological activities. For this reason, the synthesis of α,β-unsaturated lactone derivatives attracts the attention of scientist worldwide. In this thesis, asymmetric and racemic syntheses of novel α,β-unsaturated lactone derivatives were aimed.

To this aim, big scale asymmetric syntheses of (*R*)-4'-methylklavuzon and (*R*)-2'-methylklavuzon were completed successfully. Besides, syntheses of heteroatom substituted novel 5,6-dihydro-2*H*-pyran-2-one derivatives, α,β-unsaturated-γ-lactone (furan-2(5*H*)-one) derivatives and 7-membered α,β-unsaturated lactone (6,7-dihydro-5*H*-oxepin-2-one) derivatives were accomplished.

In the asymmetric syntheses of new 5,6-dihydro-2*H*-pyran-2-one derivatives, although asymmetric allylation reactions of heteroatom substituted naphthaldehydes were carried out low % yield, nevertheless racemic allylation reactions of aldehydes worked well and obtained homoallylic alcohols were converted to target 5,6-dihydro-2*H*-pyran-2-one derivatives in two steps.

Similarly, allylic alcohols which obtained by addition of vinyl magnesium bromide were converted to furan-2(5*H*)-one derivatives, but in purification stage compounds were isomerised to furan-2(3*H*)-one derivatives.

7-Membered 6,7-dihydro-5*H*-oxepin-2-one derivatives were synthesized starting from aldehydes with same strategy except *trans*-cinnamaldehyde derivative. In these molecules such an unexpected cases that C=C bond on lactone ring has *E* conformation.

In addition, a new method development studies for one-pot synthesis of α,β-unsaturated-δ-lactone were performed, and a new vinylogous aldol addition method was developed. By this method, one pot synthesis of vinylogous aldol addition product was achieved starting from methyl buten-3-oate via dienolate formation.

