NOTE TO USERS

uOttawa

L'Université canadienne
Canada's university

FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTOCTORALES

u Ottawa

L'Université canadienne
Canada's university

FACULTY OF GRADUATE AND POSDOCTORAL STUDIES

Martin Charron
AUTEUR DE LA THÈSE / AUTHOR OF THESIS

M.Sc. (Chemistry)
GRADE / DEGREE

Department of Chemistry
FACULTÉ, ÉCOLE, DÉPARTEMENT / FACULTY, SCHOOL, DEPARTMENT

Novel Naphthalene-2,3-diol Antioxidants :
Design, Synthesis and Reactivity

TITRE DE LA THÈSE / TITLE OF THESIS

T. Durst
DIRECTEUR (DIRECTRICE) DE LA THÈSE / THESIS SUPERVISOR

CO-DIRECTEUR (CO-DIRECTRICE) DE LA THÈSE / THESIS CO-SUPERVISOR

EXAMINATEURS (EXAMINATRICES) DE LA THÈSE / THESIS EXAMINERS

R. Ben

J. Wright

Gary W. Slater
LE DOYEN DE LA FACULTÉ DES ÉTUDES SUPÉRIEURES ET POSTDOCTORALES /
DEAN OF THE FACULTY OF GRADUATE AND POSTDOCORAL STUDIES

Novel Naphthalene-2,3-diol Antioxidants : Design, Synthesis and Reactivity

Martin Charron, B.Sc.

Thesis submitted to the School of Graduate Studies and Research
University of Ottawa
In partial fulfillment of the requirements for the
M. Sc. Degree in the

Ottawa-Carleton Chemistry Institute

Thèse soumise à
L'École des études supérieures et de la recherche
Université d'Ottawa
En vue de l'obtention de la maîtrise ès sciences à

L'Institut de chimie d'Ottawa-Carleton

Candidate	Supervisor
Martin Charron	Dr. Tony Durst

Your file Votre référence
ISBN: 0-494-11233-6
Our file Notre référence
ISBN: 0-494-11233-6

Novel Naphthalene-2,3-diol Antioxidants : Design, Synthesis and Reactivity

University of Ottawa

April 2005

- Acknowledgements -

First, I would like to thank my supervisor, Dr. Tony Durst, for allowing me to work in his research group and for giving me the opportunity and resources to work on this interesting project on the synthesis of novel naphthalene-2,3-diol antioxidants. I would also like to point out his great knowledge and expertise not only in organic chemistry, but also in life in general; his great ability for teaching, telling interesting stories and for his great sense to give rise of someone's interest in chemistry.

Furthermore, I would like to thank all the current and former members of the Durst research group (Ranga, Hari, Karol, Lynn, Asim and Philippe) who worked with me in the lab, for their help and interesting conversations, especially Dr. Helmi H. Hussain who was there and helped me in the beginning of my honors and graduate studies. Also, I would like to thank Dr. Wright from Carleton University and some of his current group members (Leonid, Mihaela and Alexandru) for providing me BDE calculations and for their help in DPPH$^{\cdot}$ testing, as well as Dr. Ingold and his group member, Greg, for permitting me to use the stopped-flow spectrophotometer at the NRC.

Last but most importantly, I would like to thank my family; my father Jean-Yves, my mother Johanne, my two sisters Julie and Nadine for their guidance, love and continuous support not only through out my graduate studies, but also through out my entire life. Thank you to my beautiful girlfriend, Sonia, for her everyday love, patience and support; not to forget her family: her father Jean Marie and his wife Michelle, Kim, her mother Suzanne, Mélanie and Tina for their support and advices.

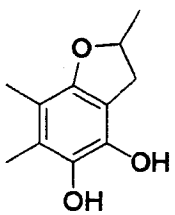
- Abstract -

Antioxidants, which are molecules capable of inhibiting or quenching free radicals, are believed to be very important molecules for preventing and limiting "oxidative stress" in human cells. This oxidative stress is caused by unwanted reactions between free radicals and cell's vital constituents, such as DNA, proteins and lipids. These reactions are responsible for lipid peroxidation, DNA and proteins breakage and mutations that are today known to be associated with degenerative diseases such as Parkinson's and Alzheimer's disease as well as with aging. The design and development of new antioxidant molecules more effective than Vitamin E, a key antioxidant in human blood, may have value in the prevention of some diseases and slow down the aging process.

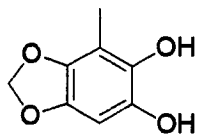
Preliminary work in the Durst lab led to the synthesis of novel catechol antioxidants, such as diols **3** and **6**, based on the Bond Dissociation Energy (BDE) of the phenolic O-H bond. These molecules were shown to be up to 55 times more reactive than Vitamin E as radical scavengers. Unfortunately, they are quite cytotoxic due to the facility with which they are converted to their respective ortho-quinones. Naphthalene-2,3-diols do not possess the same facility to be converted to their ortho-quinones, therefore these compounds can be considered as a novel antioxidant family.

A family of naphthalene-2,3-diols was prepared starting with the commercially available parent compound **16**. The key compound, 1,4-dipropyl-naphthalene-2,3-diol (**23**), was prepared by di-O-allylation of **16** followed by Claisen rearrangement and hydrogenation. Bromination of **16** followed by Heck coupling reaction gave the distyryl derivative **66**. Other analogues of **16** were prepared by using standard methods. The radical scavenging ability of this novel set of compounds was determined by reaction with DPPH radical in EtOAc under

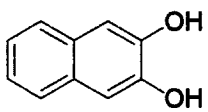
stopped-flow conditions. Compounds **23** and **66**, for example, were 2 and 84 times more effective than Vitamin E at quenching DPPH$^{\cdot}$. These compounds were also shown to be considerably less toxic to Adrenal Pheochromocytoma cells than the catechols such as **3** and **6**.



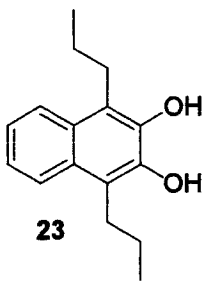
3



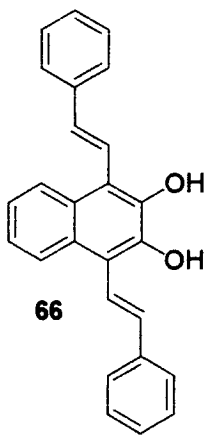
6



16



23



66

- Table of contents -

Chapter 3: Experimental

- List of Schemes -

- List of Figures –

- List of Tables -

- Symbols and Abbreviations -

acetone-d_6: deuterated acetone

aq.: aqueous

ATP: Adenosine Triphosphate

b: broad

B. Sc.: Bachelor of Science

BDE: Bond Dissociation Energy

BHT: butylated hydroxytoluene

brine: sat. aq. NaCl solution

°C: degree Celsius

calcd: calculated

^{13}C NMR: carbon Nuclear Magnetic Resonance

d: density

DCC: dicyclohexylcarbodiimide

DEPT: Distortionless Enhancement by Polarization Transfer

DIPEA: N,N-diisopropylethylamine

DMAP: N,N-dimethylaminopyridine

DMSO-d_6: deuterated dimethyl sulphoxide

DNA: Deoxyribonucleic Acid

DOPPH$^{\cdot}$: 2,2-di(4-t-octylphenyl)-1-picrylhydrazyl radical

DPPH$^{\cdot}$: 2,2-diphenyl-1-picryl-hydrazyl radical

Dr.: doctor

dt: doublet of tripet

EC_{50}: effective concentration which reduces the number of live cells to 50% of control

EI: Electron Impact

eq: equivalent

ES: Electron Spray

EtOAc: ethyl acetate

g: gram

gem: geminal

GSH: reduced form of glutathione

GSSH: oxidized form of glutathione

h: hour

HAT: Hydrogen Atom Transfer

HIV: Human Immunodeficiency Virus

HMQC: Heteronuclear Multiple Quantum Cohereance

^{1}H NMR: proton Nuclear Magnetic Resonance

HRMS: High Resolution Mass Spectrometry

Hz: hertz

in vacuo: rotatory-evaporation under vacuum followed by pump high-vacuum

IP: Ionization Potential

m: multiplet

MHz: megahertz

Mol. Wt.: Molecular Weight

MOM-Cl: chloro methyl methylether

mmol: milimoles

m. p.: melting point

MTPP-Br: methyl triphenylphosphonium bromide

MTT: (3-(3,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazoliumbromide

m/z: mass/charge

M+: molecular ion

NAD: Nicotinamide Adenine Dinucleotide

FAD: Flavin Adenine Dinucleotide

NADPH: reduced form of nicotonamide adenine dinucleotide phosphate

NRC: National Research Council

Pet.: petroleum

ppm: parts per million

Prof.: professor

qu: quintuplet

RBF: Round Bottom Flask

R_f: rate of flow

r.t.: room temperature

s: singlet

Sat.: saturated

S.M.: Starting Material

SET: Single Electron Transfer

t: tertiary

TBAF: tetrabutyl ammonium fluoride

TBDMS-Cl: *tert*-butyl-dimethylsilyl chloride

THF: tetrahydrofuran

TLC: Thin Layer Chromatography

δ: chemical shift

- Claims for original research -

- Naphthalene-2,3-diol (**16**) was selected amongst the various possible naphthalenediols as a precursor to a new family of potent antioxidants.
- It was predicted, based on simple resonance considerations, that naphthalene-2,3-diol (**16**) would not readily form 2,3-naphthoquinone. This was verified by calculations (Prof. Wright) and corroborated by observations that no quinone was isolated from air oxidation of either naphthalene-2,3-diol (**16**) or from any of the many derivatives that were synthesized during the course of this study.
- A series of derivatives of naphthalene-2,3-diol with a variety of substituents at C1, C4, C6 and/or C7 were prepared. In virtually all of these cases, the acetylated versions were also prepared and characterized for the purpose of testing their toxicity in cells and their antioxidant property. The synthesis of these compounds involved a variety of chemical reactions such as electrophilic aromatic substitution, Williamson ether synthesis, Claisen rearrangement, Heck coupling and olefin metathesis. The MOM group was usually the preferred O-H protecting group.
- The rate constant for reaction with DPPH radical was measured for ten derivatives in ethyl acetate.
- Two compounds, 1,4-dipropyl-naphthalene-2,3-diol (**23**) and 1,4-distyryl-naphthalene-2,3-diol (**66**) had $DPPH^{\cdot}$ quenching rate constant that were 2 and 83 times faster than α-tocopherol.
- A potential HIV integrase inhibitor, compound **112**, was synthesized.
- Dimeric version of naphthalene-2,3-diol, such as **107**, were prepared for evaluation as antioxidant.
- The reaction product of 1,4-dipropyl-naphthalene-2,3-diol (**23**) in air was isolated and its structure deduced as **113**.

- In vitro cell studies, by Prof. Wright's group, verified the expectation that 1,4- dipropyl-naphthalene-2,3-diol (**23**) does not participate in the redox cycle that is common to catechols which readily form *o*-quinones. This compound also does not up-regulate glutathione production unless its concentration is much higher than 100 μM. This is again consistent with its reluctance to from an *o*-quinone.

- Publications -

1. Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L.; Willmore, W. G.; Durst, T.; Hussain, H. H.; Charron, M. *Free Radical Biol. Med.* **2005**, *38*, 344-355.

- References -

1. Rice-Evans, C. A.; Burdon, R. H. Free Radical Damage and its Control, Elsevier: Amsterdam, **1997**.
2. Karlsson, J. Antioxidants and Exercice, Human Kinetics: Champaign, IL, **1997**.
3. Knight, J. A. Free Radicals, Antioxidants, Aging, and Disease, American Association for Clinical Chemistry (AACC) Press Inc.: Washington, **1999**.
4. Babic, G. Synthesis and kinetic testing of novel antioxidants, Master thesis, University of Ottawa: Ottawa, **2002**.
5. Voet, D.; Voet, J. G. Biochimie, DeBoeck Université : Bruxelles, **1998**.
6. Roberfroid, M. B.; Buc Calderon, P. Free Radicals and Oxidation Phenomena in Biological Systems, Marcel Dekker Inc.: New York, **1995**.
7. Gutteridge, J. M. C.; Halliwell, B. Antioxidants in Nutrition, Health, and Disease, Oxford University Press Inc.: New York, **1994**.
8. Karp, G. Biologie cellulaire et moléculaire, DeBoeck Université : Bruxelles, **1998**.
9. Valgimigli, L.; Banks, J. T.; Lusztyk, J.; Inglold, K. U. *J. Org. Chem.* **1999**, *64*, 3381-3383. Wright, J. S.; Carpenter, D. J.; McKay, D. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1997**, *119*, 4245-4252.
10. Burton, G. W.; Ingold, K. U. *Acc. Chem. Res.* **1986**, *19*, 194-201.
11. Machlin, L. J. Vitamin E: A comprehensive treatise, Marcel Dekkar Inc.: New York, **1980**.
12. Lucarini, M.; Pedrielli, P.; Pedulli, G. F. *J. Org. Chem.* **1996**, *61*, 9259-9263.
13. Wright, J. S.; Johnson, E. R.; DiLabio, G. A. *J. Am. Chem. Soc.* **2001**, *123*, 1173-1183.
14. Niki, E.; Noguchi, N. *Acc. Chem. Res.* **2004**, *37*, 45-51.
15. Niki, E.;Takahashi, M.; Komuro, E. *Chem. Lett.* **1986**, 1573-1576.
16. Barclay, L. R. C.; Vinqvist, M. R.; Antunes, F.; Pinto, R. E. *J. Am. Chem. Soc.* **1997**, *119*, 5764-5765.

17. Takahashi, M.; Tsuchiya, J.; Niki, E. *J. Am. Chem. Soc.* **1989**, *111*, 6350- 6353.
18. Hussain, H. H.; Babic, G.; Durst, T.; Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L. *J. Org. Chem.* **2003**, *68*, 7023-7032.
19. Charron, M. First look at the synthesis of novel dendritic antioxidants, Honors thesis, University of Ottawa: Ottawa, 2003.
20. Dewik, P. M. Medicinal Natural Products, Wiley, England, **2002.**
21. Halliwell, B.; Gutteridge, J. M. C. Free radicals in Biology and Medecine; Oxford University: Oxford, UK, 1999.
22. Valgimigli, L.; Banks, J. T.; Lusztyk, J.; Ingold, K. U. *J. Org. Chem.* **1999**, *64*, 3381-3383.
23. Burton, G.W.; LePage, Y.; Gabe, E. J.; Ingold, K. U. *J. Am. Chem. Soc.* **1980**, *102*, 7791-7792.
24. Burton, G. W.; Hugues, L.; Ingold, K. U. *J. Am. Chem. Soc.* **1983**, *105*, 5950-5951.
25. Brunmark, A.; Cadenas, E. *Free Radical Biol.* Med. **1989**, *80*, 435-477.
26. O'Brien, P. J. *Chem. Biol. Int.* **1991**, *80*, 1-31.
27. Wright, J. S.; Flueraru, M.; Chichirau, A.; Chepelev, L. L.; Willmore, W. G.; Durst, T.; Hussain, H. H.; Charron, M. *Free Radical Biol. Med.* **2005**, *38*, 344-355.
28. Han, S.-K.; Mytilineou, C.; Cohen, G. *J. Neurochem.* **1996**, *66*, 501-510.
29. Shi, M. M.; Kugelman, A.; Iwamoto, T.; Tian, L. Forman, H. J. *J. Biol. Chem.* **1994**, *269*, 26512-26517.
30. Foti, M. C.; Johnson, E. R.; Vinqvist, M. R.; Wright, J. S.; Ross, L.; Barclay, C.; Ingold, K. U. *J. Org. Chem.* **2002**, *67*, 5190-5196.
31. Hussain, H. H, unpublished results.
32. Litwinienko, G.; Ingold, K. U. *J. Org. Chem.* **2003**, *68*, 3433-3438.
33. Wright, J. S. unpublished results.
34. Valgimigli, L.; Banks, J. T.; Ingold, K. U.; Lusztyk, J. *J. Am. Chem. Soc.* **1995**, *117*, 9966-9971.

35. Naito, Y.; Sugiura, M.; Yamaura, Y.; Fukaya, C.; Yokoyama, K.; Nakagawa, Y.; Ikeda, T.; Senda, M.; Fujita, T. *Chem. Pharm. Bull.* **1991**, *39*, 1736-1745.
36. Littke, A. F.; Fu, G. C. *J. Am. Chem. Soc.* **2001**, *123*, 6989-7000.
37. Hundertmark, T.; Littke, A. F.; Buchwald, S. L.; Fu, G. C. *Org. Lett.* **2000**, *2*, 1729-1731.
38. Guiso, M.; Marra, C; Farina, A. *Tet. Lett.* **2002**, *43*, 597-598.
39. Greenwald, R.; Chaykovsky, M; Corey, E. J. *J. Org. Chem.* **1963**, *28*, 1128-1129.
40. Andrus, M. A.; Liu, J.; Meredith, E. L.; Nartey, E. *Tet. Lett.* **2003**, *44*, 4819-4822 and references therein.
41. Toda, F.; Tanaka, K.; Iwata, S. *J. Org. Chem.* **1989**, *13*, 3007-3009.
42. Zhao, H.; Neamati, N.; Mazumder, A.; Sunder, S.; Pommier, Y.; Burke, T. R. *J. Med. Chem.* **1997**, *40*, 1186-1194.
43. Horak, V.; Foster, F. V.; de Levie, R.; Jones, J. W.; Svoronos, P. *Tet. Let.* **1981**, *37*,3577-3578.
44. Bradshaw, D. P.; Jones, D. W.; Nongrum, F. M. *J.C.S. Perkin 1*, **1991**, 19-23.
45. Casiraghi, G.; Casnati, G.; Puglia, G.; Sartori, G.; Terenghi, G. *J.C.S. Perkin 1*, **1980**, 1862-1865.
46. Pryor, W. A.; Gu, J.-T.; Church, D. F. *J. Org. Chem.* **1985**, *50*, 185-189.
47. Sartor, V.; Henderson, P, T.; Schuster, G. B. *J. Am. Chem. Soc.* **1999**, *121*, 11027.

Chapter 1:

- Introduction -

1.1. *Oxygen*, as toxic as essential for life

"It took but a moment to cut off that head, though a hundred years perhaps would be required to produce another like it". This sentence was pronounced by the mathematician Lagrange on Antoine Laurent Lavoisier, who was decapitated in 1794 after he had identified *oxygen* as the element responsible for combustion and essential for respiration. The execution took place because the Revolutionary Tribunal thought that the French Republic had no use for savants like him; shortly before *oxygen* was isolated and characterized independently by Scheele and Priestley around 1772-1774 [1]. But it is far earlier than the French Revolution Period that the level of atmospheric *oxygen* reached the approximately 21-24% level that is required for a variety of life including human beings to thrive on Earth.

When the first living organisms appeared on the Blue Planet 4 to 5 billion years ago, *oxygen* was present only in chemically bound form, for example as oxides. These anaerobic organisms based their metabolism on fermentation of these energy-rich compounds for their energy needs. Some 2 billion years later, photosynthesis by marine bacteria obtained their energy from radiation energy supplied by the sunlight. These primitive forms of bacteria used hydrogen sulfide (H_2S) as the source of hydrogen as reducing equivalents in their oxido-reduction reactions. The biggest step of evolution was with the development of blue-green algae 2 billion years ago, where water (H_2O) replaced the highly toxic hydrogen sulfide as the source of reducing equivalents and where *oxygen* was formed as a by-product. It is only then that the atmospheric *oxygen* level increased from around 1% at that time to the present level of about 21-24%. This phenomenal production of *oxygen* eventually led to the ozone formation and some of the fermentative organisms that were not killed by the increased amount of *oxygen* in

the atmosphere evolved to *oxygen*-using aerobic organisms where cellular respiration, just like for humans, was their source of life [2].

In humans, just like in other aerobic organisms, cellular respiration occurs in the cell mitochondria where *oxygen*, transported through the body by a plasma transport protein called haemoglobin, is the last electron acceptor of the electron transport chain. This process occurs in a controlled and stepwise "breakdown of fuels" reaction manner, illustrated in **Scheme 1** [3]:

(1) $O_2 + e^- \rightarrow O_2^{\bullet -}$ (superoxide radical)

(2) $O_2^{\bullet -} + 2H^+ + e^- \rightarrow H_2O_2$ (hydrogen peroxide)

(3) $H_2O_2 + e^- \rightarrow OH^- + OH^\bullet$ (hydroxyl radical)

(4) $OH^\bullet + e^- \rightarrow OH^-$ (hydroxyl ion)

(5) $2OH^- + 2H^+ \rightarrow 2H_2O$

$\longrightarrow$ $O_2 + 4H^+ + 4e^- \rightarrow H_2O$

Scheme 1 [4]: The reduction of *oxygen* in the electron transport chain

As demonstrated in **Scheme 1**, molecular *oxygen* has the ability to accept or receive one or several electrons from its immediate neighbors, where the electrons are transferred essentially by transport vehicles such as Nicotinamide Adenine Dinucleotide (NAD) and Flavin Adenine Dinucleotide (FAD). These electrons carriers are important enzyme cofactors in almost all metabolic pathways, where our body can produce Adenosine Triphosphate (ATP), which acts as the energy source for our cells, in the catabolism of fat, sugars and other important substrates [5]. It is in these processes that *oxygen* gained is enormous reputation of "source of life".

Even though the final product in the reduction of *oxygen* is water (**Scheme 1**), the two radical intermediates (the hydroxyl radical and the superoxide radical), as well as hydrogen peroxide (which can be easily converted to the

hydroxyl radical by accepting one electron) are, if they manage to escape the metabolic pathways in which they are involved, very dangerous and lead to many unwanted reactions that may be toxic for living cells. Thus *oxygen,* which is required to sustain life, has also the potential to be toxic.

1.2. *Free radicals* are very reactive species

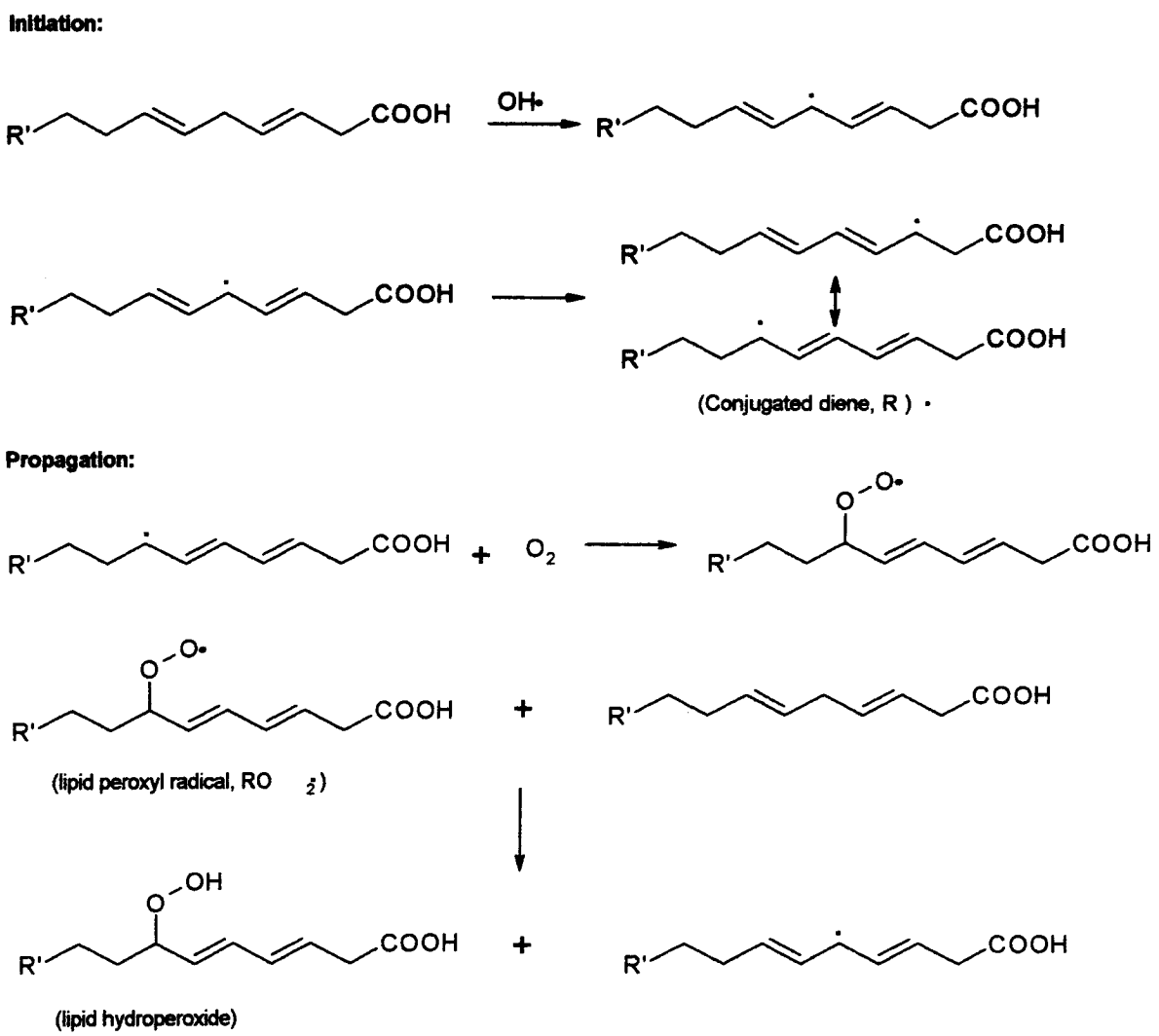
Any chemical species that has one or more unpaired electrons that occupy an atomic or molecular orbital can be called a *free radical*. Furthermore, the term "*free*" is there to tell us that these species are capable of independent existence [6]. Since *free radicals* are very reactive species, it is crucial for living organisms to control, by means of enzymes and electron carriers (cofactors) in metabolic pathways, these *free radicals* so that they can react only with wanted and specific substrates. Indeed, these *free radicals* can have an important protective role, since they are associated to the breakdown of poisonous molecules in our body, such as drugs, toxins and *D*-amino-acids [3].

Unfortunately, some manage to escape the metabolic pathways by which they are suppose to be neutralized or converted back to electron paired compounds by the end of the pathways (**Scheme 1**). As they migrate through the cell, one radical may encounter an important molecule; such as a lipid in lipid peroxidation (**Scheme 2**), a protein or a nucleotide (**Table 1**). This interaction creates a very reactive carbon-centered radical species ($R^{\cdot}$) in an initial reaction, which then can react with molecular oxygen to produce a peroxyl radical ($ROO^{\cdot}$). This peroxyl radical can further react with a "healthy" molecule to form a hydroperoxide and a new radical; thereby continue the "deadly" chain reaction.

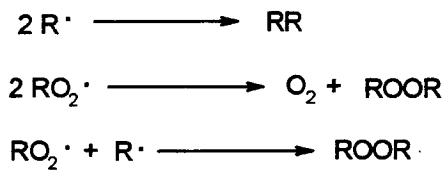
As pointed out in the above paragraph, all these reactions taken together can be compared to the "domino effect" and that is why *free radicals* are known to undergo cascade reactions.

Radical species	Targets	Products
$HO_2^{\cdot}$, $OH^{\cdot}$	Lipids	Lipid peroxides (PUFA), aldehydes
$HO_2^{\cdot}$, $OH^{\cdot}$	Proteins	Cross linking
$HO_2^{\cdot}$, $OH^{\cdot}$	Hyaluronic acid	Glycosides
$OH^{\cdot}$	DNA / RNA	Strand breaks, 8-hydroxyguanosine

Table 1 [2]: *Free radicals* and their targets in uncontrolled reactions

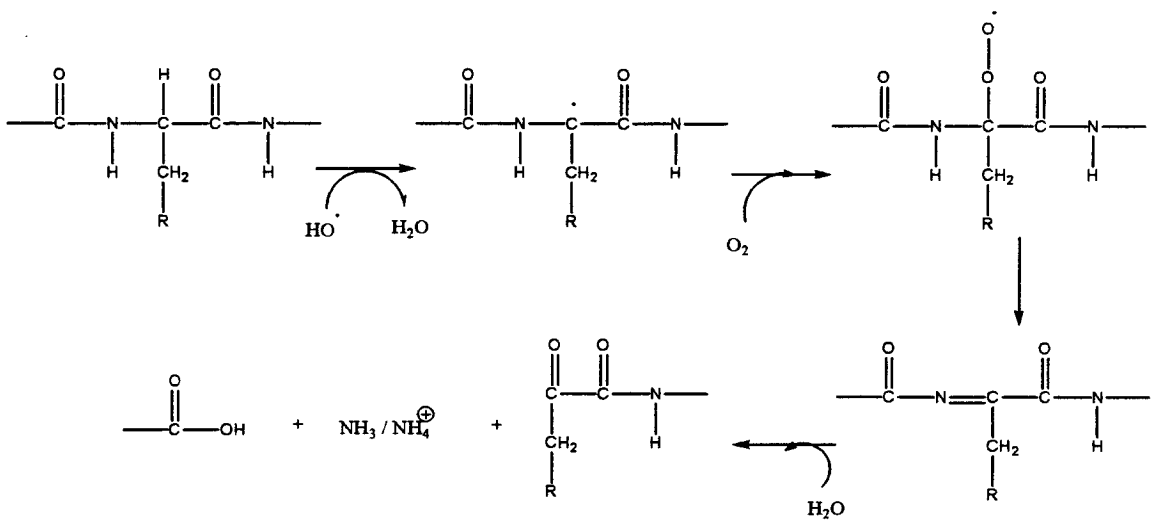


Termination:



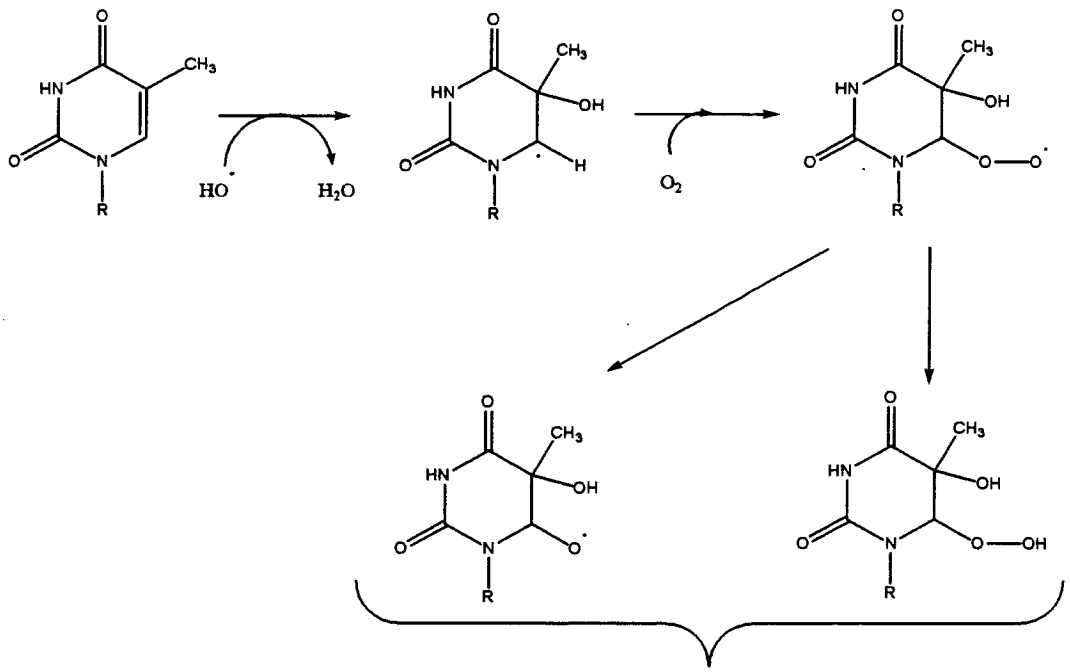
Scheme 2 [6]: Lipid peroxidation, where a chain reaction is produced

Such cascade reactions are a serious threat to living cells or organisms, because they can involve vital constituents, such as peptides (**Scheme 3**) and DNA (**Scheme 4**).



Scheme 3 [6]: An OH· -mediated scission of polypeptides

As seen in **Schemes 3** and **4**, these unwanted reactions with important constituents of the cell can be responsible for DNA mutation and breakage. Thus *free radicals* have been associated with many genetic diseases over the years, such as the Parkinson's disease, muscular dystrophy and Alzheimer's disease. Also, since *free radicals* can cleave peptides, they have been associated with degenerative diseases, such as cancer, arteriosclerosis, stroke and rheumatoid arthritis [7].



Scheme 4 [6]: A typical $OH^{\cdot}$ attack on and subsequent degradation of a pyrimidine base (thymine) in DNA

Finally, scientists have attempted over the years to explain the processes involved in aging. The hypotheses proposed include [3,4]:

- "Stochastic theory" explain aging simply as a random event, where our body deteriorate over time;
- "Developmental theory" sees aging as a decreasing efficacy of our immune system over the years;
- "Programmed theory" says that aging is controlled by our gene, where our cells are programmed to self-destruct after a certain period of time;
- "*Free radical* aging theory", which was first proposed in the mid 1950's, states that aging is basically the result of all *free radical* damages in our body over the years.

Much of the available evidence supports the *free radical* aging theory (as discussed in this subsection). However, there is a general agreement that aging is probably associated, at some extent, with each theory mentioned above.

1.3. *Antioxidants* as free radical scavengers

Since our body can produce the "deadly" free radicals as by-products to the essential catabolism and metabolic pathways, it must also have protective molecules to neutralize and/or destroy these free radicals when they manage to escape their metabolic pathways. These protective molecules, called *antioxidants*, are molecules capable of inhibiting or quenching free radicals. These processes can occur by a number of different mechanisms in order to avoid oxidative damage on various targets. These mechanisms include [7]:

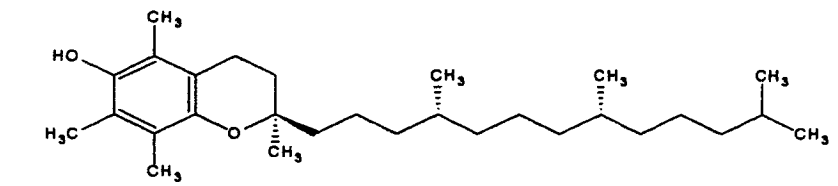
- Oxygen-derived radical scavenging, which happens either by enzymes or by a chemical reaction involving the antioxidant molecule;
- Reducing the formation of oxygen-derived species;
- Binding to metal ions capable of providing free electrons to relatively unreactive species, such as H_2O_2, and making them into very reactive ones (free radicals);
- Repairing damage to the targets;
- Destroying damaged molecules and replacing them by new ones.

To undergo all of these protective reactions, *antioxidants* must exist as various types of molecules (**Table 2**) and be present in all parts of cells, especially in the lipid membranes of cell organelles, where the majority of enzyme processes take place and free radical species are generated and quenched by *antioxidants* [2].

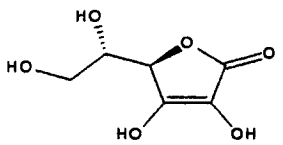
Antioxidants **enzymes**	***Antioxidants*** **proteins**	**Well known** ***antioxidants***	**Metal ions** ***antioxidants***
Catalases	Ferritin	Vitamins A, C, E	Cu
Gluthatione peroxidase and reductase	Haemoglobin	Uric acid	Mn
Superoxide dismutase	Myoglobin	Thiols	Zn
	Bilirubin	Carotenoids	Se

Table 2 [8]**:** Biological *antioxidant* troops

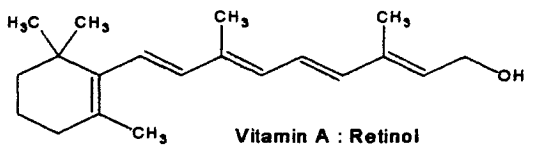
Vitamin E (α-tocopherol) (**Scheme 5**) can be considered as the "General of the *antioxidant* army troops" because it is the most concentrated lipophilic *antioxidant* in human plasma (**Table 3**). Its key function is to destroy free radicals made in lipidic tissues since these cause lipid peroxidation (**Scheme 2**) that destroys the membranes [9].



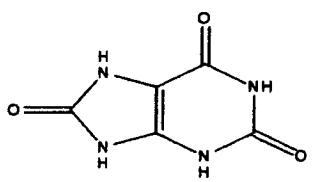
Vitamin E : Tocopherol



Vitamin C : Ascorbic Acid



Vitamin A : Retinol



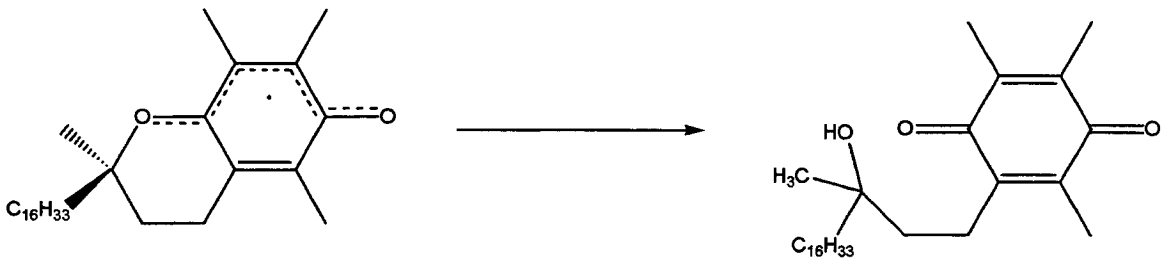
Uric Acid

Scheme 5: Structure of some important biological *antioxidants*

Vitamin E is part of the very important family known as phenolic *antioxidants*. These *antioxidants* have the ability to quench the chain-carrying peroxyl radicals (ROO·), by donation of the phenolic hydrogen atom (equation **(1)**, **Scheme 6**). The quenching reaction is known to be a much faster reaction than the attack of these peroxyl radicals on organic substrates (equation **(2)**, **Scheme 6**) [9].

$$ROO^{\cdot} + ArOH \longrightarrow ROOH + ArO^{\cdot} \quad \textbf{(1)}$$

$$ROO^{\cdot} + RH \longrightarrow ROOH + R^{\cdot} \xrightarrow{O_2} ROO^{\cdot} \quad \textbf{(2)}$$



Resonance stabilized radical

Quinone form of Vitamin E

Scheme 6 [10,11]: Reactions involved in the trapping of peroxyl radicals by phenolic *antioxidants* (chain-breaking *antioxidants*) applied to Vitamin E

The result of equation **(2)**, in the case of Vitamin E, is a resonance stabilized radical, which does not continue the chain reaction but is eventually destroyed by reacting with a second peroxyl radical to form its quinone form (**Scheme 6**), but more likely, the tocopheroxyl radical (equation **(3)**). These will be in turn trapped by water-soluble *antioxidants*, such as ascorbic acid (Vitamin C) to afford a much more stable radical and regenerate the ArO-H tocopherol molecule (see subsection 1.4) [10,11].

Compound	Concentration (μM)
Lipophilic *antioxidants*	
Vitamin E	25 - 40
Vitamin Q	0.4 - 1.0
Lycopene	0.5 - 1.0
β-Carotene	0.3 - 0.6
Hydrophilic *antioxidants*	
Protein thiols	350 - 550
Uric acid	160 – 470
Vitamin C	30 – 150
Bilirubin	5 - 20

Table 3 [2]: Solubility and typical concentration (μM) of compounds with *antioxidant* properties in human plasma

Since phenolic *antioxidants* owe their activity to the abstraction of the phenolic hydrogen by radicals (hydrogen atom transfer, HAT) (**Scheme 7**), we can expect that the rate of the reaction will strongly correlate with the O-H Bond Dissociation Enthalpy (BDE), since the weaker the O-H bond is, the faster the atom transfer reaction should be. Keeping this in mind, knowledge of the O-H bond dissociation energies in molecules can be a very powerful tool in the design of novel *antioxidants*.

A second radical quenching process is known, called Single Electron Transfer (SET), where the correlation is with the Ionization Potential (IP) of the *antioxidants*, since an electron transfer is involved. As shown in **Scheme 7**, the overall reaction is the same for both mechanisms, and it is known that these two mechanisms can happen simultaneously but at different rates [12,13].

- Hydrogen Atom Transfer (HAT):

$$ArOH + ROO^{\bullet} \rightarrow ArO^{\bullet} + ROOH$$

- Single Electron Transfer (SET)

$$ArOH + ROO^{\bullet} \rightarrow ArOH^{+} + ROO^{-}$$

$$ArOH^{+} + H_2O \leftrightarrow ArO^{\bullet} + H_3O^{+}$$

$$ROO^{-} + H_3O^{+} \leftrightarrow ROOH + H_2O$$

Scheme 7: The two possible mechanisms involved in the chain-breaking *antioxidant* preventing activity

1.4. Factors which contribute to antioxidant *activity*

Beyond the mechanism involved in the *activity* of antioxidants, numerous other factors determine if a molecule will have good *in vivo* antioxidant *activity*. Of course, the reactivity of an antioxidant toward free radicals is probably the most important factor, since the primary role of an antioxidant is to quench or neutralize these free radicals. But before being able to do so, the antioxidant molecules must reach these free radicals, therefore the localization, mobility, fate of the antioxidants radical and the ability for these antioxidants for synergistic inhibition with other antioxidant molecules are also very important factors. These factors are discussed below:

a) **Localization**

As mentioned earlier, phenolic antioxidants have the ability to donate their phenolic hydrogen to free radicals in order to neutralize them. Therefore various experiments were conducted to determine the rate of this reaction (**(1)** in **Scheme 6**) for many antioxidant molecules under different reaction conditions. These rate constants have been measured mostly in organic solutions (*in vitro*), but the *activity* of an antioxidant *in vivo* depends more on the location

than on the chemical reactivity towards free radicals. For example, when the activity of α–tocopherol (Vitamin E), Trolox (2-carboxy-2,5,7,8-tetramethyl-6-chromanol) and BHT (2,6-di-*t*-butyl-4-methylphenol) was conducted in an homogeneous solution, the rate constant for Trolox and Vitamin E was essentially the same, while BHT was much less reactive.

When the same experiment was conducted in the oxidation of membranes suspended in water, it was assumed that the lipophilic antioxidants (Vitamin E and BHT) were incorporated in the membranes, while the hydrophilic antioxidant was localized in the aqueous phase. The radicals where then generated in the aqueous phase and the rate constant for Trolox was now higher than the lipophilic antioxidants, Vitamin E followed by BHT. These results suggest that the *activity* of antioxidants does not always reflect the antioxidant efficacy towards free radicals [14].

b) **Mobility**

It is now well known that the phytyl side chain of α-tocopherol is essential for incorporation and retention of this lipophilic antioxidant in membranes and lipoproteins. Unfortunately, this side chain also decreases the mobility of α-tocopherol in membranes. It has been shown that the reactivity of α-tocopherol is substantially lower in membranes compared to homogeneous solutions [15,16]. Furthermore, when the free radicals were placed at different depths in the membranes, the apparent reactivity of α-tocopherol decreased when the radicals were deeper in the membranes [17]. These results show that in order for α-tocopherol to scavenge free radicals, it must go into the interior of the membranes or the free radicals have to float to the surface.

c) **Fate of the antioxidant radical and synergy**

As shown in **Scheme 7**, reaction of an antioxidant with a free radical via the HAT mechanism converts the antioxidant to a new free radical. Therefore the fate

of this antioxidant-derived radical should be considered as an important factor in the *in vivo* antioxidant *activity* of a molecule. When this happens, several reactions can occur between the new radical and other species in cells. It could quench other free radicals and form a more stable product, react with another antioxidant-derived radical to give a dimer or it may be reduced by a reductant to regenerate the original antioxidant molecule.

In the case of Vitamin E, the pathway most likely taken by the α-tocopheroxyl radical is the reduction of this radical by ascorbate ion, since ascorbic acid (Vitamin C, pKa = 4.2) is present predominantly as a monoanion under physiological conditions (equation **(3)**) [14]. This is where the synergistic inhibition of this combination of antioxidants comes from, preventing at the same time the attack on other potential substrates by the α-tocopheroxyl radical.

$$\alpha\text{-TO}^{\bullet} + \text{ascorbic acid} \rightarrow \alpha\text{-TOH} + \text{ascorbic acid}^{\bullet} \quad \textbf{(3)}$$

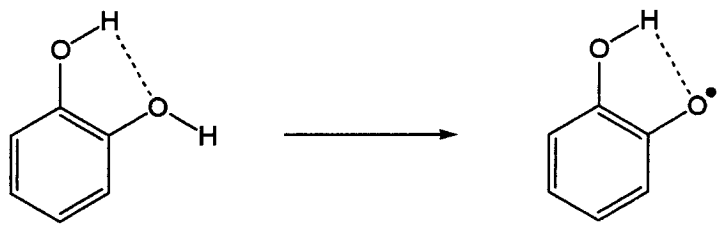
1.5. Designing *novel* antioxidants

Based on a comprehensive analysis of the antioxidant activity of Vitamin E, many scientists, especially K. U. Ingold and James S. Wright and their collaborators, were able to identify the molecular structure and parameters that were optimum in the design of synthetic *novel* antioxidants. These properties are listed below [18]:

- *Novel* antioxidants must not have weak C-H bonds because homolytic rupture of such bonds leads to carbon-centered radicals that can react with oxygen and afford chain propagating radicals;
- *Novel* antioxidants can contain sulfur or nitrogen atom, but most likely they should contain oxygen, because oxygen-centered radicals do not react with molecular oxygen to form trioxyl radical (ROOO·);

- *Novel* antioxidants should have a BDE value for the phenolic O-H bond below 88 kcal/mol, which is the BDE value of the formation of ROO-H bond from ROO· radical, because *novel* antioxidants must react rapidly with ROO·;
- *Novel* antioxidants should also have a BDE value lower than the one of Vitamin E, which is 77 kcal/mol, considering that the purpose of this is to generate more effective antioxidants;
- *Novel* antioxidants should have a BDE value higher than the 68 kcal/mol BDE value of ascorbate ion, because as mentioned earlier, antioxidants works cooperatively;
- Finally, *novel* antioxidants should have functional groups to improve transport, absorption and metabolism, e.g. lipophilic chains, as discussed in subsection 1.4.

It is known that electron-donating substituents (OMe, NH_2) in phenols decrease the strength of the O-H bond by stabilizing the phenoxy radical formed due to delocalization of the lone paired electron toward the substituent, especially when those substituents are placed in ortho or para relative to the OH group [12]. For some ortho functional groups an additional interaction, the possibility of hydrogen bonding, must also be taking into account. Indeed, in ortho hydroxyphenols (catechols), hydrogen bonding stabilizes the radical to a much higher extent than the parent molecule (**Scheme 8**). This reduces the BDE significantly relative to phenol itself.



Parent molecule Formed radical

Scheme 8: Hydrogen bond formation in catechols and in the derived radical

Theoretical calculations have been carried out by Prof. Wright's group at Carleton University in order to quantify the expected substituent effects. The calculations were initially carried out on phenol itself (87 kcal/mol) in order to validate the method. These calculations agreed within ± 0.2 kcal/mol with the experimental results. Similar calculations on a truncated version of Vitamin E also gave essentially the same BDE, 78 kcal/mol, as has been observed experimentally. A list of ortho-substituent effects on O-H bond dissociation energies in substituted phenols is given in **Table 4** (data for para- and meta-substituted phenols are also reported [13]). Since the effect of several substituents are additive, one can therefore quickly make quite good predictions of the BDE value of *novel* polysubstituted phenols using the data in **Table 4**.

Group	Electronic effect	H-bond parent	H-bond radical	Total (± 1 kcal/mol)
NH_2	- 7.5	+ 4.0	- 8.0	- 11.5
OMe	- 5.4	+ 4.0	0.0	- 1.4
OH	- 5.2	+ 4.0	- 8.0	- 9.2
$CHCH_2$	- 4.0	0.0	0.0	-4.0
tert-Butyl	- 2.2	+ 0.5	- 1.0	- 2.7
CH_3	- 2.0	0.0	0.0	- 2.0
Cl	-1.0	+ 2.0	0.0	+ 1.0
CN	+ 1.6	+ 2.0	0.0	+ 3.6

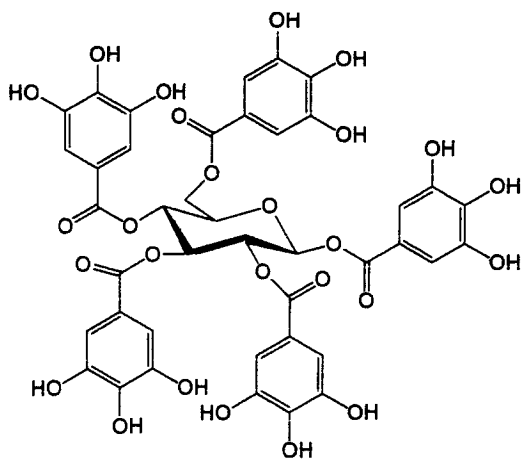
Table 4 [13]: Additive effects on the BDE value on the parent and formed radical molecules by different ortho substituents relative to phenol (87 kcal/mol)

Newly designed antioxidant molecules should have a BDE value between 68 and 75 kcal/mol, which is substantially lower than the BDE value of α-tocopherol, but higher than the BDE value of the ascorbate anion. This range is called the design window. Based on **Table 4**, such molecules would have the 1,2-dihydroxy or catechol motif and several other alkyl or alkoxy groups on the

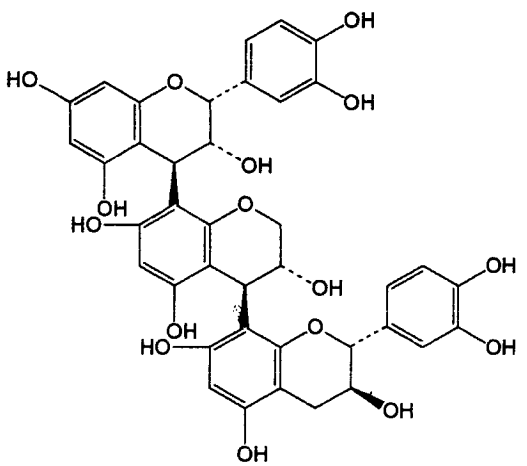
aromatic ring. One can envisage an even better activity when two or more of such units are present on the same molecule, as in dimers, trimers, even dendrimers [19]. Ortho or para nitrogen substituents were not considered since these compounds, by reacting via the SET rather than the HAT mechanism, can produce radical cation and lead to genetic damage [13, 47].

1.6. *Nature*, source of ideas

As in almost all scientific areas, chemists have learned a great deal by studying the molecules that Mother *Nature* designed as antioxidants in living systems, not only in mammals, but even more in plants. Such molecules include the already mentioned Vitamin E and C. Additionally, many plants synthesize a number of secondary metabolites via the shikimate pathway (which does not exist in mammals) that serves as excellent antioxidants [20]. Several of these compounds have the phenol, the catechol or the 1,2,3-trihydroxybenzene motif in their structures and some like pentagalloylglucose and the epicatechin trimer (**Scheme 9**), which contribute to the astringency of foods and beverages (wines, coffee and tea) have the beginning of dendrimer-like structures. These structures indicate the potential of dimers, trimers or even dendrimers as antioxidants.



Pentagalloylglucose



epicatechin trimer

Scheme 9: *Natural* dendrimer-like antioxidants

Chapter 2:

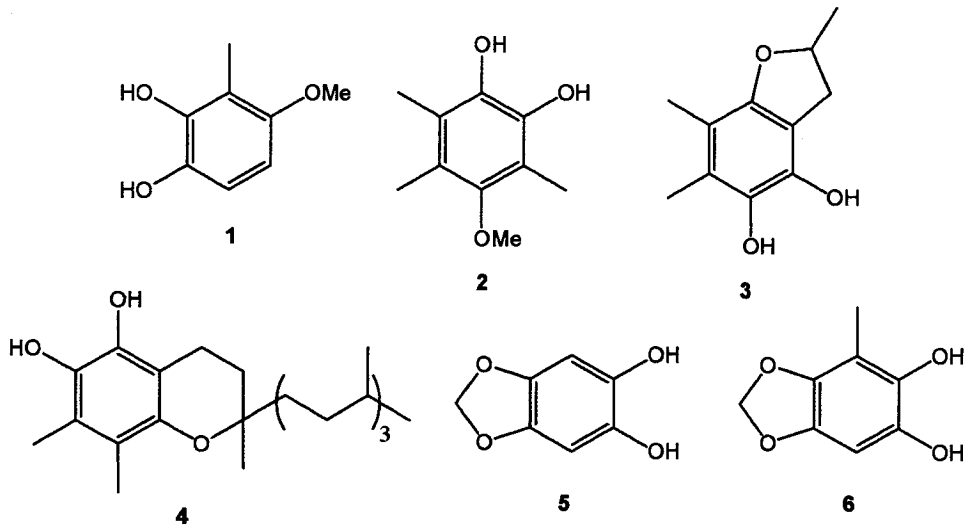
- Results and Discussion -

2.1. Preliminary investigation on catechol antioxidants

As described in the introduction, many groups have studied the properties of natural occurring antioxidants, such as the catechins, flavonoids, stilbenes and most importantly, α-tocopherol [21]. In contrast, relatively few novel synthetic antioxidants have been investigated in past years, despite the potential of such compounds capable of better antioxidant activity than Vitamin E for human health.

Since Vitamin E is the standard lipid-soluble antioxidant and phenolic compounds represent an important family of antioxidants, a logical first choice for designing novel antioxidants would be to modify various phenolic compounds with substituents that increase the antioxidant activity. The increase in antioxidant activity is reflected by a decrease of the O-H BDE. As mentioned in the introduction, catechol represents a good design motif due to the stabilization of the initially formed radical by H-bonding (**Scheme 8**). Indeed, if we take the -9.2 kcal/mol total effect of a second OH group ortho to the first (**Table 4**) relative to phenol (BDE: 87 kcal/mol), it gives a BDE value for the design motif of about 78 kcal/mol. By adding other substituents such as alkyl groups to this motif, the design window for BDE value between 68 and 75 kcal/mol should be easily reached.

Hussain et al. [18] designed and synthesized novel potent catechol antioxidants based on their predicted BDE_1 value. All compounds **1** to **6** are fully substituted aromatics. In addition, they all have an alkoxy substituent para to one of the O-H groups. These features relate these new catechols quite closely to the core structure of Vitamin E (**Scheme 10**).

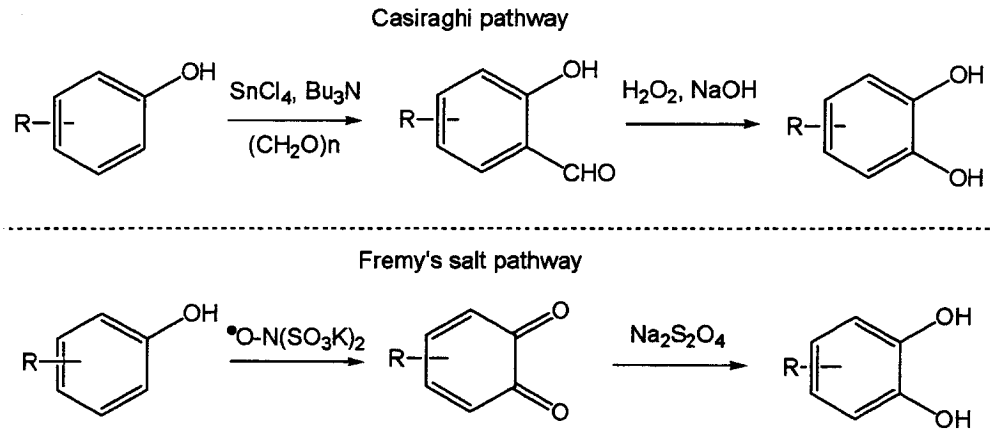


Scheme 10: Catechols synthesized by Hussain et al. [18]

The key step in each synthesis was the introduction of the ortho OH group, since one of the two OH groups was present in all the starting materials. Two different approaches were taken by the authors to introduce the second OH group. The first one being the *o*-formylation using the Casiraghi [45] reagents followed by Baeyer-Villiger oxidation coupled with hydrolysis of the intermediate formate ester using H_2O_2/NaOH (compounds **1** to **4**). Alternatively, the Fremy's salt oxidation of a phenol having an open ortho position resulted in the formation of *o*-quinones that were reduced with sodium dithionite (compounds **5** and **6**) (**Scheme 11**).

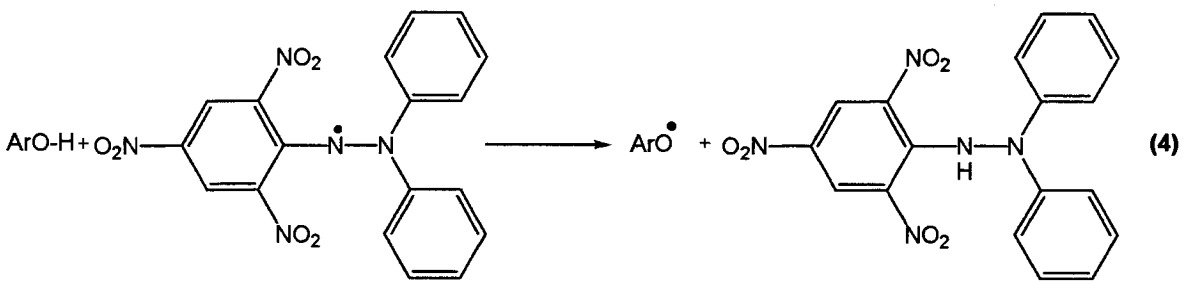
- DPPH· Quenching Studies -

These compounds were tested for their antioxidant activity to verify if their antioxidant activity could be correlated to their BDE values. This was accomplished by kinetic measurements with DPPH· carried out in a stopped-flow spectrophotometer apparatus at the National Research Council in Ottawa (NRC) [18]. This apparatus measures the decay of DPPH· in the presence of varying excess concentrations of antioxidants, following a second-order reaction (equation **(4)**, **Scheme 12**).



Scheme 11: Two pathways for the installation of the catechol motif

Since the antioxidants concentrations were in large excess, the observed rate constants k_{obs} follow pseudo-first-order kinetics, given by equation **(5)** (**Scheme 12**), where the second-order rate constant k_{dpph} is the slope of the plot of k_{obs} vs [antioxidant]. These results as well as calculated BDE values, both for the abstraction of the first and second O-H hydrogen atom (**Scheme 14**), for compounds **1** to **6** are given in **Table 5** [18].



(4)

$$K_{obs} = k_o + k_{dpph}[ArOH] \qquad \textbf{(5)}$$

Scheme 12: Reaction of DPPH· with phenolic antioxidants giving the rate constant k_{dpph} under pseudo-first-order conditions

Compounds	k_{dpph} ($M^{-1}s^{-1}$) (EtOAc)	BDE_1 (kcal/mol)	BDE_2 (Kcal/mol)
1	200	72.5	75.8
2	210	73.6	72.6
3	3000	68.7	71.7
4	4500	69.3	70.5
5	5040	69.0	67.5
6	8870	66.9	67.3
α-tocopherol	160[22]	75.0[a]	—

[a] The $C_{16}H_{33}$ phytyl tail was replaced by a methyl group for the calculation.

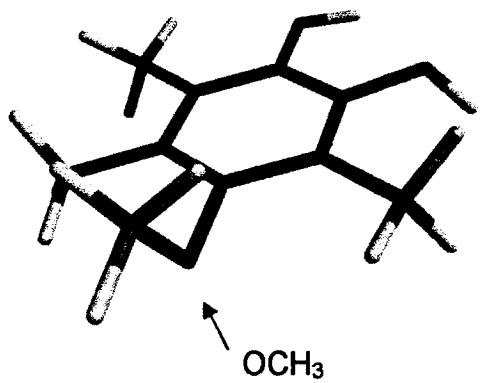
Table 5: Results for the rate constants (k_{dpph}) in EtOAc as well as BDE values for compounds **1** to **6**, compared to α-tocopherol

Analysis of the results in **Table 5** allows one to draw the following conclusions. First, the results for k_{dpph} clearly identified these novel catechol molecules to be more effective radical scavengers than Vitamin E. The calculated BDE_1 values for **1** and **2** are slightly lower than the value for α-tocopherol. As expected, the antioxidant activity of these compounds is slightly larger than that of α-tocopherol, (k_{dpph} is 220 for **2** vs 160 for α-tocopherol). For the others, compounds **3** to **6**, rate constants (k_{dpph}) are 15 to almost 50 times larger than that of Vitamin E, therefore these compounds have much better radical quenching activity than the standard molecule.

The importance of the catechol motif was clearly demonstrated by comparing α-tocopherol and compound **4**, in which one of the methyl groups ortho to the phenol in α-tocopherol was replaced by a hydroxyl group. This change resulted in a twenty five fold increase in k_{dpph}. The correlation of their BDE_1 calculations with the experimentally determined rate constants was generally very good, meaning that molecules with higher k_{dpph} have a lower BDE_1 value. The results for diol **2** also indicated how the simple use of additivity values given in **Table 4** must be tempered with caution. If we consider simple additivity, -9 (catechol motif), -2 (*o*-methyl group), -1 (two *m*-methyl group) [13] and -6

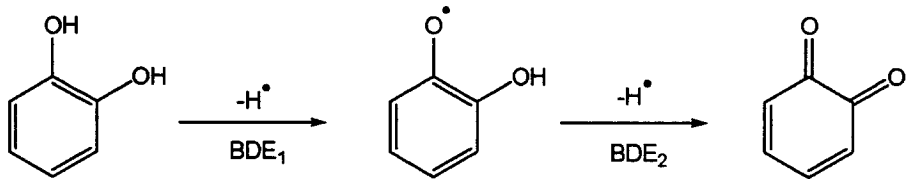
(*p*-methoxy) [13], we obtain 69 kcal/mol relative to phenol (87 kcal/mol) compared to the calculated BDE_1 of 73.6 kcal/mol. This large difference between predicted and calculated BDE_1 values was explained by the position of the *p*-methoxy group in **2**. Determination of the optimal geometry for compound **2** [18], showed that the *p*-methoxy group is forced out of the plane of the molecule by almost 90° due to steric interactions with the adjacent methyl groups, resulting in a less electron-donating substituent than predicted because of the reduced overlap of the methoxy oxygen orbitals with the aromatic ring (**Scheme 13**). The para alkoxy function in diol **3** behaves as expected since favorable overlap of the oxygen p orbitals is assured because of the planarity of the five-membered ring. This feature was realized by earlier workers in their studies of α-tocopherol analogues [23,24].

This investigation [18] on designed and synthesized catechol antioxidants suggested that the design criteria for novel catechol antioxidants based on BDE values as discussed in the introduction is useful and can lead to potent antioxidants with substantially higher activity against the DPPH radical than Vitamin E. One of the goals of this research was to determine whether these new catechols would provide protection against oxidative stress. It was necessary to determine both the potential protective action and the possible toxicity of these compounds, and show that these novel compounds, since they all have better activity against DPPH radical than Vitamin E, might be protective to cells against oxidative stress. It was first necessary to determine their toxicity, if any, against typical cell cultures.



Scheme 13 [18]: Structure of catechol **2**, showing that the methoxy group is rotated 90° out of plane due to interactions with adjacent methyl groups

Prior to describing the cell testing results for these novel catechol antioxidants, several aspects need to be pointed out. Each of these catechols was easily oxidized in air to their *o*-quinone. This transformation is accompanied by formation of a deep orange or red color when one of these compounds or its solution was kept in an open vessel at room temperature. The ease of oxidation to the corresponding *o*-quinones is in agreement with the data in **Table 5** which compares the second BDE value (BDE_2) with the first (BDE_1).

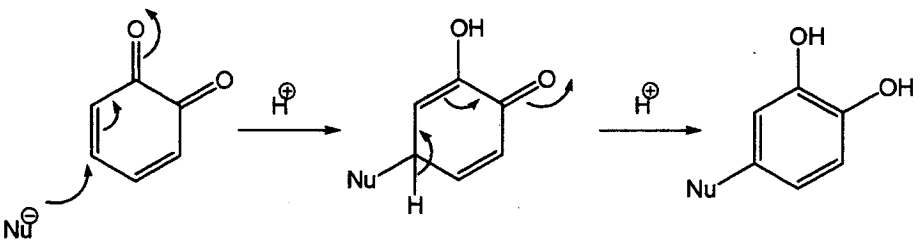


Scheme 14: Two consecutive hydrogen abstractions leading to quinone formation

Indeed, in these compounds, the abstraction of the first hydrogen atom bonded to oxygen by a radical (or simply by molecular oxygen) gives the semiquinone, while a second abstraction of the other hydrogen atom give rise to quinone formation (**Scheme 14**). As shown in **Table 5**, all these catechols (**1** to **6**) have a BDE_2 value similar to their BDE_1, meaning that after the abstraction of the first H atom, the second abstraction is as easy or even easier, leading to the formation of the corresponding *o*-quinones. One might think that two consecutive hydrogen abstractions could quench or neutralize two free radicals instead of only one, thus making catechols even more effective antioxidants than phenols. Unfortunately, the resulting *o*-quinones formed by this process are known to be very toxic for living cells, mainly via two mechanisms [25,26].

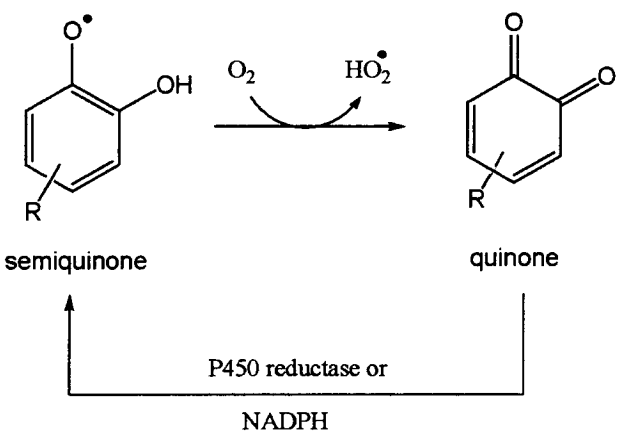
In the first mechanism, *o*-quinones can act as Michael acceptors and react with typical biological nucleophiles such as proteins, DNA or glutathione. This can eventually lead to loss of protein function, arylation of DNA bases which causes transcription errors and subsequently tumor-initiating mutations. Depletion of

glutathione in cells can upset the redox environment by changing the GSH/GSSG ratio which can eventually lead to cell death [5] (**Scheme 15**).



Scheme 15: Possible mechanism involved in the cytotoxicity of catechols

In the second mechanism, the quinones can be reduced back to semiquinones by reducing agents or enzymes present in the cells, most probably P450 reductase or NADPH. These semiquinones can then produce a redox cycle, by being oxidized back to quinones by molecular oxygen which is in this process reduced to superoxide radical. The system is now acting as a radical generator instead of a radical scavenger (**Scheme 16**).

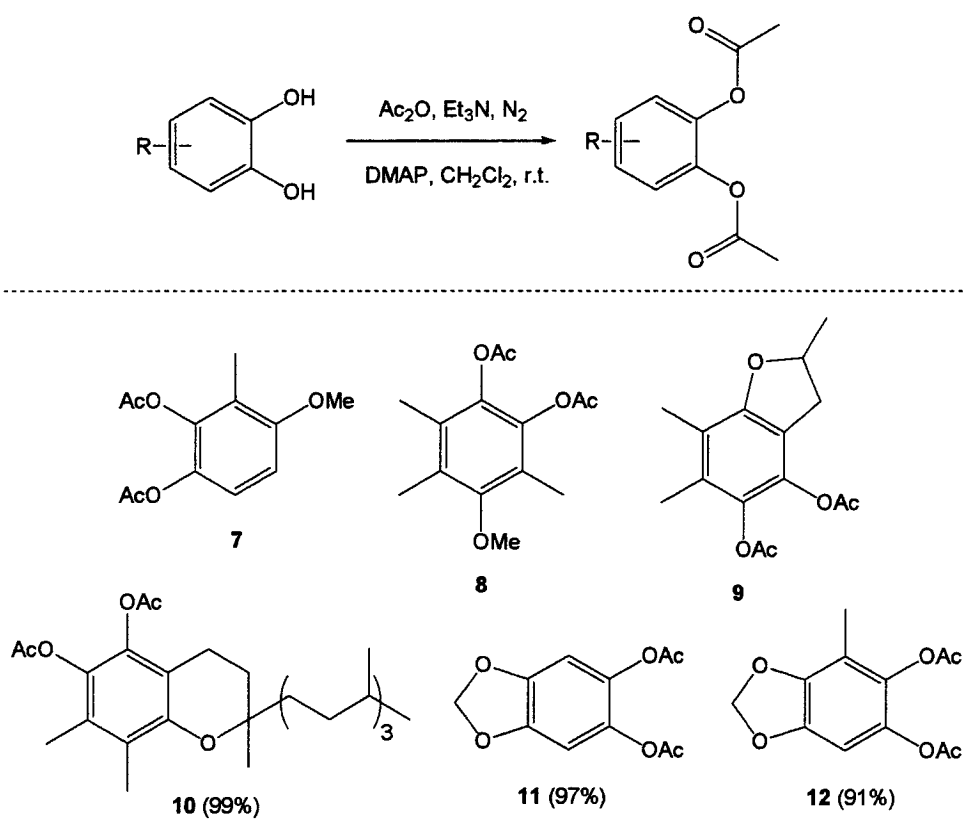


Scheme 16 [27]: Possible redox cycle for catechols where they are easily oxidized to *o*-quinones

Knowing this, compounds **2**, **3** and **6** where submitted for different cell culture testing in order to verify if these novel catechols were cytoprotective or

cytotoxic and if so, to identify the mechanism by which cytotoxicity is expressed. These testing were conducted at Carleton University in Ottawa by Dr. Wright's group [27].

Since these molecules are very easily oxidized to their respective *o*-quinones simply by exposure to air, it was necessary to protect them by acetylation of the two OH groups prior to testing. Acetylation also facilitated the incorporation of these molecules into the cells, because cell membranes are known to be very lipophilic [8], therefore polar functionalities, like catechols, will tend to pass through cell walls with difficulty. Acetylation was not expected to affect the activity of these compounds, since it is also known that cells contain intracellular esterases that will hydrolyze the acetates back to their corresponding catechols, once in the cells. Acetylation of these compounds was accomplished using the standard procedure; acetic anhydride in the presence of triethylamine and catalytic amount of N,N-dimethylaminopyridine (DMAP) illustrated in **Scheme 17**.



Scheme 17: Acetylation of compounds **1** to **6**

Prior to this step it was necessary to treat the starting catechols with sodium dithionite, except for **5** and **6**, in order to reduce any *o*-quinones that might have formed during storage back to the catechols. It was also necessary to re-synthesize Vitamin E analogue **4** and its diacetate version **10**, since the samples originally prepared by Dr. Hussain had decomposed during storage. The synthesis of compounds **4** and **10** proceeded as described by Hussain et al. [18] with yields similar to those reported. It is noteworthy that the synthesis of **10** involved a rather difficult Casiraghi / Baeyer-Villiger combination, which was complicated by the formation of several by-products, especially in the *o*-formylation reaction (yield reported: 19%, best yield obtained: 23%) where the major by-product was identified as the *p*-quinone form of the starting material δ-tocopherol [31] (**Scheme 6**). The procedure and characterization for diacetate **10** is reported in subsection 3.2.

The acetylations were carried out in an inert atmosphere in order to overcome oxidation to their respective *o*-quinones by exposure to air and obtain high yields. When carried out as such, these reactions showed only one spot on TLC after the reaction was completed. A very fast and easy purification by flash chromatography gave essentially quantitative yields. The ^{1}H NMR of these compounds showed the appearance of one or two singlets around 2.0-2.5 ppm (**Figure 1**, **2** and **3**), depending on the symmetry of the molecules, corresponding to the characteristic peak of the methyl groups on acetates.

- Toxicity Studies -

Toxicity studies were carried out by Dr. Wright's group using Adrenal Pheochromocytoma cells [27] on compounds **8**, **9** and **12**, both alone and in the presence of ascorbate (Vitamin C anion). The diacetates **7**, **8** and **9** were synthesized by Hussain et al. [31] and diacetate **10** was available for a related study [33]. Dr. Wright's group determined the EC_{50} (effective concentration which reduced the number of live cells to 50% of control) for compounds **8**, **9** and **12** (**Table 6**) [27].

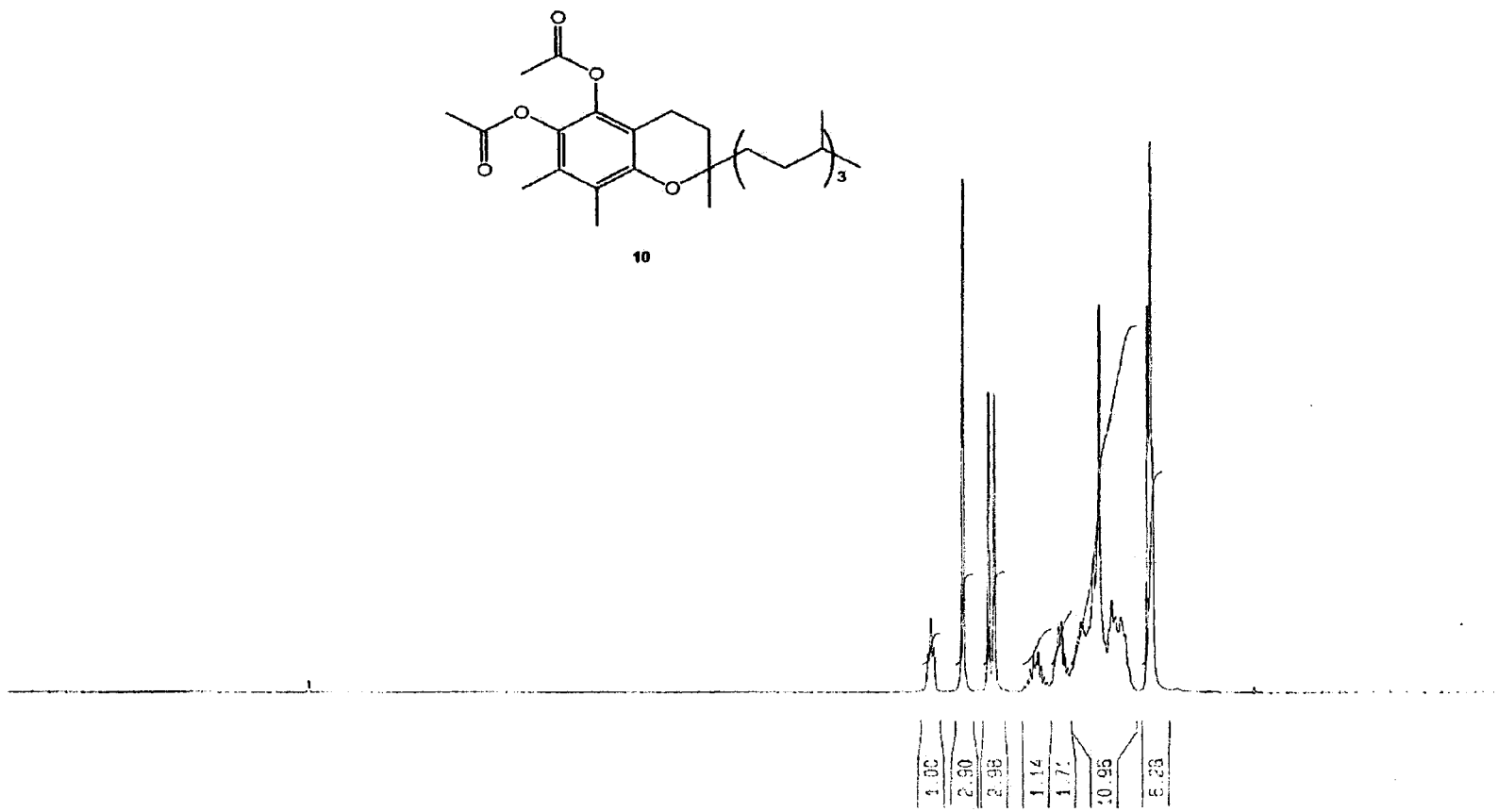


Figure 1: 300 MHz ^{1}H NMR of diacetate **10** in $CDCl_3$

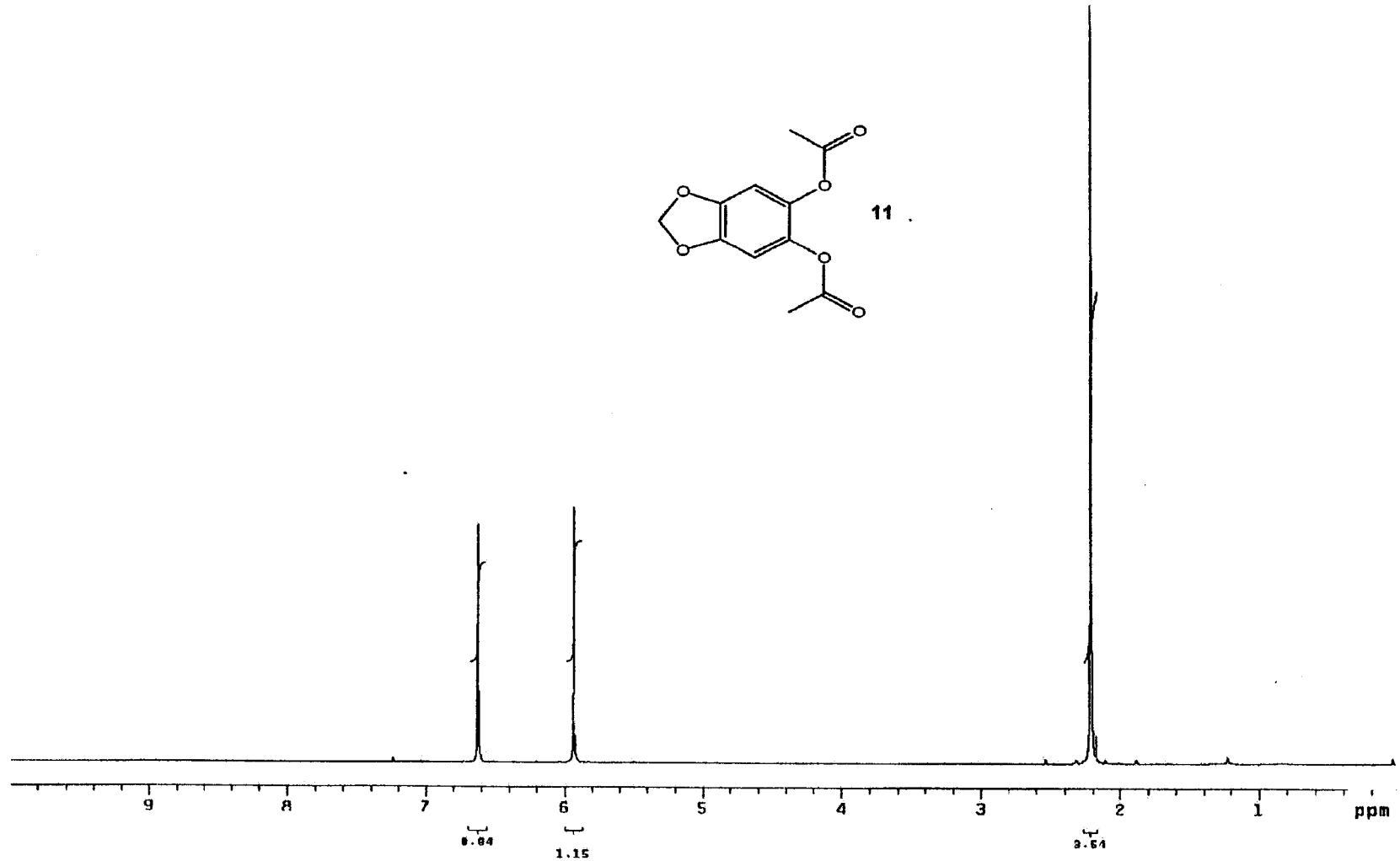


Figure 2: 200 MHz ^{1}H NMR of diacetate **11** in $CDCl_3$

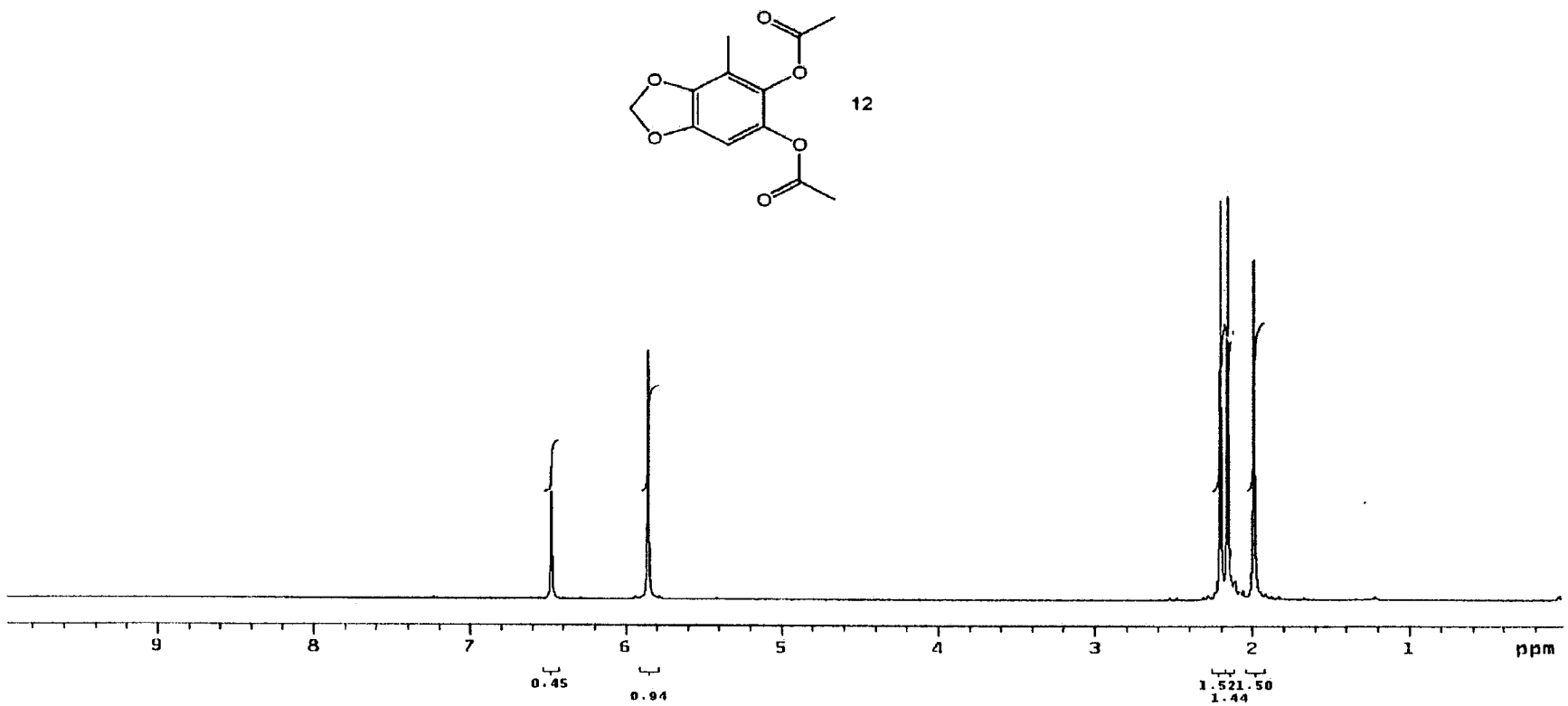


Figure 3: 200 MHz ^{1}H NMR of diacetate **12** in $CDCl_3$

Compounds	EC_{50} (μM)	$[H_2O_2]^a$ (μM)
8	100	20
8 + ascorbate[b]	110	—
9	28	32
9 + ascorbate[b]	39	—
12	26	8
12 + ascorbate[b]	27	—

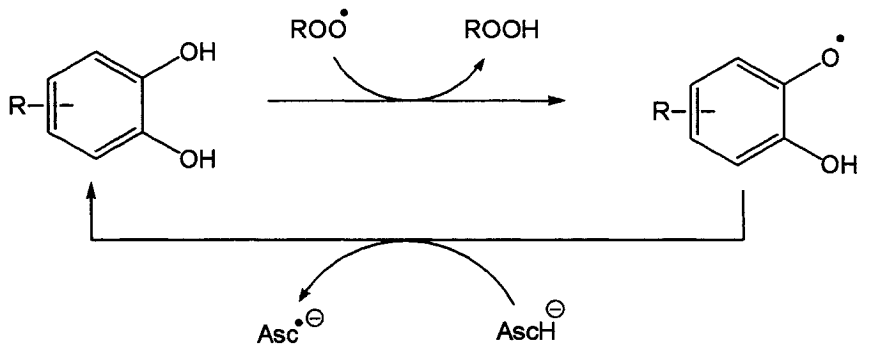
[a] Concentration of H_2O_2 when [compounds] : 200 μM, [b] [ascorbate]: 50 μM

Table 6 [27]: Results obtained for EC_{50}, as well as the H_2O_2 produced, in cell culture testing of diols **8**, **9** and **10**

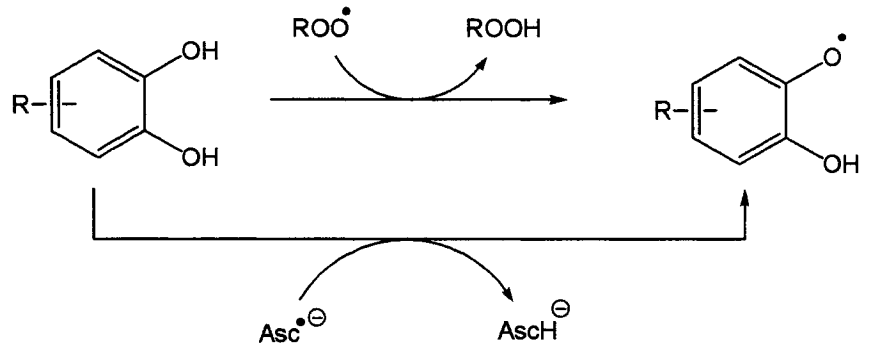
As shown in **Table 6**, these compounds are relatively cytotoxic, since the concentration required to kill 50% of cells was in the μM range, diacetate **8** being the least toxic. As discussed in the introduction, addition of ascorbate should decrease the cytotoxicity, since ascorbate should regenerate the catechols from semiquinones, thus preventing the formation of quinones. This expectation was observed for compounds **8** and **9**, where the EC_{50} increased by approximately a factor of 10.

For compound **12**, the addition of ascorbate failed to give additional protection to the cells. This can be explained by considering the BDE_1 value of the parent catechol **6** (66.9 kcal/mol) (**Table 5**), which lies outside of the design window. If the BDE_1 of the antioxidant is higher than that of ascorbate, its corresponding semiquinone can be reduced back to the catechol, therefore adding ascorbate is protective (case 1, **Scheme 18**). On the other hand, if the BDE_1 of the molecule is lower than that of ascorbate, adding ascorbate anion will now be destructive, since now the semiquinone is competing with ascorbate radical anion to regenerate ascorbate anion, which creates more semiquinone. Thus ascorbate radical anion which is normally non-toxic, is now acting as a pro-oxidant in converting the catechol into the semiquinone (case 2, **Scheme 18**).

These results again proved the importance of the design window (68-75 kcal/mol) and showed that an "ultra low" BDE_1 is not desirable.



Case 1. BDE > 68.5 kcal/mol, ascorbate anion is protective



Case 2. BDE < 68.5 kcal/mol, ascorbate anion is destructive

Scheme 18 [27]: Effect of adding ascorbate relative to BDE_1 value

Also shown in **Table 6** is the concentration of H_2O_2 produced when the concentration of the antioxidants was 200 μM. This production of hydrogen peroxide was correlated to the second mechanism by which catechols are known to exert their cytotoxicity. In this pathway, the superoxide radical generated by a redox cycle (**Scheme 16**) will likely disproportionate to form hydrogen peroxide and molecular oxygen. There was an increase in the production of H_2O_2 for compounds **8** and **9**, meaning that these molecules are capable of redox cycling and therefore harmful to cells. For diacetate **12**, there was a much lower production of H_2O_2, suggesting that this molecule exerts its cytotoxicity by another mechanism, possibly by a Michael addition reaction.

Examination of the structure of compounds **8**, **9** and **12** suggests that only the *o*-quinone of compound **12** can be considered as a potentially good Michael acceptor, since it is the only one with a sterically open β-position.

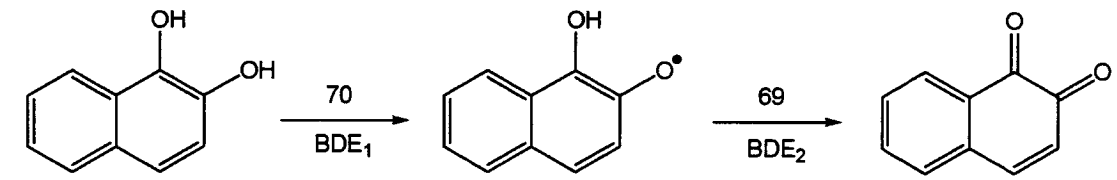
To investigate this possibility, these three compounds (as well as their respective catechols [27]) were submitted for a glutathione response test where it is possible to determine the concentration of up-regulated glutathione in cells. Indeed, if these molecules were able to deplete glutathione in cells by Micheal addition, this will force the cells to up-regulate the production of glutathione to overcome the oxidative stress [8,27]. Since the authors predicted that only compounds **12** should be a good Micheal acceptor, the up-regulation of glutathione should be higher for this compound than the other two.

Surprisingly, they observed a dramatic increasing of glutathione concentration for each compounds. The explanation for the up-regulation of glutathione for compounds **8** and **9**, also reported in other systems studied [28, 29], was that by redox cycling, these molecules increases the oxidative stress of the cells, which response to this by up-regulation of glutathione, even if the molecule is not necessarily depleting glutathione by Michael addition.

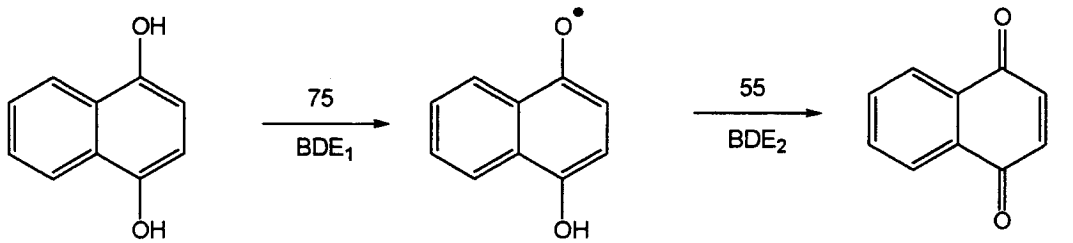
This preliminary work on the design, synthesis and reactivity of novel catechol antioxidants clearly showed that these molecules were definitely able to quench free radicals, demonstrated with DPPH$^{\cdot}$ testing, with a much better reactivity than Vitamin E. Unfortunately, these molecules were not only good antioxidants, but they could also act as pro-oxidants, therefore relatively toxic for living cells, demonstrated with different cell culture tests. It was assumed that this cytotoxicity was predominantly due to easy conversion of the catechol motif to their corresponding *o*-quinones. Thus, future designs of novel antioxidants with the potential of protecting cells against oxidative stress should avoid or minimize the ability of the design motif (now aryl-1,2-diols) to be converted to toxic *o*-quinones.

2.2. Design

In order to diminish the ability of the design motif to be converted to *o*-quinones, a new family of potential antioxidants, the naphthalenediols, was considered. Since the ability to form *o*-quinones can be correlated to the BDE values, extensive calculations of these values on naphthalenediols were carried out to suggest a new design motif, potentially less toxic and with similar reactivity against free radicals as the catechols discussed above. These calculations were also done by Dr. Wright's group at Carleton University in Ottawa; the results are summarized in **Scheme 19** below [27,33].

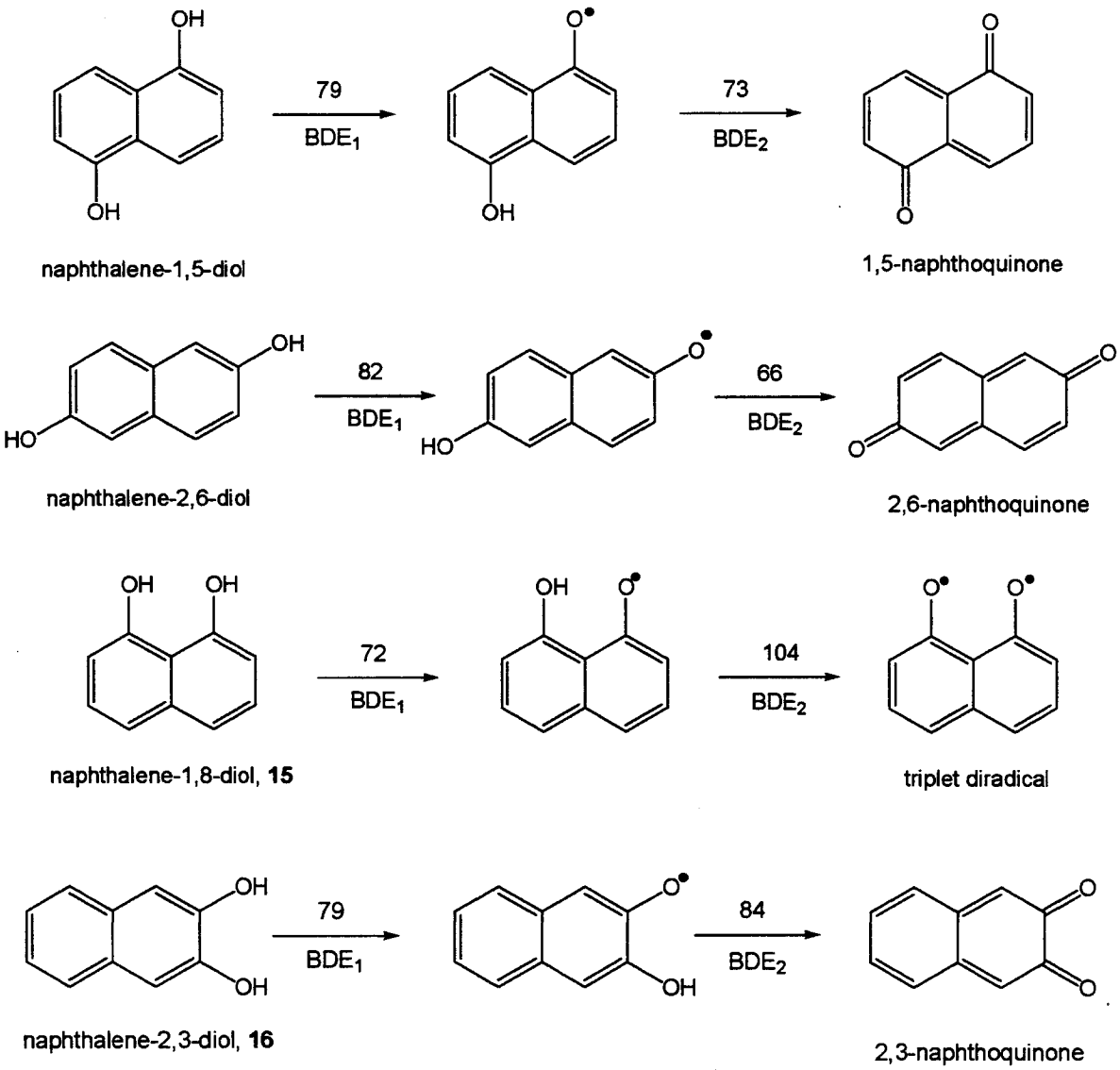


naphthalene-1,2-diol, **13** 1,2-naphthoquinone



naphthalene-1,4-diol, **14** 1,4-naphthoquinone

naphthalene-2,4-diol



Scheme 19: Results of BDE calculations on naphthalenediols

The simple exercise of drawing resonance structures for the radical obtained by removing two hydrogen atoms from the two O-H groups allowed us to eliminate some naphthalenediols, namely 1,2-(**13**), 1,4-(**14**), 1,5- and 2,6-naphthalenediols, which are capable of generating stable quinones.

This decision was re-enforced by the calculations for 1,2- and 1,4-naphthalenediols that gave significantly lower BDE_2 than BDE_1 values. Furthermore, it is well documented in the literature that these compounds are very

easily oxidized to their respective *o*- or *p*-quinones only by exposure to air; therefore their cytotoxicity should be similar to catechols.

The 2,4-,1,5- and 2,6-naphthalenediols were also eliminated because they do not possess the 1,2-diol functionality required for H-bonding stabilization of the formed radical, and thus do not have a sufficiently low BDE_1 value. For example the BDE_1 of 1,5-naphthalenediol is 79 kcal/mol.

The two remaining naphthalenediols, namely 1,8-(**15**) and naphthalene-2,3-diol (**16**) are unique. Both have the possibility of hydrogen bonding of the initially formed radical and thus the potential of a BDE_1 sufficiently low to fit the design window. Secondly, naphthalene-1,8-diol (**15**) can only yield a diradical and not a quinone after the loss of a second hydrogen atom, thus a predicted larger BDE_2. The prediction is supported by the calculations that showed BDE_1 = 74 kcal/mol and BDE_2 = 105 kcal/mol for this compound (**Scheme 19**). For these reasons, Foti and al. [30] synthesized **15** as well as 4-methoxy-naphthalene-1,8-diol and tested them for their antioxidant ability. These experiments were conducted the same way as with catechols, but in hexane and against a more lipophilic free radical, 2,2-di(4-*t*-octylphenyl)-1-picrylhydrazyl radical (DOPPH·) (**Table 7**).

Compounds	k_{DOPPH} (x 10^{-3} $M^{-1}s^{-1}$) (hexane)
catechol	1.8
15	310
16	1.3
4-methoxy-naphthalene-1,8-diol	2000
α-tocopherol	7.4[a]

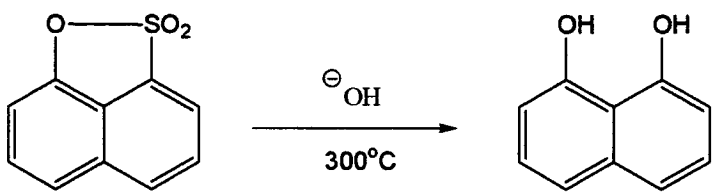
[a] The $C_{16}H_{33}$ phytyl tail was replaced by a methyl group for the experiment.

Table 7: DOPPH· rate constants for naphthalenediols [30]

Comparison between the results with DOPPH· in hexane (**Table 7**) and results previously shown with DPPH· in EtOAc (**Table 5**) is difficult, since the radical used is not the same and that it is known that "solvent effects" can alter results [32]. For example, the rate constant for *p*-methoxyphenol in EtOAc is much

lower than in hexane (1.1 versus 240 $M^{-1}s^{-1}$), due to the ability of the solvent to form H-bonds with the substrate [34].

As shown in **Table 7** and as predicted using BDE_1 values, Naphthalene-1,8-diol (**15**) is a very good radical scavenger, and its methoxy analogue is excellent, compared to catechol itself and Vitamin E (310 and 2000 versus 1.8 and 7.4 $M^{-1}s^{-1}$ respectively). Unfortunately, **15** is not a commercially available compound. The synthesis of **15** reported by Foti et al. [30] (**Scheme 20**) was achieved starting with 1,8-naphthosultone and required very harsh conditions. For example, it was necessary to melt a mixture of sodium and potassium hydroxide at 300°C and then add the naphthosultone in a deep stainless steel cylinder. Furthermore, preliminary results from my colleague, Dr. Helmi H. Hussain, showed that this compound tends to change color simply by exposure to air, from a white to a black solid, probably due to oxidation [31].



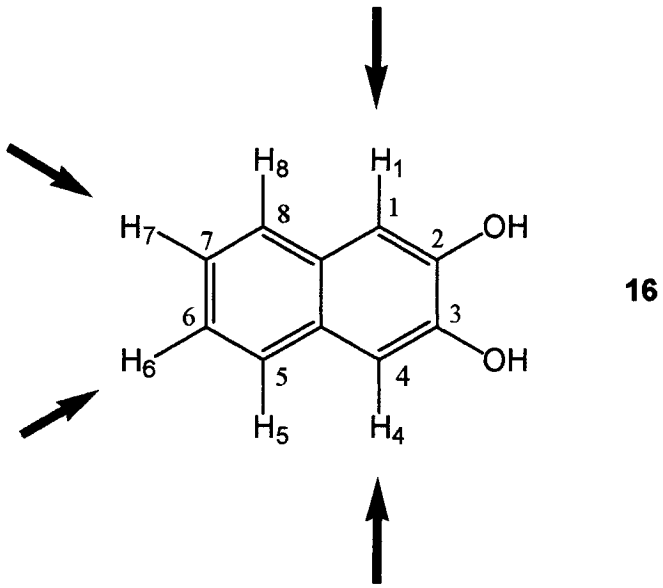
naphthosulfone **15**

Scheme 20: Reported synthesis of diol **15** by Foti et al. [30]

Naphthalene-2,3-diol (**16**) can form 2,3-naphthoquinone upon loss of two hydrogen atoms. However, the formation of the *o*-quinone results in the loss of aromaticity in both aromatic rings as compared to only in one ring for naphthalene-1,2-diol (**13**). It was therefore predicted; purely on a qualitative basis, that BDE_2 should be larger for this compound than BDE_1. A search of the literature seemed to support this notion. Several groups had attempted the preparation of this *o*-quinone and reported very limited stability of this compound even at low temperature [43,44]. Theoretical calculations gave BDE_1 = 79 kcal/mol and BDE_2 = 84 kcal/mol (**Scheme 19**), supporting the qualitative prediction and the

experimental observation that the formation of 2,3-naphthoquinone should be less favorable than the formation of the initial oxygen centered radical (semiquinone).

