Synthesis of homo A-CD estrogens for potential use in hormone replacement therapy

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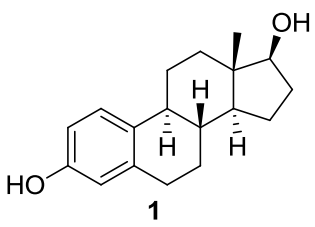
بسم الله الرحمن الرحيم

Abstract

Hormone replacement therapy (HRT) has been subject to much debate due to concerns that long term use of such treatment of menopause increases the risk of breast and uterine cancer. This is thought to be caused by estradiol (**1**) binding to the estrogen receptor α (ERα) resulting in increased cell proliferation. Another possible mechanism relates to toxicity of the estrodiol metabolites, which are thought to be genotoxic *ortho*-quinones. In a previous project, a series of A-CD estrogens (**2**) were synthesised as non-carcinogenic estradiol agonists where the *cis* CD ring junction was thought to be the cause of the desirable selectivity for ERβ. In this thesis, homo A-CDs were synthesised (**3**) with expansion of the D ring thought to increase the selecitivty for ERβ. Relative Binding Affinities (RBA) were determined with selectivity to ERα and ERβ. Most ligands showed decreased selectivity when compared to the original A-CD series. However, compounds carrying the CF_3 moiety continued to show very high potency. In addition, novel synthetic routes were employed in the preparation of certain compounds.



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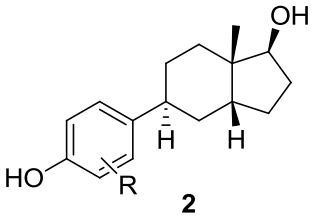

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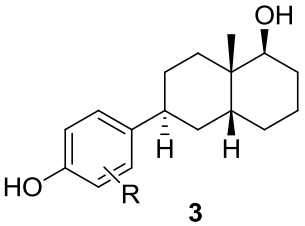

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Acknowledgments

I would first like to start by thanking God for the innumerable blessings He has bestowed upon me. I would like to also by thanking my family for their continuous support in achieving academic excellence. Thanks to my parents for helping me and pushing me throughout my studies. It would not have been possible without you.

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List of Abbreviations and Symbols

^{1}H	Proton NMR
^{13}C	Carbon 13 NMR
AcOH	Acetic acid
BuLi	Butyllithium
$CDCl_3$	Deuterated chlorofrom
d	Doublet
DCM	Dichloromethane
DEAD	Diethyl azodicaborxylate
DIPEA	*N*,*N*-diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	*N*,*N*-Dimethylformamide
E2	17β-estradiol
ee	Enantiomeric excess
ER	Estrogen Receptor
EtOAc	Ethyl Acetate
EtOH	Ethanol
HCl	Hydrochloric acid
HRMS	High resolution mass spectrometry
HRT	Hormone replacement therapy
H_2SO_4	Sulfuric acid
Hz	Hertz
J	Coupling constant
LDA	Lithium diisopropylamide
m	Multiplet
Me	Methyl
$MeNO_2$	Nitromethane
MeOD	Deuterated methanol
MeOH	Methanol

$MgSO_4$	Magnesium sulfate
MHz	Megahertz
mmol	Millimoles
MOM	Methyl ethyl ether
NBS	*N*-bromosuccinimide
NH_4Cl	Ammonium chloride
NMR	Nuclear magnetic resonance
OH	Hydroxyl
Pd/C	Palladium on carbon
ppm	Parts per million
pTSA	*para*-toluenesulfonic acid
RBA	Relative Binding Affinity
rf	Retention factor
rt	Room temperature
RTA	Relative Transcription Activation
s	Singlet
t	Triplet
TBDMS (TBS)	*Tert*-Butyldimethylsilyl ether
THF	Tetrahydrofuran
THP	Tetrahydropyranyl
TLC	Thin Layer Chromatography
TsOH	Tosylic acid

1.0 INTRODUCTION

1.1 Hormone Replacement Therapy

Hormone Replacement Therapy (HRT) has been subject to much debate over the past years. Its safety has been of much concern as different reports suggest that the long-term use of such treatment of menopause increases the risk of breast and uterine cancer, stroke, etc.[1] The number one treatment used until recently has been Premarin, manufactured by Wyeth Pharmaceuticals, which consists of estrogens isolated from mares' urine. Despite the recent discoveries of the risk this drug carries, Premarin's ability at relieving hot flashes and other menopausal side effects remains unquestionable and total sales of the drug were more than $1 billion in 2013;[2] twenty six million estrogen HRT prescriptions issued in the US in 2010. This clearly demonstrates the potential in this market and the willingness of women and their doctors to use this treatment, despite its known dangers, to treat the symptoms of menopause.

1.2 Menopause

Menopause occurs when a woman undergoes her last menstrual cycle, where a final ovulation takes place thereby indicating that there are no more active follicles in the ovary.[3] As a result, hormone levels produced by these follicles decline, including estrogen and progesterone. This on average occurs at the age of 51.7 in the United States, however some women start experiencing menopause as early as in their late thirties. Having said that, the stage of rapid decline of these hormonal levels occurs during a stage called perimenopause. By definition the latter includes all the stages leading to the last menstrual cycle plus 1 year after the fact.[3] According to a large research conducted by the

Massachusetts Women's Health Study, women who smoke tend to have an earlier onset of menopause and a shorter period to completion while women who have never given birth reach it faster than those who have. However, as is the case of menstrual cycles, menopause has different effects on each individual and as a result time of onset and duration vary. The World Health Organization defined perimenopause as the first break in the regular cycling a woman experiences.

The main symptoms experienced during menopause are a result of the hormone level fluctuations which occur due to the feedback cycle between ovary and the hypothalamus. As previously described, estrogen production decreases as the number of active ovarian follicles declines. The hypothalamus detects this change and stimulates the pituitary gland to produce more follicle-stimulating hormone (FSH). This hormone then activates the follicles in the ovary to produce more estrogen. As the levels of the latter increase in the body, feedback occurs to the hypothalamus which in turn signals to decrease FSH and subsequently estrogen production declines. This cyclic feedback explains the dynamic changes in hormones levels women experience from an hourly to a daily basis. Indeed these fluctuations may explain mood swings and headaches experienced by women. This is why diagnosis of perimenopause by measuring the FSH levels is a tricky affair since at any given time there can be a fluctuation which would represent an inaccurate indication of the overall physiological state of the individual.

Of the main indications of menopause are hot flushes, which generally appear around the first cycle irregularity and last from 1 to 5 years after menopause. In fact, it is thought that up to 85% of women are subject to this symptom.[3] The explanation behind hot flushes is linked to low level of estrogens, which in turn affect the hypothalamus. Since

the latter is most active during the night, hot flushes take place more often which is why they are also called night sweats. These occurrences more often give place to sleeping disturbances that result in sleep deprivation. Of the other symptoms include mood changes which can be attributed to depressive tendencies and weight gain. No direct correlation has been established between the latter and menopause, whoever some evidence suggests that weight gain related to the aging process is affecting the fat distribution in the body at the time of menopause.[4]

1.3 Carcinogenicity

As previously mentioned, current issues dealing with HRT are directly related to breast cancer prevalence. The issues encountered with Premarin should not mark the end of HRT, however looking at the mechanism by which the estrogens administered can cause breast cancer is key in better understanding the issue at hand. To date, two mechanisms were reported in the literature. The first mechanism suggesting carcinogenicity refers to the stimulation of estrogen receptors causing cellular proliferation.[5] Upon the binding of estrogen, a signal is sent to stimulate the transcription of genes involved in cell proliferation. With each cycle of DNA replication come mutations which are not repaired, and as these mutations accumulate chances of developing cancer increase. This explains why anti-estrogen ligands reduce the risk of breast cancer.[5]

It is important to note that there exist two estrogen receptors, ERα and ERβ, that modulate different activities. Studies have shown that the receptor ERα is mostly responsible for stimulating cell proliferation and is needed for normal mammary gland development, as seen in mice.[6] The absence of the receptor resulted in no incidence of

tumour development. Moreover, ERβ for long has been thought to have opposite effects compared to ERα. Indeed it is reported that the former acts as a transdominant repressor of the latter by forming a heterodimer upon binding of esterdiol (estrogen, E2) and altering transcriptional activity.[7] As a result, an ideal compound would be an agonist selective for ERβ with some ERα activity, thereby alleviating menopausal symptoms without promoting proliferation. This is further supported by emerging data suggesting that developing subtype-selective ligands that target either of the ER receptors could be an optimal approach in relieving hot flashes, and preventing cancer, cardiovascular disease, and osteoporosis.[8]

The second mechanism by which carcinogenicity is increased is via the formation of quinone metabolites. The suggested pathway (**Figure 1.2**) requires enzymatic hydroxylation by cytochrome P450 of the phenolic A ring, forming a catechol estrogen, before the generation of the *ortho*-quionone estrogen[9]. This highly electrophilic metabolite then goes on to cause alkylation or oxidative damage to DNA and protein. For instance, guanine or adenine can easily covalently bond to the quinine, as seen in **Figure 1.1**, and the resulting adduct is released from the DNA leaving an abasic site on the strand.[5] If missed by the DNA repair mechanism, point mutations results which upon accumulation may cause cancer.

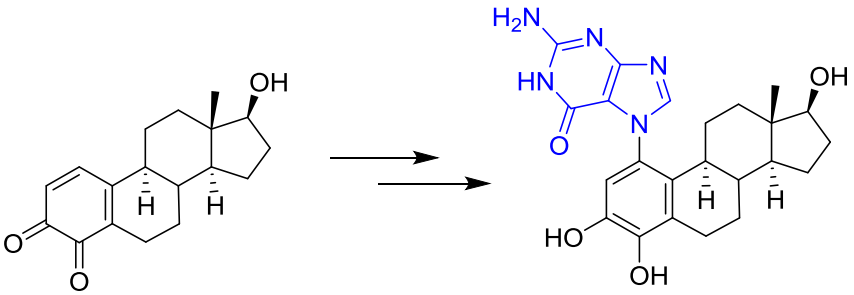


Figure 1.1 Example of 3,4-estradiol quinone forming adduct with guanine.

Further supporting this proposed mechanism is the fact that several studies have shown that levels of catechol-O-methyltranferase (COMT) affect the probability of developing breast cancer.[10] In fact, this enzyme alkylates the formed catechol thereby preventing the further formation of the quinone. The aforementioned studies have claimed that lower levels of COMT lead to higher risk of breast cancer.[11] Moreover, *o*-quinones are thought to bind or alkylate to ERs, generating highly redox-active "Trojan horse", which selectively target estrogen-sensitive genes.[9]

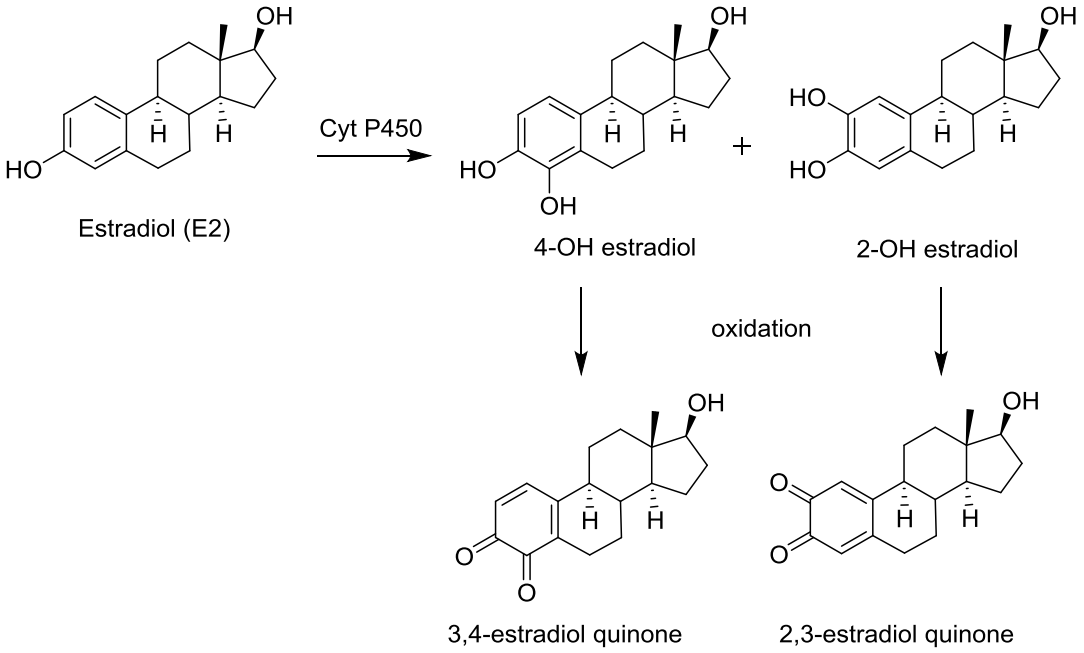


Figure 1.2 Pathway to quinone formation of estradiol via hydroxylation and oxidation.

1.4 A-CD Estrogen Project

Based on the factors mentioned above, our goal has been to design new estrogen agonists that would have selectivity for ERβ over ERα and be less prone to quinone formation when metabolised. The designed agonists closely resemble the structure of estradiol (E2), with the removal of the B ring (2 CH_2 groups) being the only difference. These subtle

changes give rise to compounds called A-CD estrogens, with the ring numbering system shown for practicality in the following **Figure 1.3**.

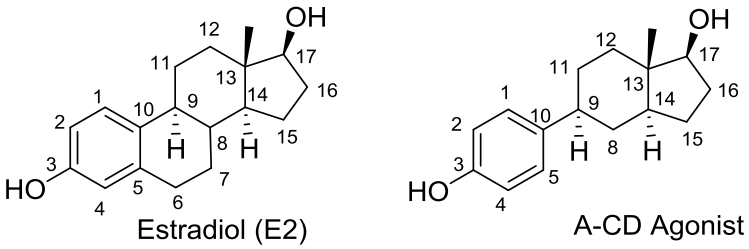


Figure 1.3 Structure of estradiol and A-CD prototype shown with ring numbering system.

The initial target of this project was the synthesis of compound **1**, a simple A-CD estrogen. However a different isomer was accidentally produced, compound **2**, which brought forth unexpected results. In fact, compound **2** showed better Relative Binding Affinity (RBA) to the estrogen receptors than **1**. Moreover, **2** demonstrated greater selectivity for ERβ over ERα than **1** and estradiol. Considering that the active site volume of E2 is 282 $Å^3$ and that of **2** is 259 $Å^3$, the selectivity may be due to the active site volume of each receptor, since it was determined that ERβ is smaller than ERα (279 $Å^3$ and 379 $Å^3$, respectively).[12] This suggests that a ligand fitting too tightly within the receptor results in a lower binding affinity as seen with **2** having selectivity to ERβ. Another important parameter is the relative transcriptional activation (RTA) which ultimately portrays the activity of the ligand. As mentioned previously, ERβ binding is preferred over ERα, however, RTAα activity is still required to relieve some of the undesirable menopause symptoms, such as hot flashes. To note that ratios for RTA are predictable using known RBA values. The difficulty comes in achieving the right proportions of activation without causing excessive cell proliferation thereby increasing the risk of breast cancer.

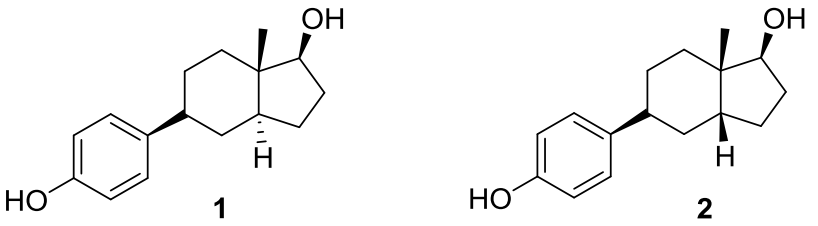


Figure 1.4 Structure of compound **1** containing the *trans* ring junction and **2** with the *cis* junction

Finally, in addition to the selectivity and activity discussed earlier, we have thought of adding substituents to Ring A in order to reduce or eliminate the formation of catechols and quinones during the metabolism to avoid DNA damage. Numerous compounds have been synthesised and tested so far, ranging from modified estradiols to substituted A-CD estrogens, in the form of SAR analysis in order to attain a better understanding of what structural features should be sought for. To date, the two compounds which show the best combination of ERα and ERβ ratios, combined with low propensity to form *o*-quinones and thus low toxicity have been designated as **L17** and **TD81**.

