Synthesis of Non-Steroidal Estrogen Agonists for Hormone Replacement Therapy

and

Synthesis and Reactivity of 2,3-Substituted 5-Silyl-7-Oxa-Bicyclo[2.2.1]Heptenes and Heptadienes

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List of Abbreviations

^{1}H	proton NMR
^{13}C	carbon 13 NMR
AC2O	acetic anhydride
AcOH	acetic acid
aq.	aqueous
COSY	correlation spectroscopy
d	doublet
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DCM	dichloromethane
DIBAL-H	diisobutylaluminium hydride
DIPEA	N,N-diisopropylethylamine
DMAP	dimethyl amino pyridine
dppp	1,3-Bis(diphenylphosphino)propane
eq.	equivalents
EtOAc	ethyl acetate
Et_3N	triethylamine
hr	hours
HRMS	high resolution mass spectrometry
i-PrOH	isopropanol
IR	infrared spectrometry
LAH	lithium aluminum hydride
m	multiplet
MEM	methyl ethyl ether
MEMCl	chloromethyl ethyl ether
MeOH	methanol
MHz	megahertz
min	minutes

mL	milliliters
mmol	millimoles
MOM	methoxymethyl ether
MOMCl	chloromethyl methyl ether
NMR	nuclear magnetic resonance
o.n.	over night
PA	p-Anisaldehyde
PIFA	phenyl iodide(III) bis(trifluoroacetate)
PIDA	phenyliodonium(III) diacetate
ppm	parts per million
PSI	parts per square inch
*p*TSA	*p*-toluene sulfonic acid
q	quadruplet
r.t.	room temperature
s	singlet
t	triplet
TBDMS	*tert*-butyldimethylsilyl
TBDMSCl	*tert*-butyldimethylsilyl chloride
tmeda	*N,N,N',N'*-tetramethylethylenediamine
TFA	trifluoroacetic acid
TLC	thin layer chromatography
Δ	heat

Abstract

The focus of the research described in this section of the thesis is the synthesis of compounds expected to bind strongly to both the estrogen β and α receptors and act as estrogen agonists. Based on earlier results in our group and docking studies we prepared a series of A-CD analogs, compounds **1**, in which the usual 13-methyl group was replaced by an ethyl group. Docking studies also indicated that substituents at C8 could lead to enhancement of binding to the estrogen receptor. With this in mind two such derivatives, compounds 2 were prepared.

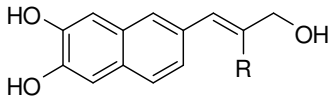
A major concern in the use of estradiol in hormone replacement therapy is its potential metabolism of dangerous ortho-quinones. The 1,2-naphthalenediol derivatives 3 avoid this possibility. They were predicted to be potent binders to the estrogen receptors with the naphthalene diol portion serving as rings A and B and the hydroxyl group taking the place of the 17-OH group of estradiol. The preparation of several derivatives of 2 is reported.

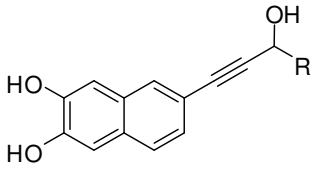
The estrogen receptor binding [ERB] relative to estradiol as standard has been determined at the University of Illinois for a number of the compounds prepared in this thesis. Unfortunately, the results were not as encouraging as expected. Importantly, all of the 13-ethyl derivatives tested showed lower binding affinity compared to the 13-methyl analogs. Similarly, the derivatives with substituents at C8 do not show higher activity than those having only hydrogens at C8. Finally, the situation with the naphthalene derivatives is, at this stage, still not completely resolved. The binding for the compounds thus tested is quite low, but it must be admitted that the structures thus far synthesized have a much lower LogP than estradiol, a factor known to greatly decrease the binding constants to the estrogen receptors.

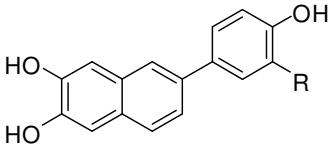
First are the AB-D analogues, which are made to resemble the first two and fourth estradiol rings with 2,3-naphthalenediol as the common scaffold. The second are the A-CD analogues, which contain an *o*-hydroxy-phenyl moiety as a mimic of the first estradiol ring, and a six and

five membered fused ring system as the third and fourth estradiol rings. Within the latter class, two subcategories of compounds were synthesized, one with an ethyl moiety at the C13 position, and a second with a methyl moiety at C13 as well as both methyl and benzyl moieties at the C8 position. Finally, some attempts at synthesizing an A-CD analogue with an aldehyde at the C5 position were made and will be discussed.

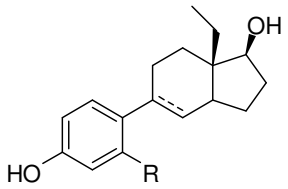
1:







2a:



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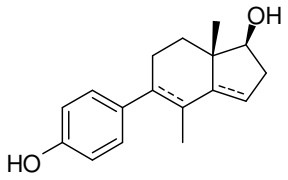
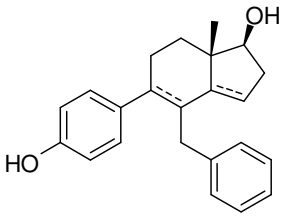




1.0 Introduction

The female lifespan is defined by many physiological changes, which can be attributed to a large extent to the changes in the production of female sex hormones experienced during various stages of development.[1] Estradiol (E2,**1**), also known as 17-β estradiol, is most abundant in non-pregnant females following menarche, estriol (E3, **2**) is the primary estrogen of pregnancy, while estrone (E1, **3**) is produced during menopause (Figure 1.1).[2]

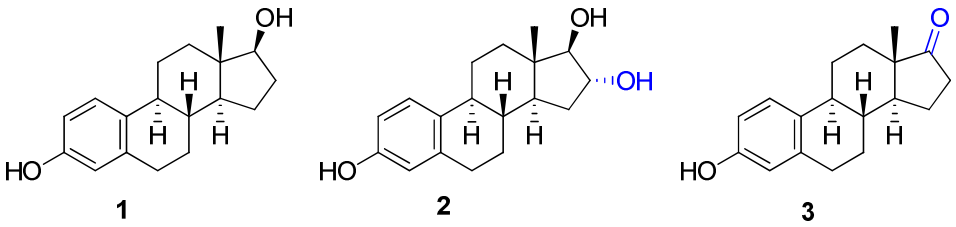


Figure 1.1 Chemical structures of steroid hormones estradiol, estriol and estrone from left to right

The estrogens are a family of steroid hormones comprised of an 18 C scaffold of four fused rings derived from cholesterol. This is referred to as an ABCD-ring system, where ring A is the fused phenol, and ring D is the fused cyclopentane moiety (Figure 1.2).

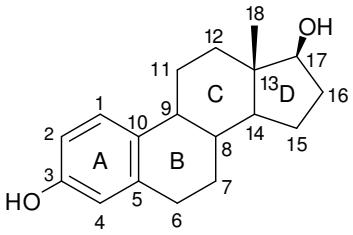


Figure 1.2 Estrogenic ABCD structure and numbering scheme

As a result of longer life expectancy and a typical onset of menopause at 50-55 ears of age, women in developed countries can spend up to a third of their lives in a hypoestrogenic state.[3-4] The changes associated with the fluctuations in estradiol levels characteristic of menopause include hot flashes, insomnia, weight gain, mood changes, breast pain, vaginal dryness and

headaches; these are termed climacteric symptoms.[5] Also associated with the onset of menopause is increased risk of coronary artery disease (CAD), or coronary heart disease (CHD)[6] and osteoporosis.

Relief of climacteric symptoms can be attained by controlling the hormonal fluctuations with the administration of exogenous hormones, or hormone replacement therapy (HRT). This treatment's popularity suffered an instantaneous decline in 2002 following a study published by the Women's Health Initiative (WHI) that labeled HRT users as being at an elevated risk of breast cancer, heart attacks and strokes.[7] These results were supported by the Million Women Study conducted in the UK.[8] The cessation of HRT by many women was not replaced by alternate treatments to control the climacteric symptoms and the development of an effective and virtually side-effect-free alternative has become the focus of ongoing research. This thesis will focus on the synthesis and biological activity of novel estrogen agonists as alternatives to HRT.

1.1 Estrogens in Women: Menarche, Menopause and Cancer

Healthy, reproductively mature women experience regular, coordinated uterine and ovarian cycles that are controlled by uterine and pituitary hormones respectively (Figure 1.3, Developmental Biology 8e Online, 2006).[9]

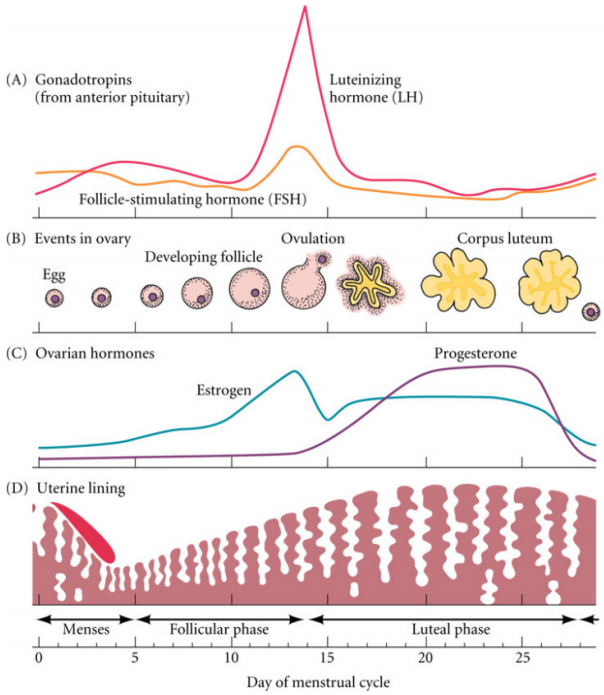


Figure 1.3 Visual representation of (A) gonadotorpic levels, (B) follicle development in the ovary, (C) ovarian hormone levels, and (D) changes in uterine lining during a 28 day menstrual cycle[9]

During the proliferative or follicular phase the pituitary gland releases the gonadotropin follicle stimulating hormone (FSH), which stimulates the growth and cellular proliferation of maturing follicles in the ovaries. This is followed by the release of a second gonadotropin called luteinizing hormone (LH). The combined effect of FSH and LH induces an increase of estrogen secretion by the follicle, promoting uterine endometrial proliferation in preparation for ovulation. Gonadotropin release peaks in the middle of the cycle and within 10-12 hours ovulation occurs and the corpus luteum is formed at the beginning of the luteal phase. The corpus luteum is responsible for the production of small quantities of estrogen and progesterone, which blocks FSH release from the pituitary gland thereby inhibiting the maturation of multiple follicles within one cycle. Progesterone is released until the corpus luteum degenerates and the cycle begin anew with menstruation, also referred to as menses.

1.1.1 Menopause Physiology

At the end of a woman's reproductive cycle the quantity and quality of the follicles necessary for ovulation and the continuation of the menstrual cycle decline until amenorrhea, the permanent cessation of menstruation occurs. In the 5-8 years preceding menopause the follicles' sensitivity to FSH decreases thereby causing increased release of FSH as well as LH, initiating a signaling cascade in the stroma of the ovaries that results in an increase in circulating estrone levels and a decrease in estradiol levels (Figure 1.4, Yen, S. S. C., 1977).[10] Clinically, elevated FSH levels are used to assess the onset of menopause, and a woman is diagnosed as postmenopausal a year after amenorrhea.

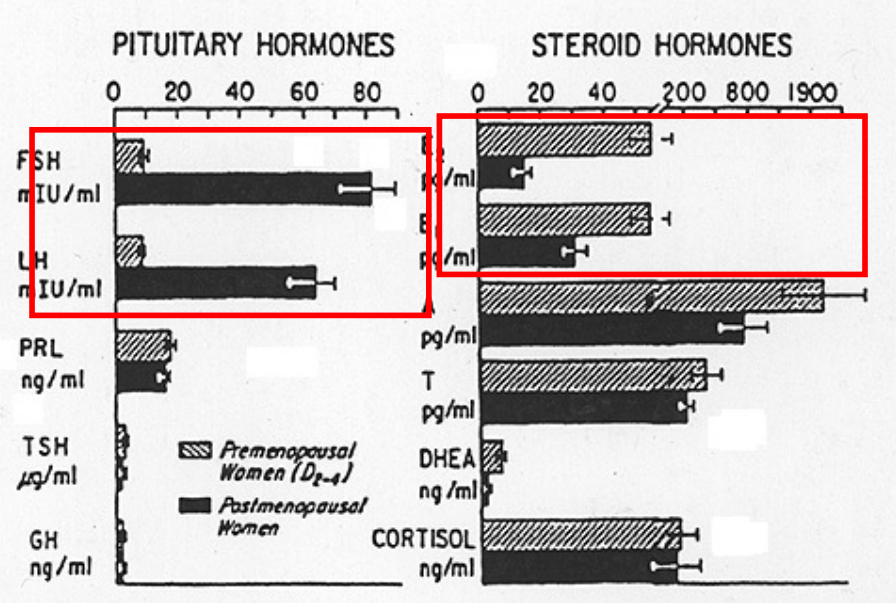


Figure 1.4 Pituitary and steroid hormone levels in postmenopausal women compared with levels in premenopausal women studied during the first week (days 2 to 4) of the menstrual cycle. Most significant are levels of FSH, LH, E_2 and E_1 (also includes levels of prolactin (PRL), thyroid-stimulating hormone (TSH), growth hormone (GH), androstenedione (A), testosterone (T), and dehydroepiandrosterone (DHEA))[10]

Menopause does not only affect the relative concentration of estrogens, it also leads to a shift in the localization of estrogen synthesis. Between the commencement of menstruation, also known as menarche and menopause the majority of circulating estrogens are produced in the ovaries by the granulosa cells where androstenedione is converted to estradiol directly or via a testosterone intermediate (Figure 1.5, Boron, W. F.; Boulpaep, E. L., 2003).[11] In turn, androstenedione is synthesized from cholesterol in the ovarian theca interna cells.

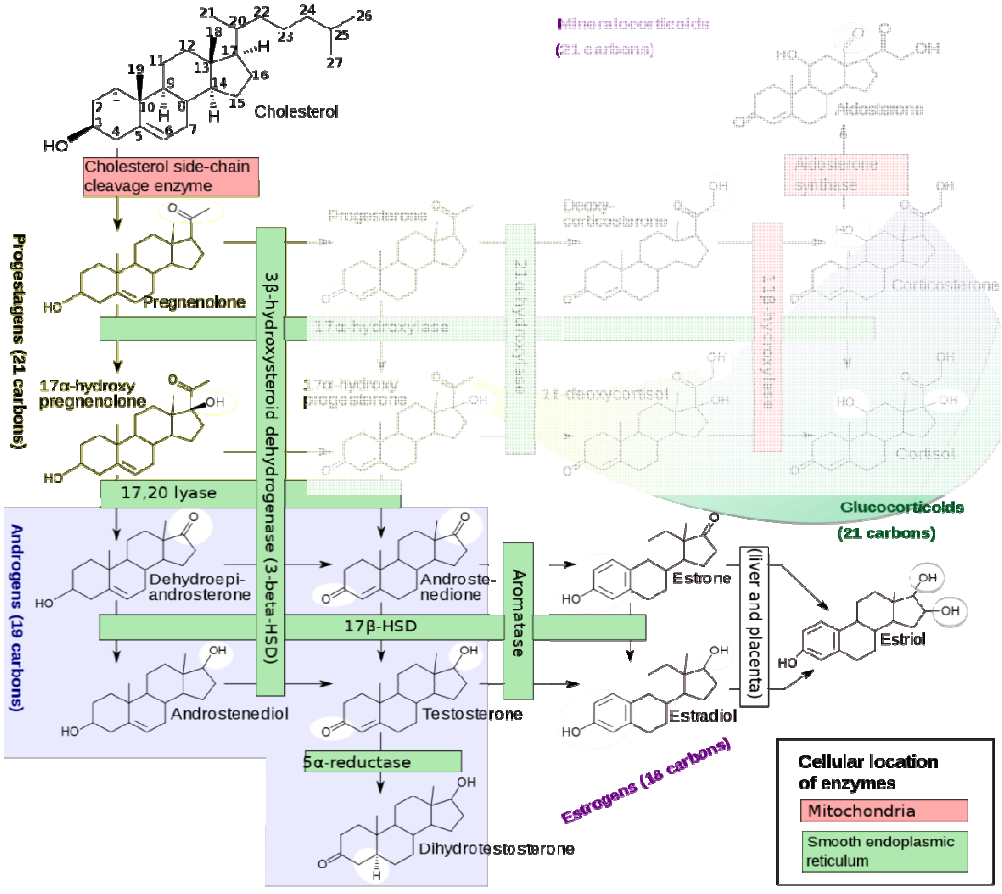


Figure 1.5 Biological pathway to cholesterol-derived steroids[11]

Secondary extragonadal sources of estrogens include the liver, adrenal glands, muscle, bone, bone marrow fibroblasts, adipose tissue and the breasts.[12] These are essential for postmenopausal women, and are responsible for the total production of estrogens after

amenorrhea. Also, the depletion of follicles results in a sharp drop in progesterone levels. Estrogens that are not counterbalanced by progesterone are termed unopposed estrogens and have been shown to cause excessive breast and uterine growth and weight gain.[5]

1.1.2 Hormone Replacement Therapy

Vasomotor and genitourinary symptoms associated with the hormonal changes previously described begin during follicular decline, up to eight years preceding menopause, at which time the woman is termed to be in perimenopause.[13] These symptoms may include hot flashes and night sweats, mood swings, depression,[14] anxiety, vaginal dryness, dyspareunia, and urge incontinence and can continue five to ten years following the onset of menopause.[15] More concerning are the elevated risks of osteoporosis, cardiovascular disease and the effects on the central nervous system. The intensity and duration of these symptoms is significantly higher in perimenopausal women as compared to both pre- and postmenopausal patients.[16]

Perimenopausal women can alleviate these symptoms by regulating the levels of circulating estrogens in the body with oral contraceptive pills (OCP), or HRT.[5] While OCP is a viable option for women in perimenopause who continue irregular ovulation and may still become pregnant, HRT is the standard treatment for women following amenorrhea. This treatment is typically comprised of estrogen with or without progestin and can be administered through various routes including orally, topically as well as locally through the vagina. Progestogens have been linked to the prevention of endometrial hyperplasia and neoplasya, which can lead to endometrial cancer, as well as the prevention of potential uterine bleeding in HRT patients.[15]

Quality of life (QoL) studies indicate that HRT users have an overall higher QoL than nonusers with reduced frequency and intensity of vasomotor symptoms.[17] HRT is also prescribed as a profilactic treatment to reduce the risk of developing chronic conditions such as cardiovascular

disease and osteoporosis.[18] A randomized study by the WHI supports the benefits of HRT on bone density,[7] which is affected by estrogen levels in women. The implications of this result are significant as one in every three women develop osteoporosis and suffer a related fracture with a 20% mortality rate for women suffering hip fractures.[19] This study also supports the use of HRT as prevention for colon cancer.[20]

Alternatively, there are many side-effects associated with this treatment, including mastodynia, or pain of the breasts, bloating and vaginal bleeding. Results of the WHI study disputed the benefits of HRT on CHD prevention in postmenopausal women. Furthermore, study subjects receiving long-term HRT were at a greater risk of stroke, and cholecystitis. In a 2004 study, statistical analysis of peri- and postmenopausal patients of the Groups Health Cooperative (GHC) demonstrated that users of HRT were at a higher risk of venous thrombosis (VT) events including deep VT (DVT) and pulmonary embolism (PT), where 35.8% of the PT cases were fatal. Of the HRT users, women administered oral conjugated equine estrogens **4** and **5** (CEEs) were at a higher risk of suffering VT events than women who used esterified estrogens (EEs) such as **6** (Figure 1.6).[21] These results were in accordance with both the WHI and Heart and Estrogen/Progestin Replacement Study (HERS).[7, 12]

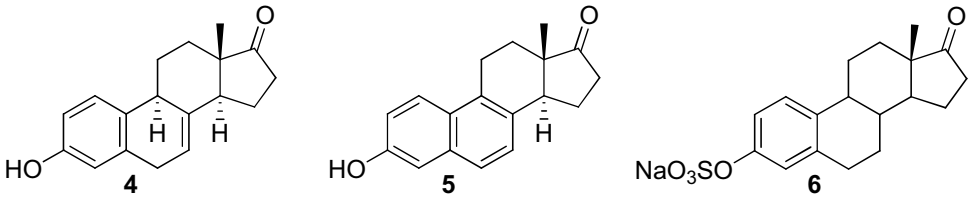


Figure 1.6 From left to right conjugated equine estrogens equilin (**4**) and equilenin (**5**), and esterified estrogen (**6**)

Another notable concern is the potential for elevated risk of breast cancer in long-term users of HRT.[7, 12, 22] Although the direct link between prolonged exposure to exogenous estrogens and

cancer is not well understood[23] statistical evidence from numerous international studies indicates that there are 6-8 additional cases of breast cancer per 1,000 HRT recipients, as compared to non-users.[7, 24] This is significant when considering the large population of peri- and menopausal women who seek treatment for the vasomotor symptoms described above.

1.2 Breast Cancer Pathology, Estrogen and HRT

Hormonal risk factors for breast cancer include early menarche, late menopause, later age of first pregnancy and causes of increased production of peripheral estrogens such as obesity.[25-27] Statistical evidence exists that suggests that exogenous estrogen sources such as OCP, especially before the first pregnancy, and HRT lead to an increase in breast cancer occurrence. Furthermore, these factors have also been linked to development and proliferation of endometrial cancer in the uterus. The common characteristic of these factors is a prolonged period of unopposed estrogen in circulation. To date, two mechanisms for estrogen carcinogenesis have been proposed.

1.2.1 Estrogen Receptor Involvement in Endometrial and Breast Epithelial Proliferation

Estrogen receptors (ERs) were first identified in 1962 by Jensen and Jacobson, who demonstrated that radiolabeled estradiol was only retained by estrogen target tissues such as the uterus, vagina and pituitary gland in female rats.[28] Subsequent investigations showed that ERs are nuclear proteins and members of the steroid and thyroid hormone receptor super family of ligand-responsive transcription factors.[29] Isolation of this protein and elucidation of the estrogen action cascade demonstrated that when the ER binds to circulating estrogen it is shuttled to the nucleus where it dimerizes and binds to estrogen response elements (EREs) in

the promoter region of an estrogen responsive-gene (Figure 1.7, Deroo, B. J. and Korach, K. S., 2006).[30]

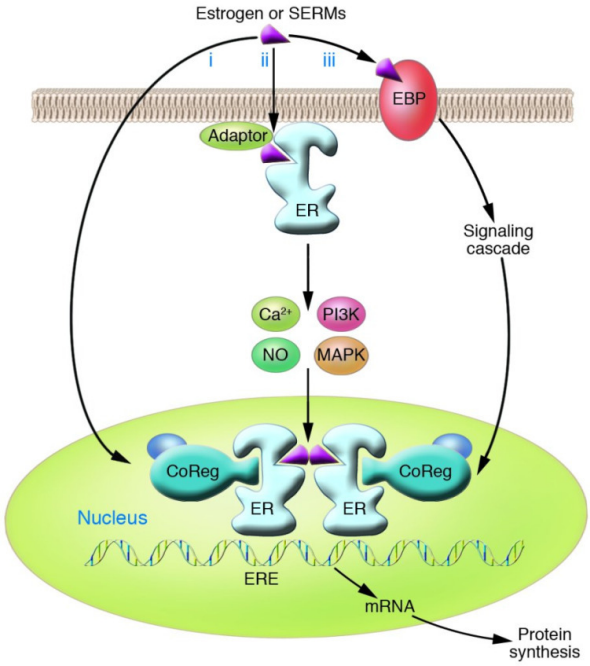


Figure 1.7 Estrogen and SERM activation of ER and biochemical cascade leading to transcription of an estrogen responsive-gene in target cell[30]

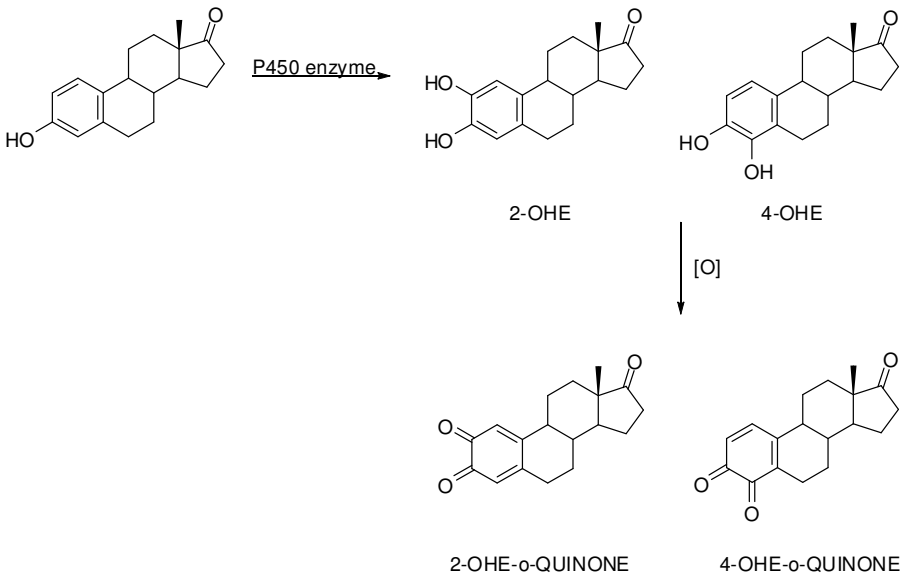
Studies of ER concentration in endometrial tissue show that it is most abbundant during the first two weeks of the menstrual cycle when estrogen is released in large amounts, unopposed by progesterone. The concentration of ER is also highest during the proliferative phase of the cycle, when in the presence of estrogen a proliferative effect is observed in endometrial and breast tissue. It is hypothesized that a marked increase in circulating estradiol leads to increased rates of proliferation and therefore increased risk of mutation and tumorigenesis in the uterus and breast tissues. This is of particular concern to postmenopausal women who no longer menstruate, and therefore cannot eliminate damaged cells in the uterine lining. It is known now that over three quarters of endometrial carcinomas contain ERs and progesterone receptors (PgR).

After locating ERs in estrogen target tissues, Jensen was able to show through a clinical ER assay a mechanistic link between estrogen and the responsiveness of breast cancer: increase in estrogen concentration resulted in increased growth of breast cancer tissue.[31] Jensen also discovered that there are two classes of ERs, ERα and ERβ; both have six functional domains (A through F) and a 58% conservation at the ligand-binding domain and 95% at the DNA-binding domain.[32] ERα contains a ligand-independent activation function AF-1, while ERβ contains a ligand-dependent activation function AF-2. These activation functions can initiate transcription independently or in combination as promoters.[33] Natural estrogens are non-selective for ERα and ERβ, while some synthetic estrogen analogues termed selective ER modulators (SERMs) can differentiate between the two receptors.

In women, ERα is found in endometrium, breast cancer cells, ovarian stroma cells and in the hypothalamus,[34] while ERβ is predominantly found in kidney, brain, bone, heart, lungs, intestinal mucosa and endothelial cells.[35] Some studies also suggest that ERβ may oppose the proliferative action of ERα.[36]

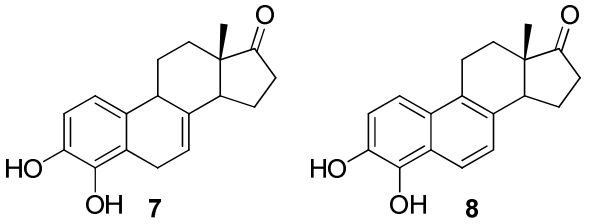
1.2.2 Carcinogenesis by Metabolites of Estrogen

Estrogens are not impervious to enzymatic modification by cellular enzymes and some well documented metabolites of estradiol 17β and estrone should be considered as potential causes of cancers. The major metabolic pathway of estrogens is the oxidation by cytochrome P450 to the 2-hydroxyestrogen (2-OHE) or the 4-hydroxyestrogen (4-OHE) in a 1:1 ratio in human extra hepatic tissues (Scheme 1).[37] These intermediates are termed catechols and can be further oxidized to the respective *ortho*-quinones, 2-OHE-*o*-quinone and 4-OHE-*o*-quinone.



Scheme 1.8 Metabolism of estrone to 2-OHE and 4-OHE and subsequent oxidation to the respective *ortho*-quinones 2-OHE-*o*-quinone and 4-OHE-*o*-quinone

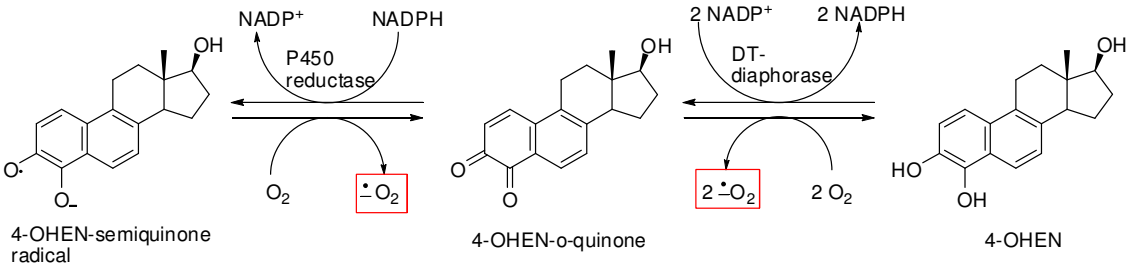
The 4-OHE appear to be significantly more carcinogenic than 2-OHE; higher levels of 4-OHE have been found in cancerous breast tissue than in healthy breast tissue.[38] Furthermore, common HRT hormones equilin and equilenin (ingredients in Premarin) are metabolized primarily to 4-hydroxyequilin, **7**, (4-OHEQ) and 4-hydroxyequilenin, **8**, (4-OHEN).[39]



Catechols of estrone and estradiol can be further oxidized by any of a large family of oxidizing enzymes to the respective *ortho*-quinones, whereas 4-OHEN can undergo spontaneous oxidation without enzymatic intervention and generate reactive oxygen species (ROS) including superoxide anion radicals ($O_2^{\cdot -}$), hydrogen peroxide and free hydroxyl radicals.

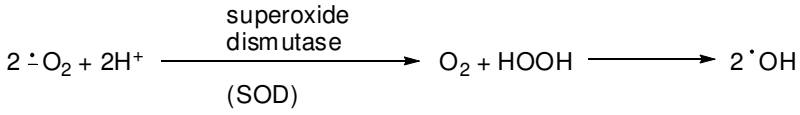
There is also a marked difference between the half lives of the quinones, where 2-OHE-*o*-quinone is much less persistent than 4-OHE-*o*-quinone with $t_{1/2}$ equal to 47 seconds and 12 minutes respectively.[40] 4-OHEQ-*o*-quinone isomerizes to 4-OHEN-*o*-quinone, which is much more stable than the equilin quinone and than the endogenous quinone estrogens with a half life of 2.3 hours.[41]

The spontaneous transformation between 4-OHEN and its quinone can be reversed in the presence of DT-diaphorase enzyme and two molar equivalents of NADPH. In addition, 4-OHEN-*o*-quinone can undergo a conversion to a 4-OHEN-semiquinone radical in the presence of P450 reductase and one molar equivalent of NADPH; this intermediate self-oxidizes back to the quinone while generating the superoxide anion radical through a process called redox cycling (Scheme 1).[42]



Scheme 1. Formation of the superoxide anion radical, $O_2^{\bullet -}$ through redox cycling between 4-OHEN, 4-OHEN-*o*-quinone and 4-OHEN-semiquinone radical

Superoxide anion radicals can be converted by superoxide dismutase in an acidic environment to molecular oxygen and peroxide, which in turn decomposes to two free hydroxyl radicals (Scheme 2). These ROS have been shown to cause oxidation of DNA bases and oxidative cleavage of phosphate-sugar bond to for 8-oxo-deoxyguanosine (8-oxo-dG) (Figure 1.9), a known biomarker for oxidative damage to DNA and an important factor in carcinogenesis.[43-45]



Scheme 2. Formation of free hydroxyl radicals from superoxide

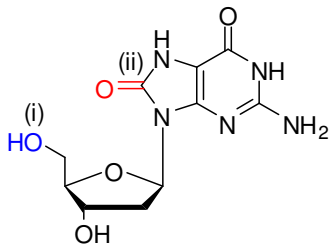


Figure 1.9 8-oxo-deoxyguanisine, formed by (i) oxidative cleavage of the phosphate-oxygen bond and the (ii) oxidation of the guanosine base

Endogenous quinone estrogens are Michael acceptors that can readily react with DNA bases, more specifically with purines adenine (A) and guanine (G). Although the mechanism is not known, it has been suggested that the bases react with the semiquinone radical intermediates rather than the *o*-quinones.[42] Additions onto the 4-OHE-*o*-quinones occur at C^1 either by N^3 of A or N^7 of G. The resulting adducts are unstable and undergo instantaneous cleavage of the deoxyribose-base bond, thereby loosing the ribose moiety and disrupting the DNA helix. These adducts are termed depurinating and are presumed to initiate the carcinogenic process (Figure 1.10).[46] Of the two possible products of 4-OHE-*o*-quinone, the guanine adduct is the most unstable and therefore the most likely to initiate mutagenesis.

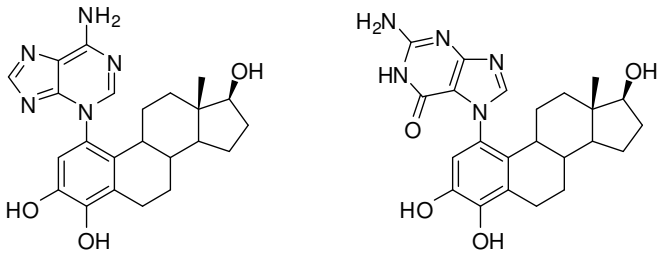


Figure 1.10 Depurinating 4-OHE adducts 4-OHE-N^3-A and 4-OHE-N^7-G from left to right

2-OHE-*o*-quinones on the other hand form stable adducts between the quinone's C^6 and N^6 of A and N^2 of G, called 2-OHEN-N^6-A and 2-OHEN-N^2-G respectively (Figure 1.11).[42] Because of the stability of these adducts they are presumed to be benign, and are not associated with carcinogenesis.

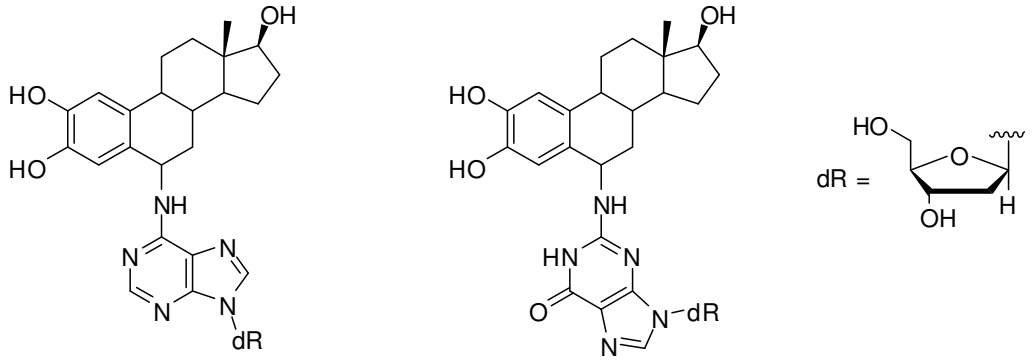


Figure 1.11 Stable 2-OHE adducts 2-OHEN-N^6-A and 2-OHEN-N^2-G from left to right

Similarly, 4-OHEN-*o*-quinone can also react with DNA bases to form stable cyclic adducts, which have been found in breast cancer cells.[47] Unlike endogenous quinone estrogens, it can also react with cytosine, C (Figure 1.12). Each base can form four stereoisomeric adducts with 4-OHEN-*o*-quinone.

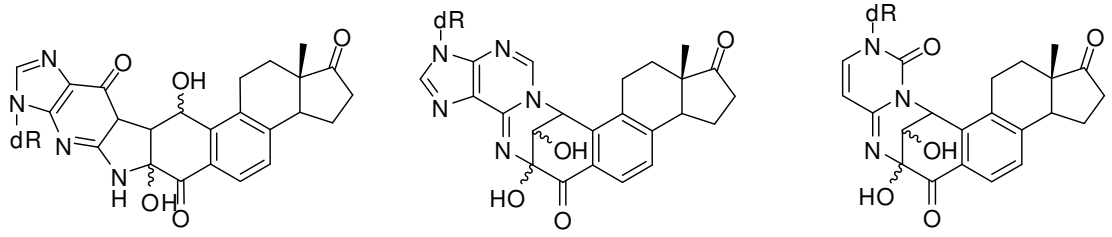


Figure 1.12 Cyclic adducts of 4-OHEN with guanine (G), adenine (A) and cytosine (C) 4-OHEN-G, 4-OHEN-A, 4-OHEN-C respectively from left to right

1.3 Synthetic HRT Drugs

In light of the risks of HRT, considerable effort has been focused on attaining a synthetic estrogen analogue with minimal side effects that will alleviate climacteric symptoms. Currently there are several HRT alternatives on the market; some of the most successful are raloxifene, tibolone and genistein (Figure 1.13).

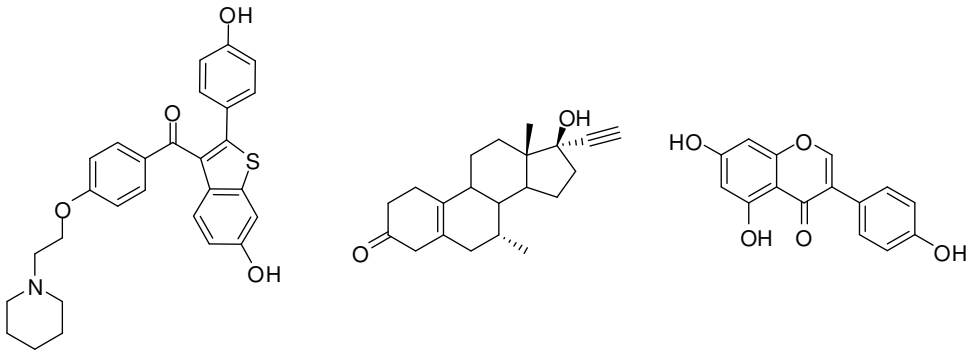


Figure 1.13 Synthetic estrogen analogues: raloxifene, tibolone and genistein from left to right

1.3.1 Raloxifene

Raloxifene is an oral SERM prescribed for the prevention and treatment of osteoporosis in post-menopausal women and has been suggested as a prophylactic in women with an elevated risk of developing invasive breast cancer. This drug's selectivity allows it to act as an agonist in bones, where it stimulates osteoblasts to increase bone deposition by the same route as endogenous estrogens are known to do. Alternatively, raloxifene does not exhibit estrogen agonist effects in breast and uterine tissues, therefore reducing the risk of occurrence of cancers in these organs as compared to traditional HRT.[48]

The drug however is not a reliable treatment for climacteric symptoms and common side effects of treatment with raloxifene include the continuation of hot flashes, leg cramps, and VT and PE. A randomized study entitled Raloxifene Use for The Heart (RUTH) was launched to investigate its

potentially beneficial effects on the reduction of CHD in postmenopausal women. Although the study showed no change in the risk of developing CHD, a statistically significant increase in mortality do to stroke in patients receiving the drug was observed compared to the rate in patients receiving a placebo.[49] These potentially adverse effects make raloxifene an unsuitable treatment for women at risk of strokes and VT events.

1.3.2 Tibolone

Tibolone is a synthetic steroid hormone with estrogenic, progestogenic and androgenic properties, and has no binding selectivity and its affinity for all type I steroid receptors.[50] It is administered orally and has a high absorption rate; in circulation it is metabolized to afford biologically active metabolites 3α-hydroxytibolone (3α-OH-tibolone) and 3β-OH-tibolone.

Similarly to raloxifene, it is used to treat osteoporosis in postmenopausal women, but unlike the SERM, tibolone also provides relief from the vasomotor and genitourinary symptoms of menopause. The Long-term Intervention on Fractures with Tibolone (LIFT) study shows a statistically significant decrease in vertebral fractures in women treated with tibolone, however the study was terminated after 34 months due to an increase in the occurrence of strokes. This study also suggests that other side effects comparable to those of raloxifene were common among women who were administered the steroid hormone drug.[51]

1.3.3 Genistein

Genistein is an isoflavone compound from the flavonoid family of phytochemicals and is naturally occurring in soybeans and in small quantities in chickpeas and other legumes. This compound is also a phytoestrogen, meaning that it has estrogen agonist properties.[52] A few short term trials have been conducted to evaluate genistein's efficacy as treatment for postmenopausal women. These studies show that ongoing administration of this phytoestrogen

diminishes vasomotor symptoms such as hot flashes without visible negative effects on endometrial tissue and vaginal epithelium.[53]

Results and Discussion

The focus of this project was to synthesize non-steroidal estrogen agonists with a higher affinity to ERβ than ERα and reluctance to form *o*-quinones. The work presented in this thesis will be comprised of three sections describing the design and synthesis of A-CD analogues with modifications at C8 and C13, non-steroidal AB-D analogues containing 2,3-naphthalenediol, and attempts towards the synthesis of compounds having carbonyl substituents at C5 in the A ring of the A-CD steroids. The findings reported in this section include contributions from honours students Ana Gargaun and Lina Chan, and co-op student Sarah Mavula.

2.0 Part A: Modification of Steroid Skeleton

2.1 Previous Efforts Towards ERβ Selective Estrogen Analogues Based on the A-CD Steroids

In recent years the Durst research group at the University of Ottawa has collaborated with the Wright group from Carleton University to design novel non-steroidal SERMs with the aid of computer models. The group's research focus lies in the design and synthesis of estrogen analogs that retain the hormone's essential structure, and therefore maintaining estradiol's proportions and pharmacophores while adding flexibility. Another potential advantage of synthesizing analogues with a close structural relationship to the endogenous estrogen is similarity in bioavailability.

To achieve these aims the 17β-estradiol structure was deconstructed, and with the help of computational analysis it was determined that the removal of the B-ring would give the analogue improved access to the ER active site while retaining the essential functionalities (Figure 2.1).

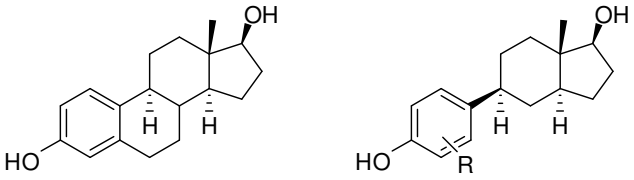


Figure 2.1 17β-estradiol structure compared to the proposed A-CD analogue from left to right

In consideration of the structural resemblance between the proposed analogues and the endogenous estrogen, the numbering system has been retained.

2.1.1 Computational Studies of A-CD Analogues

In order to model the compounds' interactions with the active site of the desired ER the X-ray crystal structure of the protein was found in the protein databank (PDB) and a gradual energy minimization was performed using PDB-Thaw. The docking software uDock is used to insert and minimize the energy of a random conformation of each analogue.[54] The values used to represent the theoretical binding energy of the analogue are those of the ligand-binding site complex with the lowest energy. The free energy required to move the ligand from aqueous blood into the hydrophobic active site of the receptor, termed the de-solvation energy, is also taken into consideration. It is unfavorable to increase this energy, which is typically caused by adding polar groups on the estradiol scaffold.

IF-E 6.0 software was used to evaluate the binding affinity of the analogue to seven residue groups deemed important for binding with estradiol's pharmacophores. The most important groups are HB12, comprised of a Glu353, Arg395 and water triad that forms two hydrogen bonds with the A-ring's hydroxyl group. HB3 represents His524, which makes a third hydrogen bond with the 17β-hydroxyl group. The groups named A, B, C and D interact with estradiol's A, B, C and D rings respectively, and the ME group with the 13β-methyl group. After calculating the relative interaction energies between the ligand and these seven groups the values are

subtracted from those derived through the modeling of the estradiol for comparison. Positive values indicate a decrease in affinity for the active site and negative represent improved binding.

Each ligand is modeled in the ERα and ERβ binding sites to compare and predict selectivity. Two marked difference between the ER active sites can be targeted to design a highly selective analogue: ERβ contains a Met336, which is replaced for Leu384 in ERα, and Ile373 in ERβ for Met421 ERα (Figure 2.2).[55] There is potential for unfavorable steric interactions between the D-ring of an analogue with increased flexibility and the Met421 residue of ERα, further supporting the assumption that the analogues in this series would be ERβ selective.

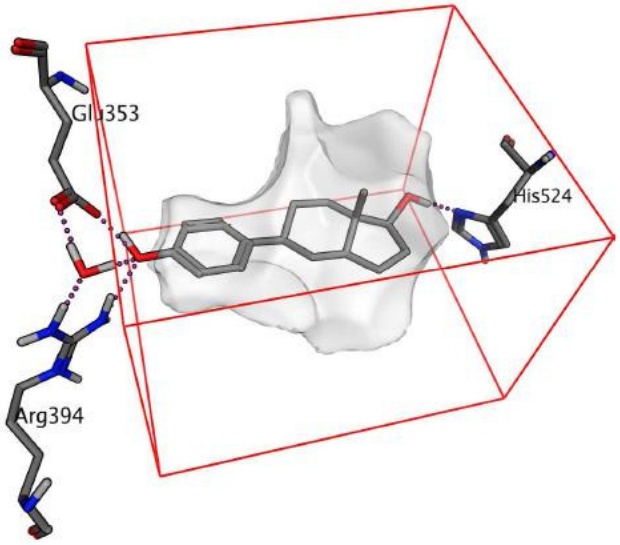


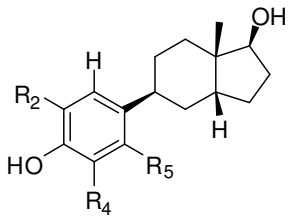
Figure 2.2 Overlay of parent A-CD-ring in active site of ERα (residues in beige) and ERβ (residues in green)

2.1.2 SAR of A-CD Analogues

The Durst lab has synthesized a number of derivatives of the A-CD strucure. SAR was conducted for substitutions on the A-ring, while maintaining a close structural relationship in the synthetic CD-rings with the corresponding rings in estradiol. This includes maintaining the absolute (S) stereochemistry at all chiral centers. Bio-assays were conducted on compounds with inverted (R) stereochemistry at C9 and showed binding to the estrogen receptors that was more than 100 times less than those of the parent A-CD compound with the natural stereochemistry, and were not pursued further. Despite the group's aim to retain the natural stereocenters in the analogues, the synthetic route chosen to attain the saturated CD-ring system resulted in the (*R*) stereochemistry at C14 instead of the natural (*S*) stereochemistry. This misassignment was corrected after a significant number of analogues had been synthesized and tested. This misassignment does not affect the compounds described in this thesis however the results of bioassays of the (*R*) C14 compounds will be presented for comparative purposes.

The results of the relative binding assays (RBAs) and relative transcription activities (RTAs) for some important analogues are summarized in Table 1.1 (the methods and implications of these techniques are further explained in Section 1.6).[55]

Table 2.1 SAR of A-ring substituents of parent A-CD compound



Compound	Ring A			RBA[a] (estradiol=100)			RTA[b] (estradiol=100)	
	R_2	R_4	R_5	ERα	ERβ	β/α	ERα	ERβ
A	H	H	H	1.5	21.5	14	4.3	164
B	H	F	H	1.0	8.7	8.7	-8.3	14
C	H	H	CH_3	2.8	33.6	12	-9.7	149
D	H	H	F	27	135	5.0	44	146
E	H	H	Cl	49	168	3.4	-	-
F	H	F	F	4.6	43	9.3	-	-
G	F	H	F	0.38	3.3	8.7	-	-
H	F	F	F	0.19	1.73	9.1	-	-
I	F	F	H	0.04	0.28	7.0	-	-
J	Cl	Cl	H	0.004	0.002	0.5	-	-
K	H	H	CF_3	90	205	2.3	-	-

[a] The relative binding affinity (RBA) assays were carried out by the Katzenellenbogen group at the University of Illinois. Relative binding was measured as the competition for binding between ^{3}H-labeled estradiol and increasing concentrations of the analogue. RBA was quantified as a measure of displacement in radioactivity of estradiol where the value for estradiol is set to 100 % for both receptors.

[b] The relative transcription activation (RTA) assays were carried out by the Pratt group at the University of Ottawa. COS-7 cells were transfected with plasmids containing sequences for the ERE-luciferase reporter and either ERα or ERβ. The RTA of the ligand at concentration 10 nM was compared to the one of estradiol at that concentration for each receptor.

These analogues were tested against the parent compound A-CD compound (entry a). Substitution of F at C4 (entry b), which could block the formation of malignant 4-OHE-*o*-quinone type metabolites gave decreased binding RBA and lower β/α selectivity. This is in accordance with the recptor models which indicate that substituents at the 2 and 4 positions are not well

tolerated. In agreement with this, the binding for the 2,4-difluoro cmpound, entry i, is almost 100 times lower than that of the parent compound, entry a. Replacement of the flourine atoms with the larger chlorine (entryj) resulted in an even greater decrease in the binding constants. In contrast, the addition of F at C5 (entry d) showed increased binding relative to the parent compound such that ERβ was now 135, that is greater than the ERβ for estradiol. This increase in binding constants was accompanied by a decreased selectivity compared to entry b and entry i. Substitution at this position with Cl (entry e) gave even higher RBAs but with a greater loss in selectivity, while a methyl group (entry c) showed lower RBA but significantly improved selectivity.

Furthermore, RTA data shows that entry d is a strong ERβ agonist with some ERα activity, while entry c is a mild ERα agonist. This is relevant information, which has led the group to believe that the synthesis of pure ERβ agonists is possible using this scaffold.

The results of these SAR studies in combination with computational analyses show that substitutions at C2 and C4 are sterically unfavorable and prevent the ligand from entering the tight region normally occupied by the A-ring, thus decreasing the relative binding of the molecule. The addition of electron withdrawing substituents at C5 increases the relative binding of the compound. These groups also impede the formation of 4-OH-*o*-quinone metabolites of the analogue by deactivating the ortho and para positions. Based on these results and observations, it was proposed that the A-CD compound with a C5 CF_3 substituent would bind even more strongly, but likely with low selcetivity. Indeed, this proved to be the case with RBAα =90 and RBAβ = 205.

2.1.3 Proposed Structures of New A-CD Analogues

A well documented characteristic of the ER active site is an enlargement of the pocket in the region containing the C and D rings. Computational analyses of the active site show that when

bound to endogenous estrogen there remain unoccupied hydrophobic pockets. This is unfavourable, and decreases binding of the ligand to the targe active site. The addition of non-polar moieties on the C and D rings could potentially lower the de-solvation energy thereby increasing the relative binding affinity of the analogue.

A potentially favorable modification can be made at C8, where the CH_2CH_2 segment of the B-ring was removed. This additional moiety could reduce binding to ERα due to unfavorable steric interactions with ERα's Met-421, thereby increasing these analogues' relative selectivity to ERβ. Computational studies were done using molecules with 8β-OH (Figure 2.3), F, Cl, Br, I and Me. The best binding affinity was afforded by the 8β-OH, however, due to its polar nature there would be an increase in de-solvation energy that is unfavorable.

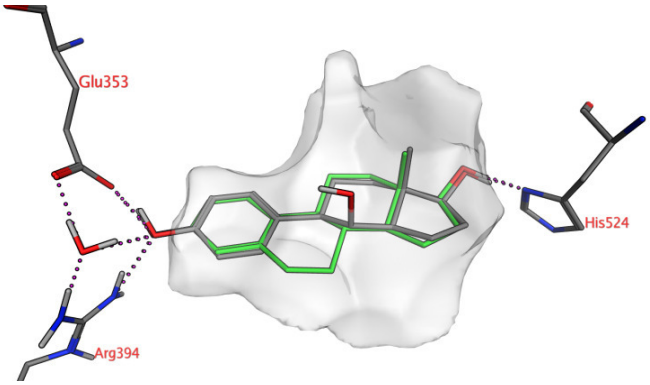


Figure 2.3 β8-OH, 13-Me A-CD analogue (grey) and estradiol (green) docked into ERα active site

According to the modeling study, Cl, Br, and Me all give increased binding in the active site, however an analogue with C8 F shows a lower binding affinity for ER than estradiol. Furthermore, it has been predicted that an analogue with a large group at C8, especially one containing a terminal tertiary amine, would act as an ER antagonist.

Possibly the easiest modification is the synthesis of a CD ring component with a 13β-ethyl rather than estradiol's 13β-methyl in order to attain improved interaction with the ME group of the

active site. When the parent A-CD-ring is modeled containing 13β-ethyl, the hydrogen bonding interactions with the HB12 residues are improved and the energy reduced by 1.9 kcal/mol. This can be attributed to a slight shift of the entire ligand in order to allow the ethyl group to enter the active site without pushing onto the surface of the pocket's wall (Figure 2.4). The ethyl group also lowers the de-solvation energy of the ligand, which is generally an indication of improved binding.

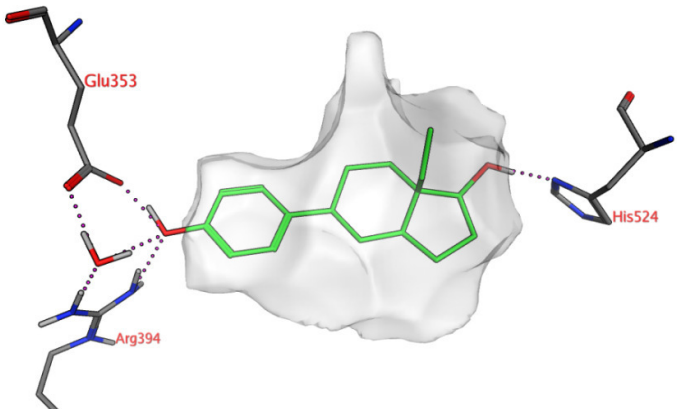
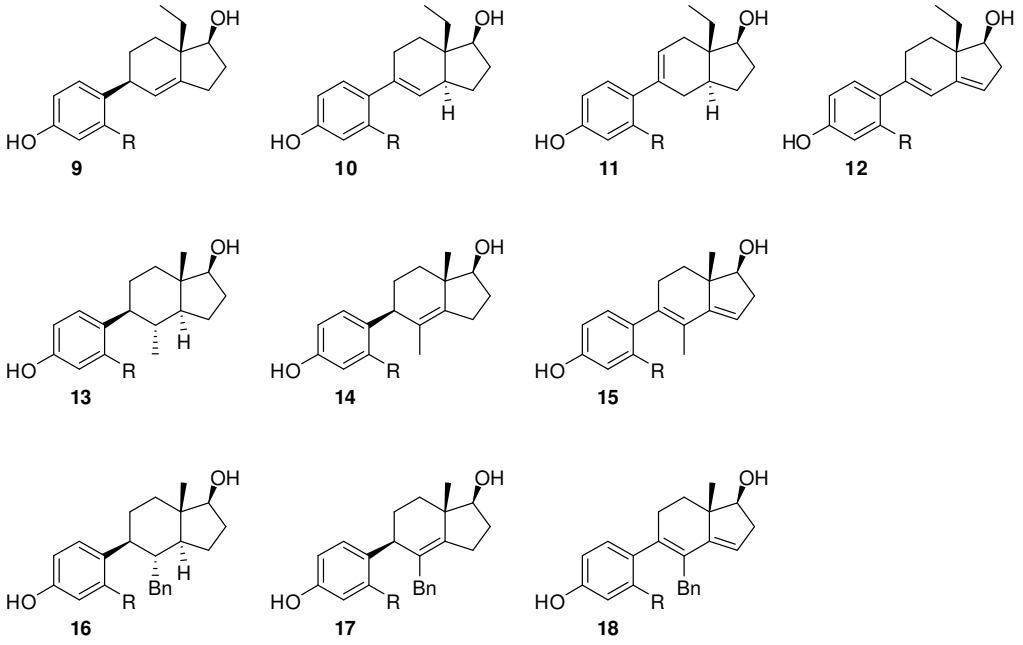


Figure 2.4 Model of parent A-CD analogue with 13β-ethyl as bound to ERα

Based on these computational studies, and in combination with SAR the compounds shown below have been proposed as potential new candidates.



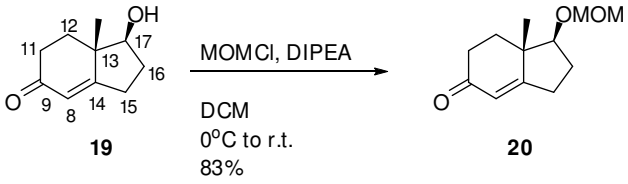
2.2 A-CD Analogues with Modifications at the C8 Position

The efforts made by the Durst group in the development of new estrogen agonists focused on the synthesis of the CD-rings of the endogenous estrogen for coupling with A-ring moieties. This bicyclic structure can be synthesized using the Hajos-Parrish reaction sequence.[56] The starting material used in the reactions described in this section was made by Dr. Asim on a large scale.

So far, most analogues of the A-CD class have had little modifications on the CD moiety ranging from single to multiple unsaturations. Computational analyses of modeled analogues suggest that modifying the CD-rings may lead to a noticeable improvement in ERβ selectivity while retaining moderate to high activity. The first modification that was proposed is the addition of a hydrophobic group at position C8 that could access a hydrophobic pocket in the active site of ERβ exclusively. Interestingly, the addition of a group that is too bulky, such as a benzyl group, could result in the analogue becoming an antagonist rather than an agonist.

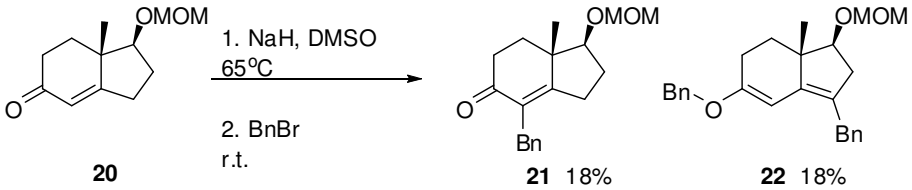
2.2.1 Synthesis of Unsaturated, 8-Methyl and 8-Benzyl CD-rings

Since the synthesis of the CD-rings is well established, the most cost and time effective method to attain the desired analogues **13**-**18** is through the modification of the C8 position of the protected, uncoupled, unsaturated ring; MOM ethers were chosen as protecting groups for this transformation. The unsaturated CD-ring **19** was diluted with dry DCM and MOMCl and DIPEA were added at 0°C, warmed to room temperature and stirred overnight. After column chromatography the MOM-protected CD-ring **20** was recovered in 83% yield. The numbering of the carbons in the CD compounds reflects their position in the steroid. This numbering is used to allow the reader to follow more easily the structure of the final A-CD product.



19 **20**

The first substrate to be synthesized using the method described above was the benzylated CD-ring. Sugimura and Paquette reported a similar alkylation using DMSO deprotonated by NaH as the base;[57] these conditions were reproduced using **20** as the starting material. DMSO was heated to 65°C for one hour in the presence of NaH before adding **20.** The mixture was stirred for one hour at room temperature prior to the addition of benzyl bromide and then stirred overnight.



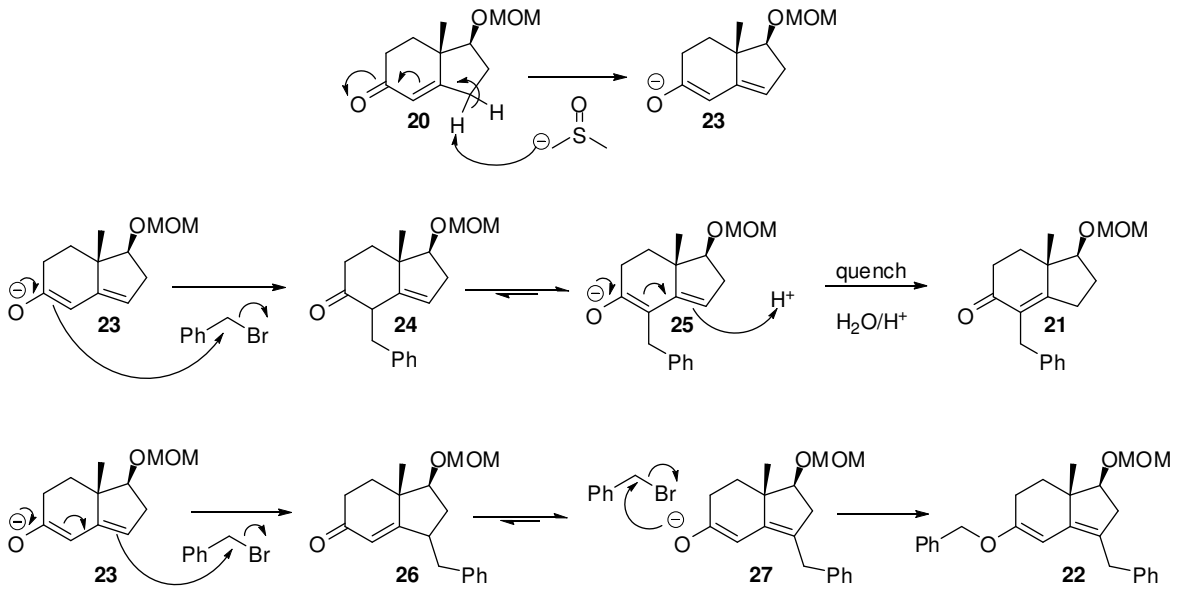
20 **21** 18% **22** 18%

The desired product (1S,7aS)-4-benzyl-1-(methoxymethoxy)-7a-methyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (**21**) was obtained in 18% yield. The characterization by ^{1}H NMR of this compound was easy due to the disappearange of the C8 proton, the addition of one benzyl group and little other changes in the rest of the molecule. A second product was also isolated in

18% yield; ^{1}H NMR showed that a C8 allyl proton was still present at 5.47 ppm, but was upfield in comparison to the the starting material's C8 allyl proton at 5.78 ppm.

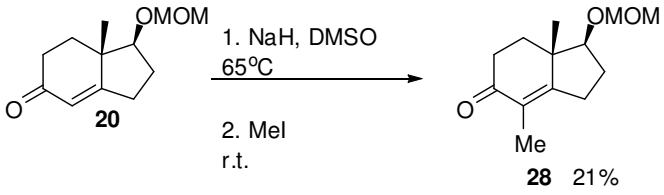
The introduction of two benzyl groups was clearly visible by peaks at 3.55 ppm and 2.81 ppm due to the O and C benzylation, respectively. The first alkylation occurred at C15, with a second benzyl group trapping at the enolate oxygen to give (**22**). Some starting material (**20**) was also re-isolated.

These results were somewhat disappointing based on literature reports of much cleaner alkyations using a similar procedure.[58] They are however not surprising when considering the mechanism of this reaction (Scheme 3). The conjugated enolate **23**, formed *in situ,* can react via two pathways to afford alkylation at both C8 (**24**) and C15 (**26**). In the presence of excess base both these intermediates can revert back to the respective conjugated enolates, which may be quenched and revert back to the conjugated carbonyl form, or the oxygen may attack excess benzyl bromide effectively trapping the enolate. It is important to note that although Scheme 3 only shows the formation of **21** and **22** all enolates (**23**, **25** and **27**) can be trapped by benzylation of the hydroxyl moiety. It is likely that the poor isolated yield is due to the formation of additional side products that could not be purified and successfully characterized.



Scheme 3. Mechanism for the transformation of **20** to **21** and **22** through enolate **23**

The methylated CD-ring was synthesized using the same procedure as described above. Compound **20** was treated with the deprotonated DMSO species and reacted with MeI at room temperature to afford the desired methylation product (**28**) in 21% yield. By ^{1}H NMR analysis, not only was the allylic C8-H gone, but also a second methyl group at 1.58 ppm was present, which is consistant with the chemical shift of a vinyl methyl group. Furthermore, the NMR of **28** was consistant with that attained by Ana Gargaun in her thesis,[59] also confirming that the desired product was isolated.



A small quantity of side product was also recovered as a mixture with some desired product. Based on the comparison of ^{1}H spectra, it appears that this compound is the reduced CD-ring, possibly due to contamination of the enone **20** with the saturated compound.

2.2.2 Attempted Alkylation of Saturated Ketone 32

Attempts at synthesizing the C8-benzyl CD ring ketones (**33**) were made honours student Ana Gargaun. Such compounds are of particular interest given that computational studies show that if A-CD analogues with equatorial C8 substituents (such as **30**) should give the highest ERβ selectivity of this class of compounds. It was also proposed that the axially substituted C8 analogues (such as **29**) should act as ER antagonists (Figure 2.5).

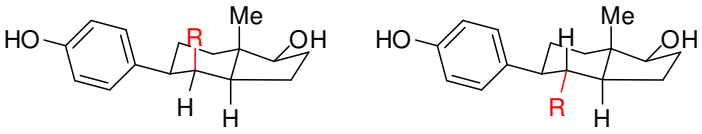
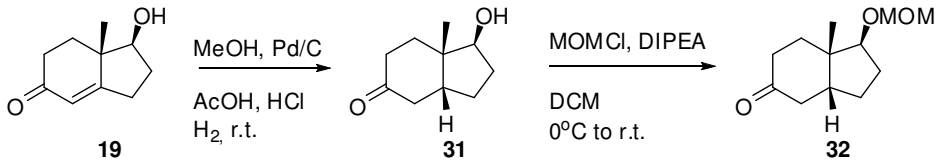
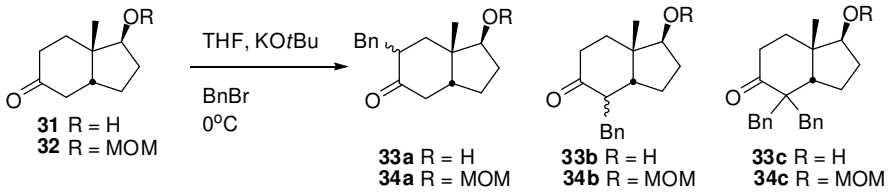


Figure 2.5 Axial (**29**) and equatorial (**30**) C8 alkylated analogues

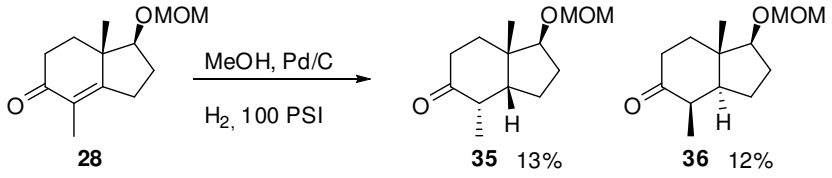
Similarly to the unsaturated CD-rings, direct alkylation of saturated CD-rings was attempted. The CD-ring enone was reduced[56] and the free hydroxyl group was protected with a MOM group using the standard protection conditions to afford **32**. It is important to note that this reaction was carried out based on the assumption that the double bond would only be reduced from the opposite face to the C13-Me resulting in a *trans* conformation. However, X-ray crystallography experiments showed that the reduction gave mainly the *cis* product.



Both the OH unprotected ketone **31** and the MOM protected ketone **32** were subjected to alkylation conditions in basic medium. In the absence of the double bond, which directed the formation of the conjugated enolate, two possible enolates were formed. As anticipated, the NMR and TLC of the crude reaction products showed a mixture of products suggesting alkylation at C8 (**33b** and **34b**), C11 (**33a** and **34a**), and bisalkylation, probably (**33c** and **34c**). We had hoped that the products might be separable via silica gel flash chromatography but despite repeated attempts this was not successful; therefore this route was not pursued further.



An alternate pathway to these compounds is via the reduction of alkylated, unsaturated CD-rings described in *Section 2.2.1*. The first attempt to reduce **28** was carried out by Ana Gargaun using Pd/C under H_2 atmosphere at 100 PSI. The reduction was successful, however the separation of the two resulting stereoisomers (**35** and **36**) was challenging and only a small fraction of the two products could be separated. The remainder of the product was obtained as a mixture of the two stereoisomers.



By ^{1}H NMR, the C8-methyl singlet at 1.58 ppm disappeared and was replaced by a doublet at 1.12 ppm, integrating for 3H, and a second doublet at 0.94 ppm (Figure 2.7 and Figure 2.8). This data indicated that the hydrogenation was successful and a tentative structural assignment was made on the assumption that axial hydorgens or hydrogens on axial substituents on 6-membered rings and typically further upfield relative to the equatorial isomers.

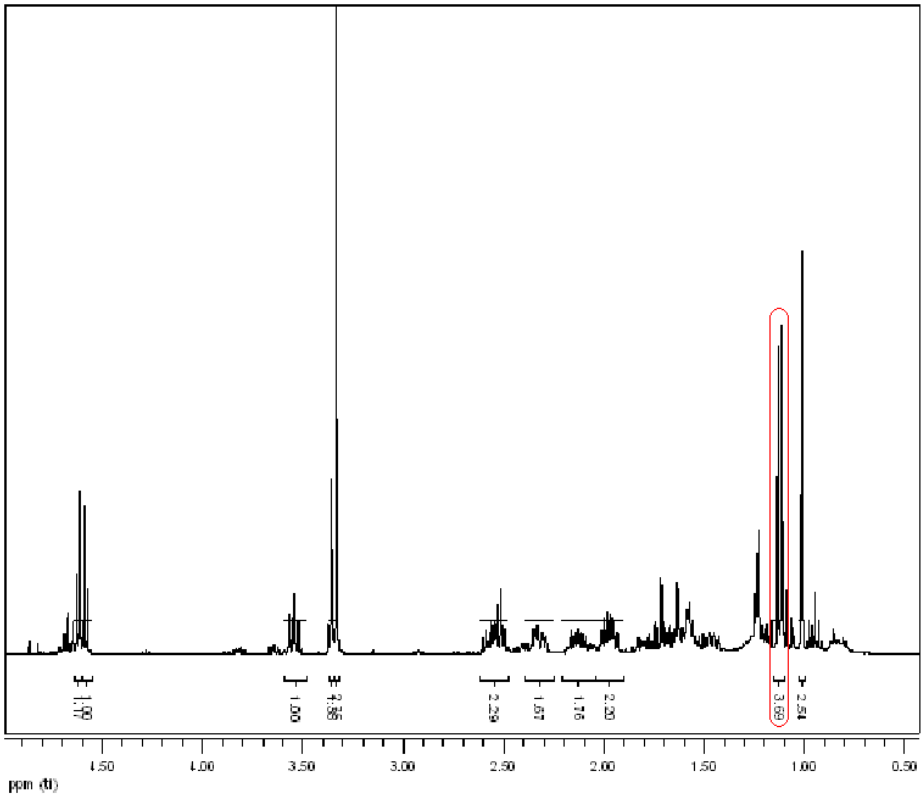


Figure 2.6 ^{1}H NMR spectrum of the first isolated isomer (**a**) with a doublet at 1.12 ppm integrating for 3H

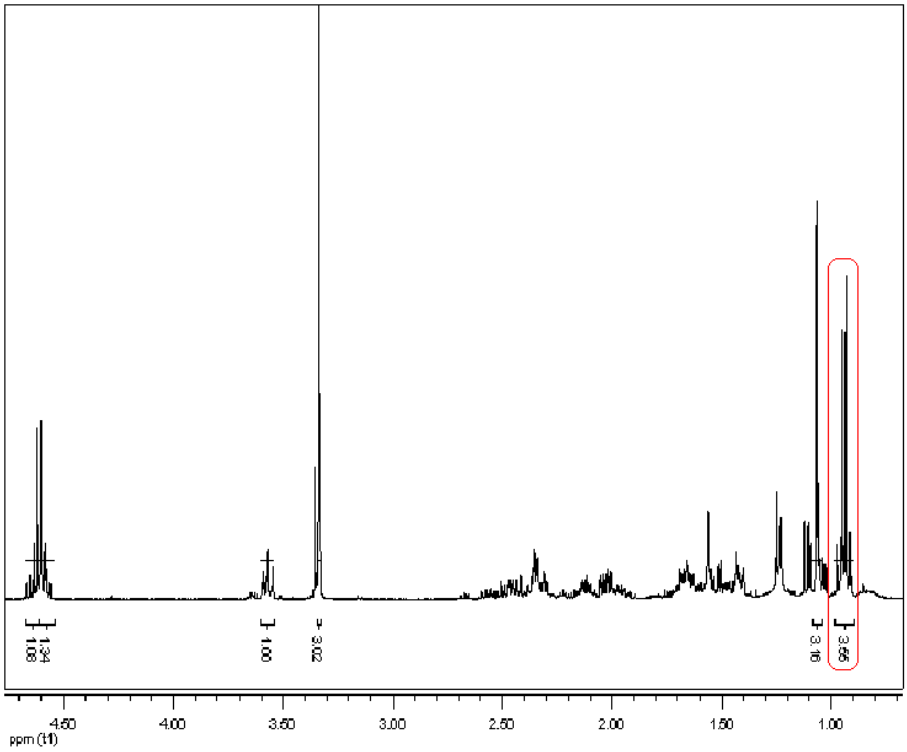


Figure 2.7 ^{1}H NMR spectrum of the second isolated isomer (**b**) with a doublet at 0.97 ppm integrating for 3H

Due to the difficulty in isolation and the small quantity of product attained, it was not possible to run more extensive NMR analyses, such as NOE. Also, the C8-H could not be clearly identified; this signal could have given a clearer indication of the stereochemistry at C8 where $J_{ax\text{-}ax}$ is typically approximately 8.0-10.0 Hz and $J_{eq\text{-}ax}$ approximately 2.0-4.0 Hz. Therefore, in order to make structural assignments the mixture was subjected to isomerization conditions. NaOMe was formed *in situ* by adding sodium metal to methanol. The mixture containing an almost 1:1 ratio of the uncharacterized diasteriomers was added and stirred at room temperature over night.