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APPENDIX A

^{1}H AND ^{13}C NMR SPECTRUM OF SELECTED COMPOUNDS

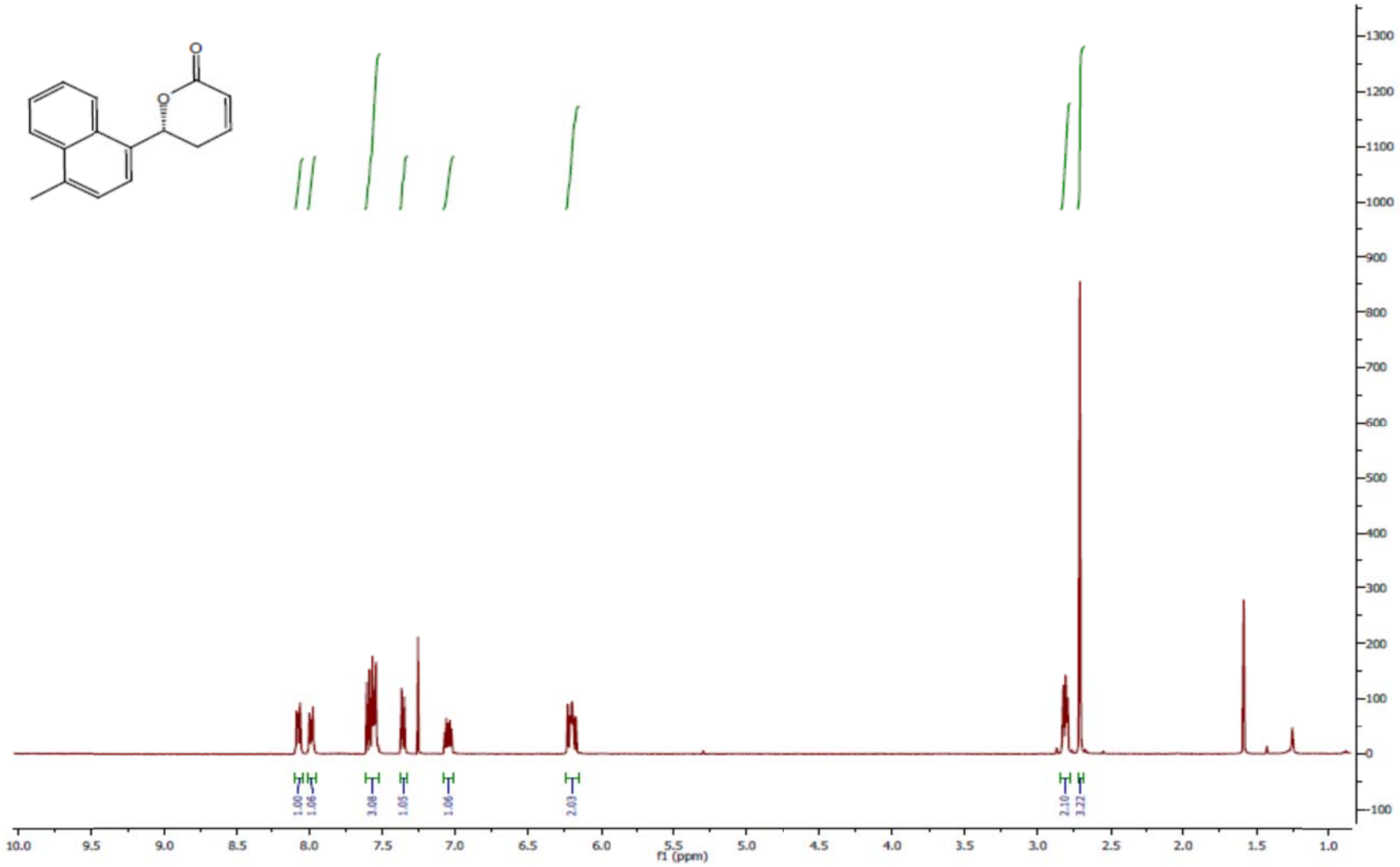

Figure A.1. ^{1}H NMR spectra of (*R*)-6-(4-methylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one