Figure 1.5 Structures of the two main compounds of interest L17 and TD-81.

In order to counter the formation of genotoxic metabolites, two strategies were employed: steric block of the positions susceptible to hydroxylation and reducing electron density of the aromatic ring. For instance synthesis of compounds with subsituents at C5 with

electron withdrawing properties (EWG) was attempted. In such compounds, the presence of a substituent at the meta position, relative to the C3 hydroxyl group, would affect the ortho-hydroxylation, part of the formation of catechols. This takes place through inductive and steric effects.

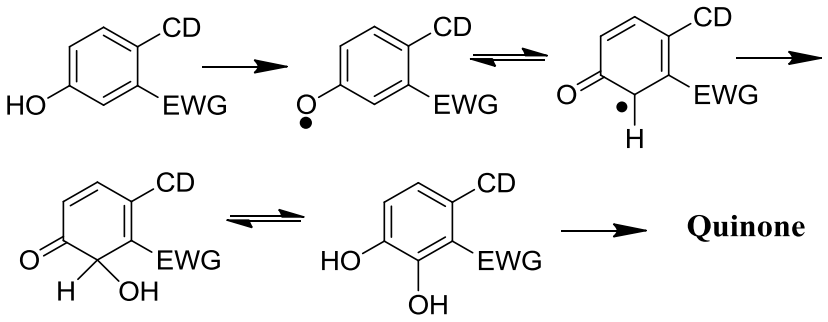


Figure 1.6 Proposed pathway of hydroxylation in the presence of a EWG at position C-5.

The inductive effect is understood to decrease the electron density in the A-ring, thereby increasing the bond dissociation energy (BDE) of the phenolic O-H.[12] The homolytic cleavage of that bond is the rate determining step in the formation of the catechol, the key intermediate in obtaining quinones. Therefore increasing the BDE will make it more difficult to achieve this step. Thus, compounds were prepared such as the ones found in **Figure 1.7**.

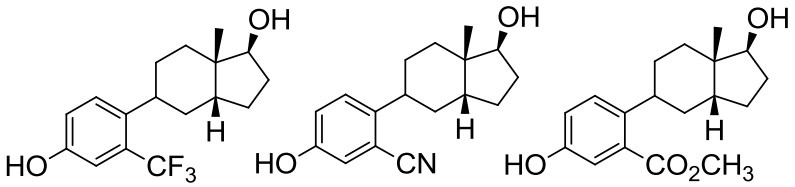


Figure 1.7 Examples of A-CD estrogens containing EWG at position C-5.

Synthesis of compounds containing CF_3 at the position of interest was completed and yielded significant results in terms of activity, with an RBA value of 205 recorded for ERβ.[12] All compounds equipped with the CF_3 moiety displayed higher activity than

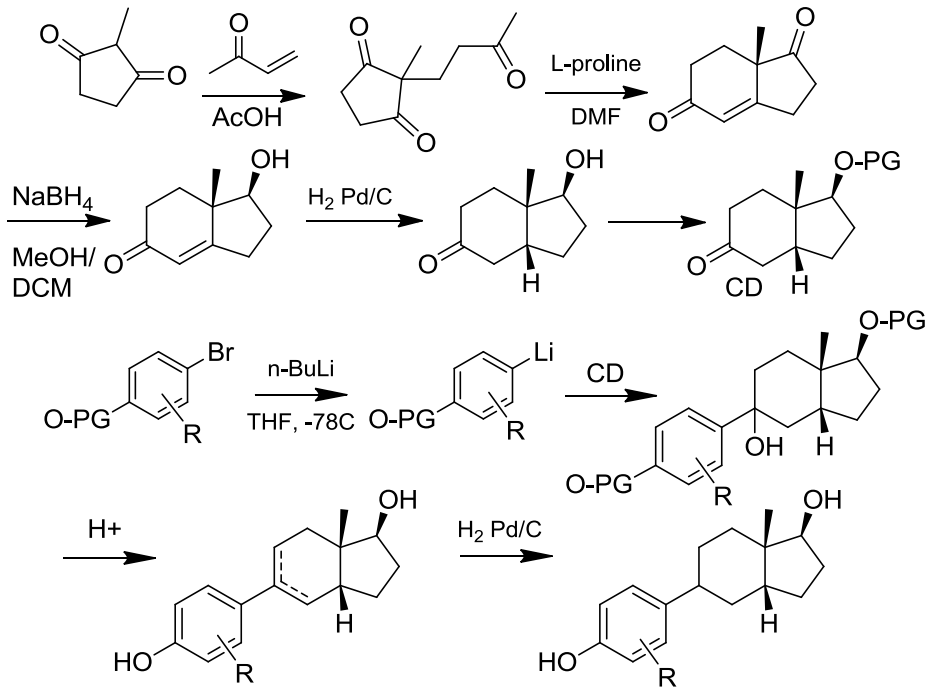
estradiol, leading to the designate name of "super estrogen". However the downside of these estrogen agonists was the low selectivity for the receptor ERβ compared to ERα (β/α) ranging in the value of around 2. Similar results were obtained with F attached at the same position, with RBAβ receptor binding reaching 136, with slightly better comparable selectivity as the CF_3 series. Indeed, these results further strengthened the desire to have EWGs at the C-5 position.

In the beginning of the A-CD project, the original target was to construct a prototype with similar skeleton structure as estradiol i.e. with a *trans* CD junction as this was expected to give closer activity to the natural ligand. However in the first synthesis a *cis* A-CD was produced unknowingly and proved to show significant selectivity for ERβ. Synthesis of *trans* followed and RBA results suggested lower affinity to both receptors in most cases and decreased selectivity.[13] The following **Table 1.0** depicts some of the key results comparing *trans* and *cis* compounds.

Table 1.0 RBA values to ER α and β for *cis* and *trans* A-CD compounds with selectivity ratio.[13] Compounds are described with indication of substituent and position number.

Compound	***cis* A-CD Structure**			***trans* A-CD Structure**		
	ERα	ERβ	β/α	ERα	ERβ	β/α
Parent H	1.47±0.26	21.5±14.6	14.6	2.38±0.19	10±1.13	4.2
4-F	1.04±0.09	8.7±1.5	8.4	1.68±0.15	6.84±0.41	4.1
5-F	27.3±0.70	135.5±7.3	5	4.22±0.06	13.6±0.35	3.2
4,5-di F	4.62±0.93	42.8±5.5	9.3	0.92±0.15	7.3±1.8	7.9
2,4,5-tri F	0.186±0.01	1.73±0.02	9.3	0.029±0.004	0.097±0.025	3.3
5-CF_3	89.7±13.8	205±23	2.3	4.8±1.1	4.9±0.1	1
5-CH_3	2.82±0.45	33.6±6.2	11.9	0.47±0.1	1.3±0.3	2.8
5-OH	0.26±0.07	3.97±0.08	15.3	0.037±0.003	0.15±0.04	4.1

Points worthy to be made include stronger affinity to ERα by parent *trans* at 2.38 compared to 1.47 for *cis* with the same phenomenon observed for compound 4-F. The rest of the results on the other hand suggest decreased affinity and selectivity across the board albeit 4,5-diF did show considerable selectivity for the *trans* (7.9). In terms of average selectivity ratio, *cis* compounds gave 9.1 compared to 3.7 for *trans* ligands which simply put concludes that *cis* is 2.5 more times more selective than *trans*. A final note of interest was the large difference in affinity for CF_3 due to the change in the bend of the molecule. Indeed values for ERβ dropped from 205 in *cis* to 4.9 in *trans*, representing 41 times less affinity.



Scheme 1.1 General synthetic route for the A-CD compounds.

1.5 Homo A-CD Estrogens

As seen in the previous work done by the group with regards to the A-CD estrogens, promising results were obtained providing a hopeful future for HRT. Although it was

possible to obtain compounds with activity stronger than estradiol itself, both in binding and transcription, the key to having the "perfect" compound lies in the selectivity between ERα and ERβ. In the series in which the CD ring fusion was *cis*, as exemplified by the parent compound **2** obtained the best selectivity β/α 14.6 and all subsequent compounds failed to improve in this aspect significantly. As a result the idea of modifying the current skeleton of the A-CD prototype came to being by increasing the size of the D ring from 5-membered to 6-membered.

The logic behind such design was inspired by considering the structural differences between compound **1** and **2**. As mentioned previously, the original intention was to synthesise **1** due to its similar flat shape to estradiol. However **2** was synthesised instead but proved to have better activity and selectivity. The main difference lies in the spatial arrangement of the D ring caused by the inversion of stereochemistry of the carbon at position 14. Indeed a switch of stereochemistry at that position results in a significant bend in the molecule. It is thought that exaggerating this "kink" by increasing the ring size would accentuate that bend even more and increase ERβ selectivity if that were a key reason for the selectivity. The following **Figure 1.8** aids in demonstrating the aforementioned structural features.

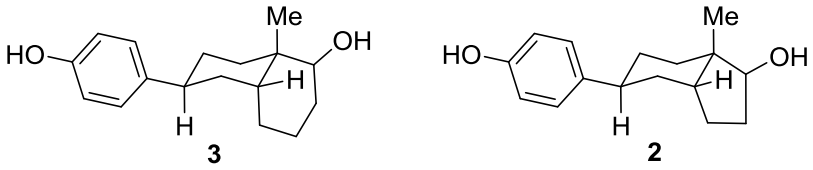


Figure 1.8 Depiction of the parent compound **2** and homo parent **3** in chair conformation.

Further rationalizations involved superimposing molecular models of the parent CD-*cis* fused A-CD **2** with the proposed homo analogue **3** in order to assess differences in the

spatial distribution of the atoms, specially the key hydroxyl group at position 17. Indeed its position and its distance to the C3 OH group are paramount in the binding of the ligand.[14] Superimposing the two models indicated that the 17-OH in **2** and **3** had very similar orientations.

Finally, computational calculations were performed by Wright and coworkers, as has been done before in the group with similar compounds.[12] Calculations attempting to predict RBAs seemed to yield a promising future for the homo A-CDs. The optimism arose from the fact that the binding affinity is greatly dependent on the logS (solubility parameter) therefore the addition of the methylene group should decrease the aqueous solubility. This effect in return would lead to increased binding affinity. Preliminary calculations gave RBA values for ERα at 35% with values of up to 468% for ERβ. This represented a ratio β/α of 13.6 for the parent homo A-CD which was promising when comparing with the previous A-CD series.

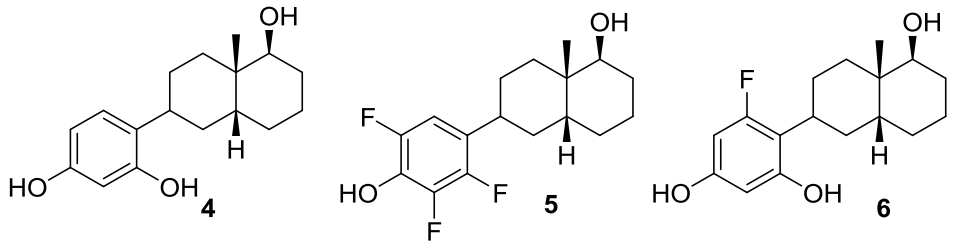


Figure 1.9 Other targets for the homo A-CD used for computational calculation of RBA values.

Further calculations for other potential targets were performed, including for homologues from the 6-5 series TD81 and L17, with RBAs of 358/33 β/α (15.4 ratio) for target **4** and 54.4/26.5 (2.05) for **5**. Moreover, target **6** was subject to the same process as the previous and led to surprisingly high values, ranging up to 100 times more active than estradiol. In this regard Wright wrote:

> "Binding affinity data: RBA for compound above in ERbeta is predicted to be 9650% !!!No that is not a misprint. The extra F-atom at 1-position (actually it is at the 5-position) fits perfectly into the receptor. I used a new method to generate conformers, there are more of them now although every one i have examined is of the chair-chair type. There are now 124 starting conformers so there are 124x90 docked poses = 11,160 poses to generate and dock, so this will probably take about a day. The intermediate output i have generated so far is only up to conformer no. 16 lowest (out of 124 total so the predicted RBA can only get better (or stay the same), but not worse. This means that by combining the 1a-homo frame (improves binding) with the 5-OH and the 1-F group we are predicting that the binding to ERbeta is almost 100x greater than E2".

This was explained due to the F atom fitting in perfectly into the receptor when looking at the generated surface maps of the compound bound into the receptor (see **Figure 1.10**). Although some scepticism arose from the latter set of data, the project looked promising especially that the synthesis would be straightforward and similar to the method used for the previous A-CD series.

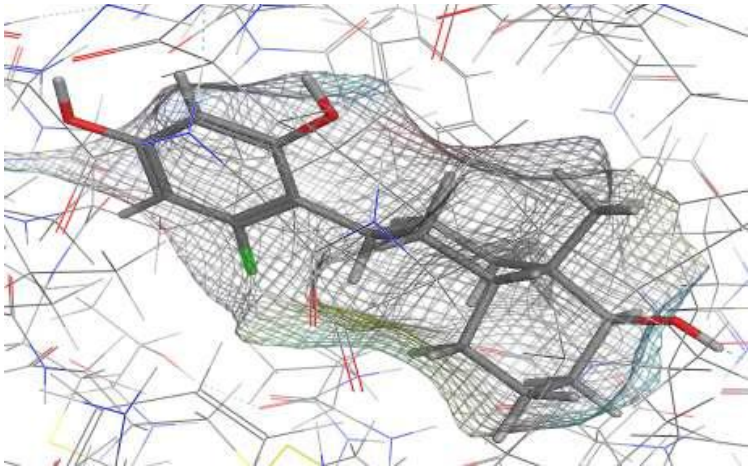


Figure 1.10 Surface map of compound **5** in ERβ obtained by Wright.

2.0 RESULTS AND DISCUSSION

2.1 Introduction

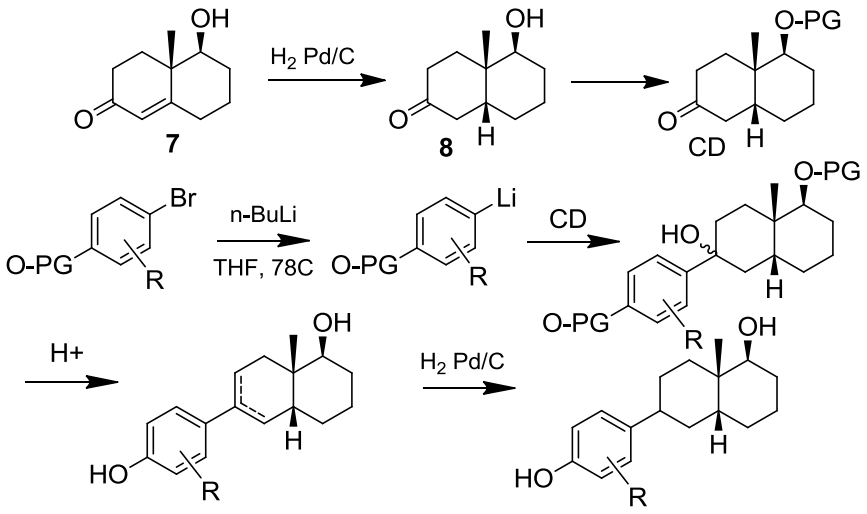
As discussed in the Introductory Chapter, the hypothesis behind expanding the D ring in the A-CD estrogens from 5 carbons to 6 carbons originated from the observations that compounds having the *cis* CD junction proved to increase selectivity for ERβ over ERα when compared to the isomers with a *trans* CD ring fusion; which is the sought-after effect. This *cis* ring fusion gives the compounds a bent shape at the CD ring junction. Increasing the D-ring size should increase the effect of the bend and in the best case increase selectivity.

