SYNTHESIS OF SIMPLE 2'-ALKOXYMETHYL SUBSTITUTED KLAVUZON DERIVATIVES

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by
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İZMİR

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ABSTRACT

SYNTHESIS OF SIMPLE 2'-ALKOXYMETHYL SUBSTITUTED KLAVUZON DERIVATIVES

α,β-Unsaturated δ-lactones are the members of lactones, which are cyclic esters. They are quite valuable compounds because of their Michael acceptor property at unsaturated carbonyl functional group. It is believed that soft nucleophilic parts of the enzymes react with the β-carbon of lactone and form a covalent bond. If that is occurred at the active site of an enzyme, its activity is inhibited irreversibly. (*R*)-goniothalamin is a α,β-unsaturated lactone and it was shown that it has a selective cytotoxic activity over cancer cells. It is less cytotoxic in healthy cells. Later, Kasaplar and coworkers synthesized the klavuzon derivatives, which can be considered as the close relatives of goniothalamins. In this study novel derivatives of simple 2'-alkoxymethyl substituted klavuzon derivatives were synthesized.

For this purpose, we started with 2-methyl-1-naphtoic acid, which can be transferred to ethyl 2-methyl-1-naphtoate by reacting with iodoethane under basic condition. Next, formed ester reacted with Br_2 molecules generated in situ by $NaBrO_3$ and $NaHSO_3$. Then formed ethyl 2-(bromomethyl)-1-naphtoate reacted with various alcohols under basic conditions to form ethyl-2-alkoxymethyl-1-naphtoate. These esters are coverted to the target klavuzon products in five steps that are reduction with $LiAlH_4$, oxidation with PCC, addition of allylmagnesium bromide, acrylate ester formation and ring closing metathesis reactions.

ÖZET

BASİT 2’-ALKOKSİMETİL SÜBSTİTÜELİ KLAVUZON TÜREVLERİNİN SENTEZLENMESİ

α,β-Doymamış laktonlar, halkalı ester yapılarına sahip olan lactonların bir üyesidir. Bunlar, yapılarındaki doymamış karbonil fonksiyonel grubunun Michael akseptör özelliklerinden dolayı oldukça değerli bileşiklerdir. Enzimlerin nükleofilik kısımlarının laktonun β-karbonuyla reaksiyona girdiği ve bir kovalent bağ oluşturduğu düşünülmektedir. Eğer bu bağ enziminin aktif bölgesinde gerçekleşirse, aktivitesi geri dönüşsüz olarak engellenir. (*R*)-goniothalamin bir α,β-doymamış lakton olup kanser hücreleri üzerinde seçici bir sitotoksik aktiviteye sahip olduğu gösterilmiştir. Sağlıklı hücrelerde daha az sitotoksiktir. Daha sonra Kasaplar ve iş arkadaşları, goniothalaminlerin yakın akrabaları sayılabilecek klavuzon türevlerini sentezledi. Bu çalışmada basit 2'-alkoksimetil sübstitüe klavuzon türevleri sentezlenmiştir.

Bu amaçla, normal şartlar altında 2-metil-1-naftoik asit iyodoetan ile reaksiyona sokarak etil-2-metil-1-naftoata dönüştürüldü. Daha sonra, oluşan ester $NaBrO_3$ ve $NaHSO_3$ tarafından üretilen Br_2 molekülleri ile reaksiyona sokuldu. Bu tepkimeden elde edilen etil 2-(bromometil)-1-naftoat bazik koşullar altında çeşitli alkollerle reaksiyona sokularak etil 2-alkoksimetil-l-naftoat oluşturuldu. Bu esterler hedef klavuzon ürünlerine $LiAlH_4$ ile indirgeme, PCC ile oksidasyon, allilmagnezyum bromür ilavesi, akrilat ester oluşumu ve halka kapanış metatezis reaksiyonları kullanılarak beş basamakta dönüştürülmüştür.

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ABBREVIATIONS

μL	Microliter
Ac	Acetate
Boc	*Tert*-butoxycarbonyl
d	Doublet
DCM	Dichloromethane
dd	Doublet of doublets
ddd	Doublet of doublet of doublets
dddd	Doublet of doublet of doublet of doublets
dddt	Doublet of doublet of doublet of triplets
ddt	Doublet of doublet of triplets
DMF	Dimethylformamide
dq	Doublet of quartets
dt	Doublet of triplets
eq	Equivalent
h	Hour
HDA	Hetero-Diels-Alder
Hex	Hexane
m	Multiplet
M	Molarity
mg	Milligram
min.	Minute
mL	Milliliter
mmol	Millimoles
N.P.	No product
N.R.	No reaction
NBS	N-Bromosuccinimide
NMR	Nuclear magnetic resonance
PCC	Pyridinium chlorochromate
Ph	Phenyl
q	Quartet
s	Singlet

sep	Septet
t	Triplet
td	Triplet of doublets
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran

CHAPTER 1

INTRODUCTION

Cell growth and division occur very rapidly in the early life of human. While human body is getting older cell growth a division get slower in some organs. But still there are types of cells, which undergo cell division process. If this cell growth and division process became uncontrolled due to the possible mutations then tumor or cancer will be formed in that tissue.

Cancer is getting more common disease in the World. Cancer is the brief name of more than 120 diseases for example, breast, bladder, kidney, skin, pancreas, carcinoma, sarcoma, leukemia, lymphoma, melanoma, brain and spinal cord tumors. Their specific behaviour is abnormal cell division. Also cancer can start one part of the body and then start to spread to the other parts of the body and start to destroy the non-malignant cells. If the cell divisions couldn't be prohibited, cancer can cause to deaths ("Cancer Facts and Figures 2016," 2016).

When DNA becomes damaged, the cell can go to death or it tries to repair the DNA. If the damaged DNA can not be repaired in cancer cells, these cells can continously multiply itself, the result is called as tumor. These tumors are called as benign or malignant, benign is noncancerous and malignant is cancerous (Gringauz, 1996).

According to research of the American Cancer Society, there are nearly 14.5 million Americans diagnosed with cancer disease on January 1, 2014. in 2016, 1,685,210 new cancer cases are predicted to be diagnosed and 595,690 Americans are expected die because of the cancer. It means that 1,630 people can die per day ("Cancer Facts and Figures 2016," 2016).

There are a lot of reasons that can contribute to the formation of cancer. These reasons are classified in two group. First one, external factors these are tobacco, unhealthy diet, body fatness, physical inactivity, excess alcohol consumption, contagious organisms, the Sun, ultraviolet light radiation exposure. On the other hand, the second internal factors are genetic mutations, immune conditions, and hormones. The external reasons could be prevented through behavioral changes and taking

measures. The most essential thing is early diagnosis to have better chance to cure the cancer ("Cancer Facts and Figures 2016," 2016).

The most common treatments of the cancer are that, surgery, radiation, chemotherapy, immunotherapy, hormone therapy and targeted therapy. The other treatments are stem cell transplant, hyperthermia photodynamic therapy, blood product donation and transfusion lasers in cancer treatment ("Cancer Facts and Figures 2016," 2016).

Chemotherapy is the well known method and it may be appllied before surgery or radiation therapy in order to shrink the tumor. This method is called neo-adjuvant chemotherapy. If the chemoterapy is applied after surgery or radiation therapy, it is used to destroy cancer cells that may remain. This method is called adjuvant chemotherapy (Schott & Hayes, 2012).

People researches looking for the cure from the natural resources. They apply to traditional treatment methods by using the different parts of the *Goniothalamus genus* which is one of the genera from the *Annonaceae family* in many countries around the world (Abdullah et al., 2013). Nearly 40% of the drugs that have been sanctioned over the last decades are either natural products or derivatives and analogues thereof (Butler, 2004; Clardy & Walsh, 2004; K. H. Lee, 2004).

Four main groups of secondary metabolites are based in the *Goniothalamus* species, which are styryl lactones (Mu et al., 1999), flavonoids (Seidel, Bailleul, & Waterman, 2000), acetogenins (Alali, Zhang, Rogers, & McLaughlin, 1998; Chen, Jiang, Chen, & Yu, 1998), and alkaloids (Lekphrom, Kanokmedhakul, & Kanokmedhakul, 2009; Zhang, Kong, Chen, & Yu, 1999). Nonetheless, only two valerolactone derivatives, (*R*)-goniothalamin (**(*R*)-1)** and its derivative **(*R*)**-goniothalamin oxide (**2**), (Figure 1.1.) were announced from *G. macrophyllus* along with the flavonoid, pinocembrin (Ee, Ng, Rahmani, & Taufiq-Yap, 2001; Sam et al., 1987).

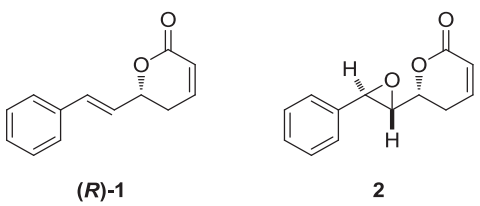

Figure 1.1. Structure of (*R*)-goniothalamin **((*R*)-1)** and (*R*)-goniothalamin oxide (**2**). (Source: (de Fatima, Marquissolo, de Albuquerque, Carraro-Abrahao, & Pilli, 2006))

1.1. 5,6-Dihydro-*2H*-pyran-2-one Pharmacophore as a Source of Biological Activity

Chiral unsaturated lactones commonly found in the structures of natural products of medicinal importance (Figure 1.2.) (Sundby, Perk, Anthonsen, Aasen, & Hansen, 2004). The 5,6-dihydro-*2H*-pyran-2-one (α,β-unsaturated-δ-lactones) moiety can be found in the structure of variety of biologically active natural products, for example, (*R*)-goniothalamin (**(*R*)-1)**), goniothalamin oxide (**2**) (Figure 1.1.) and argentilactone (**18**) (Figure 1.3.) (de Fatima, Marquissolo, et al., 2006).

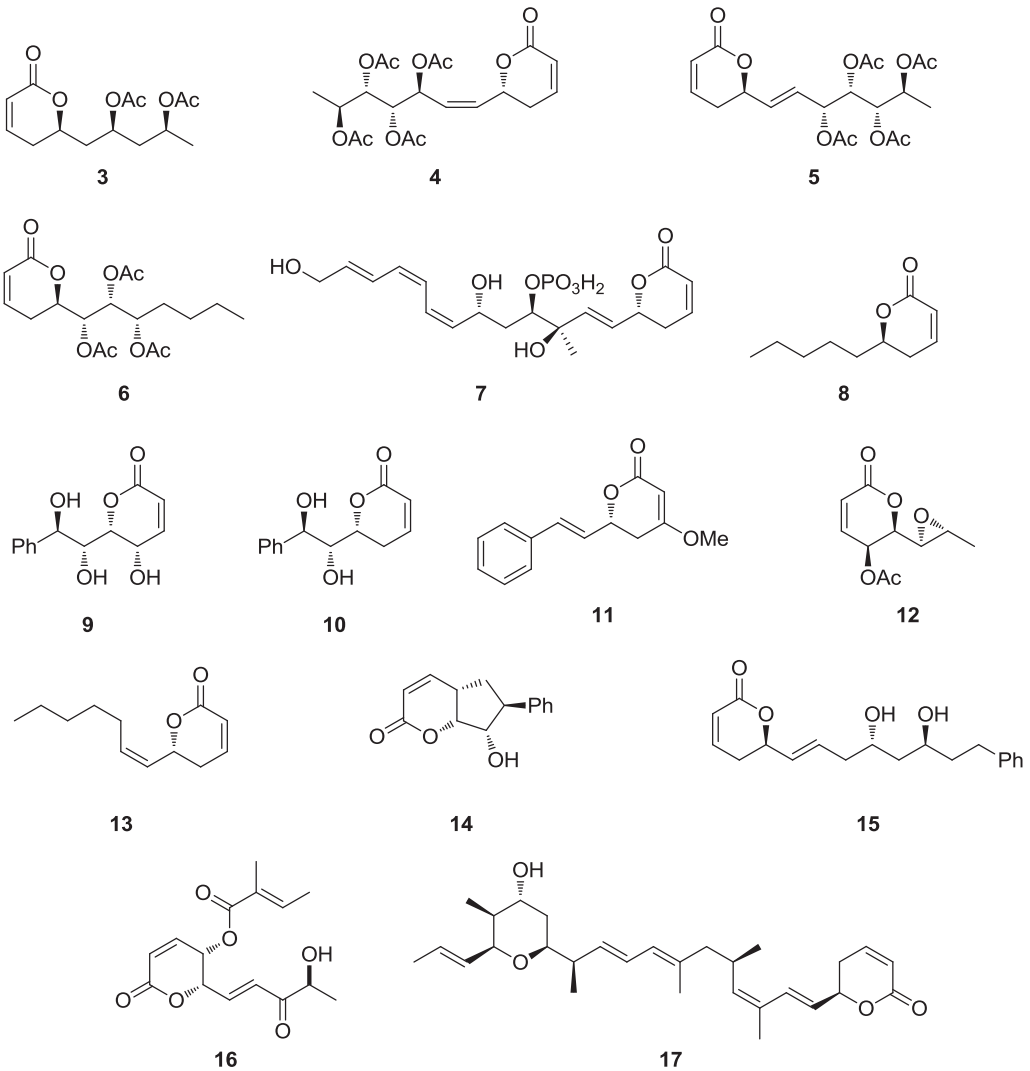

Figure 1.2. Selected examples of naturally occuring α,β-unsaturated δ-lactones. (Source: (Boucard, Broustal, & Campagne, 2007))

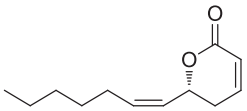

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Figure 1.3. Structure of argentilactone.
(Source: (de Fatima, Marquissolo, et al., 2006))

Derivatives of α,β-unsaturated δ-lactones are biologically active compounds and covers in the context of HIV protease inhitors (Hagen et al., 1997), protein phosphatase inhibitors (Buck et al., 2003), antioxidants (Tanaka et al., 2010), antiprotozoals (Carmona et al., 2003), antibacterials (Hester, Steven Joseph Brickner, Barbachyn, Hutchinson, & Toops, 1998)(Hester, Steven Joseph Brickner, Barbachyn, Hutchinson, & Toops, 1998), and anticancer agents (Zhou et al., 2005). Also, they have protective activity properties against oxidative stress-induced neuronal cell death.

It is believed that the Michael acceptor part in their structure is accountable for their biological properties (Carrera, Brovetto, & Seoane, 2013). The nucleophilic part of the enzyme can bind to the β-carbon of these unsaturated carbonyls (Figure 1.4.) (Kasaplar, Cakmak, & Cagir, 2010).

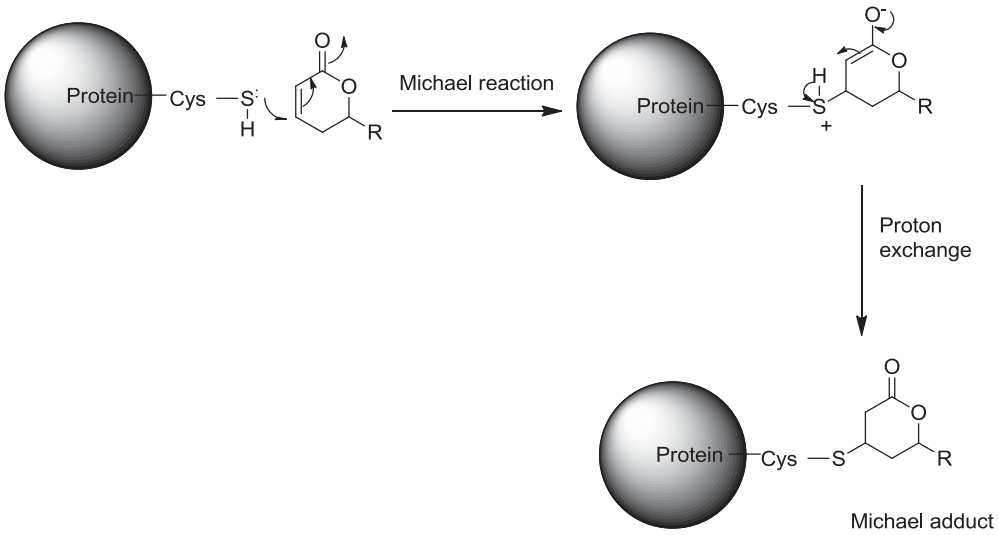


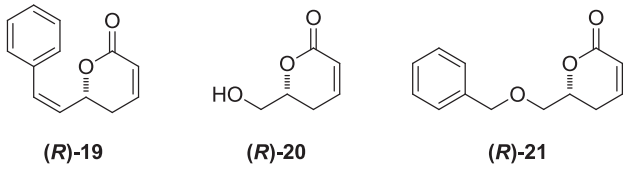
Figure 1.4. Suggested mechanism for the binding of α,β-unsaturated δ-lactones to enzymes. (Source: (Cardona, Guerra, & Restrepo, 2013))

Styryl lactone, (*R*)-goniothalamin (**(*R*)-1)**) was first isolated in 1967 by Hlubucek from the dried bark of *Cryptocarya caloneura* (Hlubucek & Robertson, 1967). Then it was isolated from *Cryptocarya moschata*, (Cavalheiro & Yoshida, 2000)

Bryonopsis laciniosa (Kabir, Khan, & Mosaddik, 2003) and also various species of *Goniothalamus* (Ahmad, Tukol, Omar, & Sharif, 1991; Goh, Ee, Chuah, & Wei, 1995; Jewers et al., 1972). Cytotoxic activity of this natural compound was studied on different cancer cell lines which are cervical carcinoma (Hela); gastric carcinoma (HGC-27); breast carcinoma (MCF-7, NCI-ADR, T47D, MDA-MB-231); leukemia (HL-60), ovarian carcinoma (Caov-3, OVCAR03), lung carcinoma (NCI-H460), skin carcinoma (UACC62), kidney carcinoma (786-0), prostate carcinoma (PC-3) and colon carcinoma (HT29). Results show that, this natural compound has significant cytotoxicity activity against to these cancer cell lines. On the other hand it has limited cytotoxicity against to non-malignant cell lines (Ali et al., 1997; Chien & Pihie, 2003; de Fatima, Kohn, Antonio, de Carvalho, & Pilli, 2005; Inayat-Hussain, Annuar, Din, Ali, & Ross, 2003; Inayat-Hussain et al., 1999; Pihie, Stanslas, & Bin Din, 1998).

1.2. Structure Activity Relationship (SAR) of Goniothalamin Derivatives

Fatima and co-workers synthesized Z-isomers of (*R*)-goniothalamin **(*R*)-19** and two different kind of linker part enhanced derivatives of 5,6-dihydro-*2H*-pyran-2 ones that are **(*R*)-20** and **(*R*)-21** (Figure 1.5.) (de Fatima et al., 2005).



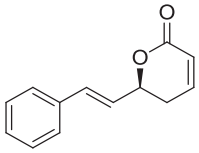
(*R*)-19 (*R*)-20 (*R*)-21

Figure 1.5. Structure of Z-isomers of (*R*)-goniothalamin **(*R*)-19** and derivatives of 5,6-dihydro-*2H*-pyran-2 ones, **(*R*)-20** and **(*R*)-21**. (Source: (de Fatima et al., 2005))

Their biologically activities were studied on MCF-7, NCI ADR, NCI 460, UACC62, 786-0, OVCAR03, PC-3, and HT29 cancer cell lines. They observed that, compound **(*R*)-19** is more cytotoxic in prostate (PC-3) cells and **(*R*)-21** is more cytotoxic in breast (MCF-7) and ovarian (OVCAR03) cancer cell lines than (*R*)-goniothalamin (**(*R*)-1**)). These results find out that compound having ether funcionality in the linker part (**(*R*)-21**) was 2-6 times lower cytotoxic than (*R*)-goniothalamin (**(*R*)-**

1)) and the presence of the *trans* oriented double bond in the linker part and Michael acceptor groups are the most important functional groups for the biological activity (de Fatima et al., 2005).

In another study, Fatima and co-workers synthesized (*S*)-goniothalamin (**(*S*)-1**) (Figure 1.6.) which is the enantiomer of (*R*)-goniothalamin (**(*R*)-1**)). Results showed that (*S*)-goniothalamin (**(*S*)-1**) has higher potency against kidney cancer cell line (786-0) and NCI ADR (breast expressing the resistance phenotype for adryamycin) than doxorubicin. For 786-0 cell line (*S*)-goniothalamin (**(*S*)-1**) is 600 times more effective than its enantiomer (*R*)-goniothalamin (**(*R*)-1**). Additionally, this synthesized compound is more effective in ovarian (OVCAR03) and prostate (PC03) cancer cell lines than the natural product (*R*)-goniothalamin (de Fatima, Kohn, de Carvalho, & Pilli, 2006).



(*S*)-1

Figure 1.6. Structure of (*S*)-goniothalamin (**(*S*)-1**).
(Source: (de Fatima, Kohn, et al., 2006))

After these results the same group synthesized eight different derivatives of (*S*)-goniothalamin (**(*S*)-1**) (Figure 1.7.). It is reported that the whole analogues are more potent against to breast cancer cell line that expressing the resistance phenotype for Adriamycin (NCI ADR) than doxorubicin (DOX) but the most potent compound is **28** has 4 nM IC_{50} value. For melanoma cell line (UACC.62), (*R*)-goniothalamin (**(*R*)-1)** was more potent than (*S*)-goniothalamin (**(*S*)-1**), although analogues **22**, **25**, and **28** were 3-, 7- and 3-times more potent, respectively, than (*R*)-goniothalamin (**(*R*)-1**).

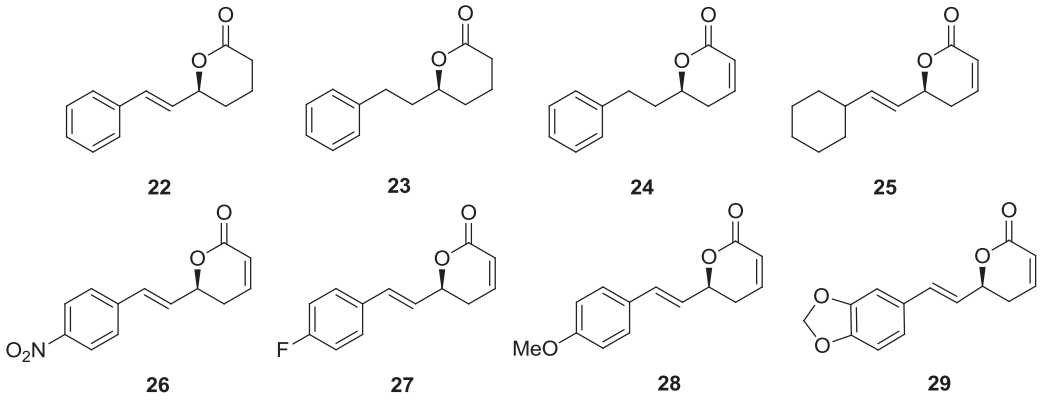


Figure 1.7. Structure of derivatives of (*S*)-goniothalamin.
(Source: (de Fatima, Kohn, et al., 2006))

Compound **25** and **28** has more antiproliferative activity against breast cancer cell line (MCF-7) than (*S*)-goniothalamin (**(*S*)-1**). By this result, authors noted that the cyclohexyl group (**25**) and addition of 4-OMe group to benzene (**28**) increase potency. Equivalently, these two compounds (**25**, **28**) are more effective than (*S*)-goniothalamin (**(*S*)-1**) and significantly more potent than (*R*)-goniothalamin (**(*R*)-1**) against to prostate cancer cell line (PC-3). Compound **22** and **25** 5- and 7- more potent than (*S*)-goniothalamin (**(*S*)-1**) against to ovarian cancer cells (OVCAR03). On the other hand, colon cancer cells (HT-29) were more sensitive to analogue **23**. If necessary to compare the positive control (DOX), DOX has lower potency for melanoma cancer cell line (UACC62) than analogues **22**, **25**, **28**. On ovarian cancer cells (OVCAR03) the compouns **22**, **25** and **26** are more potent than DOX. For prostate cancer cells (PC-3) DOX and compounds **25** and **28** have approximately the same results (de Fatima, Kohn, et al., 2006).

To sum up, (*S*)-goniothalamin (**(*S*)-1**) and compound **25** more selective cytotoxic compounds against kidney cancer cell growth (786-0) with IC_{50}= 4 and 5 nM, respectively. On the other hand, compound **28** is more potent against NCI ADR with IC_{50}= 4 nM. Their results show that presence of Micheal acceptor part, *S* configuration and C=C double bond are essential for activity against to kidney cancer cell line (786-0) (Figure 1.8.) (de Fatima, Kohn, et al., 2006).

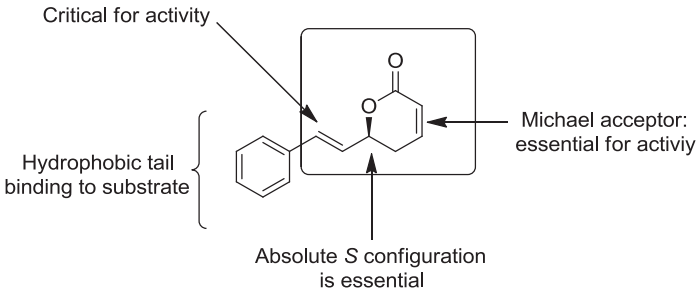


Figure 1.8. Essential groups of (*S*)-goniothalamin diagnosed by their cytotoxicity against 786-0 cancer cell line. (Source: (de Fatima, Kohn, et al., 2006))

Barcelos and co-workers were synthesized the racemic mixtures of methoxylated and trifluoromethylated goniothalamin (X=O) and aza-goniothalamin (X=N) derivatives (Compounds **30-45**) (Figure 1.9.). Cytotoxic property of these compounds was studied on glioma (U251), MCF7, NCI ADR, 786-0, lung (NCI-H460), OVCAR03, HT-29 cancers and human keratinocytes (HaCat) cell lines. Results of the study indicates that, 4-methoxy analogue **34** and 2,4-dimethoxy derivative **36** showed higher potency against all the seven human cancer cell lines similar to 3,5-dimethoxy analogue **40**. They find out that 2,4-dimethoxy analogue, compound **36**, showed higher potency than goniothalamin against all cancer cell lines evaluated. Moreover, this compound (**36**) was more cytotoxic for NCI-ADR, OVCAR03 and HT-29 cancer cell lines while it has less cytotoxicity against to HaCat. The 3,5-dimethoxy analogue **40** and 2,4,5-trimethoxy analogue **44** also displayed promising antiproliferative activity compared to that of (*R*)-goniothalamin (**(*R*)-1**) (Barcelos et al., 2012).

Kasaplar et al., synthesized 6-bicycloaryl substituted 5,6-dihydro-*2H*-pyran-2-one derivatives (Figure 1.10. and 1.11.). Among them naphthalen-1-yl substituted klauzon derivative was named as klavuzon by the inventors (Figure 1.10.). Especially, compounds **47** and **48** can be considered as conformationally constrained derivatives of goniothalamin. Biological activity of the synthesized naphthalen-1-yl, naphthalen-2-yl and quinoline-3-yl derivatives was also reported (Figure 1.11.) (Kasaplar, Yilmazer, & Cagir, 2009). According to their findings, compounds **(*R*)-47**, **48**, **49**, **(R)-51** and **(*R*)-52** are more cytotoxic for PC-3 and MCF-7 cancer cell lines than (*R*)-goniothalamin (**(*R*)-1**). Additionally, compound **(*R*)-52** is 80 and 40 times more potent than (*R*)-goniothalamin (**(*R*)-1**) in PC-3 and MCF-7 cancer cells, respectively. On the other hand, compound **(*R*)-51** is 31 and 7 times more cytotoxic than (*R*)-goniothalamin (**(*R*)-1**) for PC-3 and MCF-7 cancer cells, respectively (Kasaplar et al., 2009).

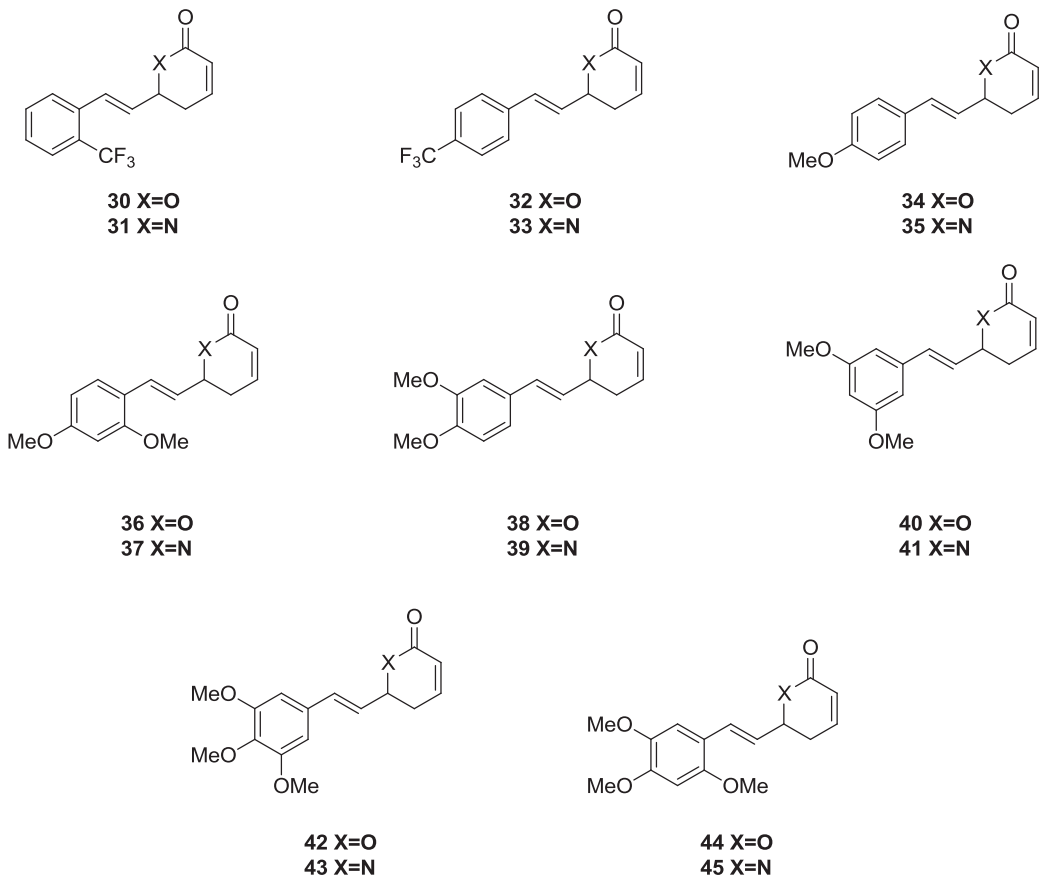


Figure 1.9. Structures of methoxylated and trifluoromethylated goniothalamin (X=O) and aza-goniothalamin (X=N) analogues. (Source: (Barcelos et al., 2012))

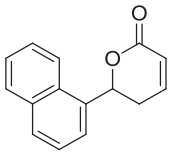


Figure 1.10. Chemical structure of klavuzon (**46**).

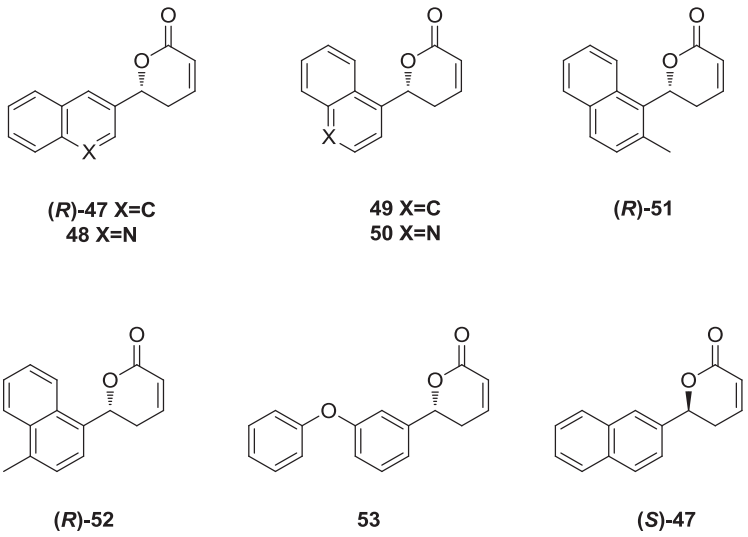


Figure 1.11. Chemical structures of 6-bicycloaryl substituted 5,6-dihydro-*2H*-pyran-2-one derivatives. (Source: (Kasaplar et al., 2009))

1.3. Synthesis of 5,6-Dihydro-*2H*-pyran- 2-one Derivatives

As it was summarized above, α,β-unsaturated δ-lactones have great potential in terms of biological activity. Due to this importance many research groups developed synthetic strategies for the synthesis of α,β-unsaturated δ-lactone derivatives. In this part of the thesis, these racemic and asymmetric synthesis methodologies will be discussed shortly.

1.3.1. Racemic Synthesis of α,β-Unsaturated δ-Lactones Starting from Aldehydes

This method starts with using the aldehydes (**54**) as reactants. The R groups consist of naphthalene, benzene, substituted benzene, quinolone, furan, benzothiophene, thiophene, benzyloxy, styryl, diphenyl and adamantine. In the first step, this reactant is treated with allyl magnesium bromide or allyl zinc bromide to produce homoallylic alcohol (**55**). In the second step, acrylic acid is reacted with compound **55** under basic (TEA) conditions in the presence of EDC to obtain **56**. Finally, via ring closing metathesis by using second generation Grubbs' catalyst in DCM, compound **56** was

converted to α,β unsaturated δ-lactone (**57**) (Figure 1.12.) (S. M. Lee, Lee, Kim, & Ko, 2011).

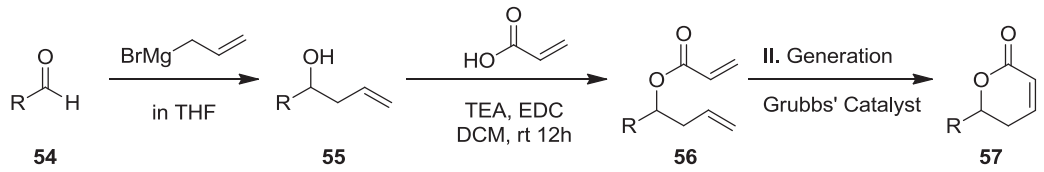


Figure 1.12. Racemic synthesis method of α,β-unsaturated δ-lactone starting from aldehydes. (Source: (S. M. Lee et al., 2011))

1.3.2. Cyclocarbonylation of Unsaturated (Allenyl, Homopropargylic, Homoallylic) Alcohols

Dupont and Donato were synthesized α,β-unsaturated δ-lactones by starting with O-protected homopropargyl alcohols (**58**). They reacted these alcohols with the same equivalent of Schwartz reagent $Cp_2Zr(H)Cl$ as s suspension in benzene at room temperature. After 12–15 h reaction was stopped and formed product was used without isolation. Then carbonylation of these hydrozirconated alkynes under 1.1 atm of carbon monoxide followed by the addition of molecules iodine gave intermediate **60**. By applying aqueous workup and column chromatography of the reaction mixture they succesfully produced the lactones (**61**) (Figure 1.13.) (Dupont & Donato, 1998).

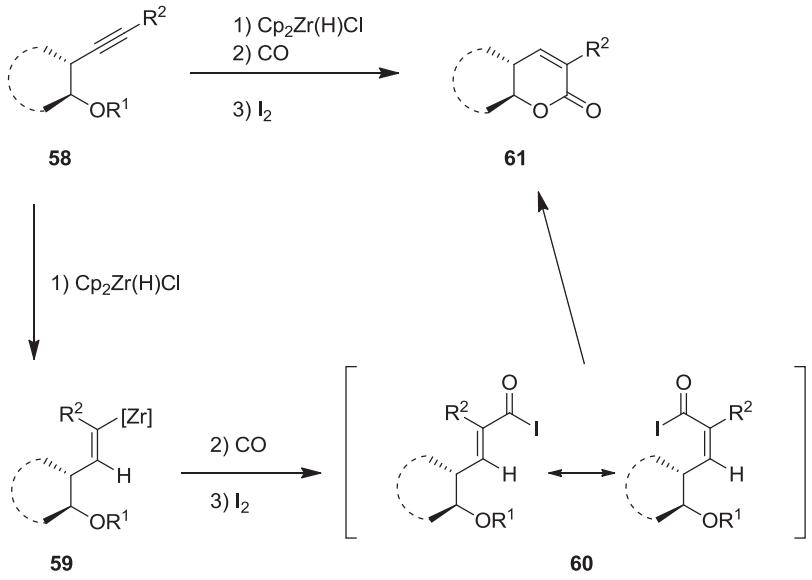


Figure 1.13. Racemic synthesis method of α,β-unsaturated δ-lactone starting from homopropargyl alcohols. (Source: (Dupont & Donato, 1998))

1.3.3. Asymmetric Allylboration of *Trans*-cinnamaldehyde for the Enantioselective Synthesis of (*R*)- and (*S*)-Goniothalamin

Reddy and co-workers synthesized α,β-unsaturated δ-lactones via asymmetric allylboration method. They used *trans*-cinnemaldehyde (**62**) as starting compound for the preparation of both enantiomers. To prepare the (*R*)-enantiomer, (-)-B-allyldiisopinocampheylborane (**(-)-63**) was added to *trans*-cinnemaldehyde to produce homoallylic alcohol ((***R***)-**64**) in Et_2O-pentane mixture at -100 °C. Esterification of the formed alcohol by acryloyl chloride (**65**) yielded the corresponding ester (***R***)-**66**. Then treatment of ester **66** with 1st generation Grubbs' catalyst (**67**) gave α,β-unsaturated δ-lactone in DCM. In the preparation of (*S*)-enantiomers, the same sequence of reactions were used, except that (+)-B-allyldiisopinocampheylborane (**(-)-63**) was used as chiral auxiliary in the first step (Figure 1.14.) (Reddy, Brown, & Ramachandran, 2001).