Since some work had already been reported by other members of this project group [30], and naphthalene-2,3-diol (**16**) is a commercially available and stable compound, we decided to focus on the synthesis of novel naphthalene-2,3-diol analogues. As shown in **Table 7**, the parent molecule **16** is not a good radical scavenger compared to Vitamin E, therefore substituted derivatives of **16** needed to be prepared in order to decrease this BDE_1 value and increase the antioxidant activity of these compounds. Examination of the structure of **16** indicates four possible derivatization sites; two ortho and two para to the 1,2-diol functionality (**Scheme 21**). Based on previous experience and being aware of substituent effects on the BDE of phenols (**Table 4**), we proceeded to the design, synthesis and testing of the antioxidant reactivity of a number of novel naphthalene-2,3-diol derivatives.

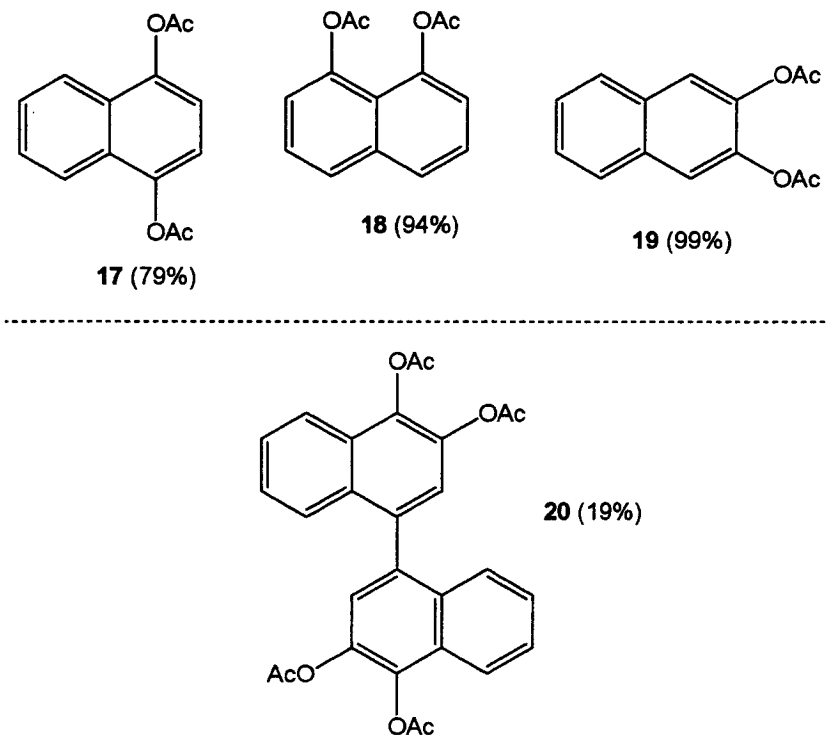


16

Scheme 21: Possible derivatization sites in the new design motif, naphthalene-2,3-diol

Concurrent with the synthesis of new naphthalene-2,3-diols, it was decided to investigate whether the cytotoxicity of naphthalenediols could be correlated with their ability or tendency to form quinones; no data of this type was available. For this reason and those mentioned in subsection 2.1, it was again decided to test these compounds as their diacetates.

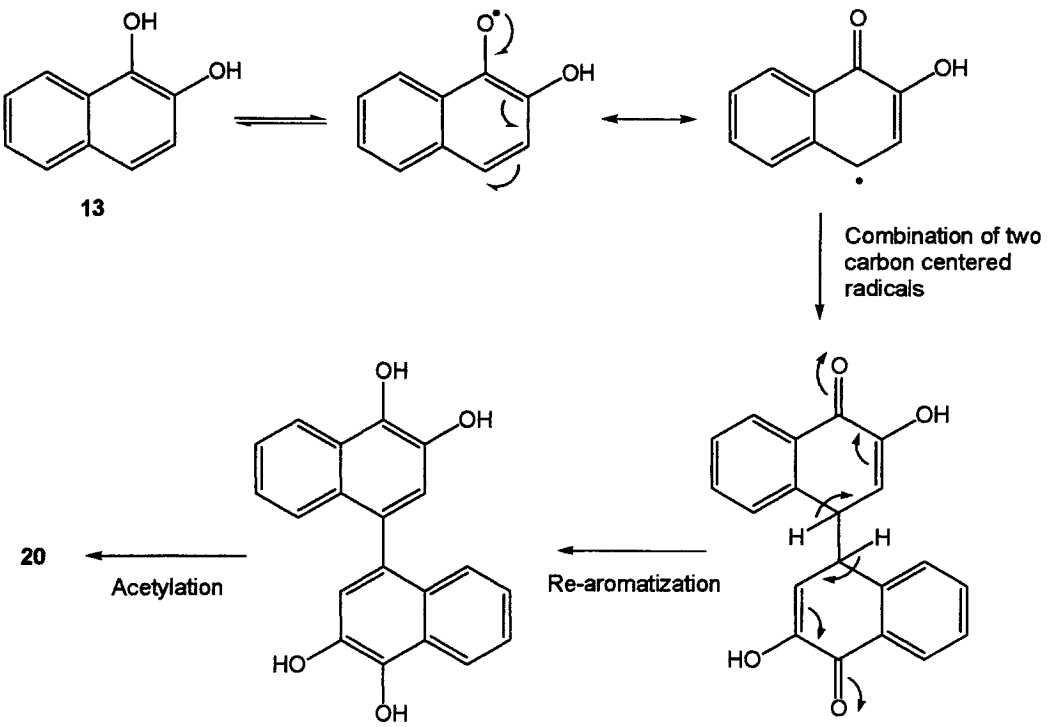
Acetylation of these molecules was accomplished using the same procedure as with the catechols (**Scheme 21**). Again, inert atmosphere was used in order to achieved high yields, since some of these compounds are easily converted to their respective *o*-quinones, especially diol **14**, where 16% of its corresponding *p*-quinone was isolated in addition to the desired 1,4-diacetate **17**.



Scheme 22: Results obtained in the acetylation of naphthalenediols, as well as the discovery of an unexpected product

Even with this precaution, initial attempts to carry out the acetylation of **13**, yielded none of the expected product, but only a small amount of the tetraacetylated dimer **20**. The structure of this unexpected product was assigned

on the basis of the mass spectrum and ^{1}H NMR data; the latter is shown in **Figure 7**. Examination of the mass spectrum of sample **13**, purchased from Aldrich, showed that no **13** was present in the sample and that the compound had dimerized. Fortunately, reduction of 1,2-naphthoquinone followed by immediate acetylation could easily yield the desired product. A mechanism for the formation of dimer **20** is shown in **Scheme 23**. The acetylation of 1,8- (**15**), 1,4- (**14**) and 2,3- (**16**) naphthalenediols proceeded in excellent yield. The ^{1}H NMR spectra of the three key products are shown in **Figures 4**, **5** and **6**.



Scheme 23: Proposed mechanism for the formation of dimer **20**

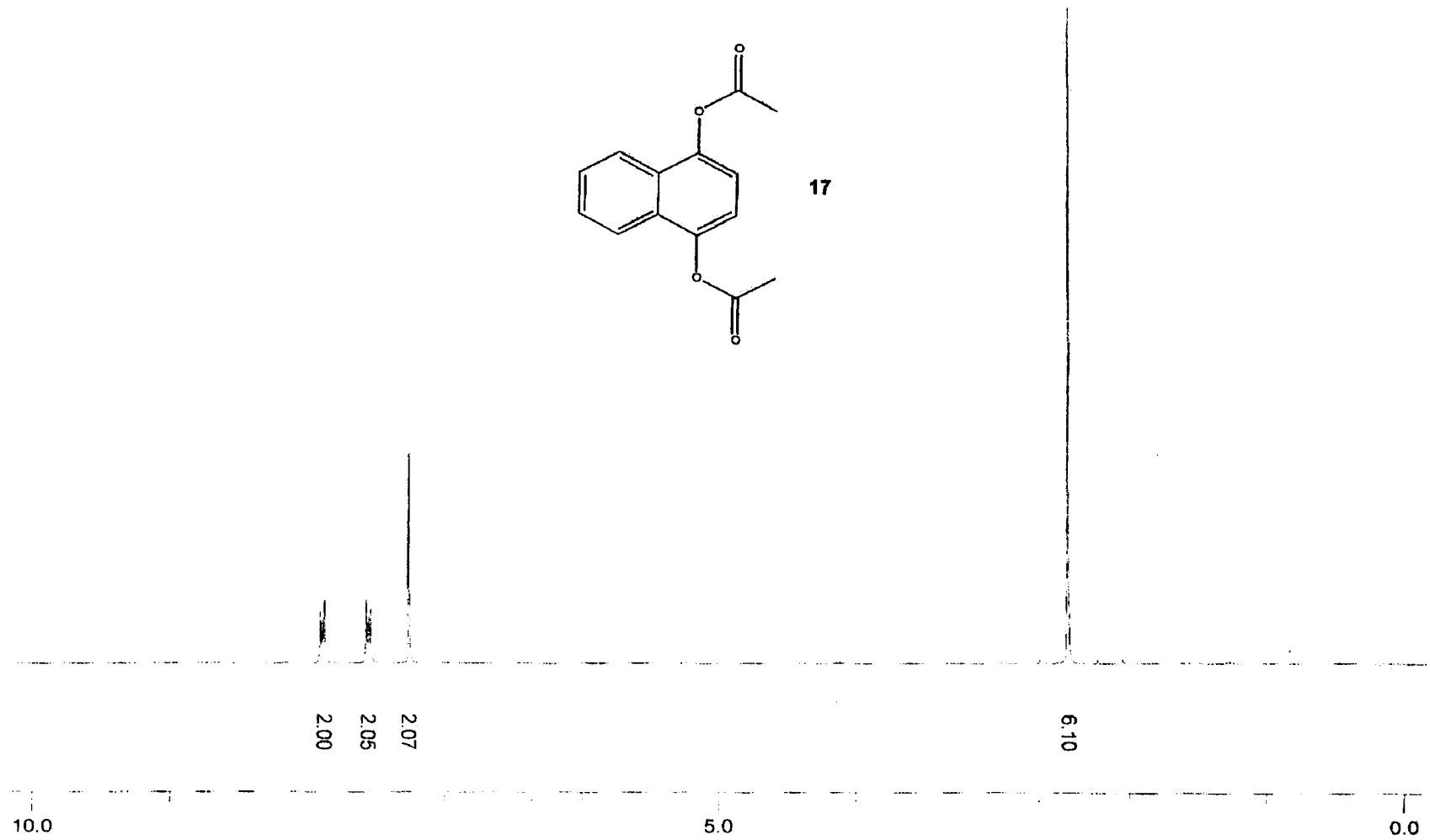


Figure 4: 300 MHz ^{1}H NMR of diacetate **17** in $CDCl_3$

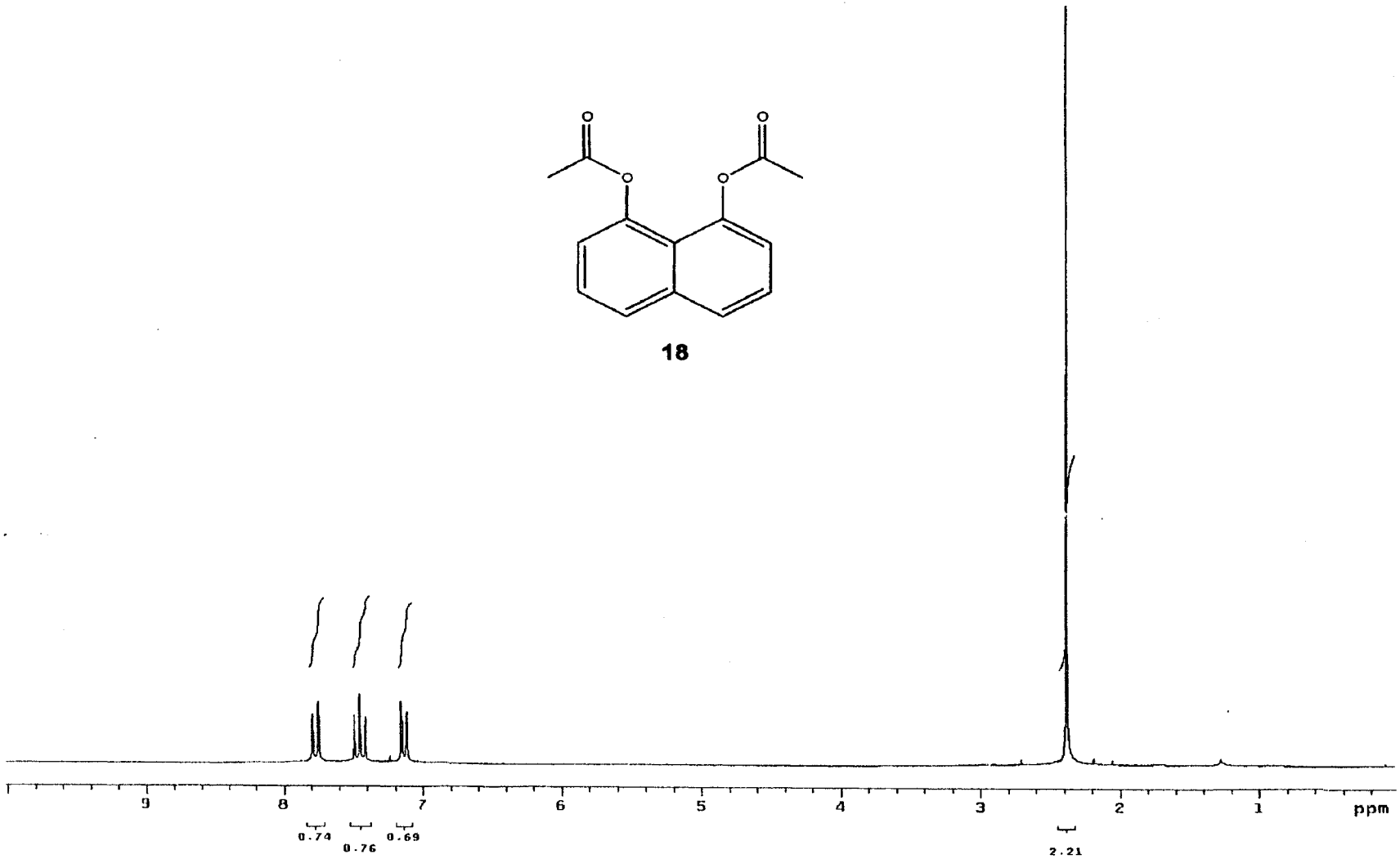


Figure 5: 200 MHz ^{1}H NMR of diacetate **18** in $CDCl_3$

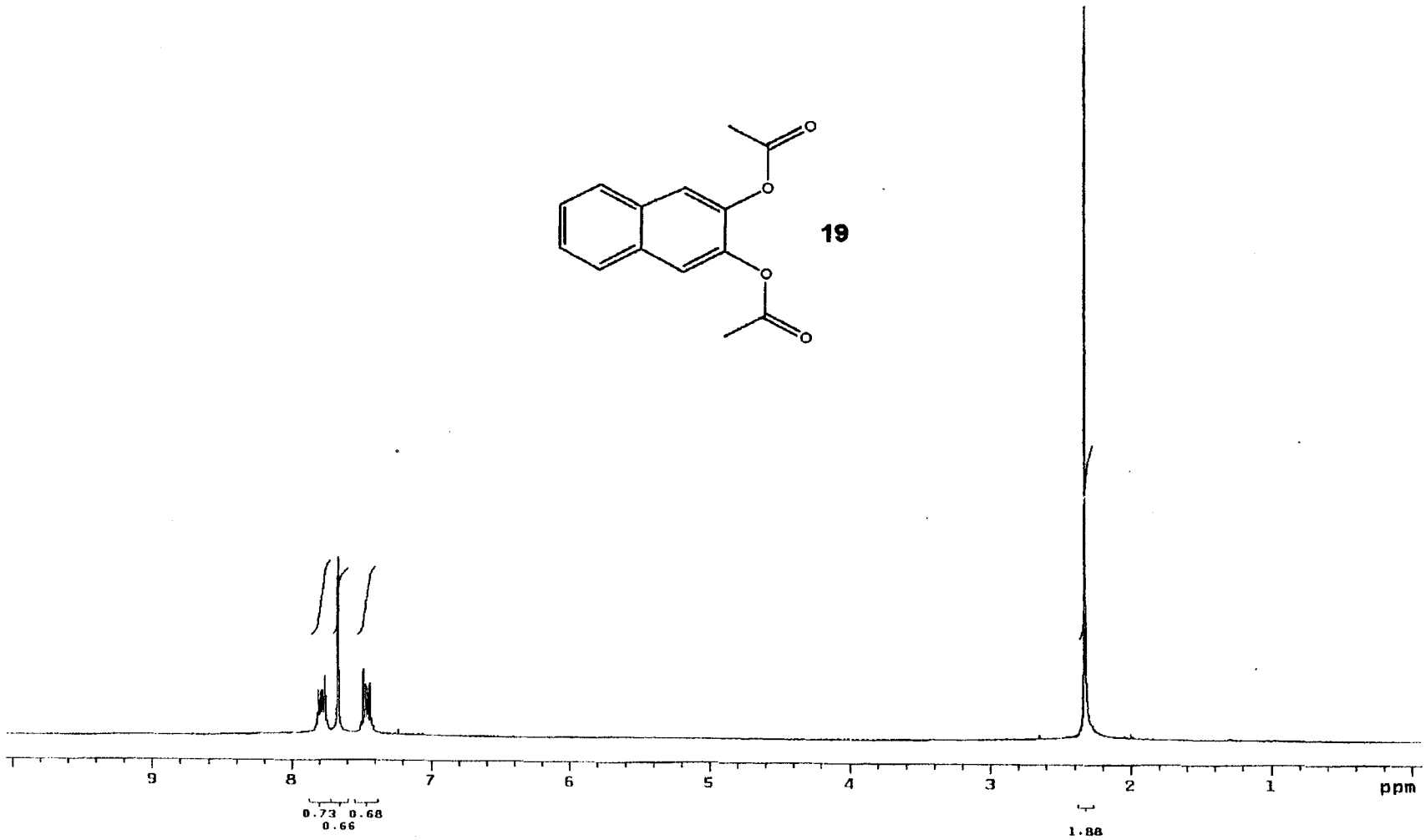


Figure 6: 200 MHz ^{1}H NMR of diacetate **19** in $CDCl_3$

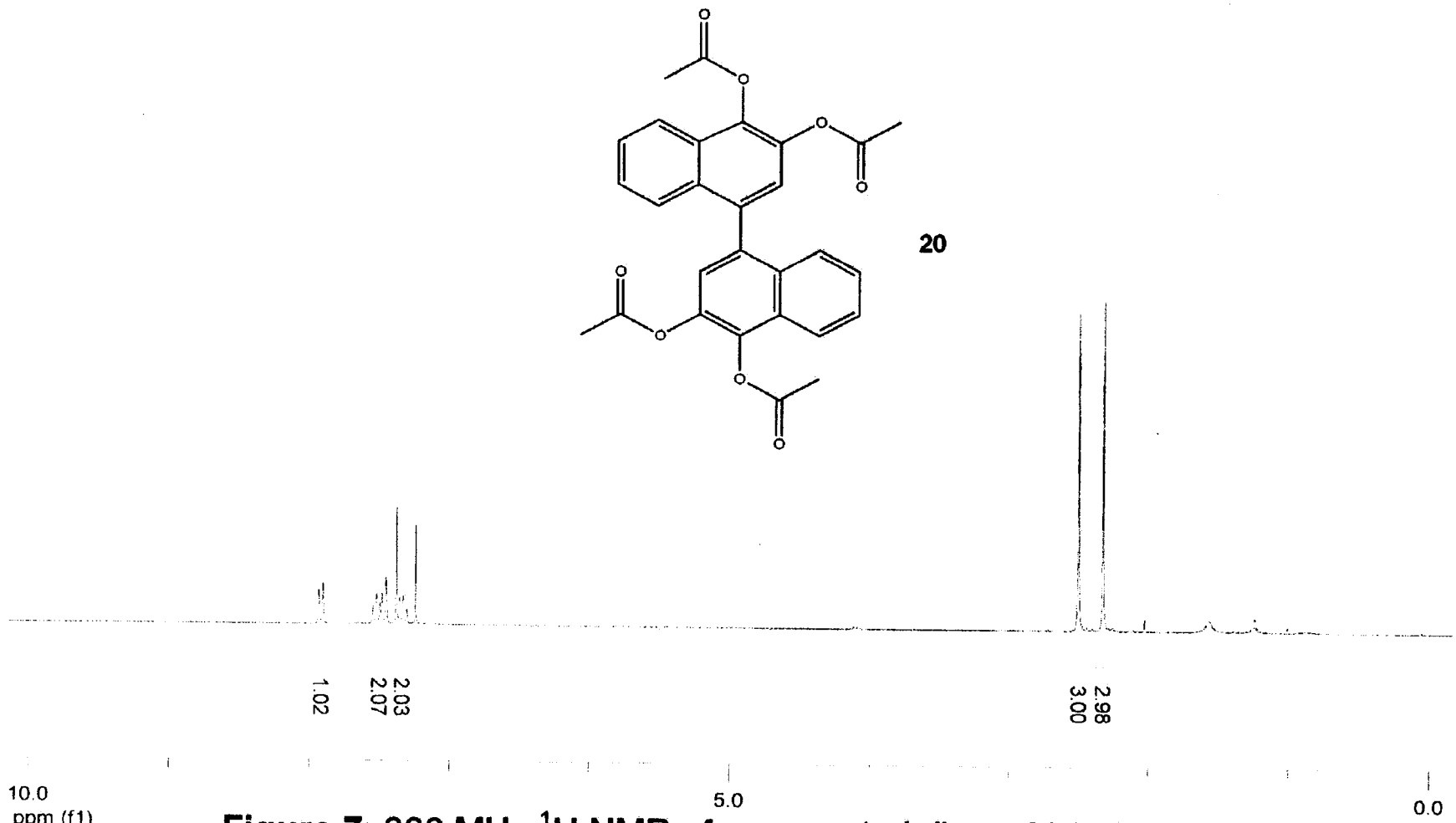
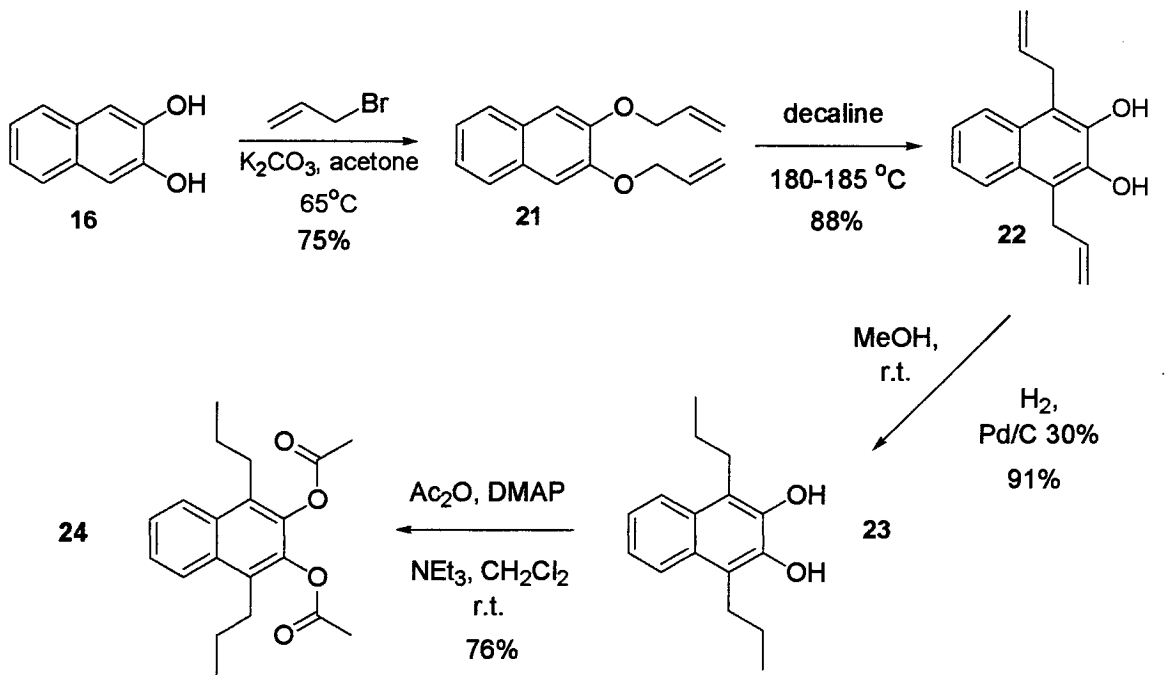


Figure 7: 300 MHz ^{1}H NMR of unexpected dimer **20** in $CDCl_3$

2.3. Synthesis

The commercially available naphthalene-2,3-diol (**16**), was calculated to have BDE_1 = 79 and BDE_2 = 84 kcal/mol. This suggested a reluctance of the compound to form 2,3-naphthoquinone and thus indicated a potentially less toxic catechol-type compound than those synthesized by Hussain et al [18].

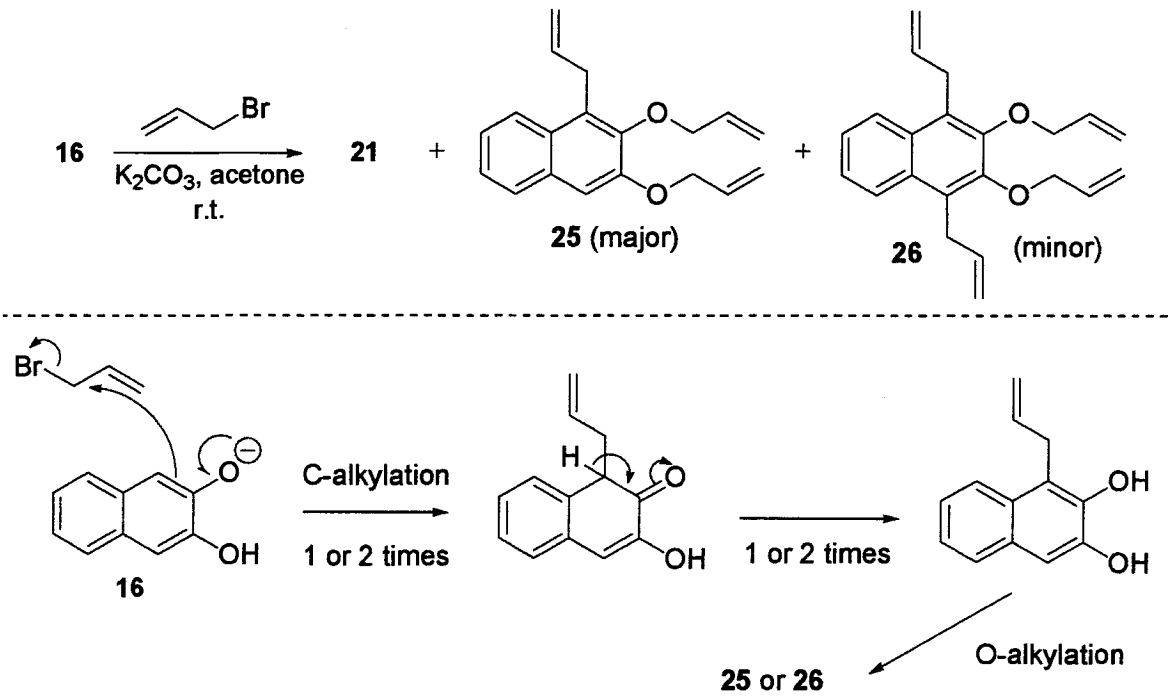
In order to fit the design window having a BDE_1 in the 68-75 kcal/mol range, it was necessary to add substituents to **16**. A logical first move was to alkylate both at C1 and C4 (**Scheme 21**), since alkyl groups (like CH_3, **Table 4**) in ortho position represent a beneficial total effect on BDE_1 of -2 kcal/mol relative to phenol. A similar beneficial effect if applicable to **16** should result in a compound reaching the top edge of the design window, around 74-75 kcal/mol. One of the easiest ways to do so was by Claisen rearrangement of the corresponding diallyl ether, followed by hydrogenation of the resulting double bonds to give a 1,4-dipropyl analogue of **16**. This procedure was followed and as expected, resulted in very good yields for the synthesis of 1,4-dipropyl-naphthalene-2,3-diol (**23**), outline in **Scheme 24**.



Scheme 24: Preparation of 1,4-dipropyl analogue **23**, and its diacetate **24**

The first step was accomplished by reacting **16** with allyl bromide in the presence of potassium carbonate in refluxing acetone, which afforded diallyl ether **21** in 75% yield. However, one might think that 75% yield for such a simple reaction should be considered as low, but in fact, this was the highest yield obtained in this reaction. The reason was that the expected product **21** was not the only product obtained in this reaction.

Indeed, when using 3eq of allyl bromide and a large excess of potassium carbonate (4eq), compounds **25** (major) and **26** (minor) were also produced (**Scheme 25**), probably by a competition between O-allylation and C-allylation reactions, since the temperature (65°C) should not be high enough to achieve Claisen rearrangement of product **21** followed by O-allylation.



Scheme 25: Proposed mechanism by which by-products **25** and **26** are formed in the allylation of diol **16**

The NMR of the mixture of by-products (**Figure 8**) shows an approximate 7.5:1 ratio of **25** and **26**. This is based on the relative integration of various areas of absorption, such as the ratio of the peaks at 7.6-7.8 and 7.8-8.0 ppm, or the ratio of the singlet at 7.1 ppm corresponding to H4 in the mono-adduct vs the peaks at

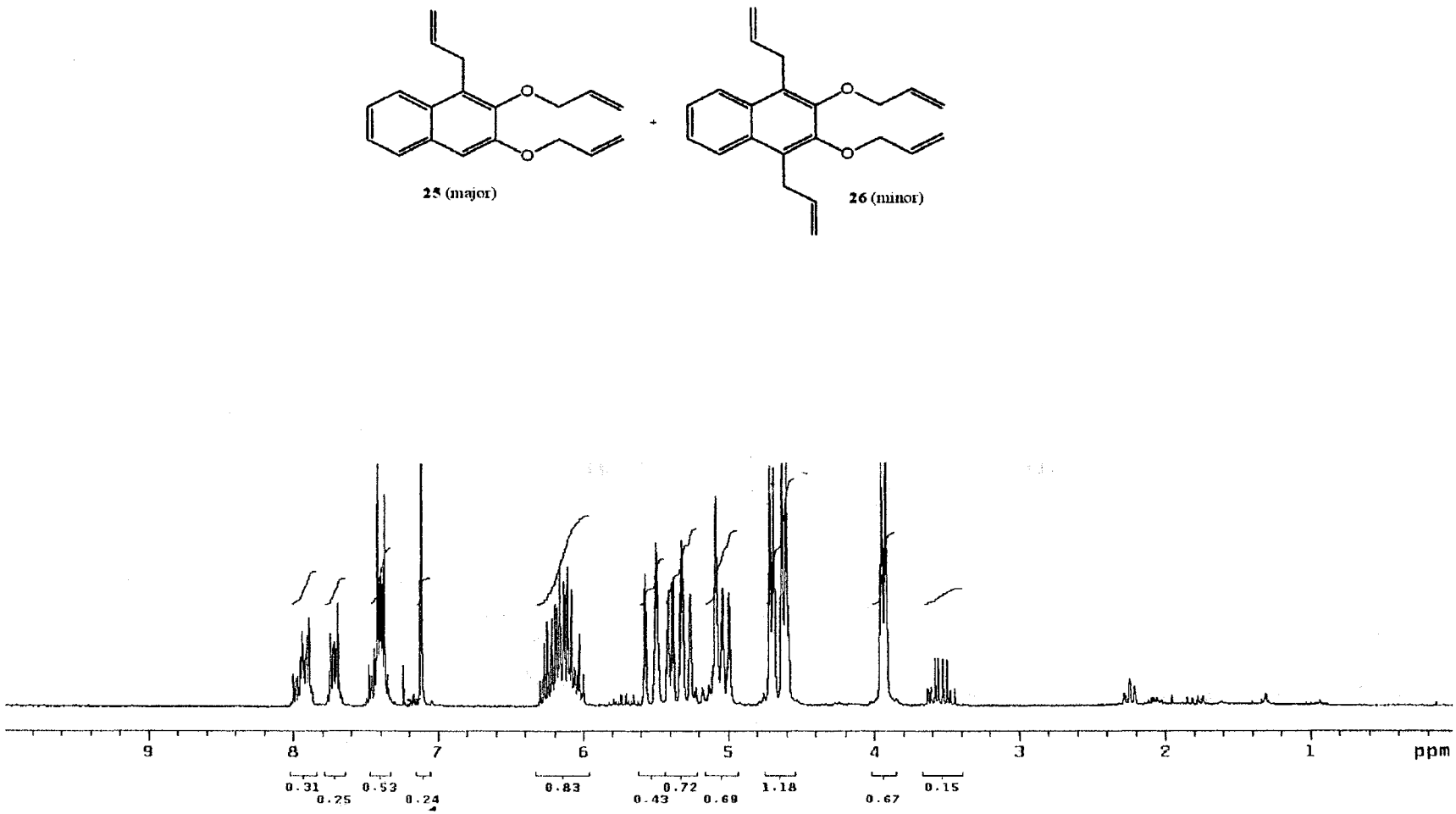


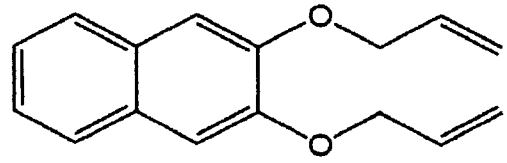
Figure 8: 200 MHz ^{1}H NMR of by-product mixture **25** and **26** in $CDCl_3$

7.8-8.0 ppm. The peaks in the 7.6-7.8 ppm region is assigned to H5 in the mono-adduct while that at 7.8-8.0 ppm is due to both H8 in the mono-adduct and H5 and H8 in the di-adduct. A similar conclusion regarding the ratio of **25** to **26** is obtained when one considers that the peaks between 3.9-4.0 ppm is due to the benzylic CH_2 groups in both **25** and **26** and those between 4.6-4.8 ppm are caused by the OCH_2 in both adducts.

In order to decrease formation of by-products **25** and **26** and increase the yield, the same reaction was also conducted with only 2.2 eq of allyl bromide, which resulted in lower yield (66-67%) attributed to the formation of the mono-O-allylated product and the NaOH washings required to get rid of this other by-product. No improvement was observed even when the original reaction was conducted at r.t. Since by-products **25** and **26** were very close to the desired product **21** on TLC, best results were achieved when the crude was purified by column chromatography followed by recrystallization (100% hexanes) of the remaining mixture. The ^1H NMR of diallyl ether **21** (**Figure 9**) showed peaks in the 5.0-6.5 ppm region, corresponding to the olefinic protons, which clearly showed the addition of allyl groups on diol **16**. Furthermore, the correlation between aromatic protons and allylic protons integrations showed the addition of two allyl groups, indicating a symmetric molecule **21**.

Diallyl ether **21** was then submitted to Claisen rearrangement in decalin at high temperature, 180-185°C. This reaction provided only one spot on TLC, which corresponded to the desired product **22**, but the yield for this Claisen rearrangement could not increased beyond 88%, due to production of tarry matter. After cooling down the reaction mixture overnight, this tar could be separated from the crude solid produced by simple filtration and washings with hexanes.

The remaining light-brownish color was more problematic to eliminate. Though the purity of **22** was high enough to go to the next step, two consecutive column chromatography followed by hexanes washings were required to finally obtain an off-white solid. In order to decrease formation of tarry matter, the reaction was conducted at 160-165°C and unfortunately, the only changes observed was the longer time period required to complete the transformation.



21

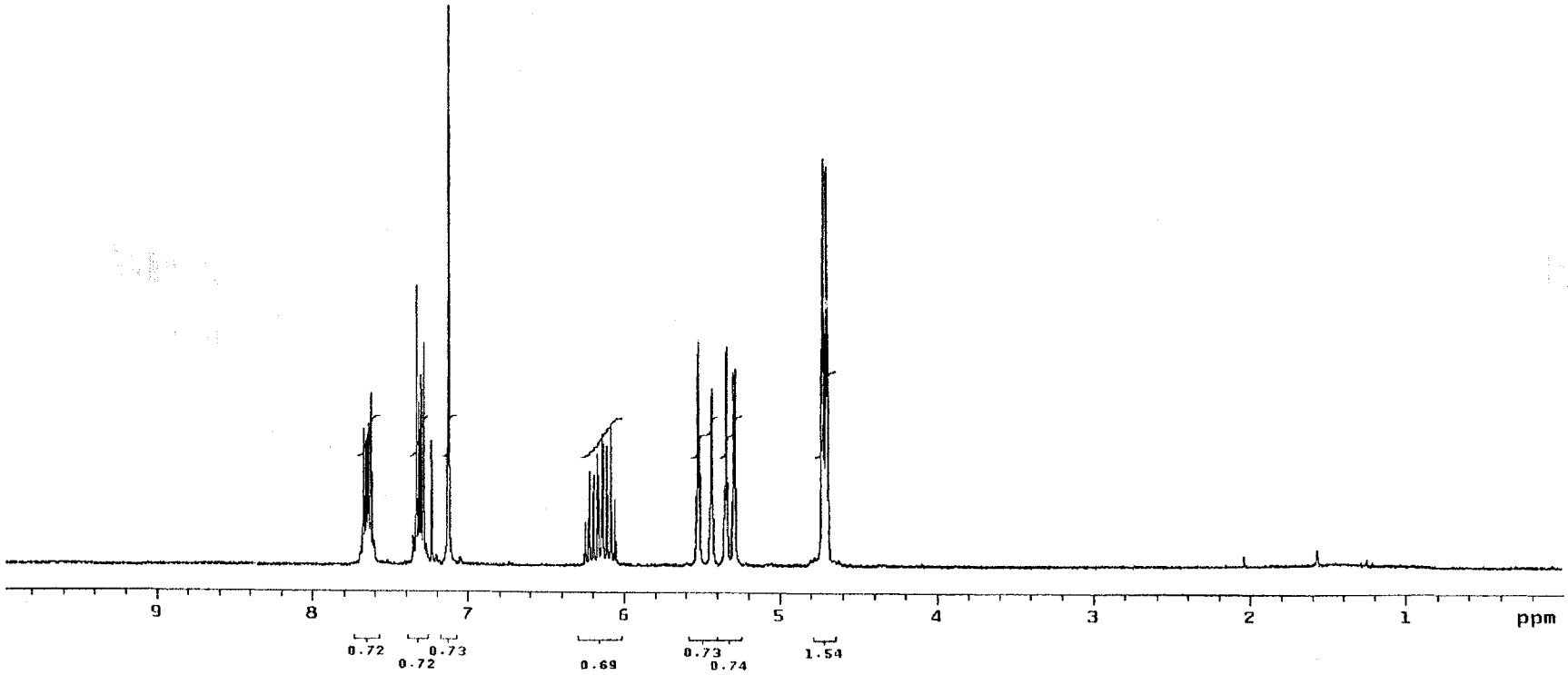
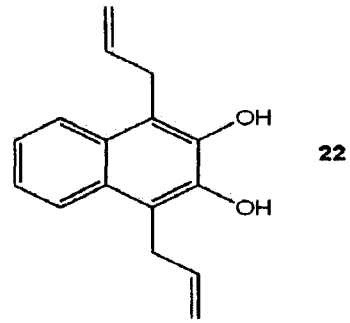


Figure 9: 200 MHz ^{1}H NMR of diallyl ether **21** in $CDCl_3$



22

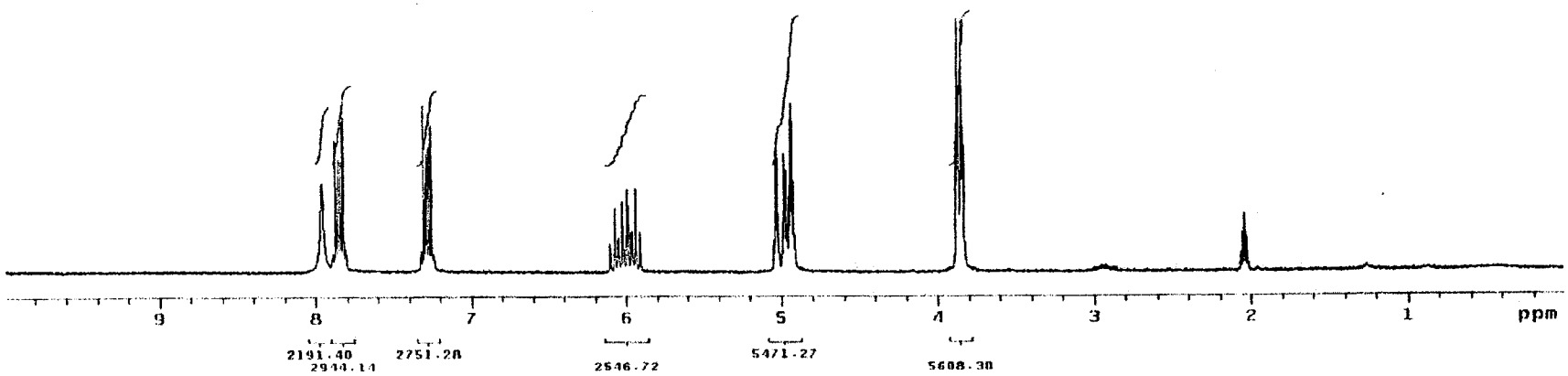


Figure 10: 200 MHz ^{1}H NMR of diol **22** in acetone-d_6

Structure **22** was proved by the disappearance of the H1 and H4 singlet at around 7.1 ppm (**Figure 9**) and the appearance of another singlet around 8 ppm corresponding to the two free OH groups in **22** (**Figure 10**). Hydrogenation of the resulting double bonds in **22** was performed by using Pd/C 30% in a hydrogen atmosphere, which provided the first potential antioxidant analogue **23** in 91% yield. The TLC showed essentially one spot, but a small greenish spot was also observed below the spot of **23**, indicating that this minor by-product was more polar than the desired diol **23**. After removing Pd/C by filtration through celite, the resulting greenish solution was washed with saturated sodium dithionite solution, which caused the color to change from green to pale yellow. This type of color change was also observed when *o*-quinones where reduced back to their respective catechols, indicating that the greenish by-product was possibly the *o*-quinone form of **23**. This observation was also supported by the fact that on TLC, the by-product spot was more polar than the desired diol **23**, characteristic of a more polar *o*-quinone than its corresponding diol, due to intramolecular hydrogen bonding in the diol form. This by-product was never isolated after silica gel chromatography of the crude product, indicating that this by-product was present in a very tiny amount. This was the only indication ever observed of possible *o*-quinone formation in this family of potential antioxidant. The ^{1}H NMR of **23** (**Figure 11**) showed the absence of olefinic protons around 5.0-6.5 ppm and the presence of two triplets and a sextuplet at the appropriate chemical shifts, characteristic of a propyl chain, due to complete hydrogenation of olefins in **22**.

The last step in the sequence illustrated in **Scheme 24** was the protection as acetates of diol **23**, which provided diacetate **24** (**Figure 12**) in reasonable yield. This step was necessary for the same reasons mentioned in subsection 2.1.

The calculated BDE_1 for **23** was 75 kcal/mol [27]. The introduction of linear alkyl groups into naphthalene-2,3-diol (**16**) had a slightly smaller effect than the same change in phenols. Since ortho *t*-butyl groups have a larger effect on phenols and have led to important antioxidants such as BHT (2,6-di-t-butyl-4-methylphenol), it was decided to attempt the preparation of 1,4-di-t-butyl-naphthalene-2,3-diol (**25**). This compound had a predicted BDE_1 between 74-75 kcal/mol, which is at the top edge of the design window.

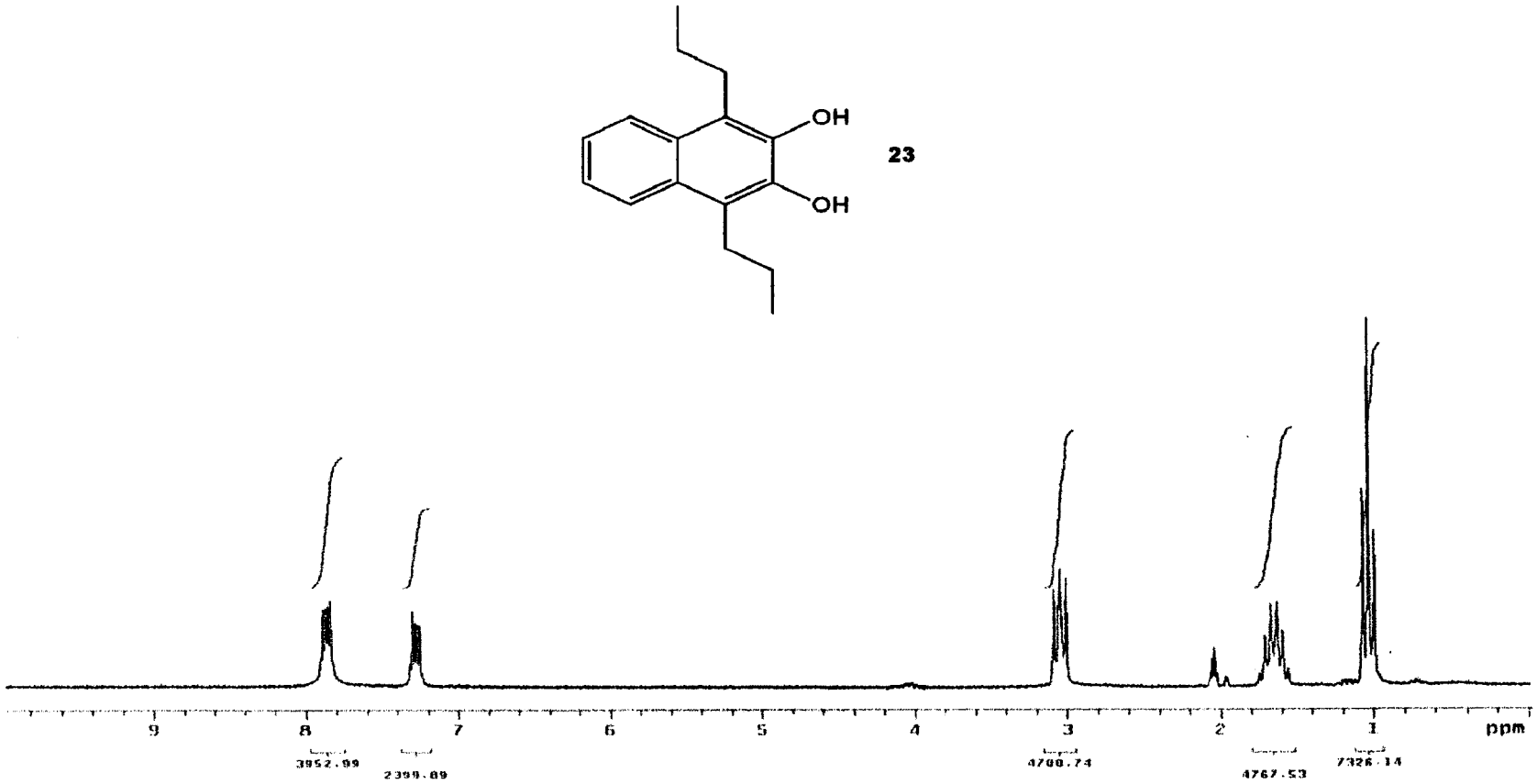


Figure 11: 200 MHz ^{1}H NMR of **23** in acetone-d_6

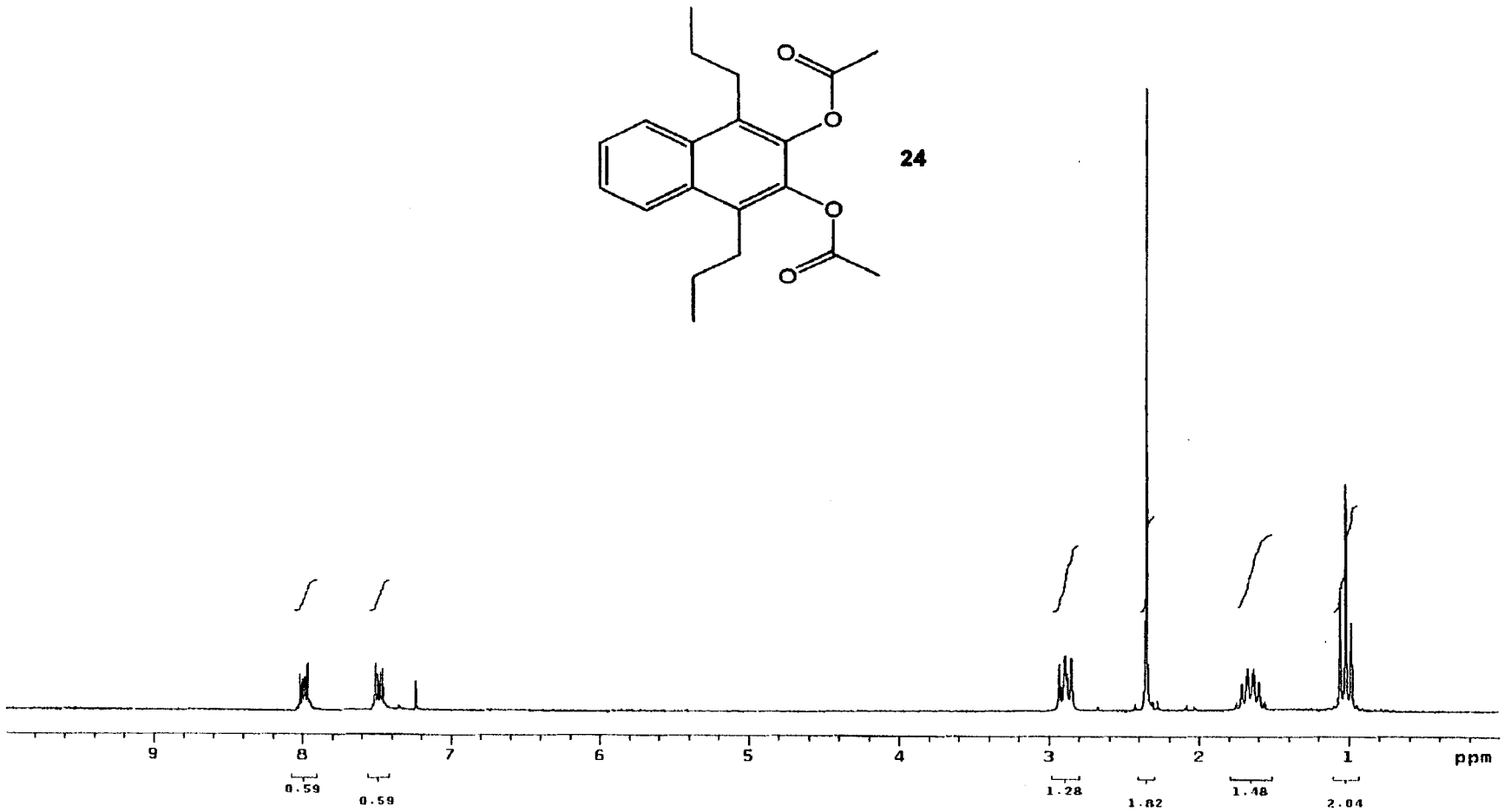
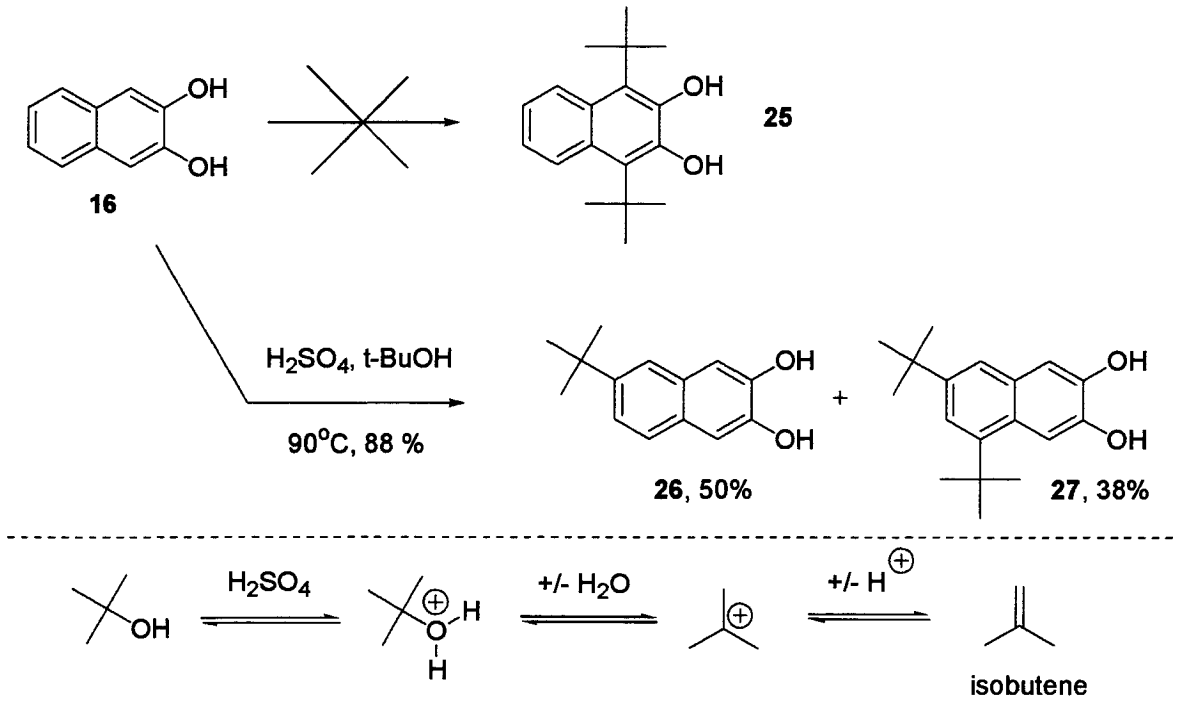


Figure 12: 200 MHz ^{1}H NMR of diacetate **24** in $CDCl_3$

As shown in **Scheme 26**, diol **16** was treated with *t*-butanol and concentrated sulfuric acid at 90°C in a closed thick glass bulb. This procedure was necessary to ensure that the pressure was high enough so that the electrophile was present in the solution, since the active electrophile in this reaction, *t*-butyl carbocation, is in equilibrium with its precursors, *t*-butanol and the gas isobutene. Unfortunately, the desired product **25** was not obtained, but a mixture of diols **26** and **27** were isolated after column chromatography as a 1.3/1 mixture, respectively.



Scheme 26: Attempt synthesis of 1,4-di-*t*-butyl-naphthalene-2,3-diol (**25**)

The ^1H NMR of diol **26** (**Figure 13**) showed a large singlet integrating for one *t*-butyl group, the presence of two singlets for H1 and H4 around 7.1-7.2 ppm, a doublet of doublets at around 7.3-7.4 ppm with J_o = 8.8 Hz and J_m = 2.0 Hz corresponding to H6 and two doublets for H5 (J_o = 8.7 Hz) and H8 (J_m = 2.0 Hz (overlapping between 7.5 and 7.6 ppm)) (**Scheme 27**). These data clearly showed that the *t*-butyl group in **26** was at C7.

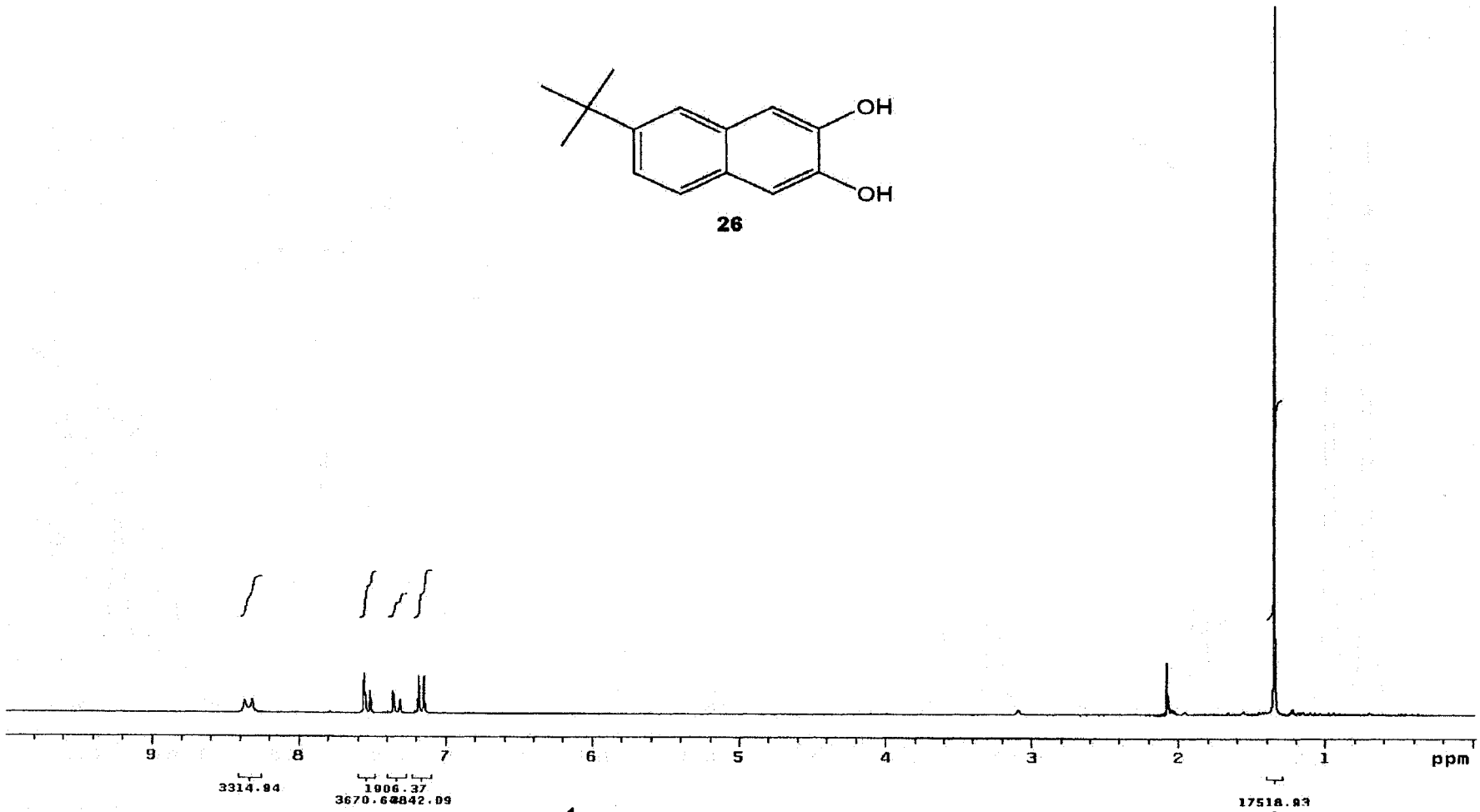
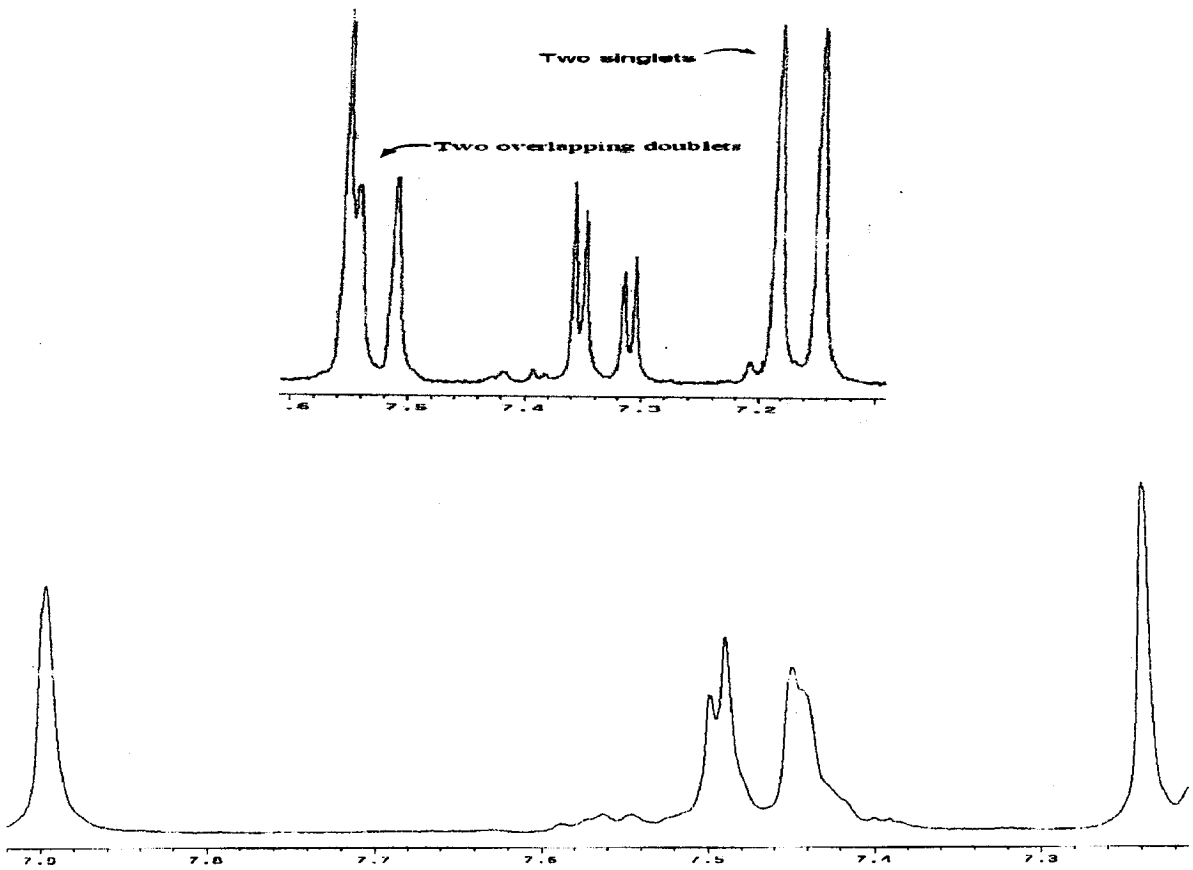


Figure 13: 200 MHz ^{1}H NMR of unexpected diol **26** in acetone-d_6



Scheme 27: Expanded aromatic region for diols **26** (top) and **27** (bottom)

For diol **27**, the presence of two large singlets around 1.5 ppm indicated the presence of two *t*-butyl groups. These were placed at C5 and C7, due to the two doublets around 7.4-7.5 ppm with J_m = 2.0 Hz (**Scheme 27**), and the C1 and C4 singlets at 7.2 and 7.9 ppm respectively (**Figure 14**). Apparently, introduction of the t-butyl groups at C1 and C4 is less favorable than into the less activated remote ring, likely for steric reasons.

The mass spectrum of **27** (**Figure 15**) showed a small peak at m/z = 328, which correspond to the introduction of three *t*-butyl groups. For this reason, the same reaction was carried out for a longer period of time with the hope of introducing additional *t*-butyl groups possibly at C1 and C4 (unlikely) (**Scheme 28**). Unfortunately, even after one week at 90°C, the TLC showed essentially the same mixture observed after 4h of reaction.

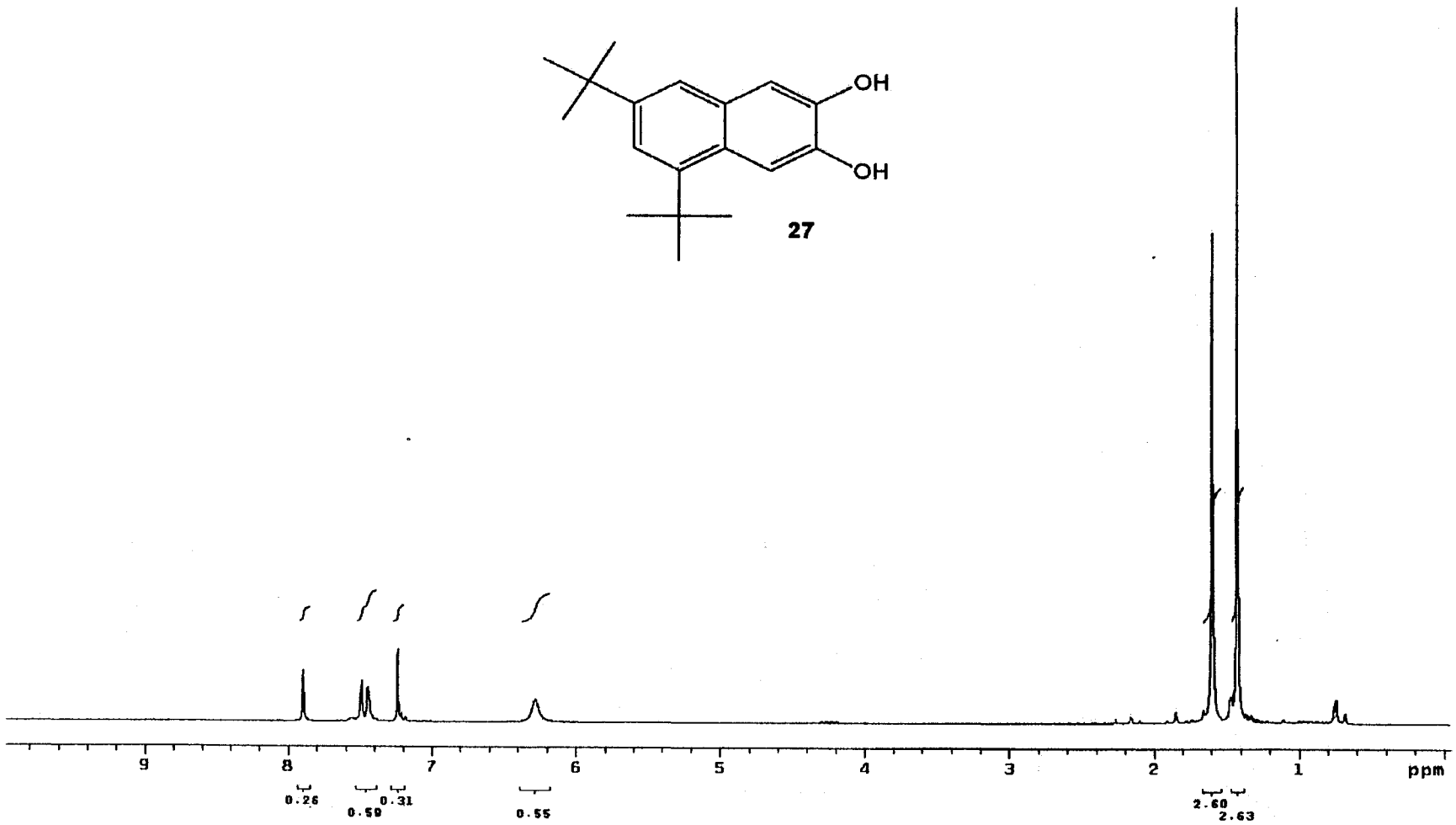


Figure 14: 200 MHz ^{1}H NMR of unexpected diol **27** in $CDCl_3$

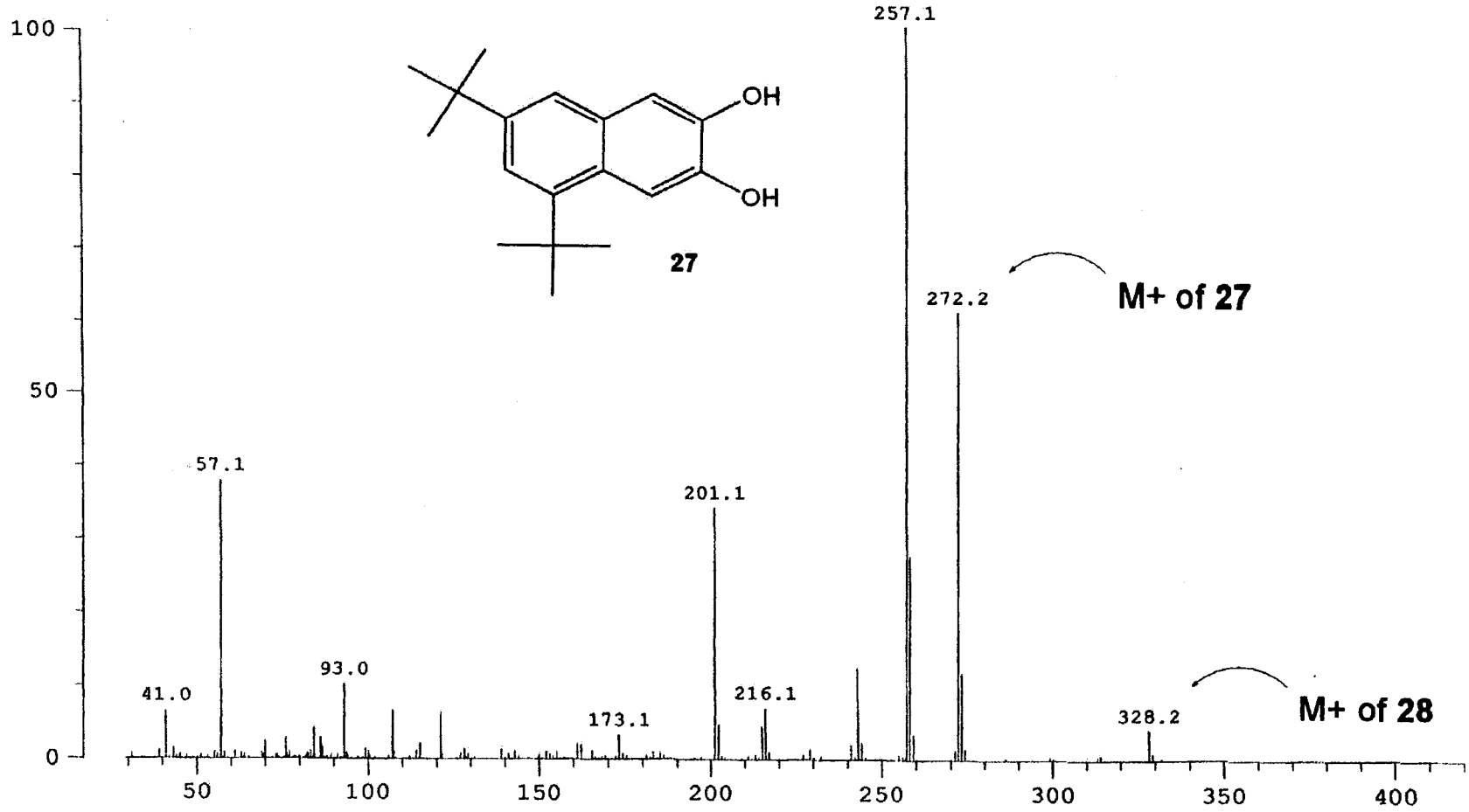
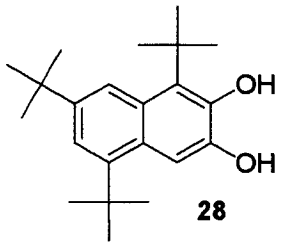


Figure 15: EI mass spectra of diol **27**, showing possible presence of diol **28**



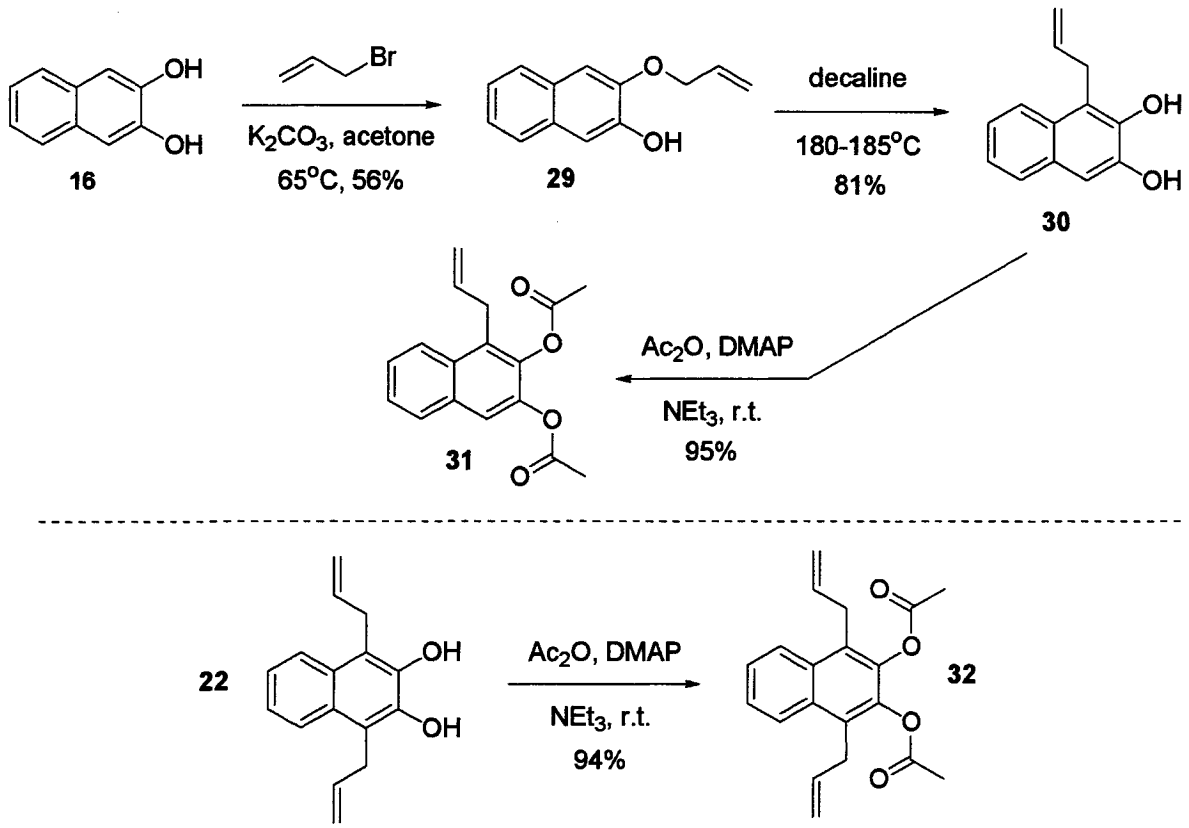
28

Scheme 28: Possible structure corresponding to the m/z = 328 peak observed in **Figure 15**

Compounds **26** and **27** were not considered as useful new antioxidants, since the effect of alkyl groups at C5 and C7 in naphthalene-2,3-diol should not decrease BDE_1 value enough to reach the design window.

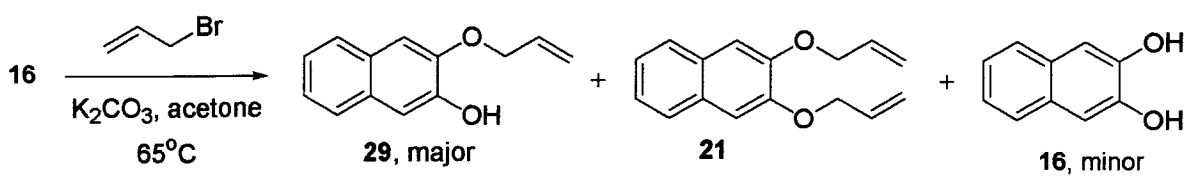
In planning this series of alkylated analogues, we also considered introducing only one alkyl chain ortho to the reactive OH groups in order to investigate the differences in reactivity and have the opportunity to change the hydrophobic character of the side chain. Since the alkylation of the starting material **16** followed by subsequent Claisen rearrangement worked well in the synthesis of diol **23**, the same pathway was followed for the introduction of only one propyl chain.

As shown in **Scheme 29**, the first step was the allylation of only one OH group accomplished by the same way used in the synthesis of diol **23**, but this time, only one equivalent of allyl bromide was used. This provided mono-allyl ether **29** in 56% yield. The ^1H NMR of **29** (**Figure 16**) showed the same kind of pattern for the allyl double bond. A singlet around 6.0 ppm, corresponding to the free OH group left, was present within the multiplet corresponding to the olefinic hydrogens.

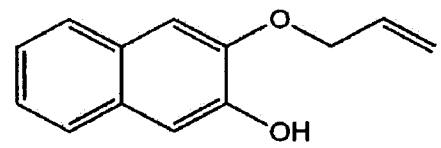


Scheme 29: Synthesis of 1-allyl analogue **30** and diacetates **31** and **32**

Furthermore, the aromatic protons did not showed the same symmetry pattern present in **Figure 9**, since two singlets, corresponding to H1 and H4, were present. As expected, compound **29** was not the only product obtained in this reaction. TLC showed a mixture of the desired product **29**, starting material **16** and diether **21** (**Scheme 30**). Careful column chromatography was required in order to isolate pure mono-allyl ether **29**.



Scheme 30: Mixture produced in the allylation of **16** with 1eq of allyl bromide



29

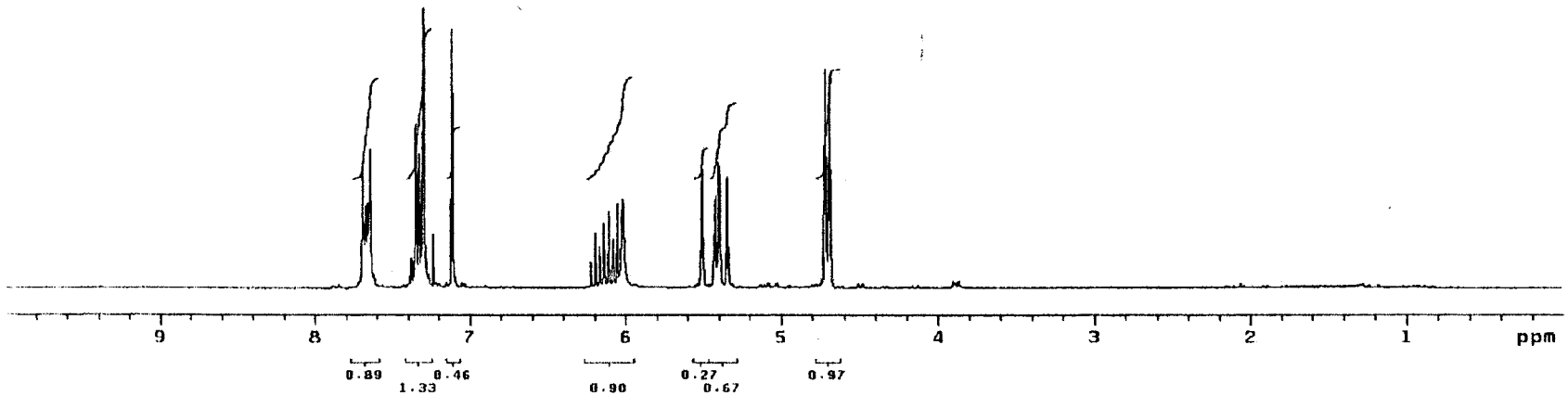


Figure 16: 200 MHz ^{1}H NMR of mono-allyl ether **29** in $CDCl_3$

Claisen rearrangement of **29** gave the diol **30**, again along with some tarry by-product. The ^{1}H NMR of diol **30** (**Figure 17**) showed only one singlet, corresponding to H4, compared to two singlets in compound **29**. This feature proved that the allyl group was now at C1.

Acetylation of diols **22** and **30** provided an excellent yield of diacetates **31** and **32** (**Scheme 29**). Two large singlets around 2.4-2.5 ppm (**Figure 18**) and only one around 2.5 ppm (**Figure 19**) proved the presence of acetate groups in compounds **31** and **32**, respectively.

As discussed in the introduction, the *in vivo* reactivity of an antioxidant is not only correlated with its ability to quench free radicals in organic solutions, but also to its lipophilicity. For future investigation on the effect of the lipophilicity of this new family of antioxidants, we decided to generate one compound with a more hydrophilic side chain and another with a more lipophilic side chain compared to diol **30**. We reasoned that the C1 substituent in **36** would increase the lipophilicity of the carbon side chain. Additionally, it should mimic the phytyl chain of Vitamin E. The preparation of this lipophilic analogue is outlined in **Scheme 31**.

Protection of the phenolic hydroxyl groups in **30** with MOM-Cl and N, N-diisopropylethylamine provided diether **33** in 80% yield. The presence of four large singlets in ^{1}H NMR of diether **33** (**Figure 20**), two of them around 5.2-5.4 ppm corresponding to the two CH_2 groups in MOM groups and two more around 3.5-3.7 ppm corresponding to the two CH_3 groups, proved that both OH groups were protected.

Hydroboration of **33** was accomplished using sodium borohydride and $BF_3{\cdot}OEt_2$ followed by sodium hydroxide and hydrogen peroxide. This afforded an 85% yield of the desired primary alcohol **34** (**Figure 21**).

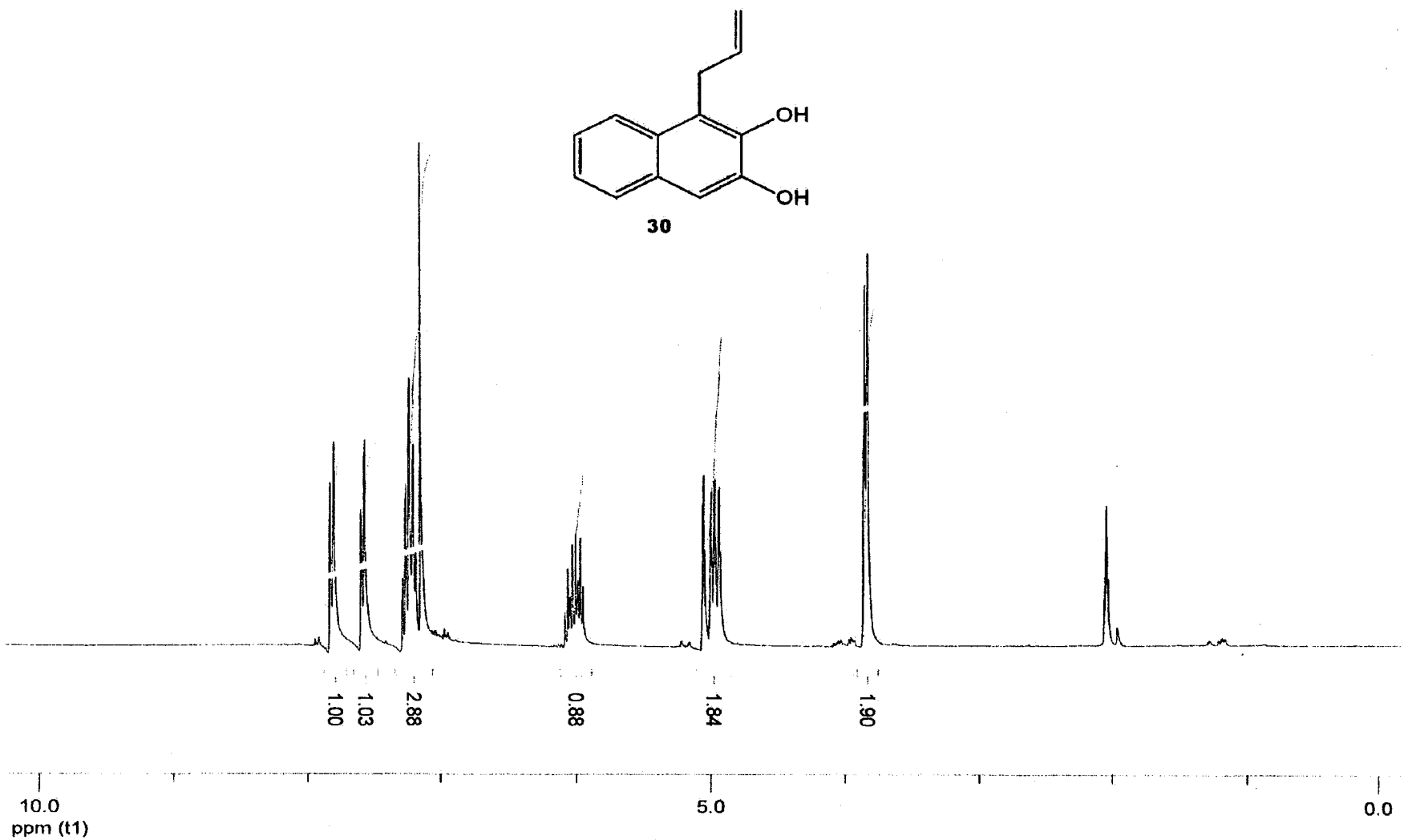


Figure 17: 300 MHz ^{1}H NMR of diol **30** in acetone-d_6

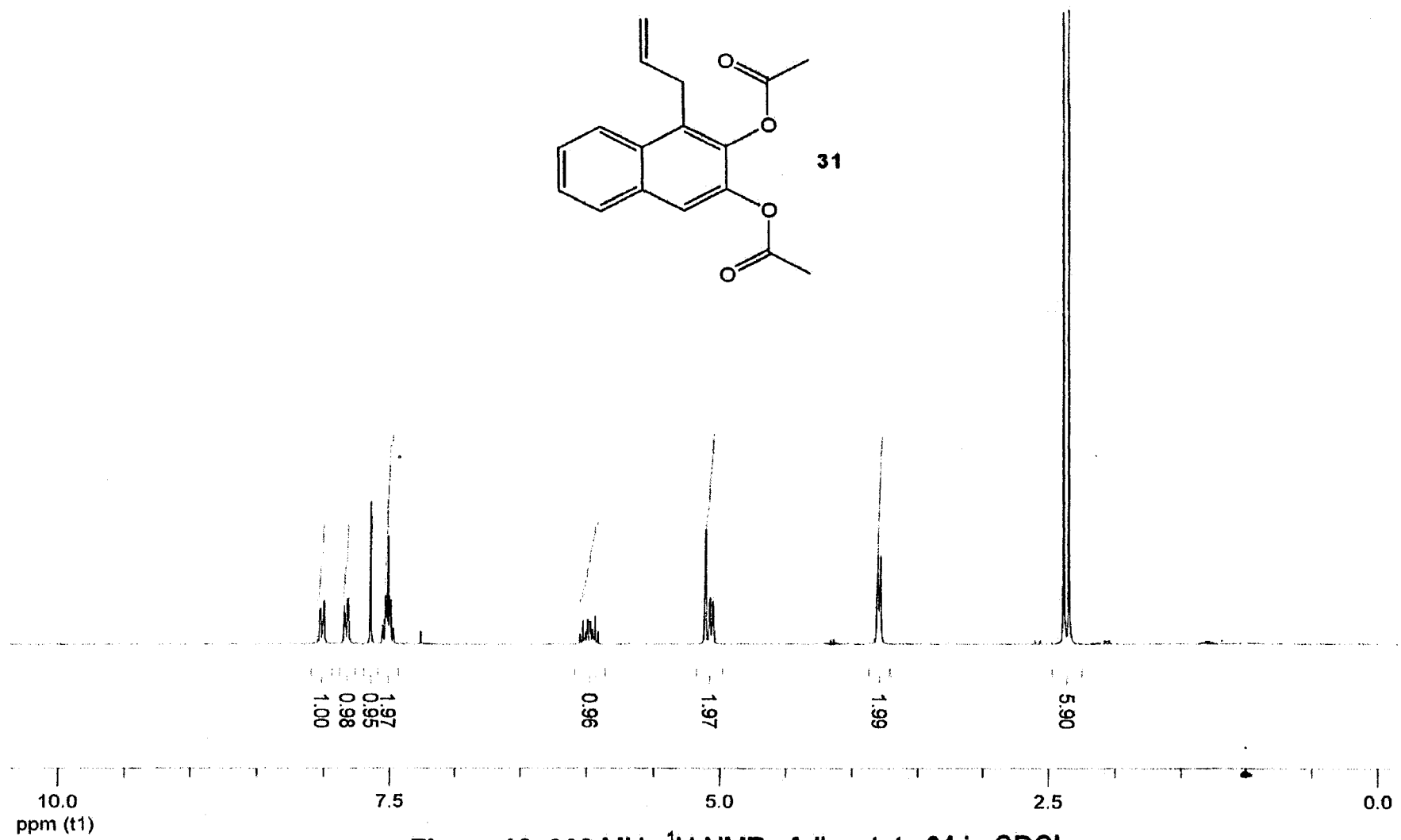


Figure 18: 300 MHz ^{1}H NMR of diacetate **31** in $CDCl_3$

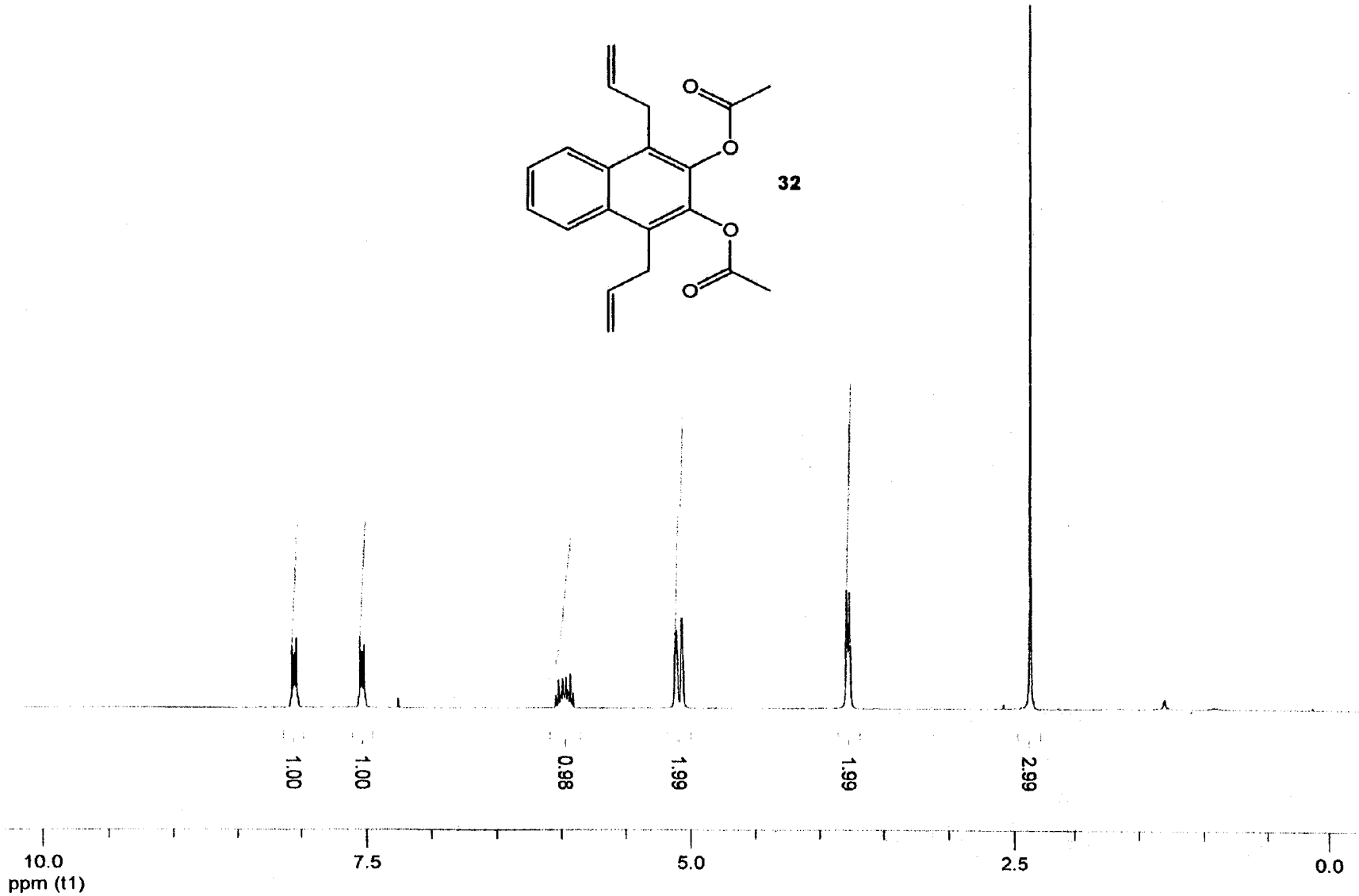
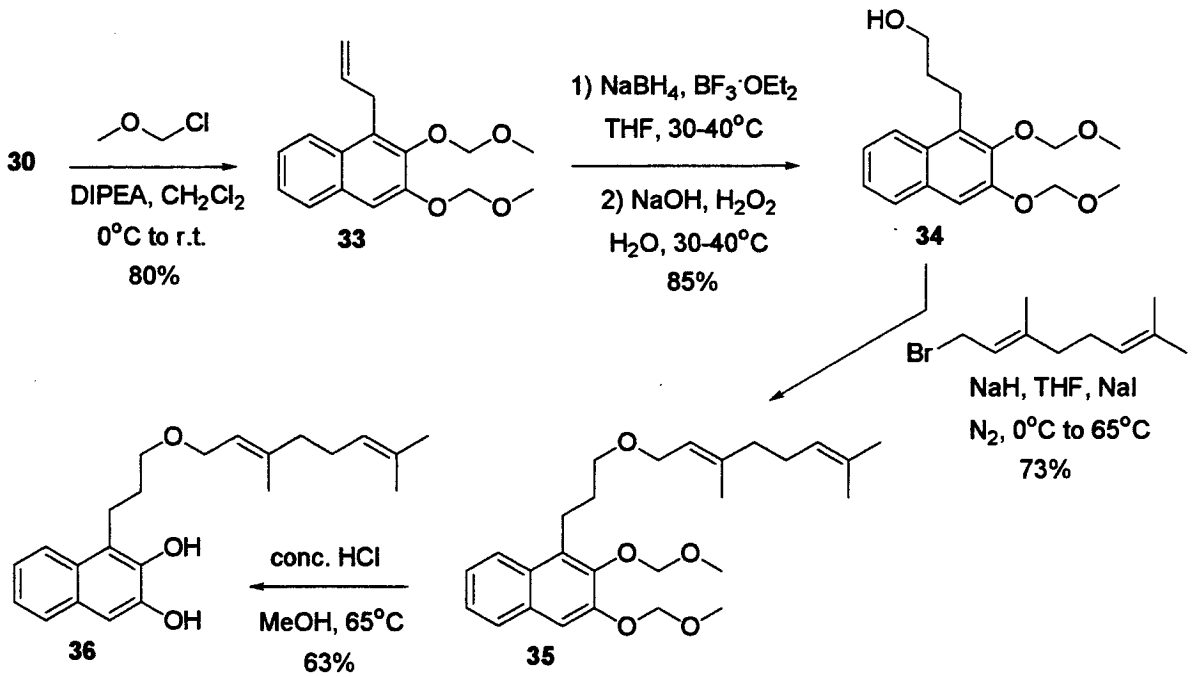


Figure 19: 300 MHz ^{1}H NMR of diacetate **32** in $CDCl_3$



Scheme 31: Preparation of lipophilic analogue **36**

Alkylation of **34** was carried out using NaH in THF to generate the alkoxide anion followed by the addition of geranyl bromide, and a catalytic amount of sodium iodide, which afforded the desired product **35** (**Figure 22**) in 73% yield.

Deprotection of the MOM groups in **35** regenerated the very important 1,2-diol functionality. This was accomplished by using a solution of 5% conc. HCl in methanol at 65°C, which provided the target diol **36** in 63% yield. The ^1H NMR of diol **36** (**Figure 23**) showed two singlets, one around 6.2 ppm and the other around 8.7 ppm corresponding to the two free OH groups in **36**. The spectrum also showed all the required features of **36** including three C-methyl groups and the two CH_2's flanking the ether oxygen. The relatively low yield of this reaction was attributed to an unwanted decomposition of the product under the reaction conditions. Indeed, when the reaction was left more than one hour, the TLC started to show the appearance of two more spots, one less polar than the starting material **35** and one more polar.