By ^{1}H NMR the C13-methyl groups of both isomers were easily identifiable as singlets at 1.01 ppm (**a**) and 1.07 ppm (**b**) ppm, and the C8-methyl signals appeared as doublets at 1.12 ppm (**a**) and 0.97 ppm (**b**). To our surprise, following the isomerization reaction the crude mixture was

almost exclusively product (**b**) where concentration of product (**a**) was significantly reduced (Figure 2.9).

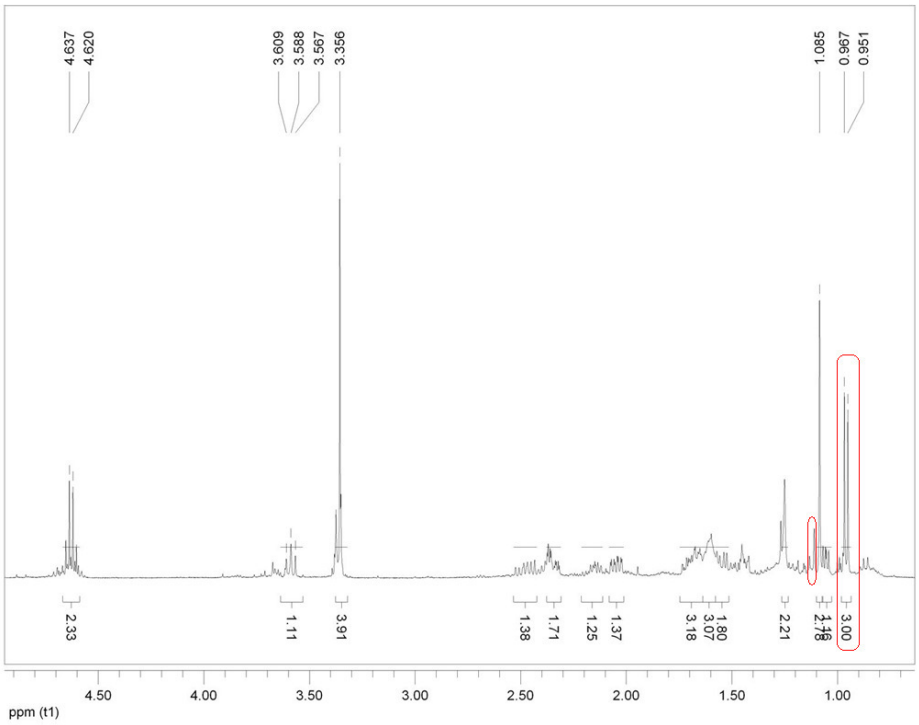


Figure 2.8 ^{1}H NMR spectrum of the product of the isomerization of a mixture of **35** and **36**, where the doublet of 1.12 ppm disappeared following the reaction

This result was surprising since the two isomers that had been proposed were not interconvertible under isomerization conditions. This and the previous evidence that showed that this type of reduction gave the *cis* saturated CD ring led us to believe that no *trans* product had been formed. This also suggests that epimerization must occur during the reduction reaction, which results in two saturated *cis* CD rings, one with 8-Me *cis* to 13-Me and another with 8-Me *trans* to 13-Me.

In order to identify the conformation of the two isomers that Ana Gargaun was able to isolate, and to understand which is favoured it is important to consider that *cis* CD rings are more labile than *trans* CD rings. Thus the two isomers with the CD *cis* can each exist as two conformers as shown in Figure 2.6. This is the result of a C ring chair-chair interconversion.

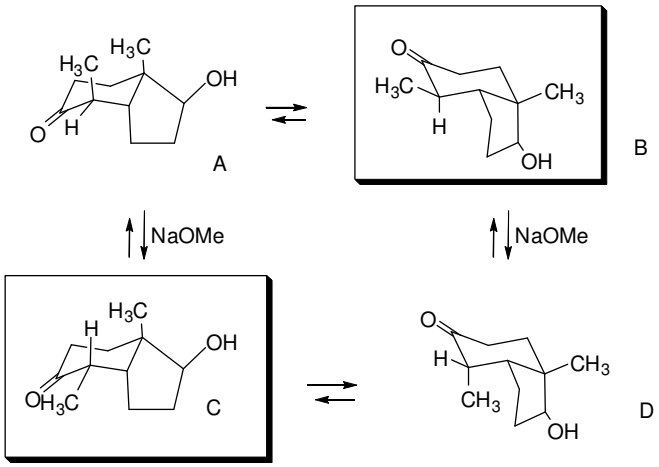


Figure 2.9 Possible conformations of compounds **35** and **36**, B and C are the most stable conformers due to the reduced steric interactions of the ring substituents

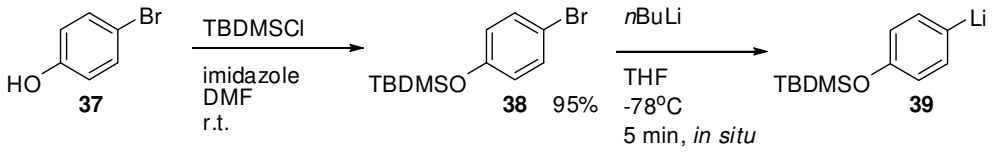
When the 13-Me and the newly introduced methyl are *cis* as in A and B, A is disfavored since it has three axial substituents and B has only one. For the other isomer it is difficult to assume in which direction the equilibrium lays. Both isomers have two axial and two equatorial substituents, although C could be somewhat preferred since it has no 1,3–diaxial intereactions whereas D has one.

A large scale synthesis of **35** was attempted using the same sequence as described above. A first attempt at the reduction of the double bond under H_2 atmosphere at 100 PSI gave no reduction product and was repeated at 200 PSI with no success. Several more attempts at reproducing the reaction conditions carried out by Ana Gargaun were made, however to date the reduction of this highly sterically hindered double bond has not been achieved.

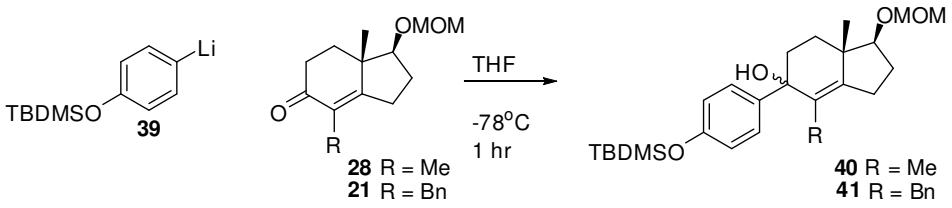
2.2.3 Preparation of A-CD compounds with C8 Substituents

The formation of A-CD compounds via coupling of CD-ketones to appropriately protected A rings has been well established within the Durst group. The most effective route is through a nucleophilic attack of a lithiated A-ring onto the CD-ring's carbonyl group. This gives a mixture of the axial and equatorial adducts at the C9 position. The C9 hydroxyl group is the source of some synthetic flexibility and can be used to confer various degrees of unsaturation.

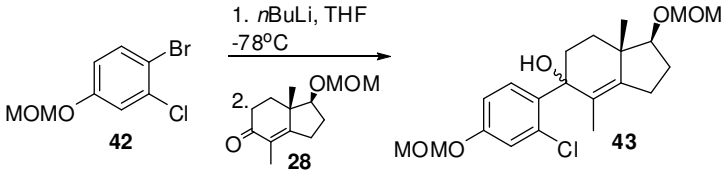
Commercially available 4-bromophenol (**37**) was protected with TBDMSCl in the presence of imidazole in DMF to afford **38** in 95% isolated yield. Halogen-lithium exchange was performed with nBuLi in in dry THF, at -78°C for 5 minutes to form **39** *in situ*.



The aryllithium intermediate **39** was allowed to react at the low temperature with the desired CD-ring ketones and the reaction was quenched with a saturated NH_4Cl solution. Workup afforded the A-CD-ring adduct with a hydroxyl group at C9. This reaction sequence was carried out with both **28** and **21** to afford **40** and **41** in 25% and 47% yield, respectively after column chromatography (Scheme 60). Although **39** was used in excess some starting material (**28** and **21**) is recovered by flash column chromatography. The ^{1}H NMR spectra of the purified products indicated that there is negligible stereoselectivity as shown be the appearance of two almost equal size peaks for the C13 quaternary methyl groups.



Coupling of a MOM-protected, C5-Cl A-ring (**42**) with **28** was also carried out under the same coupling conditions to afford **43**.

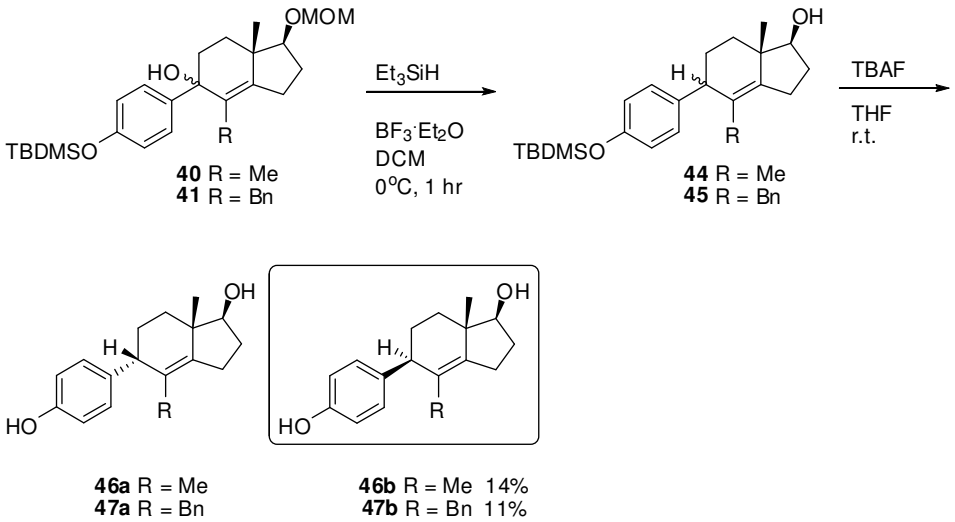


2.2.4 Reduction and Elimination of C9 Hydroxyl Groups of A-CD Analogues

The C9 hydroxyl intermediates of A-CD analogues are somewhat unstable since the hydroxyl group undergoes elimination in mildly acid environments, including during purification on silica. Because of this instability they are not useful for further development and must be further modified to more stable species. As previously mentioned, the group's aim is to create compounds that retain estradiol's natural stereochemistry, and therefore it was of interest to reductively substitute the hydroxyl moiety by a hydrogen. A method for this transformation has been previously developed by the group.

Treatment of both **40** and **41** with Et_3SiH and $BF_3{\cdot}Et_2O$ at 0 ^{o}C in DCM for 1h follwed by quenching of the reaction mixture with ammonium chloride afforded **44** and **45** respectively as mixtures of diastereomers at C9. This sequence results both in the MOM deprotection and the reductive substitution of the hydroxyl group. There is a significant amount of stereoselectivity in the reduction step. Models suggest strongly that hydride should be delivered most readily from the side opposite the C13 methyl group and the the natural isomer having the (S) stereochemistry at C9 should be favoured. The stereochemistry of the major product in the triethylsilane reduction has been proven in the sequence leading to the parent compound in this series, **46c** (R=H).[60]

The TBDMS group was removed with TBAF in THF at room temperature to afford the final product as a mixture of diasteriomers where the natural isomer was present in much higher concentration than the unnatural one (**46a-b** and **47a-b** respectively). The desired isomers with (*S*) stereochemistry at C9 (**46b** and **47b**) were then isolated using prep-HPLC with a reverse phase C18 prep-HPLC column (10µm particle size, 21.2 x 250 mm).



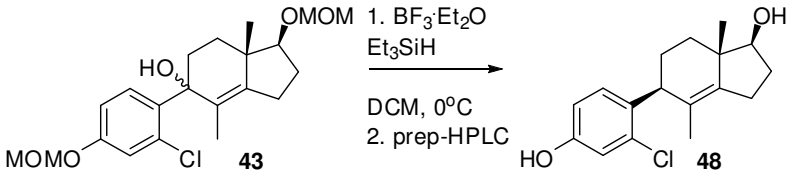
The assignments described in this section are largely based on significant investigation conducted on the monounsaturated parent compounds such as **46c** (R =H) synthesized by Daria Klonowska. In her thesis, Ms. Klonowska describes multiple 2D-NMR and NOE experiments to identify the benzylic allylic proton and its stereochemistry.[60]

Assignment of stereochemistry was based on the splitting and shifts of the C17-H signal, which have been shown to follow specific trends in these classes of compounds based on the stereochemistry at C9. When the phenol group is in the "natural" β-position, (S at C9) C17-H which is axial appears as a doublet of doublets at higher field, 3.7-3.9 ppm, than the "unnatural", (R at C9) , isomer, 4.2-4.3 ppm, which appears as a triplet. In the case of **47a** and **47b** the C17-H peaks were present at 4.03 ppm and 3.77 ppm respectively. [55] Since these values fall in the range of analogues with C8-H, they are consistent with the trend from our previous findings. This was also true about the relative splitting partern. In **46b**, the C17-H peak appears at 3.80 ppm.

Furthermore, ^{13}C NMR analysis of the parent A-CD compounds showed that the C17 peak undergoes a significant shift upfield in the "unnatural" isomer and is typically present between 72-74 ppm, where the "natural" isomer's C17 is present at 80-82 ppm. The C17 signals for **46b**

and **47b** are present at 81.4 ppm and 82.3 ppm respectiviely, again, indicating that correct assignments.

The reductive substitution of the hydroxyl group of **43** was also attempted using Et_3SiH and $BF_3{\cdot}Et_2O$ in DCM, however the product mixture was extremely complex and insufficient product was recovered to pursue purification by prep-HPLC.



It is also possible to eliminate the C9 hydroxyl group under acidic conditions to give interesting analogues with a practically flat CD plane that could force the A-ring to be virtually perpendicular (Figure 2.10).

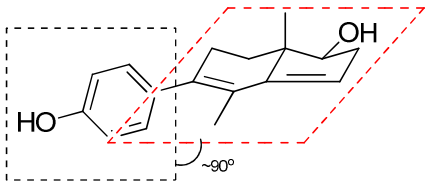
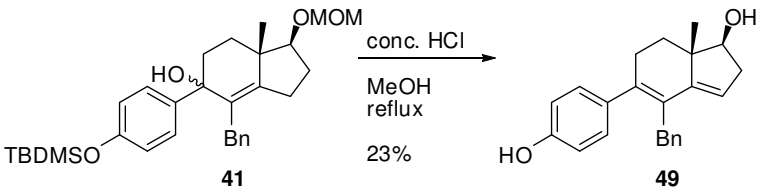


Figure 2.10 Visual representation of the proposed relative geometry of the A-ring versus the CD-ring system

Intermediate **41** was dissolved in MeOH and a few drops of concentrated HCl were added and the reaction mixture was stirred at reflux for one hour. Both the MOM and TBDMS group were removed under these conditions, as well as the C9 hydroxyl group, which gave the conjugated double bond system via an E1 mechanism. The final product (**49**) was isolated by flash column chromatography in 23% yield.



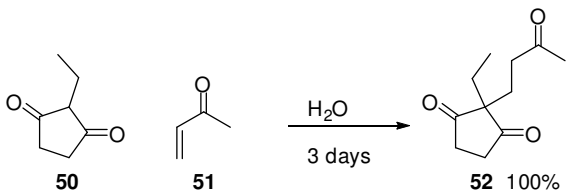
The compound is easily identifiable by ^{1}H NMR where a new allylic proton appears at 5.22 ppm, indicating that a new tri-substituted double bond was created. As compared to **47b**, the C17-H peak shifted downfield to 4.06 ppm, which can be attributed to the anisotropic effect of the double bond between C14 and C15 on C17-H, confirming that the dehydration did not give the C9-C11 double bond. The structure was further confirmed by HRMS.

2.3 A-CD Analogues with Modifications at the C13 Position

Another proposed modification to the CD-ring structure is the replacement of the C13 methyl moiety with a larger ethyl group as shown by the computational models described into *Section 2.1.3*. The simplest method to synthesize molecules **9**-**12** is by introducing the ethyl group at the beginning of the Hajos-Parrish sequence. It is important to note that all of the intermediates in the synthesis of the CD-ring containing the C13-ethyl are known, and that the structure and stereochemistry of each compound in the sequence was confirmed based on ^{1}H NMR data from literature. The literature also reports that the proline catayzed cyclization of **52** results in essentially enantiomerically pure **53**.[74]

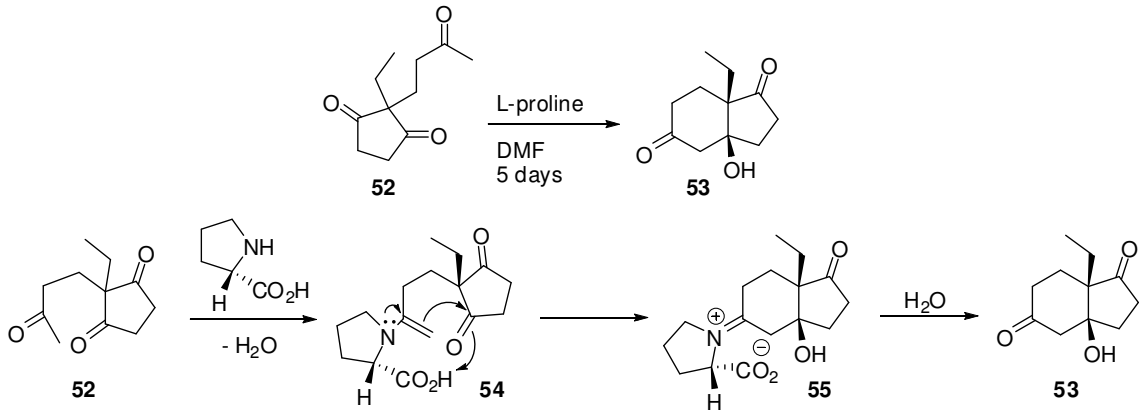
2.3.1 Synthesis of protected CD-Rings 60, 61 and 62

Commercially available 2-ethylcyclopentane-1,3-dione (**50**) was suspended in water and methyl vinyl ketone (**51**) was added and the mixture stirred for three days at room temperature. The Michael addition product (**52**) is extracted with EtOAc and concentrated under reduced pressure; **52** was recovered in a quantitative yield.



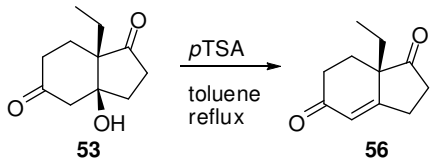
50 **51** **52** 100%

The intermediate **52** was diluted with DMF and L-proline was added to the mixture; the reaction was wrapped in aluminum foil and stirred at room temperature under ambient atmosphere for five days (Scheme 4). In this asymmetric Robinson annulation L-proline forms enamine **54** that undergoes an asymmetric enamine aldol condensation to give intermediate **55**. Finally, the hydrolysis of the iminium salt by water affords **53**, where the ethyl and hydroxyl group are *cis* to one another.



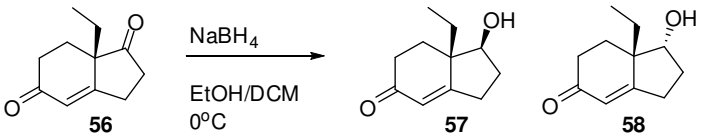
Scheme 4. Asymmetric Robinson annulation of **52** in the presence of a catalytic amount of L-proline in DMF; **53** is formed via intermediates **54** and **55**

This intermediate has never been isolated and following distillation of the DMF the crude mixture was dissolved in toluene and refluxed for 5 minutes in the presence of a catalytic amount of *p*TSA to dehydrate **53** to **56**. The product was isolated from the complex crude mixture using flash column chromatography. The desired product **56** was recovered in a 13% yield, as well as 7% of **53**, which was quantitatively dehydrated to increase the total yield to 20%. Several other cyclization products were observed with various unsaturations that could not be taken further in the synthesis of the CD-ring.



The yield of this transformation was poor as compared to the literature, which describes an isolated yield of 65% over the cyclization and dehydration steps.[56] In the paper by Mechili *et al.* the authors stated that these reactions were run on a scale of 50g-250g, partly due to the improved recrystallization of intermediate **53**. On account of working with less than 40g of staring material **52**, recrystallization was unsuccessful and the crude mixture was subjected to dehydration conditions. The products resulting from this reaction were close in R_f values and difficult to separate on a silica column, which lead to the loss of final product so as to get a sample of sufficiently high purity.

The final step in the CD-ring synthesis is the regio- and stereo-selective reduction of the C17 carbonyl to the 17β-hydroxyl group. This transformation was previously carried out on the C13 methyl-containing CD-ring with $NaBH_4$ in a 1:1 mixture of MeOH and DCM at -78°C for one hour. These conditions were repeated using **56** but showed no reduction of the carbonyl. When the temperature was increased to 0°C and the reaction was run in a 1:1 mixture of EtOH and DCM for an hour and a half the reaction of the desired carbonyl went to completion. Reduction of **56** with $NaBH_4$ in EtOH and DCM afforded **57** in 65% yield and **58** in 26%.



56 **57** **58**

The presence of the unsaturation on the C ring is essential to infer selectivity in the reduction, which made the conjugated C9 carbonyl more stable and unwilling to react with the $NaBH_4$. The C13 moiety acts as a directing group for the reduction, effectively blocking access of the reducing agent from the top face of the CD-ring. This stereoselectivity is very high in the reduction of **85**, but is not as efficient in the reduction of **56**, which results in the formation of both **57** and **58**. Even when the reaction was cooled to between -10°C and -5°C the same ratio was observed. The lower stereoselctivity in the reduction of the ethyl vs the methyl ketone is

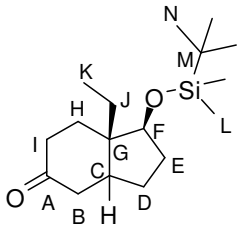
somewhat surprising; it is in fact opposite what one might have predicted based on the fact that an ethyl group is larger than a methyl group and should have provided greater hindrance to attack of hydride from the same side as the ethyl group.

Although this results in the loss of product, these diasteriomers are easily separable by flash column chromatography. These two diasteriomers could be differentiated based on, once again, the shift and splitting of the C17-H by ^{1}H NMR. Following reduction the desired isomer, **57**, showed a doublet of doublets at 3.92 ppm, while the "unnatural" isomer's C17-H peak appeared at 3.75 ppm as a triplet. Furthermore, it was expected that the "natural" isomer would be favoured due to proximity to the stereocenter at C13, and in fact **57** was more abbundant than **58**. Lastly, the spectra of these compounds were compared to the literature and confirmed this stereochemical assignment.[56]

The double bond of the CD-ring was reduced using Pd/C in MeOH, glacial acetic acid and concentrated HCl under H_2 atmosphere, which gave the saturated CD-ring (**59**) in 75% yield. Both ^{1}H and ^{13}C NMR confirmed complete reduction by the disappearance of the allyl proton peak and the two alkene carbon peaks respectively. The method for this reaction was chosen based on similar reductions performed in our group on 13-Me compounds. These conditions were decided on prior to the X-ray study that determined that CD rings made in this way had a *cis* conformation rather than the desired *trans.* These conditions were developed based on the assumption that the presence of the sufficiently bulky 13β-substituents was enough to prevent reduction of the double bond from the same phase thereby giving exclusively the *trans* product. However, the geometry of the unsaturated CD ring was not taken in consideration. This bicyclic system takes a bowl-like conformation where the five-membered ring is bent away from the 13β-Me or 13β-Et and blocks the addition of the hydrogen across the double bond from the bottom phase of the molecule.

Unlike the 13-Me CD rings, some desired *trans* product was observed and could be separated from **59** by flash column chromatography. The stereochemistry of this minor product was confirmed with ^{1}H NMR studies which paralled those in the literature. Prior to the reduction of the double bond, the C17-H peak is a dd with *J* = 9.8, 7.8 Hz, but after saturation it become a t with *J* = 8.4 Hz.[76] In our reaction sequence, **57** had a clear dd at 3.92 ppm with *J* = 9.98, 7.87 Hz by ^{1}H NMR. Following the reduction, the major compound **59** has a C17-H signal at 3.85 as a dd with *J* = 6.2, 1.5 Hz, while the minor product appears at 3.85 ppm with *J* = 8.1 Hz, which is in accordance with the literature.[76]

Table 2.2 Comparison of ^{1}H NMR data for literature values of (+)-(1S,3aS,7aS)-Hexahydro-1-(tert-butyldimethylsiloxy)-7a-ethyl-5-indanone and (+)-(1S,3aR,7aS)-Hexahydro-1-(tert-butyldimethylsiloxy)-7a-ethyl-5-indanone and **60**



Carbon	Natural Isomer[a]	Other Isomer[b]	**60**[c]
	^{1}H	^{1}H	^{1}H
F	3.70 (t, *J* = 8.4 Hz, 1H)	3.85 (dd, *J* = 5.3, 3.7 Hz, 1H)	3.87 (dd, J = 5.39, 3.73 Hz, 1H)
K	1.08 (t, *J* = 7.5 Hz, 3H)	0.89 (t, *J* = 7.5 Hz, 3H)	1.07 (t, J = 7.5 Hz, 3H)
L	0.01 (s, 3H), 0.00 (s, 3H)	0.03 (s, 6H)	0.05 (s, 6H)
N	0.87 (s, 9H)	0.87 (s, 9H)	0.89 (s, 9H)

[a] (+)-(1S,3aS,7aS)-Hexahydro-1-(tert-butyldimethylsiloxy)-7a-ethyl-5-indanone in $CDCl_3$ at 400 MHz

[b] (+)-(1*S*,3a*R*,7a*S*)-hexahydro-1-(*tert*-butyldimethylsiloxy)-7a-ethylindan-5-one in $CDCl_3$ at 500 MHz

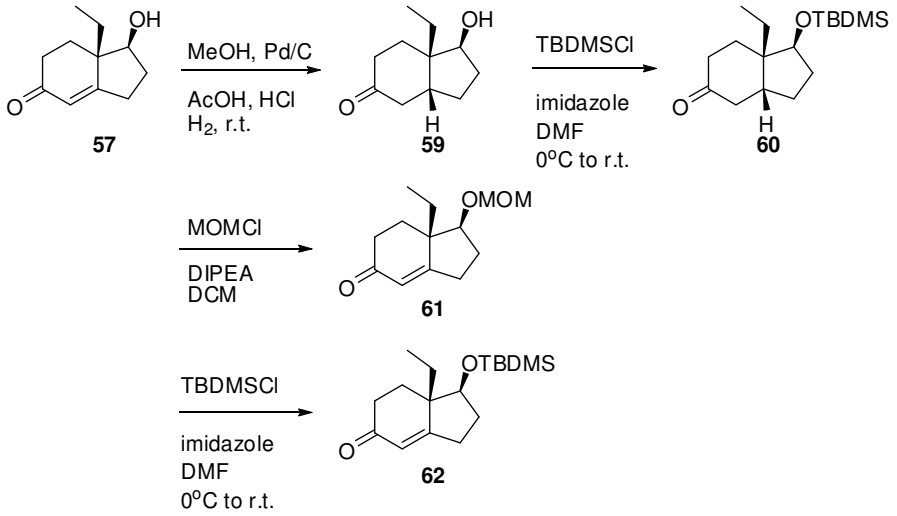
[c] NMR of **60** in $CDCl_3$ at 400 Hz

When an X-ray crystallography experiment revealed that the stereochemistry at C-14 was inverted as compared to the "natural" isomer in 13-Me compounds, a literature search of the saturated 13-Et CD ring showed that no synthesis of the unprotected, saturated compound was available, however, Corey et al. had devised a route to the TBDMS protected 13-Et CD ring.

The spectral data for this compound is compared to the spectral data of **60** in *Table 2.2*. Also shown in this table is the ^{1}H NMR data of the unnatural isomer that was reported in the Corey et al. publication with a 2.8% yield. It is clear when looking at the data that **60** is in fact the unnatural isomer, as the CD rings in the 13-Me series.

The compounds presented in this chapter will therefore contain the *cis* compounds only, however efforts are currently underway in the group to construct the desired *trans* CD rings. The analogues created in this series with the *cis* conformation are valuable for comparison with similar compounds in the 13-Me series.

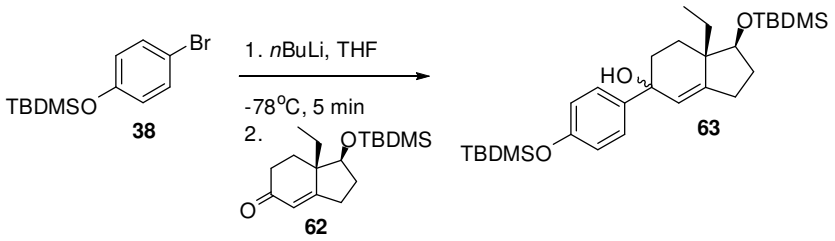
Following the reduction to afford the *cis*-keto alcohol **59** the free hydroxyl group was then protected with TBDMSCl under standard conditions to afford **60** in 85% yield. MOM groups were first considered, however the yields for this transformation under standard conditions ranged from 10% to 12%.



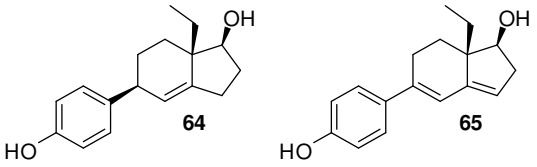
For synthetic purposes, a small amount of **57** was protected with TBDMSCl under standard conditions to attain a yield of 62%.

2.3.2 Synthesis of A-CD Compounds 64 and 65

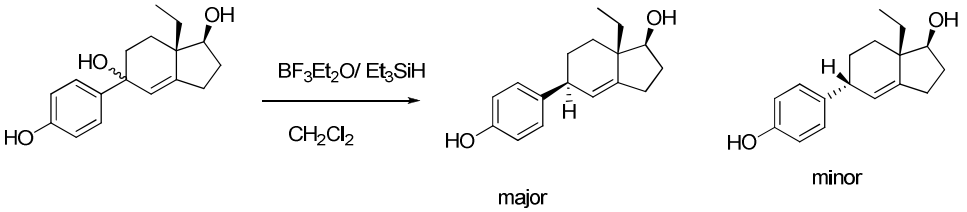
The first analogues synthesized in this series contained the unsaturated CD-ring structure. The same coupling method was used as for other members of the A-CD series, where 4-bromophenol was chosen as the parent A-ring.



This coupling gave **63** as a mixture of diasteriomers in a 48% crude yield. This intermediate was subjected to both hydrogenolysis followed by deprotection with TBAF in THF and dehydration conditions, which also removed the TBDMS groups, to afford two variations of the parent compound for this series.



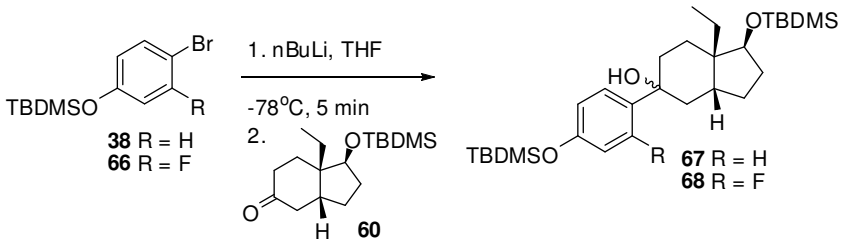
The main product of the $BF_3{\cdot}Et_2O/Et_3SiH$ reduction reaction was **64** while its diasteriomer was a minor product and was easily separated by prep-HPLC. To correctly identify **64** as the "natural" isomers the same method was used as in the compounds described in *Section 2.2.4*. The C17-H proton signal appeared as a doublet of doublets at 3.25 ppm in **64** once again complying with the previously observed trend. The "unnatural" isomer was isolated in a very small amount and could not be reliably identified by spectroscopic analysis.



Lastly, **65** was synthesized in one pot from **63** by treatment with catalytic amounts of concentrated HCl in MeOH at reflux. The dehydration yields a single product, which can be isolated using flash column chromatography thanks to the lack of new steriogenic centers being formed. The structure of this compound was determined both by comparing to the parent C13-methyl compound, as synthesized by Daria Klonowska and well as by ^{1}H NMR analysis and HRMS. The conjugated diene system appeared as two singlets at 5.46 ppm and 6.51 ppm, where the C8-H is significantly further downfield than that of monounsaturated compound **64**, due to the conjugation.

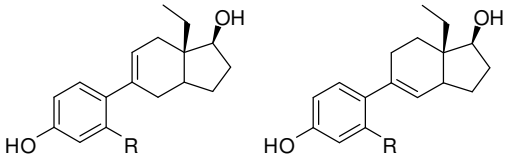
2.3.3 Synthesis of Unsaturated A-CD Compounds **71** and **72**

Saturated CD-ring **60** was also coupled using the standard coupling conditions described in previous sections with 4-bromo-(*tert*-butyl)dimethylsilane (**38**), and (4-bromo-3-fluorphenoxy)(*tert*-butyl)dimethylsilane (**66**) to afford the respective C9 hydroxyl A-CD intermediates in 44 % and 38% yield respectively.



The C9 hydroxyl intermediates **67** and **68** were subjected to dehydration conditions only; under these conditions the protecting groups of both hydroxyl groups are removed to afford final compounds. In the absence of an unsaturation in ring C, there is no control over the formation of the double bond and a mixture of regioisomers having the double bond at C9-C11 and C9-C8,

respectively is attained. Both of these products are of interest for biological assays; they were separated and isolated in high purity using prep-HPLC.



69 R = H
70 R = F

71 R = H
72 R = F

The structure assignments for the two unsaturated isomers were based on the shift and splitting of the C17 proton; this signal was expected to follow a similar trend to that seen seen in the C13-methyl series by Daria Klonowska.[60] In these compounds the H17 of the isomer with the C9-C11 double bond is further upfied (3.74-3.81 ppm) than that of the C9-C8 isomer (3.88-3.91 ppm). Furthemore, H17 appears as a doublet of doublets in the C9-C11 double bond isomer whereas the same hydrogen is a triplet when the double bond is between C9 and C8.

In the case of analogous 13β-methyl compounds the double bond regioisomers are easily separable by prep-HPLC. The method used for the parent compounds was adapted and used for the purification of 13β-ethyl analogues and two peaks could be isolated with high resolution and a high degree of symmetry. The first peak appeared to be the pure regioisomers with C9-C8 double bonds. The proton NMR for compound **71** shows the H17 peaks as a double of triplets at 3.86 ppm, the allylic proton peak as a multiplet at 5.98 ppm and two signals integrating for four protons in the aromatic region with the expected para-substituted phenyl splitting pattern.

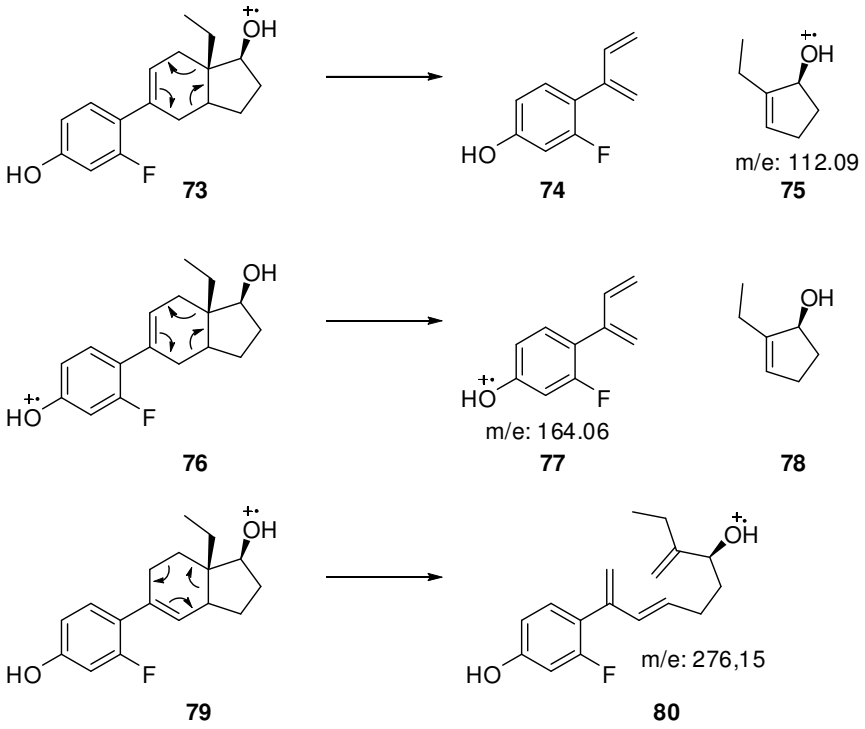
In the proton NMR of compound **72** the H17 singnal was a triplet at 3.85 ppm, while the allylic peak was a multiplet at 5.80 ppm.

The compound within the second prep-HPLC peak, surprisingly appeared to have a splitting of the H11, H17 and H18 peaks as well as doubling of the ethyl CH_3 signal. It is important to point out that the H17 signal is doubled and that both the larger and the smaller of the two resulting signals are triplets. This may suggest that both components of this mixture have a *cis* CD ring

and we may discount the possibility that the second isomer was the result of coupling of the A ring with trace amounts of the *trans* CD ring.

The same prep-HPLC peak was again subjected to modified conditions on both the analytical and prep-HPLC instruments only to afford the same mixture of products within one peak.

Another way to asses that the correct assignments were made was to analyze the MS fragmentation data for a potential reverse Diels-Alder reaction. Based on a trend observed by D. Klonowska in the study of analogous C13-methyl compounds, the reverse Diels Alder in the C9-C11 compounds results in the formation of two even *m/e* products, while in the C9-C8 isomers this rearrangement results in a linear triene (Scheme 5). When an HRMS of the mixture of isomers was performed, the mass expected for **71** was observed (*m/e* = 276.14) as well as both *m/e* = 164.06 (**77**) and *m/e* = 112.1 (**75**) were present, which corresponded to of the fragments of the reverse Diels-Alder reaction. This result suggests that the mixture of isomers contains the C9-C11 double bond compound, but does not give any insight on the nature of the unknown isomer. This was not the case for the first HPLC peak where these fragments were absent suggesting that the pure isomer was in fact the C9-C8 compound.

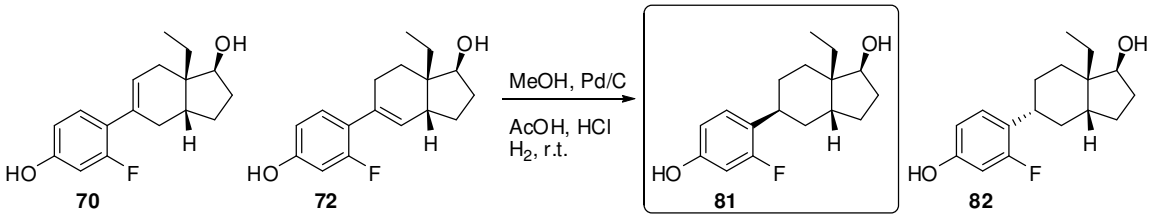


Scheme 5. Proposed reverse Diels-Alder fragmentation of radical ions **73** and **79**

This test was repeated with the compound mixture **69**. The expected mass of the A-CD compound, *m/e* = 258.2, was found as well as the reverse Diels-Alder fragments. The spectral trends for this compound are similar to those of the C5-F unknown compound and indicate that the C9-C8 isomer was isolated, while the C9-C11 isomer could only be recovered as a mixture with an unknown compound.

2.3.4 Synthesis of Saturated A-CD Compound **81**

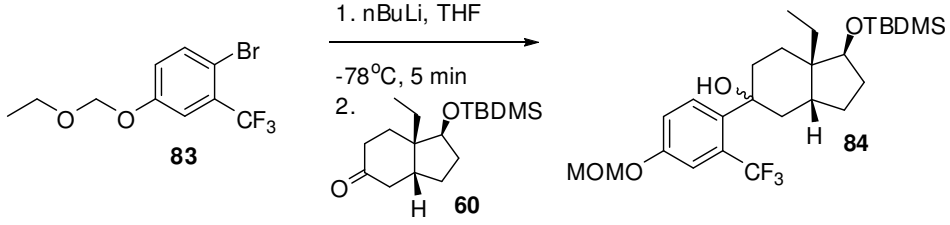
A small quantity of **70** and **72** was subjected to hydrogenation conditions in MeOH, glacial acetic acid and concentrated HCl in the presence of Pd/C, under H_2 atmosphere to afford a mixture of diasteriomers. In this instance there wwas some selectivity for the desired diasteriomer (**81**), which was present in a higher concentration by ^{1}H NMR as compared to **82**.



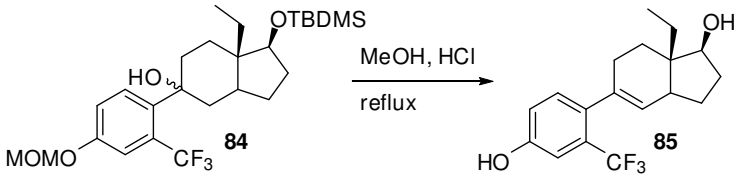
Analogue **81** was isolated in 55% yield with prep-HPLC using the method previously optimized for this class of compounds. Once again, the correct isomer was determined based on the shift of the C9-H in the ^{1}H spectrum as well as the shift of C17 in the ^{13}C spectrum, which coincides with the trends previously described in this thesis.

2.3.5 Synthesis of C5-CF_3 Mono-Unsaturated A-CD Compound

A final analogue in this series was made by coupling 1-bromo-4-(ethoxymethoxy)-2-(trifluoromethyl)benzene (**83**), which was synthesized by Dr. Cristian Dobrota, with **60**.



When subjected to dehydration conditions a single regioisomer, **85** was obtained exclusively in 23% yield. The regiochemistry is evident by the H17 peak as a triplet at 3.86 ppm, which follows the trends described in this chapter. There is no explanation to date for this phenomenon however, it is apparent that the presence of the C13-ethyl group is a driving force in these reactions.



The absence of the analogue with a C9-C11 double bond is not of immediate concern, as trends seen in previous analogue families show that compounds with a C9-C8 double bond are more powerful.

2.5 Bioassay Results

The activity of the analogues synthesized in this thesis is evaluated using two different bioassays. The first is a relative binding assay (RBA) conducted by the Katzenellenbogen group that uses radio-labeled estradiol bound to either ER receptor and evaluates the competitive binding of the desired analogue with respect to the radio-labeled estradiol. The other is a relative transcription assay (RTA), which is carried out by the Pratt group, which looks at the analogues' ability to elicit estrogen agonist activity on transcriptional proteins that control the transcription of luciferase, a luminescent protein.

It is important to recall that HRT is a treatment that alleviates symptoms that affect post-menopausal women's quality of life, as well as potential prophylaxis for some health risks associated with age-related hormone decline. As a non-essential medical treatment, a novel drug must not only be effective, but also highly selective and virtually side-effect free. In order to determine potential candidates for HRT it is therefore important to subject new analogues to different biological assays to better understand their possible *in vivo* effects.

2.5.1 Relative Binding Affinity

An effective analogue must demonstrate a comparable or better affinity to the desired receptor binding site than the endogenous estrogen. This is important for competition within a biological system with endogenous steroids. To test a compound's affinity for a receptor a relative binding assay (RBA) using tritium-labeled estradiol is commonly used. In this assay the RBA of each analogue tested is defined as the ratio of the concentration of 17β-estradiol to analogue

required to replace one-half of the bound [^{3}H]-estradiol, with the affinity of 17β-estradiol set at 100%.[61] The RBAs presented within this thesis were conducted by the Katzenellenbogen group at the University of Illinois.

2.5.2 Relative Transcription Activation

Although it is important to determine competitive binding of new analogues as compared to endogenous estrogen, RBAs are not indicative of the analogues' ability to activate ERs. To determine their efficacy at stimulating the transcriptional cascade controlled by ER, the Pratt group at the Ottawa Hospital Research Institute (OHRI) has conducted relative transcription assays (RTAs) using the luciferase reporter gene in COS-7 cells on HRT analogues.[62] The cells are treated with a standard concentration of compound for a set period of time, when the concentration of luciferase produced is evaluated and compared to the values of estradiol, and a blank. These analyses not only test whether the analogues are agonists towards the target receptor, but also whether they may function as antagonists or are inactive for ERα and ERβ. Analogues are tested against 17β-estradiol, as well as known SERMs raloxifene and tamoxifen.

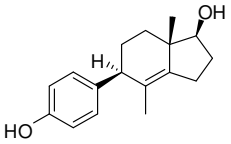
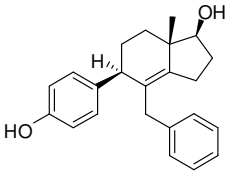
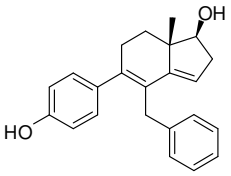
2.5.3 Further Biological Evaluation

The compounds described within this thesis are at the beginning stages of SAR and only RTA and RBA data will be reported for the purpose of determining trends in activity and specificity of these novel sub-categories. Analogues that show improved activity and selectivity for ERβ will be further studied using computational specificity prediction of receptor binding to other proteins, cytotoxicity studies in hepatic cells, proliferation/inhibition assays using MCF-7 breast cancer cells, cardio-protective effects in vascular epithelial cells and rodent uterotrophic assays to confirm *in vivo* activity.

2.5.4 Bioassay Results for C8-Alkyl Analogues

While evaluating the efficacy of RBA and RTA bioassays as a diagnostic tool for analogue activity, the Durst group has observed that these two assays are predictive of one another, and therefore only one or the other were carried out per analogue. It is important to note, however that RBAs do not indicate whether a compound is an agonist or antagonist to the respective ER, only how selectively the analogues bind to each active site.

Table 2.3 RBA data for **46b** and **47b**, and RTA data for **49**

Entry	Analogue	RBA (estradiol=100)[a]			RTA (estradiol=100)[b]		
		ERα	ERβ	β/α	ERα	ERβ	RTA(β)/RTA(α)
1		-	-	-	0	13.8	Pure β
2		0.329	0.302	0.9	-	-	-
3		2.93	3.28	1.1	-	-	-

[a] The relative binding affinity (RBA) assays were carried out by the Katzenellenbogen group at the University of Illinois. Relative binding was measured as the competition for binding between ^{3}H-labeled estradiol and increasing concentrations of the analogue. RBA was quantified as a measure of displacement in radioactivity of estradiol where the value for estradiol is set to 100 % for both receptors.

[b] The relative transcription activation (RTA) assays were carried out by the Pratt group at the University of Ottawa. COS-7 cells were transfected with plasmids containing sequences for the ERE-luciferase reporter and either ERα or ERβ. The RTA of the ligand at concentration 10 nM was compared to the one of estradiol at that concentration for each receptor.

The first compounds to be tested were from the C8-alkyl series. Analogues **46b** and **47b** were expected to give very different results. Although both were predicted to show a higher affinity

for ERβ, **47b**, with the much larger C8-moiety may be potentially an antagonist of ER based on computational models. The RTA results for **46b** complied with the hypothesis, and in fact there appeared to be no activity at ERα and good activity at ERβ. This is an extrememly promising result, which indicates that alkylation at C8 may be a viable method to confer selectivity to our alalogues.

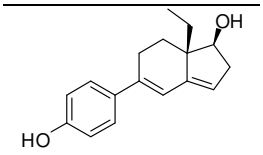
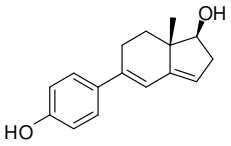
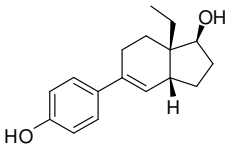
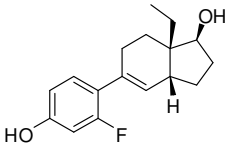
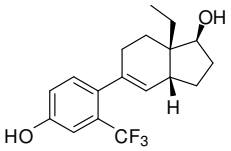
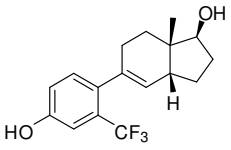
When **47b** was tested for RBA there appeared to be almost no selectivity for either receptor. This bioassay does not determine whether the compound acts as an agonist or antagonist, however, it demonstrates that perhaps the size of the moiety causes a twisting of the analogue within both activite sites, such that any selectivity is lost. These properties appear to be inherent of C8-benzyl compounds, where **49** showed negligible selectivity for ERβ, although it had increased binding compared to **47b** which may be due to steric interactions forcing the benzyl group to rotate away from the A-ring, thereby placing the moiety in a conformation that is more desirable for binding to the ERs.

From these values it can be deduced that it is important to build more C8-methyl compounds to evaluate whether modifications of the unsaturations of the CD-rings or moieties at C5 have an effect on the selectivity, and also on the potency. It is also important to investigate various sizes and types of substituents at C8, such as ethyl, iso-propyl and other alkyl groups to determine the optimal length of chain for both activity and selectivity.

2.5.5 Bioassay Results from C13-Ethyl Analogues

A few compounds of the C13-Ethyl family were also tested using RBA only. Based on computational analysis these compounds were expected to have high activity and ERβ selectivity.

Table 2.4 RBA data for **65**, **51**, **72** and **85**

Entry	Analogue	RBA (estradiol=100)[a]		
		ERα	ERβ	β/α
1		0.115	0.342	3.0
2[b]		3.3	15.9	4.8
3		1.07	6.57	6.1
4		29.3	44.2	1.5
5		16.7	8.08	0.5
6[b]		7.3	4.9	0.7

[a] The relative binding affinity (RBA) assays were carried out by the Katzenellenbogen group at the University of Illinois. Relative binding was measured as the competition for binding between ^{3}H-labeled estradiol and increasing concentrations of the analogue. RBA was quantified as a measure of displacement in radioactivity of estradiol where the value for estradiol is set to 100 % for both receptors.

[b] Entries 2 and 6 were synthesized by Daria Klonowska.[60]

The diunsaturated **65** (entry 1) was the first analogue tested in this series and performed poorly with low affinity to the ER binding sites, although it had some selectivity toward ERβ. This is especially true when comparate to the 13-Me analogue in entry 2, which has significantly higher affinity for either receptor, and an overall better selectivity for ERβ.

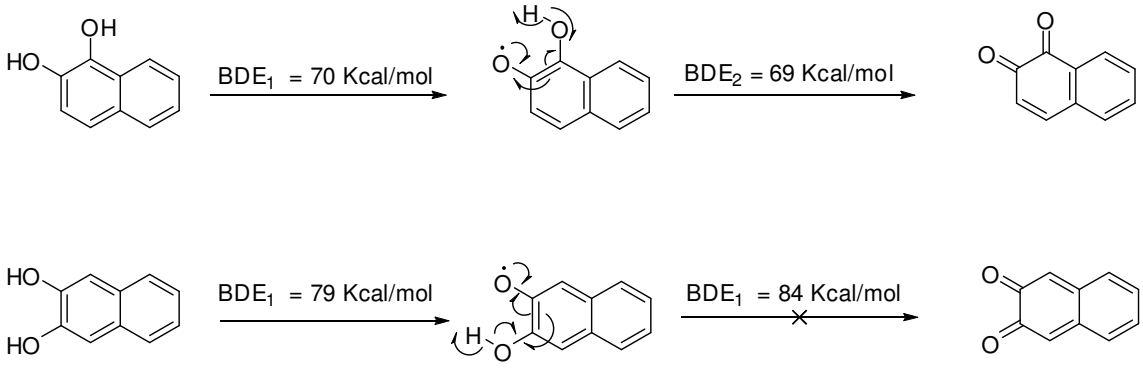
The monounsaturated parent compound **72** (entry 4) however showed a significant increase in binding, as well as better selectivity than the flatter analogue. Considering the SRA conducted on the parent C13-Me compounds, the most potent C13-Et compound was optimized by adding electron withdrawing groups at C5. As expected, addition of F in compound **72** (entry 4) further improved the binding of the analogue, but selectivity was reduced significantly. When an analogue with C5-CF_3 (**85**) was tested, a stronger binding affinity to ERα than ERβ was observed. These results parallel those seen in the SAR of C13-Me compounds, although they appear to have overall lesser ERβ selectivity. This compound also showed a twofold increase in binding affinity than its 13-Me analogue (entry 6) although **85** appeared to have a slightly higher affinity to ERα, which may pose some problems in RTA assays as well as *in vivo* assays if chosen to be investigated further.

These results could potentially indicate that the ethyl group impedes the entrance of the analogue into the active site, or, through twisting in the active site, it is not properly retained. More compounds with modifications in the degree of unsaturation as well as with different C5-substituents have been submitted for analysis to further evaluate this subclass of analogues. More 13-Et analogues of the most effective 13-Me compounds should be synthesized in order to understand whether a reasonable trend exists by which we can decide whether 13-Me or 13-Et would be a better subclass to pursue in the future.

3.0 Part B: Non-Steroidal Analogues

3.1 Introduction: Evidence to Support Naphthalenediol Investigation

Research conducted by the Durst group in an attempt to design improved and non-toxic antioxidants demonstrated that 2,3-dihydroxynapthalene (2,3-ND) does not undergo quinone formation due to the high energetic price of loosing aromaticity in both of the fused benzene rings (Scheme 6).[63] In contrast, 1,2-ND readily formed quinones and was therefore much more toxic. These tendencies are readily apparent when one examines the BDE_1 and BDE_2 of both 1,2- and 2,3-naphthalene diols. BDE_2 is smaller than BDE_1 for 1,2-ND indicating facile orthoquinone formation. In contrast BDE_2 for 2,3-ND is signifcantly larger thant BDE_1 indicating that that ortho-quinone formation would be energetically unfavourable.



Scheme 6. Mechanism of quinone formation from free radical catechol intermediates of 2,3-ND and 1,2-ND from top to bottom. Formation of 2,3-ND-quinone induces loss of aromaticity and does not proceed, while 1,2-ND-quinone is formed

In 2005 research by Wyeth researchers showed that phenylnaphthalenes could be incorporated into novel estrogen agonists for hormone replacement therapy.[64] X-ray crystallography was

used to determine the orientation of these analogues in the ER binding site and it was shown that 3-(3-Fluoro-4-hydroxyphenyl)-7-hydroxy-1-naphthonitrile acts as an A-CD-ring system.

Based on these separate studies, the Durst/Wright group decided to pursue the synthesis of novel estrogen agonists with a 2,3-ND backbone. Computational analysis conducted by the Wright group on 2,3-ND-containing compounds with a non-aromatic moiety showed that such a system would fit in the active site with a reverse orientation, where the 2,3-ND would replace estrogen's AB-rings. This is also true for analogues containing 2,6-disubstituted phenols due to the limited space in the active site for the A-ring. Based on Wyeth's results, it is presumed that 6-phenol-2,3-naphthalenediol would enter the ER active site as an A-CD system, however computational studies show that the binding affinity of such an analogue would be significantly improved when the diol bound to HB12 rather than the single hydroxyl group (Figure 1.19). Therefore, while no crystallography studies have been made on such an analogue it can be argued that it may enter the active site in either orientation.

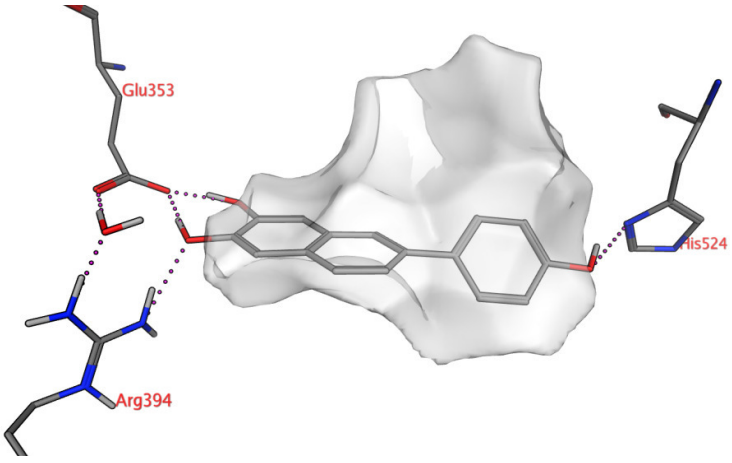
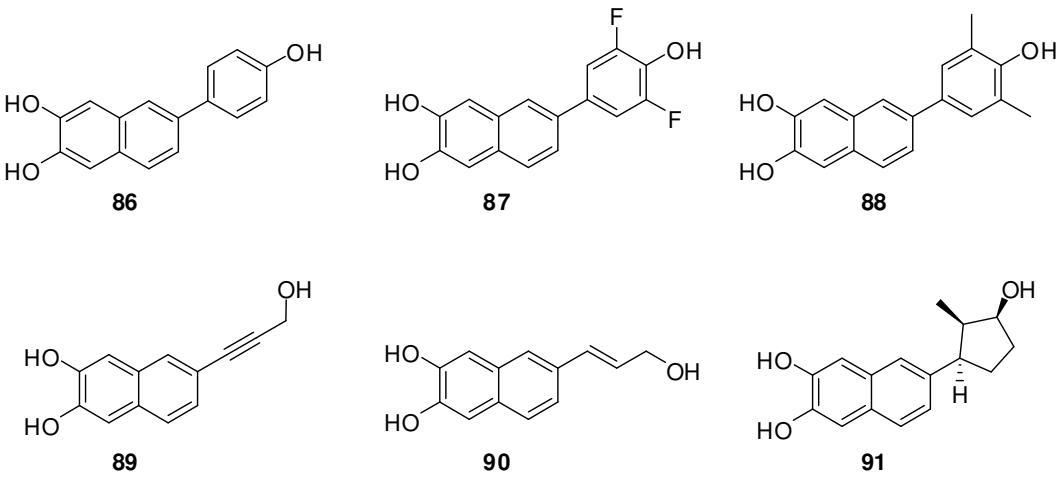


Figure 3.1 Model of 6-phenol-2,3-naphthalenediol bound to ERα active site in the AB-D orientation

After computational analyses of possible candidates were conducted, several AB-D analogues were proposed that would contain the necessary pharmacophores.

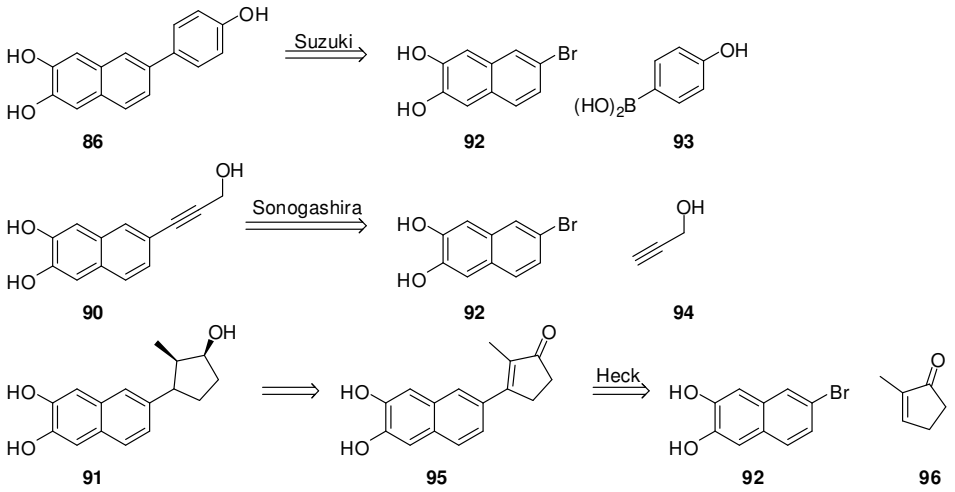


It is relevant to note that these compounds are more polar than estradiol or the A-CD compounds that have been prepared by our group and therefore have higher de-solvation energy. This however is counterbalanced by their calculated binding affinity, which is significantly greater than that of single hydroxyl group A-ring analogues and may potentially dictate their overall activity.

3.2 Synthesis of 2,3-ND Containing Analogs

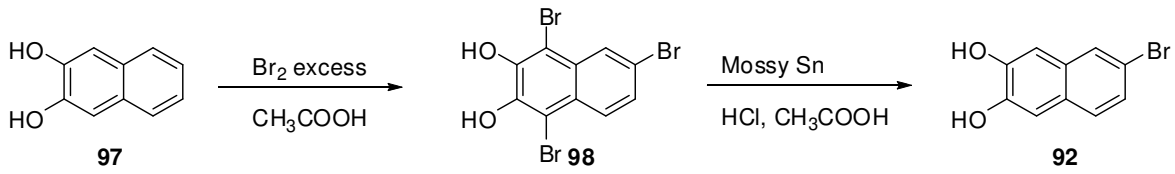
Thus far our group has focused on the investigation of A-CD analogues of estrogen where the removal of the B-ring increases favorable interactions within the receptor's active site through increased flexibility. Research reported by Wyeth scientists in 2005 proposed that 2-phenylnaphthalene be used as an A-CD-ring system where the phenol moiety replaces the estrogen A-ring and the naphthalene act as the CD-rings.[64] The underlying theme in our group has been to generate estrogen agonists that, unlike estradiol itself, would be unlikely to form potentially dangerous o-quinones. As mentioned above, 2,3-naphthalene diols form ortho quinones very reluctantly. The combination of these factors prompted us to investigate the synthese of 2,3-ND based AB-D ring systems such as 86-91 in order to investigate their binding affinity and transcription activity.

The simplest route to the desired analogues should be via transition metal catalyzed cross couplings of 6-bromo-2,3-naphthalenediol (**92**) with a functionalized D-ring. This method appears to be both economical in steps and versatile allowing for Heck or Sonogashira coupling for non-aromatic moieties and Suzuki or Stille couplings for *para*-halophenols. Furthermore, a synthetic route to the 6-bromo-2,3-ND had been partly developed by others in the group.



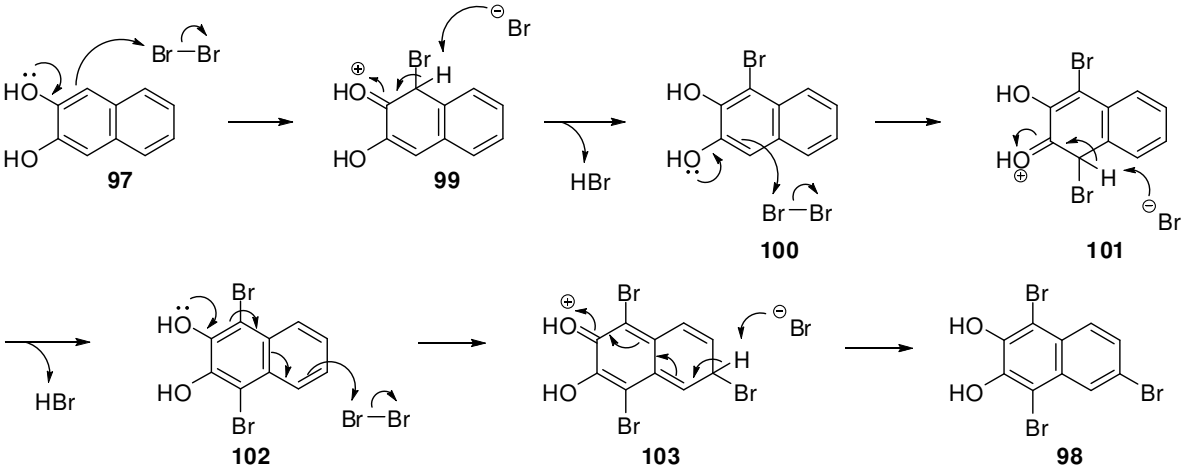
3.2.1 Preparation of the 6-bromo-2,3-Naphthalenediol Scaffold

To attain these compounds inexpensive, commercially available 2,3-naphthalenediol (**97**) was tribrominated at positions one, four and six in sequence in the presence of excess bromine in acidic conditions then selectively reduced at positions one and four.



This reaction was adapted from a procedure from the thesis by Martin Charron, who observed the formation of the tribromo intermediate after treatment of **97** with excess bromine.[65] As this was not a desired product for him, the formation of this product was not optimized. In our

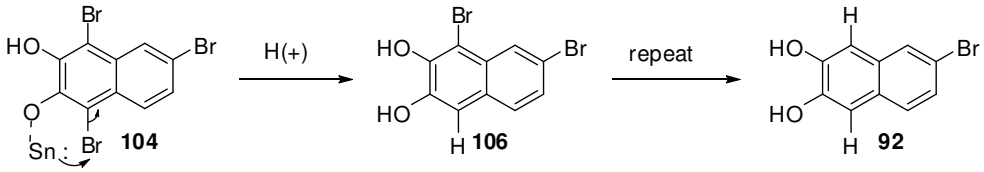
hands we observed inconsistent results when 2,3-ND was reacted with 3.1 eq. of bromine mainly because of the insolubility of both the 1,4-dibromo-2,3-naphthalenediol (**102**) and desired product **98**. Typically, the reaction products were recovered through filtration of the precipitate in an ice-water mixture and generally a mixture of starting material **97**, 1,4-dibromo-2,3-naphthalenediol (**102**) and desired product **98** were attained (Scheme 7). When this isolation was performed the yields varied from 12% to 75% with no consistency in the ratio of product to intermediates and starting material. The monobrominated intermediate **100** was never observed, as the conversion from **100** to **102** is very fast. Tretra-brominated product was not observed when the reaction was carried out at room temperature. This is attributed to the significant decrease in the nucleophilicity of **98**. When the reaction was carried out at reflux some 1,4,8,9-tetrabromo-2,3-naphthalenediol was formed. Mixtures of the various intermediates are not separable by column chromatography.



Scheme 7. Tribromination reaction of 2,3-ND to form the **98** via the electrophilic aromatic bromination mechanism via intermediates **100** and **102**

The tribromo-intermediate is commercially available, however it is very costly. The structure of **98** was confirmed by comparing the ^{1}H NMR spectrum of the product synthesized in the lab with that of the commercial product; the structure was confirmed by HRMS.

Bromines at positions 1 and 4 were selectively removed using mossy tin in the presence of acid at reflux. It was proposed that the selectivity of this reaction was the result of coordination of the tin with a hydroxyl group, therefore making the reduction of the bromine at position six unlikely. In this proposed mechanism the tin coordinates to a hydroxyl oxygen. This is followed by a two electron transfer to the bromine and cleavage of the Br-C bond in the highly acidic medium. This process is carried out a second time to afford 6-bromo-2,3-naphthalenediol **92** (Scheme 8).



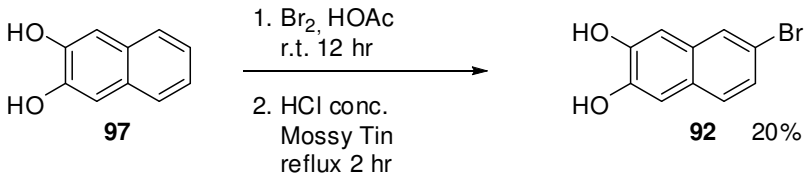
Scheme 8. Proposed mechanism for the reduction of **104** to attain **92**

The structure of **92** was easily identifiable by the appearance of the C1 and C4 proton signals as singlets at 7.20 ppm and 7.23 ppm. Signals for protons 6, 7 and 9 remain mostly unaffected, except for a slight shift upfield.

Although this sequence appears quite straight forward the overall yield of isolated **92** was very inconsistent. This is due mainly to the formation of a several products in the initial bromination stage, the difficulty of separating these products cleanly and the isolation of **92** from the inorganic byproducts obtained in the miosy tin reduction of the tribromide.

When the mixture of **97**, **102** and **98** was subjected to these reduction conditions a mixture of **97** and **92** was obtained. Although these products are inseparable by silica column, **97** is readily soluble in DCM, while **92** remains undissolved and can be filtered off. This separation method allows for the recovery of the desired product, however results in inconsistent yields ranging from as low as 43% to as high as 99%. Furthermore, large quantities of tin byproduct are produced in this reaction and precipitate with the product as high weight contaminants. These contaminants often make the purification of **92** very problematic.

A first attempt to improve the overall yield over the two steps was made by eliminating the isolation of **98** and carrying on to the tin reaction in one pot.



The equivalents of bromine were not increased, but it was assumed that this procedure would minimize product loss due to poor crystallization of **98**. The reaction with the mossy tin was carried out as per the original procedure, however the work up was modified and the product was recovered by extraction of the aqueous phase with EtOAc and then filtered repeatedly over celite to remove the inorganic contaminants. The resulting crude contained mainly **92** and was of generally of sufficiently high purity such that no further purification was performed. Although this method improved the ease of recovery and afforded a pure product, the yield was low making it a non viable route to the synthesis of **92**. The low yield is attributed to the compound's partial solubility in water.

To improve the conversion and yield of this reaction sequence it was first imperative that a reliable method for converting **97** to **98** be designed. Taking into consideration that the tribromination did not consistently go to completion, the reaction was carried out using 5 eq. of Br_2 and stirred overnight at room temperature in glacial acetic acid. This was done under the assumption that excess bromine would promote the slower addition at position six, while maintaining a low temperature that would not incite addition at position nine.

At the beginning of the reaction, the starting material was soluble in glacial acetic acid; as the reaction progressed the product begun to precipitate until the solution was rendered a thick orange slurry. The reaction was monitored by TLC and after 12 hours diluted with ice water and stirred until the ice was melted. The addition of water caused further precipitation of the product as well as any starting material and partially reacted **102**. The solid was filtered off and

washed with hexanes until the color no longer persisted to afford **98** in moderate purity in an almost quantitative yield with only trace amounts of **97** and **102**. This reaction was repeated and the yield and purity were reproduced.

The mossy tin reduction gave high conversion, however the product was difficult to isolate. It was possible to isolate the product following the reflux by diluting the cooled reaction mixture with ice-water, at which point an off white precipitate formed and could be filtered off. This method was only effective in the recovery of approximately 45%-48% of **92** in high purity, while a substantial quantity remained in the aqueous phase (this was confirmed by TLC). Furthermore, a second crop of precipitate afforded a yellow solid with a high tin content.

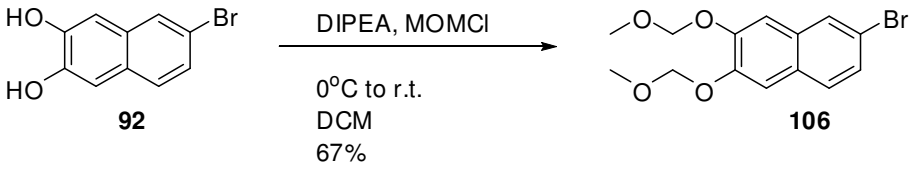
To recover the desired product the aqueous phase was extracted with EtOAc until no product was visible by TLC and the combined organic layers were filtered over a pad of celite to remove the remaining tin then concentrated under reduced pressure. Unlike the precipitate this mixture required purification by flash column chromatography. Following both stages of purification a combined yield of up to 96% could be attained.

In summary, some improvements have been made to the synthesis of this starting material, and although the highest yields that were achieved were attained using the two step method, the inconsistency of the first reaction made it inpractical. For the compounds presented in this chapter, the second one pot method was used. Although it afforded lower overall yields would give only two products that were separable by solubilization and filtration allowing for the recovery of the commercial 2,3-naphthalenediol.