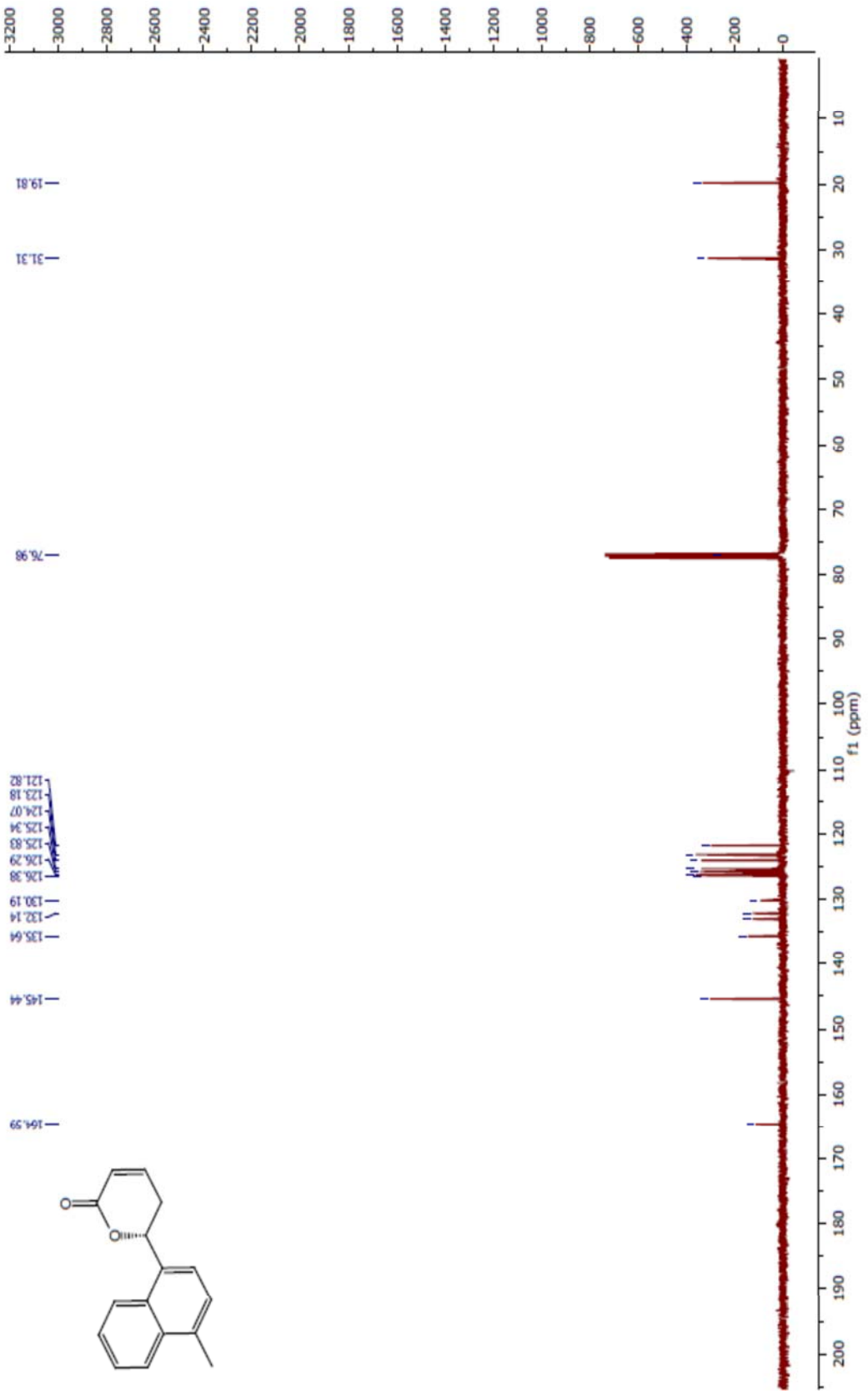

Figure A.2. ^{13}C NMR spectra of (*R*)-6-(4-methylnaphthalen-1-yl)-5,6-dihydro-2*H*-pyran-2-one