Estrogen receptor docking simulations conducted by Dr. Wright at Carleton University yielded encouraging results with higher potency and selectivity for select targets (see previous Chapter). We were excited by those numbers since they indicated very potent overall binding and good to excellent selectivity for the β receptor. Even at one tenth the potency values, the D-ring homo-CD ring *cis* fused compounds promised to have excellent potential, certainly well worth the effort required to prepare them.

2.2 General synthesis

The synthetic route for the preparation of the various compounds in the homo series was anticipated to be the same used in the synthesis of the original A-CD ligands, with the only difference being the size of the D ring. The CD ring moiety would be obtained via the Hajos-Parrish method, and both the 6-5 and 6-6 ketone series have been previously synthesised with ease.[15] The remaining steps would be the same sequence as before, with A ring preparation with desired protecting groups and subsequent coupling to the CD ring

ketone. Finishing the synthesis would in most cases require acid treatment to cause dehydration followed by hydrogenation. The following **Scheme 2.1** depicts the overall synthesis starting with the CD ring ketone **7** or **8**.



Scheme 2.1 Overall synthesis of homo A-CD compounds starting from CD ring ketone.

2.3 Synthesis of OH protected CD rings 9 and 10

The Hajos-Parrish ketone **7** was prepared on a large scale using the method originally published by the authors and previously used by the group to give comparable yields (overall 22%). The selective reduction of the cyclopenanone over the enone carbonyl resulting in the generation of the C17 β OH group was adapted from our group's work on the original 6-5 series. The angular methyl group blocks the approach from top face resulting in the hydride adding *trans* to the CH_3, as described by Ward and coworkers.[16] Structural confirmation was later achieved by the x-ray crystallography.

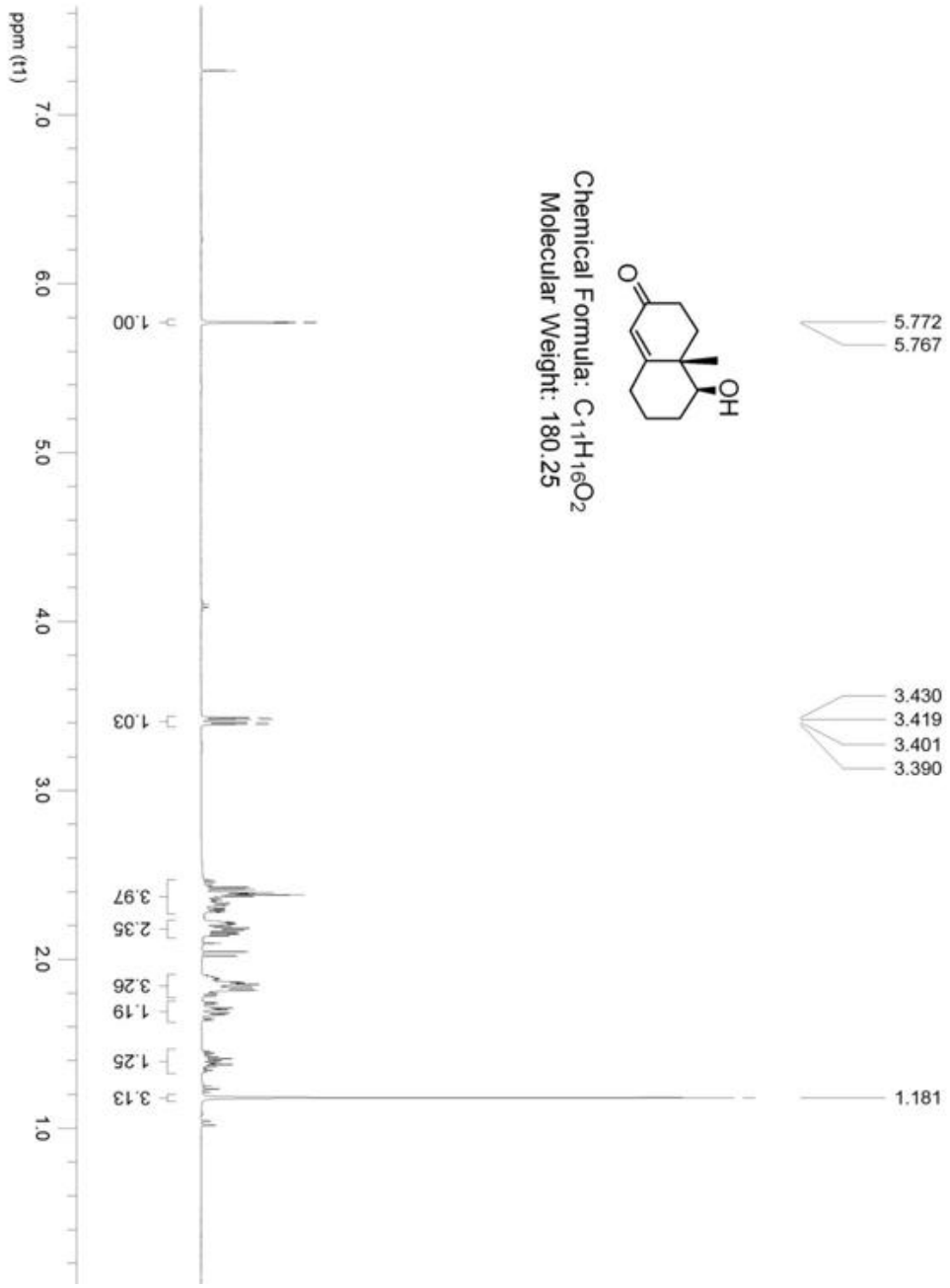


Figure 2.1 ^{1}H NMR of CD ring ketone **7** taken in $CDCl_3$ at 400MHz.

Since the intramolecular Aldol condensation was catalyzed with l-proline it was anticipated that **7** would be formed with high enantiomeric excess and the CHOH carbon would have the desired *S* stereochemistry. The enantiomeric purity was determined by converting it into its Mosher ester using a standard procedure starting from (*R*)-(+)-α-

methoxy-α-(trifluoromethyl) phenylacetic acid ((+)-MTPA). The ee was determined via the ^{19}F resonance of the CF_3 groups in the diastereomeric esters. The ratio of the two peaks was approximately 6:1 (see **Figure 2.2**) which translates to an enantiomeric excess of 74%. While not spectacular (the literature reports an average ee of 76%)[17], the enantiomeric purity was deemed to be adequate at this stage of the project. In the event that the compounds showed desired potency and β/α selectivity we planned to revisit this step in order to increase the enantiomeric purity either by further investigation into the enantioselective cyclization of **6** to **7** or converting **7** into a set of diastereomeric esters followed by separation and regeneration of enantiomerically pure **7**.

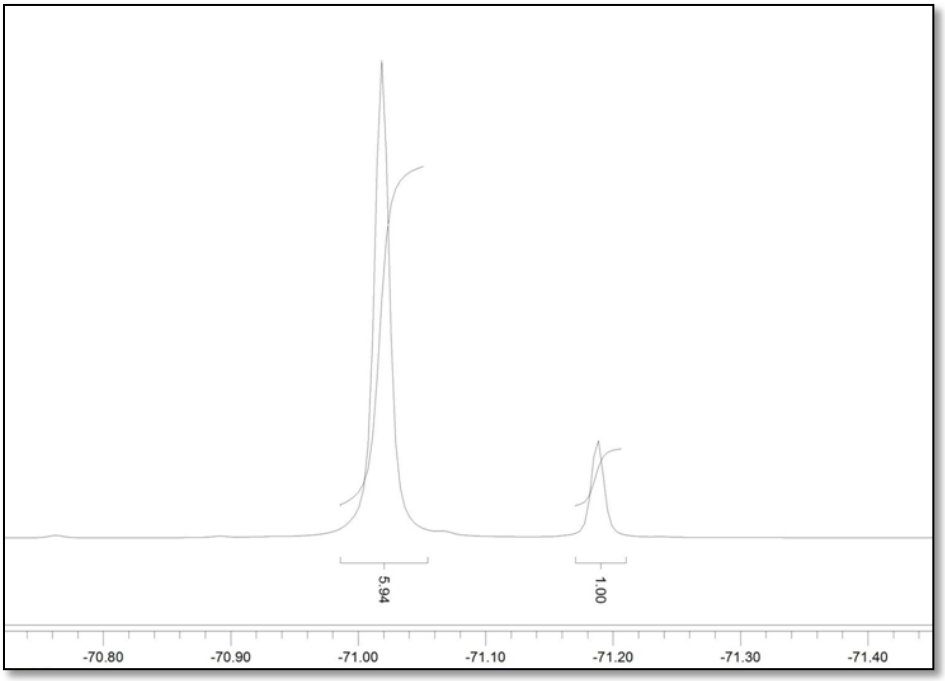


Figure 2.2 ^{19}F NMR of the Mosher ester of Hajos-Parrish alcohol depicting integration of the CF_3 group for optical purity determination.

In the synthesis of *trans* CD ring compounds, the free OH group was protected via the standard method using chloromethylmethyl ether and diisopropylethyl amine giving

yields at around 86% in several different examples.[18] Hydrogenation of the unprotected alcohol **7** yielded a 3:1 mixture of **8a** and **8b** having the *cis* and *trans* geometry at the CD ring junction respectively. It proved to be difficult to separate the two components by flash chromatography. The ratio was determined based on the integration of the methyl peaks of each isomer, with *cis* located at 1.13 ppm and *trans* at 1.01 ppm (see **Figure 2.3**).

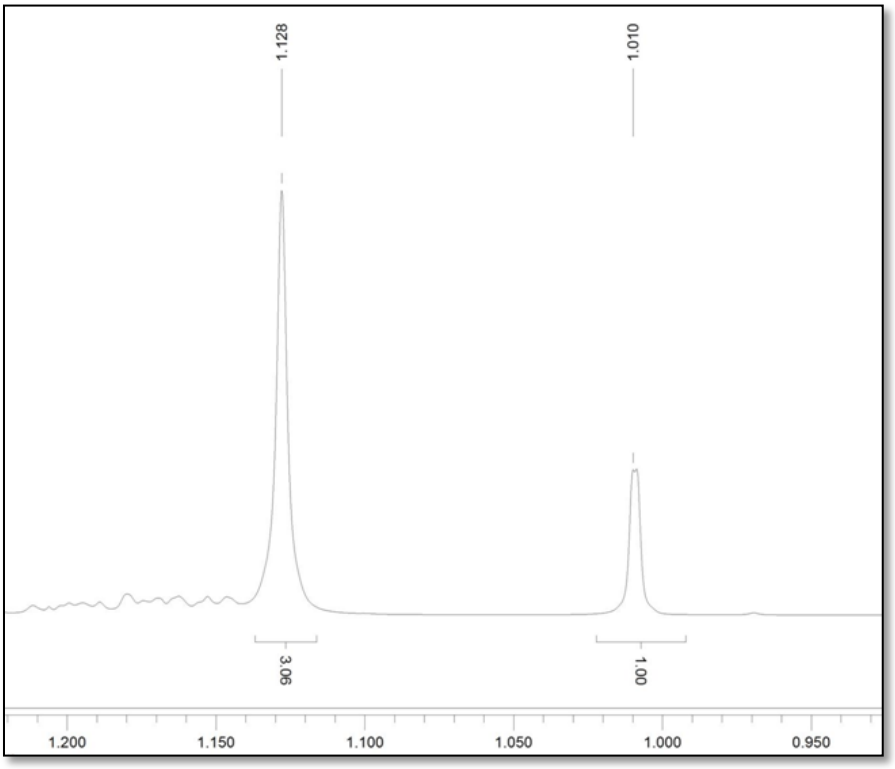
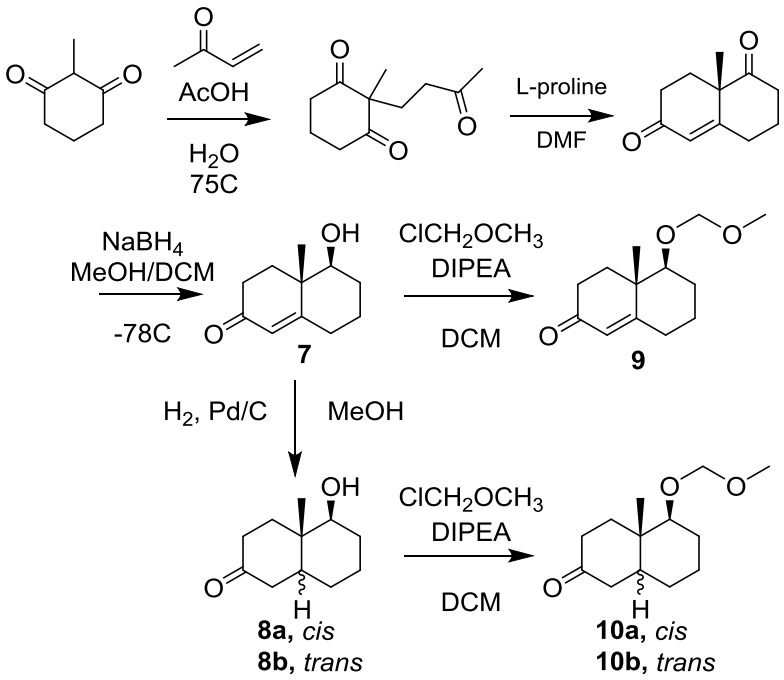


Figure 2.3 ^{1}H NMR of saturated Hajos-Parrish alcohol with attention to the methyl peaks of both *cis* and *trans* with chemical shift and relative integration.

The isomeric mixture was protected using chloromethymethyl ether once again obtaining excellent yields (93%) and coupling reaction ensued. It is noteworthy that following the coupling reaction there is a significant polarity difference between the two CD ring isomers which is easily separated by column chromatography.



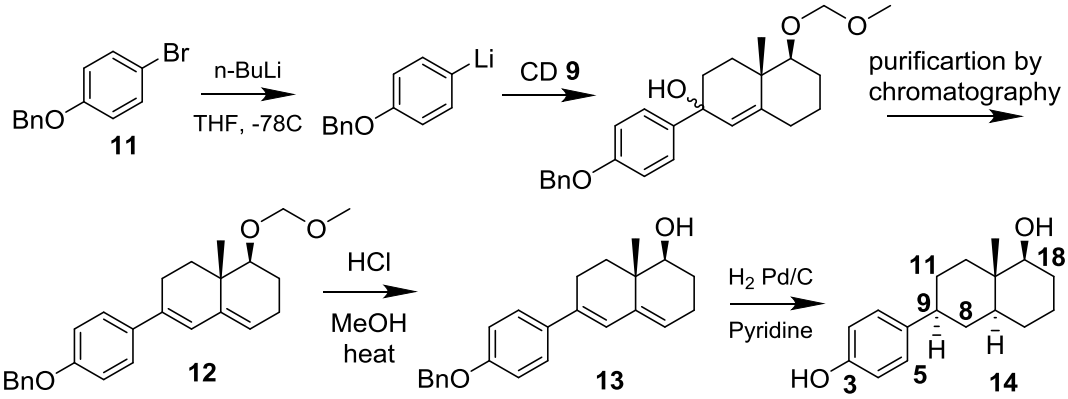
Scheme 2.2 Synthesis of the CD ring portion of the homo *trans* and cis A-CD compounds.