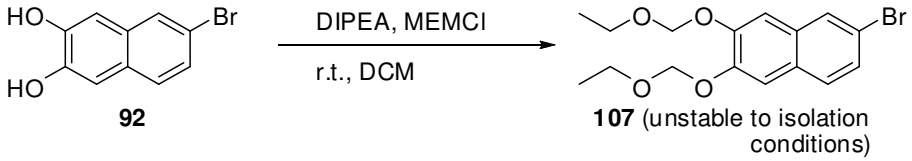
3.2.2 Protection of 6-bromo-2,3-naphthalenediol

Protection of the two hydroxyl groups was necessary prior to subjecting **92** to transition metal catalyzed cross couplings. Over the course of the project several protecting groups were tested based on the requirements of the coupling reactions. Protection with MOM groups was chosen

first due to their stability in basic conditions as well as for ease of deprotection using catalytic amounts of acid.



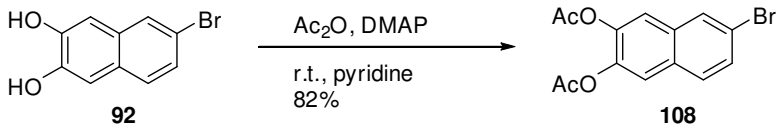
Even when MOMCl was used in significant excess, the yields for this protection were moderate. The quality of the DIPEA played an important role in the conversion, as well as the dryness of the solvent, which could impede the protection reaction. The ^{1}H NMR of **106** showed the presence of two singlets integrating for two each at 5.34 ppm and 5.344 ppm and two singlets integrating for three protons each at 3.495 ppm and 3.497 ppm proving the presence of two chemically unique MOM protecting groups. Furthermore, due to distribution problems, MOMCl became expensive and not as readily available from commercial sources. MEMCl was used as a potential alternative, which has comparable properties to the MOM equivalent, however it was lower in price and easily attained from commercial sources.



MOM protection conditions were used to add the desired MEM groups onto **92** assuming similar reactivity. This reaction afforded no product and only starting material was recovered. A second attempt was carried out starting directly at room temperature and letting the reaction stir for two days. Again, only a trace amount of product was present in the crude. Finally, the reaction was carried out using 3.7 equivalents of MEMCl and let react over two days while monitoring by TLC at which time no starting material could be observed. Following work up with sat. NH_4Cl aq. solution and extraction, the crude was purified by flash column

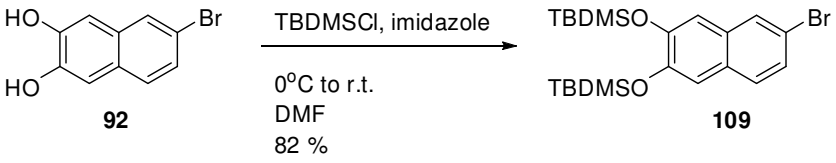
chromatography; no product was recovered from the column, however starting material was found in the aqueous layer demonstrating that the MEM groups were labile in saturated NH_4Cl solution. Due to its labile nature, MEM was not further used as a protecting group for this class of compounds.

In an attempt to improve the yield of the protection step, the hydroxyl groups were protected with acetyl groups. These groups were chosen for their ease of addition and removal as well as their stability in acidic conditions.



This protection was much more efficient than that using ether groups, it afforded significantly improved yields and was complete after reacting for one hour at room temperature. The ^1H NMR showed two acetyl singlets at 2.33 ppm and 2.34 ppm integrating for three protons each.

Lastly, **92** was protected with TBDMS groups, which are compatible with a large range of coupling reactions, as well as easily cleaved through various pathways. The protection reaction was carried out using freshly recrystallized imidazole to afford good yields with easy purification. Compound **108** was obtained as a colourless oil, and its NMR showed the correct number of *t*But and Me signals.



3.3 Coupling reaction involving 6-bromo-2,3-naphthalenediol

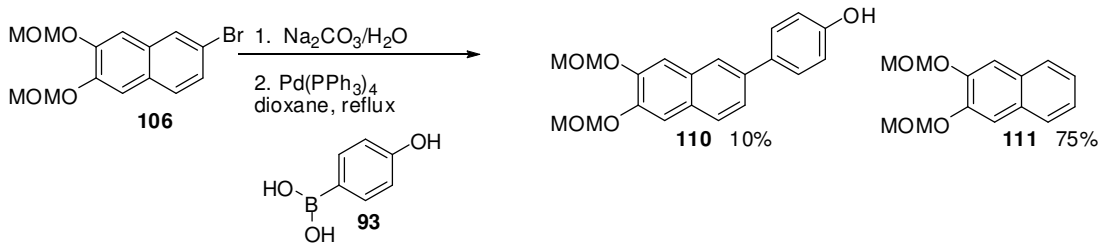
In the planning stages, the generation of compounds **86**-**91** and additional analogues was expected to be straight forward using a variety of well known transition metal coupling reactions such as the Stille, Suzuki and Kumada reactions. In the end, the preparation of these compounds proved very frustrating since generally low yields of desired products were obtained. Often times, the reaction conditions led to either the reduction of **92** or its dimerization at the six position. At other times, when the desired coupling was observed, removal of the protecting group proved problematic. The sections below illustrate the difficulties and frustrations encountered. It appears that the protected 6-bromonaphthalene-2,3-diol is not a good partner in the various organometallic coupling reactions because it is dimerized and reduced more readily than cross coupling. The disappointing reactivity of the 6-bromo-2,3-naphathalene diol including in variously protected derivatives was not anticipated; it made the planning of reaction sequences problematic. In the end despite considerable efforts only a limited number of the desired compounds were prepared. Perhaps the difficulties encountered and described in this thesis could be used to plan further variations or alternate approaches to these molecules.

3.3.1 Synthesis of 6-(4-hydroxyphenyl)naphthalene-2,3-diol (86)

The first compounds to be synthesized in this series contained aromatic D-rings with a *p*-hydroxyl group to satisfy the geometrical requirements to bind to His524 in the ER active site. Although it is still unclear what orientation it would take in the active site, the first compound to be synthesized was the parent 6-(4-hydroxyphenyl)-2,3-naphthalenediol (**86**). Several coupling reactions and substrates were tested to determine the most viable synthetic route to be used as

a general procedure to the synthesis of the analogues in this class with the greatest substrate scope and highest yields.

The most obvious synthetic route to this analogue was to couple protected 6-bromo-2,3-naphthalenediol (**106**) with commercially available 4-hydroxyphenylboronic acid (**93**) via a Suzuki cross coupling reaction. Following the procedure described by *Mewshaw et. al* (2005), compound **106** was dissolved in dioxane and treated with 2N aqueous Na_2CO_3 before adding the Pd catalyst and refluxing in the presence of phenolboronic acid overnight. The reaction mixture was cooled and diluted with sataurated NH_4Cl solution and extracted with EtOAc. Following purification by flash column chromatography only 10% of the desired product **110** were obtained, while the major product isolated in 75% yield was the reduced 2,3-bis(methoxymethoxy)naphthalene (**111**). Compound **110** was not deprotected due to insufficiently low isolated yield.

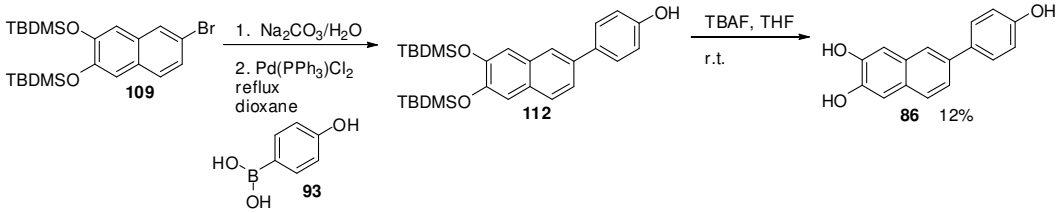


Compound **110** was easy to characterize by ^1H NMR. The five protons from the 2,3-ND scaffold retained the same spitting pattern while H7 and H9 migrated downfield with respect to the starting material. Four sets of singlets, two in the 3.3 to 3.7 ppm region integrating for 4 protons and two in the 1.2 to 1.6 ppm region integrating for 6 protons demonstrated that the MOM protecting groups were intact. Also, four protons signals in the aromatic region as two symmetric multiplets could be identified as *para*-hydroxy D-ring protons. Unfortunately, due to computer problems the NMR data for this compound was lost and cannot be accurately reported in this thesis. This compound was not carried on further due to low isolated yield.

Major product **111** was identified by ^{1}H NMR and HRMS: other than the four protons belonging to the MOM groups, which appeared as singles considerably more upfield than the aromatic protons, the aromatic signals integrated for six protons. The splitting pattern indicated that the molecule was symmetrical and three peaks integrating for two were observed. This material has been prepared by Martin Charron.[65]

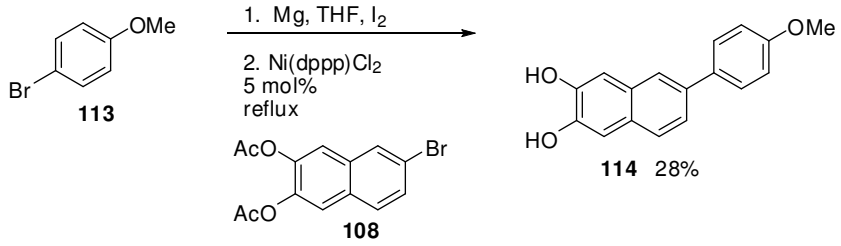
It is possible to rationalize the outcome of this reaction with two reduction pathways. Firstly, reduction can occur following the oxidative insertion of the aryl halide via metal-aryl bond protonolysis in the presence of a proton source.[68] Although this reaction is carried out in a basic medium, water is present in a significant amount and as it is known to complex with Pd it is not unlikely that the water serves as a proton donor and leads to the formation of **111**. This mechanism is possible even in a basic medium. A second route to **111** is through the redox cycling of the palladium in the presence of a hydride source.[69] This is unlikely however as no hydride source exhists in the reaction mixture.

TBDMS-protected starting material **109** was subjected to similar reaction conditions with $Pd(PPh3)_2Cl_2$ as the catalyst. The resulting product **112** could not be purified by flash column chromatography due to its low polarity, and would elute in a mixture of products using 100% hexanes, therefore the crude mixture was subjected to deprotection conditions using a 1 M TBAF in THF solution at room temperature. Following purification by flash column chromatography **86** was isolated in 12% yield over two steps with a 2:1 **97** to **86** ratio by NMR of the crude demonstrating that the reduction of the aryl halide in the cross coupling step is the favored transformation.



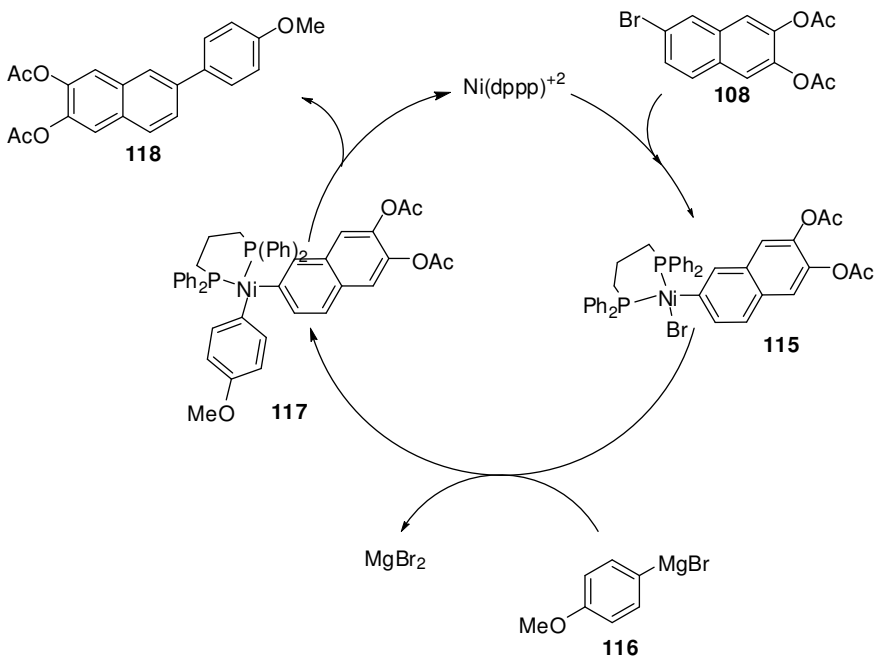
HRMS confimed that **86** had the correct mass. In the ^{1}H NMR spectrum, the D-ring proton signals could be identified at 6.89 ppm and 7.48 ppm as multiplets integrating for 2H each.

Kumada coupling conditions were also investigated for the convenience of using two aryl halides rather than the more expensive aryl boronic acids in Suzuki couplings. Commercially available 4-bromoanisole (**113**) was refluxed with magnesium filings in freshly distilled THF with catalytic amounts of iodine to attain the corresponding Grignard reagent *in situ*. 6-bromonaphthalene-2,3-diyl diacetate (**108**) was added and refluxed in the presence of Ni(dppp)Cl_2 catalyst for 12 hours.



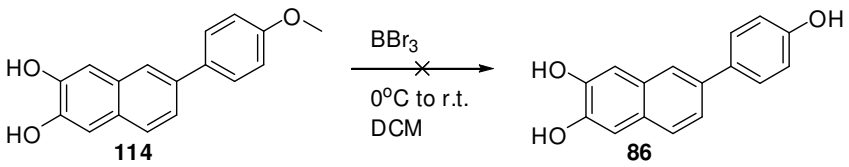
By ^{1}H NMR, **114** was very similar to **86**, however, the methoxy peak between 3.3 and 3.5 ppm demonstrated that the protecting group on the D-ring was present, while no acetyl methyl peaks were present in the upfield region. Again, the NMR data for this compound was lost due to computer problems and cannot be accurately described.

The catalytic cycle for this reaction is similar to that of Pd catalyzed cross coupling reactions (Scheme 9) where oxidative addition of **108** onto the Ni(II) catalyst is followed by transmetalation between the Grignard **116** and the Ni-complex **115** to give Ni-complex **117** and release $MgBr_2$, followed by reductive elimination of the desired product **118**. This reaction was carried out in a large excess of the Grignard, which attacked the acyl carbonyl thereby deprotecting **118** to afford **114**. The product was purified using flash column chromatography to attain the desired coupling product in 28% yield. Unfortunately, the NMR data for these transformations was lost due to a computer malfunction and could not be recovered and is not presented in this thesis.

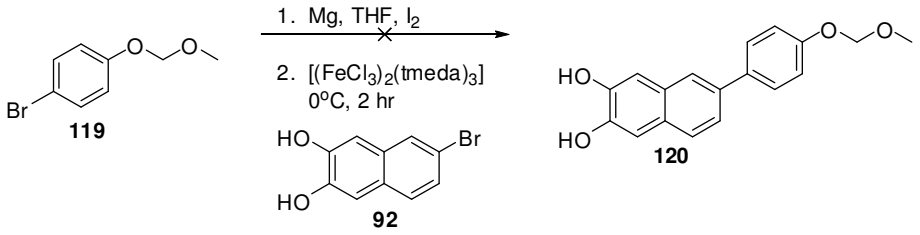


Scheme 9. Catalytic cycle of the Kumada coupling reaction

Although this method showed an improved yield as compared to the Suzuki coupling the subsequent deprotection of the methoxy moiety proved to be a challenge. Upon treatment of **114** with BBr_3 in dry DCM at 0°C to room temperature a complex mixture of products was obtained. Several attempts at isolating the components derived from this reaction were made, but no conclusive evidence of the formation of the product **86**, or identification of the side products was found. The Kumada coupling and demethylation reactions were repeated in an attempt at optimizing the deprotection step, but no final product could be isolated. This unexplained reactivity under standard demethylation conditions suggested that reaction pathways that used methoxy protecting groups should be avoided when synthesizing analogues containing 2,3-naphthalenediols.



A third method was investigated using an iron catalyzed cross coupling reaction.[70] The catalyst for this reaction was first synthesized by slowly adding TMEDA to a solution of $FeCl_3$ in dry THF, at which time $[FeCl_3)_2(tmeda)_3]$ precipitated out of solution as dark red-brown solid. The precipitate was filtered and dried to attain quantitatively the desired catalyst. This complex has been shown to successfully catalyze cross coupling between alkyl Grignards and aryl halides, but no experimental evidence exists to show that this transformation can be carried out between an aryl Grignard and an aryl halide.

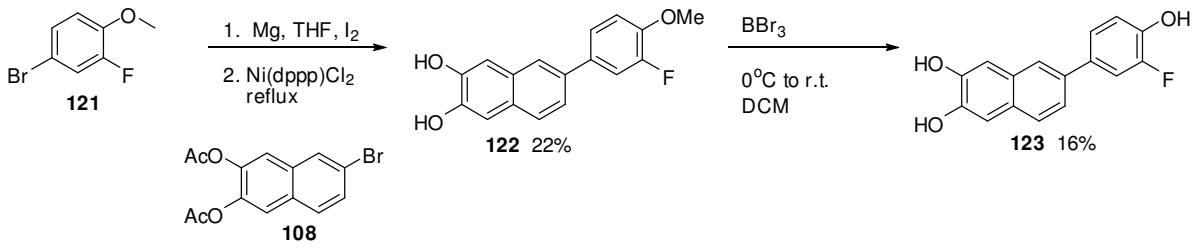


After forming the Grignard of 1-bromo-4-(methoxymethoxy)benzene (**119**) *in situ* by refluxing in THF with magnesium filings and catalytic iodine, **92** and the iron complex were added at 0°C and stirred at this temperature for two hours before the reaction was quenched with 30% HCl and extracted with EtOAc. After purification by flash column chromatography **120** was not recovered, however a large quantity of 4-(methoxymethoxy)benzene dimer was recovered.

3.3.2 Synthesis of 6-(3-fluoro-4-hydroxyphenyl)naphthalene-2,3-diol (123)

The synthesis of 6-(3-fluoro-4-hydroxyphenyl)naphthalene-2,3-diol (**123**) was carried out in parallel to that of **86**. $Ni(dppp)Cl_2$ catalyzed cross coupling was used for this synthesis due to the improved results of the Kumada reaction as compared to the yields attained in the Suzuki reaction.

Commercially available 4-bromo-2-fluoroanisole (**121**) was reacted with magnesium filings to give the respective Grignard *in situ* and coupled with **108**. This reaction afforded **122** in a modest 22% isolated yield (NMR data for **122** was lost).



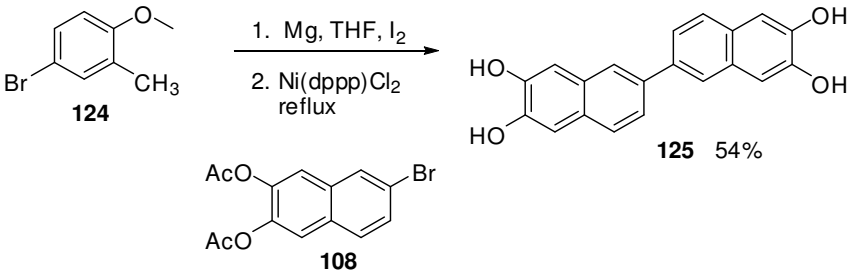
In the last step, **122** was subjected to demethylation conditions in parallel to compound **114**. Surprisingly, the reaction gave a significantly cleaner crude product and 16% of 6-(3-fluoro-4-hydroxyphenyl)naphthalene-2,3-diol (**123**) was isolated. Only 4.8 mg of **123** were synthesized and sent for RTA following characterization. Unfortunately, the NMR data for these transformations was lost due to a computer malfunction and could not be recovered. This compound's poor RTA result (see *Section 2.5.1*) did not necessitate the synthesis of more product and therefore due to lack of spectral data the two reactions described above have not been incorporated into the experimental section of this thesis.

3.3.3 Work Toward the Synthesis of 6-(4-hydroxy-3-methylphenyl)naphthalene-2,3-diol (132)

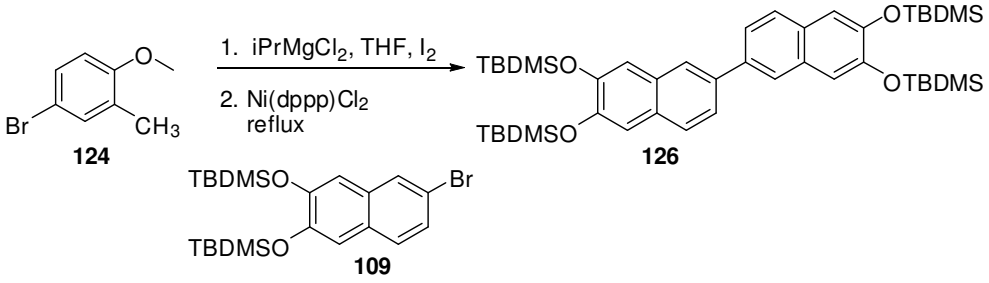
In order to force binding in the AB-D conformation the next compound of interest was 6-(4-hydroxy-3-methylphenyl)naphthalene-2,3-diol (**132**). The computational studies suggested that the addition of the methyl group would prevent the phenol moiety from fitting into the pocket in the active site where the A-ring is normally found. Furthermore, the methyl group would increase the analogue's lipophilicity, which would improve its bioavailability as well as decrease the de-solvation energy when bound to the active site.

Following the success of the Kumada reaction and subsequent demethylation of **123**, 4-bromo-1-methoxy-2-methylbenzene (**124**) was subjected to Grignard conditions, then **108** and the Ni(II) catalyst were added and refluxed for 24 hours. Following work up and purification no desired product was recovered, only the 2,3-naphthalenediol dimer **125** in 54% yield, and **92** was

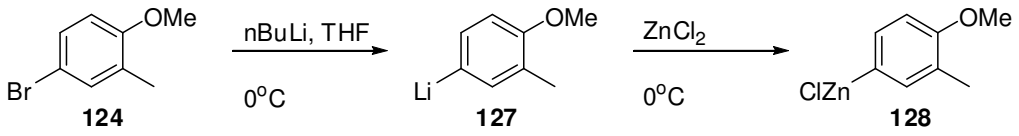
recovered in 45%. The dimer was identified by a combination of ^{1}H NMR and HRMS. At first, the spectrum appeared to be very similar to that of the unprotected starting material although the peaks for protons at positions 6, 7, and 9 were more downfield than those of **92**, while protons 1 and 4 were virtually unaffected. To investigate this furtner, a sample was sumbmitted for mass spectrometry. The compound's mass was found to be 318.087, which corresponded with the dimer and explained the shift of the proton peaks.



1-methoxy-2-methylbenzene was also recovered indicating that the Grignard did not participate in the coupling, but acted as a base. It is known in the literature that Ni(II) can catalyze homocoupling of aryl halides in the presence of a base, although Zn is also typically added.[56] Although **124** was added in large excess to account for the deprotection of **108**, the Kumada coupling was attempted using TBDMS protected **109** instead. The reaction conditions were closely preserved, although instead of magnesium filings *i*PrMgCl$_2$ was used to ascertain a complete conversion to the Grignard intermediate. Once again, the homocoupling product **126** was the major product; the crude mixture was significantly more complex than that of the previous reaction, and isolation by column chromatography of **126** was not successful due to its extremely low polarity, therefore a yield was not obtained. No desired product was observed.

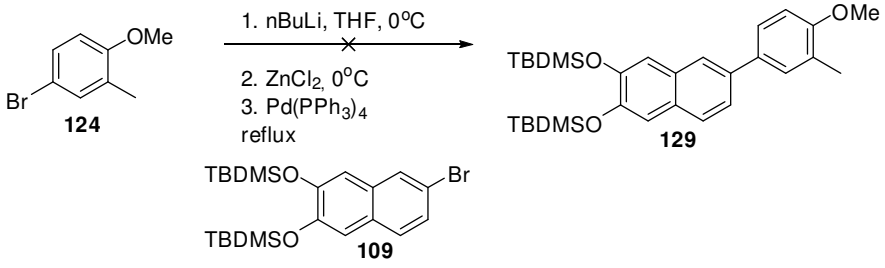


It was apparent that Ni(II) catalyzed cross coupling was not an effective method to attain the desired analogue. Negishi cross coupling conditions were chosen as an alternative, where a Pd(0) is used instead of Ni(dppp)Cl_2. **124** was first converted *in situ* to the organo-lithium intermediate **127** at 0°C in dry THF; $ZnCl_2$ was then dried at high heat under vacuum and added to the reaction mixture to afford organo-zinc chloride intermediate **128** (Scheme 10).

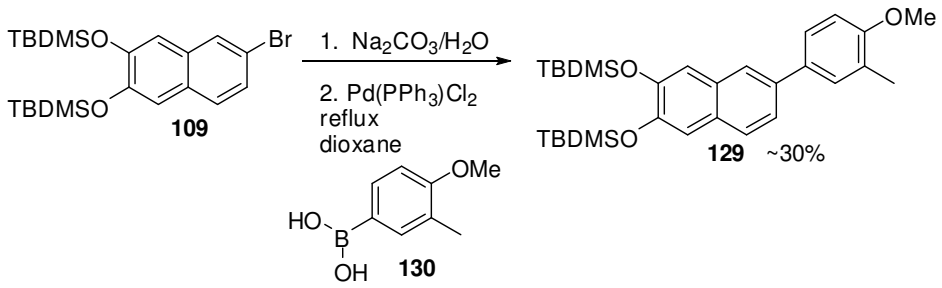


Scheme 10. *In situ* formation of organo-zinc chloride **128** from 4-bromo-1-methoxy-2-methylbenzene (**124**) via the organo-lithium species **127**

Compound **109** was added to the mixture together with palladium tetrakis and the reaction was refluxed for 12 hours, then cooled and filtered over celite and concentrated under reduced pressure. The crude was purified by flash column chromatography and only starting material was isolated.

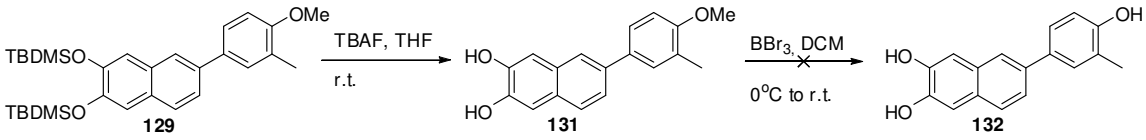


A Suzuki cross coupling reaction was carried out using commercial 4-methoxy-3-methylphenylboronic acid (**130**) and **109**. After refluxing for 12 hours and work up, the desired product **129** was isolated with flash column chromatography. Due to the non-polar nature of this compound, it could not be completely purified from other non-polar contaminants, but it was estimated by NMR that an approximate yield of 30% was obtained.

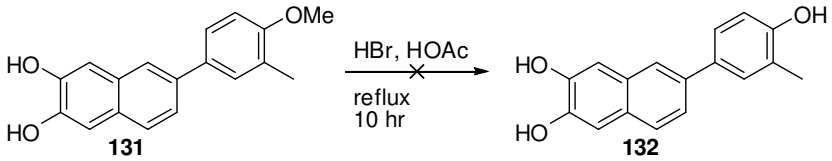


The product **129** was identified based on the presence of the TBDMS methyl groups as two singlets at 0.301 ppm and 0.295 ppm, the *t*Bu groups at 1.054 ppm. The necessary methyl peaks from the D-ring were present at 3.330 ppm for the benzylic methyl and 3.897 ppm for the methoxy group.

This compound was first subjected to desylilation conditions to afford complete conversion to **131** and an estimated yield of 80%. By ^{1}H NMR the TBDMS groups had been removed, while the methyl groups at 2.29 ppm for the benzyling methyl and 3.85 ppm for the methoxy moiety were still present. The aromatic protons for the AB and D rings were in agreement with the predicted shift and splitting. Demethylation was carried out using the same conditions as in the synthesis of **123**, however no **132** was isolated after column chromatography of the complex product mixture.



Demethylation in acidic conditions was attempted using a 33% by volume solution of HBr in glacial acidic acid. Compound **131** was dissolved in HOAc and the HBr solution was added; the resulting mixture was refluxed for 10 hours, then cooled, diluted with water and extracted with EtOAc. No final product was recovered from the complex product mixture.



These conditions were attempted again and for only 5 hours and with ongoing monitoring by TLC, but gave similar results and no product. After these results, two alternative alkyl-containing D rings were investigated (Figure 2.1).

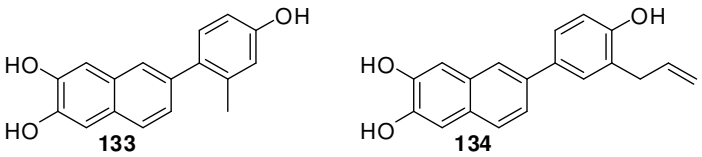
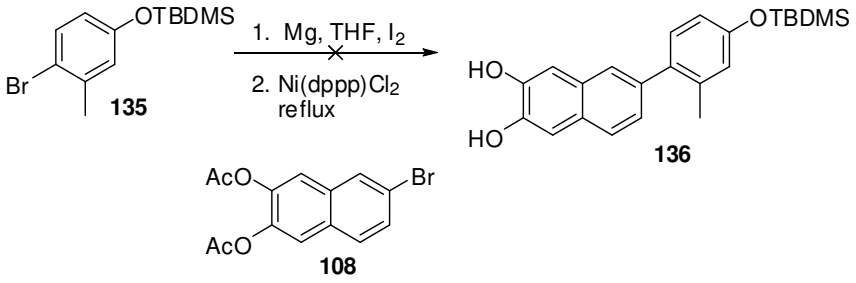


Figure 3.2 Proposed analogues with alkyl (**133**) and allyl (**134**) groups on D ring to increase lipophilicity

3.3.4 Attemped Synthesis of 6-(4-hydroxy-2-methylphenyl)naphthalene-2,3-diol (133)

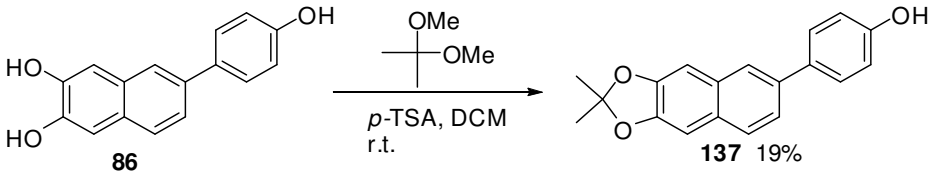
Several attempts at coupling (4-bromo-3-methylphenoxy)(tert-butyl)dimethylsilane (**135**) with **108** and **109** using the Kumada cross coupling conditions were previously described. No desired product was isolated from either reaction, likely due to the increased sterics afforded by the methyl group which may inhibit the transmetalation step in the catalytic cycle. A search of commercially available 4-methoxyphenylboronic acids shows that only the methoxy-protected compound can be purchased; due to previous problems with the demethylation of the final products the Suzuki route was not investigated and this analogue was not pursued further.



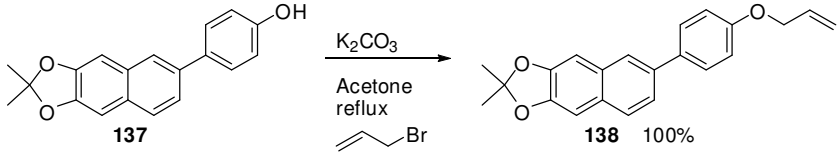
3.3.5 Work Toward the Synthesis of 6-(3-allyl-4-hydroxyphenyl)naphthalene-2,3-diol (134)

Thus far, three distinct routes to the parent compound 6-(4-hydroxyphenyl)naphthalene-2,3-diol (**86**) have been designed. Analogue 6-(3-fluoro-4-hydroxyphenyl)naphthalene-2,3-diol (**123**) was also synthesized using a comparable route. Although these pathways afford the final products in modest yields they are not viable for the synthesis of analogues with bulky methyl groups on the D-ring. A possible solution to this problem was to allylate the D-ring's hydroxyl group on the parent compound and carry out an oxy-Cope rearrangement to allylate *ortho* to the hydroxyl group. Again, allylation of the D-ring would increase lipophilicity and potentially improve the bioavailability and binding to the active site.

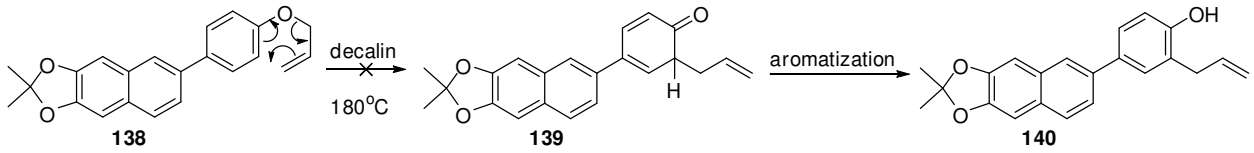
The dihydroxy-moiety of **86** was selectively protected with 2,2-dimethoxypropane in the presence of *p*-TSA. Although the conversion is not very high as 19% of **137** were isolated, 80% of **86** were recovered. The methyls of the protecting groups appeared by ^{1}H NMR at 1.26 ppm as a singlet, while the D-ring hydroxyl proton appeared as a broad signal 4.90 ppm.



The free hydroxyl group was then allylated using allyl bromide at reflux in acetone in the presence of K_2CO_3. This reaction afforded the desired product (**138**) in 100 % yield. By ^{1}H NMR the terminal allylic protons were present at 5.45 ppm and 5.31 ppm as doublets of doublets, while the third allylic proton was a multiplet at 6.09 ppm. The O-CH_2 alkyl protons appeared at 4.58 ppm as a multiplet.



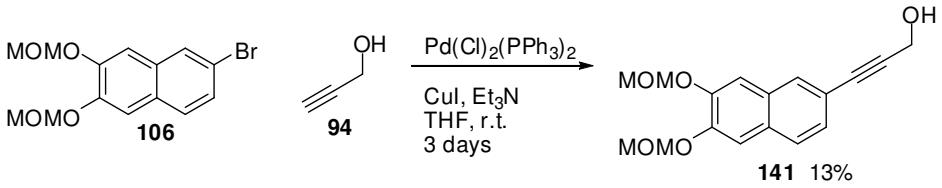
Following allylation, **138** was subjected to oxy-Cope rearrangement conditions at 180°C for four hours. This reaction gave a complex mixture of products that did not appear to contain the desired product **140**. This reaction was only attempted once due to time constraints.



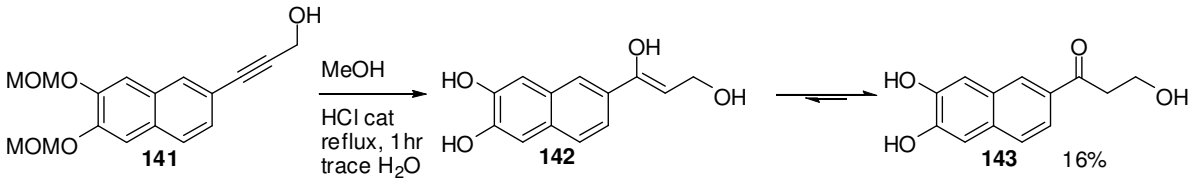
3.3.6 Synthesis of 6-(3-hydroxyprop-1-ynyl)naphthalene-2,3-diol (90)

When considering the synthesis of analogues with a non-aromatic D-ring equivalent the first priority is to introduce a hydroxyl moiety approximately 10.9 Å from the 3-hydroxyl group of the A-ring. This distance is satisfied when a propargyl alcohol or derivative is coupled to the protected 6-bromo-2,3-dihydroxynapthalene. The first compound to be synthesized in this subclass is the parent 6-(3-hydroxyprop-1-ynyl)naphthalene-2,3-diol (**90**).

The first attempt at synthesizing 6-(3-hydroxyprop-1-ynyl)naphthalene-2,3-diol was carried out by Lina Chan. The Sonogashira cross coupling of MOM protected **106** and unprotected propargyl alcohol (**94**) was performed with $Pd(Cl)_2(PPh_3)_2$ as catalyst in the presence of CuI, Et_3N in THF at room temperature for three days. This reaction afforded the desired product in poor yield (13%). The isolated prodcut **141** showed the methylene protons as a singlet at 4.44 ppm.

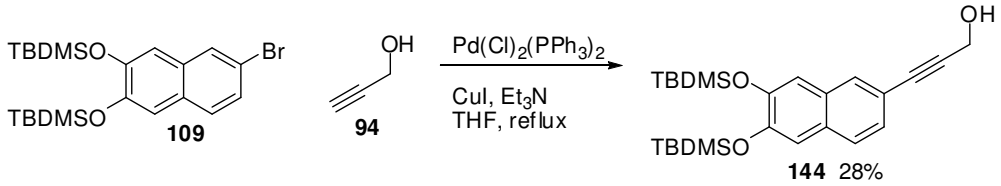


The Sonogashira product (**141**) was carried forward to the deprotection in methanol with a catalytic amount of concentrated HCl at reflux.

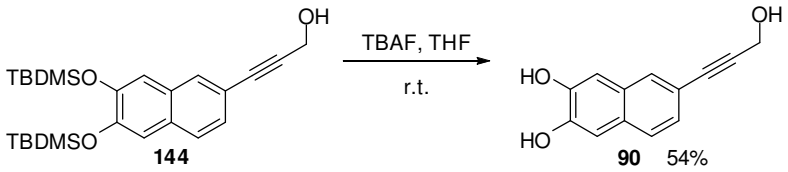


During this transformation, a single product was isolated. By ^{1}H NMR this product did not have the methylene proton singlet instead the spectrum contained two triplets at 2.72 ppm and 3.74 ppm. The spectrum showed the absence of peaks due to the MOM groups, indicating that the compound was no longer protected. Furthermore, it was apparent that the unknown molecule no longer contained a triple bond as two alkyl protons had been added. By ^{13}C NMR a carbonyl peak had formed at 198.1 ppm leading us to believe that the triple bond had been hydrate to the diol **142**, which tautomerized to give the final product **143**. Unfortunately this compound is probably too polar to be of value for bioassays.

The Sonogashira cross coupling was repeated with a protecting group that could be removed under non–acidic conditions. Thus the TBDMS protected substrate **109** was refluxed for 16 hr under typical Sonagishra reaction conditions to afford **144** in an improved yield of 28%. ^{1}H NMR of **144** showed that the methylene proton was present at 4.44 ppm as a singlet, also the methyls of the TBDMS protecting groups appeared as singlets 0.31 ppm and 0.32 ppm and the *t*Bu groups as singlets at 1.043 ppm and 1.044 ppm.



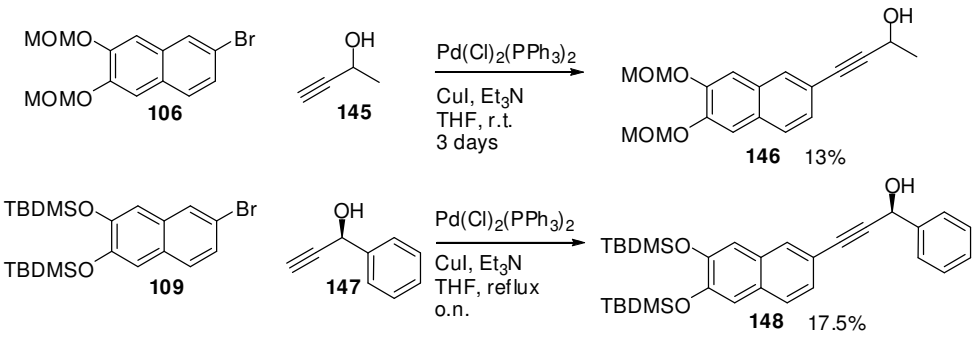
Product **144** was then subjected to deprotection conditions in THF with TBAF. The desired product, 6-(3-hydroxyprop-1-ynyl)naphthalene-2,3-diol (**90**) was isolated in 54% yield.



The ^{1}H NMR of **144** was consistent with the assigned structure showing a 2H singlet at 4.42 ppm which corresponds to the methylene protons in addition to the expected five aromatic hydrogens belonging to the naphthalene moiety.

3.3.7 Synthesis of 6-(3-hydroxybut-1-ynyl)naphthalene-2,3-diol (149) and (S)-6-(3-hydroxy-3-phenylprop-1-ynyl)naphthalene-2,3-diol (150)

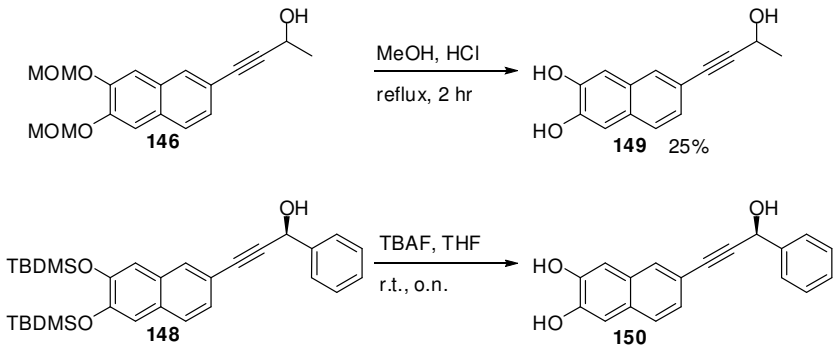
The subsequent targets in this subclass of AB-D ring compounds were chosen to be more lipophilic with small to large substituents on the D-ring-type moiety. Readily available but-3-yn-2-ol (**145**) and (R)-1-phenylprop-2-yn-1-ol (**147**) were chosen for coupling with the AB-ring moiety.



As expected, compound **146** contained a quartet at 4.77 ppm for the methine proton and a doublet at 1.55 ppm belonging to the terminal methyl group. The protons due the MOM protecting groups remained unchanged indicating that no deprotection occurred during this reaction. Similarly, the methine proton of **148** could be easily identified as a singlet at 5.72 ppm. Although the phenyl peak overlapped with the naphthalene peaks, the correct number of protons was present in the aromatic region.

Intermediates **146** and **148** were deprotected using the appropriate conditions. The deprotection of **146** to attain 6-(3-hydroxybut-1-ynyl)naphthalene-2,3-diol (**149**) gave a modest purified yield of 25%.

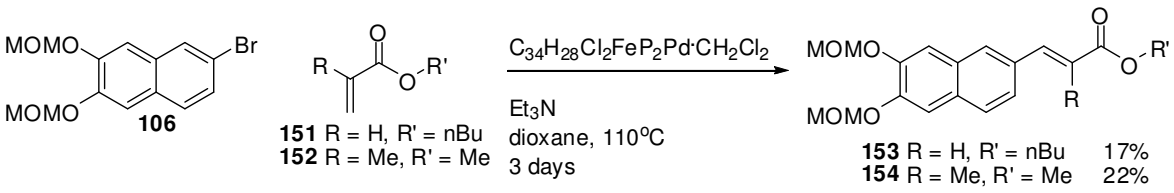
The deprotection of **148** was more problematic. The ^{1}H NMR of the product after chromatography showed the presence of residual N(*n*Bu)$_3$ in addition to the desired (S)-6-(3-hydroxy-3-phenylprop-1-ynyl)naphthalene-2,3-diol (**150**). The ^{1}H NMR of **150** showed the required number of aromatic H's in addition to the benzylic proton peak at 5.72 ppm. Recrystallization was attempted using Et_2O and hexanes and although this successfully eliminated the N(nBu)$_3$ contamination, the alkyne had parially hydrated during this procedure. The presence of the desired prodcut was indicated by the NMR of the mixture which showed the expected methyl group as a 3H doublet at 1.46 ppm and the methane proton as a quadruplet at 4.70 ppm. Beacuse of its facile hydration, this product was not pursued further.



3.3.8 Synthesis of AB-D (E)-3-(6,7-bis(methoxymethoxy)naphthalen-2-yl)prop-2-en-1-ol (155) and (E)-6-(3-hydroxy-2-methylprop-1-enyl)naphthalene-2,3-diol (158)

The geometry of the pharmacophores can also be satisfied when an allyl alcohol is used as the D-ring moiety, which can be accessed via a Heck cross coupling between **106** and commercially available butyl acrylate (**151**) and methyl methacrylate (**152**) with **106**. The coupling was

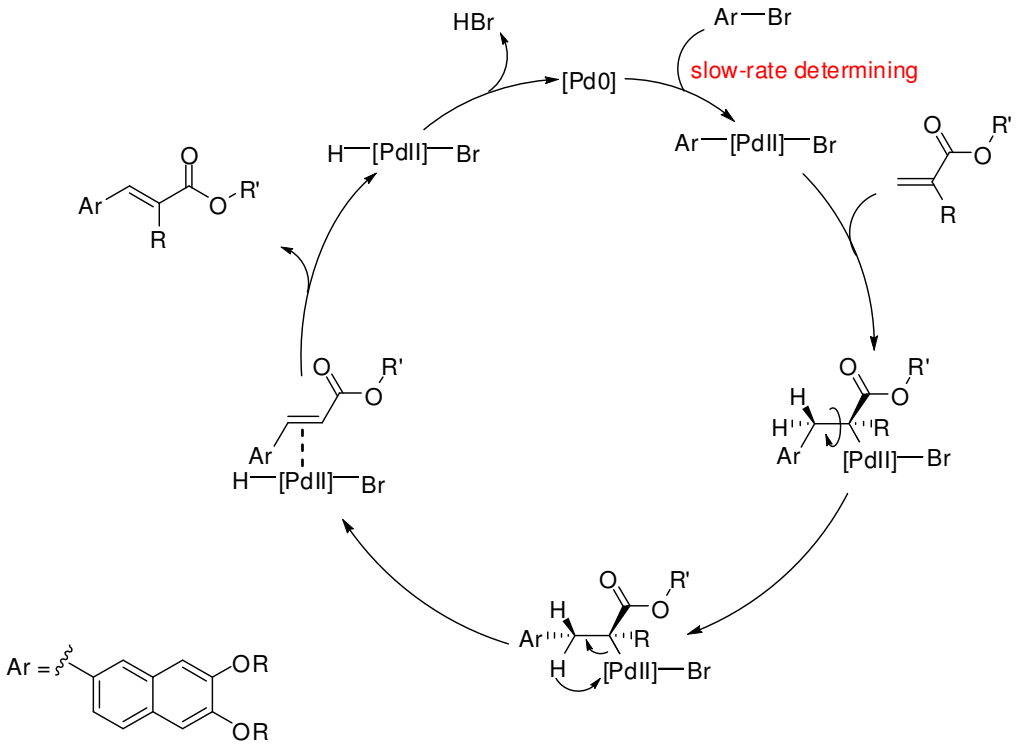
catalyzed by 1,1'-bis(diphenylphosphino)ferrocene-palladium(II)dichloride dichloromethane complex, which gave a two fold increase in yield compared to palladium acetate; nevertheless, the yields for the cross couplings were low. NMR studies of **153** showed that the coupling gave exclusively the *trans* double bond.



The formation of compound **153** was confirmed by proton NMR where the terminal methyl group of the butyl chain appeared at 0.96 ppm as a triplet, with the rest of the chain's protons as a sextet at 1.43 ppm, a quintuplet at 1.68 ppm and a triplet at 4.21 ppm. The vinyl proton appeared as doublets at 6.48 ppm and 7.77 ppm, where the coupling constant was equal to 16 Hz, which demonstrates that they are *trans* to one another.

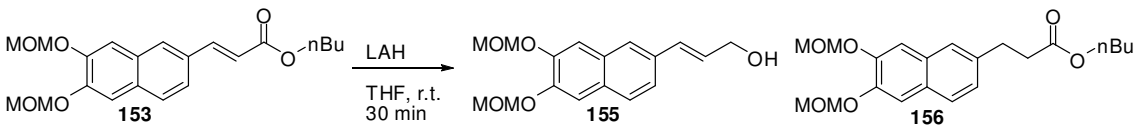
In the proton spectrum of **154** the allylic methyl proton peak was at 2.13 ppm and had a weak coupling to the allylic proton at 7.37 ppm. The methyl ester peak appeared as a singlet at 3.82 ppm. By ^{13}C NMR, both **153** and **154** contained carbonyl groups at 167.3 ppm and 169.3 ppm respectively.

The overall poor performance of 2,3-ND compounds in transition metal catalyzed cross couplings may be due to the deactivating effect of the dihydroxyl group, which reduces the rate of oxidative insertion of the transition metal into the 2,3-ND-Br bond and limiting the conversion (Scheme 11). Suggestions for future improvement of such transformations are described in *Section 3.3.13*.



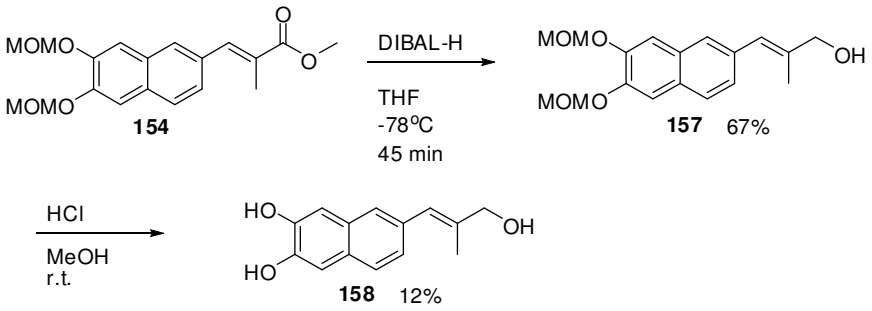
Scheme 11. Catalytic cycle of a generic Heck reaction; the nature of the aryl group decreases the rate of the oxidative insertion at the top of the cycle thereby limiting the conversion of the reaction

Subsequently, **153** was carried forward to the reduction step with LAH in THF at room temperature. After work up and purification by flash column chromatography only a trace amount of (E)-3-(6,7-bis(methoxymethoxy)naphthalen-2-yl)prop-2-en-1-ol (**155**) was attained. The reduction of the double bond via a 1,4-hydrdide addition and subsequent tautomerization of the enol to the ester (**156**) was the major reaction. This reaction was carried out on the small amount of **153** obtained from the Heck coupling leaving no more starting material to subject to reduction conditions.



Methyl methylacrylate analogue **154** was subjected to reduction conditions at -78°C in the presence of DIBAL-H for 45 min. This transformation was much more successful and (E)-3-(6,7-

bis(methoxymethoxy)naphthalen-2-yl)-2-methylprop-2-en-1-ol (**157**) was isolated in 67%. In the case of compound **157** the methyl peak by ^{1}H NMR once again appeared at a doublet at 1.96 ppm with weak coupling to the allylic proton at 7.27 ppm. The reduction was shown to be successful by the appearance of the CH_2-O as a singlet at 4.21 ppm.

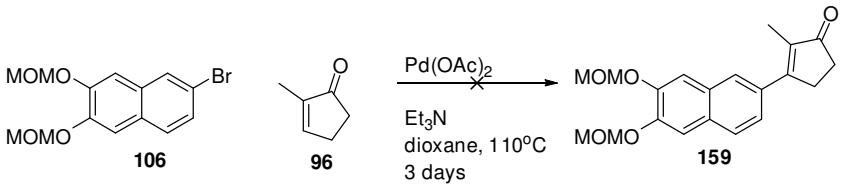


The final deprotection of **157** was carried out by honour's student Lina Chan using standard conditions in MeOH with catalytic amounts of conc. HCl at room temperature. Based on ^{1}H NMR analysis the reaction resulted in a mixture of the desired product (E)-6-(3-hydroxy-2-methylprop-1-enyl)naphthalene-2,3-diol (**158**), as well as the mono-protected intermediate indicating that the deprotection conditions were not rigorous enough to attain complete conversion. Only 12% of impure **158** was isolated from the mixture. The proton NMR of the impure product showed the absence of the MOM groups and the presence of the expected vinyl methyl, vinyl and alkyl protons at 1.92 ppm, 4.13 ppm, and 7.19 ppm respectively. Due to time constraints, no further attempts at deprotecting the intermediates were made.

3.3.9 Work Toward the Synthesis of 6-((1R,2R,3S)-3-hydroxy-2-methylcyclopentyl)naphthalene-2,3-diol (91)

Computational studies of AB-D compounds suggest that 6-((1R,2R,3S)-3-hydroxy-2-methylcyclopentyl)naphthalene-2,3-diol (**91**) could be an excellent ER agonist. This is explained by its close resemblance to the endogenous estrogen and increased flexibility resulting from the removal of the C ring. An attempt at coupling **106** with the commercially available 2-

methylcyclopent-2-enone (**96**) via Heck coupling was carried out by honours student Lina Chan but was unsuccessful and no product was observed.



This is not surprising when considering the alkene-Pd-aryl complex **159** in Figure 3.3, which is much bulkier than that formed when performing a Heck coupling with the acrylates previously described in this chapter, and therefore less likely to undergo this coupling. It can also be hypothesized that the restricted rotation of the ring prevents the alignment of the Pd(II) and βH, thereby impeding the β-elimination and decomposing back to the starting materials.

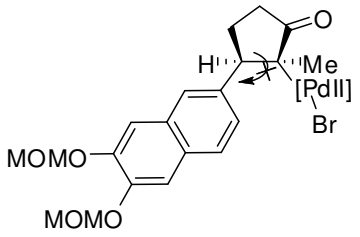
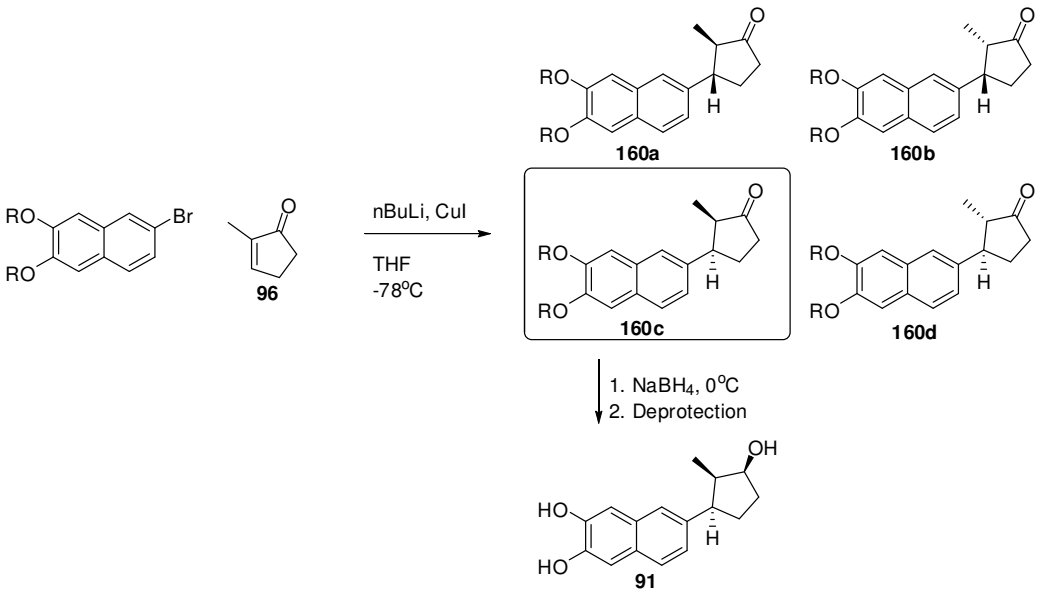


Figure 3.3 2-methylcyclopent-2-enone, 6-bromo-2,3-bis(methoxymethoxy)naphthalene, Pd complex with restricted rotation

An alternative method of coupling these substrates is via a halide-lithium exchange to give the (6,7-dihydroxynaphthalen-2-yl)lithium species *in situ*, followed by a 1,4-addition onto 2-methylcyclopent-2-enone (**96**) in the presence of CuI (Scheme 12). This method is not stereoselective and will give a mixture of four diasteriomers (**160a-d**) that may be separated by prep-HPLC. The desired stereoisomer (**160c**) can then be reduced from the ketone to the free alcohol; similar reduction in the synthesis of CD-ring scaffolds yields exclusively the desired diastereoisomer, and it can therefore be assumed that it is possible to selectively attain **91** as the final product to this transformation.

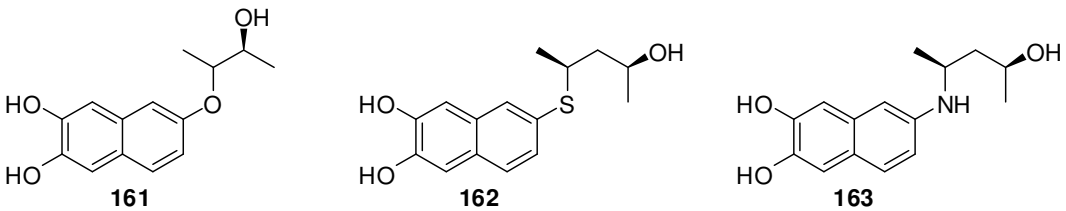


Scheme 12. 1,4-addition onto **96** with lithiated 6-bromo-2,3-ND derivative to give a mixture or diastereoisomers (**160a-d**); isomer **160c** is reduced and deprotected to afford the desired product **91** as the major product

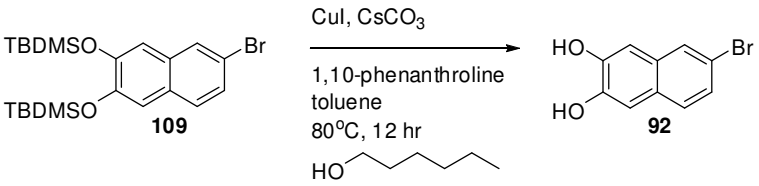
Due to time constraints and the high cost of **96** this reaction sequence has not been investigated, but may be of interest if biological assays show that this family of compounds has potential to produce competitive drug candidates.

3.3.10 Optimization of Ullmann and Buchwald-Hartwig Coupling Conditions Toward the Synthesis of Ether-Containing Analogues

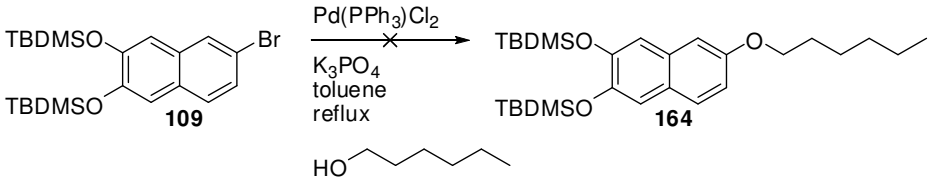
Some interesting analogues may be synthesized by linking the AB and D rings via an ether, thiol, or amine linkage. These compounds can all be attained using Buchwald-Hartwig coupling or Ullmann coupling reactions.



In an attempt to optimize reaction conditions for these couplings a trial reaction was performed using (6-bromonaphthalene-2,3-diyl)bis(oxy)bis(tert-butyldimethylsilane) (**109**) and *n*-hexanol as the substrate. The first reaction attempted was an Ullmann coupling using CuI and $CsCO_3$ in the presence of 1,10-phenanthroline in toluene at 80°C. After reacting for 12 hours, no product was formed and only deprotected starting material was recovered.



A second attempt at coupling **109** with *n*-hexanol using Buchwald-Hartwig conditions was attempted, but no desired product (**164**) was recovered.

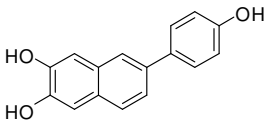
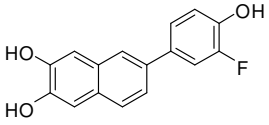
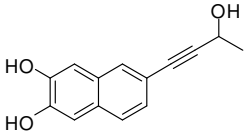
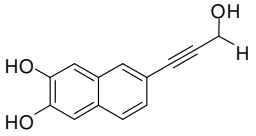


Further investigation into these transformations should be conducted, but was not carried out due to time constraints.

3.4 Bioassay Results

Several compounds from this class were sent for RTA bioassay, including two analogues with aromatic D-rings, **86** and **123**, **149** and **90**. The data from these bioassays is summarized in *Table 3.1*.

Table 3.1 RTA data for **86**, **123** and **149**, and RBA for **90**

Entry	Analogue	RTA (estradiol=100)		
		ERα	ERβ	RTA(β)/RTA(α)
1		0 (negative)	6.98	Pure β
2		0 (negative)	5.93	Pure β
3		2.42	0 (negative)	Pure α or noise
		RBA (estradiol=100)		
		ERα	ERβ	β/α
4		0.153	0.360	2.4

[a] The relative binding affinity (RBA) assays were carried out by the Katzenellenbogen group at the University of Illinois. Relative binding was measured as the competition for binding between ^{3}H-labeled estradiol and increasing concentrations of the analogue. RBA was quantified as a measure of displacement in radioactivity of estradiol where the value for estradiol is set to 100 % for both receptors.

[b] The relative transcription activation (RTA) assays were carried out by the Pratt group at the University of Ottawa. COS-7 cells were transfected with plasmids containing sequences for the ERE-luciferase reporter and either ERα or ERβ. The RTA of the ligand at concentration 10 nM was compared to the one of estradiol at that concentration for each receptor.

Although the RTA values for **86** and **123** are not very high as compared to estradiol, they are markedly selective for ERβ and in fact, it appears that there is no binding to ERα. This trend is very promising, and further SAR should be conducted. The reduced binding may be attributed to lower bioavailability of these analogues. As discussed in *Section 3.1* the increased polarity of 2,3-ND compounds may impede the delivery of the analogue to the active site due to its predominantly non-polar surface. Therefore, the next compounds in this series should contain alkyl substituents to reduce desolvation energy. Furthermore, evidence exists to support the theory that flat, non-polar structures are capable of intercalating into DNA, which not only prevents the compounds from reaching the active site, but can also lead to potentially severe side effects.[71]

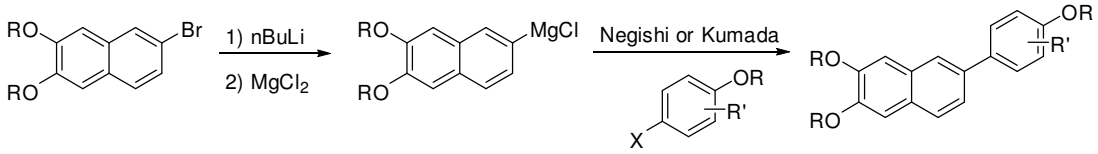
Analogue **90** was not tested for RTA, but appears to be only mildly selective for ERβ. Furthermore the binding is weak, which may be due to the poor lipophilicity of this compound due to the absence of most of the C and D rings, which would reduce the desolvation energy of binding and make it less favourable.

The most surprising result was compound **149**, which did not bind to ERβ but had some affinity for ERα. Considering the computational data, it is possible that this reversal of selectivity is due to the orientation of the compound when it enters the active site, since **86** and **123** are more likely to act as A-CD analogues than **149** and **90**. More compounds with a linear, or non-aromative D-ring should be tested to evaluate the validity of this theory, as well as some compounds with alkylated, aromatic D-rings, which are also most likely to enter the active site as A-CD systems.

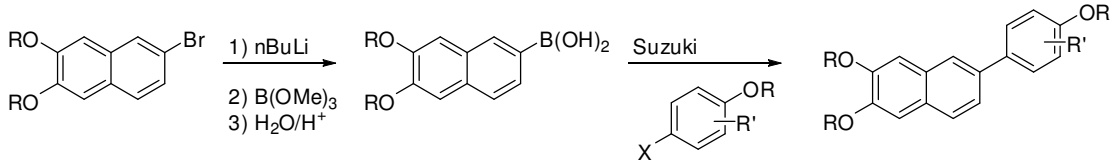
3.5 Future Perspective on the Synthesis of AB-D Analogues

The most viable route to a large variety of AB-D, 2,3-napthalenediol containing analogues is through transition metal catalyzed coupling reactions. The syntheses achieved thus far show that using protected 6-bromo-2,3-naphthalenediol as the aryl halide in such reactions leads to low yields. It is possible to invert the role of the starting materials, which may improve the conversion and yield of cross-coupling reactions with this substrate.

To optimize the Negishi and Kumada reactions, it is possible to treat protected 6-bromo-2,3-naphthalenediol with nBuLi to afford the lithiated intermediate *in situ*, which would give the Grignard reagent when reacted with $MgCl_2$. The same can be done to make the zinc derivative and used in a cross coupling reaction with either aryl or alkyl halides.

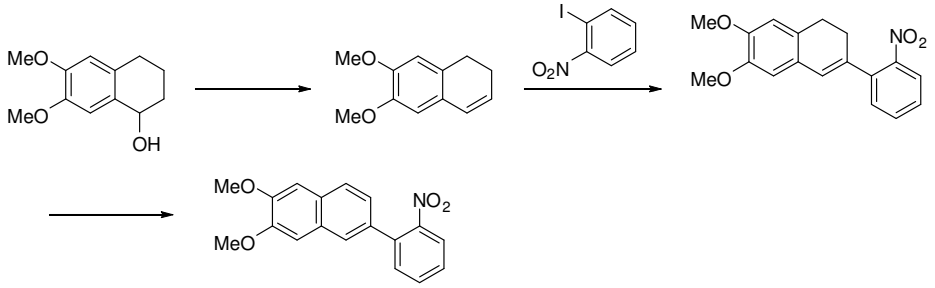


It is also possible that the conversion and yields of Suzuki couplings can be improved by making the boronic acid from the procted 6-bromo-2,3-naphthalenediol by treating it with nBuLi, followed by reaction with trimethyl borate, which is hydrolyzed to the respective boronic acid under acidic conditions (Scheme 47). This acid may then be reacted with a wide range of D rings and may allow access to a variety of analogues.



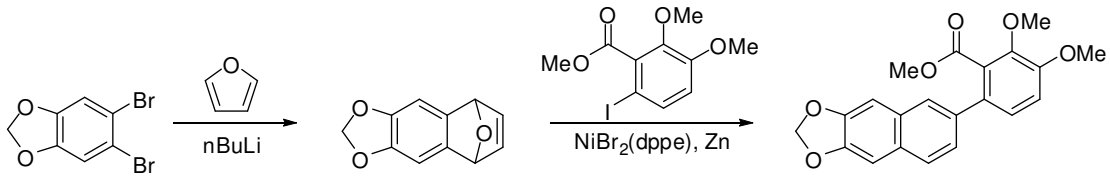
Literature searches for compounds containing the desired dihydroxy pattern show that the standard synthetic routes to these structures do not use 2,3-ND as the substrate, in fact they begin with a monoaryl starting material, which is later cyclized and aromatized to the naphthalene subunit following couping with the D-ring type moiety. Some examples of such

transformations include work carried out by *La Voie et al.* where commercially available 6,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-ol was dehydrated to attain the respective benzylic alkene which was coupled with the desired aryl halide (Scheme 13).[72]



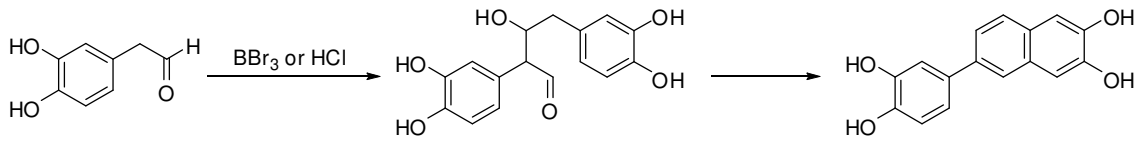
Scheme 13. Dehydration, Heck coupling and aromatization of 6,7-dimethoxy-1,2,3,4-tetrahydronaphthalen-1-ol to attain the desired A-CD type structure

A synthetic route described by *Cheng and Madan* showed the use of a nickel catalyst to couple an aryl halide to a 7-oxabicyclo[2.2.1]hept-5-ene system fused to the A-ring equivant (Scheme 14).[73]



Scheme 14. Formation of the 7-oxabicyclo[2.2.1]hept-5-ene system on 5,6-dibromobenzo [1,3]dioxole

A last example of the synthesis of 2,3-ND containing compounds starting from simple mono-aryl substrates was demonstrated by *Cotelle et al.* in 2001. Commercially available 2-(3,4-dihydroxyphenyl)acetaldehyde underwent an aldol condensation with itself in the presence of HCl or a Lewis Acid to form the aldol intermediate *in situ*. This intermediate cyclizes onto itself and dehydrates twice to attain the aromatized product (Scheme 15).



Scheme 15. Aldol condensation of 2-(3,4-dihydroxyphenyl)acetaldehyde to give the aldol intermediate, which cyclizes and aromatizes to 6-(3,4-dihydroxyphenyl)naphthalene-2,3-diol

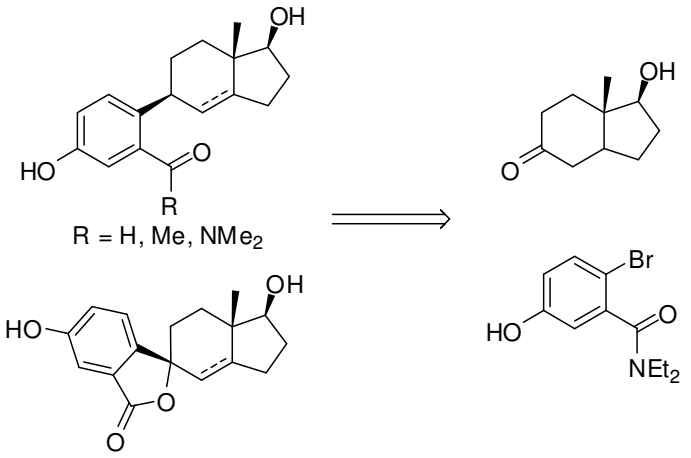
Based on these examples in literature the possibility of starting with mono-aryl substrates should be investigated. Due to time constraints these methods were not pursued, however, given future interest in this class of compounds these alternate routes should be considered.

4.0 Part C: C5-CHO and C5-Amide Analogues

4.1 Synthesis and Coupling of Novel A-rings

As previously discussed in *Section 2.1.2* our group has identified that substitutions at C5 on the A-ring are not only beneficial for the analogue's activity, but can also discourage the formation of undesirable quinines through deactivation at C4. So far, halides such as F and Cl, methyl, and trifluoromethyl have been tested, however A-rings with C5 aldehydes, ketones or amides have yet to be synthesized.

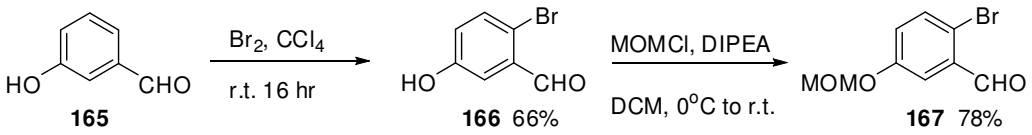
A small component of my master's research focused on the synthesis of A-rings with a protected C5 aldehyde or amide that may be coupled to a CD complex using standard coupling conditions (Scheme 16). This A-ring is particularly interesting to expand our understanding of the effect of C5 substitution on binding and transcription of analogues, as well as prevention of quinone formation. The availability of a derivative with an aldehyde, ketone or ester function at C5 could easily lead to many other derivatives via typical carbonyl group chemistry.