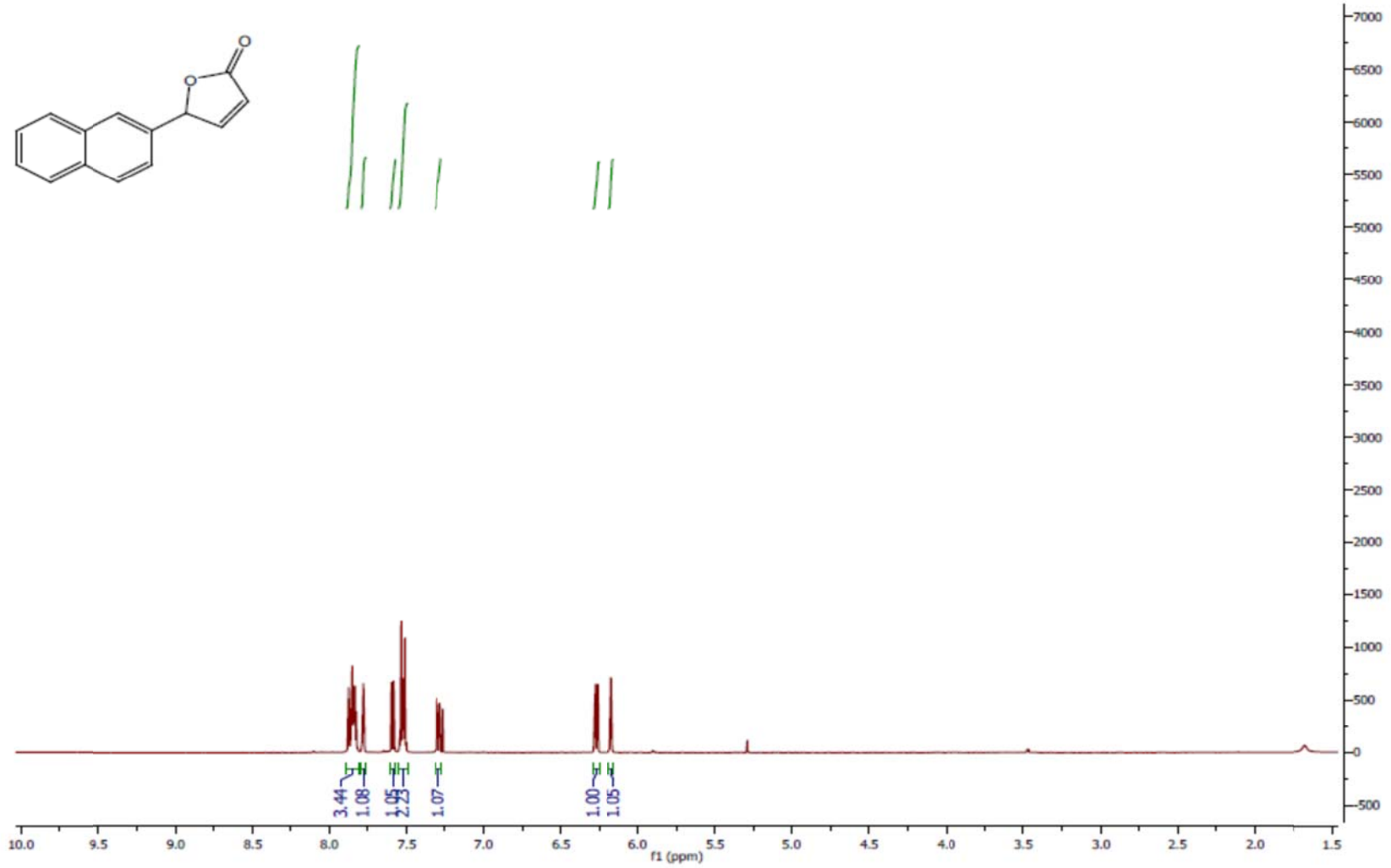

Figure A.3. ^{1}H NMR spectra of 5-(naphthalen-2-yl)furan-2(5*H*)-one

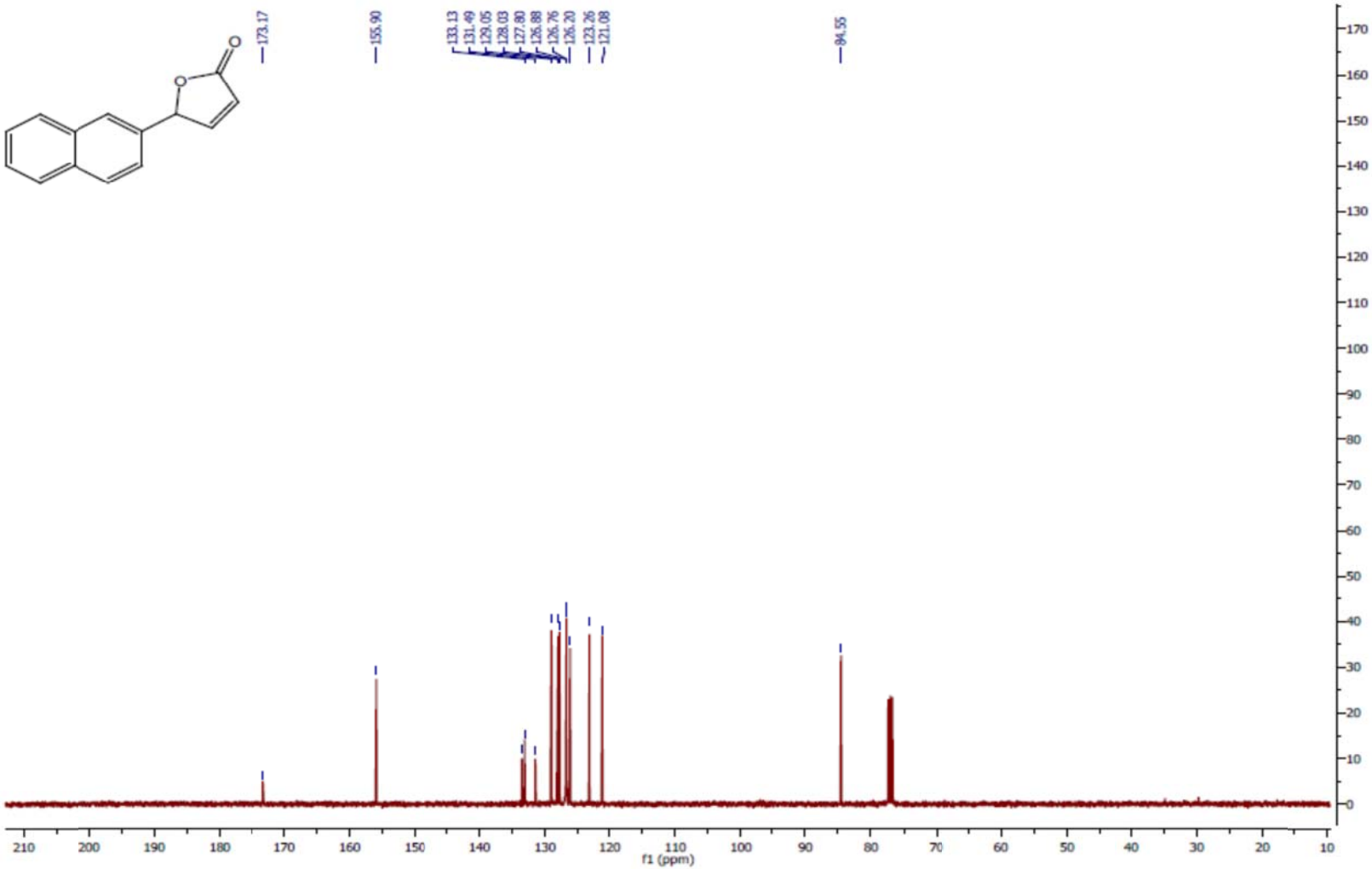