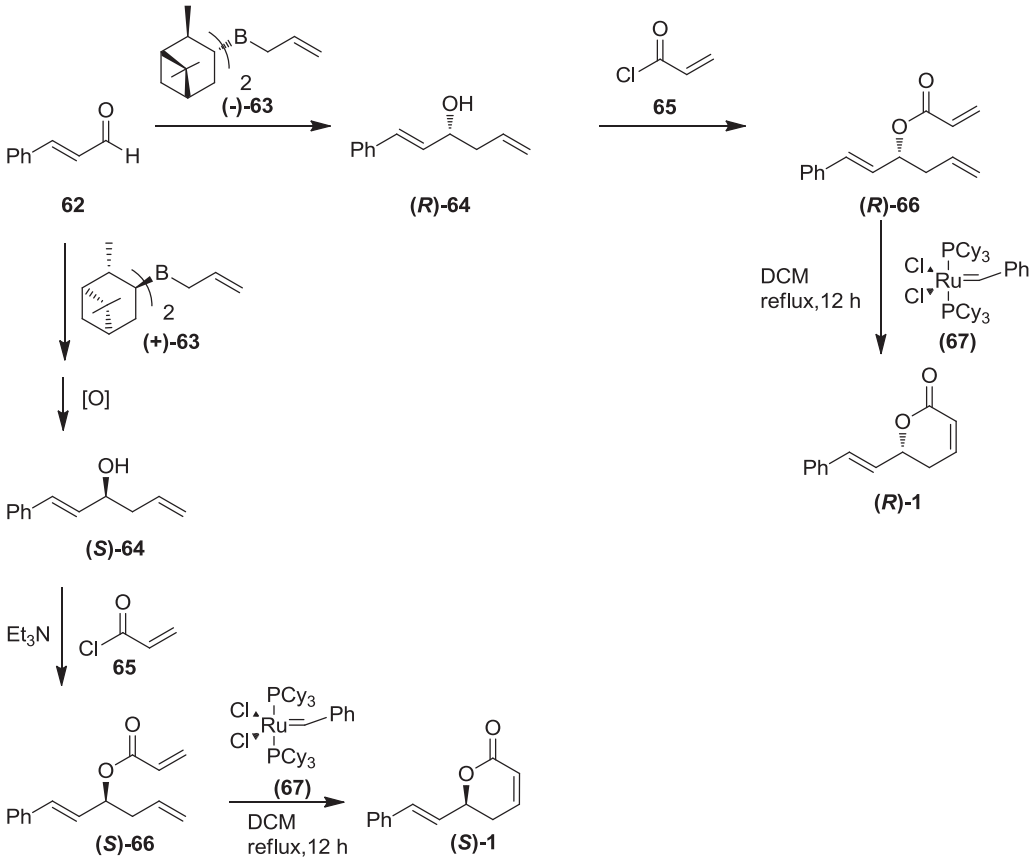


Figure 1.14. Asymmetric synthesis of (*R*)-goniothalamin **(*R*)-1** and (*S*)-goniothalamin **(*S*)-1** via allylboration with (-)-B-allyldiisopinocampheylborane **(-)-63** and (+)-B-allyldiisopinocampheylborane **(+)-63**, respectively. (Source: (Ramachandran, Reddy, & Brown, 2000; Reddy et al., 2001))

1.3.4. Enantioselective Allylation Method of α,β-Unsaturated δ-Lactones

Hanawa and co-workers developed a new titanium *R*-BINOL complex (***R*,*R*-69**) which is highly selective for the enantioselective allylation of aldehydes. This complex was prepared starting from $Ti(OiPr)_4$, $TiCl_4$ and *R*-BINOL (**(*R*)-68**) (Figure 1.15.) (Hanawa, Hashimoto, & Maruoka, 2003).

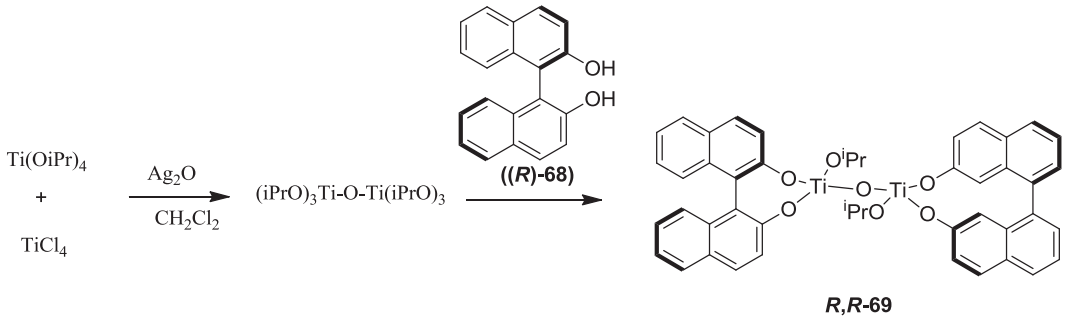


Figure 1.15. Preperation of (*R*)-BINOL-Ti complex (**69**).

Kasaplar and co-workers synthesized enantiomers of both enantiomers of conformationally constraired analog of goniothalamin starting from 2-naphthaldehyde (**70**). In the first part, (*R*)-enantiomer was prepared by using the catalyst prepared from *R*-BINOL (**(*R*)**-68). In the next one, Ti complex of *S*-BINOL was used as a source of chirality. Both Ti-BINOL complexes were used in the allylation of 2-naphthaldehyde (**70**) in the presence of allylbutyltin. Formed homoallylic alcohols (**R-71** and **S-71**) were reacted with acryloyl chloride under basic condition to produce acrylate esters (**R-72** and **S-72**). Application of Grubbs' catalyst to these esters yield the target products **R-47** and **S-47** in DCM at 60 ^{o}C, respectively (Figure 1.16.) (Kasaplar et al., 2009).

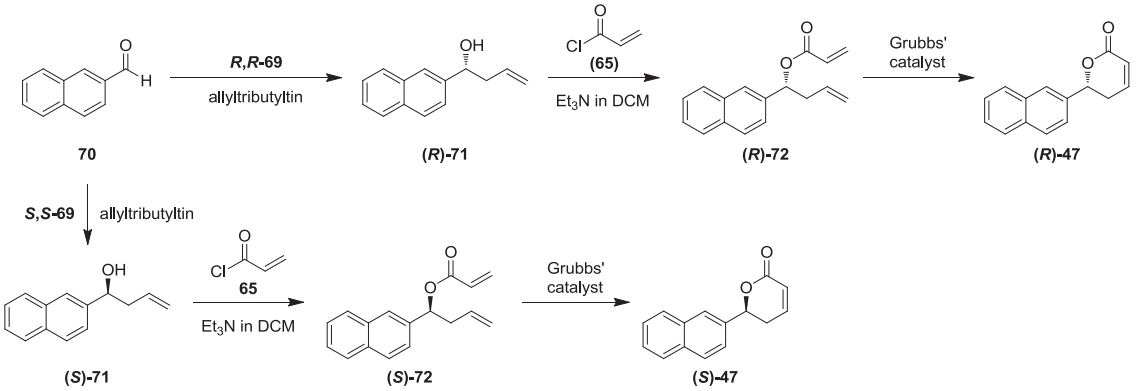


Figure 1.16. Enantioselective allylation of aldehydes which can be used in the synthesis of α,β-unsaturated δ-lactones. (Source: (Kasaplar et al., 2009))

1.3.5. Chemoenzymatic Synthesis from Homoallylic Alcohol

Lipases are used to separate the racemic mixtures in organic chemistry. They have high enantioselectivity for a large range of substrates and this enzyme widely exist and readily avaliable, so it is quite cheap (Gruttadauria, Lo Meo, & Noto, 2004).

Sundby and co-workers converted *trans*-cinnemaldeyhde into homoallylic alcohol (**73**) by using allylmagnesium bromide, and then kinetically resolved the racemic alcohol (**73**) by a transesterification reaction in hexane using vinyl acrylate as acyl donor and Candida Antarctica lipase B (CALB) as catalyst. Then, by acryloyl chloride and triethyl amine in THF **(*S*)-64** was converted to **(*S*)-66**. In the final step, by treating with Grubbs' catalyst in DCM **(*R*)-66** and **(*S*)-66** were altered to **(*R*)-1** and **(*S*)-1**, respectively (Figure 1.17.) (Sundby et al., 2004).

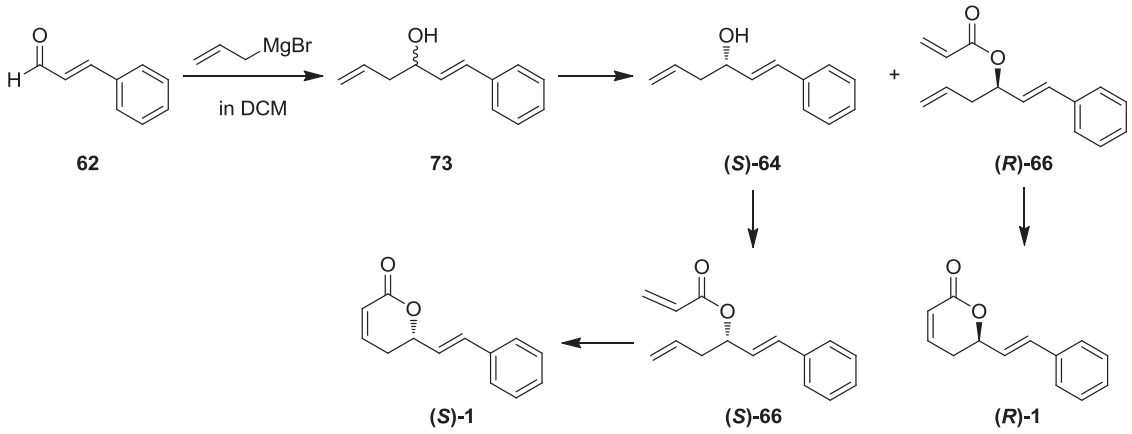


Figure 1.17. Synthesis of enantiomers of goniothalamin **(*R*)-1** and **(*S*)-1**.
(Source: (Sundby et al., 2004))

1.3.6. Hetero-Diels-Alder Reactions of Brassard Diene with Aromatic Aldehydes

Hetero-Diels-Alder (HDA) reaction of Brassard diene (**74**) is an easy way (by one step) to get α,β-unsaturated δ-lactones from aromatic aldehydes in the presence of titanium based chiral Lewis acids. However, the aliphatic aldehydes have lower selectivities to form lactones (Boucard et al., 2007).

Fan et al., applied HDA reaction and synthesized compound **77**, which is a kind of α,β-unsaturated δ-lactone, in high yield by reacting the Brassard diene (**74**) and benzaldehyde (**75**) in the presence of titanium complexes of **76** and trifluoroacetic acid (TFA) in toluene at 0 ^{o}C (Figure 1.18.) (Fan et al., 2004).

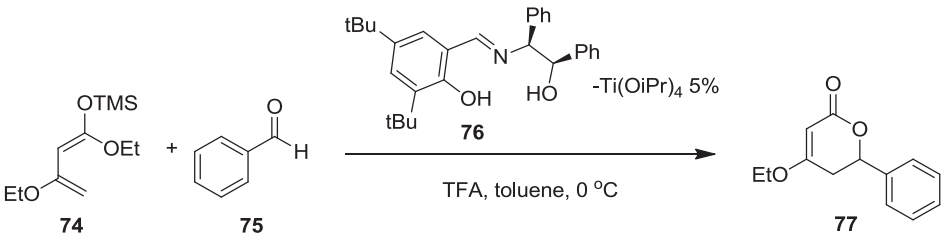


Figure 1.18. Synthesis of α,β-unsaturated δ-lactone in one step with Brassard diene (**74**) and benzaldehyde (**75**). (Source: (Fan et al., 2004))

1.3.7. Keck's Annulation

Keck and co-workers enhanced an another method. A derivative of β-acetoxy aldehyde (**78**) was treated with lithium enolate of methyl acetate (**79**) and successfully the compound **(*S*)-21** was obtained in high yield (69%). This reaction occured with a sequence of reactions; aldol type reaction, acyl migration, lactonization and irreversible β-elimination, respectively (Figure 1.19.) (Keck, Li, & Knutson, 1999).

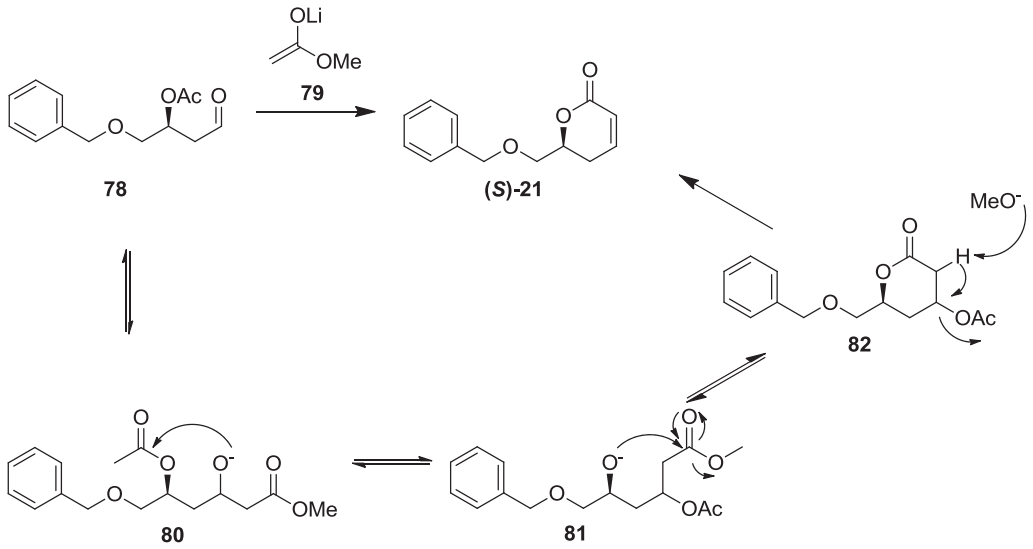


Figure 1.19. Keck Annulation method and reaction mechanism.
(Source: (Keck et al., 1999))

CHAPTER 2

RESULT AND DISCUSSION

Among the previously reported klavuzon derivatives 2'-methylklavuzon **(R)-51** had second highest cytotoxic activity against PC-3 and MCF-7 cancer cell lines (Kasaplar et al., 2009). Therefore, in this work racemic synthesis of simple 2'-alkoxymethyl substituted klavuzons (**83-91**) will be studied to evaluate the structure activity relationship of the synthesized compounds (Figure 2.1.).

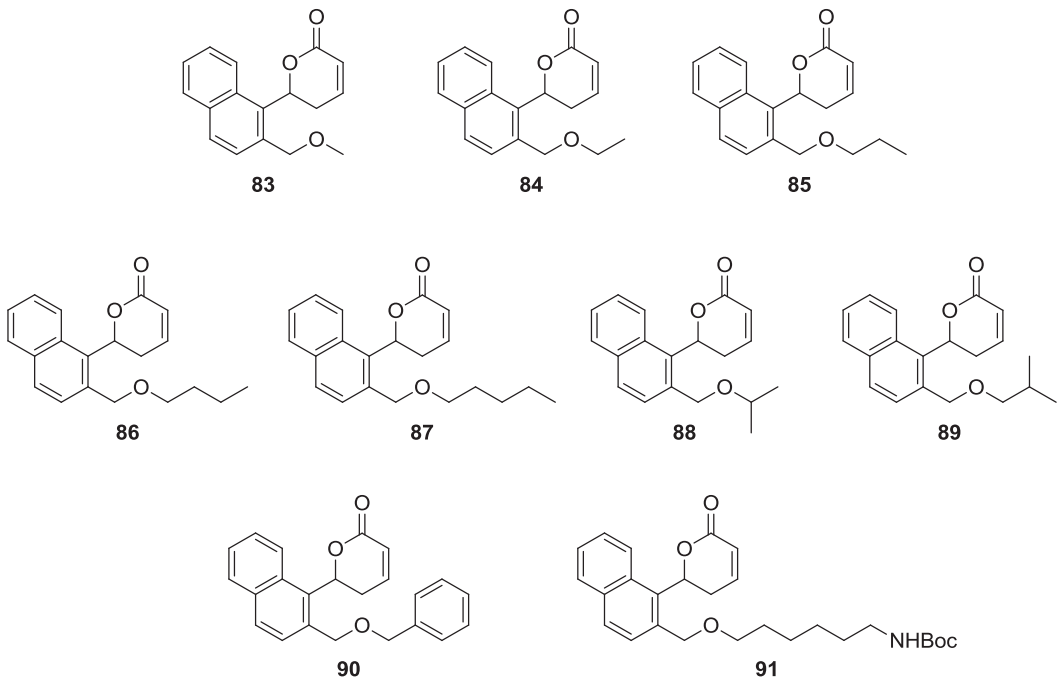


Figure 2.1. Structures of proposed 2'-alkoxymethyl substituted klavuzon derivatives.

2.1. Our Strategy Toward the Synthesis of 2'-Alkoxymethyl Klavuzon Derivatives

To perform the racemic synthesis of compounds **51** and **83-91** a synthesis strategy was proposed as shown in Figure 2.2. Although, it was known that radicalic bromination of aldehydes yield acyl halides. Small amount of compound **131** can also be formed as reported in our previous works (Kanbur, 2015; Kara, 2015).

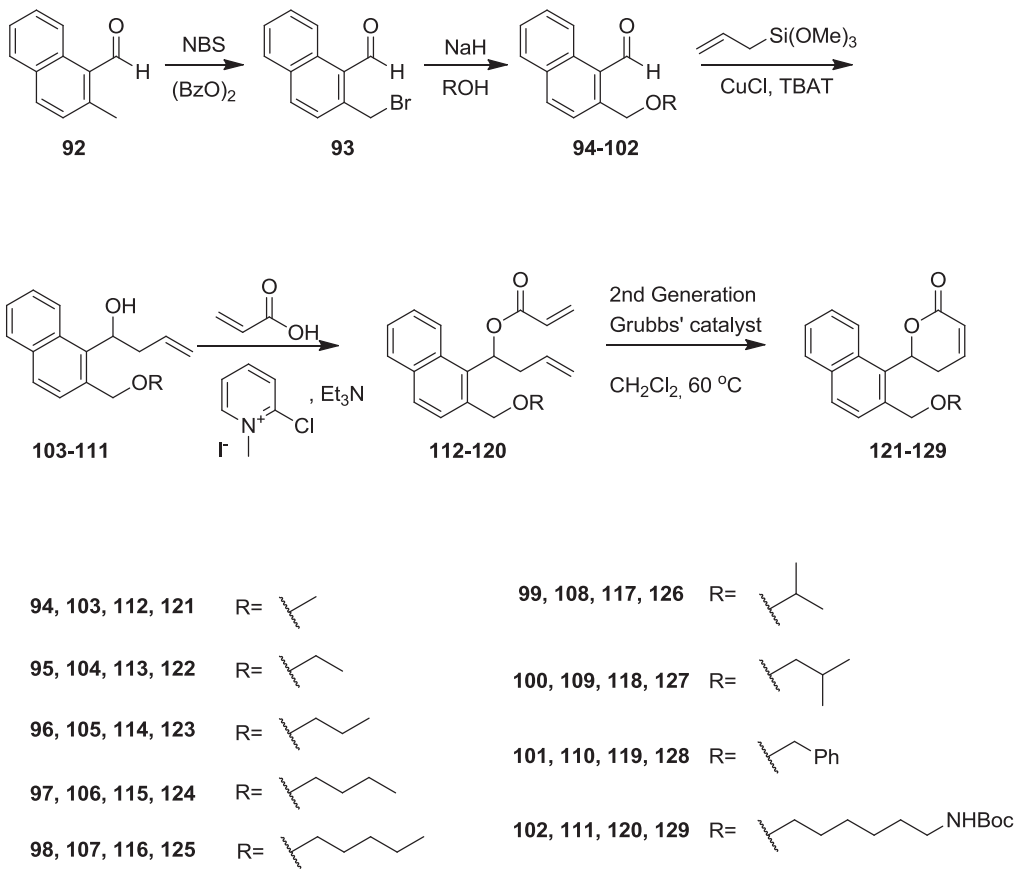
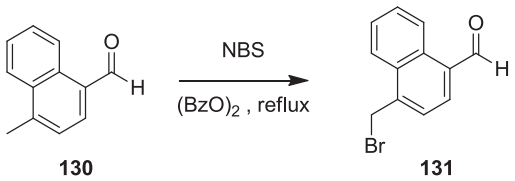


Figure 2.2. The strategy of synthesis of α,β-unsaturated-δ-lactone from 2-methyl-1-naphthaldehyde.

In this strategy, formation of compound **93** was a keypoint. Because reaction of this with various alcohols under basic condition would give diverse 2-alkoxymethyl-1-naphthaldehyde derivatives (**94**-**102**) only in two steps. Unfortunately, all attempts toward the formation of compound **93** was failed. Benzylic bromination of 4-methyl-1-naphthaldehyde (**130**) was studied previosly in our group, and it was found that small amount of brominated aldehyde could be obtained at the end of the reaction. The same reaction was also tried as a model stuy just to setup the optimium reaction conditions (Table 2.1.). Unfortunately, all attempts were failed in our hands.

Table 2.1. Results of the benzylic bromination of 4-methyl-1-naphthaldehyde with NBS.



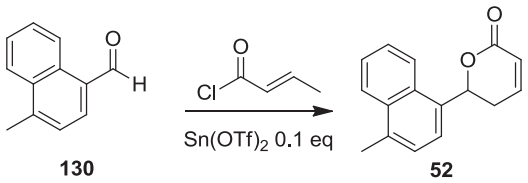
130 131

Entry	NBS (eq)	CCl_3Br (eq)	$(BzO)_2$ (eq)	$Ti(O\text{-}i\text{-}Pr)_4$ (eq)	Solvent	Yield%
1	1.1	-	0.02	-	Benzene	N.P.
2	1.2	-	0.02	-	CH_3CN	N.P.
3	-	17	0.02	-	Benzene	N.P.
4	-	17	0.038	-	Benzene	N.P.
5	-	17	0.17	-	Benzene	N.P.
6	-	17	0.17	1	Benzene	N.P.

2.2. Attempts Toward the Catalytic Asymmetric Formation of δ-Lactones from Unsaturated Acyl Halides

As an alternatine, previously Tiseni and coworkers reported that aldehydes can react with α,β-unsaturated acylhalides in the presence of tin II triflate and a tertiary base Quinidine (Table 2.2.) (Tiseni & Peters, 2010). They reported that reaction of acylhalides having at least 5-carbons length chain with aldehydes gave 5,6-disubstituted-5,6-dihydro-*2H*-pyran-2-one derivatives. It can be applied to produce only 6-substituted-5,6-dihydro-*2H*-pyran-2-one derivatives. For this purpose 4-methyl-1-naphthaldehyde was treated with crotonoyl chloride in the presence of variety of tertiary amine (Et_3N) or ether functionalized tertiary ethers (*tris*(2-(benzyloxy)ethyl)amine and quinidine). Unfortunately, all of the attempts were failed.

Table 2.2. Preperation of α,β-unsaturated δ-lactone starting from 4-methyl-1-naphthaldehyde.



Entry	Crotonoyl chloride (eq)	DIPEA (eq)	Et_3N (eq)	tris(2-(benzyloxy)ethyl)amine (eq)	Quinidine (eq)	Yield %
1	1	5	0.2	-	-	N.R.
2	2	5	0.2	-	-	N.R.
3	1.5	3	-	0.1	-	N.R.
4	2	5	-	-	0.2	N.R.

2.3. Esterification of 1-Naphthoic acid under Acidic and Basic Conditions

Another approach is the preparation of ethyl 2-(bromomethyl)-1-naphthaldehyde (**134**) starting from 2-methyl-1-naphtoic acid (**132**). Previous studies performed in our laboratory showed that 4-methyl-1-naphtoic acid could be esterified under acidic condition in ethanol. A similar approach was tried for the synthesis of ethyl 2-methyl-1-naphtoic acid, but yield of the reaction was 48 % in the presence of acidified ethanol solution (Figure 2.3.).

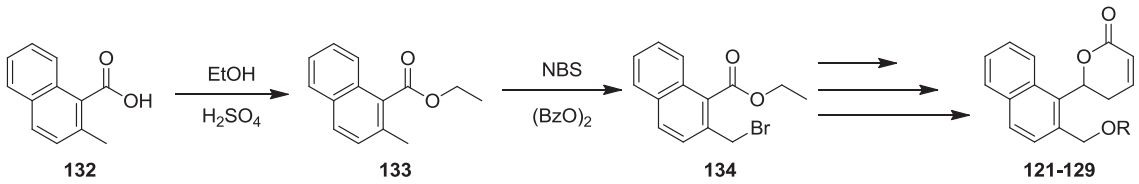


Figure 2.3. Preparation of ethyl 2-(bromomethyl)-1-naphthaldehyde (**134**) starting from 2-methyl-1-naphtoic acid (**132**).

On the other hand, 2-methyl-1-naphtoic acid (**132**) was treated with potassium carbonate and iodoethane to produce ethyl 2-methyl-1-naphtoate (**133**). Yield of this reaction was quantitative and reproducibility was quite high (Figure 2.4.).

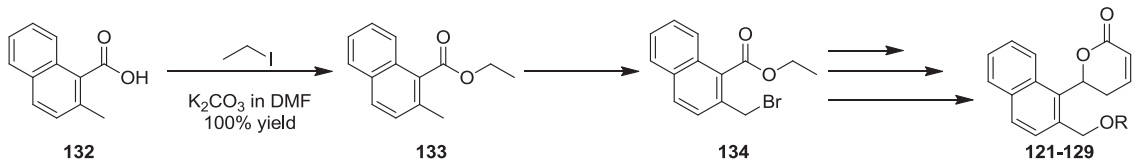


Figure 2.4. Preparation of ethyl 2-methyl-1-naphtoate (**133**) starting from 2-methyl-1-naphtoic acid (**132**).

2.4. Benzylic Bromination of Ethyl 2-Methyl-1-naphthoate (133)

In the next step, benzylic bromination reaction of ethyl 2-methyl-1-naphtoate was performed under various conditions. In earlier attempts compound **133** was treated with benzoylperoxide and bromotrichloromethane instead of carbon tetrachloride, which is prohibited chemical in Turkey, in benzene (Mestres & Palenzuela, 2002) but there was no product formation. Then benzylic bromination was performed in acetonitrile by using NBS and benzoylperoxide but these reactions also failed (Table2.3.) (Carreno, Ruano, Sanz, Toledo, & Urbano, 1995).

Table 2.3. Benzylic bromination reaction of ethyl 2-methyl-1-naphtoate.

Entry	NBS (eq)	CCl_3Br (eq)	$(BzO)_2$ (eq)	Solvent	Yield %
1	-	17	0.02	Benzene	N.R.
2	1.1	-	0.03	CH_3CN	N.R.
3	1.1	-	0.1	CH_3CN	N.R.
4	1.1	-	0.3	CH_3CN	N.R.
5	1.5	-	0.02	CH_3CN	N.R.

Ishii and coworkers developed an alternative method for benzylic bromination reaction by using $NaBrO_3/NaHSO_3$ mixture in EtOAc-water (Kikuchi, Sakaguchi, & Ishii, 1998). In the light of this study, compound **133** was converted to corresponding brominated product **134** via the formation of small amount of Br_2 in situ by mixing

$NaBrO_3/NaHSO_3$. This reaction is quite sensitive to temperature and amount of solvent used in the reaction. The yield of this reaction was quantitative under optimized conditions. Otherwise, a unseperable mixture of compounds **133** and **134** can be obtained. Because the purification of compound **134** was quite problematic, this compound was used without purification in the next steps (Figure 2.5.).

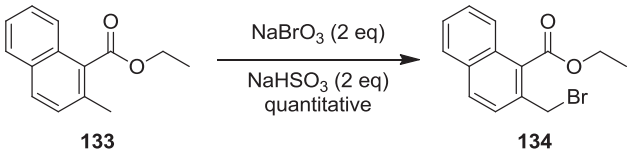


Figure 2.5. Benzylic bromination reaction by using $NaBrO_3/NaHSO_3$ mixture.

2.5. Toward to the Synthesis of 2-Alkyl Substituted 1-Naphthaldehyde Derivatives

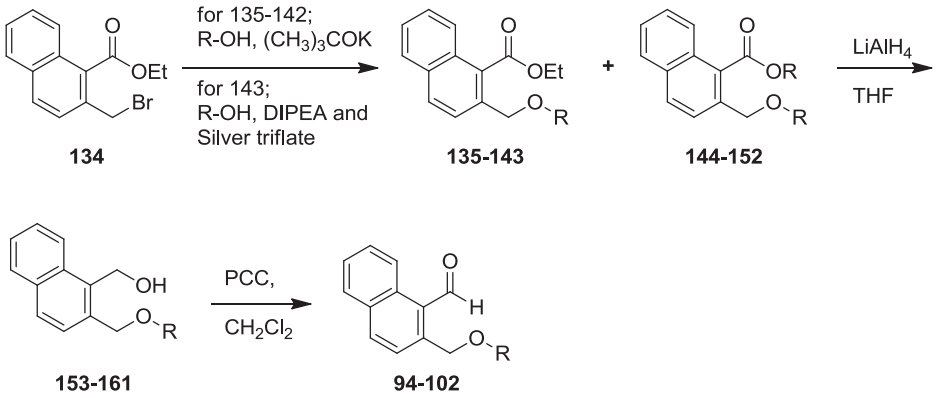
At this point, the formed 2'-alkoxymethyl-1-naphthaldehyde (**134**) can easily be transformed into 2-alkoxy-1-naphthaldeyde derivatives (**94-102**) in three steps. First primary alcohols were treated with potassium *tert*-butoxide to yield the corresponding primary alkoxide, which then can be reacted with compound **134** to produce the corresponding ethyl 2-alkoxymethyl-1-naphtoate derivatives (**135-143**) along with their transesterification products (**144-152**).

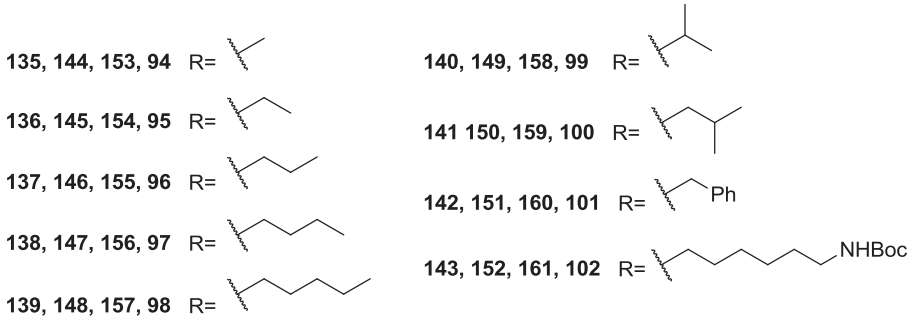
Yield of this reactions were given in Table 2.4. In the case of methyl, ethyl, propyl, pentyl, benzyl alcohol, and 6-(Boc-amino)-1-hexanol corresponding (**135**, **136**, **139**, **141**, **142** and **143**) ethyl esters were isolated successfully. In the case of propyl only transesterification products (**146**) could be isolated in 52 % yield for the last two steps. On the other hands, transesterification products for methoxide, butoxide and isopropoxide couldn't be purified in this step; so their products were used as a mixture in the next step. In the case of benzyl alcohol addition, two repetitive experiments were resulted the formation of different amounts of ethyl ester (**142**) and transesterification (**151**) product. Both of these products were isolated and characterized in two different reactions.

In the next step, formed 2-alkoxymethyl substituted 1-naphtoate derivatives were reduced to corresponding alcohols by $LiAlH_4$ to produce alcohols **153-161**. Except

isopropyl substituted derivative **158**, all reduced alcohols were obtained in relatively good yields. Lastly, 1-naphtylmethanol derivatives (**153-161**) were oxidized to 1-naphthaldehyde derivatives (**94-102**) by PCC in CH_2Cl_2 successfully (Table 2.4.).

Table 2.4. Synthesis of 2-alkoxymehyl-1-naphthaldeyhdes (**94-102**).





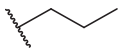
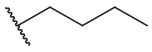
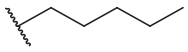
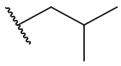
Entry	R	135-143 Yields %	144-152 Yields %	153-161 Yields %	94-102 Yields %
a		66[a]	-[b]	83	77
b		60[a]	-	85	78
c		-	52[a]	85	74
d		-	-[b]	12[c]	76
e		44[a]	-	81	86
f		-[b]	-[b]	-[b]	23[d]
g		42[a]	-	97	84

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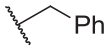
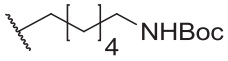
Table 2.4. (cont.)

h		80[a]	-	90	86
		28[a]	30[a]		
i		14[a]	-	65	68

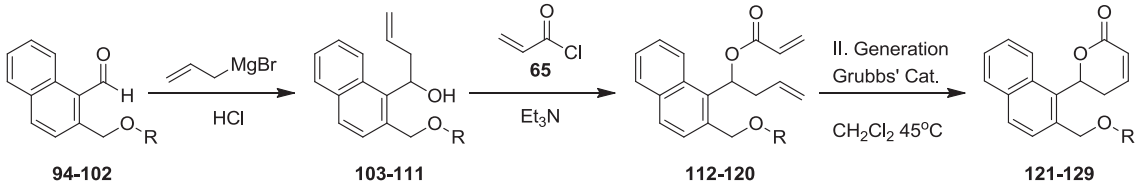
[a, c, d]Yields for the last 2,3 and 4 steps, respectively. [b]Yields couldn't reported because compounds couldn't purified.

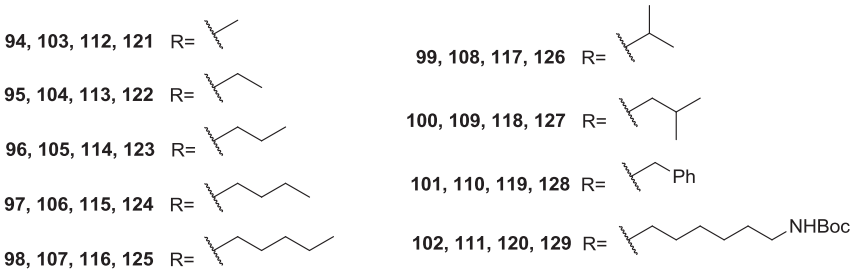
2.6. Synthesis of 2'-Alkyl Substituted Klavuzon Derivatives

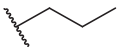
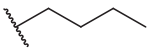
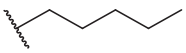
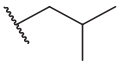
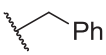
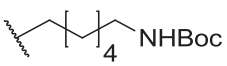
In the first stage of the synthesis, allymagnesium bromide was reacted with 2-alkoxymethyl substituted 1-naphthaldehydes (**94-102**) to produce the correspondıng homoallylic alcohols (**103-111**), with 72-98 % yields. Interestingly for the allylic form of 2-propoxymethyl substituted derivative **106** ^{1}H-NMR in $CDCl_3$ indicates the formation of atropisomer. When the ^{1}H-NMR was acquired in CD_3OD this atropisomers were disappeared. It seems that atropisomers were formed by intramoleculer hydrogen bonding.

Treatment of these alcohols (**103-111**) with acryloyl chloride under basic condition gave the acrylate esters (**112-120**) with 44-97 % yields. At last, ring closing metathesis reactions of acrylate esters (**112-120**) with II. generation Grubbs' catalyst gave the target klavuzon derivatives with 68-99 % yields (Table 2.5.).

Table 2.5. Synthesis of α,β-unsaturated-δ-lactone (**121-129**) from aldehydes (**94-102**).