Scheme 16. Proposed retrosynthesis for C5 substituted and C5 spiro analogues starting from 2-bromo-N,N-diethyl-5-hydroxybenzamide

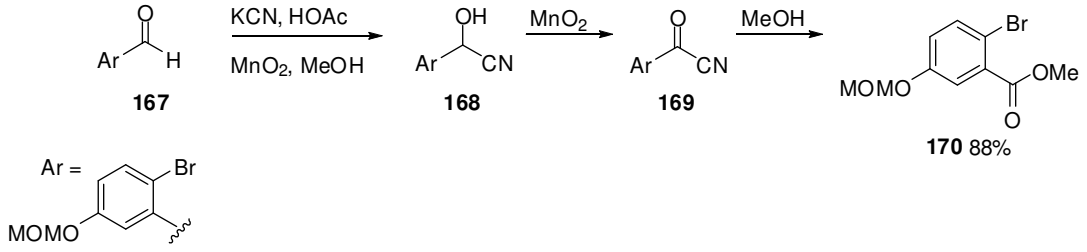
4.1.1 Attempts to Synthesize A-ring 171

The bromination of commercially available 3-hydroxybenzaldehyde (**165**) is a well documented transformation. The dryness of the solvent is of utmost importance, and the CCl_4 must be distilled over calcium hydride before solubilizing **165**; is also important to remove residual quantities of DCM. Liquid Br_2 was added drop wise over 15 minutes to the mixture and stirred at room temperature under N_2 atmosphere. The reaction was stirred for 16 hours before being diluted with DCM and quenched with water. The crude compound was then diluted in a minimal volume of EtOAc and **166** precipitated with hexanes. The prodcut thus obtained was of sufficient purity and subjected directly to MOM protection conditions without further purification. The ^1H NMR data for compound **166** was in accordance with that from the literature, and clearly dispayed a 1,2,4-trisubstitution pattern based on the splitting of the aromatic proton peaks.[60]

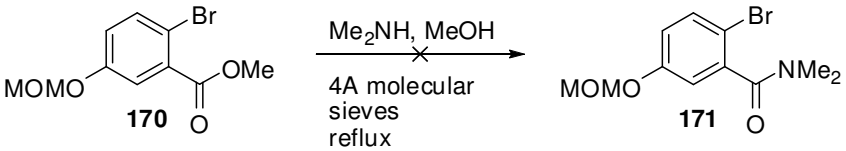


165 **166** 66% **167** 78%

Protected intermediate **167** was then reacted under esterification conditions described by *Corey et al.*, to afford the methyl ester **170**.[74] The aldehyde was sulibilized in MeOH and acetic acid, then potassium cyanide and MnO_2 were added and the reaction was stirred for 12 hours. In this one pot reaction, the first product is cyanohydrin **168**, which is oxidized *in situ* by MnO_2 to give acyl cyanide **169** that is attacked by MeOH to release cyanide and afford the methyl ester (**170**). This reaction sequence was carried out by Daria Klonowska but not taken further toward the synthesis of 5-amino A rings.[60]



To attempt coupling the A-ring the ester was converted to an amine intermediate based on work conducted by Victor Snieckus on ortho-deprotonation of benzylic esters and amides with *sec*-BuLi showing that such substrates can withstand reaction conditions in the presence of Bu^-.[75] More specifically, there is precedent to believe that diethylamide can be coupled using standard conditions without resulting in the alkylation of the carbonyl carbon. The first attempted amide synthesized was done with an excess of dimethylamine at reflux in MeOH in the presence of 4Å molecular sieves. The reaction was refluxed for approximately 14 hours and only staring material was recovered, no carboxylic acid was detected indicating that hydrolysis of the ester was not a problem.



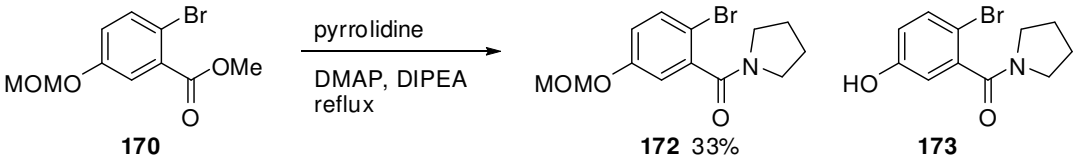
4.1.2 Synthesis of (2-bromo-5-(methoxymethoxy)phenyl)(pyrrolidin-1-yl)methanone (172)

The same reaction was carried out with the somewhat more nucleophilic pyrrolidine, however the reaction did not yield any product and only starting material was recovered.

Ester **170** was reacted then with pyrrolidine in the presence of DMAP and DIPEA at reflux for three days to afford the desired product (**172**) in 33% yield. The pyrrolidine protons could be identified by ^{1}H NMR as a multiplet at 1.92 ppm and two triplets at 3.19 ppm and 3.69 ppm,

which corresponded to the two CH_2 protons alpha to the nitrogen. Due two hindered rotation around the amine bond, these appear as separate signals.

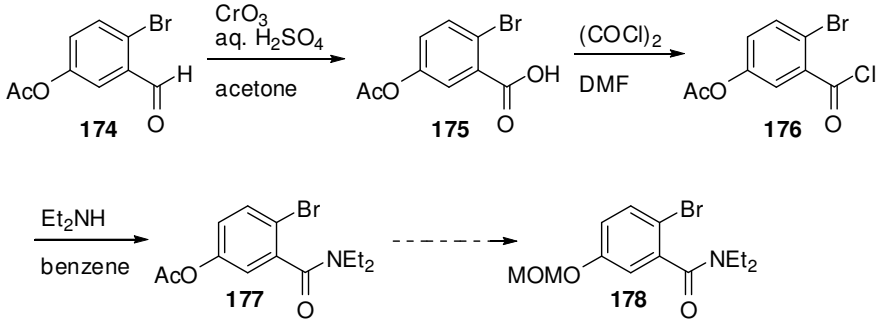
The protecting group was also present, with the MOM methyl as a singlet at 5.13 ppm and the MOM $–CH_2-$ protons at 3.44 ppm. The major product however was the deprotected amide (**173**). The two compounds, **172** and **173** were easily separated on column chromatograaphy; no starting material was recovered.



170 **172** 33% **173**

These reaction conditions were attempted using diethyl amine in place of pyrrolidine to prepare diethylamide, which was used prominently in the publications by Victor Snieckus. Even following three days at reflux no product was formed based on complete recovery of the starting material.

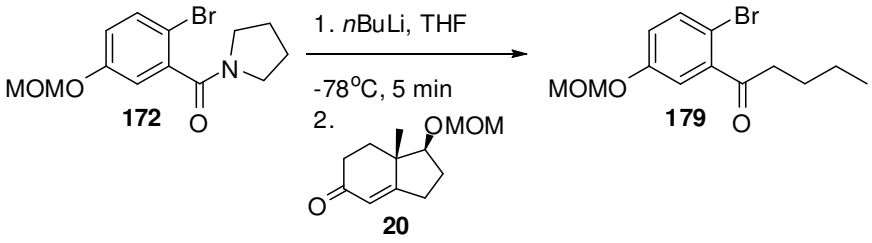
A potential new route to the dietylamide has been designed starting from brominated benzaldehyde **174**. The first proposed step is the oxidation to the carboxylic acid (**175**) using Jones reagent, followed by formation of the acid chloride (**176**), which is reacted with diethylamine to afford the desired product (**177**). This compound would have to be reprotected with a MOM ether to ensure that it could withstand coupling conditions. Due to time constraints this route has not been investigated.



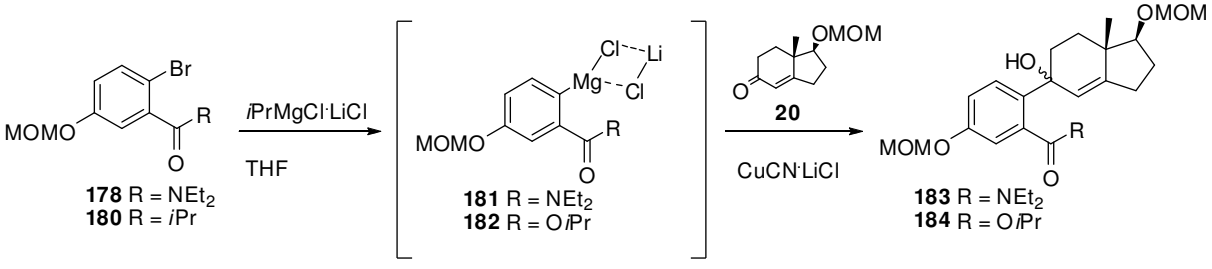
174 **175** **176** **177** **178**

4.1.3 Attempted Coupling of 5-amide A-Rings

A model study was carried out to evaluate the stability of **172** under standard coupling conditions using **178** as the model for the CD-ring system. No coupling product was recovered. The product isolated was shown to be the ketone **179** based on its unambiguous proton NMR which showed the loss of the pyrrolidine group and the introduction of the *n*butyl unit; the original three aromatic H's were still present. Surprisingly, it appears that addition of *n*BuLi to the amide which leads to a tetrahedral intermdiate and then the ketone **179** upon aqueous workup is preferred over the bromine lithium exchange.



Although this coupling reaction may prove to be more successful using **178**, an alternative coupling method using Knochel chemisty can be suggested. Using **178**, or a more hindered benzylic ester, such as **180** a Grignard reagent stabilized by LiCl salt can be formed *in situ*, and reacted with the defired CD ring system, such as **20**.[76] The reaction can be run at higher temperatures than the standard coupling described in this thesis and may be a useful route to synthesizing A-CD analogues containing more sensitive functional groups. This sequence was not attempted as part of this thesis.



5.0 General Conclusions

A varied array of estrogen agonists have been synthesized to be tested as HRT medications. Some compounds have already undergone the first, most basic bioassay screening to determine whether they are viable drug candidates. So far, the best candidates in the series discussed in this thesis are the C8-substituted analogues, which bind estrogen receptors at a sufficiently low concentration and also demonstrate a high level of selectivity for ERβ.

13-Et analogues on the other hand underperformed and not only did they have a low binding affinity to the estrogen receptors, but also little selectivity. This may be due to the inverted stereochemistry at C14 and before these compounds are discounted as possible HRT drugs then natural isomer should be synthesized and tested.

The non-steroidal AB-D compounds showed some promise, however, the synthesis of these molecules was not simple and resulted in few analogues being made and tested. A new route should be explored that would allow for the synthesis of more compounds with aromatic D rings, which had the highest ERβ selectivity.

6.0 Experimental

General information. All reactions were performed in oven-dried evacuated vessels under argon atmosphere unless otherwise specified in the procedure. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 μm). Analytical thin layer chromatography was performed on aluminum sheets pre-coated with silica gel 60 F254, cut to size. Visualization was accomplished with ultraviolet light and PA stain followed by heating.

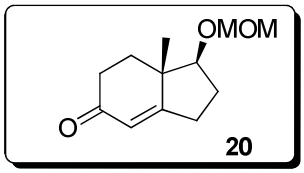
^{1}H NMR spectra were recorded on a Bruker Avance300 (300 MHz) or Avance400 (400 MHz) spectrometer at ambient temperature and are reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm, DMSO-d_6 at 2.50 ppm). Data are reported as: multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz. ^{13}C NMR spectra were recorded on an Avance400 (100 MHz) spectrometer. High-resolution mass spectra were recorded on a Kratos-Concept IIH instrument operated by the Ottawa-Carleton Mass Spectrometry Centre.

Materials. THF was dried by distillation over sodium. Unless otherwise noted, all commercial materials were used without further purification. Reagents were purchased from Sigma-Aldrich and Fluka.

Products. The yields presented in this experimental section are based on the amount of product obtained, regardless of the isolation of starting material.

6.1 Synthesis of the (1S,7aS)-1-hydroxy-4,7a-dimethyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one Component

6.1.1 (1S,7a S)-1-(methoxymethoxy)-7a-methyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (20)

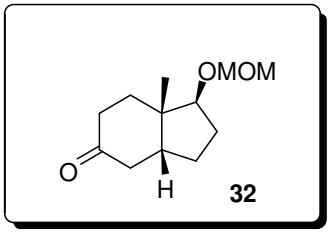


A solution of the Hajosh Parrish enone, **19,** (5.0 g, 30.1 mmol) in 300 mL of DCM was purged with N_2 gas and cooled to 0°C. MOMCl (3.4 mL, 45.15 mmol) was added and the mixture stirred at 0°C for 20 min, DIPEA (6.3 mL, 36.1 mmol) was added drop wise and then the solution was warmed to room temperature and stirred overnight. The reaction was quenched using a saturated NH_4Cl solution (200 mL) and extracted with DCM (3x200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 7:3 Hex/EtOAc elution gradient to afford **20**[77] as a pale yellow oil (5.23 g, 83%), starting material was also recovered (0.9 g, 5.5 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.17 (s, 3H), 1.81-1.86 (m, 2H), 2.22-2.09 (m, 2H), 2.46-2.33 (m, 2H), 2.53 (ddd, J = 17.9, 14.4, 5.3 Hz, 1H), 2.71 (ddt, J = 19.6, 11.6, 2 Hz, 1H), 3.38 (s, 3H), 3.69 (dd, J = 10.2, 7.5 Hz, 1H), 4.65 (dd, J = 6.8 Hz, 1H), 4.70 (dd, J = 6.8 Hz, 1H), 5.78 (s, 1H)

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 199.0, 174.3, 123.2, 96.0, 85.3, 55.3, 44.8, 34.3, 33.2, 26.8, 26.4, 15.8

6.1.2 (1S,3aR,7aS)-1-(methoxymethoxy)-7a-methylhexahydro-1H-inden-5(6H)-one (32)



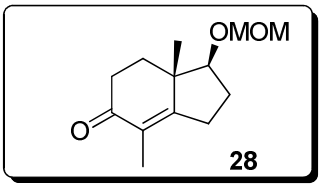
32

A solution of 1.00 g (5.95 mmol) of ketone **31** dissolved in 15 mL of DCM was purged with N_2 and cooled to 0°C prior to the dropwise addition of 0.623 g (7.74 mmol) of MOM-Cl followed 5 min later with 0.923 g (7.14 mmol) of DIPEA. The reaction mixture was stirred for 3 hours at 0°C then quenched with a solution of saturated NH_4Cl (5 mL), diluted with water (10 mL) and extracted with DCM (3 x 10mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc elution solvent to afford **32**[78] as a yellow oil (0.200 g, 16%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 1.17 (s, 3H), 1.59-1.78 (m, 4H), 1.89-1.98 (m, 1H), 2.01-2.11 (m, 1 H), 2.14-2.29 (m, 3H), 2.34-2.47 (m, 2H), 3.37 (s, 3H), 3.74 (t, J = 5.6 Hz, 1H), 4.60 (d, J=6.8 Hz, 1H), 4.67 (d, J = 6.8 Hz, 1H)

^{13}C NMR ($CDCl_3$, 400 MHz) δ ppm 212.5, 95.3, 83.8, 55.1, 43.8, 42.5, 42.1, 36.4, 32.2, 28.9, 28.1, 20.2

6.1.3 (1S,7aS)-1-(methoxymethoxy)-4,7a-dimethyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (28)

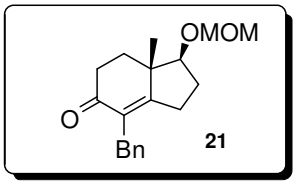


A round bottom flask was charged with NaH, 60% in oil then washed with hexanes (2 x 3 mL). The solvent was removed by pipetting and the resulting slurry was dried under vacuum then weighed (0.10 g, 4.19 mmol). The flask was purged with N_2 gas and freshly distilled DMSO (20 mL) was added. The mixture was stirred and heated to 60°C-65°C for 1h, then cooled to room temperature. A solution of **20** (0.40 g, 1.9 mmol) in distilled DMSO (5 mL) was added and the resulting mixture was stirred at room temperature for 1h. MeI (0.13mL, 2.09 mmol) was added and the reaction mixture was stirred overnight at room temperature. The reaction was quenched with water and extracted with Et_2O (3 x 30 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 1:4 Hex/EtOAc elution solvent to afford **28**[59] as a clear oil (0.090 g, 21 %); (0.030 g, 0.14 mmol) of the starting ketone was also recovered.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 1.06 (s, 3H), 1.58 (s, 3H), 1.87-1.72 (m, 2H), 2.17-2.00 (m, 3H), 2.40-2.27 (m, 2H), 2.57-2.44 (m, 2H), 3.31 (s, 3H), 3.60 (dd, J = 10.4, 7.2 Hz, 1H), 4.59 (d, J = 6.7 Hz, 1H), 4.63 (d, J = 6.7 Hz, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 10.7, 16.0, 25.7, 27.2, 33.2, 34.3, 44.7, 55.2, 85.7, 96.0, 128.7, 167.2, 198.6

6.1.4 (1S,7aS)-4-benzyl-1-(methoxymethoxy)-7a-methyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (21)



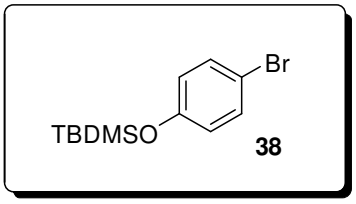
A round bottom flask was charged NaH 60% in oil then washed with hexanes (2 x 3 mL), the solvent was removed by pipetting and the resulting slurry was dried under vacuum then weighed (0.050 g, 2.09 mmol). The flask was purged with N_2. then freshly distilled DMSO (10 mL) was added and stirred at 60°C-65°C for 1 h The solvent wa cooled to room temperature and **20** (0.20 g, 0.95 mmol) in distilled DMSO (2.5 mL) was added. The resulting mixture was stirred at room temperature for 1 h before adding BnBr (0.13mL, 1.05 mmol) and stirring overnight at room temperature. The reaction was quenched with water and extracted with Et_2O (3 x 15 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 4:1 Hex/EtOAc elution solvent to afford **21** as a clear, yellow oil (0.051 g, 18 %) and (3S,3aS)-1,6-bis(benzyloxy)-3-(methoxymethoxy)-3a-methyl-2,3,3a,4,5,6-hexahydro-1H-indene (0.070 g, 0.17 mmol) was also recovered.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 1.16 (s, 3H), 1.90-1.78 (m, 2H), 2.19-2.09 (m, 2H), 2.48-2.36 (m, 2H), 2.67-2.53 (m, 2H), 3.37 (s, 3H), 3.53 (dd, J = 24.4, 14.70 Hz, 2H), 3.69 (dd, J = 10.5, 7.3 Hz, 1H), 4.65 (d, J = 6.7 Hz, 1H), 4.69 (d, J = 6.7 Hz, 1H), 7.12 (m, 3H), 7.24-7.19 (m, 2H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 16.16, 25.7, 27.2, 30.8, 33.3, 34.1, 45.0, 55.3, 85.5, 96.0, 125.7, 128.2, 128.3, 132.3, 139.8, 169.1, 197.8

HRMS: calculated $C_{19}H_{24}O_3$ = 300.1725, found = 300.1712

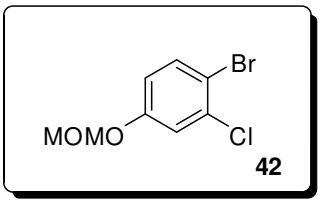
6.1.5 (4-bromophenoxy)(tert-butyl)dimethylsilane (38)



A solution of 4-bromophenol (2.08 g, 12.0 mmol) in DMF (34 mL) was purged with N_2 gas and cooled to 0°C. Imidazole (1.64 g, 24.0 mmol) and TBDMSCl (4.53 g, 30.1 mmol) were added and the mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (30 mL) and washed with 10% HCl (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 100% hexanes elution solvent to afford **38**[79] as a colourless oil (3.27 g, 95 %).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 0.18 (s, 6H), 0.97 (s, 9H), 6.74-6.68 (m, 2H), 7.34-7.29 (m, 2H)

6.1.6 1-bromo-2-chloro-4-(methoxymethoxy)benzene (42)

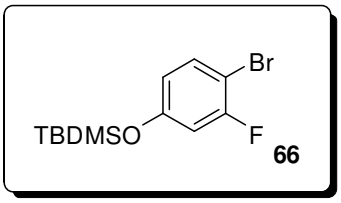


42

A solution of commercially available 4-bromo-3-chlorophenol (1.0 g, 4.82 mmol) in dry DCM (10 mL) was purged with N_2 gas and cooled to 0^{o}C. DIPEA (0.7478 g, 5.79 mmol) was added drop wise to the reaction mixture, stirred for 5 min, and MOMCl (0.582 g, 7.23 mmol) was added. The mixture was stirred for 3 hours at 0°C then quenched with a solution of saturated NH_4Cl (10 mL) and diluted with water (5 mL) and extracted with DCM (3 x 10mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography using a 19:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford **42**[59] as a colourless oil (1.05 g, 86%).

^{1}H NMR: (400MHz, $CdCl_3$) δ 7.48 (d, 1H, J=9.2Hz), 7.18 (d, 1H, J=2.8), 6.83 (dd, 1H, J=6Hz, 2.8Hz), 5.14 (s, 2H), 3.47 (s, 3H)

6.1.7 (4-bromo-3-fluorophenoxy)(tert-butyl)dimethylsilane (66)

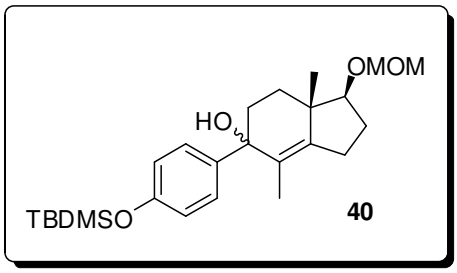


66

A solution of commercially available 4-bromo-3-fluorophenol (2.0 g, 10.5 mmol) in DMF (33 mL) was purged with N_2 and cooled to 0°C, then imidazole (1.43 g, 20.9 mmol) and TBDMSCl (2.37 g, 15.71 mmol) were added. The solution was warmed to room temperature and stirred overnight then diluted with EtOAc (30 mL) and washed with 10% HCl (3 x 30 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 100% hexanes elution solvent to afford **66**[80] as a colourless oil (1.31 g, 62%); starting material was also recovered (0.94 g, 46.8%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 0.18 (s, 6H), 0.95 (s, 9H), 6.52 (ddd, J = 8.74, 2.69, 1.05 Hz, 1H), 6.61 (dd, J = 10.09, 2.69 Hz, 1H), 7.33 (t, J = 8.48 Hz, 1H)

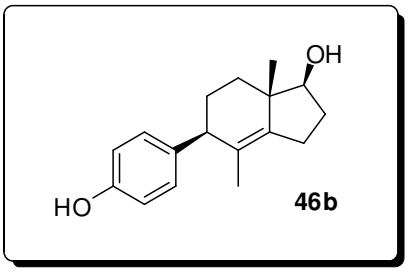
6.1.8 (1S,7aS)-5-(4-hydroxyphenyl)-1-(methoxymethoxy)-4,7a-dimethyl-2,3,5,6,7,7a-hexahydro-1H-inden-5-ol (40)



A solution of protected phenol **38** (0.686 g, 2.39 mmol) in THF (15 mL) was purged with N_2 gas and cooled to -78°C. *n*BuLi (0.21 mL, 2.39 mmol) was added drop wise and the reaction mixture was stirred for 10 minutes. A solution of ketone **28** (0.357g, 1.59mmol) in THF (2 mL) was added drop wise at -78°C and the mixture was stirred for 1 hour then warmed to room temperature. The reaction was quenched with a saturated solution of NH_4Cl (10 mL), diluted with water (10 mL) and extracted with EtOAc (3 x 10mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified using flash column chromatography with a 9:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford **40**[59] as an oil (0.253 g, 25%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 0.19 (s, 6H), 0.97 (s, 9H), 1.08 (s, 3H), 1.45 (s, 3H), 1.61 (dt, J= 13.6, 3.2 Hz, 1H), 2.07 (s, 1H), 2.10-2.22 (m, 2H), 2.26-2.45 (m, 2H), 3.33 (s, 3H), 3.59 (dd, J = 8, 2 Hz, 1H), 4.62 (d, J = 6.8 Hz, 1H), 4.66 (d, J = 6.8 Hz, 1H), 6.77 (d, J = 8.4Hz, 2H), 7.18 (d, J = 8.4 Hz, 2H)

6.1.9 (1S,5R,7aS)-5-(4-hydroxyphenyl)-4,7a-dimethyl-2,3,5,6,7,7a-hexahydro-1H-inden-1-ol (46b)



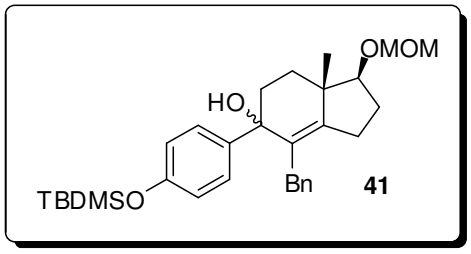
A solution of protected phenol **40** (0.253 g, 0.56 mmol) in anhydrous DCM (10 mL) was cooled to 0°C. Et_3SiH (0.564 g, 4.85 mmol) and $BF_3{\cdot}Et_2O$ (0.414 g, 2.92 mmol) were added and the solution was stirred for 1 hour then warmed to room temperature. The reaction was quenched with a saturated solution of NH_4Cl (10 mL) and extracted with DCM (3 x 10mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude intermediate (**44**) (0.080 g, 0.21 mmol). The crude was dissolved in THF (5 mL) and TBAF (0.236 mL, 24 mmol) was added drop wise to the solution. The mixture was stirred at room temperature overnight then diluted with EtOAc (10 mL) and brine (10 mL). The mixture was extracted with EtOAc (2 x 10mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified using flash column chromatography with 9:1 Hex/EtOAc to 3:2 Hex/EtOAc elution gradient, then by prep-HPLC using a 9:11 MeCN/H_2O sovent system to afford **46b** as a yellow oil (0.020 g, 14%).

^{1}H NMR (400MHz, $CO(CD_3)_2$) δ ppm 1.02 (s, 3H), 1.26 (d, J = 1.2 Hz, 3H), 1.60-1.75 (m, 2H), 1.80 (dt, J = 12.4, 3.2Hz, 1H), 1.87-1.96 (m, 2H), 2.05-2.01 (m, 1H), 2.18-2.36 (m, 2H), 3.07-3.04 (m, 1H), 3.58 (t, J = 8.8 Hz, 1H), 6.75 (dt, J = 2.8, 8.4 Hz, 2H), 6.95 (dt, J = 2.8, 8.4 Hz, 2H)

^{13}C NMR (400MHz, $CO(CD_3)_2$) δ ppm 16.3, 17.3, 23.9, 29.3, 31.3, 35.1, 43.4, 47.8, 81.4, 115.2, 126.8, 128.8, 137.7, 140.2, 155.5

HRMS: calculated $C_{17}H_{22}O_2$ = 258.1620, found = 258.16

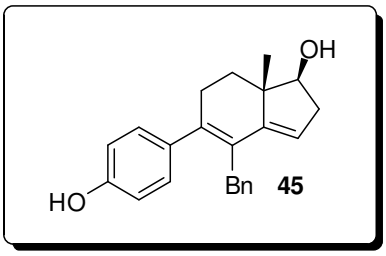
6.1.10 (1S,7aS)-4-benzyl-5-(4-(tert-butyldimethylsilyloxy)phenyl)-1-(methoxymethoxy)-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-5-ol (41)



A solution of protected phenol **38** (0.199 g, 0.69 mmol) in freshly distilled THF (6.5 mL) was purged with N_2 gas and cooled to -78°C. *n*BuLi (0.42 mL, 1.04 mmol) was added slowly and the mixture was stirred for 5 min. A solution of ketone **21** (0.311 g, 1.04 mmol) in freshly distilled THF (1.5 mL) was purged with N_2 gas then cannulated into the reaction mixture at -78°C. The solution was stirred at this temperature for 1 hour, then warmed to room temperature and quenched drop wise with a saturated NH_4Cl solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a Hex to 9:1 Hex/EtOAc elution gradient to afford **41** as a yellow oil (0.166 g, 47%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 0.22 (s, 6H), 1.00 (s, 9H), 1.18 (s, 3H), 1.47-1.35 (m, 1H), 1.67 (dt, J = 13.2, 3.6 Hz, 1H), 1.89 (dt, J = 12.4, 3.2 Hz, 1H), 2.19-2.09 (m, 1H), 2.56-2.21 (m, 5H), 3.06 (d, J = 16.02 Hz, 1H), 3.35 (s, 3H), 3.54 (dd, J = 37.69, 15.99 Hz, 1H), 3.65 (dd, J = 9.98, 7.82 Hz, 1H), 4.64 (d, J = 6.4 Hz, 1H), 4.68 (d, J = 6.4 Hz, 1H), 6.84-6.76 (m, 2H), 7.14-7.05 (m, 2H), 7.25-7.15 (m, 5H)

6.1.11 (1S,7aS)-4-benzyl-5-(4-hydroxyphenyl)-7a-methyl-2,6,7,7a-tetrahydro-1H-inden-1-ol (45)



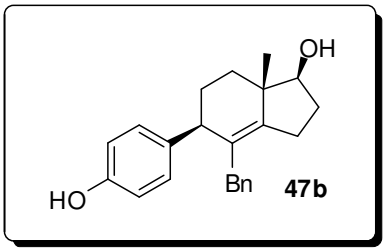
45

Three drops of concentrated HCl were added to a solution of **41** (0.049 g, 0.10 mmol) in MeOH (5 mL) and the reaction mixture was refluxed for 1 hour under ambient atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude was diluted with DCM (2 mL) and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford **45** as a yellow oil (0.0075 g, 23%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 1.07 (s, 3H), 1.60 (dt, J = 12.42, 5.76 Hz, 2H), 2.03-1.95 (m, 1H), 2.32 (d, J = 9.17 Hz, 1H), 2.64 (s, 1H), 2.59-2.43 (m, 2H), 3.62-3.45 (m, 2H), 4.06 (dd, J = 9.06, 7.71 Hz, 1H), 5.22 (s, 1H), 6.75-6.70 (m, 2H), 7.05-6.99 (m, 2H), 7.08 (d, J = 6.95 Hz, 2H), 7.13 (t, J = 7.31 Hz, 1H), 7.23 (dd, J = 10.11, 4.53 Hz, 2H)

HRMS: calculated $C2_3H_{24}O_2$ = 332.1776, found = 332.1751

6.1.12 (1S,5R,7aS)-4-benzyl-5-(4-hydroxyphenyl)-7a-methyl-2,3,5,6,7,7a-hexahydro-1H-inden-1-ol (47b)



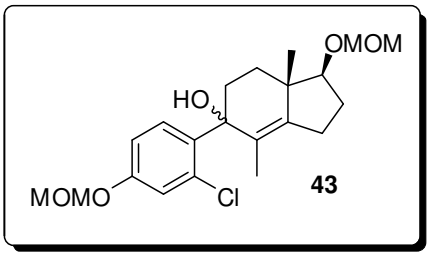
A solution of **41** (0.166 g, 0.33 mmol) in anhydrous DCM (5 mL) was purged with N_2 gas and cooled to 0°C. $BF_3{\cdot}Et_2O$ (0.21 mL, 1.64 mmol) and Et_3SiH (0.43 mL, 2.71 mmol) were added and the reaction mixture was stirred at 0°C for 1 hour. The solution was warmed to room temperature and then quenched with a saturated NH_4Cl solution (5 mL) and extracted with EtOAc (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford the crude intermediate (**41**) as a pale oil. The intermediate was diluted with freshly distilled THF (3 mL) and 1M TBAF solution in THF (0.39 mL, 0.390 mmol) was added under ambient pressure and atmosphere, and the reaction mixture was stirred overnight. The solution was diluted with 10% HCl solution (4 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford a mixture of two isomers. This mixture was purified using prep-HPLC using a 45% MeCN, 55% water elution solvent to afford **47b** as a colourless oil (12.5 mg, 11.3%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 1.11 (s, 3H), 1.37-1.23 (m, 2H), 1.87-1.63 (m, 3H), 1.99-1.90 (m, 1H), 2.15-2.03 (m, 1H), 2.60-2.37 (m, 2H), 2.79-2.70 (m, 1H), 3.10-3.00 (m, 1H), 3.38 (d, J = 15.24 Hz, 1H), 3.82-3.74 (m, 1H) , 4.68-4.57 (m, 1H) , 6.76-6.70 (m, 2H), 6.91-6.84 (m, 4H), 7.15 (d, J = 7.20 Hz, 1H), 7.20 (dd, J = 7.89, 6.41 Hz, 2H)

^{13}C NMR (400MHz, $CO(CD_3)_2$) δ ppm 18.12, 24.99, 32.20, 36.19, 36.93, 40.22, 44.89, 45.95, 82.99, 116.2, 126.7, 129.6, 129.9, 130.3, 132.5, 138.5, 141.2, 143.1, 156.5

HRMS: calculated $C2_3H_{26}O_2$ = 334.1933, found = 334.1908

6.1.13 (1S,7aS)-5-(2-chloro-4-(methoxymethoxy)phenyl)-1-(methoxymethoxy)-4,7a-dimethyl-2,3,5,6,7,7a-hexahydro-1H-inden-5-ol (43)



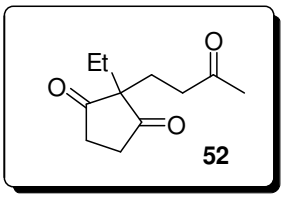
43

A solution of protected phenol **42** (0.227 g, 0.91 mmol) in freshly distilled THF (15 mL) was purged with N_2 gas and cooled to -78°C. *n*BuLi (0.09 mL, 1.36 mmol) was added drop wise and the mixture was stirred for 5 minutes. A solution of ketone **28** (0.390 g, 1.36 mmol) in dry THF (2 mL) was added drop wise into the reaction mixture, which was then stirred for 10 minutes and let warm to room temperature. The reaction was quenched with a saturated NH_4Cl solution (10 mL) and diluted with water (5 mL) then extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography using a 9:1 Hex/EtOAc elution solvent to afford **43**[59] as a yellow oil (0.237 g, 66%).

^{1}H NMR: (400MHz, $CdCl_3$) δ 7.08 (d, 1H, J=1.4Hz), 6.92-6.95 (m, 1H), 6.84 (dd, 1H, J=2.8Hz, 6Hz), 5.15 (s, 1H), 4.66 (d, 1H, J=2.0), 4.64 (d, 1H, J=3.2), 4.60 (d, 1H, J=6.4Hz), 3.48 (s, 3H), 3.37 (s, 2H), 3.33 (s, 3H), 2.41-2.47 (m, 2H), 2.27-2.38 (m, 2H), 1.98-2.19 (m, 4H), 1.54 (s, 22H), 1.08 (s, 3H), 1.02 (s, 2H), 0.89 (t, 2H, J=7.2Hz)

6.2 Synthesis of the (1S,7aS)-7a-ethyl-1-hydroxy-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one Component

6.2.1 2-ethyl-2-(3-oxobutyl)cyclopentane-1,3-dione (52)

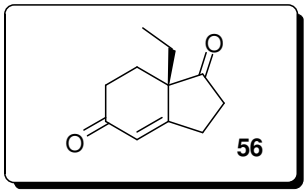


52

To a suspention of commercially available 2-ethylcyclopentane-1,3-dione (24.89 g, 197.3 mmol) in water (125 mL), methyl vinyl ketone (32.4 mL, 394.6 mmol) was added and the mixture was stirred at ambient pressure and temperature for 5 days until the solution became clear. The water was then extracted with EtOAc (3 x 150 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to attain **52**[81] in quantitative yield as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.79 (t, *J* = 7.6 Hz, 3H), 1.58 (s, 3H), 1.65 (quintuplet, *J* = 7.6 Hz, 2H), 1.88 (t, *J* = 7.2 Hz, 2H), 2.41 (t, *J* = 7.2 Hz, 2H), 2.86-2.63 (m, 4H)

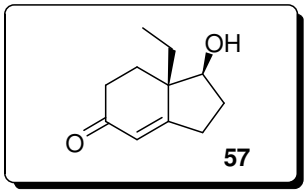
6.2.2 (S)-7a-ethyl-2,3,7,7a-tetrahydro-1H-indene-1,5(6H)-dione (56)



To a solution of **52** (38.7 g, 197.3 mmol) in DMF (110 mL), L-proline (6.8 g, 59.2 mmol) was added and the reaction mixture was stirred at ambient pressure and temperature for three days. The solvent was then distilled off under vacuum and the crude was purified using flash column chromatography with a 100% Hex to 9:1 Hex/EtOAc elution gradient to afford **56**[81] as a yellow oil (7.03 g, 20%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.97 (t, *J* = 7.51 Hz, 3H), 1.75 (m, 4H), 2.26 (ddd, *J* = 13.84, 4.95, 2.37 Hz, 1H), 2.49-2.36 (m, 3H), 2.86-2.64 (m, 2H), 3.04-2.90 (m, 1H), 5.98 (d, *J* = 2.38 Hz, 1H)

6.2.3 (1S,7aS)-7a-ethyl-1-hydroxy-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (57)

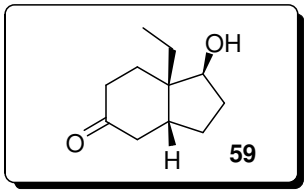


57

A solution of diketone **56** (2.67 g, 14.96 mmol) in a 1:1 mixture of EtOH and DCM (60 mL) was cooled to -5°C and $NaBH_4$ (0.198 g, 5.24 mmol) was added before purging the reaction vessel with N_2 gas. The mixture was stirred for 1 hour, then quenched with acetone (5.5 mL) at -5°C and stirredstirred until the bubbling stopped. The solution was warmed to room temperature and diluted with DCM (60 mL) and washed with a 1 M NaOH solution (60 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 3:2 Hex/EtOAc elution gradient to afford **57**[82] as a colourless oil (1.75 g, 64.7%). (1R,7aS)-7a-ethyl-1-hydroxy-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one was also isolated (0.706 g, 3.92 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.07 (t, J = 7.6 Hz, 3H), 1.63-1.53 (m, 1H), 1.94-1.70 (m, 3H), 2.15 (m, 2H), 2.55-2.29 (m, 4H), 2.75-2.62 (m, 1H), 3.92 (dd, J = 9.98, 7.87 Hz, 1H), 5.83 (s, 1H)

6.2.4 (1S,7aS)-7a-ethyl-1-hydroxyhexahydro-1H-inden-5(6H)-one (59)



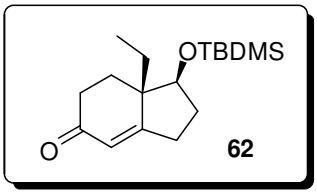
59

Pd (10% on C) (0.34 g) was added to a solution of ketone **57** (3.39 g, 18.2 mmol) in MeOH (33 mL), acetic acid (12 mL) and 10% HCl solution (1 mL). The reaction flask was purged with H_2 gas and stirred overnight. The mixture was filtered over celite and washed with MeOH, then concentrated under reduced pressure. The crude was diluted with brine (40 mL) and extracted with EtOAc (100 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 3:2 Hex/EtOAc elution gradient to afford **59** as a colourless oil (2.49 g, 75%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.89 (t, J = 7.2 Hz, 3H), 1.57-1.23 (m, 9H), 1.71-1.57 (m, 2H), 1.91-1.73 (m, 2H), 2.21-2.10 (m, 1H), 3.85 (dd, J = 6.2, 1.5 Hz, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 8.93, 14.12, 23.26, 25.28, 26.64, 31.59, 32.13, 36.85, 41.33, 43.55, 46.82, 78.08, 212.7

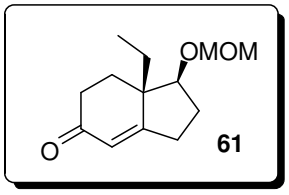
6.2.5 (1S,7aS)-1-(tert-butyldimethylsilyloxy)-7a-ethyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (62)



A solution **57** (0.58 g, 3.2 mmol) in DMF (35 mL) purged with N_2 gas and cooled to 0°C, then imidazole (0.44 g, 6.44 mmol) and TBDMSCl (0.72 g, 4.8 mmol) were added and the mixture was warmed to room temperature and stirred overnight. The solution was diluted with EtOAc (35 mL) and washed with 10% HCl (3 x 35 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 100% Hex elution solvent to afford **62**[82] as a colourless oil (0.587 g, 62.3 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.06 (s, 6H), 0.90 (s, 9H), 1.04 (t, J = 10.22 Hz, 3H), 1.61-1.49 (m, 2H), 1.74-1.61 (m, 2H), 1.93-1.74 (m, 3H), 2.06-1.93 (m, 1H), 2.25-2.30 (m, 2H), 2.45 (dd, J = 14, 5.6 Hz, 1H), 2.65 (ddt, J = 22, 14.4, 2.4 Hz, 1H), 3.81 (dd, J = 9.86, 7.86 Hz, 1H), 5.81 (s, 1H)

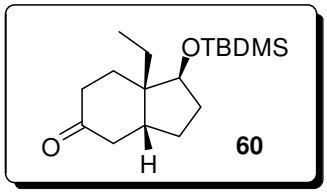
6.2.6 (1S,7aS)-1-(methoxymethoxy)-7a-ethyl-2,3,7,7a-tetrahydro-1H-inden-5(6H)-one (61)



A solution of ketone **57** (0.29 g, 1.6 mmol) in DCM (3.0 mL) was purged with N_2 gas and cooled to 0°C. MOMCl (0.18 mL, 2.4 mmol) was added and the mixture stirred for 20 minutes, then DIPEA (0.34 mL, 1.9 mmol) was added drop wise and the solution was warmed to room temperature and stirred overnight. The reaction was quenched using a saturated NH_4Cl solution (3.0 mL) and extracted with DCM (3 x 2.0 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 7:3 Hex/EtOAc elution gradient to afford **61** as a pale yellow oil (0.041 g, 11.4%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.04 (t, J = 7.6 Hz, 3H), 1.58 (quartet, J = 7.6 Hz, 2H), 1.83 (m, 3H), 2.17-2.13 (m, 1H), 2.37-2.31 (m, 2H), 2.48-2.42 (m, 1H), 2.72-2.62 (m, 1H), 3.36 (s, 3H), 3.73 (dd, J = 9.9, 7.9 Hz, 1H), 4.62 (d, J = 6.7 Hz, 1H), 4.66 (d, J = 6.4 Hz, 1H), 5.81 (s, 1H)

6.2.7 (1S,7aS)-1-(tert-butyldimethylsilyloxy)-7a-ethylhexahydro-1H-inden-5(6H)-one (60)

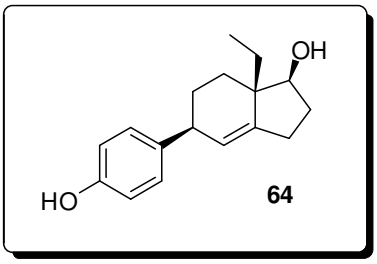


A solution of ketone **59** (2.56 g, 14.0 mmol) in DMF (42 mL) was purged with N_2 gas and cooled to 0°C, then imidazole (1.91 g, 28.1 mmol) and TBDMSCl (5.29 g, 35.1 mmol) were added and the mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% HCl (3 x 50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 100% Hex elution solvent to afford **60**[82] as a colourless oil (3.53 g, 85 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.05 (s, 6H), 0.89 (s, 9H), 1.07 (t, J = 7.5 Hz, 3H), 1.23 (m, 2H), 1.48-1.36 (m, 1H), 1.60-1.52 (m, 2H), 1.69 (m, 1H), 1.84-1.75 (m, 1H), 2.03-1.85 (m, 2H), 2.26-2.16 (m, 3H), 2.36-2.28 (m, 3H), 2.45 (dd, J = 14.8, 6.3 Hz, 1H), 3.87 (dd, J = 5.39, 3.73 Hz, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm -5.01, -4.05, 8.97, 17.98, 23.90, 25.81, 25.87, 28.43, 32.26, 36.82, 41.99, 42.70, 46.85, 78.21, 212.8

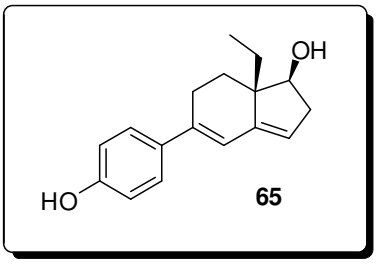
6.2.8 (1S,5S,7aS)-7a-ethyl-5-(4-hydroxyphenyl)-2,3,5,6,7,7a-hexahydro-1H-inden-1-ol (64)



A solution of protected phenol **38** (0.301 g, 1.05 mmol) in freshly distilled THF (7 mL) was purged with N_2 gas and cooled to -78°C. *n*BuLi (0.25 mL, 1.05 mmol) was added slowly into the mixture and stirred for 5 minutes. A solution of ketone **62** (0.205 g, 0.70 mmol) in freshly distilled THF (3 mL) was purged with N_2 gas then cannulated into the reaction mixture at -78°C. The mixture was stirred at this temperature for 1 hour, then warmed to room temperature and quenched drop wise with a saturated NH_4Cl solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude intermediate (**63**) was dissolved in anhydrous DCM (10 mL), purged with N_2 gas and cooled to 0°C. $BF_3{\cdot}Et_2O$ (0.66 mL, 5.23 mmol) and Et_3SiH (1.40 mL, 8.68 mmol) were added and the reaction mixture was stirred at 0°C for 1 hour. The solution was warmed to room temperature, quenched with a saturated NH_4Cl solution (10 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure and dissolved in freshly distilled THF (10 mL). Under ambient pressure and atmosphere, 1M TBAF solution in THF (3.1 mL, 3.14 mmol) was added and the reaction mixture was stirred overnight. The solution was diluted with 10% HCl solution (15 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure.The crude was purified using flash column chromatography with a 4:2 Hex/EtOAc to 3:2 Hex/EtOAc elution gradient to afford a mixture of two isomers. This mixture was purified using prep-HPLC using a 45% MeCN, 55% water elution solvent to afford **64** as a yellow oil (36.9 mg, 20.4 %).

^{1}H NMR (400MHz, $CO(CD_3)_2$) δ ppm 1.01 (t, J = 7.6 Hz, 3H), 1.28 (dt, J = 13.6, 3.1 Hz, 1H), 1.64-1.47 (m, 2H), 1.78-1.64 (m, 2H), 1.92 (m, 2H), 2.18-2.09 (m, 2H), 2.53-2.39 (m, 1H), 3.29-3.21 (m, 1H), 3.71 (dt, J = 9.2, 4.3 Hz, 1H), 3.85 (br, OH), 5.33 (s, 1H), 6.80-6.70 (m, 2H) , 7.06-6.97 (m, 2H), 8.08 (br, OH)

6.2.9 (1S,7aS)-7a-ethyl-5-(4-hydroxyphenyl)-2,6,7,7a-tetrahydro-1H-inden-1-ol (65)



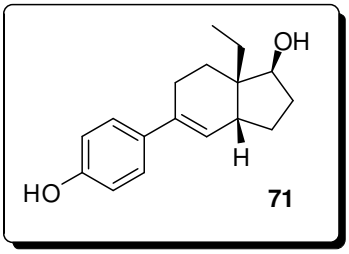
65

A solution of protected phenol **38** (0.307 g, 1.07 mmol) in freshly distilled THF (7 mL) was purged with N_2 gas and cooled to -78°C. *n*BuLi (0.26 mL, 1.07 mmol) was added slowly into the mixture, which was stirred for 5 minutes. Compound **62** (0.210 g, 0.710 mmol) was diluted with freshly distilled THF (3 mL) in a round bottom flask and purged with N_2 gas then cannulated into the reaction mixture at -78°C. The reaction was stirred at this temperature for 1 hour, then warmed to room temperature and quenched drop wise with a saturated NH_4Cl solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude intermediate was charged to a round bottom flask with a stirring bar MeOH (5 mL). Three drops of concentrated HCl were added and the reaction mixture was refluxed for 1 hour under ambient atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude was diluted with DCM (2 mL) and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 10% EtOAc, 90% hexanes to 20% EtOAc, 80% hexanes elution gradient to afford **65** as a yellow oil (0.047 g, 17.2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.99 (t, J = 7.5 Hz, 3H), 1.54-1.43 (m, 2H), 1.65-1.61 (m, 1H), 1.89 (br, OH), 2.23 (ddd, J = 12.8, 4.5, 2.5 Hz, 1H), 2.44 (dd, J = 16.4, 8.9 Hz, 1H), 2.69-2.53 (m, 3H), 4.18 (t, J = 8.5 Hz, 1H), 5.46 (s, 1H), 5.75 (br, OH), 6.51 (s, 1H), 6.83-6.78 (m, 2H), 7.36 (m, 2H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 9.68, 22.57, 25.85, 32.95, 39.64, 47.52, 83.275, 115.2, 118.5, 119. 9, 126.5, 133.4, 137.3, 145.0, 155.3

6.2.10 (1S,7aS)-7a-ethyl-5-(4-hydroxyphenyl)-2,3,3a,6,7,7a-hexahydro-1H-inden-1-ol (71)



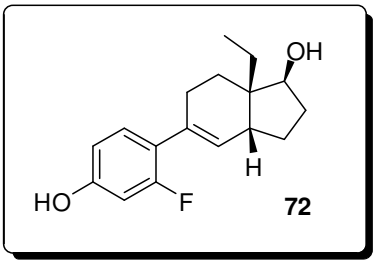
71

A solution of protected phenol **38** (3.07 g, 10.7 mmol) in freshly distilled THF (110 mL) was purged with N_2 gas and cooled to -78°C. nBuLi (5.34 mL, 10.7 mmol) was added slowly into the mixture and stirred for 5 minutes while ketone **60** (2.11 g, 7.12 mmol) was diluted with freshly distilled THF (30 mL) and purged with N_2 gas. This solution was then cannulated into the reaction mixture at -78°C. The solution was stirred at this temperature for 1 hour, then warmed to room temperature and quenched drop wise with a saturated NH_4Cl solution (200 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a Hex 9:1 Hex/EtOAc elution gradient. The intermediate was charged diluted with MeOH (20 mL). Three drops of concentrated HCl were added and the reaction mixture was refluxed for 1 hour under ambient atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude was diluted with DCM (20 mL) and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford the mixture of isomers. This mixture was purified using prep-HPLC equipped with a 45% MeCN, 55% water elution solvent to afford **71** as a yellow oil (36.9 mg, 13.6 %). The other isomers were inseparable from one another and only one could be identified.

^{1}H NMR (400MHz, $CO(CD_3)_2$) δ ppm 0.99 (t, J = 7.6 Hz, 3H), 1.33-1.21 (m, 1H), 1.54-1.41 (m, 2H), 1.86-1.60 (m, 4H), 2.01 (m, 1H), 2.22 (m, 1H), 2.40 (m, 1H), 2.63 (ddd, J = 17.4, 6.0, 1.6 Hz, 1H),

3.75 (d, J = 4.5 Hz, 1H), 3.86 (dt, J = 8.50, 3.97 Hz, 1H), 5.98 (m, 1H), 6.80-6.74 (m, 2H), 7.31-7.22 (m, 2H), 8.28 (br, OH)

6.2.11 (1S,7aS)-7a-ethyl-5-(2-fluoro-4-hydroxyphenyl)-2,3,3a,6,7,7a-hexahydro-1H-inden-1-ol (72)



72

A solution of **66** (2.33 g, 7.6 mmol) in freshly distilled THF (70 mL) was purged with N_2 gas and cooled to -78°C. nBuLi (3.82 mL, 7.6 mmol) was added slowly into the mixture and stirred for 5 minutes while **60** (1.51 g, 5.1 mmol) was diluted with freshly distilled THF (30 mL), purged with N_2 gas and cannulated into the reaction mixture at -78°C. The solution was stirred at this temperature for 1 hour, then warmed to room temperature and quenched drop wise with a saturated NH_4Cl solution (100 mL). The mixture was extracted with EtOAc (3 x 100 mL) and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a Hex to 9:1 Hex/EtOAc elution gradient. The intermediate was isolated and diluted in MeOH (50 mL). Three drops of concentrated HCl were added and the reaction mixture was refluxed for 1 hour under ambient atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude was diluted with DCM (20 mL) and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOac to 4:1 Hex/ EtOAc gradient to afford the mixture of isomers. This mixture was purified using prep-HPLC equipped with a 45% MeCN, 55% water elution solvent to afford **72** as a yellow oil (36.9 mg, 13.6 %). The other isomers were inseparable from one another and only one could be identified.

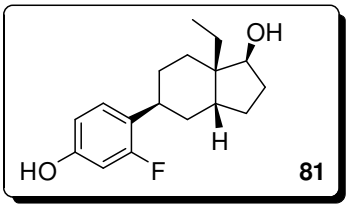
^{1}H NMR (400MHz, $CO(CD_3)_2$) δ ppm 1.02 (t, J = 7.55 Hz, 3H), 1.39 (m, 2H), 1.52 (dd, J = 14.16, 7.13 Hz, 1H), 1.72-1.58 (m, 2H), 1.90-1.72 (m, 2H), 2.04-1.95 (m, 1H), 2.28 (m, 2H), 2.67-2.56 (m,

1H), 2.71 (br, OH), 3.70 (br, OH), 3.85 (t, J = 8.7 Hz, 1H), 5.84-5.77 (m, 1H), 6.58 (ddd, J = 15.2, 10.6, 2.4 Hz, 2H), 7.10 (t, J = 8.8 Hz, 1H)

^{13}C NMR (400MHz, $CO(CD_3)_2$) δ ppm 12.0, 18.8, 27.0, 32.3, 33.90, 33.93, 36.6, 44.2, 44.4, 84.5, 84.7, 104.5, 104.8, 112.9, 113.0, 128.1, 128.2, 131.7, 131.7, 135.0, 135.0, 161.1, 163.5

HRMS: calculated $C_{17}H_{21}FO_2$ = 276.1526, found = 276.1528

6.2.12 (1S,7aS)-7a-ethyl-5-(4-hydroxyphenyl)octahydro-1H-inden-1-ol (81)



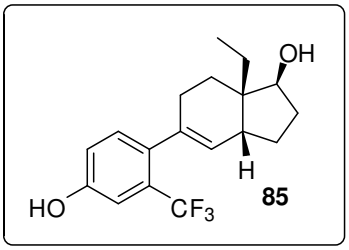
To a solution of **72** (0.208 g, 0.75 mmol) in MeOH (7 mL), acetic acid (5 mL) and 10% HCl solution (2 mL) Pd (10% on C) (10 mol%) was added and the reaction flask was purged with H_2 gas and stirred overnight. The mixture was filtered over celite and washed with MeOH, then concentrated under reduced pressure. The crude was diluted with brine and extracted with EtOAc (10 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 3:2 Hex/EtOAc elution gradient to afford the mixture of two isomers. This mixture was purified using prep-HPLC equipped with a 45% MeCN, 55% water elution solvent to afford **81** as a colourless oil (0.114 g, 55%).

^{1}H NMR (400MHz, $CO(CD_3)_2$) δ ppm 0.89 (t, J = 7.4 Hz, 3H), 1.17-1.03 (m, 1H), 1.66-1.48 (m, 6H), 1.78-1.66 (m, 2H), 1.89-1.78 (m, 2H), 2.08 (s, 1H), 2.50-2.15 (m, 1H), 2.81 (s, OH), 3.06-2.92 (ttt, J = 24.4, 12.4, 3.6 Hz, 1H), 3.77 (t, J = 5.3 Hz, 1H), 6.51 (dd, J = 12.4, 2.4 Hz, 1H), 6.45 (dd, J = 8.4, 2.4 Hz, 1H), 7.15 (t, J = 8.7 Hz, 1H), 8.48 (br, OH)

^{13}C NMR (400MHz, $CO(CD_3)_2$) δ ppm 10.27, 24.32, 28.11, 28.26, 29.40, 32.60, 32.80, 33.97, 34.03, 43.90, 48.91, 48.94, 80.06, 80.20, 104.21, 104.46, 113.09, 113.12, 130.17, 130.24

HRMS: calculated $C_{17}H_{23}FO_2$ = 278.1682, found = 278.1696

6.2.13 (1S,7aS)-7a-ethyl-5-(4-hydroxy-2-(trifluoromethyl)phenyl)-2,3,3a,6,7,7a-hexahydro-1H-inden-1-ol (85)



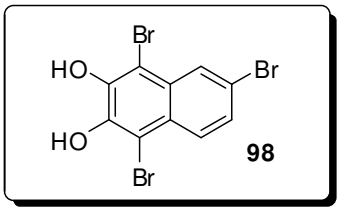
A solution of protected phenol **83** (0.307 g, 1.07 mmol) in freshly distilled THF (7 mL) was purged with N_2 gas and cooled to -78°C. nBuLi (0.26 mL, 1.07 mmol) was added slowly into the mixture and stirred for 5 minutes. **60** (0.210 g, 0.710 mmol) was diluted with freshly distilled THF (3 mL) and purged with N_2 gas then cannulated into the reaction mixture at -78°C. The mixture was stirred at this temperature for 1 hour, then warmed to room temperature and quenched drop wise with a saturated NH_4Cl solution (10 mL). The mixture was extracted with EtOAc (3 x 10 mL) and the organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a Hex to 9:1 Hex/EtOAc elution gradient. The intermediate was isolated as a colourless oil and diluted in MeOH (5 mL). Three drops of concentrated HCl were added and the reaction mixture was refluxed for 1 hour under ambient atmosphere. The mixture was cooled to room temperature and concentrated under reduced pressure. The crude was diluted with DCM (2 mL) and washed with brine. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford almost exclusively a single isomer with some traces of the second less favoured isomer. This mixture was purified using prep-HPLC equipped with a 45% MeCN, 55% water elution solvent to afford **85** as a yellow oil (0.0075 g, 23%).

^{1}H NMR (400MHz, $CO(CD_3)_2$) δ ppm 1.03 (t, J = 7.5 Hz, 3H), 1.46-1.34 (m, 2H), 1.50 (m, 1H), 1.70-1.57 (m, 2H), 1.78 (m, 2H), 2.03-1.96 (m, 1H), 2.21-2.12 (m, 2H), 2.60 (ddd, J = 17.2, 5.7, 1.0 Hz, 1H), 3.77 (br, OH), 3.86 (t, J = 8.8 Hz, 1H), 5.49 (dd, J = 3.3, 1.8 Hz, 1H), 7.13-7.07 (m, 2H), 7.03-6.99 (m, 1H)

^{13}C NMR (400MHz, $CO(CD_3)_2$) δ ppm 10.2, 16.7, 25.1, 30.39, 34.44, 34.5, 42.4, 42.4, 82.8, 112.3, 112.4, 118.6, 126.7, 132.1, 135.8, 156.0

6.3 Synthesis of the Naphthalene-2,3-diol Component

6.3.1 1,4,8-tribromo-2,3-naphthalenediol (98)

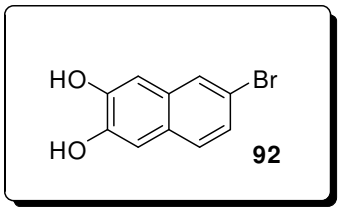


A solution of commercially available 2,3-naphthalenediol (1.0g, 6.24 mmol) in with glacial acetic acid (20 mL) was stirred until all the solid was dissolved. To this translucent, colorless mixture Br_2 (1 mL, 19.35 mmol) was added under ambient atmosphere and the solution was stirred overnight. During the course of the reaction an orange precipitate was formed and the resulting slurry was poured into ice water (30 mL) and stirred until the ice had melted. The precipitate was filtered and washed with hexanes until **98**[83] was isolated as a white, crystalline solid (0.97g, 75%). Once dried, **98** was sufficiently pure to be used in subsequent reactions.

^{1}H NMR (300 MHz, $CO(CD_3)_2$) δ (ppm) 7.60 (dd, *J* = 8.7, 1.8 Hz, 1H), 7.99 (d, *J* = 8.7 Hz, 1H), 8.23 (d, *J* = 1.8 Hz, 1H), 8.33 (br, OH)

^{13}C NMR (400 MHz, $CO(CD_3)_2$) δ (ppm) 103.8, 105.2, 119.4, 126.6, 127.6, 128.1, 128.7, 129.0, 144.6, 145.2

6.3.2 6-bromonaphthalene-2,3-diol (92)



Method 1: A solution of commercially available naphthalene-2,3-diol (10.1 g, 62.9mmol) in glacial acetic acid (200 mL) was stirred under ambient atmosphere until the solid was dissolved then Br_2 (10 mL, 195.1 mmol) was added, resulting in an orange solution containing a yellow precipitate. This mixture was stirred overnight, then mossy tin (7.47 g, 62.9 mmol) and concentrated HCl (60 mL) were added and the solution was refluxed for three hours during which time the solid dissolved to afford a brown, translucent solution. The mixture was cooled and poured into ice water (500 mL) and stirred for two hours. During this time, a yellow precipitate appeared. The precipitate was filtered to dryness and dissolved in EtOAc (700 mL) and filtered over a pad of celite then concentrated under reduced pressure to afford **92** as a white solid (3.03 g, 20 %).

Method 2: A solution of **98** (11.99 g, 30.2 mmol) and mossy tin (3.59 g, 30.2 mmol) in conc. HCl (60 mL) and glacial acetic acid (100 mL) was refluxed for 3hr under ambient atmosphere and then cooled to room temperature and poured into ice water (100 mL). The resulting precipitate was filtered, washed with distilled water and air-dried to afford compound **92** (3.40 g, 47%).

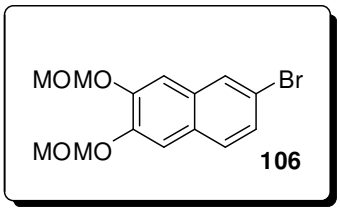
The aqueous layer was extracted with EtOAc (5 x 50 mL) and the organic layers were combined, dried over $MgSO_4$, filtered over celite and concentrated under reduced pressure. The crude was purified by flash column chromatography using 100% DCM as the elution solvent to afford **92** as a white solid (3.75 g, 52%).

^{1}H NMR (400 MHz, $CO(CD_3)_2$): δ (ppm) 7.20 (s, 1H), 7.23 (s, 1H), 7.27 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.55 (d, *J* = 8.8 Hz, 1H), 7.80 (d, *J* = 1.6 Hz, 1H), 7.99 (s, OH)

^{13}C NMR (400 MHz, $CO(CD_3)_2$): δ (ppm) 109.4, 109.6, 117.8, 125.8, 126.1, 128.9, 129.1, 129.2, 146.9, 147.2

HRMS calculated 237.9629, found at 237.9627

6.3.3 6-bromo-2,3-bis(methoxymethoxy)naphthalene (106)

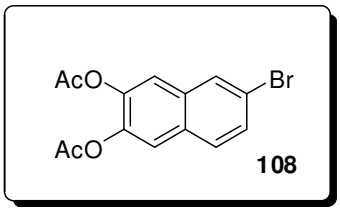


A solution of **92** (0.80 g, 3.35 mmol) in DCM (5 mL) was purged with N_2 gas and cooled to 0°C. MOMCl (0.76 mL, 10.0 mmol) was added and the mixture was stirred at 0°C for 20 minutes, then DIPEA (1.3 mL, 7.37 mmol) was added drop wise and the solution was warmed to room temperature and stirred overnight. The reaction was quenched using a saturated NH_4Cl solution (10 mL) and extracted with DCM (3x10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 7:3 Hex/EtOAc elution gradient to afford **106** as a white solid (0.739 g, 67 %).

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ (ppm) 3.495 (s, 3H), 3.497 (s, 3H), 5.340 (s, 2H), 5.344 (s, 2H), 7.43 (dd, *J* = 8.8, 2.0 Hz, 1H), 7.48 (s, 1H), 7.51 (s, 1H), 7.70 (d, *J* = 8.8 Hz, 1H), 7.96 (d, *J* = 2.0 Hz, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ (ppm) 56.3, 56.4, 95.3, 95.3, 110.6, 111.4, 118.3, 127.8, 128.2, 128.3, 128.7, 130.9, 147.5, 147.9

6.3.4 6-bromonaphthalene-2,3-diyl diacetate (108)

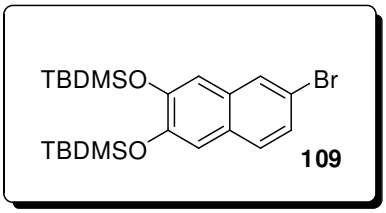


108

A solution of **92** (1.86 g, 7.78 mmol) in pyridine (9 mL) with a few crystals of DMAP was purged with N_2 gas then Ac_2O (2.4 mL, 18.67 mmol) was added and the mixture was stirred for 1 hour at room temperature. The reaction was quenched with water (15 mL) to afford **108** as a pale pink precipitate after filtration (2.04 g, 82 %).

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ ppm 2.33 (s, 3H), 2.34 (s, 3H), 7.64 (dd, *J* = 8.80, 2.01 Hz, 1H), 7.78 (d, *J* = 14.36 Hz, 2H), 7.89 (d, *J* = 8.93 Hz, 1H), 8.14-8.18 (m, 1H)

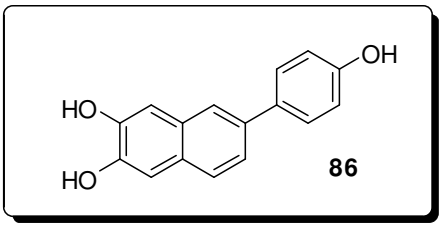
6.3.5 (6-bromonaphthalene-2,3-diyl)bis(oxy)bis(tert-butyldimethylsilane) (109)



A solution of **92** (3.49 g, 14.6 mmol) in DMF (10 mL) was purged with N_2 gas and cooled to 0°C then imidazole (4.00 g, 58.4 mmol) and TBDMSCl (6.60 g, 43.8 mmol) were added and the mixture was warmed to room temperature and stirred overnight. The reaction mixture was diluted with EtOAc (50 mL) and washed with 10% HCl (3 x 50 mL). The organic phase was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography using a dry pack loading method with a Hex to 9:1 Hex/EtOAc elution gradient to afford **109** as a white solid (5.61 g, 82 %).

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ ppm 0.31 (s, 6H), 0.32 (s, 6H), 1.04 (s, 9H), 1.04 (s, 9H), 7.35 (d, *J* = 4.94 Hz, 2H), 7.38 (dd, *J* = 8.72, 2.02 Hz, 1H), 7.68 (dd, *J* = 8.70, 0.43 Hz, 1H), 7.95 (d, *J* = 1.47 Hz, 1H)

6.3.6 6-(4-hydroxyphenyl)naphthalene-2,3-diol (86)



86

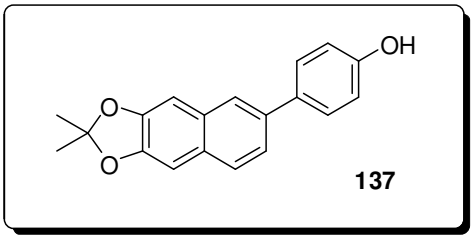
$Pd(PPh_3)_2Cl_2$ (0.007 g, 0.107 mmol) was added to a solution of **109** (1.00 g, 2.14 mmol) in dioxane (30 mL) and purged with N_2 gas. The mixture was stirred at room temperature for 10 minutes and a 2M Na_2CO_3 solution (4 mL) was added then stirred for 1 hour at room temperature. 4-methoxy-3-methylphenylboronic acid (0.354 g, 2.57 mmol) was added and the mixture was refluxed for 4 hours. The reaction mixture was cooled and diluted with DCM (30 mL) then washed with water (60 mL). The aqueous phase was extracted with DCM (3 x 60 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was immediately dissolved in freshly distilled THF (5 mL) and purged with N_2 gas and a 1M solution of TBAF in THF (2.57 mL, 2.57 mmol) was added drop wise. The mixture was stirred at room temperature overnight and then diluted with 10% HCl solution (7 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography with a 4:1 Hex/EtOAc elution solvent to afford **86** as a beige solid (0.065 g, 12%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 6.92-6.86 (m, 2H), 7.32-7.26 (m, 1H), 7.43-7.36 (m, 2H), 7.50-7.44 (m, 2H), 7.505-7.54 (m, 2H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 29.7, 29.7, 115.6, 126.7, 128.4, 128.7, 134.0, 140.8, 155.1

HRMS: calculated $C_{16}H_{12}O_3$ = 252.0786, found = 252.08

6.3.7 4-(2,2-dimethylnaphtho[2,3-d][1,3]dioxol-6-yl)phenol (137)



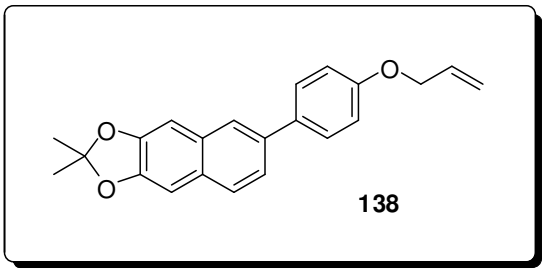
137

Commercially available 2,2-dimethythoxy propane (0.04 mL, 0.314 mmol) and PTSA (in a catalytic amount) were added to a solution of **86** (66.0 mg, 0.26 mmol) in DCM (2.5 mL) and the flask was purged with N_2 gas. The reaction mixture was stirred at room temperature for three hours then washed with water (3 mL) and extracted with DCM (3 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 4:1 Hex/EtOAc elution solvent to afford **51** as a white solid (14.5 mg, 19%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.86 (br, OH, 1H), 6.91 (d, J = 8.40 Hz, 2H), 7.31 (t, J = 7.33 Hz, 1H), 7.42 (t, J = 7.55 Hz, 2H), 7.49 (d, J = 8.37 Hz, 2H), 7.54 (d, J = 7.59 Hz, 2H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 14.1, 22.7, 29.7, 31.9, 115.6, 126.7, 128.4, 128.7, 134.0, 140.7, 155.0

6.3.8 6-(4-(allyloxy)phenyl)-2,2-dimethylnaphtho[2,3-d][1,3]dioxole (138)

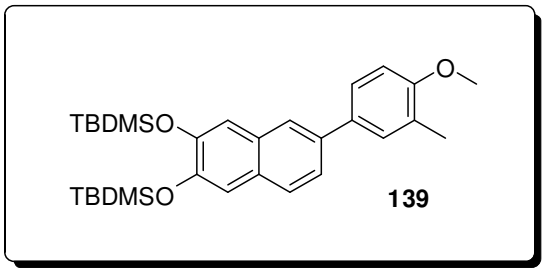


138

K_2CO_3 (34.6 mg, 0.25 mmol) and allyl bromide (0.02 mL, 0.25 mmol) were added to a solution of **137** (14.5 mg, 0.05 mmol) in acetone (1 mL) and the flask was purged with N_2 gas and refluxed for 2 hours. The solvent was evaporated under reduced pressure and the crude was diluted in DCM (1 mL) and washed with water (1 mL). The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography using a dry pack loading method with a Hex to 9:1 Hex/EtOAc elution gradient to afford **138** as a pale yellow oil (16.6 mg, quantitative yield).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 4.59 (td, J = 5.26, 1.44 Hz, 2H), 5.31 (dd, J = 10.51, 1.38 Hz, 1H), 5.45 (dd, J = 17.26, 1.55 Hz, 1H), 6.15-6.03 (m, 1H), 7.04-6.96 (m, 2H), 7.34-7.27 (m, 1H), 7.42 (m, 2H), 7.58-7.49 (m, 4H)

6.3.9 (6-(4-methoxy-3-methylphenyl)naphthalene-2,3-diyl)bis(oxy)bis(tert-butyldimethylsilane) (129)

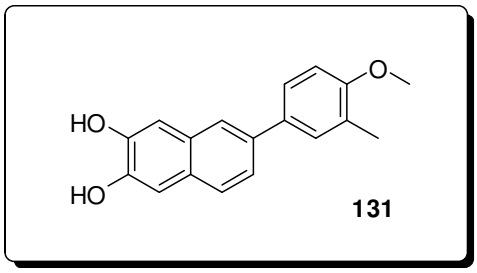


139

$Pd(OAc)_2$ (0.005 g, 0.02 mmol) and PPh_3 (0.011 g, 0.04 mmol) were added to a solution of **109** (0.31 g, 0.67 mmol) in DME (3 mL) and purged with N_2 gas then stirred at room temperature for 10 minutes. A 2M Na_2CO_3 solution (1 mL) was added and mixture was stirred for 1 hour at room temperature. 4-methoxy-3-methylphenylboronic acid (0.16 g, 1.0 mmol) was then added to the solution and the mixture was refluxed for 4 hours. The reaction mixture was cooled and diluted with DCM (3 mL) then washed with water (6 mL). The aqueous layer was extracted with DCM (3 x 6 mL) and the combined organic phases were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a Hex to 9:1 Hex/EtOAc elution gradient to afford **129** as a yellow oil (0.14 g, 41 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.295 (s, 6H), 0.30 (s, 6H), 1.05 (s, 18H), 2.33 (s, 3H), 3.90 (s, 3H), 6.93 (d, J = 9.2 Hz, 1H), 7.21 (s, 1H), 7.25 (s, 1H), 7.53-7.48 (m, 2H), 7.55 (dd, J = 8.4 Hz, 1.6 Hz, 1H),7.68 (d, J = 8.58 Hz, 1H), 7.79 (d, J = 1.2 Hz, 1H)

6.3.10 6-(4-methoxy-3-methylphenyl)naphthalene-2,3-diol (131)

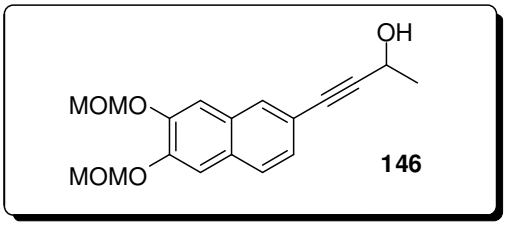


131

To a solution of **129** (0.14 g, 0.28 mmol) in freshly distilled THF (3 mL) a 1M TBAF solution in THF (0.83 mL, 0.83 mmol) was added under ambient pressure and atmosphere and the reaction mixture was stirred overnight. The mixture was diluted with 10% HCl solution (4 mL) and extracted with EtOAc (3 x 3 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 4:1 Hex/EtOAc to 3:2 Hex/EtOAc elution gradient to afford **131** as a yellow oil (0.065 g, 84 %).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.29 (s, 3H), 3.85 (s, 3H), 6.88 (d, J = 8.92 Hz, 1H), 7.20 (s, 1H), 7.23 (s, 1H), 7.44-7.47 (m, 2H), 7.49 (dd, J = 8.76, 0.43 Hz, 1H), 7.62 (d, J = 8.47 Hz, 1H), 7.74 (s, 1H)

6.3.11 4-(6,7-bis(methoxymethoxy)naphthalen-2-yl)but-3-yn-2-ol (146)

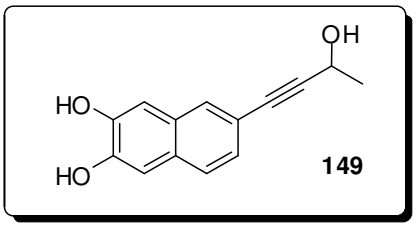


A solution of CuI (15.2 mg, 0.08 mmol) and $Pd(Cl)_2(PPh_3)_2$ (56.1 mg, 0.08 mmol) in THF (5 mL) was purged with N_2 gas and **106** (261 mg, 0.80 mmol) and Et_3N (1.08 mL, 7.7 mmol) were added. The reaction mixture was stirred for 15 minutes then 3-butyn-2-ol (0.08 mL, 1.02 mmol) was added and the mixture was stirred for 3 days at room temperature then filtered over celite and concentrated under vacuum. The crude mixture was purified by flash column chromatography using a 13:7 Hex/CH_2Cl_2 elution solvent to afford **146** as a yellow oil (31.4 mg, 13%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.56 (d, *J* = 6.4 Hz, 3H), 2.08 (br, OH, 1H), 3.53 (s, 3H), 3.53 (s, 3H), 4.77 (q, *J* = 6.4 Hz, 1H), 5.34 (s, 2H), 5.35 (s, 2H), 7.31 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.398 (s, 1H), 7.42 (s, 1H), 7.58 (d, *J* = 8.4 Hz, 1H), 7.77 (s, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 24.5, 56.3, 56.4, 58.9, 84.5, 90.7, 95.2, 95.3, 111.3, 111.3, 118.4, 126.7, 127.3, 129.2, 129.3, 130.4, 147.6, 147.9

6.3.12 6-(3-hydroxybut-1-ynyl)naphthalene-2,3-diol (149)

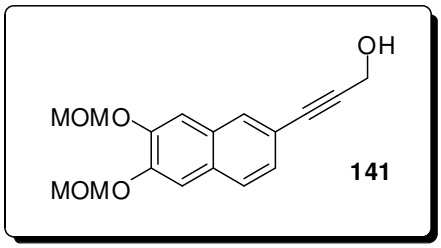


Conc. HCl (2 drops) was added solution of **146** (30 mg, 0.095 mmol) in methanol (1 mL) under ambient atmosphere and the mixture was stirred at room temperature for 1h. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried with $MgSO_4$, filtered and concentrated under reduced pressure. The crude was purified using flash column chromatography using a 13:7 Hex/EtOAc to 1:1 Hex/EtOAc elution gradient to afford **149** (6 mg, 25%) as a yellow oil.