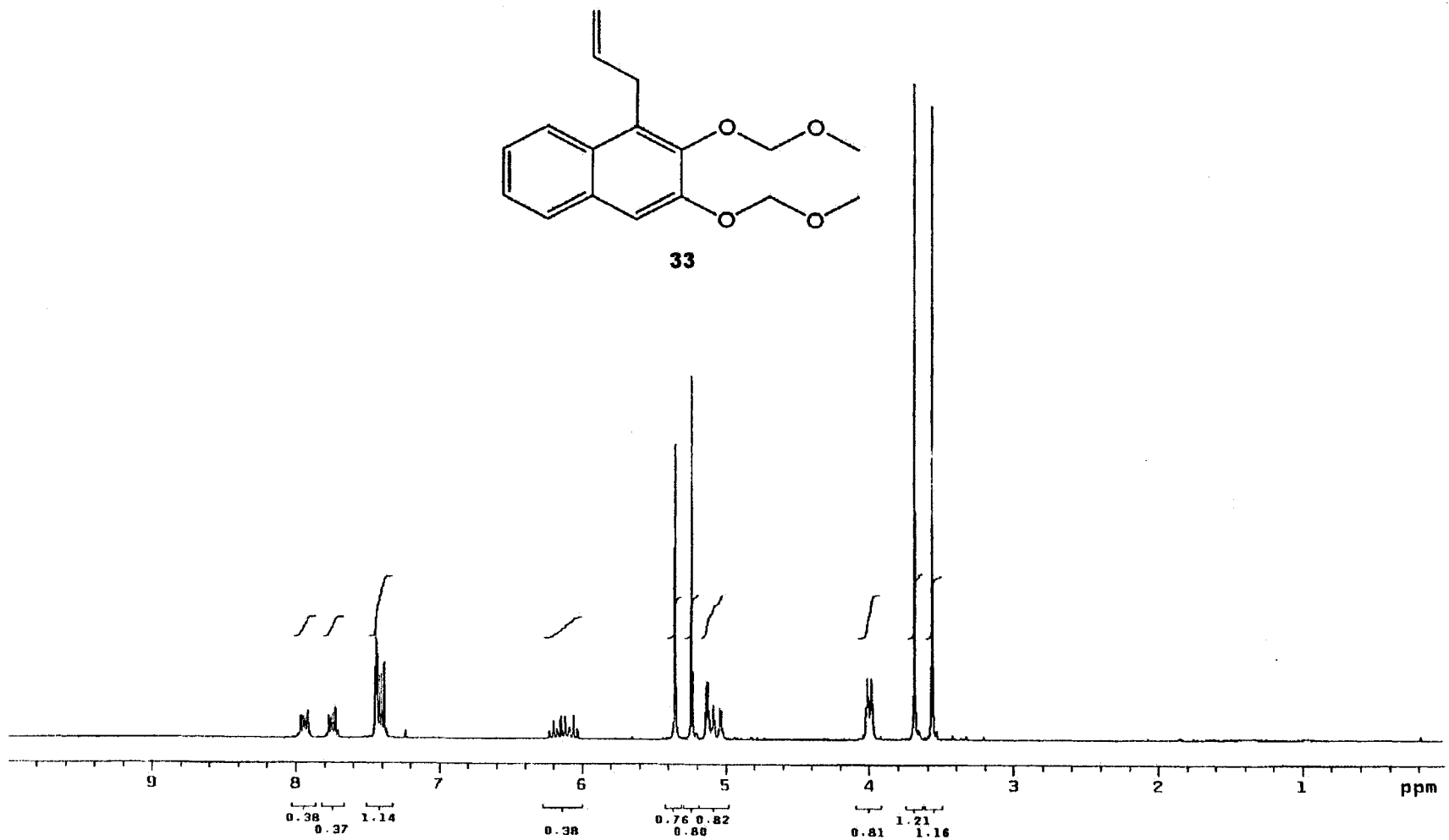


Figure 20: 200 MHz ^{1}H NMR of diether **33** in $CDCl_3$

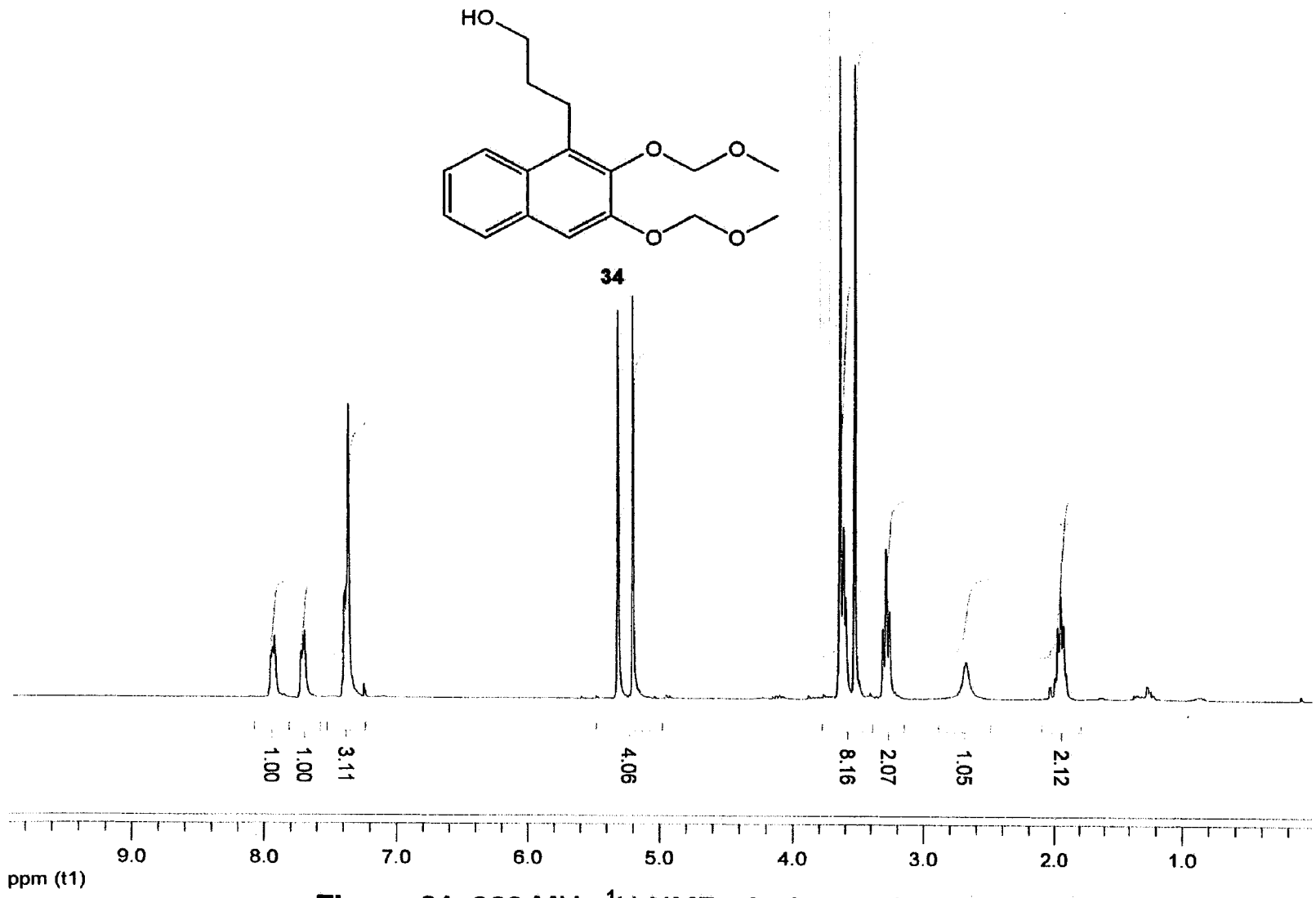


Figure 21: 300 MHz ^{1}H NMR of primary alcohol **34** in $CDCl_3$

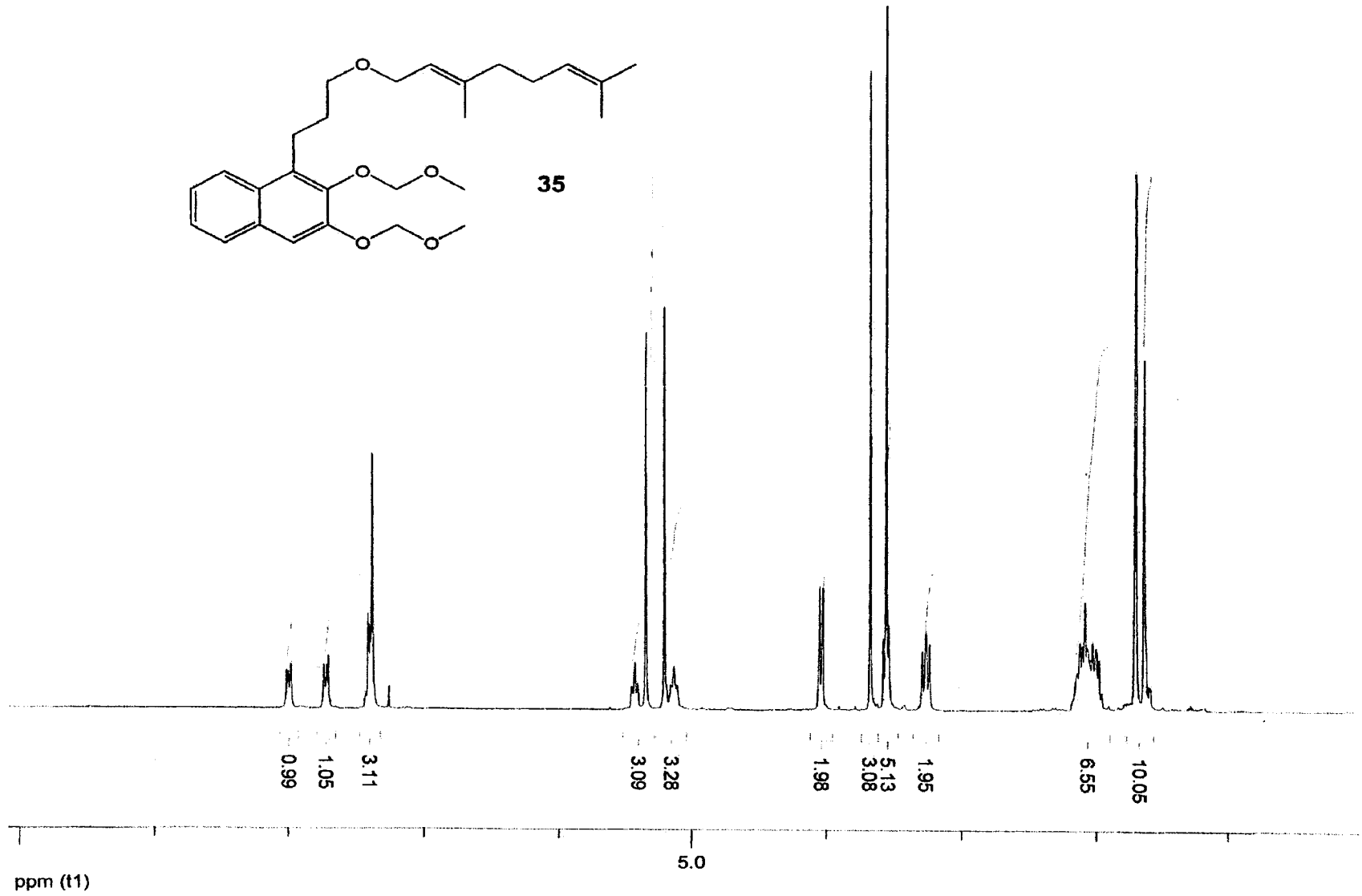


Figure 22: 300 MHz ^{1}H NMR of **35** in $CDCl_3$

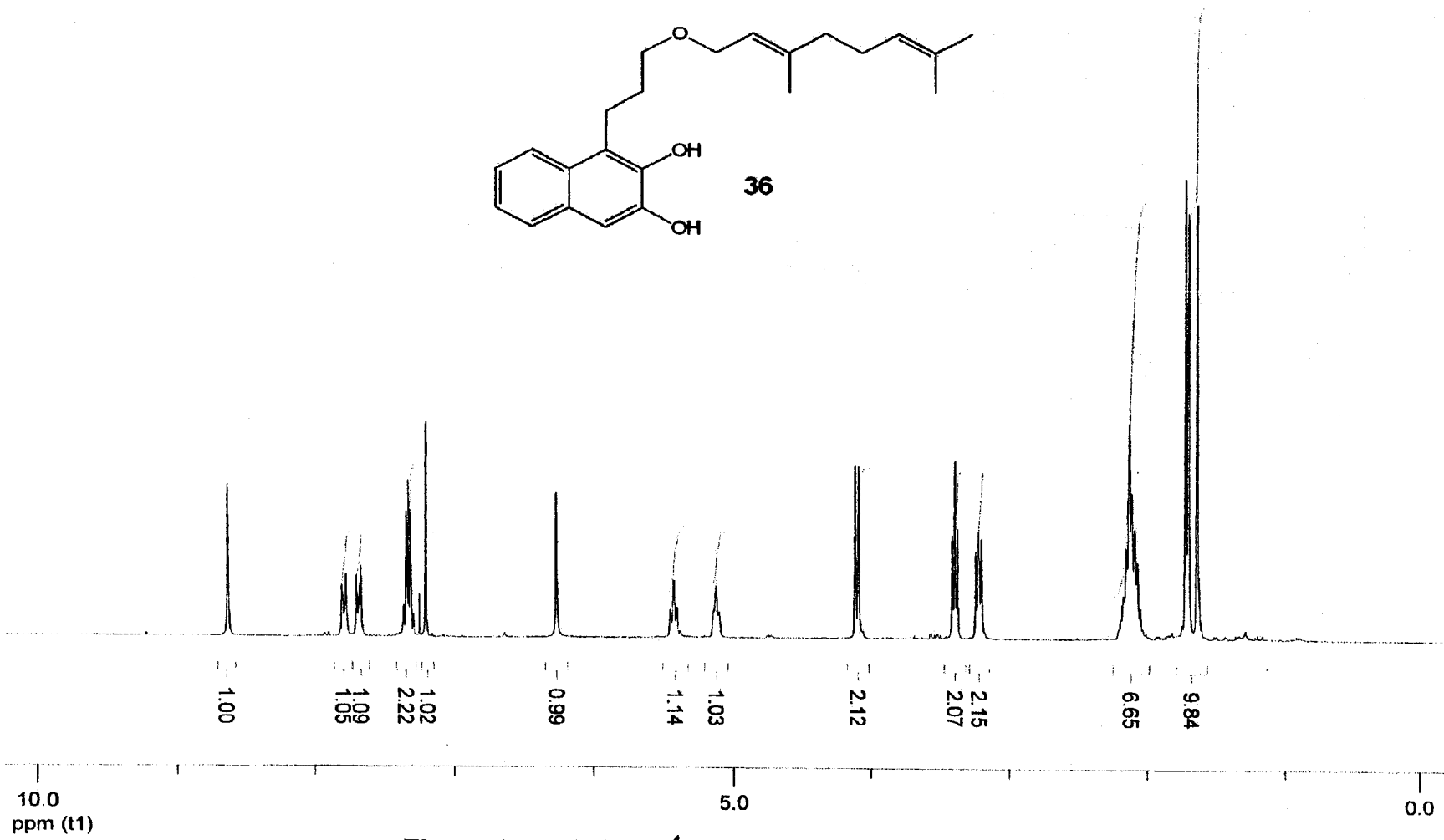
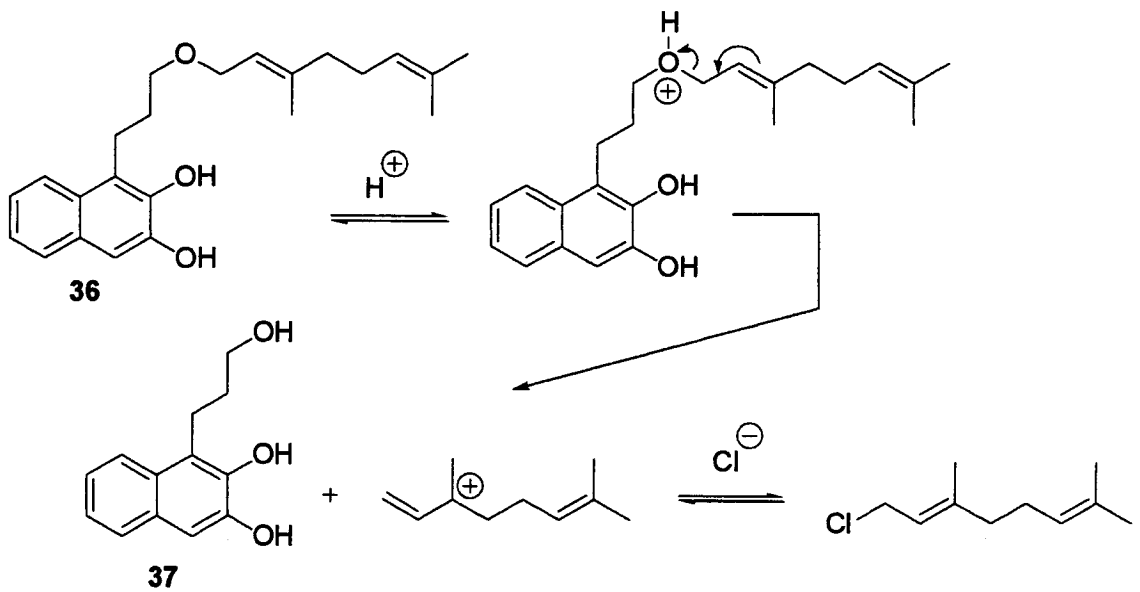


Figure 23: 300 MHz ^{1}H NMR of analogue **36** in $CDCl_3$

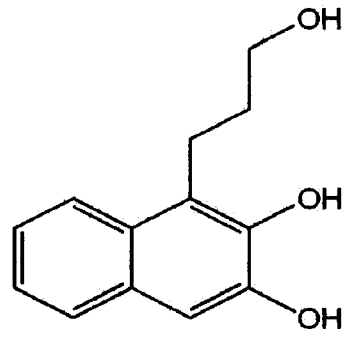
The R_f of the non-polar spot was similar to that of geranyl bromide, which suggested cleavage of the geranyl ether side chain in acidic conditions to yield geranyl chloride and compound **37**, corresponding to the more polar side product on TLC. The close proximity of one alkene function on the geranyl side chain during the ether cleavage could support a mechanism by which a stabilized carbocation is formed (**Scheme 32**).



Scheme 32: Proposed mechanism by which side-product **37** is formed

Finally, due to the expected high lipophilicity of the geranyl side chain in analogue **36**, it was thought that acetylation of its 1,2-diol functionality would not be required for cell incorporation.

The likely formation of compound **37**, according to TLC, in the final step of the synthesis of diol **36** suggested that MOM deprotection of primary alcohol **34** would be a simple route to the more hydrophilic antioxidant **37** (**Scheme 33**). Deprotection of **34** was accomplished the same way as in the MOM deprotection of compound **35**; this provided the expected product **37** (**Figure 24**) in 80% yield.



37

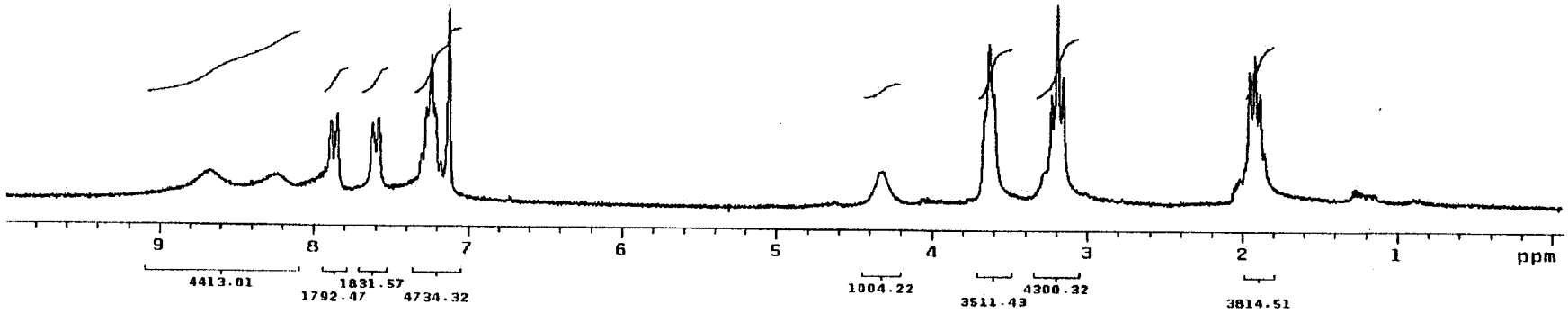
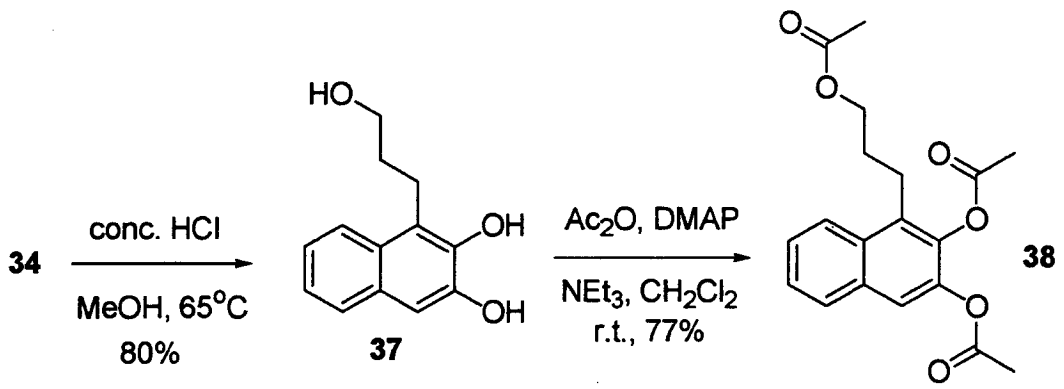


Figure 24: 200 MHz ^{1}H NMR of analogue **37** in acetone-d_6



Scheme 33: Synthesis of hydrophilic analogue **37**, and its triacetate version **38**

Acetylation of **37**, using the same procedure as in the acetylation of catechols, provided triacetate **38** in 77% yield. This structure was proved by the appearance of three large singlets between 2.0-2.5 ppm, characteristic of the methyl groups in acetates in the ^{1}H NMR of triacetate **38** (**Figure 25**). The relatively low yield of 77% was correlated to the relative instability or purity of the starting material **37**, which tend to gained some reddish color on storage. One evidence of the questionable purity of **37** was in the mass spectrum (**Figure 26**), which was taken 5 days after the reaction was conducted. This spectrum showed a peak at m/z = 252 which indicated the presence of one chlorine (natural abundance: 75% ^{35}Cl and 25% ^{37}Cl) in the side-product, since there is also the presence of a peak at m/z = 254 which is almost 1/3 the height of the previous one. This feature tends to support the impurity of the starting material **37**, compared to the change of color which tends to support the instability of **37**, possibly caused by air oxidation.

Since we anticipated that the calculated BDE_1 value of these alkylated analogues would probably be around 74-75 kcal/mol, it was thought that installing an electron-donor group, like a methoxy group, at C6 or C7 of these analogues would decrease the BDE_1 value further into the design window and consequently increase their reactivity against free radicals.

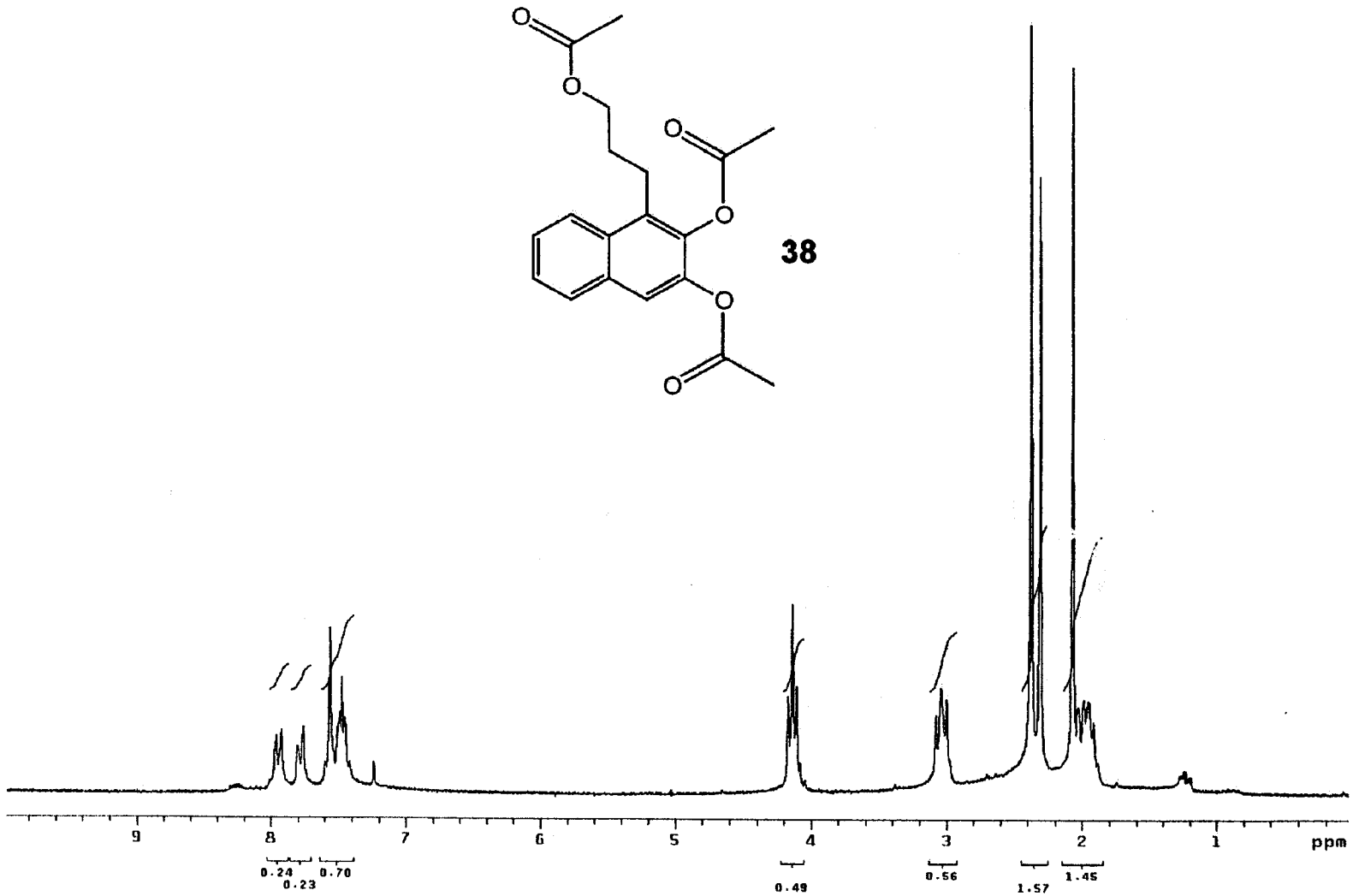


Figure 25: 200 MHz ^{1}H NMR of triacetate **38** in $CDCl_3$

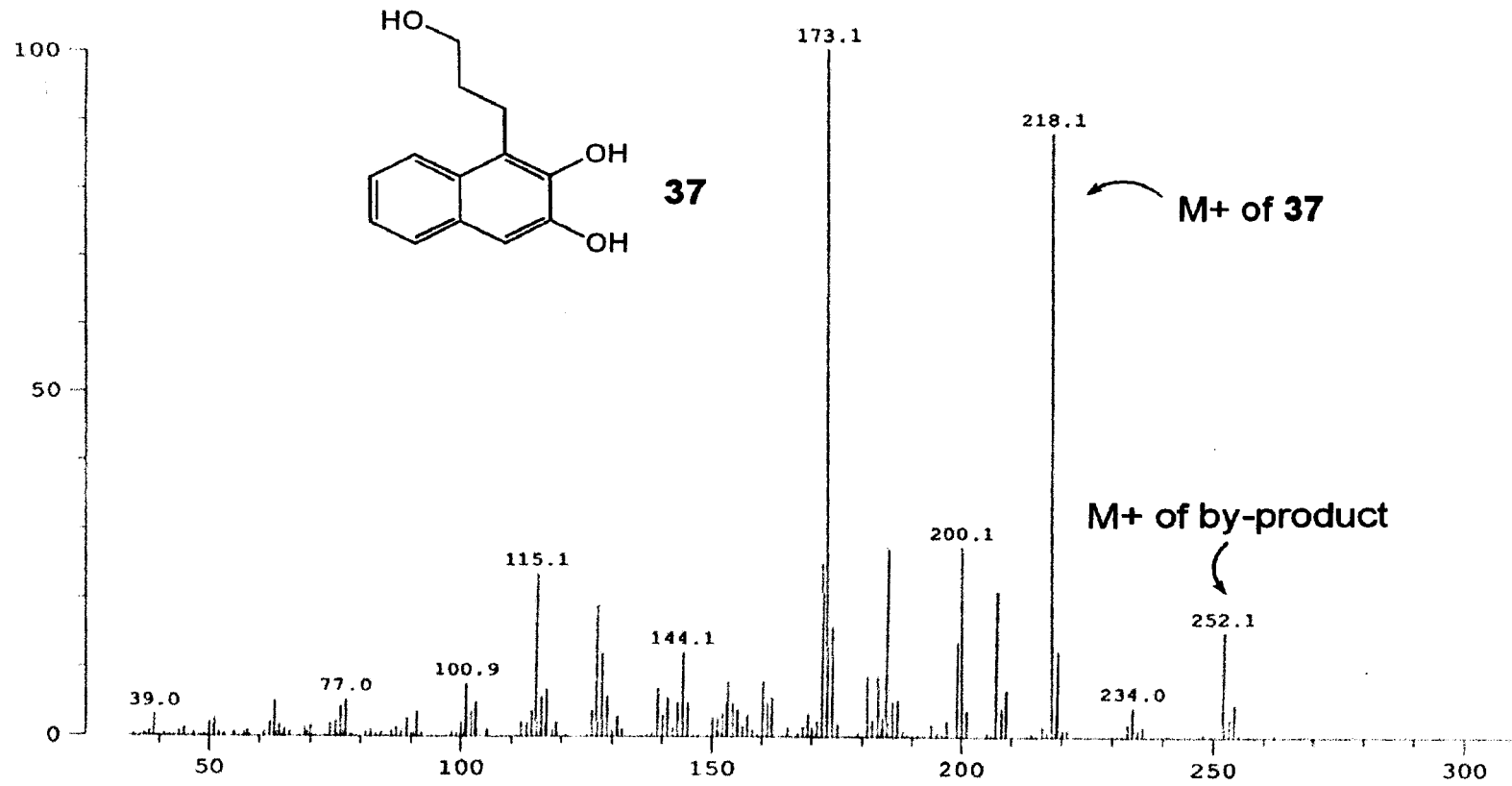
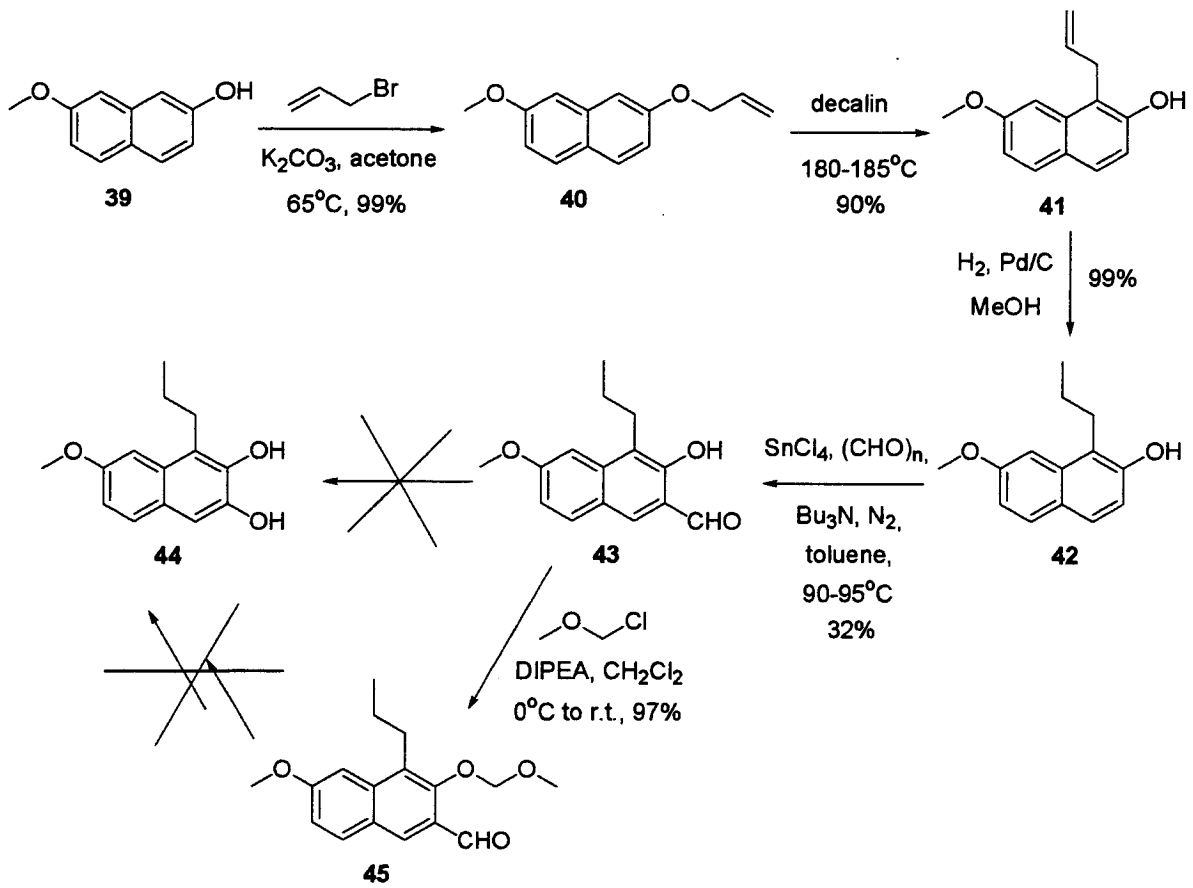


Figure 26: Mass spectrum of analogue **37**, showing evidence of possible by-product

The commercially available 7-methoxy-2-naphthol **39** was chosen as the starting material for the designed target **44**. The proposed route from **39** to **44** is shown in **Scheme 34**.



Scheme 34: Attempted synthesis of **44**

O-allylation of **39** gave mainly the desired allylether **40**. The mass spectrum of **40** (**Figure 27**) indicated the formation of some C1 and O-allylated products, similar to that observed in earlier allylation of naphthalene-2,3-diol (**16**) (**Scheme 25**). This by-product must be quite minor since the ^{1}H NMR of the product (**Figure 28**) showed that the integration of the low field vinyl hydrogen signal (6.0-6.5 ppm) vs the methoxy group was close to the expected 1:3 for **40** and not 2:3 for the doubly allylated by-product.

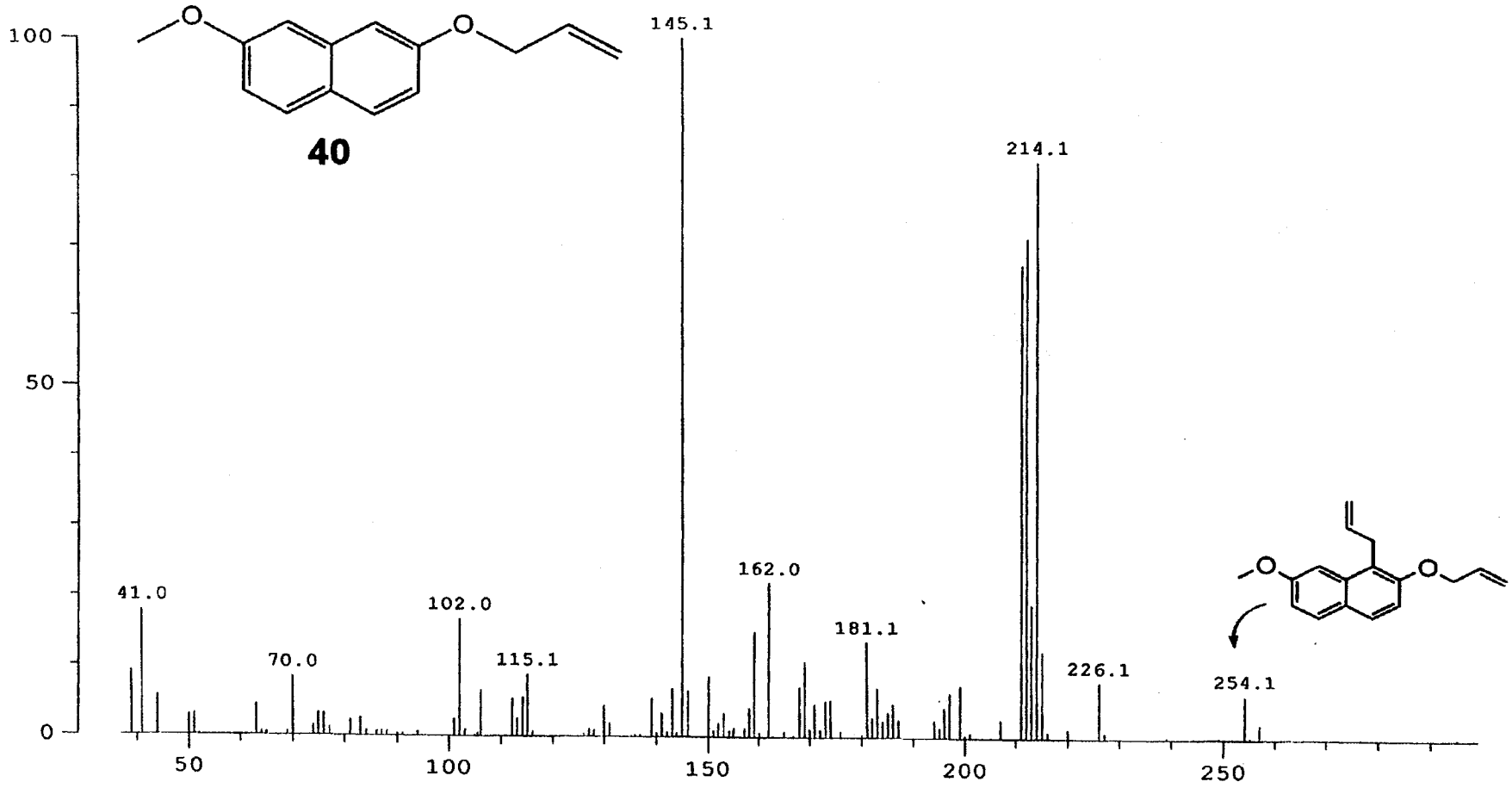


Figure 27: Mass spectrum of allylether **40**, showing evidence of by-product

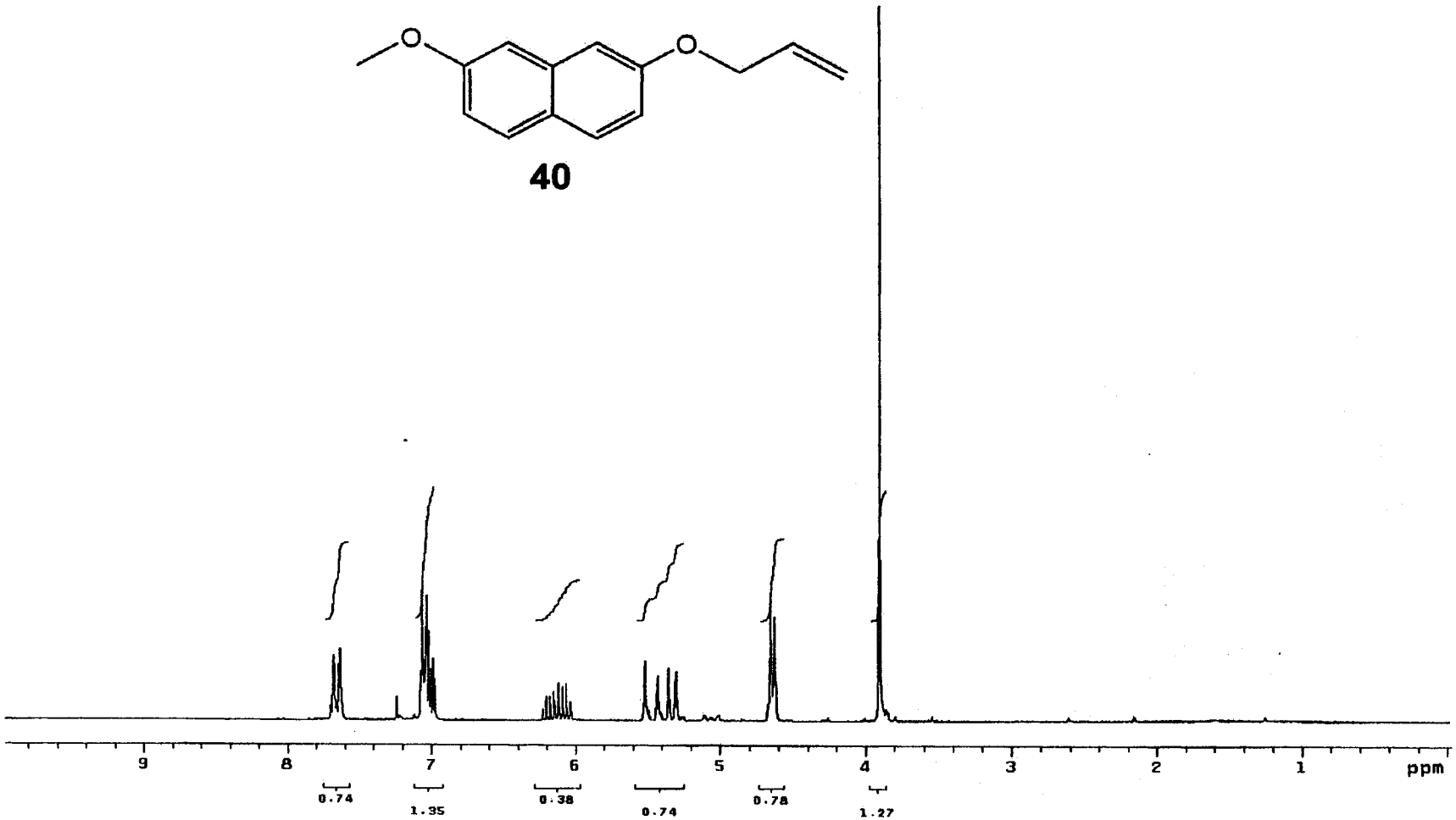


Figure 28: 200 MHz ^{1}H NMR of allylether **40** in $CDCl_3$

Furthermore, **40** underwent the expected Claisen rearrangement to form **41** in 90% isolated yield. Since this product contained only one OH group, the work-up and purification was little easier than in the other Claisen rearrangement reactions explained so far, because the crude was brought to the aqueous phase with aq. 10% NaOH solution, reacidified and extracted; which reduced the effect of the production of tarry matter on the purification. The ^{1}H NMR of **41** (**Figure 29**) showed all the expected peaks. Hydrogenation of **41** to **42** using H_2, Pd/C 30% in methanol gave **42** in quantitative yield. Again, the ^{1}H NMR (**Figure 30**) confirmed the structure.

The first few steps of **Scheme 34** proceeded with very high yields, as expected, since these steps were analogous to those used in the preparation of **23**. Unfortunately, the last two steps were more problematic. *o*-Formylation provided the expected aldehyde **43**, but the best yield obtained was only 32%. When the reaction was conducted on a larger scale (5.4g of **42**), with a larger excess of paraformaldehyde (5eq) and larger amounts of tin tetrachloride (0.5eq), the yield dropped as low as 7%. Furthermore, when the reaction mixture was heated to reflux temperature (120°C), some of the paraformaldehyde evaporated and then condensed and remained stuck in the condenser, resulting in less paraformaldehyde available for the reaction. Similar low yields were reported by Hussain et al. [18] in the synthesis of their catechol antioxidants. The presence of the desired aldehyde functionality in **43** was easily demonstrated by the singlet around 9.8 ppm in the ^{1}H NMR of **43** (**Figure 31**). Furthermore, the singlet around 10.7 ppm, corresponding to the OH proton, showed that the aldehyde functionality was ortho to the OH group.

Baeyer-Villiger type conversion of **43** to **44** was unsuccessful under a variety of reaction conditions, including those that were successful in other compounds studied previously by our group [18]. The attempts are summarized in **Table 8**.

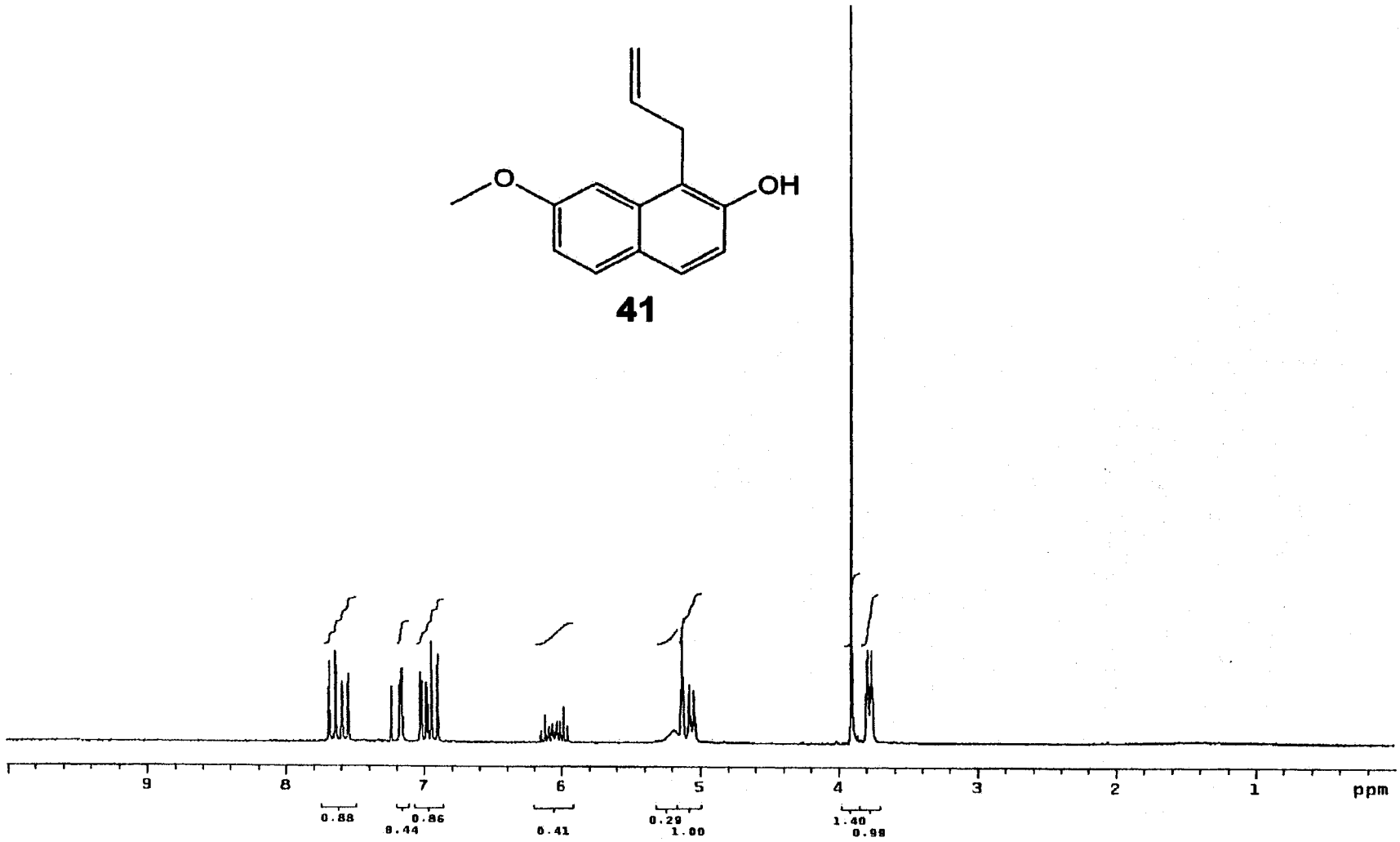


Figure 29: 200 MHz ^{1}H NMR of alcohol **41** in $CDCl_3$

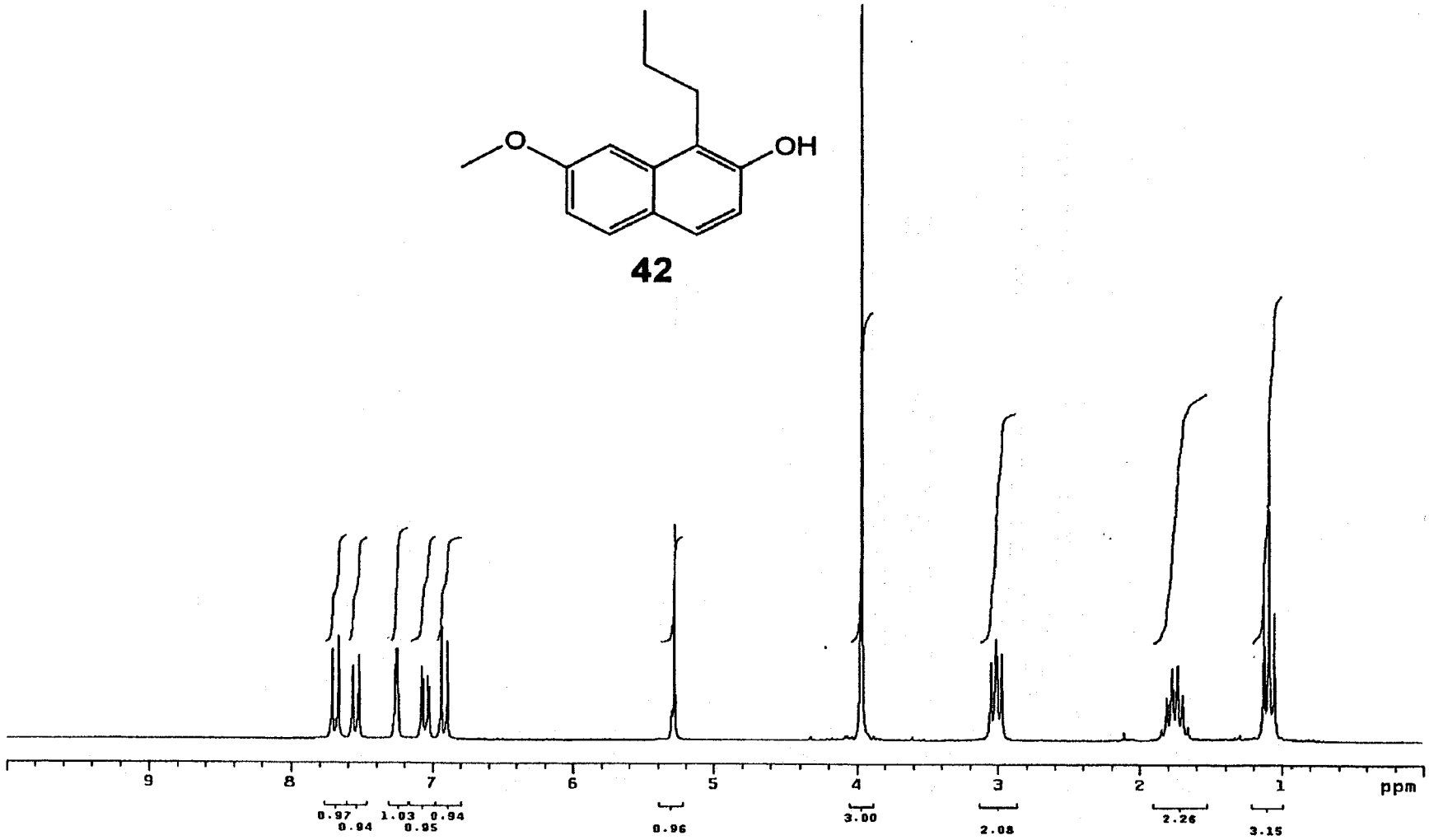
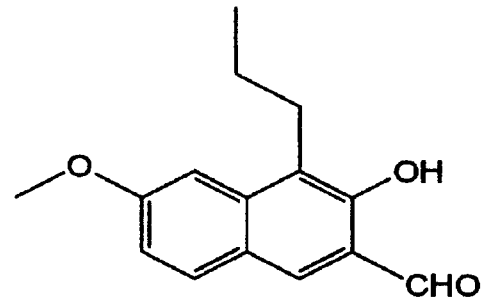


Figure 30: 200 MHz ^{1}H NMR of naphthol **42** in $CDCl_3$



43

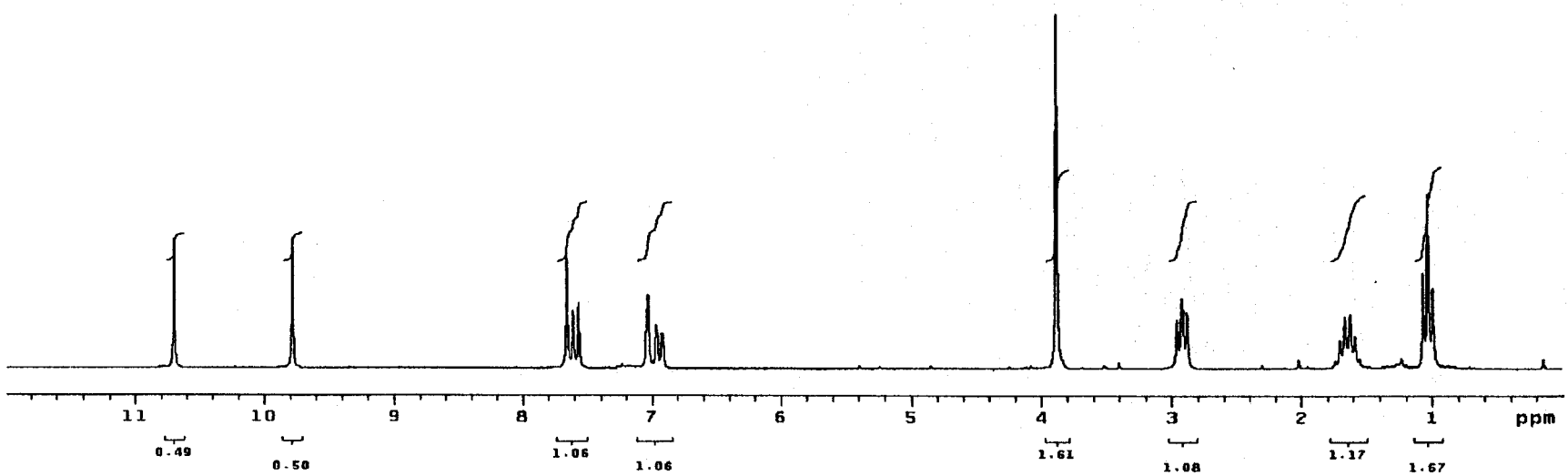


Figure 31: 200 MHz ^{1}H NMR of aldehyde **43** in $CDCl_3$

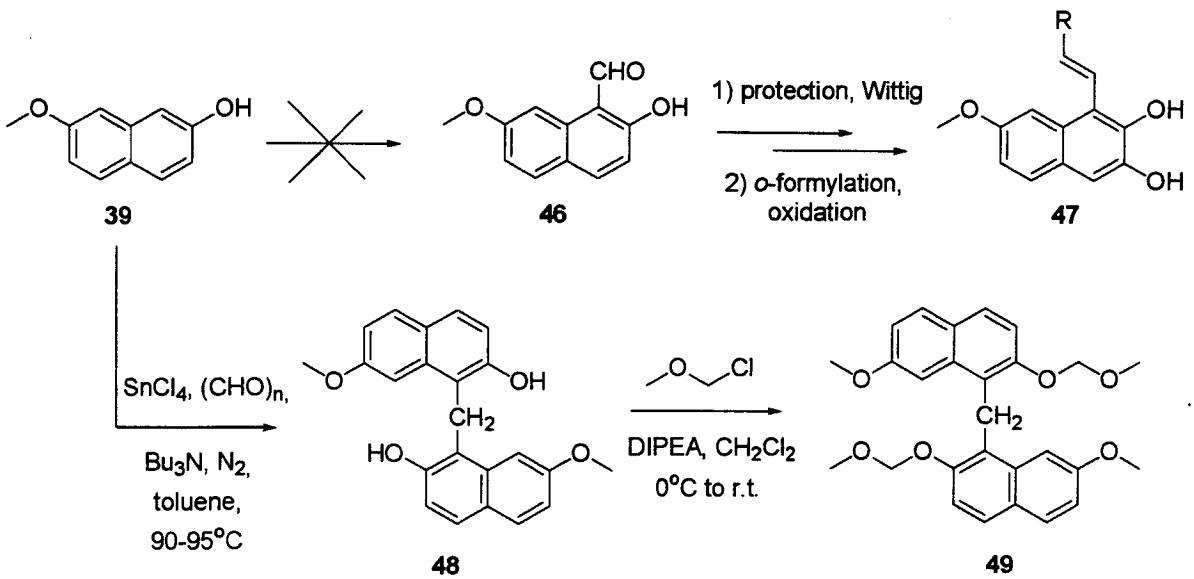
Attempts	S. M.	Reagents	Solvents	Temperature (°C)	Reaction time	TLC appearance
1	**43**	H_2O_2 30%, 0.36eq NaOH, 1eq	9/1 H_2O/THF	30	1h	S.M.
2	**43**	H_2O_2 30%, 1.2eq NaOH, 1eq	9/1 H_2O/THF	30	overnight	S.M.
3	**43**	H_2O_2 30%, 1.2eq NaOH, 1eq	1/9 H_2O/THF	30	overnight	S.M.
4	**43**	H_2O_2 30%, 1.2eq NaOH, 1eq	9/1 H_2O/THF + 4mL EtOH	30	overnight	Several spots after work-up
5	**43**	mCPBA 77%, 1.2eq	CH_2Cl_2	0° to reflux	overnight	Several spots after column
6	**45**	H_2O_2 30%, 1.2eq NaOH, 1eq	9/1 H_2O/THF + 4mL EtOH	40	2h	Several spots after work-up

Table 8: Attempted conversion of **43** to **44**

For example, the attempts 1 to 3 used the conditions reported by Hussain et al. [18] and gave essentially starting material, even when the solvent was changed to 1/9 H_2O/THF. Addition of ethanol to the reaction mixture to aid solubility (attempts 4 and 6) afforded some reaction as judged by a new spot on TLC.

Unfortunately, the yellowish crude mixture changed to dark red after work-up or column chromatography (attempt 5) and the initial single spot possibly due to the instability of the desired product **44**. In a final attempt, the OH group in **43** was first protected as a MOM group (**Figure 32**). Unfortunately, the oxidative step was again unsuccessful.

Concurrent with **44**, we attempted the preparation of the alkene **47** which has an alkenyl substituent ortho to one of the OH group of the diol functionality, since such substituents are known to decrease BDE value more than simple alkyl groups (**Table 4**). A possible route to **47** is shown in **Scheme 35**. At the time this was planned, the problems for the final oxidation step were unknown.



Scheme 35: Synthesis attempt on diol **47**, as well as the formation of the unexpected product **48**

Unfortunately the first step, the *o*-formylation of naphthol **39** was not successful, not giving **46** but **48**. The ^{1}H NMR of **48** (**Figure 33**) showed singlets around 9.1 ppm and 5.1 ppm, which we attributed to the aldehyde and to the OH group of what we initially believed was the desired compound **46**. In order to prepare for Wittig reaction, the OH group was protected as a MOM group.

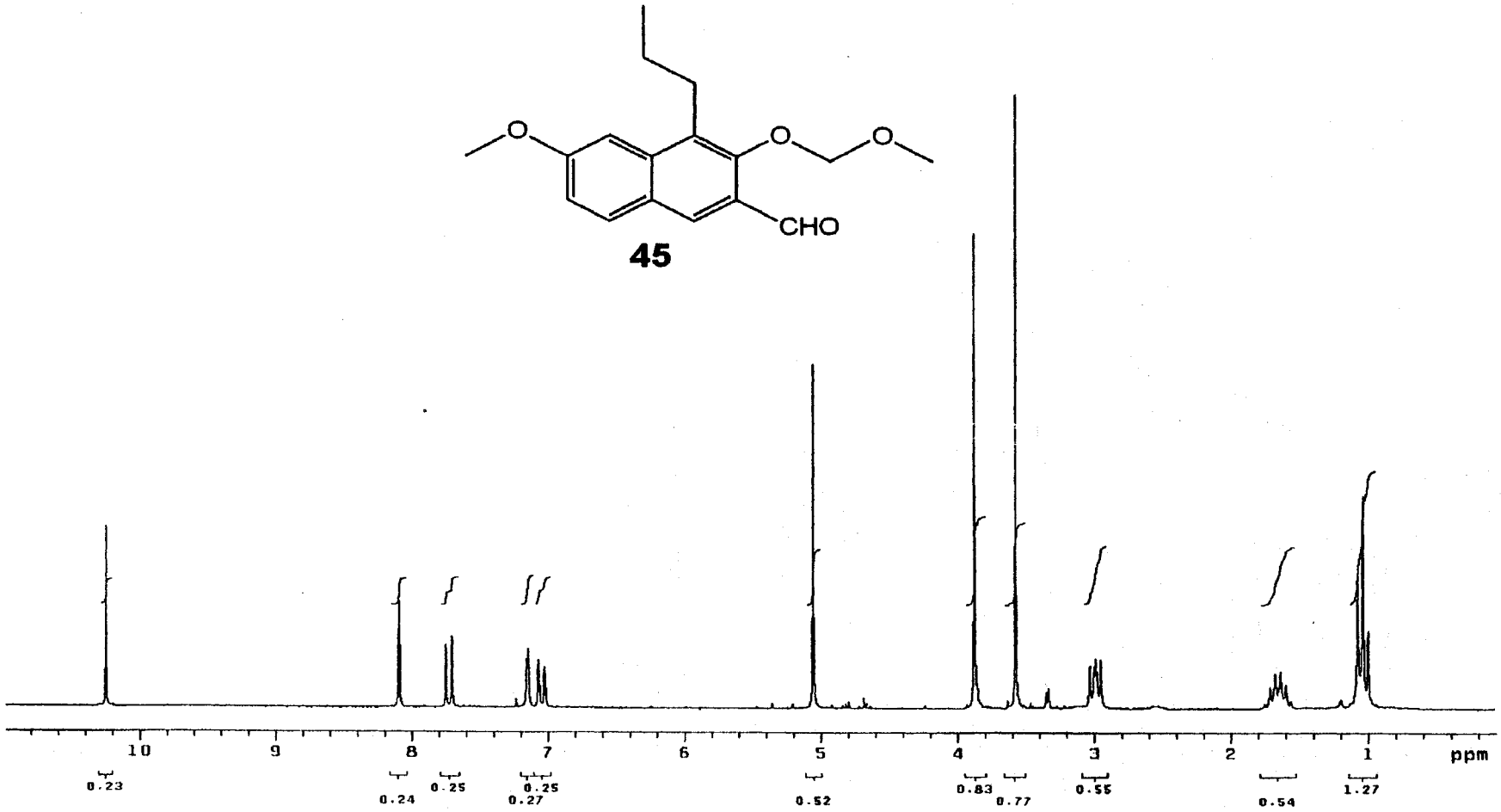


Figure 32: 200 MHz ^{1}H NMR of aldehyde **45** in $CDCl_3$

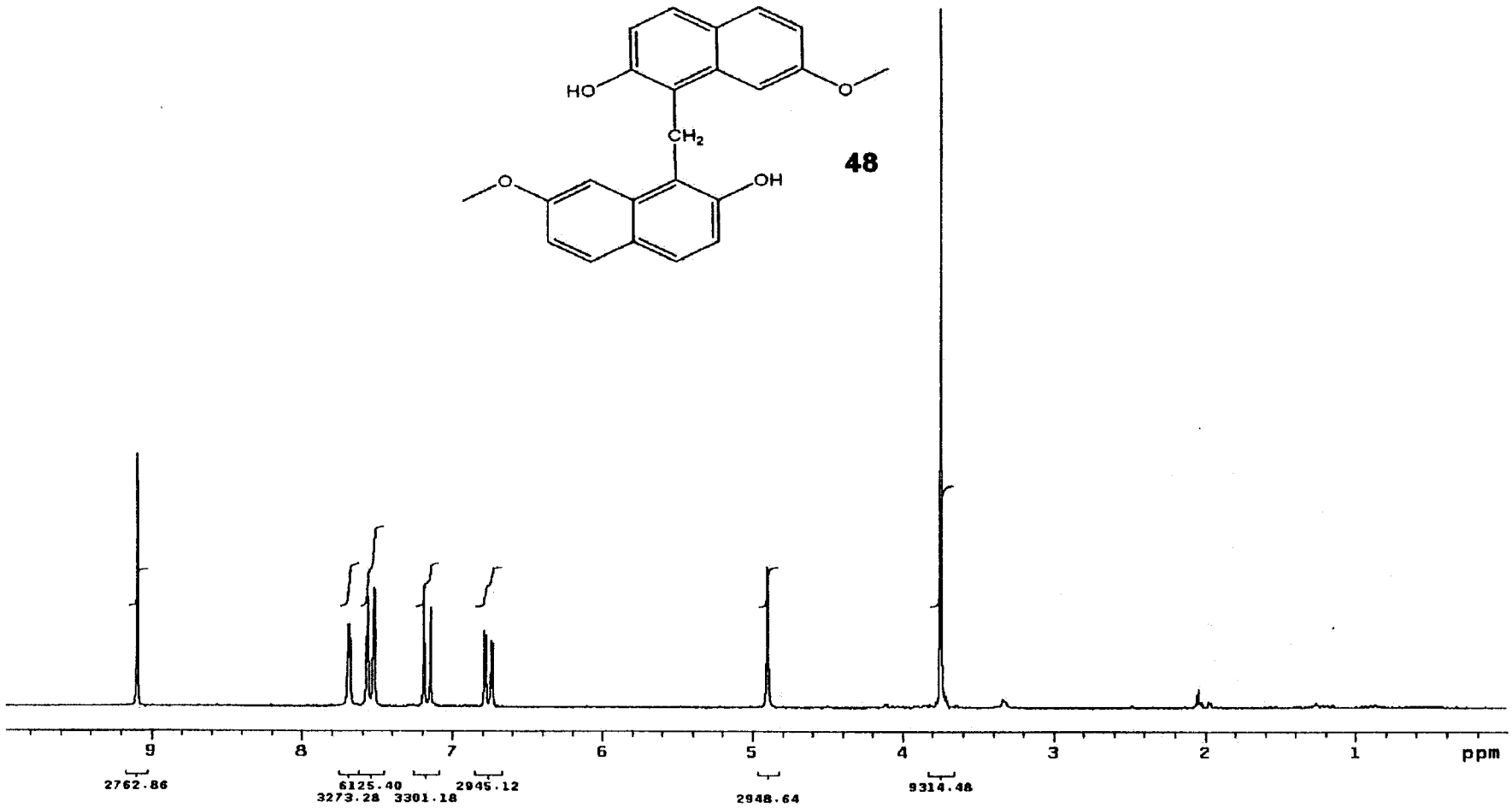
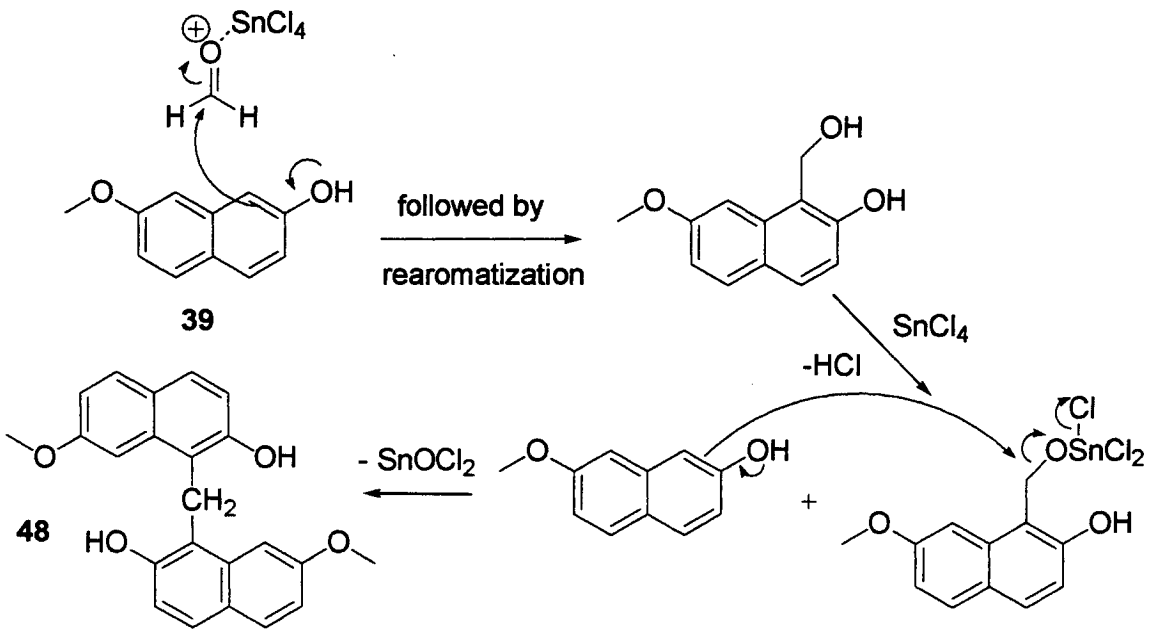


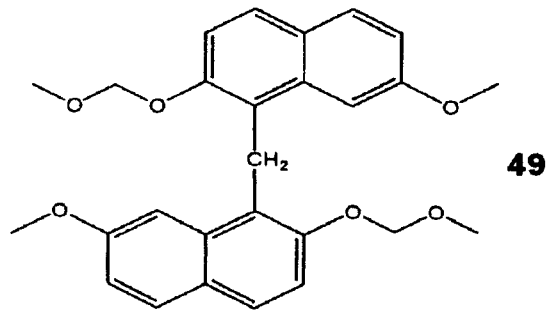
Figure 33: 200 MHz ^{1}H NMR of unexpected product **48** in acetone-d_6

The resulting ^{1}H NMR (**Figure 34**) no longer showed the aldehyde peak and thus it could not be **46**. The structure of the product obtained in the *o*-formylation reaction was reassigned as **48**, based on its mass spectra (**Figure 35**), ^{13}C NMR (**Figure 36**) and DEPT NMR (**Figure 37**). The mass spectra showed the molecular ion peak at m/z = 448, which provided the hint that the compound contained two naphthalene units. The singlet around 9.1 ppm in **Figure 33** was assigned to the OH groups and that near 5.1 ppm to the CH_2 group between the two aryl rings. The peak near 22 ppm in the ^{13}C NMR was shown to be due to the CH_2 by DEPT NMR. The formation of **48** was rationalized by the mechanism outlined in **Scheme 36**.



Scheme 36: Proposed mechanism for the formation of unexpected product **48**

An alternate approach to 7-substituted naphthalene-2.3-diols is outlined in **Scheme 37**. Acylation of **16** was expected to produce the 7-acetyl derivative **50** from which should serve as precursor to a number of target compounds such as the alkene **53** and the ether **55**.



49

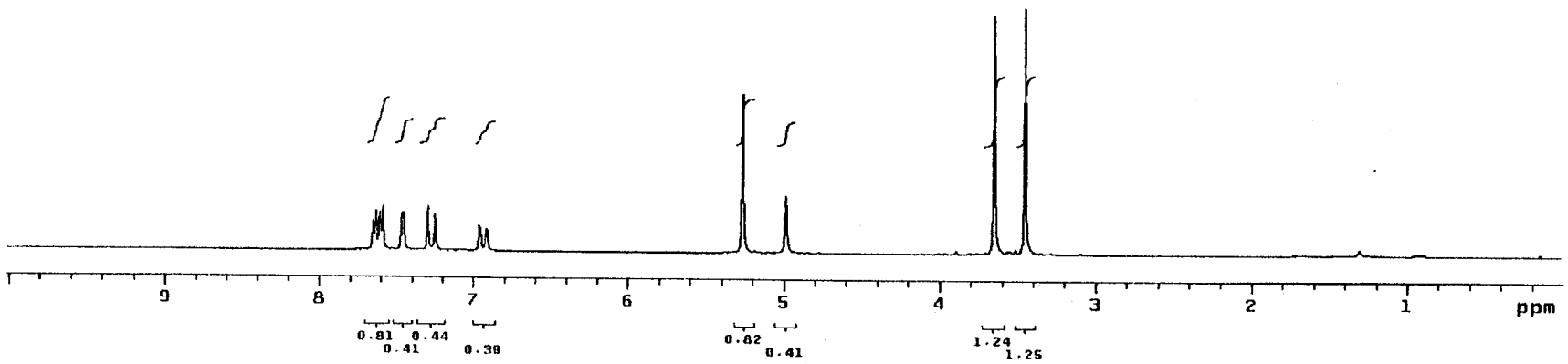


Figure 34: 200 MHz ^{1}H NMR of **49** in $CDCl_3$

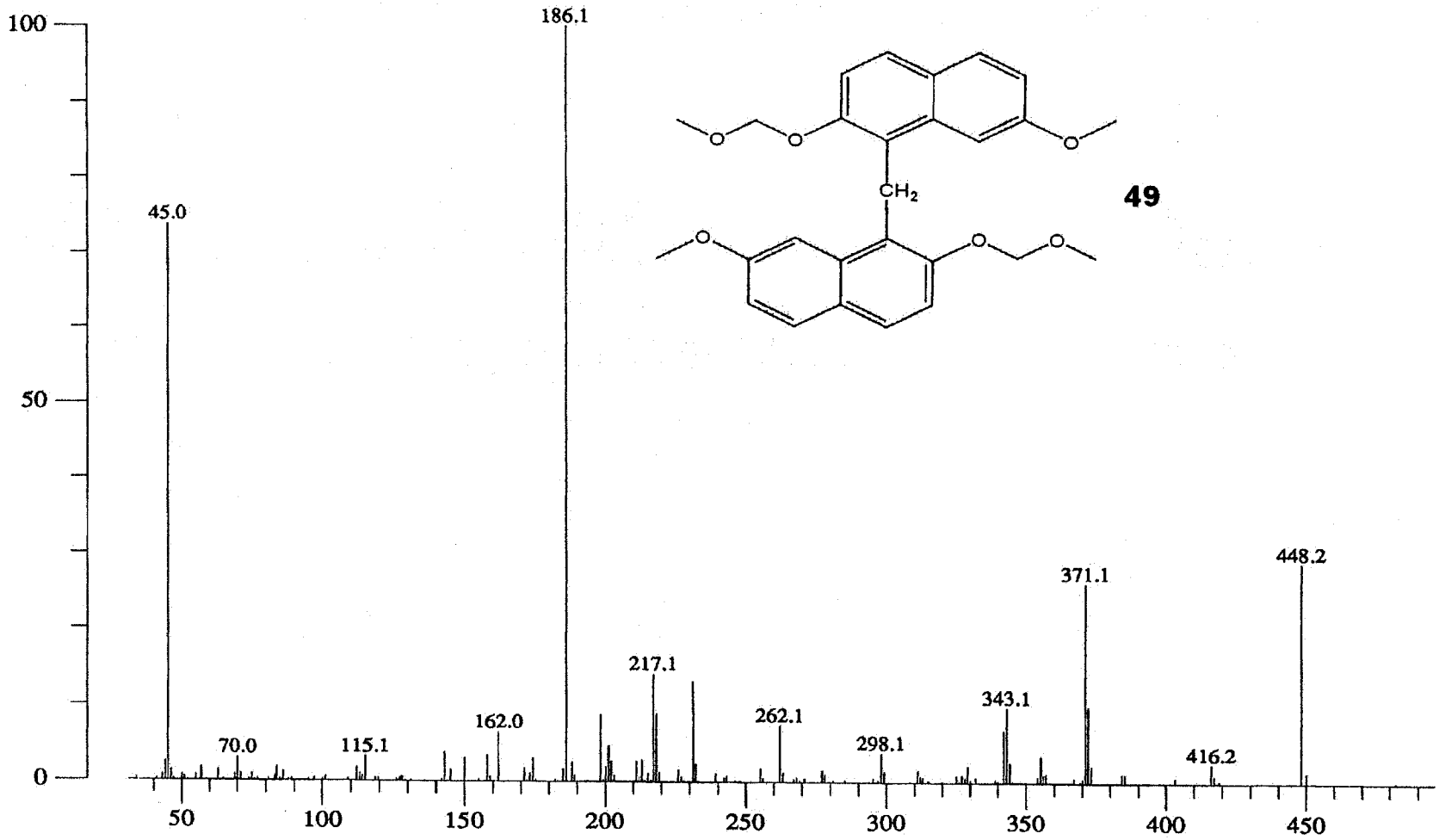


Figure 35: Mass spectrum of dimer **49**

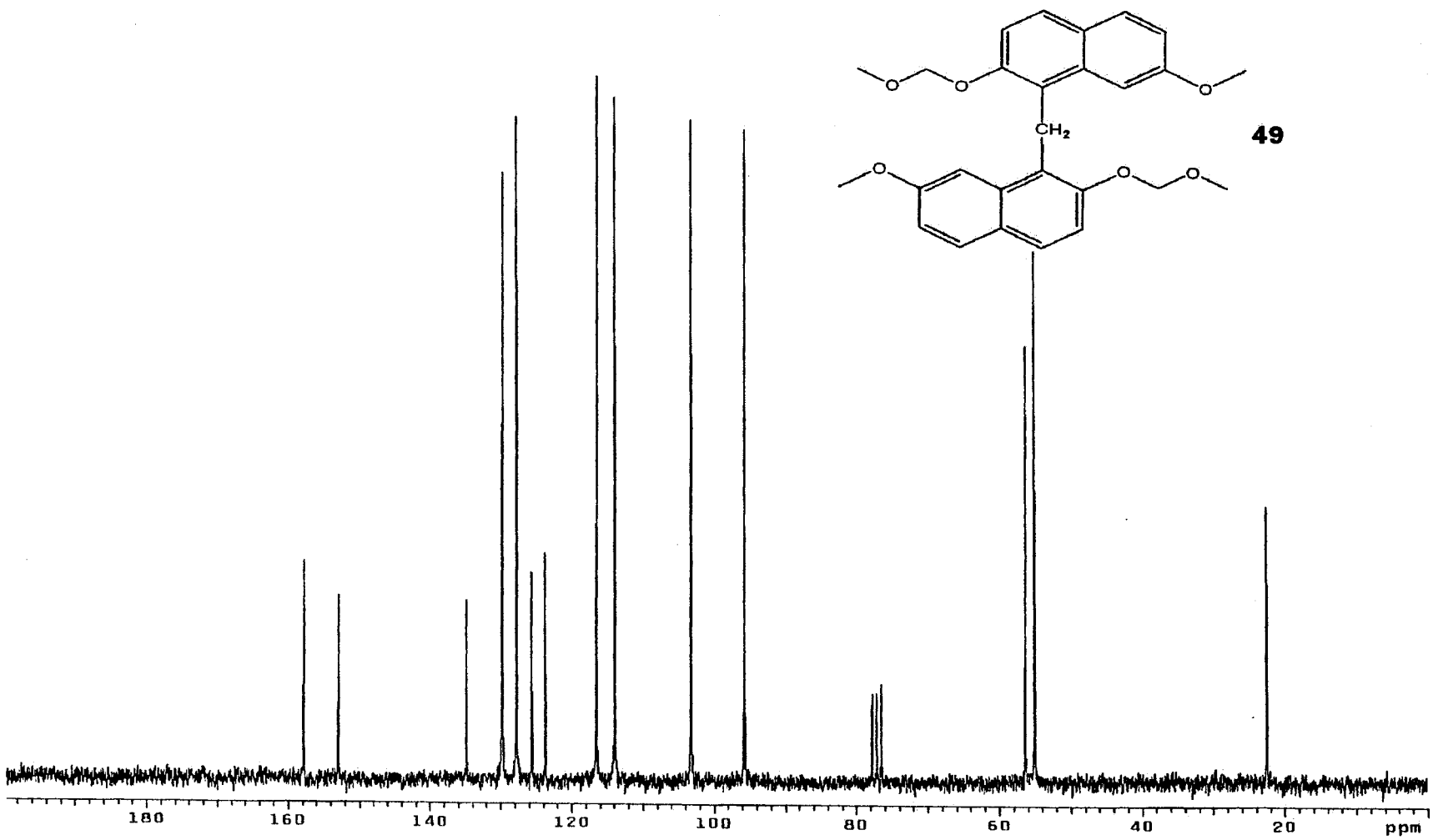


Figure 36: 200 MHz ^{13}C NMR of **49** in $CDCl_3$

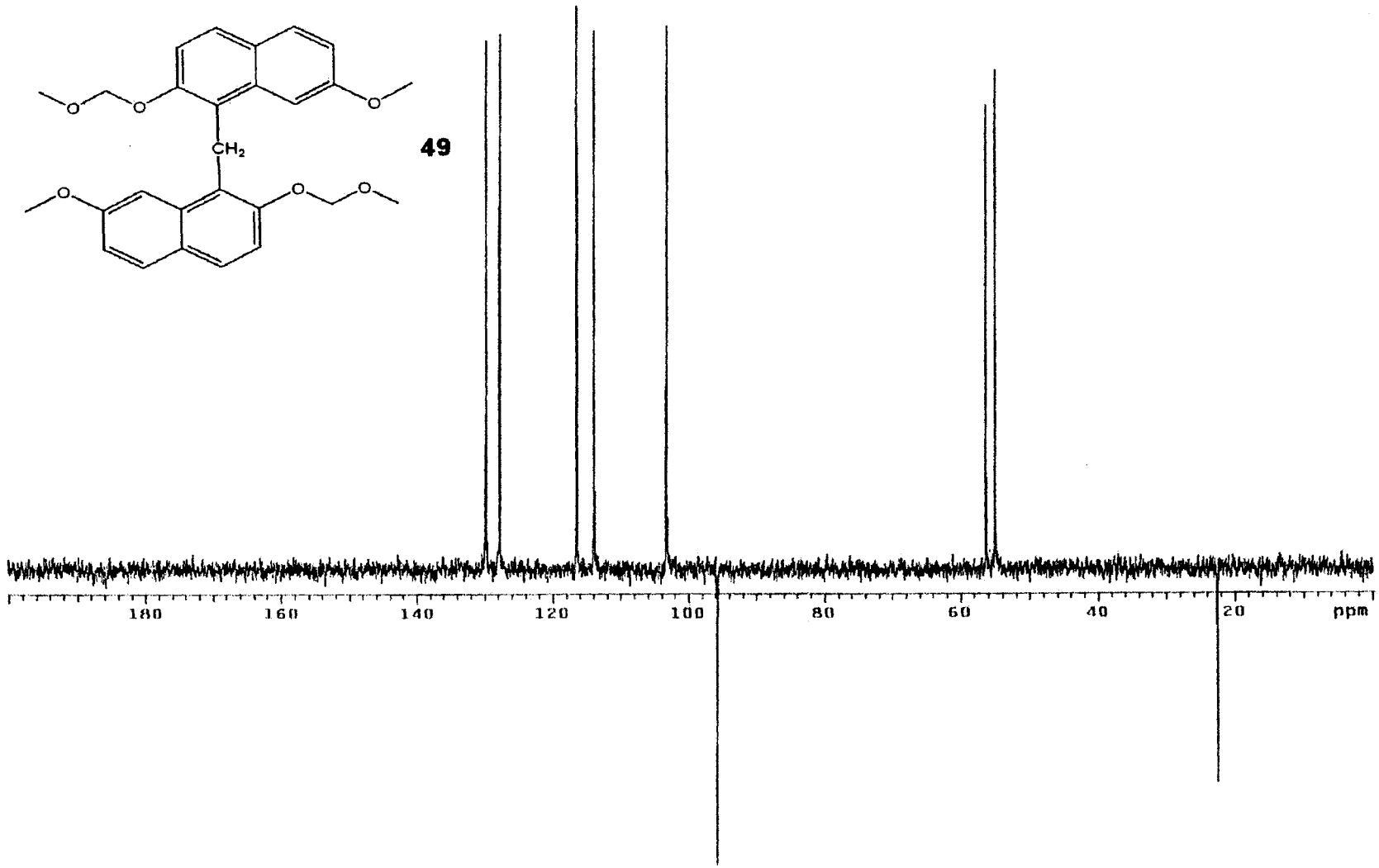
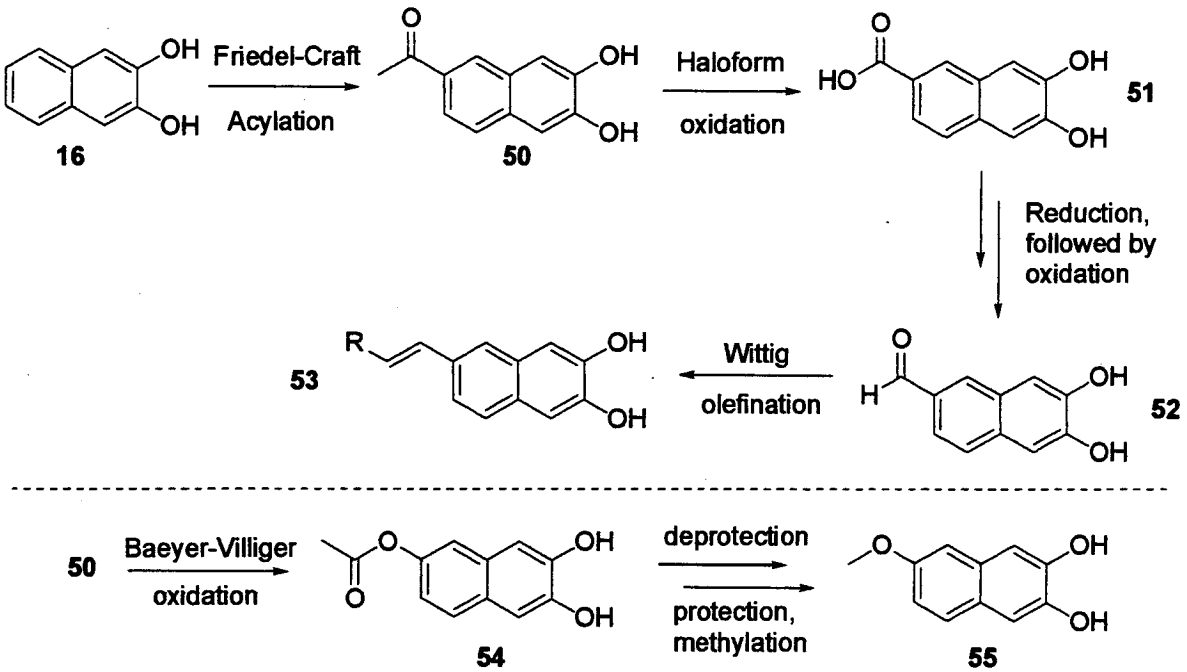
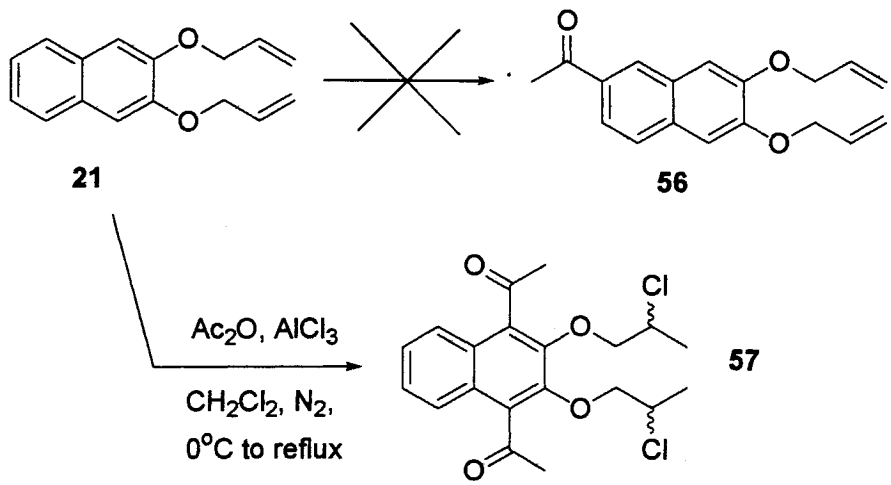


Figure 37: 200 MHz dept NMR of **49** in $CDCl_3$



Scheme 37: Possible pathways envisioned with acylated version of **16**

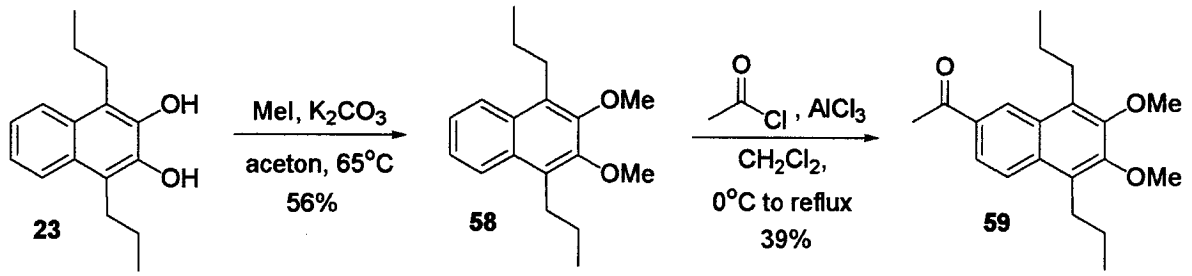
Naito et al. [35] reported the acylation of the dimethyl ether of **16** in nitrobenzene as solvent. In order to avoid the protection-deprotection steps and the problem of removing the nitrobenzene, we attempted the acylation of compound **21** in CH_2Cl_2. Claisen rearrangement would generate the naphthalene-2,3-diol function when desired (**Scheme 38**).



Scheme 38: Unwanted product **57** formed in Friedel-Craft acylation of **21**

The ^{1}H NMR (**Figure 38**) of the isolated product showed no singlets in the aromatic region, suggesting that substituents (acyl groups) were introduced at C1 and C4. The mass spectrum (**Figure 39**) of the product showed a molecular peak at m/z = 396 and indicated the presence of two chlorines in the product, because of the characteristic pattern 9:6:1 at m/z = 396, 398 and 400 due to the different chorines isotopes. These data are consistent with HCl addition to both alkene groups in **21** and the structure assignment of the product as **57** (**Scheme 38**).

Since the above sequence was unsuccessful, we returned to the paper published by Naito et al. [35] and protected diol **23** with methyl iodide (**Scheme 39**). Despite using excess of methyl iodide (4eq), only 56% of diether **58** was isolated (**Figure 40**).



Scheme 39: Friedel-Craft acylation of **58**, protected version of analogue **23**

Friedel-Craft reaction of **58** in refluxing CH_2Cl_2 gave 39% yield of the desired product **59**, the rest being essentially the starting material **58** as shown by TLC. The position of the acylation was confirmed by the ^{1}H NMR of **59** (**Figure 41**), since H8 appeared as a singlet near 8.6 ppm.

It is noteworthy that direct formylation reactions on **58** and **16** to get analogues of **52** were also tried, but all of these attempts were unsuccessful, and led essentially to recovered starting material or decomposition. The reaction types and conditions tried are listed in **Table 9**.

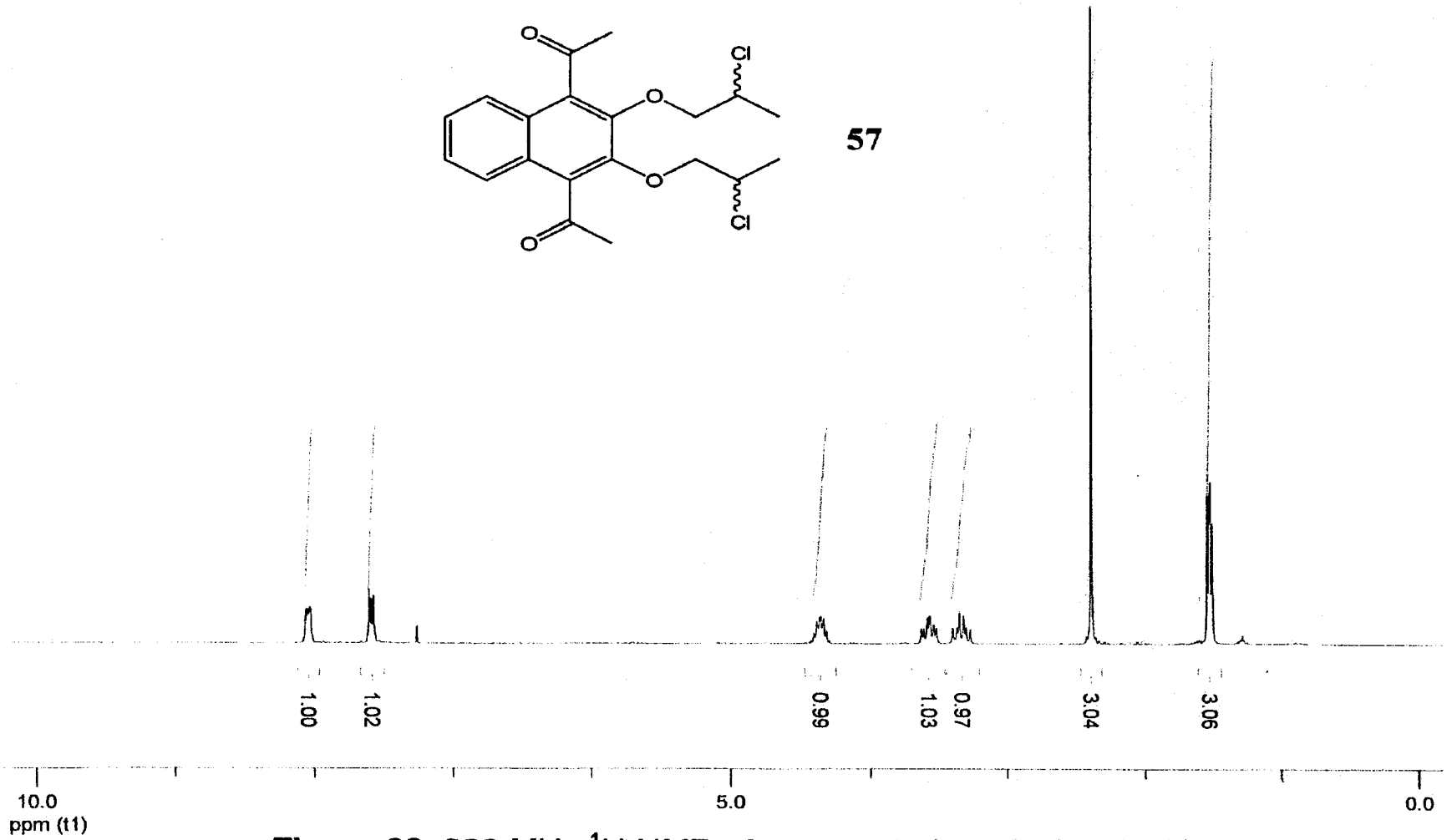


Figure 38: 300 MHz ^{1}H NMR of unexpected product **57** in $CDCl_3$

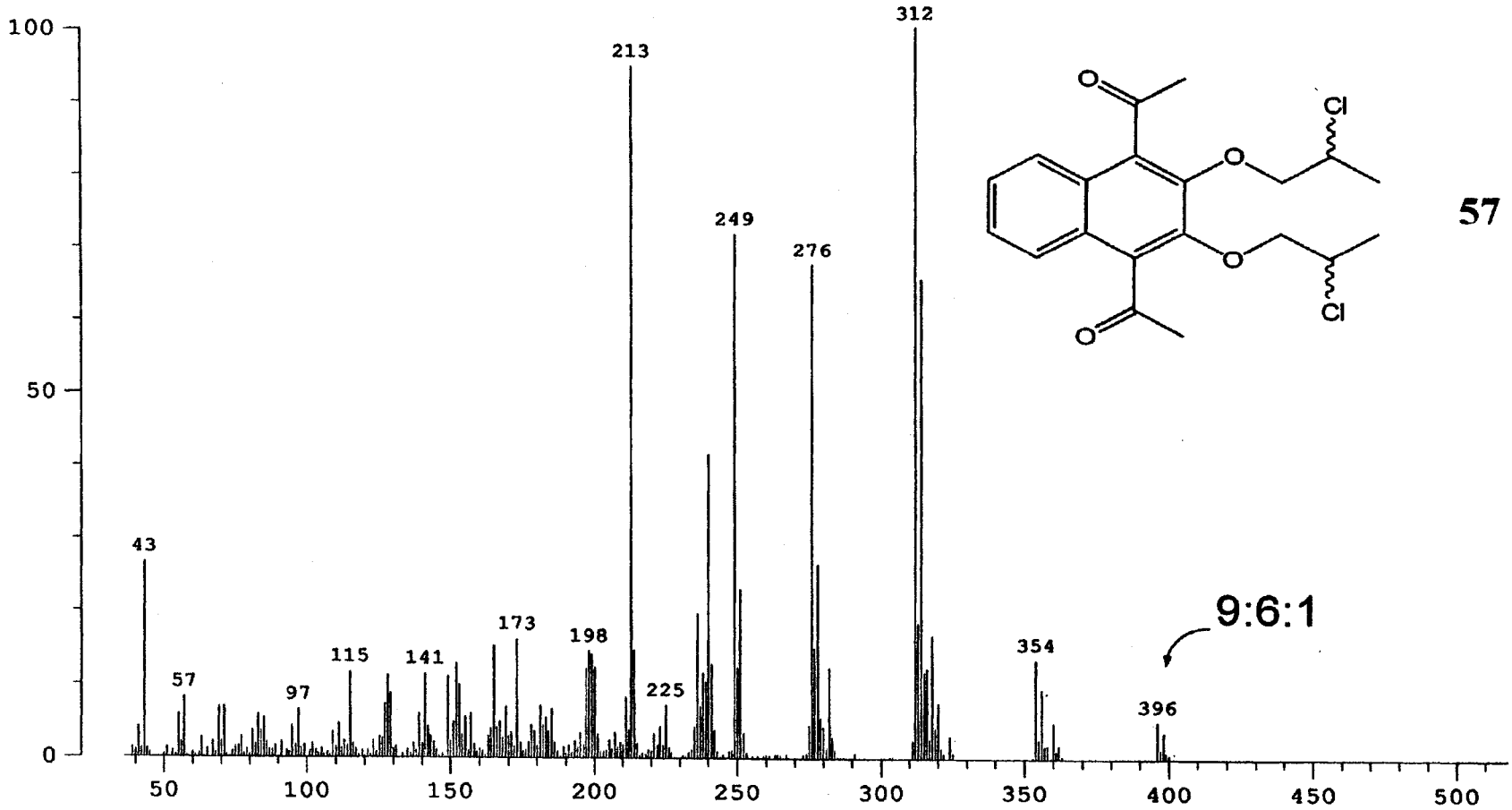


Figure 39: Mass spectrum of unexpected product **57**

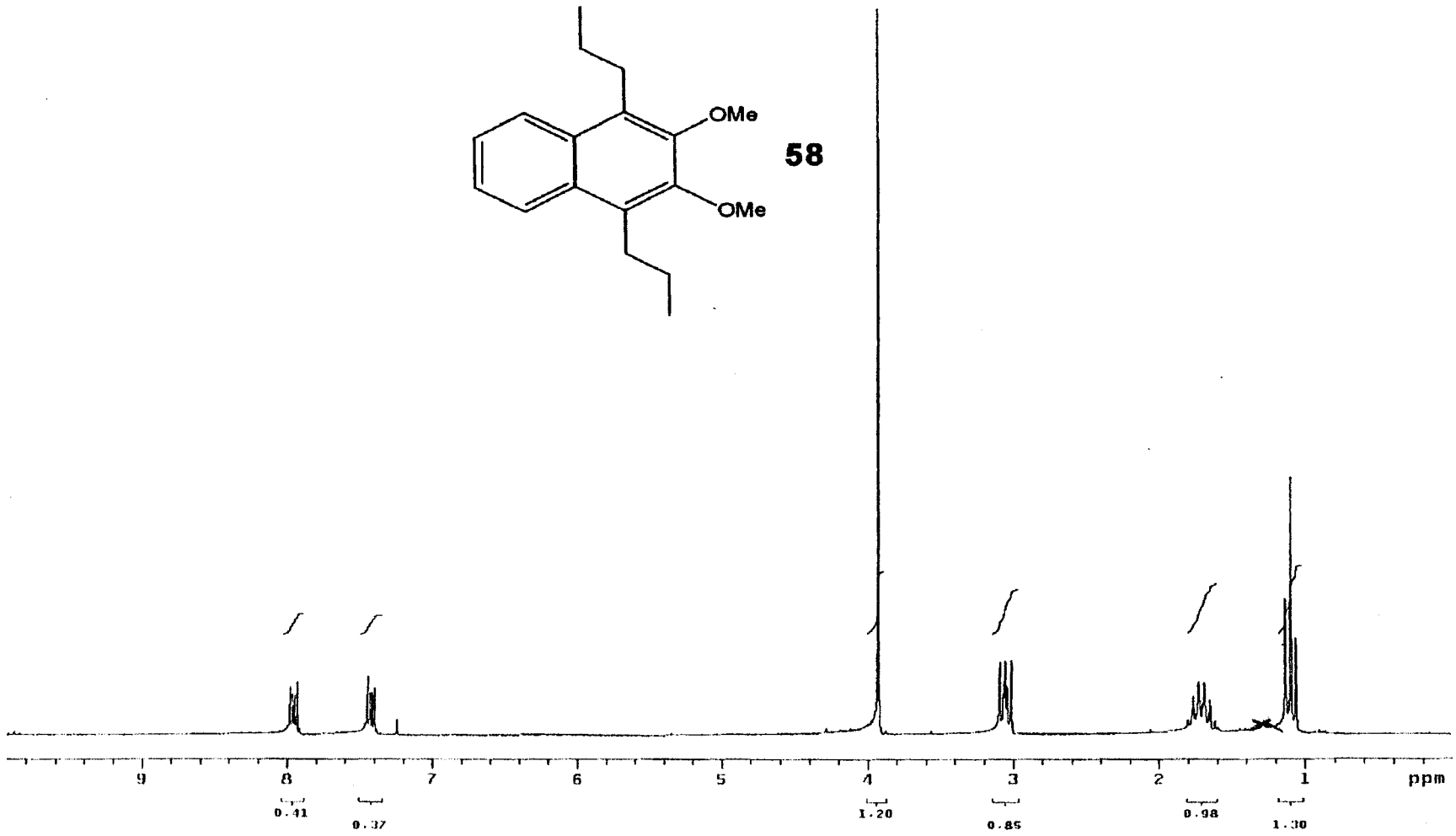


Figure 40: 200 MHz ^{1}H NMR of dimethylether **58** in $CDCl_3$

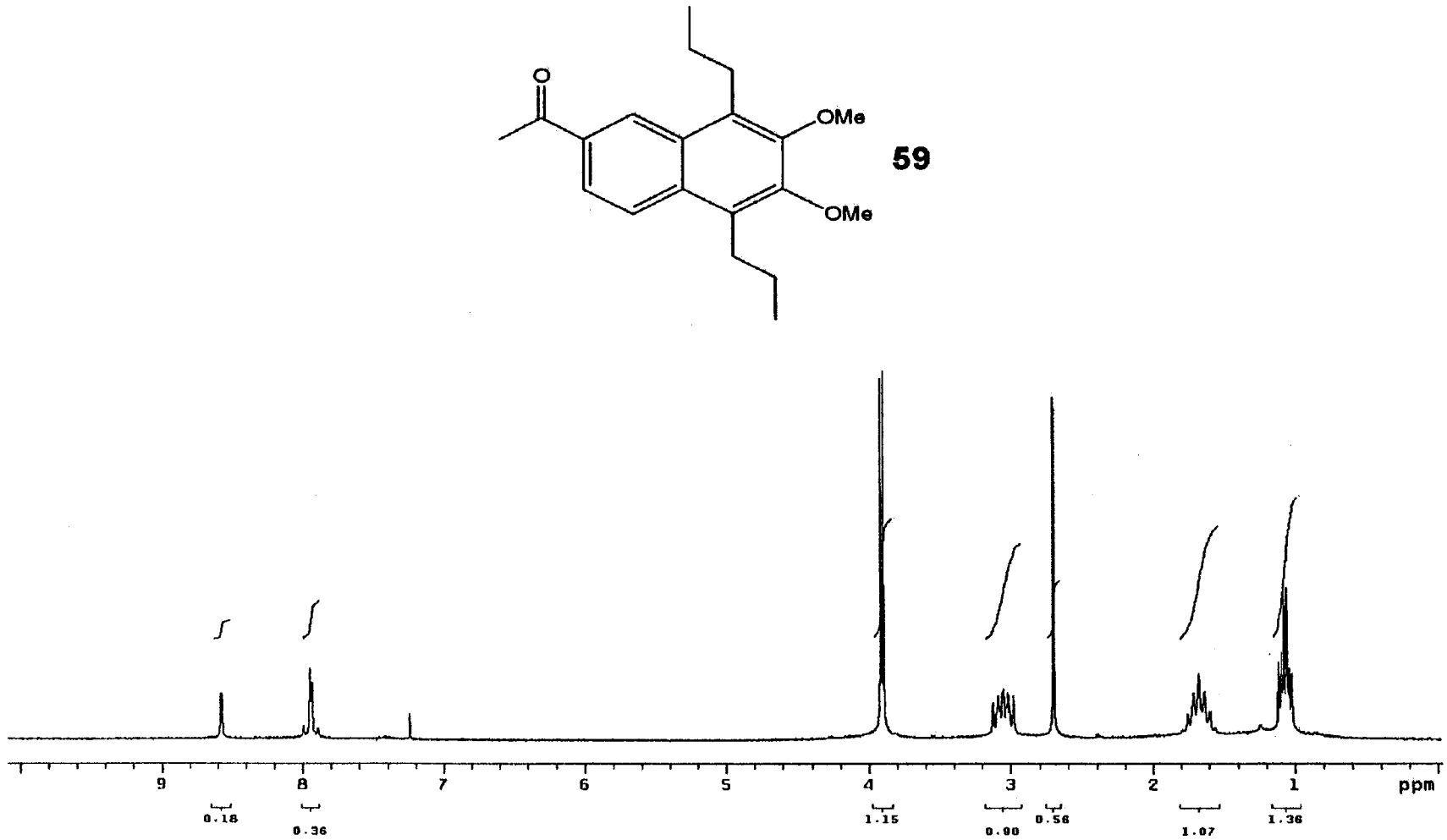


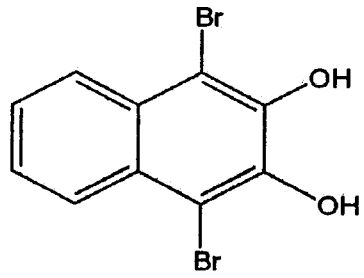
Figure 41: 200 MHz ^{1}H NMR of ketone **59** in $CDCl_3$

S.M.	Reaction name	Reagents	TLC appearance
58	Vilsmeier	$POCl_3$, DMF, reflux	S.M.
16	Reimer-Tiemann	$CHCl_3$, TEBAC, NaOH, H_2O, i-PrOH, 1,4-dioxane, 70°C	S.M.
16	Vilsmeier	$POCl_3$, DMF, reflux	S.M.
16	Gatterman	NaCN, HCl $ZnCl_3$, ether, r.t.	S.M.
16	—	Dichloromethyl methyl ether, $SnCl_4$, N_2 0°C to r.t.	Turns black in work-up

Table 9: Reactions tried in the direct formylation of **16** and **58**

Since we encountered significant difficulties in introducing alkene substituents at the C1, C4 and C7 positions via the Wittig strategy outlined in **Schemes 34**, **35** and **37**, we shifted the focus to introducing bromine substituents at these positions with the intent of using these atoms as handles for the introduction of the desired substituents. Aryl bromides are known to be reactive partners in metal-catalyzed coupling reactions, such as palladium-catalyzed Heck [36] and Sonogashira [37] coupling reactions and we intended to investigate these possibilities.