Entry	R	103-111 Yield %	112-120 Yield %	121-129 Yield %
a		94	88	78
b		94	97	85
c		94	89	85
d		98	91	67
e		77	76	73
f		96	79	68
g		89	75	88
h		72	95	74
i		98	44	99

CHAPTER 3

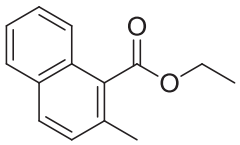
EXPERIMENTAL

3.1. General Methods

Reagents and solvents were purchased from Sigma-Aldrich and used as supplied. The whole experiments were under N_2 gaseous purchased from Habaş. Reactions were monitored by using Merck TLC plates (Silica gel 60 F254). The products were isolated by chromatographic purification by flash column using 70-230 mesh sized silica gel. ^{1}H, ^{13}C NMR data were recorded on Varian 400-MR (400 MHz) spectrometer. Chemical shifts for ^{1}H, ^{13}C-NMR are reported in δ (ppm) and $CDCl_3$ peaks were used as reference in ^{1}H-NMR (7.26 ppm), and ^{13}C-NMR (77.36 ppm) respectively.

3.2. Preparation of Ethyl 2-Methyl-1-naphthoate (133) from 2-Methyl-1-naphthoic Acid (132)

In a two-necked flask (25 mL), 1.00 g of 2-methyl-1-naphthoic acid (5.37 mmol, 1.00 eq) was placed and dissolved in 6.0 mL of dry dimethylformamide (DMF) then 1.48 g of potassium carbonate (10.74 mmol, 2.00 eq) and 1.26 g of iodoethane (648 µL, 8.05 mmol, 1.50 eq) was added and the mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, resulting mixture was extracted with ethyl acetate (3x10 mL) and combined organic phase washed with distilled water (3x10 mL) and 10 mL of saturated brine solution and 10 mL of 1M NH_4Cl solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:4) to give 1.15 g of desired product in quantitative yield.



Yield: > 99%; colourless viscous liquid;

R_f: 0.57 (1:4 EtOAc-Hex);

R_f: 0.50 (1:8 EtOAc-Hex containing 1% acetic acid);

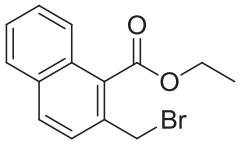
R_f: 0.33 (1:25 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.86 – 7.78 (m, 3H), 7.51 (ddd, *J* = 8.4, 4.2, and 1.2 Hz, 1H), 7.46 (dd, *J* = 11.3, and 4.4 Hz, 1H), 7.32 (d, *J* = 8.4 Hz, 1H), 4.59 – 4.50 (q, J = 7.2 Hz 2H), 2.52 (s, 3H), 1.51 – 1.42 (t, J = 7.2 Hz 3 H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.75, 133.17, 131.63, 130.29, 129.99, 129.55, 128.36, 128.04, 126.99, 125.44, 124.42, 61.32, 20.08, 14.40.

3.3. Benzylic Bromination of Ethyl 2-Methyl-1-naphthoate (133)

In a two-necked flask (25 mL), 423 mg of sodium bromate (2.8 mmol, 2.00 eq) was added and dissolved in 4.0 mL of distilled water. Into this flask, a solution of 300 mg of 2-methyl-1-naphtoic acid (1.4 mmol, 1.00 eq) was placed after dissolved in 6.0 mL of ethyl acetate. In another flask (25 mL), 291 mg of 58.5% sodium bisulfite (2.8 mmol, 2.00 eq) dissolved in 2 mL of distilled water. Then the first mixture was added to the second flask by dropwise in 10 min at 0 ^oC. The resulting mixture was stirred at room temperature under nitrogen atmosphere for 16 h. After that, reaction mixture was extracted with 3x10 mL of ethyl acetate and combined organic phase was washed with 10 mL of saturated brine solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. Crude NMR indicates the quantitative yield of the target product (**133**).



Yield: Quantitative by NMR; yellow viscous liquid;

R_f: 0.56 (1:8 EtOAc-Hex);

R_f: 0.24(1:25 EtOAc-Hex);

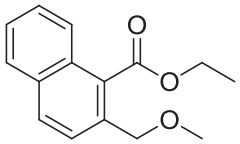
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.96 – 7.91 (m, 1H), 7.88 (d, *J* = 8.5 Hz, 1H), 7.83 (dd, *J* = 7.3, and 1.9 Hz, 1H), 7.60 – 7.47 (m, 3H), 4.71 (s, 2H), 4.60 (q, *J* = 7.1 Hz, 2H), 1.50 (t, *J* = 7.1 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.75, 133.17, 131.63, 130.29, 129.99, 129.55, 128.36, 128.04, 126.99, 125.44, 124.42, 61.32, 20.08, 14.40.

3.4. Preparation of Ethyl 2'-Alkoxymethyl-1-naphthoate Derivatives

3.4.1. Ethyl 2-(Methoxymethyl)-1-naphthoate (135-144)

In a two-necked flask (25 mL), the crude product (527 mg) of bromination reaction was placed and dissolved in 3.0 mL of methanol then 303 mg of potassium tert-butoxide (2.7 mmol, 1.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 2 hours, the reaction mixture was treated with 5 mL of 1M HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:12) resulted 217 mg of desired product in 66% yield for two steps.



Yield: 66% for two steps; colourless viscous liquid;

R_f: 0.46 (1:8 EtOAc-Hex);

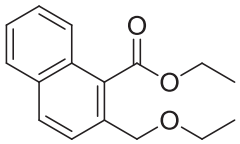
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 (ddd, *J* = 3.2, 1.5 and 0.8 Hz, 1H), 7.90 (d, *J* = 8.6 Hz, 1H), 7.87 – 7.83 (m, 1H), 7.57 – 7.47 (m, 3H), 4.69 (s, 2H), 4.54 (q, *J* = 7.2 Hz, 2H), 3.39 (s, 3H), 1.46 (t, *J* = 7.1 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.05, 133.90, 132.83, 130.03, 129.94, 129.87, 128.12, 127.12, 126.21, 125.49, 124.88, 72.56, 61.44, 58.24, 14.32;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{15}H_{16}O_3Na$): 267.0997; found: 267.0992.

3.4.2. Ethyl 2-(Ethoxymethyl)-1-naphthoate (136)

In a two-necked flask (25 mL), the crude product (176.8 mg) of bromination reaction was placed and dissolved in 7.0 mL of ethanol then 102 mg of potassium tert-butoxide (0.9 mmol, 1.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 2 hours, the reaction mixture was treated with 5 mL of 1M HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:25) resulted 111 mg of desired product in 60% yield for two steps.



Yield: 60% for two steps; colourless viscous liquid;

R_f: 0.35(1:8 EtOAc-Hex);

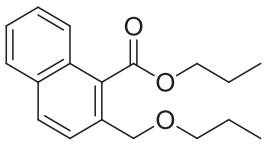
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.93 – 7.87 (m, 2H), 7.84 (dd, *J* = 7.9 and 1.4 Hz, 1H), 7.58 – 7.45 (m, 3H), 4.73 (s, 2H), 4.53 (q, *J* = 7.1 Hz, 2H), 3.52 (q, *J* = 7.0 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H), 1.23 (t, *J* = 7.0 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.11, 134.32, 132.78, 129.91, 129.88, 128.10, 127.09, 126.13, 125.57, 124.83, 70.65, 65.91, 61.43, 15.15, 14.31;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{16}H_{18}O_3Na$): 281.1154; found: 281.1150.

3.4.3. Propyl 2-(Propoxymethyl) naphthalene-1-carboxylate (146)

In a two-necked flask (25 mL), the crude product (289 mg) of bromination reaction was placed and dissolved in 4.0 mL of propanol then 277 mg of potassium tert-butoxide (2.5 mmol, 2.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 16 hours, the reaction mixture was treated with 5 mL of 1M HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:16) resulted 147 mg of desired product in 52% yield for two steps.



Yield: 52% for two steps; colourless viscous liquid;

R_f: 0.67 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.3 Hz, 1H), 7.87 (d, J = 8.5 Hz, 1H), 7.81 (d, J = 7.7 Hz, 1H), 7.56 (d, J = 8.5 Hz, 1H), 7.54 – 7.43 (m, 2H), 4.74 (s, 2H), 4.43 (t, J = 6.7 Hz, 2H), 3.42 (t, J = 6.7 Hz, 2H), 1.92 – 1.77 (m, 2H), 1.71 – 1.58 (m, 2H), 1.04 (t, J = 7.4 Hz, 3H), 0.94 (t, J = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.17, 134.47, 132.79, 129.95, 129.93, 129.87, 128.10, 127.05, 126.10, 125.57, 124.90, 72.30, 70.79, 67.11, 22.95, 22.05, 10.64, 10.63.

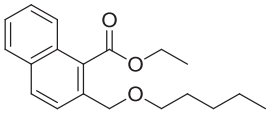
3.4.4. Butyl 2-(Butoxymethyl)-1-naphthoate (147)

In a two-necked flask (25 mL), the crude product (250 mg) of bromination reaction was placed and dissolved in 4.0 mL of butanol then 244 mg of potassium tert-butoxide (2.17 mmol, 2.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 16 hours, the reaction mixture was treated with 5 mL of 1M HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, product could not purified because of the product of the transesterification reaction. Weight of crude product was 245.8 mg.

3.4.5. Ethyl 2-((Pentyloxy)methyl)-1-naphthoate (139)

In a two-necked flask (25 mL), the crude product (450 mg) of bromination reaction was placed and dissolved in 5.0 mL of pentanol then 431 mg of potassium tert-butoxide (3.84 mmol, 2.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 16 hours, the reaction mixture was treated with 5 mL of 1M

HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:25) resulted 213 mg of desired product in 44% yield for two steps.



Yield: 44% for two steps; colourless viscous liquid;

R_f: 0,59 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.95 (d, *J* = 8.3 Hz, 1H), 7.90 (d, *J* = 8.5 Hz, 1H), 7.84 (dd, *J* = 8.3 and 1.0 Hz, 1H), 7.58 (d, *J* = 8.5 Hz, 1H), 7.56 – 7.46 (m, 2H), 4.75 (s, 2H), 4.54 (q, *J* = 7.2 Hz, 2H), 3.47 (t, *J* = 6.7 Hz, 2H), 1.69 – 1.59 (m, 2H), 1.47 (t, *J* = 7.2 Hz, 3H), 1.40 – 1.30 (m, 4H), 0.92 (t, J = 7.1 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.04, 134.50, 132.80, 129.91, 129.87, 128.12, 127.08, 126.12, 125.59, 124.87, 70.80, 70.76, 61.40, 29.45, 28.34, 22.56, 14.33, 14.04;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{19}H_{24}O_3Na$): 323.1623; found: 323.1610.

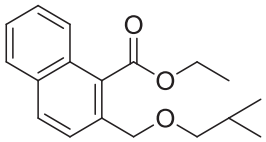
3.4.6. Ethyl 2-(Isopropoxymethyl)-1-naphthoate (140-149)

In a two-necked flask (25 mL), the crude product (512.4 mg) of bromination reaction was placed and dissolved in 4.0 mL of isopropyl alcohol then 294 mg of potassium tert-butoxide (2.62 mmol, 1.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 16 hours, the reaction mixture was treated with 5 mL of 1M HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure product could not purified

because of the product of the transesterification reaction. Weight of crude product is 207.7 mg.

3.4.7. Ethyl 2-(Isobutoxymethyl)-1-naphthoate (141)

In a two-necked flask (25 mL), the crude product (375.4 mg) of bromination reaction was placed and dissolved in 5.0 mL of 2-methyl-1-propanol then 359 mg of potassium tert-butoxide (3.2 mmol, 2.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 16 hours, the reaction mixture was treated with 5 mL of 1M HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:25) resulted 159 mg of desired product in 42% yield for two steps.



Yield: 42% for two steps; colourless viscous liquid;

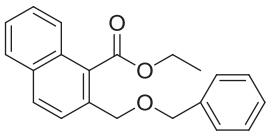
R_f: 0.79 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 (d, J = 8.4 Hz, 1H), 7.90 (d, J = 8.5 Hz, 1H), 7.88 – 7.81 (m, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.52 (dddd, J = 19.0, 8.0, 6.9 and 1.3 Hz, 2H), 4.74 (s, 2H), 4.54 (q, J = 7.1 Hz, 2H), 3.25 (d, J = 6.7 Hz, 2H), 2.00 – 1.86 (m, 1H), 1.47 (t, J = 7.2 Hz, 3H), 0.94 (d, J = 6.7 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.03, 134.57, 132.78, 129.93, 129.89, 129.81, 128.13, 127.10, 126.13, 125.61, 124.87, 77.51, 70.89, 61.43, 28.55, 19.45, 14.33.

3.4.8. Ethyl 2-((Benzyloxy)methyl)-1-naphthoate (142) and Benzyl 2-((Benzyloxy)methyl)-1-naphthoate (151)

In a two-necked flask (25 mL), 290 mg of 2-bromomethyl-1-naphtoate (0.99 mmol, 1.00 eq) was placed and dissolved in 8.0 mL of benzyl alcohol then 278 mg of potassium tert-butoxide (2.48 mmol, 2.50 eq) was added and the mixture was stirred at reflux under nitrogen atmosphere. After 16 hours, the reaction mixture was treated with 5 mL of 1M HCl solution and then 10 mL of distilled water and the extracted with dichloromethane (3x10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:12) resulted 255 mg of desired product (**8h**) in 80% yield.



Yield: 80%; colourless viscous liquid;

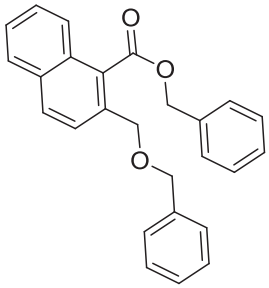
R_f: 0.42 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.94 – 7.89 (m, 2H), 7.88 – 7.83 (m, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.57 – 7.48 (m, 2H), 7.39 – 7.27 (m, 5H), 4.79 (s, 2H), 4.55 (s, 2H), 4.45 (q, *J* = 7.2 Hz, 2H), 1.38 (t, *J* = 7.2 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.04, 138.01, 133.94, 132.87, 130.16, 129.98, 129.91, 128.37, 128.13, 127.81, 127.66, 127.14, 126.23, 125.70, 124.90, 72.35, 70.17, 61.47, 14.25;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{21}H_{20}O_3Na$): 343.1310; found: 343.1317.

In another experiment, transesterification product, benzyl 2-((benzyloxy)methyl)-1-naphthoate (**151**) was obtained in 30% yield and characterized.



Yield: 30%; colourless viscous liquid;

R_f: 0.34 (1:8 EtOAc-Hex);

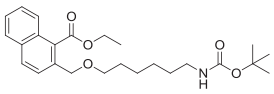
^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.91 (m, 2H), 7.88 (dd, *J* = 6.4 and 2.9 Hz, 1H), 7.61 (d, *J* = 8.5 Hz, 1H), 7.58 – 7.51 (m, 2H), 7.51 – 7.46 (m, 2H), 7.45 – 7.31 (m, 8H), 5.48 (s, 2H), 4.80 (s, 2H), 4.51 (s, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 168.93, 138.07, 135.55, 134.26, 132.90, 130.18, 130.02, 129.78, 128.76, 128.67, 128.49, 128.43, 128.18, 127.84, 127.70, 127.25, 126.31, 125.75, 124.96, 72.40, 70.29, 67.36;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{26}H_{22}O_3Na$): 405.1467; found: 405.1462

3.4.9. Ethyl 2-(((6-((*Tert*-butoxycarbonyl)amino)hexyl)oxy)methyl)-1-naphthoate (143)

In a two-necked flask (25 mL), the crude product (296 mg) of bromination reaction was placed and dissolved in 5.0 mL of dry DCM and 219 mg of 6-(Boc-amino)-1-hexanol (1.01 mmol, 1.00 eq) were placed. Then 241 mg of silver trifluoromethanesulfonate (0.94 mmol, 0.93 eq) and 121 mg of N-ethyldiisopropylamine (161 μL, 0.94 mmol, 0.93 eq) were added, respectively. The mixture was stirred at 0 ^oC under nitrogen atmosphere for 2 h and then at room temperature under nitrogen for 16 h. After that, the residue was filtered off by Et_2O. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:14) resulted 73 mg of desired product with 14% yield for two steps.



Yield: 14% for two steps; colourless viscous liquid;

R_f: 0.65 (1:2 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 7.98 – 7.77 (m, 3H), 7.61 – 7.44 (m, 3H), 4.71 (s, 2H), 4.51 (q, *J* = 7.1 Hz, 3H), 3.43 (t, *J* = 6.6 Hz, 2H), 3.14 – 3.01 (m, 2H), 1.65 – 1.55 (m, 2H), 1.53 – 1.20 (m, 18H);

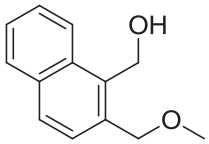
^{13}C-NMR (100 MHz, $CDCl_3$) δ 169.01, 155.97, 134.37, 132.77, 129.91, 129.87, 129.85, 128.10, 127.08, 126.13, 125.56, 124.84, 78.94, 70.79, 70.50, 61.41, 40.50, 29.98, 29.67, 29.62, 28.41, 26.61, 25.84, 14.32;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{25}H_{35}NO_5Na$): 452.2413; found: 452.2427

3.5. Reduction of Esters to Alcohol

3.5.1. (2-(Methoxymethyl)naphthalen-1-yl)methanol (153)

In a two-necked flask (25 mL), 303 mg of ethyl 2-(methoxymethyl)-1-naphthoate (1.24 mmol, 1.00 eq) was placed and dissolved in 8.0 mL of dry THF then the dissolved 71 mg of lithium aluminium hydride (1.5 mmol, 1.21 eq) in 5.0 mL of dry THF was slowly added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 208 mg of desired product in 83% yield.



Yield: 83%; colourless viscous liquid;

R_f: 0.15 (1:4 EtOAc-Hex);

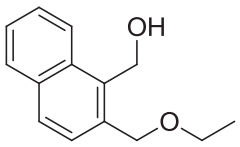
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.5 Hz, 1H), 7.88 – 7.84 (m, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8 and 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.0, 6.8 and 1.2 Hz, 1H), 7.43 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 2H), 4.72 (s, 2H), 3.46 (s, 3H), 2.81 (s, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.02, 134.23, 133.85, 132.31, 128.47, 127.63, 126.74, 125.97, 124.00, 74.34, 58.32, 57.96;

HRMS (ESI-TOF) m/z calculated for $[M+H]^+$ ($C_{13}H_{15}O_2$): 203.1072; found: 203.1071.

3.5.2. (2-(Ethoxymethyl)naphthalen-1-yl)methanol (154)

In a two-necked flask (25 mL), 359 mg of ethyl 2-(ethoxymethyl)-1-naphthoate (1.39 mmol, 1.00 eq) was placed and dissolved in 6.0 mL of dry THF then the dissolved 79 mg of lithium aluminium hydride (2.1 mmol, 1.50 eq) in 3.0 mL of dry THF was slowly added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 255 mg of desired product in 85% yield.



Yield: 85%; colourless viscous liquid;

R_f: 0.22 (1:4 EtOAc-Hex);

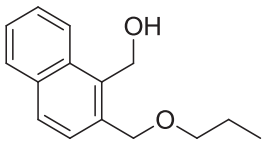
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.6 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8 and 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 6.8 and 1.2 Hz, 1H), 7.44 (dd, *J* = 8.4 and 4.2 Hz, 1H), 5.13 (s, 2H), 4.76 (s, 2H), 3.64 (q, *J* = 7.0 Hz, 2H), 2.71 (s, 1H), 1.27 (t, *J* = 7.0 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.11, 134.55, 133.82, 132.33, 128.46, 128.43, 127.65, 126.71, 125.91, 123.96, 72.49, 66.23, 57.95, 15.27;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{14}H_{16}O_2Na$): 239.1048; found: 239.1051.

3.5.3. (2-(Propoxymethyl)naphthalen-1-yl)methanol (155)

In a two-necked flask (25 mL), 187 mg of propyl 2-(propoxymethyl)naphthalene-1-carboxylate (0.65 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then the dissolved 37 mg of lithium aluminium hydride (0.98 mmol, 1.50 eq) in 3.0 mL of dry THF was slowly added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 128 mg of desired product in 85% yield.



Yield: 85%; colourless viscous liquid;

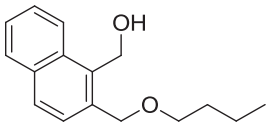
R_f: 0.44 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.28 (d, *J* = 8.4 Hz, 1H), 7.85 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.62 – 7.48 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 5.07 (s, 2H), 4.71 (s, 2H), 3.50 (t, *J* = 6.7 Hz, 2H), 3.32 (s, 1H), 1.73 – 1.60 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.87, 134.56, 133.79, 132.36, 128.47, 128.42, 127.63, 126.67, 125.89, 124.13, 72.62, 72.37, 57.75, 23.00, 10.67.

3.5.4. (2-(Butoxymethyl)naphthalen-1-yl)methanol (156)

In a two-necked flask (25 mL), 246 mg of butyl 2-(butoxymethyl)-1-naphthoate (0.78 mmol, 1.00 eq) was placed and dissolved in 5.0 mL of dry THF then the dissolved 45 mg of lithium aluminium hydride (1.17 mmol, 1.50 eq) in 3.0 mL of dry THF was slowly added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:4 in 1% EtOH) resulted 49 mg of desired product in 34% yield for three steps.



Yield: 34% for three steps; colourless viscous liquid;

R_f: 0.54 (1:4 EtOAc-Hex containing 1% ethanol);

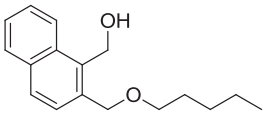
R_f: 0.08 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (d, *J* = 8.4 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.80 (d, *J* = 8.3 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8 and 1.4 Hz, 1H), 7.50 (ddd, *J* = 7.9, 6.9 and 1.1 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 5.13 (s, 2H), 4.76 (s, 2H), 3.58 (t, *J* = 6.7 Hz, 2H), 2.95 (s, 1H), 1.68 – 1.57 (m, 2H), 1.47 – 1.31 (m, 2H), 0.92 (t, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.10, 134.59, 133.82, 132.32, 128.46, 128.41, 127.68, 126.70, 125.90, 123.97, 72.73, 70.81, 57.96, 31.83, 19.36, 13.90.

3.5.5. (2-((Pentyloxy)methyl)naphthalen-1-yl)methanol (157)

In a two-necked flask (25 mL), 212 mg of ethyl 2-((pentyloxy)methyl)-1-naphthoate (0.71 mmol, 1.00 eq) was placed and dissolved in 5.0 mL of dry THF then the dissolved 40 mg of lithium aluminium hydride (1.1 mmol, 1.50 eq) in 3.0 mL of dry THF was slowly added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 160 mg of desired product in 87% yield.



Yield: 87%; colourless viscous liquid;

R_f: 0.21 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.3 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8 and 1.5 Hz, 1H), 7.50 (ddd, *J* = 8.0, 6.8 and 1.2 Hz, 1H), 7.44 (d, *J* = 8.4 Hz, 1H), 5.14 (d, *J* = 6.3 Hz, 2H), 4.77 (s, 2H), 3.58 (t, *J* = 6.7 Hz, 2H), 2.96 – 2.88 (m, 1H), 1.69 – 1.58 (m, 2H), 1.40 – 1.29 (m, 4H), 0.96 – 0.85 (m, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 136.14, 134.59, 133.82, 132.31, 128.46, 128.41, 127.69, 126.71, 125.90, 123.94, 72.77, 71.11, 57.98, 29.46, 28.30, 22.49, 13.98;

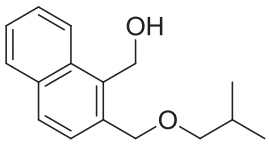
HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{17}H_{22}O_2Na$): 281.1517; found: 281.1523.

3.5.6. (2-(Isopropoxymethyl)naphthalen-1-yl)methanol (158)

Ethyl 2-(isopropoxymethyl)-1-naphthoate couldn't purified. In this experiment the crude product was used. In a two-necked flask (25 mL), this crude product (208 mg) was placed and dissolved in 5.0 mL of dry THF then the dissolved 43 mg of lithium aluminium hydride (1.14 mmol, 1.50 eq) in 3.0 mL of dry THF was slowly added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, the desired product couldn't by SiO_2 column chromatography. Weight of crude product was 137 mg.

3.5.7. (2-(Isobutoxymethyl)naphthalen-1-yl)methanol (159)

In a two-necked flask (25 mL), 159 mg of ethyl 2-(isobutoxymethyl)-1-naphthoate (0.56 mmol, 1.00 eq) was placed and dissolved in 5.0 mL of dry THF then the dissolved 32 mg of lithium aluminium hydride (0.83 mmol, 1.50 eq) in 3.0 mL of dry THF was slowly added at 0 ^{o}C. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 130 mg of desired product in 97% yield.



Yield: 97%; colourless viscous liquid;

R_f: 0.19 (1:8 EtOAc-Hex);

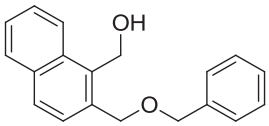
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1H), 7.89 – 7.84 (m, 1H), 7.81 (d, *J* = 8.3 Hz, 1H), 7.57 (ddd, *J* = 8.5, 6.8 and 1.5 Hz, 1H), 7.51 (ddd, *J* = 8.0, 6.8 and 1.2 Hz, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 5.12 (s, 2H), 4.74 (s, 2H), 3.35 (d, *J* = 6.6 Hz, 2H), 3.00 (s, 1H), 1.93 (sep, *J* = 6.7 Hz, 1H), 0.95 (d, *J* = 6.7 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 135.95, 134.59, 133.80, 132.32, 128.48, 128.42, 127.70, 126.69, 125.90, 124.05, 77.88, 72.75, 57.87, 28.54, 19.46.

3.5.8. (2-((Benzyloxy)methyl)naphthalen-1-yl)methanol (160)

In a two-necked flask (25 mL), 255 mg of ethyl 2-((benzyloxy)methyl)-1-naphthoate (0.79 mmol, 1.00 eq) was placed and dissolved in 5.0 mL of dry THF then

the dissolved 45 mg of lithium aluminium hydride (1.19 mmol, 1.50 eq) in 3.0 mL of dry THF was slowly added at 0 ^{o}C. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Reaction mixture was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 198 mg of desired product in 90% yield.



Yield: 90%; colourless viscous liquid;

R_f: 0.19 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.31 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.0 Hz, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.62 – 7.56 (m, 1H), 7.56 – 7.49 (m, 1H), 7.45 (d, *J* = 8.4 Hz, 1H), 7.43 – 7.31 (m, 5H), 5.13 (d, *J* = 5.3 Hz, 2H), 4.81 (s, 2H), 4.64 (s, 2H), 2.81 (s, 1H);

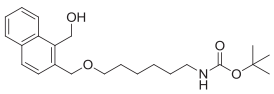
^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.54, 135.98, 134.24, 133.86, 132.41, 128.61, 128.53, 128.49, 128.09, 128.02, 127.70, 126.76, 126.00, 124.12, 72.76, 71.64, 57.97;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{19}H_{18}O_2Na$): 301.1204; found: 301.1211

3.5.9. *Tert*-butyl (6-((1-(Hydroxymethyl)naphthalen-2-yl)methoxy) hexyl)carbamate (161)

In a two-necked flask (25 mL), 117 mg of ethyl 2-(((6-((tert butoxycarbonyl)amino)hexyl)oxy)methyl)-1-naphthoate (0.27 mmol, 1.00 eq) was placed and dissolved in 5.0 mL dry THF then the dissolved 17 mg of lithium aluminium hydride (0.41 mmol, 1.50 eq) in 3.0 mL dry THF was slowly added at 0 ^{o}C. The

mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 10 mL of 1M HCl solution. Crude product was extracted with ethyl acetate (3x10 mL) and then combined organic phase was washed with 1M HCl (10 mL) solution. The organic phase was dried anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 68 mg of desired product with 65% yield.



Yield: 65%; colourless viscous liquid;

R_f: 0.32 (1:2 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.29 (d, *J* = 8.1 Hz, 1H), 7.86 – 7.81 (m, 1H), 7.79 (d, *J* = 8.3 Hz, 1H), 7.55 (ddd, *J* = 8.5, 6.8 and 1.5 Hz, 1H), 7.48 (ddd, *J* = 8.0,6.8 and 1.2 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.12 (s, 2H), 4.74 (s, 2H), 4.61 (s, 1H), 3.55 (t, *J* = 6.6 Hz, 2H), 3.13 – 2.98 (m, 3H), 1.60 (dd, *J* = 14.5 and 6.7 Hz, 2H), 1.48 – 1.22 (m, 15H);

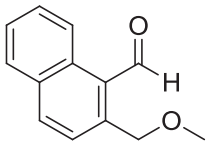
^{13}C-NMR (100 MHz, $CDCl_3$) δ 156.01, 136.00, 134.49, 133.79, 132.31, 128.44, 128.42, 127.65, 126.67, 125.88, 123.99, 78.97, 72.63, 70.80, 57.89, 40.41, 32.53, 29.91, 29.68, 29.61, 28.43, 26.47, 25.78;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{23}H_{33}NO_4Na$): 410.2307; found: 410.2317

3.6. Oxidation of Alcohols to Aldehydes

3.6.1. 2-(Methoxymethyl)-1-naphthaldehyde (94)

In a two-necked flask (25 mL) 279 mg of PCC (1.29 mmol, 1.10 eq) was placed and dissolved in 5.0 mL of dry DCM then a solution of 238 mg of (2-(methoxymethyl)naphthalen-1-yl)methanol (1.17 mmol, 1.00 eq) in 3.0 mL of dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL of DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 179 mg of desired product in 77% yield.



Yield: 77%; brown viscous liquid;

R_f: 0.52 (1:4 EtOAc-Hex);

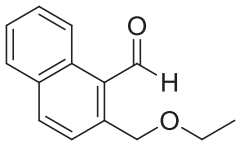
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.85 (d, *J* = 8.7 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.85 (d, *J* = 8.1 Hz, 1H), 7.64 (d, *J* = 8.9 Hz, 1H), 7.61 (dd, *J* = 4.6 and 4.0 Hz, 1H), 7.55 – 7.49 (m, 1H), 4.91 (s, 2H), 3.46 (s, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.89, 141.69, 134.17, 133.19, 131.47, 128.58, 128.51, 128.49, 126.42, 125.99, 124.24, 72.19, 58.52;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{13}H_{12}O_2Na$): 223.0735; found: 223.0742.

3.6.2. 2-(Ethoxymethyl)-1-naphthaldehyde (95)

In a two-necked flask (25 mL), 473 mg of PCC (2.19 mmol, 1.10 eq) was placed and dissolved in 8.0 mL of dry DCM then a solution of 289 mg of (2-(ethoxymethyl)naphthalen-1-yl)methanol (1.34 mmol, 1.00 eq) in 4.0 mL of dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL of DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:11) resulted 226mg of desired product in 78% yield.



Yield: 78%; brown viscous liquid;

R_f: 0.57 (1:4 EtOAc-Hex);

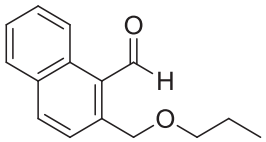
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.95 (s, 1H), 8.92 – 8.85 (m, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.91 – 7.85 (m, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.63 (ddd, *J* = 8.6, 6.8 and 1.5 Hz, 1H), 7.53 (ddd, *J* = 13.3, 7.2 and 3.8 Hz, 1H), 4.98 (s, 2H), 3.63 (q, *J* = 7.0 Hz, 2H), 1.28 (t, *J* = 7.0 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.08, 142.10, 134.17, 133.21, 131.46, 128.58, 128.57, 128.49, 126.39, 126.16, 124.34, 70.24, 66.33, 15.19;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{14}H_{14}O_2Na$): 237.0891; found: 237.0889.

3.6.3. 2-(Propoxymethyl)-1-naphthaldehyde (96)

In a two-necked flask (25 mL), 131 mg of PCC (0.61 mmol, 1.10 eq) was placed and dissolved in 8.0 mL of dry DCM then a solution of 127 mg of (2-(propoxymethyl)naphthalen-1-yl)methanol (0.55 mmol, 1.00 eq) in 4.0 mL of dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:11) resulted 93 mg of desired product in 74% yield.



Yield: 74%; brown viscous liquid;

R_f: 0.44 (1:8 EtOAc-Hex);

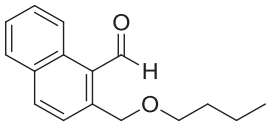
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.90 (s, 1H), 8.88 (dd, *J* = 8.6 and 0.7 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.84 (dd, *J* = 8.1 and 0.6 Hz, 1H), 7.65 (d, *J* = 8.5 Hz, 1H), 7.61 (ddd, *J* = 8.6, 6.8 and 1.4 Hz, 1H), 7.53 (d, *J* = 1.1 Hz, 1H), 4.94 (s, 2H), 3.51 (t, *J* = 6.6 Hz, 2H), 1.73 – 1.59 (m, 2H), 0.96 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.05, 142.25, 134.14, 133.19, 131.39, 128.57, 128.51, 128.47, 126.37, 126.18, 124.38, 72.65, 70.42, 22.97, 10.71.

3.6.4. 2-(Butoxymethyl) -1-naphthaldehyde (97)

In a two- necked flask (25 mL), 125 mg of PCC (0.58 mmol, 1.10 eq) was placed and dissolved in 8.0 mL of dry DCM then a solution of 129 mg of (2-(butoxymethyl)naphthalen-1-yl)methanol (0.53 mmol, 1.00 eq) in 4.0 mL of dry DCM

was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 98 mg of desired product in 76% yield.



Yield: 76%; brown viscous liquid;

R_f: 0.60 (1:8 EtOAc-Hex);

R_f: 0.37 (1:25 EtOAc-Hex);

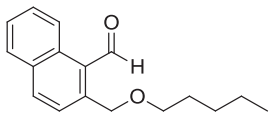
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.93 (s, 1H), 8.89 (dd, *J* = 8.7 ve 0.9 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.87 (dd, *J* = 8.1 and 0.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.63 (ddd, *J* = 8.6, 6.9 and 1.4 Hz, 1H), 7.53 (ddd, *J* = 8.0, 6.9 and 1.1 Hz, 1H), 4.97 (s, 2H), 3.57 (t, *J* = 6.5 Hz, 2H), 1.68 – 1.58 (m, 2H), 1.47 – 1.35 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.08, 142.25, 134.16, 133.20, 131.43, 128.59, 128.55, 128.48, 126.38, 126.18, 124.38, 70.81, 70.47, 31.81, 19.41, 13.92.

3.6.5. 2-((Pentyloxy)methyl)-1-naphthaldehyde (98)

In a two-necked flask (25 mL), 263 mg of PCC (1.22 mmol, 1.10 eq) was placed and dissolved in 8.0 mL of dry DCM then a solution of 286 mg of (2-((pentyloxy)methyl)naphthalen-1-yl)methanol (1.1 mmol, 1.00 eq) in 4.0 mL of dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the

solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 242 mg of desired product in 86% yield.



Yield: 86%; brown viscous liquid;

R_f: 0.58 (1:8 EtOAc-Hex);

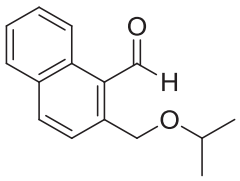
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.94 (s, 1H), 8.89 (dd, *J* = 8.7 and 0.8 Hz, 1H), 8.04 (d, *J* = 8.5 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 1H), 7.63 (ddd, *J* = 8.5, 6.8 and 1.4 Hz, 1H), 7.54 (ddd, *J* = 8.0, 6.9 and 1.1 Hz, 1H), 4.97 (s, 2H), 3.56 (t, *J* = 6.6 Hz, 2H), 1.70 – 1.61 (m, 2H), 1.42 – 1.29 (m, 4H), 0.94 – 0.87 (m, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.06, 193.05, 142.24, 134.15, 133.21, 131.44, 128.58, 128.47, 126.38, 126.17, 124.38, 71.12, 70.46, 29.42, 28.36, 22.51, 14.01;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{17}H_{20}O_2Na$): 279.1361; found: 279.1378.

3.6.6. 2-(Isopropoxymethyl)-1-naphthaldehyde (99)

(2-(isopropoxymethyl)naphthalen-1-yl)methanol couldn't purified. In this experiment the crude product was used. In a two-necked flask (25 mL), 151 mg of PCC (0.69 mmol, 1.10 eq) was placed and dissolved in 8.0 mL of dry DCM then a solution of this crude product (136.6 mg) in 4.0 mL of dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:50) resulted 92 mg of desired product in 23% yield for four steps.



Yield: 23% for four steps; brown viscous liquid;

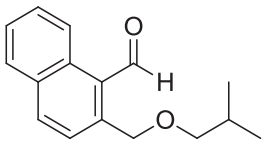
R_f: 0.44 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.87 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.51 (t, *J* = 7.4 Hz, 1H), 4.95 (s, 2H), 3.75 (sep, *J* = 6.1 Hz, 1H), 1.25 (d, *J* = 6.1 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.19, 142.52, 134.13, 133.17, 131.40, 128.54, 128.52, 128.46, 126.34, 124.38, 71.86, 67.75, 22.11.

3.6.7. 2-(Isobutoxymethyl)-1-naphthaldehyde (100)

In a two-necked flask (25 mL), 126 mg of PCC (0.59 mmol, 1.10 eq) was placed and dissolved in 8.0 mL of dry DCM then a solution of 130 mg of (2-(isobutoxymethyl)naphthalen-1-yl)methanol (0.53 mmol, 1.00 eq) in 4.0 mL of dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 108 mg of desired product in 84% yield.