Figure A.4. ^{13}C NMR spectra of 5-(naphthalen-2-yl)furan-2(5*H*)-one

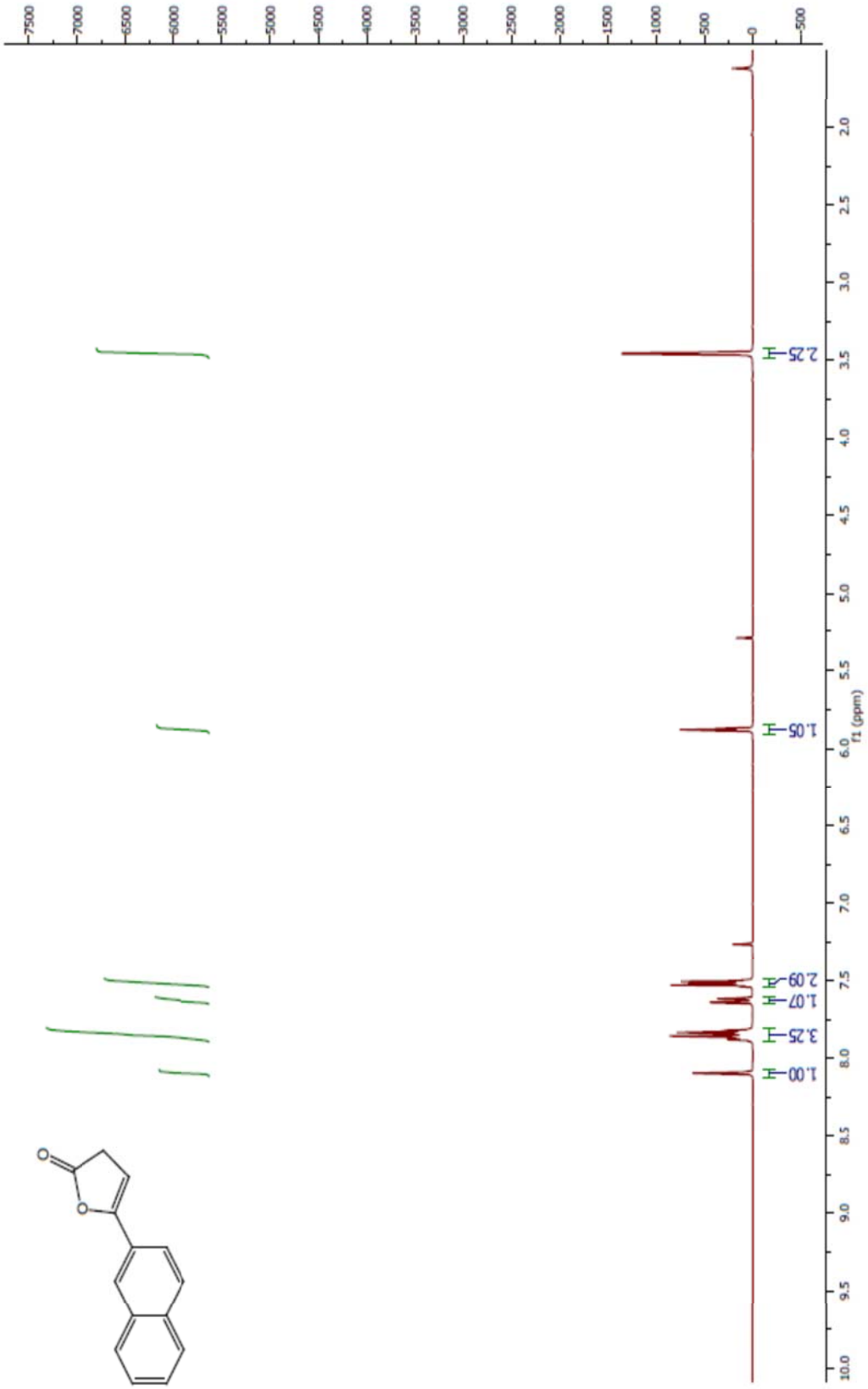

Figure A.5. ^{1}H NMR