Reactions of **16** with one equivalent of bromine resulted in an inseparable mixture of products (**Scheme 40**). When 2eq of bromine were used, the TLC of the reaction mixture showed only one spot. Isolation of the product from such a reaction afforded 1,4-dibromo-naphthalene-2,3-diol (**60**). The ^1H NMR (**Figure 42**) of **60**, showed, as expected, no singlets in the aromatic region.



60

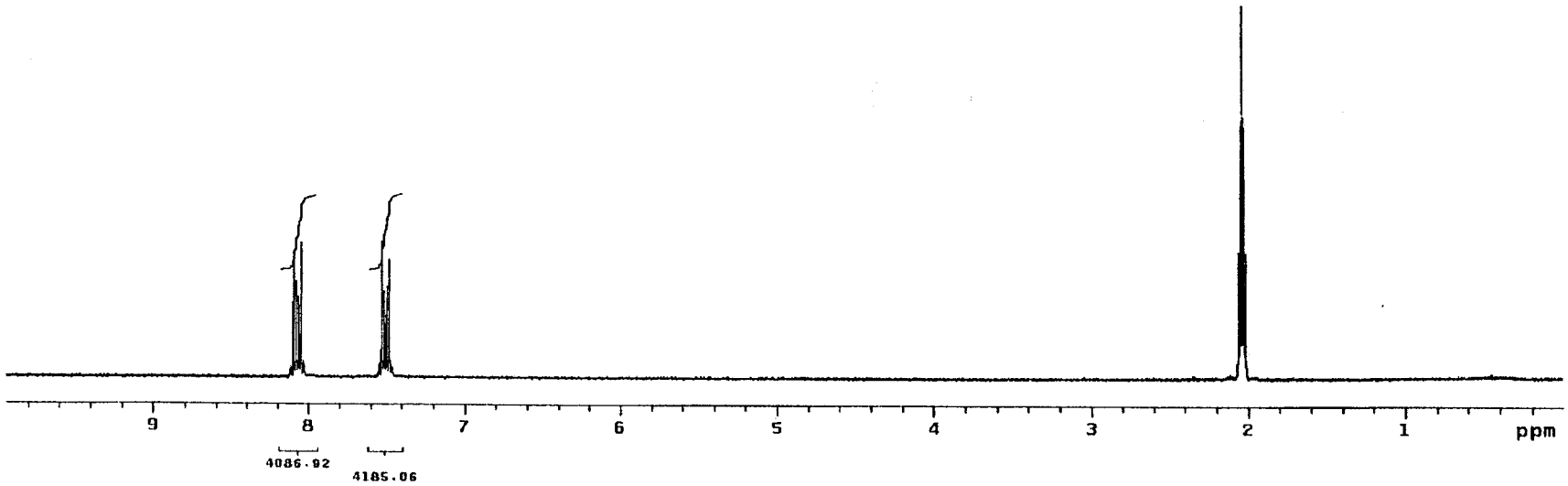
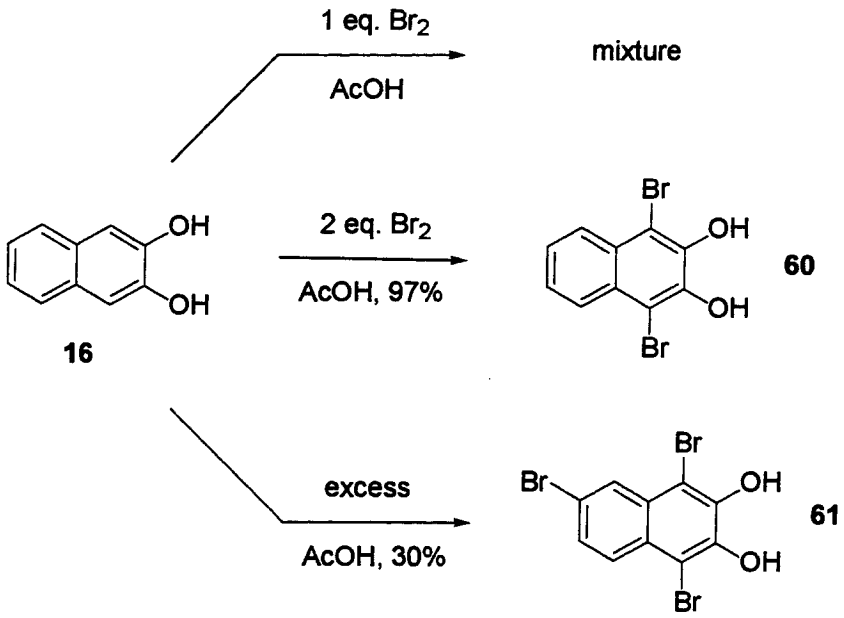


Figure 42: 200 MHz ^{1}H NMR of diol **60** in acetone-d_6



Scheme 40: Results for bromination experiments on design motif **16**

Furthermore, the characteristic pattern 1:2:1 (natural abundance: ^{79}Br 50.5% and ^{81}Br 49.5%) in the mass spectrum of **60** (**Figure 43**) for the molecular ion peaks (m/z = 316, 318 and 320) proved that this compound contained two bromine atoms.

When bromine was used in excess, the only isolated product was the tribromodiol **61**, whose mass spectrum (**Figure 44**) showed a set of molecular ion peaks (m/z = 394, 396, 398 and 400) having the 1:3:3:1 pattern characteristic for three bromines in the molecule. The location of the third bromine was confirmed by the appearance of a doublet around 8.2 ppm with J_m = 1.97 Hz in the ^1H NMR of **61** (**Figure 45**). This reaction was carried out only once. The product **61** precipitated in the reaction flask and was filtered off and characterized. No attempt was made to recover the product remaining in the solution; the yield of **61** was 30%.

The first Heck coupling reaction was tried on the MOM protected dibromide **60** with methyl acrylate using the same conditions found in the paper published by Littke et al. [36] on Heck reactions of aryl bromides, where Pd/P(*t*Bu)$_3$ in the presence of a bulky base (Cy_2NMe) is used as the active catalyst (**Scheme 41**).

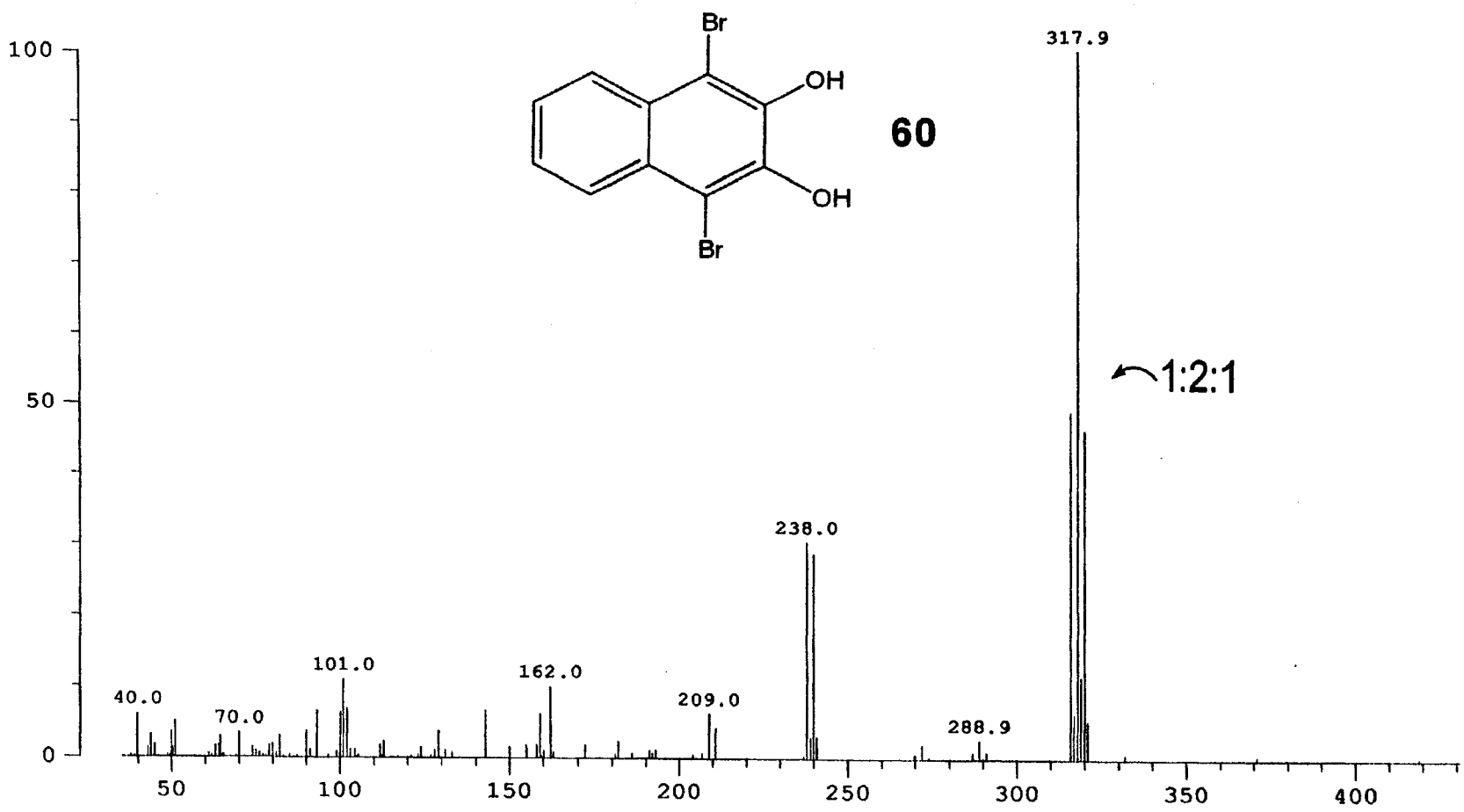


Figure 43: Mass spectrum of diol **60**

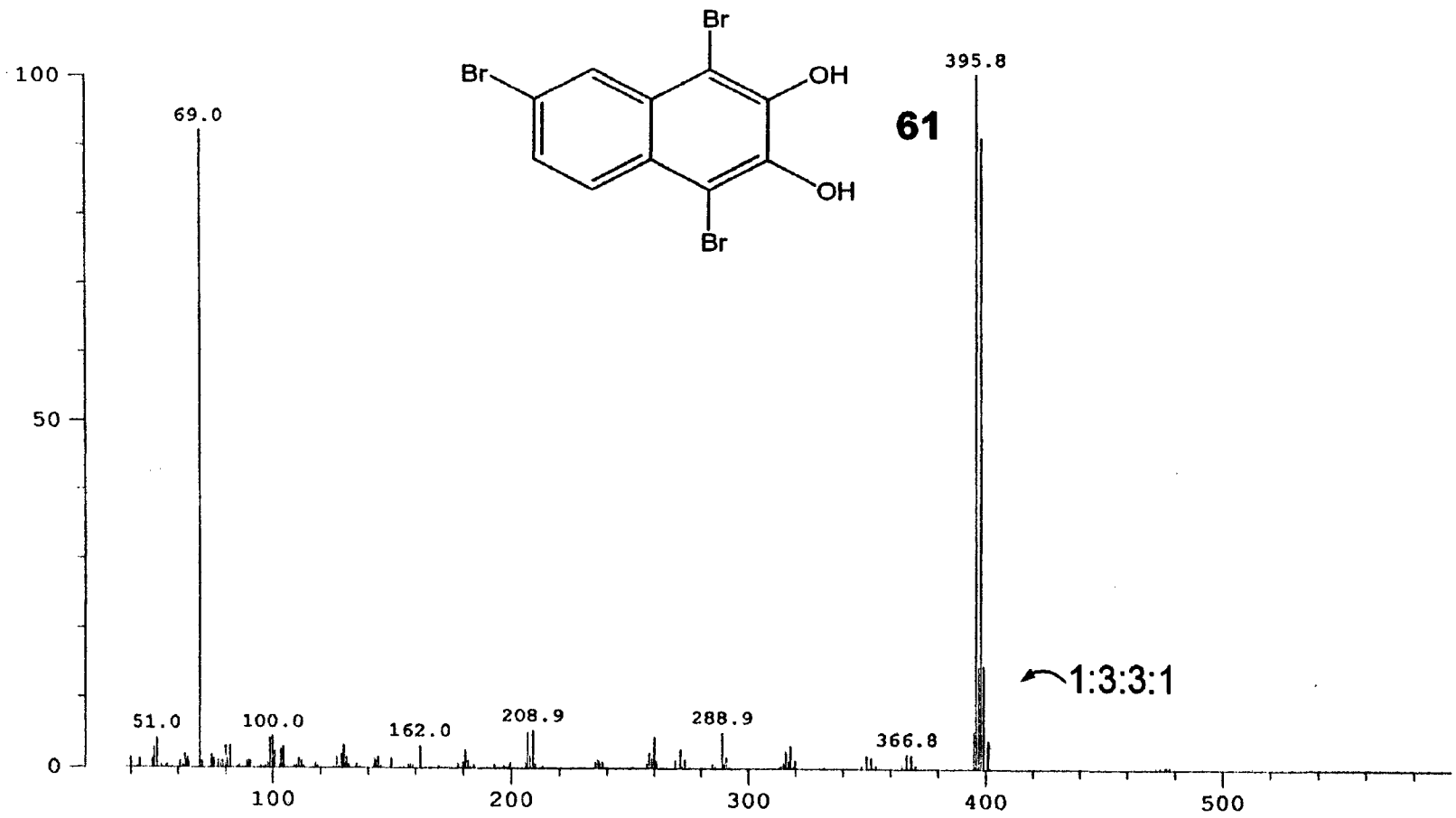
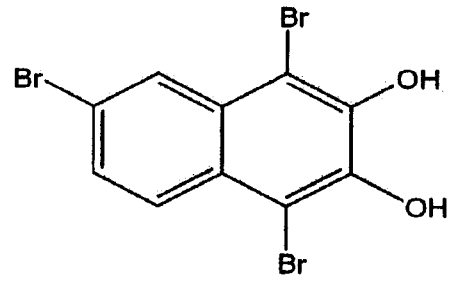


Figure 44: Mass spectrum of diol 61



61

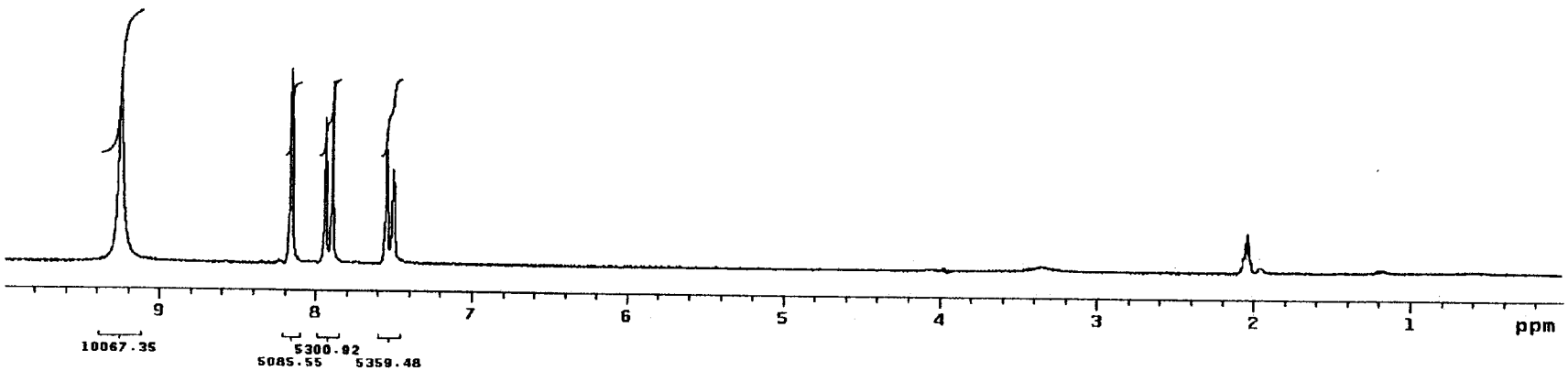
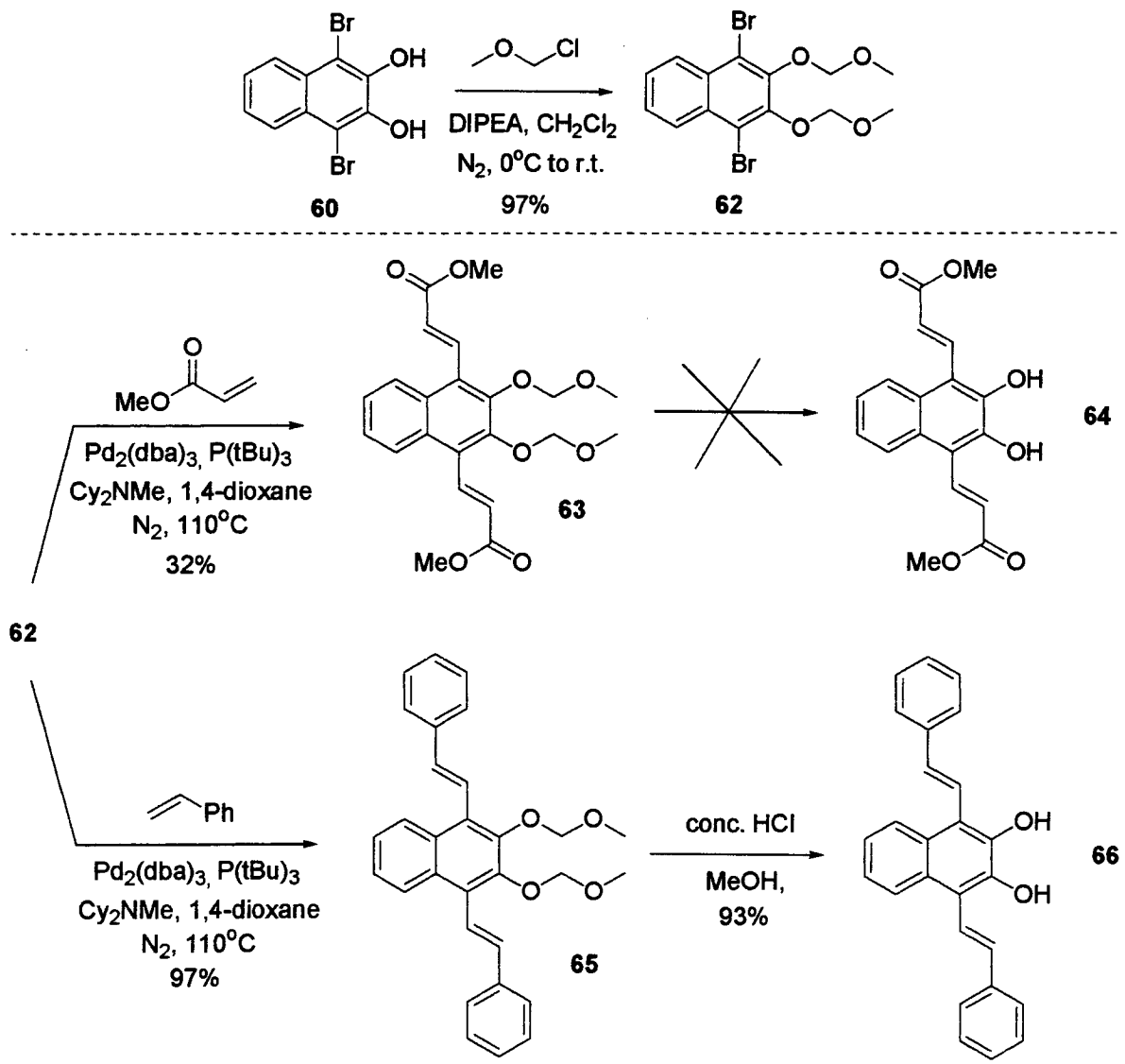


Figure 45: 200 MHz ^{1}H NMR of diol **61** in acetone-d_6

The introduction of an electron-withdrawing group should allow us to investigate the effect on BDE values of ortho conjugated olefins. Protection of the diol functionality was required prior to the coupling reaction, since the Littke paper suggested that a free alcohol may alter reactivity.



Scheme 41: Synthesis of distyrenyl analogue **66**, as well as the attempt synthesis of analogue **64**

Protection of **60** using MOM-Cl gave **62** in good yield. Its ^{1}H NMR (**Figure 46**) showed the presence of the characteristic peaks of the MOM groups, around 3.7 ppm for the CH_3 groups and around 5.2 ppm for the CH_2 groups. Heck coupling with methyl acrylate gave a surprisingly low yield (32%) of the desired product **63** partly due to formation of a by-product that was very difficult to separate from the desired product **63**. The ^{1}H NMR of **63** (**Figure 47**) showed a singlet around 3.6 ppm, corresponding to the two ester methyl groups, which proved that the addition of methyl acrylate was successful at both C1 and C4. Furthermore, the presence of two doublets, one around 6.6 ppm and the other around 8.2 ppm with a coupling constant of 16.3 Hz, corresponding to the olefins protons, demonstrated that the geometry of the olefins were trans. Unfortunately, removal of the MOM groups in **63** to give **64** was not successful; since submission of **63** to the standard conditions for MOM deprotection gave extensive decomposition as shown by the TLC of the reaction mixture.

In contrast with the previous coupling reaction, the reaction conditions with styrene as the coupling partner gave essentially one spot on TLC, which translated to a 97% of **65** (**Scheme 41**). The ^{1}H NMR of distyrenyl **65** (**Figure 48**) showed the required number of hydrogen in the aromatic region and two doublets with characteristic coupling constants of trans olefins (16.6 Hz). In contrast to **63**, deprotection of **65** went smoothly and afforded 1,4-distyryl-naphthalene-2,3-diol (**66**) in 93% yield. The structure assignment as **66** was confirmed by the presence of the singlet around 8.4 ppm integrating for two protons, corresponding to the two free OH groups in ^{1}H NMR of diol **66** (**Figure 49**).

Compound **66** was obtained as a bright yellow solid after column chromatography and tended to change to a red-colored solid on storage. Surprisingly, no changes in TLC appearance and ^{1}H NMR of the resultant solid were observed. The mass spectrum of this compound (**Figure 50**) was highly unusual. The compound did not show the expected molecular ion at m/z = 364, but gave the highest m/z peak at 360, indicating the loss of four mass units, most likely four hydrogen. We believe that chemistry shown in **Scheme 42** occurred in

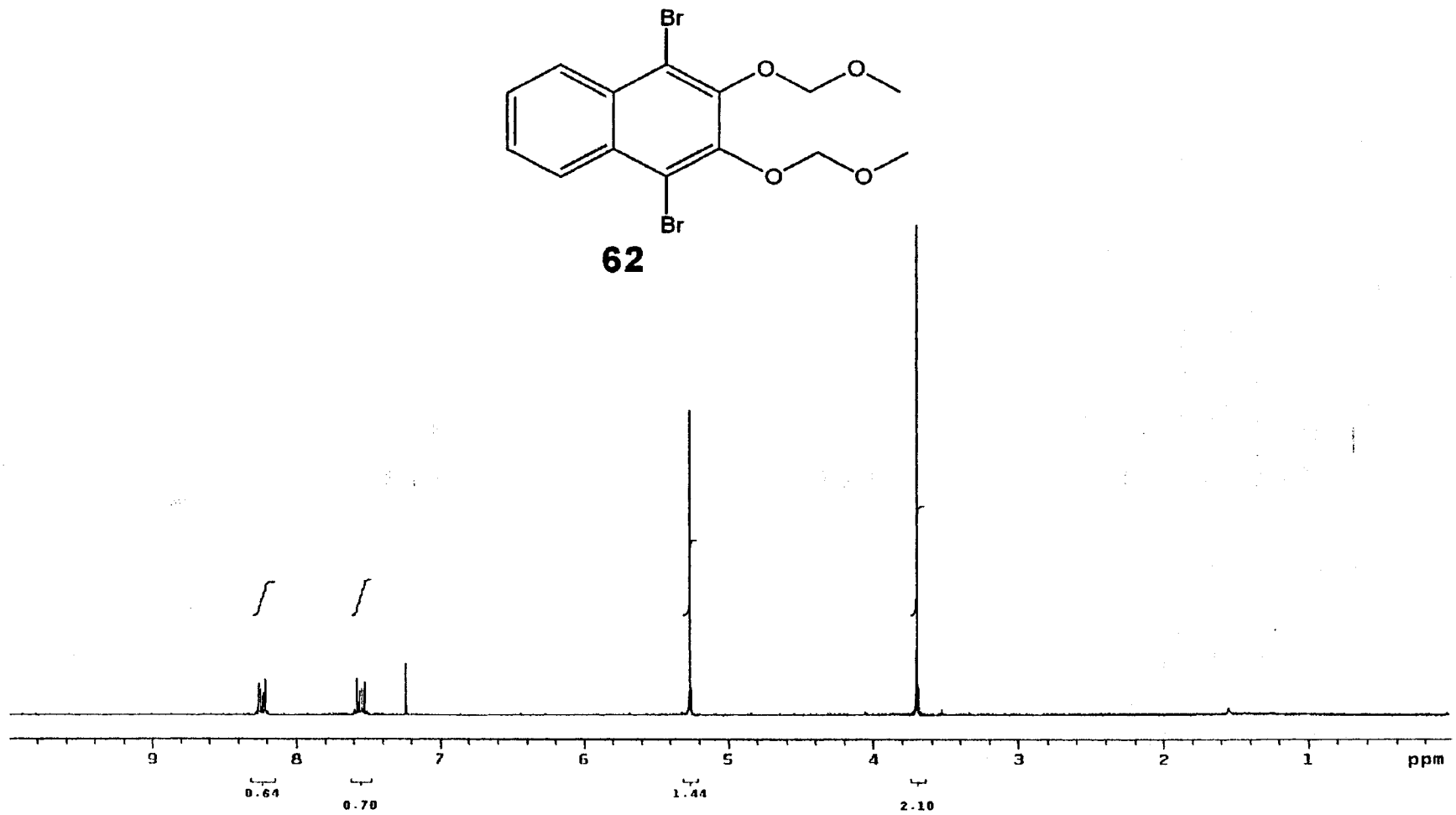


Figure 46: 200 MHz ^{1}H NMR of dibromide **62** in $CDCl_3$

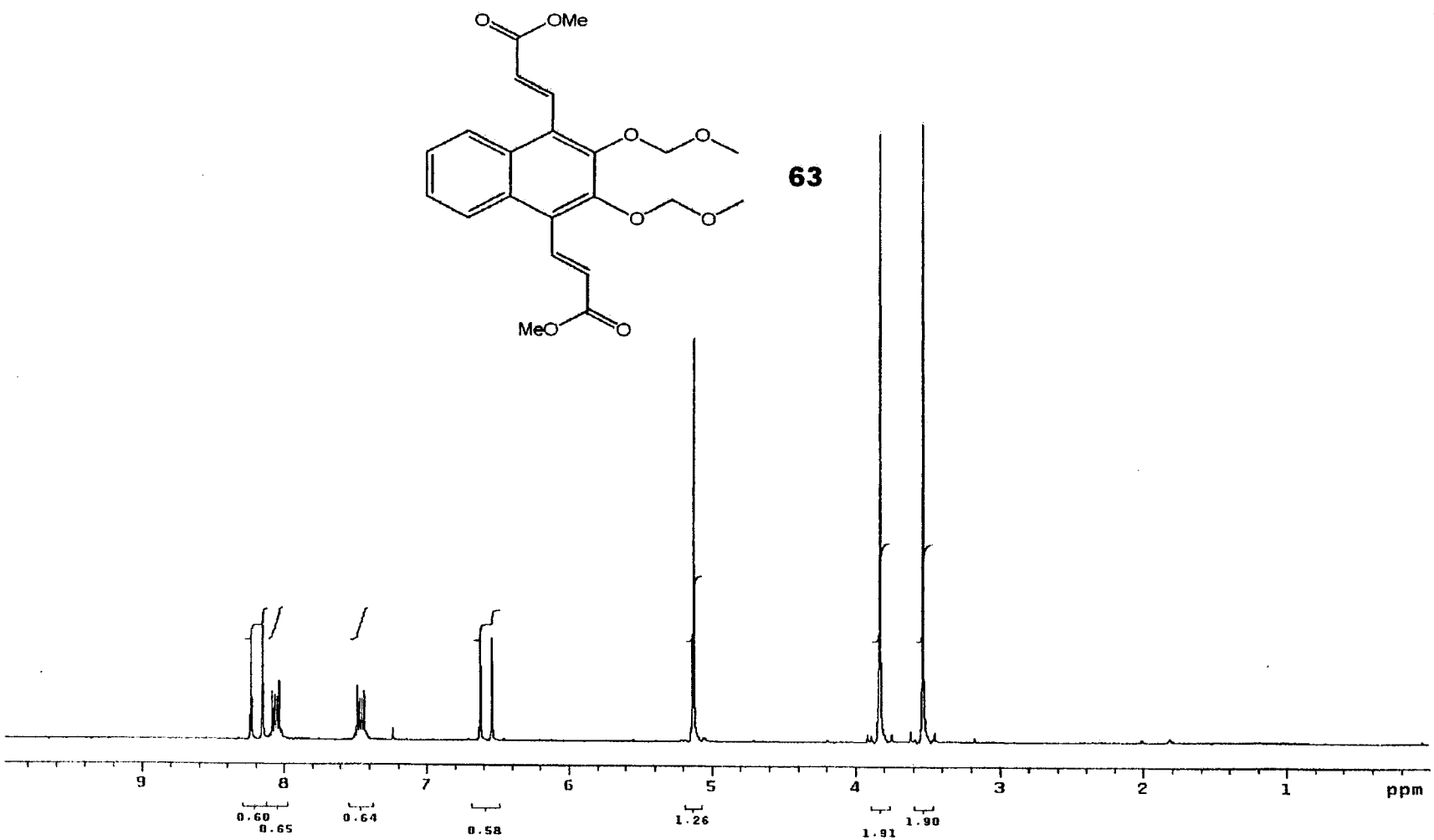


Figure 47: 200 MHz ^{1}H NMR of diester **63** in $CDCl_3$

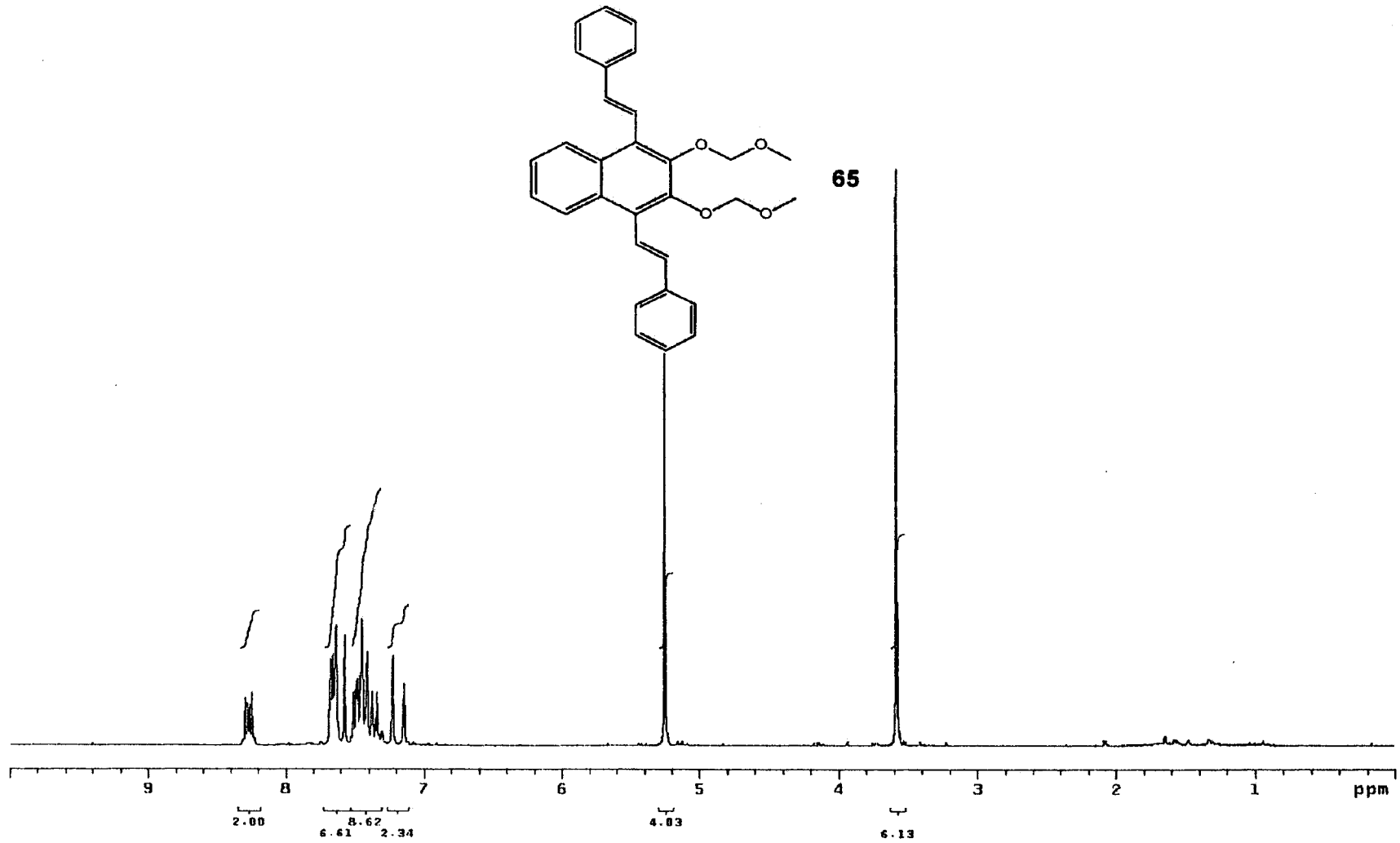


Figure 48: 200 MHz ^{1}H NMR of distyryl **65** in $CDCl_3$

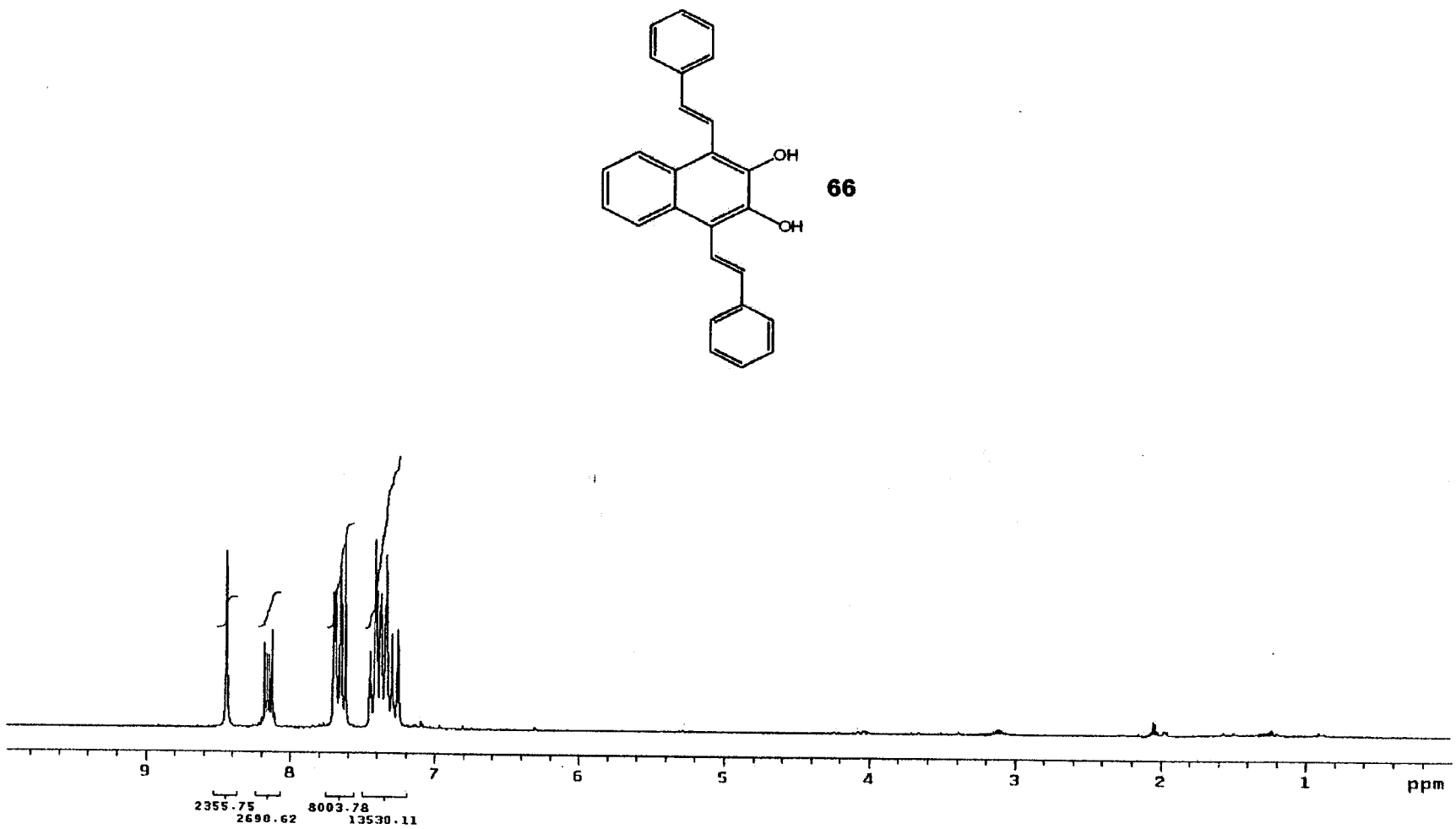


Figure 49: 200 MHz ^{1}H NMR of diol **66** in acetone-d_6

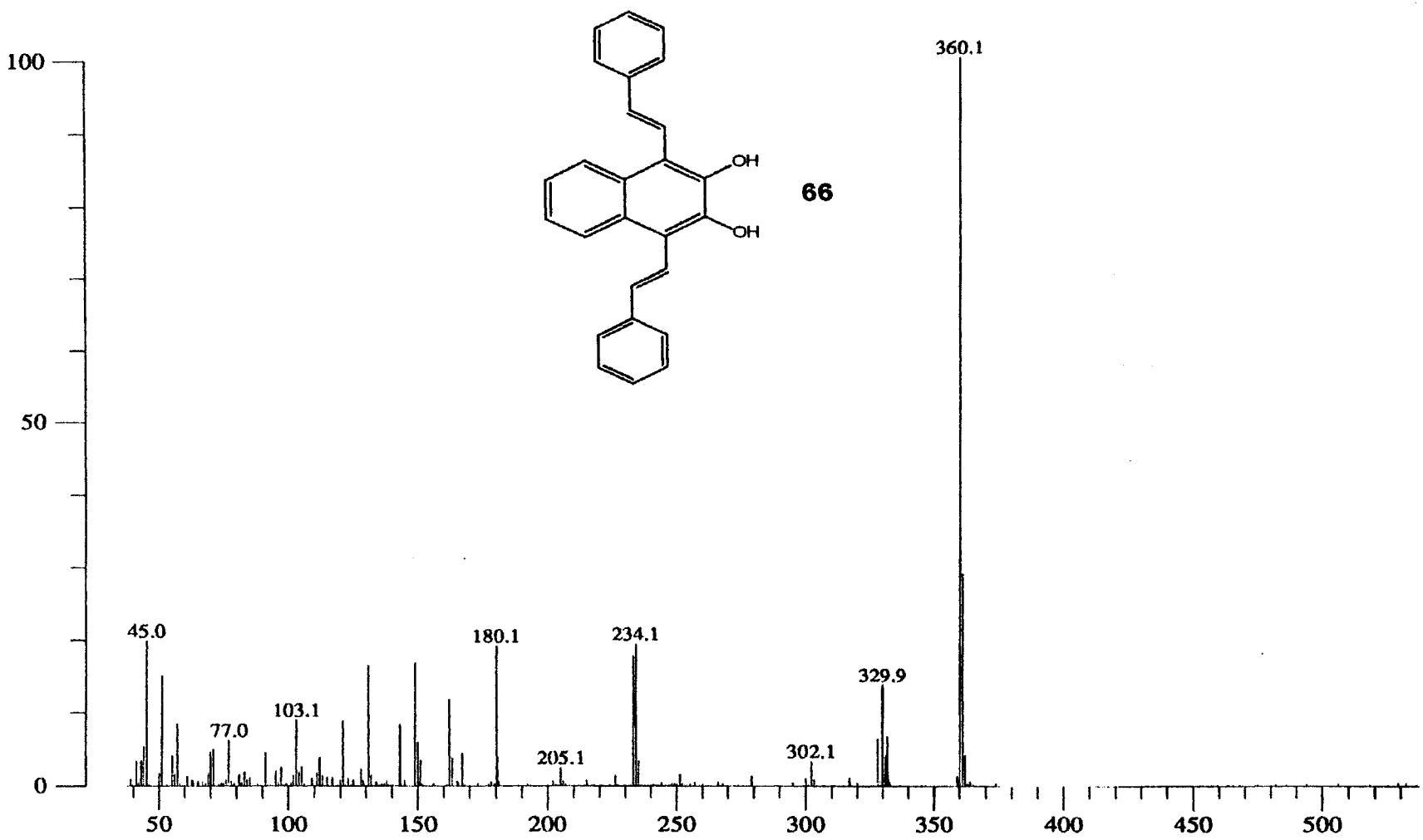
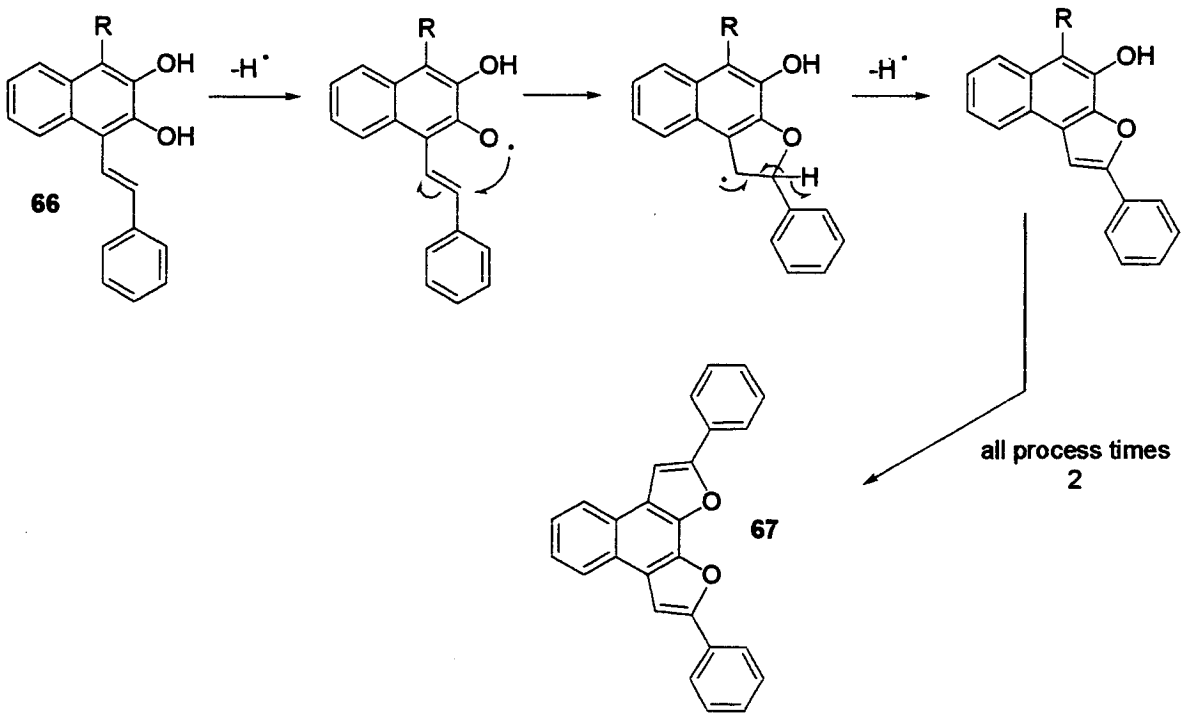


Figure 50: Mass spectrum of diol 66

the mass spectrometer. It involves cyclization of the phenol on the ortho styrenyl units followed by loss of 2H to give a stable furan.

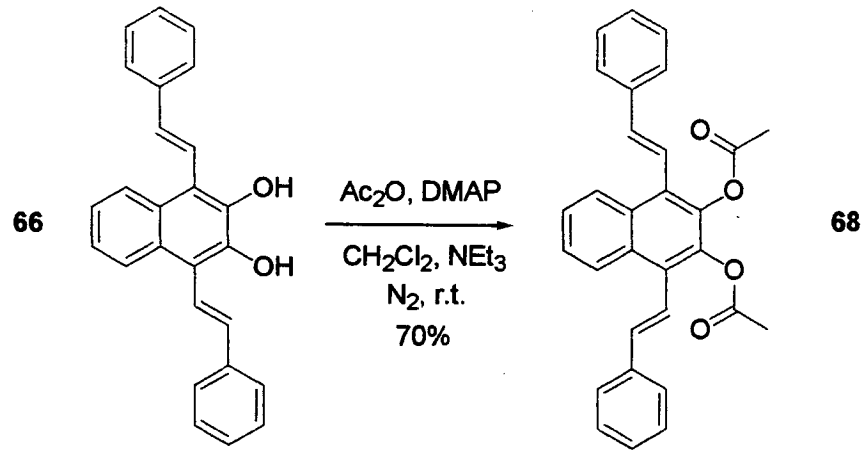


Scheme 42: Proposed mechanism for the formation of the m/z = 360 product **67**

Acetylation of **66** (**Scheme 43**) gave the expected diacetate **68** whose ^{1}H NMR (**Figure 51**) showed the characteristic peak of the acetates methyl groups around 2.3 ppm. The mass spectrum of **68** gave correct molecular ion and thereby provided confirmation of the correct structure assignment of **66**. The unusual mass spectrum of **66** described above has not been investigated further.

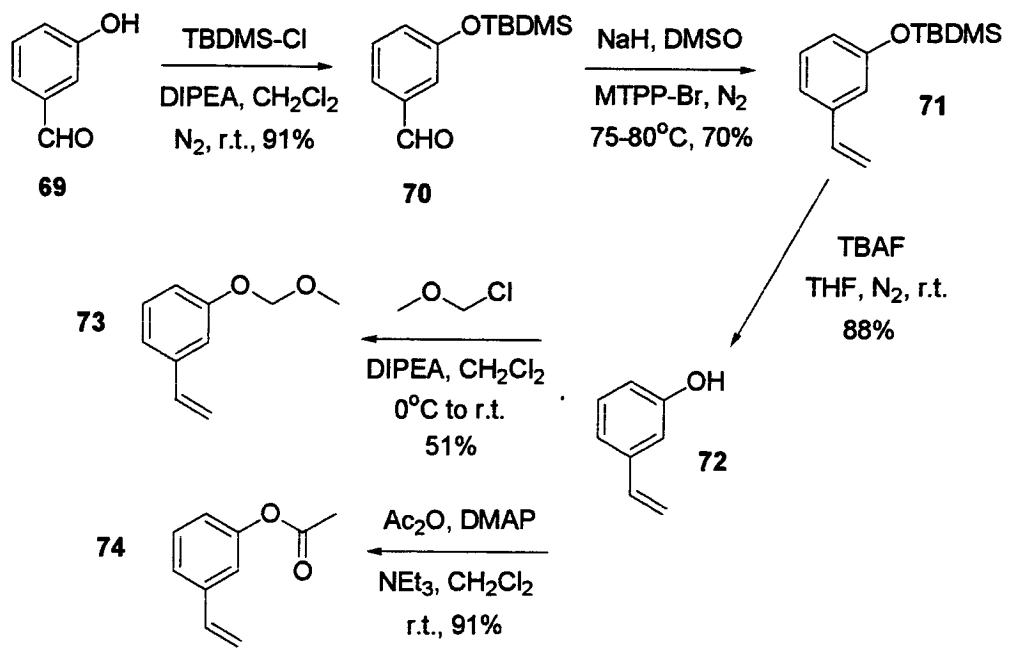
A somewhat less lipophilic analogue of **66**, one that carried a meta hydroxyl group in the benzene ring became the next target molecule. For this purpose, we needed the protected 3-hydroxystyrene such as **73** and **74**. These compounds were prepared in routine fashion [38,39] from 3-hydroxybenzaldehyde **69**, which is commercially available (**Scheme 44**) .

The first step was the protection of the OH in **69** with TBDMS-Cl, which provided the desired product **70** in good yield (91%).



Scheme 43: Acetylation of analogue **66**

Purification of this product by column chromatography was not required, since the only by-product observed by TLC was the excess of TBDMS-Cl, which evaporated under high vacuum overnight.



Scheme 44: Synthesis of 3-hydroxystyrene **72**, as well as its MOM and acetoxy versions **73** and **74**

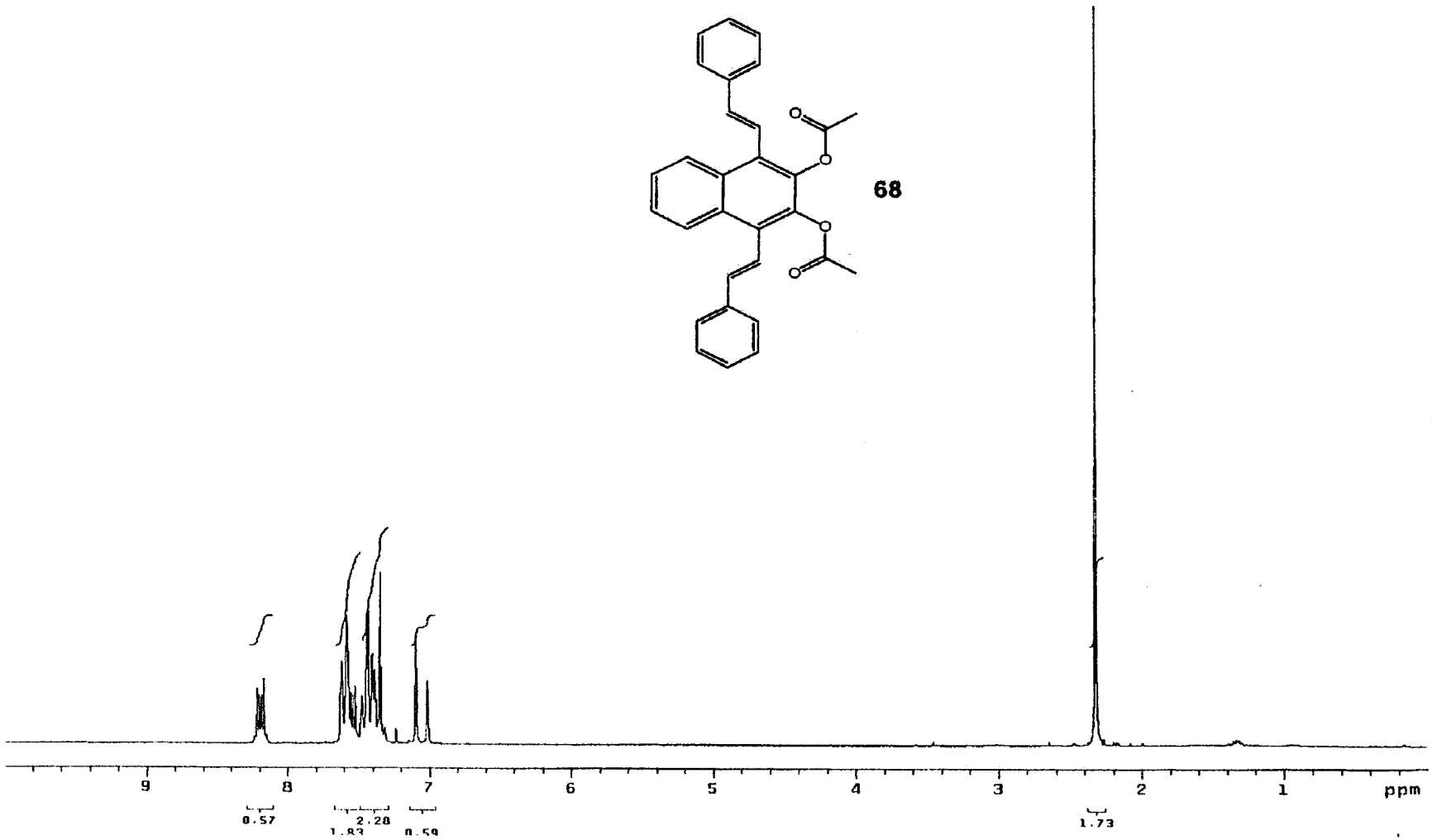


Figure 51: 200 MHz ^{1}H NMR of diacetate **68** in $CDCl_3$

^{1}H NMR of **70** (**Figure 52**) showed the characteristic peaks of TBDMS, a singlet around 0.2 ppm for the CH_3 groups and another singlet around 1.0 ppm for the *t*-butyl group.

Then, the Greenwald et al. [39] conditions of the Wittig reaction, where methylsulfinyl carbanion is first formed by NaH-DMSO and then used to generate the alkylidene phosphorane or Wittig reagent by treatment with a phosphonium salt, gave styryl **71** in 70% yield after column chromatography.

^{1}H NMR of **71** (**Figure 53**) clearly demonstrated the presence of the desired olefin with two doublets of doublets corresponding to the two terminal protons, one around 5.2 ppm (J_{cis} = 10.9 Hz) and the other around 5.7 ppm (J_{trans} = 17.5 Hz). Furthermore, in the paper published by Guiso et al. [38], deprotection of the TBDMS group was not done, since they reported that the Wittig reaction also deprotected the alcohol functionality. Only small amount of deprotected **72** was observed by TLC (< 20%) after the Wittig reaction on **70**. Full deprotection using TBAF gave 3-hydroxystyrene **72** in 88% yield (**Figure 54**).

Finally, 3-hydroxystyrene **72** was protected both as acetate **74** (see below) and MOM ether **73**, in 91% and 51% respectively. The relatively low yield obtained for the MOM protection was due to the presence of a second spot, possibly remaining starting material according to TLC, even after reacting overnight. ^{1}H NMR of MOM ether **73** (**Figure 55**) showed the characteristic peaks for the MOM group, singlet around 3.5 ppm for the CH_3 group and singlet around 5.2 ppm for the CH_2 group, as well as the characteristic peak for the acetate methyl group in ^{1}H NMR of **74** (**Figure 56**), around 2.3 ppm.

Having protected styrene **73** in hands, same conditions as in the Heck coupling reaction between **62** and styrene were applied in the coupling with **73**, which provided desired distyrenyl **75** in 96% yield (**Scheme 45**). Its structure was confirmed by ^{1}H NMR (**Figure 57**) which showed the presence of two singlets around 3.5 ppm for the MOM CH_3 groups and two more singlets around 5.2 ppm for the MOM CH_2 groups, as well as two doublets around 7.1 ppm and 7.6 ppm with J_{trans} = 16.6 Hz.

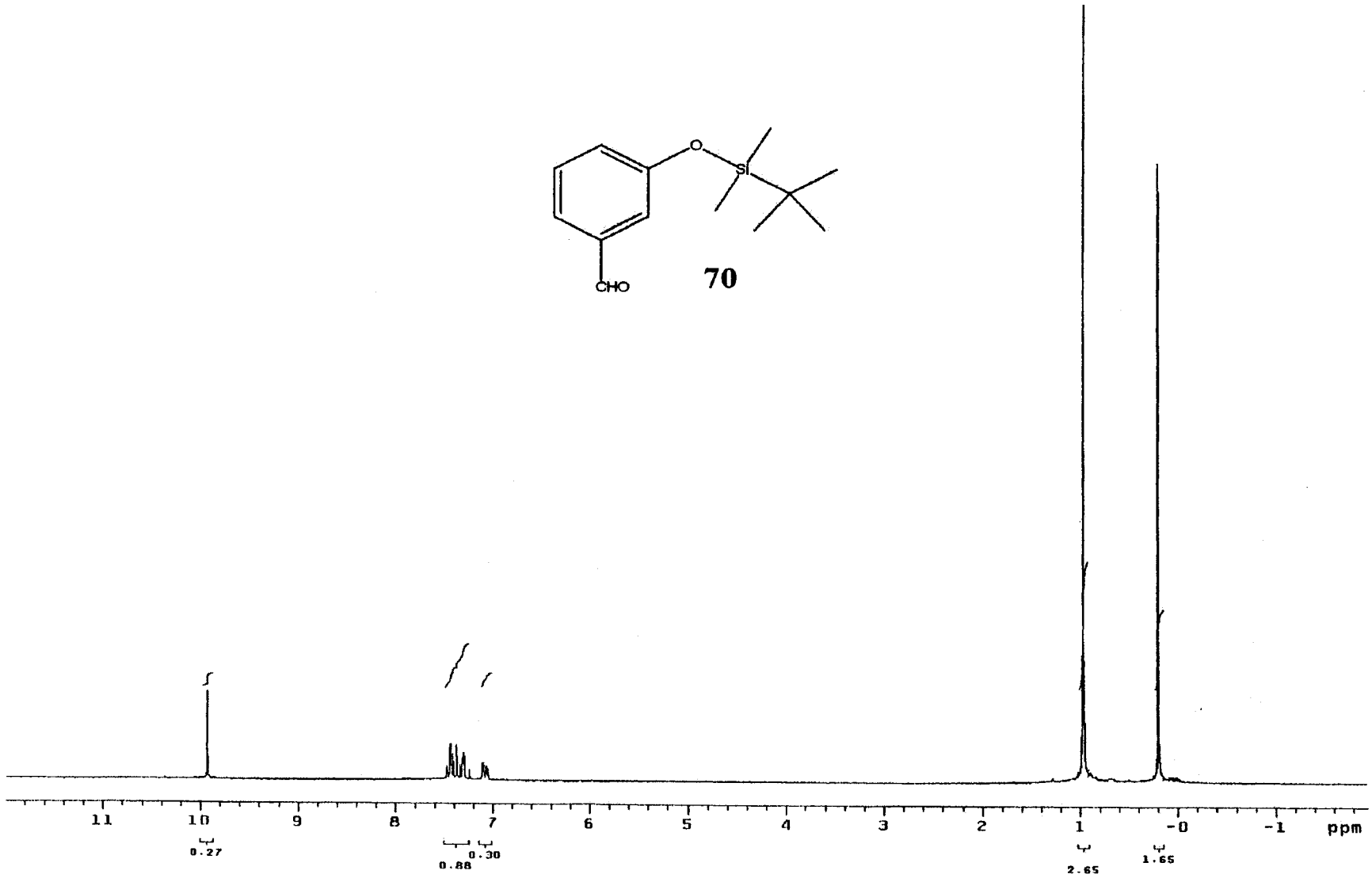


Figure 52: 200 MHz ^{1}H NMR of protected aldehyde **70** in $CDCl_3$

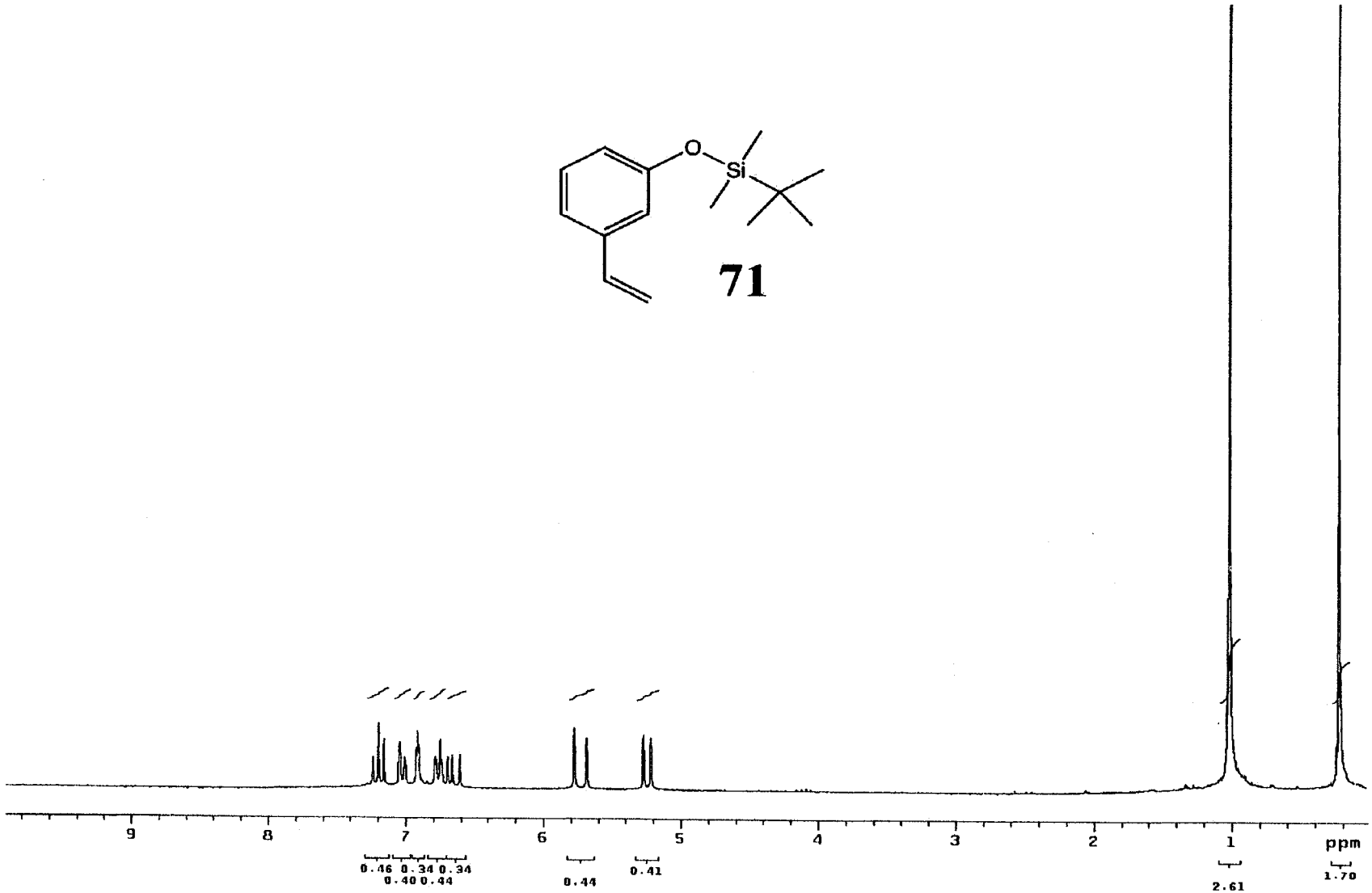
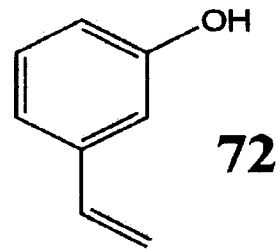


Figure 53: 200 MHz ^{1}H NMR of styryl **71** in $CDCl_3$



72

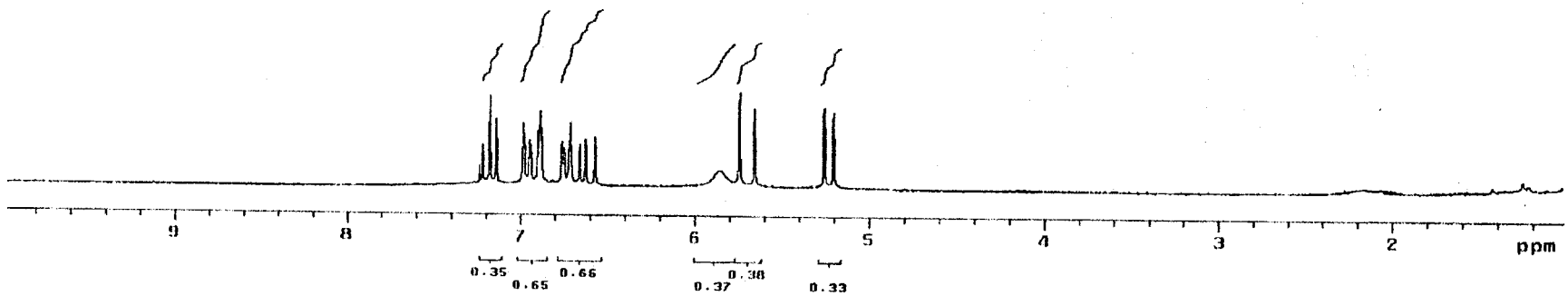


Figure 54: 200 MHz ^{1}H NMR of hydroxystyrene **72** in $CDCl_3$

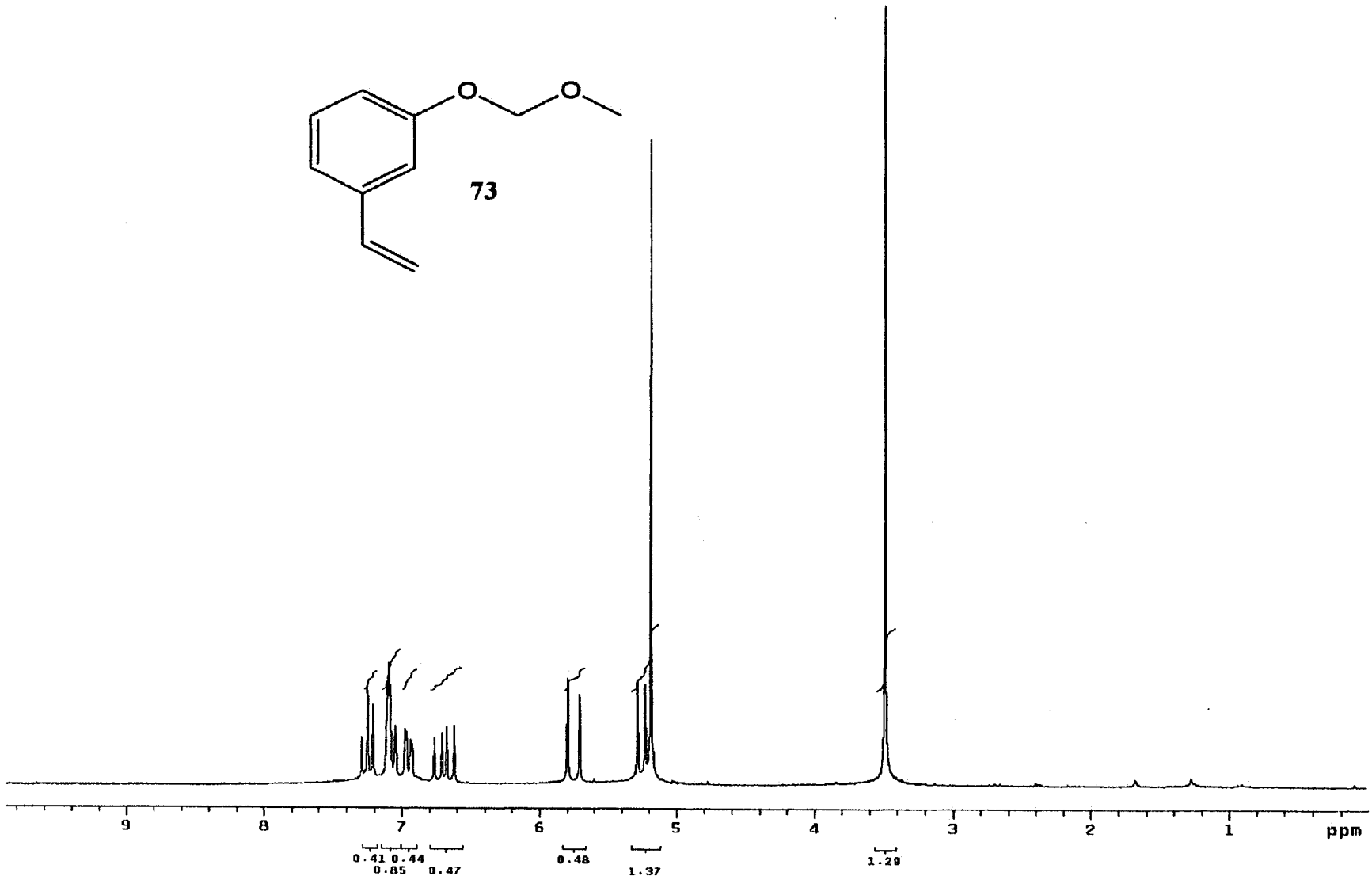


Figure 55: 200 MHz ^{1}H NMR of MOM ether **73** in $CDCl_3$

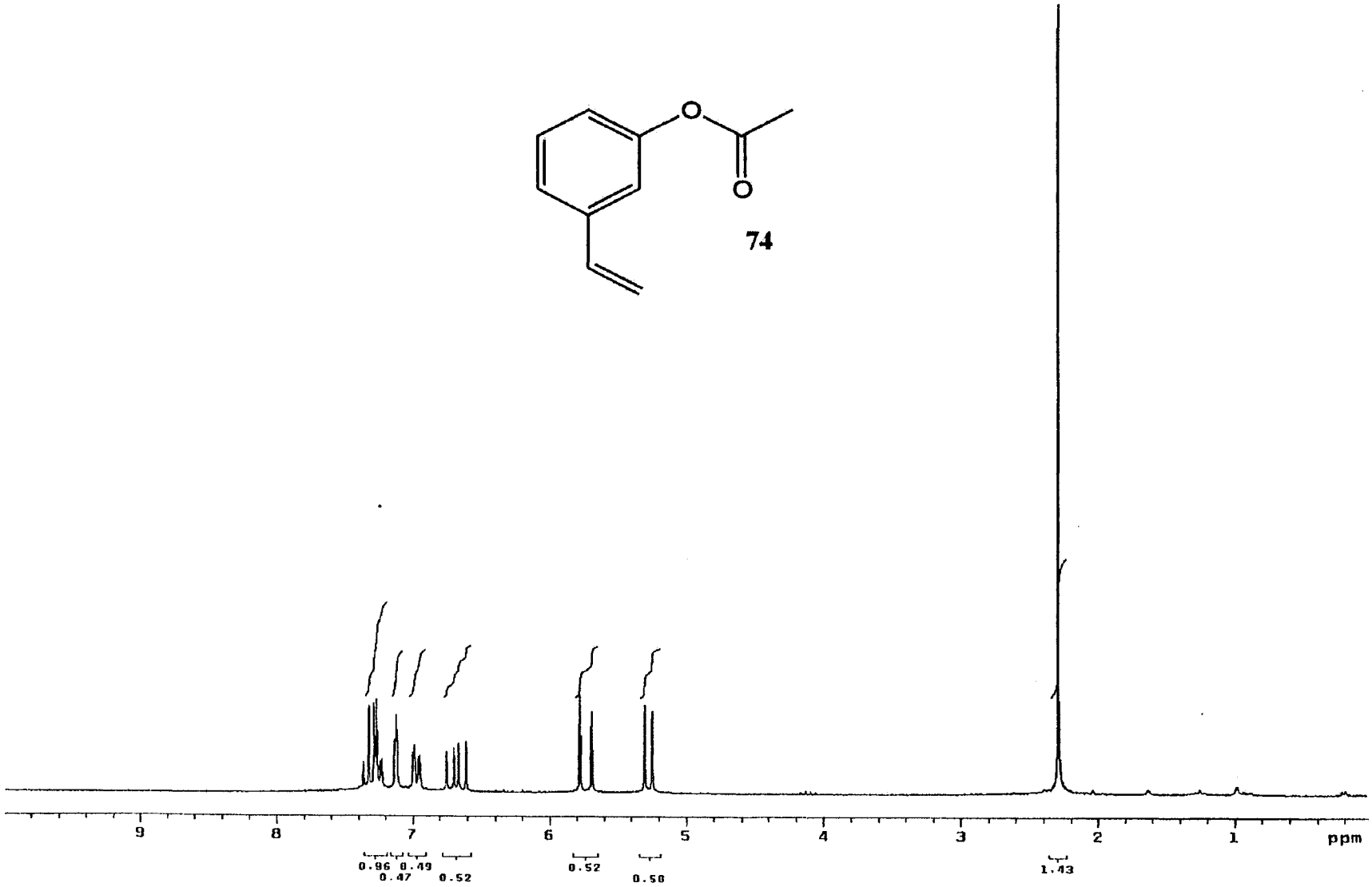


Figure 56: 200 MHz ^{1}H NMR of acetoxystyrene **74** in $CDCl_3$

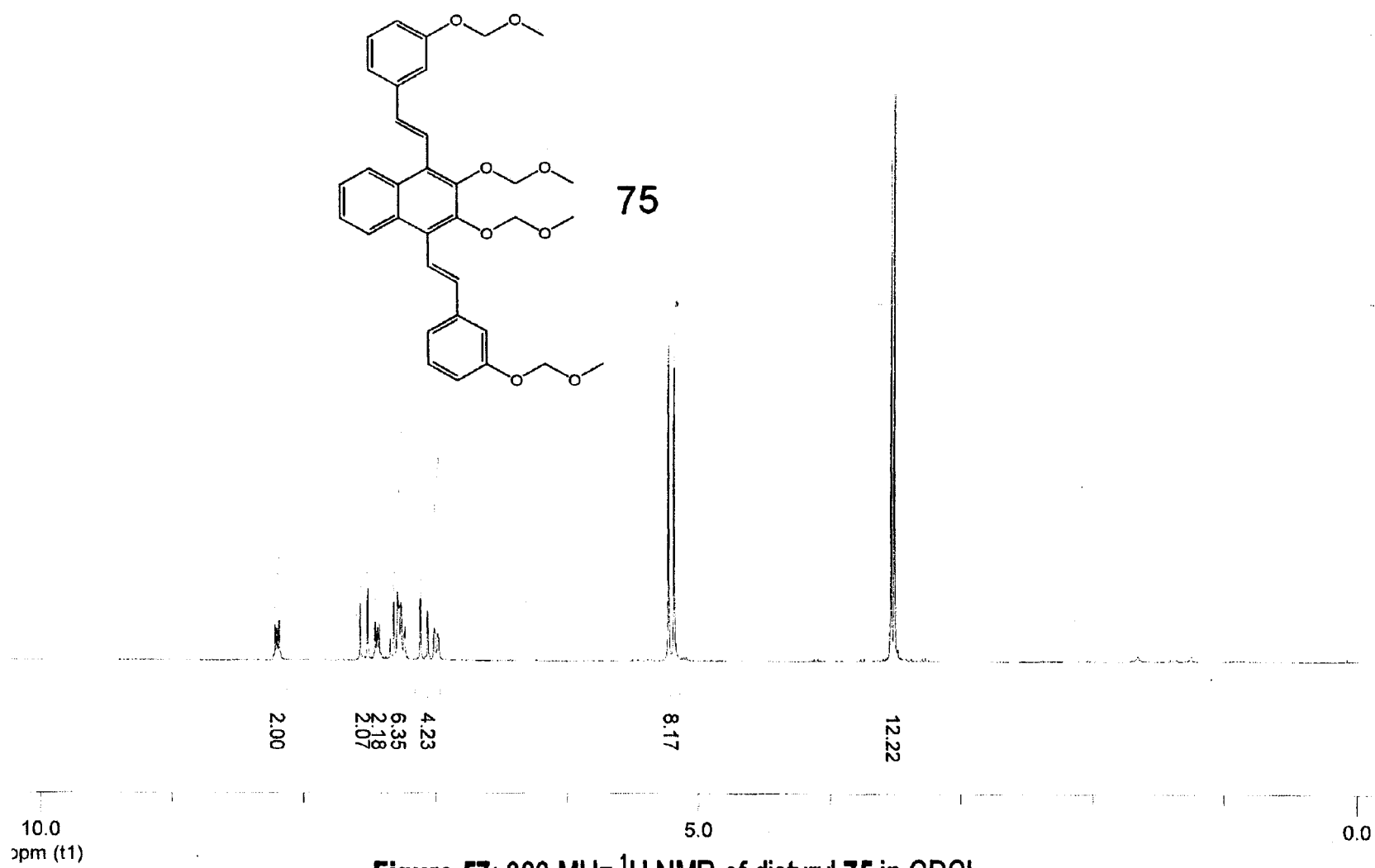
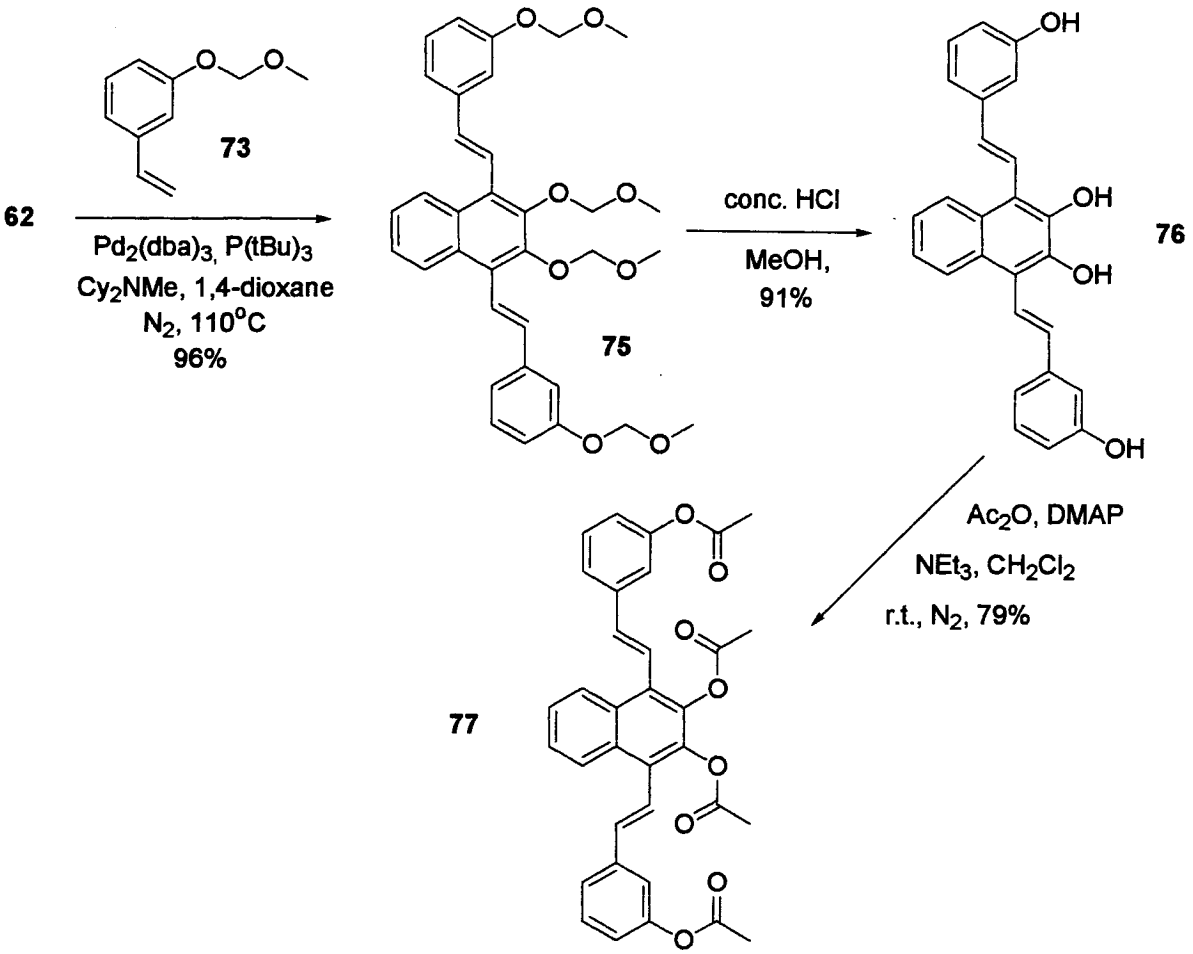


Figure 57: 300 MHz ^{1}H NMR of distyryl **75** in $CDCl_3$



Scheme 45: Synthesis of the more hydrophilic version of analogue **66** providing **76**, as well as its acetate version **77**

Deprotection of MOM groups using the standard conditions provided the desired more hydrophilic analogue **76** in 91% yield, whose ^{1}H NMR (**Figure 58**) showed a broad singlet around 8.4 ppm integrating for two of the four free OH groups in **76**.

Finally, ^{1}H NMR of **77** (**Figure 59**) showed the presence of two singlets around 2.3 ppm, integrating for 6H each, proved that each free OH groups in **76** was successfully acetylated in 79% yield.

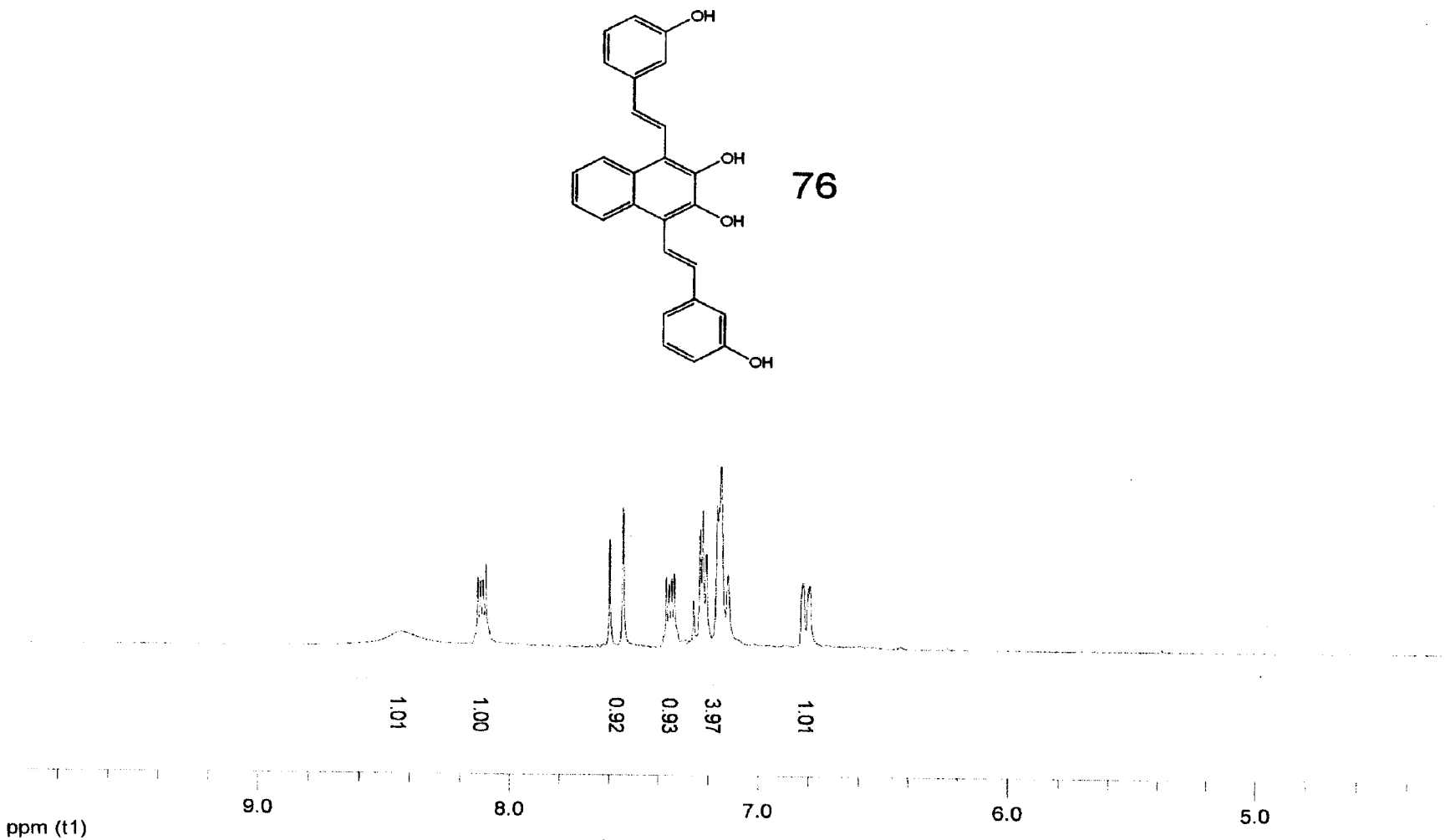


Figure 58: 300 MHz ^{1}H NMR of analogue **76** in acetone-d_6

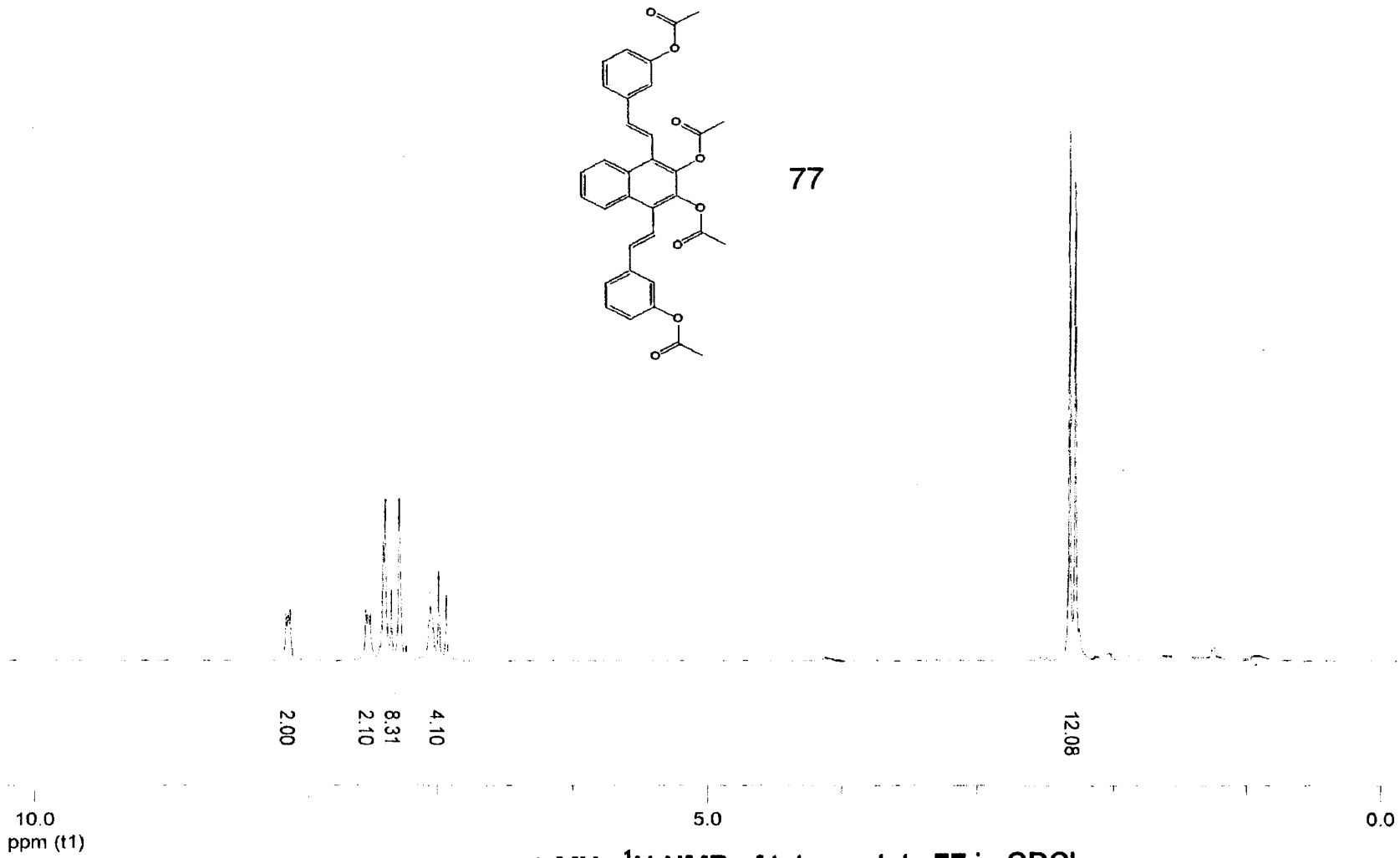
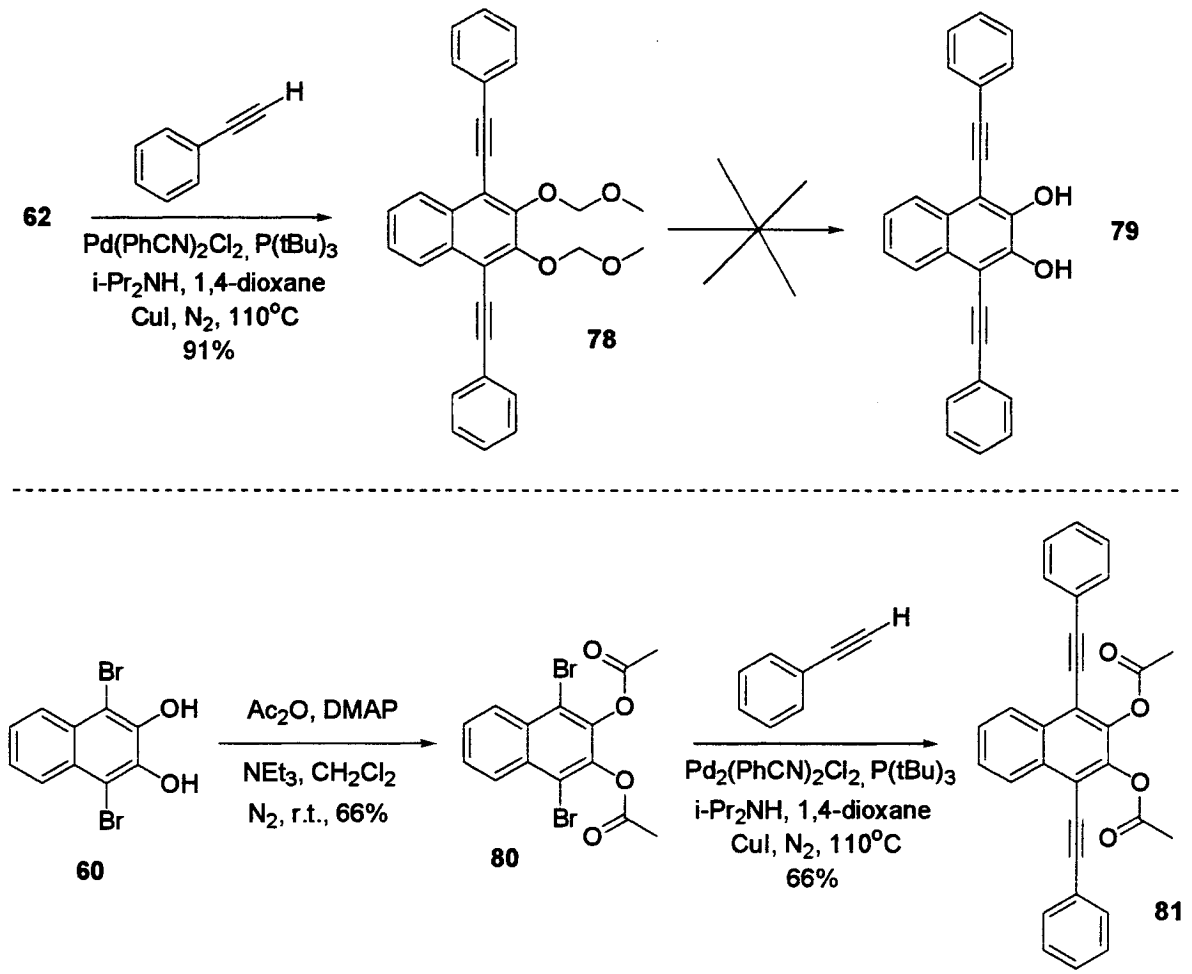


Figure 59: 300 MHz ^{1}H NMR of tetraacetate **77** in $CDCl_3$

At this point, we had analogues substituted at C1 and C4 of the design motif **16** with alkyl chains **23** and with conjugated olefins **66** and **76**. To complete this series, we decided to synthesize an analogue with conjugated triple bonds, and this was achieved by Sonogashira coupling reaction, using conditions developed by Fu et al. [37], between protected version of **60** and phenylacetylene (**Scheme 46**).



Scheme 46: Synthesis of **81**, as well as the attempted synthesis of **79**

The first Sonogashira coupling reaction afforded **78** in excellent yield (91%). The addition of two multiplets in the aromatic region of the ^{1}H NMR of **78** (**Figure 60**), around 7.4 and 7.7 ppm, corresponding to the added phenyl protons, showed that the coupling reaction was successful. Unfortunately, MOM

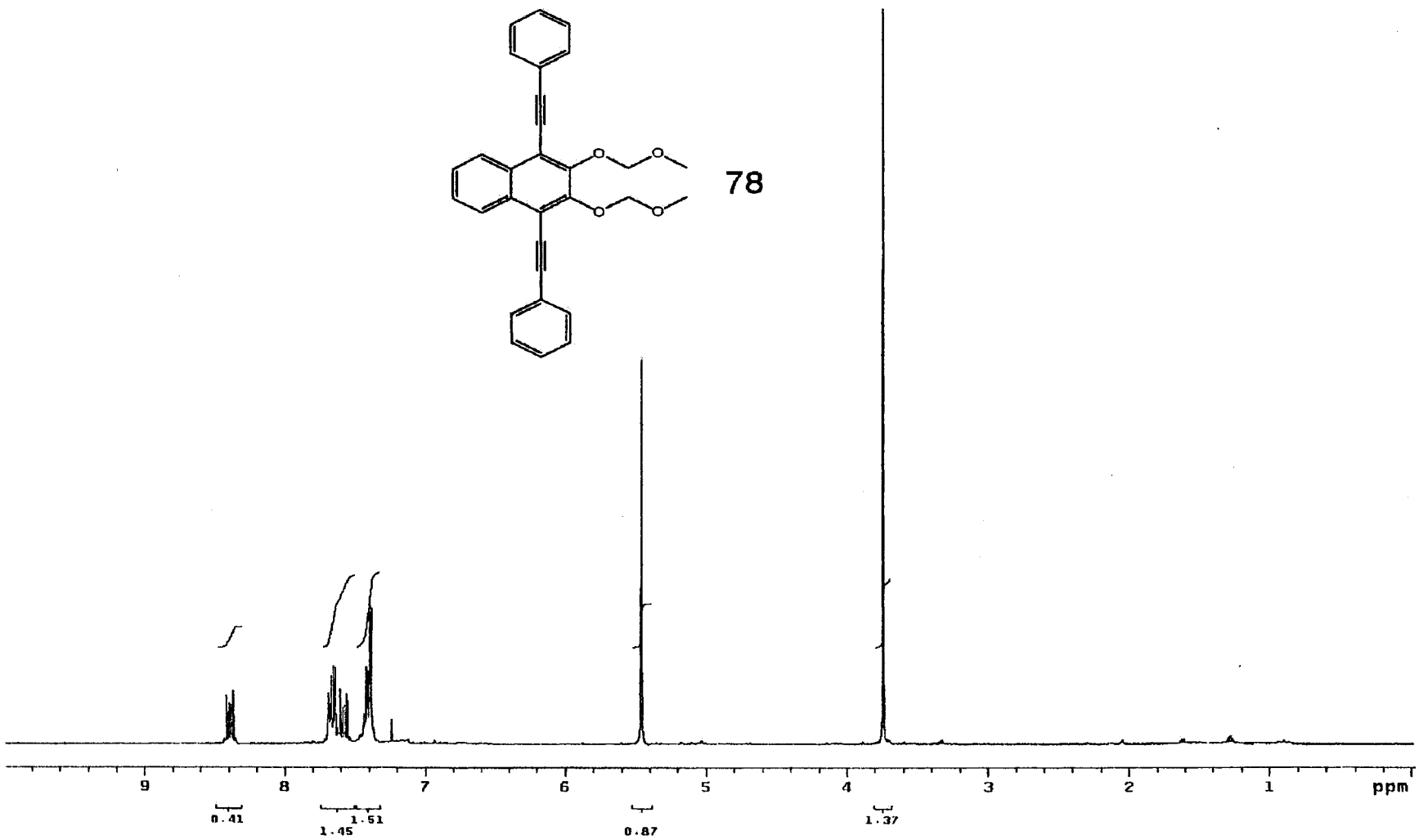
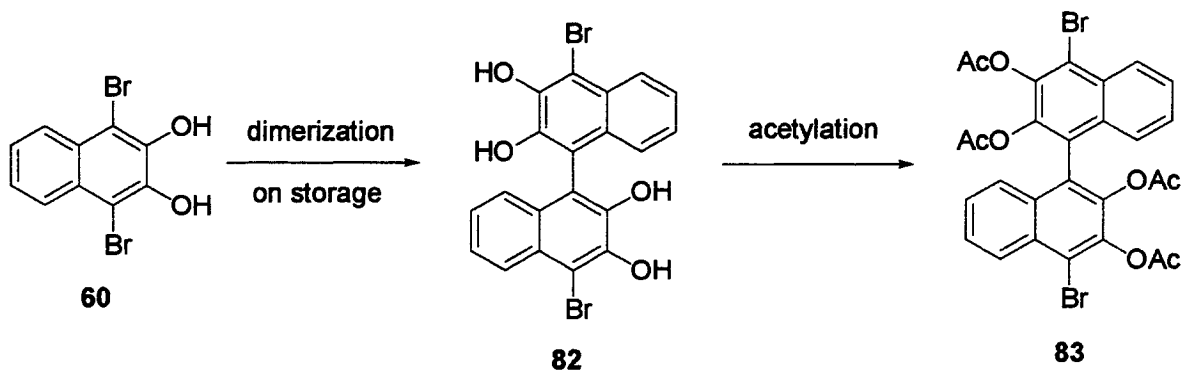


Figure 60: 200 MHz ^{1}H NMR of **78** in $CDCl_3$

deprotection of **78** resulted in the formation of many spots on TLC, probably due to the instability of the product; no **79** was isolated.