Yield: 84%; brown viscous liquid;

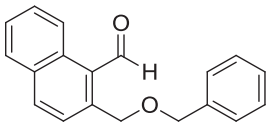
R_f: 0.58 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.89 (d, *J* = 8.7 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.86 (dd, *J* = 8.1 and 0.6 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 7.62 (ddd, *J* = 8.4, 6.9 and 1.4 Hz, 1H), 7.53 (t, *J* = 7.5 Hz, 1H), 4.96 (s, 2H), 3.33 (dd, *J* = 6.6 and 0.5 Hz, 2H), 2.01 – 1.89 (m, 1H), 0.95 (d, *J* = 6.7 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.05, 142.34, 134.12, 133.20, 131.40, 128.58, 128.52, 128.48, 126.37, 126.18, 124.40, 77.83, 70.61, 28.58, 19.44.

3.6.8. 2-((Benzyloxy)methyl)-1-naphthaldehyde (101)

In a two-necked flask (25 mL), 169 mg of PCC (0.78 mmol, 1.10 eq) was placed and dissolved in 8.0 mL of dry DCM then a solution of 198 mg of (2-((benzyloxy)methyl)naphthalen-1-yl)methanol (0.71 mmol, 1.00 eq) in 4.0 mL of dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 170 mg of desired product in 86% yield.



Yield: 86%; brown viscous liquid;

R_f: 0.35 (1:8 EtOAc-Hex);

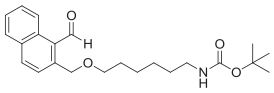
^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.96 (s, 1H), 8.89 (d, *J* = 8.7 Hz, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.89 (d, *J* = 8.1 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.65 (ddd, *J* = 8.5, 6.8, and 1.4 Hz, 1H), 7.55 (ddd, *J* = 8.0, 6.9 and 1.1 Hz, 1H), 7.44 – 7.30 (m, 5H), 5.05 (s, 2H), 4.66 (s, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 192.99, 141.71, 137.73, 134.22, 133.25, 131.50, 128.63, 128.52, 128.50, 127.87, 127.85, 126.47, 126.23, 124.31, 72.81, 69.73;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{19}H_{16}O_2Na$): 299.1048; found: 299.1058.

3.6.9. *Tert*-butyl (6-((1-Formylnaphthalen-2-yl)methoxy)hexyl) carbamate (102)

In a two-necked flask (25 mL), 42 mg of PCC (0.19 mmol, 1.10 eq) was placed and dissolved in 8.0 mL dry DCM then a solution of 68 mg of tert-butyl (6-((1-(hydroxymethyl)naphthalen-2-yl)methoxy)hexyl)carbamate (0.18 mmol, 1.00 eq) in 4.0 mL dry DCM was added. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the crude product was filtered off with 10 mL DCM. The organic phase was washed with 10 mL of 1M NaOH and 10 mL of 1M HCl. The organic phase was dried anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 46 mg desired product with 68% yield.



Yield: 68%; brown viscous liquid;

R_f: 0.54 (1:2 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 10.92 (s, 1H), 8.88 (d, *J* = 8.6 Hz, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.87 (d, *J* = 8.2 Hz, 1H), 7.73 – 7.59 (m, 2H), 7.53 (ddd, *J* = 8.0, 6.9 and 1.1 Hz, 1H), 4.96 (s, 2H), 4.56 (s, 1H), 3.54 (t, *J* = 6.5 Hz, 2H), 3.09 (d, *J* = 6.3 Hz, 2H), 1.62 (dd, *J* = 14.4 and 6.7 Hz, 2H), 1.51 – 1.21 (m, 15H);

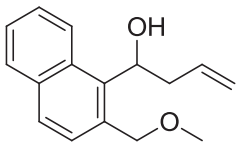
^{13}C-NMR (100 MHz, $CDCl_3$) δ 193.06, 193.05, 155.98, 142.12, 134.15, 133.22, 131.41, 128.59, 128.47, 126.40, 126.18, 124.37, 78.95, 70.85, 70.48, 40.49, 29.98, 29.60, 28.41, 26.56, 25.88.126.23, 124.31, 72.81, 69.73;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{23}H_{31}NO_4Na$): 408.2151; found: 408.2146

3.7. Synthesis of Homoallylic Alcohol with Allylmagnesium Bromide

3.7.1. 1-(2-(Methoxymethyl)naphthalen-1-yl)but-3-en-1-ol (103)

In a two-necked flask (25 mL), 179 mg of 2-(methoxymethyl)-1-naphthaldehyde (0.89 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then 155 mg of allylmagnesium bromide (183 μL, 1.07 mmol, 1.20 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:12) resulted 203 mg of desired product in 94% yield.



Yield: 94%; yellow viscous liquid;

R_f: 0.35 (1:4 EtOAc-Hex);

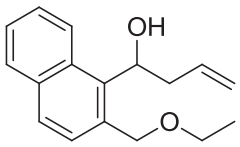
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.57 (d, *J* = 5.8 Hz, 1H), 7.87 – 7.80 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.54 – 7.44 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.03 – 5.84 (m, 1H), 5.59 (s, 1H), 5.22 – 5.10 (m, 2H), 4.78 – 4.62 (m, 2H), 3.39 (s, 3H), 3.06 (s, 1H), 3.02 – 2.88 (m, 1H), 2.76 – 2.61 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.88, 135.39, 134.23, 132.59, 131.24, 128.71, 128.11, 127.90, 125.76, 125.58, 117.57, 73.76, 70.89, 58.10, 42.10;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{16}H_{18}O_2Na$): 265.1204; found: 265.1204.

3.7.2. 1-(2-(Ethoxymethyl)naphthalen-1-yl)but-3-en-1-ol (104)

In a two-necked flask (25 mL), 243 mg of allylbromide (175 µl, 2.01 mmol, 3.00 eq) was dissolved in 4.0 mL of dry ether and then 48 mg of Mg (2.01 mmol, 3.00 eq) was added. In another two necked flask (25 mL) 144 mg of 2-(ethoxymethyl)-1-naphthaldehyde (0.67 mmol, 1.00 eq) was placed and dissolved in 6.0 mL of dry THF then the synthesized allylmagnesium bromide in first two necked flask was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:12) resulted 75 mg of desired product in 44% yield.



Yield: 44%; yellow viscous liquid;

R_f: 0.46 (1:4 EtOAc-Hex);

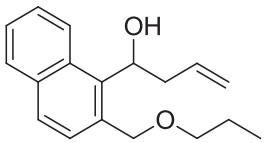
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.86 – 7.80 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.44 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.01 – 5.87 (m, 1H), 5.60 (dd, *J* = 8.4 and 4.5 Hz, 1H), 5.19 (ddd, *J* = 17.1, 3.1 and 1.6 Hz, 1H), 5.15 – 5.09 (m, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.68 (d, *J* = 11.3 Hz, 1H), 3.57 (q, *J* = 7.0 Hz, 2H), 3.20 (s, 1H), 3.02 – 2.88 (m, 1H), 2.74 – 2.62 (m, 1H), 1.24 (t, *J* = 7.0 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.94, 135.46, 134.22, 132.80, 131.28, 128.70, 128.10, 128.00, 125.73, 125.52, 117.51, 71.96, 70.88, 65.96, 42.06, 15.20;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{17}H_{20}O_2Na$): 279.1361; found: 279.1376.

3.7.3. 1-(2-(Propoxymethyl)naphthalen-1-yl)but-3-en-1-ol (105)

In a two-necked flask (25 mL), 92 mg of 2-(propoxymethyl)naphthalene-1-carbaldehyde (0.4 mmol. 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then 3.40 g of allylmagnesium bromide (4 mL, 23.4 mmol, 58.50 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 102 mg of desired product in 94% yield.



Yield: 94%; yellow viscous liquid;

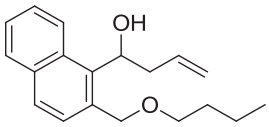
R_f: 0.18 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.86 – 7.80 (m, 1H), 7.74 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 5.98 – 5.85 (m, 1H), 5.56 (dd, *J* = 8.6 and 4.6 Hz, 1H), 5.18 (d, *J* = 17.1 Hz, 1H), 5.12 (d, *J* = 10.1 Hz, 1H), 4.74 (d, *J* = 11.2 Hz, 1H), 4.66 (d, *J* = 11.3 Hz, 1H), 3.46 (t, *J* = 6.7 Hz, 2H), 3.38 (s, 1H), 3.02 – 2.88 (m, 1H), 2.75 – 2.63 (m, 1H), 1.69 – 1.56 (m, 2H), 0.93 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.94, 135.47, 134.21, 132.83, 131.28, 128.70, 128.09, 128.00, 125.91, 125.72, 125.53, 117.51, 72.43, 72.10, 70.79, 42.05, 22.93, 10.69.

3.7.4. 1-(2-(Butoxymethyl)naphthalen-1-yl)but-3-en-1-ol (106)

In a two-necked flask (25 mL), 98 mg of 2-(butoxymethyl)naphthalene-1-carbaldehyde (0.4 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then 1.70 g of allylmagnesium bromide (2 mL, 11.7 mmol, 29.30 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 112 mg of desired product in 98% yield.



Yield: 98%; yellow viscous liquid;

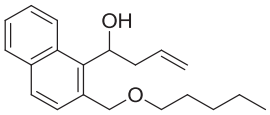
R_f: 0.41 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, MeOH-d_4) δ 8.70 (s, 1H), 7.81 (dd, J = 6.9, and 2.2 Hz, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.48 – 7.39 (m, 3H), 5.95 – 5.83 (m, 1H), 5.58 (dd, *J* = 8.1 and 6.0 Hz, 1H), 5.11 – 5.03 (m, 1H), 5.03 – 4.98 (m, 1H), 4.87 (s, 1H), 4.81 – 4.68 (m, *J* = 11.5 Hz, 2H), 3.53 (td, *J* = 6.5 and 1.9 Hz, 2H), 3.02 – 2.91 (m, 1H), 2.71 – 2.60 (m, 1H), 1.68 – 1.55 (m, 2H), 1.41 (dq, *J* = 14.6 and 7.4 Hz, 2H), 0.93 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, MeOH-d_4) δ 137.98, 135.48, 134.35, 132.94, 131.32, 128.24, 127.45, 127.15, 126.19, 125.02, 124.90, 115.80, 71.22, 70.10, 70.07, 41.81, 31.59, 19.08, 12.91.

3.7.5. 1-(2-((Pentyloxy)methyl)naphthalen-1-yl)but-3-en-1-ol (107)

In a two-necked flask (25 mL), 241 mg of 2-((pentyloxy)methyl)-1-naphthaldehyde (0.94 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then 818 mg of allylmagnesium bromide (961 μL, 5.63 mmol, 5.99 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 216 mg of desired product in 77% yield.



Yield: 77%; yellow viscous liquid;

R_f: 0.27 (1:8 EtOAc-Hex);

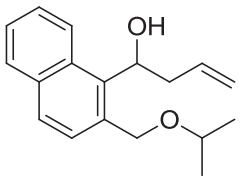
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 6.6 Hz, 1H), 7.85 – 7.81 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 6.02 – 5.89 (m, 1H), 5.69 – 5.61 (m, 1H), 5.20 (dd, *J* = 17.1 and 1.6 Hz, 1H), 5.17 – 5.12 (m, 1H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.69 (d, *J* = 11.4 Hz, 1H), 3.55 – 3.48 (m, 2H), 3.09 – 2.88 (m, 2H), 2.74 – 2.63 (m, 1H), 1.68 – 1.56 (m, 2H), 1.39 – 1.28 (m, 4H), 0.95 – 0.85 (m, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.87, 135.43, 134.19, 132.92, 131.26, 128.71, 128.11, 125.76, 125.52, 117.60, 72.25, 70.89, 70.83, 42.09, 29.44, 28.37, 22.52, 14.01;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{20}H_{26}O_2Na$): 321.1831; found: 321.1833.

3.7.6. 1-(2-(Isopropoxymethyl)naphthalen-1-yl)but-3-en-1-ol (108)

In a two-necked flask (25 mL), 91 mg of 2-(isopropoxymethyl)-1-naphthaldehyde (0.4 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then 3.40 g of allylmagnesium bromide (4 mL, 23.4 mmol. 58.50 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 104 mg of desired product in 96% yield.



Yield: 96%; yellow viscous liquid;

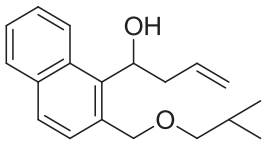
R_f: 0.18 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.87 – 7.77 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.44 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 6.01 – 5.83 (m, 1H), 5.55 (dd, *J* = 9.0 and 4.8 Hz, 1H), 5.22 – 5.08 (m, 2H), 4.69 (s, 2H), 3.72 (dt, *J* = 12.2 and 6.1 Hz, 1H), 3.47 (s, 1H), 2.94 (ddd, *J* = 18.4, 12.4 and 5.8 Hz, 1H), 2.78 – 2.62 (m, 1H), 1.23 (d, *J* = 6.1 Hz, 3H), 1.22 (d, *J* = 6.1 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.98, 135.53, 134.20, 133.03, 131.31, 128.68, 128.12, 125.90, 125.67, 125.48, 117.44, 71.57, 70.77, 69.39, 42.00, 22.11, 22.06.

3.7.7. 1-(2-(Isobutoxymethyl)naphthalen-1-yl)but-3-en-1-ol (109)

In a two-necked flask (25 mL), 108 mg of 2-(isobutoxymethyl)-1-naphthaldehyde (0.4 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then 1.93 g of allylmagnesium bromide (2.3 mL, 13.3 mmol, 33.30 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:4) resulted 111 mg of desired product in 89% yield.



Yield: 89%; yellow viscous liquid;

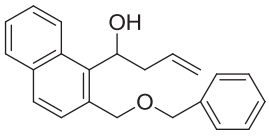
R_f: 0.31 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (s, 1H), 7.86 – 7.82 (m, 1H), 7.75 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 5.98 – 5.87 (m, 1H), 5.63 – 5.56 (m, 1H), 5.20 (ddd, *J* = 17.1, 3.0 and 1.4 Hz, 1H), 5.14 (dd, *J* = 10.1 and 0.7 Hz, 1H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.67 (d, *J* = 11.4 Hz, 1H), 3.29 (d, *J* = 6.6 Hz, 2H), 3.02 – 2.91 (m, 1H), 2.73 – 2.64 (m, 1H), 1.99 – 1.85 (m, 2H), 0.94 (d, *J* = 6.7 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.84, 135.45, 134.19, 132.96, 131.28, 128.72, 128.09, 128.02, 125.85, 125.74, 125.52, 117.57, 77.68, 72.28, 70.77, 42.05, 28.52, 19.51, 19.50.

3.7.8. 1-(2-((Benzyloxy)methyl)naphthalen-1-yl)but-3-en-1-ol (110)

In a two-necked flask (25 mL), 169 mg of 2-((benzyloxy)methyl)-1-naphthaldehyde (0.61 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry THF then 530 mg of allylmagnesium bromide (622 µL, 3.65 mmol, 5.98 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 140 mg of desired product in 72% yield.



Yield: 72%; yellow viscous liquid;

R_f: 0.28 (1:8 EtOAc-Hex);

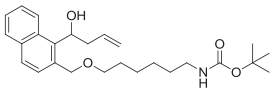
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 5.9 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.76 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.44 (d, *J* = 8.4 Hz, 1H), 7.39 – 7.28 (m, 5H), 5.99 – 5.81 (m, 1H), 5.64 (dd, *J* = 8.3 and 3.9 Hz, 1H), 5.18 – 5.07 (m, 2H), 4.86 (d, J = 11.5 Hz, 1H), 4.79 (d, J = 11.4 Hz, 1H), , 4.60 (s, 2H), 3.02 – 2.86 (m, 1H), 2.79 – 2.61 (m, 2H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 137.86, 135.27, 134.25, 132.69, 131.25, 128.73, 128.46, 128.19, 128.04, 127.92, 127.80, 125.78, 125.59, 117.77, 72.41, 71.26, 70.89, 42.01;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{22}H_{22}O_2Na$): 341.1517; found: 341.1518.

3.7.9. *Tert*-butyl (6-((1-(1-hydroxybut-3-en-1-yl)naphthalen-2-yl) methoxy)hexyl)carbamate (111)

In a two-necked flask (25 mL), 46 mg of tert-butyl (6-((1-formylnaphthalen-2-yl)methoxy)hexyl)carbamate (0.12 mmol, 1.00 eq) was placed and dissolved in 4.0 mL dry THF then 1.02 g of allylmagnesium bromide (1.2 mL, 7.02 mmol, 59.00 eq) was added at 0 ^oC. The mixture was stirred at room temperature under nitrogen atmosphere. After 2 hours, the reaction was ended up with 5 mL of 1M HCl solution at 0 ^oC and extracted with ethyl acetate (3x10 mL) and then combined organic phase washed with 1M HCl (10 mL) solution. The organic phase was dried anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 50 mg desired product with 98% yield.



Yield: 98%; yellow viscous liquid;

R_f: 0.49 (1:2 EtOAc-Hex);

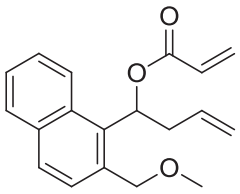
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.56 (s, 1H), 7.89 – 7.79 (m, 1H), 7.73 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.43 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 5.98 – 5.85 (m, 1H), 5.62 (dd, *J* = 9.0 and 4.8 Hz, 1H), 5.21 – 5.08 (m, 2H), 4.77 (d, *J* = 11.4 Hz, 1H), 4.68 (d, *J* = 11.4 Hz, 1H), 4.56 (s, 1H), 3.49 (t, *J* = 6.0 Hz, 2H), 3.07 (d, *J* = 6.2 Hz, 2H), 3.01 – 2.88 (m, 1H), 2.72 – 2.63 (m, 1H), 1.65 – 1.55 (m, 2H), 1.48 – 1.21 (m, 16H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 155.98, 137.91, 135.43, 134.18, 132.85, 131.27, 128.68, 128.07, 128.00, 125.72, 125.51, 117.50, 79.00, 72.15, 70.81, 70.59, 42.09, 40.43, 29.94, 29.68, 29.62, 28.41, 26.53, 25.97, 25.86.

3.8. Acrylate Ester Synthesis

3.8.1. 1-(2-(Methoxymethyl)naphthalen-1-yl)but-3-enyl Acrylate (112)

In a two-necked flask (25 mL), 201 mg of 1-(2-(methoxymethyl)naphthalen-1-yl)but-3-en-1-ol (0.83 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 138 mg of acryloyl chloride, 98% (121 µL, 1.49 mmol, 1.80 eq) and 302 mg of triethylamine (416 µL, 2.98 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:10) resulted 216 mg of desired product in 88% yield.



Yield: 88%; colourless viscous liquid;

R_f: 0.68 (1:4 EtOAc-Hex);

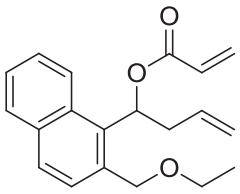
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.59 (d, *J* = 7.9 Hz, 1H), 7.88 – 7.84 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.57 – 7.45 (m, 3H), 6.64 (s, 1H), 6.45 – 6.38 (m, 1H), 6.22 – 6.13 (m, 1H), 5.91 (ddt, *J* = 17.0, 10.1 and 7.0 Hz, 1H), 5.80 (dd, *J* = 10.4 and 1.4 Hz, 1H), 5.17 (dt, *J* = 5.7 and 2.9 Hz, 1H), 5.14 – 5.08 (m, 2H), 4.66 (d, *J* = 11.6 Hz, 1H), 3.49 – 3.47 (s, 3H), 3.24 (dt, *J* = 15.7 and 10.9 Hz, 1H), 2.79 (dddd, *J* = 9.4, 6.9, 5.3 and 3.2 Hz, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.59, 134.20, 131.10, 130.82, 128.95, 128.79, 128.48, 127.15, 125.88, 125.44, 117.64, 73.47, 72.80, 58.17, 39.74;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{19}H_{20}O_3Na$): 319.1310; found: 319.1310.

3.8.2. 1-(2-(Ethoxymethyl)naphthalen-1-yl)but-3-enyl Acrylate (113)

In a two-necked flask (25 mL), 20 mg of 1-(2-(ethoxymethyl)naphthalen-1-yl)but-3-en-1-ol (0.078 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 13 mg of acryloyl chloride, 98% (11 µL, 0.14 mmol, 1.80 eq) and 28 mg of triethylamine (39 µL, 0.28 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:10) resulted 23 mg of desired product in 97% yield.



Yield: 97%; colourless viscous liquid;

R_f: 0.34 (1:8 EtOAc-Hex);

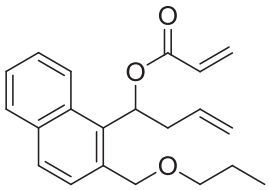
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.58 (d, *J* = 8.1 Hz, 1H), 7.86 – 7.82 (m, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.56 – 7.44 (m, 3H), 6.65 (s, 1H), 6.44 – 6.37 (m, 1H), 6.21 – 6.11 (m, 1H), 5.97 – 5.85 (m, 1H), 5.80 (dd, J = 10.4 and 1.5 Hz, 1H), 5.23 – 5.08 (m, 3H), 4.72 – 4.64 (d, 1H), 3.70 – 3.60 (m, 2H), 3.28 – 3.17 (m, 1H), 2.79 (dddt, *J* = 14.5, 6.4, 4.9, and 1.4 Hz, 1H), 1.29 (t, J = 7.0 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.61, 134.46, 134.24, 131.14, 130.77, 128.93, 128.79, 128.50, 127.30, 125.81, 125.37, 117.58, 72.77, 71.69, 65.96, 39.64, 15.28;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{20}H_{22}O_3Na$): 333.1467; found: 333.1456.

3.8.3. 1-(2-(Propoxymethyl)naphthalen-1-yl)but-3-enyl Acrylate (114)

In a two-necked flask (25 mL), 102 mg of 1-(2-(propoxymethyl)naphthalen-1-yl)but-3-en-1-ol (0.38 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 63 mg of acryloyl chloride, 98% (58 µL, 0.68 mmol, 1.80 eq) and 138 mg of triethylamine (190 µL, 1.36 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 110 mg of desired product in 89% yield.



Yield: 89%; colourless viscous liquid;

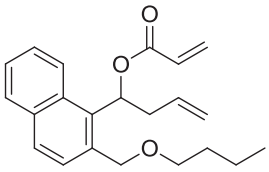
R_f: 0.52 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 7.6 Hz, 1H), 7.90 – 7.83 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.44 (m, 3H), 6.67 (s, 1H), 6.42 (dd, *J* = 17.3 and 1.4 Hz, 1H), 6.17 (dd, *J* = 17.3 and 10.4 Hz, 1H), 6.01 – 5.85 (m, 1H), 5.80 (dd, *J* = 10.4 and 1.4 Hz, 1H), 5.24 – 5.09 (m, 3H), 4.70 (d, *J* = 10.8 Hz, 1H), 3.63 – 3.49 (m, 2H), 3.32 – 3.19 (m, 1H), 2.80 (dddt, *J* = 14.4, 6.4, 4.9 and 1.4 Hz, 1H), 1.76 – 1.65 (m, 2H), 0.99 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.62, 134.58, 134.29, 134.22, 134.12, 131.14, 130.83, 128.95, 128.81, 128.50, 127.31, 125.83, 125.38, 117.65, 77.41, 72.69, 72.47, 71.85, 39.65, 23.08, 10.75.

3.8.4. 1-(2-(Butoxymethyl)naphthalen-1-yl)but-3-enyl Acrylate (115)

In a two-necked flask (25 mL), 111 mg of 1-(2-(butoxymethyl)naphthalen-1-yl)but-3-en-1-ol (0.39 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 65 mg of acryloyl chloride, 98% (59 µL, 0.7 mmol, 1.80 eq) and 142 mg of triethylamine (197 µL, 1.4 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 121 mg of desired product in 91% yield.



Yield: 91%; colourless viscous liquid;

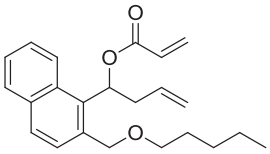
R_f: 0.50 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 7.4 Hz, 1H), 7.86 (d, *J* = 8.0 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.44 (m, 3H), 6.67 (s, 1H), 6.42 (dd, *J* = 17.4 and 1.3 Hz, 1H), 6.18 (dd, *J* = 17.3 and 10.4 Hz, 1H), 6.00 – 5.85 (m, *J* = 17.2, 10.1 and 6.9 Hz, 1H), 5.80 (d, *J* = 10.4 Hz, 1H), 5.25 – 5.07 (m, 3H), 4.70 (d, *J* = 10.8 Hz, 1H), 3.67 – 3.53 (m, 2H), 3.30 – 3.21 (m, 1H), 2.86 – 2.76 (m, 1H), 1.71 – 1.62 (m, 2H), 1.45 (dq, J = 14.9, and 7.4 Hz, 2H), 0.96 (t, *J* = 7.4 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.62, 134.61, 134.29, 134.22, 134.09, 131.14, 130.83, 128.96, 128.82, 128.51, 127.30, 125.83, 125.38, 117.65, 72.70, 71.89, 70.60, 39.65, 31.97, 19.47, 14.03.

3.8.5. 1-(2-((Pentyloxy)methyl)naphthalen-1-yl)but-3-enyl Acrylate (116)

In a two-necked flask (25 mL), 216 mg of 1-(2-((pentyloxy)methyl)naphthalen-1-yl)but-3-en-1-ol (0.72 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 120 mg of acryloyl chloride, 98% (107 µL, 1.3 mmol, 1.80 eq) and 263 mg of triethylamine (463 µL, 2.6 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:6) resulted 194 mg of desired product in 76% yield.



Yield: 76%; colourless viscous liquid;

R_f: 0.55 (1:8 EtOAc-Hex);

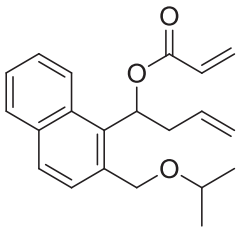
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.60 (d, *J* = 8.0 Hz, 1H), 7.88 – 7.83 (m, 1H), 7.80 (d, *J* = 8.4 Hz, 1H), 7.58 – 7.44 (m, 3H), 6.68 (s, 1H), 6.46 – 6.38 (m, 1H), 6.23 – 6.12 (m, 1H), 5.92 (ddt, *J* = 17.2, 10.2 and 6.9 Hz, 1H), 5.80 (dd, *J* = 10.4 and 1.5 Hz, 1H), 5.24 – 5.09 (m, 3H), 4.71 (d, *J* = 11.3 Hz, 1H), 3.69 – 3.53 (m, 2H), 3.32 – 3.18 (m, 1H), 2.88 – 2.77 (m, 1H), 1.74 – 1.62 (m, 2H), 1.47 – 1.32 (m, 4H), 0.94 (t, *J* = 7.1 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.58, 134.64, 134.22, 131.16, 130.75, 128.94, 128.79, 128.53, 127.28, 125.82, 125.36, 117.61, 72.68, 71.87, 70.91, 39.65, 29.57, 28.46, 22.60, 14.06;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{23}H_{28}O_3Na$): 375.1936; found: 375.1946.

3.8.6. 1-(2-(Isopropoxymethyl)naphthalen-1-yl)but-3-enyl Acrylate (117)

In a two-necked flask (25 mL), 104 mg of 1-(2-(isopropoxymethyl)naphthalen-1-yl)but-3-en-1-ol (0.39 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 64 mg of acryloyl chloride, 98% (59 µL, 0.69 mmol, 1.80 eq) and 141 mg of triethylamine (194 µL, 1.39 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:6) resulted 101 mg of desired product in 79% yield.



Yield: 79%; colourless viscous liquid;

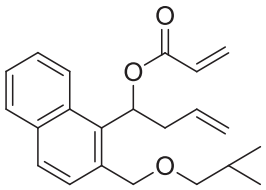
R_f: 0.52 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.61 (d, J = 7.8 Hz, 1H), 7.90 – 7.82 (m, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.59 – 7.41 (m, 3H), 6.70 (s, 1H), 6.42 (dd, J = 17.4 and 1.4 Hz, 1H), 6.18 (dd, J = 17.3 and 10.4 Hz, 1H), 5.95 (ddt, J = 17.1, 10.2 and 6.9 Hz, 1H), 5.80 (dd, J = 10.4 and 1.4 Hz, 1H), 5.26 – 5.18 (m, 1H), 5.14 (d, J = 10.3 Hz, 2H), 4.71 (d, J = 10.2 Hz, 1H), 3.85 (dt, J = 12.2 and 6.1 Hz, 1H), 3.39 – 3.15 (m, 1H), 2.91 – 2.72 (m, 1H), 1.34 (d, J = 6.1 Hz, 3H), 1.29 (d, J = 6.1 Hz, 3H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.68, 134.74, 134.36, 134.29, 131.20, 130.83, 128.96, 128.89, 128.54, 127.52, 126.00, 125.79, 125.34, 117.63, 72.73, 71.52, 69.26, 39.61, 22.33, 22.12.

3.8.7. 1-(2-(Isobutoxymethyl)naphthalen-1-yl)but-3-enyl Acrylate (118)

In a two-necked flask (25 mL), 111 mg of 1-(2-(isobutoxymethyl)naphthalen-1-yl)but-3-en-1-ol (0.39 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 65 mg of acryloyl chloride, 98% (60 µL, 0.7 mmol, 1.80 eq) and 142 mg of triethylamine (196 µL, 1.4 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 99 mg of desired product in 75% yield.



Yield: 75%; colourless viscous liquid;

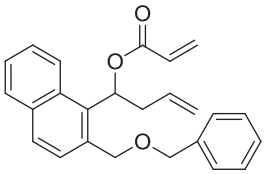
R_f: 0.48 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.62 (d, *J* = 7.0 Hz, 1H), 7.90 – 7.85 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.52 (m, 2H), 7.49 (ddd, *J* = 7.9, 6.8 and 1.1 Hz, 1H), 6.70 (s, 1H), 6.44 (dd, *J* = 17.3 and 1.4 Hz, 1H), 6.21 (d, *J* = 10.4 Hz, 1H), 6.01 – 5.87 (m, 1H), 5.84 – 5.78 (m, 1H), 5.26 – 5.10 (m, 3H), 4.72 (d, *J* = 10.4 Hz, 1H), 3.45 – 3.34 (m, 2H), 3.34 – 3.21 (m, 1H), 2.87 – 2.79 (m, 1H), 2.08 – 1.94 (m, 1H), 1.00 (t, *J* = 6.8 Hz, 6H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.63, 134.71, 134.29, 134.20, 134.00, 131.15, 130.88, 130.76, 128.99, 128.83, 128.52, 127.31, 125.86, 125.40, 117.74, 77.76, 72.59, 72.00, 39.64, 28.68, 19.61, 19.60.

3.8.8. 1-(2-((Benzyloxy)methyl)naphthalen-1-yl)but-3-enyl Acrylate (119)

In a two-necked flask (25 mL), 139 mg of 1-(2-((benzyloxy)methyl)naphthalen-1-yl)but-3-en-1-ol (0.44 mmol, 1.00 eq) was placed and dissolved in 4.0 mL of dry DCM then at 0 ^oC 73 mg of acryloyl chloride, 98% (65 µL, 0.79 mmol, 1.80 eq) and 160 mg of triethylamine (220 µL, 1.58 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried with anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 156 mg of desired product in 95% yield.



Yield: 95%; colourless viscous liquid;

R_f: 0.39 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.61 (d, *J* = 6.5 Hz, 1H), 7.88 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.59 – 7.30 (m, 8H), 6.72 (s, 1H), 6.42 (dt, *J* = 17.3 and 1.6 Hz, 1H), 6.18 (ddd, *J* = 17.3, 10.4 and 1.7 Hz, 1H), 5.95 – 5.83 (m, 1H), 5.83 – 5.79 (m, 1H), 5.25 (d, *J* = 11.5 Hz, 1H), 5.16 – 5.05 (m, 2H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.73 – 4.63 (m, 2H), 3.24 (s, 1H), 2.89 – 2.74 (m, 1H);

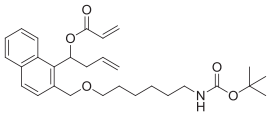
^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.59, 138.19, 134.35, 134.24, 134.08, 131.15, 130.83, 128.98, 128.86, 128.50, 128.42, 127.87, 127.69, 127.37, 125.91, 125.49, 117.73, 72.78, 72.55, 71.26, 39.63;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{25}H_{24}O_3Na$): 395.1623; found: 395.1631.

3.8.9. 1-(2-(((6-((*Tert*-butoxycarbonyl)amino)hexyl)oxy)methyl) naphthalen-1-yl)but-3-en-1-yl Acrylate (120)

In a two-necked flask (25 mL), 50 mg of tert-butyl (6-((1-(1-hydroxybut-3-en-1-yl)naphthalen-2-yl)methoxy)hexyl)carbamate (0.12 mmol, 1.00 eq) was placed and dissolved in 4.0 mL dry DCM then at 0 ^oC 20 mg of acryloyl chloride, 98% (18 µL, 0.21 mmol, 1.80 eq) and 43 mg of triethylamine (59 µL, 0.42 mmol, 3.60 eq) were added, respectively. The mixture was stirred at room temperature under nitrogen atmosphere. After 16 hours, the reaction was ended up with 5 mL of distilled water, extracted with dichloromethane (3x10 mL), and combined organic phase washed with distilled water (10 mL). The organic phase was dried anhydrous $MgSO_4$ and filtered. After removal of the solvent under reduced pressure, crude product was purified by

SiO_2 column chromatography (EtOAc/Hex; 1:8) resulted 26 mg desired product with 44% yield.



Yield: 44%; colourless viscous liquid;

R_f: 0.66 (1:2 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.55 (d, *J* = 8.0 Hz, 1H), 7.86 – 7.80 (m, 1H), 7.77 (d, *J* = 8.4 Hz, 1H), 7.55 – 7.41 (m, 3H), 6.61 (s, 1H), 6.38 (dd, *J* = 17.3 and 1.4 Hz, 1H), 6.14 (dd, *J* = 17.3 and 10.4 Hz, 1H), 5.82 (ddd, *J* = 13.8, 11.8 and 5.8 Hz, 2H), 5.19 – 5.05 (m, 3H), 4.66 (d, *J* = 11.4 Hz, 1H), 3.61 – 3.49 (m, 2H), 3.19 (dd, *J* = 15.3 and 7.7 Hz, 1H), 3.10 (d, *J* = 6.3 Hz, 2H), 2.80 – 2.71 (m, 1H), 1.69 (s, 1H), 1.63 (dd, *J* = 13.8 and 6.9 Hz, 2H), 1.51 – 1.27 (m, 15H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 165.57, 155.95, 134.50, 134.14, 131.09, 130.78, 128.90, 128.78, 128.47, 127.19, 125.80, 125.35, 117.62, 78.98, 72.60, 71.79, 70.67, 40.52, 39.60, 29.99, 29.73, 28.41, 26.67, 25.95;

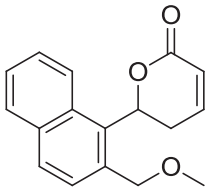
HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{29}H_{39}NO_5Na$): 504.2726; found: 504.2702.

3.9. Ring Closing Metathesis

3.9.1. 6-(2-(Methoxymethyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (121)

In a two-necked flask (50 mL), 214 mg of 1-(2-(methoxymethyl) naphthalen-1-yl) but-3-enyl acrylate (0.72 mmol, 1.00 eq) was placed and dissolved in 30.0 mL of dry DCM. Then 61 mg of 2nd generation Grubbs' catalyst (0.072 mmol, 0.10 eq) was added by dissolving in 3.0 mL of dry DCM The mixture was stirred reflux under nitrogen

atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:4) resulted 150 mg of desired product in 78% yield.



Yield: 78%; white solid;

R_f: 0.24 (1:4 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.39 – 8.25 (m, 1H), 7.95 – 7.76 (m, 2H), 7.53 – 7.46 (m, 2H), 7.42 (dd, *J* = 7.9 and 4.0 Hz, 1H), 7.07 (ddd, *J* = 9.9, 6.2 and 2.0 Hz, 1H), 6.29 (dd, *J* = 13.1 and 4.5 Hz, 1H), 6.23 (ddd, *J* = 9.9, 2.8 and 1.0 Hz, 1H), 4.86 (d, *J* = 11.7 Hz, 1H), 4.52 (d, *J* = 11.7 Hz, 1H), 3.37 (s, 3H), 3.31 – 3.20 (m, 1H), 2.65 – 2.55 (m, 1H);

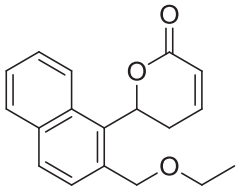
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.26, 146.26, 134.36, 133.88, 132.21, 131.17, 129.52, 129.07, 127.66, 126.29, 125.79, 125.47, 121.18, 76.46, 73.82, 58.02, 30.43;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{17}H_{16}O_3Na$): 291.0997; found: 291.0996

3.9.2. 6-(2-(Ethoxymethyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (122)

In a two-necked flask (50 mL), 66 mg of 1-(2-(ethoxymethyl) naphthalen-1-yl) but-3-enyl acrylate (0.2 mmol, 1.00 eq) was placed and dissolved in 15.0 mL of dry DCM. Then 18 mg of 2nd generation Grubbs' catalyst (0.02 mmol, 0.10 eq) was added by dissolving in 1.5 mL of dry DCM The mixture was stirred reflux under nitrogen atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was purified by SiO_2

column chromatography (EtOAc/Hex; 1:4) resulted 54 mg of desired product in 85% yield.