2.4 Synthesis of parent homo A-CD compounds

2.4.1 Synthesis of the *trans* homo CD ring A-CD isomer **14**

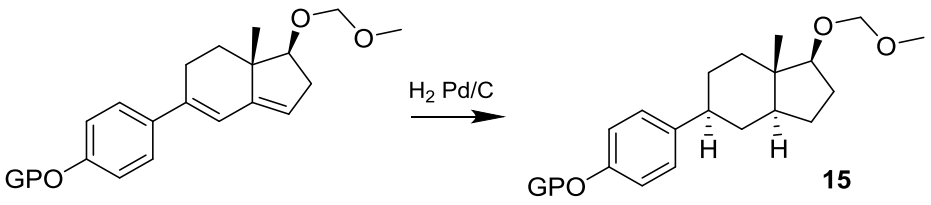
The synthesis of compound **14** was quite straightforward; it is shown in **Scheme 2.3**. The A ring moiety **11** was prepared in 88% isolated yield by simple benzylation of 4-bromophenol. The coupling reaction required a bromine-lithium exchange in **11** with nBuLi in THF at -78^{o}C. This was followed by the addition of the protected enone **9.** The resultant crude adduct was subjected to silica gel chromatography which resulted in dehydration of the allylic-benzylic tertiary alcohol by the mildly acidic silica gel to give diene **12** as the only key product in 66% overall yield. The MOM protecting group was removed with HCl in refluxing MeOH to afford the benzylated diene **13** (45%). Finally hydrogenation saturated the diene double bonds and also removed the benzyl protecting

group to afford the desired parent CD *trans*-fused compound **14.** The overall yield of **14** based on protected CD ring **9** was 18%.



Scheme 2.3 Synthetic route to parent target, compound **14** having the *trans* CD junction.

Hydrogenation, with the use of a heterogeneous catalyst (Pd/C), occurs preferentially from the bottom phase due to the flat nature of the molecule since the CH_3 and OH groups hinder the top phase. The formation of the (9*R*) stereochemistry as the major isomer in the hydrogenation of **13** was expected based on our laboratory experience in the synthesis of the parent *trans*-fused compound **15** containing a 5-membered D ring (see **Scheme 2.4**).[13] The final product compound **14** was purified by recrystallization in EtOH. The steroid numbering system adapted for this homo series is shown in structure **14**. This system is used to allow facile comparison with steroids and the original A-CD series. The key change is that in steroids and the A-CD compounds the OH in the ring D is at position 17 whereas in the homo ring D compounds described in this thesis the OH group is C18.



Scheme 2.4 Hydrogenation of diene in previous 5-membered D ring A-CD series

Structural confirmation was based on the same key pointers as in the previous A-CD series – that is the chemical shifts of the methyl and C18 H signal in the D ring. As seen in **Figure 2.5** the former appears at 0.86 ppm while the latter is represented by a distinct doublet of doublets in the region of 3.14-3.18 ppm.

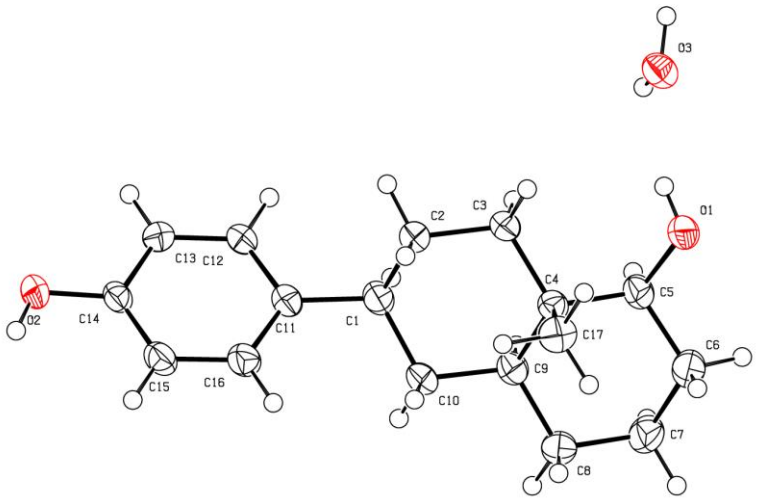


Figure 2.4 X-ray crystallography of *trans* compound **14** with H_2O molecule H-bonded to C18 OH obtained by Korobov.

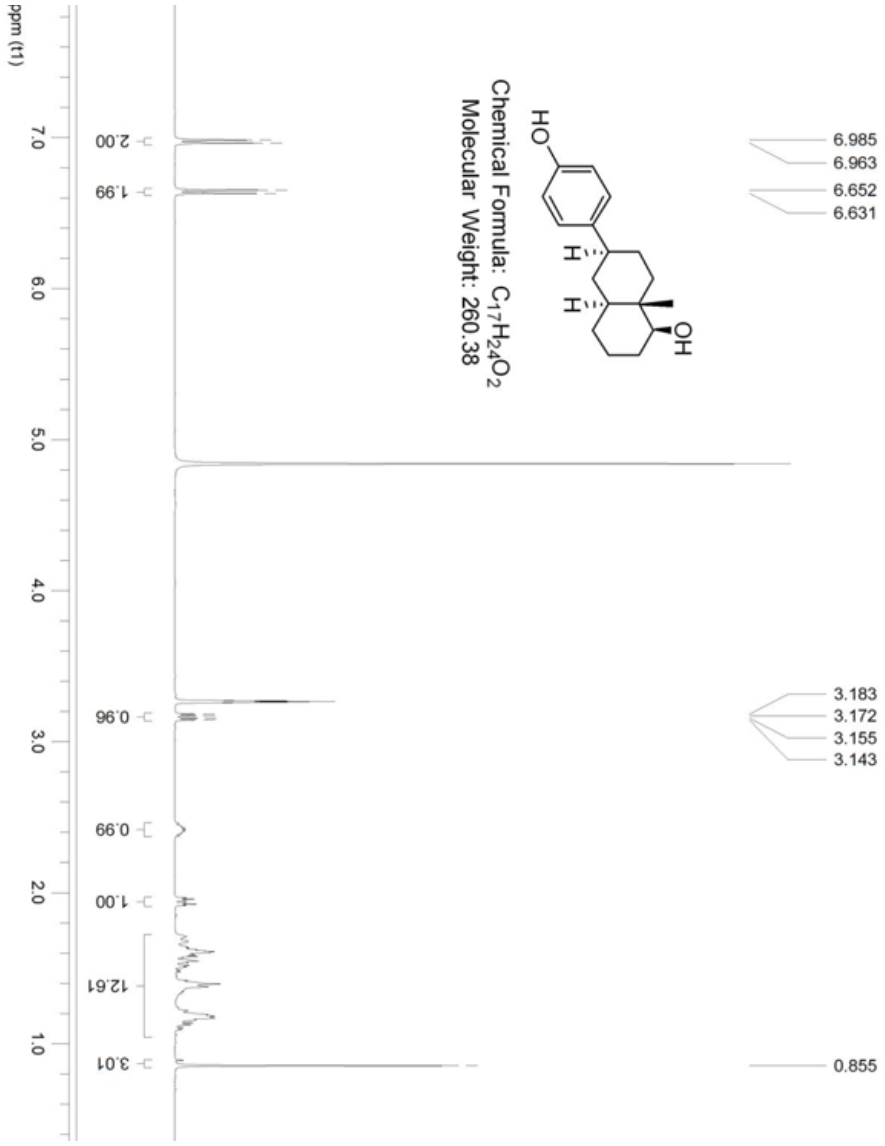


Figure 2.5 ^{1}H NMR of *trans* parent **14** taken in MeOD at 400MHz.

The structural assignment of **14**, the first in this series, was confirmed by a single crystal X-ray determination carried out by Dr. Ilia Korobov. The structure showing in **Figure 2.4** shows conclusively the *trans* CD ring geometry and the "natural" steroid arrangement in which the 9-H is *trans* to the quaternary methyl group at C13 (steroid numbering).

It is also interesting to note is that the plane of the aromatic ring in the crystal structure of **14** is essentially perpendicular to that of the C ring plane. This same feature was noted in

analog **16** in which the D ring is five rather than six-membered (**Figure 2.6**). The results of the bioassays measuring the binding of **14** and of all the other new compounds synthesized in this thesis will be presented and discussed at the end of this Chapter.

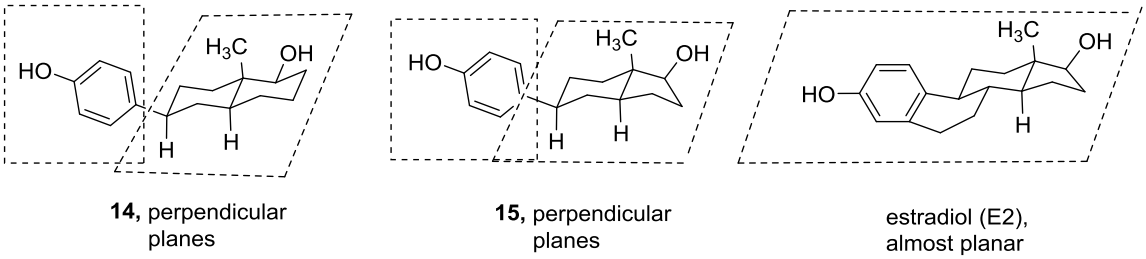


Figure 2.6 Perpendicular planes of A ring and CD ring shown for **14** and **15** in comparison to E2.

2.4.2 Synthesis of *cis* CD-fused A-CD compound **3**

The synthesis of CD *cis*-fused compound **3** commenced with the addition of lithio derivative derived from **11** to the hydroxyl group protected *cis*-fused CD ring **10**. As above the coupling reaction was straightforward resulting in a diastereomeric mixture of the tertiary alcohols at C9 with a respectable yield of 77%. Treatment of this intermediate with acid in order to remove the protecting group gave an unexpected product in addition to the desired mixture of alkenes **18**. The deprotection of **16** took more time than expected. The progress of the reaction was monitored by TLC which showed the formation of a less polar product. It was first thought that this was simply the result of dehydration of the tertiary alcohol at C9 without deprotection of the MOM group. Since this less polar spot on TLC only increased in importance with time the reaction was stopped and the mixture was purified in order to isolate the intriguing product. This unknown compound was obtained as a soft white solid, similar to $MgSO_4$. The ^1H NMR indicated the absence of the H at C17 with no signal appearing between 3.0 and 4.0 ppm.

Except for the $PhCH_2$-O group, the most downfield non aromatic signal integrating to 1H appeared at 2.86 ppm; finally the angular methyl peak was significantly deshielded to 1.28 ppm compared to that in **10** and in intermediate alcohol **16** (1.04 ppm). The upfield portion of the ^1H NMR is shown in **Figure 2.7**.

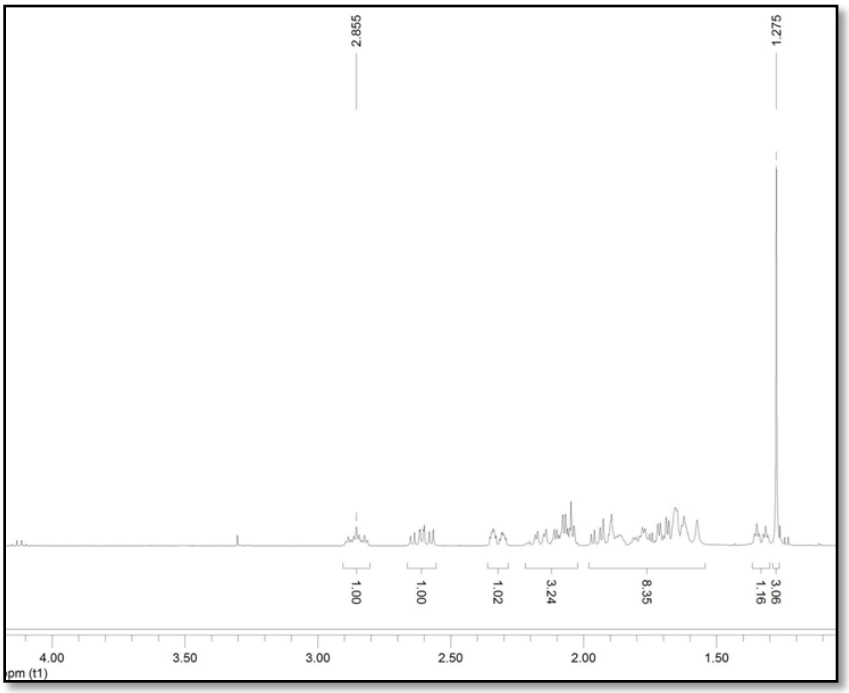


Figure 2.7 ^1H NMR of ketone **16** showing the spectral region lacking C17 H with appearance of benzylic H and shifted methyl peak.

The carbon-13 spectrum showed a peak at 216 ppm indicating that at a carbonyl was present in the molecule. These data and the molecular formluar: $C_{24}H_{28}O_2$ (HRMS) led to the assignment of structure **17** to this compound. The only plausible explanation for its formation was a hydride shift of the H from C18 to the carbocation created at C9 either by loss of water or reprotonation of the alkenes **18**. The transfer of a hydride from C18 to C9 is accompanied by loss of the hydroxyl protecting group. Long range hydride shifts have precedents in this literature; a relevant example is shown below from Prelog and

coworkers in 1956 (**Figure 2.8a**).[19] This was the earliest example of such hydride shifts involving the formation of a ketone.

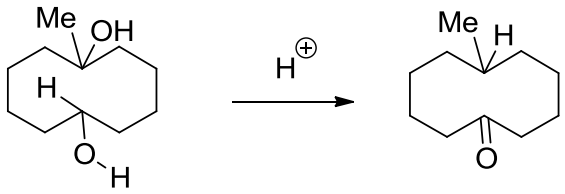


Figure 2.8a Example of a transannular hydride shift through space resulting from dehydration at a tertiary position.

Although the above example depicts a hydride transfer across one ring, work done by Parker and Stevenson in 1969 showed a similar reaction taking place in a bicyclic system; a scaffold much more analogous to the homo A-CDs (see **Figure 2.8b**).[20] This hydride shift was later explored in more detail and will be discussed in a subsequent section.

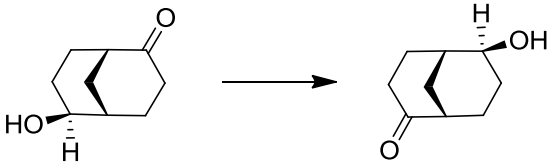
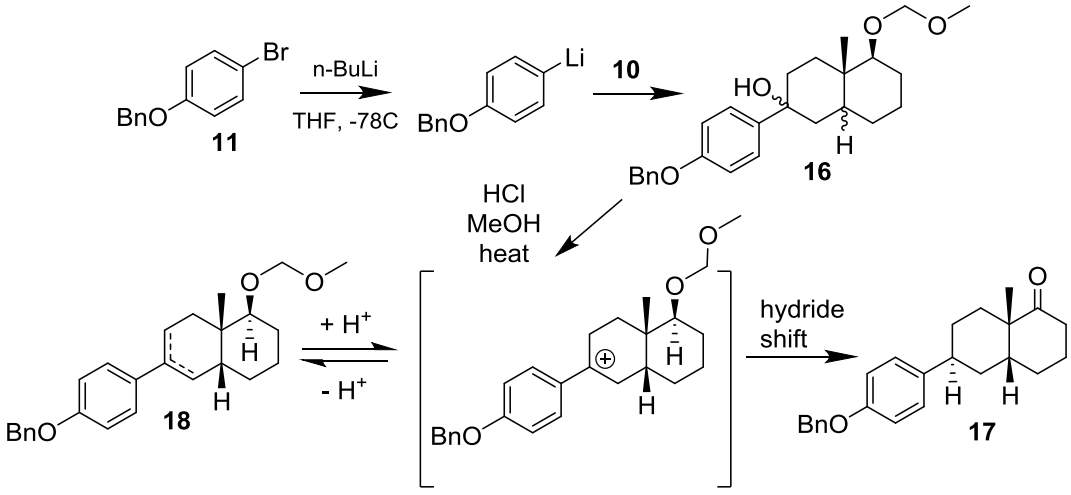
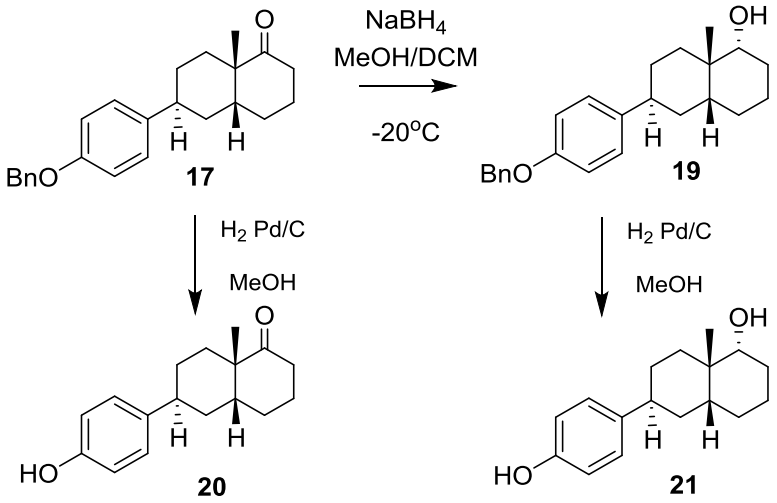


Figure 2.8b Example of a transannular 2,6-hydride shift in a bicyclononane system.