Synthesis of the diacetate of **79** was successful. Acetylation of **60** gave relatively low yield (66%) of diacetate **80** (**Figure 61**). The first time that this reaction was conducted, the yield obtained was only 42%. This was partly attributed to the dimerization of the starting material **60** on storage resulting in **82** (**Scheme 47**), possibly via the same kind of mechanism presented in **Scheme 21**. Indeed, by-product **83** was isolated in 9% yield after this reaction and its structure was confirmed by ^{1}H NMR (**Figure 62**), in which the aromatic region integrates for ten protons vs the OH groups. The mass spectra (**Figure 63**) gave the expected molecular ion peak at m/z = 642 with the characteristic 1:2:1 pattern indicating two bromine atoms.



Scheme 47: Formation of by-product **83**, isolated after the acetylation of **60**

Finally, coupling reaction with phenylacetylene provided diacetate **81** in 66% yield. The ^{1}H NMR (**Figure 64**) showed only multiplets integrating for 14H in the aromatic region vs the six acetyl hydrogens.

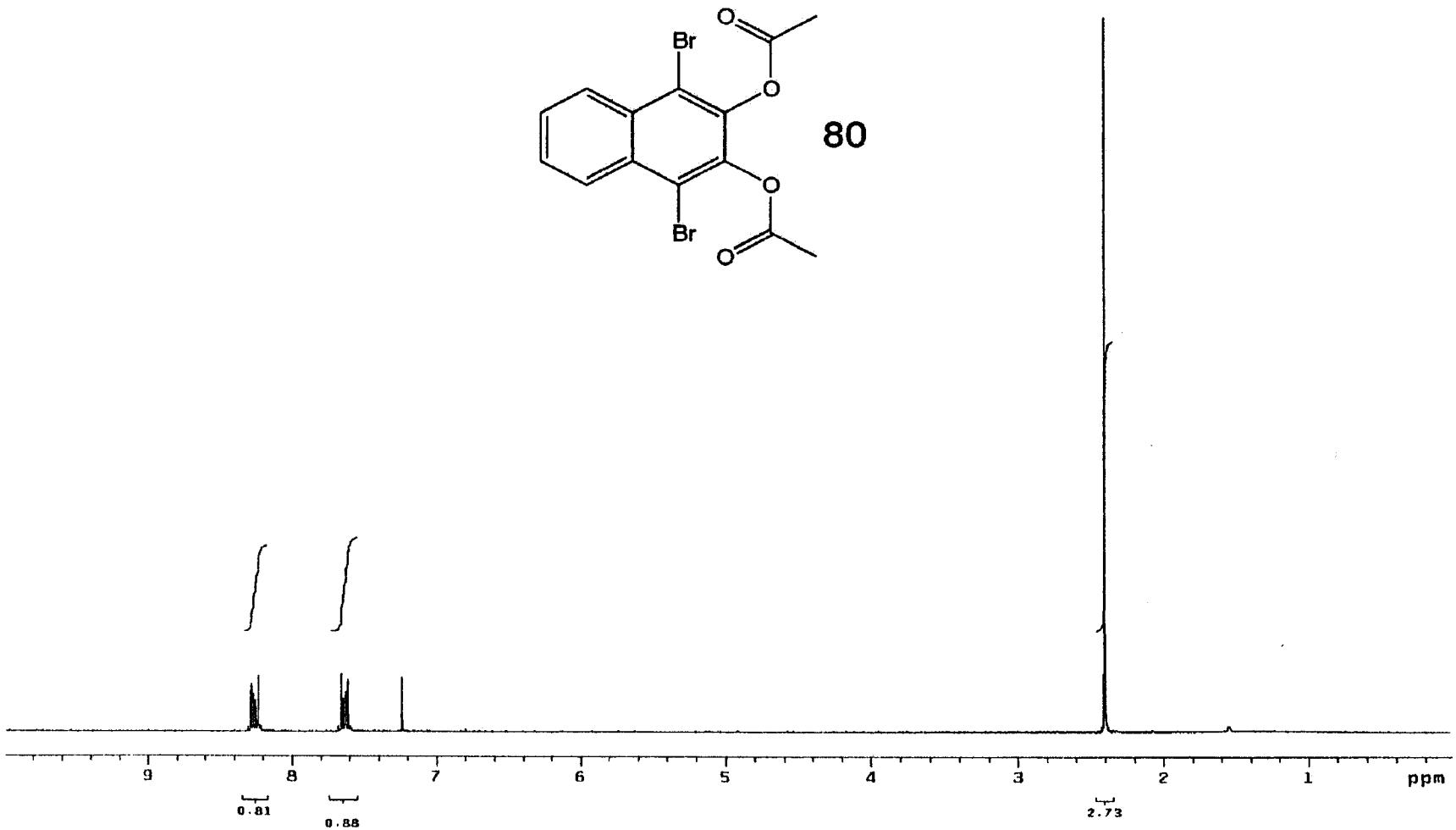


Figure 61: 200 MHz ^{1}H NMR of diacetate **80** in $CDCl_3$

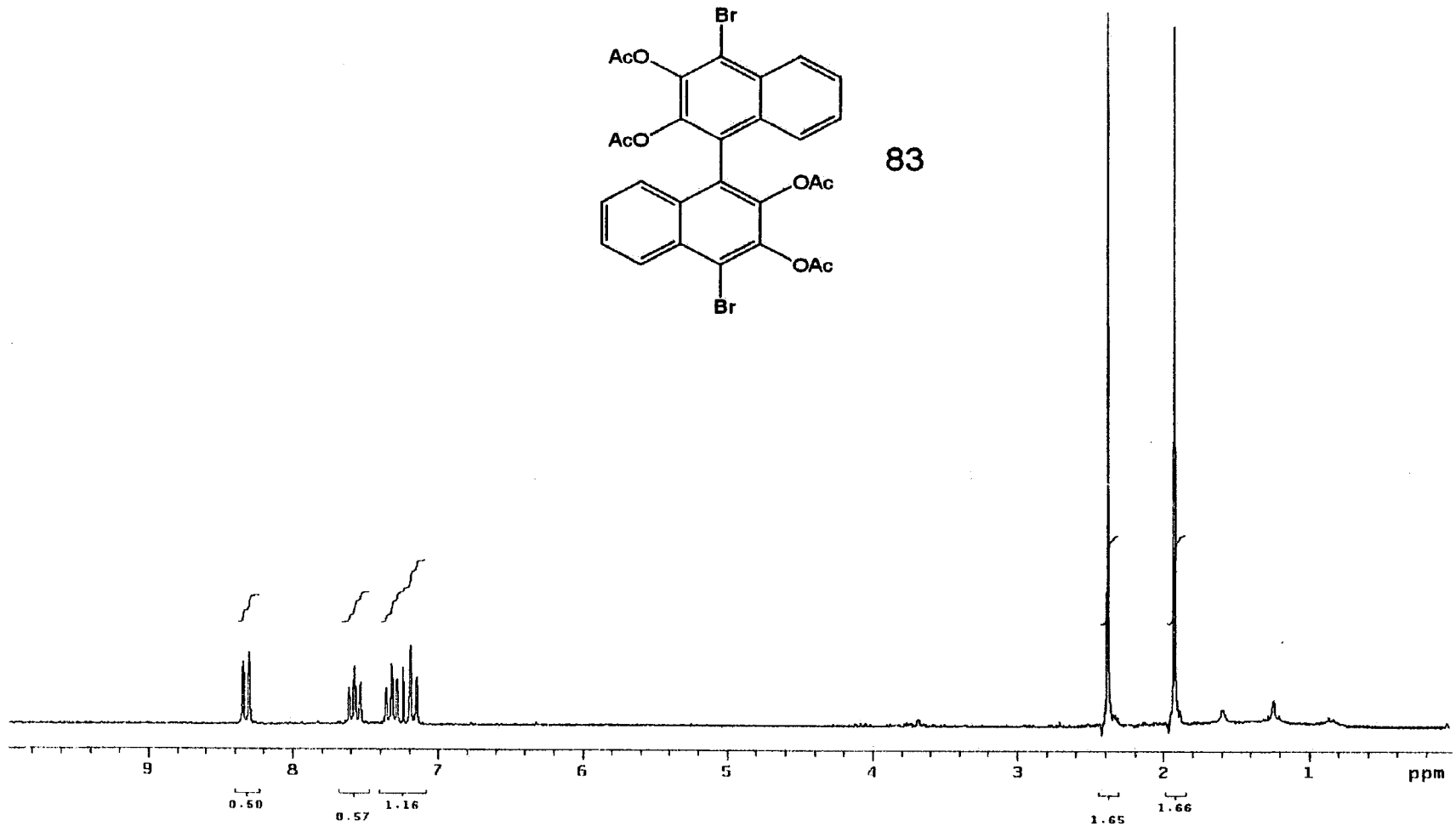


Figure 62: 200 MHz ^{1}H NMR of by-product **83** in $CDCl_3$

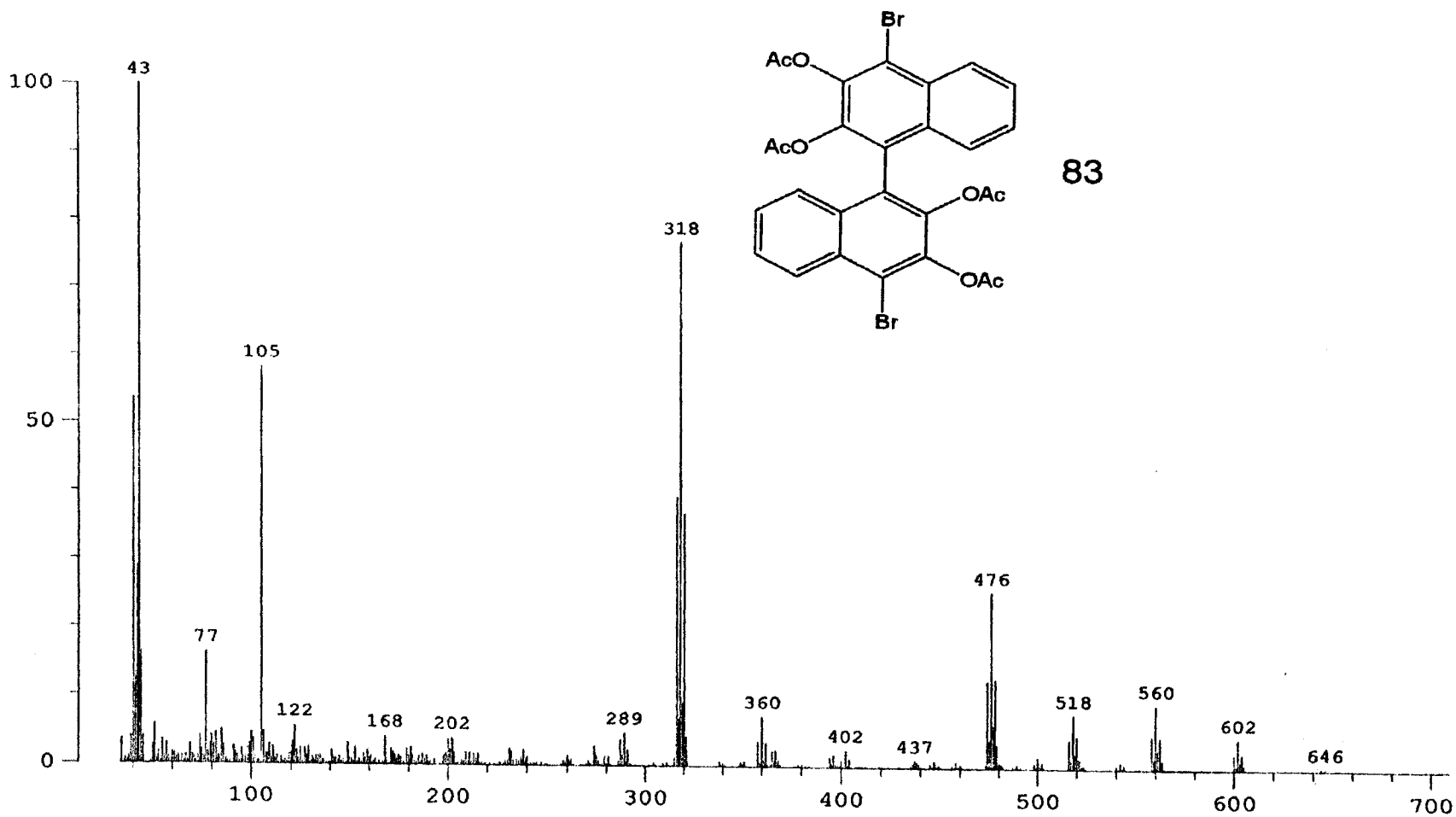


Figure 63: Mass spectrum of by-product **83**

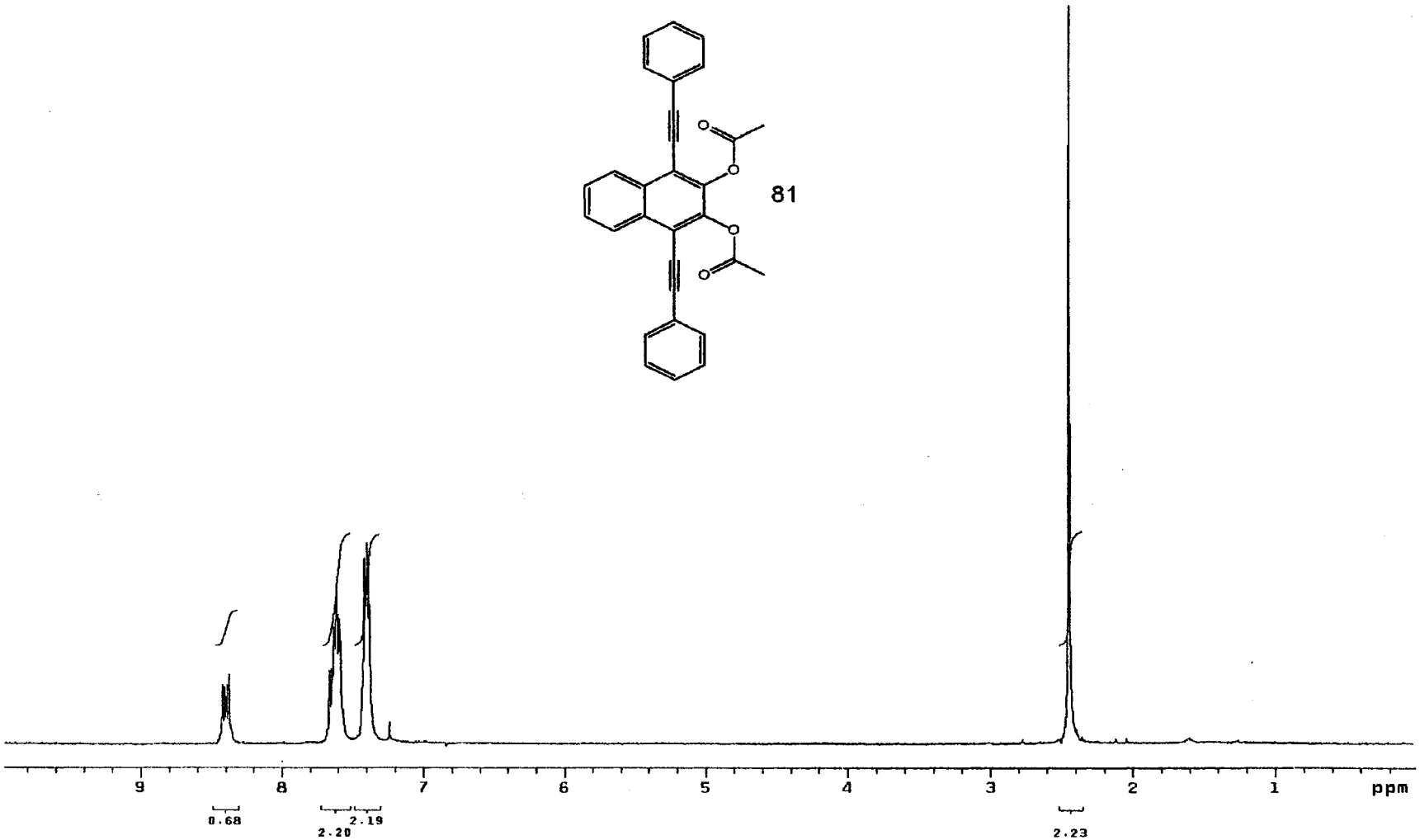
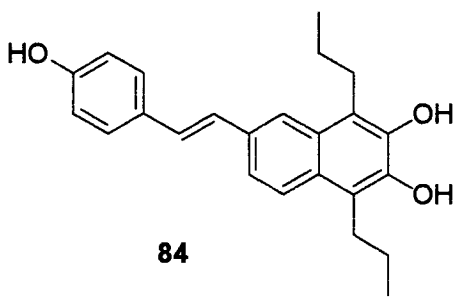


Figure 64: 200 MHz ^{1}H NMR of diacetate **81** in $CDCl_3$

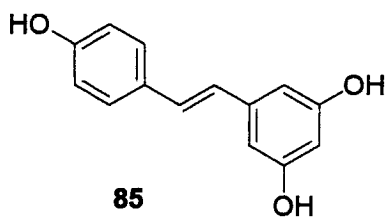
Based on the results obtained in the bromination of naphthalene-2,3-diol (**16**), we rationalized that bromination of **23** should result in bromination at either position C6 or C6 and C7. From these intermediates it should be possible to introduce new substituents, for example vinyl groups, at C6 and at C7 using the same approach as was used for the preparation of **79** and **81**.

Compound **84** (**Scheme 48**) was chosen as the first target. This compound could be considered as an analogue of the well known resveratrol, a key constituent found in the skin of the red grape. Resveratrol **85** (**Scheme 48**) is known to possess not only antioxidant activity, but also cyclooxygenase inhibition, platelet aggregation inhibition and inhibition of tumor initiation, only to mention these properties [40].



84

new target

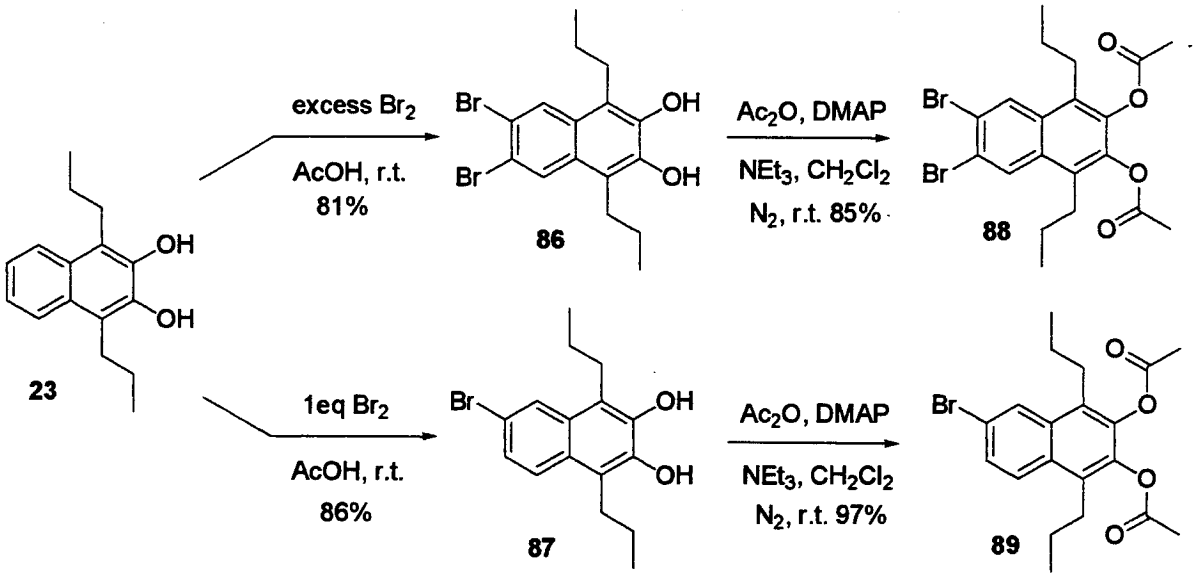


85

resveratrol

Scheme 48: Resveratrol **85** and the new target **84**

Reaction of **23** with an excess of bromine (**Scheme 49**) gave the 7,8-dibromo derivative **86** in 81% yield. The ^{1}H NMR of the product (**Figure 65**) showed only a large singlet in the aromatic region, corresponding to H5 and H8, proving that the product was diol **86**.



Scheme 49: Results of bromination reactions on **23**, as well as their acetylation

The use of 1eq of bromine afforded **87** in 86% yield after column chromatography. The ^{1}H NMR of **87** (**Figure 66**) showed the expected pattern for the aromatic protons: one doublet of doublets around 7.4 ppm for H6, a doublet around 7.8 ppm for H5 and a doublet around 8.0 ppm for H8.

Acetylation of **86** and **87** gave the diacetates **88** and **89** in good yields. The ^{1}H NMR of **88** (**Figure 67**) and **89** (**Figure 68**) showed in each cases the characteristic peak of the added acetates around 2.4 ppm.

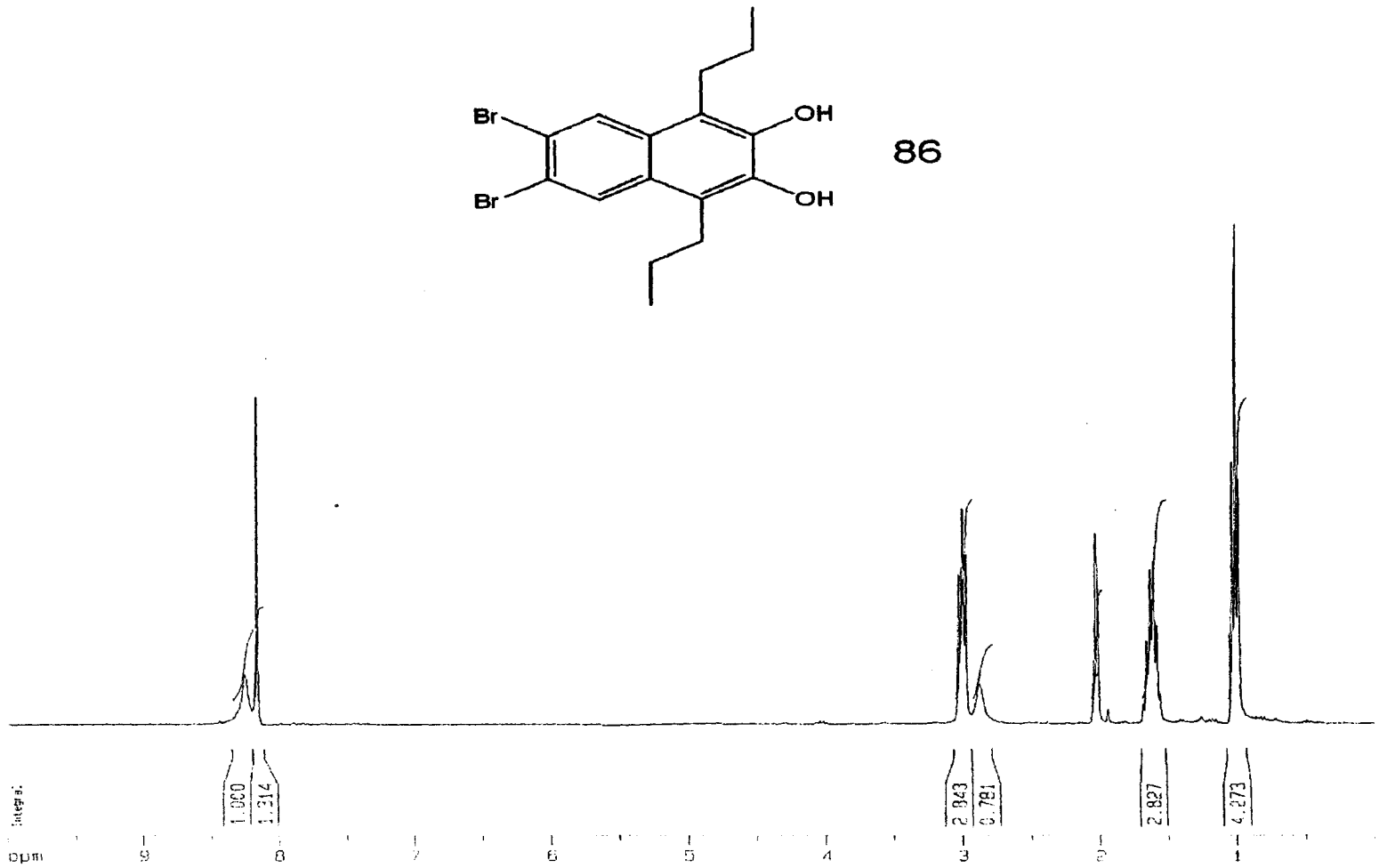


Figure 65: 300 MHz ^{1}H NMR of diol **86** in acetone-d_6

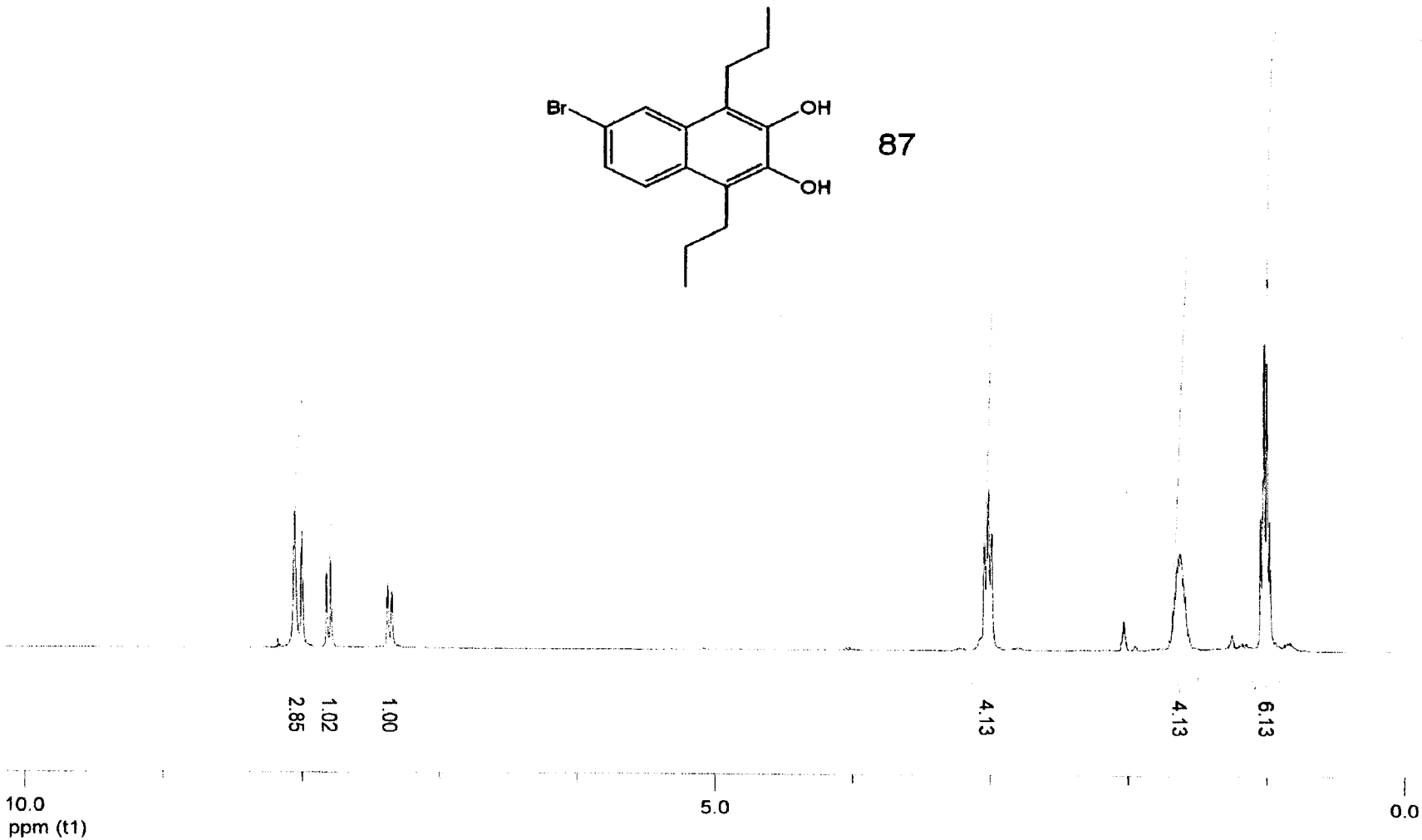


Figure 66: 300 MHz ^{1}H NMR of diol **87** in acetone-d_6

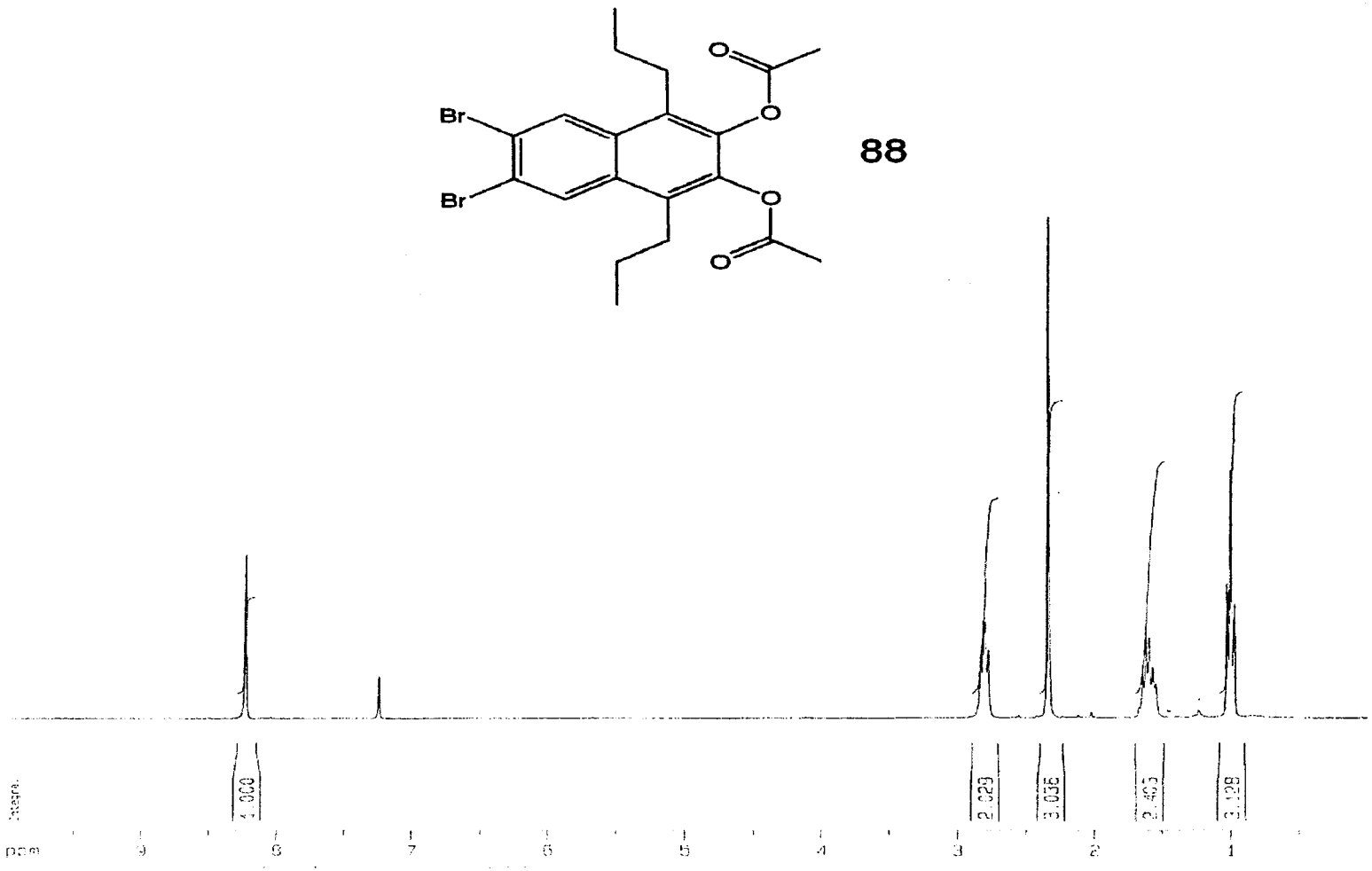


Figure 67: 300 MHz ^{1}H NMR of diacetate **88** in $CDCl_3$

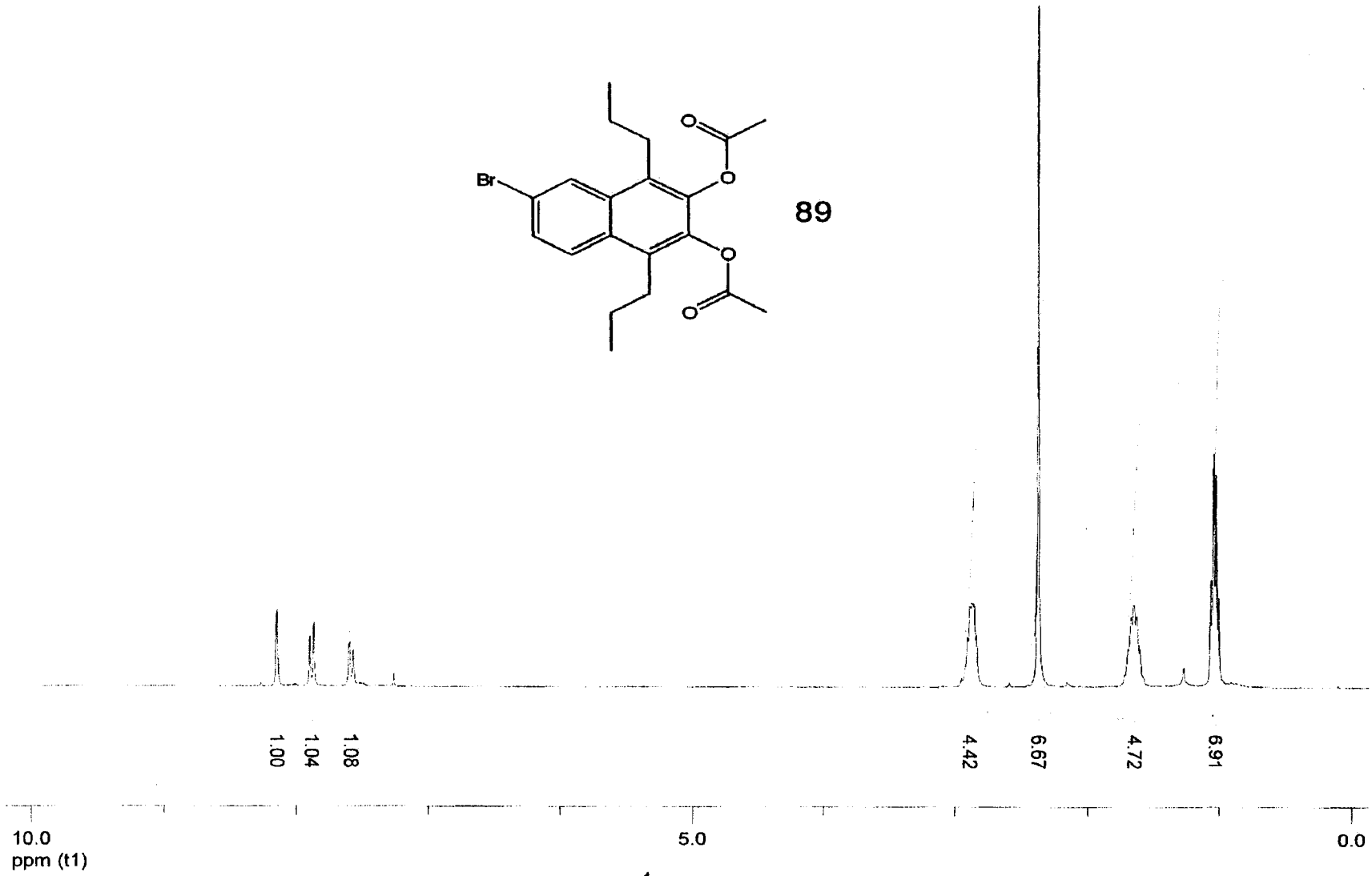
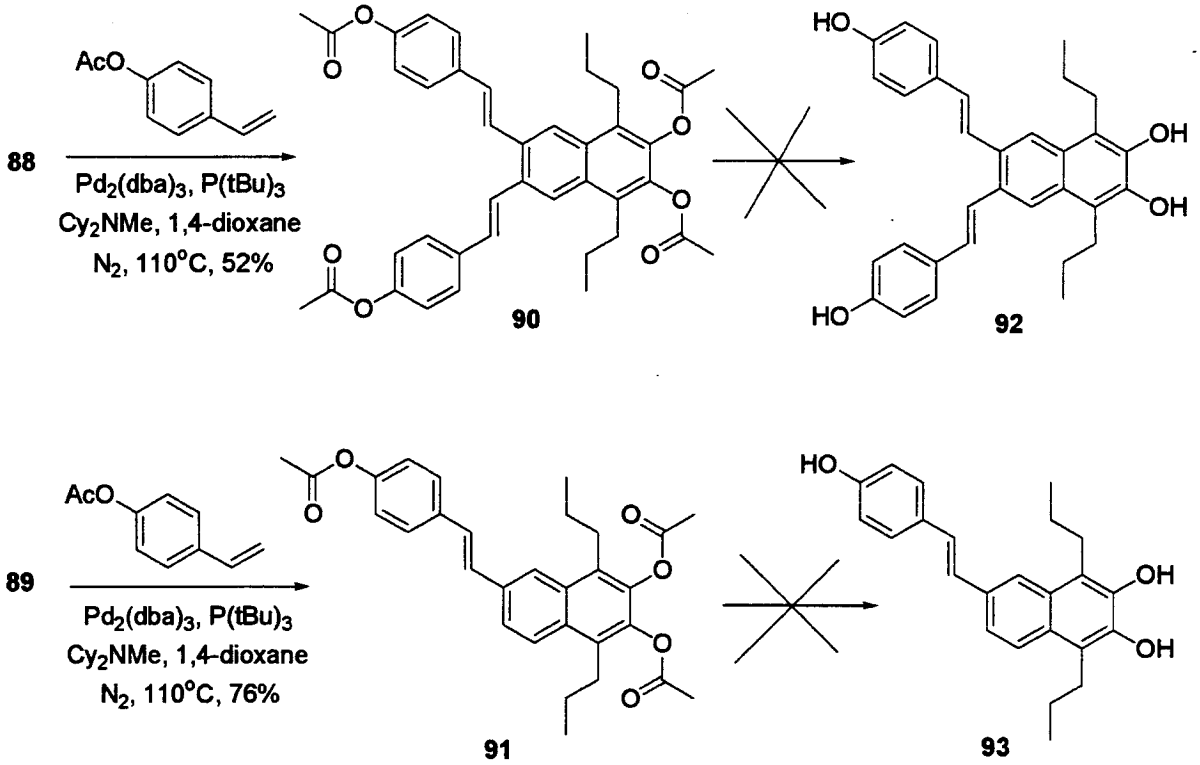


Figure 68: 300 MHz ^{1}H NMR of diacetate **89** in $CDCl_3$



Scheme 50: Results obtained in the coupling reactions with 4-acetoxystyrene

Heck coupling reactions between the acetates **88** and **89** and the commercially available 4-acetoxystyrene (**Scheme 50**) provided their respective products **90** and **91** with moderate yields. The ^{1}H NMR of **90** (**Figure 69**) clearly showed the presence of two additional acetate groups with the extra singlet around 2.3 ppm, as well as two doublets with J_{trans} = 15.8 Hz around 7.0 and 7.4 ppm, proving that the alkene stereochemistry was trans. The ^{1}H NMR of **91** (**Figure 70**) was in general agreement with the assigned structure but could not be used to assign the alkene stereochemistry which is assumed to be trans. Unfortunately, deprotection of the acetate groups using basic conditions to yield the final targets **92** and **93** was not successful.

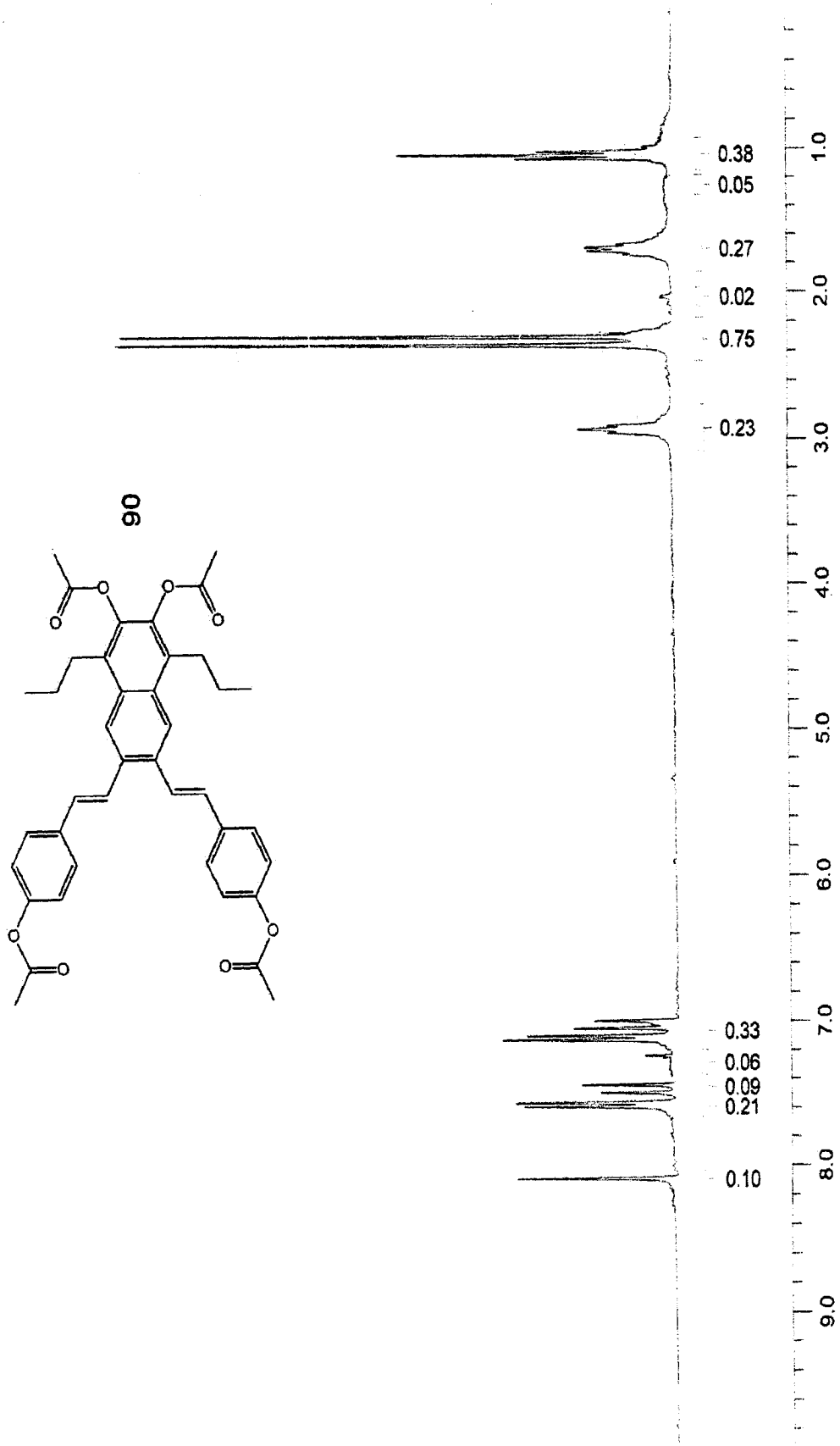


Figure 69: 300 MHz ^{1}H NMR of **90** in $CDCl_3$

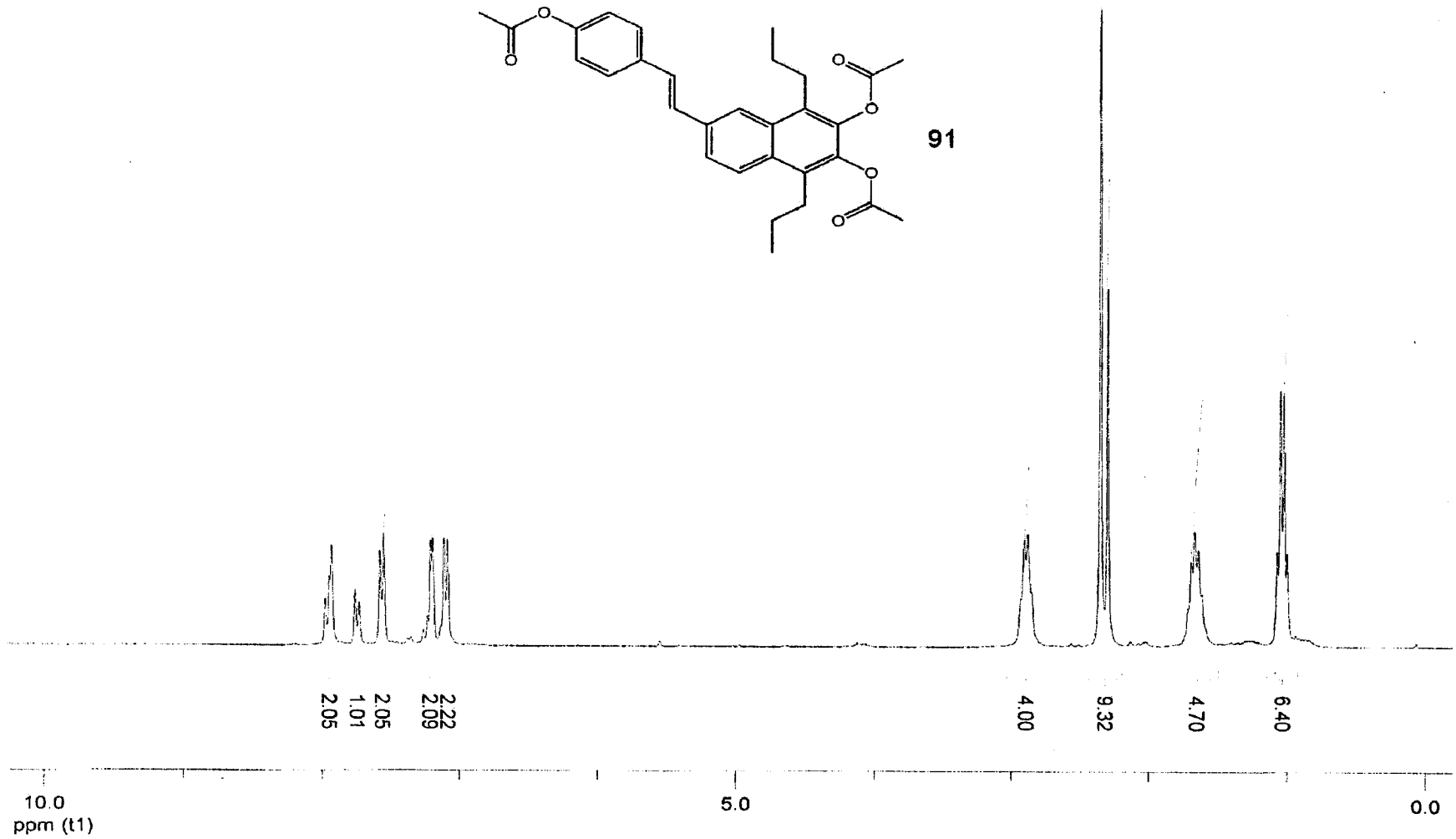
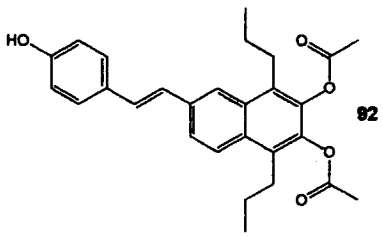


Figure 70: 300 MHz ^{1}H NMR of **91** in $CDCl_3$

In some experiments, only partially deprotected products were produced according to ^1H NMR of the crude product. When the partially deprotected products were resubmitted to the reaction conditions longer time, many spots were seen on TLC indicating a complex mixture of products. The reactions conditions and TLC appearances are resumed in **Table 10**.

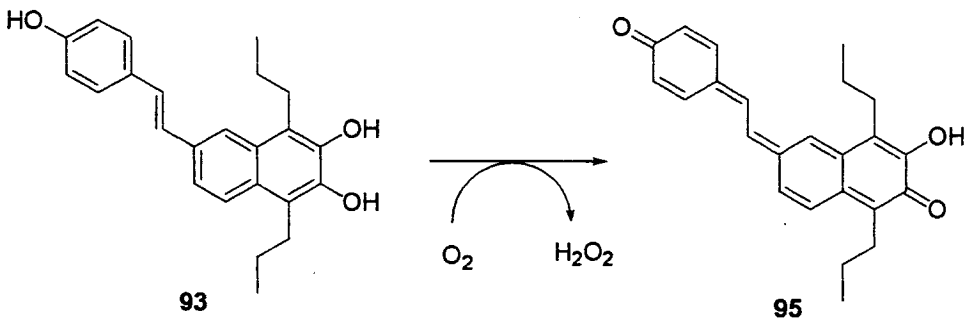
S.M.	Conditions	TLC appearance
90	KOH, THF 65°C, 2h	Many spots
91	-NaOH, THF/H_2O 9/1 40-50°C, 1h -same conditions	-1 spot, partially deprotected product **92** -many spots
91	NaOH, MeOH/H_2O 9/1 N_2, 65°C, 4h	Many spots



92

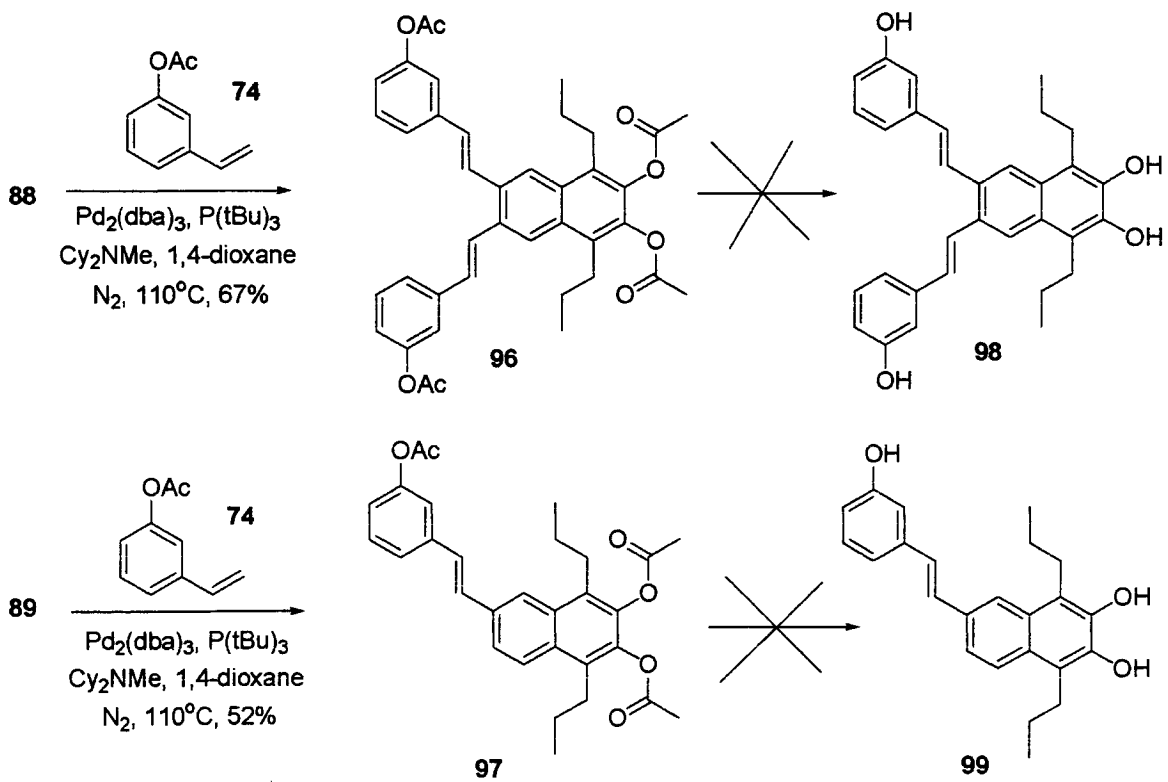
Table 10: Reaction conditions tried in the acetate deprotection of **90** and **91**

We also thought that this deprotection problem, resulting in many spots on TLC, could come from the fact that these compounds could be oxidized to their respective diketones (**Scheme 51**), even though such compounds were never isolated. In order to investigate this possibility, we decided to couple **88** and **89** with 3-acetoxystyrene **74** (**Scheme 44**), even if the products obtained from these reactions **98** and **99** would be less active as antioxidants because the meta OH group is much less effective as a radical stabilizer than when at the para position (**Scheme 52**).



Scheme 51: Possible formation of diketone **95** through oxidation by air, probably resulting in other by-products

Coupling reactions between **88** and **89** with 3-acetoxystyrene (**74**) using the same conditions gave essentially the same results as when 4-acetoxystyrene was used. Because the aromatic and olefinic protons were essentially in the same region of the ^{1}H NMR of **96** (**Figure 71**) and **97** (**Figure 72**), integration were important in order to verify the structures obtained.



Scheme 52: Coupling reactions of **88** and **89** with 3-acetoxystyrene **74**

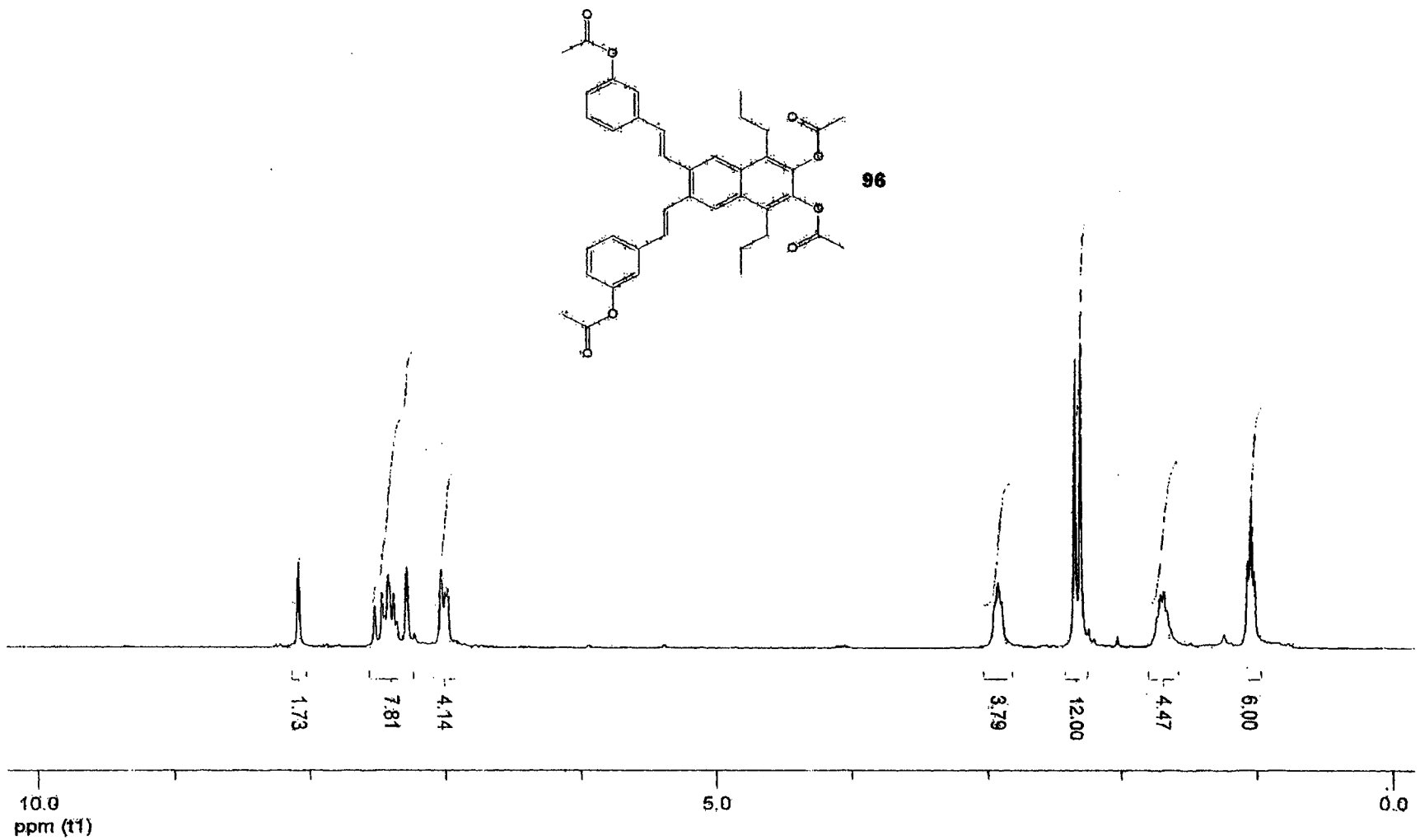


Figure 71: 300 MHz ^{1}H NMR of **96** in $CDCl_3$

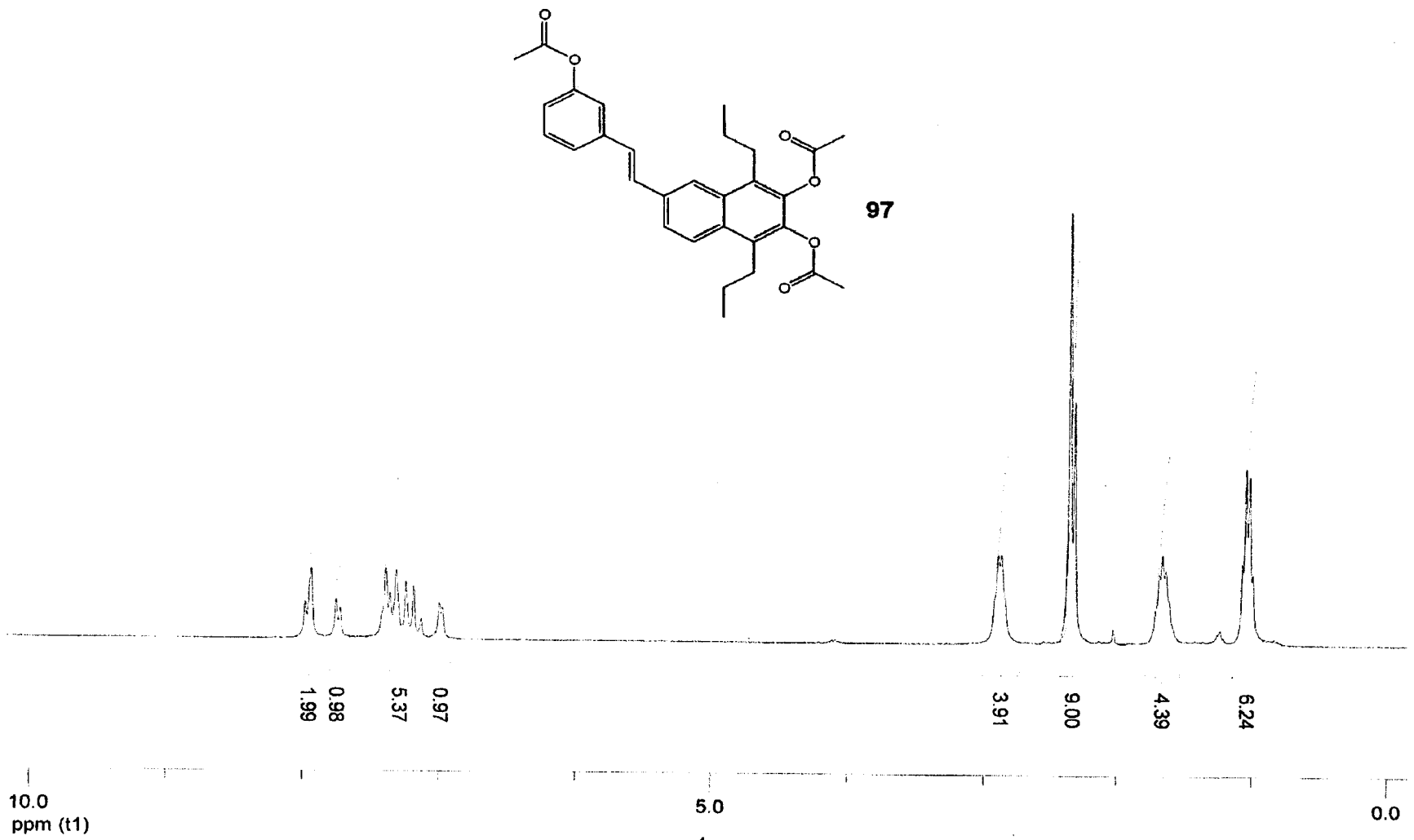
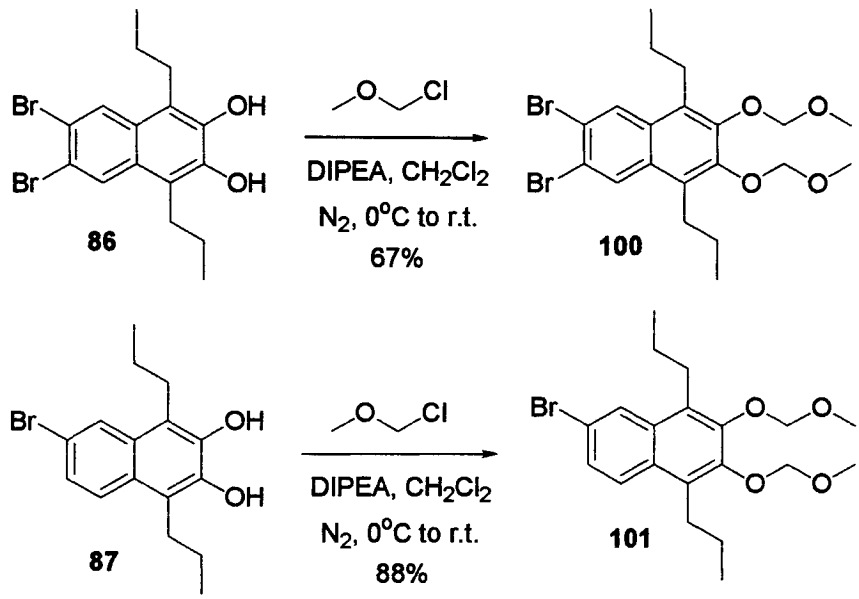


Figure 72: 300 MHz ^{1}H NMR of **97** in $CDCl_3$

Again, removal of the acetate groups under basic conditions gave the same unexpected results (**Table 10**) as with 4-acetoxystyrenyl coupling products **91** and **92**. It was thought that these compounds were probably not stable under basic conditions, thus acetate deprotection using acidic conditions (conc. HCl, MeOH/H_2O 6/4, 70°C) was tried once on **96**. This method resulted in only partially deprotected product according to ^1H NMR of the crude reaction product, suggesting that deprotection of acetate groups from 2,3-naphthol functionality was not as easy as expected. Since deprotection of MOM groups worked well for the other compounds synthesized in this subsection, we then went back to **86** and **87** and protected the two hydroxyl groups with MOM groups (**Scheme 53**).



Scheme 53: MOM protection of diols **86** and **87**

The protected bromides **100** (**Figure 73**) and **101** (**Figure 74**) were obtained in 67% and 88% yield respectively. The ^1H NMR showed the presence of the characteristic peaks for the MOM groups in each case. Having these compounds in hands, Heck coupling reactions between **100** and **101** with **73** was performed (**Scheme 54**), giving respectively 89% and 80% yield (compared to 67% and 52% for **96** and **97**), supporting the suggestion that better yields were obtained when the

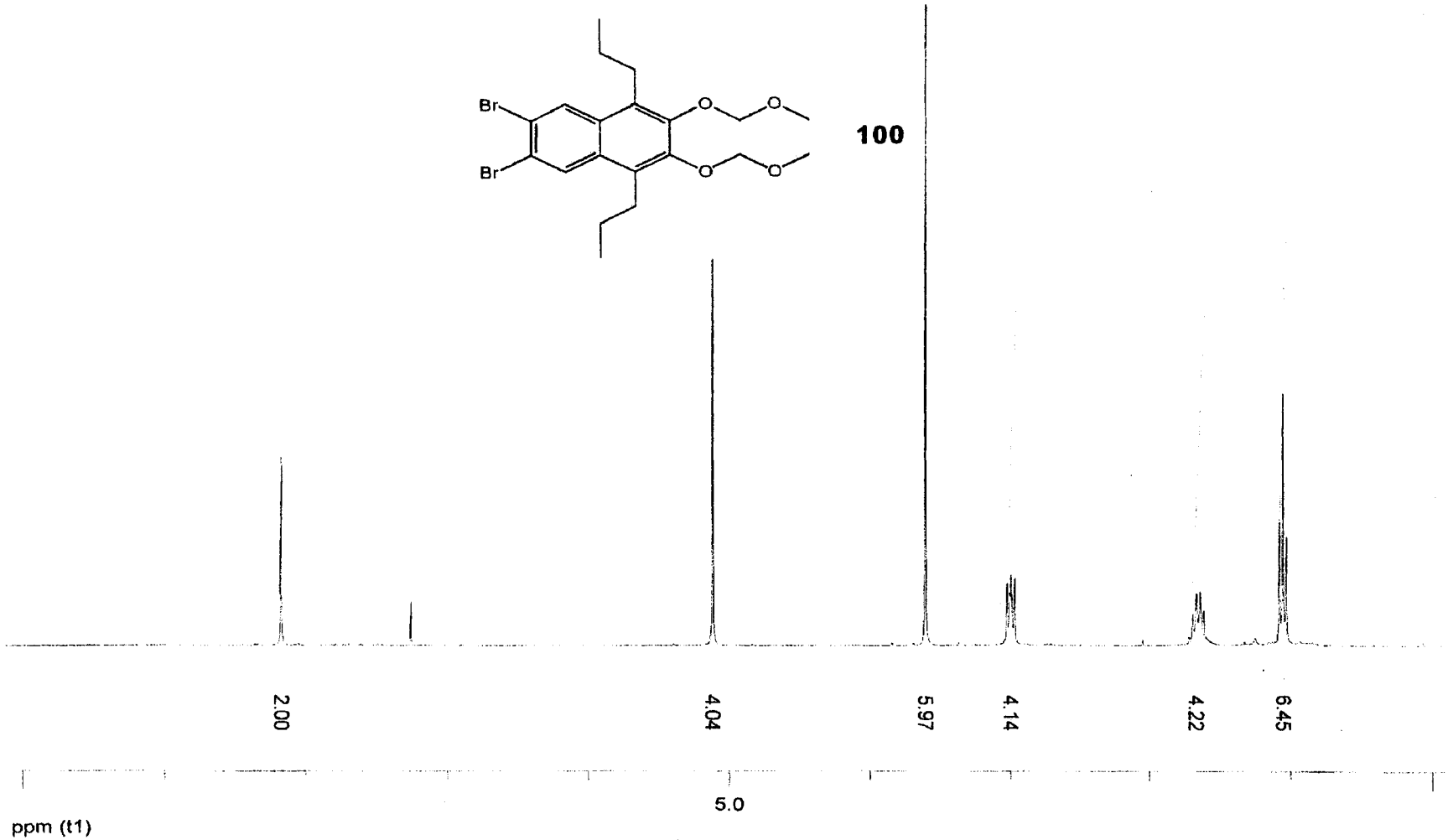


Figure 73: 300 MHz ^{1}H NMR of dibromide **100** in $CDCl_3$

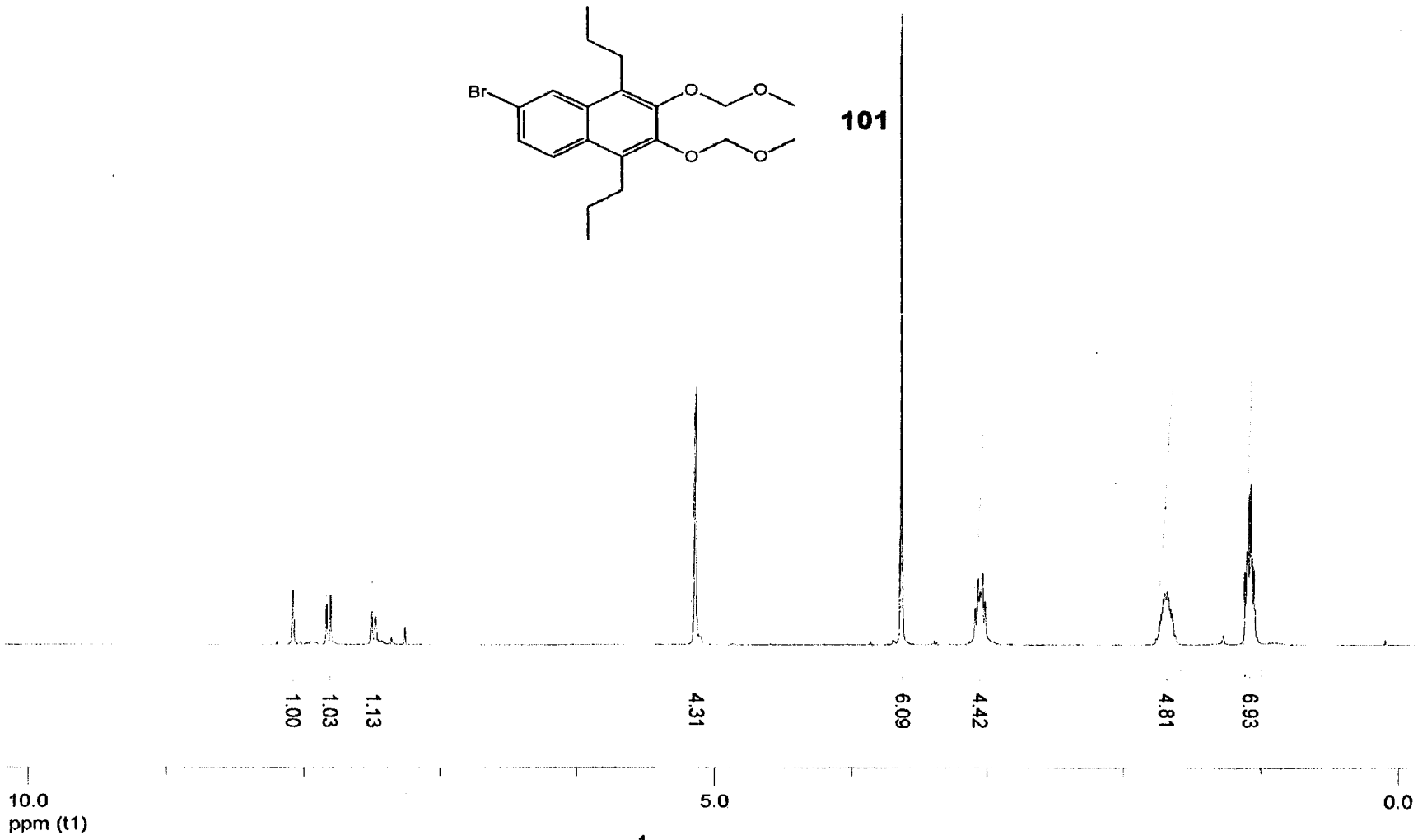
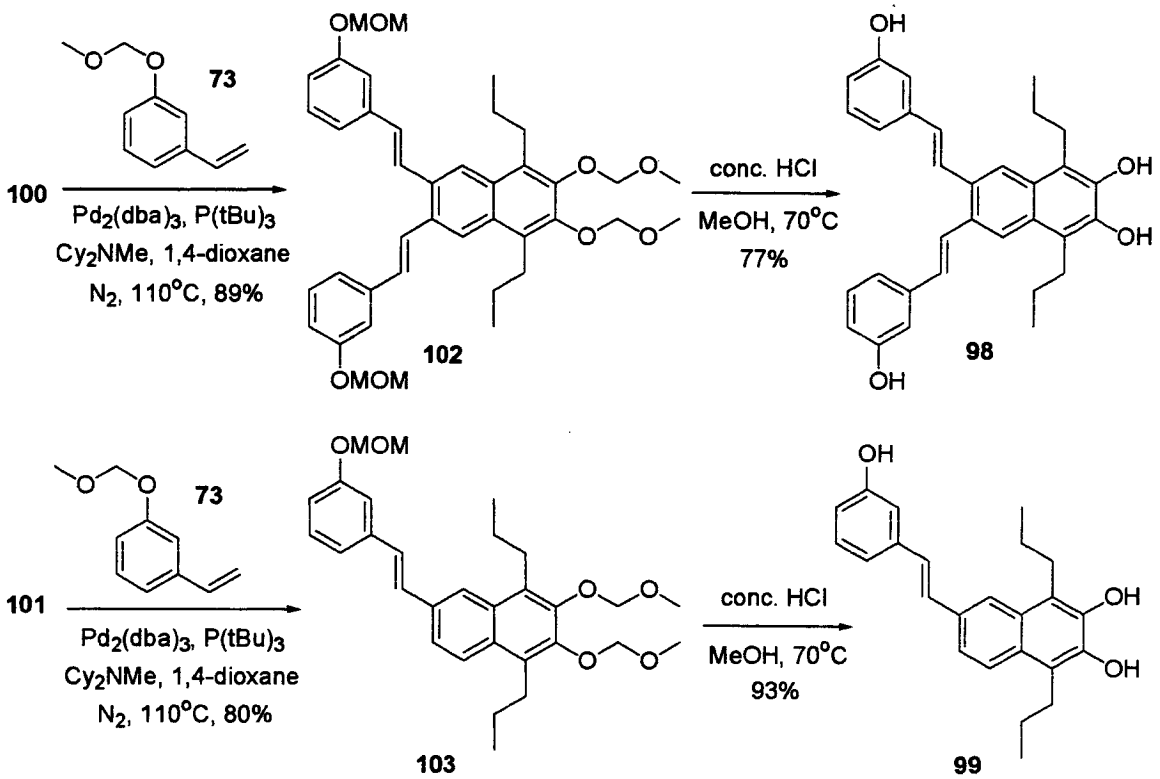


Figure 74: 300 MHz ^{1}H NMR of bromide **101** in $CDCl_3$

hydroxyl groups in coupling partners were protected as MOM groups. Again, ^{1}H NMR of distyrenyl **102** (**Figure 75**) showed clearly the presence of trans olefins with two doublets with trans coupling constants around 7.0 and 8.0 ppm.



Scheme 54: Synthesis of analogues **98** and **99**

In contrast, ^{1}H NMR of **103** (**Figure 76**) could not be used to assign the alkene stereochemistry. However, the ratio of aromatic to the various non-aromatic peaks proved that the coupling reaction was successful.

The efforts made in generating **102** and **103** as precursors for the synthesis of **98** and **99**, respectively, were not in vain. Deprotection of MOM groups using the standard conditions afforded fully deprotected analogues **98** and **99** in respectable yields after column chromatography, showing that these compounds had considerable stability under appropriate conditions.

The ^{1}H NMR of **98** (**Figure 77**) showed three singlets between 8.0-8.5 ppm, one for the two remaining identical naphthalene aromatic protons, and the other

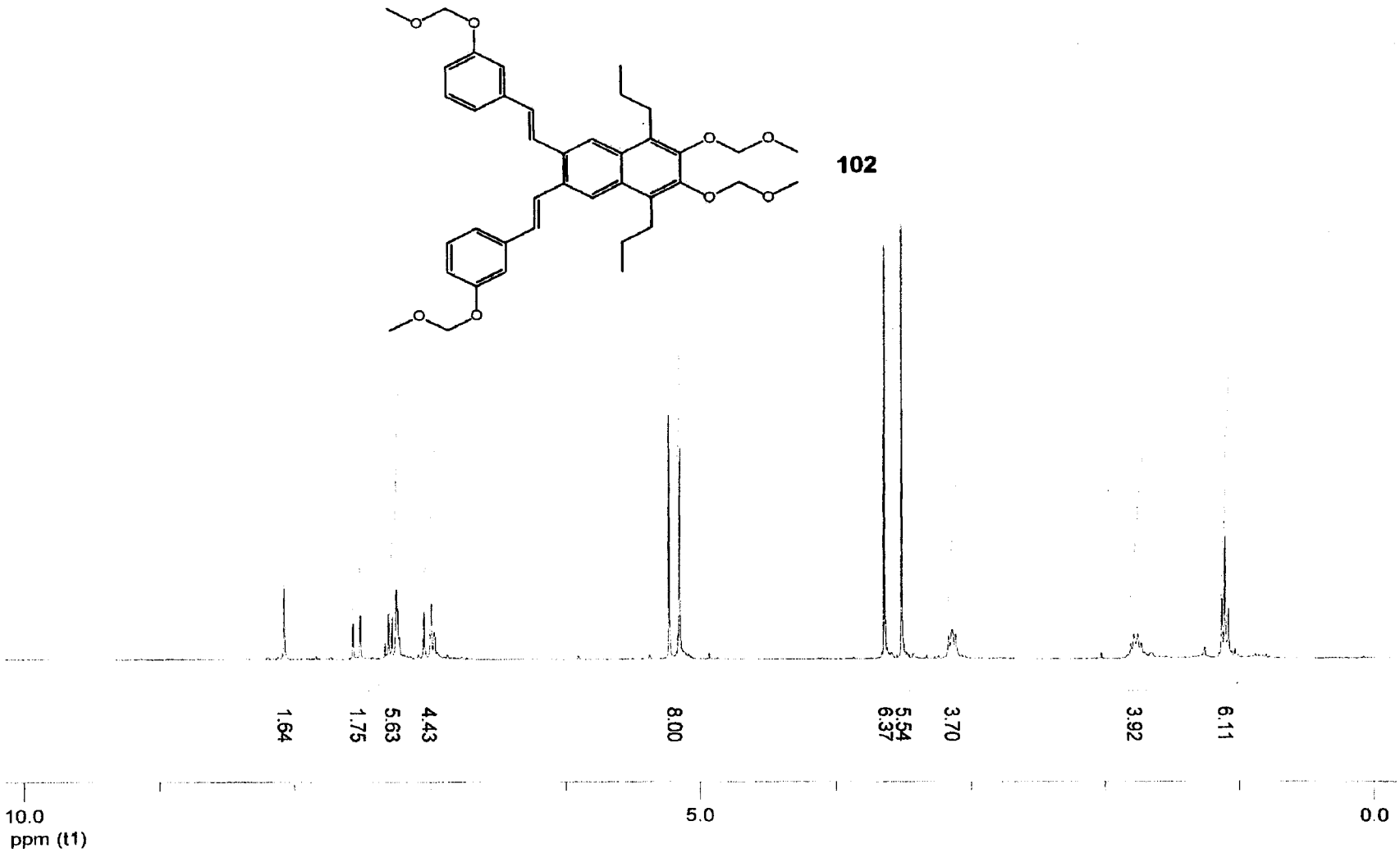


Figure 75: 300 MHz ^{1}H NMR of **102** in $CDCl_3$

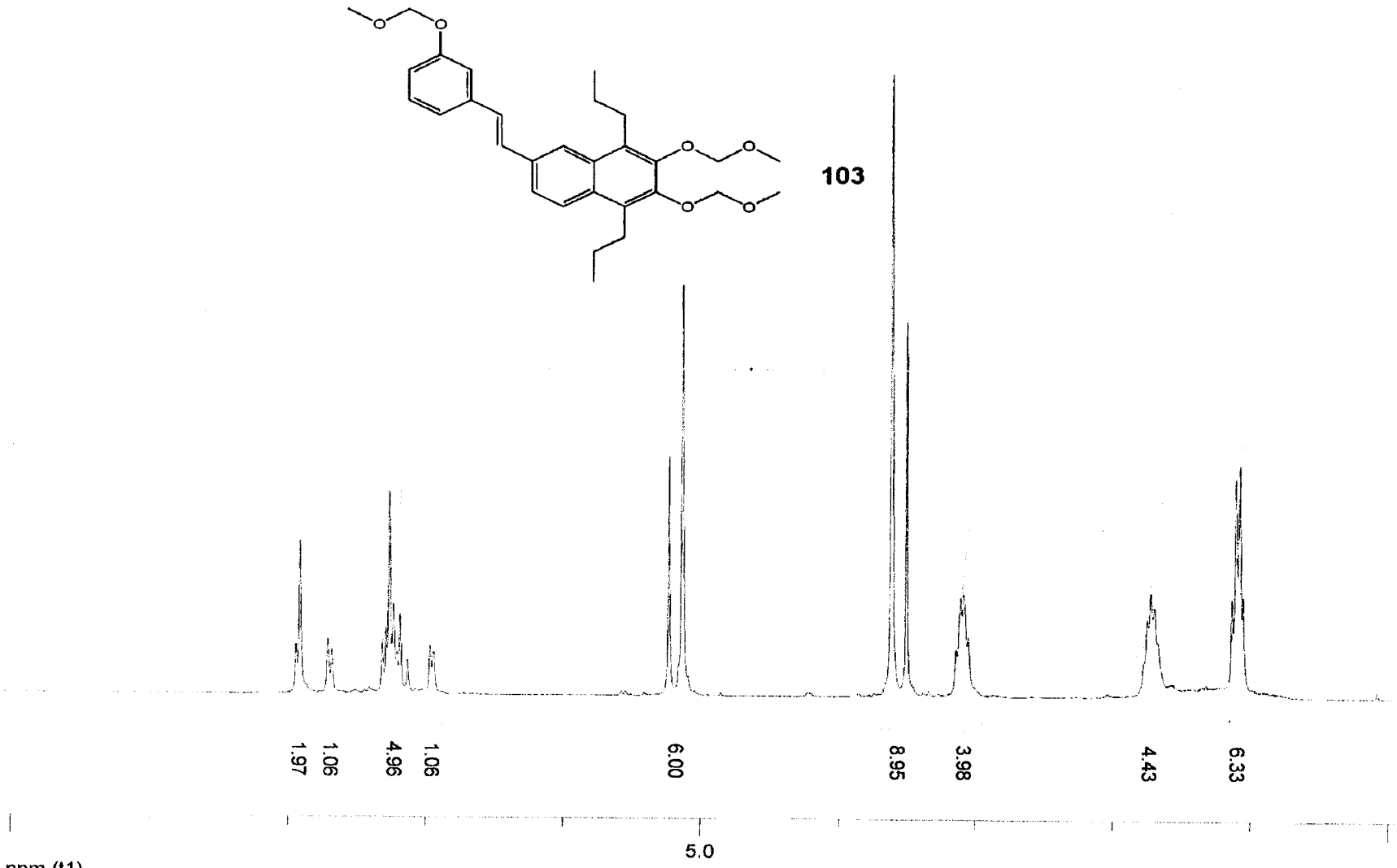


Figure 76: 300 MHz ^{1}H NMR of **103** in $CDCl_3$

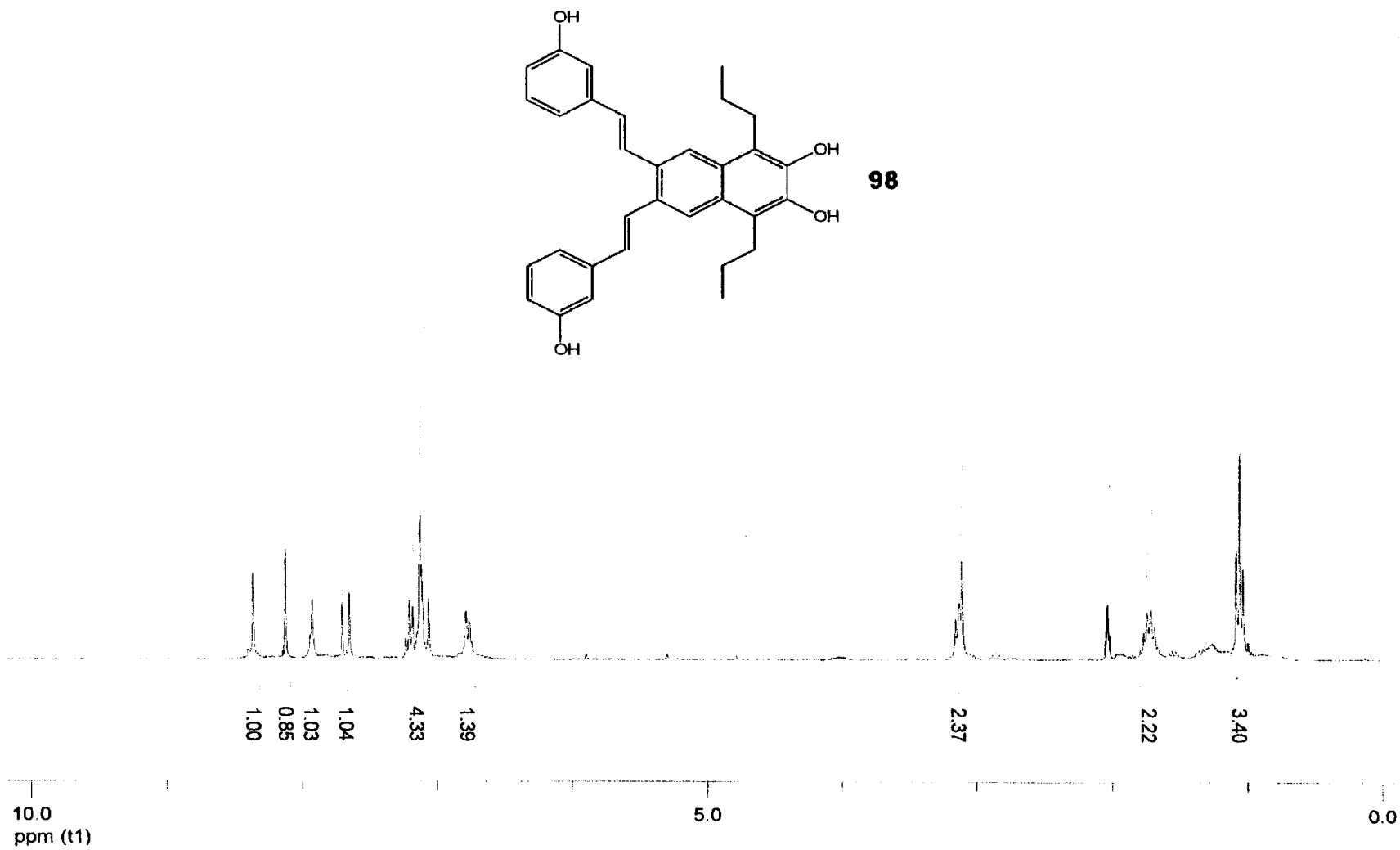
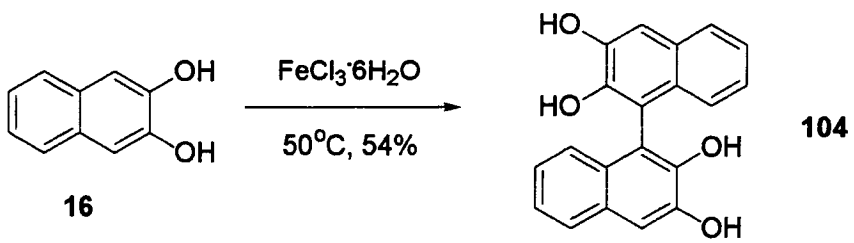


Figure 77: 300 MHz ^{1}H NMR of **98** in acetone-d_6

two for two of the three OH groups. In the case of **99** (**Figure 78**), the integration of the hydrogens of the propyl chains vs the remaining hydrogens (aromatic, alkene and OH) between 6.5 and 8.3 ppm was close to expectation.

- Synthesis of dimeric derivatives -

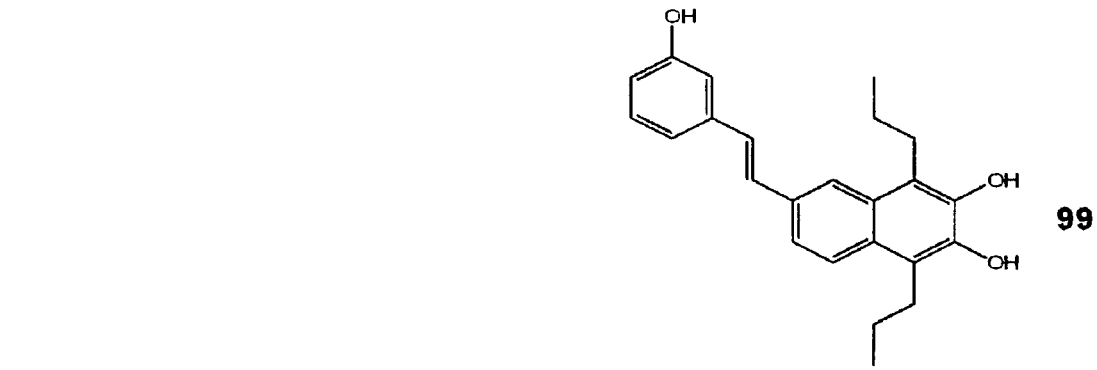
The concept of dendritic antioxidants was introduced in Chapter 1. Thus far two examples have been prepared. The first, the dimer **104** was obtained in 54% yield by oxidative coupling of naphthalene-2,3-diol (**16**) using iron trichloride [41] (**Scheme 55**). The mass spectrum (**Figure 80**) showed the expected molecular ion peak at m/z = 318 and the ^{1}H NMR (**Figure 79**) indicated five unique hydrogens bonded to carbon, including a singlet at 7.36 ppm due to the remaining H4.



Scheme 55: Solid state synthesis of naphthalene-2,3-diol dimer **104**

The synthesis of the second compound in this series, **107**, is shown in **Scheme 56**. Here the MOM protected compound **33** was reacted with the 1st generation Grubbs catalyst. This gave 80% of the desired dimer **105** as a 3:1 mixture of cis/trans olefin, the remainder being recovered starting material.

The ^{1}H NMR of **105** (**Figure 81**) showed that the product was a 3:1 mixture, since every single peak in the spectrum was related to a 1/3 partner. It was not possible to assign the stereochemistry of the major product, since there were no couplings between the olefin protons because of the plane of symmetry in the molecule.



99

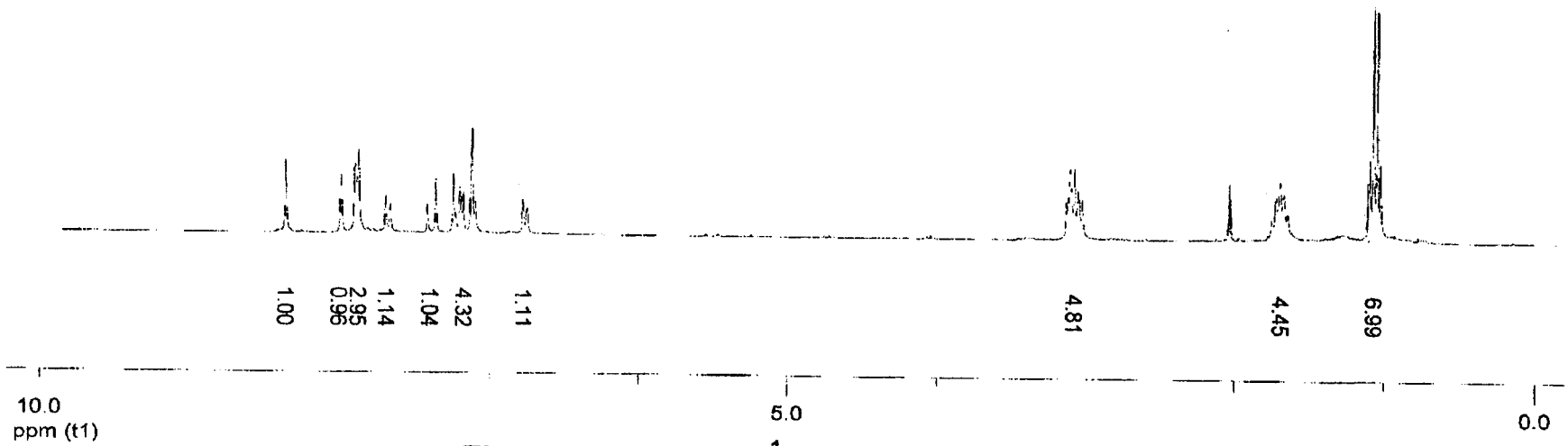
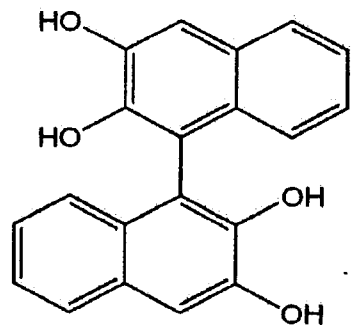


Figure 78: 300 MHz ^{1}H NMR of **99** in acetone-d_6



104

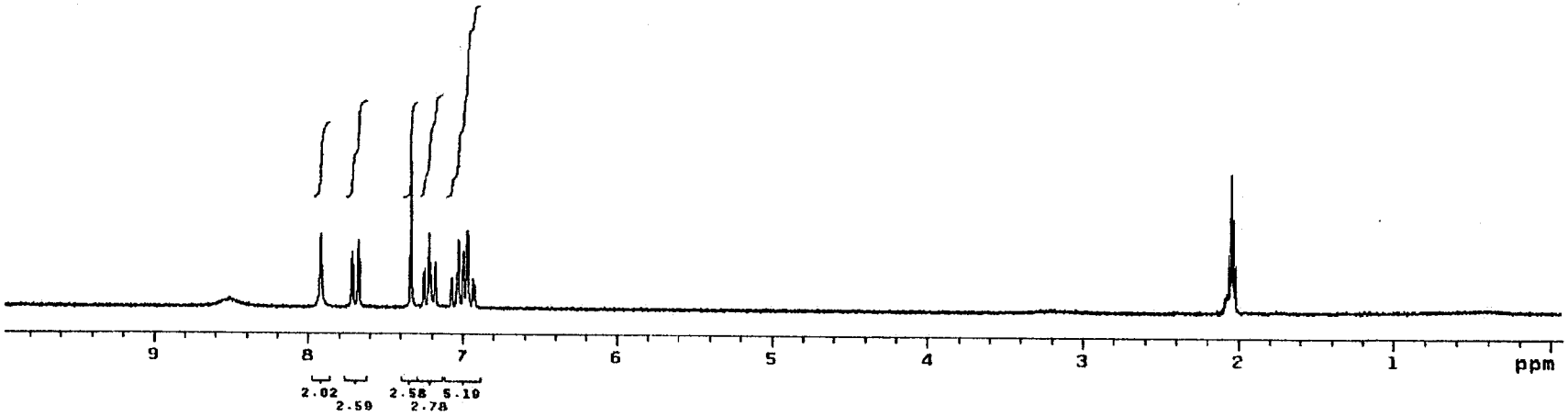


Figure 79: 200 MHz ^{1}H NMR of dimer **104** in acetone-d_6

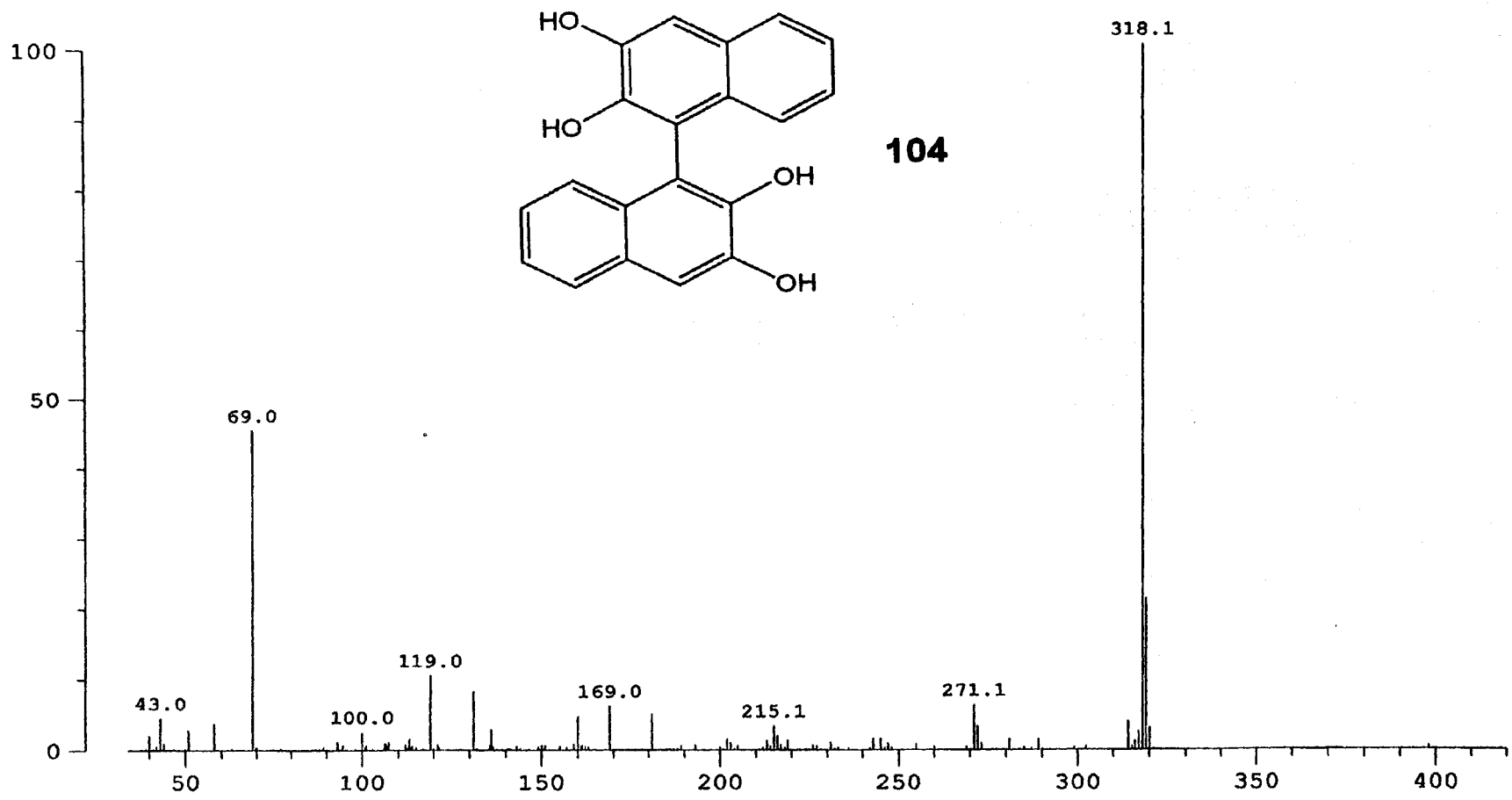


Figure 80: Mass spectrum of 2,3-naphthalenediol dimer **104**

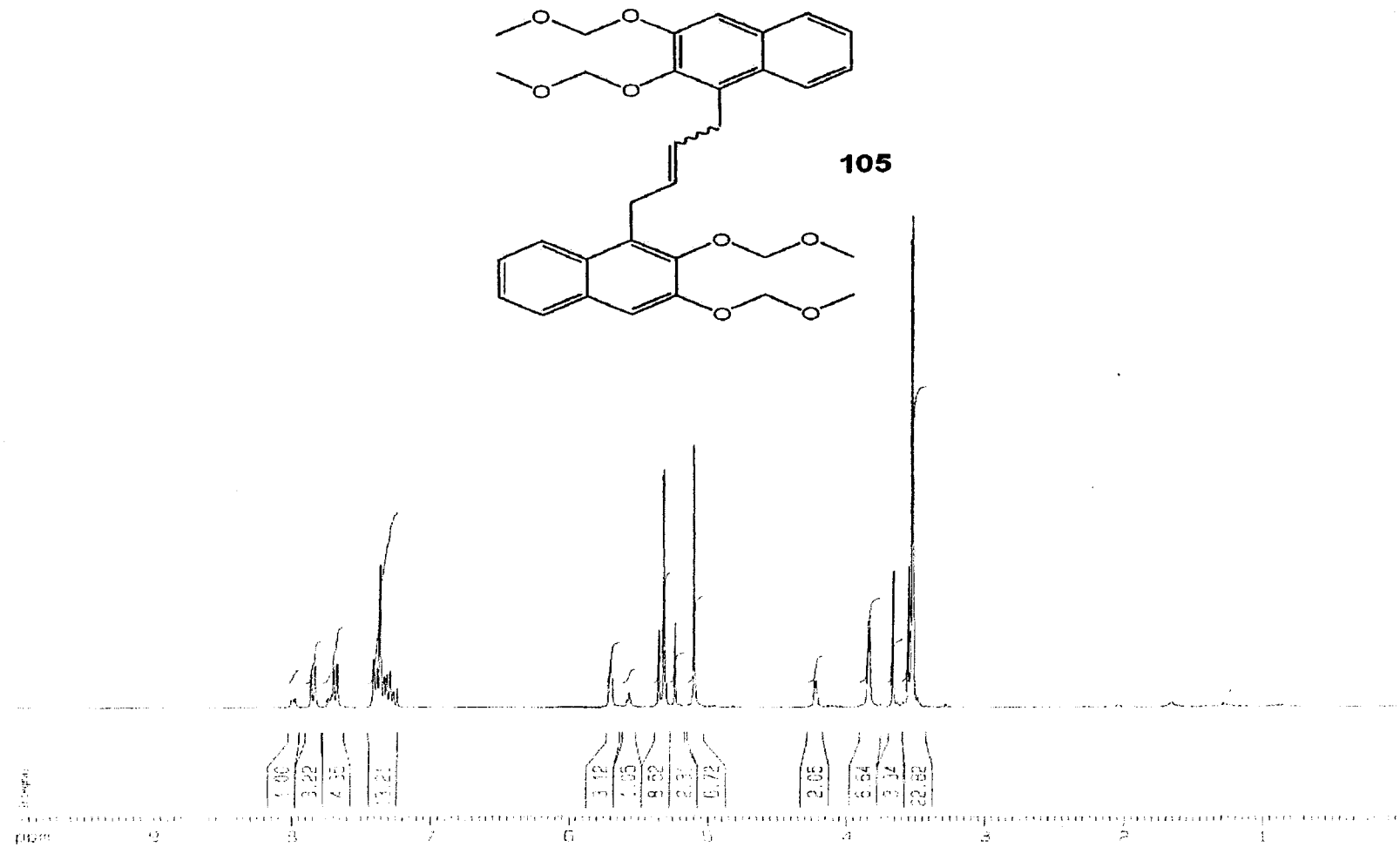
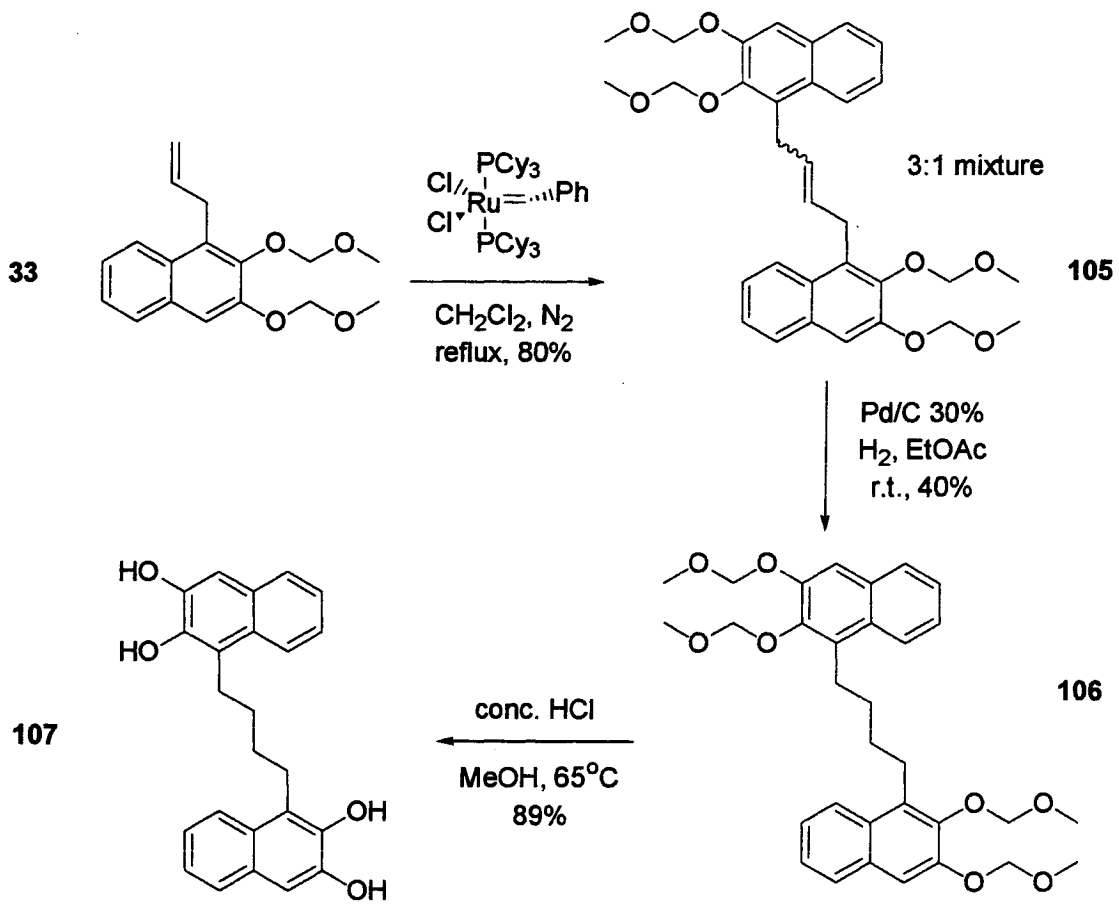


Figure 81: 300 MHz ^{1}H NMR of dimer **105** in $CDCl_3$



Scheme 56: Synthesis of dimer **107**

Hydrogenation of the olefin with Pd/C 30% was conducted in an atmosphere of hydrogen using balloons. The use of only atmospheric pressure could account for the low yield (40%) obtained for **106**. The starting material and the product were very close on TLC, therefore separation by column chromatography was very difficult. This also contributed for the low isolated yield. The ^{1}H NMR of **106** (**Figure 82**) showed two triplets for the linker CH_2's around 1.9 ppm (4H) and the other around 3.2 ppm (4H).