Yield: 85%; white solid;

R_f: 0.45 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.2 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.44 – 7.40 (m, 1H), 7.07 (ddd, *J* = 9.8, 6.2 and 1.9 Hz, 1H), 6.30 (dd, *J* = 13.1 and 4.4 Hz, 1H), 6.23 (ddd, *J* = 9.9, 2.8 and 1.0 Hz, 1H), 4.86 (d, *J* = 11.6 Hz, 1H), 4.57 (d, *J* = 11.6 Hz, 1H), 3.54 (q, *J* = 7.1 Hz, 2H), 3.25 (dddd, *J* = 19.2, 13.1, 2.7 and 2.1 Hz, 1H), 2.63 (dddd, *J* = 19.3, 6.1, 4.5 and 1.0 Hz, 1H), 1.21 (t, *J* = 7.0 Hz, 3H);

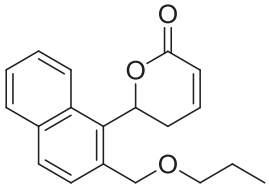
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.27, 146.13, 134.35, 134.16, 132.16, 131.21, 129.54, 129.05, 127.63, 126.27, 125.74, 125.48, 121.35, 76.57, 72.08, 65.83, 30.45, 15.25;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{18}H_{18}O_3Na$): 305.1154; found: 305.1150.

3.9.3. 6-(2-(Propoxymethyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (123)

In a two-necked flask (50 mL), 110 mg of 1-(2-(propoxymethyl) naphthalen-1-yl) but-3-enyl acrylate (0.34 mmol, 1.00 eq) was placed and dissolved in 15.0 mL of dry DCM. Then 29 mg of 2nd generation Grubbs' catalyst (0.03 mmol, 0.10 eq) was added by dissolving in 1.5 mL of dry DCM The mixture was stirred reflux under nitrogen atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was purified by SiO_2

column chromatography (EtOAc/Hex; 1:2) resulted 85 mg of desired product in 85% yield.



Yield: 85%; white solid;

R_f: 0.06 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 7.3 Hz, 1H), 7.86 – 7.83 (m, 1H), 7.81 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.44 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.05 (ddd, *J* = 9.8, 6.2 and 1.9 Hz, 1H), 6.29 (dd, *J* = 13.1 and 4.4 Hz, 1H), 6.22 (ddd, *J* = 9.8, 2.7 and 0.8 Hz, 1H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.54 (d, *J* = 11.6 Hz, 1H), 3.44 (t, *J* = 6.6 Hz, 2H), 3.31 – 3.15 (m, 1H), 2.69 – 2.56 (m, 1H), 1.66 – 1.54 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H);

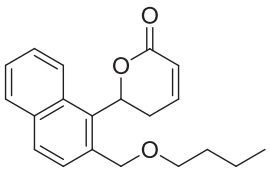
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.35, 146.26, 134.35, 134.19, 132.18, 131.21, 129.56, 129.07, 127.70, 126.26, 125.75, 125.57, 121.32, 76.60, 72.36, 72.34, 30.48, 23.00, 10.78;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{19}H_{20}O_3Na$): 319.1310; found: 319.1302

3.9.4. 6-(2-(Butoxymethyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (124)

In a two-necked flask (50 mL), 120 mg of 1-(2-(butoxymethyl) naphthalen-1-yl) but-3-enyl acrylate (0.36 mmol, 1.00 eq) was placed and dissolved in 15.0 mL of dry DCM. Then 30 mg of 2nd generation Grubbs' catalyst (0.036 mmol, 0.10 eq) was added by dissolving in 1.5 mL of dry DCM The mixture was stirred reflux under nitrogen atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was purified by SiO_2

column chromatography (EtOAc/Hex; 1:2) resulted 74 mg of desired product in 67% yield.



Yield: 67%; white solid;

R_f: 0.08 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (d, 1H), 7.89 – 7.84 (m, 1H), 7.82 (d, *J* = 8.4 Hz, 1H), 7.52 – 7.44 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.07 (ddd, *J* = 9.8, 6.2 and 1.9 Hz, 1H), 6.29 (dd, *J* = 13.1 and 4.4 Hz, 1H), 6.24 (ddd, *J* = 9.9, 2.7 and 0.8 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.55 (d, *J* = 11.5 Hz, 1H), 3.49 (t, *J* = 6.5 Hz, 2H), 3.32 – 3.20 (m, 1H), 2.69 – 2.58 (m, 1H), 1.65 – 1.49 (m, 2H), 1.41 – 1.32 (m, 2H), 0.91 (t, *J* = 7.4 Hz, 3H);

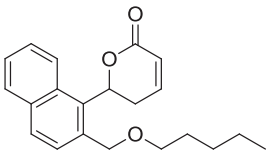
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.34, 146.20, 134.36, 134.17, 132.17, 131.21, 129.57, 129.06, 127.69, 126.27, 125.75, 125.57, 121.35, 76.60, 72.41, 70.45, 31.84, 30.50, 19.43, 13.94;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{20}H_{22}O_3Na$): 333.1467; found: 333.1469.

3.9.5. 6-(2-((Pentyloxy)methyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (125)

In a two-necked flask (50 mL), 194 mg of 1-(2-((pentyloxy) methyl) naphthalen-1-yl) but-3-enyl acrylate (0.55 mmol, 1.00 eq) was placed and dissolved in 30.0 mL of dry DCM. Then 47 mg of 2nd generation Grubbs' catalyst (0.055 mmol, 0.10 eq) was added by dissolving in 3.0 mL of dry DCM The mixture was stirred reflux under nitrogen atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was

purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 131 mg of desired product in 73% yield.



Yield: 73%; white solid;

R_f: 0.12 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.33 (d, *J* = 9.2 Hz, 1H), 7.89 – 7.78 (m, 2H), 7.53 – 7.43 (m, 2H), 7.41 (d, *J* = 8.4 Hz, 1H), 7.05 (ddd, *J* = 9.7, 6.2 and 1.8 Hz, 1H), 6.29 (dd, *J* = 13.1 and 4.4 Hz, 1H), 6.23 (dd, *J* = 9.9 and 1.9 Hz, 1H), 4.85 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 3.48 (t, *J* = 6.6 Hz, 2H), 3.30 – 3.20 (m, 1H), 2.69 – 2.55 (m, 1H), 1.65 – 1.53 (m, 2H), 1.36 – 1.28 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H);

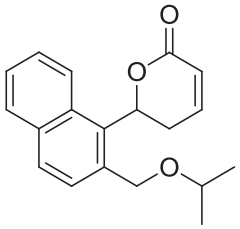
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.27, 146.15, 134.35, 134.20, 132.17, 131.22, 129.55, 129.05, 127.67, 126.25, 125.73, 125.54, 121.35, 76.58, 72.37, 70.78, 30.49, 29.46, 28.45, 22.50, 14.04;

HRMS (ESI-TOF) m/z calculated for $[M]^+$ ($C_{21}H_{25}O_3$): 325.1804; found: 325.1803.

3.9.6. 6-(2-(Isopropoxymethyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (126)

In a two-necked flask (50 mL), 101 mg of 1-(2-(isopropoxymethyl) naphthalen-1-yl) but-3-enyl acrylate (0.31 mmol, 1.00 eq) was placed and dissolved in 15.0 mL of dry DCM. Then 26 mg of 2nd generation Grubbs' catalyst (0.031 mmol, 0.10 eq) was added by dissolving in 1.5 mL of dry DCM The mixture was stirred reflux under nitrogen atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was

purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 63 mg of desired product in 68% yield.



Yield: 68%; white solid;

R_f: 0.06 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.36 – 8.29 (m, 1H), 7.89 – 7.78 (m, 2H), 7.53 – 7.44 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.08 (ddd, *J* = 9.8, 6.2 and 1.8 Hz, 1H), 6.29 (dd, *J* = 13.1 and 4.4 Hz, 1H), 6.24 (dd, *J* = 9.9 and 2.4 Hz, 1H), 4.82 (d, *J* = 11.1 Hz, 1H), 4.59 (d, *J* = 11.1 Hz, 1H), 3.81 – 3.67 (m, 1H), 3.35 – 3.20 (m, 1H), 2.68 (ddd, *J* = 19.3, 5.7 and 4.8 Hz, 1H), 1.21 (d, *J* = 11.8 Hz, 3H), 1.20 (d, *J* = 11.8 Hz, 3H);

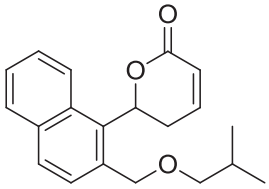
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.38, 146.23, 134.37, 134.34, 132.17, 131.24, 129.62, 129.04, 127.70, 126.24, 125.70, 125.53, 121.42, 76.72, 71.46, 69.72, 30.48, 22.16, 22.05;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{19}H_{20}O_3Na$): 319.1310; found: 319.1310.

3.9.7. 6-(2-(Isobutoxymethyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (127)

In a two-necked flask (50 mL), 98 mg of 1-(2-(isobutoxymethyl) naphthalen-1-yl) but-3-enyl acrylate (0.29 mmol, 1.00 eq) was placed and dissolved in 15.0 mL of dry DCM. Then 25 mg of 2nd generation Grubbs' catalyst (0.029 mmol, 0.10 eq) was added by dissolving in 1.5 mL of dry DCM The mixture was stirred reflux under nitrogen atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was purified by SiO_2

column chromatography (EtOAc/Hex; 1:2) resulted 79 mg of desired product in 88% yield.



Yield: 88%; white solid;

R_f: 0.08 (1:8 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.30 (m, 1H), 7.88 – 7.84 (m, *J* = 5.0 and 4.5 Hz, 1H), 7.82 (d, *J* = 8.3 Hz, 1H), 7.52 – 7.45 (m, 2H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.06 (ddd, *J* = 9.9, 6.2 and 1.9 Hz, 1H), 6.30 (dd, *J* = 13.1 and 4.4 Hz, 1H), 6.23 (ddd, J = 9.9, 2.8, and 1.0 Hz, 1H), 4.86 (d, *J* = 11.5 Hz, 1H), 4.54 (d, *J* = 11.5 Hz, 1H), 3.33 – 3.20 (m, 3H), 2.69 – 2.57 (m, 1H), 1.95 – 1.80 (m, 1H), 0.91 (d, *J* = 6.7 Hz, 3H), 0.90 (d, *J* = 6.7 Hz, 3H);

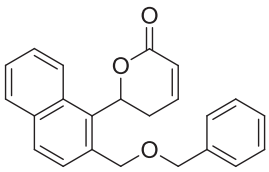
^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.32, 146.17, 134.35, 134.20, 132.16, 131.22, 129.56, 129.05, 127.72, 126.26, 125.74, 125.60, 121.39, 77.73, 76.59, 72.59, 30.50, 28.57, 19.50, 19.45;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{20}H_{22}O_3Na$): 333.1467; found: 333.1467.

3.9.8. 6-(2-((Benzyloxy)methyl)naphthalen-1-yl)-5,6-dihydro-*2H*-pyran-2-one (128)

In a two-necked flask (50 mL), 156 mg of 1-(2-((benzyloxy) methyl) naphthalen-1-yl) but-3-enyl acrylate (0.42 mmol, 1.00 eq) was placed and dissolved in 30.0 mL of dry DCM. Then 36 mg of 2nd generation Grubbs' catalyst (0.042 mmol, 0.10 eq) was added by dissolving in 3.0 mL of dry DCM The mixture was stirred reflux under nitrogen atmosphere. After 2 hours, the mixture was allowed to cool to room temperature. After removal of the solvent under reduced pressure, crude product was

purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 107 mg of desired product in 74% yield.



Yield: 74%; white solid;

R_f: 0.08 (1:8 EtOAc-Hex);

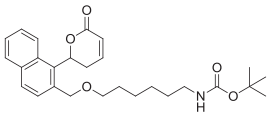
^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.38 – 8.29 (m, 1H), 7.89 – 7.85 (m, 1H), 7.83 (d, *J* = 8.4 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.43 (d, *J* = 8.4 Hz, 1H), 7.40 – 7.28 (m, 5H), 6.98 (ddd, *J* = 9.8, 6.2 and 1.9 Hz, 1H), 6.26 (dd, *J* = 13.1 and 4.4 Hz, 1H), 6.21 (ddd, *J* = 9.9, 2.8 and 1.0 Hz, 1H), 4.91 (d, *J* = 11.5 Hz, 1H), 4.63 (d, *J* = 11.5 Hz, 1H), 4.55 (q, *J* = 11.6 Hz, 2H), 3.28 – 3.12 (m, 1H), 2.62 – 2.51 (m, 1H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.24, 146.16, 137.64, 134.42, 133.79, 132.39, 131.23, 129.62, 129.08, 128.56, 128.07, 127.99, 127.81, 126.33, 125.85, 125.57, 121.24, 76.56, 72.52, 71.40, 30.40;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{23}H_{20}O_3Na$): 367.1310; found: 367.1320.

3.9.9. *Tert*-butyl (6-((1-(6-Oxo-3,6-dihydro-2H-pyran-2-yl)naphthalen-2-yl)methoxy)hexyl)carbamate (129)

In a two-necked flask (50 mL), 26 mg of 1-(2-(((6-((tert-butoxycarbonyl) amino) hexyl) oxy) methyl) naphthalen-1-yl) but-3-en-1-yl acrylate (0.05 mmol, 1.00 eq) was placed and dissolved in 10.0 mL dry DCM. Then 5 mg of 2nd generation Grubbs' catalyst (0.005 mmol, 0.10 eq) was added by dissolving in 1.0 mL dry DCM The mixture was stirred reflux under nitrogen atmosphere for 2 hours. After removal of the solvent under reduced pressure, crude product was purified by SiO_2 column chromatography (EtOAc/Hex; 1:2) resulted 22 mg desired product with 99% yield.



Yield: 99%; white solid;

R_f: 0.25 (1:2 EtOAc-Hex);

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.32 (d, *J* = 9.2 Hz, 1H), 7.92 – 7.78 (m, 2H), 7.54 – 7.39 (m, 3H), 7.08 (ddd, *J* = 9.6, 6.2 and 1.7 Hz, 1H), 6.37 – 6.17 (m, 2H), 4.85 (d, *J* = 11.6 Hz, 1H), 4.62 – 4.50 (m, 2H), 3.47 (t, *J* = 6.5 Hz, 2H), 3.37 – 3.21 (m, 1H), 3.14 – 3.03 (m, 2H), 2.70 – 2.55 (m, 1H), 1.62 – 1.51 (m, 2H), 1.52 – 1.28 (m, 15H);

^{13}C-NMR (100 MHz, $CDCl_3$) δ 164.25, 155.95, 146.09, 134.35, 134.11, 132.14, 131.20, 129.57, 129.04, 127.65, 126.29, 125.75, 125.50, 121.41,76.54, 72.35, 70.58, 40.46, 30.50, 30.29, 30.02, 29.69, 28.41, 26.59, 25.96, 22.67, 14.10;

HRMS (ESI-TOF) m/z calculated for $[M+Na]^+$ ($C_{27}H_{35}NO_5Na$): 476.2413; found: 476.2426

CHAPTER 4

CONCLUSION

α,β-Unsaturated δ-lactones which are the members of lactones are quite valuable compounds because of their Michael acceptor property of unsaturated carbonyl functional group. Klavuzons are the members of α,β-unsaturated δ-lactones and their cytotoxic propertied over cancer cells are remarkable. They are more potent then goniothalamin analogues. Due to their interesting properties, racemic preparation of nine simple klavuzon derivatives were completed. Their anticancer properties will be investigated in near future.

In this study, synthesis of klavuzon derivatives were started with 2-methyl-1-naphtoic acid (**132**), which can be transferred to ethyl 2-methyl-1-naphtoate (**133**) by reacting with iodoethane under basic condition. This formed ester **133** reacted with Br_2 molecules generated in situ by $NaBrO_3$ and $NaHSO_3$ in order to transfer to ethyl 2-(bromomethyl)-1-naphtoate (**134**). Then formed ethyl 2-(bromomethyl)-1-naphtoate (**134**) reacted with various alcohols under basic conditions to form ethyl-2-alkoxymethyl-1-naphtoate (**135-152**). These esters **135-152** are coverted to primary alcohols (**153-161**) by reduction with $LiAlH_4$. Then via oxidation reaction with PCC, the primary alcohols (**153-161**) were transformed to 2-alkoxtmethyl-1-naphtaldehydes (**94-102**). The aldehydes (**94-102**) were treated with allymagnesium bromide to obtain homoallylic alcohols (**103-111**) via Grignard reaction. Later, homoallylic alcohols (**103-111**) were reacted with acryloyl chloride (**65**) in the presence of a base to produce acrylate esters (**112-120**). In the final part, the target klavuzon products (**121-129**) were synthesized via ring closing metathesis reactions with second generation Grubbs' catalyst.

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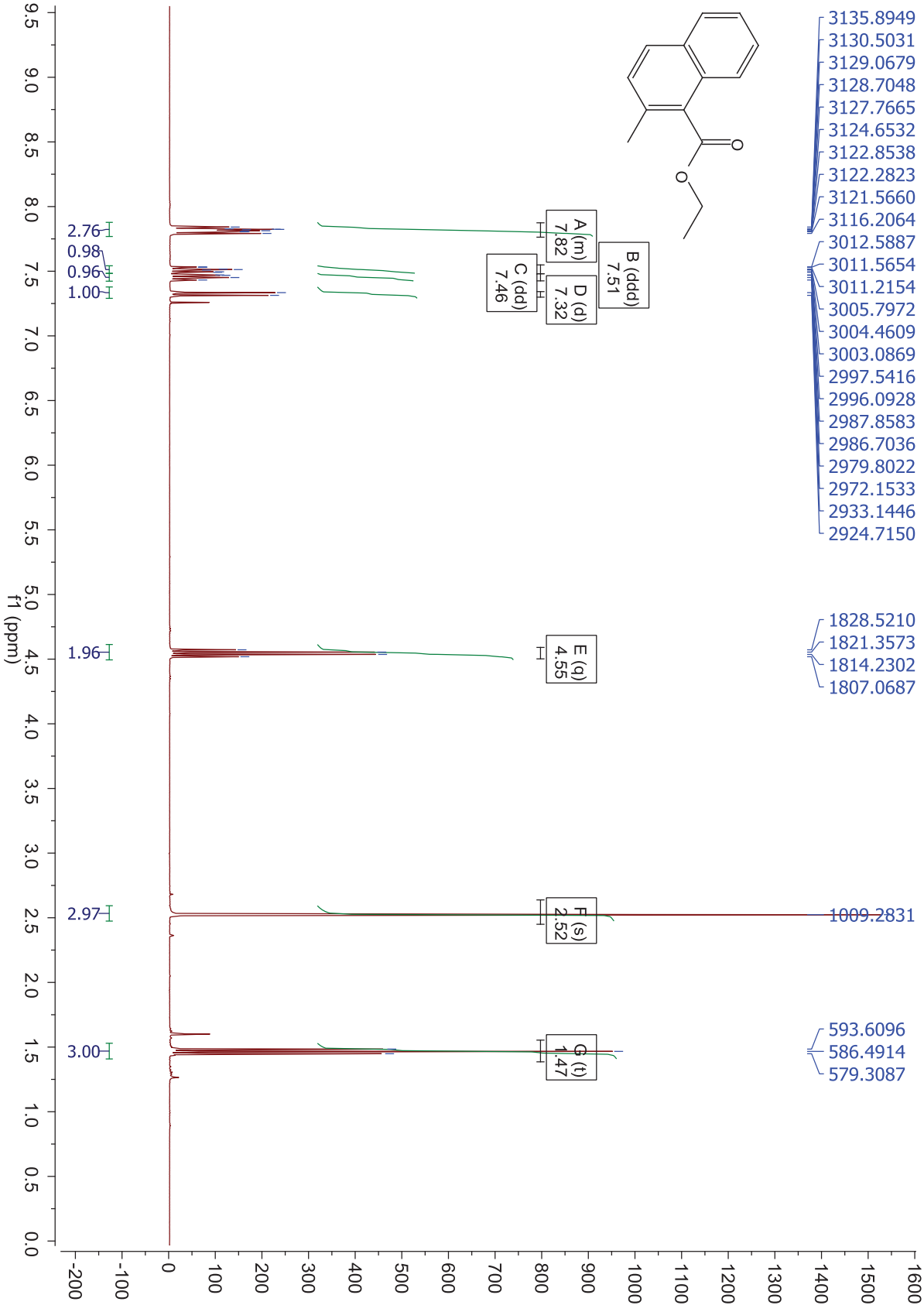
APPENDIX A

^{1}H NMR AND ^{13}C NMR SPECTRA FOR SELECTED EXAMPLES


A (m) 7.82
B (ddd) 7.51
C (dd) 7.46
D (d) 7.32
E (q) 4.55
F (s) 2.52
G (t) 1.47
2.76
0.98
0.96
1.00
1.96
2.97
3.00
3135.8949
3130.5031
3129.0679
3128.7048
3127.7665
3124.6532
3122.8538
3122.2823
3121.5660
3116.2064
3012.5887
3011.5654
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3005.7972
3004.4609
3003.0869
2997.5416
2996.0928
2987.8583
2986.7036
2979.8022
2972.1533
2933.1446
2924.7150
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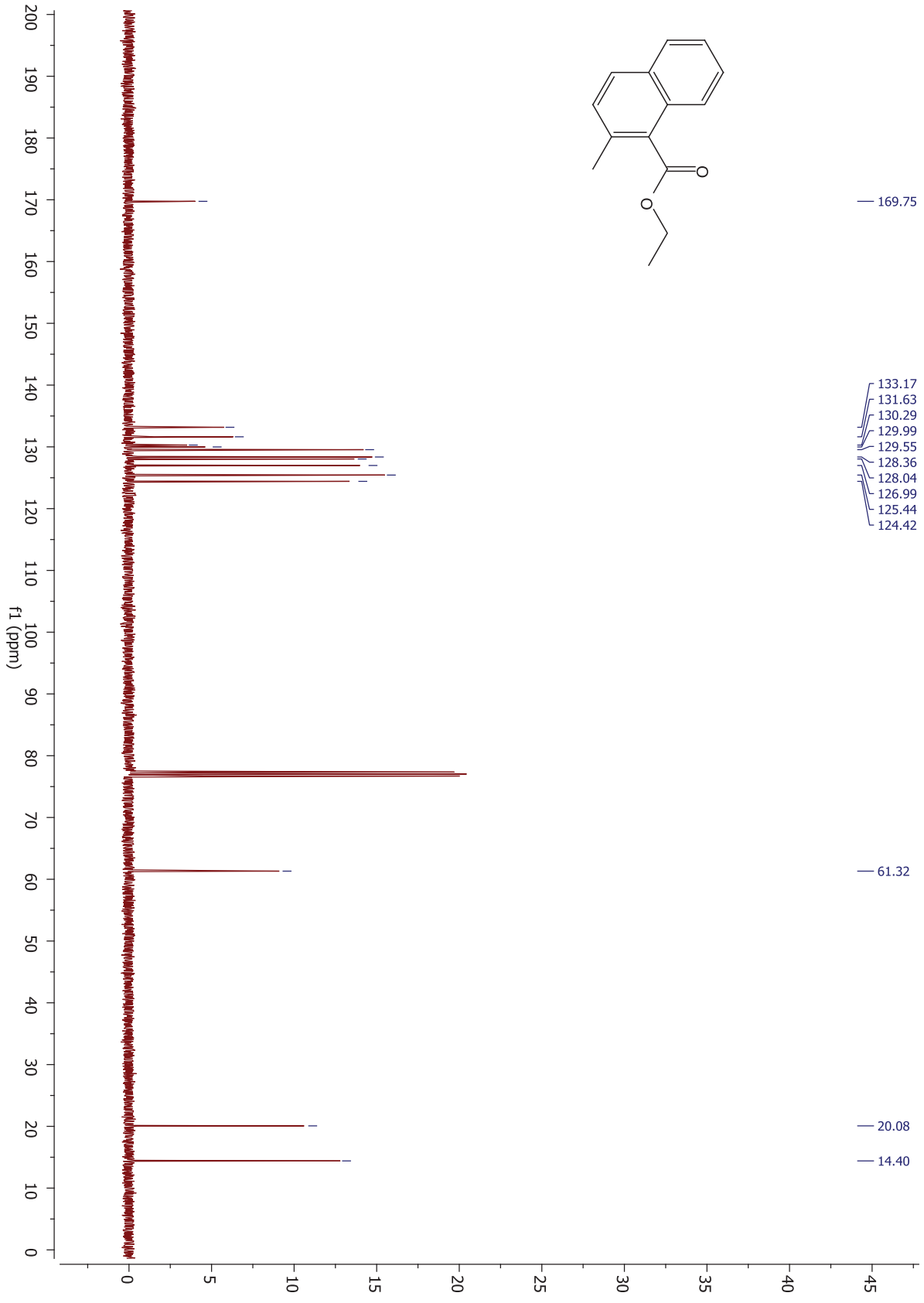
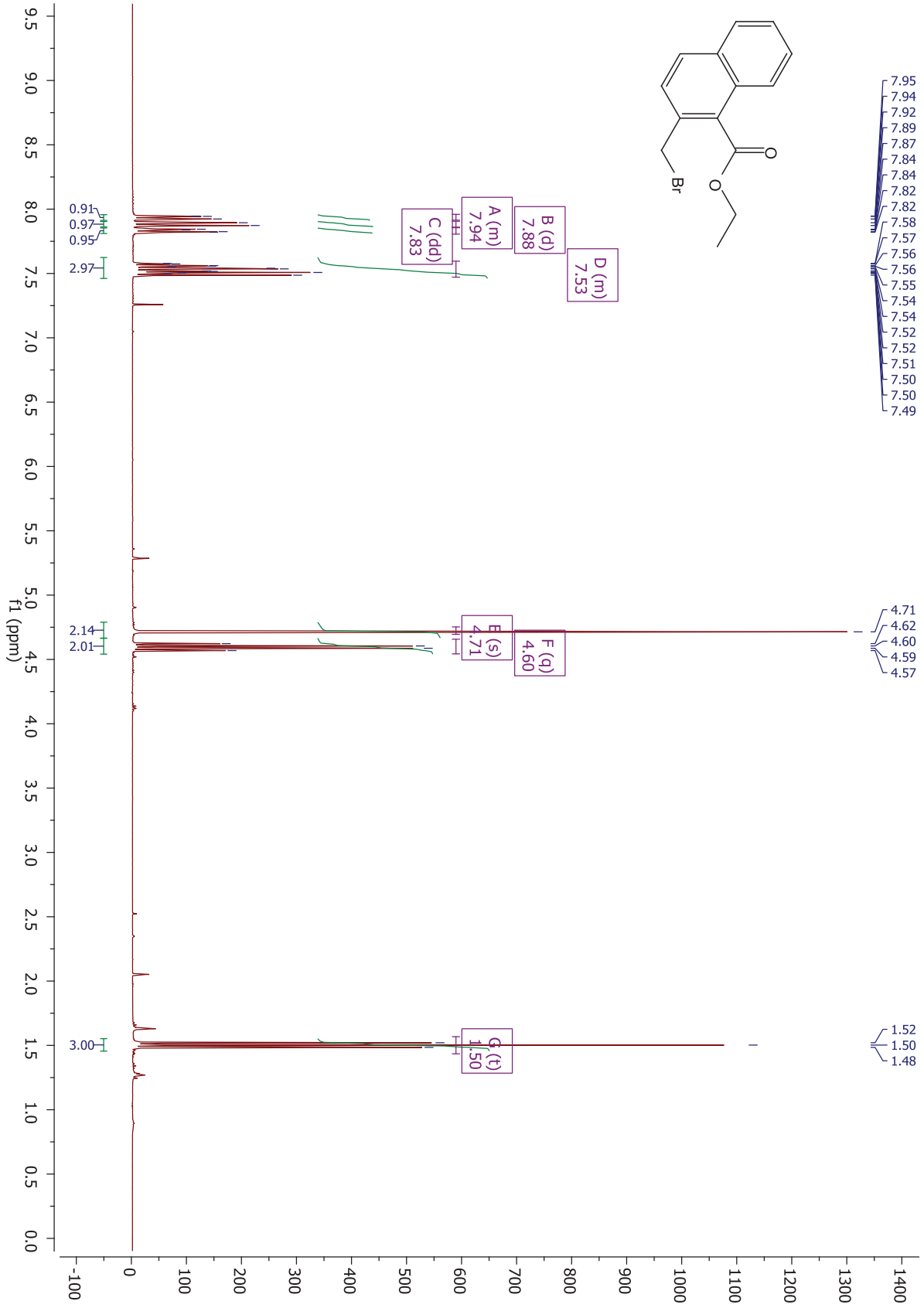
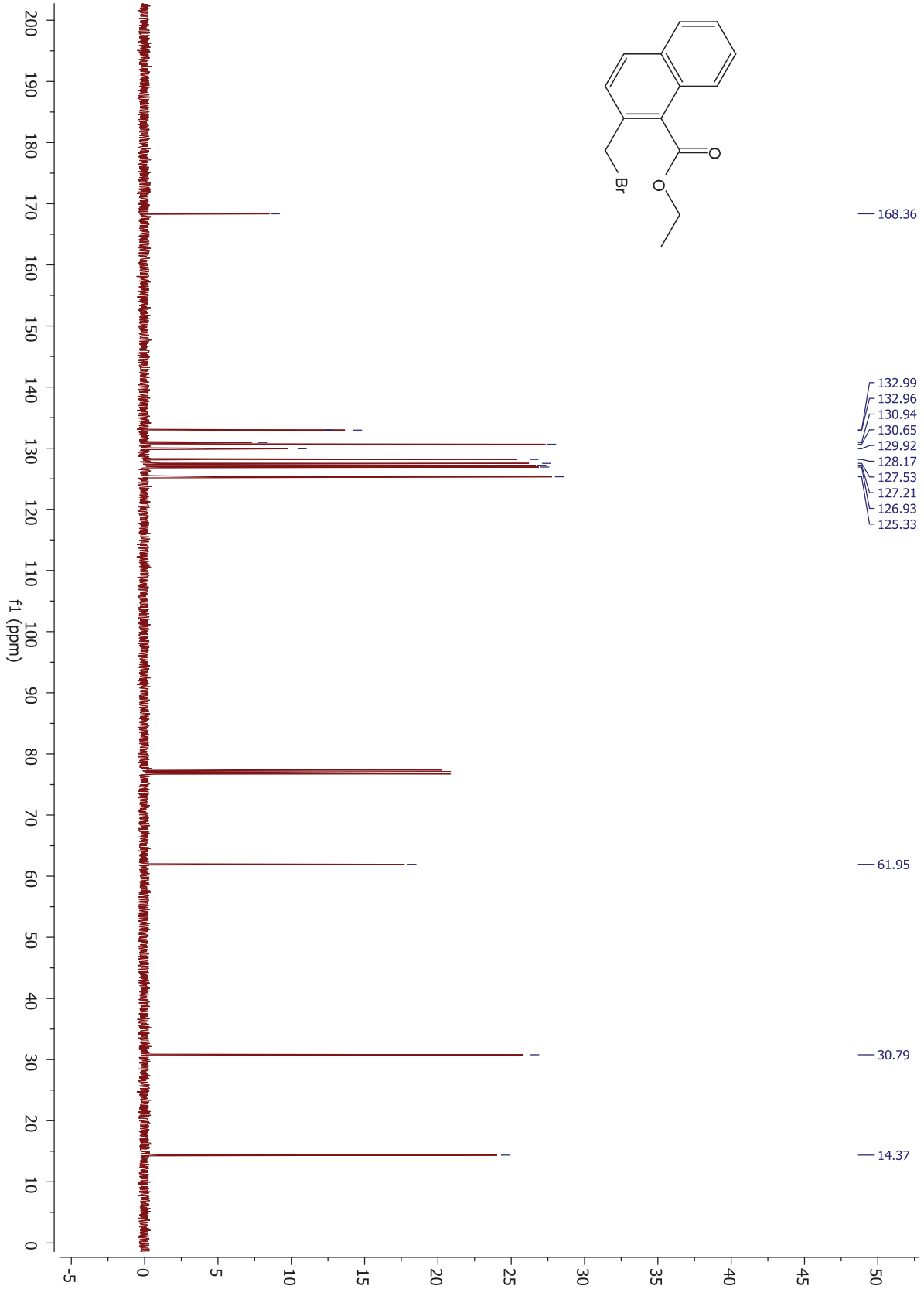
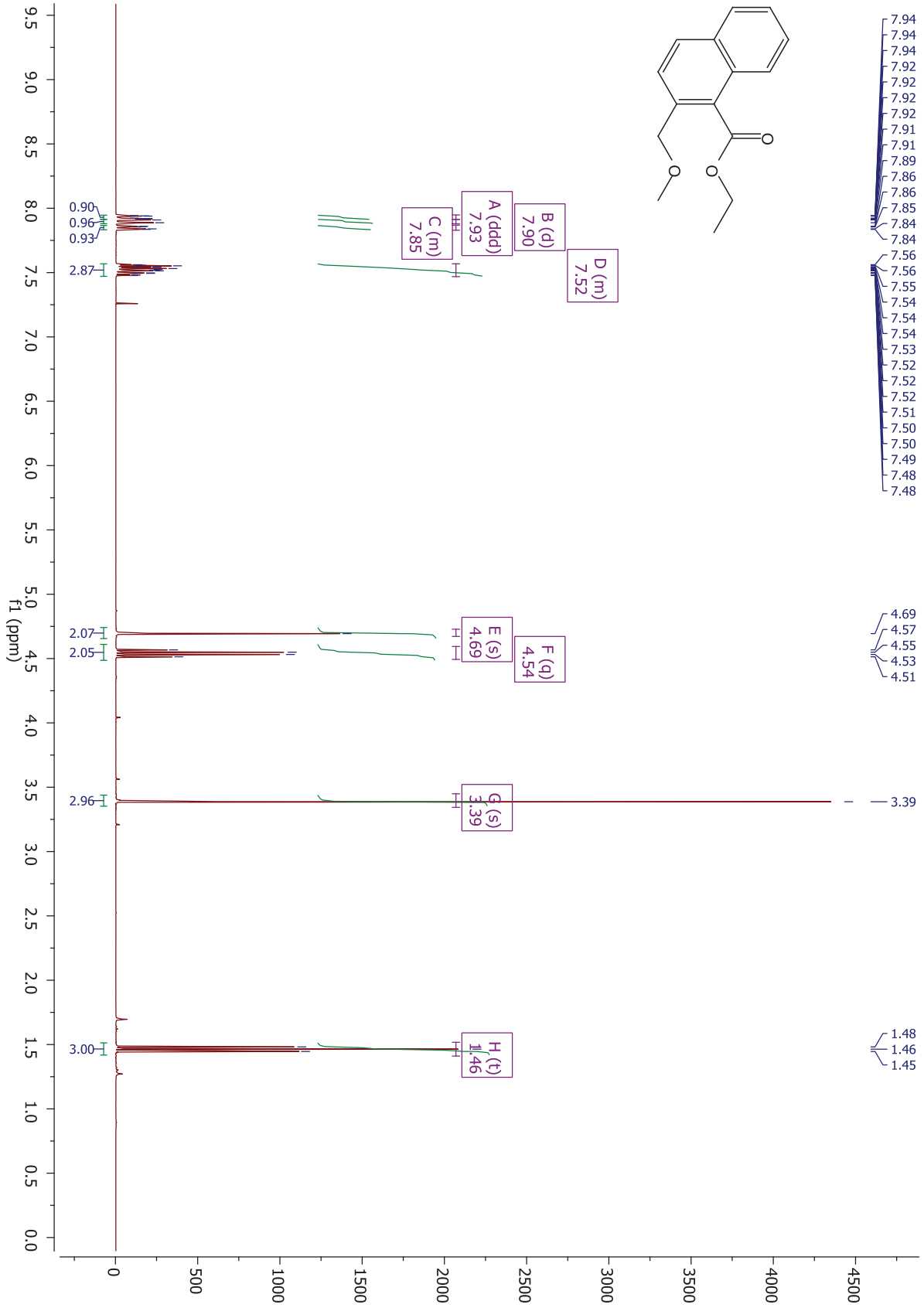
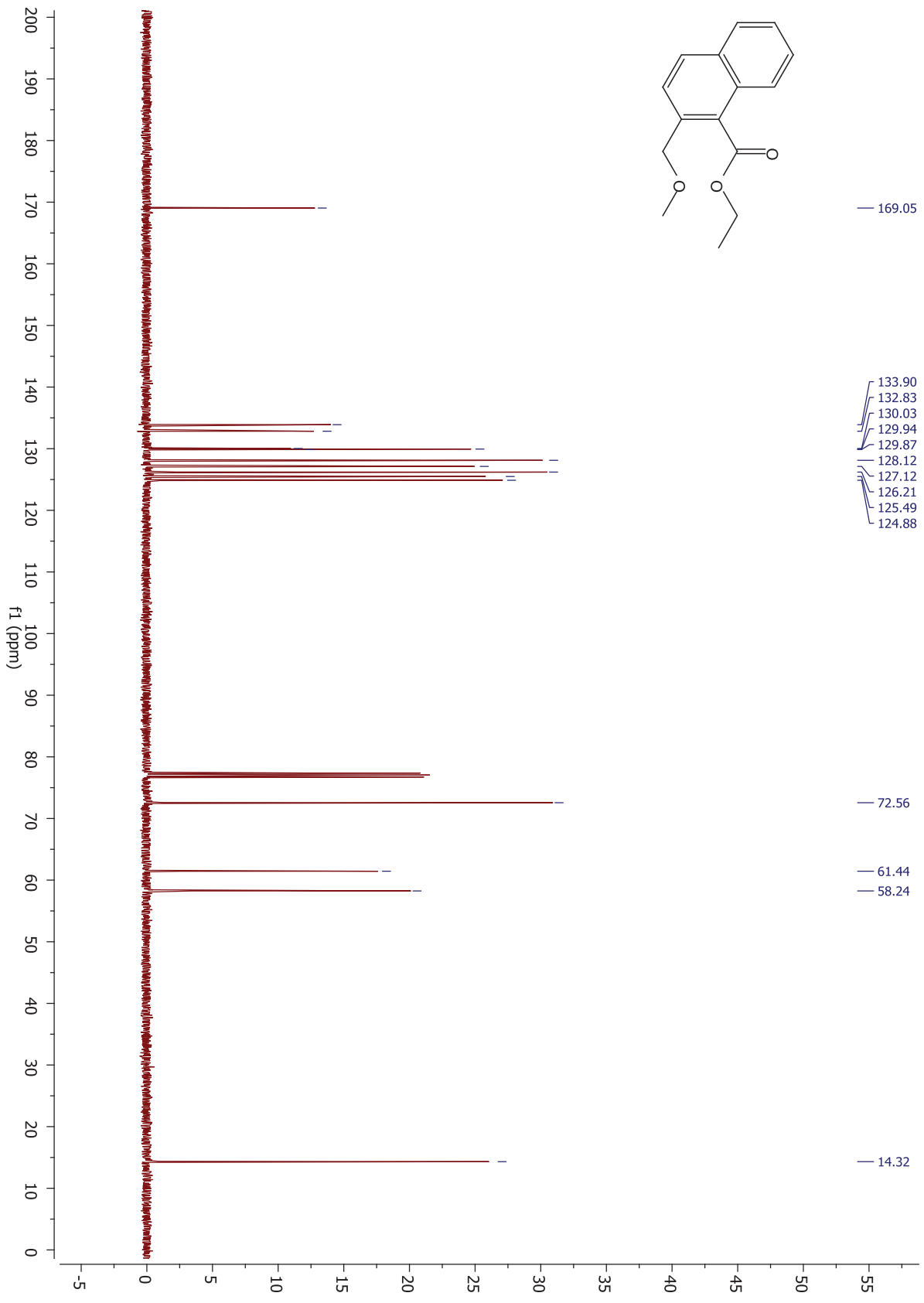
593.6096
586.4914
579.3087
f1 (ppm)