spectra of 5-(naphthalen-2-yl)furan-2(3*H*)-one

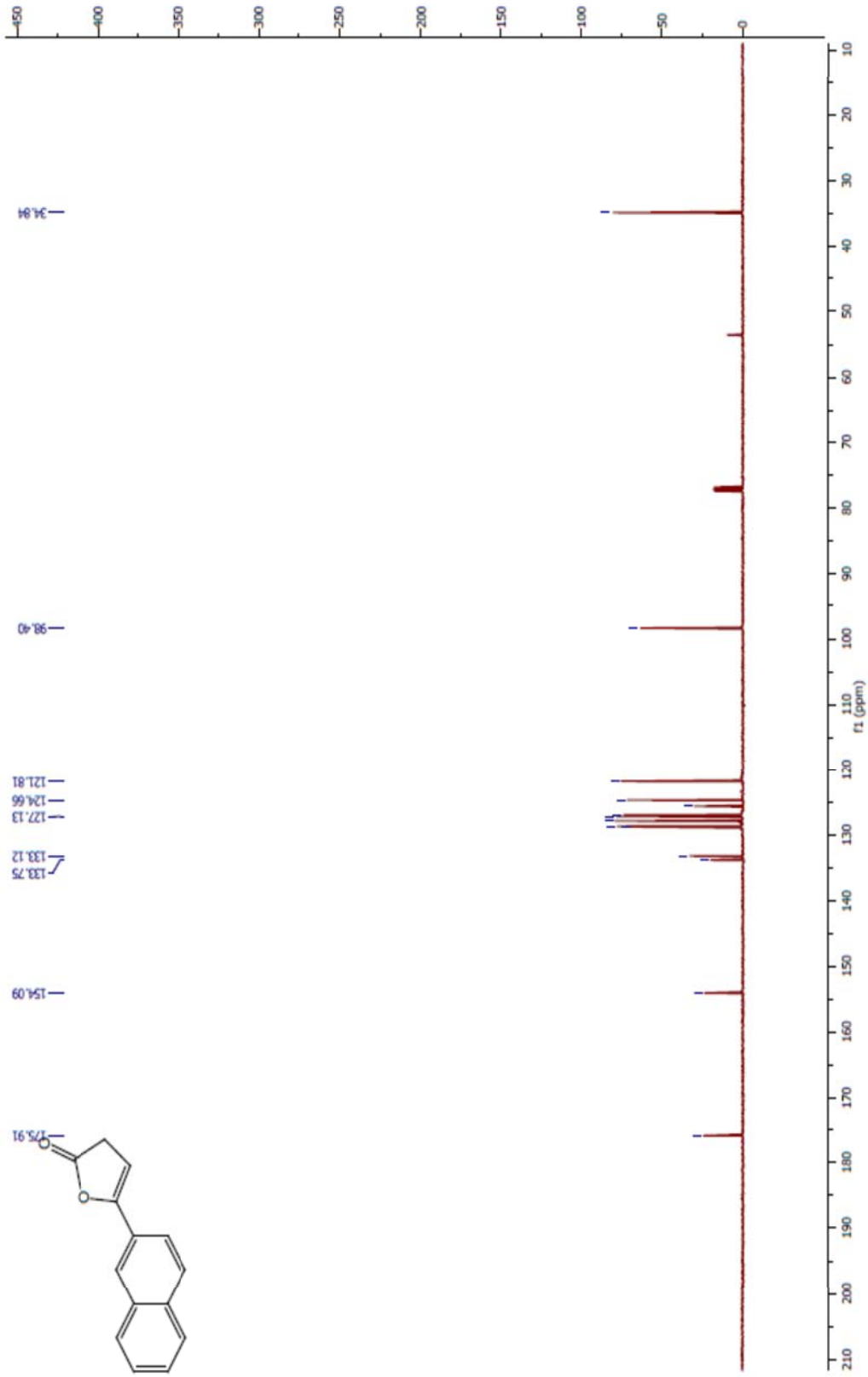

Figure A.6. ^{13}C NMR spectra of 5-(naphthalen-2-yl)furan-2(3*H*)-one