Finally, MOM deprotection under standard conditions gave the final dimer **107** in 89% yield. Its ^{1}H NMR (**Figure 83**) clearly showed two broad singlets, around 3.0 and 9.0 ppm, for the four free OH groups. This compound was obtained as a pale yellowish solid after column chromatography. It changed to a pinky solid on storage, even though TLC showed essentially no changes.

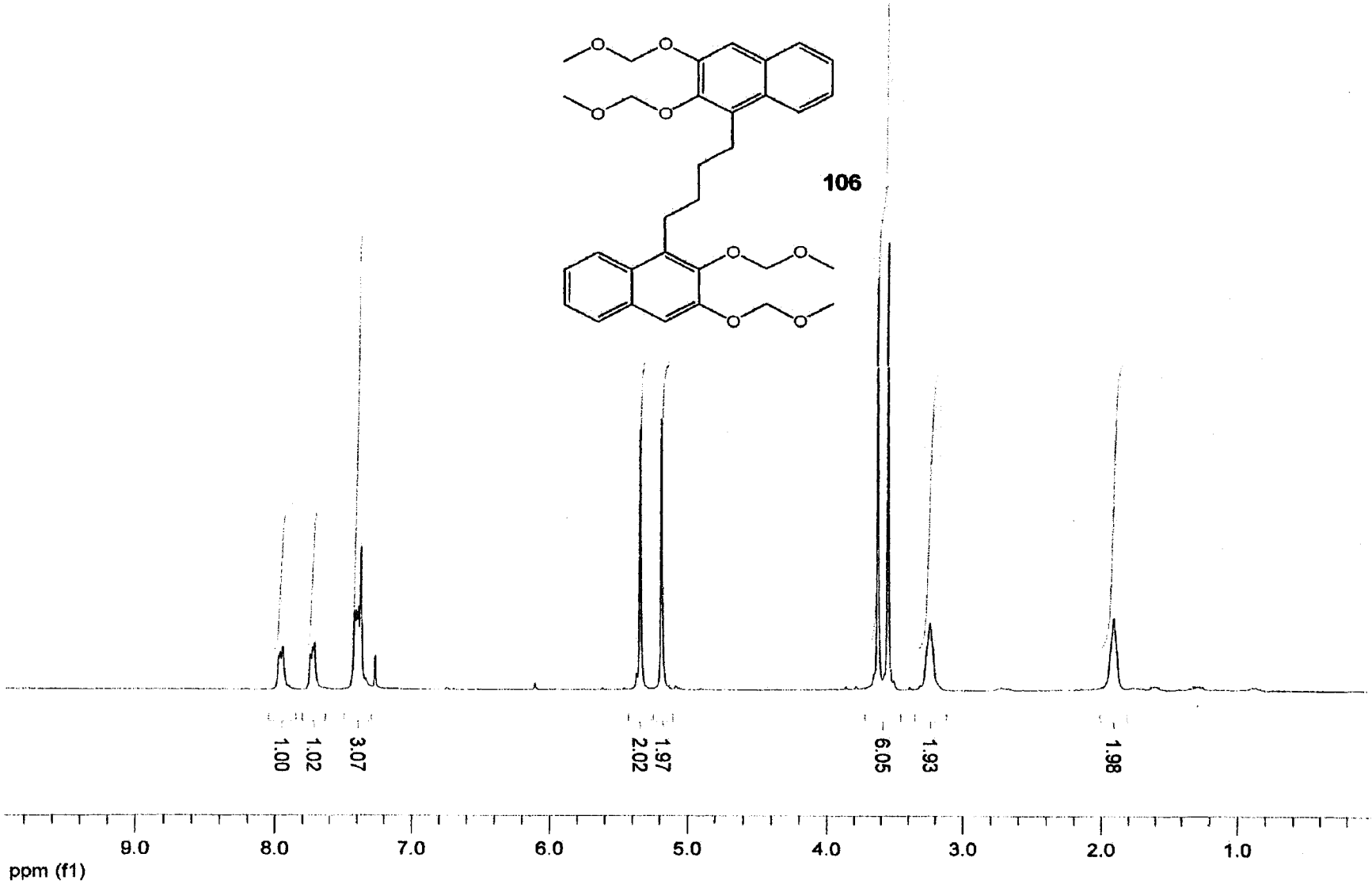


Figure 82: 300 MHz ^{1}H NMR of dimer **106** in $CDCl_3$

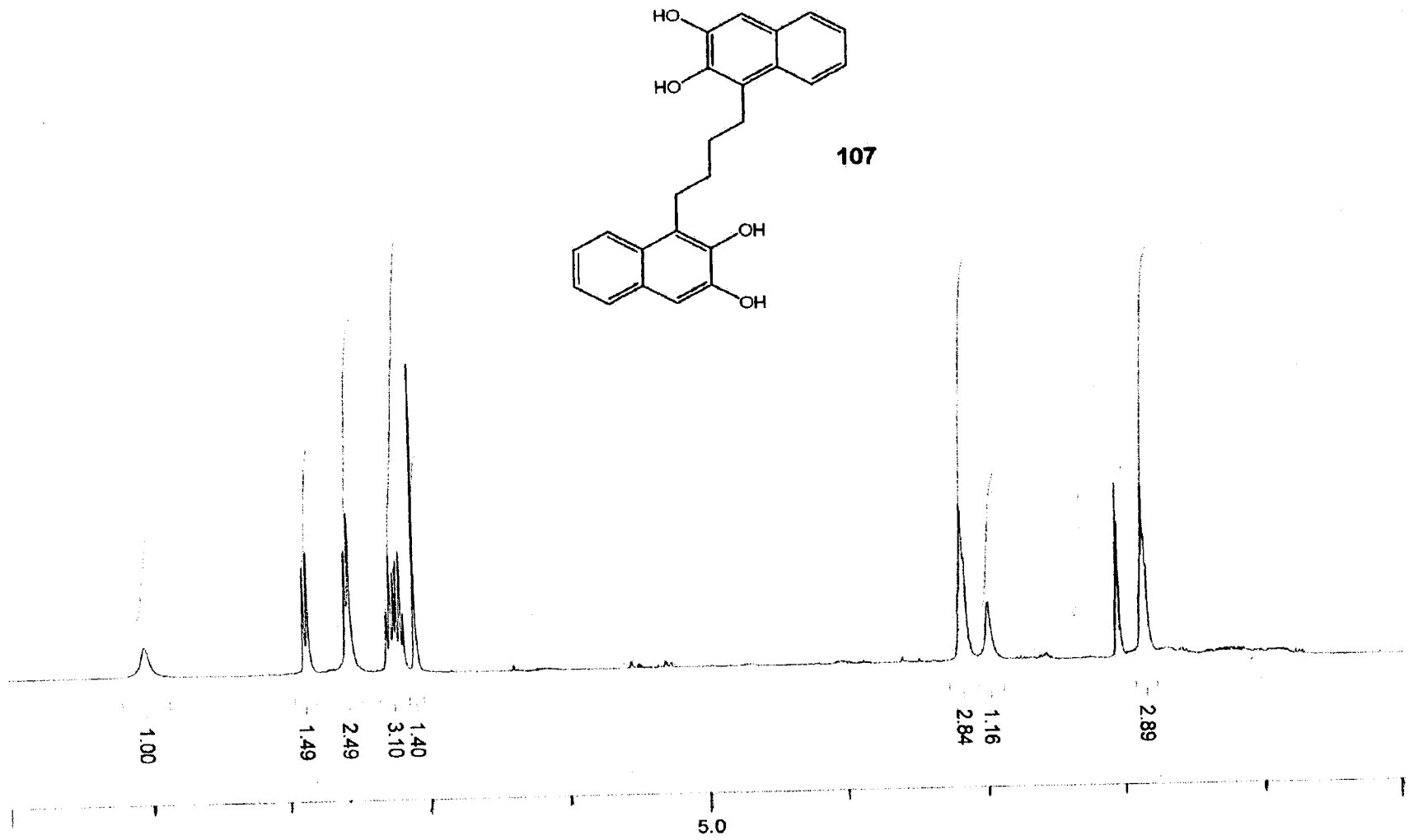
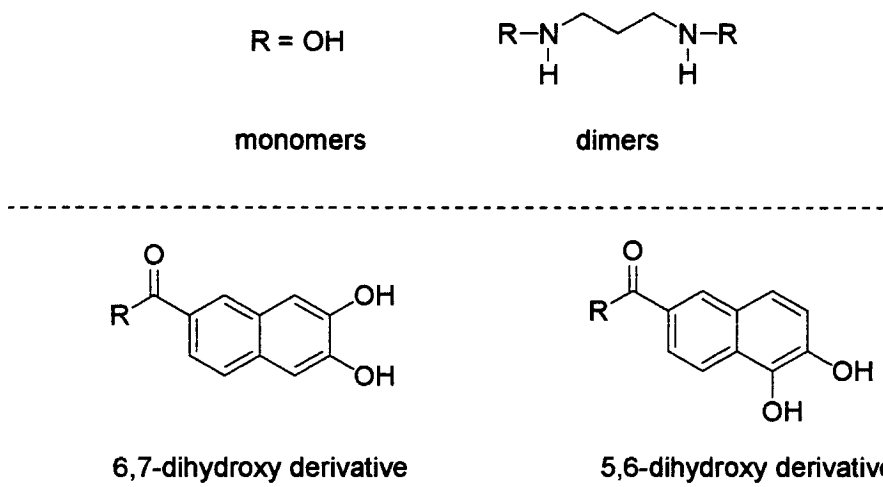


Figure 83: 300 MHz ^{1}H NMR of dimer **107** in acetone-d_6

- Naphthalene-2,3-diols as HIV integrase inhibitors -

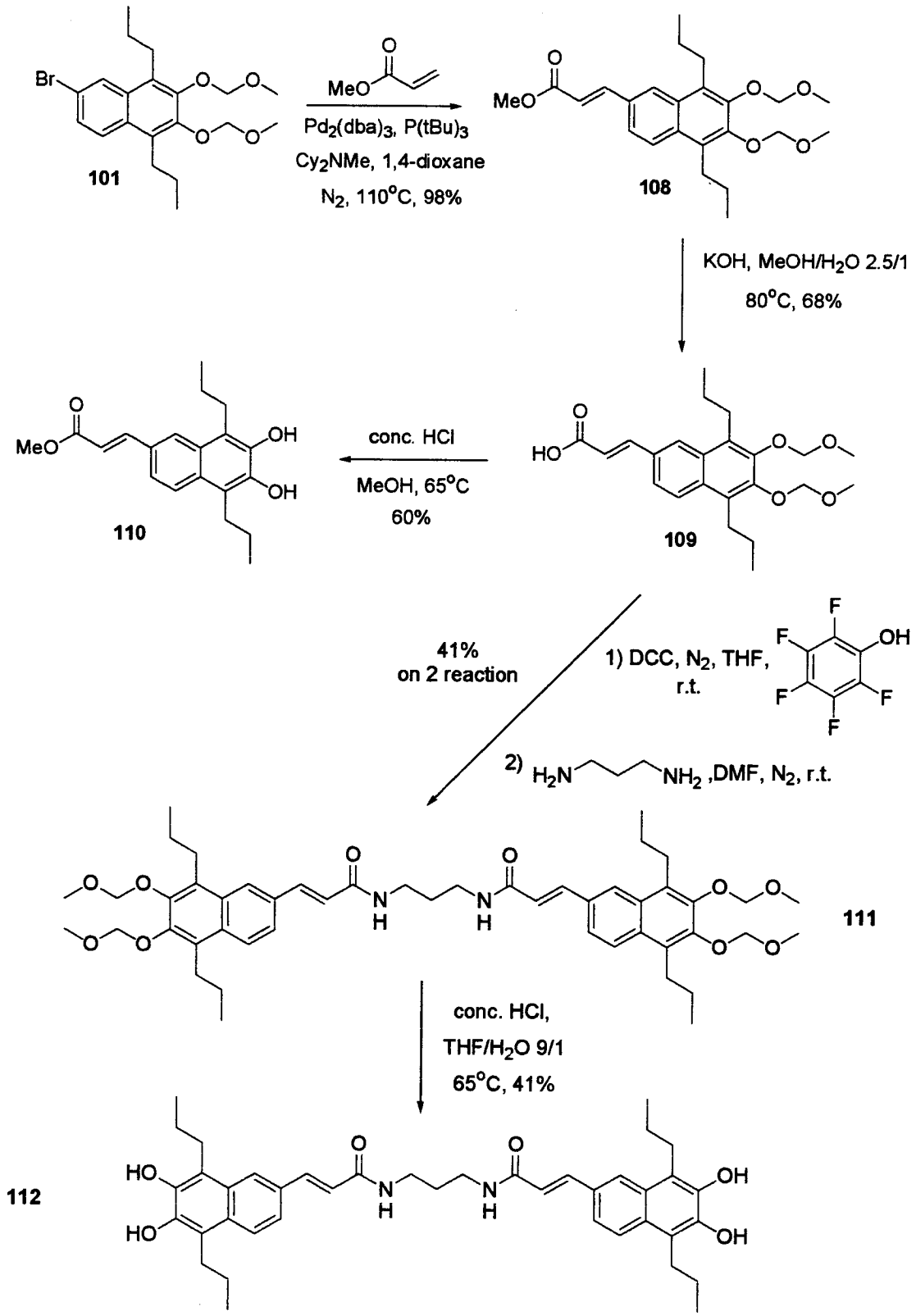
In addition of their potential as good antioxidants, naphthalene-2,3-diol analogues are also known as potent HIV integrase inhibitors, since Zhao et al. [42] demonstrated that 6,7-dihydroxy-2-naphthoic acid was a better inhibitor than its 5,6-dihydroxy isomer or any mono-hydroxy isomers, with an IC_{50} in the range of 5.0 µM compared to about 50 µM and over 200µM respectively . Furthermore, they demonstrated that dimerization of these naphthoic acid derivatives as arylamides linked with an alkyl chain resulted in a significant enhancement in potency relative to their monomeric acids, in the range of 0.9 µM for the 6,7-dihydroxy analogue and about 0.2 µM for the 5,6-dihydroxy analogue (**Scheme 57**).



Scheme 57: Most effective HIV integrase inhibitors tested by Zhao et al. [42]

Since Zhao et al. [42] didn't reported any testing on derivatives with substituents at C1 or C4, substituted diarylamide, dimer **112**, was synthesized starting from MOM protected bromide **101** (**Scheme 58**), in the perspective of submitting our analogue to the authors for future testing.

The first step involved in the synthesis of **112** was the Heck coupling reaction between MOM protected aryl bromide **101** and methyl acrylate. This afforded the desired product **108** in quantitative yield (98%).



Scheme 58: Synthesis of **112**, a potential HIV integrase inhibitor

The structure was confirmed by ^1H NMR (**Figure 84**) where the presence of an extra singlet, corresponding to the methyl group on the acrylate moiety, around 3.9 ppm, as well as two doublets with J_{trans} = 16 Hz around 6.5 and 7.9 ppm, showed the presence of the trans acrylate moiety.

Saponification of the resulting ester **108** using potassium hydroxide basic conditions provided the acrylic acid **109** in 68% yield (**Figure 85**). Treatment of **109** with conc. HCl in methanol accomplished two reactions, MOM deprotection and re-esterification of the acid. Compound **110** obtained in 60% yield (**Figure 86**) was considered as a candidate for evaluation both as an HIV integrase inhibitor and as possible antioxidant.

This acrylic acid **109** was also submitted to activation with pentafluorophenol and DCC, which provided a pentafluorophenyl ester intermediate, according to the very non-polar spot on TLC, which without characterization was reacted with 1,3-diaminopropane to finally obtained protected diamide **111** in 52% overall yield. Structure was confirmed by the integration ratio between the propyl chain linker peaks, around 3.5 ppm for the two CH_2's closest to the amide functionality (4H) and around 1.8 ppm for the central CH_2 integrating for only two protons (**Figure 87**).

Finally, the desired final potential HIV integrase inhibitor product **112** (**Figure 88**) was obtained after MOM deprotection of **111** in a relatively low yield of 41%. Attempts to purify **112** by recristallization after column chromatography were only partly successful since **112** was an oily material which solidified under high vacuum and return to oily state when removing it from the high vacuum.

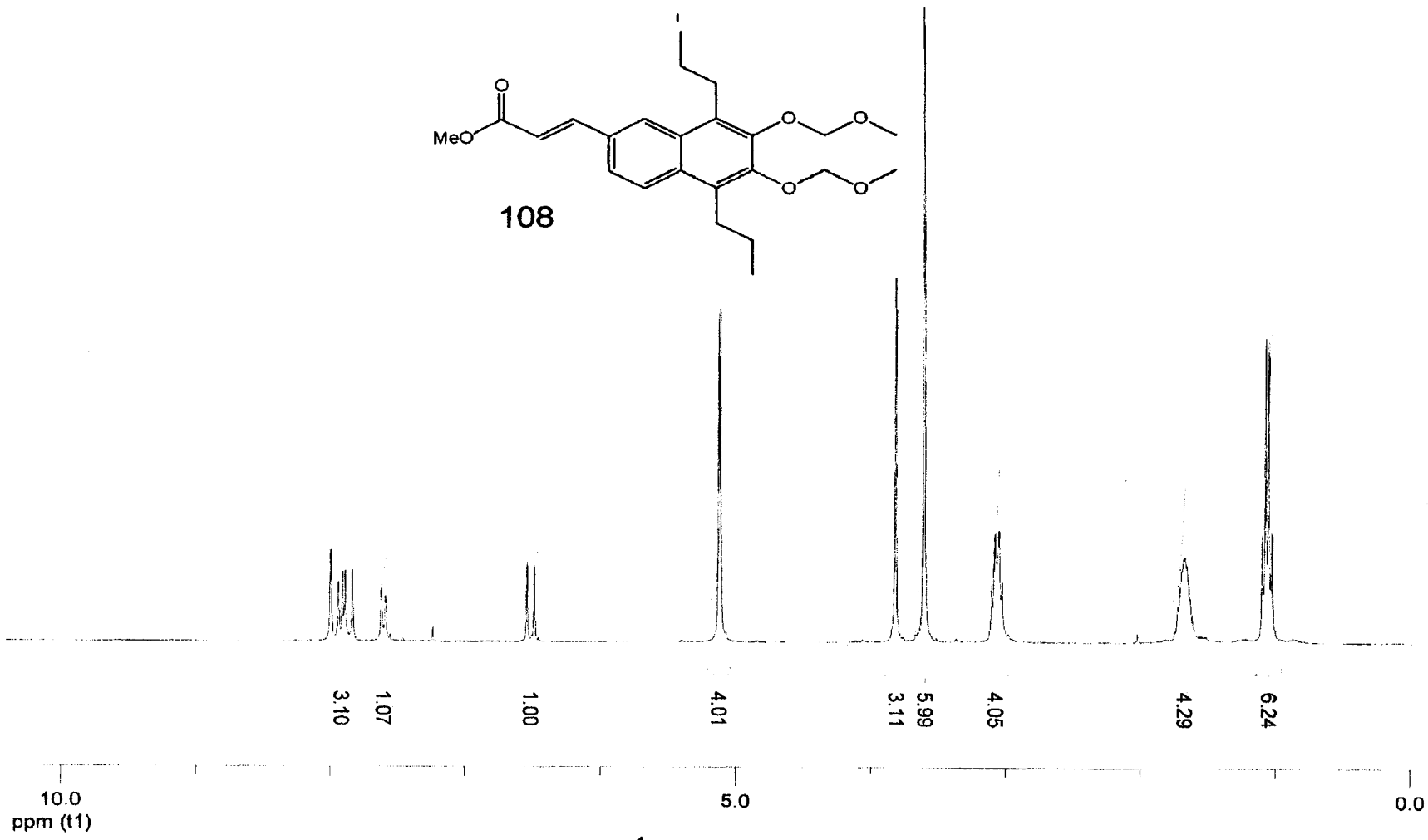


Figure 84: 300 MHz ^{1}H NMR of acrylic ester **108** in $CDCl_3$

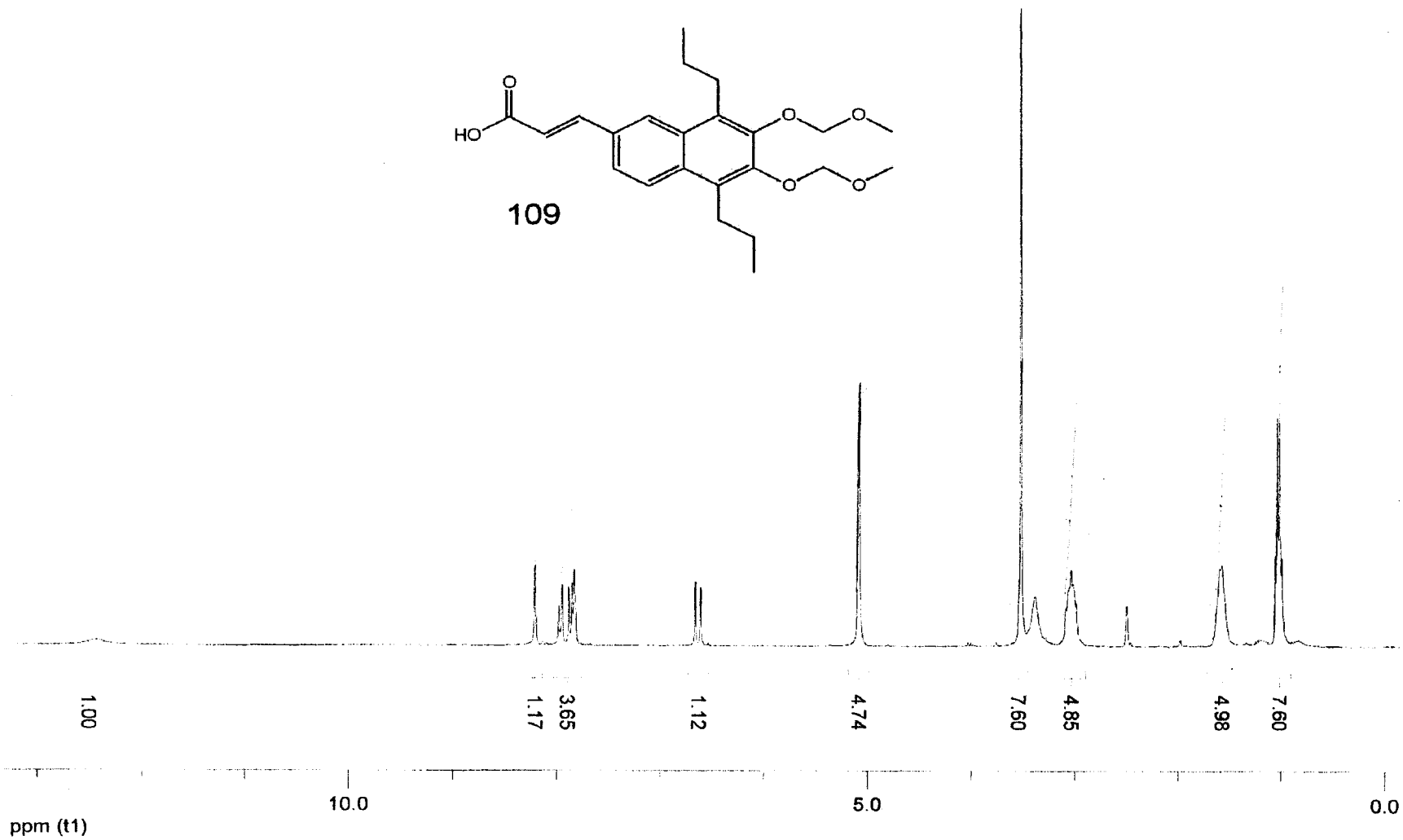


Figure 85: 300 MHz ^{1}H NMR of acrylic acid **109** in DMSO-d_6

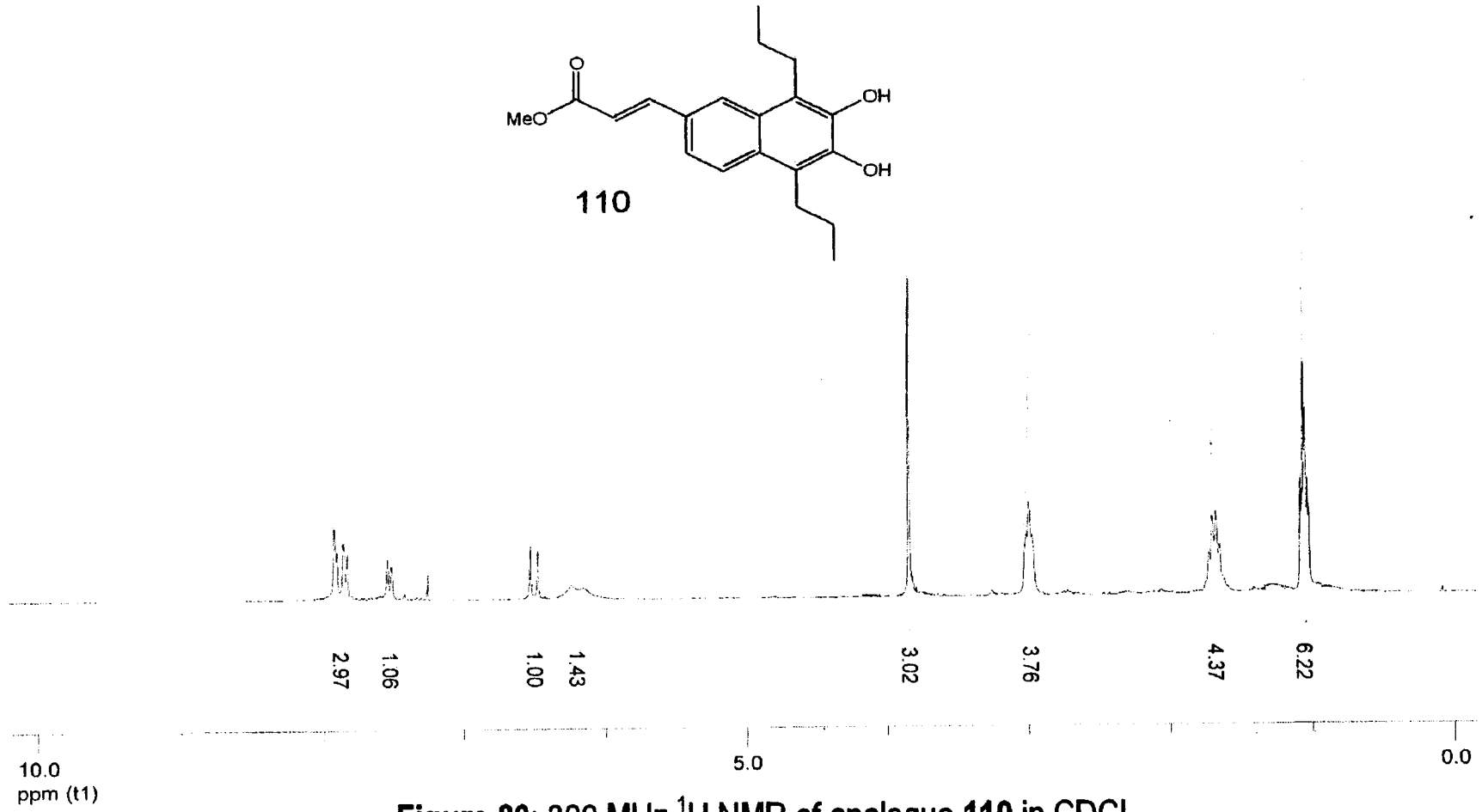


Figure 86: 300 MHz ^{1}H NMR of analogue **110** in $CDCl_3$

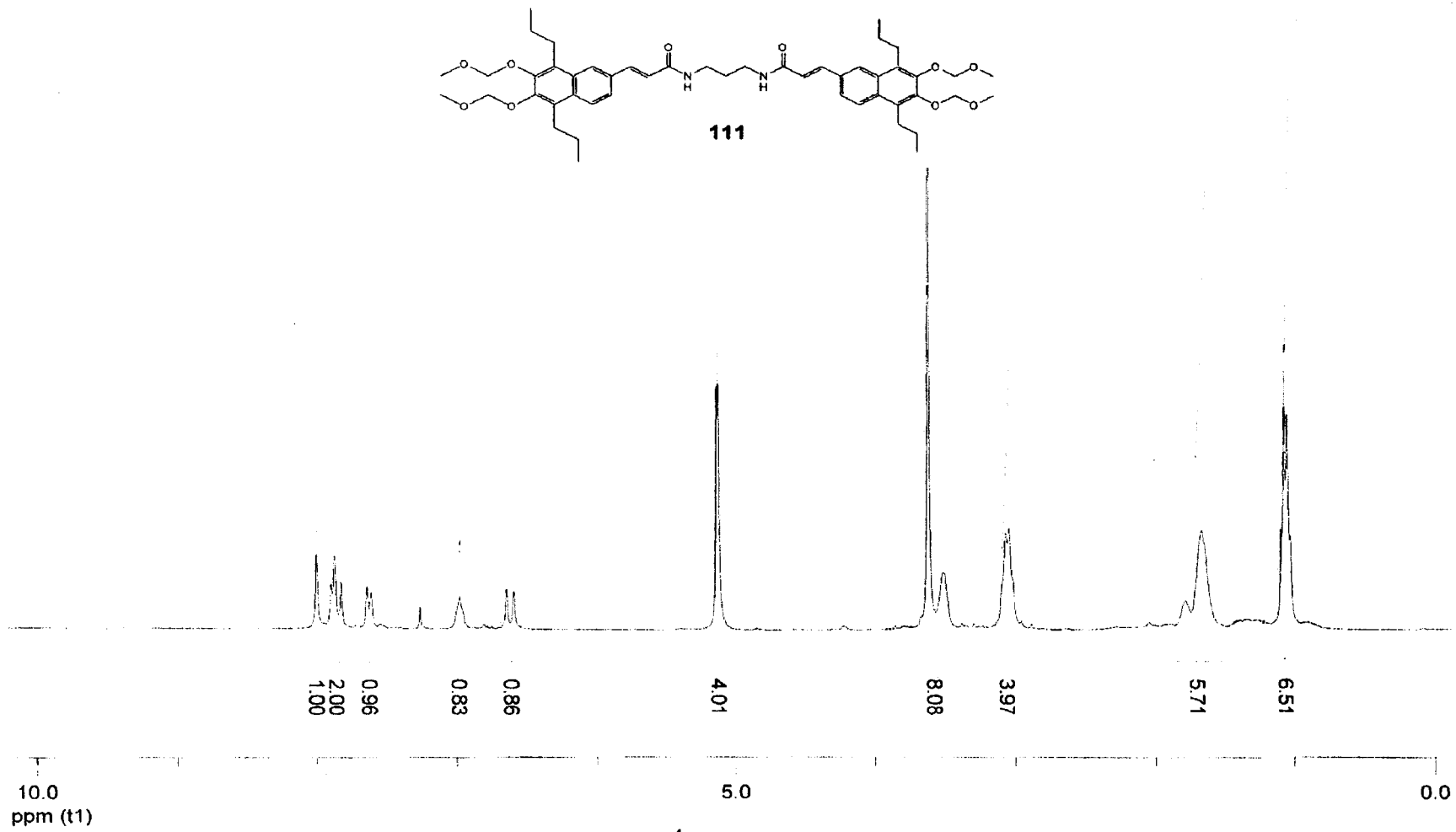


Figure 87: 300 MHz ^{1}H NMR of diamide **111** in $CDCl_3$

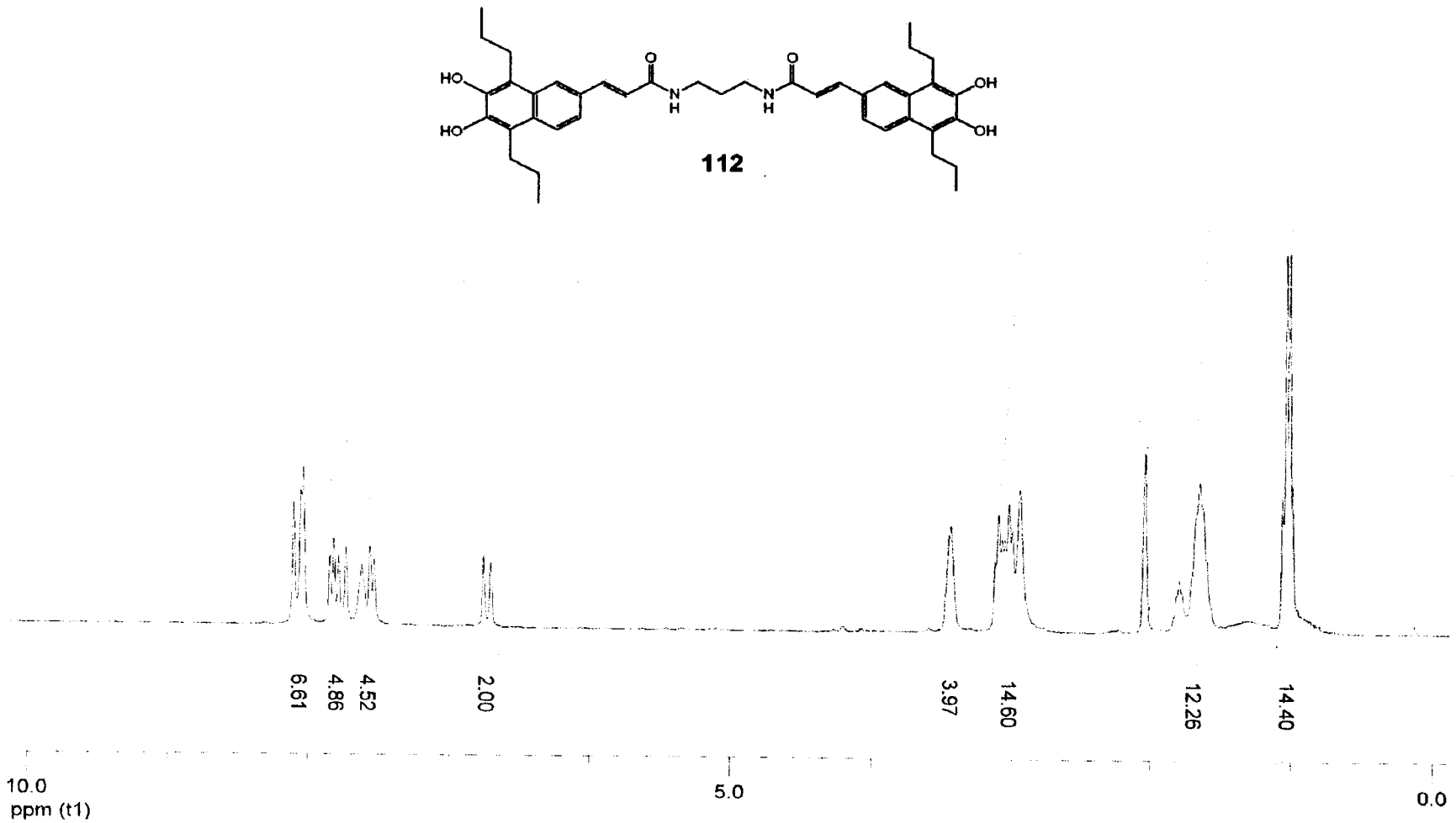


Figure 88: 300 MHz ^{1}H NMR of **112** in acetone-d_6

- Summary -

The parent compound naphthalene-2,3-diol (**16**) was derivatized at all the open positions with a variety of substituents including alkyl, alkenyl and alkynyl attached to the naphthalene ring. The substituents were selected not only to increase the antioxidant capability, but also to test the reliability of the theoretical calculations carried out by our collaborating group at Carleton University led by Prof. Wright. With one or two exceptions, the initially chosen targets were synthesized.

Towards the end of this investigation we became aware of the anti HIV integrase activity of naphthalene-2,3-diol-5-carboxylate derivatives and synthesized the dimer **112** for evaluation in this area.

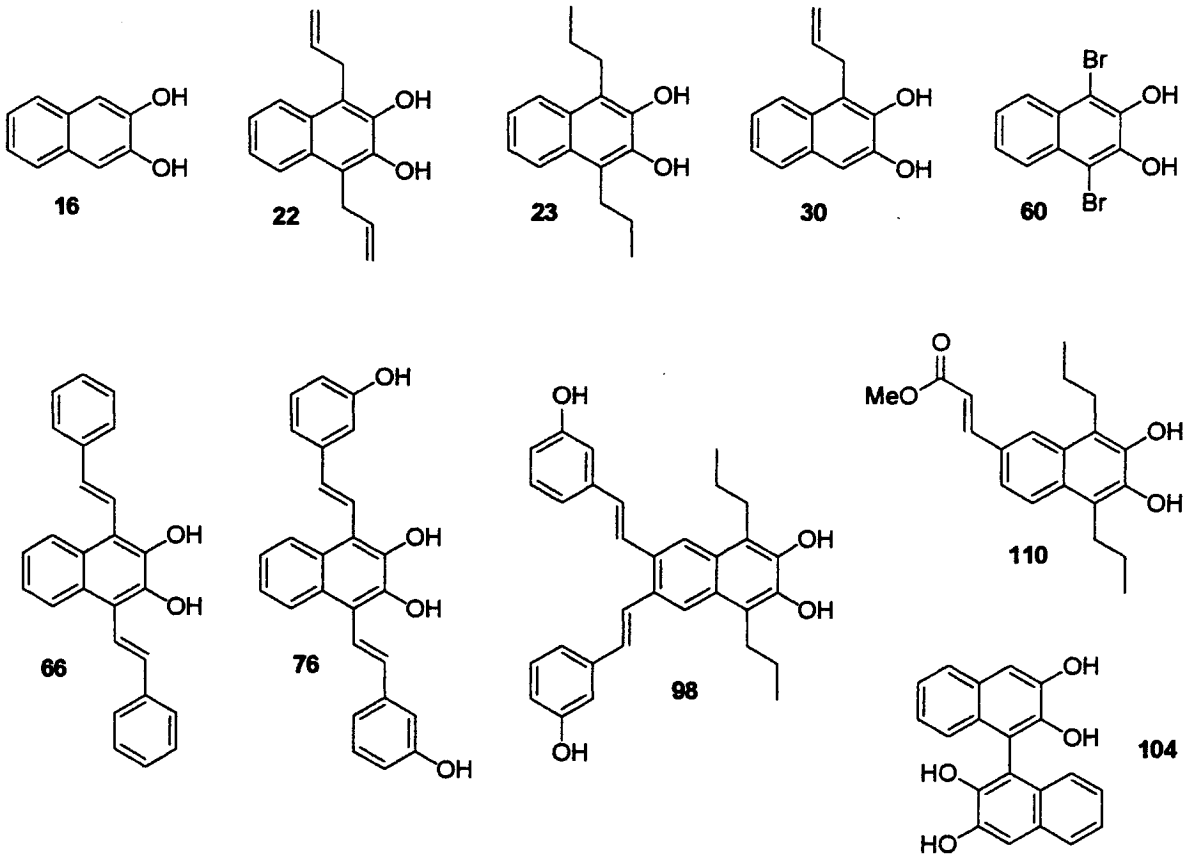
2.3. Reactivity

- Radical quenching of DPPH· -

The antioxidant reactivity of 10 naphthalene-2,3-diol derivatives against the DPPH radical was determined under the same conditions and with the same apparatus as was used to study the reactivity of catechols (subsection 2.1). This should allow for a ready comparison between the two antioxidant families. The derivatives were chosen for mainly two reasons. First, to verify whether the calculations performed by Dr. Wright's group predict the relative antioxidant rates with good accuracy and secondly to allow us to study the effect of substituents, both electron-donating and electron-withdrawing at the various derivatization sites and again verify the predictive power of the calculations.

Since these DPPH· experiments were conducted at the NRC, the time between the synthesis and the radical quenching experiment was sometimes relatively long (months), so the purity of the samples was an issue. The experimentally determined rate constants (k_{dpph}) in EtOAc for the decay of DPPH radical observed for the naphthalene-2,3-diols are presented in **Table 11** together with that of Vitamin E. To help the reader, the structures of all the compounds tested are shown in **Scheme 59**.

The parent naphthalene-2,3-diol (**16**) has a calculated BDE_1 of 79 kcal/mol, which is considerably less than 75 kcal/mol, the value of Vitamin E. The rate constant of this compound with DPPH·, (k_{dpph} = 11 $M^{-1}s^{-1}$), is substantially lower than that of Vitamin E (k_{dpph} = 160 $M^{-1}s^{-1}$). Surprisingly, despite the predictions, the replacement of one of the hydrogen in **16** by an allyl group as in **30** did not result in an increase in the rate; in fact the observe rate constant was only 3 $M^{-1}s^{-}1$. Replacement of both the hydrogen at C1 and C4 by allyl groups restored the rate constant to 11 $M^{-1}s^{-1}$. The relative antioxidant activity of the dibromo compound **60** was, as expected, the lowest amongst the compounds tested; its predicted BDE_1 value is 81 kcal/mol.



Scheme 59: Molecular structure of potential antioxidants tested against DPPH·

Compounds	k_{dpph} $M^{-1}s^{-1}$ (EtOAc)
16	11
22	11
23	312
30	3
60	2
66	13300
76	197
98	22
104	2
110	7
α-tocopherol[a]	**160**[18]

[a] The phytyl side chain was replaced by a methyl group for the experiment.

Table 11: Rate constants (k_{dpph}) for the decay of DPPH radical of the different Naphthalene-2,3-diols and for Vitamin E

The key compound in our series, 1,4-dipropyl-naphthalene-2,3-diol (**23**) (k_{dpph} = 312 $M^{-1}s^{-1}$), was twice as effective as α-tocopherol in quenching the DPPH radical. This restored considerable faith in the predictive capability of the calculations. The calculated BDE_1 for **23** is 75 kcal/mol; essentially identical to that of α-tocopherol. Based on this data, this compound was a candidate for further investigation with respect to toxicity (see below).

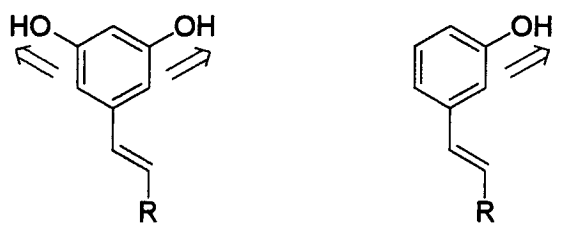
The low reactivity of the allyl derivatives **23** and **30**, if this represents their true relative reactivity, is puzzling. One would be hard pressed to suggest that an allyl group is not electron donating and radical stabilizing relative to hydrogen. It seems not unreasonable to suggest that a propyl group be somewhat more electron donating than allyl, and thus the propyl compound **23** was expected to react more rapidly with DPPH· than allyl derivative **22**. However, the difference was expected to be small, not a factor of 30.

The 1,4-distyrenyl analogue **66** was by far the most reactive radical scavenger of this series of naphthalene-2,3-diol analogues with a k_{dpph} = 13300 $M^{-1}s^{-1}$. This reactivity was better than any catechols reported by Hussain et al. [18]. The more than 80 fold increase in radical quenching activity was attributed to the tremendous beneficial effect of the two styrenyl substituents. Indeed, the calculations made by Wright et al. [13], showed an effect of -8.5 kcal/mol for a styrenyl substituent when it is in para position in phenol. Considering that the ortho effect should be similar or even better, the predicted BDE_1 value for distyrenyl **66** should be around 70 kcal/mol (79 for the design motif - 8.5 for one *o*-styrenyl substituent and assuming that the *m*-styrenyl effect (not calculated) should be small). If these estimates are verified by the calculations, then this compound sits at the bottom edge of the design window with a BDE_1 value still low enough for it to react with the ascorbate radical anion to regenerate **66**.

The derivative **76** was designed to introduce some hydrophilicity into the molecule. The hydroxyl substituent was place in a meta position so that it could not interact directly with the radical and form a quinonoid system. We were disappointed that the rate constant for quenching the DPPH radical for **76** was much lower than of **66** and quite comparable to α-tocopherol. This result was not

anticipated based on the qualitative addition of substituent effects, since the effect of a para 3,5-dihydroxystyrenyl substituent relative to phenol was calculated to be -8.2 kcal/mol [13]. Nevertheless, compound **76** can still be considered as a potent radical scavenger, since its reactivity was little higher (k_{dpph} = 197 $M^{-1}s^{-1}$) than the one of Vitamin E (k_{dpph} = 160 $M^{-1}s^{-1}$).

This difference between prediction and observation for **76** could be attributed to the presence of only one *m*-hydroxy group compared to the 3,5-dihydroxystyrenyl present in resveratrol, since the first should act as a better electron-withdrawing group than the second. First, the lower effect observed for the 3,5-dihydroxystyrenyl compared to styrenyl itself is due to the non-conjugated OH group, acting as an electron-withdrawing group by the electronegativity of the oxygen atom. Knowing that, electrons in 3,5-dihydroxystyrenyl substituent should be more available for conjugation through all the molecule stabilizing by the same way the formed phenoxyl radical, since electrons are pulled in both directions; almost totally eliminating the dipolar moment, which is not the case in the 3-hydroxystyrenyl substituent (**Scheme 60**). This hypothesis could be verify by the synthesis and testing of a 3,5-dihydroxydistyrenyl analogue. It is noteworthy that possible difference of preferred conformation between **66** and **76** could also alter the conjugation in the molecules, also contributing to the large difference of reactivity between these two similar analogues.



Scheme 60: Dipolar moment observed in 3,5-dihydroxystyrenyl compared to 3-hydroxystyrenyl

Unfortunately, this unexpected 3-hydroxystyrenyl reactivity effect was also present in the results obtained for compound **98** (k_{dpph} = 22), which was also expected to be a more potent antioxidant than Vitamin E, and certainly more

reactive than **23**. The synthesis and testing of a styrenyl analogue of **98** without OH group on the styrene moiety should demonstrate a better reactivity than Vitamin E and **23** and enable the investigation of the reactivity of analogues substituted at C6 and C7.

The results for the acrylic ester **110** was as expected, since esters are well-known electron-withdrawing groups.

The low rate of the reaction between dimer **104** and DPPH radical (k_{dpph} = 2 $M^{-1}s^{-1}$) clearly showed that this kind of binaphthyl compounds can not be considered as potential antioxidants, since its reactivity was even less than the monomer **16** (k_{dpph} = 11 $M^{-1}s^{-1}$). These results were attributed to a preferred conformation of **104**, with no conjugation between the two naphthalene cores; thus each naphthyl unit act as an electron-withdrawing group.

It would have been interesting to know the reactivity of **107** relative to 1-propyl-naphthalene-2,3-diol (not prepared). The predictions are that the 1-propyl derivative should have activity intermediate between the parent naphthalene-2,3-diol (**16**) and the 1,4-dipropyl compound **23** and that **107** should be twice as reactive.

In summary, although the DPPH quenching ability do not seem to correlate as well as we hoped with the qualitative predictions, we have identified two compounds, namely the 1,4-dipropyl-naphthalene-2,3-diol (**23**) and the 1,4-distyrenyl analog **66** as excellent antioxidants with greater reactivity than α-tocopherol.

- Tocixity studies -

Some of the above compounds were then submitted for cell viability (toxicity) and other cell based test to begin their assessment as possible antioxidants for potential *in vivo* use. We also hoped to verify the hypothesis previously made concerning the cytotoxicity of these compounds compared to catechols. We expected it to be much lower because of the likely decreased *o*-quinones formation.

The cytotoxicity of catechols was attributed to their easy conversion to *o*-quinones, mainly by two mechanisms, redox cycling (**Scheme 16**) and by Michael addition (**Scheme 15**). If naphthalene-2,3-diols are not to be converted to their respective *o*-quinones, any cytotocity should come from these two mechanisms. This expectation was verified for 1,4-dipropyl-naphthalene-2,3-diol (**23**) by an H_2O_2 response curve for the redox cycling mechanism (**Figure 89**) and by a glutathione response curve for the Michael addition mechanism (**Figure 90**), provided by our co-authors [27].

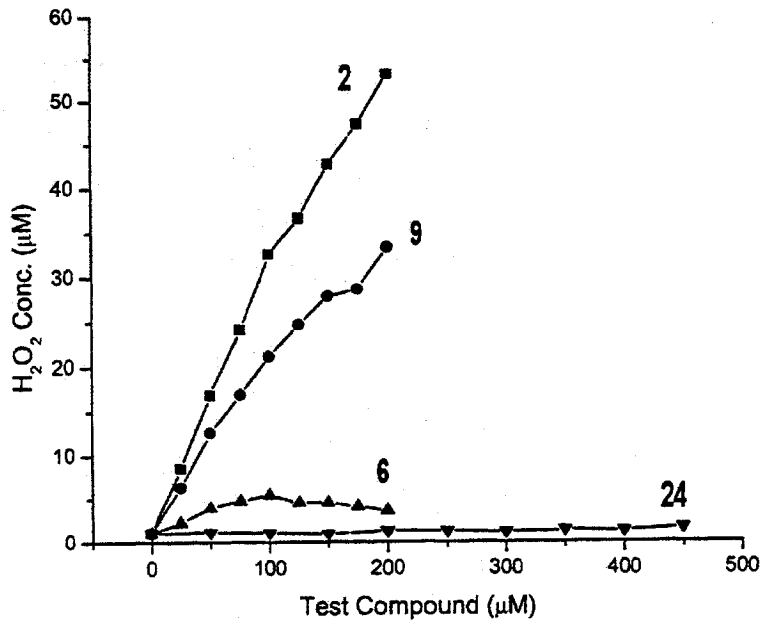


Figure 89 [27]: H_2O_2 response curve for diacetate **24** compared to representative catechols

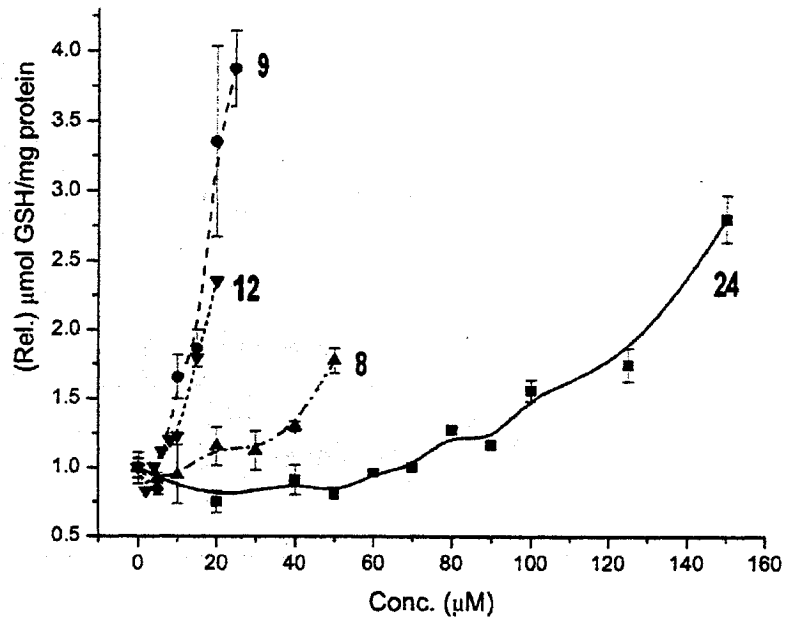


Figure 90 [27]: GSH response curve for **24**, compared to diacetates of representative catechols

As shown in **Figure 89**, 1,4-dipropyl diacetate **24** does not undergo a redox cycle, and this, even though there is two exchangeable hydrogen atoms in its unprotected version **23**, suggesting that no *o*-quinone was formed during the 24h incubation time. This is deduced from the observation of the total absence of peroxide generated compared to the catechols, keeping in mind that superoxide radical ($HO_2^{\cdot}$), if formed during redox cycling, should disproportionate to form H_2O_2. This statement is also supported by our observation that no significant quantities of *o*-quinones were observed during the synthesis of naphthalene-2,3-diol analogues.

The GSH response curve (**Figure 90**) for **24** was also consistent with the lack of redox cycling and with the lack of Micheal acceptor sites on analogue **23**, since there was no significant increase in GSH regulation up to nearly 100 µM. This is again in contrast to catechols, especially for compounds **9** and **12**. However, beyond this point, even 1,4-dipropyl analogue **24** causes GSH to increase, meaning that the cells were responding to an oxidative stress generated by other ways. It was speculated that this cytotoxicity with high concentration of **24**

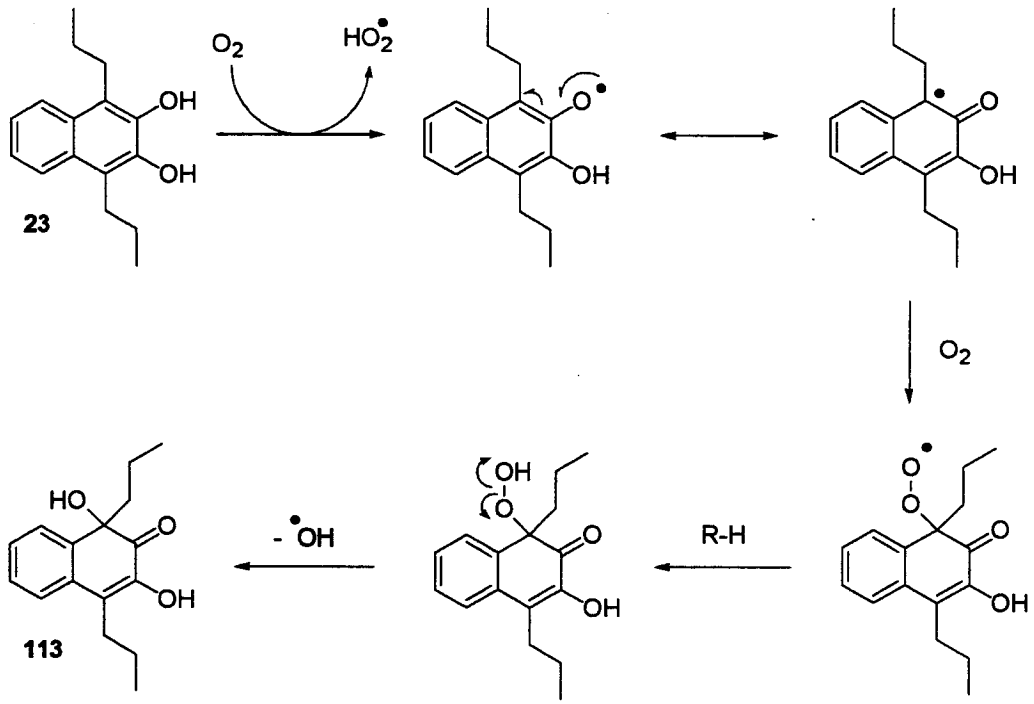
could come from oxidation of GSH and protein thiols by the phenoxyl radical (semiquinone form) or formation of lipid peroxides with subsequent cytotoxicity.

Finally, EC_{50} obtained for the diacetate **24** was 153 μM without added ascorbate and 182 μM with the presence of vitamin C anion [27]. These results also correlated the hypothesis about this family compared to catechols, since they were higher, meaning less cytotoxic, than any other catechols tested by Wright et al. [27] (**Table 6**). Furthermore, the fact that EC_{50} with added ascorbate was higher than the one without showed that Vitamin C could regenerate the active antioxidant *in vivo* and that added ascorbate was protective, agreed with the fact that the calculated BDE_1 value of 75 kcal/mol was in the design window (**Scheme 18**).

These cell culture testing clearly demonstrated that the naphthalene-2,3-diol family of potential antioxidants are not converted to their *o*-quinone form, resulting in higher EC_{50} than any other catechols tested. However, EC_{50} for the 1,4-dipropyl analogue was not negligible and thus of concern if these antioxidants were to be considered for use in humans.

1,4-Dipropyl-naphthalene-2,3-diol (**23**) and its diacetate version **24** are currently undergoing several other cytotoxicity testing, namely in adrenal cells, primary cortical neuron cells, hepatic cells, in hepatic/lung cell model as well as in nematode *C. elegans*. Since it appears that the cytotoxicity of the 1,4-dipropyl compound **23** is not due to *o*-quinone formation, it may be due to other oxidation processes.

When a sample of **23** was kept for several months in an open to air container at 4°C, evidence of change (partial liquefaction) was observed. TLC investigation showed the presence of a new product with R_f close to **23**. Careful purification and extensive characterization allowed us to assign structure **113** to the new material. A possible mechanism for its formation is proposed in **Scheme 61**.



Scheme 61: Proposed mechanism for the formation of by-product **113**

The ^{1}H NMR of **113** (**Figure 91**) showed two distinct methyl peaks as triplets at 0.75 and 1.05 ppm. In one case, the propyl group was still joined to an aromatic system as shown by the triplet for the CH_2 group near 2.9 ppm. The corresponding CH_2 group of the other propyl chain appeared as a doublet of triplets at 1.75 and 1.80 ppm. Such signals could only arise if that CH_2 was no longer joined to aromatic ring but to a saturated chiral carbon. The spectrum showed two rather different OH groups at 3.45 and 6.10 ppm and four non-identical aromatic hydrogens. These data combined with the ^{13}C NMR (**Figure 92**) and the mass data (**Figure 93**) confirmed structure as **113**.

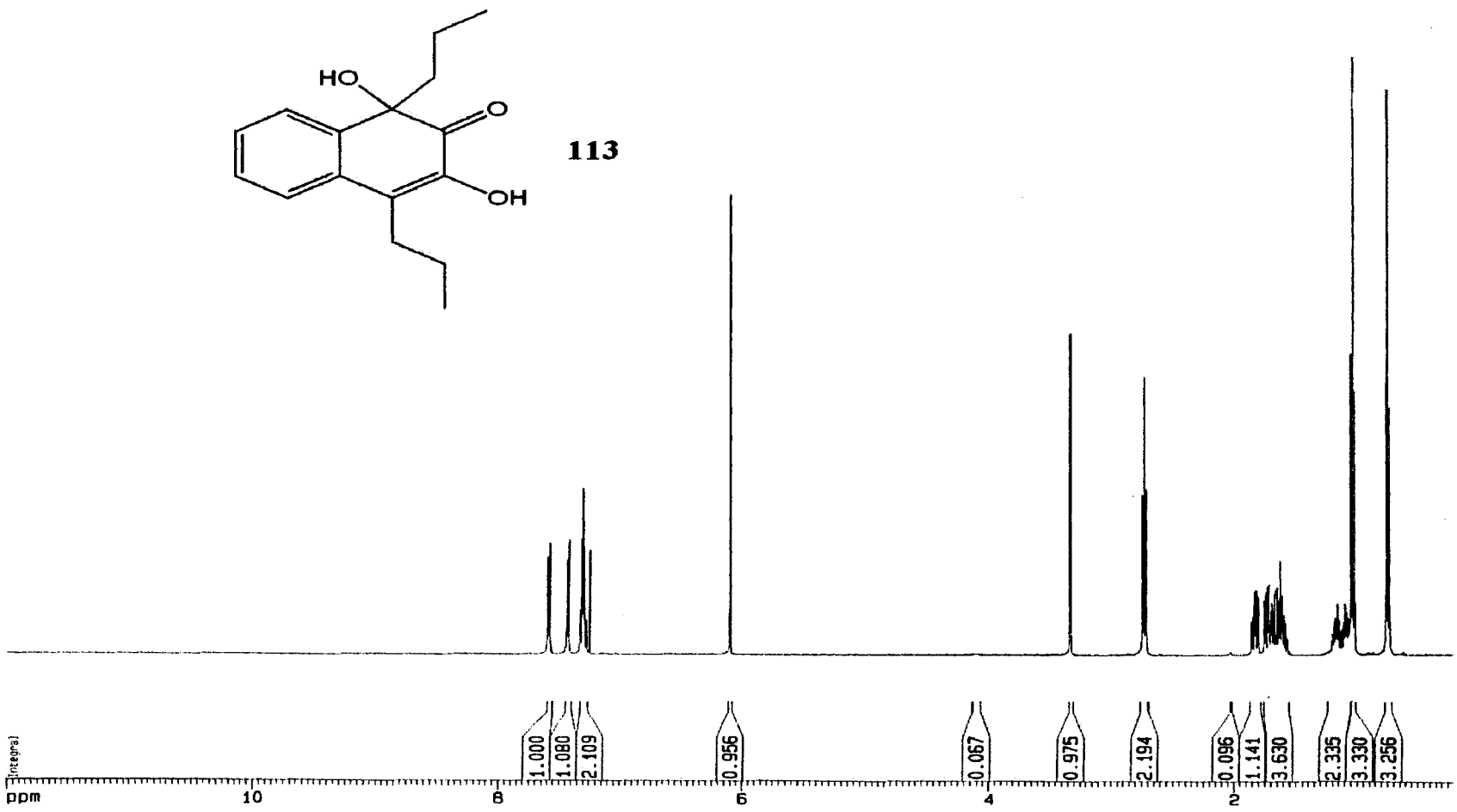


Figure 91: 500 MHz ^{1}H NMR of by-product **113** in $CDCl_3$

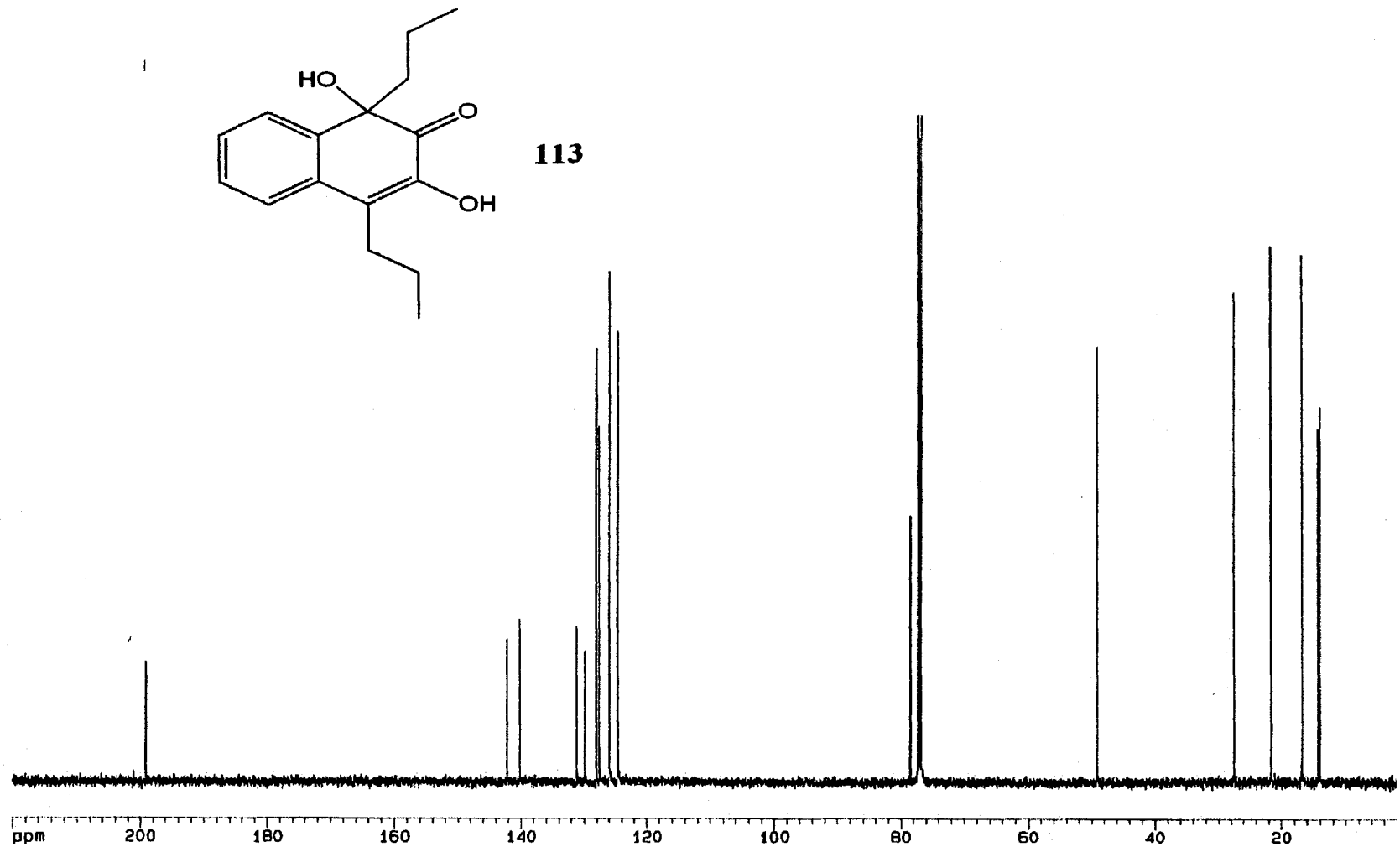


Figure 92: 500 MHz ^{13}C NMR of by-product **113** in $CDCl_3$

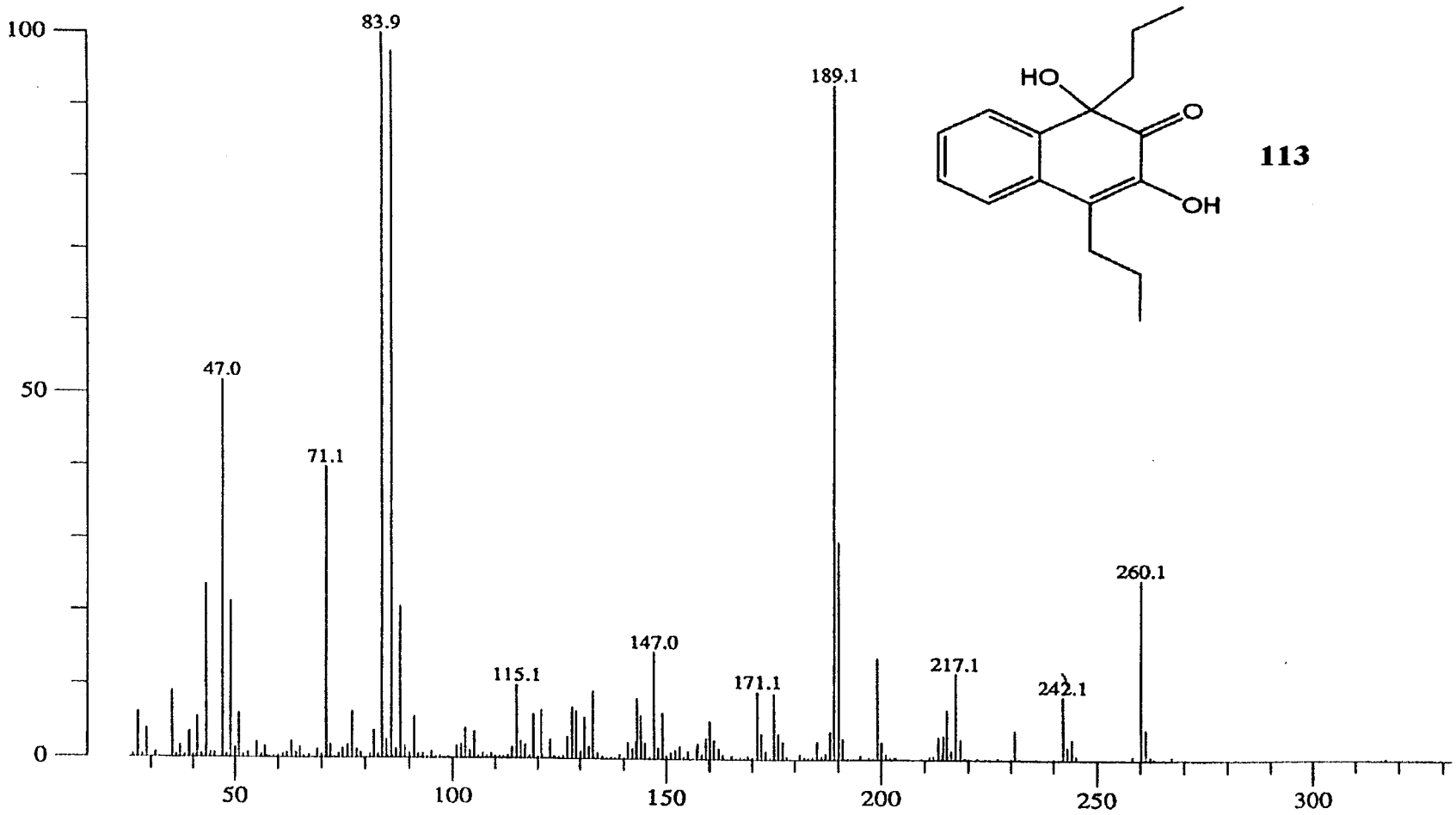
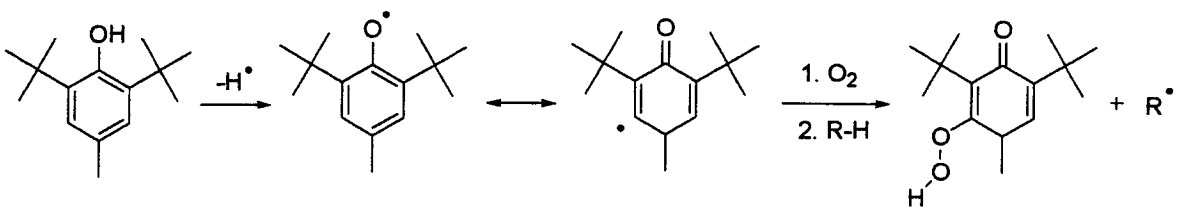


Figure 93: Mass spectrum of by-product **113**

It appears that the phenoxy radical derived from **23** can react with oxygen at the carbon center resonance form. This should generate initially a peroxide and then a hydroperoxide before finally giving **113**. Such a sequence could initiate unwanted oxidation causing cell death. This observation is reminiscent of the slow reactions of BHT with oxygen [46]. In this case the hydroperoxide, as like **114**, has been isolated. BHT is therefore also not a completely benign antioxidant.



114

Scheme 62: Reaction of BHT with molecular oxygen

- Summary -

These cell culture and DPPH· results proved that naphthalene-2,3-diols should now be considered as potential antioxidants, since some of the synthesized analogues were shown to be very good radical scavengers, better than Vitamin E. These antioxidants are less toxic than the well-known catechol antioxidants. However, the true potential in *in vivo* situation remains to be demonstrated.

Chapter 3:

- Experimental -

3.1. Notes

- **Synthesis:**

All starting materials were purchased from Aldrich and used as received. P(*t*Bu)$_3$, which was purchased from Strem Chemicals, was used to prepare the 1.0M solution of P(*t*Bu)$_3$ in anhydrous 1,4-dioxane in a glove box. Melting points were determined by using a Thomas Hoover Capillary melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained from either a Bruker AMX-500 spectrometer, Varian XL-300 or a Varian Gemini-200 spectrometer. The samples were run in spectroscopic grade deuterated chloroform, acetone or dimethyl sulphoxide. Chemical shifts are in parts per million relative to tetramethyl silane. Mass spectrum analyses and high resolution mass spectra were performed by the analytical services available at University of Ottawa. High resolution mass spectroscopy was done on a Kratos Concept-IIA mass spectrometer. Peaks reported for mass analysis are those beyond 20% except for the molecular ion peaks.

Dry solvents used for reactions came from an mBraun dry solvents distillation apparatus and the glassware used for moisture sensitive reactions were dried overnight in an oven prior to use. Oven dried syringes were used to transfer chemicals and solvents. Solvents used for non-moisture sensitive reactions were the driest and purest solvents commercially available and used as received. All reactions were monitored by thin layer chromatography using silica gel on alumina sheets, 60 F_{254}. Spots on these TLC were seen either by ultraviolet light or by staining, which was a 5% solution of ammonium molybdate in 10% aqueous H_2SO_4. The TLC plates were developed by dipping into the stain and then heated

with heat gun. Silica gel 270-400 mesh was used for column chromatography. Eluent solvent mixtures reported in procedures are solvents used for the beginning of the purification processes. The names assigned to compounds were taken from Chemdraw 2001 computer software.

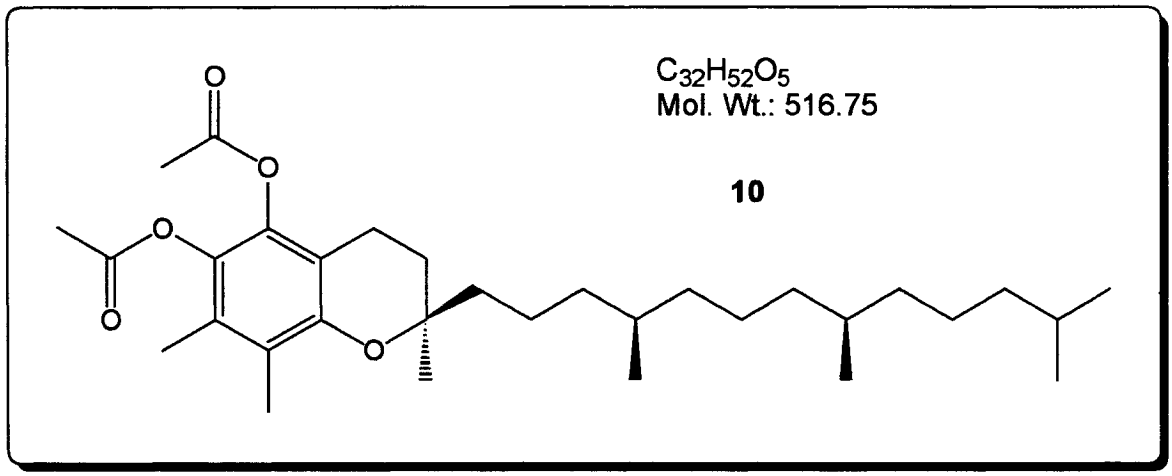
- **DPPH· testing:**

The NRC stop-flow apparatus is an Applied Photophysics SX 18MV spectrometer with a xenon 150 arc light source. DPPH· was obtained from Northern Sources, Inc. or Aldrich, and used without further purification. All compounds tested were examined by TLC or ^{1}H NMR for their relative purity prior to testing. In a typical experiment, DPPH· was deoxygenated under nitrogen, and then mixed 1:1 with deoxygenated solutions of antioxidants, where the different concentrations were usually 2 orders of magnitude greater, as to obtain pseudo-first order rate constants. The decay of DPPH· was monitored at 519 nm in the presence of a given and large excess concentrations of antioxidant at room temperature. Under these conditions, the decay curve is pseudo-first order, and it was well fitted by a single-exponential function $[DPPH] = [DPPH]_0 \exp(-k_{obs}t) +$ constant. From plots of k_{obs} vs [antioxidant] for at least five different concentrations the second-order rate constant was obtained as the slope of the plot.

All BDE calculations and cell culture testing were performed by Dr. Wright's group [18, 27] at Carleton University in Ottawa.

3.2. Procedures and characterizations

Acetic acid 6-acetoxy-2,7,8-trimethyl-2-(4,8,12-trimethyl-tridecyl)-chroman-5-yl ester:



Triethylamine (0.096mL, 0.693 mmol, d 0.726) was added via syringe to a solution of diol **4** (prepared in 3 steps from δ-tocopherol following the procedure of Hussain et al. [18])(0.1g, 0.231 mmol) and DMAP (0.006g, 0.046 mmol) dissolved in 10mL of dry CH_2Cl_2, under nitrogen atmosphere, followed by acetic anhydride (0.065mL, 0.693 mmol, d 1.082). The mixture was stirred at r.t. for 4h, then diluted with 10mL of water and the layers were separated. The organic layer was washed once with 10mL of aq. 10% HCl and the combined aqueous layers extracted twice with CH_2Cl_2 (2 x 10mL). The combined organic layers were dried over $MgSO_4$, filtered and solvent evaporated in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes to afford pure product **10** in 99% yield as pale yellowish oil (0.12g, 0.230 mmol).

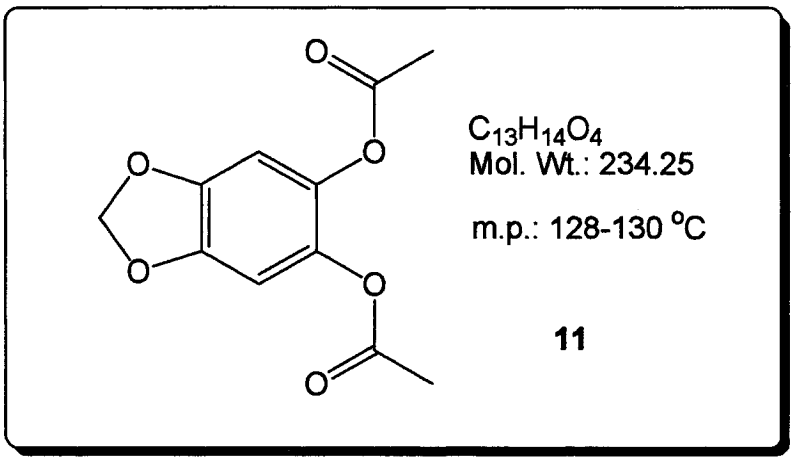
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.84-0.86 (m, 12H), 1.03-1.49 (m, 22H), 1.50-1.56 (m, 2H), 1.62-1.80 (m, 2H), 2.03 (s, 3H), 2.07 (s, 3H), 2.27 (s, 6H), 2.48-2.53 (t, 2H, J = 6.5 Hz)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 12.19, 13.27, 17.71, 20.01, 20.14, 20.72, 20.74, 21.35, 23.02, 23.12, 24.37, 24.82, 25.19, 28.35, 30.42, 33.07, 33.17, 37.65, 37.74, 37.78, 37.83, 39.74, 40.51, 76.44, 112.57, 123.57, 128.39, 133.78, 138.41, 150.15, 168.73, 169.39

Mass (EI): *m/z* (%) = 516.4 (M+, 8), 475.4 (21), 474.4 (64), 433.4 (30), 432.4 (100), 167.1 (42), 166.1 (40), 99.0 (57), 71.1 (21), 69.1 (25), 57.1 (38), 55.1 (28), 43.1 (41), 41.0 (27)

HRMS: calcd 516.3815, found 516.3806

1-[6-(2-Oxo-propyl)-benzo[1,3]dioxol-5-yl]-propan-2-one:



Acetylation of diol **5** (0.1g, 0.649 mmol) was accomplished following the same procedure as in synthesis of diacetate **10**. The crude solid was dissolved in 10mL of CH_2Cl_2 and filtered through a small pad of silica gel packed into a disposable pipet. After evaporation of all solvent in vacuo, white crystals were obtained as pure diacetate **11** (0.15g, 0.630 mmol, 97 % yield).

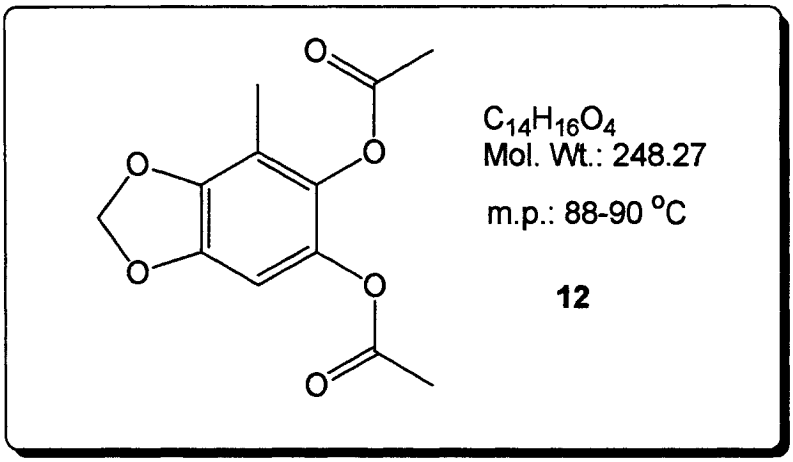
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.21 (s, 6H), 5.93 (s, 2H), 6.63 (s, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 20.46, 102.18, 103.97, 135.82, 145.30, 168.56

Mass (EI): *m/z* (%) = 238.0 (M+, 7), 154.0 (100), 43.0 (24)

HRMS: calcd 238.0477, found 238.0489

1-[4-methyl-6-(2-Oxo-propyl)-benzo[1,3-dioxol-5-yl]-propan-2-one:



Acetylation of diol **6** (0.9g, 5.35 mmol) was accomplished following the same procedure as in the synthesis of diacetate **10**. The crude solid was dissolved in 10mL of CH_2Cl_2 and filtered through a small pad of silica gel packed into a disposable pipet. After evaporation of all solvent in vacuo, pale brownish crystals were obtained as pure diacetate **12** (1.23g, 4.88 mmol, 91 % yield).

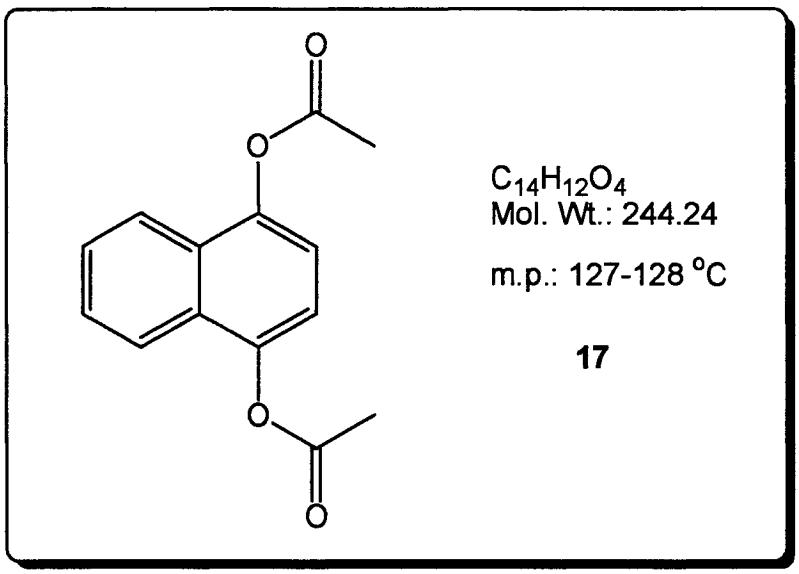
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.99 (s, 3H), 2.16 (s, 3H), 2.20 (s, 3H), 5.86 (s, 2H), 6.48 (s, 1H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 9.43, 19.98, 20.32, 101.40, 101.80, 113.51, 135.30, 136.12, 144.08, 144.31, 168.33, 168.66

Mass (EI): *m/z* (%) = 252.1 (M+, 12), 168.0 (100), 167.0 (26)

HRMS: calcd 252.0634, found 252.0650

Acetic acid 4-acetoxy-naphthalen-1-yl ester:



Acetylation of diol **14** (0.2g, 1.25 mmol) was accomplished during 4h following the same procedure as in the synthesis of diacetate **10**. The crude product was purified by column chromatography using 20% EtOAc in Hexanes as eluent, which afforded diacetate **17** as an off-white solid (0.24g, 0.983 mmol, 79%).

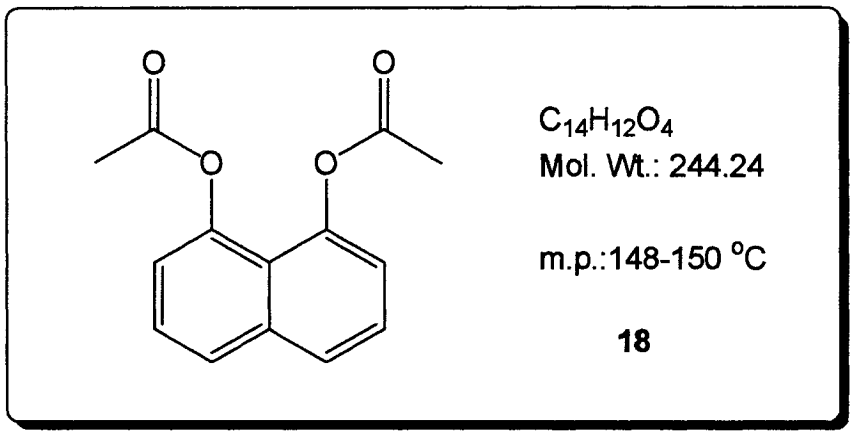
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.46 (s, 6H), 7.26 (s, 2H), 7.54-7.57 (m, 2H), 7.87-7.90 (m, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 20.93, 117.59, 121.53, 126.91, 127.54, 144.22, 169.32

Mass (EI): *m/z* (%) = 244.1 (M+, 5), 160.1 (100)

HRMS: calcd 244.0736, found 244.0739

Acetic acid 8-acetoxy-naphthalen-1-yl ester:



Acetylation of diol **15** (0.07, 0.437 mmol) was carried out during 2h following the same procedure as in the synthesis of diacetate **10**. The crude product was then diluted in 10 mL of CH_2Cl_2 and filtered through a small pad of silica gel packed in a disposable pipet, solvent evaporated in vacuo, which afforded 94 % of pure **18** as a white solid (0.1g, 0.410 mmol).

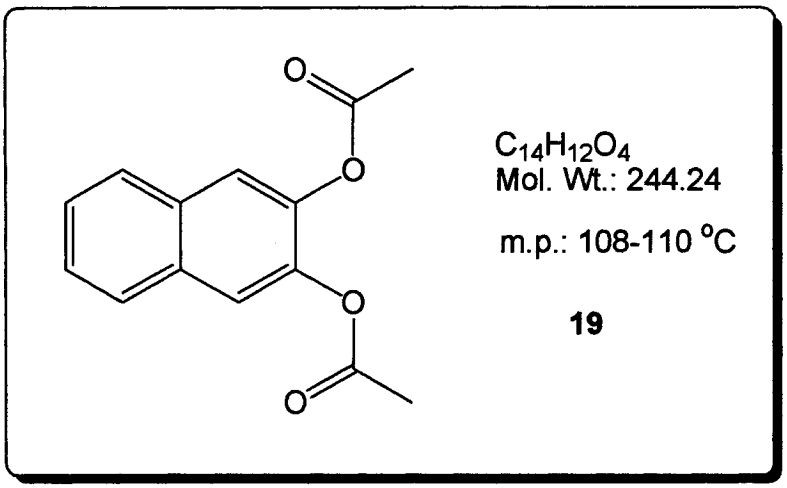
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.38 (s, 6H), 7.12-7.16 (dd, 2H, J_o = 7.54 Hz, J_m = 1.04 Hz), 7.42-7.49 (t, 2H, J_o = 7.42 Hz), 7.75-7.80 (dd, 2H, J_o = 8.47 Hz, J_m = 1.04 Hz)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 21.22, 120.61, 126.03, 126.95, 136.67, 145.04, 169.67

Mass (EI): *m/z* (%) = 244.1 (M+, 6), 160.1 (100)

HRMS: calcd 244.0736, found 244.0741

Acetic acid 3-acetoxy-naphthalen-2-yl ester:



Acetylation of diol **16** (0.1g, 0.624 mmol) was accomplished following the same procedure as in the synthesis of diacetate **10**. The crude product was purified by flash column chromatography using 7/3 Hexanes/EtOAc as eluent, which afforded diacetate **19** (0.15g, 0.618 mmol) as a white powdered solid in 99 % yield.

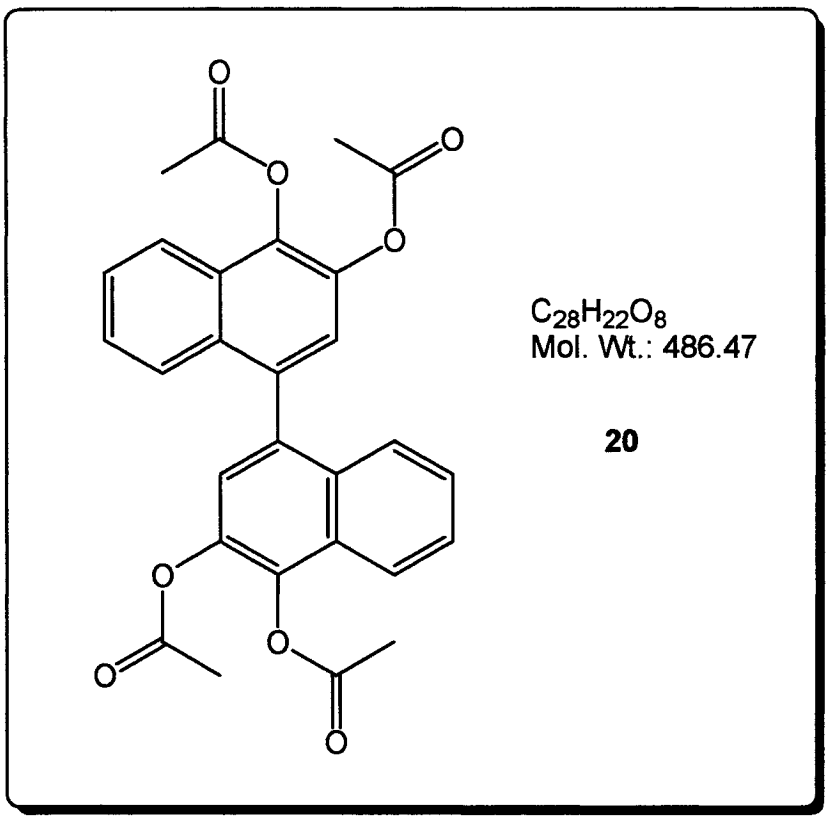
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.33 (s, 6H), 7.43-7.49 (m, 2H), 7.67 (s, 2H), 7.76-7.81 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 20.67, 120.95, 126.38, 127.47, 131.54, 140.95, 168.60

Mass (EI): *m/z* (%) = 244.1 (M+, 9), 202.1 (24), 160.1 (100), 43.0 (39

HRMS: calcd 244.0736, found 244.0731

Acetic acid 3,3',4'-triacetoxy-[1,1]binaphthalenyl-4-yl ester:



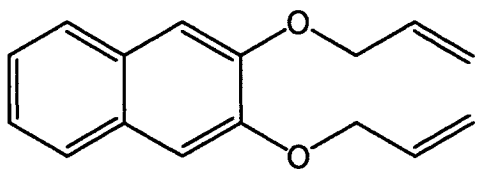
$C_{28}H_{22}O_8$
Mol. Wt.: 486.47

20

Dimer **20** (0.0565g, 0.116 mmol, 19%) was characterized as a white solid following an acetylation attempt on diol **13** (0.2g, 1.25 mmol) (see subsection 2.2), which followed the same procedure than in the synthesis of diacetate **10**.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.33 (s, 6H), 2.51 (s, 6H), 7.33-7.38 (m, 4H), 7.46-7.55 (m, 4H), 7.90-7.93 (d, 2H, J_o = 8.42 Hz)
Mass (EI): *m/z* (%) = 486.1 (M+, 16), 402.1 (36), 360.1 (55), 318.1 (100), 317.1 (24), 84.0 (24), 43.0 (78)
HRMS: calcd 486.1315, found 486.1311

2,3-Bis-allyloxy-naphthalene:



$C_{16}H_{16}O_2$
Mol. Wt.: 240.30

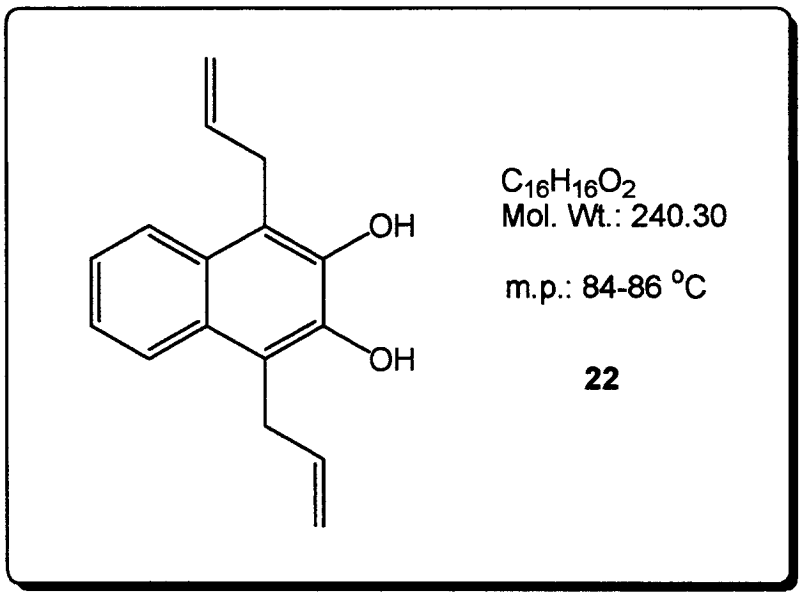
m.p.: 60-61 °C

21

Potassium carbonate (17.26g, 124.88 mmol) was added to a solution of 2,3-dihydroxynaphthalene **16** (5.0g, 31.22 mmol) in 40 mL of acetone followed by the allyl bromide (7.92mL, 93.66 mmol, d 1.43) by syringe. The resulting pinkish solution with suspension was placed under nitrogen atmosphere and refluxed (65°C) overnight. The resulting suspension was filtered by suction. The solid was washed several times with acetone and solvent evaporated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes which provided 3.48g of pure product. Several mixed fractions were further purified by recrystallization using 100% hexanes to afford an extra 2.11g of pure product, to yield a total of 5.59g of **21** (75%).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.69-4.71 (t, 2H), 4.72-7.74 (t, 2H), 5.28-5.36 (dq, 2H, J_{cis} = 10.43 Hz, J_{gem} = 1.51 Hz), 5.43-5.54 (dq, 2H, J_{trans} = 17.28 Hz, J_{gem} = 1.62 Hz), 6.06-6.25 (m, 2H), 7.13 (s, 2H), 7.24-7.34 (m, 2H), 7.63-7.67 (m, 2H)
^{13}C NMR ($CDCl_3$, 200 MHz): δ = 69.49, 108.24, 117.80, 124.15, 126.27, 129.15, 133.05, 148.61
Mass (EI): *m/z* (%) = 240.1 (M+, 87), 199.1 (100), 171.0 (25), 171.0 (40), 169.1 (61), 153.1 (21), 143.1 (33), 131.1 (25), 128.1 (53), 115.1 (31), 102.0 (44), 41.0 (59)
HRMS: calcd 240.1150, found 240.1162

1,4-Diallyl-naphthalene-2,3-diol:



$C_{16}H_{16}O_2$
Mol. Wt.: 240.30

m.p.: 84-86 °C

22

A suspension of diether **21** (5.0g, 20.81 mmol) in 25 mL of decalin was heated to 180-185°C during which time the solid dissolved. After 2h at that temperature, the resulting dark brown solution was cooled down to r.t. and left in freezer overnight. The solid produced was filtered and washed several times with cold hexanes, which afforded **22** as light brownish-colored crystals (4.43g, 18.44 mmol) in 88 % yield.