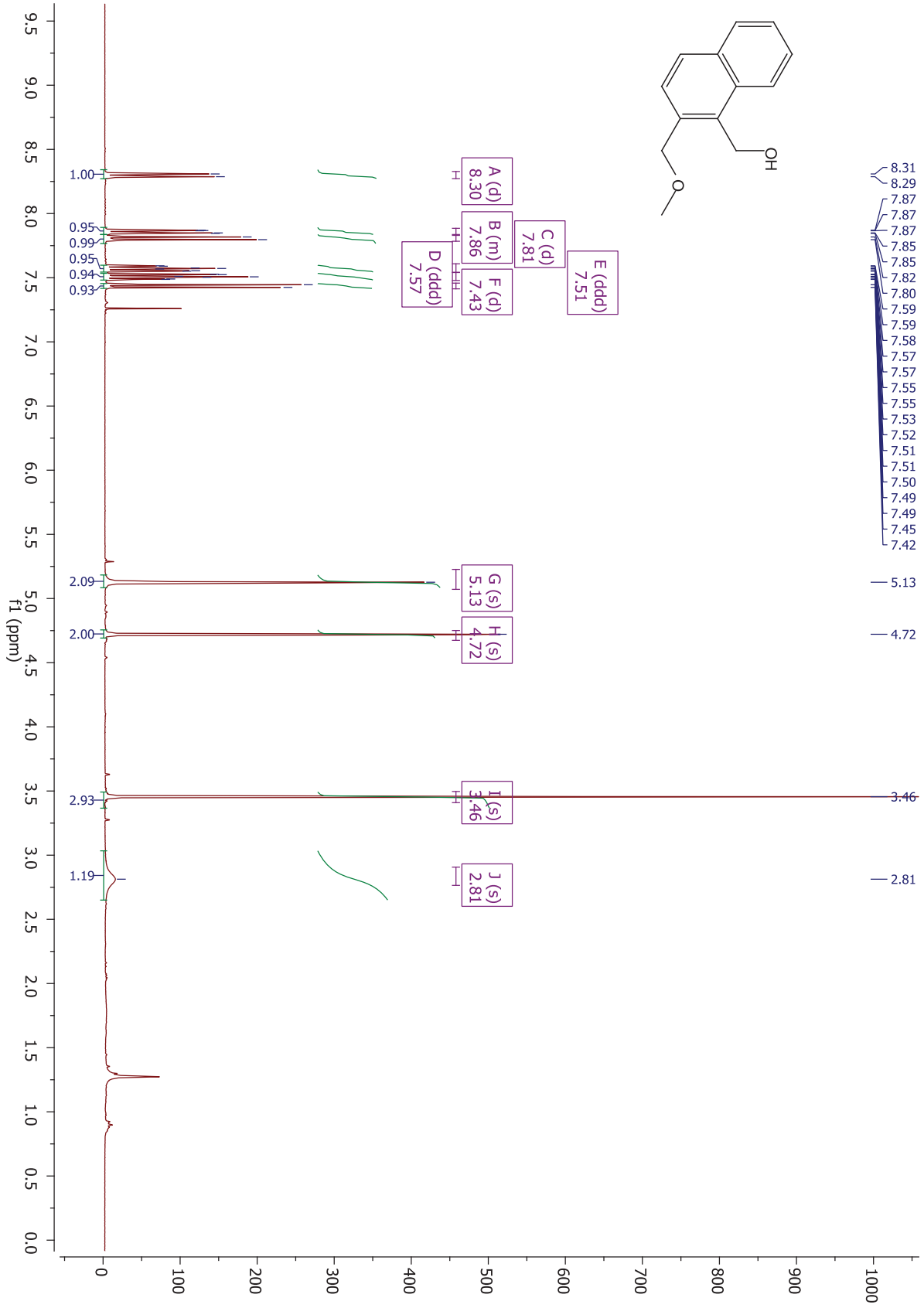

169.75
133.17
131.63
130.29
129.99
129.55
128.36
128.04
126.99
125.44
124.42
61.32
20.08
14.40
f1 (ppm)

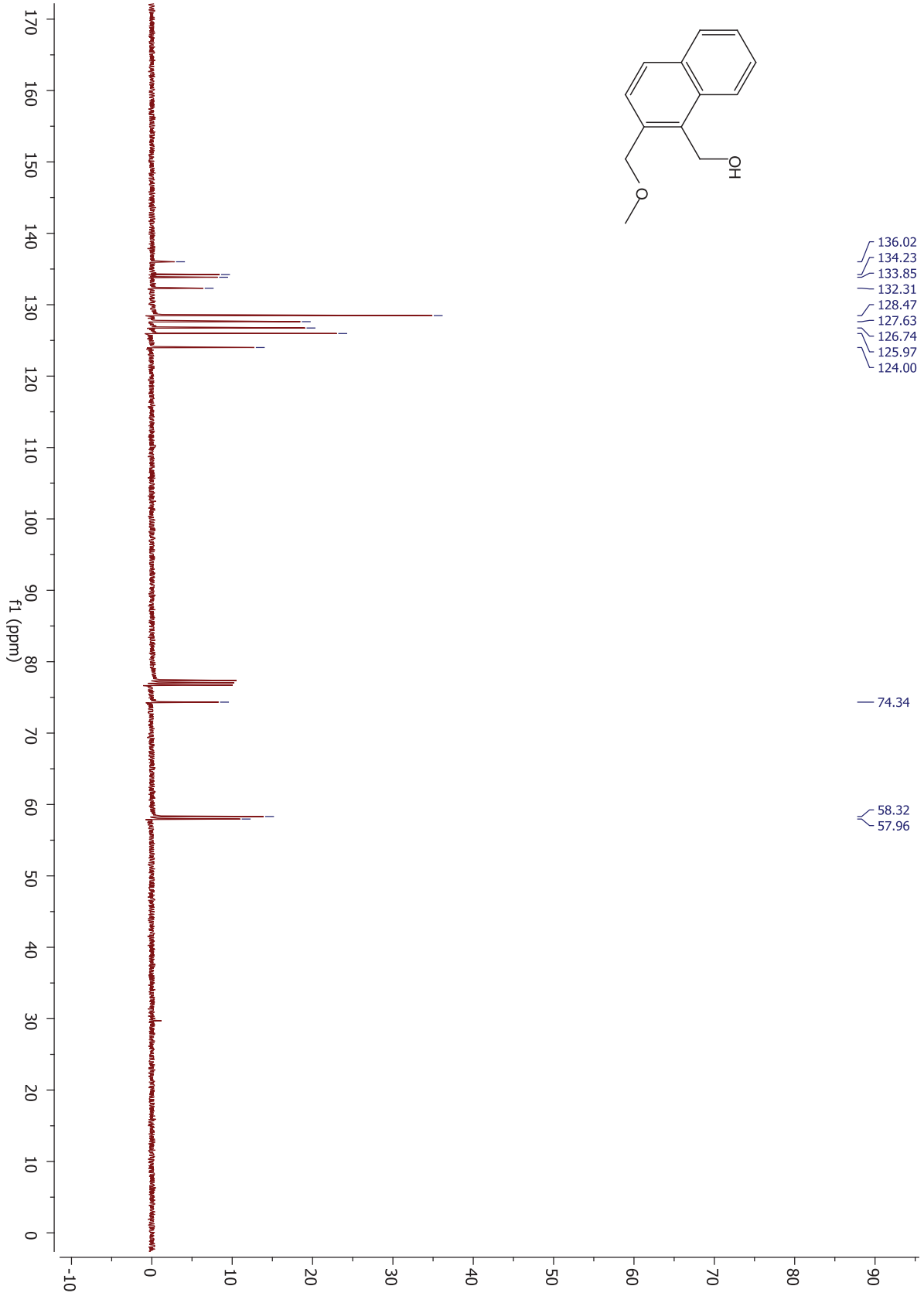

A (m) 7.94
B (d) 7.88
C (dd) 7.83
D (m) 7.53
E (s) 4.71
F (q) 4.60
G (t) 1.50
Br
O
O
0.91
0.97
0.95
2.97
2.14
2.01
3.00
7.95
7.94
7.92
7.89
7.87
7.84
7.84
7.82
7.82
7.58
7.57
7.56
7.56
7.55
7.54
7.54
7.52
7.52
7.51
7.50
7.50
7.49
4.71
4.62
4.60
4.59
4.57
1.52
1.50
1.48
f1 (ppm)

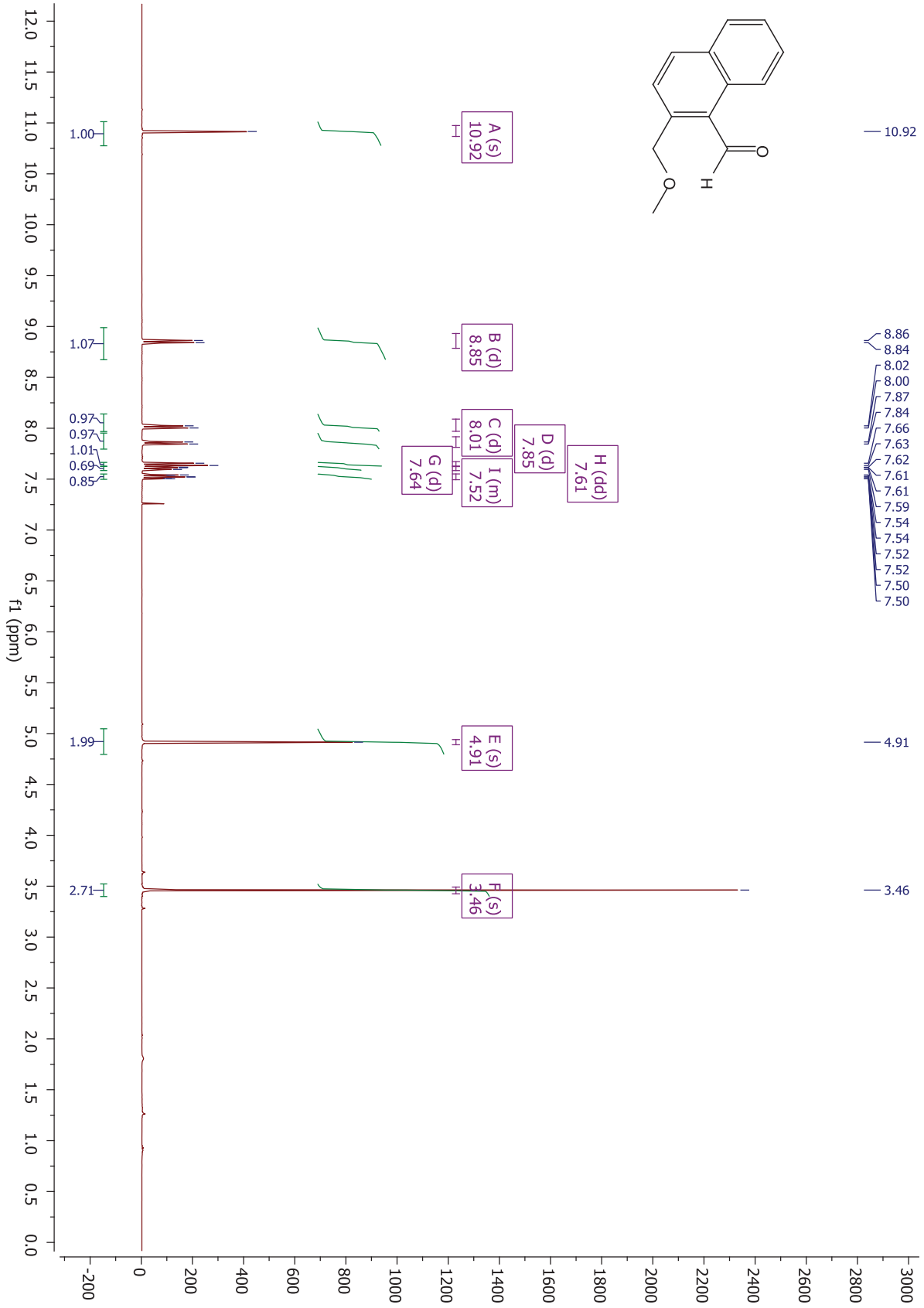

f1 (ppm)
168.36
132.99
132.96
130.94
130.65
129.92
128.17
127.53
127.21
126.93
125.33
61.95
30.79
14.37
Br
O
O

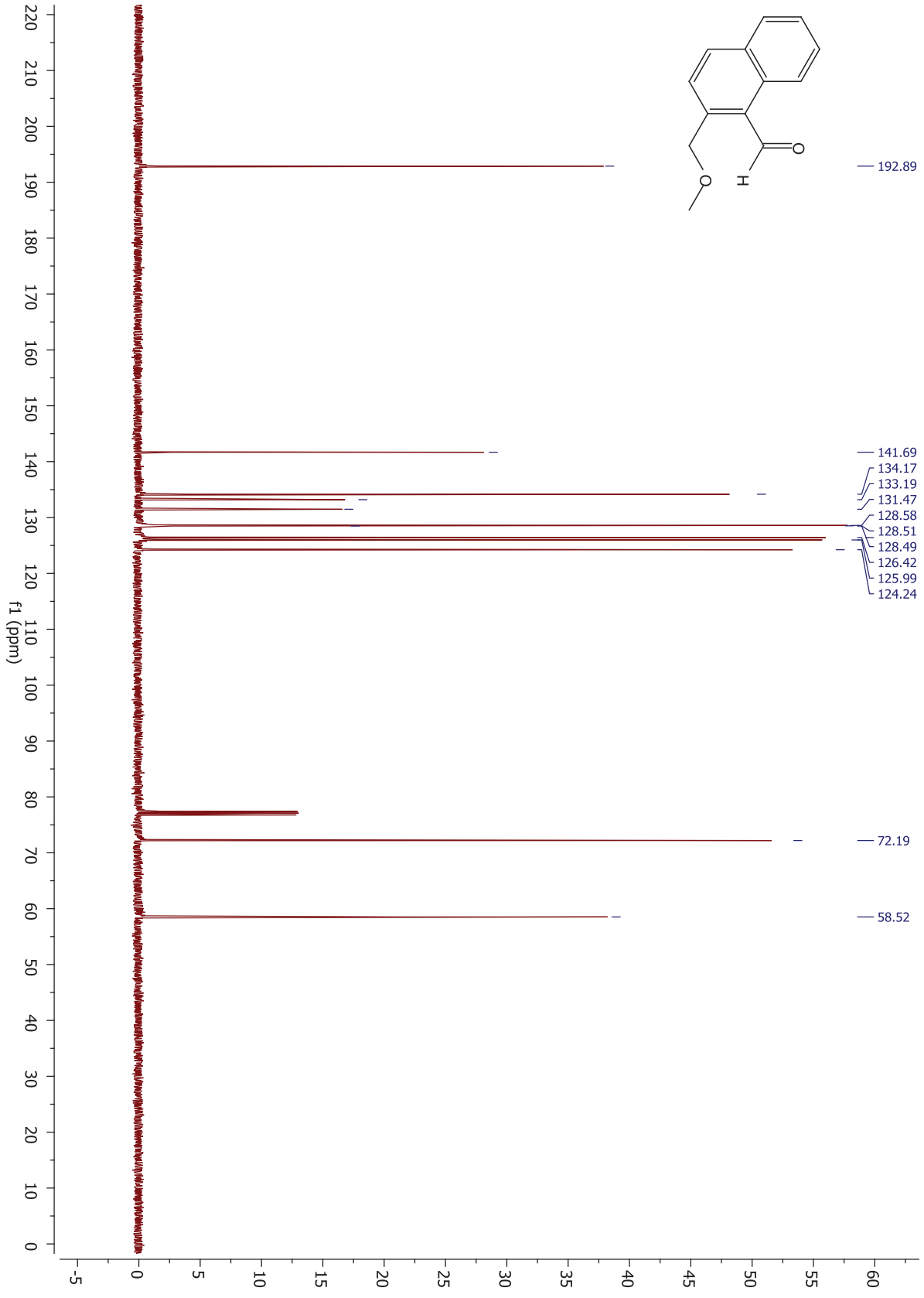

A (ddd) 7.93
B (d) 7.90
C (m) 7.85
D (m) 7.52
E (s) 4.69
F (q) 4.54
G (s) 3.39
H (t) 1.46
0.90
0.96
0.93
2.87
2.07
2.05
2.96
3.00
7.94
7.94
7.94
7.92
7.92
7.92
7.92
7.92
7.91
7.91
7.89
7.86
7.86
7.85
7.84
7.84
7.56
7.56
7.55
7.54
7.54
7.54
7.53
7.52
7.52
7.52
7.51
7.50
7.50
7.49
7.48
7.48
4.69
4.57
4.55
4.53
4.51
3.39
1.48
1.46
1.45
f1 (ppm)

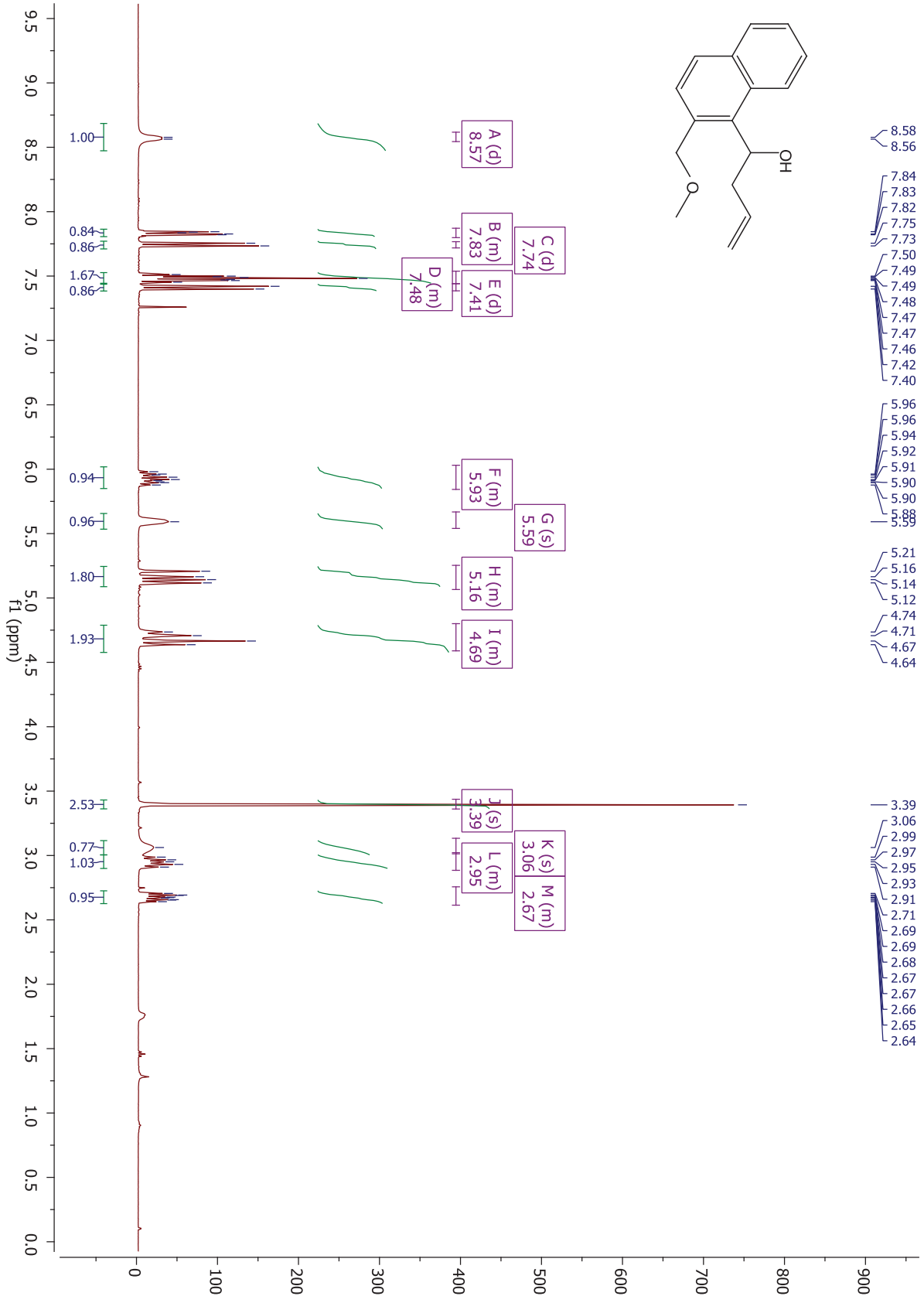

169.05
133.90
132.83
130.03
129.94
129.87
128.12
127.12
126.21
125.49
124.88
72.56
61.44
58.24
14.32
f1 (ppm)

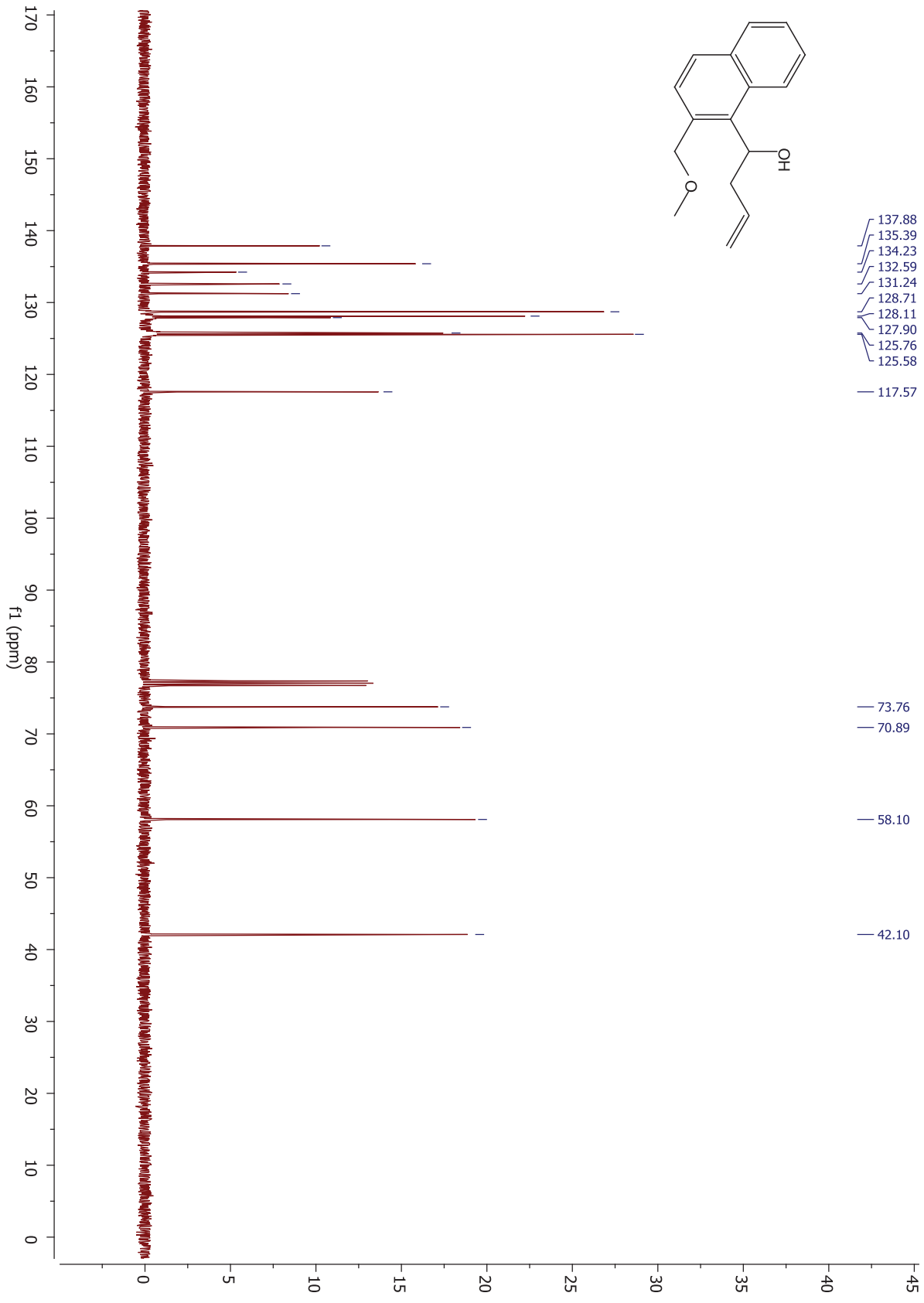

A (d) 8.30
B (m) 7.86
C (d) 7.81
D (ddd) 7.57
E (ddd) 7.51
F (d) 7.43
G (s) 5.13
H (s) 4.72
I (s) 3.46
J (s) 2.81
OH
O
f1 (ppm)

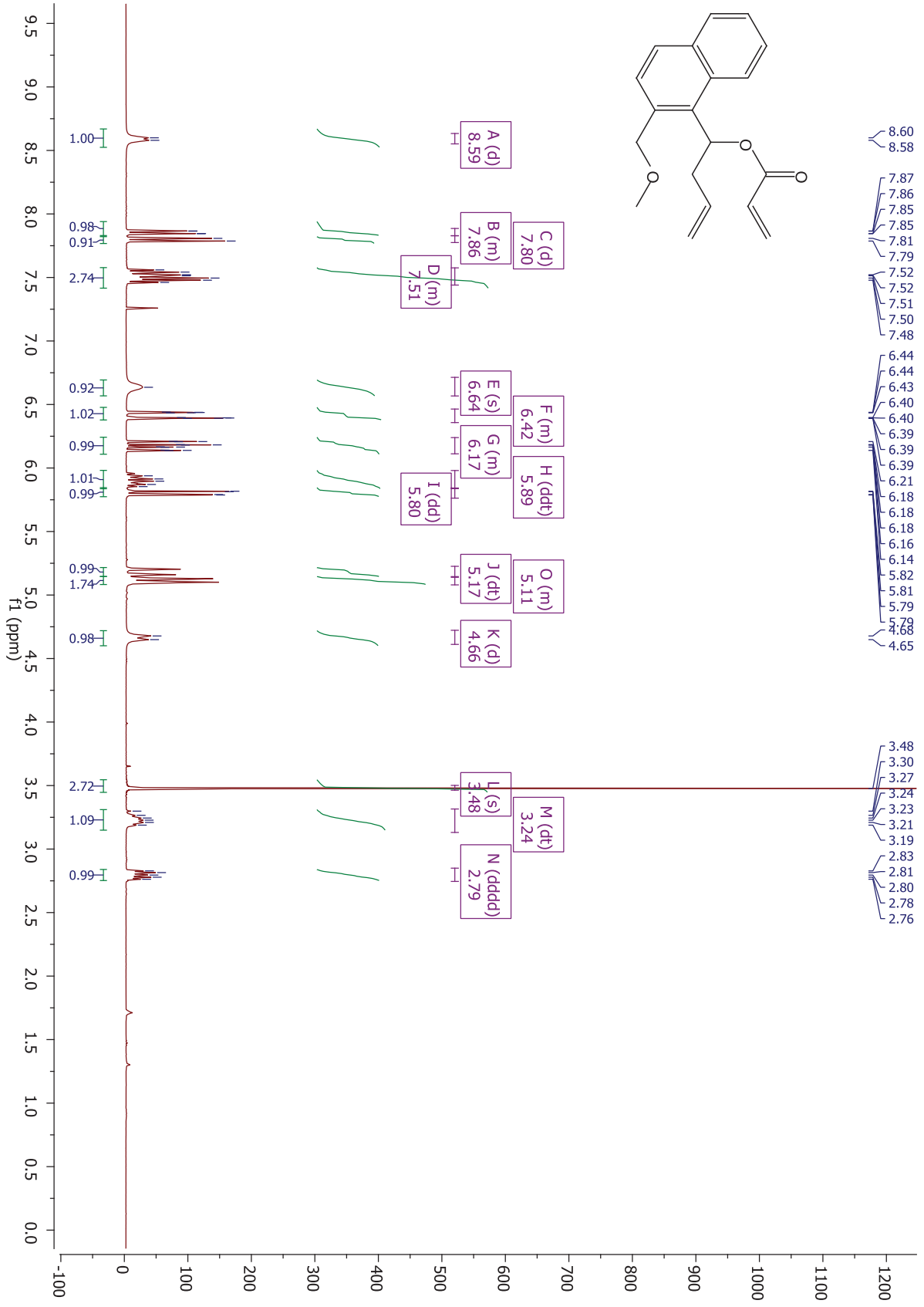

OH
O
136.02
134.23
133.85
132.31
128.47
127.63
126.74
125.97
124.00
74.34
58.32
57.96
f1 (ppm)

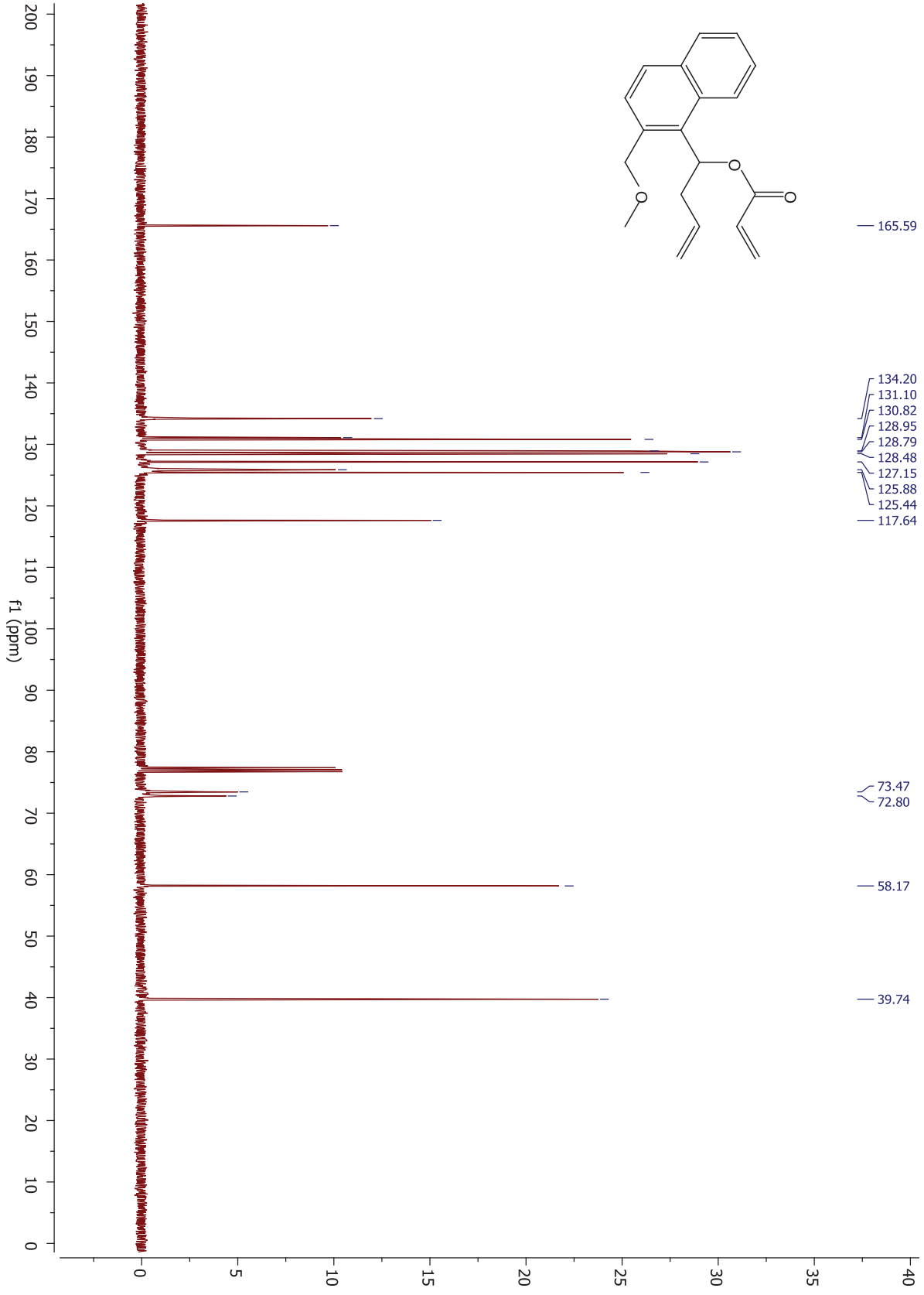

A (s) 10.92
B (d) 8.85
C (d) 8.01
D (d) 7.85
E (s) 4.91
F (s) 3.46
G (d) 7.64
H (dd) 7.61
I (m) 7.52
1.00
1.07
0.97
0.97
1.01
0.69
0.85
1.99
2.71
10.92
8.86
8.84
8.02
8.00
7.87
7.84
7.66
7.63
7.62
7.61
7.61
7.59
7.54
7.54
7.52
7.52
7.50
7.50
4.91
3.46
f1 (ppm)