^{1}H NMR (400 MHz, $CO(CD_3)_2$): δ ppm 1.462 (d, *J* = 6.4 Hz, 3H), 2.851 (br, OH), 4.698 (q, *J* = 6.4 Hz, 1H), 7.177 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.184 (s, 1H), 7.194 (s, 1H), 7.567 (d, *J* = 8.4 Hz, 1H), 7.675 (s, 1H)

HRMS calculated 228.0786, found at 228.0763

6.3.13 3-(6,7-Bis(methoxymethoxy)naphthalen-2-yl)prop-2-yn-1-ol (141)

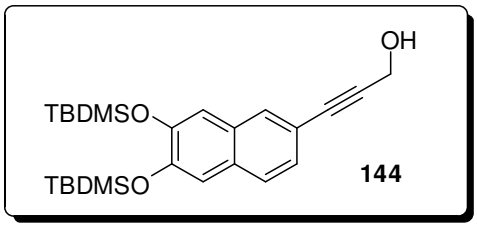


A round bottom flask was charged with stir bar, CuI (11.4 mg, 0.061 mmol) and $Pd(Cl)_2(PPh_3)_2$ (40 mg, 0.061 mmol) in dry THF (5 mL). The flask was purged with N_2 gas and **106** (200 mg, 0.61 mmol) and Et_3N (1 mL, 5.9 mmol) were added. The reaction mixture was stirred for 15 minutes followed by the addition of propargyl alcohol (0.04 mL, 0.76 mmol). After stirring for 3 days at room temperature, the reaction mixture was filtered through celite and concentrated under reduced pressure. The crude mixture was purified using flash column chromatography with a 13:7 Hex/CH_2Cl_2 elution solvent to afford **141** as a yellow oil (24.3 mg, 13%).

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ ppm 3.49 (s, 3H), 3.50 (s, 3H), 4.44 (s, 2H), 5.33 (s, 2H), 5.34 (s, 2H), 7.32 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.47 (s, 1H), 7.48 (s, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.82 (s, 1H)

^{13}C NMR (400 MHz, $CO(CD_3)_2$) δ ppm 51.8, 56.3, 86.3, 86.9, 95.2, 95.3, 111.3, 111.3, 118.4, 126.8, 127.3, 129.2, 129.4, 130.4, 147.9, 147.7

6.3.14 3-(6,7-bis(tert-butyldimethylsilyloxy)naphthalen-2-yl)prop-2-yn-1-ol (144)

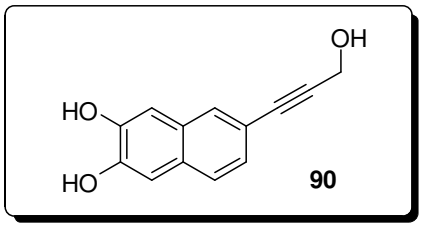


A solution of CuI (25.9 mg, 0.136 mmol) and $Pd(Cl)_2(PPh_3)_2$ (95.4 mg, 0.136 mmol) in dry THF (5.6 mL) was purged with N_2 gas and **109** (300 mg, 0.68 mmol) and Et_3N (0.92mL, 6.6 mmol) were added. The reaction mixture was stirred for 15 minutes followed by the addition of propargyl alcohol (0.049 mL, 0.85 mmol). After refluxing for 14 hours, 0.5 equivalents of propargyl alcohol (0.0196 mL, 0.34 mmol) were added and the solution was refluxed for another 6 hours. The mixture was cooled to room temperature and filtered through celite and concentrated under reduced pressure. The crude mixture was purified using flash column chromatography with a 4:1 Hex/EtOAc elution solvent to afford **144** as a yellow oil (84.3 mg, 28%).

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ ppm 0.312 (s, 6H), 0.318 (s, 6H), 1.043 (s, 9H), 1.044 (s, 9H), 4.44 (s, 2H), 7.28 (dd, J = 8.4 Hz, 1.6 Hz, 1H), 7.33 (s, 2H), 7.68 (d, J = 8.4 Hz, 1H), 7.81 (d, J = 0.88 Hz, 1H)

^{13}C NMR (400 MHz, $CO(CD_3)_2$) δ ppm -4.69, 18.3, 25.51, 25.53, 50.2, 84.5, 88.4, 115.9, 116.0, 118.6, 126.4, 126.5, 129.3, 129.5, 129.6, 148.1, 148.2

6.3.15 3-(6,7-dihydroxynaphthalen-2-yl)prop-2-yn-1-ol (90)

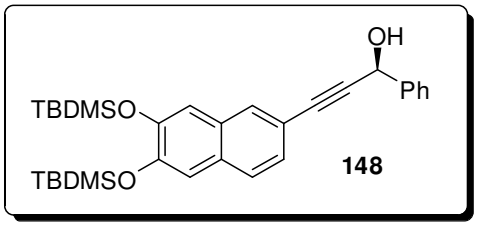


A solution of **144** (84.0mg, 0.189 mmol) in dry THF (2 mL) was purged with N_2 gas and a 1M solution of TBAF in THF (0.455mL, 0.455mmol) was added. The mixture was stirred for 14 hours then 0.5 equivalents of 1M TBAF solution (0.095 mL, 0.095 mmol) were added and the solution was stirred for an additional 24 hours. The reaction mixture was diluted with a 10% HCl solution (3 mL) and extracted with EtOAc (3 x 3 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified with flash chromatography using a 19:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford **90** as a yellow oil (21.98 mg, 54%).

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ ppm 4.42 (s, 2H), 7.21 (m, 3H), 7.58 (d, J = 8.8, 1H), 7.70 (d, J = 0.82 Hz, 1H)

^{13}C NMR (400 MHz, $CO(CD_3)_2$) δ ppm 50.2, 84.7, 87.9, 109.4, 109.5, 117.7, 125.8, 126.1, 129.0, 129.1, 129.3, 146.9, 147.2

6.3.16 (S)-3-(6,7-bis(tert-butyldimethylsilyloxy)naphthalen-2-yl)-1-phenylprop-2-yn-1-ol (148)

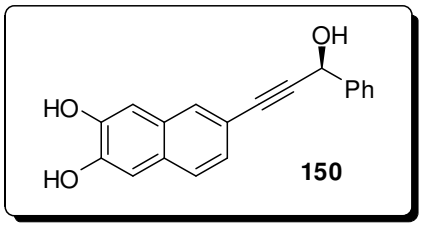


A solution of CuI (25.89mg, 0.136 mmol) and $Pd(Cl)_2(PPh_3)_2$ (95.4 mg, 0.136 mmol) in dry THF (5.6 mL) was purged with N_2 gas and **109** (300 mg, 0.68 mmol) and Et_3N (0.92mL, 6.6 mmol) were added. The reaction mixture was stirred for 15 minutes followed by the addition of (R)-1-phenylprop-2-yn-1-ol (0.147mL, 1.19mmol). The reaction mixture was refluxed for 14 hours then was cooled to room temperature and filtered through celite and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 4:1 Hex/EtOAc elution solvent to afford **148** as a yellow oil (62 mg, 17.5%).

^{1}H NMR (300 MHz, $CO(CD_3)_2$) δ ppm 0.31 (s, 6H), 0.32 (s, 6H), 1.04 (s, 18H), 5.09 (br, s, OH), 5.72 (s, 1H), 7.31 (dd, J = 8.4, 1.5 Hz, 2H), 7.33 (s, 1H), 7.34 (s, 1H), 7.399 (m, 2H), 7.62-7.67 (m, 2H), 7.69 (d, J = 8.4 Hz, 1H), 7.85 (s, 1H)

^{13}C NMR (400 MHz, $CO(CD_3)_2$) δ ppm -3.85, 19.16, 19.18, 26.35, 26.38, 64.9, 86.5, 90.9, 116.7, 116.9, 119.2, 127.3, 127.47, 128.51, 129.1, 130.3, 130.3, 130.6, 143.3, 148.9, 149.1, 206.1

6.3.17 (S)-6-(3-hydroxy-3-phenylprop-1-ynyl)naphthalene-2,3-diol (150)

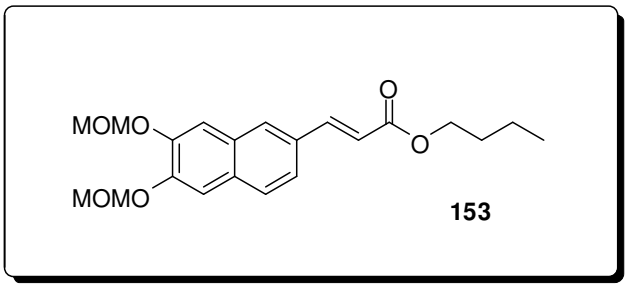


A solution of **148** (24.0mg, 0.046 mmol) in dry THF (0.5 mL) was purged with N_2 gas and a 1M solution of TBAF in THF (0.113 mL, 0.113 mmol) was added. The mixture was stirred for 14 hours then diluted with a 10% HCl solution (2 mL) and extracted with EtOAc (3 x 2 mL). The organic layers were combined and dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified with flash chromatography using a 19:1 Hex/EtOAc to 9:1 Hex/EtOAc elution gradient to afford **150** as a yellow oil (5.2 mg, 40%).

^{1}H NMR (300 MHz, $CO(CD_3)_2$) δ ppm 5.72 (s, 1H), 7.206 (s, 1H), 7.212 (s, 1H), 7.24 (dd, J = 8.4, 1.6 Hz, 1H), 7.28-7.34 (m, 1H), 7.42-7.38 (m, 2H), 7.58 (d, J = 8.4 Hz 1H), 7.63-7.67 (m, 2H), 7.73 (d, J = 1.2 Hz, 1H)

^{13}C NMR (400 MHz, $CO(CD_3)_2$) δ ppm 65.8, 87.7, 91.4, 111.3, 111.4, 119.3, 127.6, 127.9, 128.479, 129.485, 130.1, 130.6, 130.914, 130.987, 131.2, 144.3, 148.8, 149.1

6.3.18 (E)-Butyl 3-(6,7-bis(methoxymethoxy)naphthalen-2-yl)acrylate (153)

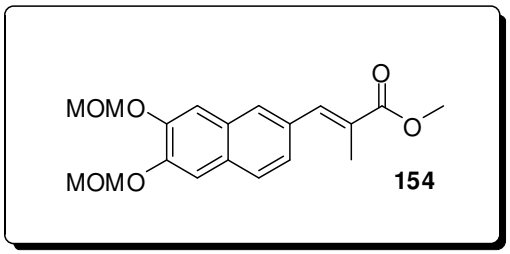


A solution of $C_{34}H_{28}Cl_2FeP_2$ Pd·CH_2Cl_2 complex (48.9 mg, 0.062 mmol) in dioxane (15 mL) was purged with N_2 gas and **106** (400 mg, 1.23 mmol), butyl acrylate (0.22 mL, 1.54 mmol), and Et_3N (0.37 mL, 2.64 mmol) were added and the mixture was refluxed for 3 days. The reaction mixture was cooled to room temperature, quenched with a saturated solution of NH_4Cl (5 mL) and then filtered through a pad of celite. The resulting mixture was washed with a solution of 10% HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude mixture was purified by flash column chromatography with a 13:7 Hex/CH_2Cl_2 elution solvent to afford **153** as a yellow oil (80 mg, 17%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 0.96 (t, *J* = 7.2 Hz, 3H), 1.43 (sextet, *J* = 7.2 Hz, 2H), 1.68 (quintet, *J* = 6.8 Hz, 2H), 3.538 (s, 3H), 3.540 (s, 3H), 4.21 (t, *J* = 6.8 Hz, 2H), 5.36 (s, 2H), 5.37 (s, 2H), 6.48 (d, *J* = 16 Hz, 1H), 7.46 (s, 1H), 7.49 (s, 1H), 7.52 (dd, *J* = 6.8, 1.6 Hz, 1H), 7.66 (d, *J* = 8.4 Hz, 1H), 7.769 (s, 1H), 7.773 (d, *J* = 16 Hz, 1H),

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 13.8, 19.2, 30.8, 56.3, 56.4, 64.3, 95.2, 95.3, 111.3, 112.1, 117.6, 122.5, 127.4, 128.6, 129.5, 130.7, 130.8, 144.9, 147.8, 148.3, 167.3

6.3.19 (E)-Ethyl 3-(6,7-bis(methoxymethoxy)naphthalen-2-yl)-2-methylacrylate (154)

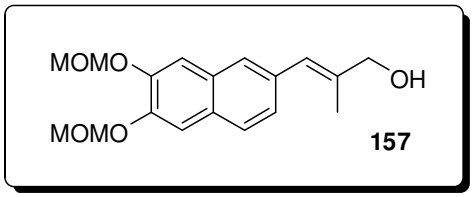


A solution of $C_{34}H_{28}Cl_2FeP_2$ Pd·CH_2Cl_2 complex (48.9 mg, 0.062 mmol) in dioxane (15 mL) was purged with N_2 gas and **106** (400 mg, 1.23 mmol), methyl methacrylate (0.16 mL, 1.25 equiv.), and Et_3N (0.37 mL, 1.54 mmol) were added to the solution and the reaction was refluxed for 3 days. The reaction mixture was cooled to room temperature, quenched with a saturated solution of NH_4Cl (5 mL) and then filtered through a pad of celite. The resulting mixture was washed with a solution of 10% HCl (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash column chromatography with 13:7 Hex/CH_2Cl elution solvent to afford **154** as a yellow oil (91.7 mg, 22%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 2.19 (d, *J* = 1.6 Hz, 3H), 3.54 (s, 3H), 3.55 (s, 3H), 3.82 (s, 3H), 7.37 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.46 (s, 1H), 7.48 (s, 1H), 7.67 (d, *J* = 8.8 Hz, 1H), 7.72 (s, 1H), 7.78 (s, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 14.3, 52.1, 56.3, 95.3, 95.3, 111.2, 111.8, 126.1, 126.3, 126.7, 127.8, 128.2, 129.4, 129.4, 132.1, 139.3, 147.7, 147.9, 169.3

6.3.20 (E)-3-(6,7-Bis(methoxymethoxy)naphthalen-2-yl)-2-methylprop-2-en-1-ol (157)

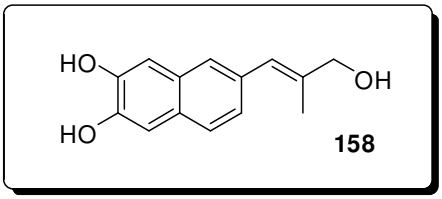


A solution of **154** (91.7 mg, 0.26 mmol) in THF (5 mL) was purged with N_2 gas and cooled to -78^{o}C then DIBALH (0.24 mL, 0.39 mmol) was added drop wise and the mixture was stirred at -78°C for 45 minutes. The mixture was warmed to 0^{o}C and was diluted with methanol (5 mL) and a saturated solution of NH_4Cl (10 mL) and extracted with EtOAc (3 x 10 mL). The organic layers were combined, dried with $MgSO_4$ and concentrated under reduced pressure. The crude was purified by flash chromatography using a 4:1 Hex/EtOAc elution solvent to afford **157** as a yellow oil (55.6 mg, 67%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.59 (br, OH), 1.96 (d, *J* = 1.2 Hz, 3H), 3.54 (s, 3H), 3.55 (s, 3H), 4.21 (s, 2H), 5.352 (s, 2H), 5.358 (s, 2H), 6.60 (s, 1H), 7.27 (dd, *J* = 8.4, 1.6 Hz, 1H), 7.442 (s, 1H), 7.446 (s, 1H), 7.57 (s, 1H), 7.60 (d, *J* = 8.4 Hz, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 15.5, 56.3, 69.2, 95.3, 111.4, 111.6, 125.3, 126.2, 126.4, 126.4, 128.4, 129.6, 133.9, 137.6, 147.2, 147.4

6.3.21 (E)-6-(3-Hydroxy-2-methylprop-1-enyl)naphthalene-2,3-diol (158)



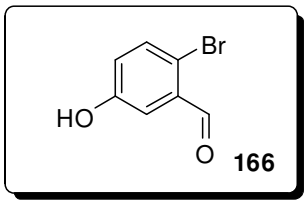
158

Conc. HCl (2 drops) was added to a solution of **157** (55.6 mg, 0.18 mmol) in methanol (1 mL) under ambient atmospehere and the mixture was stirred for 1h at room temperature. The reaction mixture was diluted with water (5 mL) and extracted with EtOAc (3 x 10 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography using a 3:2 Hex/EtOAc elution solvent to afford **158** (5 mg, 12%). The final yield was too low to complete the compound's characterization.

^{1}H NMR (400 MHz, $CO(CD_3)_2$) δ ppm 1.92 (d, *J* = 1.3 Hz, 3H), 4.13 (s, 2H), 6.60 (s, 1H), 7.17 (s, 1H), 7.18 (s, 1H), 7.19 (dd, *J* = 8.4, 2.0 Hz, 1H), 7.52 (s, 1H), 7.56 (d, *J* = 8.4 Hz, 1H)

6.4 Synthesis of the 2-bromo-N,N-diethyl-5-hydroxybenzamide Component

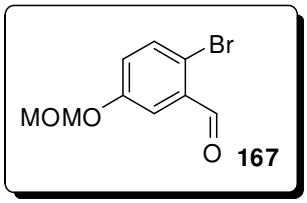
6.4.1 2-bromo-5-hydroxybenzaldehyde (166)



A solution of commercially available 3-hydroxybenzaldehyde (5.0 g, 41 mmol) in freshly distilled CCl_4 (800 mL) was purged with N_2 gas. Bromine (2.1 mL, 41 mmol) was added drop wise and the reaction mixture was stirred at room temeperature overnight. Water (700 mL) was added to the reaction mixture and extracted with DCM (3 x 700 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The resulting solid was diluted in a minimum amount of EtOAc and the product was precipitated by addition of hexanes. After filtration, **166**[84] was recovered as pale pink flakes (32.0 g, 78.2%).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 7.00 (dd, J = 8.7, 3.2 Hz, 1H), 7.39 (d, J = 3.2 Hz, 1H), 7.51 (d, J = 8.7 Hz, 1H), 10.29 (s, 1H)

6.4.2 2-bromo-5-(methoxymethoxy)benzaldehyde (167)



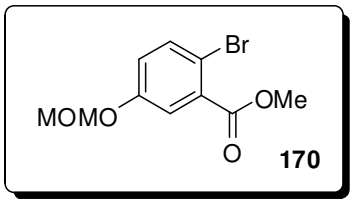
167

A solution of **166** (5.55 g, 27.6 mmol) in dry DCM (300 mL) was purged with N_2 gas. The mixture was cooled to 0°C and MOMCl (3.1 mL, 41.4 mmol) and DIPEA (5.8 mL, 33.1 mmol) were added in sequence and the reaction mixture was warmed to room temperature and stirred overnight. The reaction was quenched using a saturated NH_4Cl solution (400 mL) and extracted with DCM (3 x 400 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 9:1 Hex/EtOAc to 4:1 Hex/EtOAc elution gradient to afford **167**[60] as a white, flaky solid (5.32 g, 78%); starting material was also recovered (0.94 g, 4.7 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.46 (s, 3H), 5.19 (s, 2H), 7.15 (dd, J = 8.8, 3.1 Hz, 1H), 7.56-7.53 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 3.1 Hz, 1H), 10.30 (s, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 191.2, 156.6, 134.3, 133.9, 123.7, 118.6, 116.1, 94.2, 55.99

6.4.3 Methyl 2-bromo-5-(methoxymethoxy)benzoate (170)



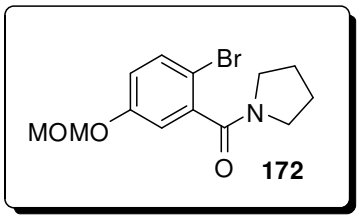
170

KCN (7.42 g, 113.95 mmol) and MnO_2 (39.2 g, 450.8 mmol) were added to a solution of **167** (5.32 g, 21.5 mmol) in MeOH (200 mL) and glacial acetic acid (1.05 mL, 34.4 mmol) and was purged with N_2 gas. The mixture was stirred at room temperature overnight and the MeOH was removed under reduced pressure and the resulting slurry was dissolved in EtOAc (200 mL) and filtered to remove MnO_2 before washing with water (200 mL) and extracting with EtOAc (3 x 200 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure to afford **170**[60] as a yellow oil (5.22 g, 88%) in sufficiently high purity to use in subsequent steps.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 3.46 (s, 3H), 3.93 (s, 3H), 5.17 (s, 2H), 7.54 (d, J = 8.8 Hz, 1H), 7.46 (d, J = 3.0 Hz, 1H), 7.02 (dd, J = 8.8, 3.0 Hz, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 165.9, 155.9, 134.6, 132.5, 120.4, 118.6, 112.6, 94.0, 55.7, 52.0

6.4.4 (2-bromo-5-(methoxymethoxy)phenyl)(pyrrolidin-1-yl)methanone (172)



172

DMAP (3.05 mg, 0.025 mmol) and DIPEA (0.13 mL, 0.75 mmol) were added to a solution of **170** (137 mg, 0.50 mmol) in pyrrolidine (3mL) and purged with N_2 gas. The mixture was stirred for three days at reflux. The mixture was cooled to room temperature, diluted with DCM (10 mL) and washed with a solution of saturated NH_4Cl (10 mL). The aqueous phase was extracted with DCM (3 x 8 mL) and the combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The crude was purified using flash column chromatography with a 4:1 Hex/EtOAc to 3:2 Hex/EtOAc elution gradient to afford **172** as a yellow oil (51.2 mg, 33%). (2-bromo-5-hydroxyphenyl)(pyrrolidin-1-yl)methanone was also recovered (17.6 mg, 0.065 mmol).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 1.92 (m, 4H), 3.19 (t, J = 6.8 Hz, 2H), 3.44 (s, 3H), 3.63 (t, J = 6.82 Hz, 2H), 5.13 (s, 2H), 6.90 (dd, J = 8.8, 2.9 Hz, 1H), 6.96 (d, J = 2.9 Hz, 1H), 7.42 (d, J = 8.8 Hz, 1H)

^{13}C NMR (400 MHz, $CDCl_3$) δ ppm 24.55, 25.91, 45.50, 48.02, 56.13, 94.55, 110.3, 115.3, 118.3, 133.6, 140.4, 167.0