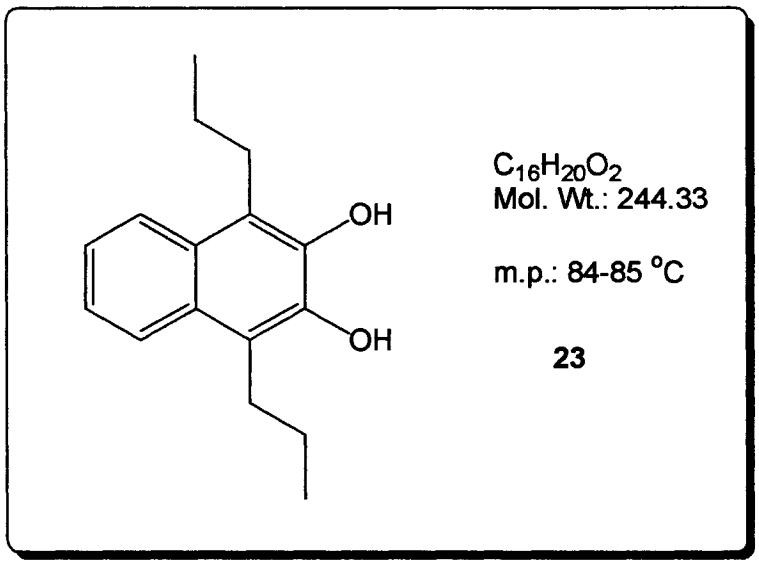
^{1}H NMR (acetone-d_6, 200 MHz): δ = 3.83-3.85 (t, 2H), 3.86-3.88 (t, 2H), 4.92-4.95 (3 x q, 4H, J_{trans} = 19.02 Hz, J_{cis} = 10.90 Hz, J_{gem} = 1.97 Hz), 5.91-6.11 (m, 2H), 7.26-7.31 (m, 2H), 7.83-7.88 (m, 2H), 7.96 (s, 2H)

^{13}C NMR (acetone-d_6, 200 MHz): δ = 115.21, 117.21, 123.99, 124.38, 129.32, 137.40, 144.10

Mass (EI): *m/z* (%) = 240.1 (M+, 100), 153.1 (23)

HRMS: calcd 240.1150, found 240.113

1,4-Dipropyl-naphthalene-2,3-diol:



$C_{16}H_{20}O_2$
Mol. Wt.: 244.33

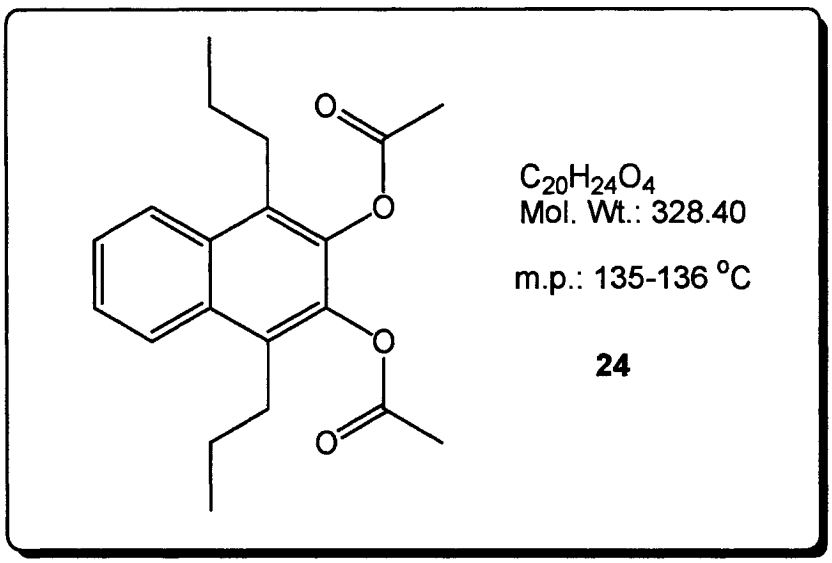
m.p.: 84-85 °C

23

Pd/C 30% (0.17g, 1.58 mmol) was added in one portion to a solution of diol **22** (3.8g, 15.81 mmol) dissolved in 15mL of MeOH and the RBF was closed tightly with septum and parafilm. The resulting black solution was then placed under hydrogen atmosphere using 2 balloons and stirred at r.t. overnight (16h). The resulting mixture was filtered through celite and washed several times with EtOAc. The combined solvents were evaporated in vacuo and the crude was dissolved in 20mL of EtOAc, washed once with saturated aq. sodium hydrosulfite solution (10mL) and the aqueous layer extracted once with 10mL of EtOAc. The combined organic layers were dried over $MgSO_4$, filtered and the solvent was evaporated in vacuo. The crude (greenish solid) was purified by column chromatography using 5% EtOAc in hexanes as eluent, which afforded diol **23** (3.5g, 14.33 mmol) in 91% yield as an off-white solid, which after hexanes washings became more white.

^{1}H NMR (acetone-d_6, 200 MHz): δ = 0.99-1.06 (t, 6H, J = 7.31 Hz), 1.59-1.96 (m, 4H), 3.01-3.08 (t, 4H, J = 7.77 Hz), 7.26-7.30 (m, 2H), 7.84-7.89 (m, 4H)
^{13}C NMR (acetone-d_6, 200 MHz): δ = 14.51, 23.82, 27.81, 119.48, 123.74, 124.08, 129.23, 143.69
Mass (EI): *m/z* (%) = 244.1 (M+, 40), 215.1 (100)
HRMS: calcd 244.1463, found 244.1482

Acetic acid 3-acetoxy-1,4-dipropyl-naphthalen-2-yl ester:



$C_{20}H_{24}O_4$
Mol. Wt.: 328.40

m.p.: 135-136 °C

24

Acetylation of diol **22** (0.4g, 1.64 mmol) was accomplished following the same procedure as in the synthesis of diacetate **10**. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent, which afforded diacetate **23** (0.41g, 1.25 mmol) in 76% yield as an off-white solid.

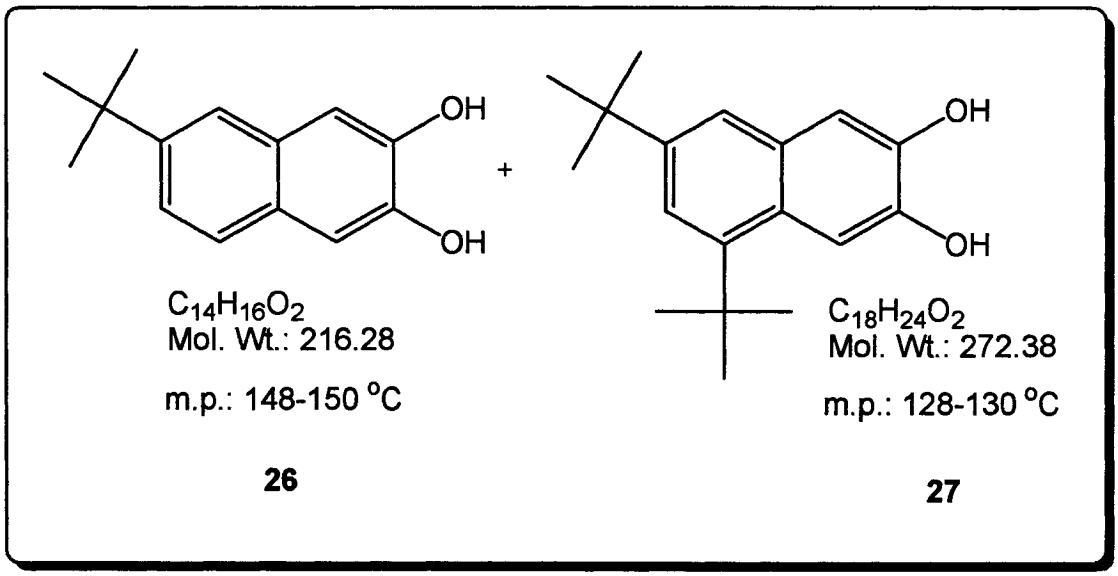
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.98-1.05 (t, 6H, J = 7.31 Hz), 1.59-1.71 (m, 4H), 2.35 (s, 6H), 2.85-2.93 (t, 4H, J = 7.89 Hz), 7.46-7.51 (m, 2H), 7.97-8.02 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.53, 20.41, 23.28, 28.44, 124.81, 125.71, 129.25, 131.04, 138.95, 168.75

Mass (EI): *m/z* (%) = 328.2 (M+, 19), 286.2 (45), 245.2 (32), 244.1 (100), 215.1 (69)

HRMS: calcd 328.1675, found 328.1660

6-*tert*-Butyl-naphthalene-2,3-diol (26) and 5,7-di-tert-butyl-naphthalene-2,3- diol (27):



2,3-Naphthalenediol **16** (2.0g, 12.49 mmol) was placed in a thick glass bulb and dissolved in 25mL of t-BuOH. To the resulting mixture was added carefully 4mL of conc. sulfuric acid and the bulb was tightly closed and stirred 4h at 90°C, during which time formation of two layers was observed. The resulting two layers solution was washed with saturated aq. $NaHCO_3$ (10mL), layers separated and the aqueous layer extracted with EtOAc (3 x 15mL). The combined organic layers were washed once with 50mL of water, dried over $MgSO_4$, filtered and solvents evaporated in vacuo. The purple colored crude solid was purified by two consecutive column chromatographies using 20% EtOAc in hexanes as eluent. This afforded diol **26** (1.36g, 6.29 mmol) followed by diol **27** (1.29g, 4.74 mmol) in a combined 88% yield.

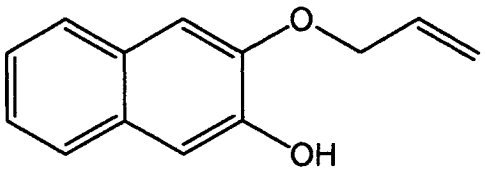
- Characterization of **26**:

^{1}H NMR (acetone-d_6, 200 MHz): δ = 1.35 (s, 9H), 7.15 (s, 1H), 7.18 (s, 1H), 7.31-7.36 (dd, 1H, J_o = 8.81 Hz, J_m = 1.97 Hz), 7.51-7.54 (d, 1H, J_o = 8.7 Hz), 7.54-7.55 (d, 1H, J_m = 2.09 Hz), 8.32 (s, 1H), 8.37 (s, 1H)
^{13}C NMR (acetone-d_6, 200 MHz): δ = 31.59, 35.00, 109.92, 110.56, 121.84, 122.83, 126.48, 128.38, 130.22, 146.42, 156.59, 147.02
Mass (EI): *m/z* (%) = 216.1 (M+, 32), 201.1 (100), 84.0 (23), 70.1 (22), 58.0 (31)
HRMS: calcd 216.1150, found 216.1141

- Characterization of **27**:

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.42 (s, 9H), 1.59 (s, 9H), 6.30 (s, 2H), 7.24 (s, 1H), 7.44-7.45 (d, 1H, J_m= 1.97 Hz), 7.49-7.50 (d, 1H, J_m= 1.97 Hz), 7.90 (s, 1H)
^{13}C NMR ($CDCl_3$, 200 MHz): δ = 31.28, 31.57, 34.78, 36.09, 110.49, 111.95, 120.70, 120.87, 125.47, 131.31, 142.25, 142.69, 144.16, 145.76
Mass (EI): *m/z* (%) = 272.2 (M+, 61), 258.1 (28), 257.1 (100), 201.1 (34), 27.1 (38)
HRMS: calcd 272.1776, found 272.1800

3-Allyloxy-naphthalen-2-ol:



$C_{13}H_{12}O_2$
Mol. Wt.: 200.23
m.p.: 48-50 °C

29

Potassium carbonate (5.18g, 37.46 mmol) followed by allyl bromide (2.64mL, 31.22 mmol, d 1.43) was added to 2,3-naphthalenediol **16** (5.0g, 31.22 mmol) dissolved in 25mL of acetone. The resulting pinkish solution was placed under nitrogen atmosphere and refluxed for 4h. The reaction mixture was cooled to r.t., filtered and the precipitate was washed several times with acetone. The filtrate was evaporated in vacuo. The crude product was dissolved in 20mL of EtOAc and washed with aq. 10% NaOH solution (3 x 10mL). The combined aqueous layers were acidified using conc. HCl then extracted with EtOAc (3 x 20mL). The combined organic layers were dried over $MgSO_4$, filtered and solvent evaporated in vacuo. The oily crude material was purified by two consecutive column chromatography using 10% followed by 5% EtOAc in hexanes as eluent, which afforded pure **29** (3.52g, 17.58 mmol, 56%) as a white solid.

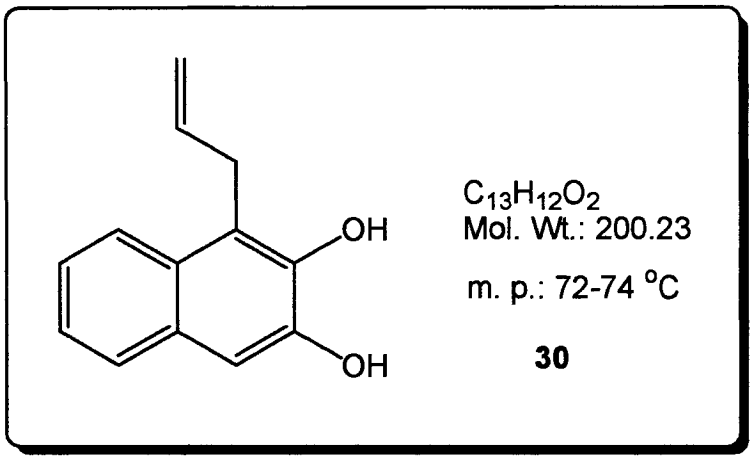
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 4.68-4.70 (t, 1H), 4.71-4.73 (t, 1H), 5.33-5.40 (dq, 1H, J_{cis} = 10.44 Hz, J_{gem} = 1.28 Hz), 5.41-5.52 (dq, 1H, J_{trans} = 17.28 Hz, J_{gem} = 1.51 Hz), 6.02 (s, 1H), 6.03-6.22 (m, 1H), 7.12 (s, 1H), 7.24-7.38 (m, 2H), 7.30 (s, 1H), 7.65-7.69 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 69.64, 106.94, 109.52, 118.72, 123.86, 124.38, 126.32, 126.50, 128.89, 129.68, 132.38, 145.73, 146.22

Mass (EI): *m/z* (%) = 200.1 (M+, 90), 159.0 (100), 131.1 (88)

HRMS: calcd 200.0837, found 200.0842

1-Allyl-naphthalene-2,3-diol:



$C_{13}H_{12}O_2$
Mol. Wt.: 200.23
m. p.: 72-74 °C

30

Rearrangement of mono-allyl ether **29** (3.52g, 17.58 mmol) was accomplished following the same procedure as in the synthesis of **22**. The crude product was purified by two consecutive column chromatography using 5% EtOAc in hexanes as eluent, which afforded **30** (2.84g, 14.18 mmol) as a slightly brownish solid in 81% yield.

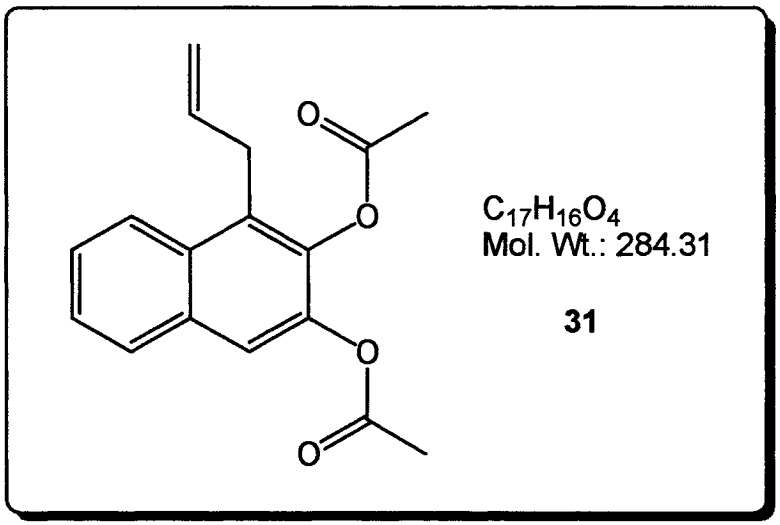
^{1}H NMR (acetone-d_6, 300 MHz): δ = 3.83-3.84 (t, 1H), 3.85-3.86 (t, 1H), 4.93-4.98 (dq, 1H, J_{cis} = 10.08 Hz, J_{gem} = 1.60 Hz), 4.99-5.07 (dq, 1H, J_{trans} = 17.13 Hz, J_{gem} = 1.80 Hz), 5.95-6.09 (m, 1H), 7.15 (s, 1H), 7.18-7.29 (m, 2H), 7.57-7.60 (dd, J_o = 6.44 Hz, J_m = 1.67 Hz), 7.81-7.83 (d, 1H, J_o = 8.20 Hz)

^{13}C NMR (acetone-d_6, 300 MHz): δ = 109.57, 116.03, 119.48, 124.73, 124.75, 124.99, 128.28, 130.15, 131.19, 138.41, 145.61, 146.95

Mass (EI): *m/z* (%) = 200.1 (M+, 100), 199.1 (21), 185.1 (43), 181.1 (25), 153.1 (26)

HRMS: calcd 200.0837, found 200.0839

Acetic acid 3-acetoxy-1-allyl-naphthalen-2-yl ester:



$C_{17}H_{16}O_4$
Mol. Wt.: 284.31

31

Acetylation of diol **30** (0.2g, 0.999 mmol) was carried out for 2h following the procedure used for the synthesis of diacetate **10**. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent, which afforded diacetate **31** (0.27g, 0.950 mol) as a yellowish oil in 95% yield.

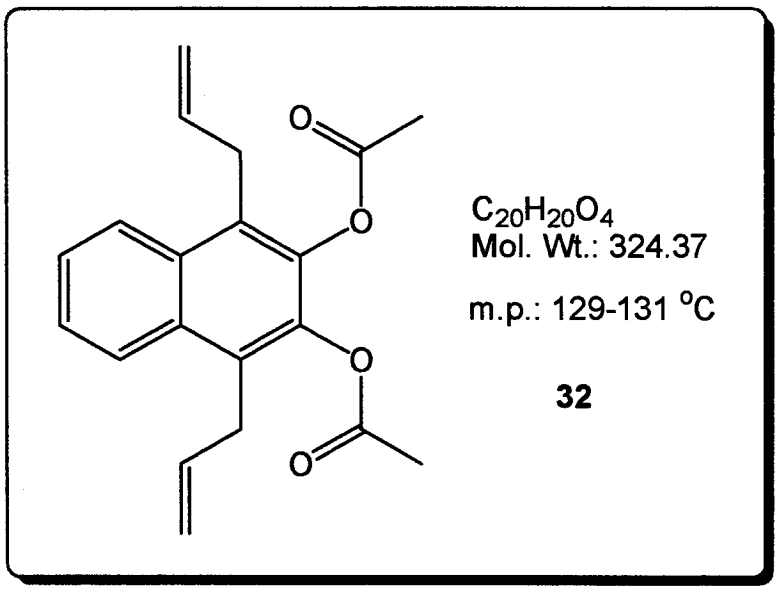
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.35 (s, 3H), 2.38 (s, 3H), 3.78-3.79 (t, 1H), 3.80-3.81 (t, 1H), 5.04-5.11 (3 x q, 2H, J_{trans} = 18.12 Hz, J_{cis} = 10.74 Hz, J_{gem} = 1.56 Hz), 5.94-6.05 (m, 1H), 7.26-7.55 (m, 2H), 7.64 (s, 1H), 7.80-7.84 (m, 1H), 7.98-8.03 (m, 1H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 20.81, 21.21, 30.85, 116.79, 120.10, 124.73, 126.56, 126.69, 128.82, 129.01, 131.01, 132.30, 135.50, 139.82, 141.30, 168.92, 168.99

Mass (EI): *m/z* (%) = 284.1 (M+, 30), 242.1 (56), 201.1 (39), 200.1 (100), 199.1 (25), 185.1 (38), 43.0 (52)

HRMS: calcd 284.1049, found 284.1039

Acetic acid 3-acetoxy-1,4-diallyl-naphthalen-2-yl ester:



Acetylation of diol **31** (0.15g, 0.624 mmol) was accomplished during 2h following the same procedure as in the synthesis of diacetate **10**. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent, which afforded diacetate **32** (0.19g, 0.586 mmol) as a white solid in 94% yield.

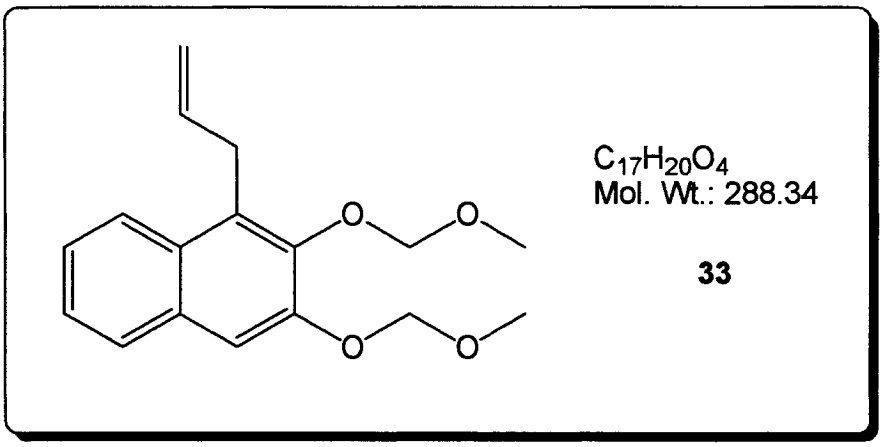
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.37 (s, 6H), 3.77 (bt, 1H), 3.79 (bt, 1H), 5.06-5.12 (2 x q, 2H, J_{gem} = 1.45 Hz), 5.91-6.04 (m, 1H), 7.51-7.56 (m, 2H), 8.03-8.08 (m, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 20.52, 30.57, 116.43, 125.09, 126.14, 127.08, 131.16, 135.31, 139.60, 168.66

Mass (EI): *m/z* (%) = 324.1 (M+, 12), 282.1 (40), 241.1 (21), 240.1 (100)

HRMS: calcd 324.1362, found 324.1380

1-Allyl-2,3-bis-methoxymethoxy-naphthalene:



DIPEA (1.86mL, 10.65 mmol, d 0.742) followed by chloromethyl methyl ether (0.81mL, 10.65 mmol, d 1.060) were added dropwise to a solution of diol **30** (0.71g, 3.55 mmol) dissolved in 15mL of dry CH_2Cl_2 at 0°C under nitrogen atmosphere. The resulting yellowish solution was stirred 30 min at 0°C and then 4h at r.t. The resulting solution was diluted with 15mL of water and the layers separated. The aqueous layer was extracted using CH_2Cl_2 (2 x 15mL) and the combined organic layers dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent to afford **33** (0.82g, 2.84 mmL) as a colorless oil in 80% yield.

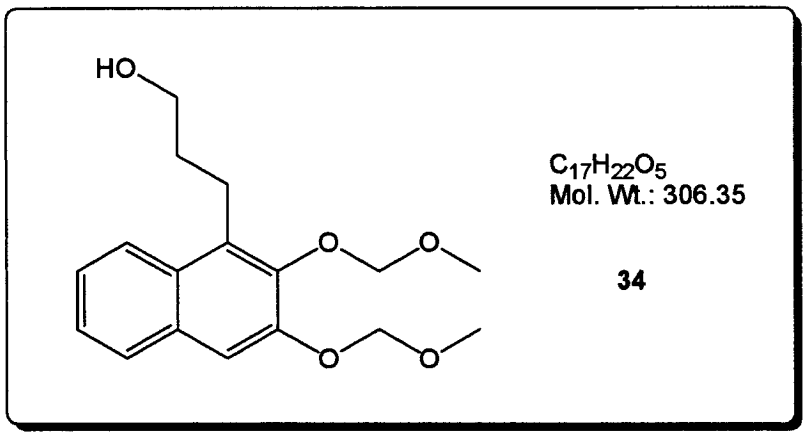
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.57 (s, 3H), 3.69 (s, 3H), 3.97-3.99 (t, 1H), 4.00-4.02 (t, 1H), 5.02-5.14 (3 x q, 2H, J_{trans} = 18.67 Hz, J_{cis} = 9.97 Hz, J_{gem} = 1.74 Hz), 5.24 (s, 2H), 5.35 (s, 2H), 6.03-6.23 (m, 1H), 7.24-7.43 (m, 2H), 7.44 (s, 1H), 7.71-7.77 (m, 1H), 7.90-7.97 (m, 1H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 30.14, 56.30, 57.61, 94.90, 99.42, 110.07, 115.71, 124.32, 124.40, 125.16, 127.50, 128.31, 128.66, 131.53, 136.78, 144.45, 149.10

Mass (EI): *m/z* (%) = 288.1 (M+, 15), 212.1 (100), 211.1 (23), 69.0 (79), 45.0 (47), 45.0 (92), 43.0 (22), 43.0 (48)

HRMS: calcd 288.1362, found 288.1372

3-(2,3-Bis-methoxymethoxy-naphthalen-1-yl)-propan-1-ol:



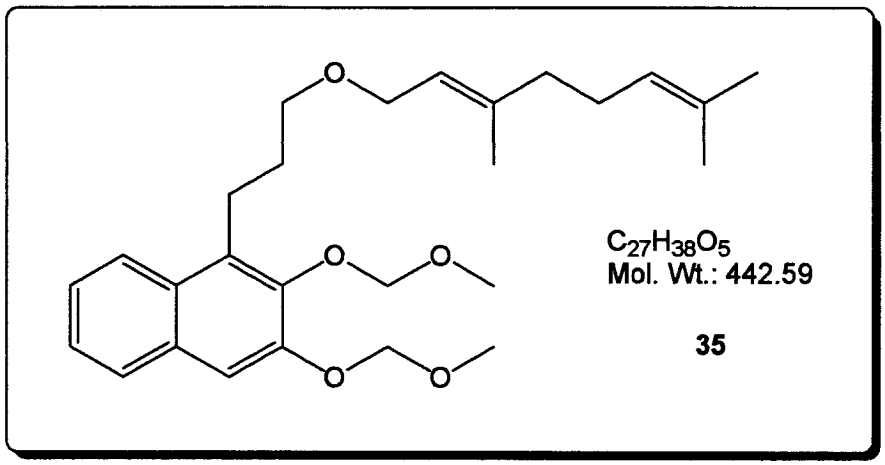
$C_{17}H_{22}O_5$
Mol. Wt.: 306.35

34

To compound **33** (0.2g, 0.694 mmol) and sodium borohydride (0.02g, 0.520 mmol) dissolved in 5mL of dry THF in a 2-neck RBF equipped with a condenser and a dropping funnel was added over 1 hour at 30-40°C a solution of $BF_3{\cdot}OEt_2$ (0.09mL, 0.699 mmol, d 1.120) in dry THF (5mL). The resulting mixture was stirred another hour at r.t. after which time 2mL of water was added. The solution was reheated to 30-40°C and 2mL of a 10% aq. NaOH solution was added followed by 2mL of H_2O_2 (30%). After 15 min, the resulting solution was neutralized using aq. 10% HCl followed by dilution with 20mL of EtOAc and 10mL of brine. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10mL) and the combined organic layers were dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude was purified by column chromatography using 30% EtOAc in hexanes as eluent. This gave the primary alcohol **34** (0.18g, 0.587 mmol) as a colorless oil in 85% yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.91-2.00 (qu, 2H), 2.68 (s, 1H), 3.26-3.31 (t, 2H), 3.53 (s, 3H), 3.60-3.65 (t, 2H), 3.65 (s, 3H), 5.21 (s, 2H), 5.32 (s, 2H), 7.37 (s, 1H), 7.37-7.40 (m, 2H), 7.69-7.72 (m, 1H), 7.92-7.95 (m, 1H)
^{13}C NMR ($CDCl_3$, 300 MHz): δ = 22.19, 33.10, 56.75, 58.27, 62.05, 95.28, 99.99, 110.16, 124.24, 124.90, 125.61, 128.02, 128.68, 130.50, 132.07, 144.64, 149.06
Mass (EI): *m/z* (%) = 306.1 (M+, 5), 200.1 (33), 185.1 (27), 45.0 (100)
HRMS: calcd 306.1467, found 306.1483

1-[3-(3,7-Dimethyl-octa-2,6-dienyloxy)-propyl]-2,3-bis-methoxymethoxy-naphthalene:



To a suspension of sodium hydride (dry, 95%) (0.03g, 1.11 mmol) in 5mL of dry THF under nitrogen atmosphere at 0°C was added dropwise compound **34** (0.17g, 0.555 mmol). The yellowish mixture was stirred 30 min while warming up to r.t. Sodium iodide (0.02g, 0.111 mmol) was added followed by geranyl bromide (0.13mL, 0.666 mmol, d 1.14) dropwise and the mixture was refluxed overnight. The resulting white mixture was cooled to r.t. and poured into a mixture of 10mL of EtOAc and 15mL of water. The layers were separated and the aqueous layer was extracted with EtOAc (2 x 10mL). The combined organic layers were dried over Na_2SO_4, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent to afford **35** (0.18g, 0.407 mmol) as a colorless oil in 73% yield.

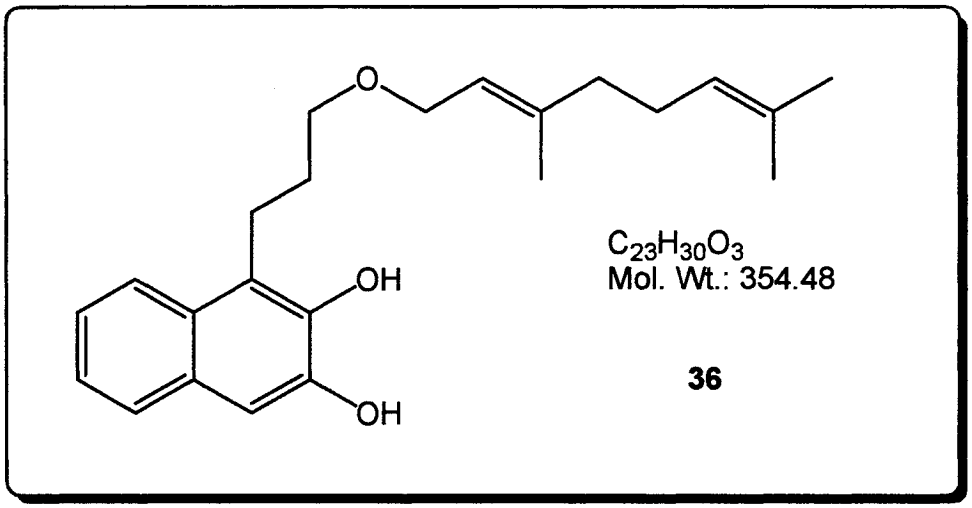
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.63 (s, 3H), 1.70 (s, 6H), 1.96-2.15 (m, 6H), 3.24-3.29 (t, 2H), 3.53-3.58 (t, 2H), 3.56 (s, 3H), 3.68 (s, 3H), 4.03-4.05 (d, 2H, J = 6.66 Hz), 5.11-5.15 (t, 1H), 5.20 (s, 2H), 5.34 (s, 2H), 5.40-5.45 (t, 1H), 7.36-7.42 (m, 2H), 7.38 (s, 1H), 7.70-7.73 (m, 1H), 7.98-8.01 (m, 1H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 16.43, 17.63, 22.71, 25.64, 26.34, 30.45, 39.55, 56.22, 57.52, 67.29, 69.86, 94.80, 99.28, 109.53, 121.13, 123.92, 123.97, 124.27, 124.97, 127.41, 128.45, 130.98, 131.42, 131.51, 139.49, 144.20, 148.85

Mass (EI): *m/z* (%) = 442.1 (M+, 1), 306.1 (28), 274.1 (21), 230.1 (53), 229.1 (27), 214.1 (33), 201.1 (24), 200.1 (100), 199.1 (29), 185.1 (55), 81.1 (23), 69.1 (68), 45.0 (87), 41.0 (26)

HRMS: calcd 442.2719, found 442.2716

1-[3-(3,7-Dimethyl-octa-2,6-dienyloxy)-propyl]-naphthalene-2,3-diol:



$C_{23}H_{30}O_3$
Mol. Wt.: 354.48

36

The starting material **35** (0.17g, 0.384 mmol) was dissolved in 10mL of MeOH and 4 drops of conc. HCl were added. This mixture was refluxed for one hour. The yellowish solution was cooled to r.t., diluted with 15mL of EtOAc and washed with 15mL of water. The aqueous layer was extracted twice with 10mL of EtOAc and the combined organic layers were dried over Na_2SO_4, filtered through cotton and the combined solvents evaporated in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent. This yielded 0.085g (0.240 mmol) or 63% of **36** as a colorless oil.

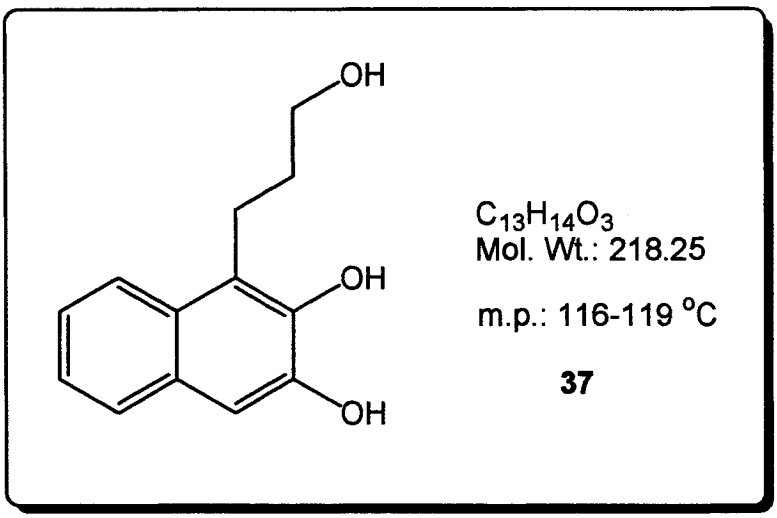
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.65 (s, 3H), 1.71 (s, 3H), 1.73 (s, 3H), 2.05-2.19 (m, 6H), 3.20-3.24 (t, 2H), 3.38-3.41 (t, 2H), 4.09-4.12 (d, 2H, J = 7.02 Hz), 5.11-5.15 (t, 1H), 5.41-5.46 (t, 1H), 6.27 (s, 1H), 7.21 (s, 1H), 7.30-7.37 (m, 2H), 7.68-7.71 (m, 1H), 7.78-7.81 (m, 1H), 8.64 (s, 1H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 16.43, 17.68, 20.78, 25.65, 26.23, 27.46, 39.56, 67.11, 67.23, 107.78, 118.71, 119.11, 122.47, 123.49, 123.67, 127.23, 127.74, 130.25, 131.84, 142.09, 142.83, 145.88

Mass (EI): *m/z* (%) = 354.2 (M+, 3), 218.1 (100), 200.1 (27), 173.1 (30), 81.1 (22), 69.1 (63)

HRMS: calcd 354.2195, found 354.2185

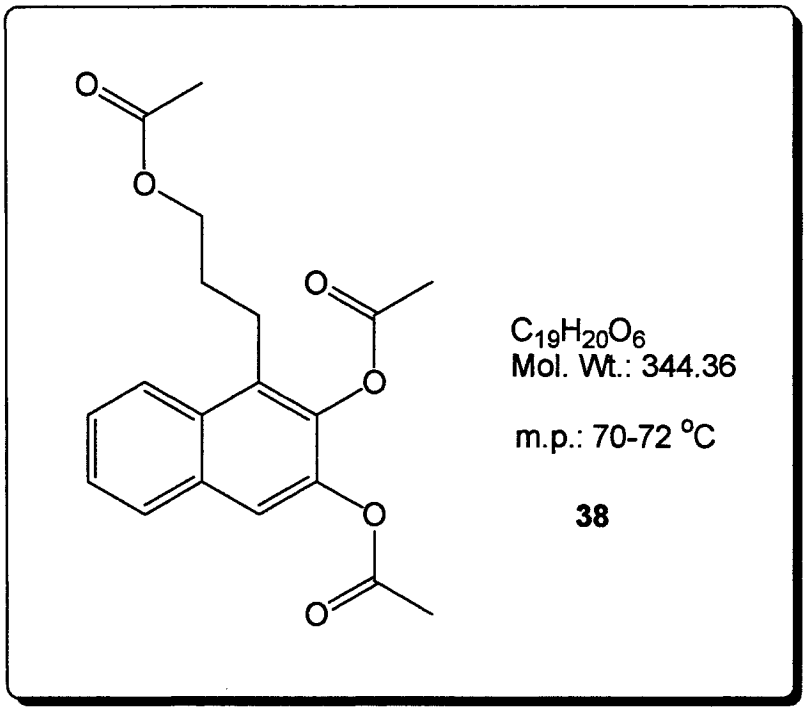
1-(3-Hydroxy-propyl)-naphthalene-2,3-diol:



MOM deprotection of **34** (0.35g, 1.14 mmol) was accomplished during 2h following the same procedure as in the synthesis of **36**. The crude product was purified by column chromatography using 7/3 hexanes/EtOAc as eluent, which afforded triol **37** (0.2g, 0.916 mmol) as a brownish oil in 80% yield.

^{1}H NMR (acetone-d_6, 200 MHz): δ = 1.86-1.99 (qu, 2H), 3.16-3.23 (t, 2H), 3.56-3.68 (t, 2H), 4.32 (s, 1H), 7.13 (s, 1H), 7.18-7.32 (m, 2H), 7.58-7.62 (d, 1H, J_o = 8.35 Hz), 7.85-7.89 (d, 1H, J_o = 8.23 Hz), 8.25 (s, 1H), 8.68 (s, 1H)
Mass (EI): *m/z* (%) = 218.1 (M+, 88), 207.0 (21), 200.1 (28), 185.1 (27), 173.1 (100), 172.1 (25), 115.1 (24)
HRMS: calcd 218.0943, found 218.0940

Acetic acid 3-acetoxy-1-(3-acetoxy-propyl)-naphthalen-2-yl ester:



$C_{19}H_{20}O_6$
Mol. Wt.: 344.36

m.p.: 70-72 °C

38

Acetylation of triol **37** (0.09g, 0.412 mmol) was accomplished following the same procedure as in the synthesis of diacetate **10**. The crude product was flash chromatographed using 50% EtOAc in hexanes as eluent to afford triacetate **38** (0.11g, 0.319 mmol) as a pale yellowish oil in 77% yield.

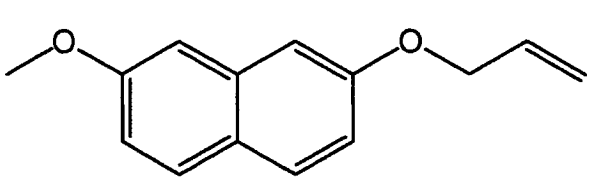
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.89-2.02 (m, 2H), 2.07 (s, 3H), 2.31 (s, 3H), 2.37 (s, 3H), 3.00-3.08 (t, 2H), 4.11-4.17 (t, 2H), 7.42-7.51 (m, 2H), 7.57 (s, 1H), 7.76-7.81 (m, 1H), 7.92-7.96 (d, 1H, J_o = 7.54 Hz)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 20.32, 20.76, 20.95, 22.79, 28.73, 64.05, 119.51, 123.68, 125.19, 126.14, 126.35, 127.11, 128.57, 130.29, 131.92, 140.72, 168.60, 168.69, 170.11

Mass (EI): *m/z* (%) = 344.1 (M+, 6), 260.1 (37), 200.1 (100)

HRMS: calcd 344.1260, found 344.1243

2-Allyloxy-7-methoxy-naphthalene :



$C_{14}H_{14}O_2$
Mol. Wt.: 214.26

m. p.: 63-65 °C

40

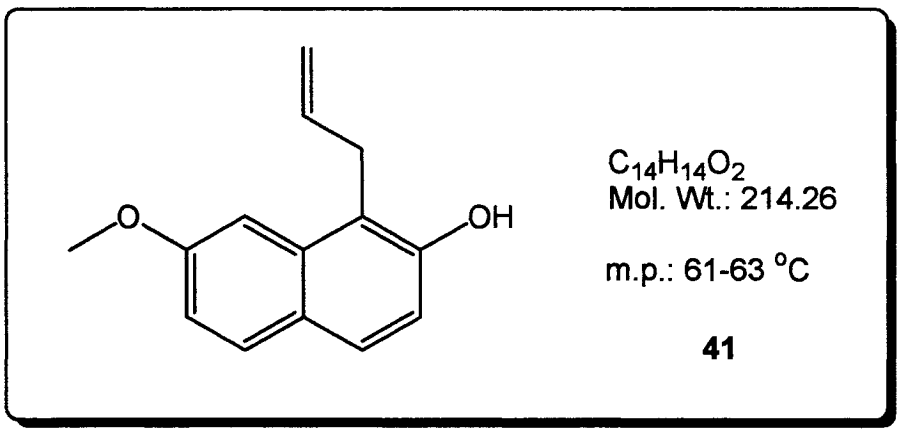
Potassium carbonate (7.93g, 57.40 mmol) followed by allyl bromide (4.86mL, 57.40 mmol, d 1.43) was added to 5.0g (28.70 mmol) of **39** dissolved in 25mL of acetone. The pinkish mixture was refluxed under nitrogen atmosphere during 4 hours. After cooling the mixture to r.t., the suspension was filtered by suction and the precipitate washed several times with acetone. The filtrate was evaporated in vacuo. The resulting oily material was placed in freezer for 30 min during which time it solidified into an off-white solid. This solid was washed with 10mL of hexanes and afforded relatively pure **40** (6.12g, 28.56 mmol) in essentially quantitative yield (99 %).

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.90 (s, 3H), 4.62-4.63 (t, 1H), 4.64-4.66 (t, 1H), 5.30-5.36 (dq, 1H, J_{cis} = 10.44 Hz, J_{gem} = 1.51 Hz), 5.42-5.52 (dq, 1H, J_{trans} = 17.28, J_{gem} = 1.62), 6.06-6.11 (m, 1H), 7.00-7.06 (m, 4H), 7.63-7.68 (dd, 2H, J_o = 8.35 Hz, J_m = 0.58 Hz)

Mass (EI): *m/z* (%) = 214.1 (M+, 83), 212.1 (72), 211.1 (68), 162.0 (22), 145.1 (100)

HRMS: calcd 214.0994, found 214.1016

1-Allyl-7-methoxy-naphthalen-2-ol:



$C_{14}H_{14}O_2$
Mol. Wt.: 214.26

m.p.: 61-63 °C

41

The allylether **40** (6.12g, 28.56 mmol) was suspended in 40mL of decalin and heated to 180-185°C for 4 hours, during which time the solid dissolved. The resulting black solution was washed several times with aq. 10% NaOH solution (4 x 25mL) and the combined aqueous layers were acidified using aq. 10% HCl solution. The aqueous solution was extracted using EtOAc (3 x 75mL) and the combined organic layers were dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo to give alcohol **41** (5.48g, 25.58 mmol, 90%) as a relatively pure brownish solid.

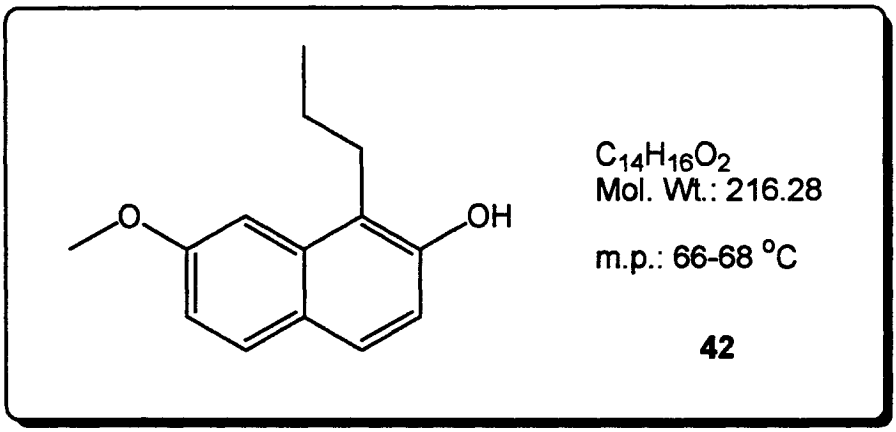
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.76-3.77 (t, 1H), 3.78-3.80 (t, 1H), 3.91 (s, 3H), 5.04-5.13 (3 x q, 2H, J_{trans} = 17.74 Hz, J_{cis} = 9.51 Hz, J_{gem} = 1.74 Hz), 5.14 (s, 1H), 5.99-6.20 (m, 1H), 6.95-6.98 (d, 1H, J_o = 8.70 Hz), 7.02-7.18 (dd, 1H, J_o = 8.93 Hz, J_m = 2.44 Hz), 7.17-7.18 (d, 1H, J_m = 2.44 Hz), 7.55-7.60 (d, 1H, J_o = 8.81 Hz), 7.64-7.69 (d, 1H, J_o = 8.93 Hz)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 29.48, 55.21, 102.21, 108.62, 115.28, 115.33, 115.82, 124.76, 128.02, 130.06, 134.57, 135.64, 151.68, 158.26

Mass (EI): *m/z* (%) = 214.1 (M+, 100), 183.1 (27)

HRMS: calcd 214.0994, found 214.1012

7-Methoxy-1-propyl-naphthalen-2-ol:



$C_{14}H_{16}O_2$
Mol. Wt.: 216.28

m.p.: 66-68 °C

42

Hydrogenation of alcohol **41** (5.40g, 25.20 mmol) was accomplished following the same procedure as in the synthesis of diol **23**. The oily crude product was placed under high vacuum overnight during which time it solidified into a brownish solid. This was washed with 15mL of hexanes through a filter pad to afford relatively pure **42** (5.39g, 24.92 mmol, 99%) as a pale brownish solid.

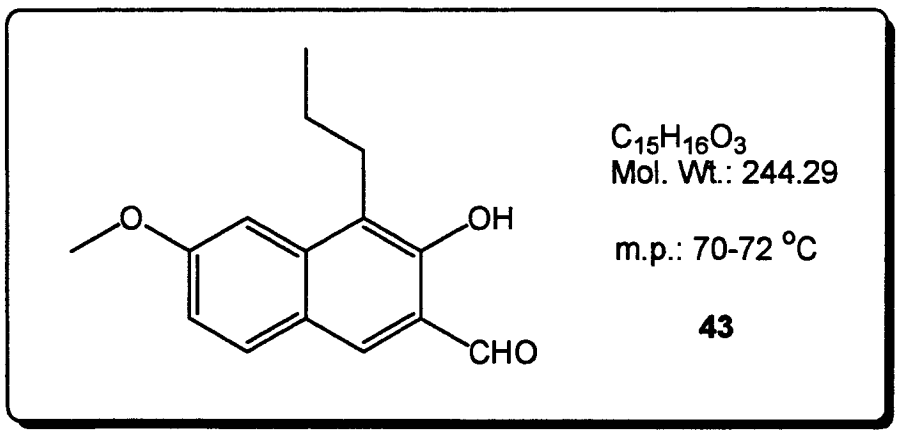
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.05-1.12 (t, 3H), 1.69-1.81 (m, 2H), 2.97-3.05 (t, 2H), 3.96 (s, 3H), 5.28 (s, 1H), 6.89-6.94 (d, 1H, J_o =8.70 Hz), 7.02-7.08 (dd, 1H, J_o = 8.93 Hz, J_m = 2.55 Hz), 7.25-7.26 (d, 1H, J_m = 2.44 Hz), 7.52-7.57 (d, 1H, J_o = 8.70 Hz), 7.67-7.71 (d, 1H, J_o = 8.81 Hz)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.44, 22.63, 27.18, 55.29, 102.52, 114.96, 115.22, 119.31, 124.85, 127.33, 130.17, 134.58, 151.07, 158.07

Mass (EI): *m/z* (%) = 216.1 (M+, 37), 187.1 (100)

HRMS: calcd 216.1150, found 216.1132

3-Hydroxy-6-methoxy-4-propyl-naphthalene-2-carbaldehyde:



$C_{15}H_{16}O_3$
Mol. Wt.: 244.29

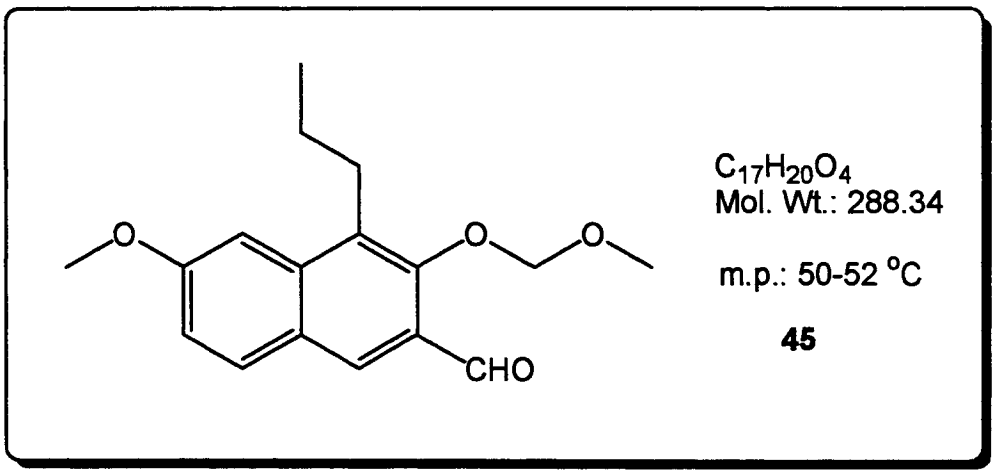
m.p.: 70-72 °C

43

The alcohol **42** (0.25g, 1.16 mmol), n-tributylamine (0.22mL, 0.928 mmol, d 0.778) and tin tetrachloride (0.28mL, 0.278 mmol, 1.0M in CH_2Cl_2) were stirred in 25mL of toluene at r.t. under an atmosphere of nitrogen for 20 min. Paraformaldehyde (0.15g, 5.10 mmol) was then added to the brownish mixture. The resulting mixture was heated to 90-95°C for 4 hours under nitrogen. After TLC showed no further changes, the reaction mixture was poured into 10mL of water, acidified to pH 3 with aq. 10% HCl solution and extracted using EtOAc (3 x 10mL). The combined organic layers were washed once with 10mL of water, dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent to give aldehyde **43** (0.09g, 0.368 mmol) as a bright yellow solid in 32% yield along with 64% (0.16g, 0.740 mmol) of recovered starting material **42**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.99-1.07 (t, 3H), 1.59-1.70 (m, 2H), 2.88-2.96 (t, 2H), 3.89 (s, 3H), 6.92-6.97 (dd, 1H, J_o = 8.93 Hz, J_m = 1.62 Hz), 7.03 (bs, 1H), 7.57-7.61 (d, 1H, J_o = 8.93 Hz), 7.66 (s, 1H), 9.79 (s, 1H), 10.70 (s, 1H)
^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.40, 22.24, 26.24, 55.15, 101.60, 116.53, 119.57, 121.31, 122.95, 131.96, 135.60, 138.70, 153.70, 161.07, 196.29
Mass (EI): *m/z* (%) = 244.1 (M+, 28), 215.1 (100), 40.0 (34)
HRMS: calcd 244.1099, found 244.1119

6-Methoxy-3-methoxymethoxy-4-propyl-naphthalene-2-carbaldehyde:



$C_{17}H_{20}O_4$
Mol. Wt.: 288.34

m.p.: 50-52 °C

45

N,N-diisopropylethylamine (0.29mL, 1.64 mmol, d 0.742) and chloromethyl methyl ether (0.12mL, 1.64 mmol, d 1.060) were added to a solution of **43** (0.2g, 0.819 mmol) in 10mL of dry CH_2Cl_2 under nitrogen atmosphere and at 0°C. The resulting yellow mixture was stirred 30 min at 0°C, then left at r.t. overnight. The orangish mixture was washed with aq. 10% NaOH (2 x 10mL) and the organic layer was dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo. The oily material solidified under high vacuum, after which time the solid produced was washed with 15mL of hexanes to afford aldehyde **45** (0.23g, 0.798 mmol) as relatively pure pale orangish solid in 97% yield.

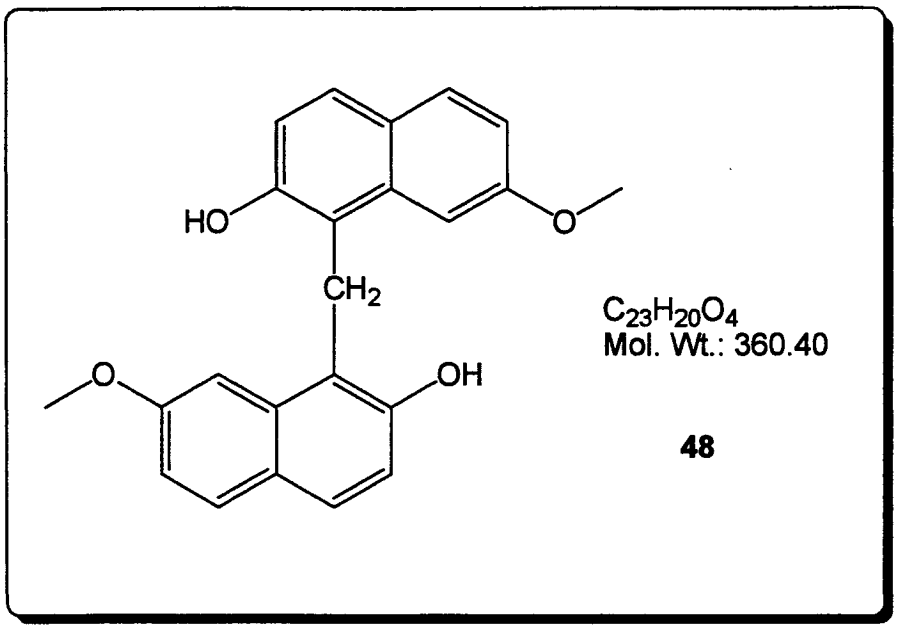
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.00-1.07 (t, 3H), 1.60-1.71 (m, 2H), 2.95-3.03 (t, 2H), 3.58 (s, 3H), 3.88 (s, 3H), 5.06 (s, 2H), 7.02-7.08 (dd, 1H, J_o = 8.93 Hz, J_m = 2.44 Hz), 7.15-7.16 (d, 1H, J_m = 2.32 Hz), 7.71-7.75 (d, 1H, J_o = 8.93 Hz), 8.10 (s, 1H), 10.22 (s, 1H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.58, 23.13, 27.91, 55.21, 57.68, 101.57, 103.10, 117.94, 125.59, 126.32, 129.89, 130.89, 132.18, 137.73, 153.38, 160.16, 190.77

Mass (EI): *m/z* (%) = 288.1 (M+, 17), 45.0 (100), 32.0 (52)

HRMS: calcd 288.1362, found 288.1347

Dimer of 39 joined by a methylene group:



$C_{23}H_{20}O_4$
Mol. Wt.: 360.40

48

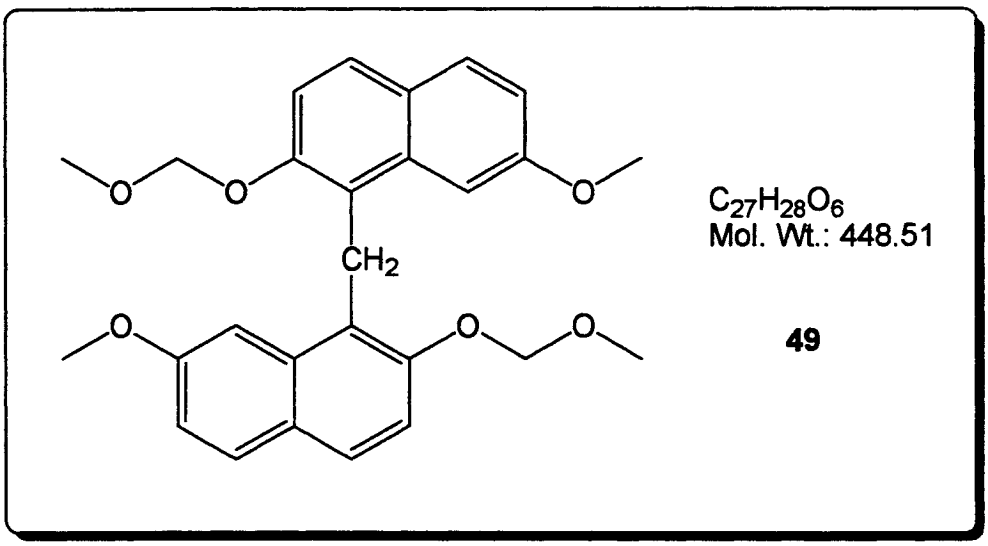
Dimer **48** was characterized following a formylation attempt on alcohol **39** (see subsection 2.2), which followed the same procedure then in the synthesis of **43**.

^{1}H NMR (acetone-d_6, 200 MHz): δ = 3.75 (s, 6H), 4.90 (s, 2H), 6.73-6.79 (dd, 2H, J_o = 8.81 Hz, J_m = 2.44 Hz), 7.14-7.19 (d, 2H, J_o = 8.70 Hz), 7.52-7.56 (d, 2H, J_o = 8.81 Hz), 7.52-7.57 (d, 2H, J_o = 8.58 Hz), 7.68-7.69 (d, 2H, J_m = 2.44 Hz), 9.09 (s, 2H)

^{13}C NMR (acetone-d_6, 200 MHz): δ = 21.56, 55.40, 103.89, 115.60, 115.90, 119.60, 125.48, 128.38, 130.38, 136.47, 153.17, 158.69

Mass (EI): *m/z* (%) = 360.1 (M+, 4), 341.1 (43), 186.3 (21), 174.2 (100), 169.2 (39), 43.0 (20)

Protected version of 46:



$C_{27}H_{28}O_6$
Mol. Wt.: 448.51

49

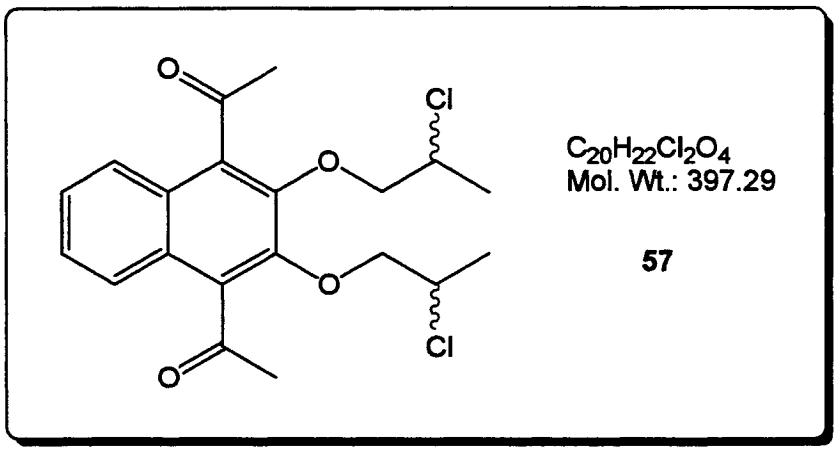
MOM protection of dimer **48** (0.45g, 1.25 mmol) was accomplished following the same procedure as in the synthesis of **45**. The crude product was purified by column chromatography using 8/2 hexanes/EtOAc as eluent, which afforded dimer **49** (0.2g, 0.446 mmol, 36%) as a yellowish oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.45 (s, 6H), 3.65 (s, 6H), 4.99 (s, 2H), 5.26 (s, 4H), 6.91-6.96 (dd, 2H, J_o = 8.81 Hz, J_m = 2.32 Hz), 7.25-7.29 (d, 2H, J_o = 8.93 Hz), 7.45-7.46 (d, 2H, J_m = 2.20 Hz), 7.59-7.63 (d, 2H, J_o = 8.93 Hz), 7.61-7.65 (d, 2H, J_o = 8.93 Hz)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 22.47, 55.00, 56.31, 95.69, 103.22, 113.92, 116.46, 123.66, 125.59, 127.74, 129.76, 134.83, 152.90, 157.78

Mass (EI): *m/z* (%) = 448.2 (M+, 29), 371.1 (26), 186.1 (100), 45.0 (74)

1-[4-Acetyl-2,3-bis-(2-chloro-propoxy)-naphthalen-1-yl]-ethanone:



$C_{20}H_{22}Cl_2O_4$
Mol. Wt.: 397.29

57

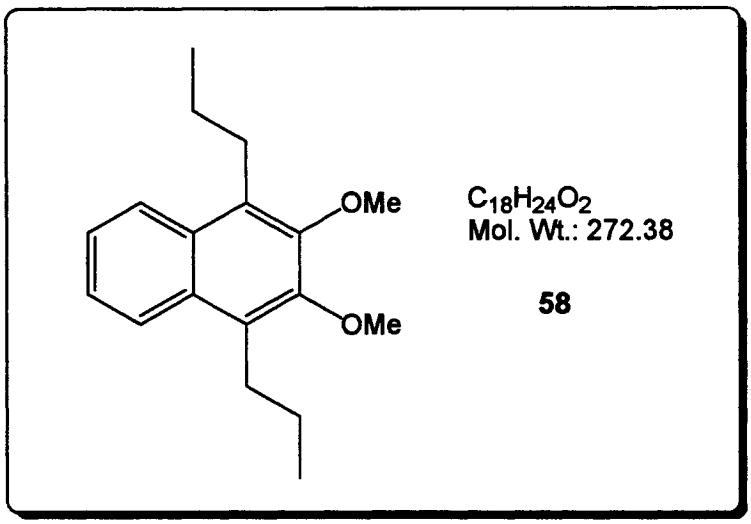
To a suspension of aluminum chloride (0.22g, 1.66 mmol) in 5mL of dry CH_2Cl_2, placed under nitrogen atmosphere and at 0°C, was added dropwise acetic anhydride (0.05mL, 0.458 mmol, d 1.082) followed by **21** (0.1g, 0.416 mmol) dissolved in 5mL of dry CH_2Cl_2. The resulting mixture was stirred at that temperature 30 min after which time the solution was refluxed 2h. The reddish mixture was poured into 10mL of water, layers were separated, and the aqueous layer extracted with CH_2Cl_2 (3x 10mL). The combined organic layers were washed with water (10mL), sat. $NaHCO_3$ solution (10mL), dried over Na_2SO_4, filtered through cotton and solvent evaporated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent to give **57** (0.092g, 0.233 mmol) in 56% yield as a pale yellowish solid.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.49-1.50 (d, 3H, J = 4.25 Hz), 1.51-1.53 (d, 3H, J = 4.30 Hz), 2.40 (s, 6H), 3.27-3.39 (dt, 2H, J_1 = 8.90 Hz, J_{gem} = 14.07 Hz), 3.52-3.62 (dt, J_1 = 5.65 Hz, J_{gem} = 13.30 Hz), 4.31-4.40 (m, 2H), 7.56-7.61 (m, 2H), 8.03-8.06 (m, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 20.76, 25.07, 25.11, 37.47, 56.81, 124.96, 125.00, 126.51, 126.53, 126.86, 131.18, 140.36, 168.46

Mass (EI): *m/z* (%) = 396 (M+, 5), 314 (66), 312 (100), 278 (27), 276 (68), 251 (23), 249 (72), 240 (42), 213 (95), 43 (27)

2,3-Dimethoxy-1,4-dipropyl-naphthalene:



$C_{18}H_{24}O_2$
Mol. Wt.: 272.38

58

Potassium carbonate (0.68g, 4.92 mmol) and methyl iodide (0.31mL, 4.92 mmol, d 2.28) was added to a solution of **23** (0.3g, 1.23 mmol) dissolved in 15mL of acetone. The yellowish mixture was refluxed overnight, after which time the resulting mixture was filtered with suction and the precipitate was washed several times with acetone. The filtrate was diluted with an equal amount of EtOAc and washed twice with aq. 10% NaOH solution. The combined aqueous layers were extracted using EtOAc (2 x 10mL) and the combined organic layers were dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by column chromatography using 100% hexanes, which afforded 98 mg of pure product, as well as 100 mg as a mixture. The mixture was submitted to preparative TLC, using 5% EtOAc in hexanes as eluent to afford 90mg of pure product. The combined yield of pure **58**, a colorless oil, was 0.19g (0.690 mmol, 56%).

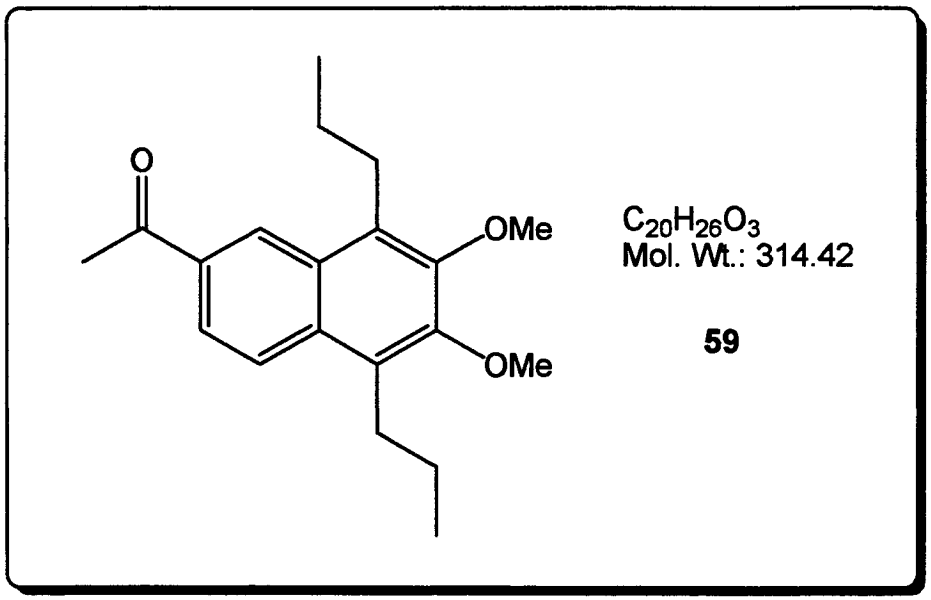
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.06-1.13 (t, 6H), 1.65-1.80 (m, 4H), 3.01-3.09 (t, 4H), 3.92 (s, 6H), 7.40-7.45 (m, 2H), 7.93-7.98 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 14.69, 24.26, 27.77, 60.80, 124.49, 129.05, 130.18, 149.80

Mass (EI): *m/z* (%) = 272.2 (M+, 64), 243.1 (100)

HRMS: calcd 272.1776, found 272.1792

1-(6,7-Dimethoxy-5,8-dipropyl-naphthalen-2-yl)-ethanone:



$C_{20}H_{26}O_3$
Mol. Wt.: 314.42

59

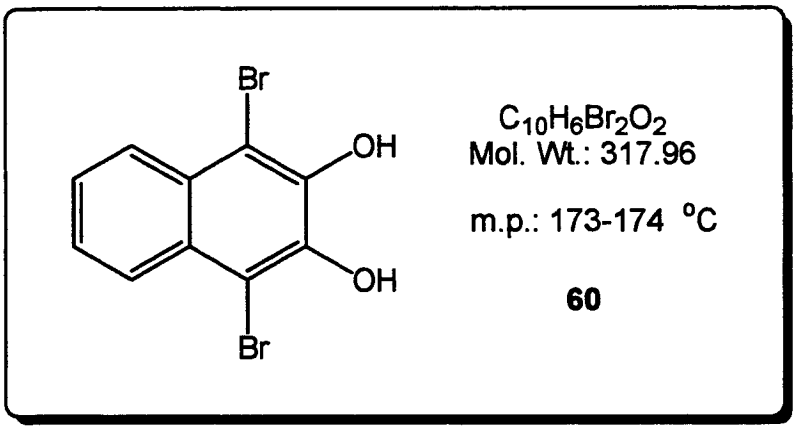
Acetyl chloride (0.1mL, 1.47 mmol, d 1.104) was added to a solution of **58** (0.1g, 0.367 mmol) dissolved in 10mL of dry CH_2Cl_2. To this cooled (0°C) yellowish solution was added in three portions aluminum chloride (0.44g, 3.30 mmol) and the solution was stirred at this temperature for 30 min, after which time it was refluxed overnight. The resulting dark red mixture was poured into 10mL of water and extracted using CH_2Cl_2 (3 x10mL). The combined organic layers were washed with 10mL of sat. $NaHCO_3$ solution and 10mL of brine, dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent. The yield of **59** was 0.045g (0.143 mmol) as a pale yellowish oil.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.02-1.09 (t, 3H), 1.04-1.11 (t, 3H), 1.60-1.75 (m, 4H), 2.70 (s, 3H), 2.97-3.12 (m, 4H), 3.90 (s, 3H), 3.92 (s, 3H), 7.93-7.99 (m, 2H), 8.57 (s, 1H)

Mass (EI): *m/z* (%) = 315.2 (20), 314.2 (M+, 100), 285.2 (99)

HRMS: calcd 314.1882, found 314.1897

1,4-Dibromo-naphthalene-2,3-diol:



A solution of bromine (1.99g, 12.48 mmol) dissolved in 5mL of acetic acid was added dropwise to diol **16** (1.0g, 6.24 mmol) dissolved in 10mL of acetic acid over a period of 5 min. The orangish solution was stirred open to air 1h after which time a precipitate formed. The precipitate was filtered with suction and washed several times with hexanes to afford 0.99g of pure product. The filtrate was diluted with 15mL of water and extracted using EtOAc (3 x15mL). The combined organic layers were dried over MgSO4, filtered through cotton and solvents evaporated in vacuo, which afforded another 0.94g of pure **60** after several washings with hexanes. The total yield of **60**, a white solid, was 1.93g (6.07 mmol, 97%).

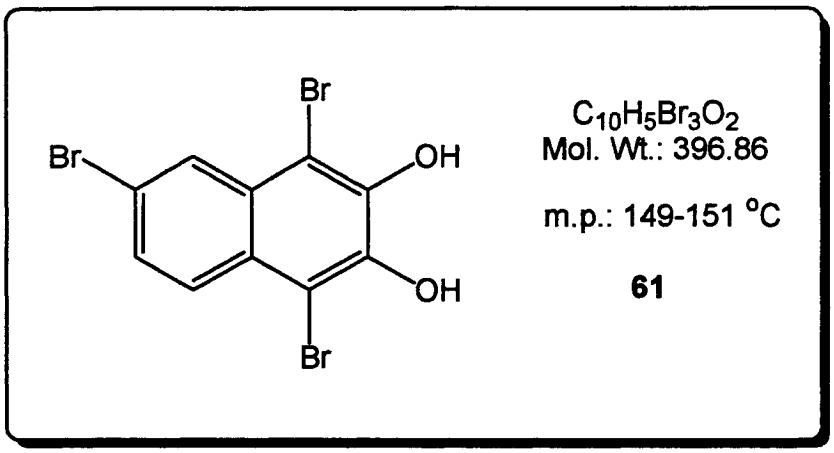
^{1}H NMR (acetone-d_6, 200 MHz): δ = 7.44-7.48 (m, 2H), 8.02-8.06 (m, 2H), 9.1 (s,2H)

^{13}C NMR (acetone-d_6, 200 MHz): δ = 106.16, 126.58, 128.61, 144.92

Mass (EI): *m/z* (%) = 319.9 (46), 317.9 (M+, 100), 315.9 (49), 240.0 (29), 238.0 (31)

HRMS: calcd 315.8735, found 315.8746

1,4,6-Tribromo-naphthalene-2,3-diol:



$C_{10}H_5Br_3O_2$
Mol. Wt.: 396.86

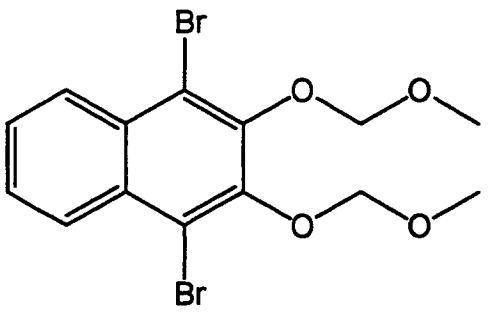
m.p.: 149-151 °C

61

Excess bromine was added to 0.2g (1.25 mmol) of **16** dissolved in 5mL of acetic acid until the red color persisted. The mixture was stirred open to air overnight, after which time a precipitate formed. This precipitate was filtered with suction and washed several times with hexanes, which afforded pure **61** (0.15g, 0.380 mmol) in 30% yield as a white solid.

^{1}H NMR (acetone-d_6, 200 MHz): δ = 7.49-7.55 (dd, 1H, J_o = 9.05 Hz, Jm = 1.51 Hz), 7.89-7.94 (d, 1H, J_o = 9.05 Hz), 8.15-8.16 (d, 1H, J_m = 1.97 Hz), 9.25 (s, 2H)
^{13}C NMR (acetone-d_6, 200 MHz): δ = 104.65, 106.01, 120.22, 127.25, 128.38, 128.79, 129.41, 129.71, 145.41, 145.95
Mass (EI): *m/z* (%) = 397.8 (91), 395.8 (100), 394.9 (M+, 5), 69.0 (92)
HRMS: calcd 393.7840, found 393.7853

1,4-Dibromo-2,3-bis-methoxymethoxy-naphthalene:



$C_{14}H_{14}Br_2O_4$
Mol. Wt.: 406.07

m.p.: 76-77 °C

62

N,N-Diisopropylethyl amine (0.50mL, 2.83 mmol, d 0.742) and chloromethyl methyl ether (0.22mL, 2.83 mmol, d 1.060) were added dropwise to a solution of **60** (0.3g, 0.944 mmol) dissolved in 20mL of dry CH_2Cl_2 placed under nitrogen atmosphere and at 0°C. The mixture was stirred at that temperature for 30 min and then left at r.t. for 4h, after which time the resulting yellowish solution was diluted with 20mL of water and extracted with CH_2Cl_2 (3 x 10mL). The combined organic layers were dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo to afford dibromide **62** (0.37g, 9.11 mmol, 97%) as a pale yellowish solid after several hexanes washings.

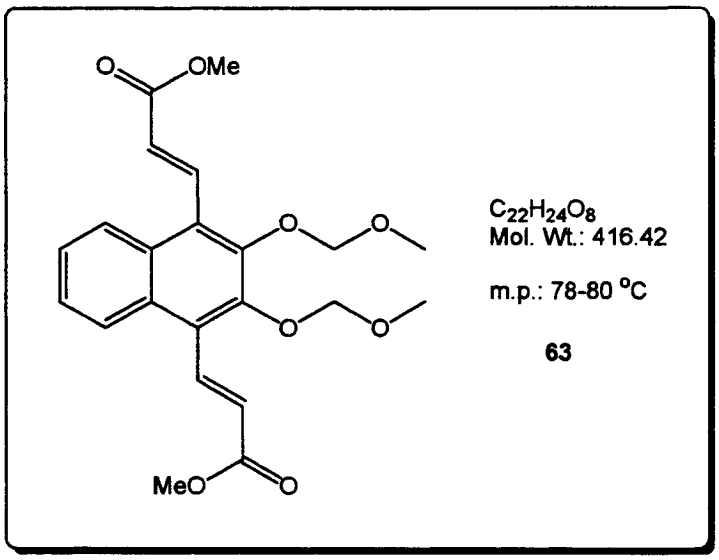
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.69 (s, 6H), 5.26 (s, 4H), 7.52-7.57 (m, 2H), 8.21-8.26 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 58.26, 99.75, 116.69, 127.31, 130.23

Mass (EI): *m/z* (%) = 405.9 (M+, 6), 331.9 (60), 329.9 (80), 327.9 (59), 45.0 (100)

HRMS: calcd 403.9259, found 403.9277

3-[4-(2-Methoxycarbonyl-vinyl)-2,3-bis-methoxymethoxy-naphthalen-1-yl]-acrylic acid methyl ester:



To **62** (0.3g, 0.739 mmol) and $Pd_2(dba)_3$ (0.02g, 0.02 mmol) under nitrogen atmosphere was added a solution of $P(tBu)_3$ in anhydrous 1,4-dioxane (0.4mL, 0.04mmol, 0.1M), Cy_2NMe (0.35mL, 1.63 mmol, d 0.921), methyl acrylate (0.16mL, 1.77 mmol, d 0.956) and 3mL of anhydrous 1,4-dioxane. The mixture was refluxed overnight, after which time the greenish solution was diluted with 3mL of EtOAc and filtered through a small pad of silica gel packed in a disposable pipet with several EtOAc washings. After the solvents were evaporated in vacuo, the crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent to give 32% of **63** (0.1g, 0.240 mmol) as a bright yellow solid.

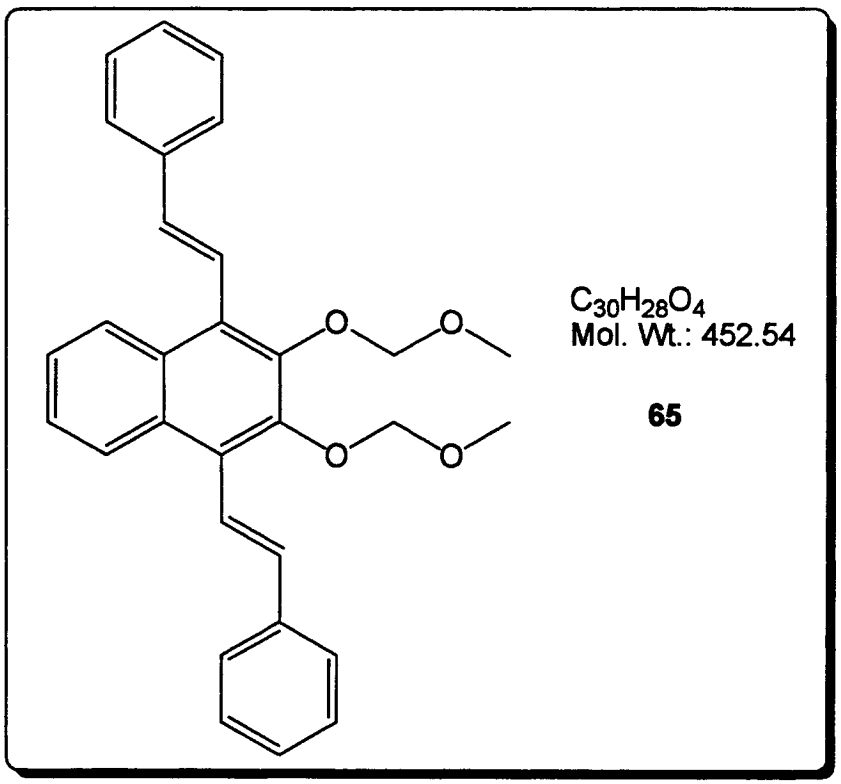
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.53 (s, 6H), 3.83 (s, 6H), 5.13 (s, 4H), 6.54-6.62 (d, 2H, J_{trans} = 16.35 Hz), 7.44-7.48 (m, 2H), 8.04-8.09 (m, 2H), 8.15-8.24 (d, 2H, J_{trans} = 16.24 Hz)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 51.81, 58.11, 99.69, 124.75, 125.76, 126.35, 127.02, 129.30, 138.38, 147.38, 167.12

Mass (EI): *m/z* (%) = 416.1 (M+, 2), 341.1 (25), 340.1 (79), 308.1 (20), 293.1 (25), 249.1 (43), 45.0 (100)

HRMS: calcd 416.1471, found 416.1468

2,3-Bis-methoxymethoxy-1,4-distyryl-naphthalene:



The coupling reaction between **62** (0.3g, 0.739 mmol) and styrene (0.19mL, 1.63 mmol, d 0.909) was accomplished following the same procedure as in the coupling reaction between **62** and methyl acrylate. The crude product was purified by column chromatography using 5 % EtOAc in hexanes as eluent to afford 97% of **65** (0.32g, 0.707 mmol) as a bright yellow solid.

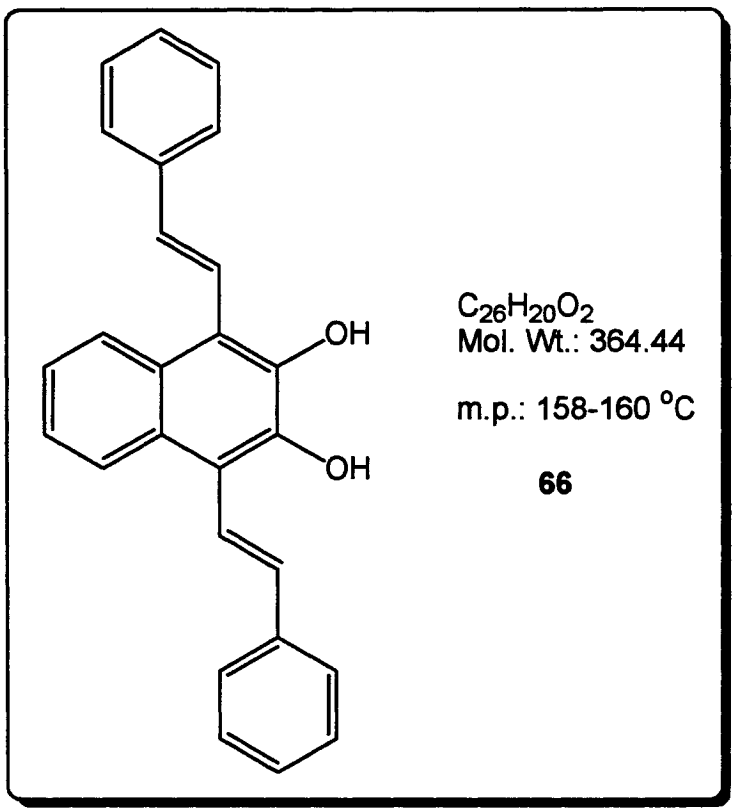
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.58 (s, 6H), 5.25 (s, 4H), 7.15-7.23 (d, 2H, J_{trans} = 16.58 Hz), 7.34-7.51 (m, 8H), 7.58-7.66 (d, 2H, J_{trans} = 16.58 Hz), 7.63-7.68 (m, 4H), 8.24-8.29 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 58.02, 99.54, 122.18, 125.40, 125.48, 126.50, 127.92, 128.18, 128.82, 130.11, 136.34, 137.60, 146.61

Mass (EI): *m/z* (%) = 452.2 (M+, 1), 376.1 (21), 361.1 (30), 360.1 (100), 234.1 (52), 233.1 (46), 131.1 (23)

HRMS: calcd 452.1988, found 452.2012

1,4-Distyryl-naphthalene-2,3-diol:



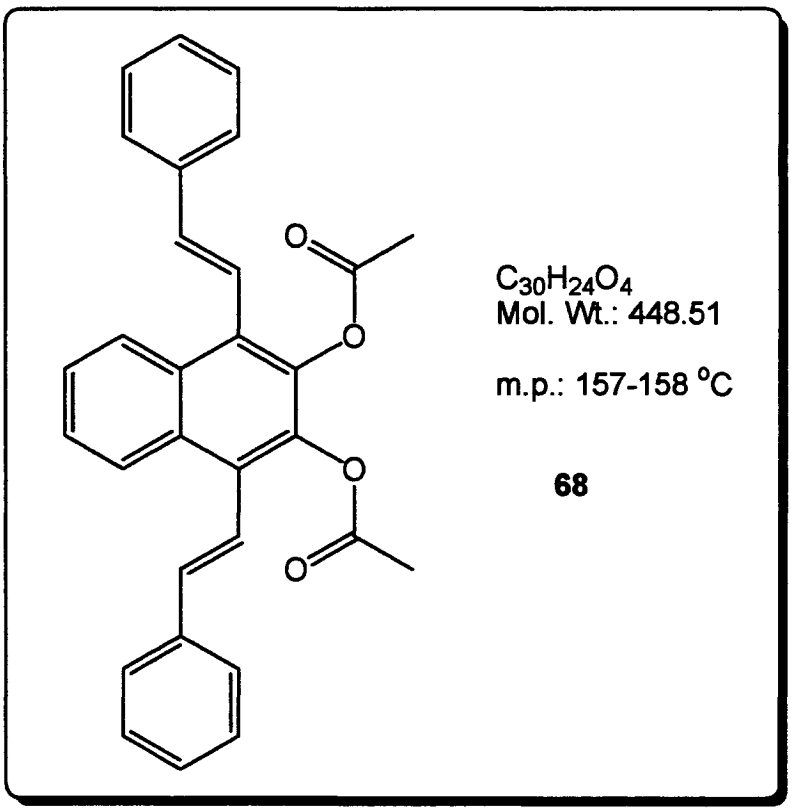
MOM deprotection of **65** (0.24g, 0.530 mmol) was carried out following the same procedure as in the MOM deprotection of **35**. The crude product was purified by column chromatography using 10% EtOAc in hexanes; this afforded diol **66** (0.18g, 0.494 mmol) as a yellow solid in 93% yield.

^{1}H NMR (acetone-d_6, 200 MHz): δ = 7.25-7.45 (m, 8H), 7.30-7.41 (d, 2H, J_{trans} = 16.93 Hz), 7.62-7.70 (d, 2H, J_{trans} = 16.58 Hz), 7.65-7.70 (m, 4H), 8.13-8.18 (m, 2H), 8.44 (s, 2H)

^{13}C NMR (acetone-d_6, 200 MHz): δ = 118.16, 122.66, 124.70, 124.93, 127.36, 128.47, 128.89, 129.52, 136.19, 138.85, 144.11

Mass (EI): *m/z* (%) = 361.1 (29), 360.1 (100)

Acetic acid 3-acetoxy-1,4-distyryl-naphthalen-2-yl ester:



Acetylation of diol **66** (0.15g, 0.412 mmol) was accomplished following the same procedure as in the acetylation of diol **4**. The crude product was recristallized from methanol to afford the diacetate **68** (0.13g, 0.290 mmol) as a pale greenish solid in 70% yield.

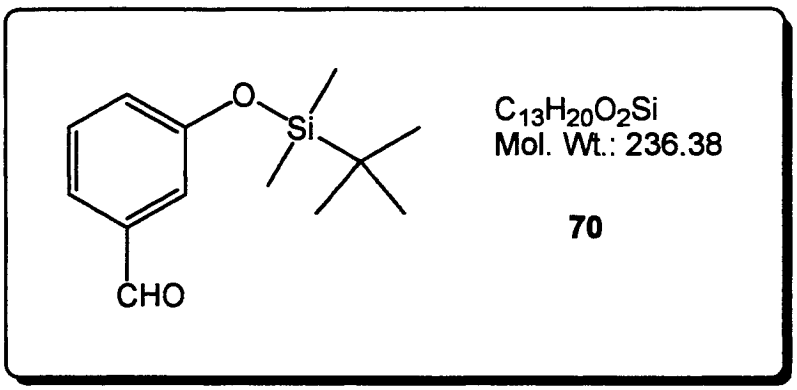
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.32 (s, 6H), 7.01-7.10 (d, 2H, J_{trans} = 16.47 Hz), 7.35-7.43 (d, 2H, J_{trans} = 16.47 Hz), 7.37-7.48 (m, 6H), 7.52-7.63 (m, 6H), 8.17-8.22 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 20.64, 120.61, 125.65, 126.50, 126.66, 128.14, 128.32, 128.86, 130.86, 136.70, 137.02, 138.90, 168.63

Mass (EI): *m/z* (%) = 448.2 (M+, 20), 406.2 (26), 365.2 (28), 364.2 (100), 362.1 (32), 360.1 (48)

HRMS: calcd 448.1675, found 448.1685

3-(*tert*-Butyl-dimethyl-silanyloxy)-benzaldehyde:



$C_{13}H_{20}O_2Si$
Mol. Wt.: 236.38

70

Benzaldehyde **69** (1.0g, 8.19 mmol) was suspended in 10mL of dry CH_2Cl_2, under nitrogen atmosphere at 0°C. DIPEA (2.85mL, 16.38 mmol, d 0.742) was added followed by *tert*-butyldimethylsilyl chloride (2.47g, 16.38 mmol) dissolved in 10mL of dry CH_2Cl_2, during which time the suspension all dissolved. The brownish solution was stirred at 0°C for 30 min after which time it was left at r.t. 2h. It was diluted with 20mL of water and layers separated. The aqueous layer was extracted using CH_2Cl_2 (2 x20mL) and the combined organic layers were dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo overnight to afford **70** (1.76g, 7.44 mmol) as a colorless liquid in 91% yield, after filtering the residue through a small pad of silica gel combined with EtOAc washings.

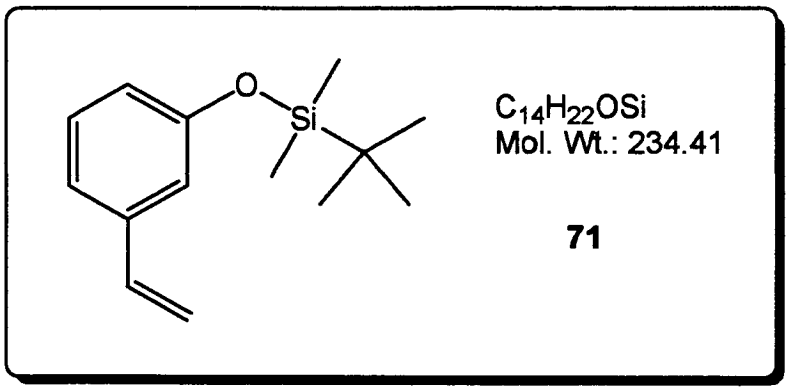
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.20 (s, 6H), 0.97 (s, 9H), 7.06-7.11 (ddd, 1H), 7.29-7.47 (m, 3H), 9.93 (s, 1H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = -4.49, 25.56, 119.82, 123.54, 126.52, 130.05, 192.12

Mass (EI): *m/z* (%) = 236.1 (M+, 11), 179.1 (100)

HRMS: calcd 236.1233, found 236.1219

***tert*-Butyl-dimethyl-(3-vinyl-phenoxy)-silane:**



$C_{14}H_{22}OSi$
Mol. Wt.: 234.41

71

A suspension of sodium hydride (95%, dry) (0.41g, 16.92 mmol) in 10mL of dimethylsulphoxide under nitrogen atmosphere was heated to 75-80°C and stirred for 45 min. Methyltriphenylphosphonium bromide (6.04g, 16.92 mmol) dissolved in 10mL of DMSO was added after cooling the reaction mixture to 0°C. The solution was warmed to r.t. and stirred 10 min after which time 1.0g of **70** (4.23 mmol) was added dropwise. The orangish mixture was stirred overnight. The reaction was quenched by adding 10mL of sat. NH_4Cl solution and extracted using EtOAc (3 x 20mL). The combined organic layers were washed once with 20mL of water, dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by column chromatography using 100% hexanes as eluent to give 0.69g of pure **71** (2.94 mmol, 70%) as a colorless liquid.

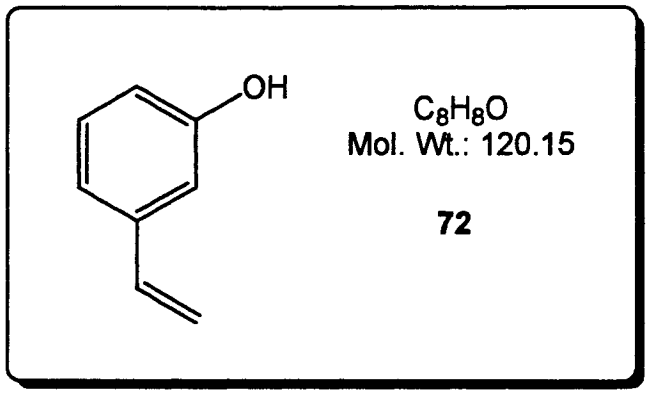
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 0.23 (s, 6H), 1.02 (s, 9H), 5.22-5.28 (dd, 1H, J_{cis} = 10.90 Hz, J_{gem} = 0.81Hz), 5.69-5.78 (dd, 1H, J_{trans} = 17.51 Hz, J_{gem} = 0.93 Hz), 6.61-6.75 (dd, 1H, J_{trans} = 17.63 Hz, J_{cis} = 10.90 Hz), 6.74-6.79 (ddd, 1H), 6.91-6.93 (t, 1H, J_m = 2.34 Hz), 7.01-7.05 (d, 1H, J_o = 7.77 Hz), 7.16-7.20 (d, 1H, J_o = 7.77 Hz)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = -4.40, 18.20, 25.70, 113.89, 117.74, 119.49, 119.56, 129.41, 136.72, 139.04, 155.84

Mass (EI): *m/z* (%) = 234.1 (M+, 18), 178.1 (20), 177.1 (100)

HRMS: calcd 234.1440, found 234.1416

3-Vinyl-phenol:



A tetrabutylammonium fluoride (5.88mL, 5.88 mmol, 1.0M) solution in THF was added dropwise to **71** (0.69g, 2.94 mmol) dissolved in 10mL of dry THF and under nitrogen atmosphere. The resulting yellowish solution was stirred at r.t. for 1h, after which time the mixture was diluted with 10mL of water and extracted using EtOAc (3 x 15mL). The combined organic layers were washed once with 10mL of brine, dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent to afford 0.31g of 3-hydroxystyrene **72** (2.58 mmol) as a colorless liquid.

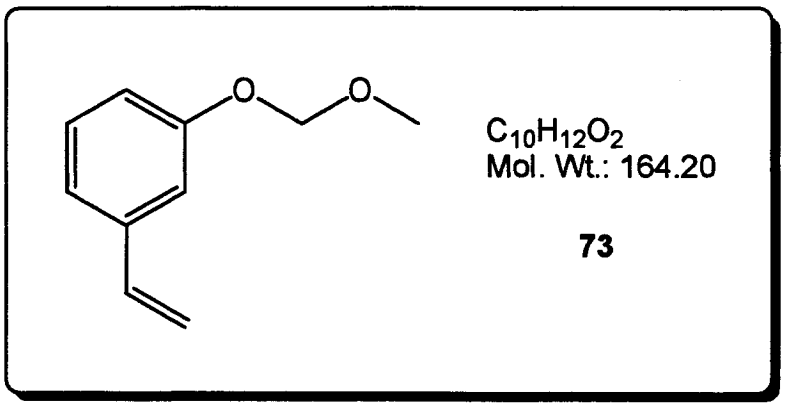
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 5.20-5.26 (dd, 1H, J_{cis} = 10.79 Hz, J_{gem} = 0.81Hz), 5.66-5.75 (dd, 1H, J_{trans} = 17.51 Hz, J_{gem} = 0.93 Hz), 5.86 (s, 1H), 6.57-6.71 (dd, 1H, J_{cis} = 10.90 Hz, J_{trans} = 17.40 Hz), 6.71-6.77 (ddd, 1H), 6.88-6.90 (t, 1H), 6.94-6.99 (d, 1H, J_o = 7.65 Hz), 7.14-7.22 (t, 1H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 112.79, 114.24, 114.90, 118.99, 129.71, 136.46, 139.25, 155.74

Mass (EI): *m/z* (%) = 120.1 (M+, 100), 91.1 (69), 65.0 (22), 39.0 (23)

HRMS: calcd 120.0575, found 120.0567

1-Methoxymethoxy-3-vinyl-benzene:



MOM protection of hydroxystyrene **72** (0.90g, 7.49 mmol) was accomplished following the same procedure as in the MOM protection of alcohol **43**. The crude product was purified by column chromatography using 100% hexanes as eluent to yield MOM ether **73** (0.63g, 3.84 mmol, 51%) as a colorless liquid.

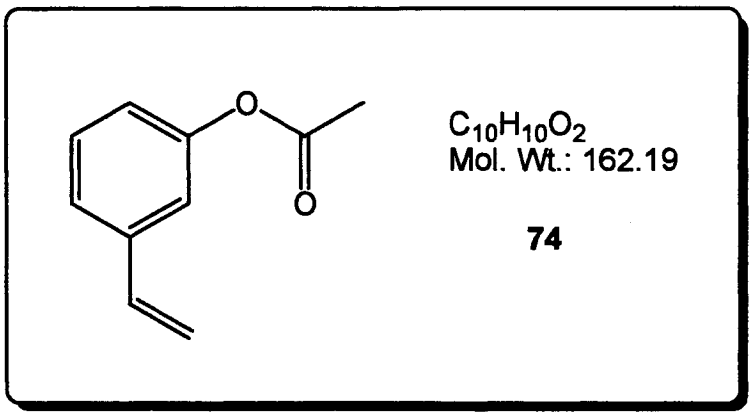
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.49 (s, 3H), 5.19 (s, 2H), 5.23-5.28 (d, 1H, J_{cis} = 10.79 Hz), 5.70-5.71 (dd, 1H, J_{trans} = 17.63 Hz, J_{gem} = 0.81 Hz), 6.62-6.76 (dd, 1H, J_{trans} = 17.63 Hz, J_{cis} = 10.90 Hz), 6.92-6.98 (ddd, 1H), 7.04-7.10 (m, 2H), 7.21-7.25 (d, 1H, J_o = 7.77 Hz)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 55.93, 94.36, 113.86, 114.23, 115.62, 119.98, 129.50, 136.58, 139.07, 157.47

Mass (EI): *m/z* (%) = 164.1 (M+, 14), 45.0 (100)

HRMS: calcd 164.0837, found 164.0841

Acetic acid 3-vinyl-phenyl ester:



$C_{10}H_{10}O_2$
Mol. Wt.: 162.19

74

Acetylation of 3-hydroxystyrene **72** (0.31g, 2.50 mmol) was accomplished following the same procedure as in the synthesis of diacetate **10**. The crude product was purified by column chromatography using 100% hexanes as eluent to afford acetate **74** (0.37g, 2.28 mmol) in 91% yield as a pale yellowish liquid.

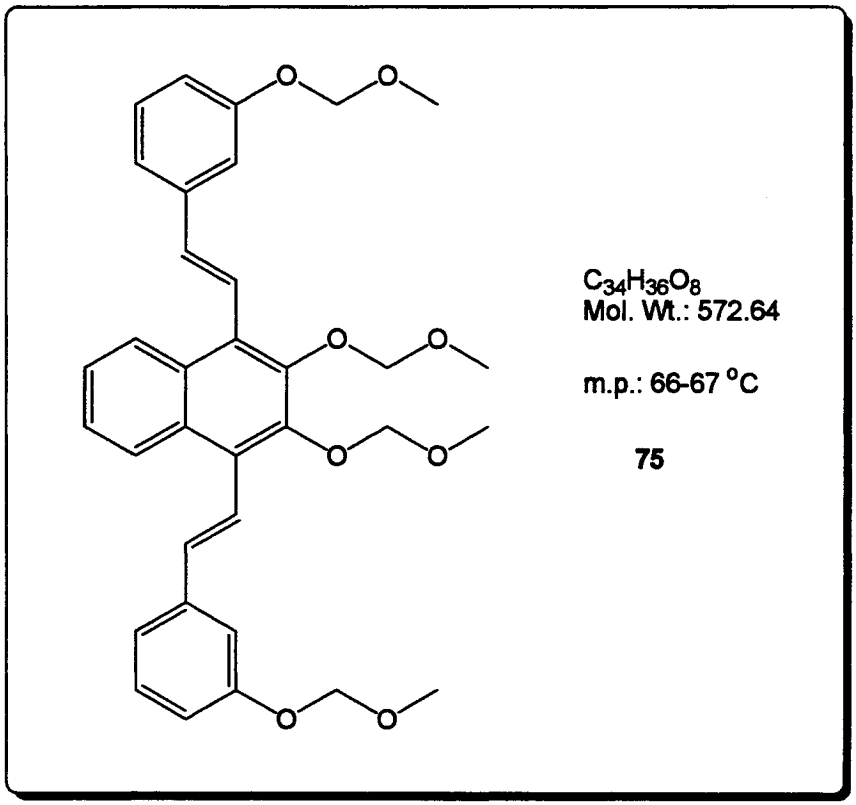
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.29 (s. 3H), 5.25-5.30 (dd, 1H, J_{cis} = 10.90 Hz, J_{gem} = 0.70 Hz), 5.69-5.78 (dd, 1H, J_{trans} = 17.63 Hz, J_{gem} = 0.70 Hz), 6.61-6.75 (dd, 1H, J_{trans} = 17.63 Hz, J_{cis} = 10.90 Hz), 6.94-7.00 (dt, 1H), 7.12-7.13 (t, 1H), 7.23-7.36 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 21.11, 114.91, 119.08, 120.87, 123.85, 129.44, 135.93, 139.21, 150.90, 169.47

Mass (EI): *m/z* (%) = 162.1 (M+, 33), 121.1 (24), 120.1 (100), 91.1 (33), 43.0 (28)

HRMS: calcd 162.0681, found 162.0682

2,3-Bis-methoxymethoxy-1,4-bis-[2-(3-methoxymethoxy-phenyl)-vinyl]-naphthalene:



$C_{34}H_{36}O_8$
Mol. Wt.: 572.64

m.p.: 66-67 °C

75

The coupling reaction between **62** (0.14g, 0.346 mmol) and **73** (0.12g, 0.761 mmol) was accomplished following the same procedure as that for **62** and methyl acrylate. The crude product was purified by column chromatography using 15% EtOAc in hexanes as eluent. The yield of pure **75** was 96% (0.19g, 0.332 mmol) as a bright yellow solid.