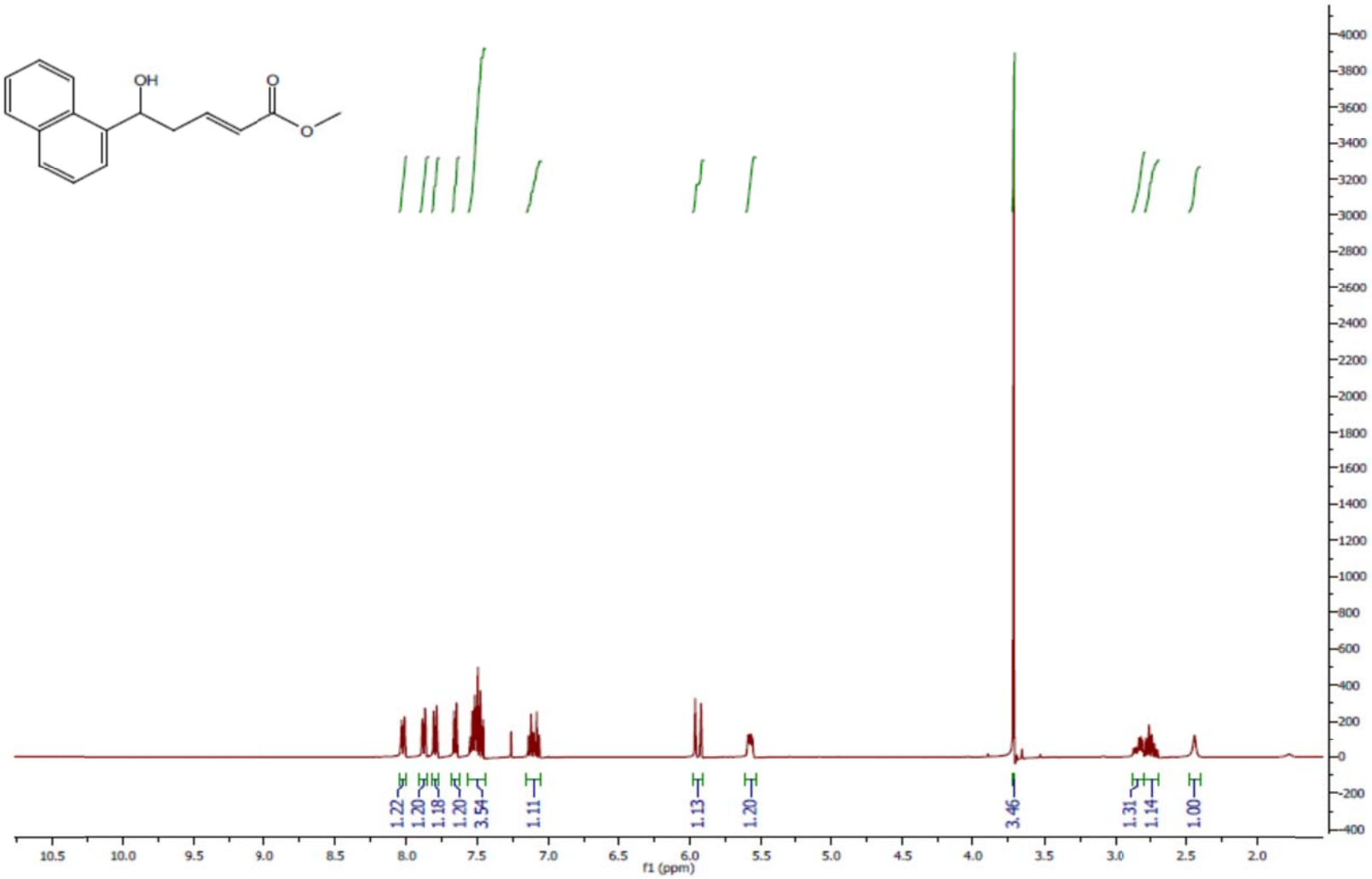

Figure A.7. ^{1}H NMR spectra of methyl (*E*)-5-hydroxy-5-(naphthalen-2-yl)pent-2-enoate