7.0 References

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APPENDIX A: NMR Data

Figure a.1 ^{1}H NMR of compound **95**, 400 Hz, Chloroform-d

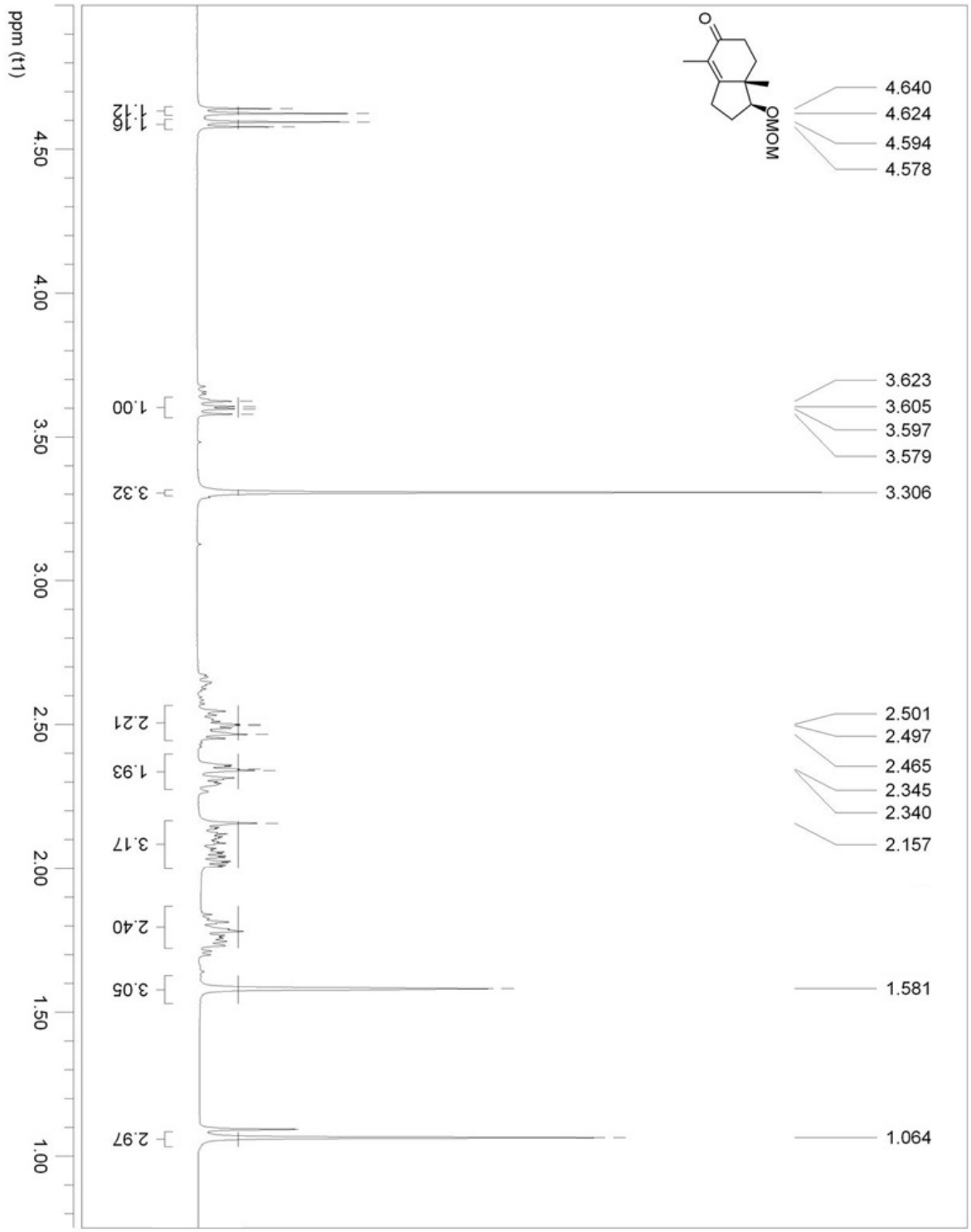


Figure a.2 ^{13}C NMR of compound **95**, 400 Hz, Chloroform-d

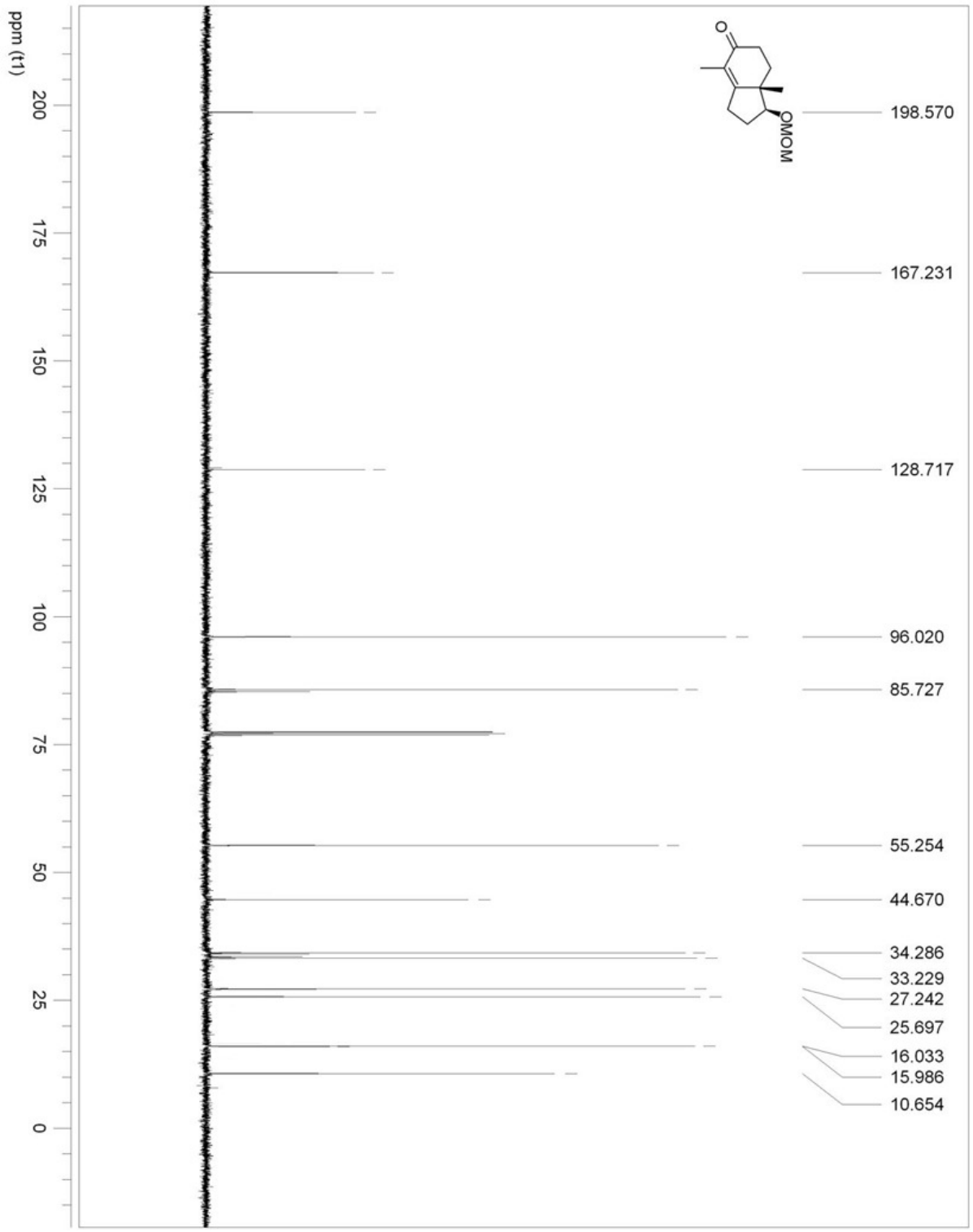


Figure a.3 ^{1}H NMR of compound **88**, 400 Hz, Chloroform-d

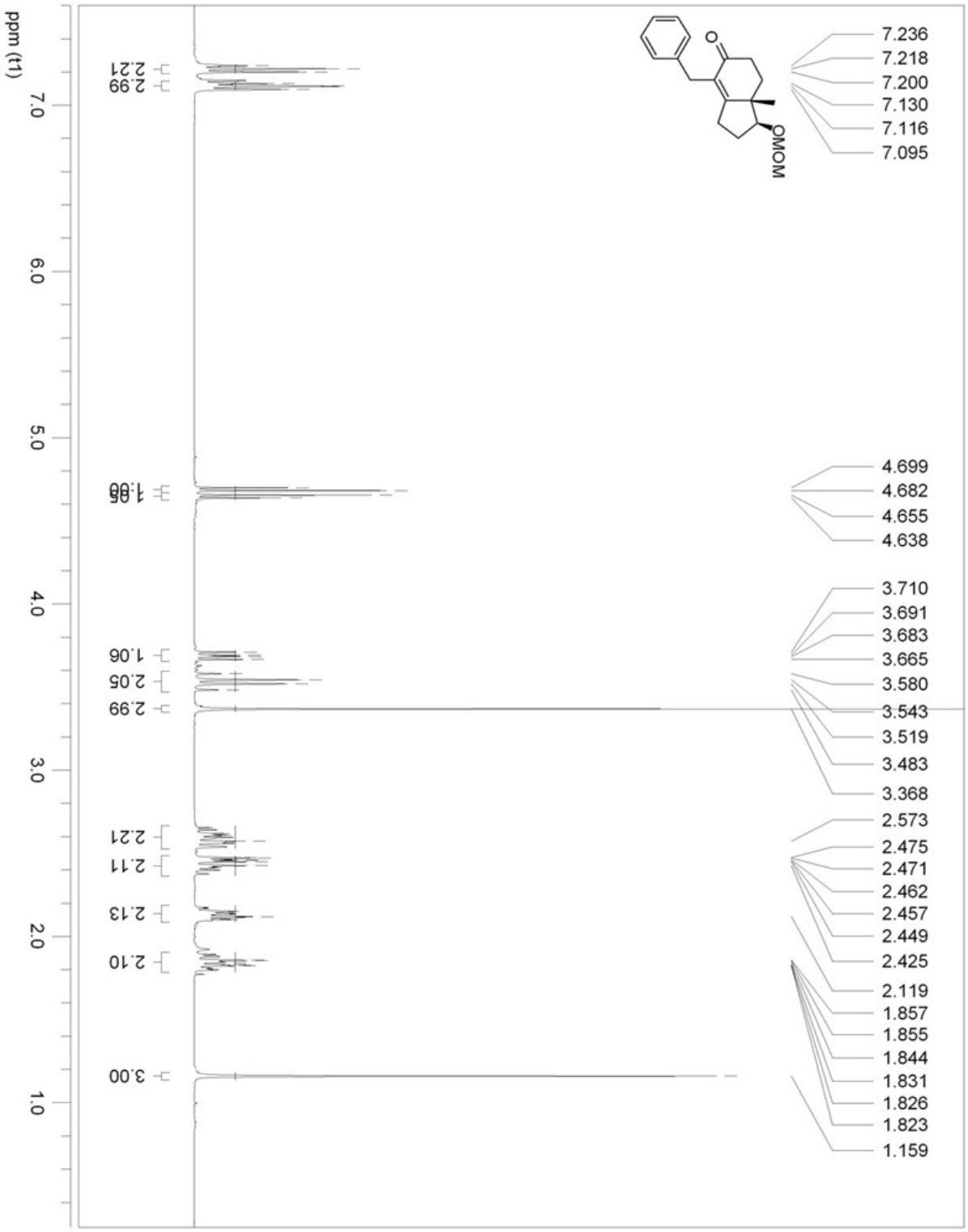


Figure a.4 ^{13}C NMR of compound **88**, 400 Hz, Chloroform-d

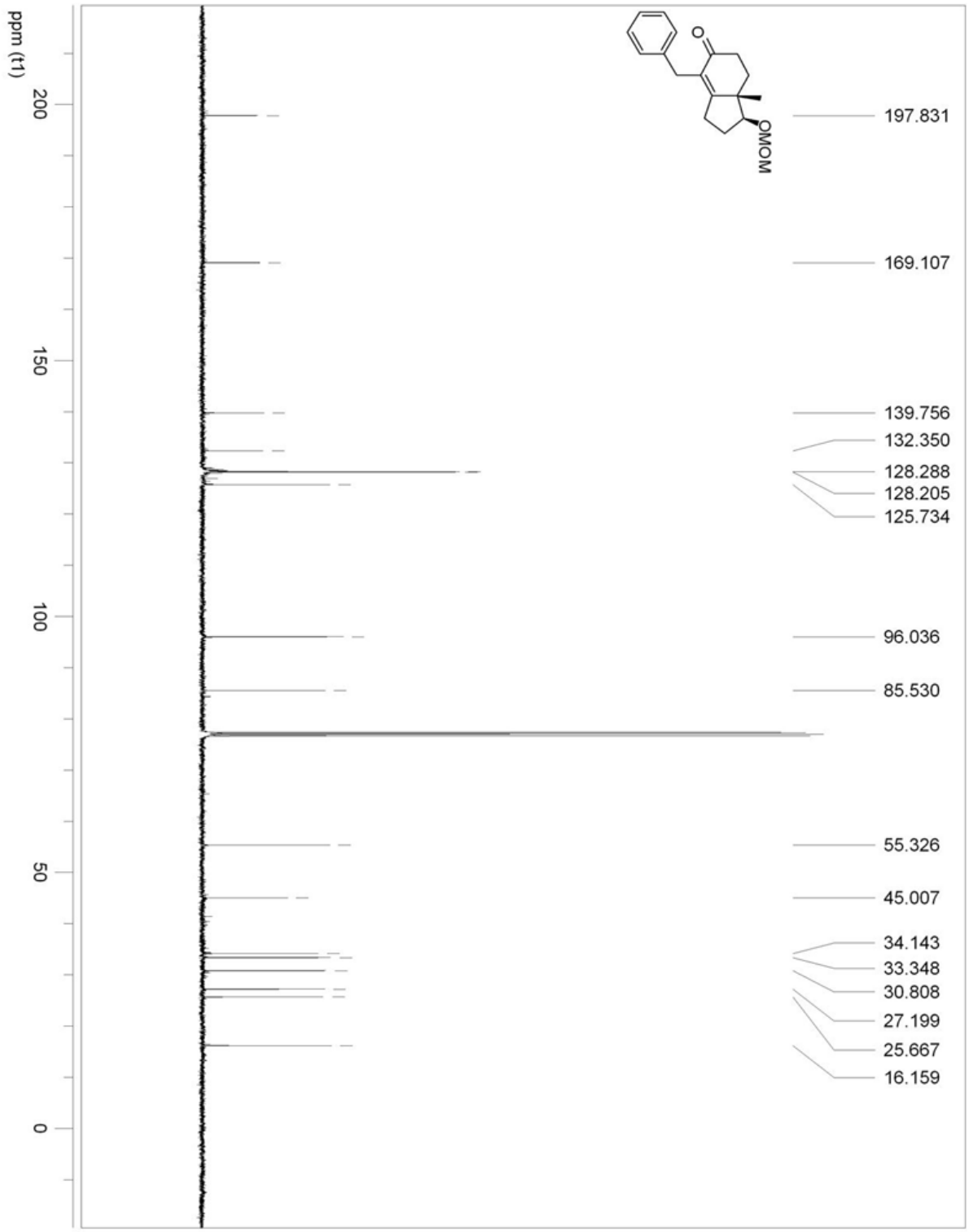


Figure a.5 ^{1}H NMR of compound **42**, 400 Hz, Chloroform-d

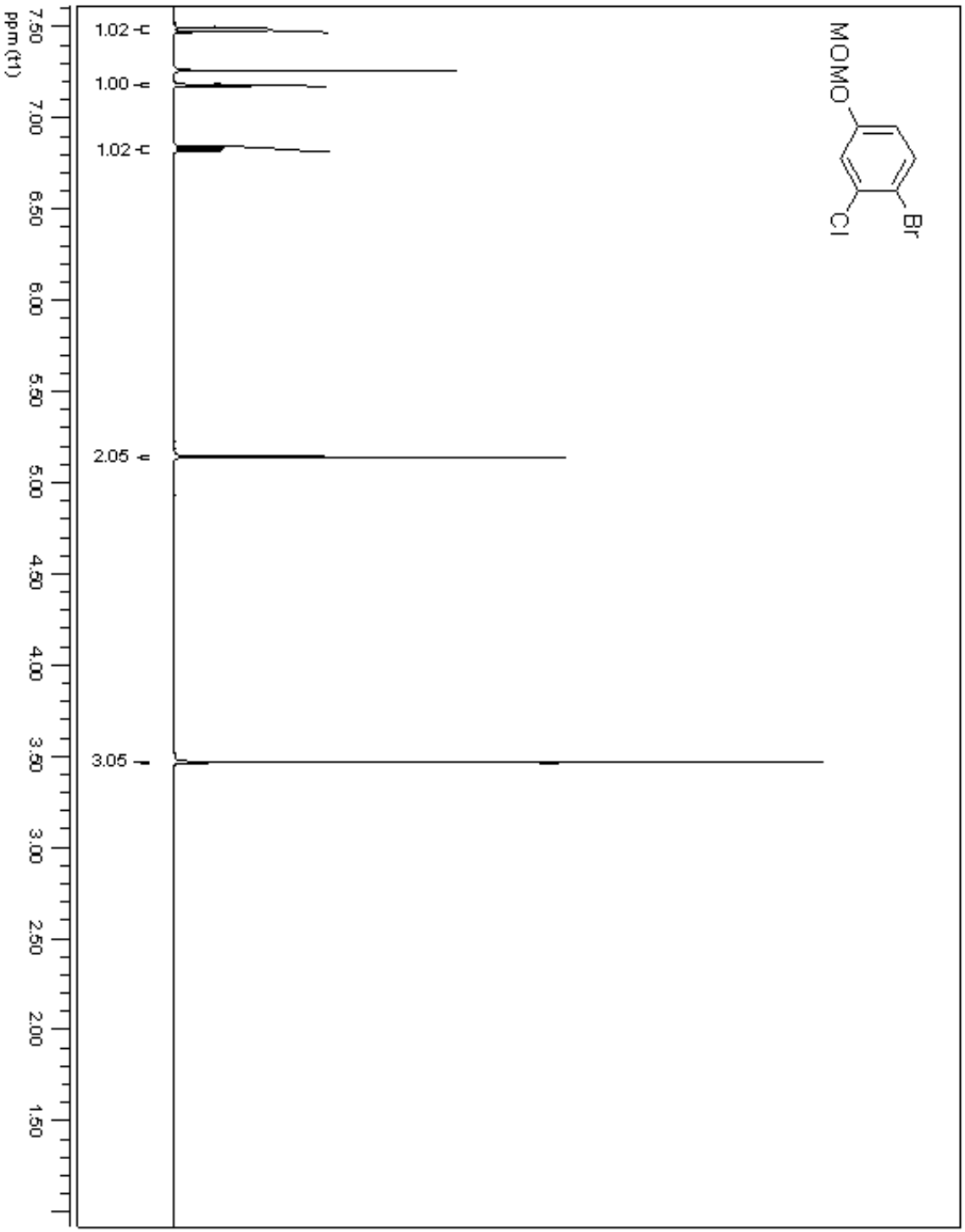


Figure a.6 ^{1}H NMR of compound **108**, 400 Hz, Chloroform-d

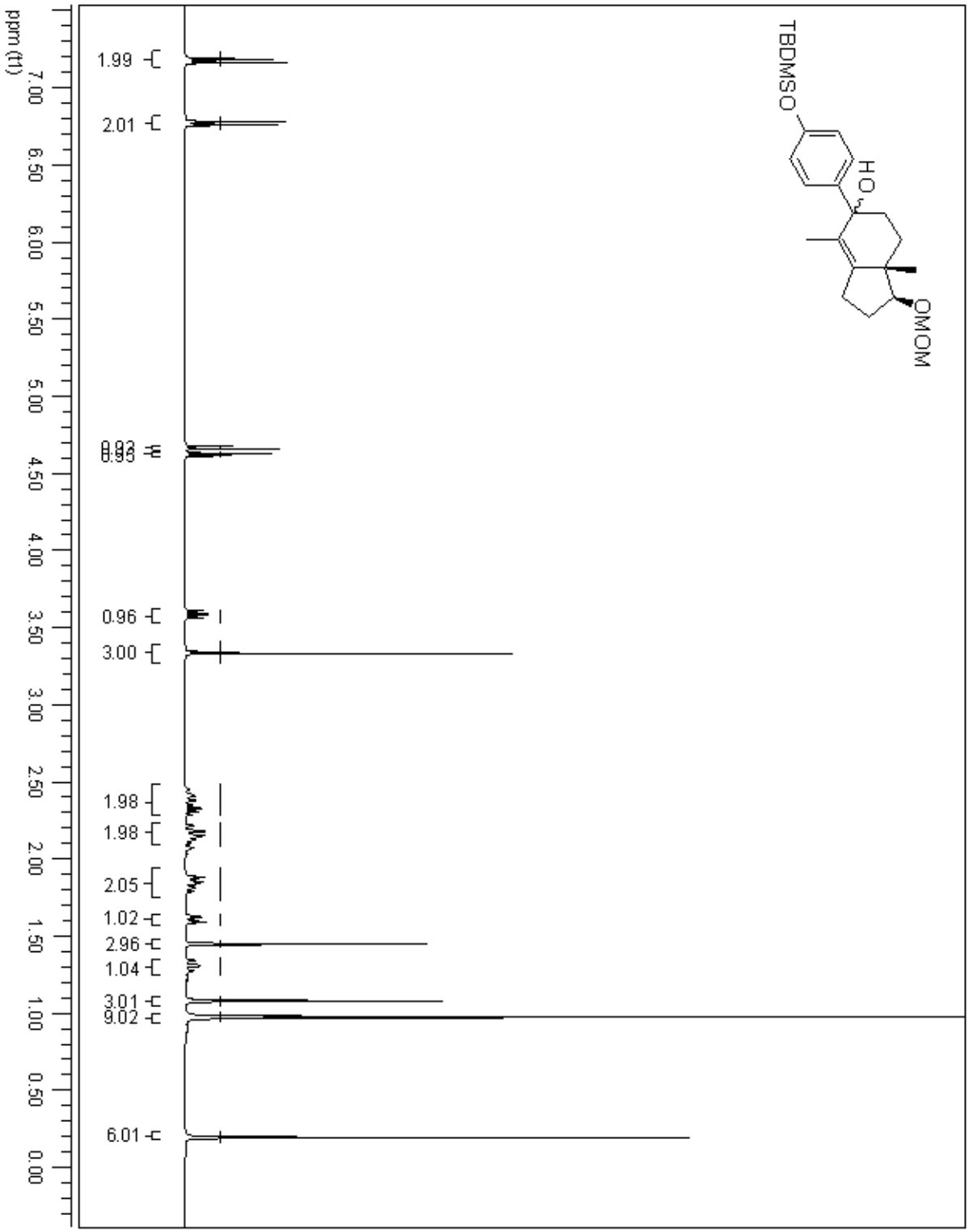


Figure a.7 ^{1}H NMR of compound **115b**, 400 Hz, Acetone-d

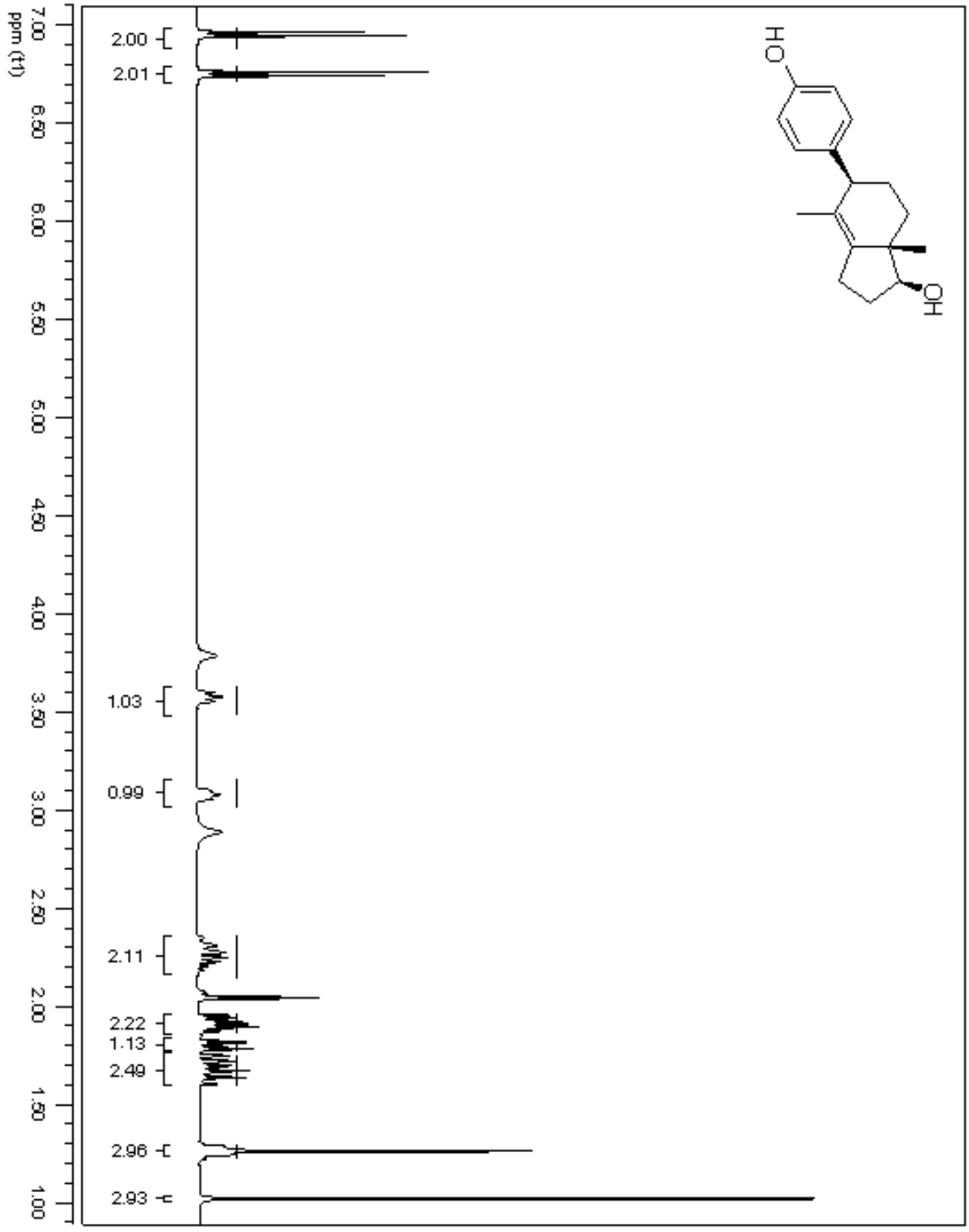


Figure a.8 ^{13}C NMR of compound **115b**, 400 Hz, Acetone-d

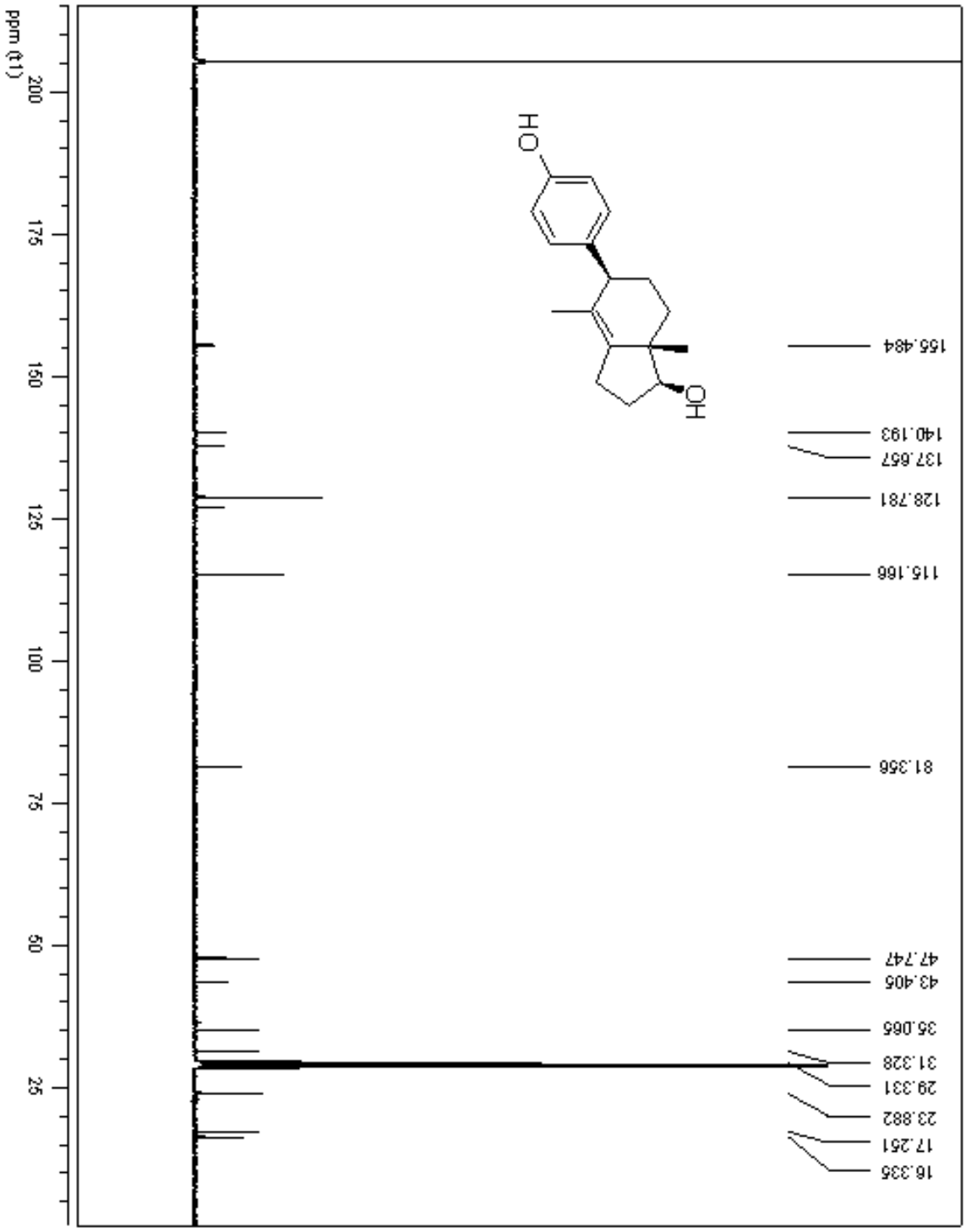


Figure a.9 ^{1}H NMR of compound **109**, 400 Hz, Chloroform-d

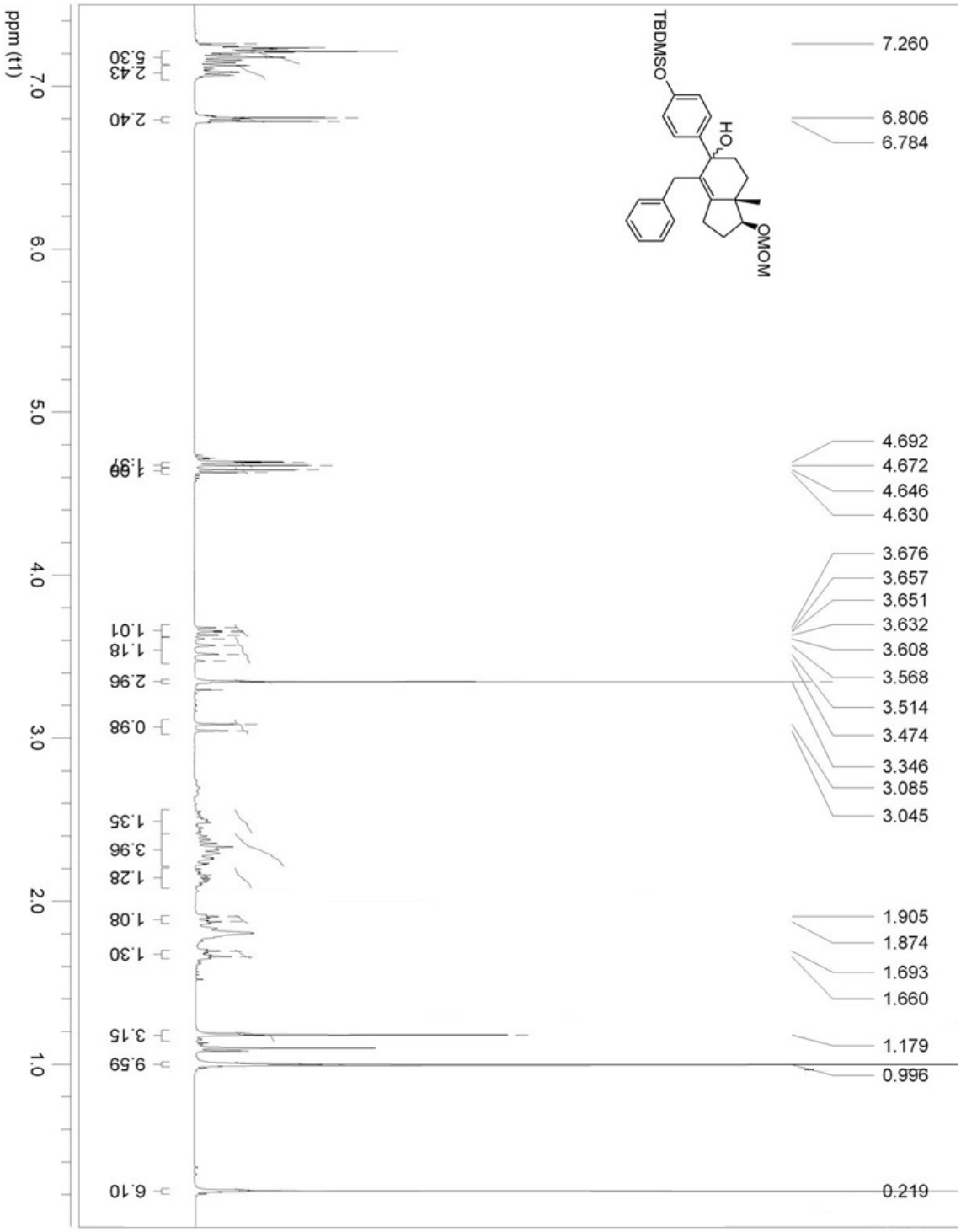


Figure a.10 ^{1}H NMR of compound **45**, 400 Hz, Chloroform-d

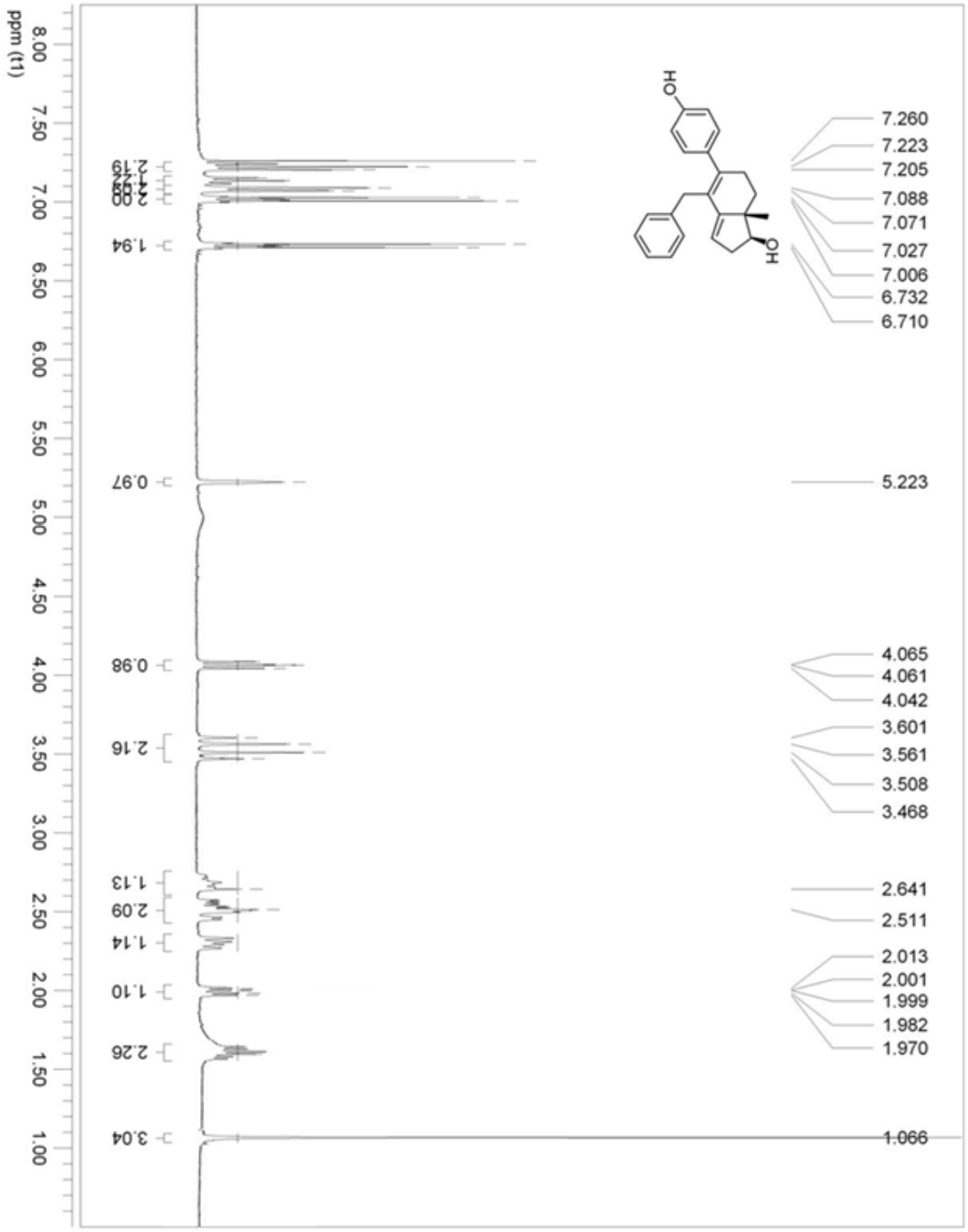


Figure a.11 ^{1}H NMR of compound **47b**, 400 Hz, Chloroform-d

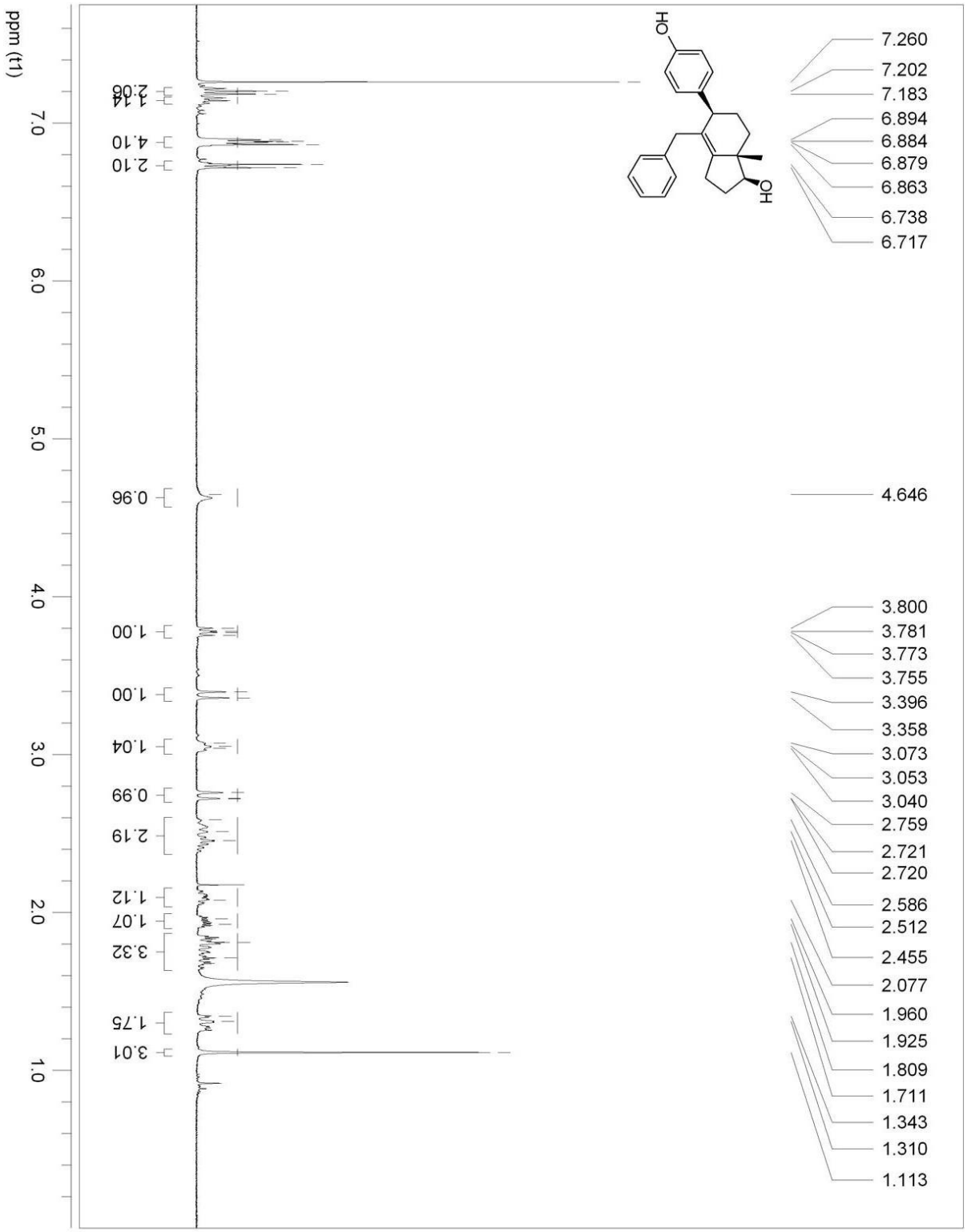


Figure a.12 ^{13}C NMR of compound **47b**, 400 Hz, Aceton-d

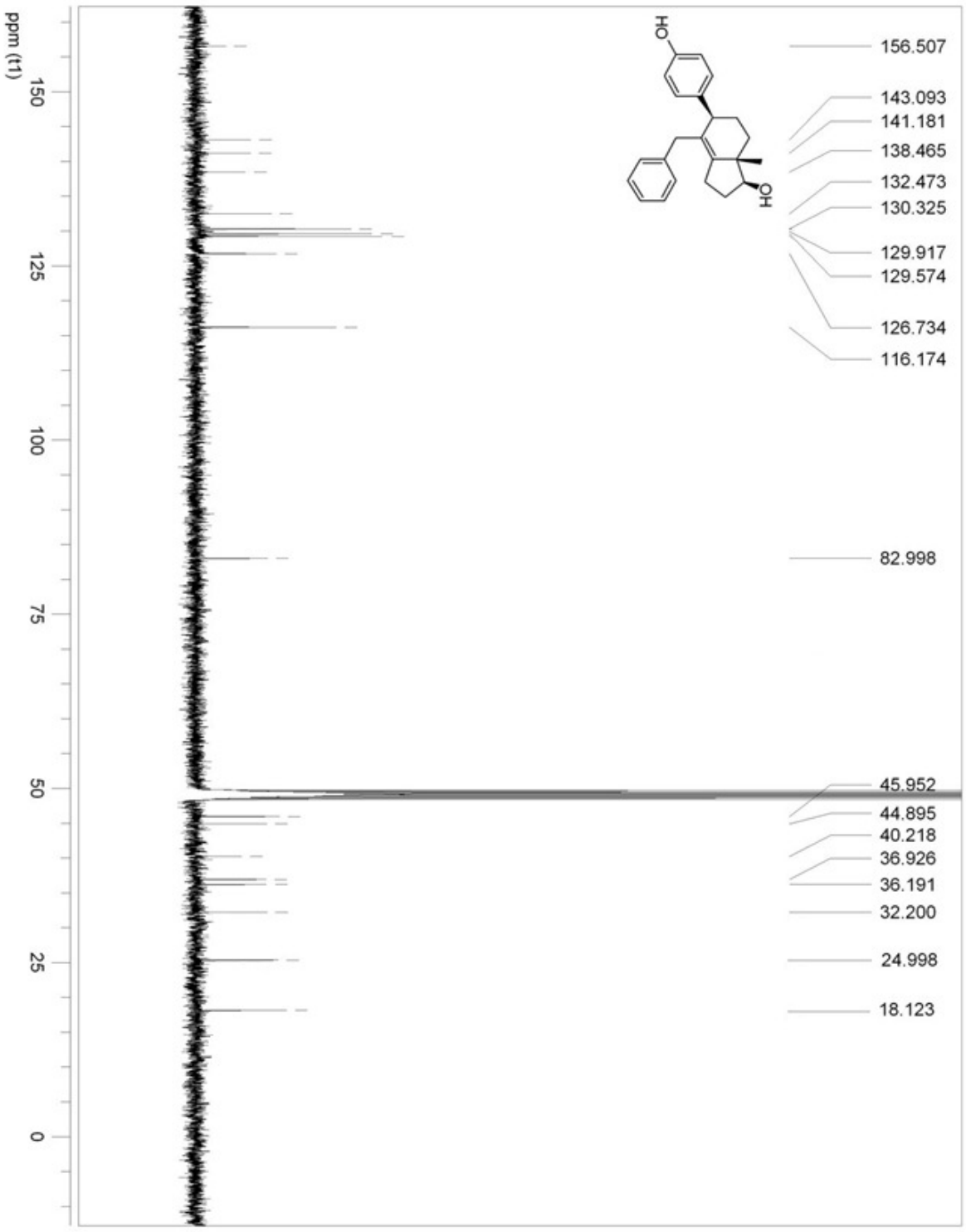


Figure a.13 ^{1}H NMR of compound **59**, 400 Hz, Chloroform-d

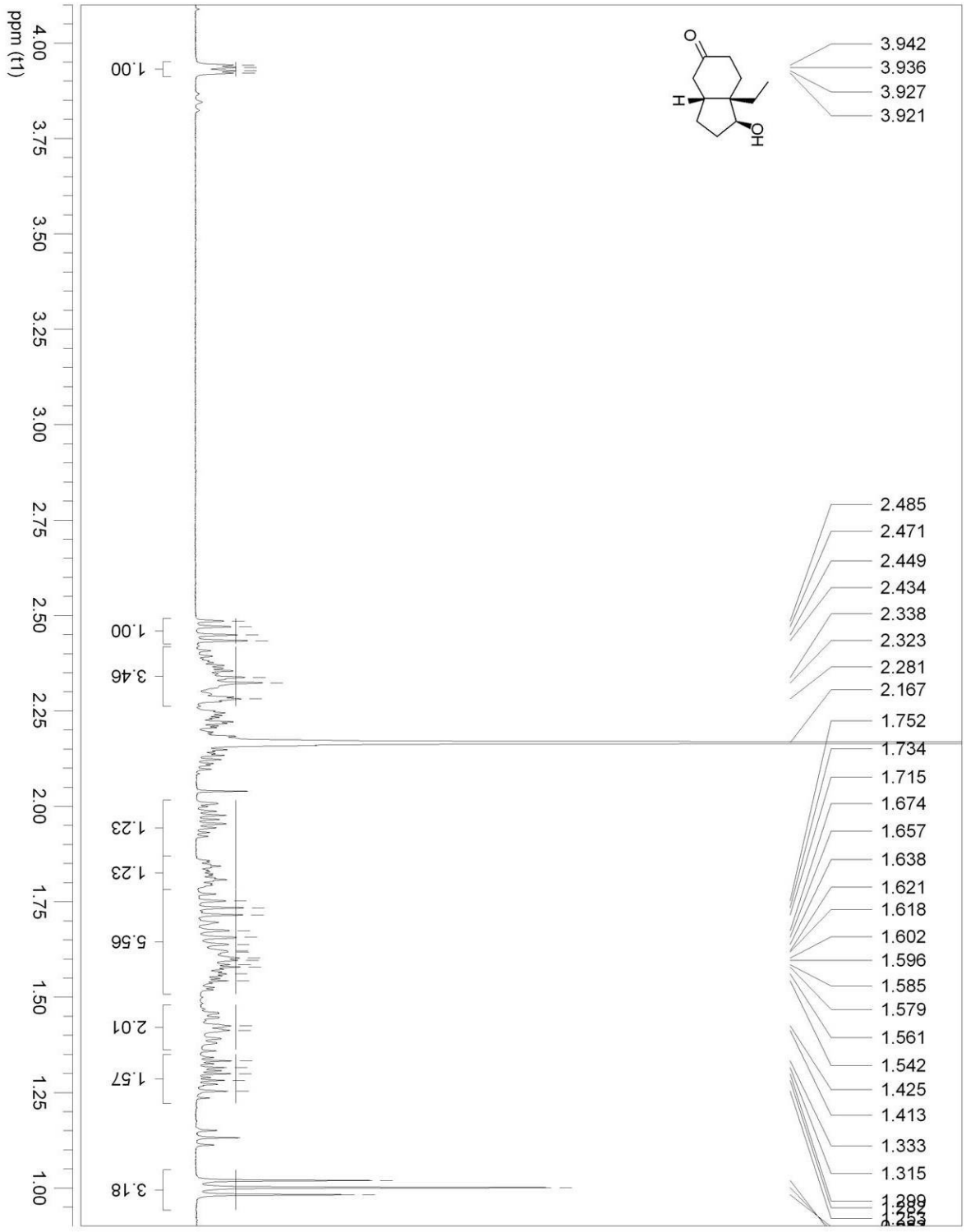


Figure a.14 ^{13}C NMR of compound **59**, 400 Hz, Chloroform-d

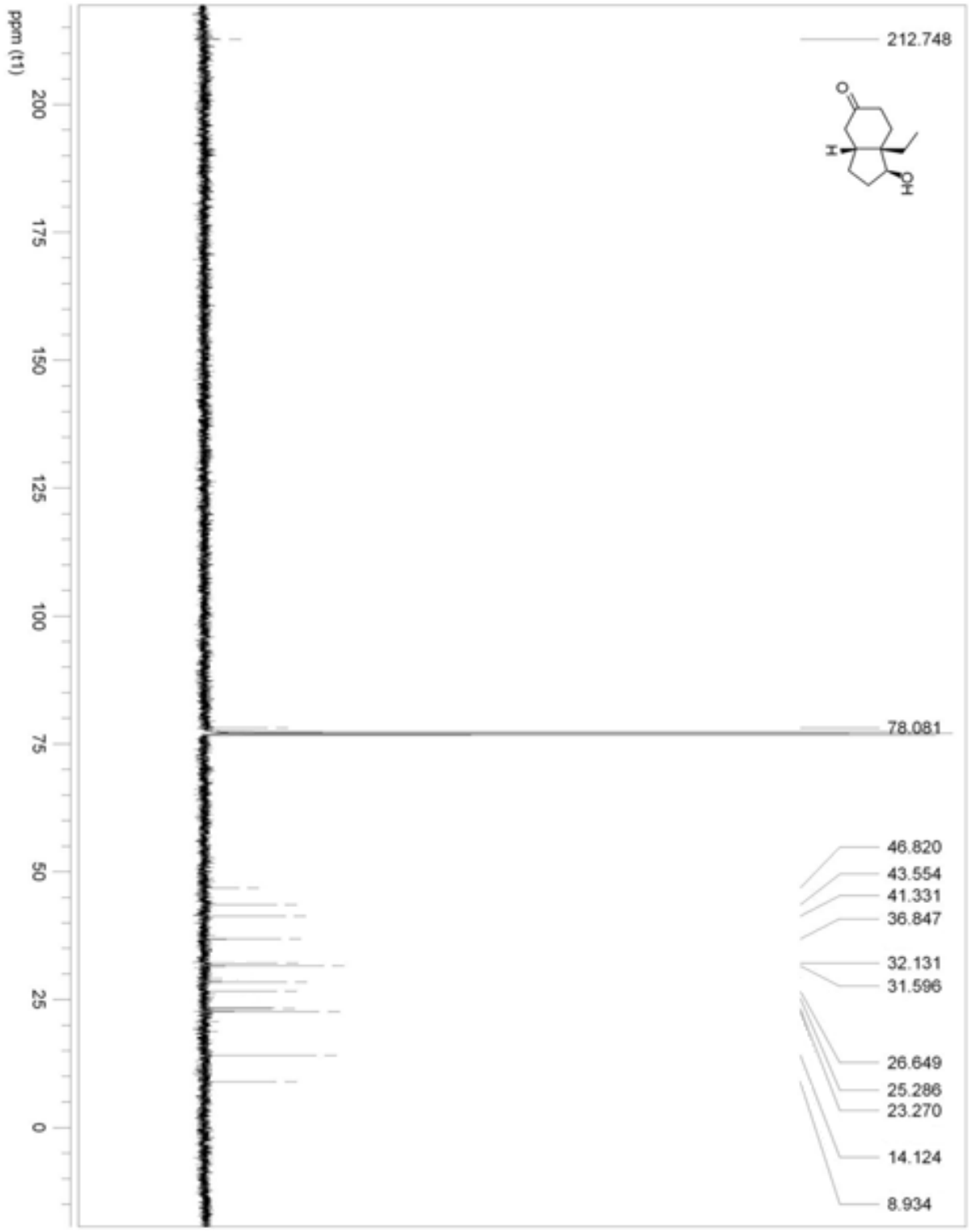


Figure a.15 ^{1}H NMR of compound **61**, 400 Hz, Chloroform-d

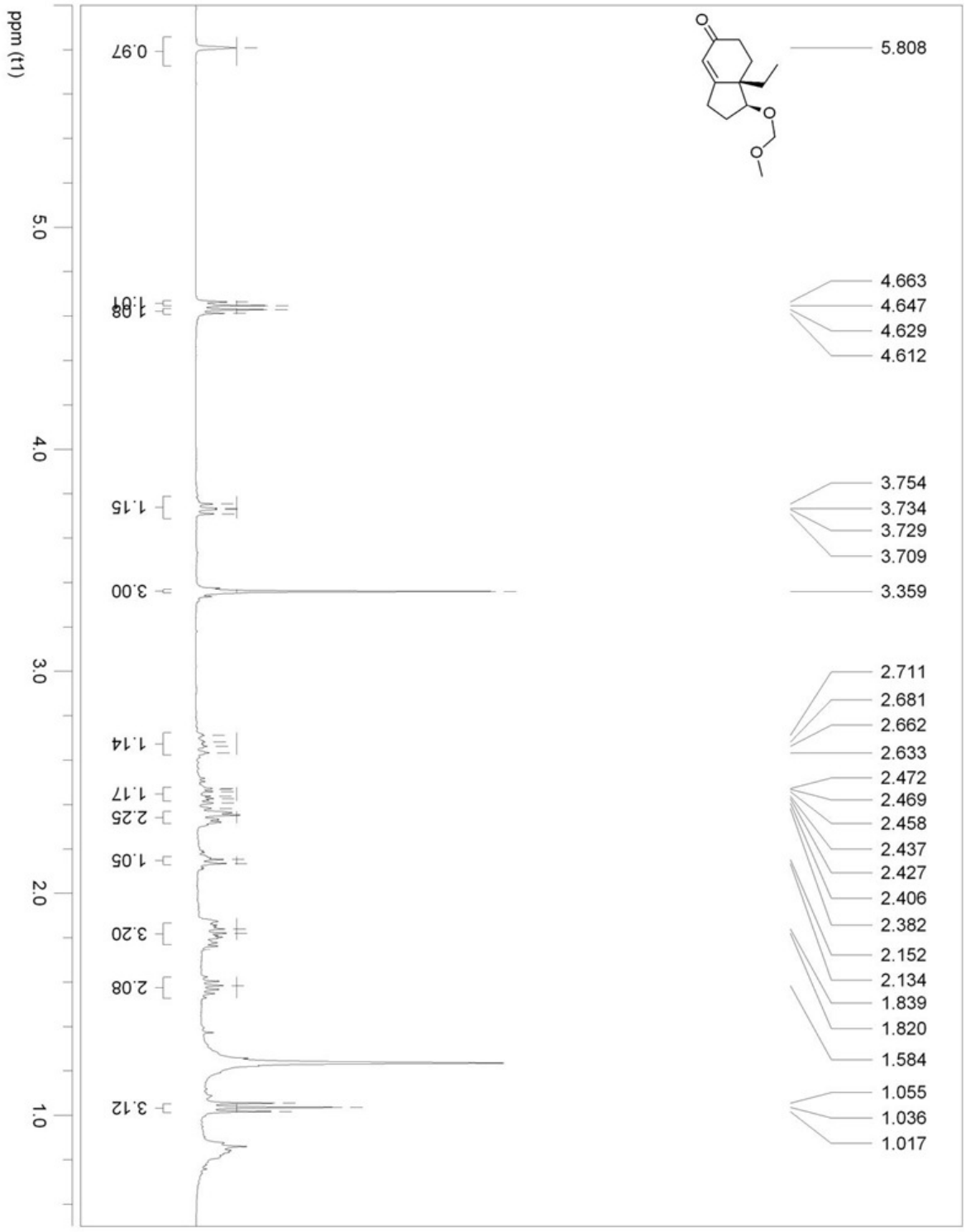


Figure a.16 ^{1}H NMR of compound **64**, 400 Hz, Acetone-d

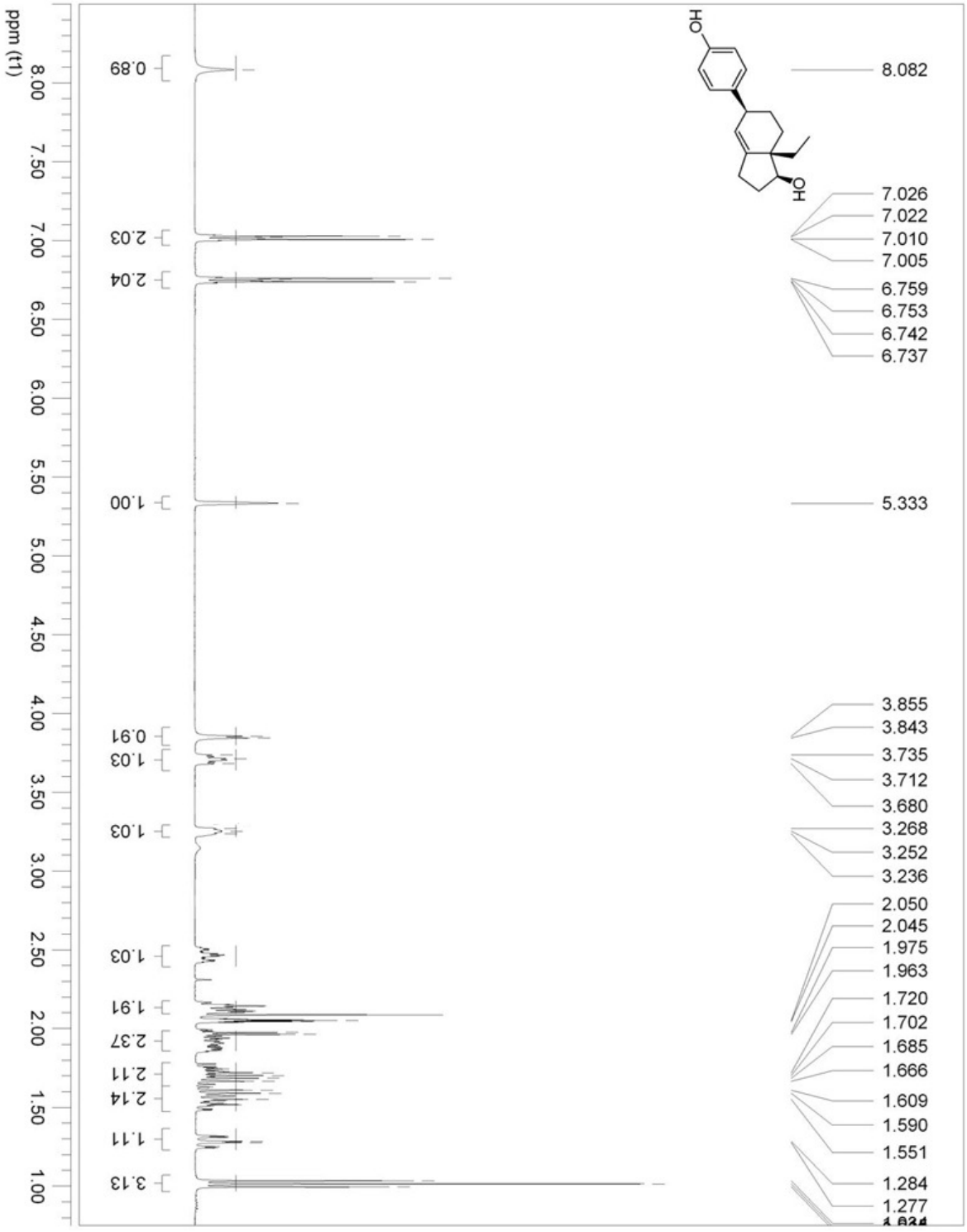


Figure a.17 ^{1}H NMR of compound **65**, 400 Hz, Chloroform-d

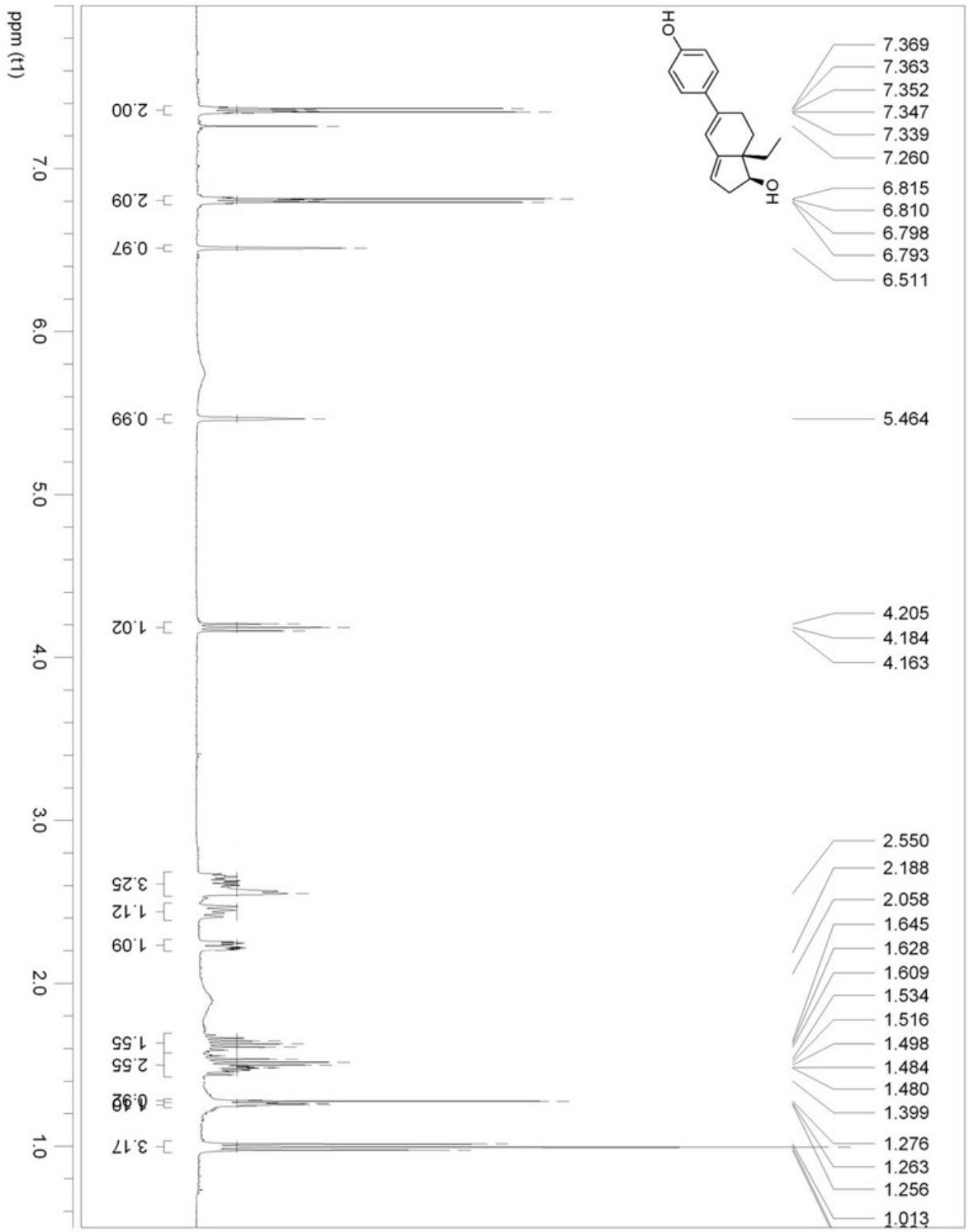


Figure a.18 ^{13}C NMR of compound **65**, 400 Hz, Chloroform-d

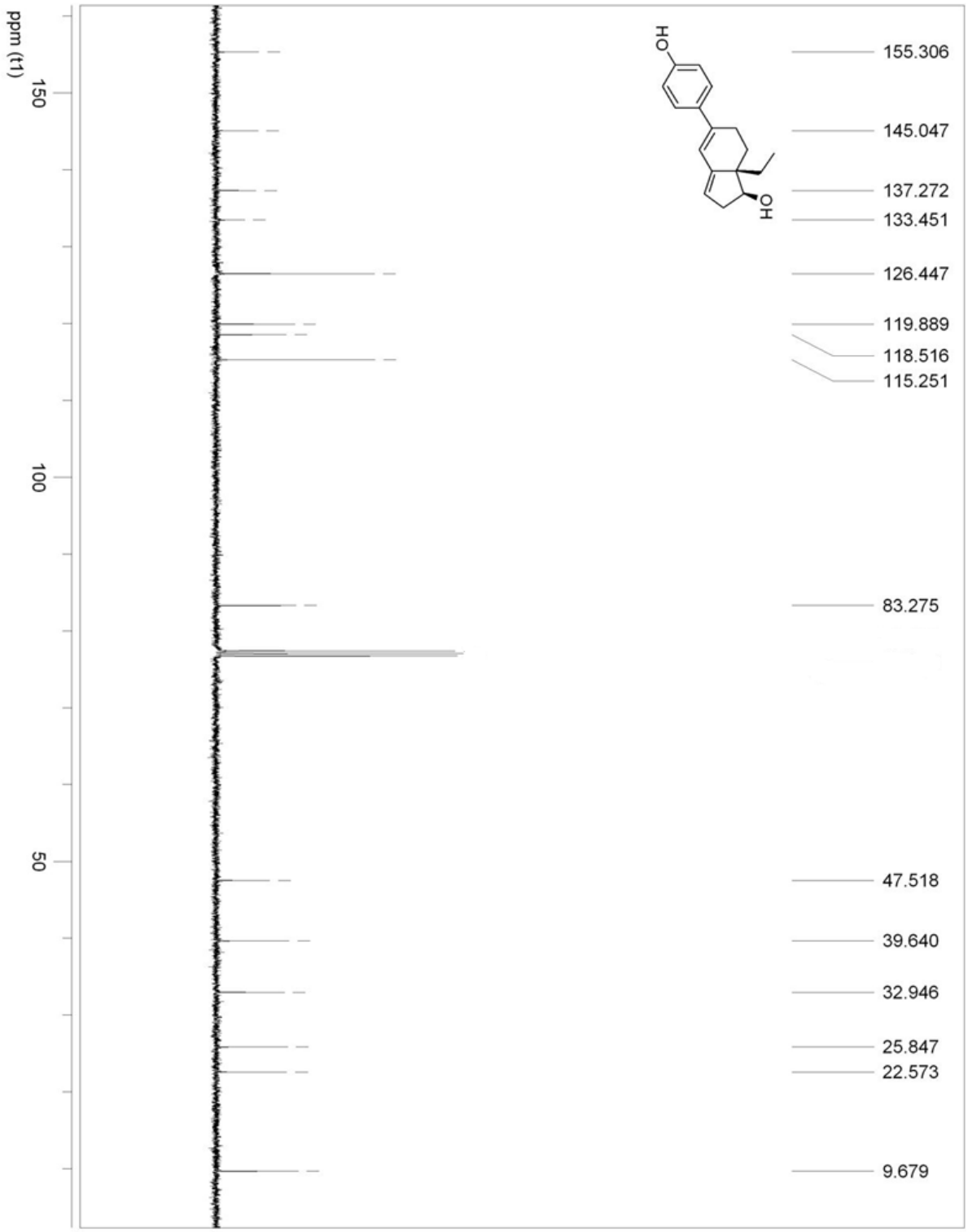


Figure a.19 ^{1}H NMR of compound **71**, 400 Hz, Acetone-d

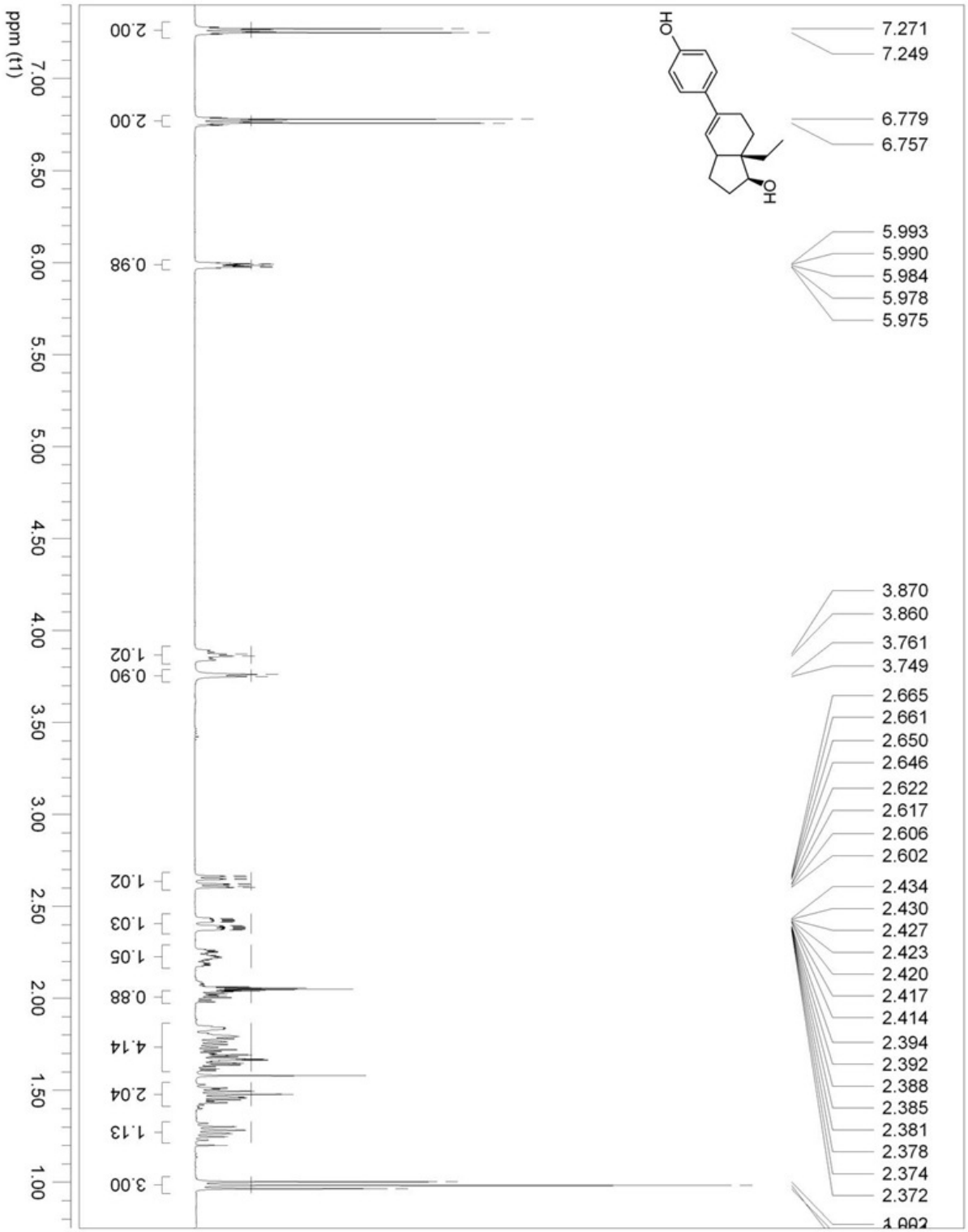


Figure a.20 ^{1}H NMR of compound **72**, 400 Hz, Acetone-d

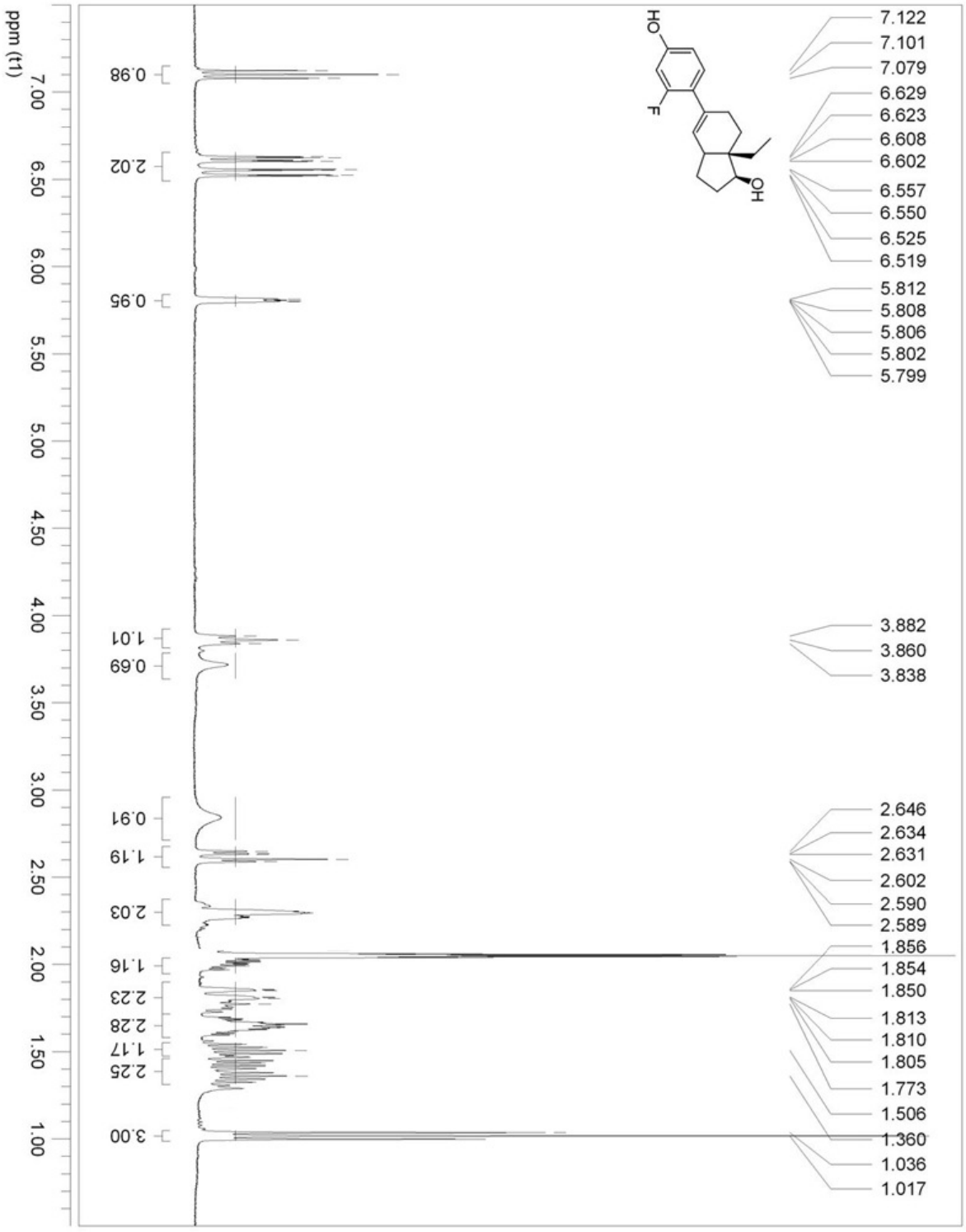


Figure a.21 ^{13}C NMR of compound **72**, 400 Hz, Acetone-d

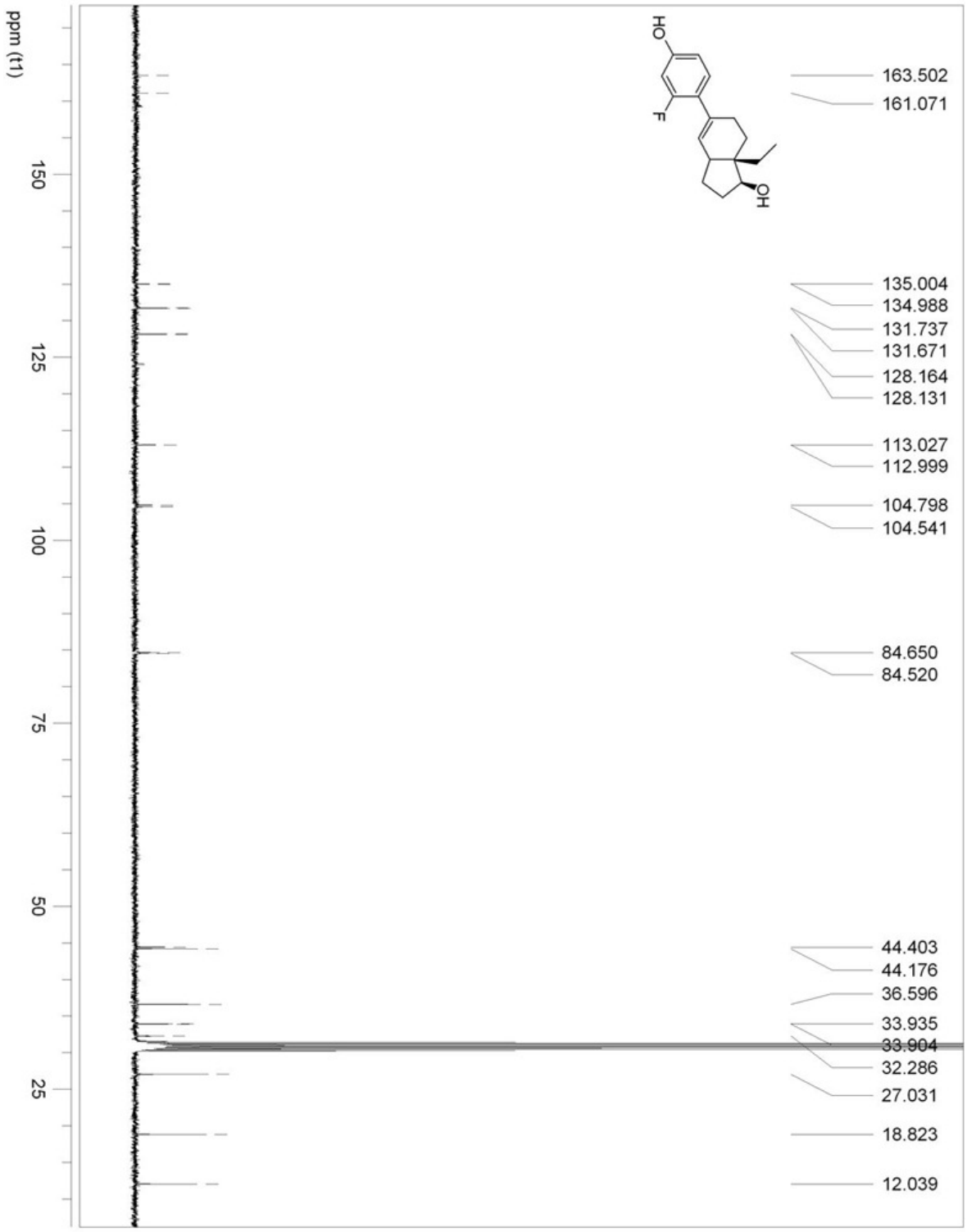


Figure a.22 ^{1}H NMR of compound **81**, 400 Hz, Acetone-d

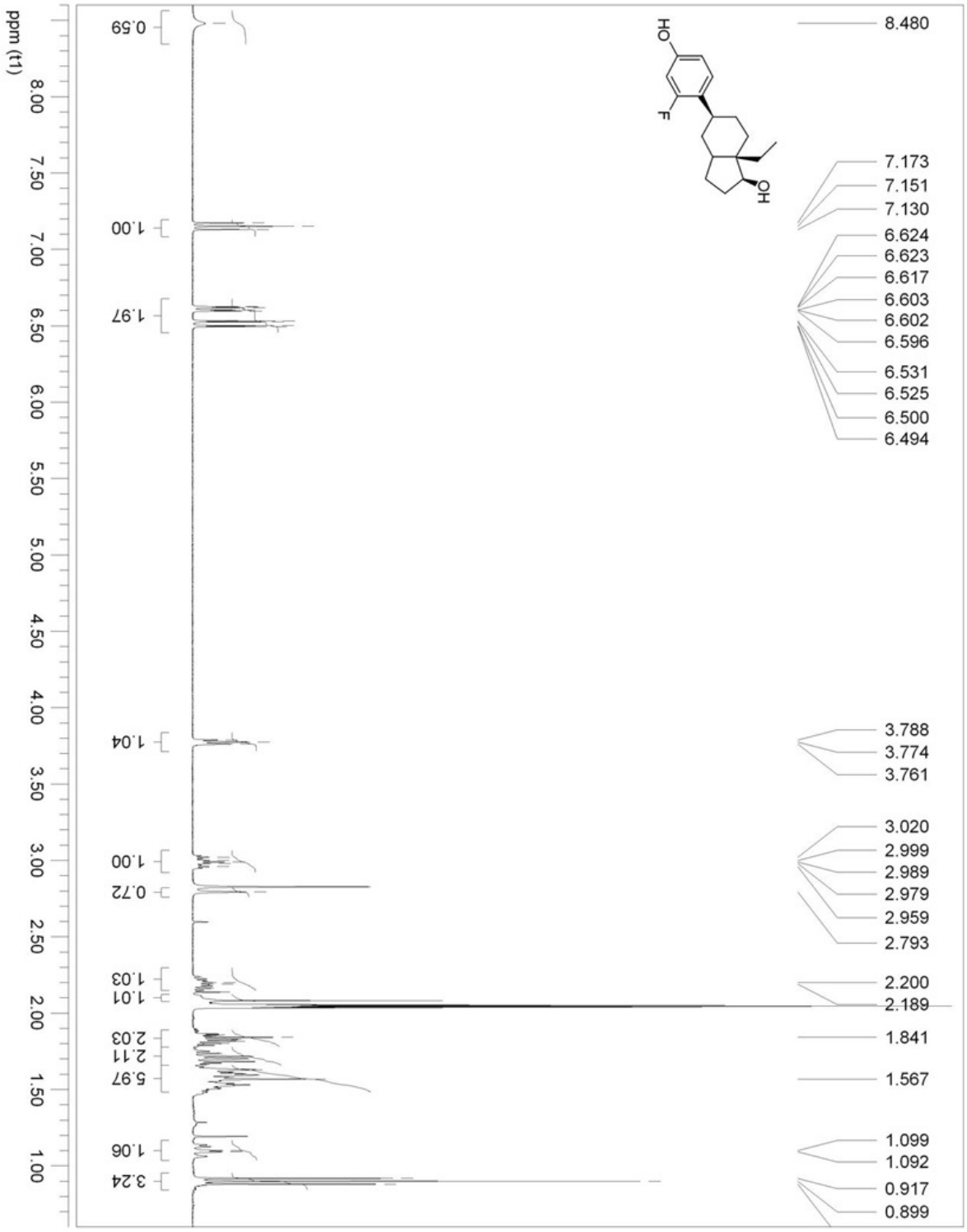


Figure a.23 ^{13}C NMR of compound **81**, 400 Hz, Acetone-d

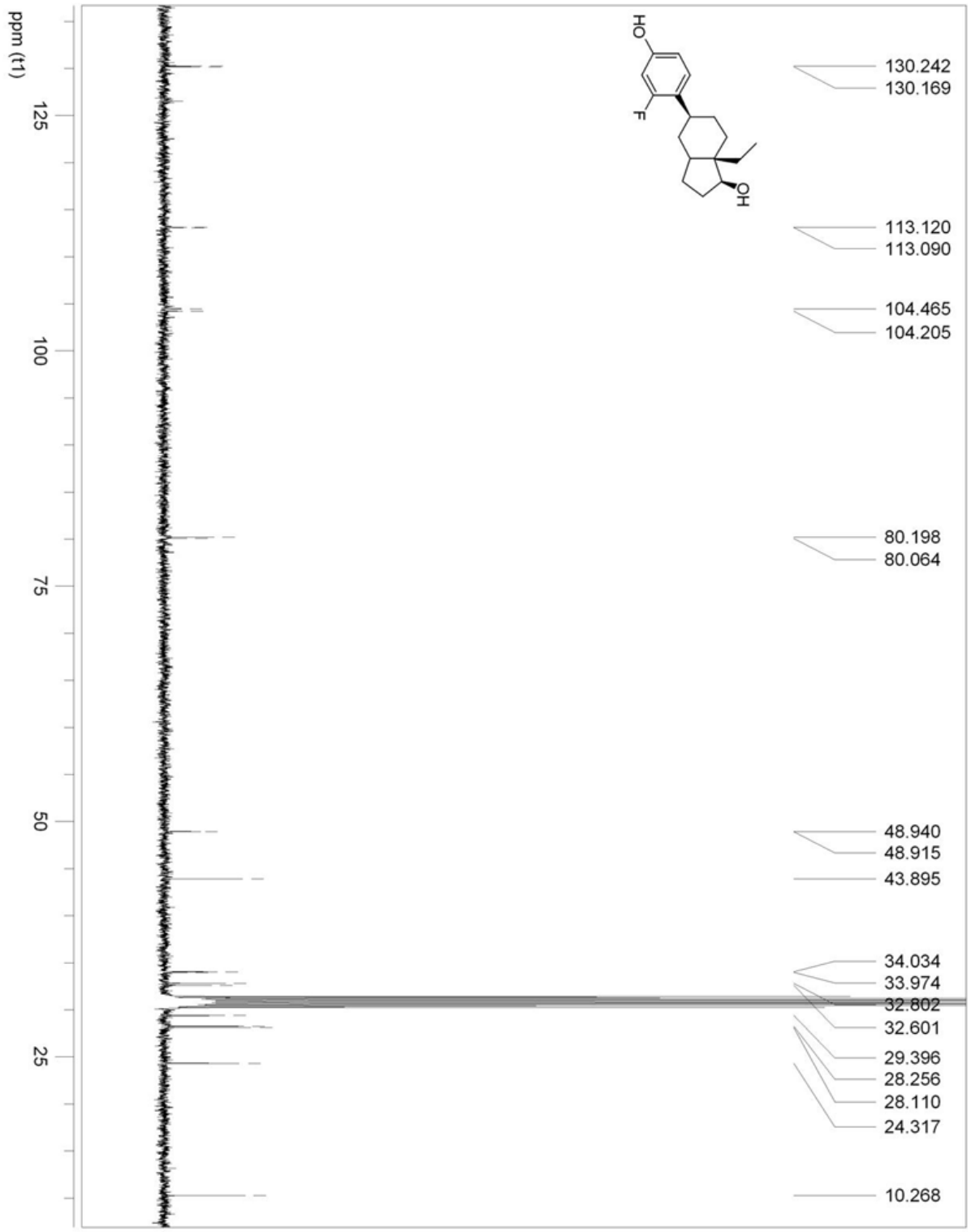


Figure a.24 ^{1}H NMR of compound **85**, 400 Hz, Acetone-d

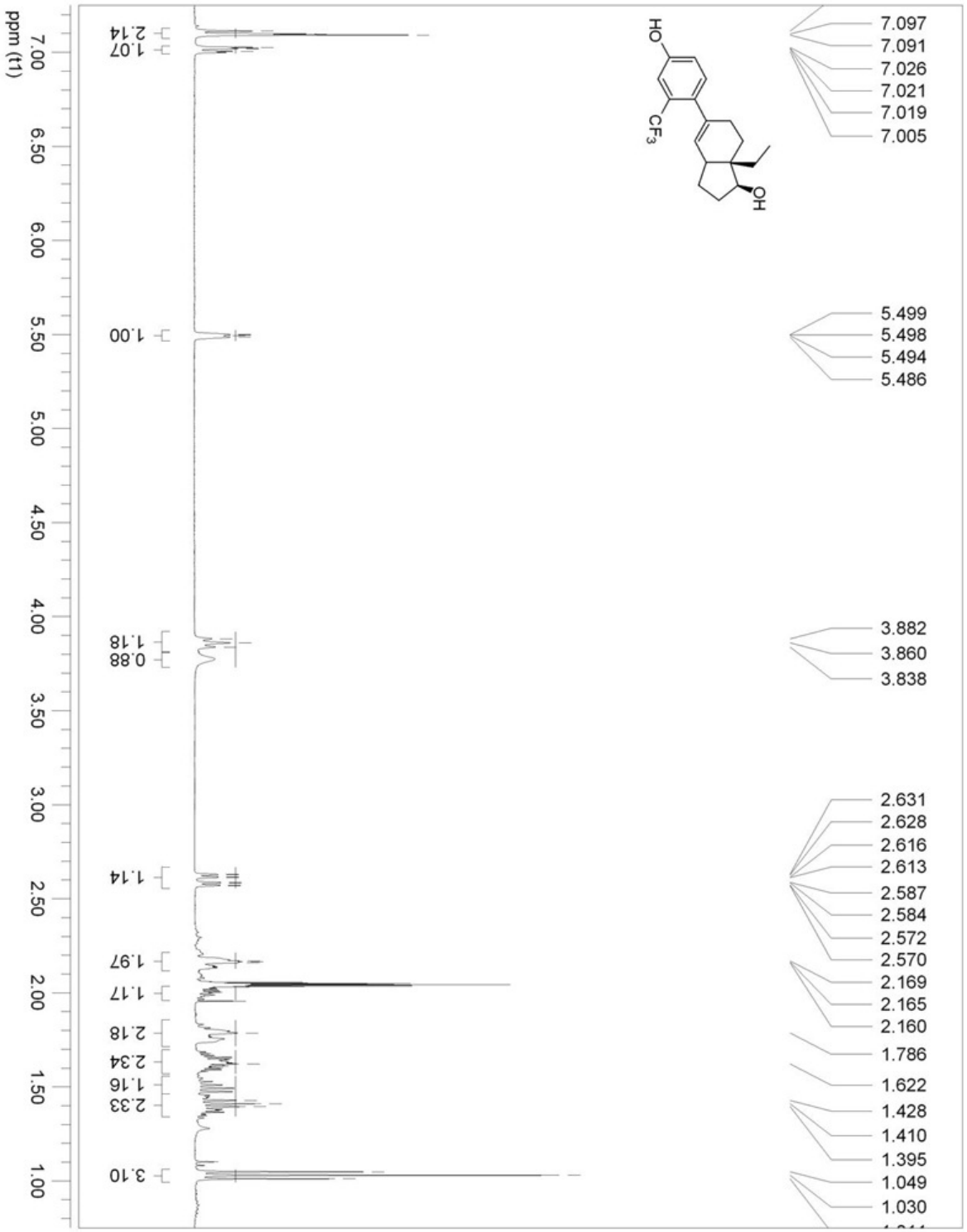


Figure a.25 ^{13}C NMR of compound **85**, 400 Hz, Acetone-d

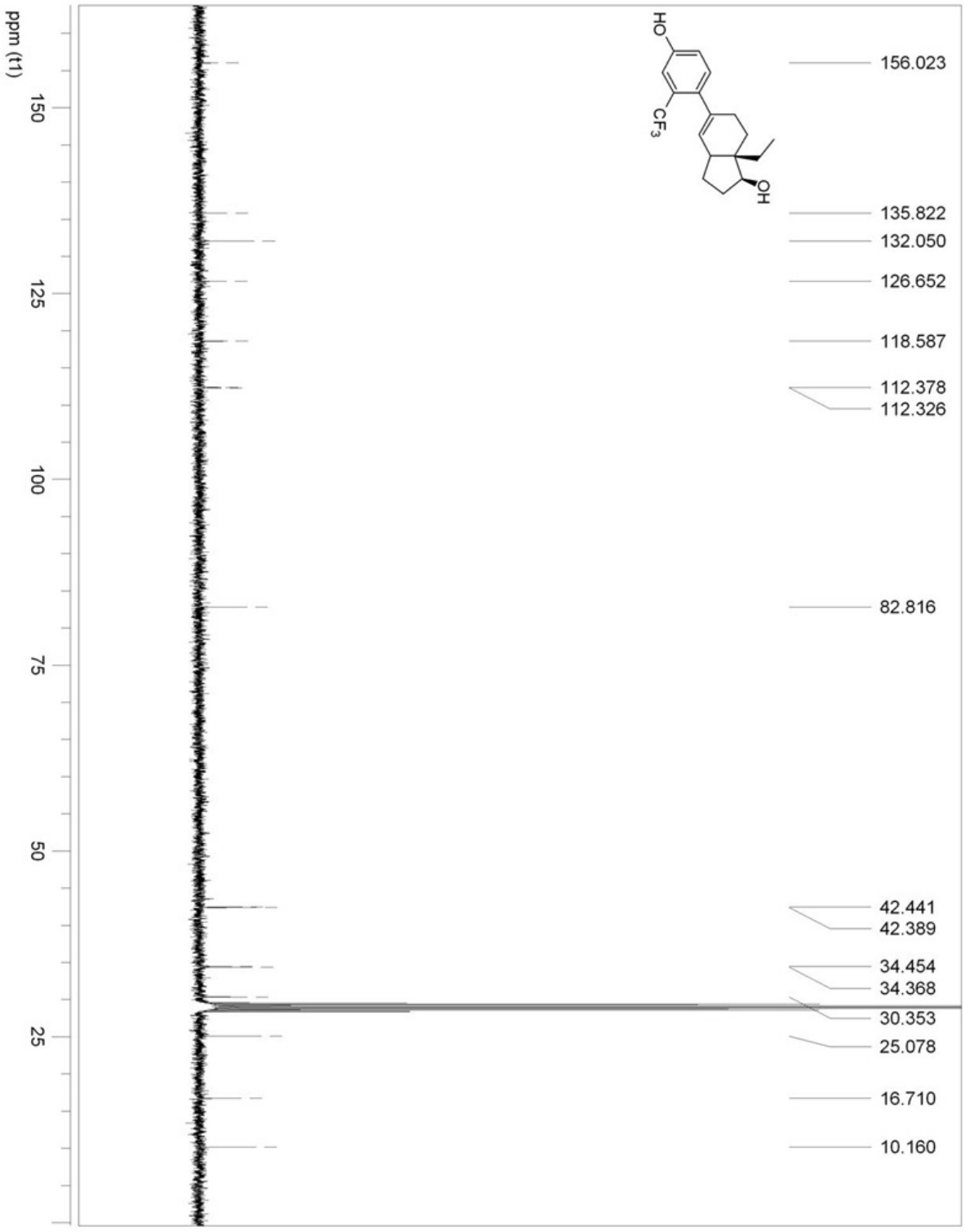


Figure a.26 ^{1}H NMR of compound **92**, 400 Hz, Acetone-d

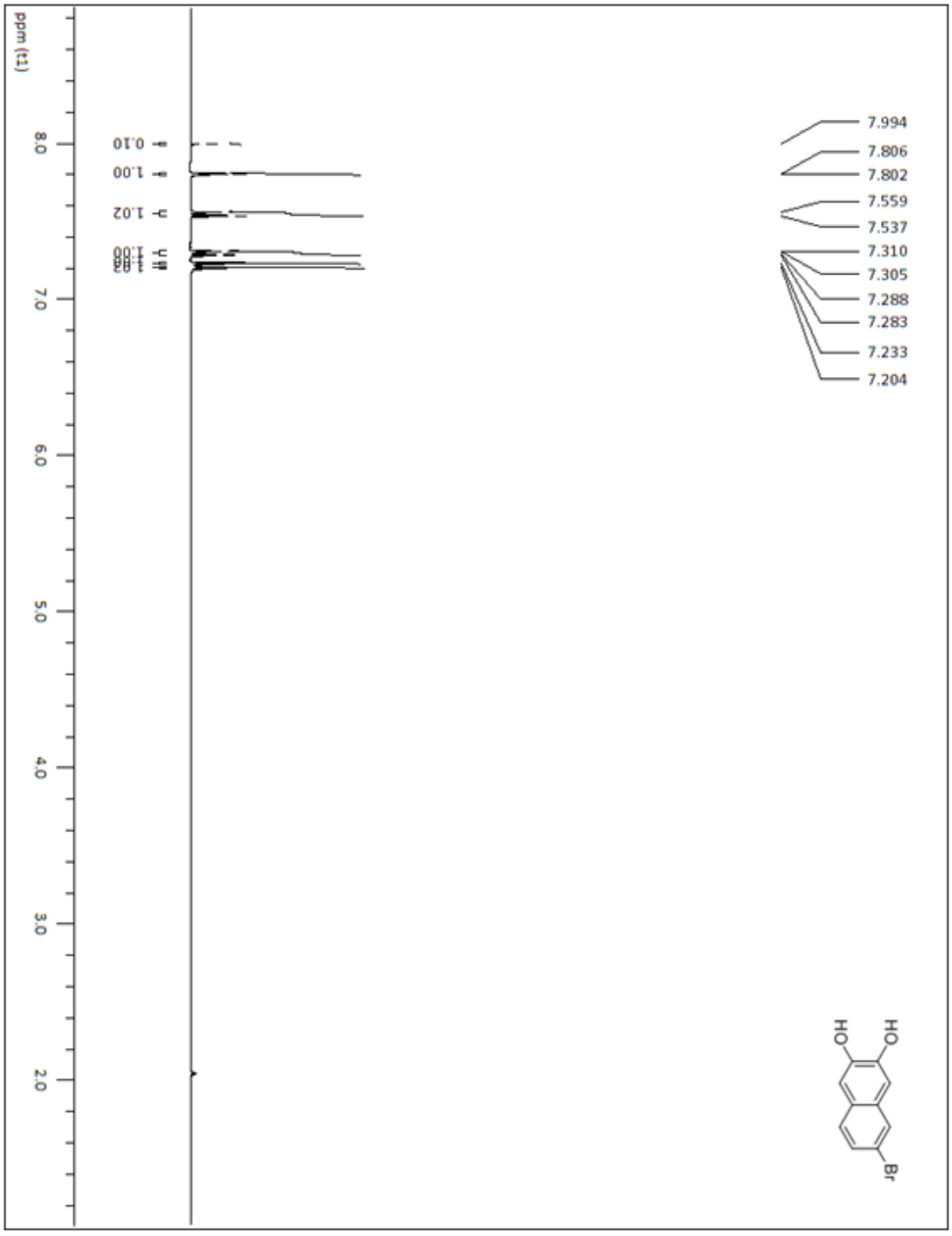


Figure a.27 ^{13}C NMR of compound **92**, 400 Hz, Acetone-d

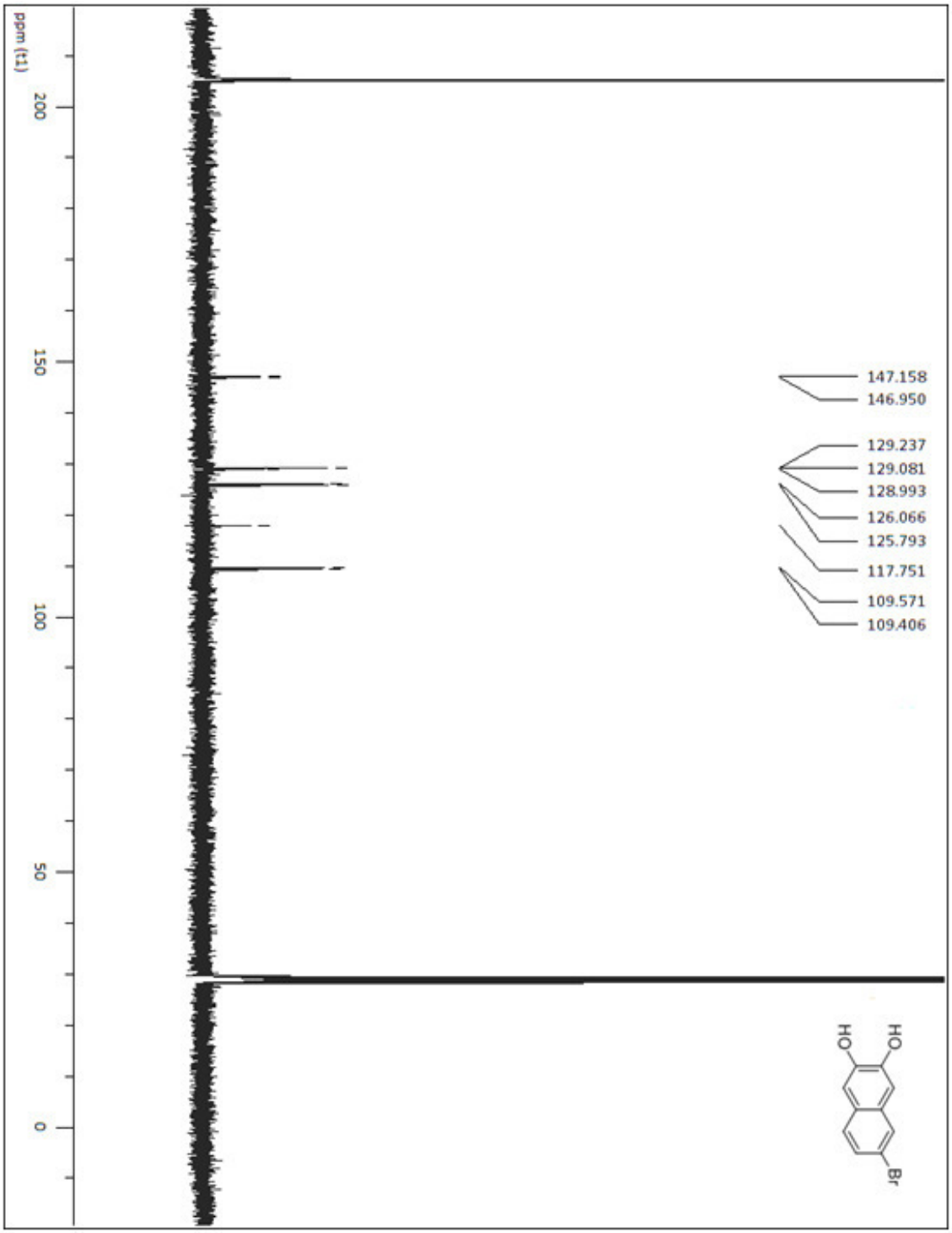


Figure a.28 ^{1}H NMR of compound **106**, 400 Hz, Acetone-d

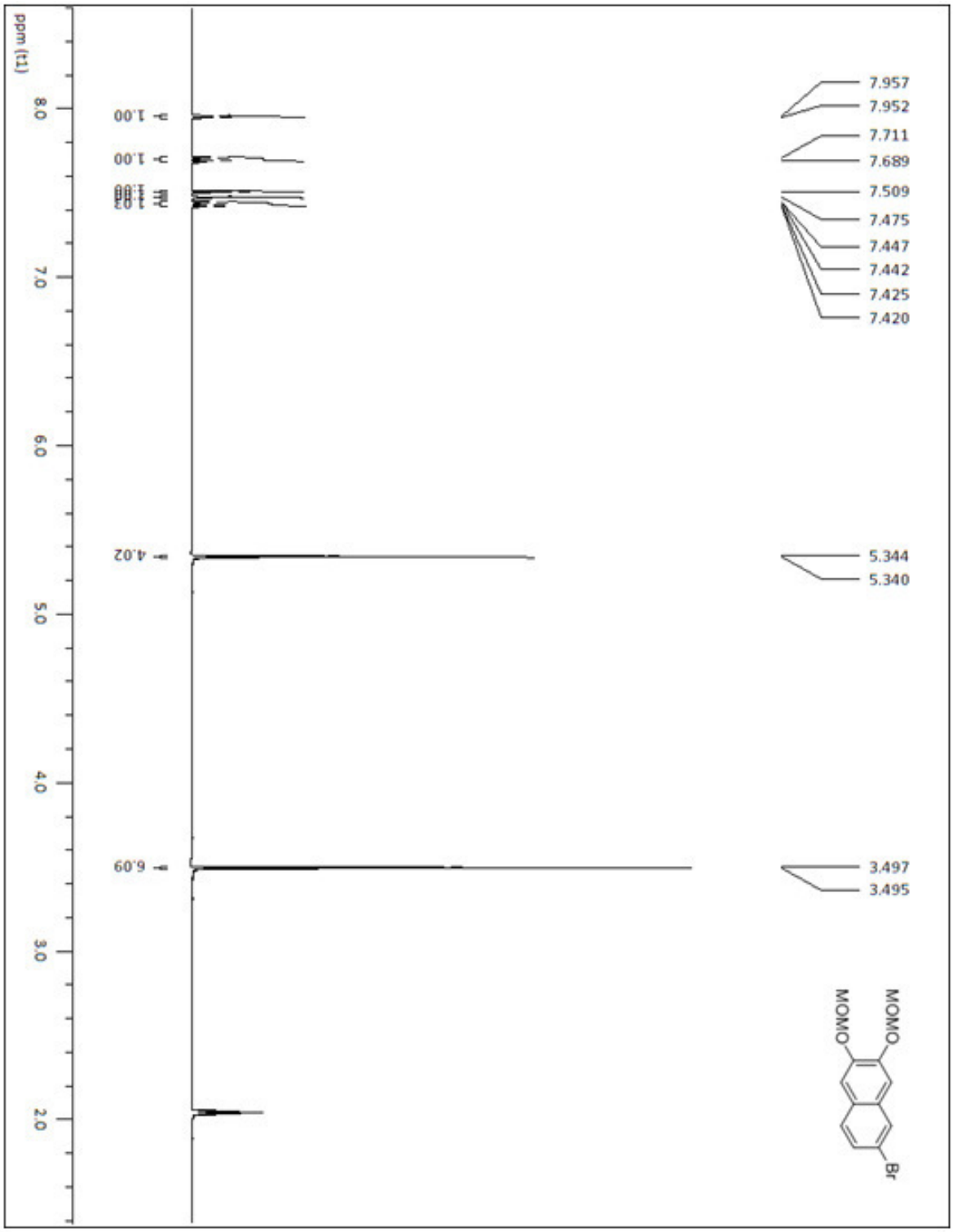


Figure a.29 ^{13}C NMR of compound **106**, 400 Hz, Acetone-d

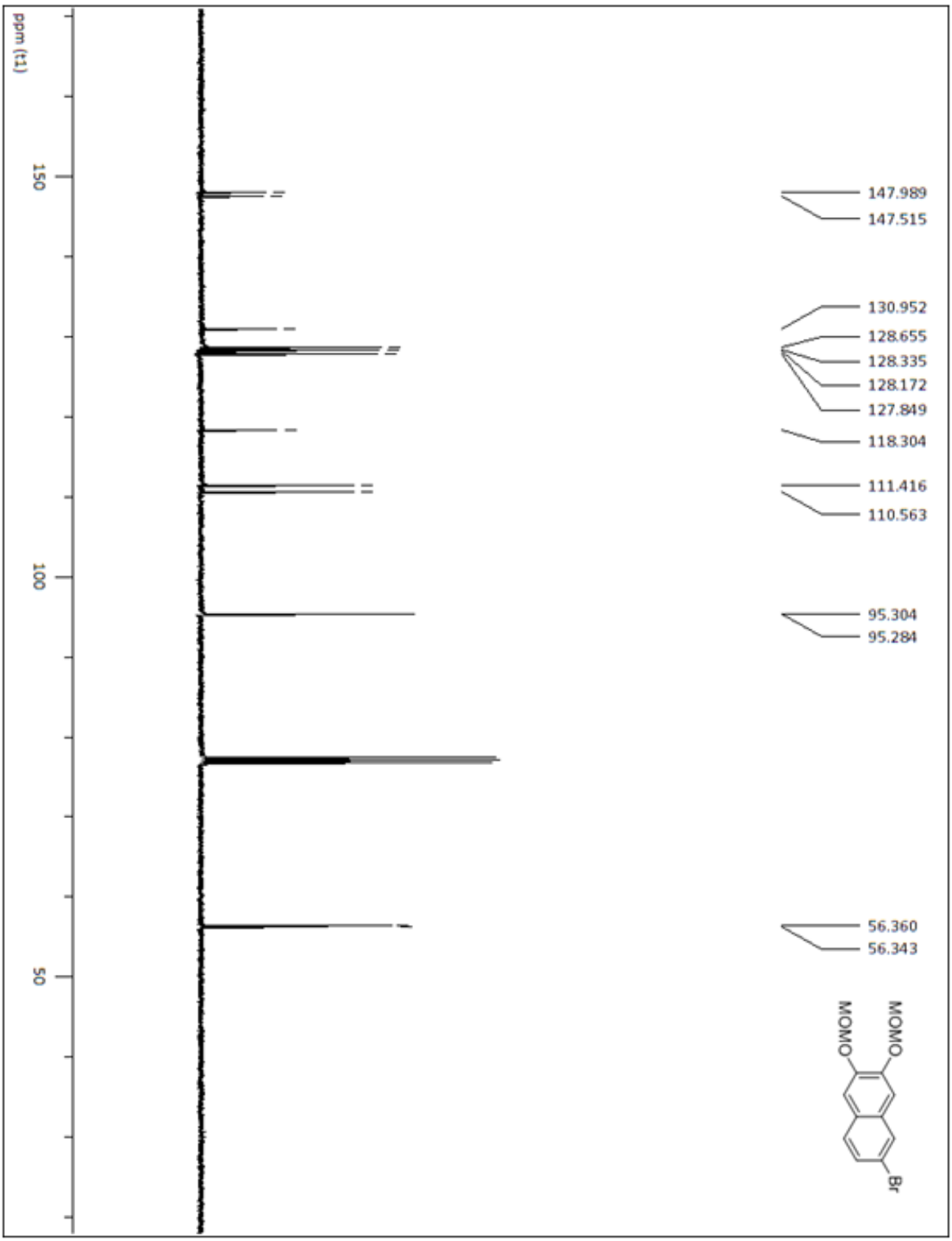


Figure a.30 ^{1}H NMR of compound **108**, 400 Hz, Acetone-d

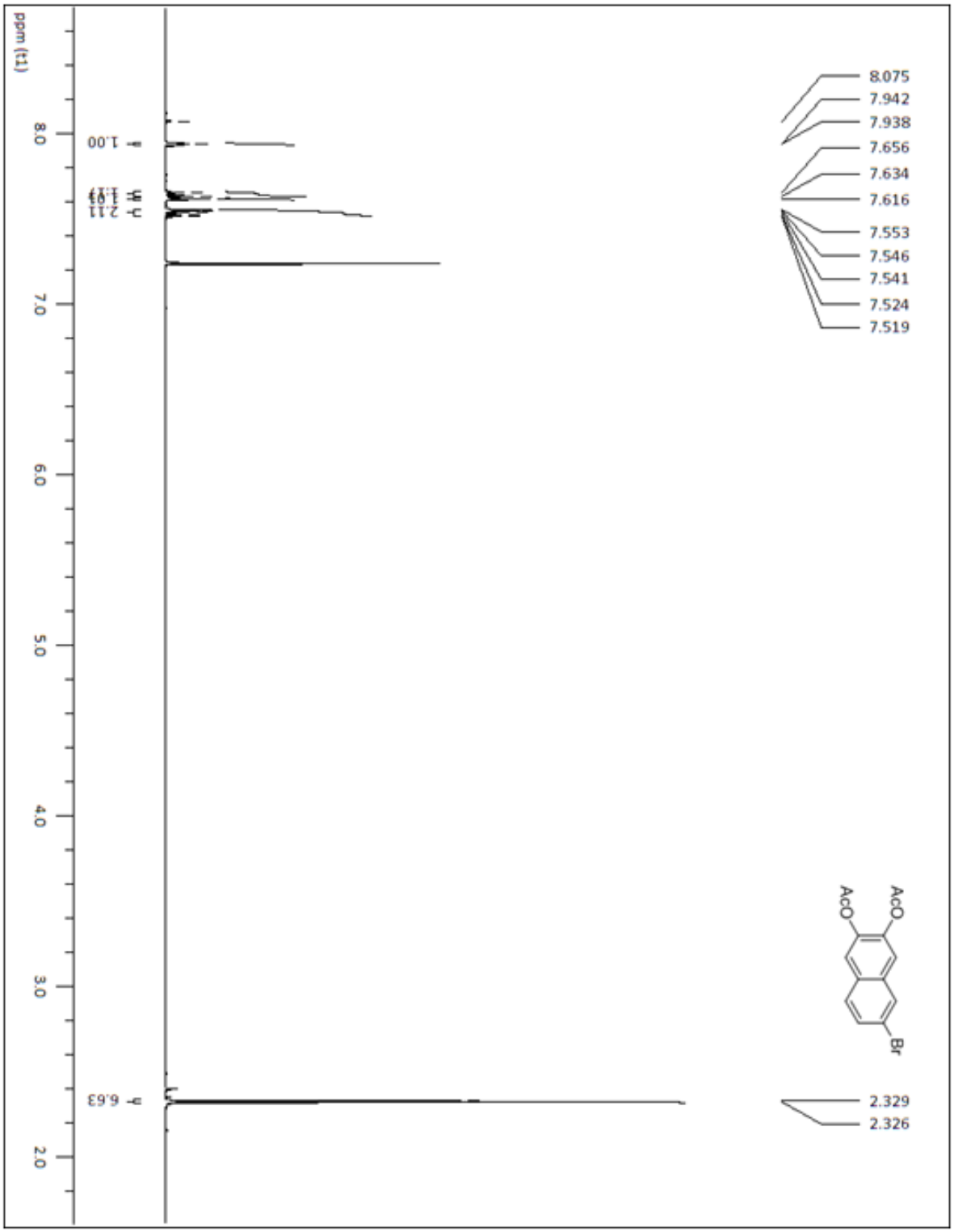


Figure a.31 ^{1}H NMR of compound **109**, 400 Hz, Acetone-d

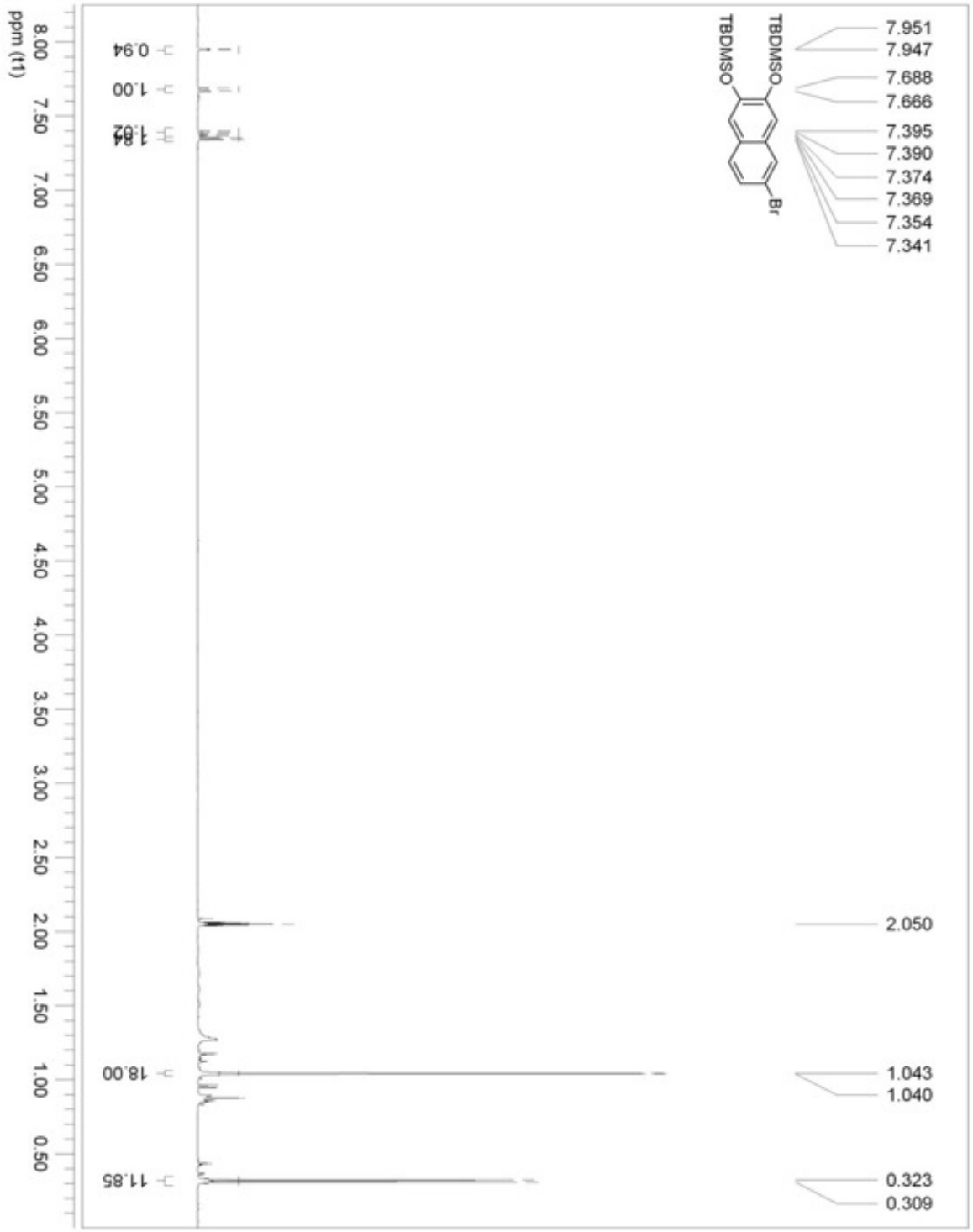


Figure a.32 ^{1}H NMR of compound **86**, 400 Hz, Acetone-d

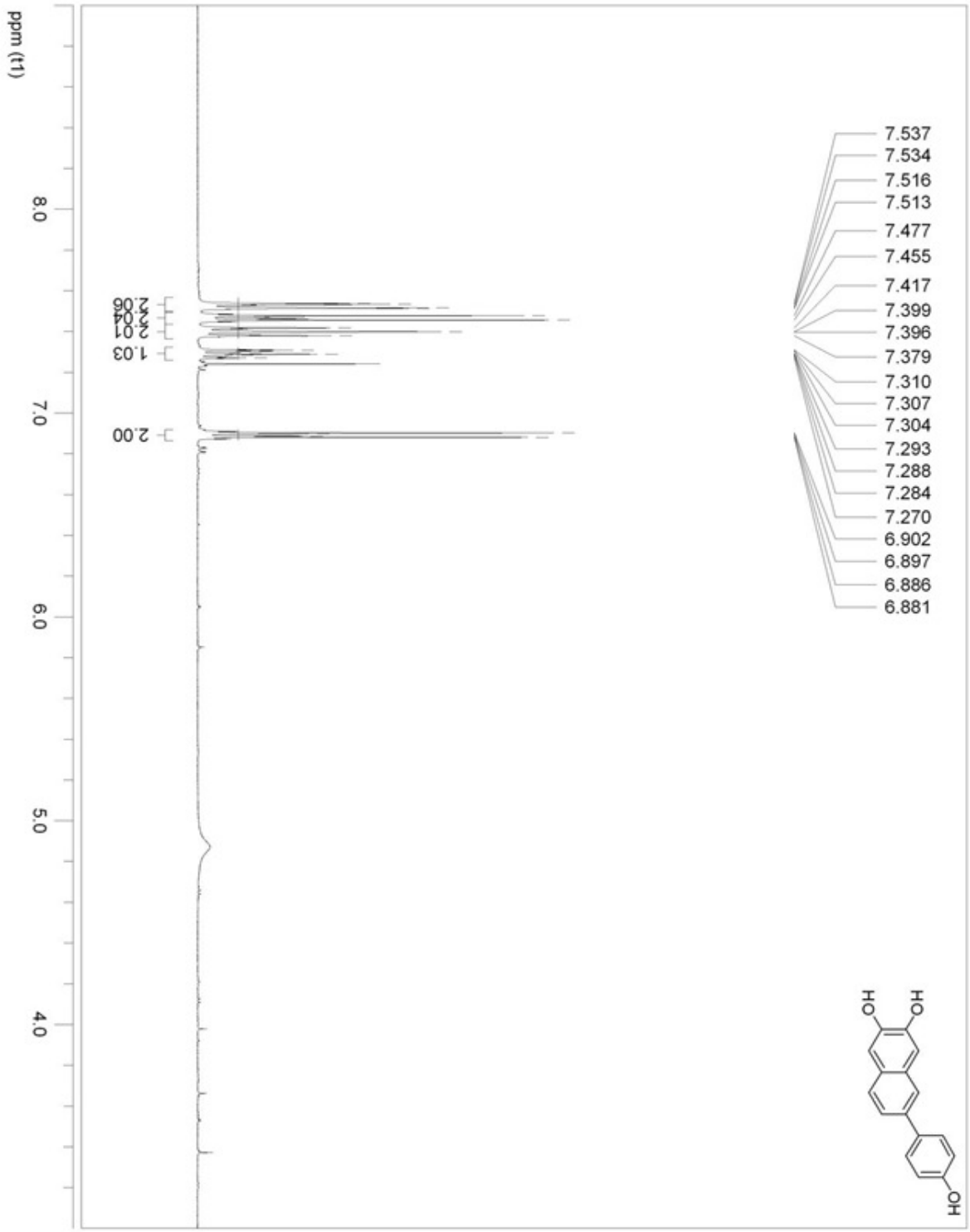


Figure a.33 ^{13}C NMR of compound **86**, 400 Hz, Acetone-d

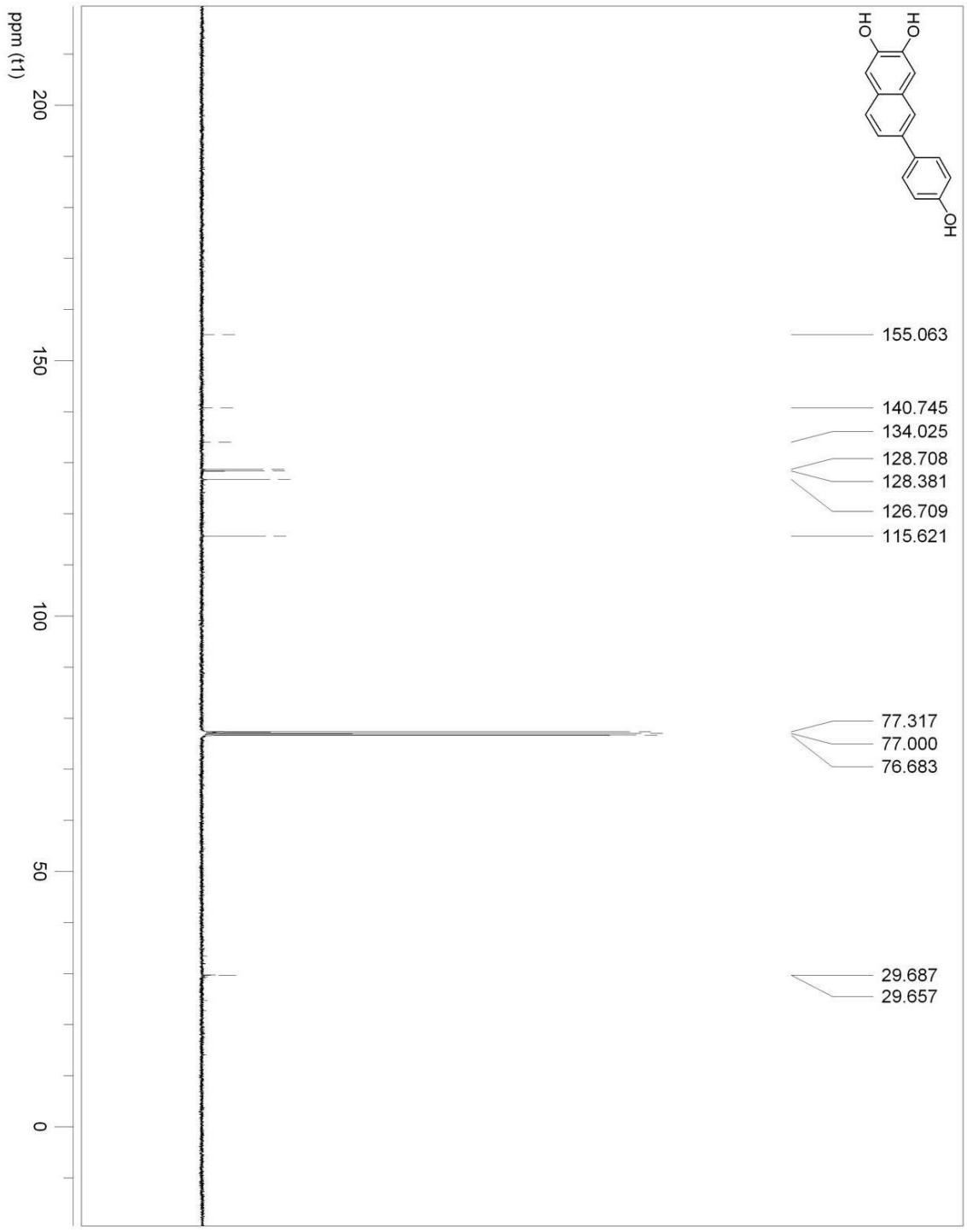


Figure a.34 ^{1}H NMR of compound **137**, 400 Hz, Acetone-d

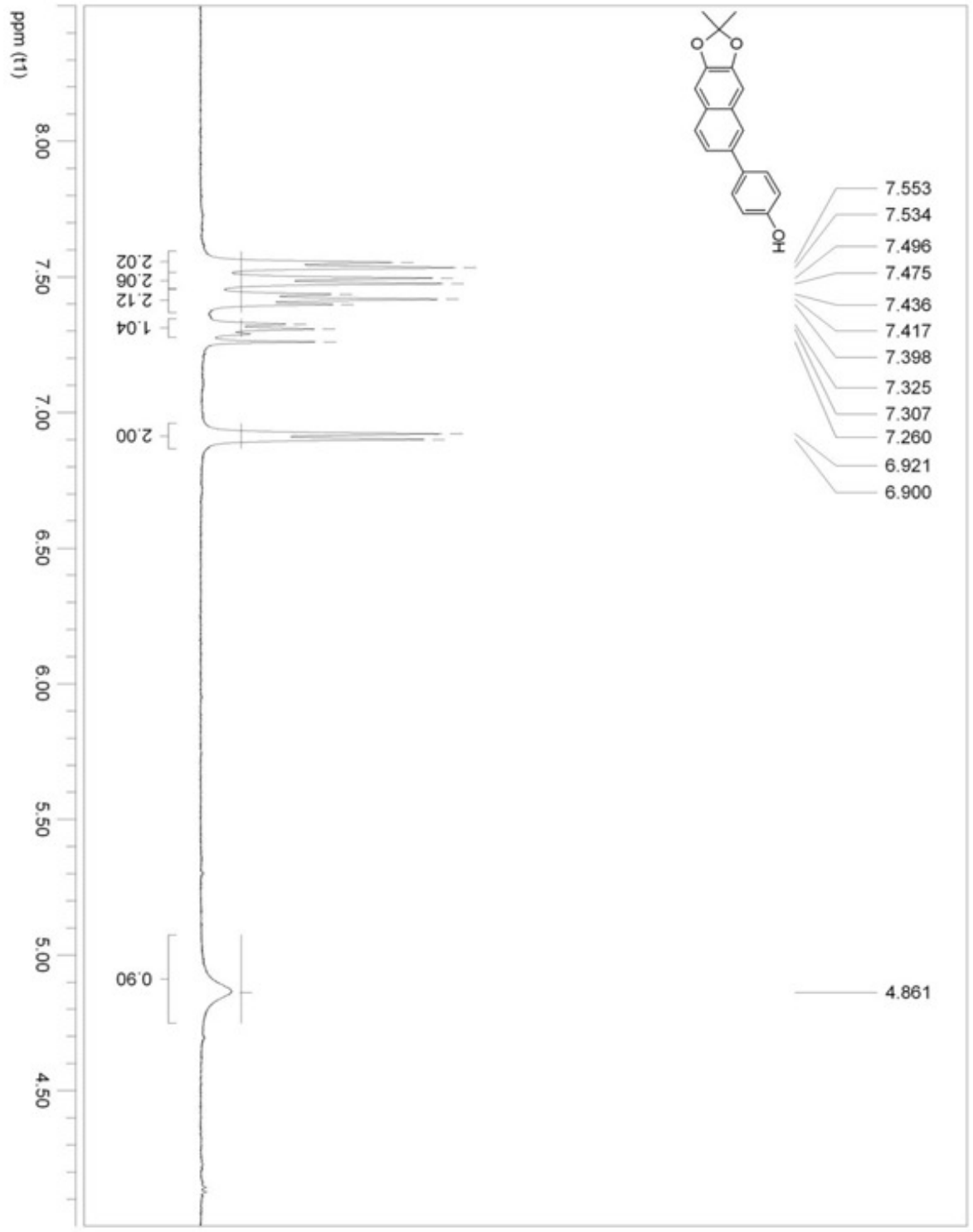


Figure a.35 ^{13}C NMR of compound **137**, 400 Hz, Acetone-d

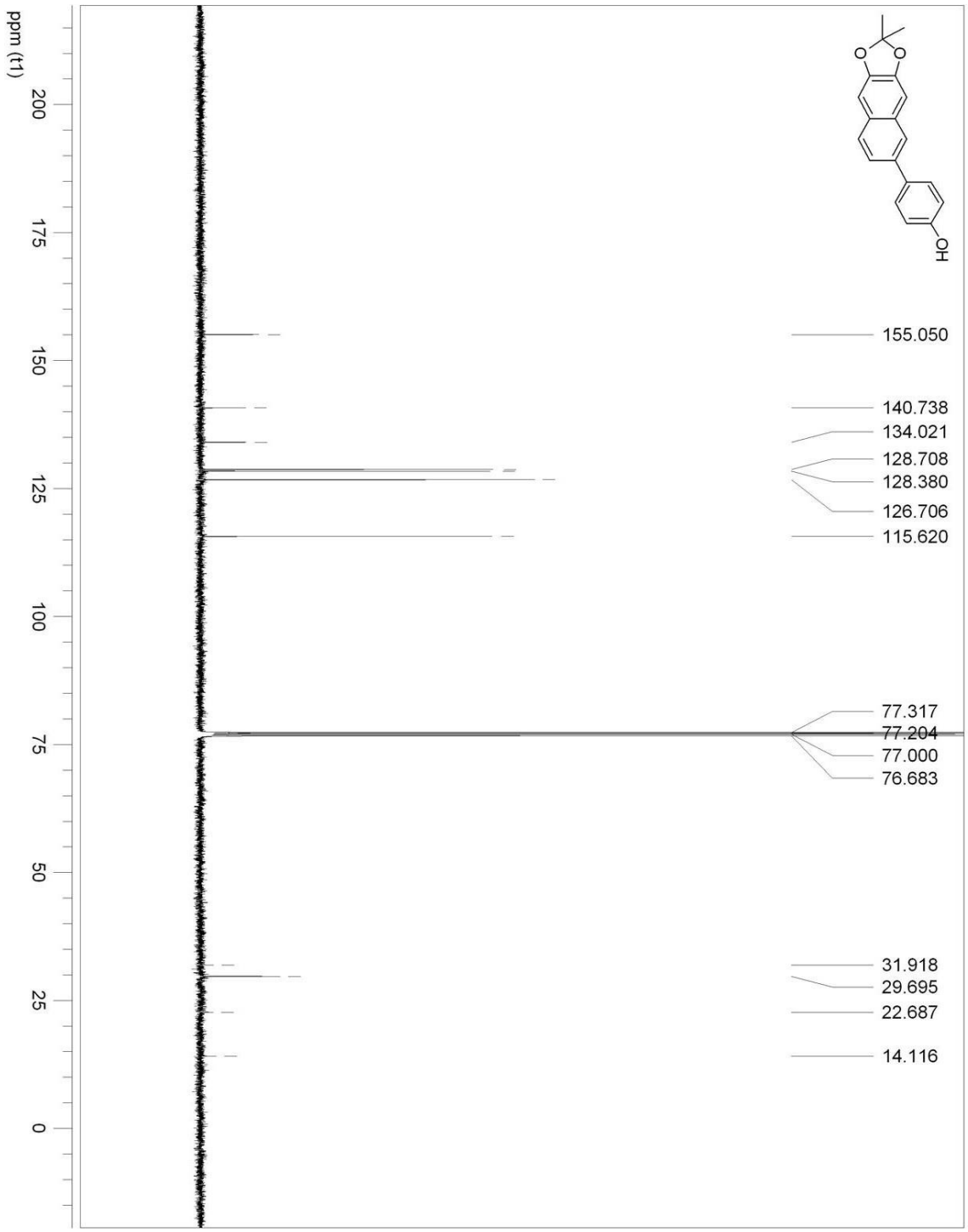


Figure a.36 ^{1}H NMR of compound **138**, 400 Hz, Acetone-d

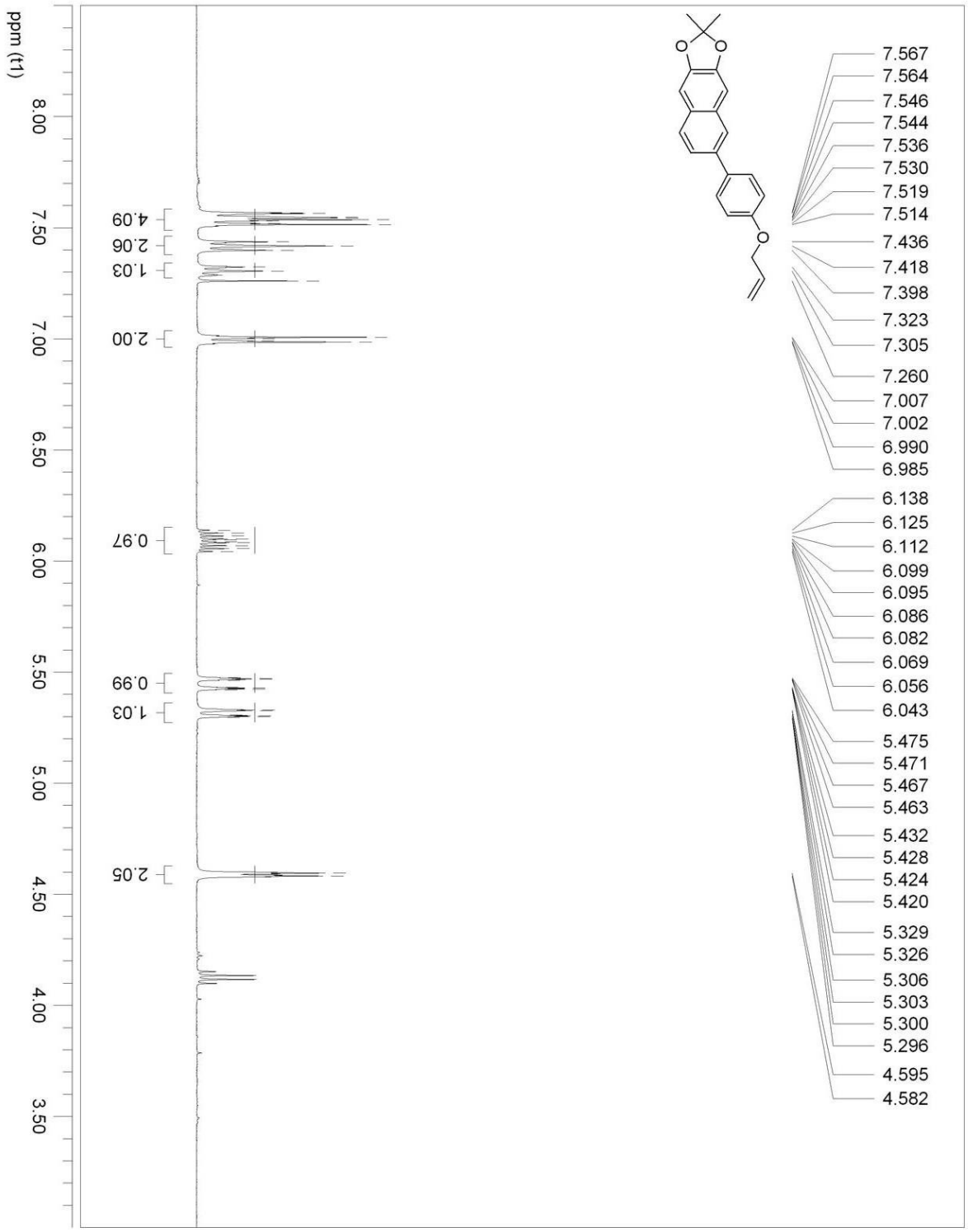


Figure a.37 ^{1}H NMR of compound **129**, 400 Hz, Acetone-d

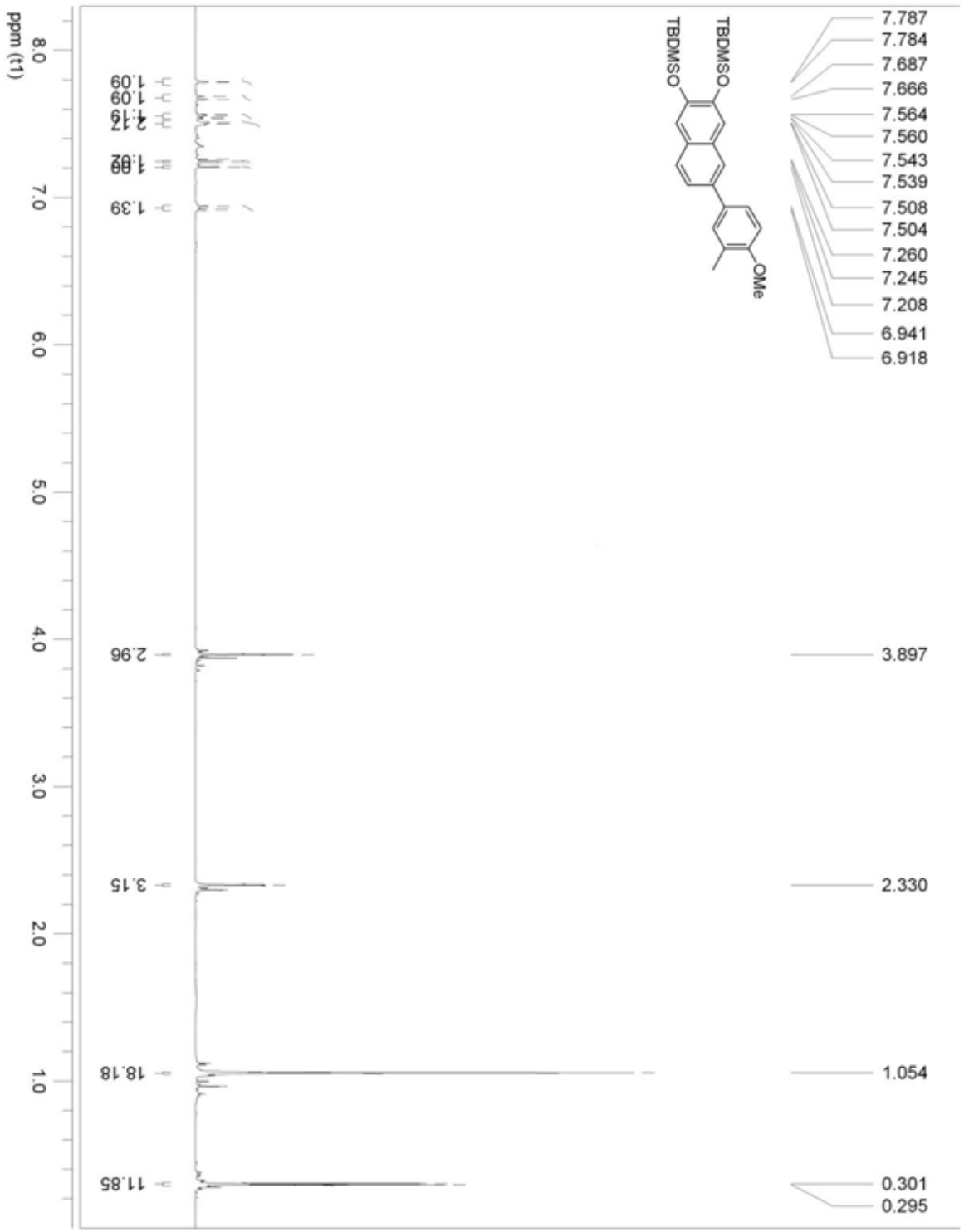


Figure a.38 ^{1}H NMR of compound **131**, 400 Hz, Acetone-d

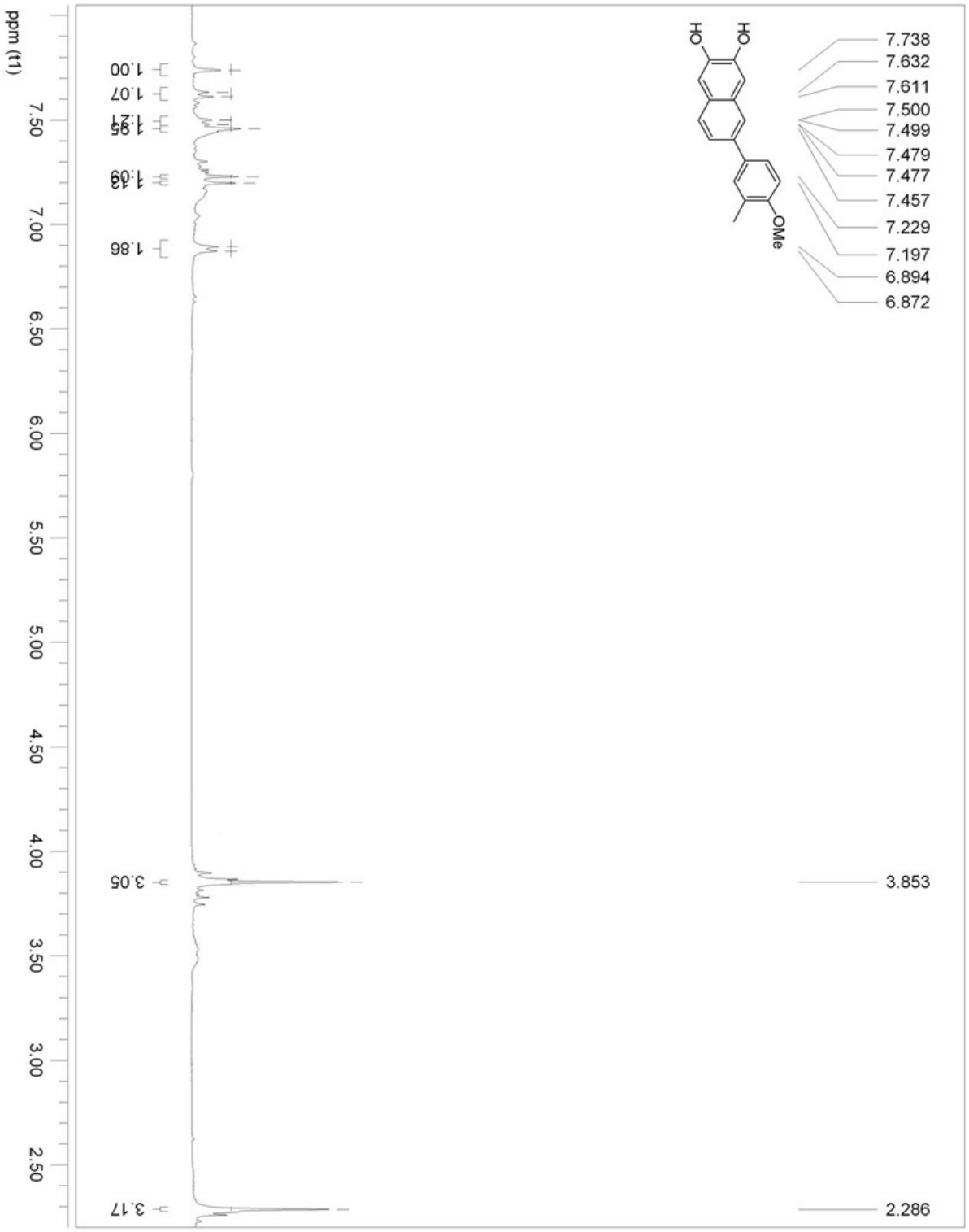


Figure a.39 ^{1}H NMR of compound **146**, 400 Hz, Acetone-d

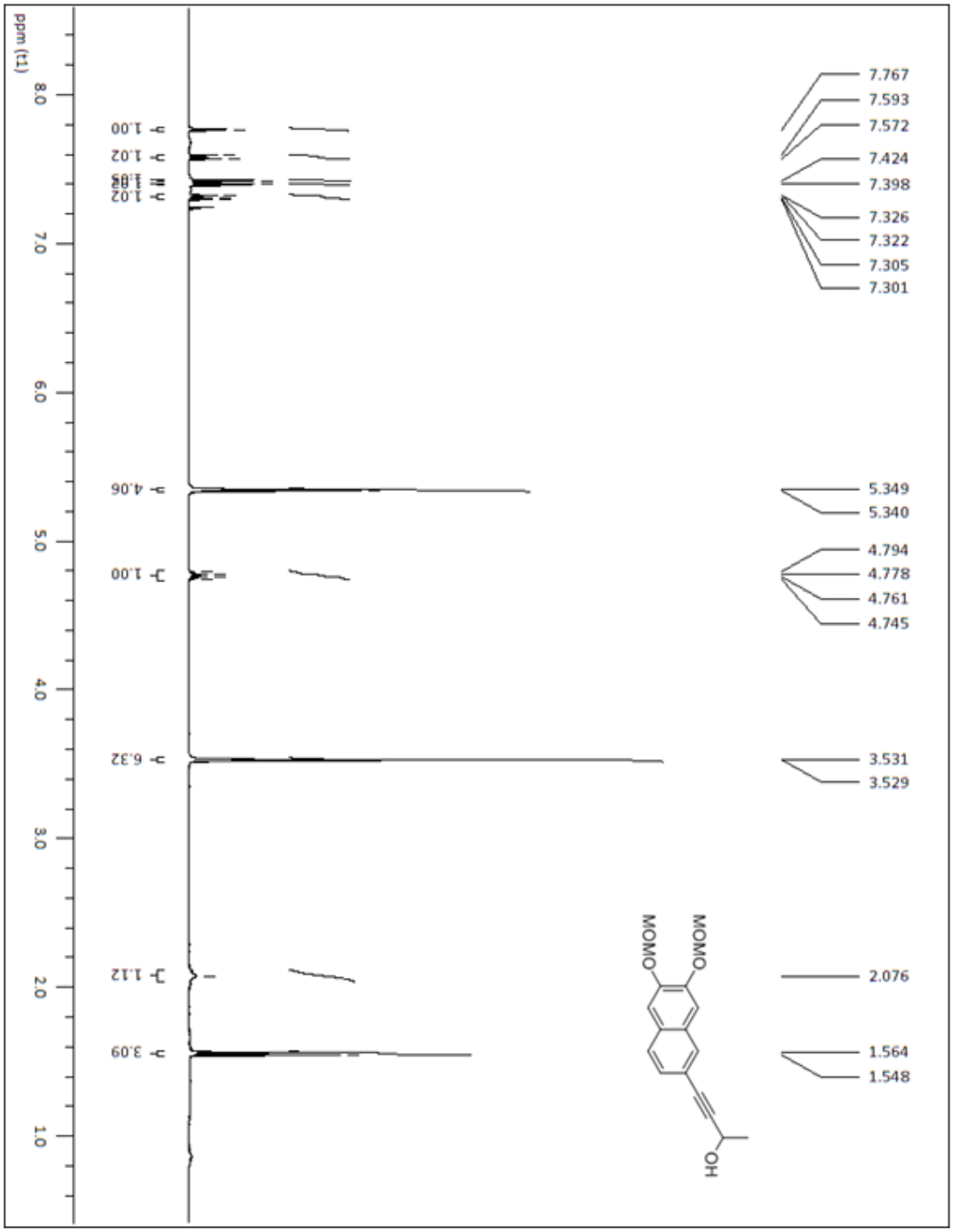


Figure a.40 ^{13}C NMR of compound **146**, 400 Hz, Acetone-d

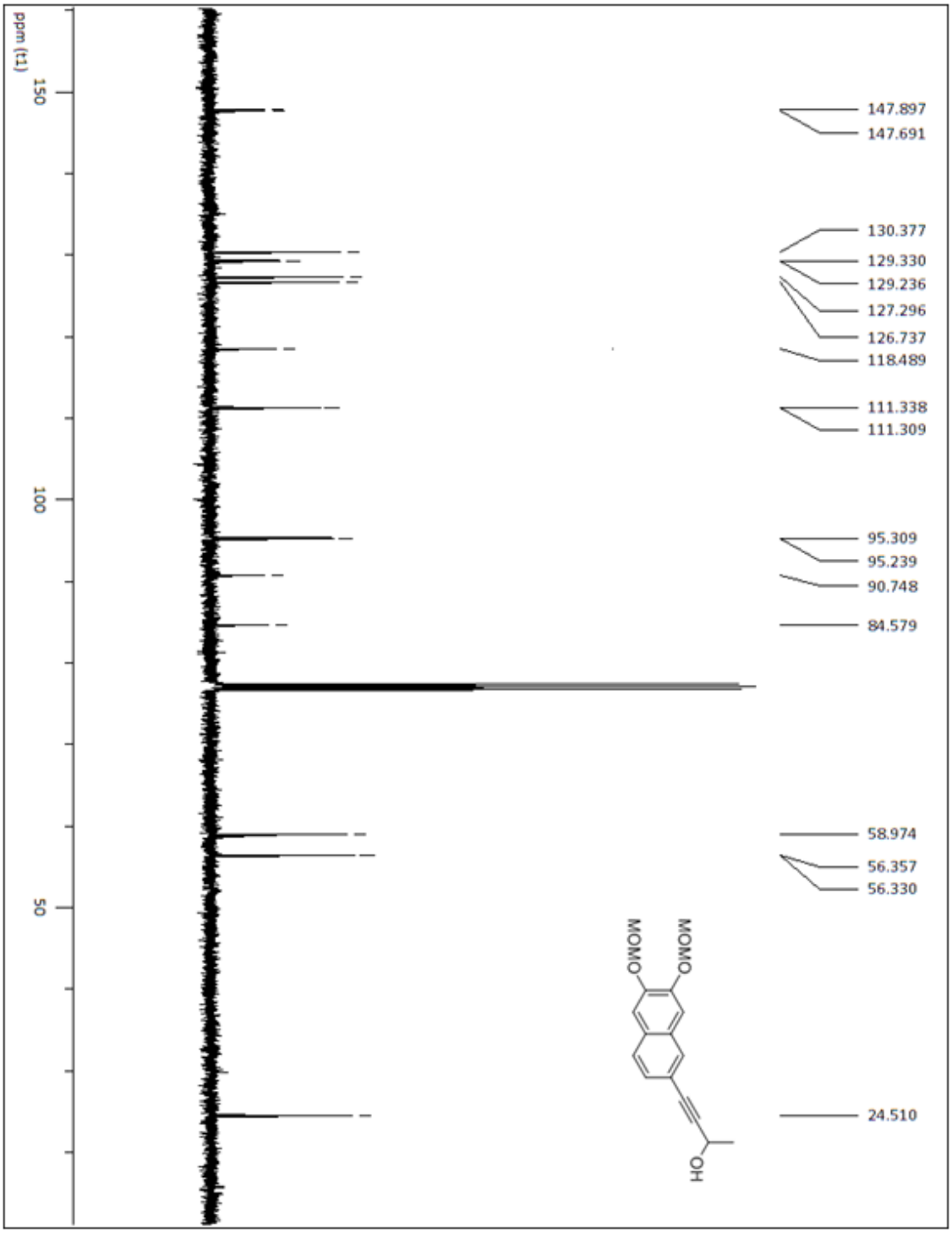


Figure a.41 ^{1}H NMR of compound **149**, 400 Hz, Acetone-d

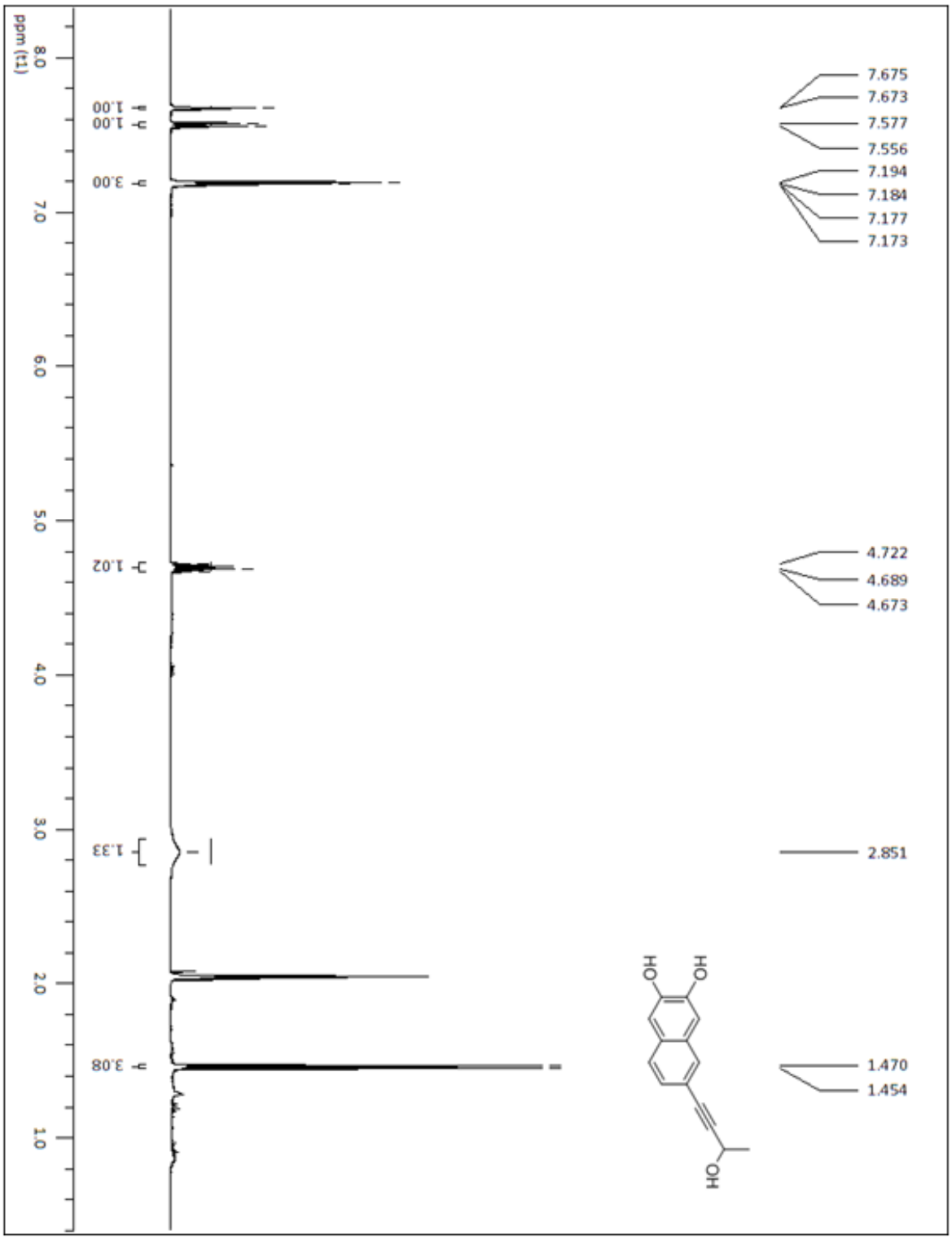


Figure a.42 ^{1}H NMR of compound **141**, 400 Hz, Acetone-d

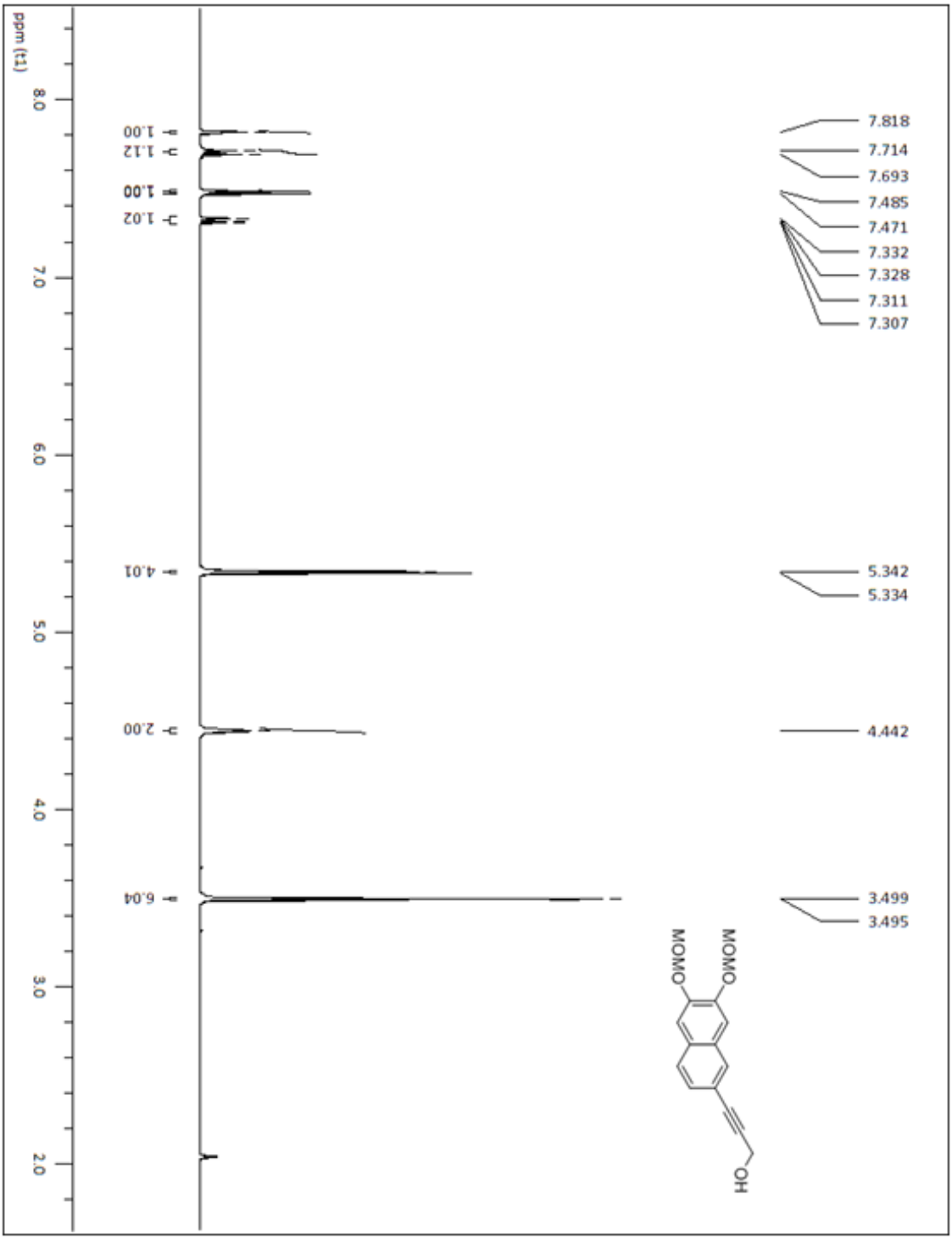


Figure a.43 ^{13}C NMR of compound **141**, 400 Hz, Acetone-d

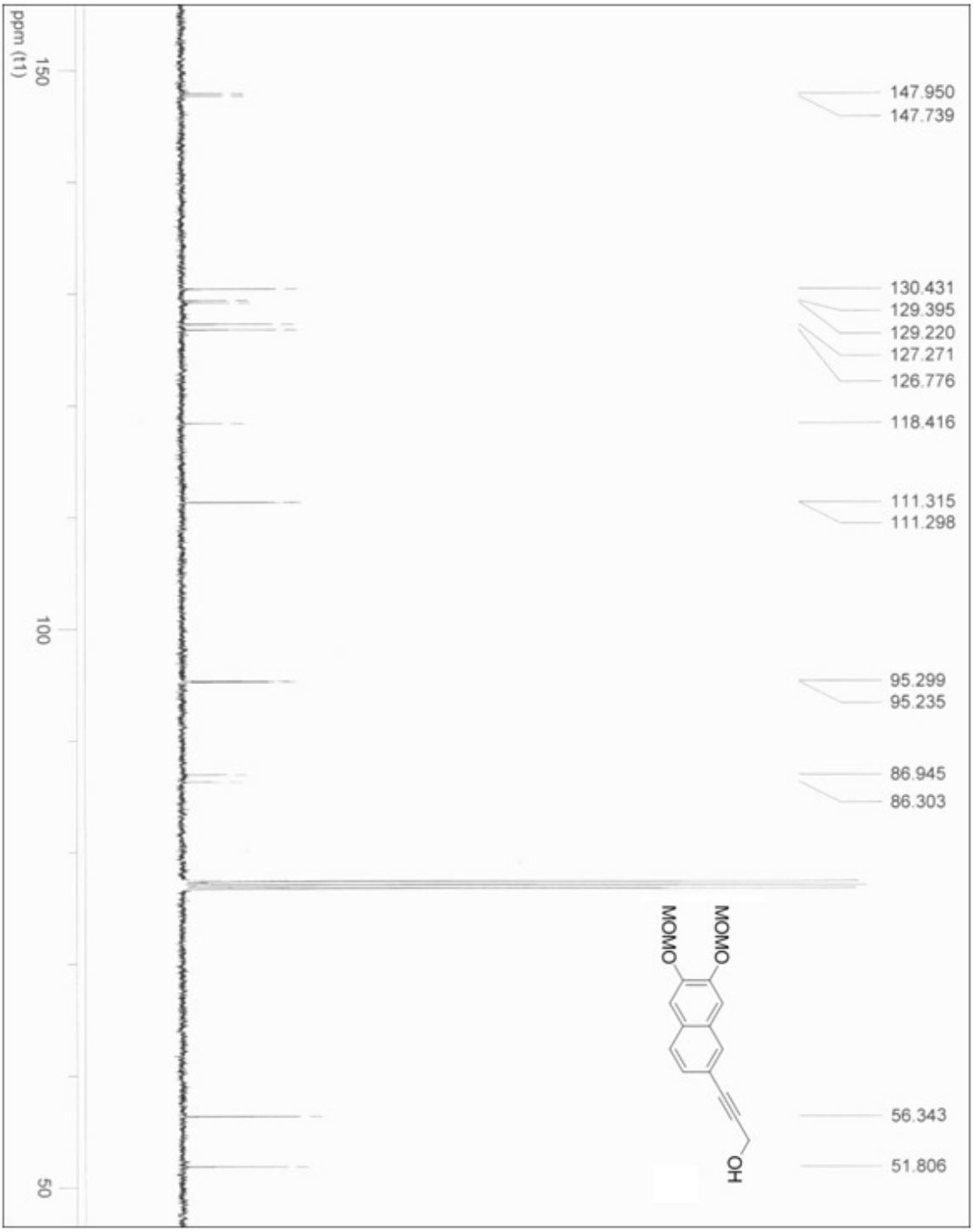


Figure a.44 ^{1}H NMR of compound **144**, 400 Hz, Acetone-d

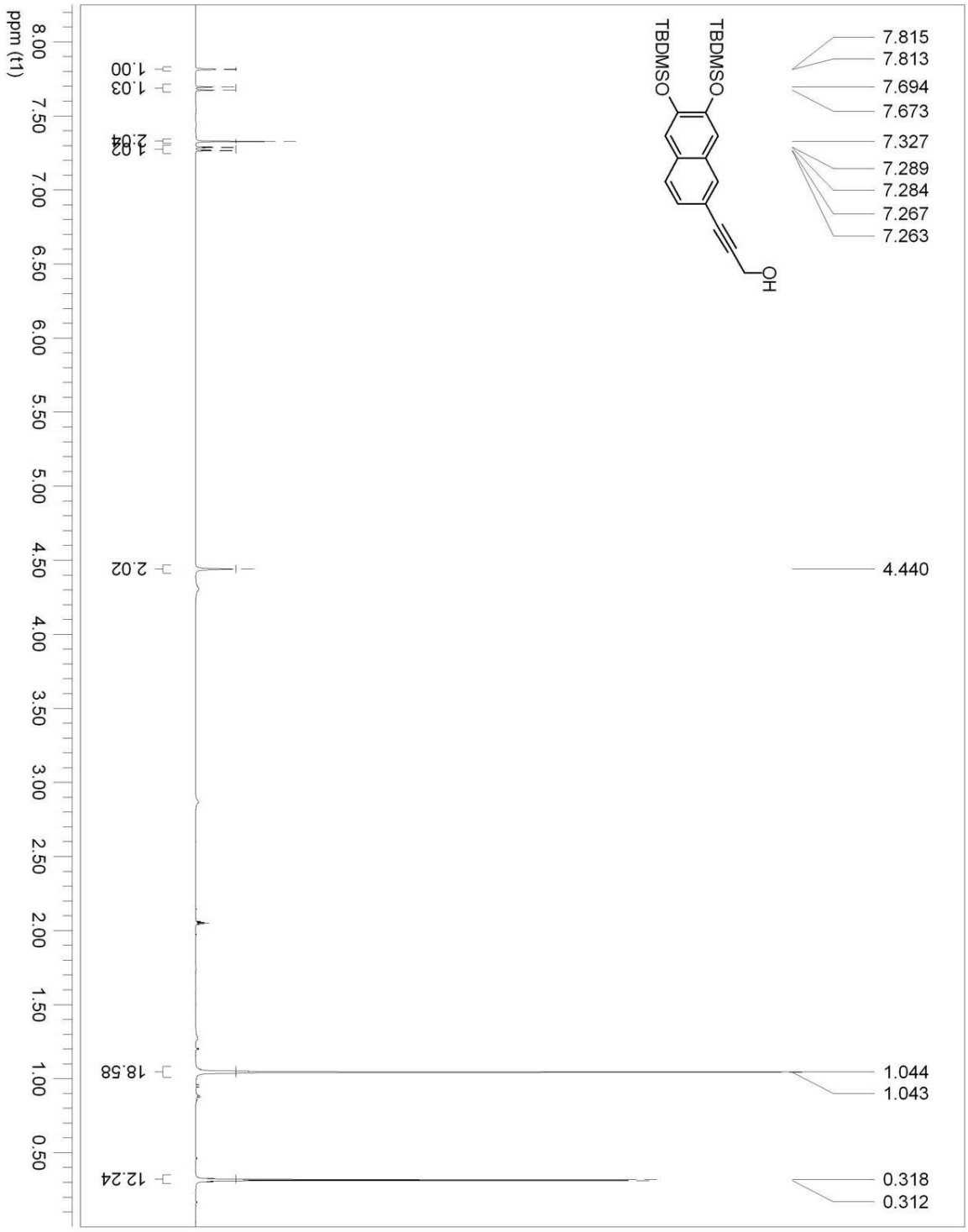


Figure a.45 ^{13}C NMR of compound **144**, 400 Hz, Acetone-d

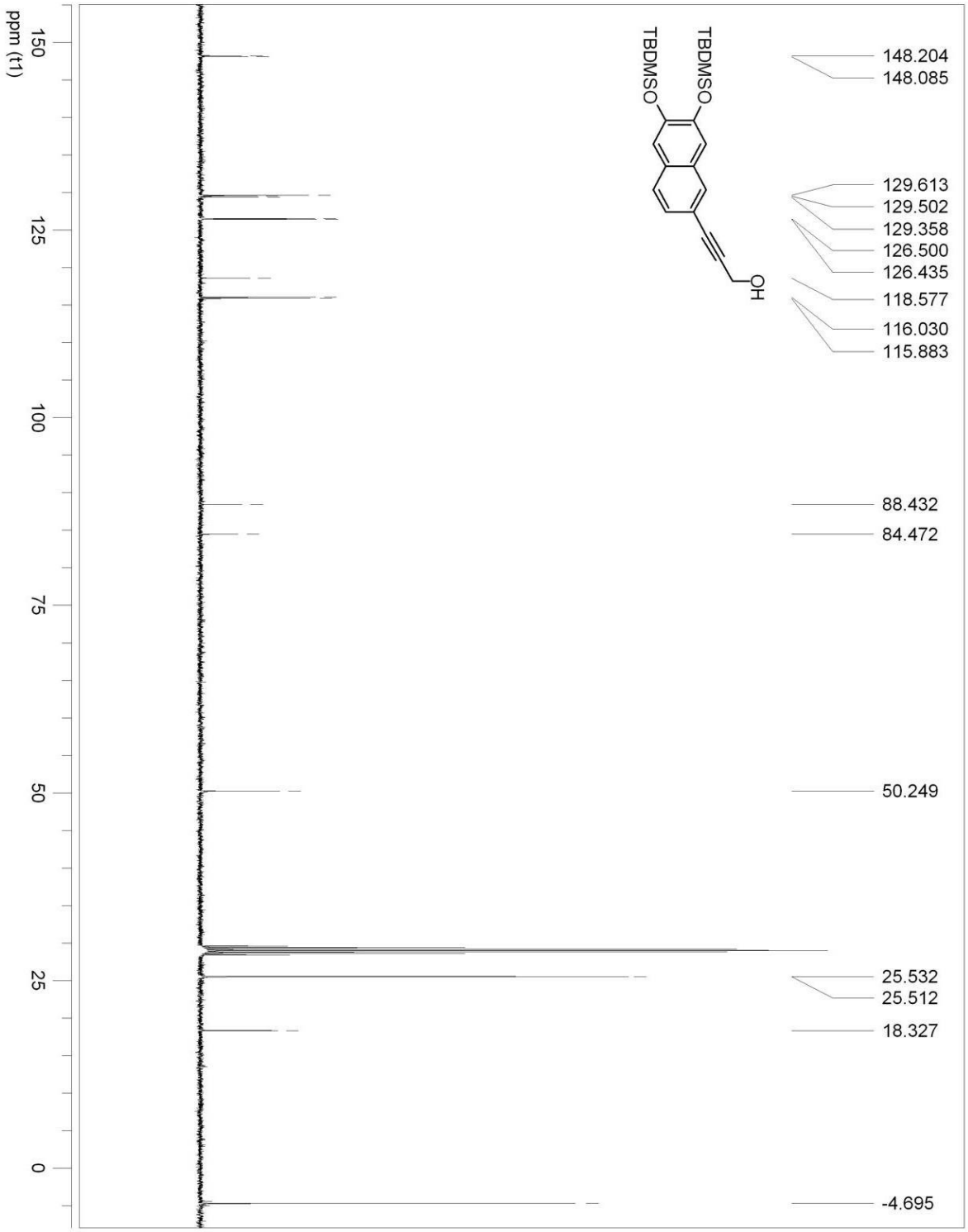


Figure a.46 ^{1}H NMR of compound **90**, 400 Hz, Acetone-d

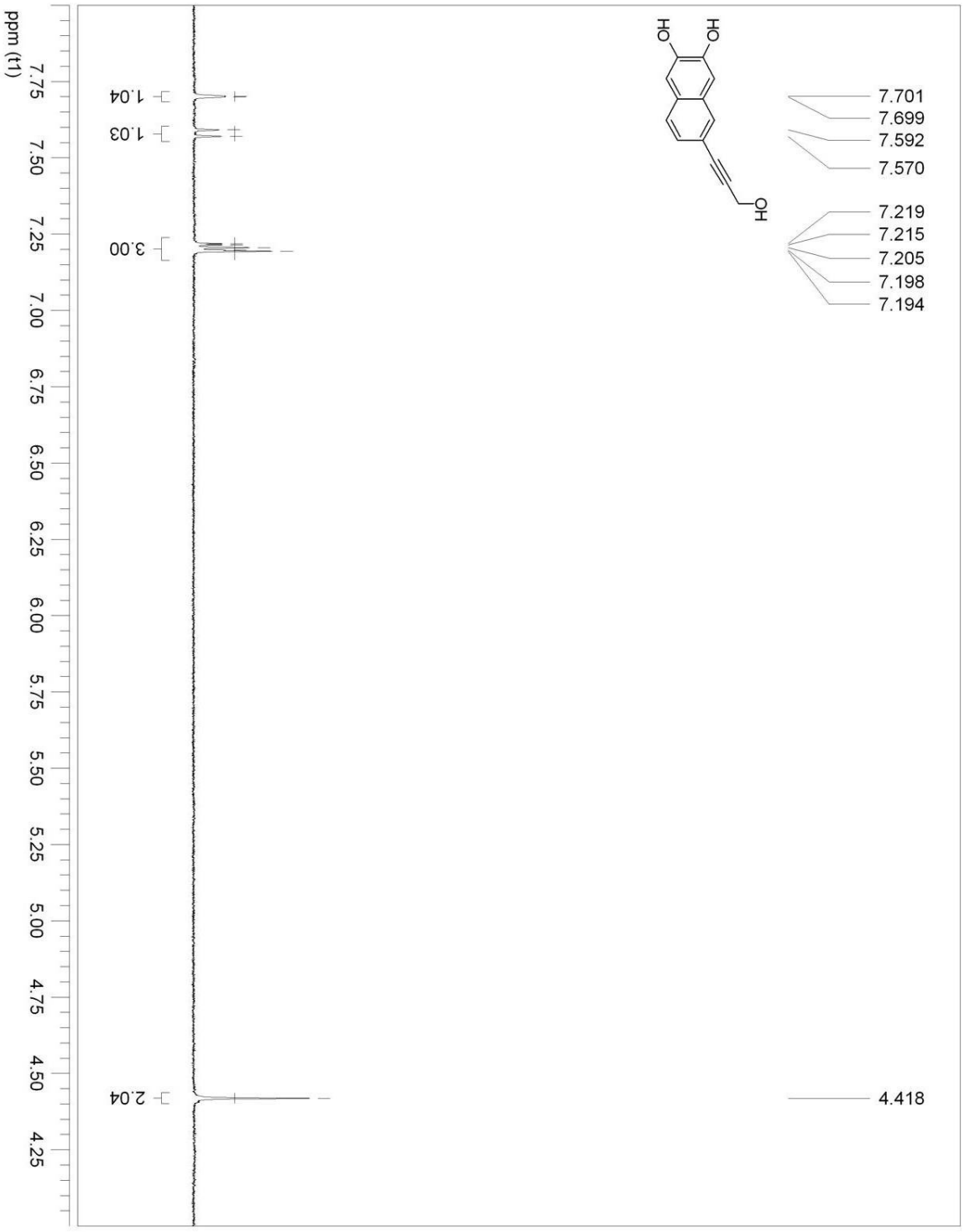


Figure a.47 ^{13}C NMR of compound **90**, 400 Hz, Acetone-d

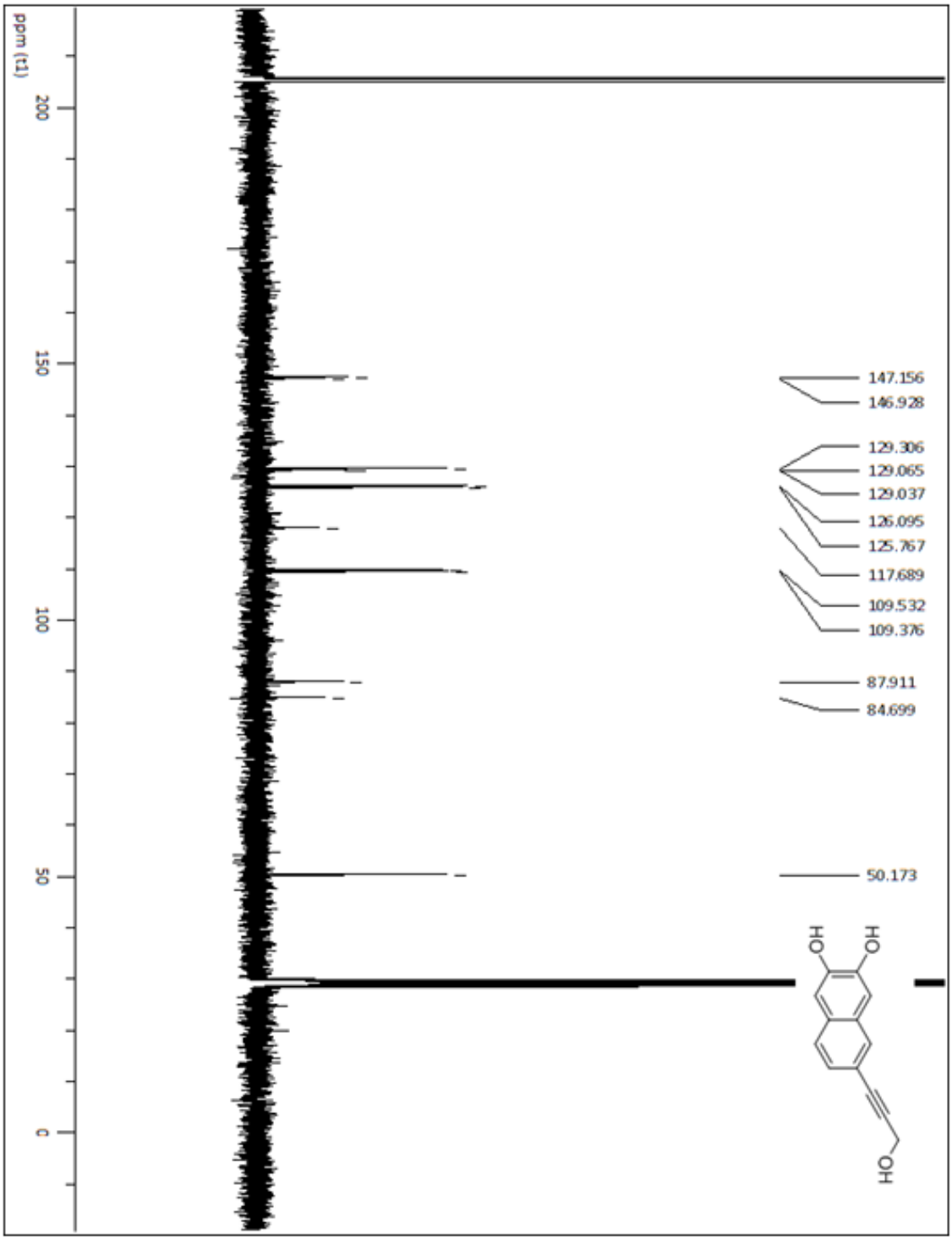


Figure a.48 ^{1}H NMR of compound **148**, 400 Hz, Acetone-d

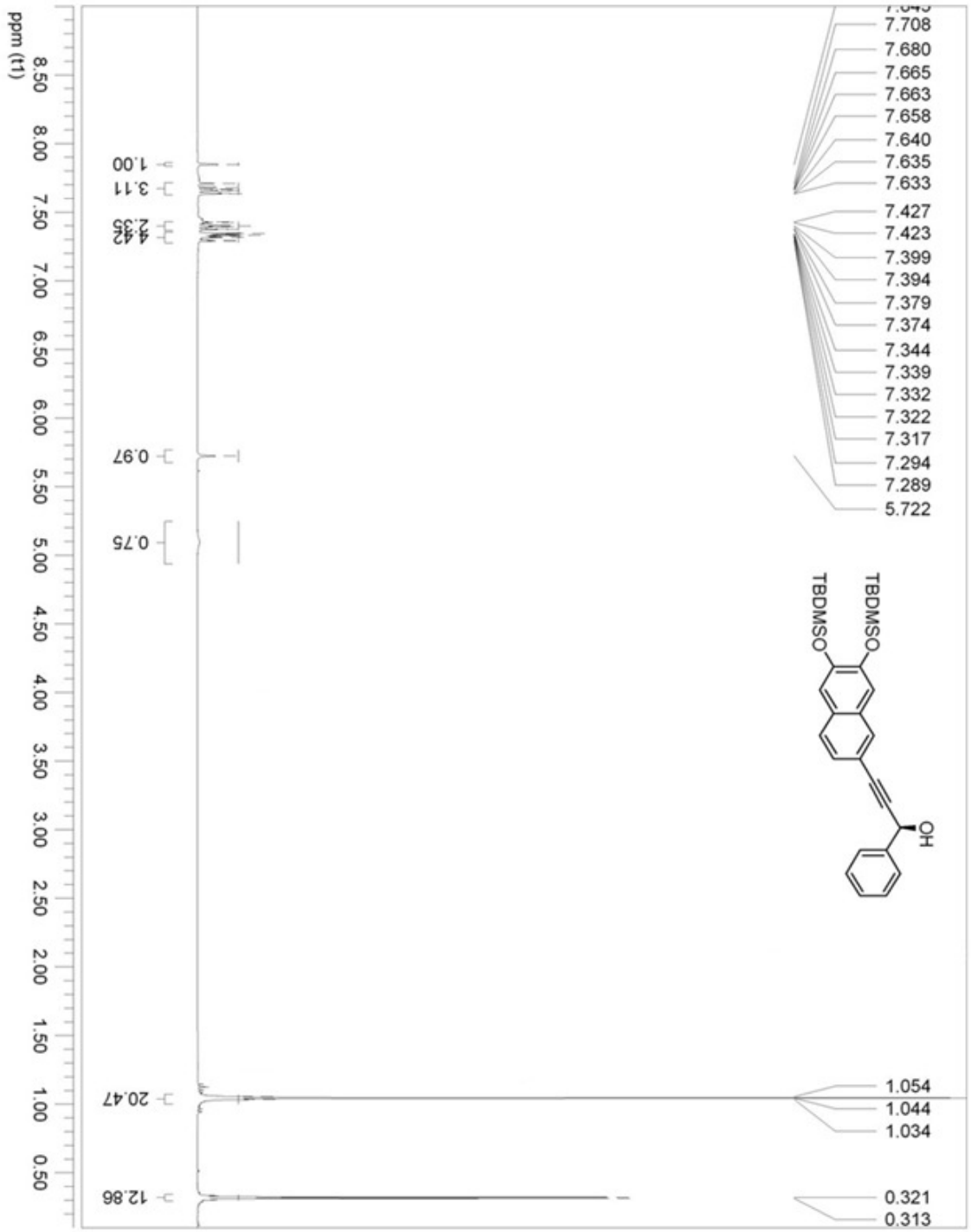


Figure a.49 ^{13}C NMR of compound **148**, 400 Hz, Acetone-d

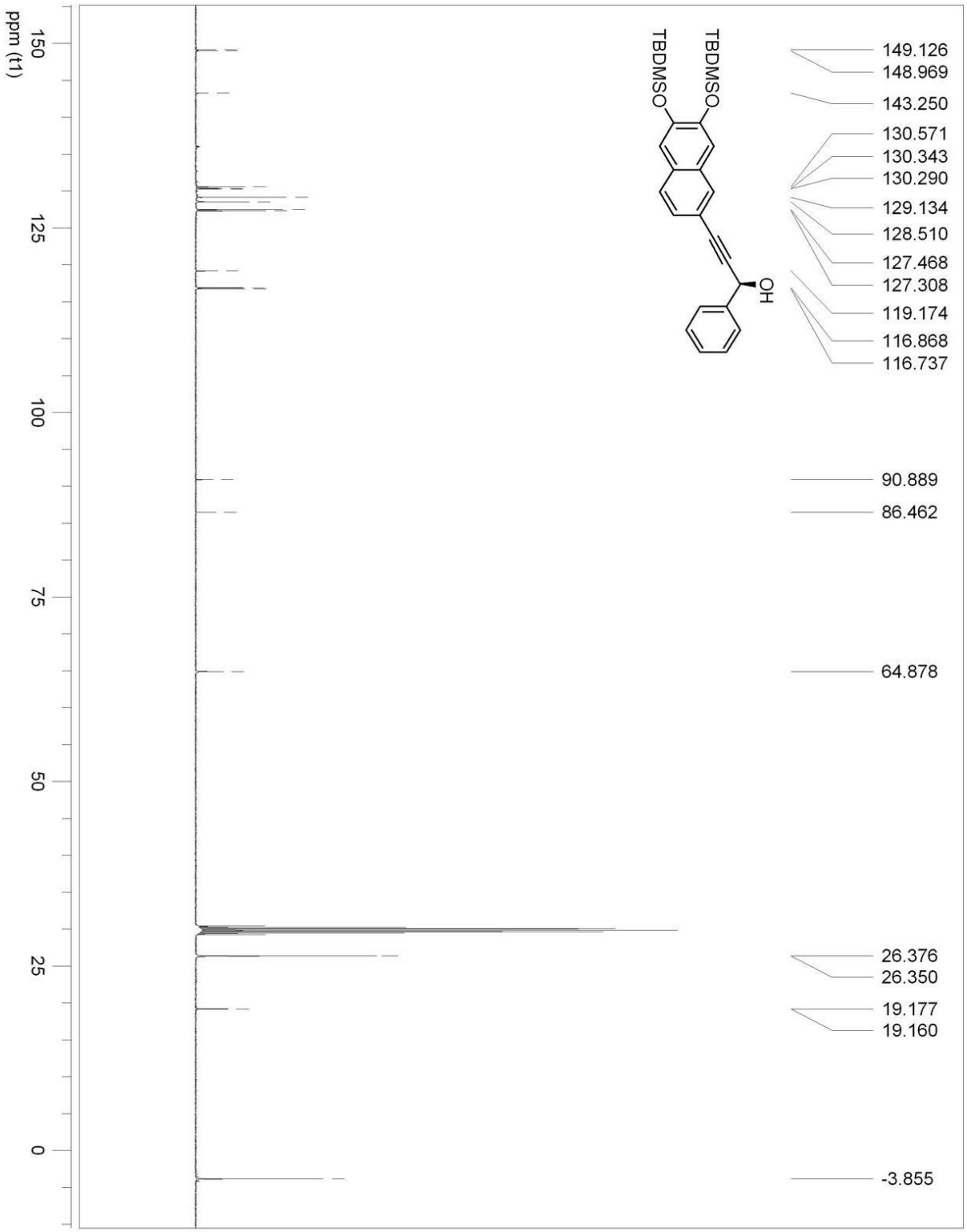


Figure a.50 ^{1}H NMR of compound **150**, 400 Hz, Acetone-d

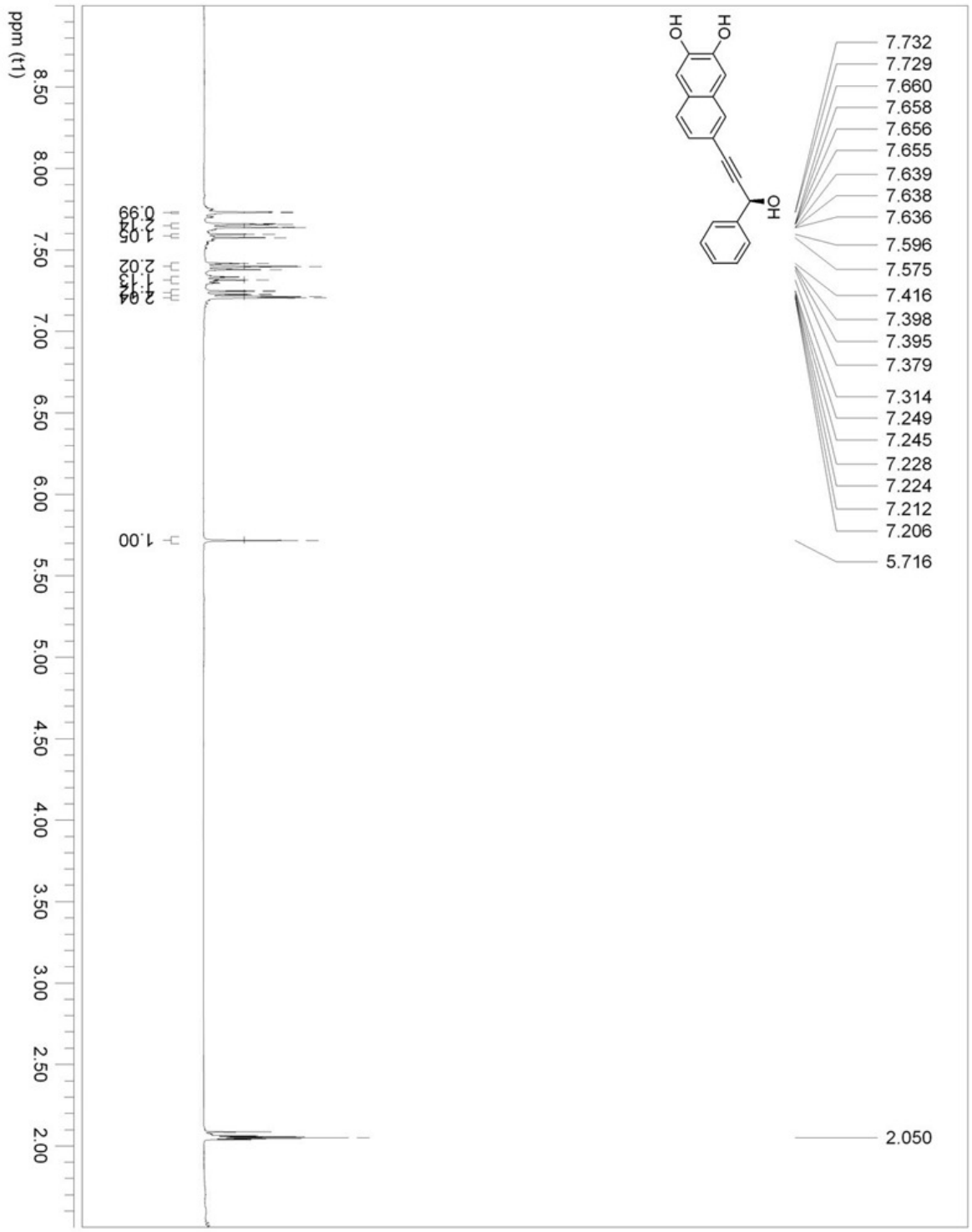


Figure a.51 ^{13}C NMR of compound **150**, 400 Hz, Acetone-d

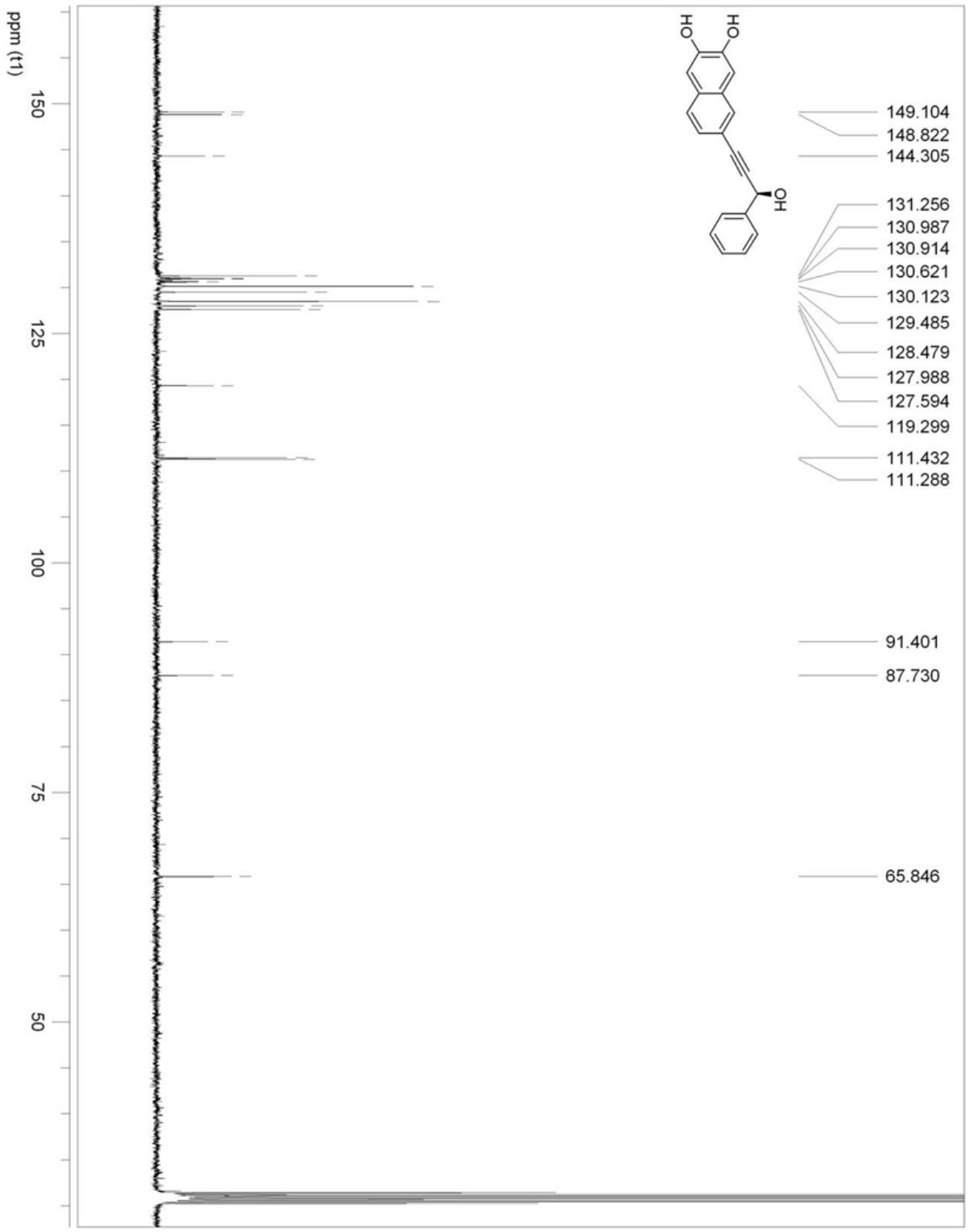


Figure a.52 ^{1}H NMR of compound **153**, 400 Hz, Acetone-d

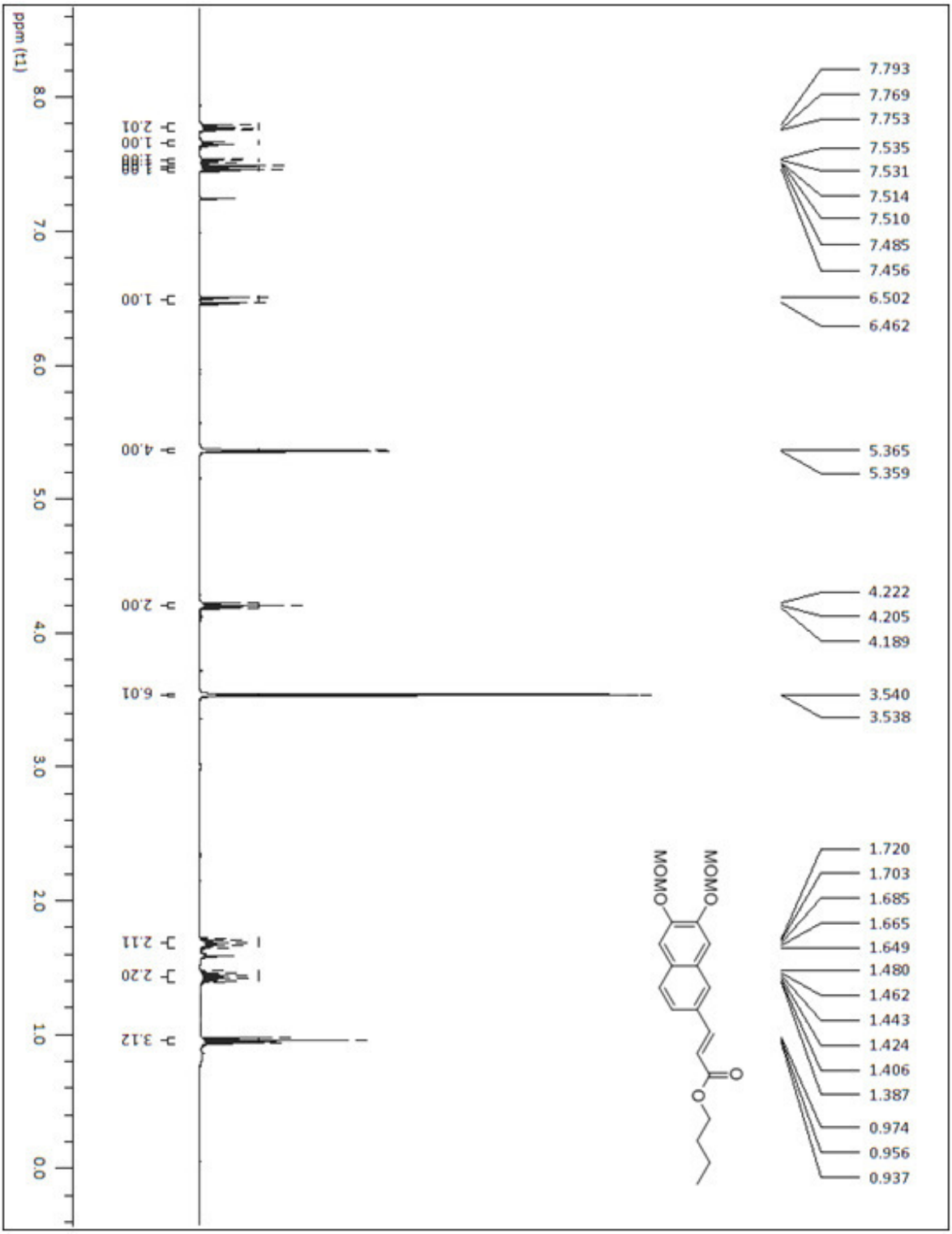


Figure a.53 ^{13}C NMR of compound **153**, 400 Hz, Acetone-d

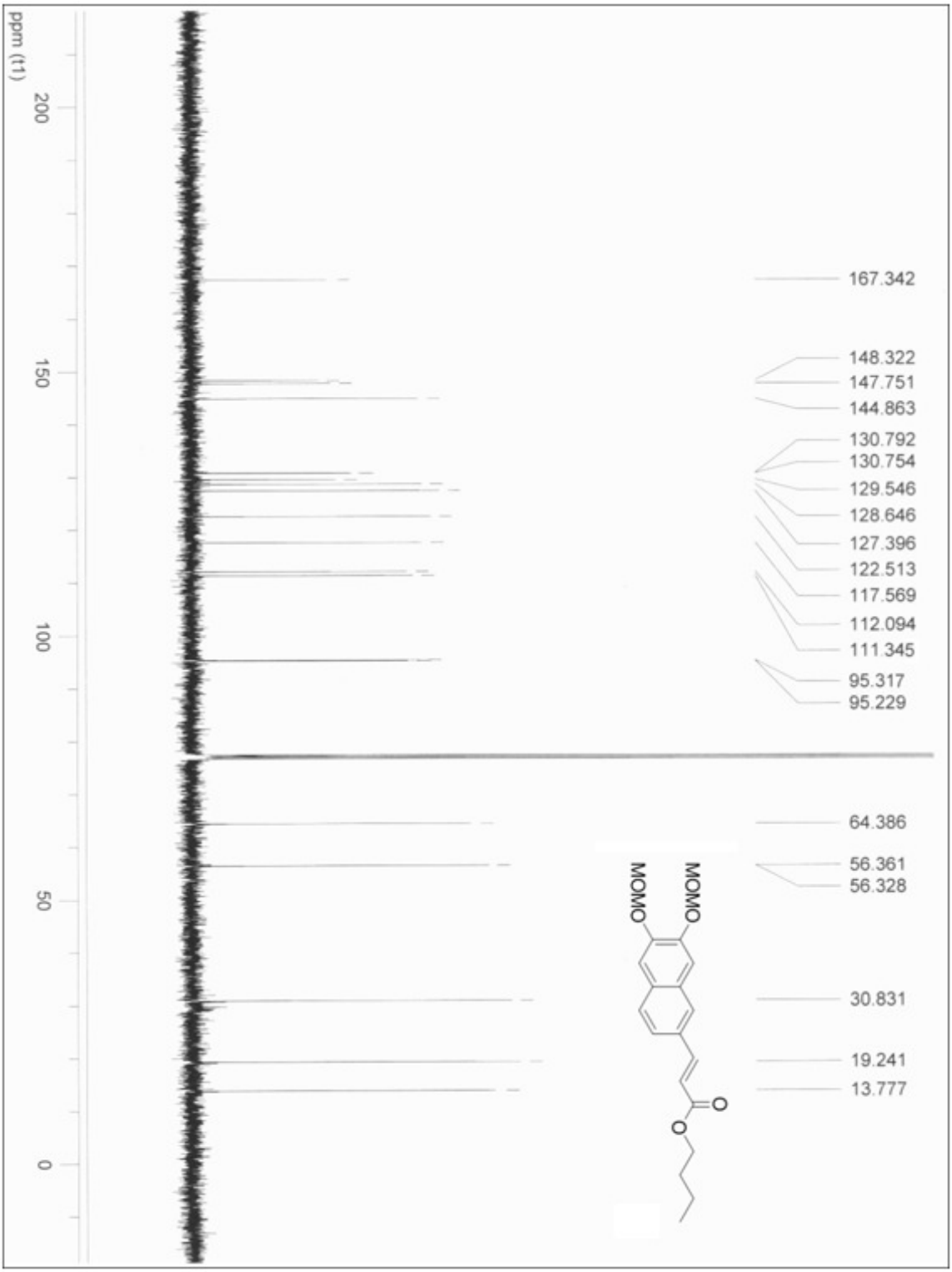


Figure a.54 ^{1}H NMR of compound **154**, 400 Hz, Acetone-d

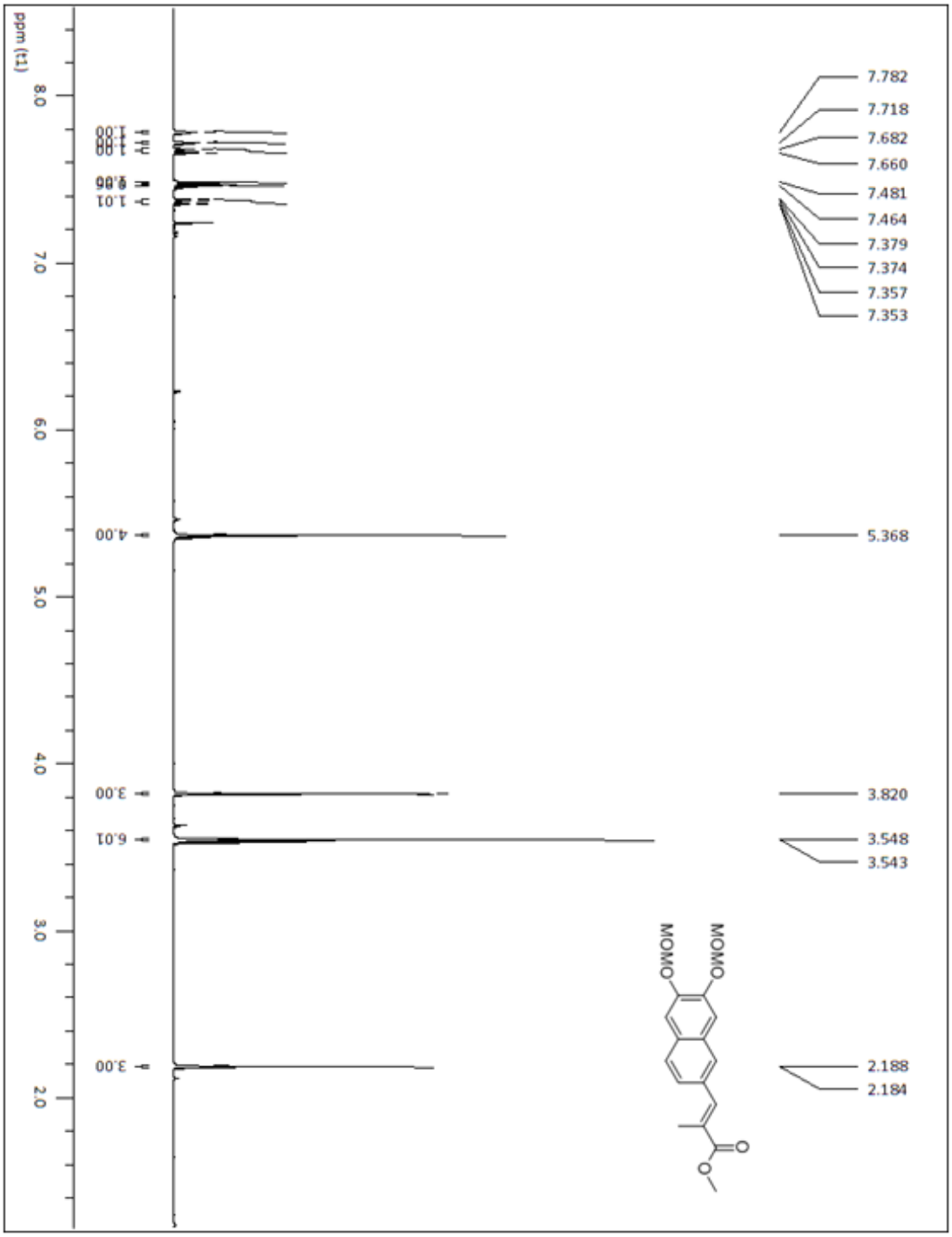


Figure a.55 ^{13}C NMR of compound **154**, 400 Hz, Acetone-d

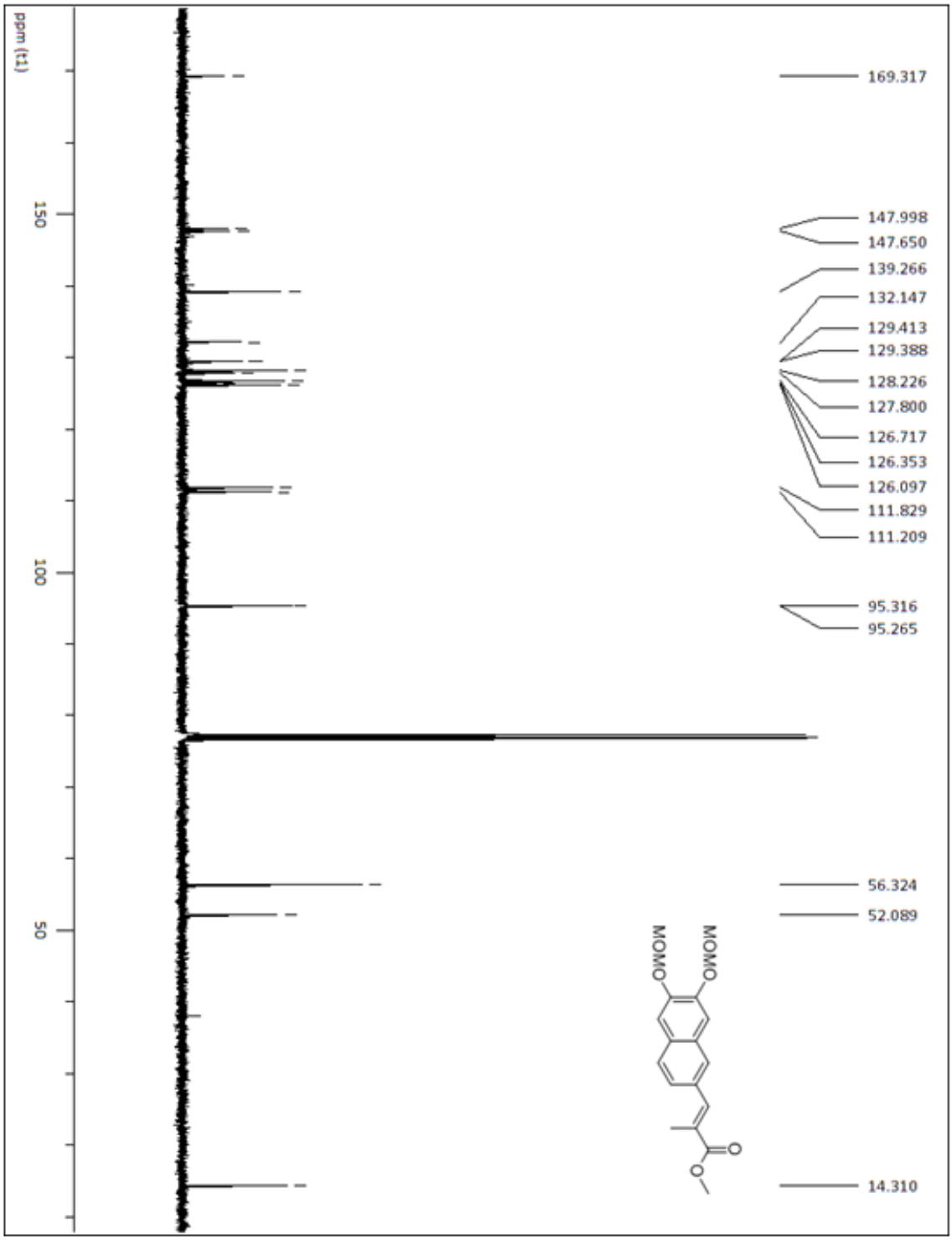


Figure a.56 ^{1}H NMR of compound **157**, 400 Hz, Acetone-d

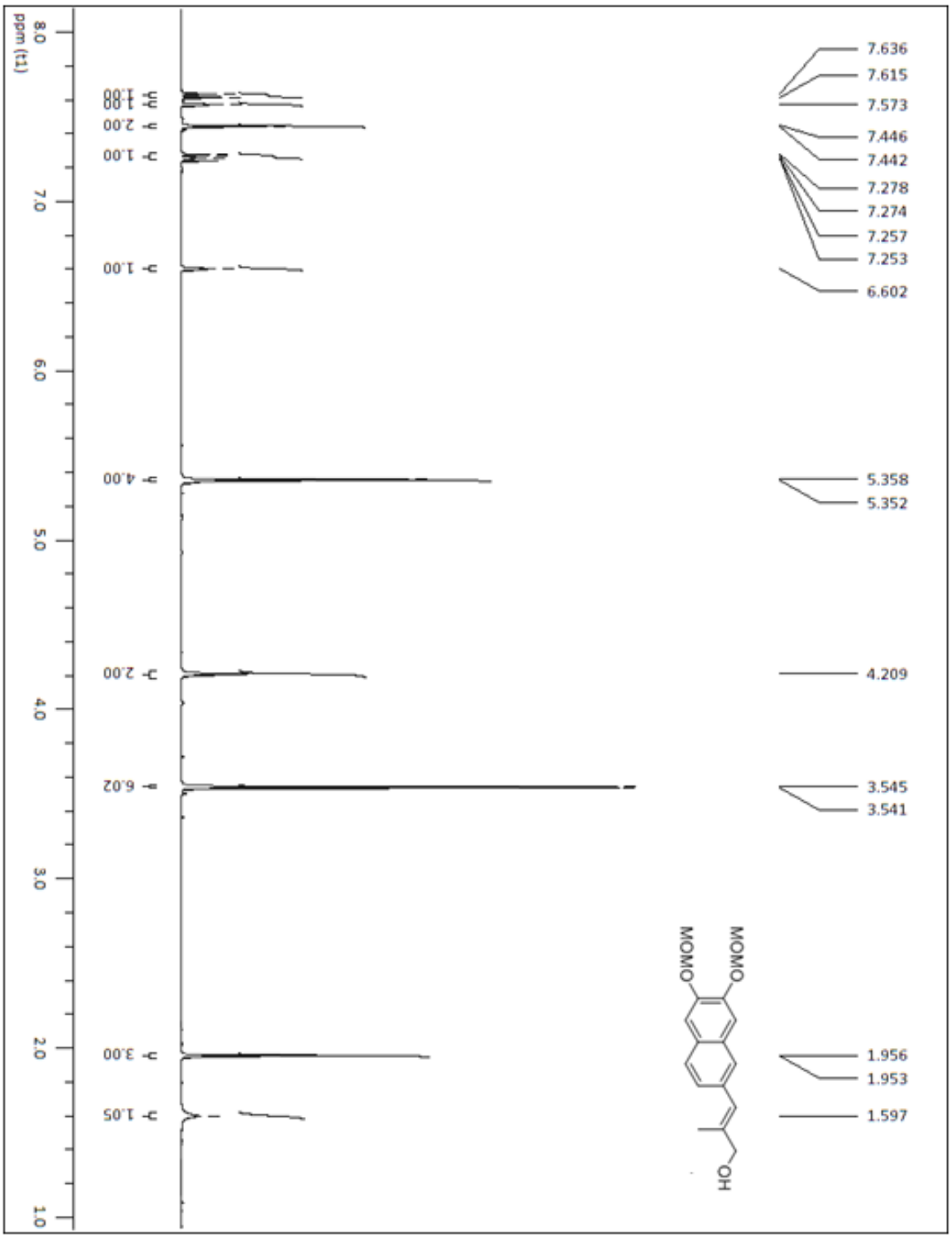


Figure a.57 ^{13}C NMR of compound **157**, 400 Hz, Acetone-d

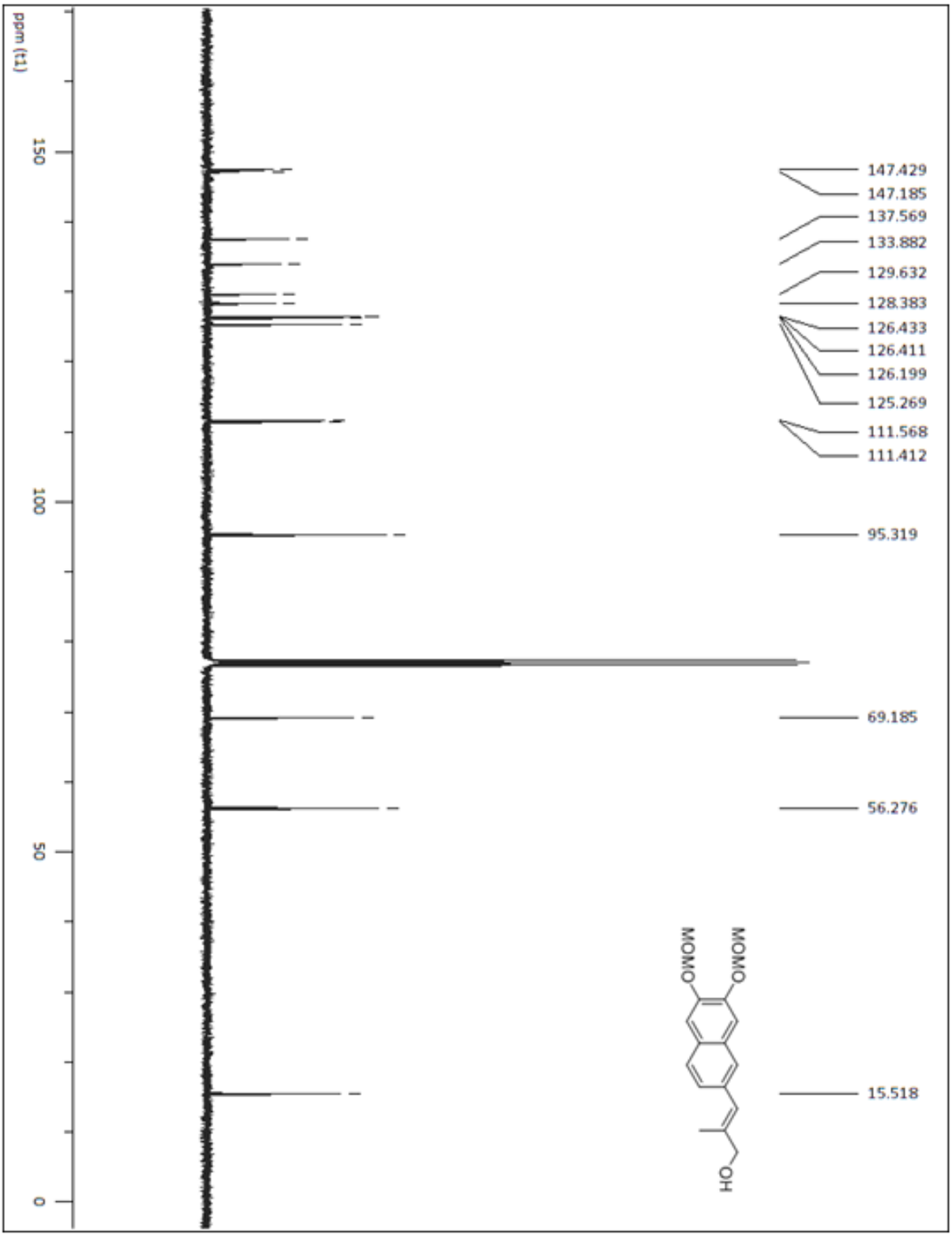


Figure a.58 ^{1}H NMR of compound **158**, 400 Hz, Acetone-d

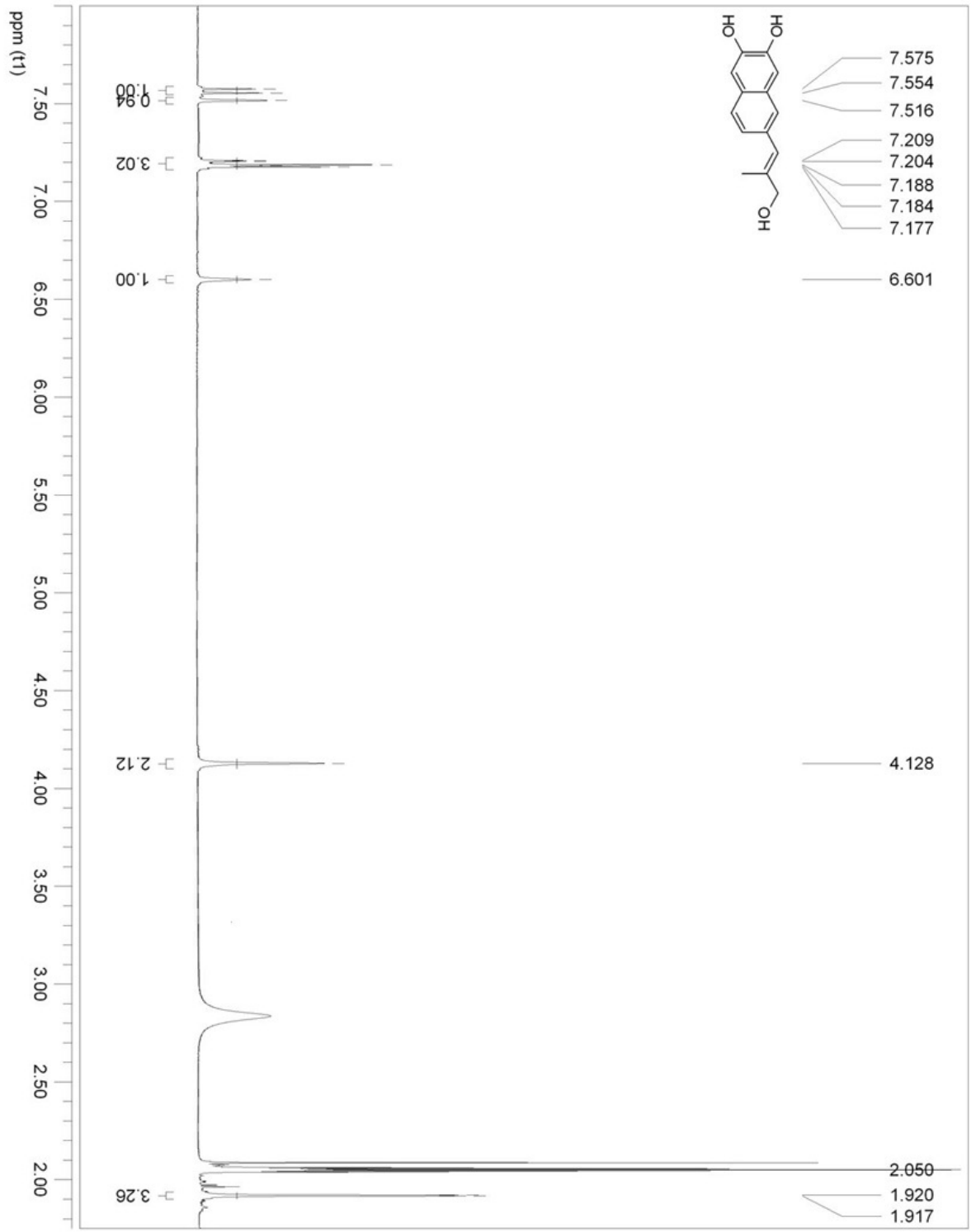


Figure a.59 ^{1}H NMR of compound **172**, 400 Hz, Acetone-d

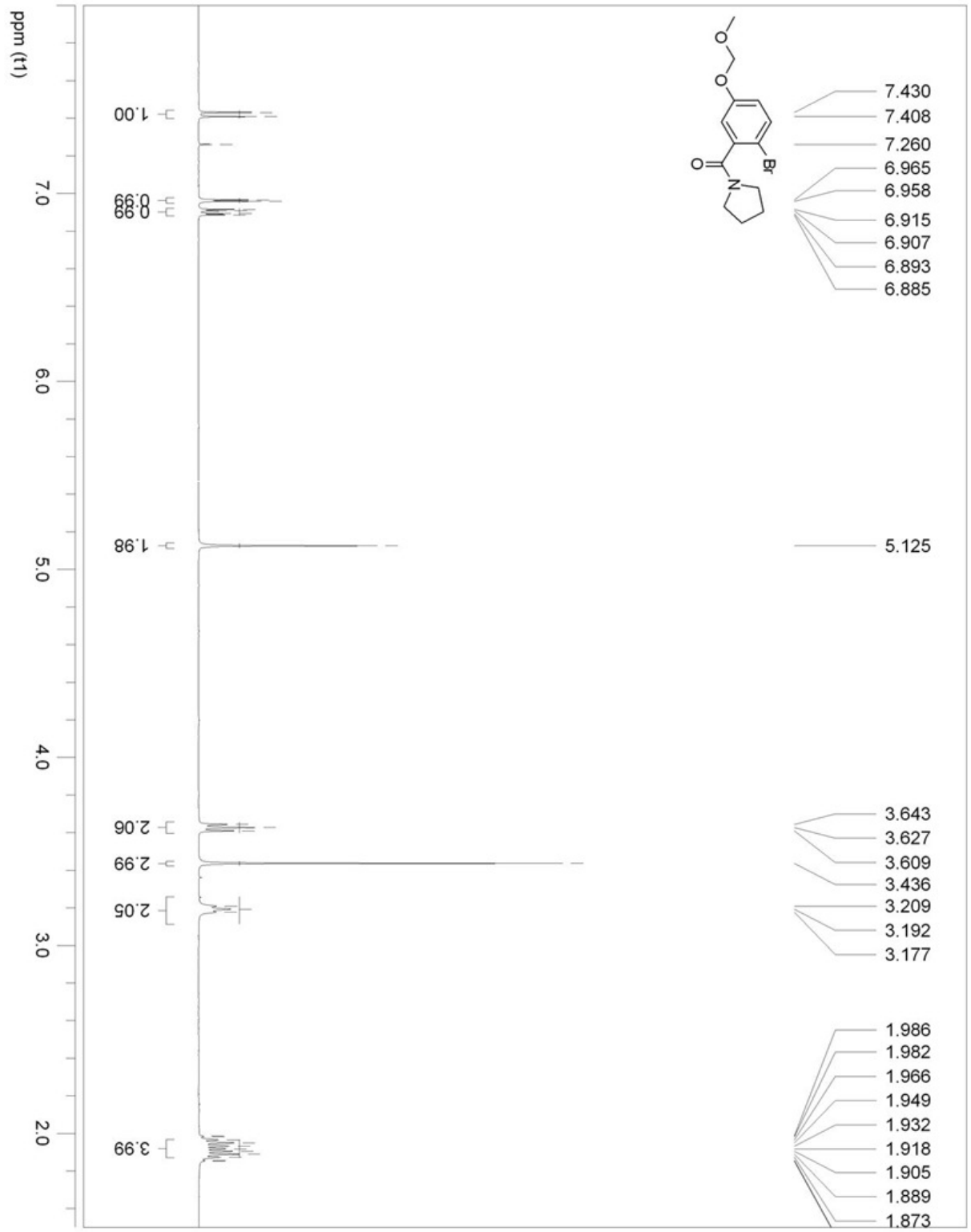
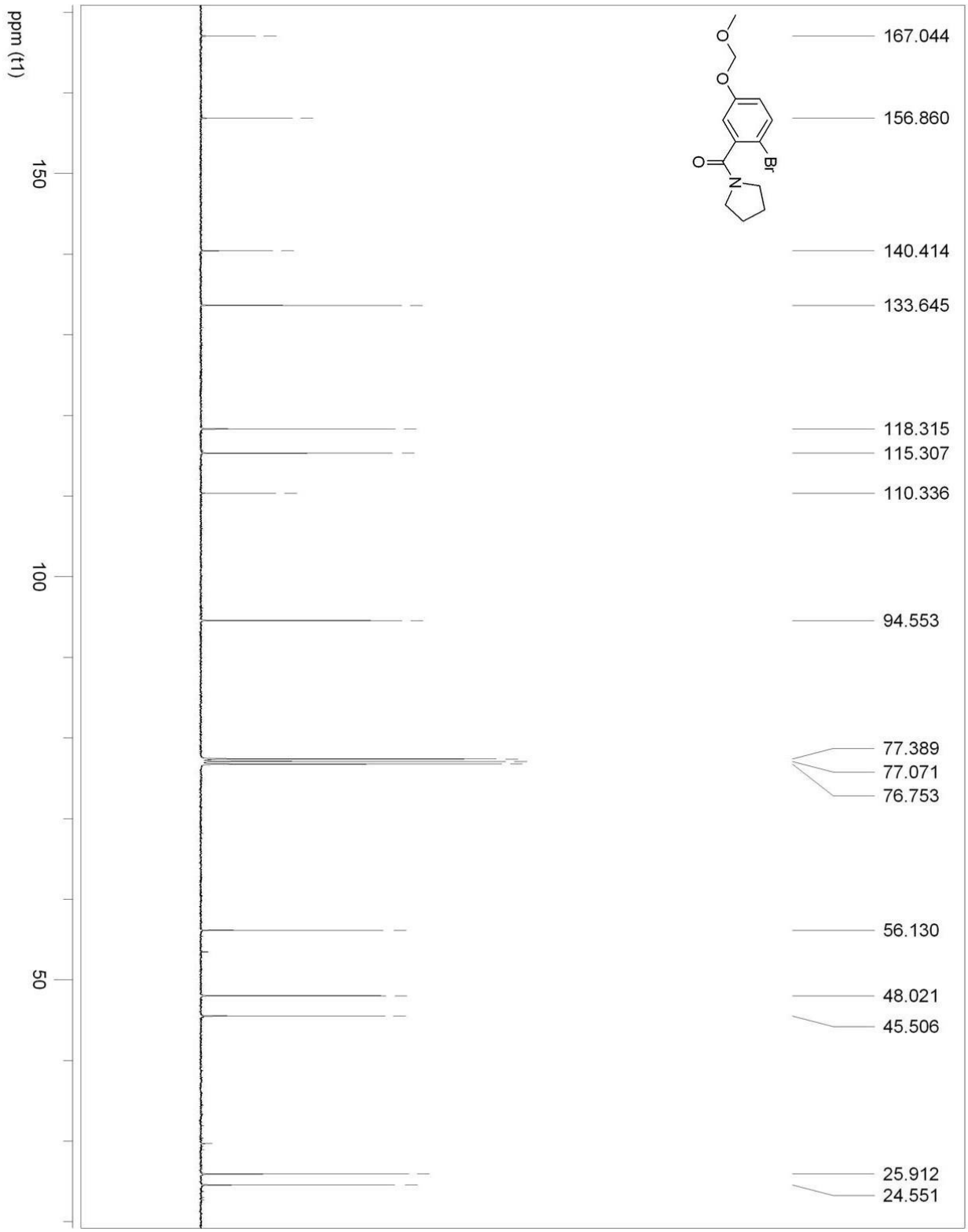


Figure a.60 ^{13}C NMR of compound **172**, 400 Hz, Acetone-d



Synthesis and Reactivity of 2,3-substituted 5-silyl-7-oxa-bicyclo[2.2.1]heptenes and Heptadienes

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Keywords: 3-Silyl furan / Diels-Alder / 5-Silyl-7-oxa-bicyclo[2.2.1] heptenes / 5-Silyl-7-oxa-bicyclo[2.2.1] heptadienes / Michael Additions

Silylated functional groups have widely demonstrated their ability to direct the regio- and stereoselectivity by stabilization of positive and negative charges at the β and α positions respectively. Research from the Malacria group indicates that silyl groups can act as directing groups in palladium catalysed allylic alkylations. This paper discusses a recent study of the properties of silyl groups as directing groups in Diels-Alder reactions using 3-silyl furans as dienes. The synthesis of these furans and the reactivity of the 7-oxabicyclo[2.2.1]heptadienes cyclo-adducts will be discussed. 3-Silyl furans have been synthesized from (*E*)-2-silylbut-2-ene-1,4-diols in a one step reaction using potassium dichromate and in good yields. It is also possible to use a less toxic two step method using palladium catalysis, but in moderate yields. These 3-silyl furans have been reacted under Lewis Acid conditions with both symmetric reagents such as dimethyl acetylenedicarboxylate (DMAD) and electron deficient olefins such as methyl acrylate. The reactivity of the resulting 7-oxabicyclo [2.2.1]heptadienes and 7-oxabicyclo[2.2.1]heptanes is also discussed.

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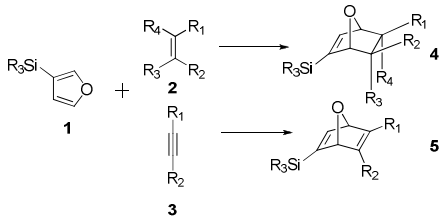
IntIntroduction

Organosilanes have a wide range of applications in organic synthesis. They are commonly used as protecting groups, and can also be transformed to different functional groups, by Tamao-Fleming[1] oxidation and Hiyama coupling[2-3] reactions. Another aspect of these functional groups is their ability to stabilize charges on adjacent atoms: in many cases, carbocations β to a silane (Si-C-C$^+$) are stabilized through interaction of the empty *p* orbital of the carbocation atom and the silicon-carbon *σ* bonding orbital. Alternately, silanes can stabilize α-carboanion (Si-C$^-$) through the interaction of the carboanion's occupied *p* orbital and the silicon's *σ* * antibonding orbital.[4-6] These trends can be used in synthesis to control regioselectivity as well as in some cases stereoselectivity.

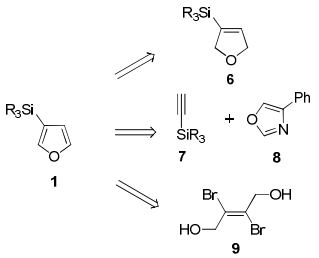
Based on these properties, silanes can be used as directing groups. In the Mizoroki-Heck reaction, an allylsilane is used to direct intramolecular coupling, resulting in the selective formation of the vinylsilane after β-elimination.[7] Nucleophilic substitution of (*E*)-2-(triethylsilyl)but-2-ene-1,4-diyl diacetate[8] and (*E*)-4-(methoxycarbonyloxy)-3-(trimethylsilyl)but-2-enyl acetate[9] under Pd(0) catalysis results almost exclusively in substitution at the β position to the silane. These reactions are both regio and stereo selective and the configuration of the double bond is retained.

Furans are capable of acting as dienes in Diels-Alder reactions with alkenes and alkynes, preferentially those with an electron withdrawing group.[13] In this study we also examine the effects of silanes at the 3 position on the regio and stereoselectivity of this reaction (Scheme 1). Previous studies conducted in the Malacria group have shown that the presence of a Lewis acid is necessary to activate the diene.[14-15]



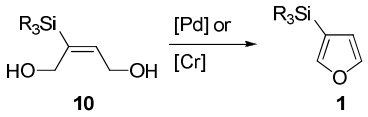
Scheme 1. Diels-Alder reaction of 3-silyl furans with substituted alkenes and alkynes

A simple synthetic route to the silylated reagents is still required. To date, there exist three routes to the synthesis of 3-silyl furans (Scheme 2), [10-12] which show poor yields, difficulty of synthesis or toxicity of reagents.



Scheme 2. Synthesis of 3-silyl furans

This paper looks at two methods for the synthesis of 3-silyl furans from (*E*)-2-(trialkylsilyl)but-2-ene-1,4-diol (Scheme 3).



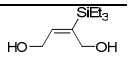
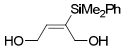
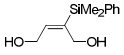
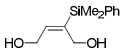
Scheme 3. Oxidation route to 3-silyl furan

It is proposed that the oxabicyclo[2.2.1]heptan-5-ene type products of the Diels-Alder reaction can be opened to give tetra, or penta substituted cyclohexenes under ring opening conditions.[16-19] These products would retain the relative stereochemistry conferred by the Diels-Alder reaction, and the silane could once again direct the attack of the nucleophile, determining the regiochemistry of the final product. Furthermore, these products can eventually be used as keystone intermediates in synthesis, where the silane can be transformed to a hydroxyl group, or used to couple the cyclohexene to alkylhalides.

Results and Discussion

The transformation of but-2-yne-1,4-diol (**11**) to the (*E*)-2-(trialkylsilyl)but-2-ene-1,4-diol (**10**), using the respective alkylsilane and platinum tetrakis (triphenylphosphine) catalyst has been previously optimized in our group. This method gives high yields for different silanes and has allowed us to prepare a variety of precursors for the cyclization and aromatization to the respective 3-silyl furans. The results attained in the previous study are presented in Table 1. The hydrosilylation reaction was also performed under $H_2PtCl_6{\cdot}6H_2O$ catalysis, however this method has not been persued due to reproducibility issues.