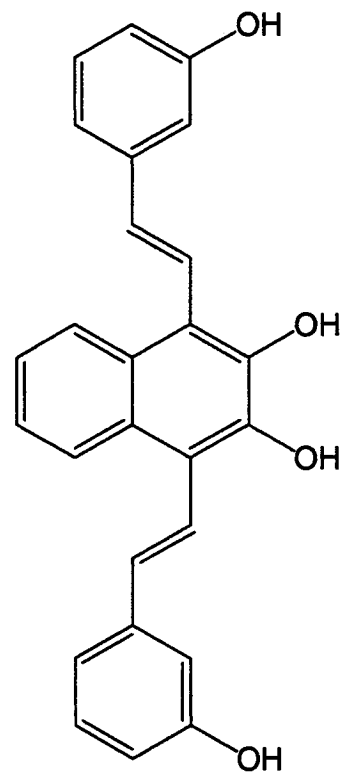
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.51 (s, 6H), 3.54 (s, 6H), 5.19 (s, 4H), 5.23 (s, 4H), 6.98-7.02 (ddd, 2H), 7.06-7.12 (d, 2H, Jtrans = 16.60 Hz), 7.24-7.35 (m, 6H), 7.43-7.46 (m, 2H), 7.52-7.57 (d, 2H, Jtrans = 16.56 Hz), 8.18-8.22 (m, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 55.70, 57.67, 94.11, 99.17, 113.77, 115.37, 119.91, 122.23, 125.00, 125.12, 127.74, 129.42, 129.67, 135.68, 138.76, 146.27, 157.34

Mass (EI): *m/z* (%) = 572.2 (M+, 18), 497.2 (31), 496.2 (95), 45.0 (100)

HRMS: calcd 572.2410, found 572.2423

1,4-Bis-[2-(3-hydroxy-phenyl)-vinyl]-nphthalene-2,3-diol:



$C_{26}H_{20}O_4$
Mol. Wt.: 396.43

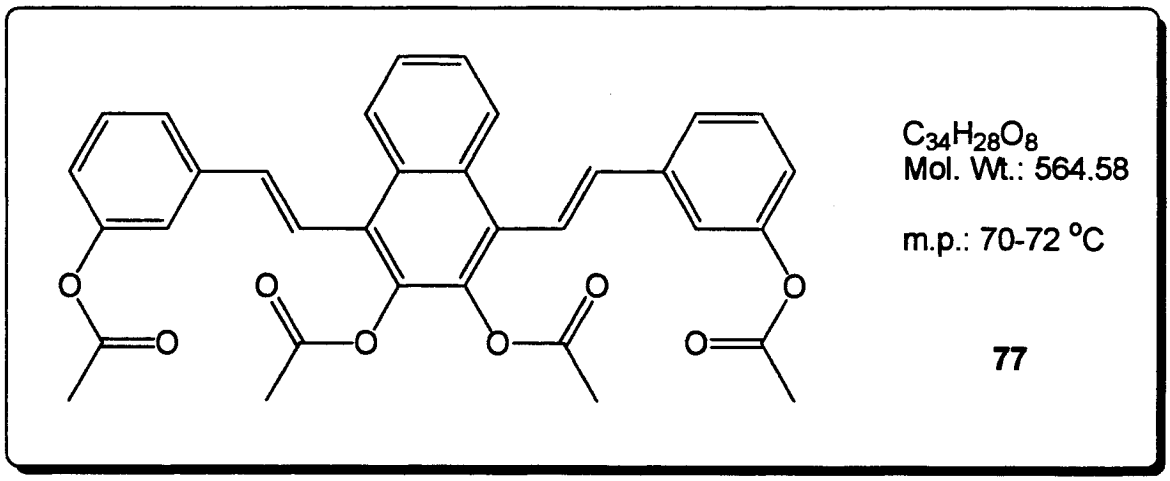
m.p.: 185-187 °C

76

MOM deprotection of **75** (0.19g, 0.332 mmol) was accomplished following the same procedure as in the MOM deprotection of **35**. The crude product was washed with 5mL of hexanes. This gave **76** as a bright yellow solid in 91% yield (0.12g, 0.303 mmol).

^{1}H NMR (acetone-d_6, 300 MHz): δ = 6.80-6.83 (dd, 2H), 7.12-7.25 (m, 8H), 7.26-7.38 (m, 2H), 7.54-7.60 (d, 2H, J_o = 16.52 Hz), 8.10-8.14 (m, 2H), 8.42 (s, 2H)
^{13}C NMR (acetone-d_6, 300 MHz): δ = 114.54, 116.35, 118.80, 119.69, 123.22, 125.36, 125.58, 129.55, 131.24, 136.91, 141.00, 144.80, 159.28
Mass (EI): *m/z* (%) = 396.1 (M+, 28), 392.1 (44), 279.1 (21), 278.1 (100), 277.1 (22), 162.0 (35), 143.0 (28), 31.0 (27)
HRMS: calcd 396.1362, found 396.1345

Acetic acid 3-acetoxy-1,4-bis-[2-(3-acetoxy-phenyl)-vinyl]-naphthalen-2-yl ester:



$C_{34}H_{28}O_8$
Mol. Wt.: 564.58

m.p.: 70-72 °C

77

Acetic anhydride (0.13mL, 1.33 mmol d 1.082) and triethylamine (0.19mL, 1.33 mmol, d 0.726) were added to **76** (0.088g, 0.222mmol) and DMAP (0.005g, 0.044 mmol) dissolved in 10mL of dry CH_2Cl_2 under N_2. The yellowish solution was stirred at r.t. 3h, after which time the solution was diluted with 10mL of water and layers separated. The aqueous layer was extracted using CH_2Cl_2 (2 x 20mL) and the combined organic layers were dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo. The crude product was purified by column chromatography using 30% EtOAc in hexanes as eluent to afford **77** (0.0487g, 0.175 mmol) as a pale yellowish solid in 79% yield.

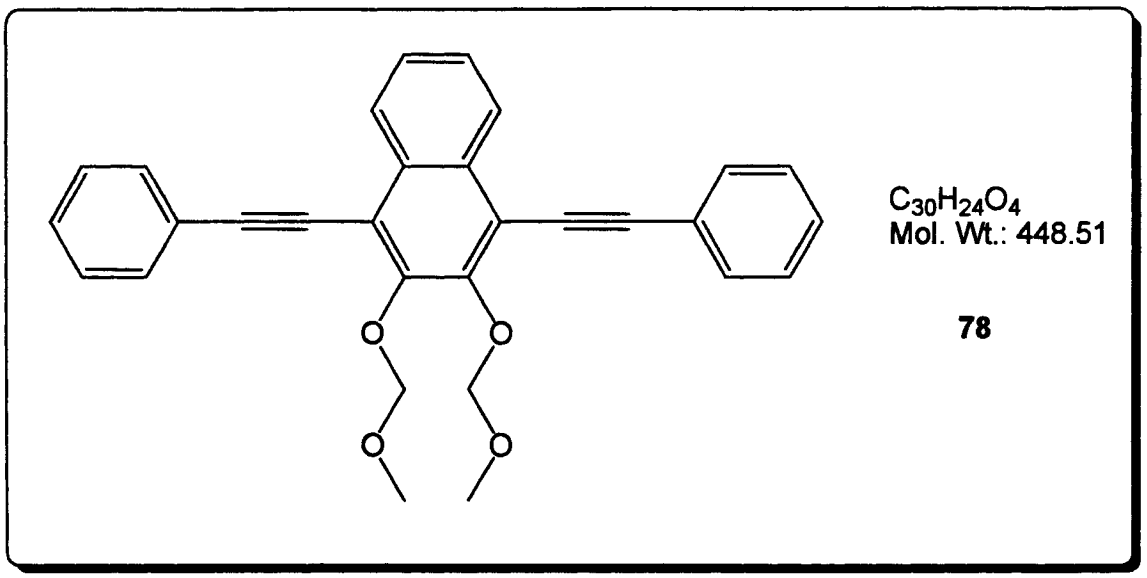
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 2.28 (s, 6H), 2.32 (s, 6H), 6.93-6.99 (d, 2H), J_{trans} = 16.52 Hz), 7.03-7.06 (m, 2H), 7.29-7.40 (m, 8H), 7.50-7.53 (m, 2h), 8.09-8.13 (m, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 20.31, 20.85, 119.10, 121.15, 121.36, 124.01, 125.26, 126.29, 127.66, 129.47, 130.41, 135.44, 138.30, 138.53, 150.81, 168.26, 169.21

Mass (EI): *m/z* (%) = 564.2 (M+, 20), 522.2 (20), 481.2 (38), 480.2 (100), 43.0 (33)

HRMS: calcd 564.1784, found 564.1775

2,3-Bis-methoxymethoxy-1,4-bis-phenylethynyl-naphthalene:



$C_{30}H_{24}O_4$
Mol. Wt.: 448.51

78

To **62** (0.3g, 0.739 mmol), $Pd(PhCN)_2Cl_2$ (0.008g, 0.022 mmol) and copper iodide (0.003g, 0.015 mmol), under nitrogen atmosphere, was added a solution of P(*t*Bu)$_3$ (0.44mL, 0.044 mmol, 0.1M) in anhydrous 1,4-dioxane, diisopropylamine (0.25mL, 1.77 mmol, d 0.722), phenylacetylene (0.19mL, 1.77 mmol, d 0.930) and 3mL of anhydrous 1,4-dioxane. The mixture was refluxed overnight, after which time the resulting reddish solution was filtered through a small pad of silica gel packed in a disposable pipet with several EtOAc washings. The solvents were evaporated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent to yield **78** (0.31g, 0.669 mmol, 91%) as a reddish oily material.

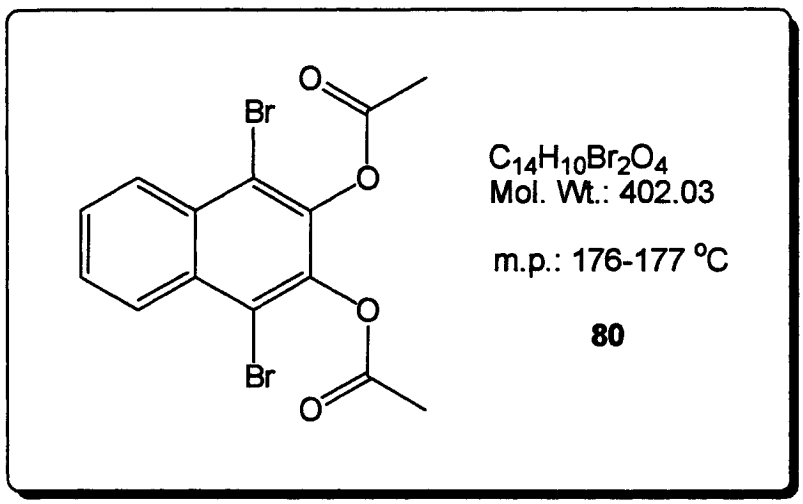
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 3.74 (s, 6H), 5.46 (s, 4H), 7.38-7.43 (m, 6H), 7.52-7.62 (m, 2H), 7.64-7.68 (m, 4H), 8.37-8.41 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 57.96, 83.99, 99.69, 100.29, 115.36, 123.14, 126.05, 126.66, 128.52, 128.73, 131.01, 131.54, 150.97

Mass (EI): *m/z* (%) = 448.2 (M+, 18), 373.1 (29), 372.1 (100), 45.0 (28)

HRMS: calcd 448.1675, found 448.1650

Acetic acid 3-acetoxy-1,4-dibromo-naphthalen-2-yl ester:



Acetylation of diol **60** (1.89g, 6.14 mmol) was carried out following the same procedure as in the acetylation of diol **4**. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent to give 66% of diacetate **80** (1.62g, 4.05 mmol) as an off-white solid.

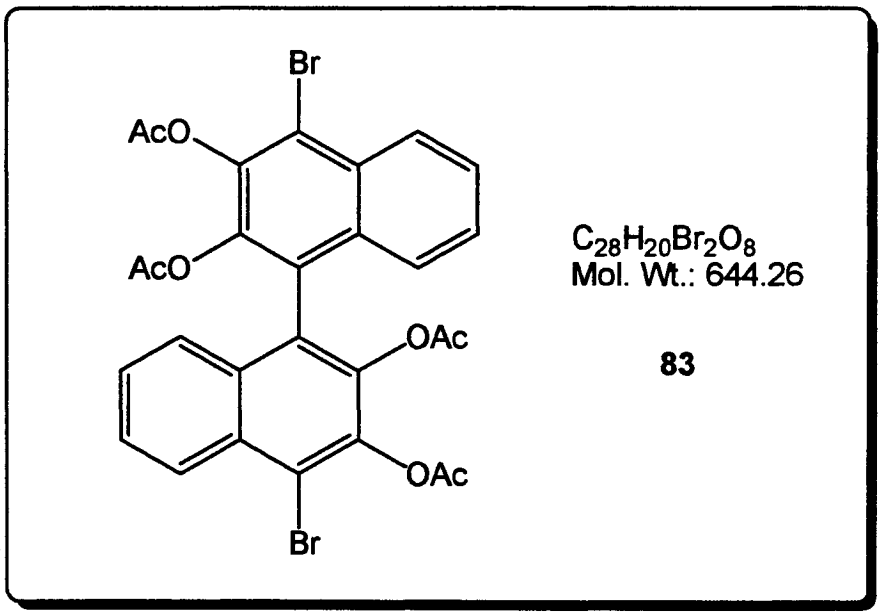
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.40 (s, 6H), 7.61-7.66 (m, 2H), 8.24-8.28 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 20.40, 116.70, 127.54, 128.35, 130.79, 140.43, 167.29

Mass (EI): *m/z* (%) = 399.9 (M+, 3), 319.9 (63), 317.9 (100), 315.9 (64), 43.0 (53)

HRMS: calcd 399.8946, found 399.8946

Acetic acid 3,2',3'-triacetoxy-4,4'-dibromo-[1,1]-binaphthalenyl-2-yl ester:



$C_{28}H_{20}Br_2O_8$
Mol. Wt.: 644.26

83

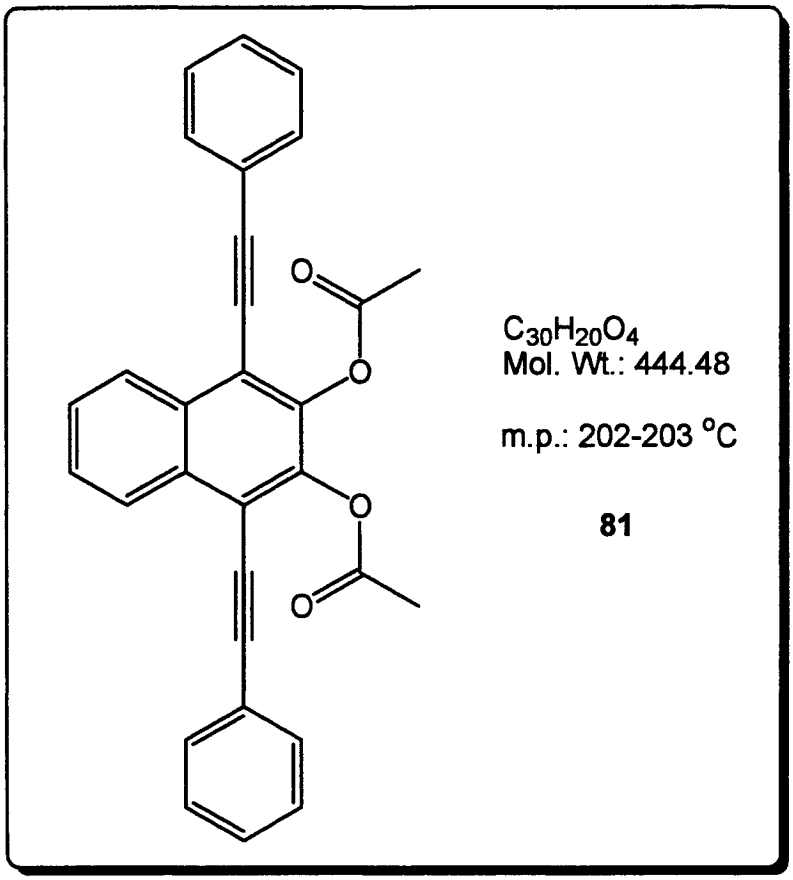
Dimer **83** was characterized as a white solid following the acetylation of diol **62** (see subsection 2.2) following the same procedure as in the acetylation of diol **4**.

^{1}H NMR ($CDCl_3$, 200 MHz): δ = 1.90 (s, 6H), 2.40 (s, 6H), 7.15-7.20 (d, 2H), 7.30-7.40 (t, 2H), 7.50-7.60 (t, 2H), 8.30-8.40 (d, 2H)

Mass (EI): *m/z* (%) = 642 (0.1), 476 (26), 320 (37), 318 (77), 316 (39), 105 (58), 43 (100), 42 (29), 40 (54)

HRMS: calcd 641.9525, found 641.9600

Acetic acid 3-acetoxy-1,4-bis-phenylethynyl-naphthalen-2-yl ester:



$C_{30}H_{20}O_4$
Mol. Wt.: 444.48

m.p.: 202-203 °C

81

The coupling reaction between **80** (0.15g, 0.375 mmol) and phenylacetylene was accomplished following the same procedure as outlined for **62** and phenylacetylene. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent to give 66% of **81** (0.11g, 0.247 mmol) as a light yellowish solid.

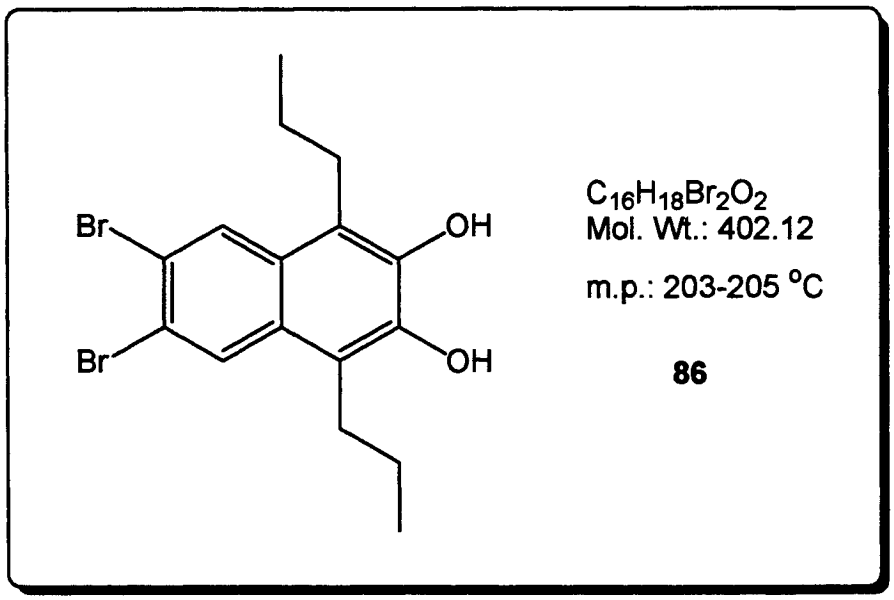
^{1}H NMR ($CDCl_3$, 200 MHz): δ = 2.45 (s, 6H), 7.38-7.41 (m, 6H), 7.58-7.66 (m, 6H), 8.37-8.42 (m, 2H)

^{13}C NMR ($CDCl_3$, 200 MHz): δ = 20.55, 82.09, 101.37, 115.97, 122.63, 126.57, 127.59, 128.55, 139.07, 131.48, 131.68, 143.33, 167.85

Mass (EI): *m/z* (%) = 444.1 (M+, 19), 402.1 (31), 361.1 (46), 360.1 (100)

HRMS: calcd 444.1362, found 444.1354

6,7-Dibromo-1,4-dipropyl-naphthalene-2,3-diol:



$C_{16}H_{18}Br_2O_2$
Mol. Wt.: 402.12
m.p.: 203-205 °C

86

Bromination of diol **23** (1.0g, 4.09 mmol) was accomplished following the same procedure as in synthesis of dibromide **60**. The crude product was washed with 10mL of hexanes to give dibromide **86** (1.32g, 3.25 mmol, 81%) as a white solid.

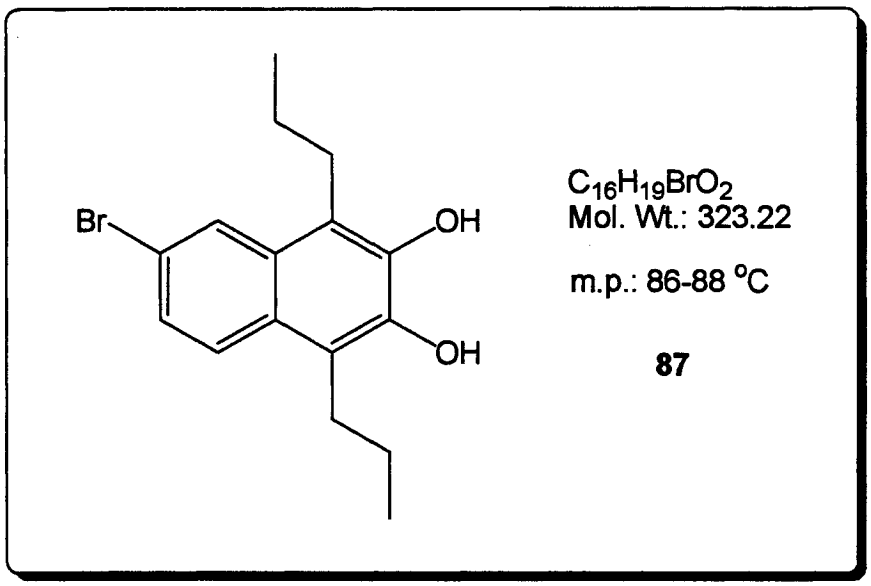
^{1}H NMR (acetone-d_6, 300 MHz): δ = 0.99-1.04 (t, 6H), 1.57-1.69 (m, 2H), 2.89 (s, 1H), 2.99-3.04 (t, 4H), 8.17 (s, 1H), 8.26 (s, 2H)

^{13}C NMR (acetone-d_6, 300 MHz): δ = 13.91, 23.32, 27.19, 118.38, 118.57, 128.35, 129.08, 144.74

Mass (EI): *m/z* (%) = 404.0 (24), 402.0 (44), 400.0 (M+, 30), 375.0 (38), 373.0 (81), 371.0 (50), 293.0 (20), 131.0 (33), 71.0 (34), 69.0 (100), 43.0 (79), 29.0 (21), 28.0 (39)

HRMS: calcd 399.9674, found 399.9668

6-Bromo-1,4-dipropyl-naphthalene-2,3-diol:



$C_{16}H_{19}BrO_2$
Mol. Wt.: 323.22

m.p.: 86-88 °C

87

A solution of bromine (0.33g, 2.05 mmol) dissolved in 10mL of acetic acid was added to a solution of **23** (0.5g, 2.05 mmol) dissolved in 10mL of acetic acid dropwise. The orangish solution was stirred overnight at r.t. open to air during which time the color became greenish. This mixture was diluted with 10mL of water and extracted using EtOAc (3 x 10mL). The combined organic layers were dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent. The yield of pure **87** was 0.57g (1.77 mmol), an off-white solid.

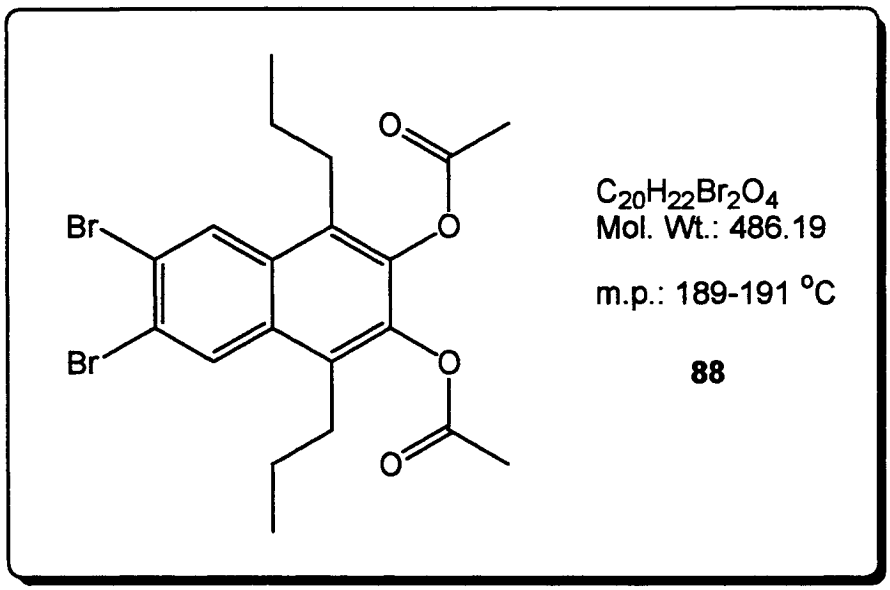
^{1}H NMR (acetone-d_6, 300 MHz): δ = 0.98-1.05 (m, 6H), 1.57-1.68 (m, 4H), 2.99-3.05 (m, 4H), 7.35-7.39 (dd, 1H, J_o = 9.00 Hz, J_m = 2.02 Hz), 7.80-7.83 (d, 1H, J_o = 9.01 Hz), 8.00-8.01 (d, 1H, J_m = 1.96 Hz), 8.06 (s, 2H)

^{13}C NMR (acetone-d_6, 300 MHz): δ = 15.47, 24.80, 24.84, 28.72, 28.81, 118.54, 119.95, 120.95, 127.12, 127.44, 127.65, 128.80, 131.75, 145.19, 145.84

Mass (EI): *m/z* (%) = 324.1 (47), 322.1 (M+, 49), 295.0 (97), 293.0 (100)

HRMS: calcd 322.0568, found 322.0569

Acetic acid 3-acetoxy-6,7-dibromo-1,4-dipropyl-npahthalen-2-yl ester:



Acetylation of diol **86** (1.3g, 3.25 mmol) was accomplished following the same procedure as in the synthesis of diacetate **10**. The crude product was washed once with 10mL of hexanes. This afforded 1.33g of diacetate **88** (2.75 mmol, 85%) as a white solid.

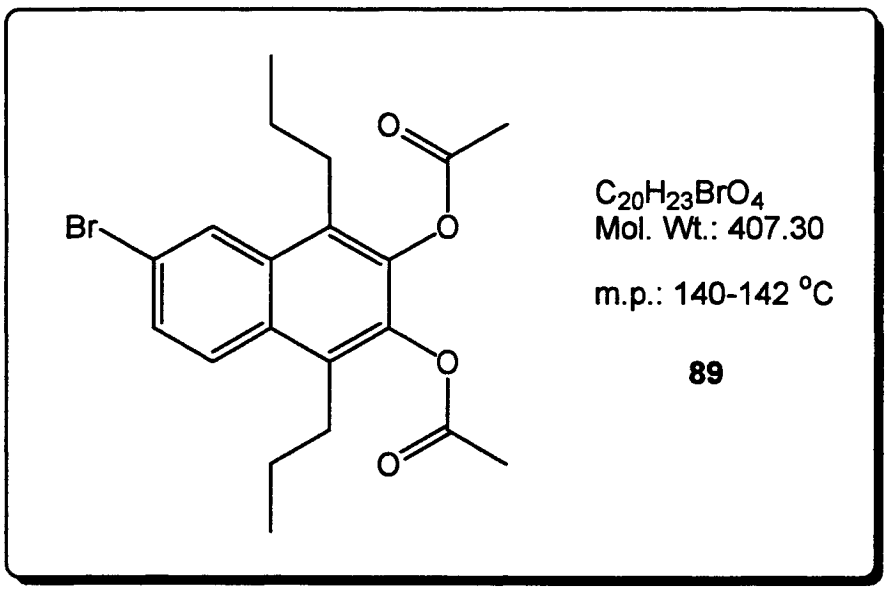
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 0.98-1.02 (t, 6H), 1.55-1.67 (m, 4H), 2.34 (s, 6H), 2.78-2.83 (t, 4H), 8.22 (s, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.85, 20.79, 23.69, 28.77, 122.76, 129.28, 129.82, 131.47, 140.52, 168.83

Mass (EI): *m/z* (%) = 484.0 (M+, 4), 404.0 (44), 402.0 (100), 372.9 (32), 162.0 (22)

HRMS: calcd 483.9885, found 483.9903

Acetic acid 3-acetoxy-7-bromo-1,4-dipropyl-naphthalen-2-yl ester:



Acetylation of diol **87** (0.90g, 2.79 mmol) was accomplished following the same procedure as in the synthesis of diacetate **10**. The crude product was washed once with 5mL of hexanes to give diacetate **89** (1.10g, 2.71 mmol) in 97% yield as a white powdered solid.

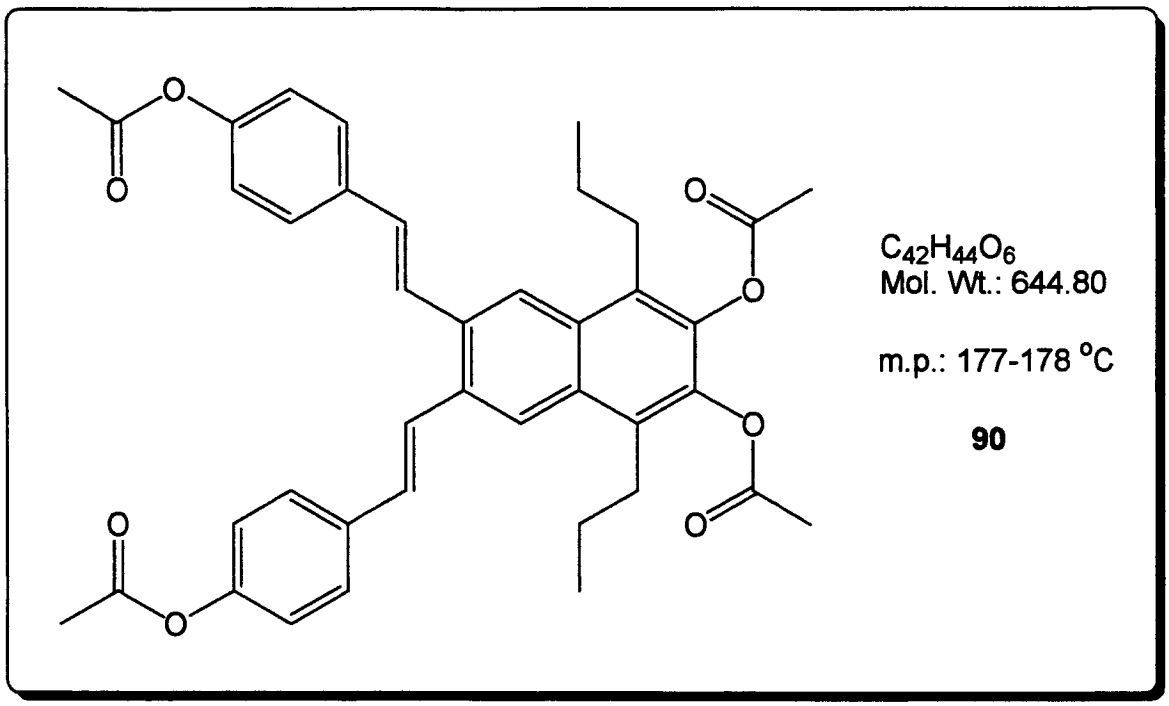
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.01-1.07 (q, 6H), 1.61-1.70 (m, 4H), 2.37 (s, 6H), 2.84-2.90 (m, 4H), 7.57-7.60 (dd, 1H, J_o = 9.03 Hz, J_m = 1.70 Hz), 7.87-7.90 (d, 1H, J_o = 9.07 Hz), 8.14-8.15 (d, 1H, J_m = 1.59 Hz)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.44, 20.35, 23.21, 23.29, 28.32, 28.37, 120.22, 126.56, 127.03, 128.68, 129.01, 129.55, 129.57, 132.36, 139.28, 139.82, 168.53, 168.54

Mass (EI): *m/z* (%) = 406.1 (M+, 11), 366.1 (20), 364.1 (23), 324.1 (89), 323.1 (20), 322.1 (100), 295.0 (38), 293.0 (37), 188.1 (23), 162.0 (24), 143.0 (27), 31.0 (23)

HRMS: calcd 406.0780, found 406.0809

Acetic acid 3-acetoxy-6,7-bis-[2-(4-acetoxy-phenyl)-vinyl]-1,4-dipropyl-naphthalen-2-yl ester:



$C_{42}H_{44}O_6$
Mol. Wt.: 644.80

m.p.: 177-178 °C

90

The coupling reaction between **88** (0.1g, 0.206 mmol) and 4-acetoxystyrene (0.08mL, 0.494 mmol, d 1.06) was accomplished following the same procedure as in the coupling reaction between **62** and methyl acrylate. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent. The yield of **90**, a yellowish solid, was 0.07g (0.108 mmol, 52%).

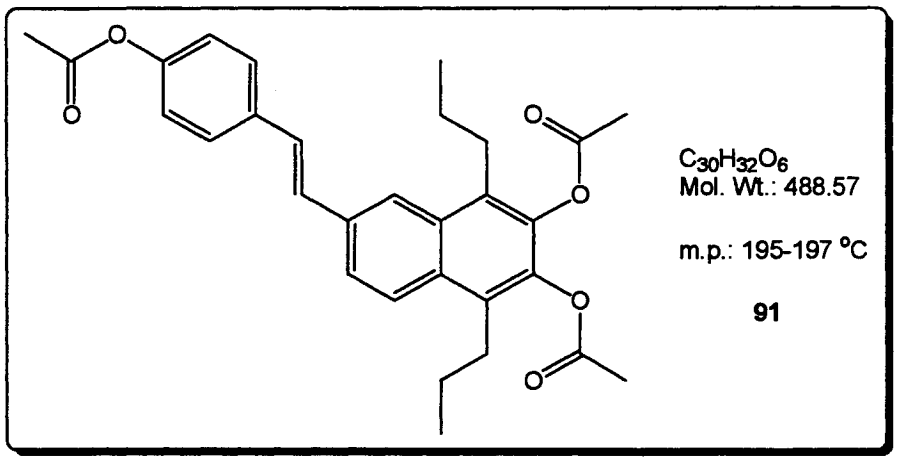
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.02-1.07 (t, 6H), 1.67-1.75 (m, 4H), 2.31 (s, 6H), 2.36 (s, 6H), 2.91-2.96 (t, 4H), 7.00-7.05 (d, 2H, J_{trans} = 15.75 Hz), 7.10-7.13 (d, 4H, J_o = 7.79 Hz), 7.44-7.50 (d, 2H, J_{trans} = 15.97 Hz), 7.57-7.59 (d, 4H, J_o = 7.91 Hz), 8.09 (s, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.99, 20.87, 21.56, 23.83, 28.84, 122.34, 123.13, 127.94, 128.12, 129.67, 131.06, 131.49, 134.90, 135.55, 139.79, 150.68, 169.15, 169.89

Mass (EI): *m/z* (%) = 648.3 (M+, 67), 607.3 (37), 606.3 (91), 565.3 (39), 564.3 (100), 373.2 (45), 162.0 (42), 143.0 (32), 107.0 (55), 31.0 (47)

HRMS: calcd 648.2723, found 648.2728

Acetic acid 3-acetoxy-7-[2-(4-acetoxy-phenyl)-vinyl]-1,4-dipropyl-naphthalen-2-yl ester:



To $Pd_2(dba)_3$ (0.015g, 0.016 mmol) placed under N_2 was added via syringe a solution of P(*t*Bu)$_3$ (0.32mL, 0.032 mmol, 0.1M) in anhydrous 1,4-dioxane, Cy_2NMe (0.14mL, 0.649 mmol, d 0.921), **89** (0.22g, 0.541 mmol) dissolved in 5mL of anhydrous 1,4-dioxane and 4-acetoxystyrene (0.1mL, 0.649 mmol, d 1.06). The mixture was stirred at 110°C overnight, while under N_2. The reaction mixture was filtered through a small pad of silica gel packed in a disposable pipet and washed several times with EtOAc; the solvents evaporated in vacuo. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent. The solid product obtained was washed with 10mL of hexanes, which afforded product **91** (0.2g, 0.410 mmol, 76%) as a white powdered solid.

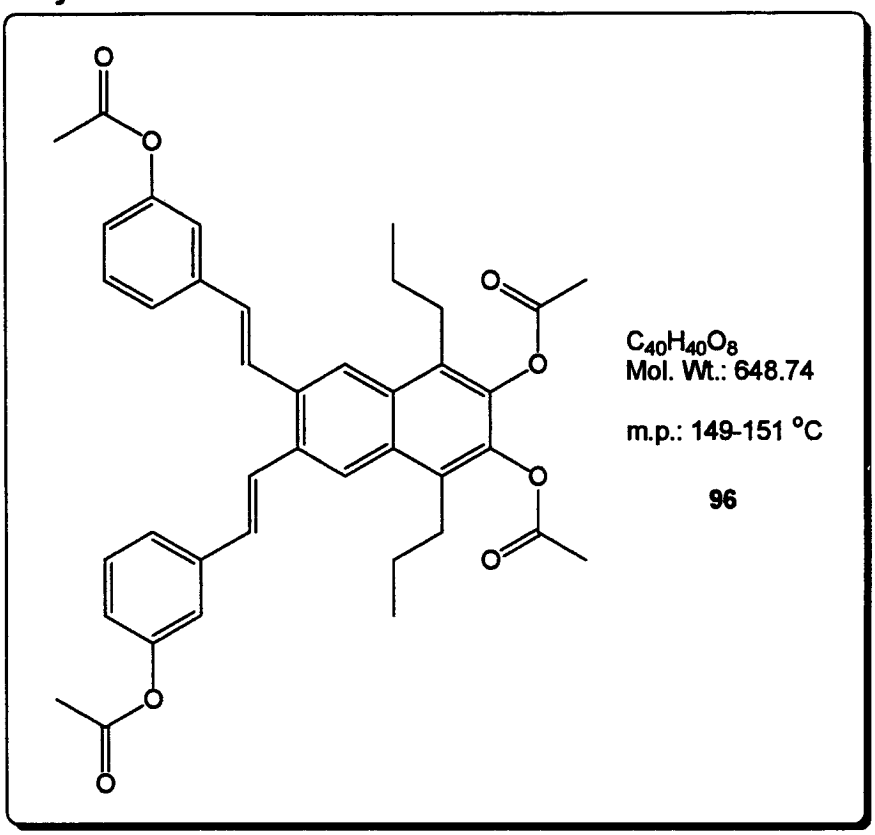
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.00-1.07 (q, 6H), 1.62-1.71 (m, 4H), 2.29 (s, 3H), 2.35 (s, 6H), 2.85-2.93 (q, 4H), 7.08-7.11 (d, 2H, J_o = 8.42 Hz), 7.19-7.23 (m, 2H), 7.55-7.58 (d, 2H, J_o = 8.35 Hz), 7.73-7.76 (d, 1H, J_o = 8.77 Hz), 7.93 (s, 1H), 7.95-7.97 (d, 1H, J_o = 9.15 Hz)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.78, 14.83, 20.66, 21.37, 23.61, 28.65, 28.69, 122.05, 123.17, 124.21, 125.53, 127.71, 128.37, 129.24, 129.60, 130.83, 131.56, 134.68, 135.25, 139.30, 139.66, 150.34, 168.97, 169.01, 169.68

Mass (EI): *m/z* (%) = 488.2 (M+, 30), 446.2 (100), 404.2 (73), 362.2 (94), 162.0 (21)

HRMS: calcd 488.2199, found 488.2194

Acetic acid 3-acetoxy-6,7-bis-[2-(3-acetoxy-phenyl)-vinyl]-1,4-dipropyl-naphthalen-2-yl ester:



The coupling reaction between **88** (0.2g, 0.413 mmol) and 3-acetoxystyrene **74** (0.16g, 0.991 mmol) was accomplished following the same procedure as in the coupling reaction between **62** and methyl acrylate. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent This afforded pure **96** (0.18g, 0.277 mmol) as a yellowish solid in 67% yield.

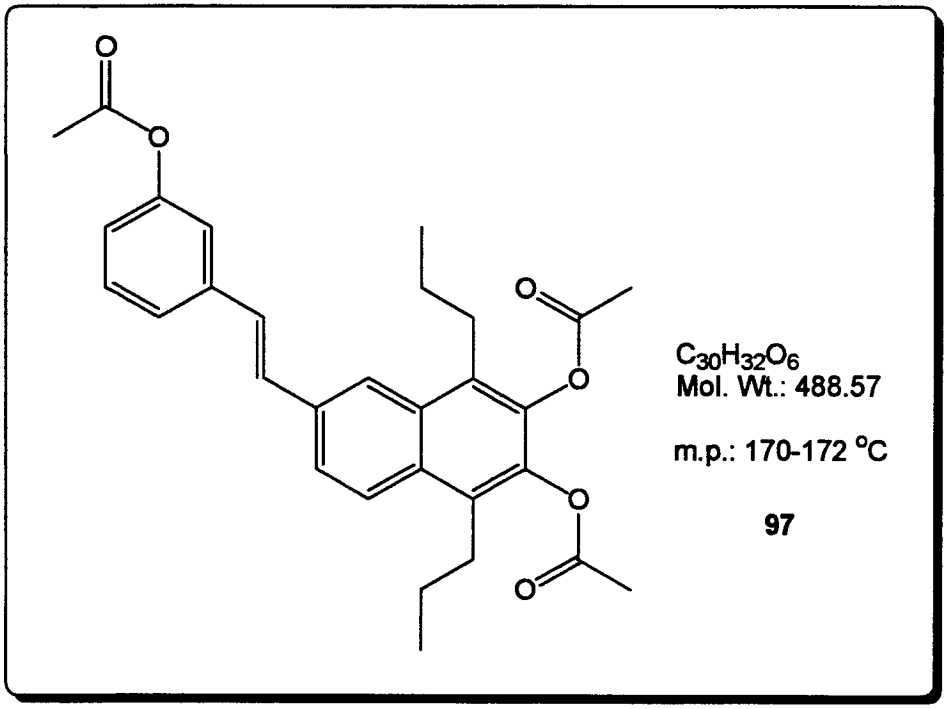
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03-1.07 (t, 6H), 1.67-1.74 (m, 4H), 2.31 (s, 6H), 2.36 (s, 6H), 2.91-2.95 (t, 4H), 7.00-7.04 (m, 4H), 7.29-7.53 (m, 8H), 8.09 (s, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.53, 20.40, 21.10, 23.36, 28.36, 119.65, 120.97, 122.93, 124.34, 128.30, 129.26, 129.68, 130.64, 131.19, 134.30, 138.93, 139.41, 151.01, 168.68, 169.53

Mass (EI): *m/z* (%) = 649.3 (31), 648.3 (M+, 71), 607.3 (27), 606.3 (66), 565.3 (39), 564.3 (100), 415.2 (25), 43.0 (51)

HRMS: calcd 648.2723, found 648.2735

Acetic acid 3-acetoxy-7-[2-(3-acetoxy-phenyl)-vinyl]-1,4-dipropyl-naphthalen-2-yl ester:



$C_{30}H_{32}O_6$
Mol. Wt.: 488.57

m.p.: 170-172 °C

97

The coupling reaction between **89** (0.2g, 0.492 mmol) and 3-acetoxystyrene **74** (0.096g, 0.591 mmol) was accomplished following the same procedure as in the coupling reaction between **89** and 4-acetoxystyrene. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent, which afforded 52% yield of pure **97** (0.0975g, 0.200 mmol) as an off-white solid.

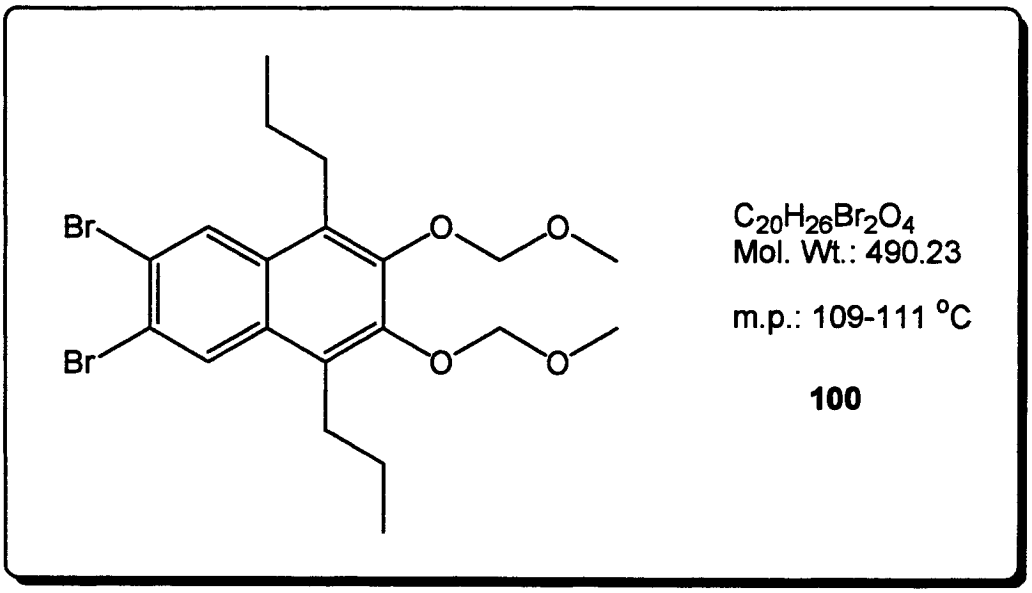
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.00-1.07 (q, 6H), 1.61-1.71 (m, 4H), 2.31 (s, 3H), 2.35 (s, 6H), 2.87-2.90 (q, 4H), 7.00 (m, 1H), 7.13-7.42 (m, 5H), 7.72-7.75 (d, 1H, J_o = 8.62 Hz), 7.93 (s, 1H), 7.93-7.98 (d, 1H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.79, 14.86, 20.67, 21.41, 23.62, 28.67, 28.70, 119.48, 120.95, 123.16, 124.45, 124.55, 125.57, 128.38, 129.62, 129.67, 129.88, 130.09, 130.93, 131.54, 134.48, 139.16, 139.37, 139.68, 151.29, 168.99, 169.02, 169.76

Mass (EI): *m/z* (%) = 488.2 (M+, 12), 446.2 (50), 404.2 (100), 162.0 (27), 69.0 (29)

HRMS: calcd 488.2199, found 488.2173

6,7-Dibromo-2,3-bis-methoxymethoxy-1,4-dipropyl-naphthalene:



$C_{20}H_{26}Br_2O_4$
Mol. Wt.: 490.23

m.p.: 109-111 °C

100

MOM protection of crude **86** (0.75g, 1.87 mmol) was accomplished following the same procedure as in the synthesis of **33**. The crude product was purified by column chromatography using 100% hexanes as eluent, which afforded pure **100** (0.61g, 1.25 mmol) as a white solid in 67% yield.

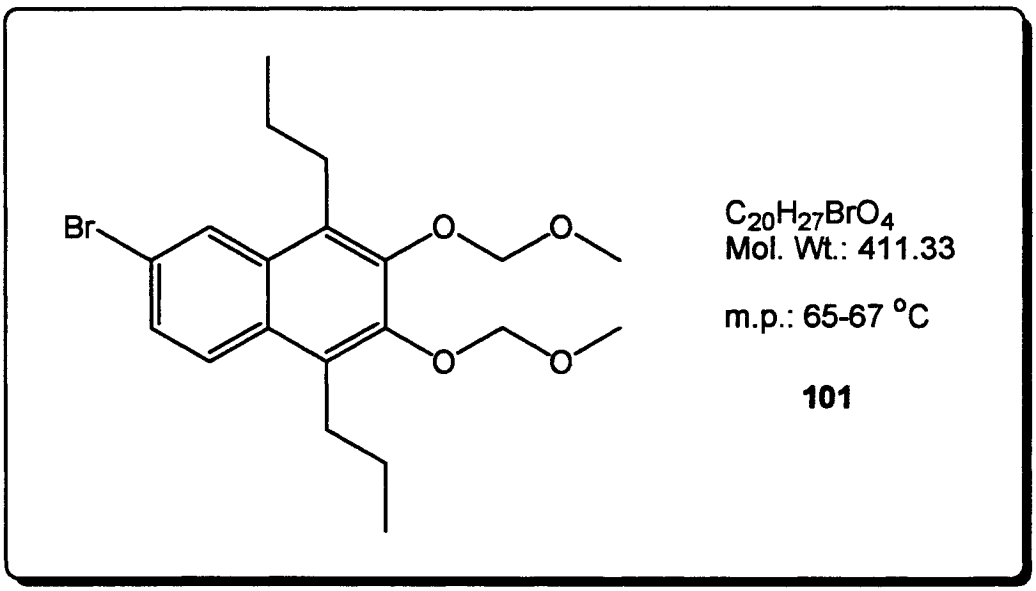
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03-1.08 (t, 6H), 1.62-1.70 (m, 4H), 2.98-3.03 (t, 4H), 3.61 (s, 6H), 5.12 (s, 4H), 8.18 (s, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.50, 23.89, 28.01, 57.79, 99.49, 120.94, 129.20, 129.31, 130.41, 147.62

Mass (EI): *m/z* (%) = 488.0 (M+, 1), 416.0 (29), 414.0 (59), 412.0 (29), 386.9 (24), 384.9 (48), 382.9 (23), 45.0 (100)

HRMS: calcd 488.0198, found 488.0170

6-Bromo-2,3-bis-methoxymethoxy-1,4-dipropyl-naphthalene:



$C_{20}H_{27}BrO_4$
Mol. Wt.: 411.33

m.p.: 65-67 °C

101

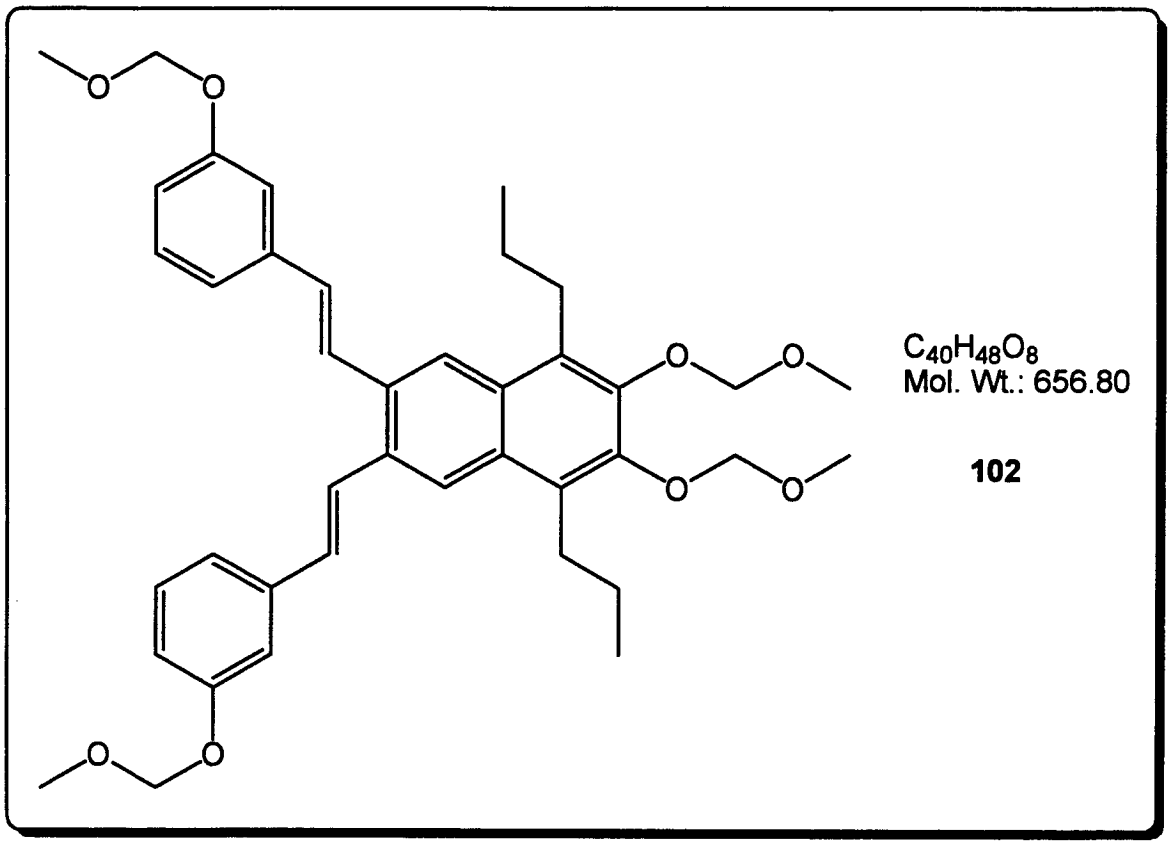
MOM protection of **87** (0.61g, 1.89 mmol) was accomplished following the same procedure as in the synthesis of **33**. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent, which afforded **101** (0.68g, 1.66 mmol) as a white solid in 88% yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.04-1.11 (m, 6H), 1.64-1.73 (m, 4H), 3.01-3.09 (m, 4H), 3.63 (s, 6H), 5.13 (s, 4H), 7.47-7.51 (dd, 1H, J_o = 9.01 Hz, J_m = 1.91 Hz), 7.80-7.83 (d, 1H, J_o = 9.07 Hz), 8.07-8.08 (d, 1H, J_m = 1.78 Hz)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.96, 24.28, 24.36, 28.43, 28.50, 58.15, 99.88, 99.92, 119.50, 126.84, 127.23, 128.32, 129.23, 129.63, 130.50, 132.12, 147.20, 147.76

Mass (EI): *m/z* (%) = 45.0 (100)

2,3-bis-methoxymethoxy-6,7-bis-[2-(3-methoxymethoxy-phenyl)-vinyl]-1,4-dipropyl-naphthalene:



$C_{40}H_{48}O_8$
Mol. Wt.: 656.80

102

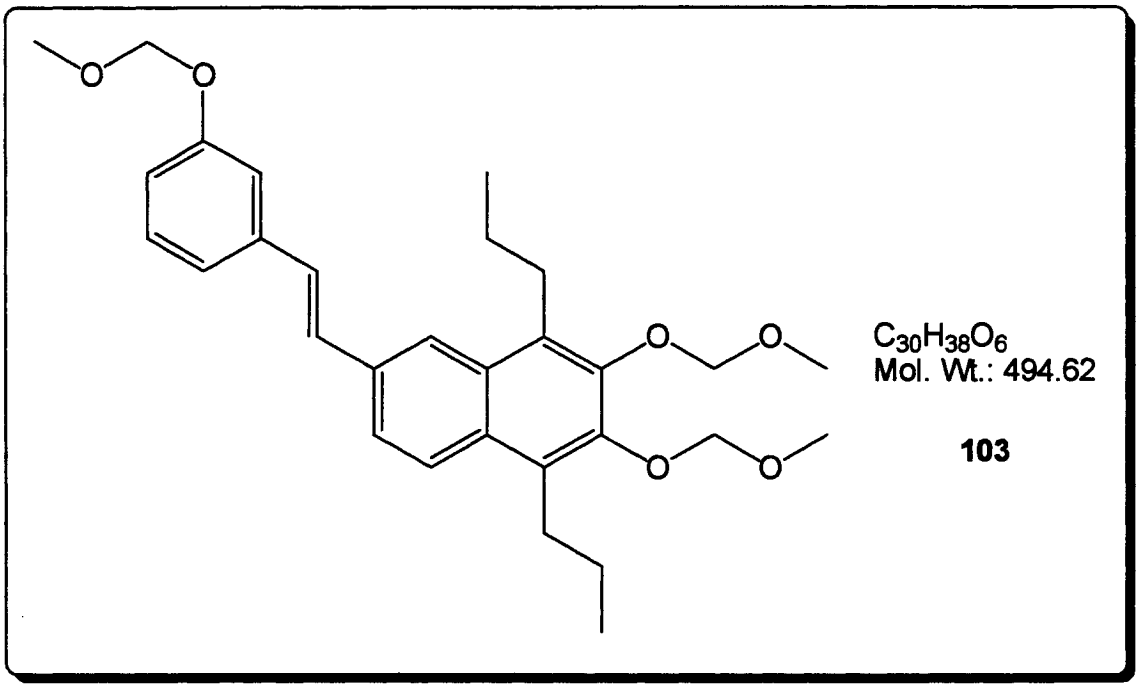
Coupling reaction between **100** (0.1g, 0.205 mmol) and **73** (0.07g, 0.451 mmol) was accomplished following the same procedure as in the coupling reaction between **62** and methyl acrylate. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent which provided pure **102** (0.12g, 0.182 mmol) as a pale yellowish oil in 89% yield

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.08-1.12 (t, 6H), 1.72-1.80 (m, 4H), 3.13-3.16 (t, 4H), 3.50 (s, 6H), 3.63 (s, 6H), 5.15 (s, 4H), 5.23 (s, 4H), 6.97-7.00 (m, 2H), 6.99-7.05 (d, 2H, J_{trans} = 15.92 Hz), 7.22-7.33 (m, 6H), 7.51-7.57 (d, 2H, J_{trans} = 16.00 Hz), 8.07 (s, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.31, 23.74, 27.76, 55.71, 57.46, 94.11, 99.23, 114.17, 115.22, 120.08, 122.35, 127.86, 129.43, 129.53, 129.66, 130.91, 133.18, 138.80, 146.59, 157.29

Mass (EI): *m/z* (%) = 656.4 (M+, 14), 581.3 (35), 580.3 (87), 45.0 (100)

2,3-bis-methoxymethoxy-6-[2-(3-methoxymethoxy-phenyl)-vinyl]-1,4-dipropyl-naphthalene:



$C_{30}H_{38}O_6$
Mol. Wt.: 494.62

103

Coupling reaction between **101** (0.1g, 0.244 mmol) and **73** (0.05g, 0.293 mmol) was carried out following the same procedure as in the coupling reaction between **89** and 4-acetoxystyrene. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent. This afforded **103** (0.096g, 0.194 mmol), a colorless oil, in 80% yield.

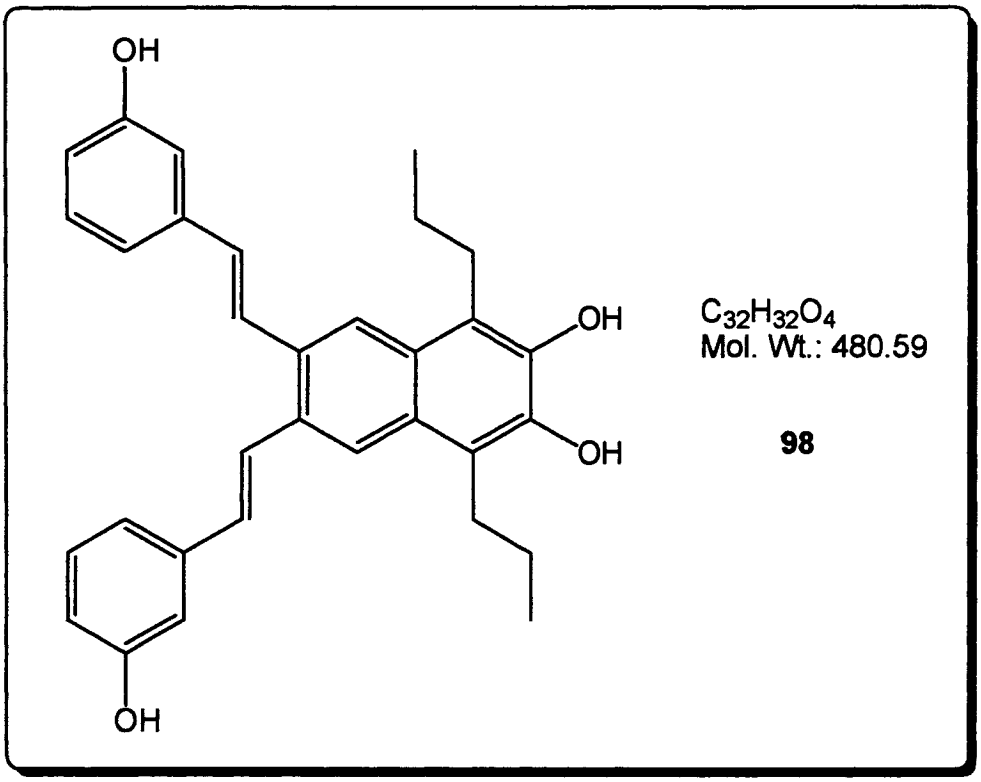
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.06-1.14 (q, 6H), 1.54-1.77 (m, 4H), 3.06-3.15 (q, 4H), 3.52 (s, 3H), 3.63 (s, 6H), 5.14 (s, 4H), 5.24 (s, 2H), 6.94-6.97 (m, 1H), 7.13-7.32 (m, 5H), 7.68-7.72 (d, 1H, J_o = 8.76 Hz), 7.91 (s, 1H), 7.91-7.94 (d, 1H, J_o = 8.69 Hz)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.74, 14.80, 24.13, 28.20, 28.25, 56.14, 57.86, 94.48, 99.64, 113.95, 115.64, 120.52, 122.05, 124.20, 125.25, 128.31, 129.69, 129.79, 130.03, 130.06, 130.63, 133.59, 139.09, 146.77, 147.02, 157.71

Mass (EI): *m/z* (%) = 494.3 (M+, 13), 419.2 (28), 418.2 (100), 162.0 (27), 143.0 (22), 45.0 (50)

HRMS: calcd 494.2668, found 494.2673

6,7-Bis-[2-(3-hydroxy-phenyl)-vinyl]-1,4-dipropyl-naphthalene-2,3-diol:



$C_{32}H_{32}O_4$
Mol. Wt.: 480.59

98

MOM deprotection of **102** (0.12g, 0.183 mmol) was accomplished following the same procedure as in the synthesis of diol **36**. The crude product was washed once with 5mL of hexanes, which afforded **98** (0.068g, 0.142 mmol) as a yellowish gummy solid in 77% yield.

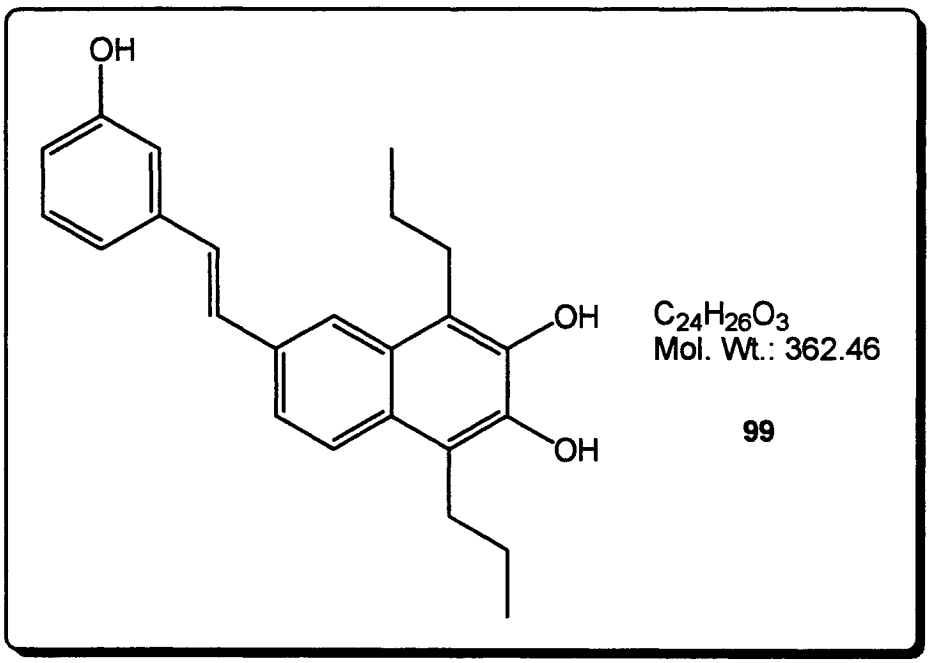
^{1}H NMR (acetone-d_6, 300 MHz): δ = 1.04-1.09 (t, 6H), 1.69-1.77 (m, 4H), 3.11-3.16 (t, 4H), 6.74-6.79 (m, 2H), 7.06-7.24 (m, 8H), 7.65-7.71 (d, 2H, J_{trans} = 16.12 Hz), 7.93 (s, 2H), 8.13 (s, 2H), 8.37 (s, 2H)

^{13}C NMR (acetone-d_6, 300 MHz): δ = 14.09, 23.52, 27.31, 113.35, 115.04, 118.67, 119.24, 121.65, 128.02, 128.60, 130.07, 130.78, 132.16, 139.77, 143.84, 158.12

Mass (EI): *m/z* (%) = 481.2 (32), 480.2 (M+, 100), 373.2 (20), 162.0 (40), 143.0 (30), 31.0 (34)

HRMS: calcd 480.2301, found 480.2283

6-[2-(3-Hydroxy-phenyl)-vinyl]-1,4-dipropyl-naphthalene-2,3-diol:



$C_{24}H_{26}O_3$
Mol. Wt.: 362.46

99

MOM deprotection of **102** (0.095g, 0.192 mmol) was accomplished following the same procedure as in the synthesis of diol **36**. The crude product was flash chromatographed using 20% EtOAc in hexanes as eluent, which afforded **99** (0.0649g, 0.179 mmol) as a yellowish gummy solid in 93% yield.

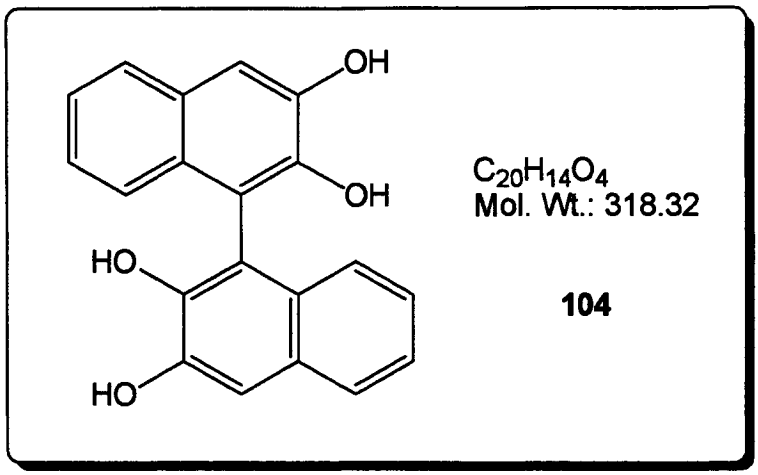
^{1}H NMR (acetone-d_6, 300 MHz): δ = 1.01-1.06 (q, 6H), 1.63-1.74 (m, 4H), 3.03-3.13 (m, 4H), 6.73-6.77 (m, 1H), 7.09-7.23 (m, 4H), 7.35-7.40 (d, 1H, J_{trans} = 16.37 Hz), 7.65-7.68 (dd, 1H, J_o = 8.86 Hz, J_m = 1.58 Hz), 7.86 (s, 1H), 7.86-7.88 (d, 1H, J_o = 7.17 Hz), 7.98 (s, 1H), 8.35 (s, 1H)

^{13}C NMR (acetone-d_6, 300 MHz): δ = 15.28, 15.32, 24.66, 24.71, 28.56, 28.61, 114.49, 115.99, 119.53, 120.66, 120.80, 121.83, 124.77, 125.46, 128.73, 129.65, 130.12, 131.19, 131.21, 133.69, 140.97, 144.76, 144.83, 159.30

Mass (EI): *m/z* (%) = 363.2 (28), 362.2 (M+, 100), 335.1 (26), 333.2 (50), 308.1 (21), 307.1 (60), 43.1 (23)

HRMS: calcd 362.1882, found 362.1877

[1,1']-Binaphthalenyl-2,3,2',3'-tetraol:



$C_{20}H_{14}O_4$
Mol. Wt.: 318.32

104

Diol **16** (1.0g, 6.24 mmol) and iron trichloride hexahydrate (3.37g, 12.48 mmol) were separately finely powdered using agate mortar and pestle. Both powders were placed in a test tube which was well shaken to give a yellowish homogeneous solid mixture and heated up using a water bath to 50°C during 2h. The resulting brownish mixture was treated with 25mL of aq. 10% HCl solution, causing the product to precipitate from the greenish solution. The residue was filtered by suction and washed several times with hexanes, after which time the resulting solid was dissolved in EtOAc, dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo. The crude product was recrystallized from EtOAc, which afforded pure **104** (0.53g, 1.67 mmol) as a white solid in 54% yield [41].

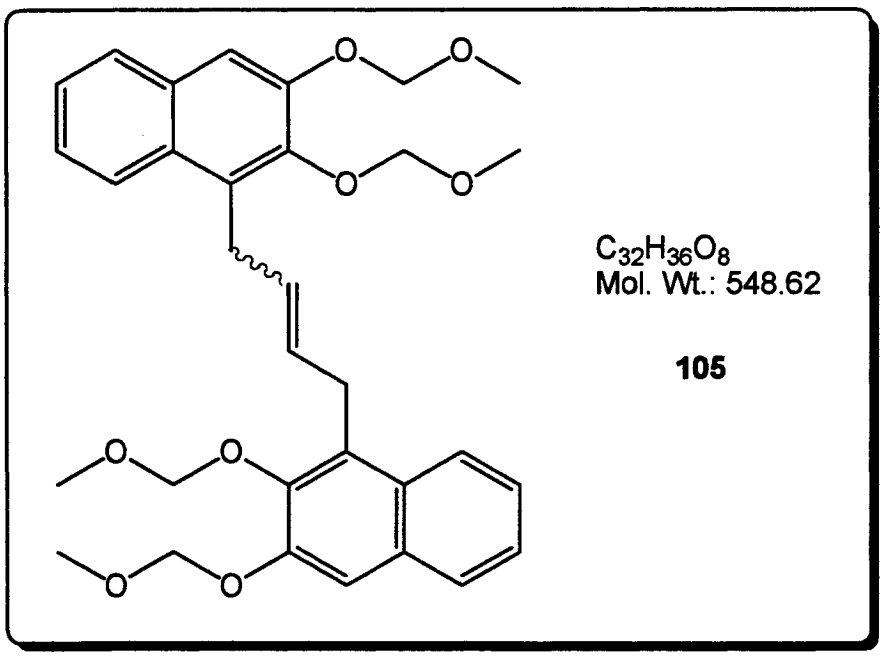
^{1}H NMR (acetone-d_6, 200 MHz): δ = 6.93-7.07 (m, 4H), 7.17-7.21 (dd, 1H, J_o = 8.00 Hz, J_m = 1.62 Hz), 7.21-7.25 (dd, 1H, J_o = 8.00 Hz, J_m = 1.51 Hz), 7.34 (s, 2H), 7.67-7.71 (d, 2H, J_o = 8.12 Hz), 7.92 (s, 2H), 8.50 (s, 2H)

^{13}C NMR (acetone-d_6, 200 MHz): δ = 110.36, 124.04, 124.10, 125.29, 127.02, 129.90, 130.52, 147.10

Mass (EI): *m/z* (%) = 319.1 (21), 318.1 9M+, 100), 69.0 (46)

HRMS: calcd 318.0892, found 318.0870

Dimerization of 33:



$C_{32}H_{36}O_8$
Mol. Wt.: 548.62

105

Dry CH_2Cl_2 (5mL) was added via syringe to **33** (0.1g, 0.347 mmol) and Grubbs 1st generation catalyst (0.02g, 0.02 mmol) under N_2. The purple mixture was refluxed overnight during which time the color became black. The solution was diluted with 10mL of CH_2Cl_2 and washed using 10mL of sat. $NaHCO_3$ solution followed by 10mL of brine. The combined aqueous layers were extracted with CH_2Cl_2 (2 x 10mL) and the combined organic layers were dried over $MgSO_4$, filtered through cotton and solvent evaporated in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent. This afforded **105**, a yellowish oily material (0.076g, 0.139 mmol), as a 3:1 mixture of alkene stereoisomers in 80% yield.

* = major product

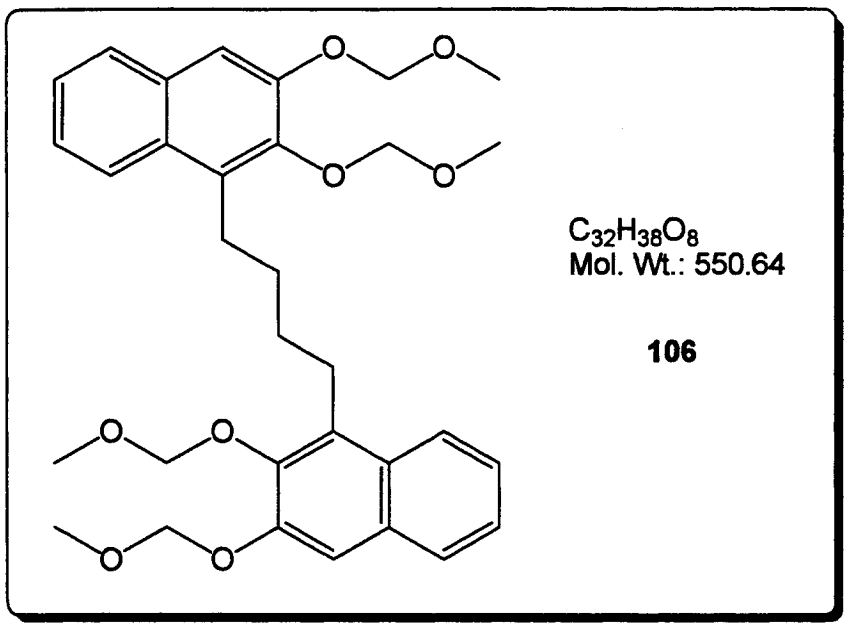
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 3.52 (s, 6H)*, 3.53 (s, 6H)*, 3.55 (s, 6H), 3.67 (s, 6H), 3.83-3.84 (bd, 4H)*, 4.22-4.23 (d, 4H, J = 3.66 Hz), 5.10 (s, 4H)*, 5.24 (s, 4H), 5.32 (s, 4H)*, 5.35 (s, 4H), 5.56-5.58 (t, 2H), 5.69 (t, 2H)*, 7.24-7.41 (m, 6H* + 6H), 7.67-7.70 (d, 2H, J_o = 7.79 Hz)*, 7.71-7.75 (m, 2H), 7.83-7.86 (d, 2H, J_o = 8.21 Hz)*, 7.98-8.01 (m, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 25.29, 29.28*, 56.70*, 57.92*, 58.17, 95.29*, 99.75*, 99.96, 110.31*, 110.37, 124.65*, 124.71, 124.82, 124.93*, 125.45*, 125.60, 127.75*, 127.93, 129.04*, 129.31*, 129.35, 130.08*, 130.15, 131.85*, 131.97, 144.56*, 144.62, 149.44*, 149.48

Mass (EI): *m/z* (%) = 548.2 (M+, 1), 440.2 (28), 396.1 (33), 224.1 (20), 223.1 (20), 211.1 (36), 198.1 (20), 197.1 (29), 185.1 (49), 45.0 (100)

HRMS: calcd 548.2410, found 548.2397

Hydrogenation of dimer 105:



$C_{32}H_{38}O_8$
Mol. Wt.: 550.64

106

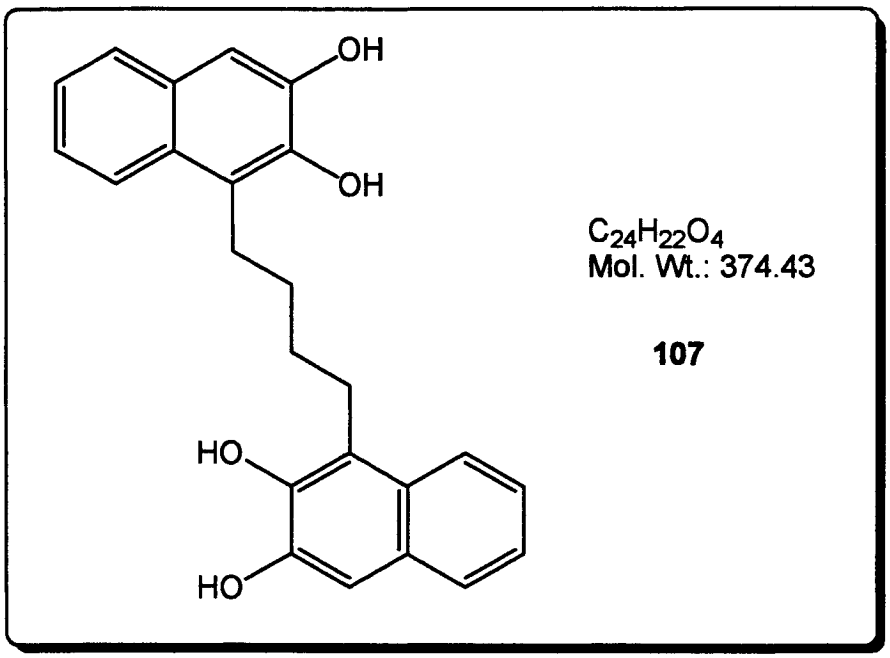
To **105** (0.07g, 0.128 mmol) dissolved in 3mL of EtOAc was added in one portion Pd/C 30% (0.0007g, 0.006 mmol) after which time the resulting black solution was closed and equipped with two balloons filled with hydrogen and stirred at r.t. over week-end. The reaction mixture was filtered through celite with several EtOAc washings, followed by evaporation of the solvent in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent, which afforded pure **106** (0.028g, 0.051 mmol) as a white solid in 40% yield.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.91 (bt, 4H), 3.24 (bt, 4H), 3.55 (s, 6H), 3.62 (s, 6H), 5.18 (s, 4H), 5.34 (s, 4H), 7.37 (s, 2H), 7.37-7.41 (m, 4H), 7.71-7.74 (m, 2H), 7.94-7.97 (m, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 25.85, 30.87, 56.06, 57.32, 94.62, 99.15, 109.21, 123.65, 124.04, 124.75, 127.32, 128.15, 131.19, 131.30, 143.86, 148.70

Mass (EI): *m/z* (%) = 442.2 (28), 398.2 (31), 225.1 (27), 199.1 (26), 185.1 (50), 45.0 (100)

MOM deprotection of dimer 106:



$C_{24}H_{22}O_4$
Mol. Wt.: 374.43

107

MOM deprotection of **106** (0.025g, 0.045 mmol) was accomplished following the same procedure as in the synthesis of diol **36**. The crude product was purified by flash chromatography using 10% EtOAc in hexanes. The yield of **107** (0.015g, 0.040 mmol), a pinky solid, was 89% after washing with sodium hydrosulfite solution.

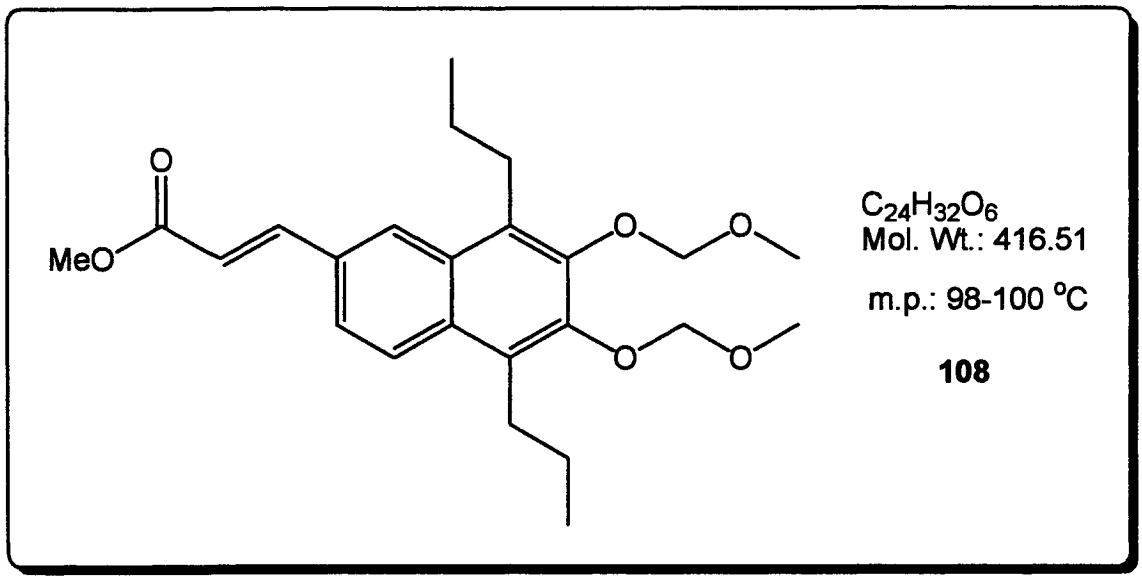
^{1}H NMR (acetone-d_6, 300 MHz): δ = 1.83-1.88 (m, 4H), 2.99 (s, 2H), 3.15-3.17 (bt, 4H), 7.10 (s, 2H), 7.17-7.29 (m, 4H), 7.56-7.58 (d, 2H, J_o = 7.85 Hz), 7.86-7.89 (d, 2H, J_o = 8.28 Hz), 9.04 (s, 2H)

^{13}C NMR (acetone-d_6, 300 MHz): δ = 26.98, 32.05, 109.33, 122.91, 124.77, 124.86, 125.15, 128.58, 130.33, 131.53, 145.49, 147.17

Mass (EI): *m/z* (%) = 375.2 (22), 374.2 (M+, 71), 173.1 (100)

HRMS: calcd 374.1518, found 374.1539

3-(6,7-Bis-methoxymethoxy-5,8-dipropyl-naphthalen-2-yl ester)-acrylic acid methyl ester:



$C_{24}H_{32}O_6$
Mol. Wt.: 416.51
m.p.: 98-100 °C

108

The coupling reaction between **101** (0.10g, 0.244 mmol) and methyl acrylate (0.03mL, 0.293 mmol, d 0.956) was accomplished following the same procedure as in the coupling reaction between **89** and 4-acetoxystyrene. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent, which afforded methyl acrylate **108** (0.10g, 0.240 mmol) as a yellowish solid in 98% yield.

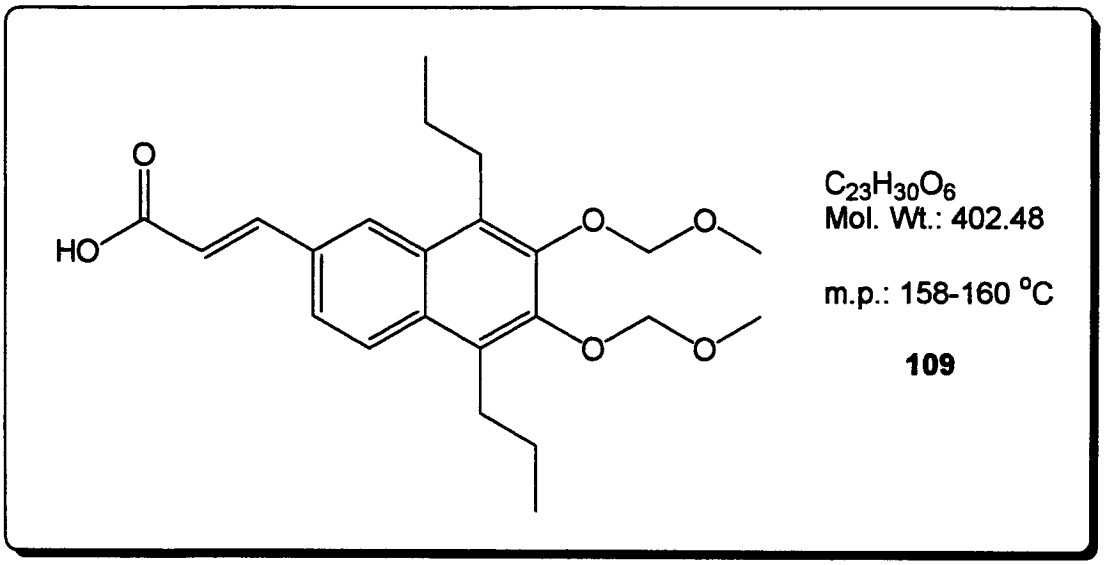
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03-1.10 (q, 6H), 1.61-1.72 (m, 4H), 3.03-3.10 (q, 4H), 3.60 (s, 3H), 3.61 (s, 3H), 3.82 (s, 3H), 5.12 (s, 2H), 5.13 (s, 2H), 6.49-6.54 (d, 1H, J_{trans} = 15.95 Hz), 7.59-7.62 (d, 1H, J_o = 8.76 Hz), 7.84-7.89 (d, 1H, J_{trans} = 16.01 Hz), 7.91-7.94 (d, 1H, J_o = 8.93 Hz), 8.00 (s, 1H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.77, 14.82, 24.17, 24.33, 28.27, 28.29, 51.91, 57.95, 99.73, 99.74, 117.37, 122.22, 125.68, 127.47, 130.35, 130.39, 130.80, 130.97, 131.54, 145.64, 147.41, 148.01, 167.856

Mass (EI): *m/z* (%) = 416.2 (M+, 4), 341.2 (24), 340.2 (100), 311.1 (93), 45.0 (58)

HRMS: calcd 416.2199, found 416.2215

3-(6,7-Bis-methoxymethoxy-5,8-dipropyl-naphthalen-2-yl)-acrylic acid:



$C_{23}H_{30}O_6$
Mol. Wt.: 402.48

m.p.: 158-160 °C

109

A solution of potassium hydroxide (0.067g, 1.20 mmol) in 2.5mL of water was added to the starting acrylic ester **108** (0.1g, 0.240 mmol) dissolved in 6.5mL of methanol. The resulting yellowish suspension was equipped with a condenser and heated up to 80°C during 3h, after which time the reaction was quenched by adding aq. 10% HCl till pH 4 and extracted using EtOAc (3 x 10mL). The combined organic layers were washed once with 10mL of brine, dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by flash chromatography using 30% EtOAc in hexanes as eluent, which afforded pure acrylic acid **109** (0.066g, 0.164 mmol) as a white solid in 68% yield.

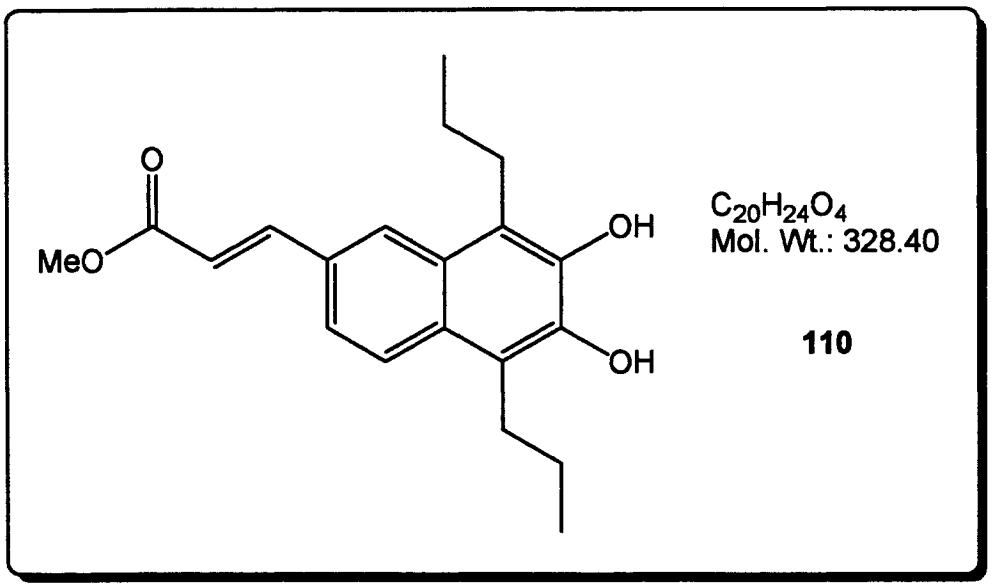
^{1}H NMR (DMSO-d_6, 300 MHz): δ = 0.99-1.05 (q, 6H), 1.58-1.62 (m, 4H), 2.99-3.09 (m, 4H), 3.52 (s, 6H), 5.08 (s, 2H), 5.09 (s, 2H), 6.61-6.66 (d, 1H, J_{trans} = 15.99 Hz), 7.83-7.85 (d, 1H), 7.83-7.88 (d, 1H, J_{trans} = 16.09 Hz), 7.95-7.98 (d, 1H, J_o = 8.97 Hz), 8.20 (s, 1H), 12.40 (s, 1H)

^{13}C NMR (DMSO-d_6, 300 MHz): δ = 14.32, 14.34, 23.61, 23.82, 27.29, 27.41, 57.14, 98.96, 98.99, 118.79, 122.39, 125.18, 127.23, 129.45, 129.59, 130.43, 130.81, 144.50, 146.84, 147.41, 167.77

Mass (EI): *m/z* (%) = 402.2 (M+, 4), 327.2 (22), 326.2 (99), 297.1 (100), 45.0 (78)

HRMS: calcd 402.2042, found 402.2027

3-(6,7-Dihydroxy-5,8-dipropyl-naphthalen-2-yl ester)-acrylic acid methyl ester:



$C_{20}H_{24}O_4$
Mol. Wt.: 328.40

110

MOM deprotection and esterification of **109** (0.07g, 0.174 mmol) was accomplished following the same procedure as in the synthesis of diol **36**. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent, which provided diol **110** (0.034g, 0.104 mmol) as yellowish oil in 60% yield, which tend to solidify in high vacuum.

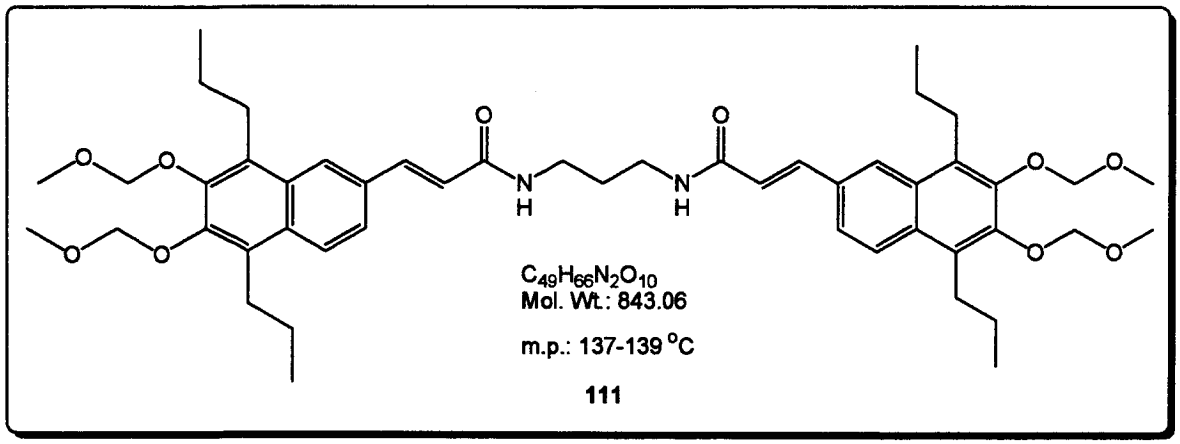
^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.02-1.08 (m, 6H), 1.63-1.73 (m, 4H), 2.97-3.01 (t, 4H), 3.84 (s, 3H), 6.20 (s, 1H), 6.30 (s, 1H), 6.46-6.52 (d, 1H, J_{trans} = 15.92 Hz), 7.51-7.54 (d, 1H, J_o = 8.84 Hz), 7.82-7.85 (d, 1H, J_o = 8.41 Hz), 7.84-7.90 (d, 1H, J_{trans} = 15.90 Hz), 7.91 (s, 1H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.51, 14.53, 23.25, 23.39, 27.49, 52.01, 116.18, 119.41, 120.00, 121.05, 124.57, 126.66, 128.26, 129.44, 129.81, 142.24, 143.19, 146.44, 168.49

Mass (EI): *m/z* (%) = 328.2 (M+, 59), 300.1 (20), 299.1 (100), 57.1 (31), 55.1 (20), 43.1 (35), 41.0 (20)

HRMS: calcd 328.1675, found 328.1683

3-(6,7-Bis-methoxymethoxy-5,8-dipropyl-naphthalen-2-yl)-*N*-{3-[3-(6,7-methoxymethoxy-5,8-dipropyl-naphthalen-2-yl)-acryloylamino]-propyl}-acrylamide:



$C_{49}H_{66}N_2O_{10}$
Mol. Wt.: 843.06

m.p.: 137-139 °C

111

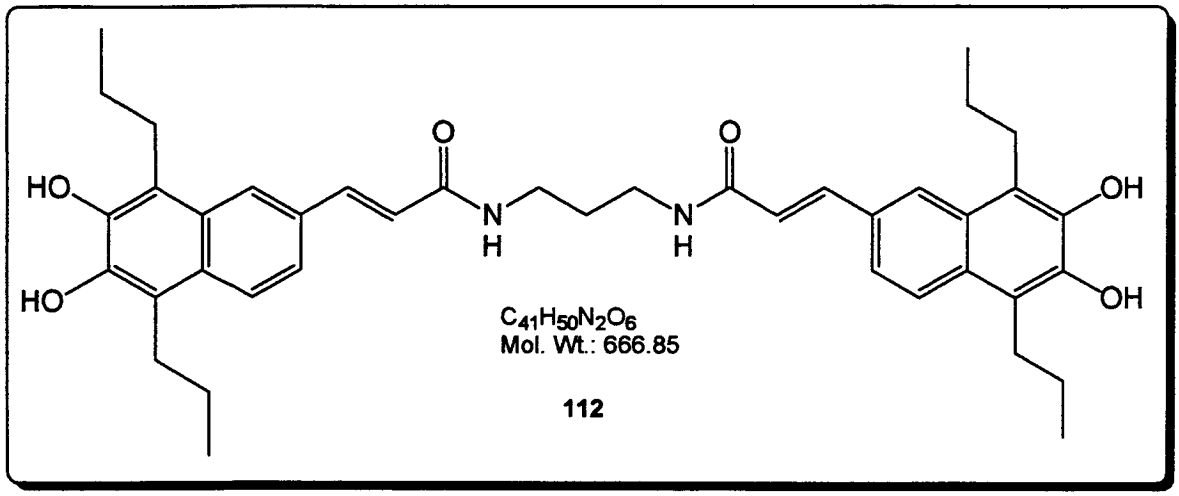
To the starting material **109** (0.15g, 0.373 mmol) dissolved in 10mL of dry THF, placed under nitrogen atmosphere, was added pentafluorophenol (0.082g, 0.448 mmol) dissolved in 2.5mL of dry THF followed by the dropwise addition of DCC (0.092g, 0.448 mmol) dissolved in 2.5mL of dry THF. The resulting colorless solution was refluxed overnight, after which time the resulting mixture was filtered with suction and the precipitate washed several times with petroleum ether. The filtrate was evaporated in vacuo. The crude product was purified by column chromatography using 10% EtOAc in hexanes as eluent, which provided the pentafluoro acrylic ester intermediate (0.18g, 0.317 mmol) as an off-white solid in 85% yield. To this intermediate dissolved in 10mL of DMF was added dropwise 1,3-diaminopropane (0.014mL, 0.159 mmol, d 0.888) dissolved in 1mL of DMF. The resulting mixture was stirred at 70°C for 4h, after which time the solution was diluted with 20mL of water and extracted using EtOAc (3 x 10mL). The combined organic layers were washed once with 20mL of brine, dried over $MgSO_4$, filtered through cotton and solvents evaporated in vacuo. The crude product was purified by column chromatography using 7/3 EtOAc/hexanes as eluent, which afforded the desired dimer **111** (0.0638g, 0.076 mmol) as an off-white solid in 41% yield over two reactions.

^{1}H NMR ($CDCl_3$, 300 MHz): δ = 1.03-1.09 (q, 12H), 1.67-1.75 (m, 8H), 1.78-1.79 (bt, 2H), 3.02-3.07 (q, 8H), 3.50-3.52 (bt, 4H), 3.62 (s, 12H), 5.12 (s, 4H), 5.13 (s, 4H), 6.59-6.69 (d, 2H, J_{trans} = 15.57 Hz), 6.98 (bt, 2H), 7.61-7.63 (d, 2H, J_o = 8.88 Hz), 7.82-7.87 (d, 2H), 7.84-7.89 (d, 2H), 8.00 (s, 2H)

^{13}C NMR ($CDCl_3$, 300 MHz): δ = 14.31, 14.35, 23.69, 23.84, 27.81, 29.66, 35.84, 57.50, 99.24, 99.27, 119.80, 121.62, 125.09, 126.84, 129.83, 130.00, 130.39, 130.67, 130.76, 141.54, 146.80, 147.26, 166.93

Mass (ES) *m/z*+1 (%) = 844.1 (M+1, 0.14), 83.1 (28), 56.2 (50), 42.3 (100)

3-(6,7-Dihydroxy-5,8-dipropyl-naphthalen-2-yl)-*N*-{3-[3-(6,7-dihydroxy-5,8-dipropyl-naphthalen-2-yl)-acryloylamino]-propyl)-acrylamide:

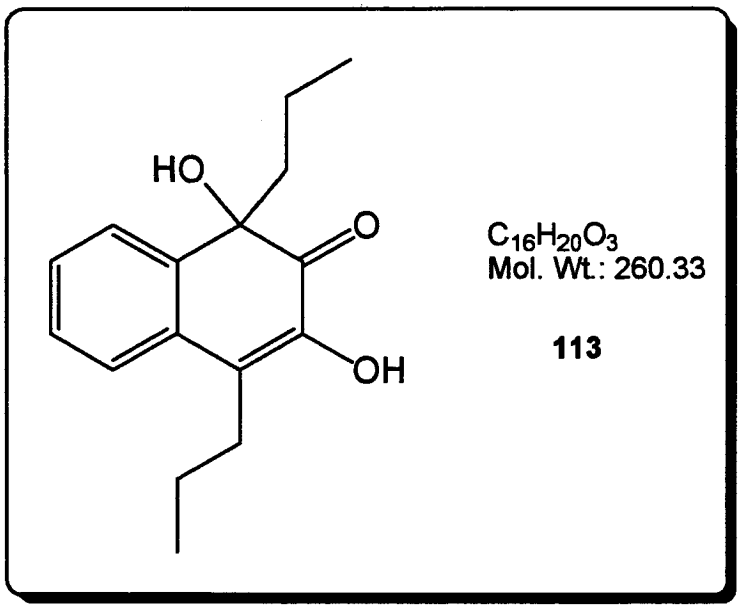


112

MOM deprotection of **111** (0.063g, 0.075 mmol) was accomplished following the same procedure as in the synthesis of diol **36**. The crude product was purified by column chromatography using 8/2 EtOAc in hexanes as eluent, which afforded dimer **112** (0.020g, 0.031 mmol) as a yellowish oily material in 41% yield.

^{1}H NMR (acetone-d_6, 300 MHz): δ = 0.99-1.06 (q, 12H), 1.60-1.74 (m, 8H), 1.78-1.82 (m, 2H), 2.98-3.13 (m, 8H), 3.44-3.46 (m, 4H), 3.71-6.76 (d, 2H, J_{trans} = 15.54 Hz), 7.54-7.56 (d, 2H, J_o = 8.67 Hz), 7.62-7.64 (bt, 2H), 7.73-7.79 (d, 2H, J_{trans} = 15.58 Hz), 7.82-7.85 (d, 2H, J_o = 8.75 Hz), 8.04 (s, 2H), 8.05 (s, 2H), 8.10 (s, 2H)
^{13}C NMR (acetone-d_6, 300 MHz): δ = 15.78, 15.81, 25.14, 25.30, 29.03, 29.08, 32.03, 38.53, 121.24, 121.87, 122.21, 122.49, 126.18, 127.62, 130.39, 131.19, 131.95, 142.87, 145.52, 146.16, 168.20
Mass (ES) *m/z*+1 (%) = 667.4 (M+1, 0.1), 83.1 (24), 59.2 (25), 56.2 (90), 42.3 (100)

1,3-Dihydroxy-1,4-dipropyl-1*H*-naphthalen-2-one:



$C_{16}H_{20}O_3$
Mol. Wt.: 260.33

113

Compound **113** was isolated and characterized after leaving diol **23** in the fridge (about 4°C) for 2 months. The crude product was purified by column chromatography using 5% EtOAc in hexanes as eluent, which afforded pure **113**, representing about 40% of the original **23**.

^{1}H NMR ($CDCl_3$, 500 MHz): δ = 0.73-0.76 (t, 3H), 1.02-1.05 (t, 3H), 1.06-1.25 (m, 2H), 1.57-1.86 (m, 2H), 1.70-1.75 (dt, 1H, J_{gem} = 12.10 Hz, J_α = 4.76 Hz), 1.80-1.86 (dt, 1H, J_{gem} = 13.15 Hz, J_α = 4.93 Hz), 2.71-2.74 (t, 2H), 3.33 (s, 1H), 6.10 (s, 1H), 7.27-7.33 (m, 2H), 7.42-7.43 (m, 1H), 7.57-7.59 (m, 1H)

^{13}C NMR ($CDCl_3$, 500 MHz): δ = 13.93, 14.24, 16.69, 21.57, 27.48, 78.49, 124.59, 125.92, 127.55, 127.99, 129.82, 131.20, 140.20, 142.19, 199.16

Mass (EI): *m/z* (%) = 260.1 (M+, 25), 190.1 (30), 189.1 (93), 87.9 (21), 85.9 (98), 83.9 (100), 71.1 (40), 49.0 (21), 47.0 (52), 43.1 (24)