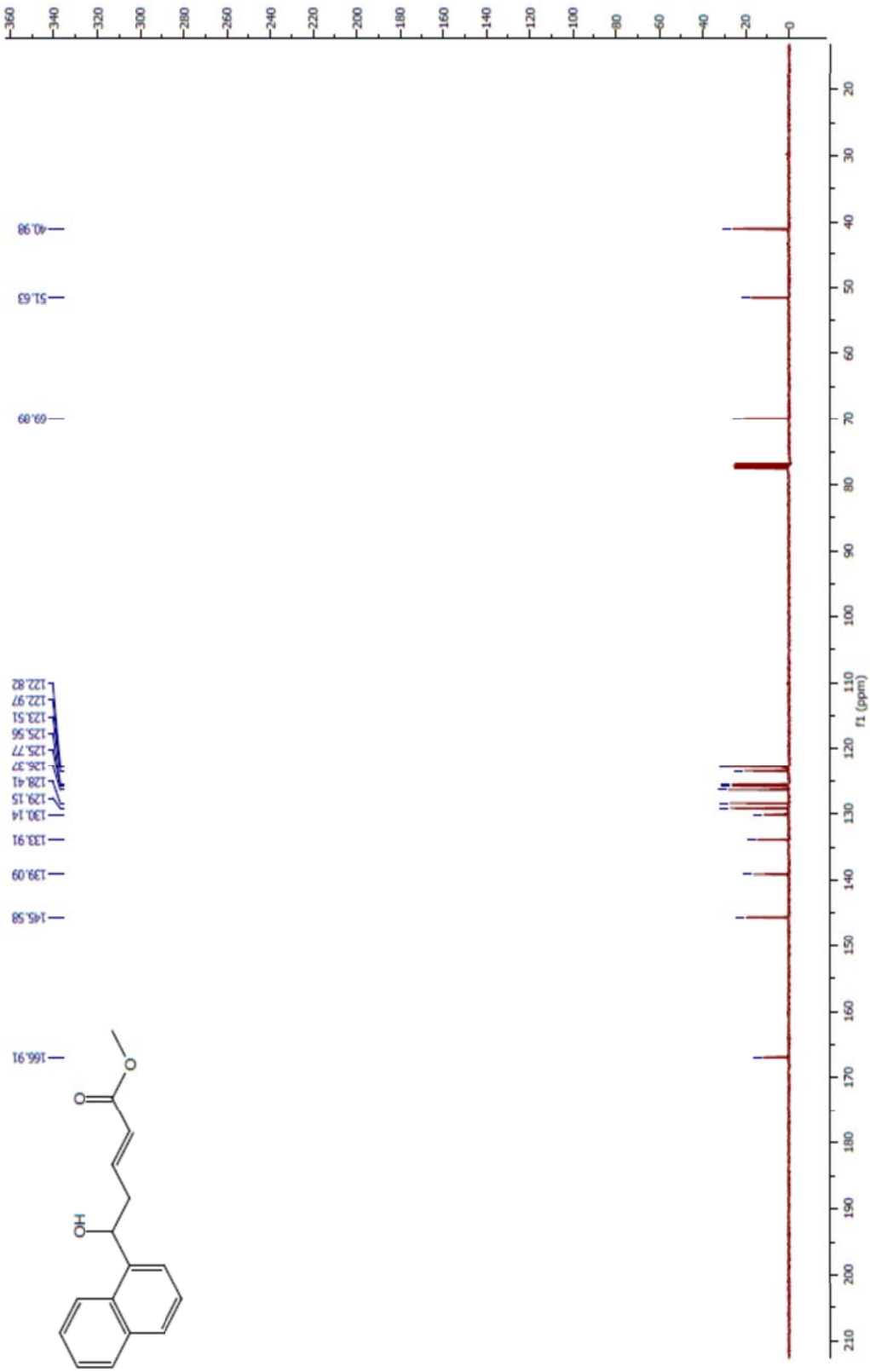

Figure A.8. ^{13}C NMR spectra of methyl (*E*)-5-hydroxy-5-(naphthalen-2-yl)pent-2-enoate

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