Table 1. Synthesis of (*E*)-2-(trialkylsilyl)but-2-ene-1,4-diol from but-2-yne-1,4-diol

Entry	Silane	Time (h)	Yield (%)	Product
10a	$HSiEt_3$	3h	> 98	
10b	$HSiMe_2Ph$	3h	> 98	
10c	$HSi(iPr)_3$	3h	96	
10d	$HSiMe_2tBu$	3h	> 98	

We chose the method described by Wong et al to prepare the furans used in the Diels-Alder reactions (Figure 1). The corresponding (*E*)-2-(trialkylsilyl)but-2-ene-1,4-diol (**10a**, **10b**) was solubilized in a *n*-hexane/H_2SO_4 aq 7.5% (w/w) and heated to reflux, at which time a solution of $K_2Cr_2O_7$ in H_2SO_4 conc. was added slowly using a dropping funnel. This reaction was fast and efficient, and the hexane layer could be separated from the aqueous layer when the addition of the oxidation agent was complete. We have been able to achieve a yield of 66% for the triethyl(furan-3-yl)silane (**10a**) and 68% for the triisopropyl(furan-3-yl)silane (**10b**) after purification by distillation and flash column chromatography respectively.

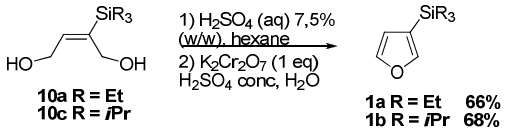


Figure 1. Preparation of furan from but-2-yne-1,4-diol, using $K_2Cr_2O_7$ as oxidizing agent

An alternate, two-step synthesis of the 3-silyl furans starting from the (*E*)-2-(trialkylsilyl)but-2-ene-1,4-diol was investigated (Figure 2).[20] First, the diol was cyclised under acidic conditions, neat with a catalytic amount of $KHSO_4$ at 100°C. The conversion was quantitative on both the triethyl and triisopropyl series. Silylated furans **1a** and **1b** were sufficiently pure to be taken directly to the next reaction.

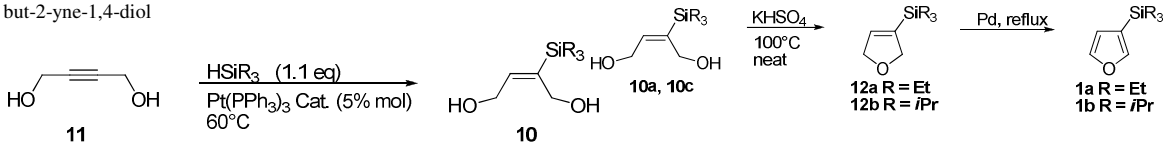
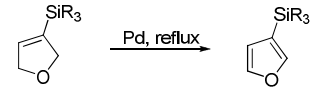


Figure 2. Preparation of furan from (*E*)-2-(trialkylsilyl)but-2-ene-1,4-diol

The subsequent step was the Pd catalyzed dehydrogenation of **12a** and **12b** (Table 2). Two catalysts were used Pd/C and $Pd(OH)_2$ at reflux in ethanol for two to three hours, and once overnight at reflux in EtOH, which did not give an improved yield. These reaction conditions saw formation of negligible amounts of the desired furans **1a** and **1b**, however, it was remarked that precursors **12a** and **12b** that had been filtered over a short pad of silica already contained trace amounts of the respective furan. To investigate this, **12a** was diluted with ethyl acetate and silica was added and stirred over three days at room temperature. By ^{1}H NMR, a higher concentration of the furan was present, as well as a substantial quantity of degradation; these reaction conditions were not investigated further. However, it was observed that after two months stored under atmospheric conditions, **12a** spontaneously and quantitatively oxidized to **1a**.

Table 2. Conditions for the palladium catalyzed dehydrogenation of (2,5-dihydrofuran-3-yl)silanes



12a R = Et
12b R = *i*Pr

1a R = Et
1b R = *i*Pr

Entry[a]	Silane	Solvent	Catalyst[a]	Temp (°C)	Yield (%)
1	**12a**	EtOH	Pd/C	Reflux	≤ 7
2	**12a**	*i*BuOH	Pd/C	Reflux	100
3	**12b**	*i*BuOH	Pd/C	Reflux	≤ 3
4	**12a**	EtOH	$Pd(OH)_2$	Reflux	≤ 11
5	**12a**	EtOAc	silica	r.t.	degradation, ≤ 47

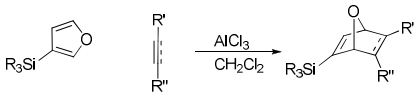
[a] entry 1 was reacted for 2 hours and overnight, with comparable results, entries 2-5 were reacted 2-3 hours; [b] 5 mol % catalyst concentration, silica was added as a 1:1 (w/w) ratio.

In order to increase the conversion to the furan, a solvent with a higher boiling point was chosen: dehydrogenation in *i*BuOH at reflux gave quantitative yield of **12a**, while under the same conditions the conversion of **12b** to **1b** was only slightly improved. It can be speculated that the difference in the sterics between the triethylsilane and triisopropylsilane was directly related to the difference in conversions. Increasing the reaction temperature and time may be sufficient to drive the dehydrogenation of **12b** to completion. This method was therefore capable of becoming a viable route to the 3-silyl furans, however it required further optimization to achieve desirable conversions.

The 3-silyl furans were then subjected to Diels-Alder cycloaddition conditions to study the efficacy of the silane as a directing group. Some reactions of triethyl(furan-3-yl)silane (**1a**), triisopropyl(furan-3-yl)silane (**1b**) and dimethylphenyl(furan-3-yl)silane with symmetrical dienophiles N-phenylmaleimide, malemic anhydride and dimethyl acetylene dicarboxylate (DMAD) have been performed.

These previous experiments have shown that the addition of a Lewis Acid is essential to reach good yields and complete conversion to the desired product. Furthermore due to the aromatic nature of the diene there was a strong tendency to undergo retro Diels-Alder[21] to give the corresponding acetylenic silane and the 3, 4-disubstituted furan. In the absence of Lewis Acid, the reaction mixture must be heated, which favours this undesired reaction. $AlCl_3$ proved to be a good catalyst,[14] which allowed us to minimize heating of the Diels-Alder products and therefore avoid retro Diels-Alder.

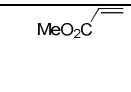
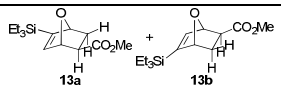
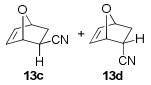
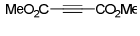
Table 3. Diels-Alder between 3-silyl furans and various dienophiles



1a R = Et
1b R = *i*Pr

2 = alkene
3 = alkyne

13
14

Entry	Furan	Dienophile	Temp (°C)	Yield (%)
1	**1a**		r.t.	 **13a** **13b**
2	**1a**		r.t.	Mixture of products
3	**1a**		r.t.	 **13c** **13d**
4	**1a**		-20°C	77
5	**1b**		-20°C	1:1 **1b**:**14b**
6	**1b**		0°C to r.t.	81

At first, a series of acrylates were reacted with **1a** to evaluate the effect of the silane on the regioselectivity of the reaction. The acrylates (1.5 eq.) were added to a solution of **1a** in CH_2Cl_2 and the reaction flask was placed in a water bath. $AlCl_3$ (1.5 eq.) was then added and the reaction mixture was stirred at ambient temperature for 30 minutes, at which point no more furan remained and the reaction was quenched and worked up. Methyl acrylate gave a mixture of two silylated products: they could not be separated by column chromatography and were recovered in a 1:1.6 ratio by ^{1}H NMR. Using the *exo* cycloaddition product of furan and methyl acrylate (*exo*-methyl-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate)[22-24] as reference, we were able to identify these compounds as the two regioisomers resulting from the *exo* directed cycloaddition of methyl acrylate onto the 3-silyl furan. On the basis of sterics, we can deduce that *exo*-methyl-5-(triethylsilyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (**13a**) is more abundant than *exo*-methyl-6-

(triethylsilyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (**13b**).

A third product was present in the crude mixture, but was lost during purification by column chromatography. This product can be identified as the *exo* Diels-Alder adduct between the desilylated furan and methylacrylate. The three products were present in a 1:1.6:1 (**13a** : **13b** : desilylation product) ratio in the crude mixture when methylacrylate was not distilled. Unexpectedly, upon distillation of the dienophile prior to reaction, the desilylated product become major, but could not be isolated. We have not addressed this problem further due to time constraints.

Reaction with the *tert*-butyl acrylate gave a complex mixture of products and no desired oxabicyclo[2.2.1]heptene type compounds could be isolated. Finally, cycloaddition of the acrylonitrile resulted in the loss of the triethyl silane. The products of the *exo* (**13c**) / *endo* (**13d**) Diels-Alder attack of the acrylonitrile on the furan were isolated in a 1:1 ratio.

On the other hand, the Diels-Alder reaction with symmetrical DMAD gave the single possible cycloaddition product in 77% and 81% yield for **14a** and **14b** respectively. It is important to note that the reaction with **1b** as the dienophile required higher reaction temperature to achieve complete conversion, which may be attributed to the increased steric effect of the triisopropyl silane during the attack on the dienophile.

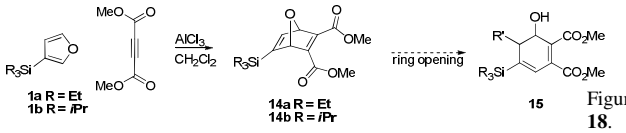


Figure 3. Investigation of ring opening of oxabicyclo[2.2.1]he ptenes

The Diels-Alder products **14a** was subjected to ring opening conditions described by Carrée et al.,[24] where the oxabicyclo[2.2.1]heptene is activated by a Lewis Acid, followed by a nucleophilic attack by benzylamine.

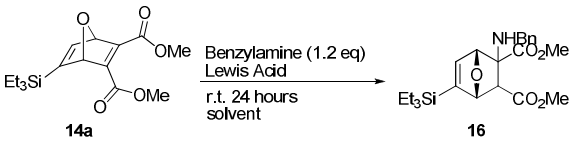


Table 4. 1,4 addition of benzylamine of Diels-Alder cycloadduct

Entry	Solvent	Lewis Acid	Yield (%)
1	THF	$FeCl_3$	44
2	CH_2Cl_2	$Sc(OTf)_3$	87

Two experiments have been performed (Table 4) and gave the Michael addition product as a single regioisomer. Unfortunately, the ring opening was not achieved and the benzylamine added 1,4 to the ester substituted double bond to give dimethyl 2-(benzylamino)-5-(triethylsilyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**16**). This is the only product formed, and a significant difference in the conversion and isolated yield were seen between the two reaction conditions. With $FeCl_3$, **16** was isolated in 44% yield based on a conversion of 50% by ^{1}H NMR, while no starting material remained when using $Sc(OTf)_3$.

To avoid 1,4-addition of the benzylamine, we are currently testing the ring opening reaction on selectively reduced dimethyl 5-(triethylsilyl)-7-oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylate (**17**) (Figure 4). Under mild reaction conditions optimized in our group, the single diasteriomer **17** was isolated.[14] This product will then be subjected to the ring opening conditions described above to attain monocyclic product **18**.

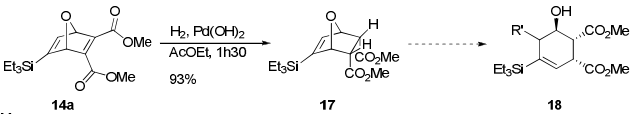


Figure 4. ReSduction of **14a** to **17** and subsequent ring opening to **18**.

Conclusions

The aim of this project was to elucidate the effect of silanes as directing groups in Diels-Alder reactions, and to show the possible applications of silane substituted oxabicyclo[2.2.1]heptene compounds in synthesis by undergoing ring opening to form substituted cyclohexenes. It has also been of interest to this study to investigate alternate methods of synthesizing the 3-silyl furans which were used as dienes; the Pd catalyzed dehydrogenation route is an attractive method for reducing the use of toxic reagents, even if the Jones oxidation route is more general and more efficient. This method requires more investigation and optimization to increase the scope of its substrates and to achieve a high yields.

Also, the Diels-Alder cycloaddition of acrylates to 3-silyl furans must be optimized. Milder reaction conditions with reduced equivalents of Lewis Acid, and longer reaction times at a reduced temperature may help to reach better

selectivities, as well an prevent undesired side reactions, such as the desilylation observed with acrylonitrile.

Finally, the conditions and reagents for the opening of the oxabicyclo[2.2.1]heptene type products must be investigated and determined. In the long term, the chemistry discussed in this paper can have great application in the synthesis of natural products, and once optimized it can be applied as the keystone transformation in such a synthesis.

Experimental Section