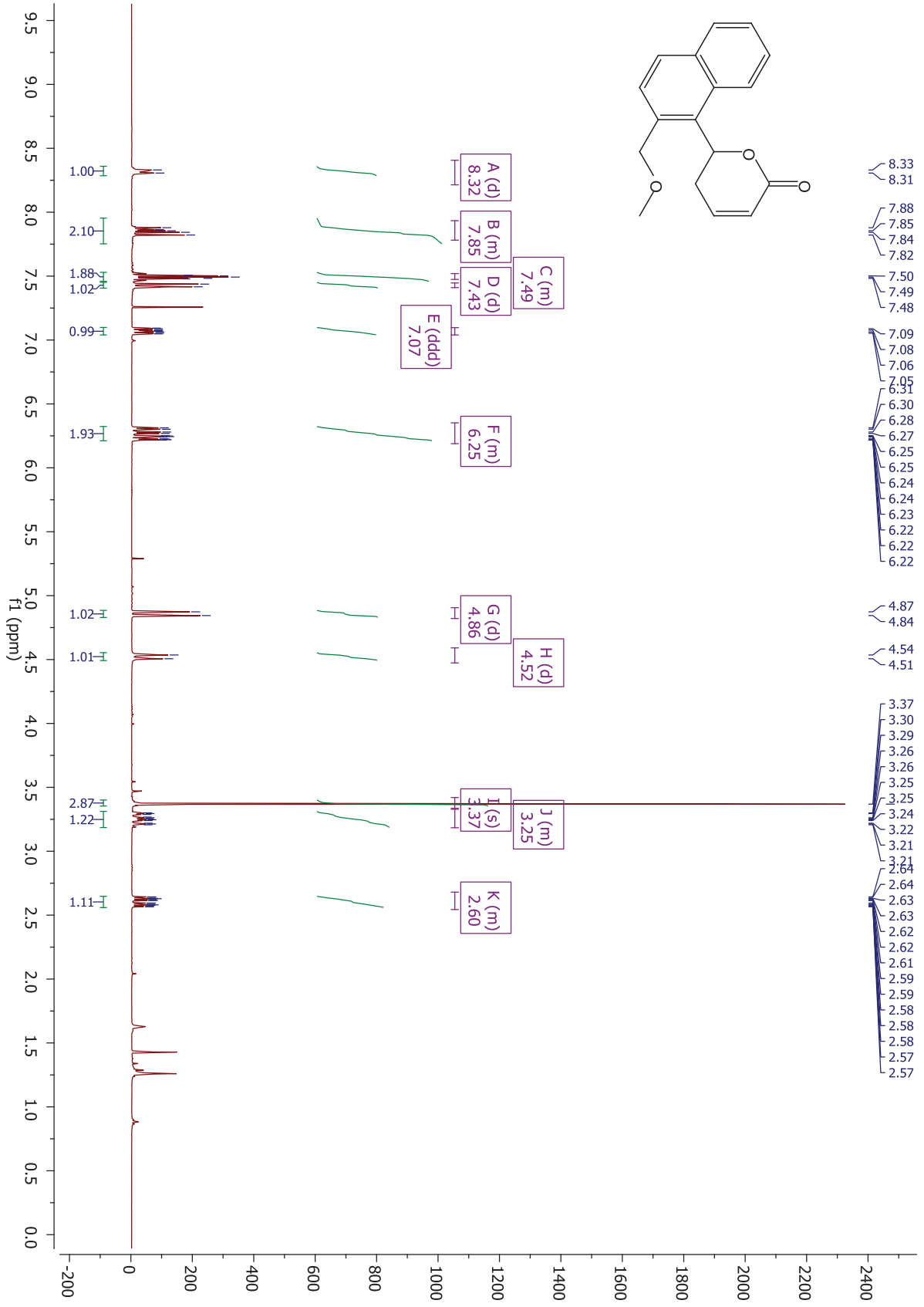

192.89
141.69
134.17
133.19
131.47
128.58
128.51
128.49
126.42
125.99
124.24
72.19
58.52
O
O
H
f1 (ppm)

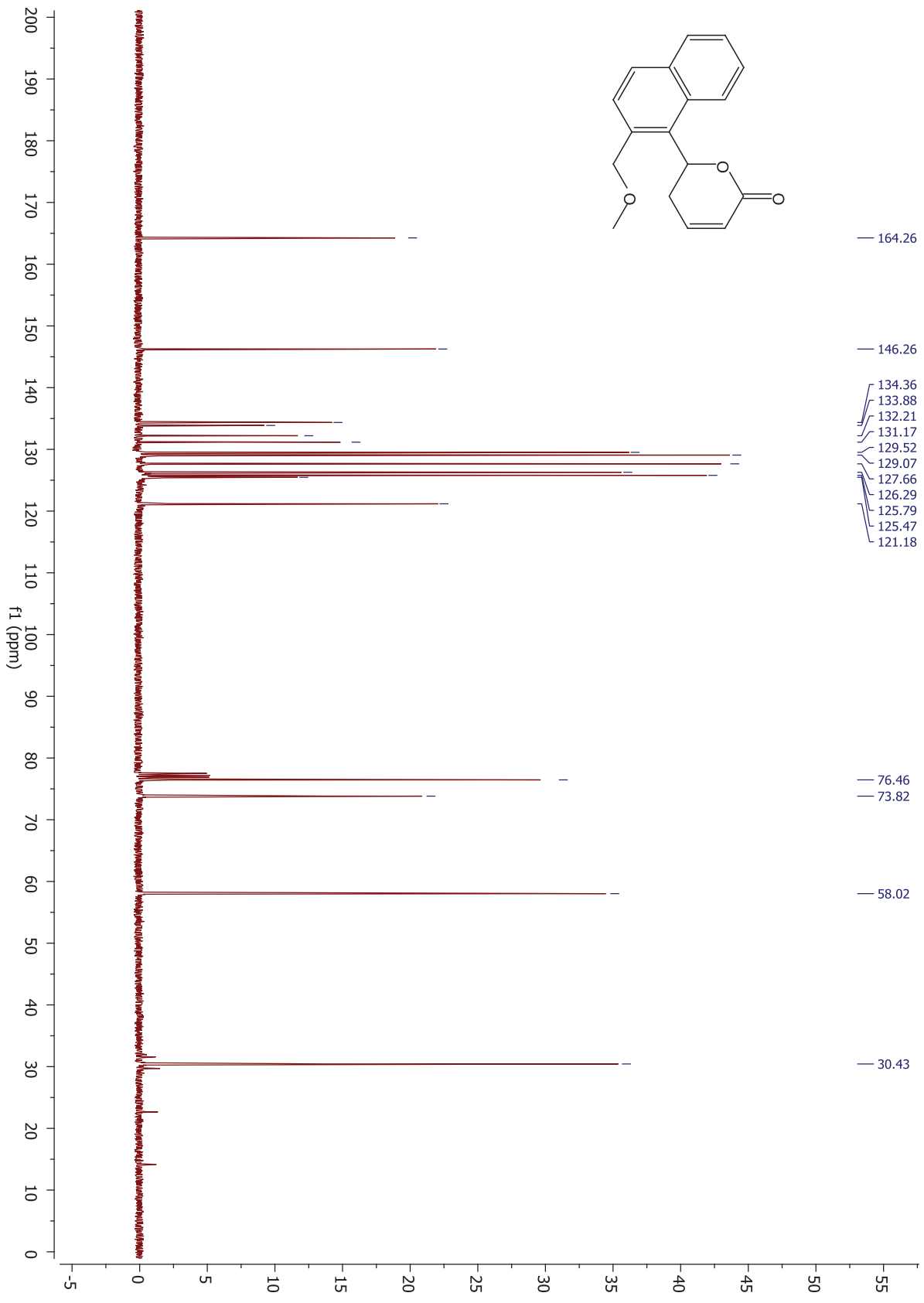

A (d) 8.57
B (m) 7.83
C (d) 7.74
D (m) 7.48
E (d) 7.41
F (m) 5.93
G (s) 5.59
H (m) 5.16
I (m) 4.69
J (s) 3.39
K (s) 3.06
L (m) 2.95
M (m) 2.67
1.00
0.84
0.86
1.67
0.86
0.94
0.96
1.80
1.93
2.53
0.77
1.03
0.95
OH
O
f1 (ppm)

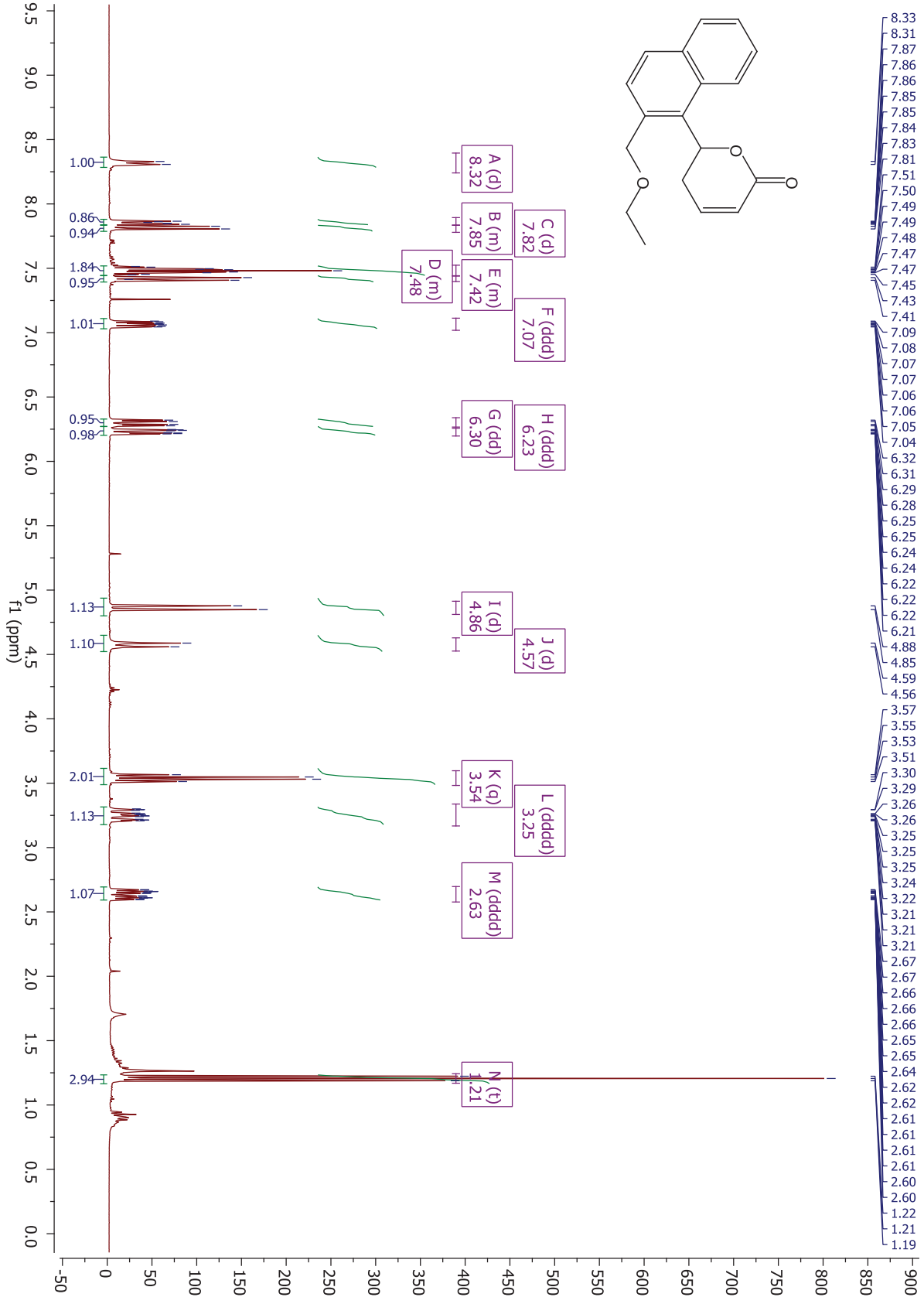

137.88
135.39
134.23
132.59
131.24
128.71
128.11
127.90
125.76
125.58
117.57
73.76
70.89
58.10
42.10
OH
O
f1 (ppm)

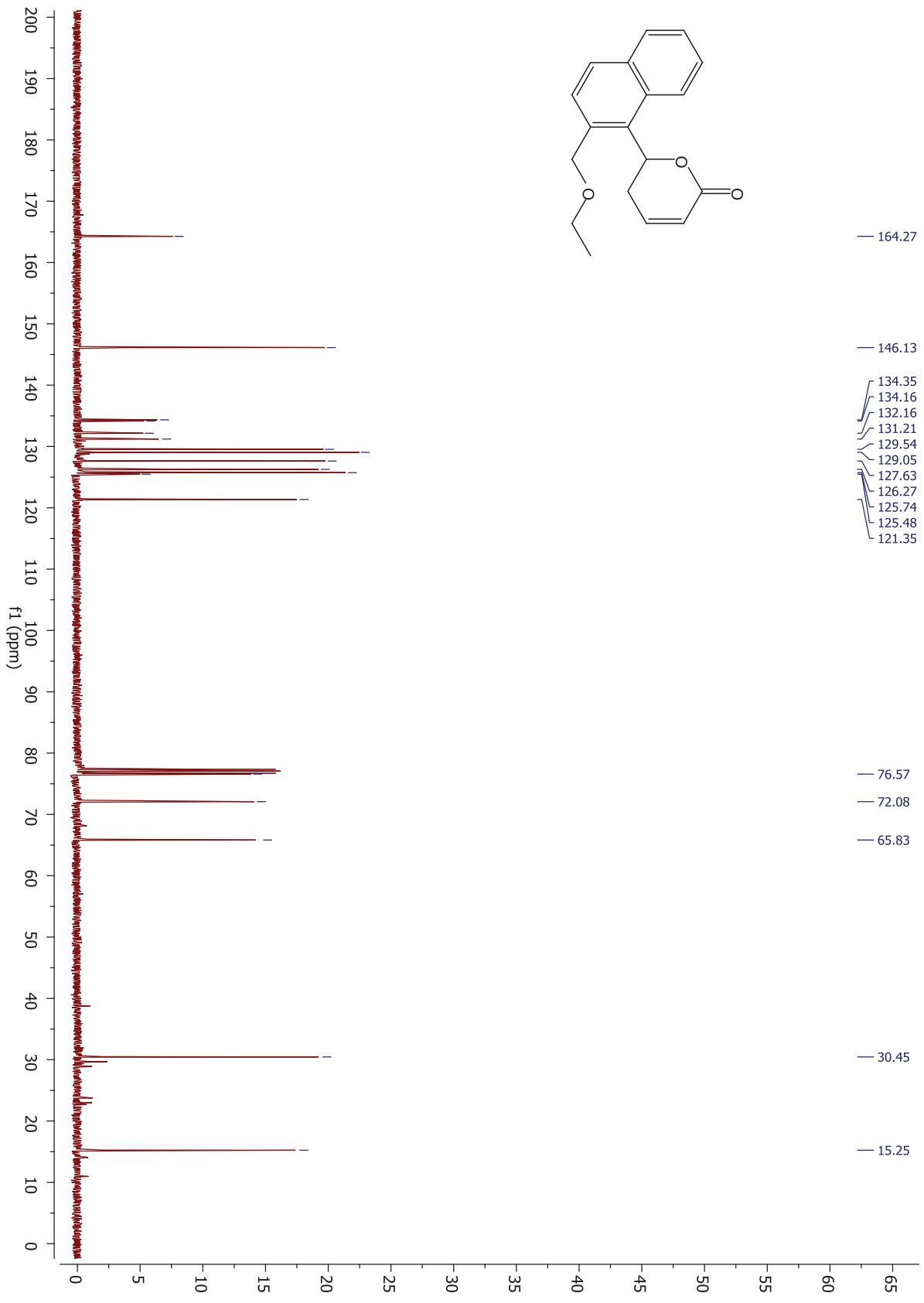

A (d) 8.59
B (m) 7.86
C (d) 7.80
D (m) 7.51
E (s) 6.64
F (m) 6.42
G (m) 6.17
H (ddt) 5.89
I (dd) 5.80
J (dt) 5.17
K (d) 4.66
L (s) 3.48
M (dt) 3.24
N (dddd) 2.79
O (m) 5.11
f1 (ppm)

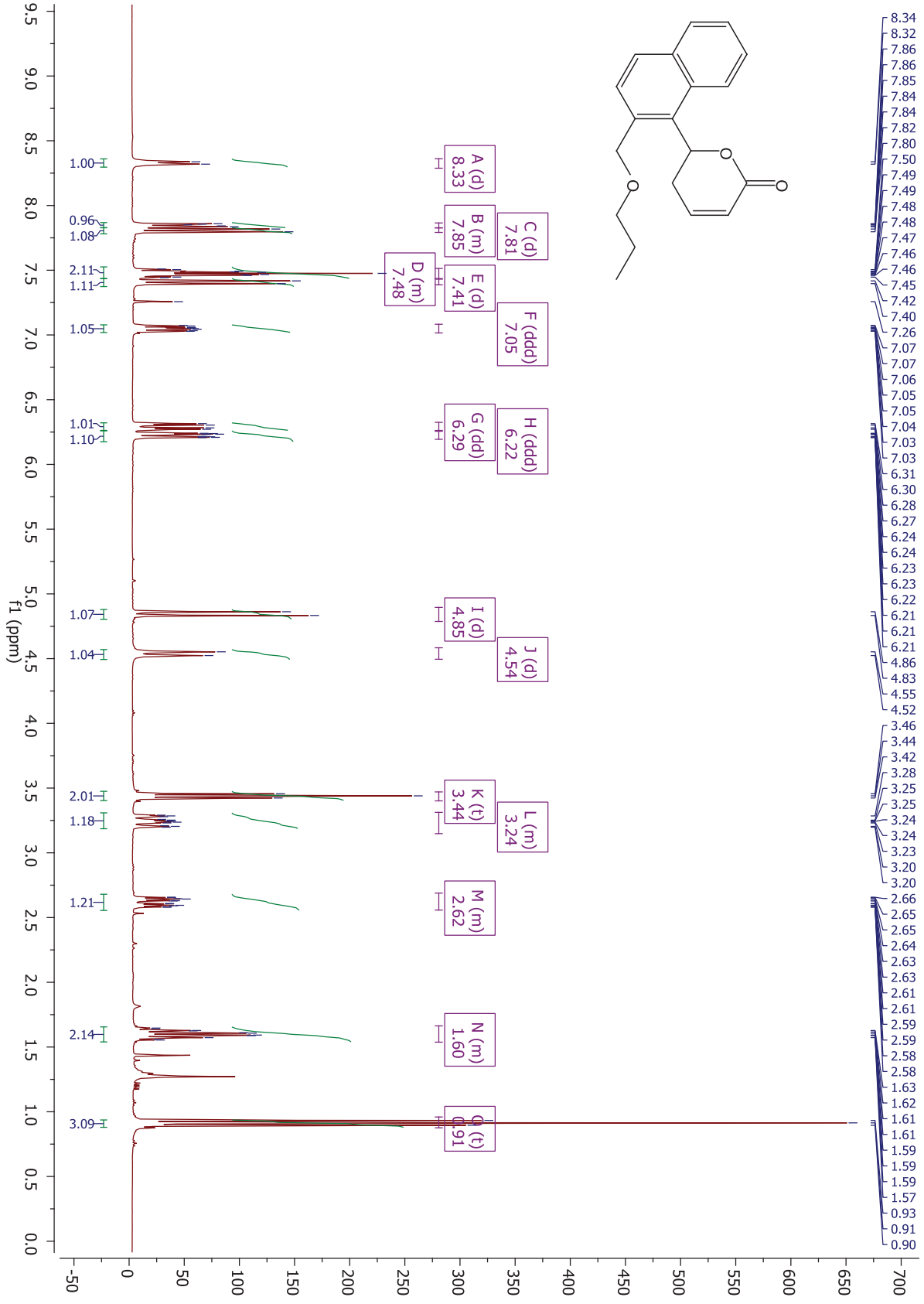

f1 (ppm)
165.59
134.20
131.10
130.82
128.95
128.79
128.48
127.15
125.88
125.44
117.64
73.47
72.80
58.17
39.74

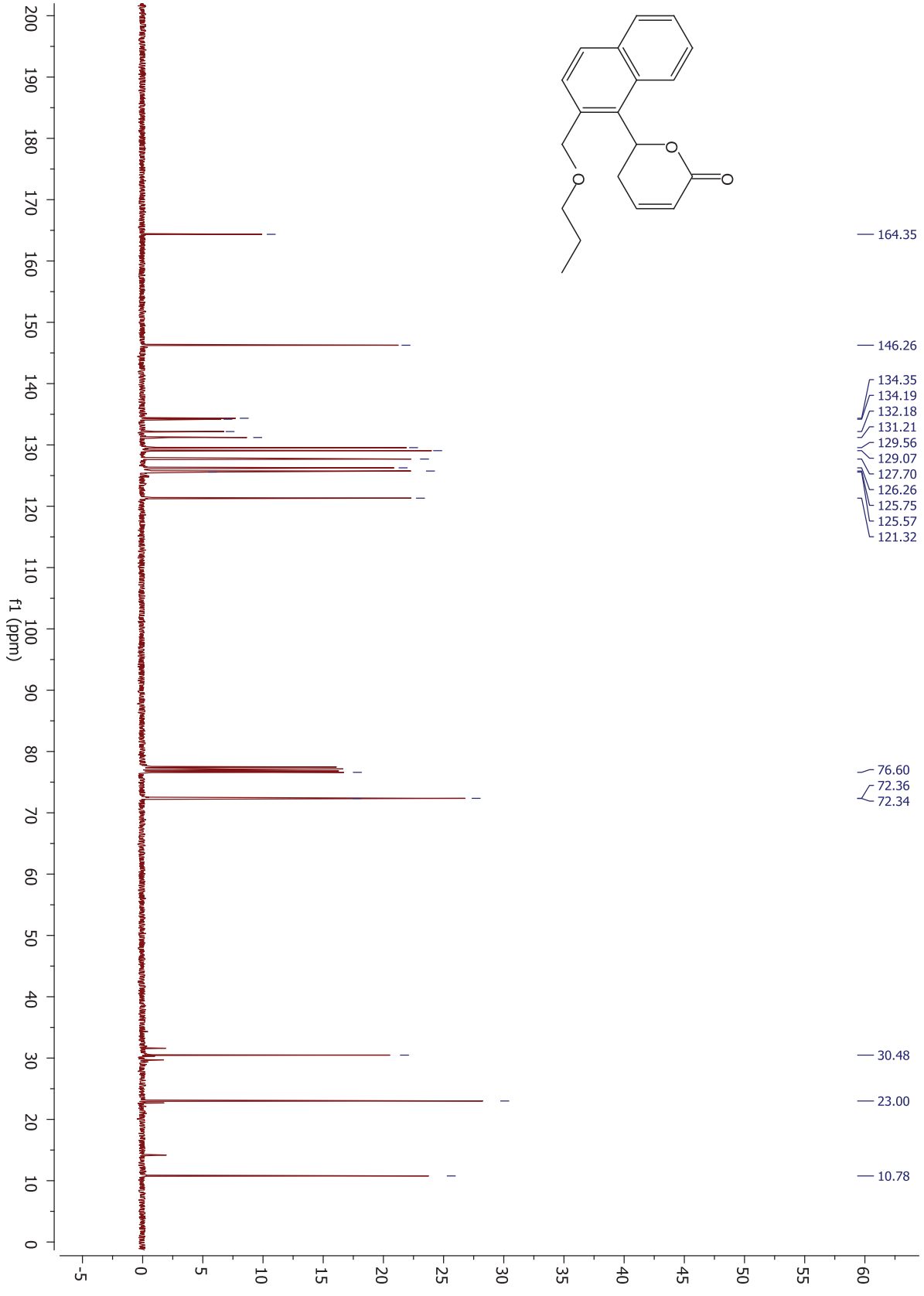

A (d) 8.32
B (m) 7.85
C (m) 7.49
D (d) 7.43
E (ddd) 7.07
F (m) 6.25
G (d) 4.86
H (d) 4.52
I (s) 3.37
J (m) 3.25
K (m) 2.60
1.00
2.10
1.88
1.02
0.99
1.93
1.02
1.01
2.87
1.22
1.11
f1 (ppm)

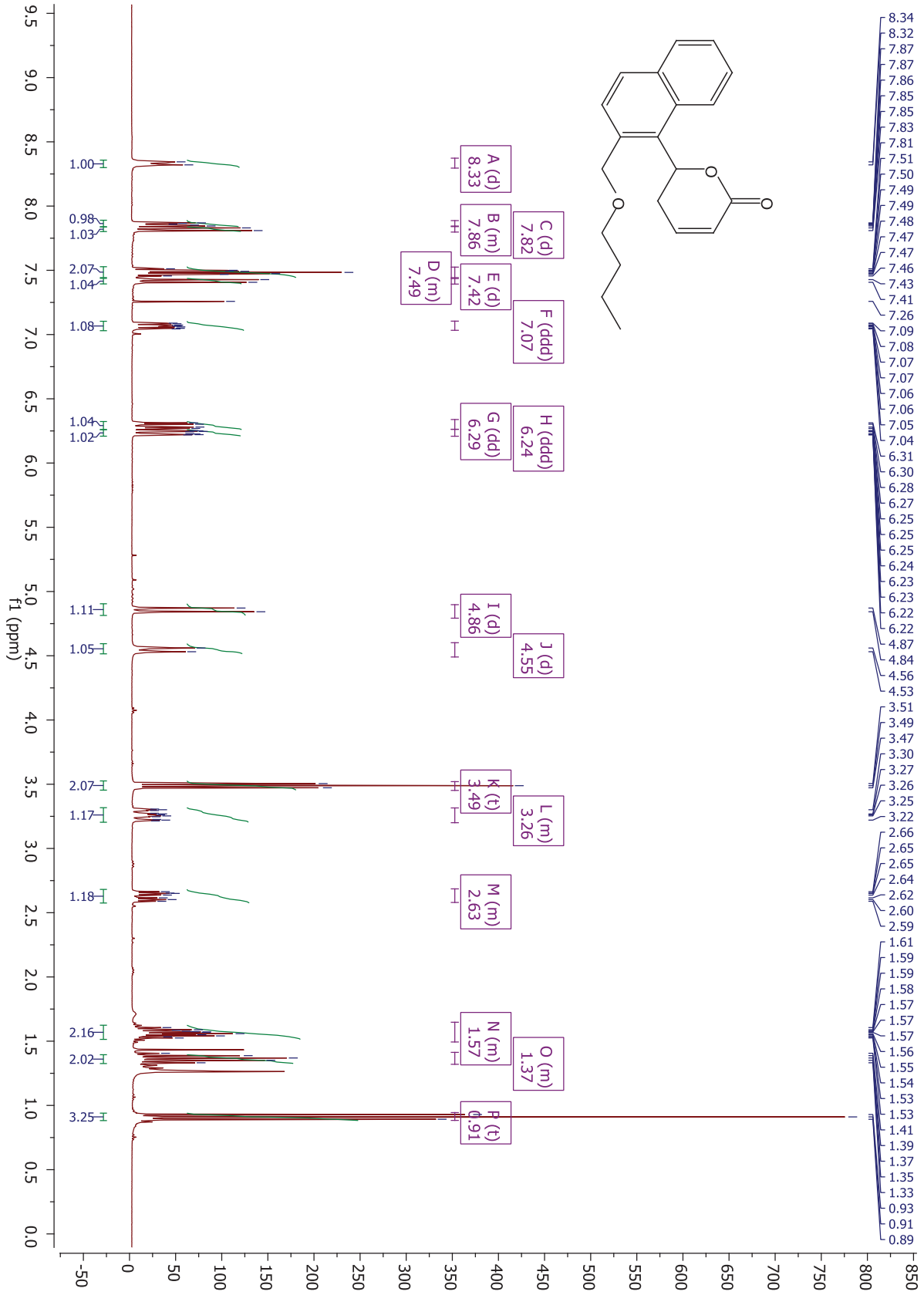

164.26
146.26
134.36
133.88
132.21
131.17
129.52
129.07
127.66
126.29
125.79
125.47
121.18
76.46
73.82
58.02
30.43
f1 (ppm)

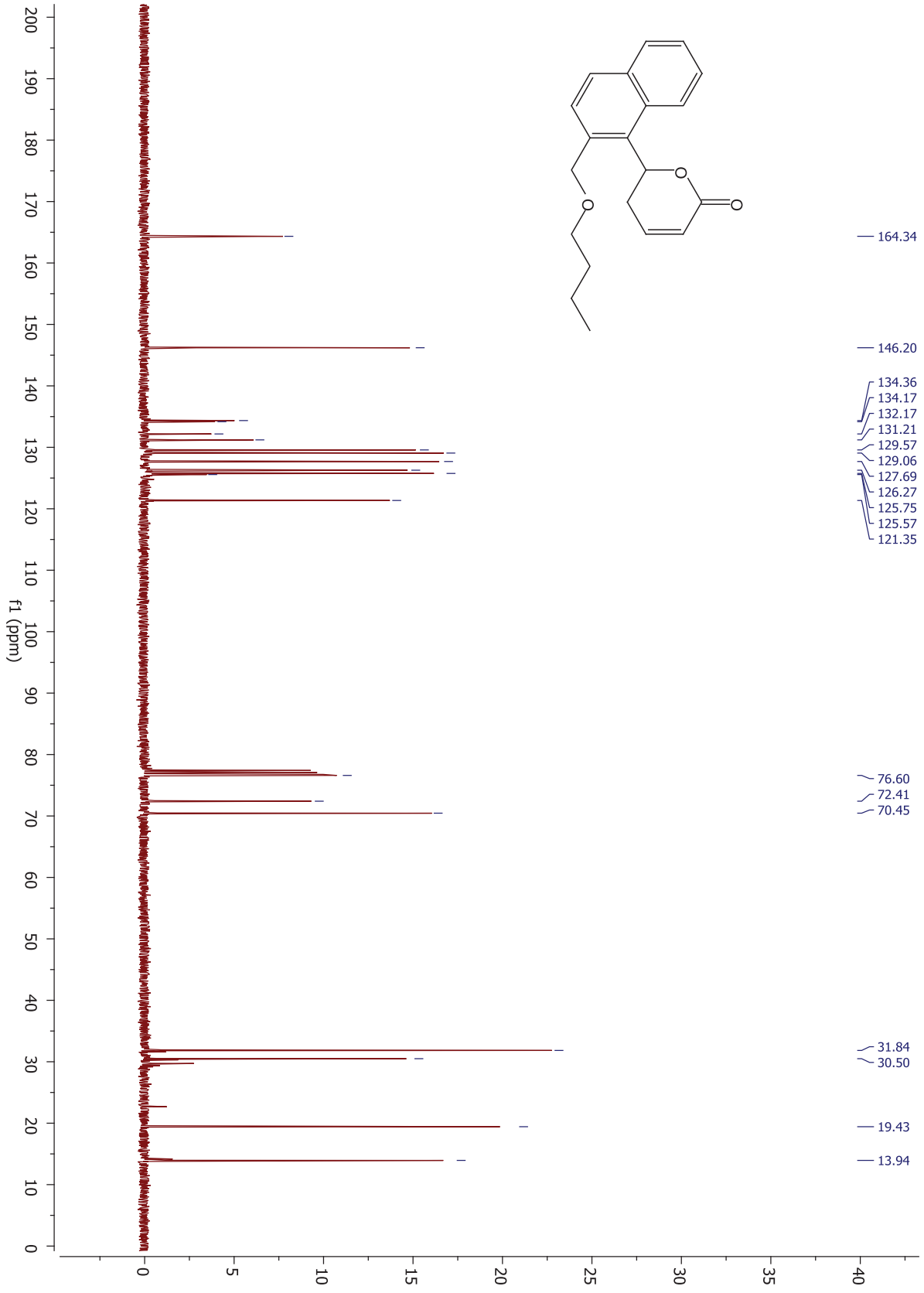

f1 (ppm)
A (d) 8.32
B (m) 7.85
C (d) 7.82
D (m) 7.48
E (m) 7.42
F (ddd) 7.07
G (dd) 6.30
H (ddd) 6.23
I (d) 4.86
J (d) 4.57
K (q) 3.54
L (dddd) 3.25
M (dddd) 2.63
N (t) 1.21
1.00
0.86
0.94
1.84
0.95
1.01
0.95
0.98
1.13
1.10
2.01
1.13
1.07
2.94

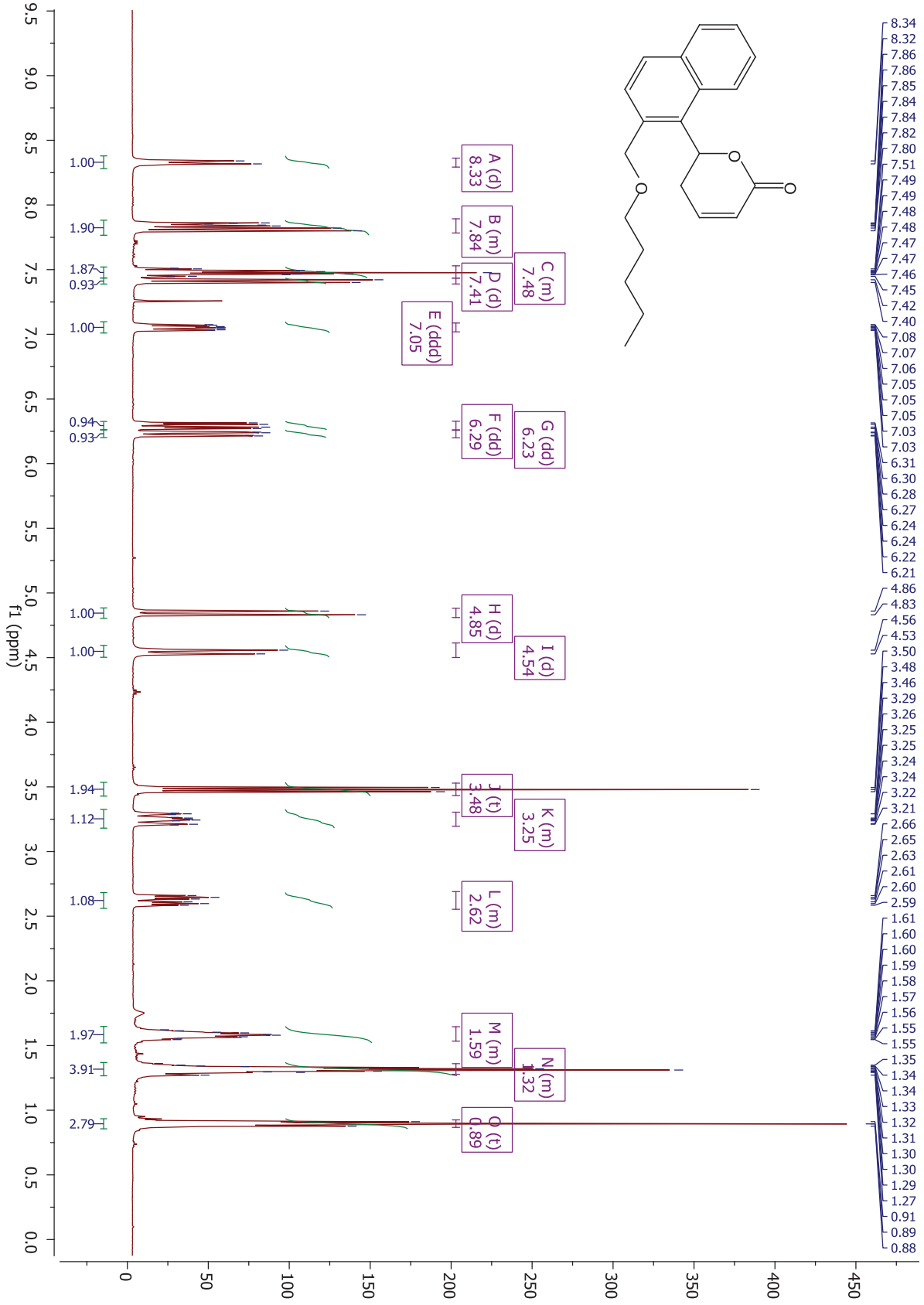

164.27
146.13
134.35
134.16
132.16
131.21
129.54
129.05
127.63
126.27
125.74
125.48
121.35
76.57
72.08
65.83
30.45
15.25
f1 (ppm)