Scheme 2.5 Coupling reaction with saturated CD ring in the synthesis of **3** followed by acid treatment resulting in the hydride shift.

This unexpected reaction installed the desired *S* C9 stereochemistry which saved us the often problematic separation of isomers following the hydrogenation; which required preparative HPLC in most cases. The next step seemed trivial at first since it entailed a reduction of the carbonyl at C18, where it was first thought that the hydride would add from the back face, away from the methyl group, as it does in typical steroid 17-ketone reductions. Sodium borohydride reduction of **17** regenerated a C18 hydroxyl group as confirmed by proton NMR, however the hydride was deemed to have added from the front face as determined by the pattern of the doublet of doublets (*J*= 4.4 and 11.6, axial-equatorial and axial-axial coupling). Both ketone **17** and alcohol **19** were hydrogenated to remove the benzyl protection. The resultant products, **20** and **21**, were sent for bioassays in order to compare their binding activities to the estrogen receptors with estradiol.



Scheme 2.6 Reduction of ketone **17** to the final compounds **20** and **21.**

More careful analysis of the model of **17** made it clear that the more accessible face of the carbonyl was the frontal one as the axial hydrogens would be the only source of hinderance. Due to the bend in the ring system caused by the *cis* fusion of the C and D

rings, the back face has a methylene group hindering the path to the carbonyl. The following **Figure 2.9** helps visualise the hydride attack on the carbonyl from both faces.

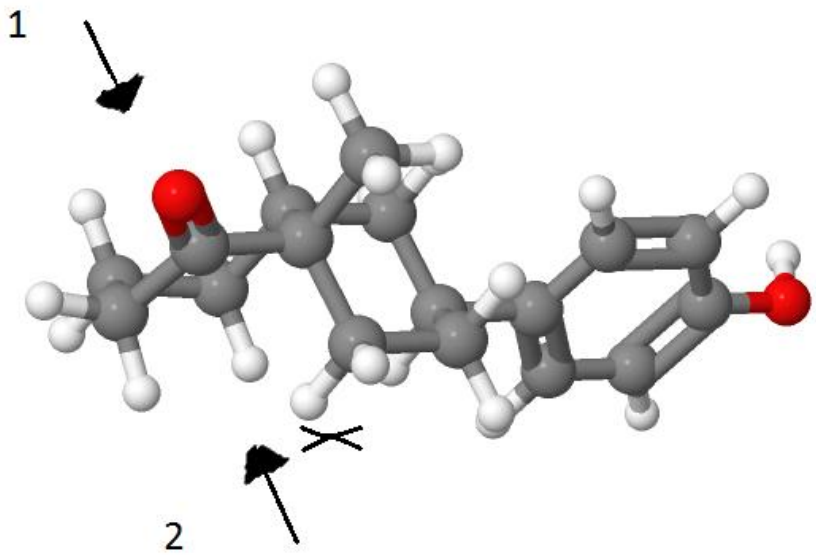
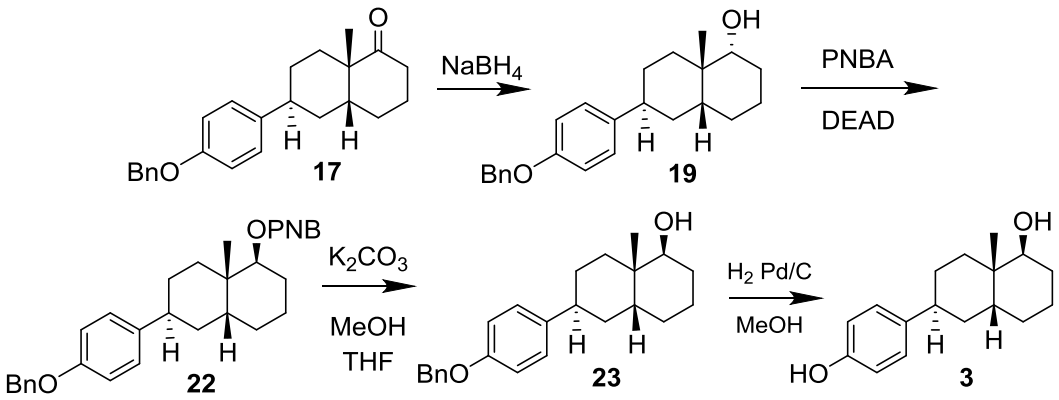


Figure 2.9 Hydride attack in the reduction of **17** (back view) with 1 representing the front attack and 2 representing the addition from the back with steric hinderance apparent in the latter.

What remained to be done in order to complete the synthesis of **3** was inversion of the C18 alcohol and deprotection of C3 OH. This was accomplished using the well established Mitsunobu reaction, first reported in 1967.[21] Indeed, the nucleophile attacking from the same face as seen for the hydride should be quite favourable and afford the desired stereochemistry at C18. Model studies of the Mitsunobu reactions were carried out on readily available estradiol (E2). Initial attempts gave yields of the inverted intermediate ester of only 15% when using estradiol (E2) as the substrate; the same reaction conditions gave alcohol **23** in 24% yield. Considerable efforts were made to optimize these transformations using estradiol as the model compound. Eventually conditions adapted from Dodge and coworkers[22] were employed. This utilized toluene as solvent with slow addition of the diethylazodicarboxylate (DEAD) at room temperature,

followed by heating at 80°C for two hours after. For compound **3**, this optimization gave yields of up to 77%. Hydrolysis of the *p*-nitrobenzoic ester and removal of the benzyl group resulted in the formation of parent homo A-CD **3**. The overall yield in the final two steps was 48%. We assume that this compound and its precursor **20** and **21** have an ee of about 74, the same as determined for the enone **7** since no enantiomeric enhancement or dilution should have taken place in the subsequent steps.



Scheme 2.7 Completion of synthesis of **3** via C-18 OH inversion using Mitsunobu.

The proton NMR of **3** confirmed the structure, with the methyl group appearing at 1.158 ppm, downfield from 1 ppm which is characteristic of *cis* CD ring compounds in the parent A-CD having the *S* configuration at C9. Compounds in which the methyl signals appear at higher field than 1.0 ppm have the *R* configuration. Another indication of the desired stereochemistry is the C18 H appearing between 3.2 and 3.5 ppm. Moreover there are key differences in methyl and C18 signals in the carbon spectra (see **Table 2.1**) which are reminiscent of the original A-CD series where the methyl signal appeared at 20 ppm while the homo analog displayed the same signal at 22 ppm. The full proton spectrum can be found in **Figure 2.10**.

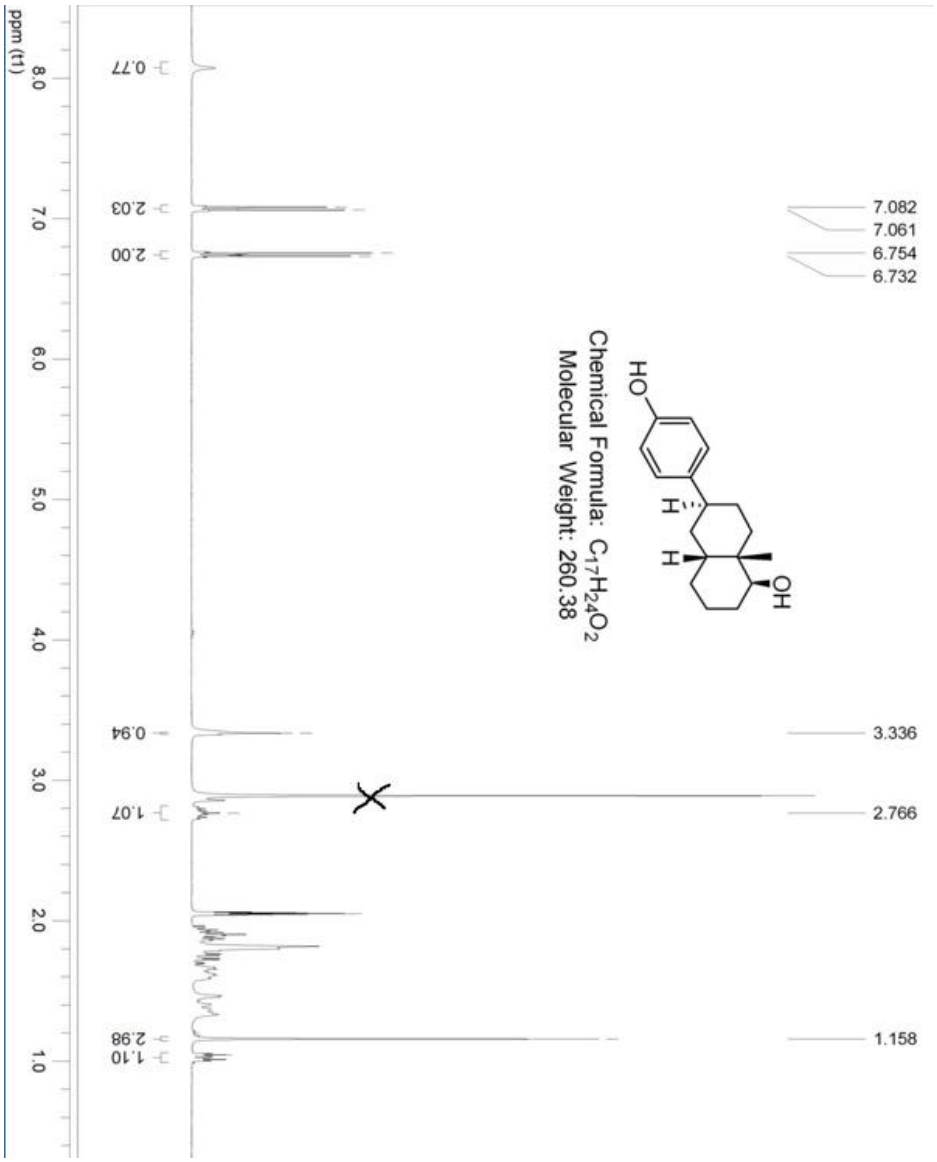


Figure 2.10 ^{1}H NMR of compound **3** in Acetone-d_6 at 400MHz.

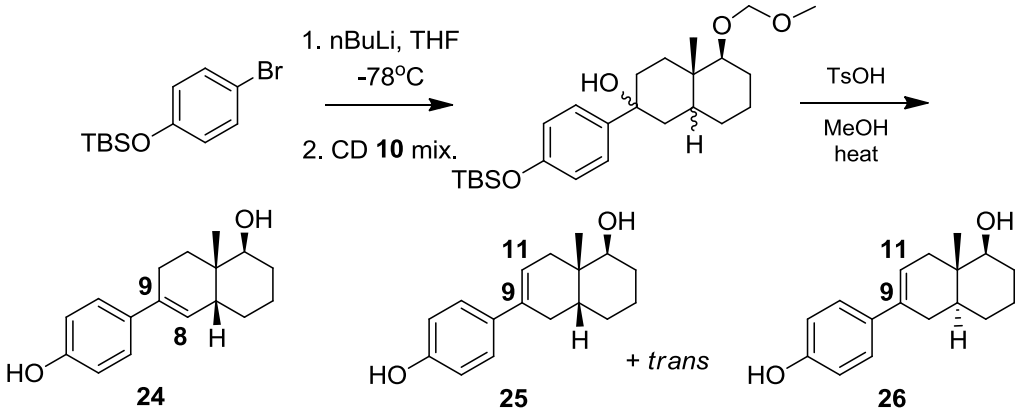
Table 2.1 Proton and carbon spectral data of distinct signals for parent **3** and **14**

	^{1}H NMR	
Signal	**14** (*trans*) δ (ppm)	**3** (*cis*) δ (ppm)
s (CH_3)	0.86	1.16

m (C-9 H)	2.418	2.77
dd (C-18 H)	3.12	3.34 (s)
d (C-1,5)	6.64	6.74
d (C-2,4)	6.97	7.0
^{13}C NMR		
CH_3	10.5	22.0
C-18	80.4	74.2
C-1,5	116.0	115.0
C-2,4	128.6	127.7

2.4.3 Synthesis of alkene isomers of *cis* CD ring A-CD **24** and **25**

To complete the parent series, compounds with unsaturations were synthesised by isolating the intermediates following the coupling reaction and acid treatment. In the previously discussed syntheses, a benzyl protecting group was used for the A ring which would be later removed by hydrogenation. However since the desired target contained an unsaturation the protecting group needed to be modified. To that effect, a TBS group was used due to its acid labiality making it easy to obtain the product following the condensation in one step, removing all protecting groups at once.



Scheme 2.8 Synthetic pathway to parent *cis* olefin **24** and **25**

As mentioned previously, CD ring **10** was synthesised as a mixture of *cis* and *trans* isomers. In this case the *cis* and *trans* isomers were not separated and therefore following the coupling reaction treatment with acid yielded mainly three isomers; the 8,9 and 9,11 olefin compounds, **24** and **25** respectively, with the *cis* CD ring, and the 9,11 isomer **26** with *trans* CD junction. A minor fourth peak appeared during the separation by HPLC which should represent the 9,8 alkene however its characterization was inconclusive. This caused a slight problem in terms of the purification since the polarities were very similar and separation by preparative HPLC only yielded compound **24** pure while the other isomer, 9,11 olefin **25**, was obtained contaminated with 10% of its *trans* isomer. The latter mixture was nonetheless sent for RBA testing in order to get an idea of the activity. No further purification steps were attempted to separate the isomers.

Structural determination was done based on results from previous work on the A-CD project. Based on the original A-CD analogs the 8,9 alkene, **24**, is expected to be the less polar compared to the 9,11 isomer while the CD *trans*-fused isomers are more polar than *cis*. Careful examination of the ^{1}H NMR of these compounds shows that the proton signal representing the unsaturation in the NMR of **24** has a much broader peak than that seen in the spectrum of **25**. This is expected since in **24** the C8 H is expected to couple to one H at the ring junction while in **25** the C11 H couples to the two protons on the adjacent methylene group.