Materials. Dichloromethane was dried by distillation over calcium hydride, and THF was dried by distillation over Na/benzophenone. Unless otherwise noted, all commercial materials were used without further purification. **General information.** All reactions were performed in oven-dried evacuated vessels under argon atmosphere unless otherwise specified in the procedure. Purification of reaction products was carried out by flash column chromatography using silica gel (40-63 µm). Analytical thin layer chromatography was performed on aluminum sheets pre-coated with silica gel 60 F254, cut to size. Visualization was accomplished with ultraviolet light and PAN and $KMnO_4$ stains followed by heating.
^{1}H NMR spectra were recorded on a Bruker Avance400 (400 MHz) spectrometer at ambient temperature and were reported in ppm using solvent as the internal standard ($CDCl_3$ at 7.26 ppm). Data were reported as: multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), integration and coupling constant(s) in Hz.
Infrared spectra were obtained using a Bruker Tensor 27 ATR diamond PIKE instrument. High resolution mass spectra were obtained by the laboratoire de structure et fonction de molécules bioactives (UMR 7613).
General Procedure for the synthesis of (*E*)-2-(trialkylsilyl)but-2-ene-1,4-diols (GP1). But-2-yne-1,4-diol (116 mmol) was recrystalized in ethyl acetate (20 mL) and ethanol (1 mL). The crystals were dissolved in THF (70 mL) and the trialkylsilane (128 mmol) was added. $(PPh_3)_4Pt$ (0.058 mmol) was added and the reaction was refluxed for three hours. The resulting solution was concentrated under reduced pressure to afford the product, sufficiently pure for use in further reactions.

General Procedure for the synthesis of trialkyl(furan-3-yl)silanes (GP2).

(*E*)-2-(trialkylsilyl)but-2-ene-1,4-diol (13 mmol) was diluted with *n*-hexane (26 mL), and 7.5% (w/w) H_2SO_4 aqueous solution (10 mL). The mixture was heated to reflux and stirred for 5 minutes, then a solution of $K_2Cr_2O_7$ (13 mmol) in water (26 ml) and concetrated H_2SO_4 (4.25 mL) was introduced slowly with a dropping funnel into the reaction vessel. Once the reagent was added, the mixture was stirred for a few minutes then the organic phase was separated and the aqueous phase was extracted with pentanes. The combined organic layers were washed with a sat. Na_2CO_3 solution, water and a sat. NaCl solution then dried over $MgSO_4$ and concentrated under reduced pressure. The product was purified by distillation or flash column chromatography.

General Procedure for the synthesis of dimethyl-5-(trialkylsilyl)-7-oxa-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (GP3). Trialkyl(furan-3-yl)silane (5.6 mmol) was diluted in CH_2Cl_2 (20 mL). Dimethyl acetylene dicarboxylate (DMAD) (8.37 mmol) and the mixture was cooled then $AlCl_3$ was added and the reaction mixture was stirred for 20 minutes. The reaction was quenched with sat. NH_4Cl solution and extracted with CH_2Cl_2; the combined organic layers were dried over Mg_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography.

(*E*)-2-(triethylsilyl)but-2-ene-1,4-diol (10a). Synthesized following GP1 using but-2-yne-1,4-diol (10g, 116 mmol), triethylsilane (20.6 mL, 128 mmol) and $(PPh_3)_4Pt$ (72 mg, 0.058 mmol), as a yellow oil, in quantitative yield (23.5 g).

^{1}**H** : δ = 6.03 (t, *J* = 6Hz, 1H, $Et_3SiC=CH$), 4.25 (d, *J* = 6Hz, 2H, $HOCH_2CH$), 4.20 (s, 2H, $HOCH_2CSiEt_3$), 3.62 (s, 2H, OH), 0.97 (t, *J* = 8Hz, 9H, $SiCH_2CH_3$), 0.65 (q, *J* = 8Hz, 6H, $SiCH_2CH_3$).

^{13}**C** : δ = 142.0 (1C, $Et_3SiC=CH$), 140.7 (1C, $Et_3SiC=CH$), 60.0 (1C, $HOCH_2CH$), 59.0 (1C, $HOCH_2CSiEt_3$), 7.3 (3C, $SiCH_2CH_3$), 2.9 (3C, $SiCH_2CH_3$).

IR : ν 3301, 3068, 3009, 2955, 2897, 1618, 1427, 1360, 1247, 1043, 1006, 817, 773cm^{-1}.

(*E*)-2-(triisopropylsilyl)but-2-ene-1,4-diol (10b). Synthesized following GP1, using but-2-yne-1,4-diol (1 g, 12 mmol) triisopropylsilane (2.6 mL, 13 mmol) and $(PPh_3)_4Pt$ (7 mg, 0.006 mmol), as a white solid (2.71 g, 96% yield).

Tf = 75°C-78°C

^{1}**H** : δ = 6.23 (t, *J* = 6Hz, 1H, $iPr_3SiC=CH$), 4.36 (d, *J* = 6Hz, 2H, $HOCH_2CH$), 4.24 (s, 2H, $HOCH_2CSiiPr_3$), 2.32 (s, 2H, OH), 1.21-1.16 (m, 3H, $SiCH(CH_3)_2$), 1.09 (d, *J* = 8Hz, 18H, $SiCH(CH_3)_2$).

^{13}**C** : δ = 144.9 (1C, $iPr_3SiC=CH$), 139.9 (1C, $iPr_3SiC=CH$), 60.5 (1C, $HOCH_2CH$), 59.9 (1C, $HOCH_2CSiiPr_3$), 18.6 (6C, $SiCH(CH_3)_2$), 10.8 (3C, $SiCH(CH_3)_2$).

IR : ν 3311, 2942, 2864, 1611, 1457, 1384, 1364, 1250, 1002, 882cm^{-1}.

HRMS : calculated $C_{13}H_{28}O_2NaSi$ = 267.1751, found = 267.1752.

(2,5-dihydrofuran-3-yl)triethylsilane (12a). (9.77 mmol, 1.977 mg) (*E*)-2-(triethylsilyl)but-2-ene-1,4-diol **(10a)** was combined with $KHSO_4$ neat and heated to 100°C while stirring for 90 minutes. The mixture was diluted with one volume petroleum ether and filtered through a short pad of silica, then washed with two volumes of petroleum ether. The solvent was evaporated at ambient pressure and 50°C to

afford a dark yellow oil. 1.2 g of crude were purified by distillation at 6.5E-1 mbar and 75°C-90°C to afford a pale yellow oil (623.6 mg, 57 %).
^{1}**H** : δ = 6.03 (s, 1 H, Et_3SiC=C*H*), 4.70 (m, 2H, OCH_2CSiEt_3), 4.65 (m, 2H, OCH_2CH), 0.90 (t, *J* = 7.9 Hz, 9H, SiCH_2CH_3), 0.61 (q, *J* = 7.7 Hz, 6H, SiCH_2CH_3).

IR : ν 2954, 2910, 2875, 1736, 1537, 1489, 1458, 1332, 1236, 1137, 1060, 1026, 1003, 877, 790 cm^{-1}.

Triethyl(furan-3-yl)silane (1a). Synthesized following GP2, using (*E*)-2-(triethylsilyl)but-2-ene-1,4-diol **(10a)** (2.64 g, 13 mmol) and $K_2Cr_2O_7$ (3.84 g, 13 mmol). The product was purified by distillation at a pressure of 6E-1 mbar and a temperature of 80°C to 90°C to afford a yellow oil (1.57 g, 66% yield).

^{1}**H** : δ = 7.50 (t, *J* = 1.5Hz, 1H, OC*H*=CH), 7.35 (dd, *J* = 1.5Hz, *J* = 0.9Hz, 1H, OC*H*=CSiEt_3), 6.36 (dd, *J* = 1.7Hz, *J* = 0.9Hz, 1H, Et_3SiC-C*H*), 0.96 (t, *J* = 8Hz, 9H, SiCH_2CH_3), 0.70 (q, *J* = 8Hz, 6H, SiCH_2CH_3).

^{13}**C** : δ = 147.6 (1C, O*C*H=CH), 142.7 (1C, O*C*H=CSiEt_3), 114.9 (1C, OCH=*C*SiEt_3), 113.6 (1C, Et_3Si*C*-CH), 7.4 (3C, SiCH_2*C*H_3), 3.9 (3C, Si*C*H_2CH_3).

IR : ν 2953, 2910, 2875, 1579, 1537, 1489, 1459, 1378, 1235, 1062, 1027, 970cm^{-1}.

Triisopropyl(furan-3-yl)silane (1b). Synthesized following GP2, using (*E*)-2-(triisopropylsilyl)but-2-ene-1,4-diol **(10b)** (2.51 g, 10.3 mmol) and of $K_2Cr_2O_7$ (3.03 g, 10.3 mmol). The product was purified by flash column chromatography (AcOEt / Pentane (6 / 94)) to afford a yellow oil (1.56 g, 68% yield).

^{1}**H** : δ = 7.53 (s, 1H, OC*H*=CH), 7.41 (s, 1H, OC*H*=CSi*i*Pr_3), 6.41 (s, 1H, *i*Pr_3SiC-C*H*), 1.30-1.20 (m, 3H, SiC*H*$(CH_3)_2$), 1.10 (d, *J* = 7 Hz, 18H, SiCH(CH_3)$_2$).

^{13}**C** : δ = 148.1 (1C, O*C*H=CH), 142.4 (1C, O*C*H=CSi*i*Pr_3), 114.5 (1C, *i*Pr_3SiC-*C*H), 112.3 (1C, *i*Pr_3Si*C*-CH), 18.6 (6C, SiCH(*C*H_3)$_2$), 11.3 (3C, Si*C*H$(CH_3)_2$).

IR : ν 2942, 2891, 2865, 1579, 1535, 1489, 1462, 1383, 1366, 1235, 1137, 877, 789cm^{-1}.

Dimethyl-5-(triethylsilyl)-7-oxa-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (14a). Synthesized following GP3, using triethyl(furan-3-yl)silane **(1a)** (1 g, 5.6 mmol) and DMAD (1.03 mL, 8.37 mmol) at −20°C. The product was purified by flash column chromatography (using CH_2Cl_2 as the elution solvent) to attain a yellow oil (1.39 g, 77% yield).

^{1}**H** : δ = 7.41 (d, *J* = 1.5Hz, 1H, C*H*=CSiEt_3), 5.78 (d, *J* = 1.8Hz, 1H, OC*H*-CSiEt_3), 5.62 (t, *J* = 1.5Hz, 1H, OC*H*-CH), 3.79 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 0.88 (t, *J* = 8Hz, 9H, SiCH_2CH_3), 0.61 (m, 6H, SiCH_2CH_3).

^{13}**C** : δ = 163.4 (1C, *C*O_2Me), 162.8 (1C, *C*O_2Me), 153.9 (1C, CH=*C*SiEt_3), 153.3 (1C, *C*H=CSiEt_3), 152.7 (1C, *C*(CO_2Me)=C(CO_2Me)), 152.6 (1C, *C*(CO_2Me)=C(CO_2Me)), 88.2 (1C, O*C*H-CH), 85.5 (1C, O*C*H-CSiEt_3), 52.3 (1C, O*C*H_3), 52.1 (1C, O*C*H_3), 7.2 (3C, SiCH_2*C*H_3), 3.0 (3C, Si*C*H_2CH_3).

IR : ν 2952, 2910, 2875, 1710, 1637, 1550, 1435, 1322, 1295, 1227, 1168, 1083, 1004, 933, 868, 844cm^{-1}.

HRMS : calculated $C_{16}H_{24}O_5NaSi$ = 347.1285, found = 347.1289.

Dimethyl-5-(triisopropylsilyl)-7-oxa-bicyclo[2.2.1]hepta-2,5-diene-2,3-dicarboxylate (14b). Synthesized following GP3, using triisopropyl(furan-3-yl)silane **(1b)** (896 mg, 2.4 mmol) and DMAD (0.45 mL, 3.7 mmol) at 0°C to room temperature. The product was purified by flash column chromatography (using CH_2Cl_2 as the elution solvent) to obtain a yellow oil (1.97 g, 81% yield).

^{1}**H** : δ = 7.53 (d, J = 1.9Hz, 1H, C*H*=CSi*i*Pr_3), 5.91 (d, J = 1.3Hz, 1H, OC*H*-CSi*i*Pr_3), 5.62 (t, J = 1.6Hz, 1H, OC*H*-CH), 3.82 (s, 3H, OCH_3), 3.77 (s, 3H, OCH_3), 1.16 (q, J = 7.2Hz, 3H, SiC*H*$(CH_3)_2$), 1.06 (d, J = 7.2Hz, 9H, SiCH(CH_3)$_2$), 0.99 (d, J= 7.2Hz, 9H, SiCH(CH_3)$_2$).

^{13}**C** : δ = 164.0 (1C, *C*O_2Me), 162.9 (1C, *C*O_2Me), 154.6 (1C, CH=*C*Si*i*Pr_3), 153.6 (1C, *C*H=CSiEt_3), 153.4 (1C, *C*(CO_2Me)=C(CO_2Me)), 153.0 (1C, *C*(CO_2Me)=C(CO_2Me)), 89.0 (1C, O*C*H-CH), 85.8 (1C, O*C*H-CSiEt_3), 52.6 (1C, O*C*H_3), 52.4 (1C, O*C*H_3), 18.9 (6C, SiCH(*C*H_3)$_2$), 11.6 (3C, Si*C*H$(CH_3)_2$).

IR : ν 2945, 2891, 2865, 1726, 1638, 1546, 1460, 1435, 1383, 1322, 1260, 1229, 1208, 1168, 1110, 1083, 1041, 1000, 911, 882, 867, 842, 786 cm^{-1}.

Methyl-5-(triethylsilyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate and methyl 6-(triethylsilyl)-7-oxabicyclo[2.2.1]hept-5-ene-2-carboxylate (13a, 13b). Triethyl(furan-3-yl)silane (**1a**) (64.0 mg, 0.35 mmol) was diluted in CH_2Cl_2 (1.5 mL) and methyl acrylate (47 µL, 0.527 mmol) was added. The solution was cooled to 0°C and $AlCl_3$ was added over a period of 2 minutes. The reaction was warmed to room temperature and let stir for 1 hour. The reaction mixture was washed with sat. $NaHCO_3$ solution and extracted with EtOAc. The combined organic layers were dried over Mg_2SO_4 and concentrated under reduced pressure. The product was purified by flash column chromatography (using a 100% petroleum ether to 10% EtOAc, 90% petroleum ether solvent gradient) to afford a pale yellow oil (73 mg, 77% yield of the two *exo* regioisomers in a 1:1.6 **13b**:**13a** ratio).

^{1}**H** : δ = 6.57 (d, *J* = 1.5 Hz, 1H, C*H*=CSiEt_3 **13b**), 6.53 (d, *J* = 1.6 Hz, 1H, C*H*=CSiEt_3 **13a**), 5.19 (s, 1H, OC*H*-CH **13b**), 5.13 (s, 1H, OC*H*-CH **13a**), 5.09 (d, *J* = 4.6 Hz, 1H, OC*H*-CSiEt_3 **13a**), 5.02 (d, *J* = 4.1 Hz, 1H, OC*H*-CSiEt_3 **13b**), 3.69 (s, 3H, OCH_3 **13a** or **13b**), 3.68 (s, 3H, OCH_3 **13a** or **13b**), 2.35 (dd, *J* = 4.0, 8.5 Hz, 1H *H*C(CO_2Me) **13a**), 2.26 (dd, *J* = 3.9, 8.5 Hz, 1H *H*C(CO_2Me) **13b**), 2.1-2.08 (m, 1H, H_{eq}-CH-CH(CO_2Me) **13b**), 2.08-2.06 (m, 1H, H_{eq}-CH-

$CH(CO_2Me)$ **13a**), 1.47 (dd, J = 8.6, 11.6 Hz, 1H, H_{ax}-CH-$CH(CO_2Me)$ **13b**),1.40 (dd, J = 8.6, 11.5 Hz, 1H, H_{ax}-CH-$CH(CO_2Me)$ **13a**), 0.91 (m, 9H, $SiCH_2CH_3$ **13a** and **13b**), 0.60 (m, 6H, $SiCH_2CH_3$ **13a** and **13b**).

^{13}**C** : δ = 174.7 (1C, CO_2Me **13a** or **13b**), 174.6 (1C, CO_2Me **13a** or **13b**), 148.7 (1C, $CH=CSiEt_3$, **13a** or **13b**), 147.2 (1C, $CH=CSiEt_3$ **13b**), 146.2 (1C, $CH=CSiEt_3$, **13a** or **13b**), 144.8 (1C, $CH=CSiEt_3$ **13a**), 84.6 (1C, OCH-CH **13b**), 81.7 (1C, OCH-CH **13a** or OCH-$CSiEt_3$ **13a**), 81.6 (1C, OCH-CH **13a** or OCH-$CSiEt_3$ **13a**), 78.8 (1C, OCH-$CSiEt_3$ **13b**), 52.5 (1C, OCH_3 **13a** and **13b**), 43.0 (1C, $HC(CO_2Me)$ **13a** and **13b**), 29.3 (1C, $CH_2CH(CO_2Me)$ **13a** or **13b**), 29.2 (1C, $CH_2CH(CO_2Me)$ **13a** or **13b**), 6.9 (3C, $SiCH_2CH_3$ **13a** and **13b**), 3.5 (3C, $SiCH_2CH_3$ **13a** and **13b**).

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