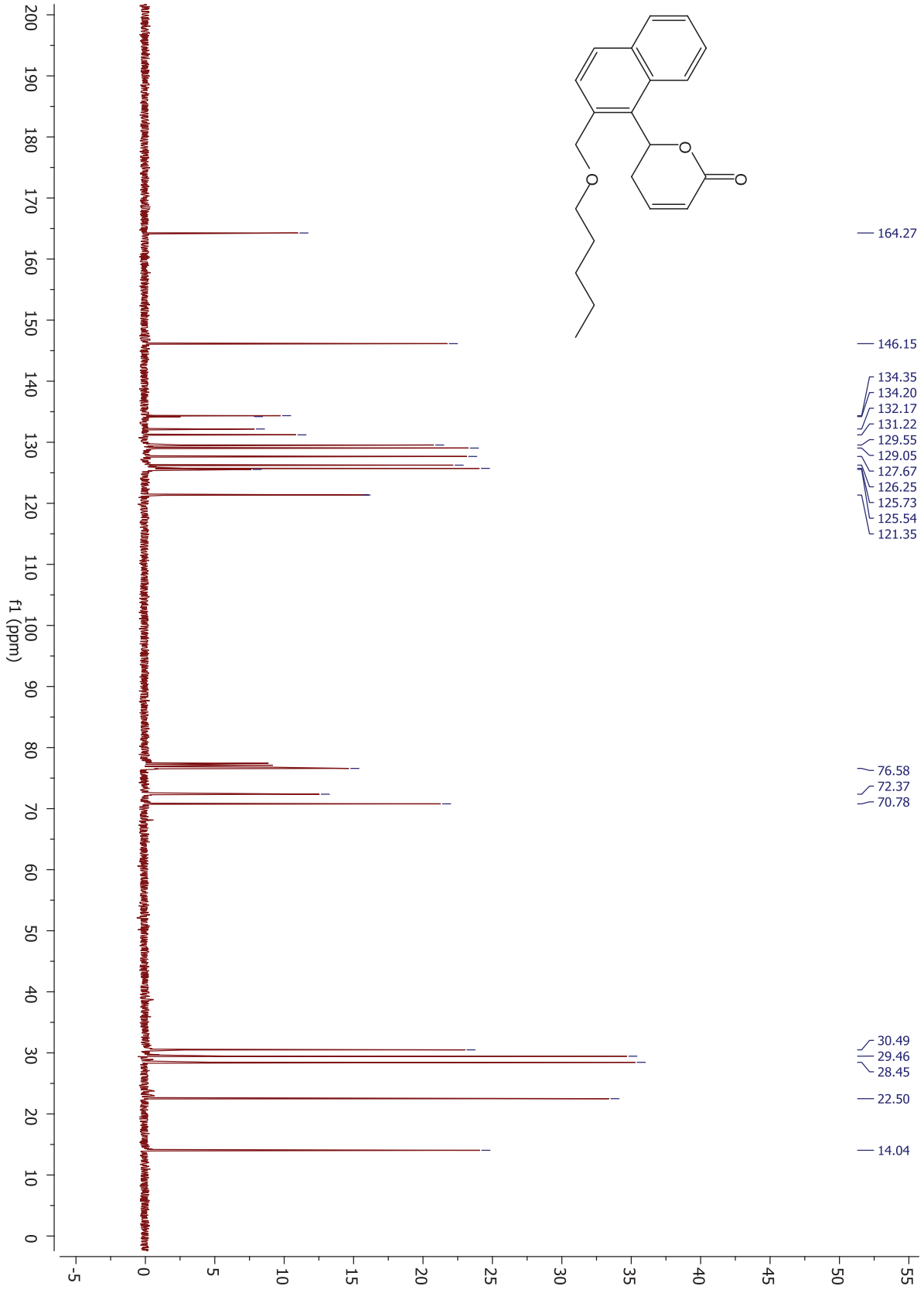

A (d) 8.33
B (m) 7.85
C (d) 7.81
D (m) 7.48
E (d) 7.41
F (ddd) 7.05
G (dd) 6.29
H (ddd) 6.22
I (d) 4.85
J (d) 4.54
K (t) 3.44
L (m) 3.24
M (m) 2.62
N (m) 1.60
O (t) 0.91
1.00
0.96
1.08
2.11
1.11
1.05
1.01
1.10
1.07
1.04
2.01
1.18
1.21
2.14
3.09
f1 (ppm)

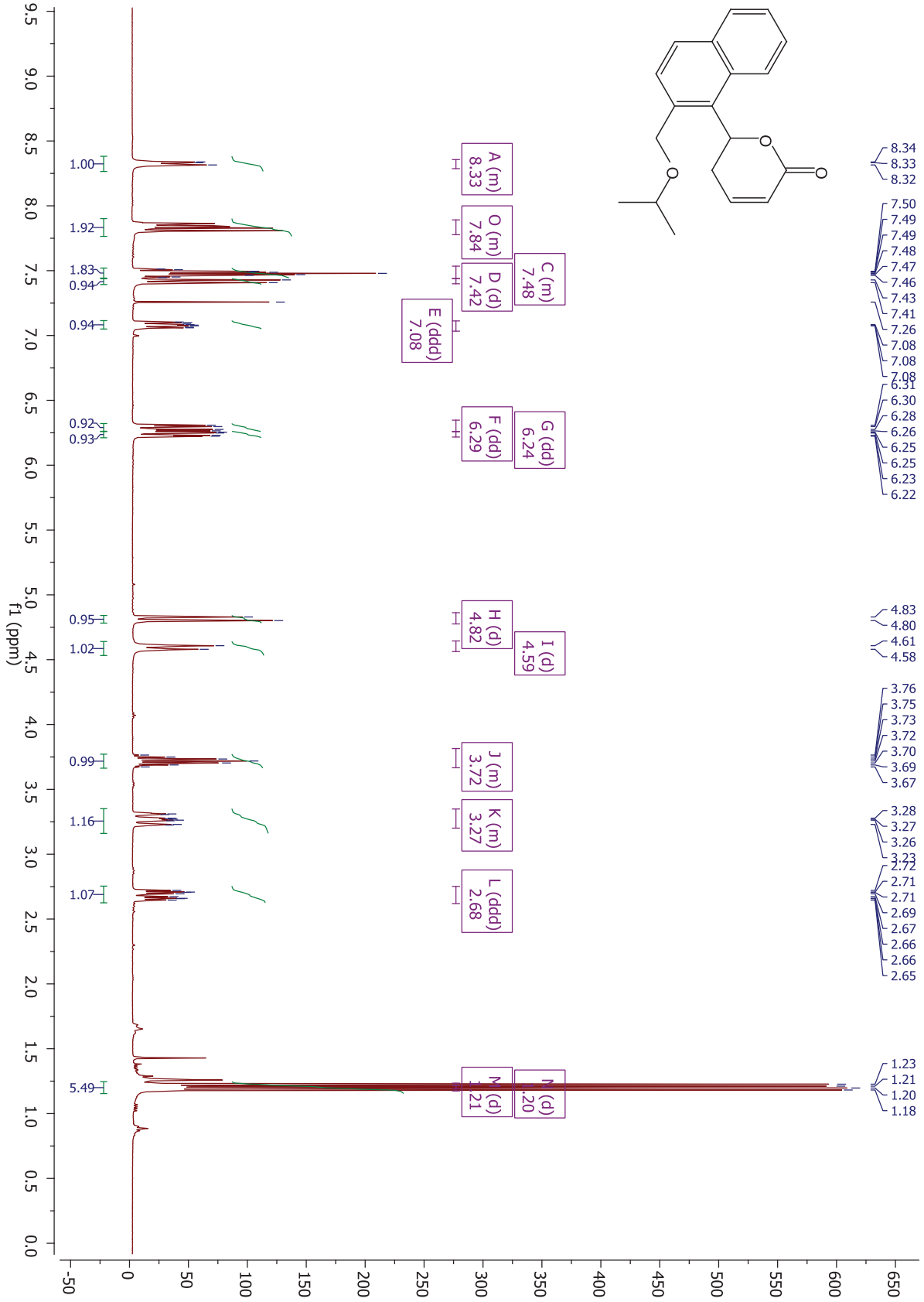

164.35
146.26
134.35
134.19
132.18
131.21
129.56
129.07
127.70
126.26
125.75
125.57
121.32
76.60
72.36
72.34
30.48
23.00
10.78
f1 (ppm)

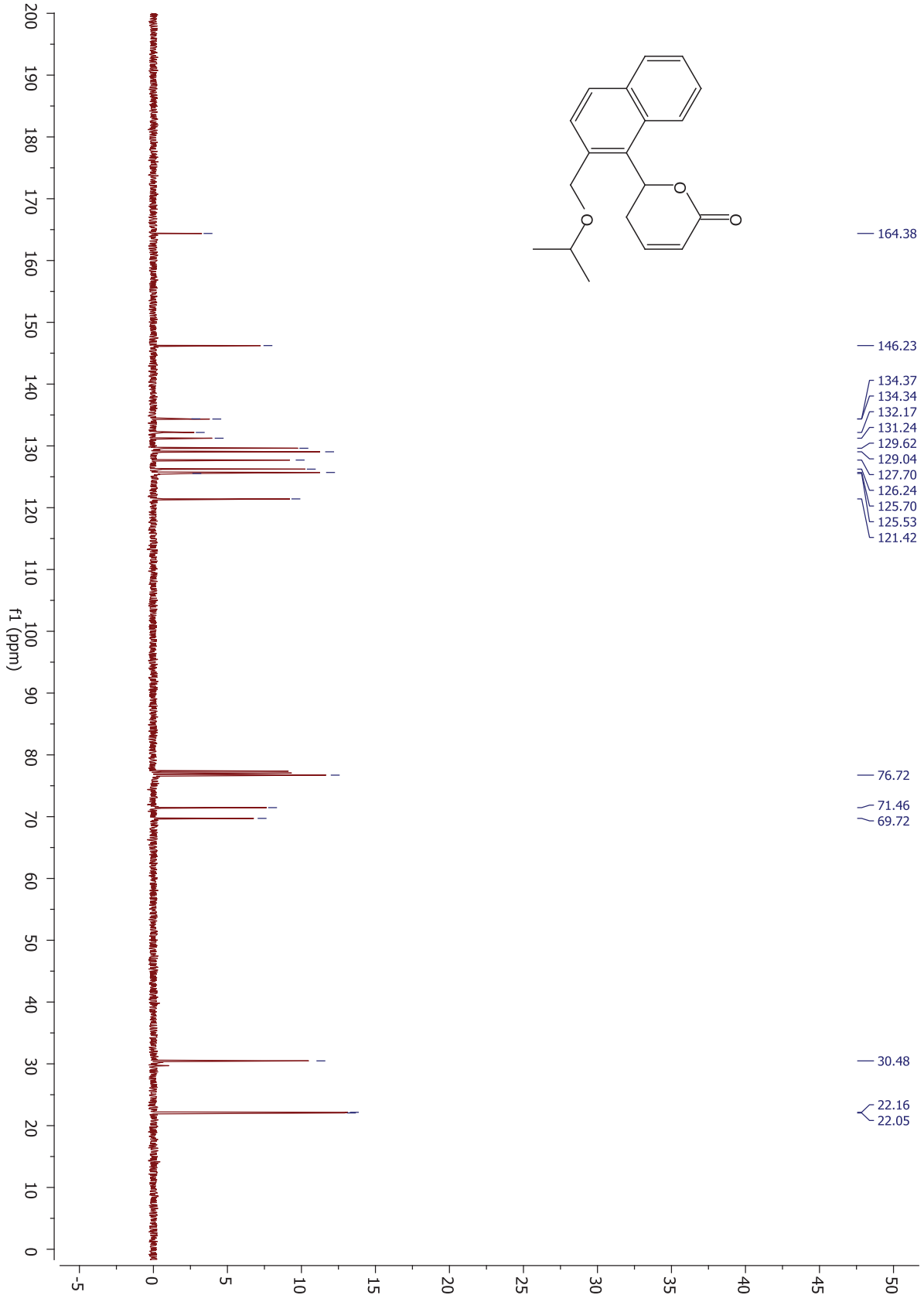

A (d) 8.33
B (m) 7.86
C (d) 7.82
D (m) 7.49
E (d) 7.42
F (ddd) 7.07
G (dd) 6.29
H (ddd) 6.24
I (d) 4.86
J (d) 4.55
K (t) 3.49
L (m) 3.26
M (m) 2.63
N (m) 1.57
O (m) 1.37
P (t) 0.91
f1 (ppm)

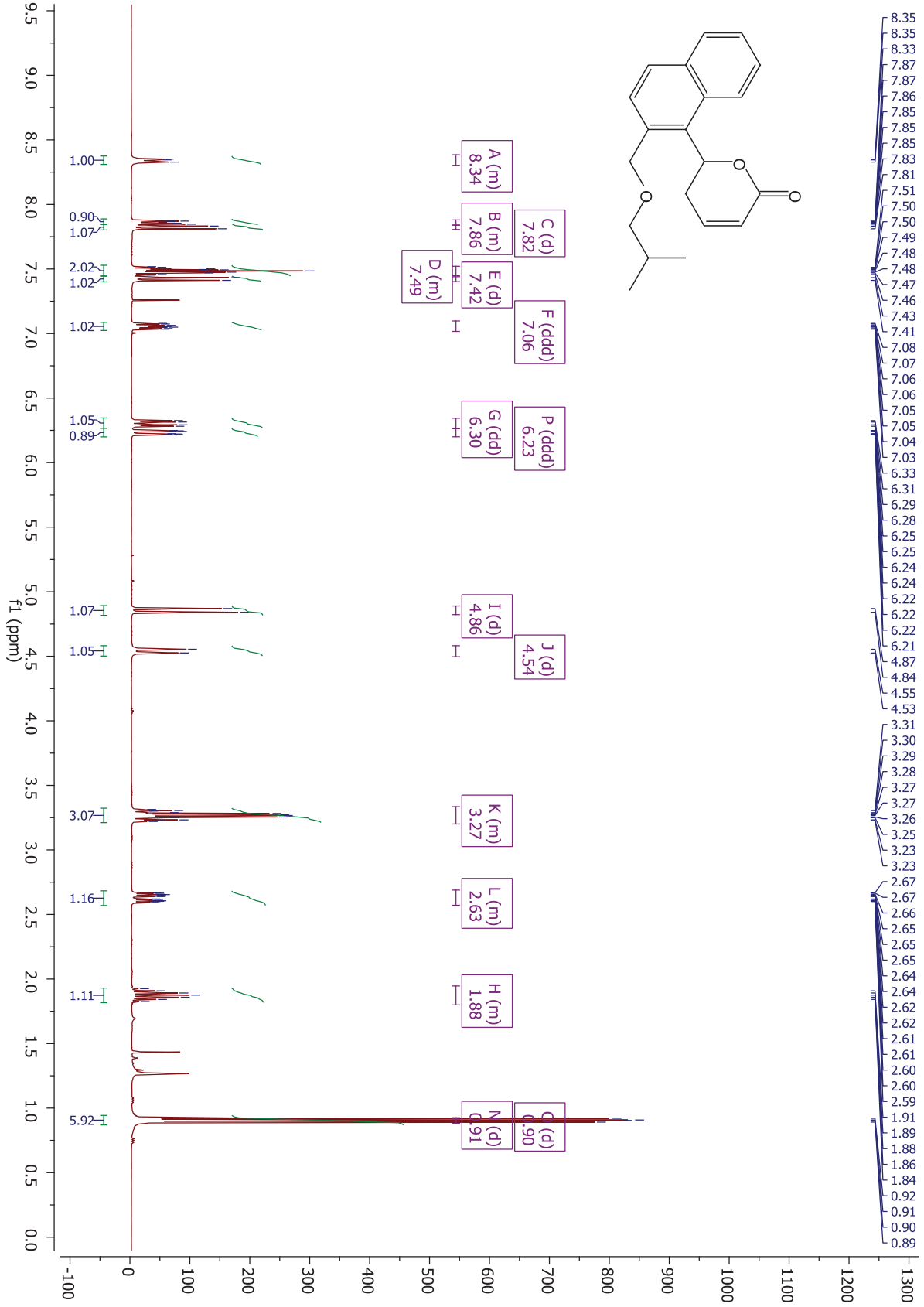

164.34
146.20
134.36
134.17
132.17
131.21
129.57
129.06
127.69
126.27
125.75
125.57
121.35
76.60
72.41
70.45
31.84
30.50
19.43
13.94
f1 (ppm)

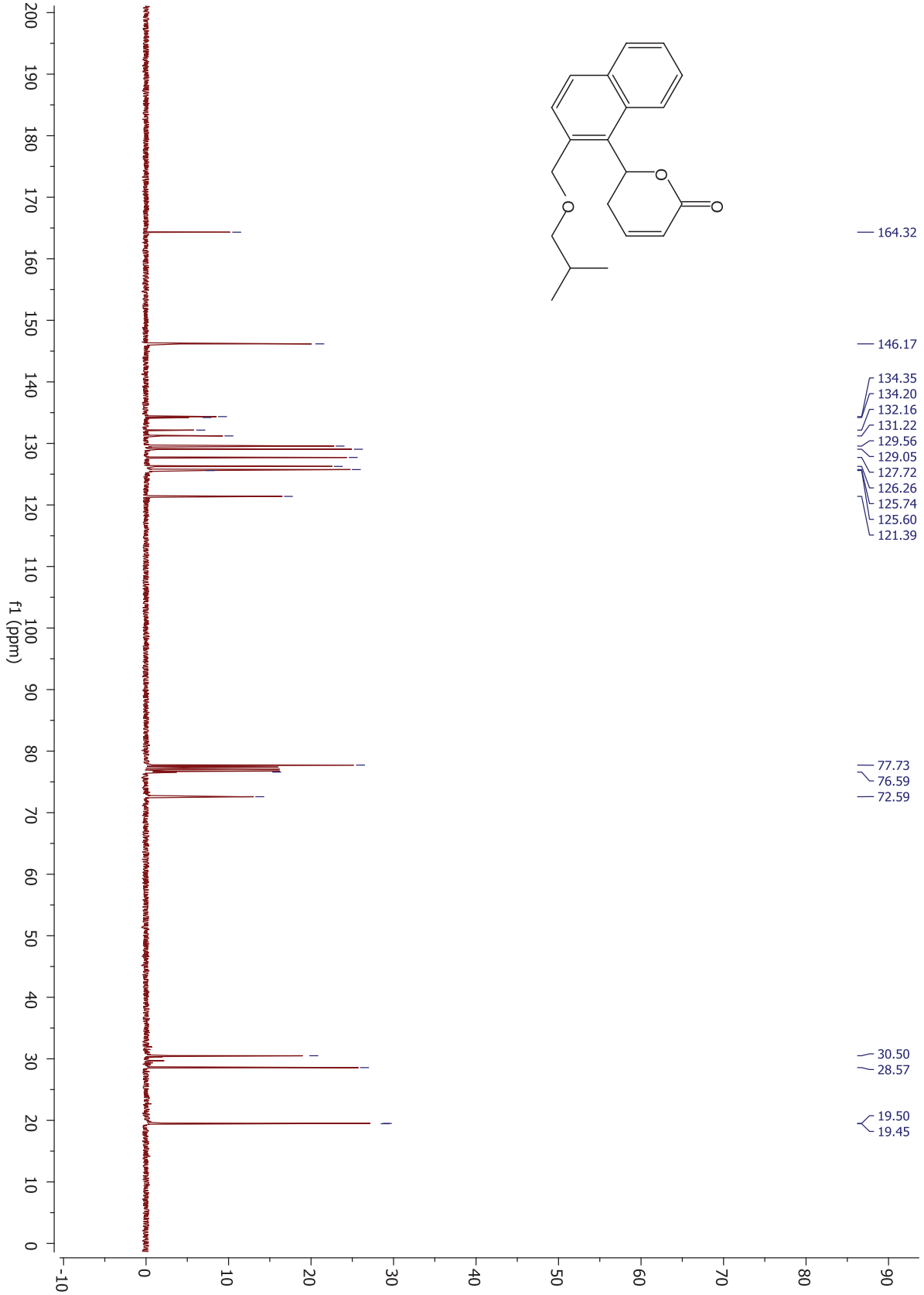

A (d) 8.33
B (m) 7.84
C (m) 7.48
D (d) 7.41
E (ddd) 7.05
F (dd) 6.29
G (dd) 6.23
H (d) 4.85
I (d) 4.54
J (t) 3.48
K (m) 3.25
L (m) 2.62
M (m) 1.59
N (m) 1.32
O (t) 0.89
1.00
1.90
1.87
0.93
1.00
0.94
0.93
1.00
1.00
1.94
1.12
1.08
1.97
3.91
2.79
f1 (ppm)


164.27
146.15
134.35
134.20
132.17
131.22
129.55
129.05
127.67
126.25
125.73
125.54
121.35
76.58
72.37
70.78
30.49
29.46
28.45
22.50
14.04
f1 (ppm)


A (m) 8.33
O (m) 7.84
D (d) 7.42
C (m) 7.48
E (ddd) 7.08
F (dd) 6.29
G (dd) 6.24
H (d) 4.82
I (d) 4.59
J (m) 3.72
K (m) 3.27
L (ddd) 2.68
M (d) 1.21
N (d) 1.20
1.00
1.92
1.83
0.94
0.94
0.92
0.93
0.95
1.02
0.99
1.16
1.07
5.49
f1 (ppm)


164.38
146.23
134.37
134.34
132.17
131.24
129.62
129.04
127.70
126.24
125.70
125.53
121.42
76.72
71.46
69.72
30.48
22.16
22.05
f1 (ppm)


A (m) 8.34
B (m) 7.86
C (d) 7.82
D (m) 7.49
E (d) 7.42
F (ddd) 7.06
G (dd) 6.30
P (ddd) 6.23
I (d) 4.86
J (d) 4.54
K (m) 3.27
L (m) 2.63
H (m) 1.88
N (d) 0.91
Q (d) 0.90
1.00
0.90
1.07
2.02
1.02
1.02
1.05
0.89
1.07
1.05
3.07
1.16
1.11
5.92
f1 (ppm)


164.32
146.17
134.35
134.20
132.16
131.22
129.56
129.05
127.72
126.26
125.74
125.60
121.39
77.73
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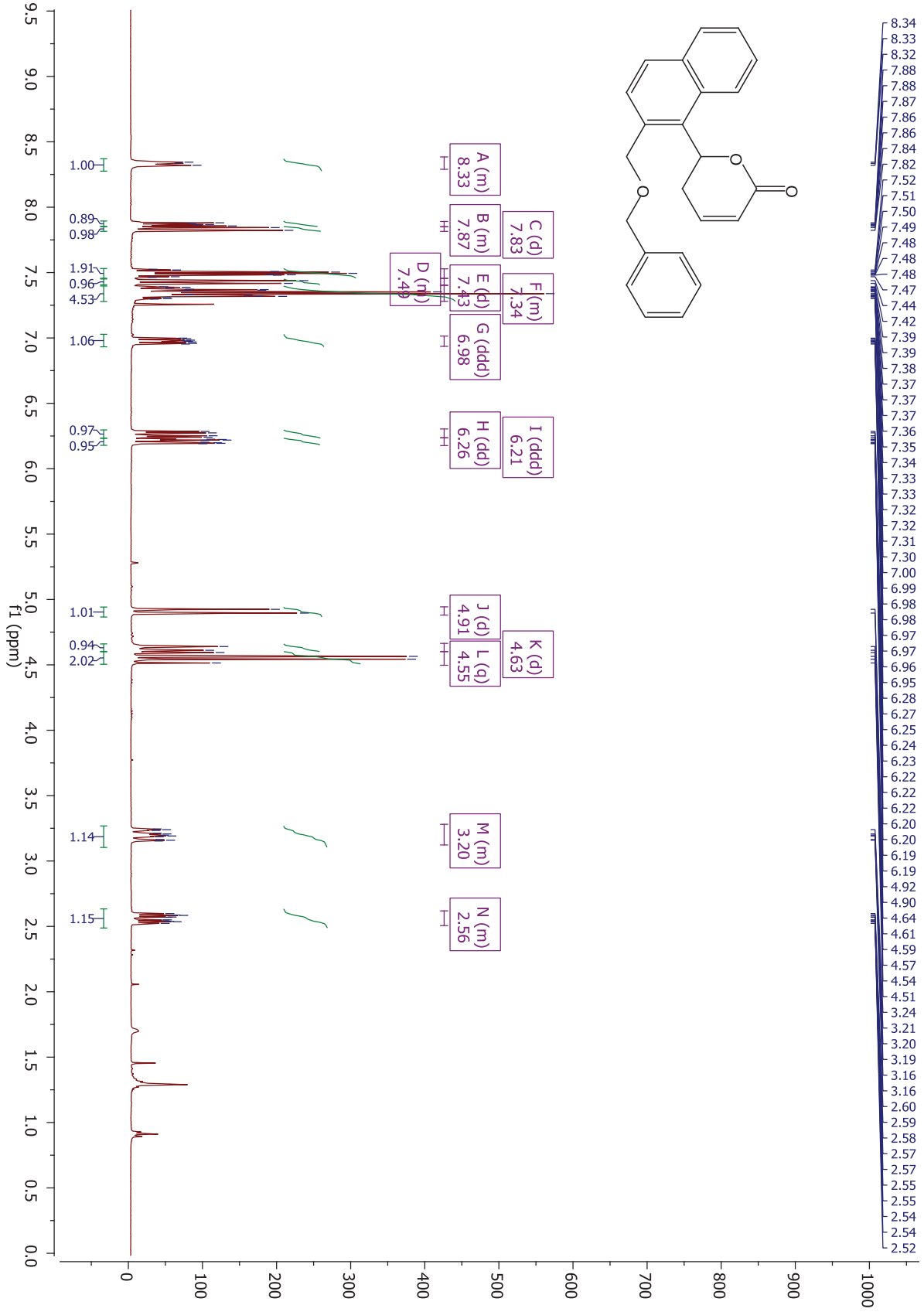
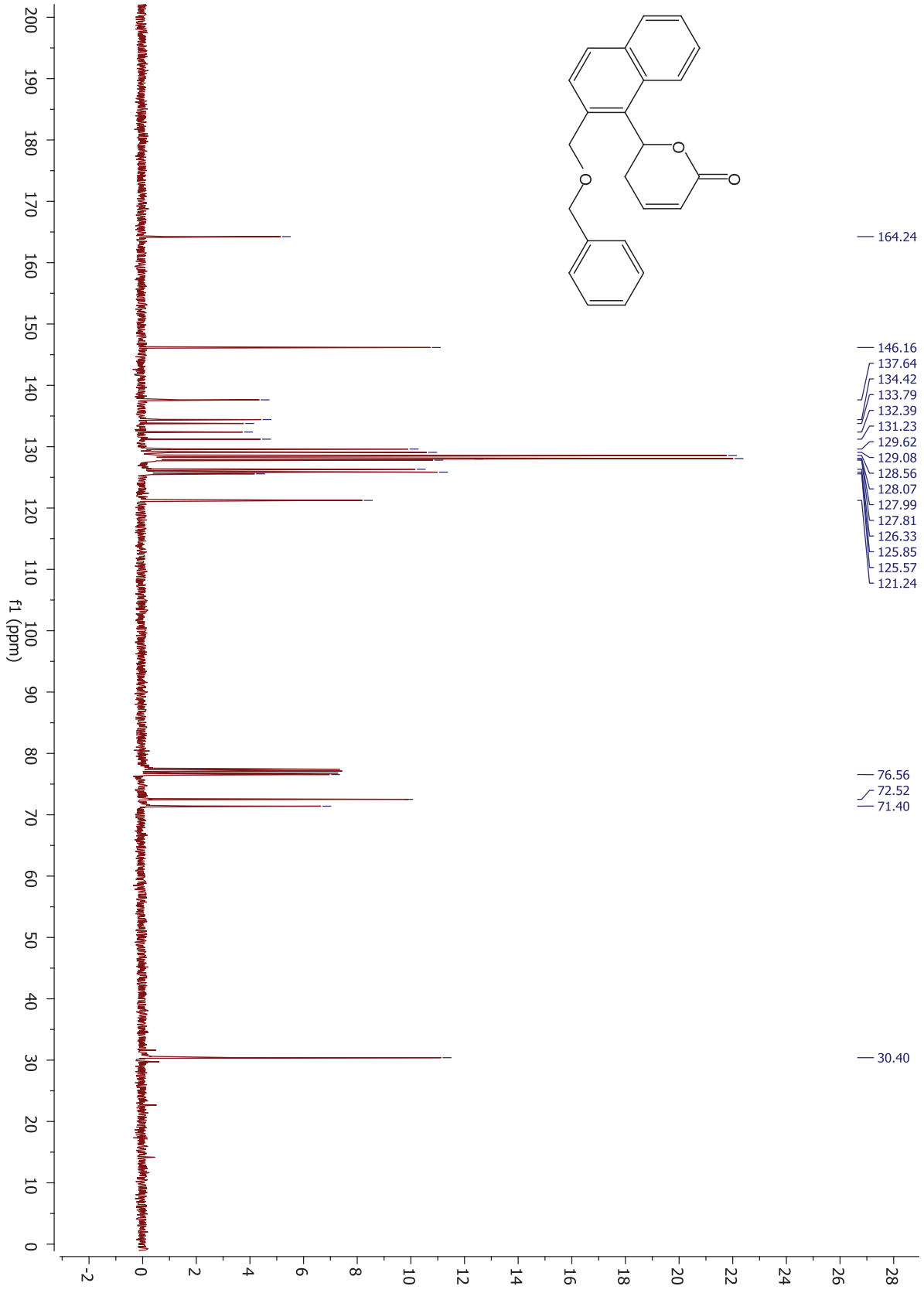
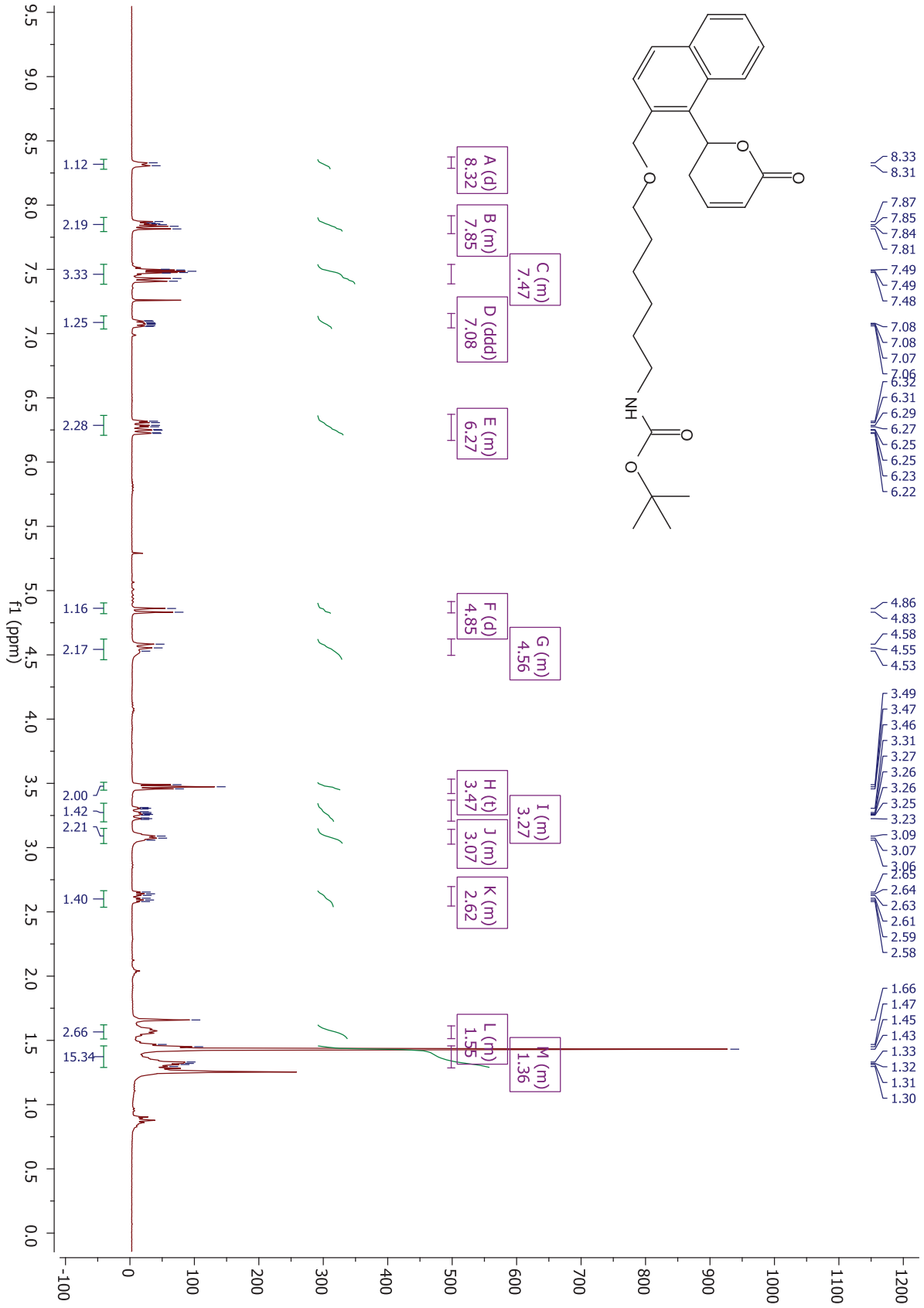
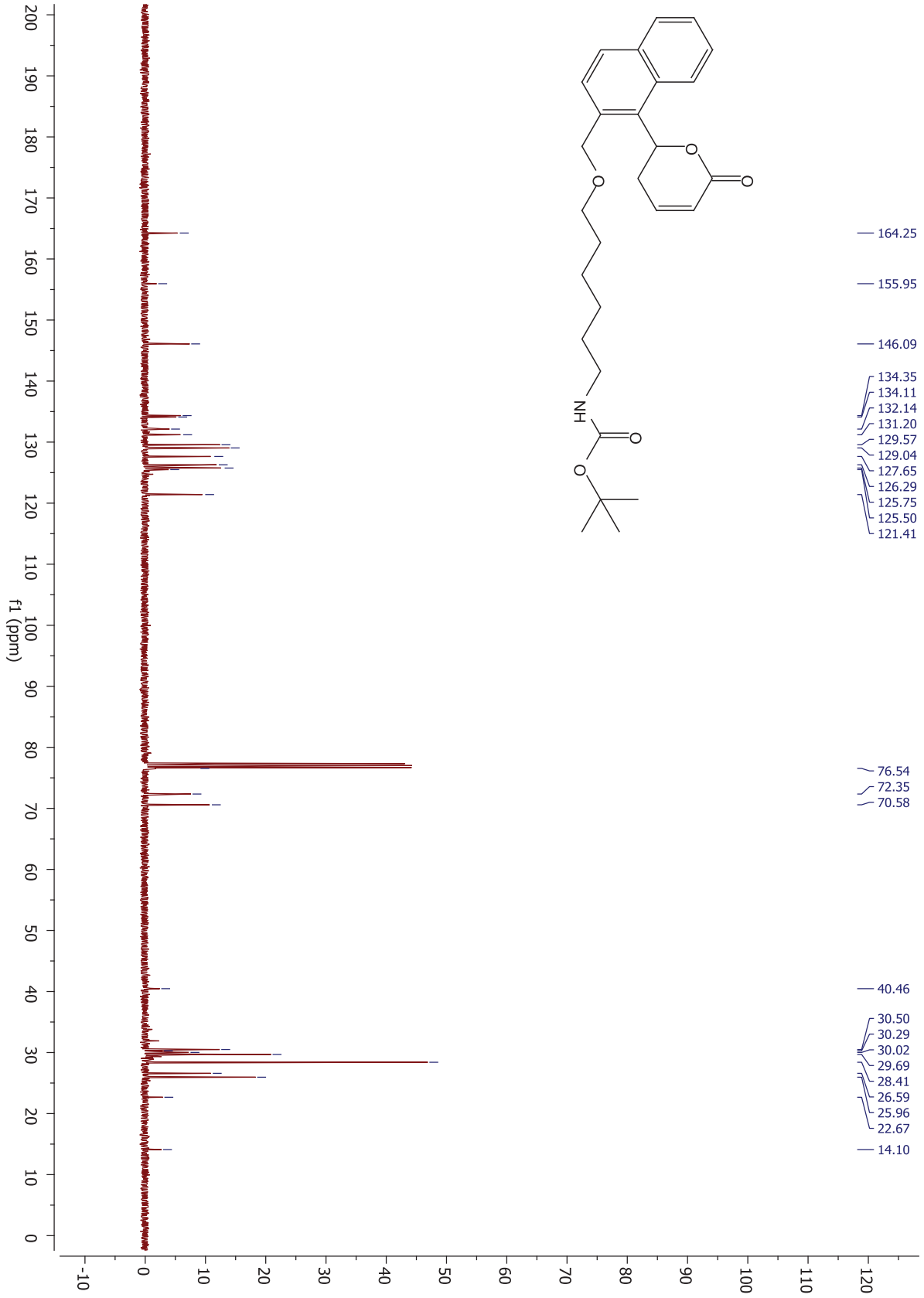
72.59
30.50
28.57
19.50
19.45
f1 (ppm)


A (m) 8.33
B (m) 7.87
C (d) 7.83
D (m) 7.49
E (d) 7.43
F (m) 7.34
G (ddd) 6.98
H (dd) 6.26
I (ddd) 6.21
J (d) 4.91
K (d) 4.63
L (q) 4.55
M (m) 3.20
N (m) 2.56
1.00
0.89
0.98
1.91
0.96
4.53
1.06
0.97
0.95
1.01
0.94
2.02
1.14
1.15
f1 (ppm)


164.24
146.16
137.64
134.42
133.79
132.39
131.23
129.62
129.08
128.56
128.07
127.99
127.81
126.33
125.85
125.57
121.24
76.56
72.52
71.40
30.40
f1 (ppm)


A (d) 8.32
B (m) 7.85
C (m) 7.47
D (ddd) 7.08
E (m) 6.27
F (d) 4.85
G (m) 4.56
H (t) 3.47
I (m) 3.27
J (m) 3.07
K (m) 2.62
L (m) 1.55
M (m) 1.36
1.12
2.19
3.33
1.25
2.28
1.16
2.17
2.00
1.42
2.21
1.40
2.66
15.34
NH
O
f1 (ppm)


164.25
155.95
146.09
134.35
134.11
132.14
131.20
129.57
129.04
127.65
126.29
125.75
125.50
121.41
76.54
72.35
70.58
40.46
30.50
30.29
30.02
29.69
28.41
26.59
25.96
22.67
14.10
NH
O
f1 (ppm)