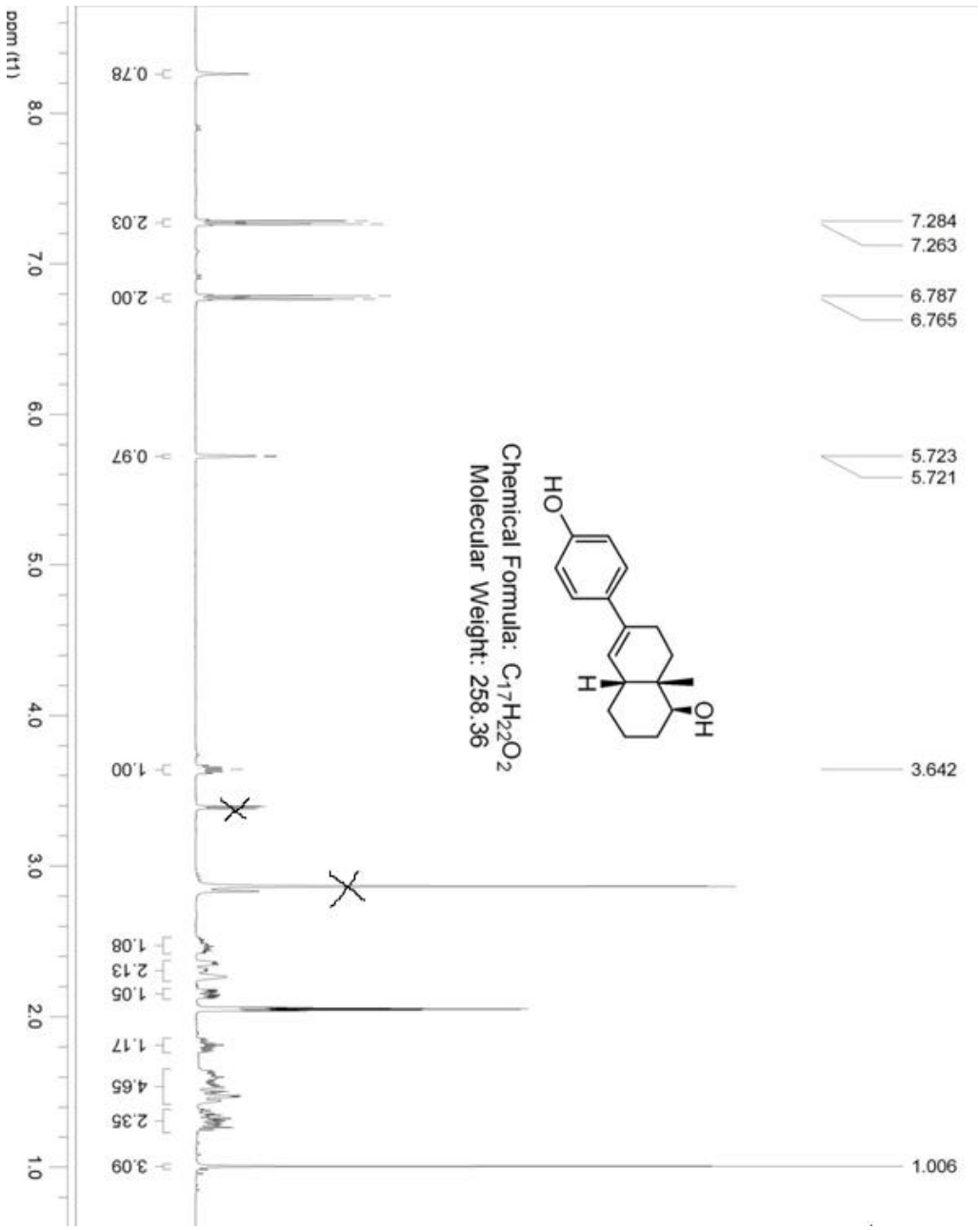


Figure 2.11 ^{1}H NMR of compound **24** in Acetone-d_6 at 400MHz.

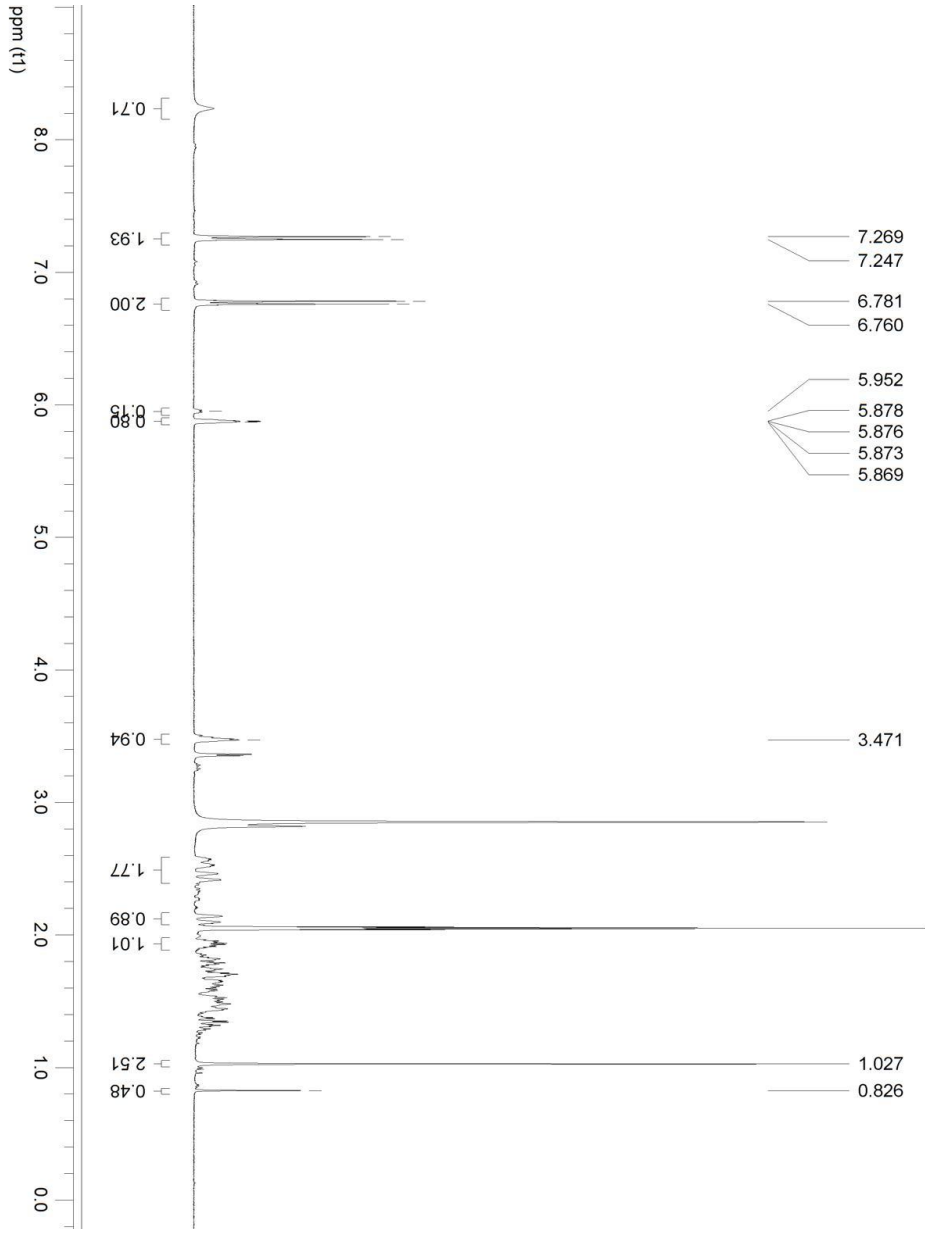


Figure 2.12 ^{1}H NMR of compound **25** in Acetone-d_6 at 400MHz.

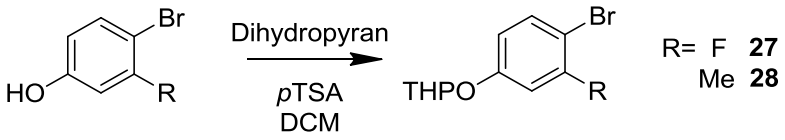
2.5 Synthesis of homo A-CDs with substitution at C5

2.5.1 Synthesis of the homo *cis* CD ring A-CD with Me and F at C5

During the original A-CD estrogen project, many substitutions were carried out on the A ring in order to determine which position would yield the most activity and selectivity.

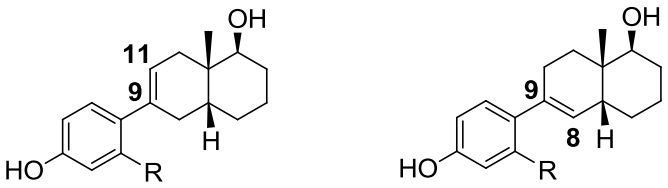
Through many trials it was found that a variety of substituents at position 5 substantially improved the binding to the estrogen receptors relative to the parent compound. In some cases such as with the 5-F, Cl, and CF_3 derivatives, the increase in potency resulted in a decrease in β/α selectivity. For other compounds such as the 5-methyl and 5-hydroxy derivatives, the β/α ratio was comparable to the parent compound.[14]

As a result several of the homologues from the 6-5 series were synthesised including compounds with CH_3, F, and CF_3 groups. Their preparation first required readying the A ring for the halo-lithium exchange reaction which usually required only protection of an available bromophenol. The commercially available 3-methyl-4-bromophenol and 3-fluoro-4-bromophenol were protected with the inexpensive 3,4-dihydro-*2H*-pyran (THP) to give **27** and **28** ,respectively, in about 75% isolated yield after purification on silica gel column (**Scheme 2.9**). The use of this protecting group would also allow access to the C ring alkenes since using a benzyl group requires hydrogenation for removal, which would saturate the alkene.



Scheme 2.9 Synthesis route for A rings of homo A-CD with C5 substitution with F and Me.

The remaining steps were straightforward. As usual the first step was bromine-lithium exchange on the protected 4-boromophenol in THF at -78^{o}C using *n*BuLi followed by addition of protected CD ring **10**. Treatment with HCl in MeOH removed both the protecting groups and caused dehydration to generate the desired olefins.



29, R= F
31, R= Me

30, R= F
32, R= Me

Figure 2.13 The two dehydration products obtained after acid treatment of coupled compounds.

The 8,9 olefins (**30** and **32**) were isolated by reverse phase preparative HPLC. As mentioned in **Section 2.4.3** the 9,11 alkenes were not obtained completely pure; compounds **29** and **31** contained 10% of the *trans* isomer (**Figure 2.13**). As was always the case in the original A-CD series, the *cis* isomers were less polar than the *trans* therefore in reverse phase the latter is isolated first. The 8,9 isomer proved to be the least polar of the two *cis* isomers as it was isolated last. This was confirmed by proton NMR by examining the olefin signal (see previous **Section 2.4.3**). Moreover, it was interesting to note that alkene 9,11 was always more dominant (2 to 3 times more abundant) compared to the second isomer as determined by integration of the olefin and methyl signals.

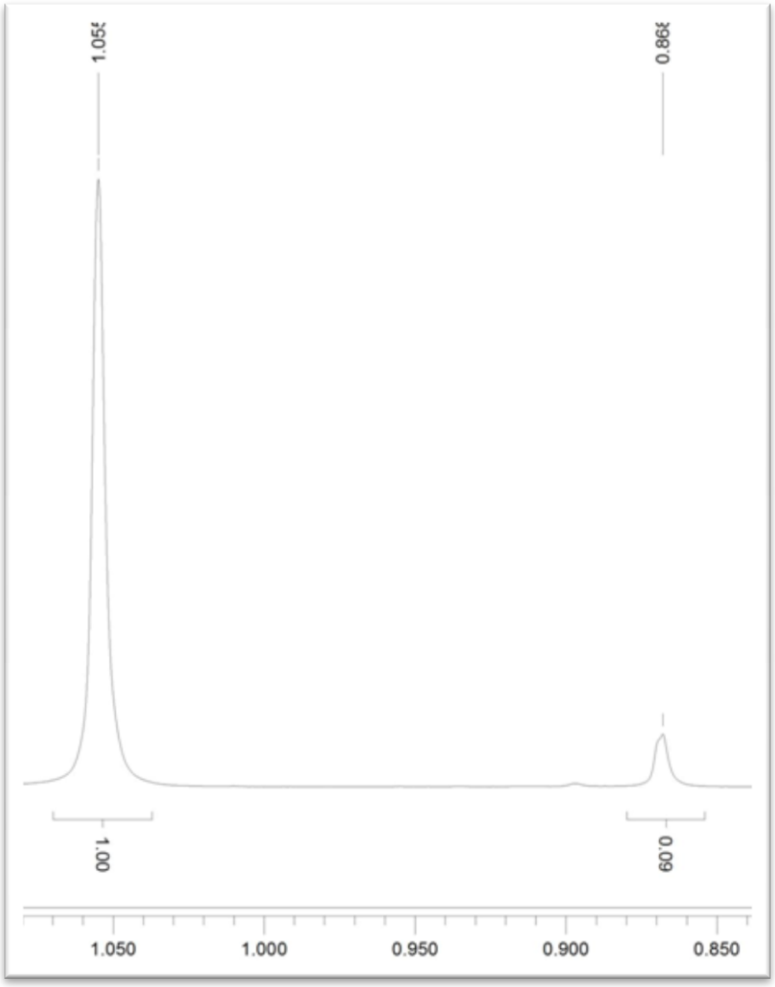


Figure 2.14 ^{1}H NMR of the methyl region of **29** showing methyl of *trans* at 0.87ppm.

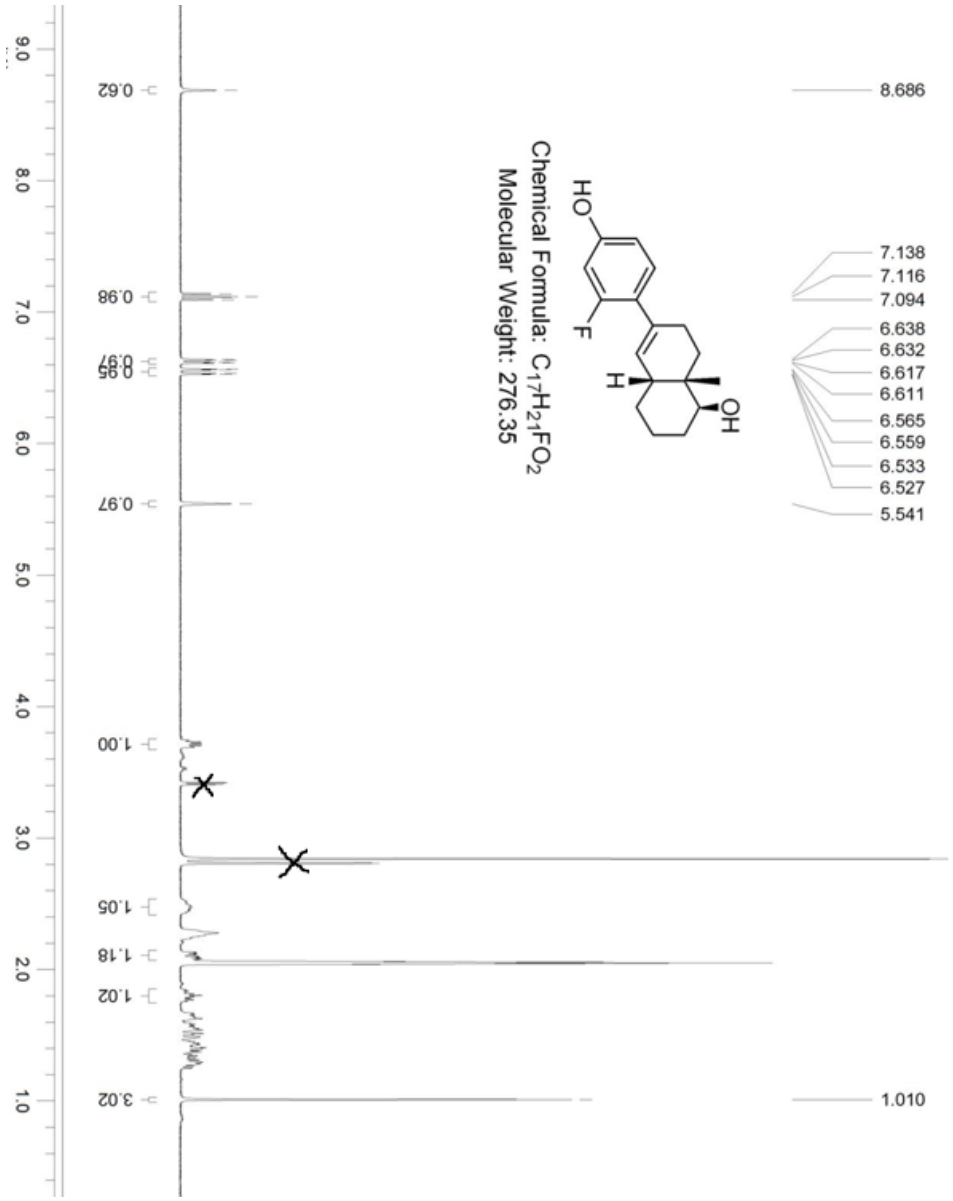


Figure 2.15 ^{1}H NMR of compound **30** in Acetone-d_6 at 400MHz.

As mentioned previously in this section, obtaining the saturated final compound was achieved in the same synthetic sequence as for the olefin products. As a result, starting from 8,9 and 9,11 alkenes, one could imagine straightforward treatment with H_2 and Pd/C to obtain the final compounds. This hydrogenation, which was supposed to be part of the original planned route as per the A-CD estrogens project, was expected to yield both the

"natural" and "non-natural" isomers (the former being *S* and latter *R* at C9). In the 6-5 CD ring *cis* series, hydrogenation of olefins usually yielded a ratio of 2:3 natural to non-natural isomer. This was explained by the bend resulting from the natural of the *cis* ring junction. Delivery of hydrogen by the catalyst is less favoured from the more hindered bottom face (face of the bend due to the *cis* fusion of the CD ring) compared to the top face which is affected by the angular methyl group resulting in mainly addition from the top to give the *R* configuration at C9.

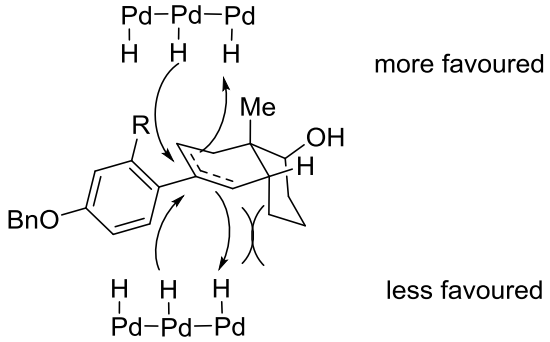
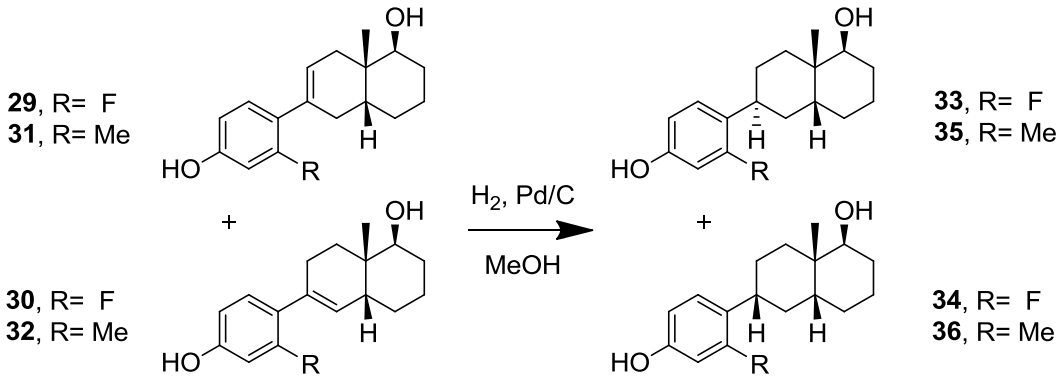


Figure 2.16 Hydrogenation of olefin compounds with approach from the bottom face less favoured due to steric hindrance with ring D.

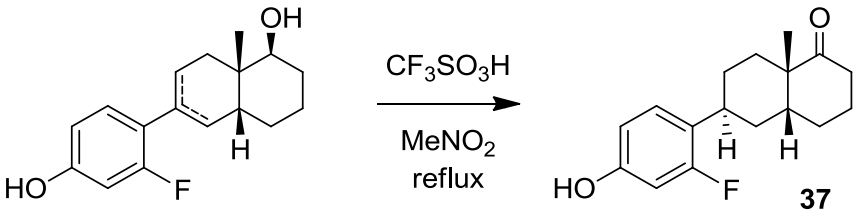
When the hydrogenation was performed on the 6-6 CD ring olefins, the majority of the product was the non-natural isomer (8:2 to 9:1). This distribution in product was rationalized similarly as mentioned above. In the present case addition to the bottom face is even more disfavoured relative to the top due to the more accentuated bend in the molecule (see **Figure 2.16**). It is noteworthy that the hydride shift resulting in the (9*R*) stereochemistry with concomitant formation of a ketone at C18 was not fully understood and reproducible at the time of these syntheses. The isomeric 5-F compounds **33** and 5-

CH_3 **35** were separated by careful flash chromatography. The NMR spectra of these compounds are reproduced in Appendix I.



Scheme 2.10 Hydrogenation of alkene mixture to obtain saturated 5-F and 5-CH_3

As described for the parent compound another approach to the (9*S*) compounds was via the C18 ketone obtained via the hydride shift accompanying dehydration of the initial coupling of the A and CD moieties. Following a study resulting in the optimization of the rearrangement reaction, the synthesis of the ketone version of 5-F was carried out on a 300mg scale of the alkene mixture **29** and **30**. After 40 minutes of reaction in refluxing $MeNO_2$ with catalytic amounts of CF_3SO_3H the ketone **37** was isolated as a yellow solid in 73% yield. Since the parent ketone **20** had shown acceptable potency with high β/α selectivity (see **Section 2.7**) the 5-F version **37** was thought to be a good candidate for bio-assay. Spectral data confirmed the desired product with the downfield methyl signal appearing at 1.23 ppm, characteristic of it being α to a carbonyl group (see **Section 2.6**); the benzylic proton occured at 3.18 ppm and no C18 proton was present. Carbon NMR depicted a ketone signal at 215 ppm, further assurance that the rearrangement product was obtained. In this case since the 5-F (9*S*) isomer had already been prepared it was not necessary to use **37** for the preparation of that compound.



Scheme 2.11 Synthesis of 5-F ketone **37** from mixture of olefins 8,9 and 9,11

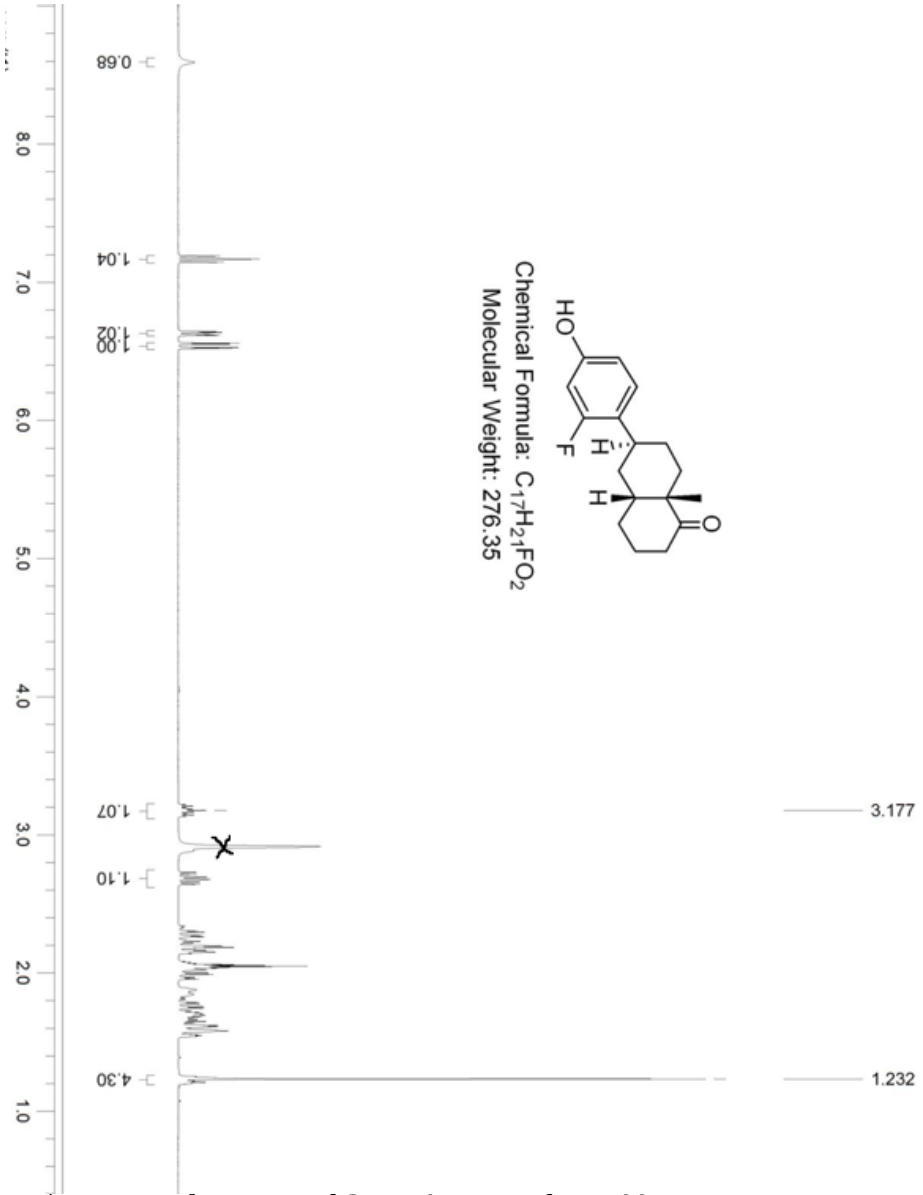
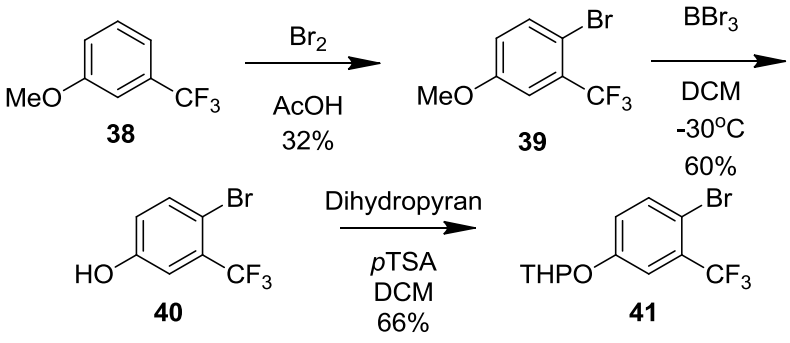


Figure 2.17 ^{1}H NMR of compound **37** in Acetone-d_6 at 400MHz.

2.5.2 Synthesis of homo A-CD compounds with CF_3 at C5

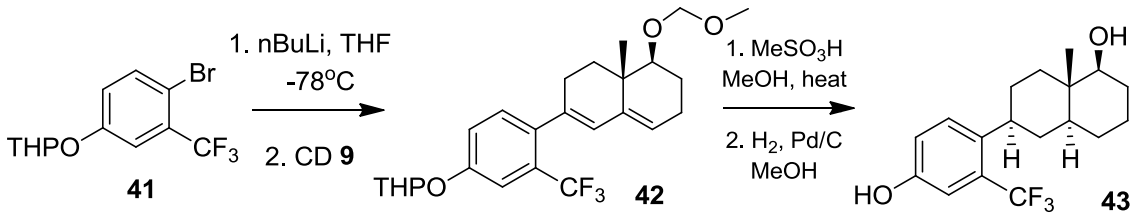
In the 6-5 A-CD series, compounds with CF_3 groups at C5 showed both RBA binding and RTA activity that was more potent than naturally occurring estradiol.[13] Unfortunately these compounds were relatively unselective with respect to the estrogen α and β receptors.[12] It was therefore of interest to prepare the homo A-CDs analogs in order to compare the activity and selectivity.

The commercially available starting material 3-trifluoromethyl anisole **38**, served as the starting for the preparation of the A ring moiety. The methoxy group could have been kept as the phenol protecting group however its conversion in the desired OH is difficult and requires harsh conditions. Thus **38** was first brominated at C4 of the aromatic ring followed by demethylation using BBr_3 in DCM at -78 ^oC.[18] Finally a THP group was placed on the C3 OH as was done for the previous compounds as laid out in **Scheme 2.12**. To note, the same steps were followed for the abovementioned preparation of CF_3 as was used in the original A-CD series.[12]



Scheme 2.12 Sequence for the preparation of the A ring in the CF_3 series.

The first compound made in this series was the *trans* CD ring A-CD **42**, following the same steps as was for the parent version. A ring **41** was coupled to CD **9** giving a yield of 67% of diene **42** after chromatography. Treatment with acid removed the protecting groups. The final hydrogenation step was quantitative yielding the desired compound **43** as a white solid.

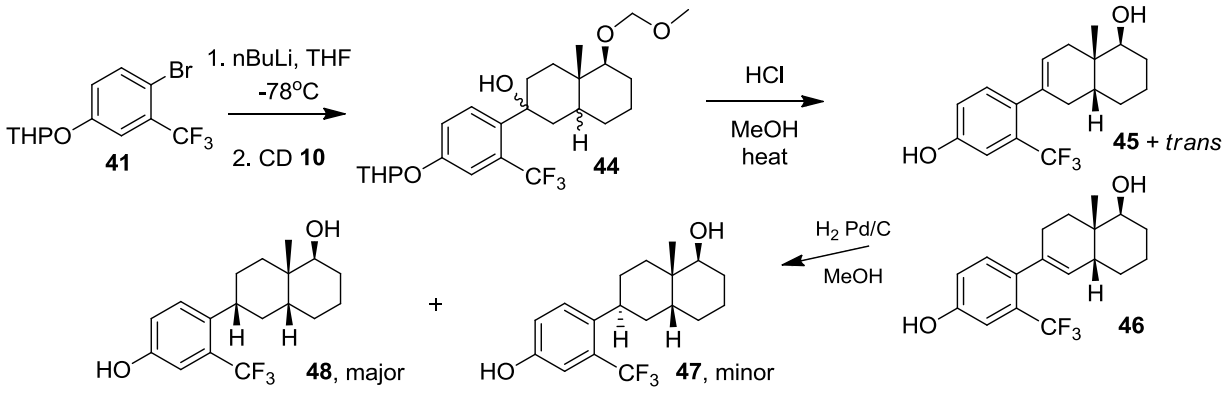


Scheme 2.13 Synthesis of *trans* CD ring 5-CF_3 **43**

Generation of the CD ring cis fused alkenes **45** and **46** followed the same steps as for the previously mentioned 5-F and 5-Me. The coupling reaction of the lithio derivative obtained from **41** with the saturated CD ketone **10** resulted in a yield of 63 % of the tertiary alcohol **44**. Treatment of this material with acid afforded the two alkenes **45** and **46** in approximately equal amounts as determined by the integration of the two alkene peak at 5.25 and 5.41 ppm. A small part of the mixture was separated by preparative HPLC using reverse phase column to yield the olefins **45** and **46**. The individual structure assignment was based on examination of the alkene region of the ^{1}H NMR with the key distinguishing features being the broader peak at 5.41 ppm representing the 9,11 olefin and a narrower peak at 5.25 ppm indicating a 8,9 olefin.

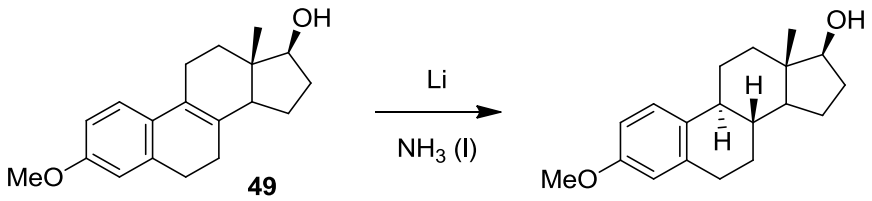
The remainder of the above alkene mixture was subjected to hydrogenation in order to obtain the saturated derivative **47**. Unfortunately, after the reduction reaction, little to no

(9*S*) isomer was recovered, indicating that virtually all of the substrate had been subjected to hydrogen addition from the top face. In fact on TLC a small less polar spot could be seen which may have represented the desired isomer but not enough compound could be collected to characterize and send for testing.



Scheme 2.14 Route to CF_3 olefin compounds **45** and **46** with synthesis of **47** and **48**

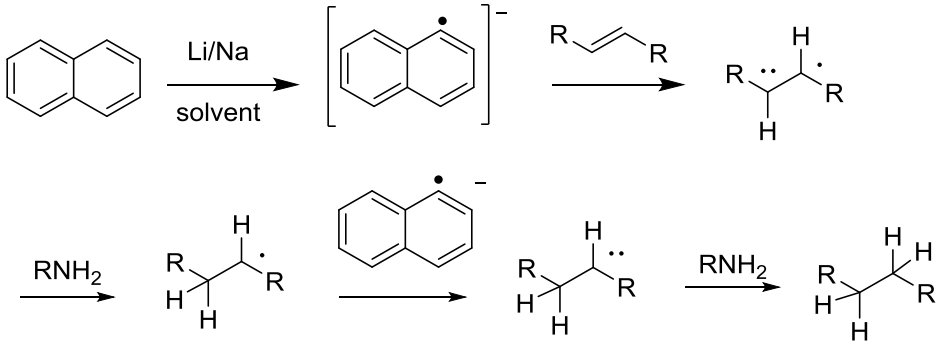
Other methods of reduction were explored. These were inspired bsed on the final step of the synthesis of estradiol conduct by Corey and coworker, where alkene **49** is hydrogenated using the Birch reduction.[23]



Scheme 2.15 Hydrogenation of alkene **49** en route to estradiol.

This method appeared promising as an alternate means of reducing the C ring double bonds. However the conditions of such a reaction meant that we ran the risk of over reduction and losing the aromatic ring which would be an irreversible process.

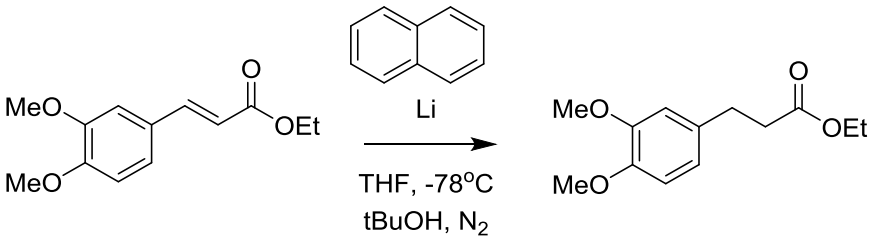
The typical Birch reduction uses lithium or sodium metal in liquid ammonia at -60 ^{o}C. Due to the extreme conditions of the reaction, a different version of the Benkeser reduction was reported by Donohoe and coworkers[24] which utilizes Li or Na as the electron source, an aromatic system as the "electron transporter" and amines or alcohols as potential proton source.



Scheme 2.16 Overview of the Benkeser reduction of a general alkene.

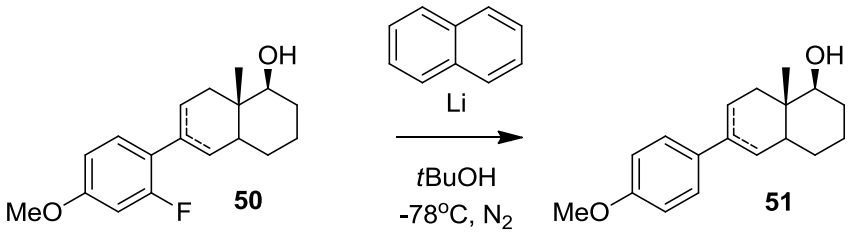
We were optimistic that the electrons would first add at C8/C11 thereby pushing the π electrons onto C9 where they would be stabilized due to the electronegativity of the CF_3 group. Since the formation of a carbocation at C9 was not favoured, as seen during the rearrangement attempts, then a caboanion should be stable. A few unsaturated compounds were tested using this method including CD ring **7** in order to attain mastery of the reaction. Following the success in saturating the CD ring, the next step was to attempt the reduction on a compound containing both an olefin and an aromatic ring. The

following **Scheme 2.17** depicts the reaction on the latter compound, where it was found that the reaction worked well but did not go to completion. Nonetheless the starting material could be recovered and the reaction repeated again.



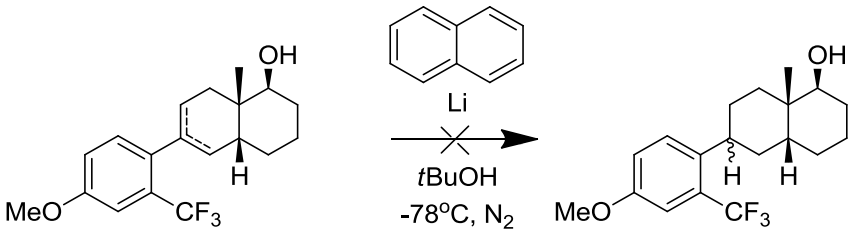
Scheme 2.17 Benkeser reduction on compound with aromatic and olefin moieties.

The abovementioned result was encouraging, albeit the compound used did contain a conjugated system with a carbonyl group, something the CF_3 compound did not have. Another compound was subject to the Benkeser reaction, this time a 5-F methylether olefin **50**; however a surprising outcome took place. The proton NMR of the product looked identical the parent methylether **51**, suggesting the loss of the F from the aromatic ring.



Scheme 2.18 Attempted reduction of double bond in 5-F methylether **50**.

Despite this result the reduction was attempted on the CF_3 olefin itself, which proved to give a disappointing result. None of the desired reduction appeared to take place; there seemed to be some reduction of the aromatic ring.



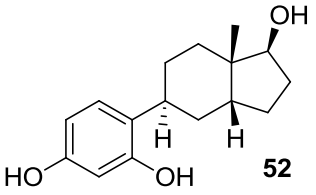
Scheme 2.19 Attempted reduction of double bond in 5-CF_3 olefin.

It is worthy to note that rearrangement reaction, one which results in the hydride shift from C18 to C9 and establishes the (9*S*) stereochemistry, was attempted numerous times on the CF_3 compound but without success. Plausible reasons for this are discussed in **Section 2.6**.

2.5.3 Synthesis of dihydroxyl homo A-CD **60**

The 5-OH compound A-CD **52** was judged particularly interesting since it had quite strong but also rather selective binding to ERβ. It was also shown to be non-toxic. Finally, the rate of metabolism of this compound was much lower than that of any compound studied in the original A-CD series. These metabolism studies were carried out by researchers at the Centre for Drug Research and Development at the University of British Columbia.[25] Whereas compounds such as estradiol and the parent A-CD compounds were metabolized by rat liver homogenates with a half-life of less than 30

minutes, the 5-OH compound was recovered essentially unchanged after more than 6 hours (see **Figure 2.18**).

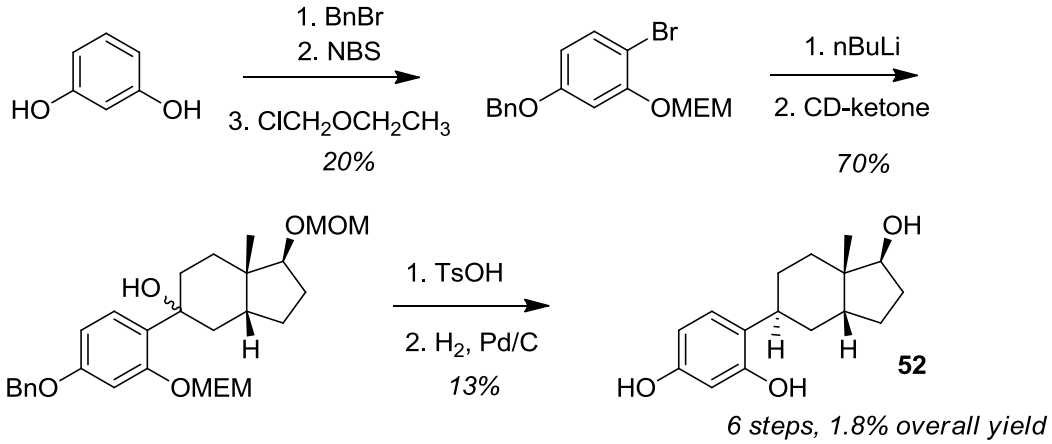


RBA(alpha)=0.26 RTA(alpha)= 3
RBA(beta)= 4.0 RTA(beta)= 85
beta/alpha= 15 beta/alpha= 28

Figure 2.18 RBA and RTA data for original 5-OH A-CD **52**

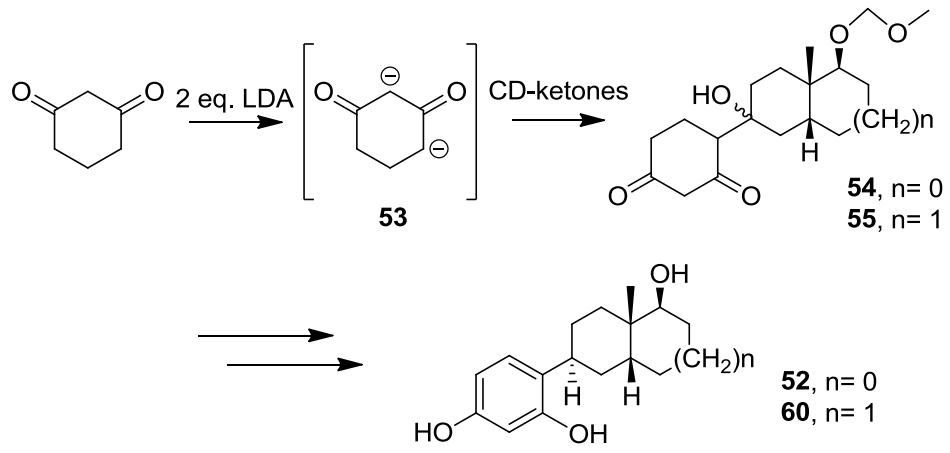
It was therefore of interest to prepare the homo analog **60** with the expectation that this compound would also be non-toxic, metabolically stable and hopefully also have useful and selective RBA and RTA activity.

In the previous A-CD project, this compound was synthesised using the regular method shown in **Scheme 2.20.**



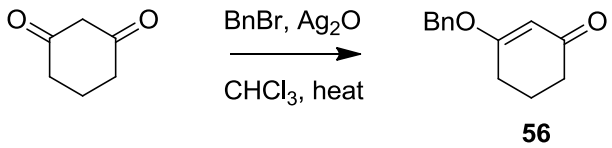
Scheme 2.20 Overall synthesis of original 5-OH A-CD **52**.

In an attempt to develop a simpler and efficient synthesis for both the original and homo 5-hydroxy A-CD compounds, we investigated the use of cyclohexan-1,3-dione as a starting material. Treatment of this diketone with two equivalents of LDA was expected to generate dianion **53**. Aldol condensation with the protected CD ring ketones would give adducts **54** and **55**. The remaining steps would include aromatization of the cyclohexan-di-one yielding the 3,5 dihydroxyl compound.



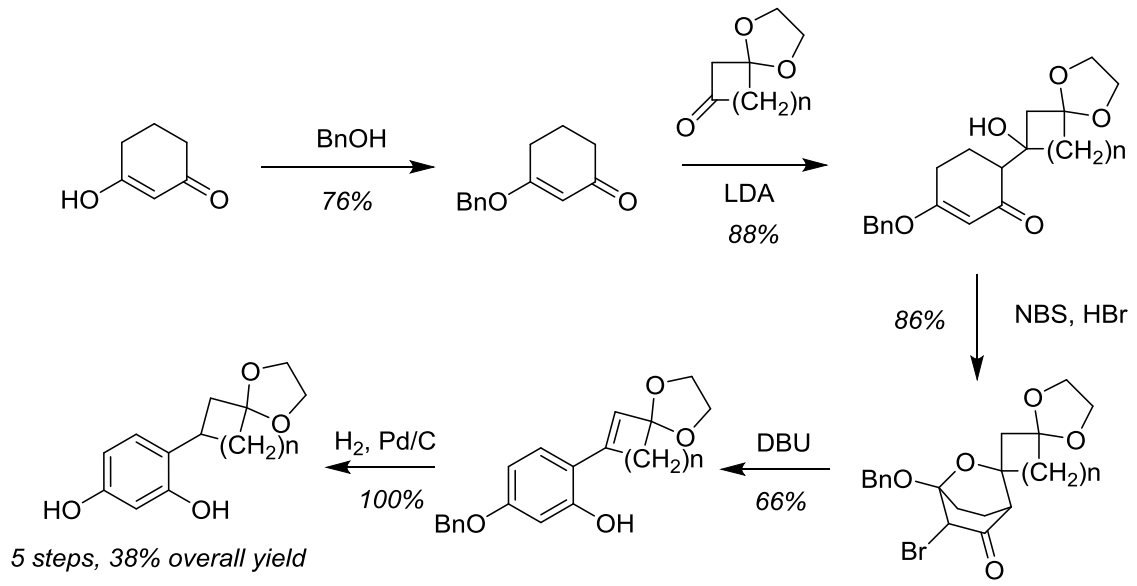
Scheme 2.21 Original proposed route to obtaining 5-OH A-CD from cyclohexan-1,3-dione.

This approach was attempted but without success since the initially formed oxy-anion was insoluble in most solvents available, including THF, resulting in a distinct orange precipitate. To avoid this we decided to form a benzyl enol ether by reaction of the 1,3-dione with BnBr and silver oxide. This resulted in the formation of **56** in 80% yield.[14]



Scheme 2.22 Synthesis of the A-ring of 5-OH compound.

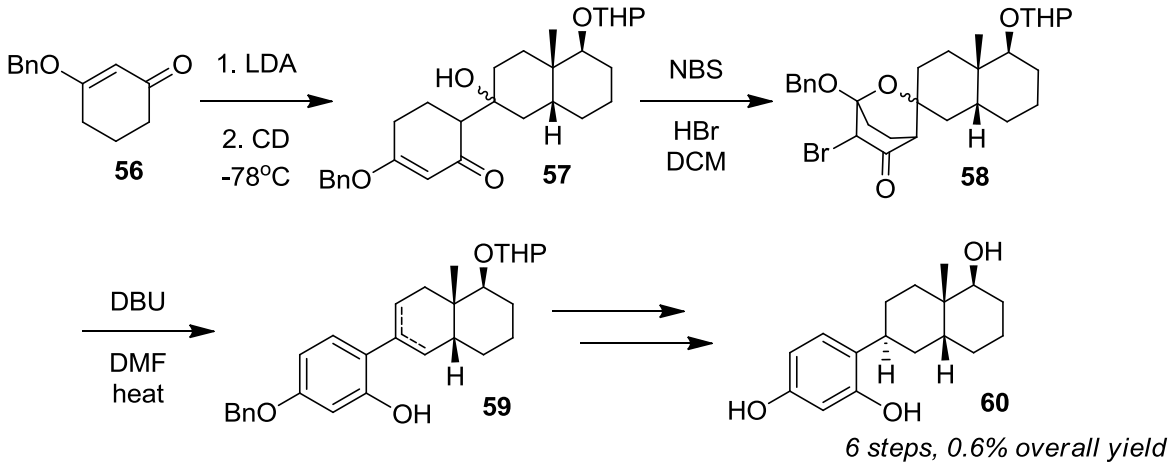
A literature search validated this approach. A Pfizer patent reported the preparation of aromatized 1,3-dihydroxylated ring systems and their use as skin lightening agents initiated by this type of condensation reaction starting from the same cyclic diketone that is 1,3-cyclohexadione.[26] The key step was the aromatization which was done by first treating the Aldol product with NBS and then heating in the presence of a base to allow for the aromatic system to form. The Pfizer route is shown in **Scheme 2.23.**



Scheme 2.23 Pfizer route starting from enol ether to aromatized dihydroxyl product.

The goal was to prepare compound **60** via this route. Thus treatment of **56** with 1 eq. of LDA followed by the condensation with the protected CD ring ketone **10a** afforded the adduct **57** as a white solid in 74% isolated yield. The ^{1}H NMR spectrum of **57** showed all of the expected features including the alkene H at 5.47 ppm and the benzyl CH_2 group at 4.89 ppm. The spectrum was somewhat complicated by the fact that **57** can be formed as a mixture of a number of diastereomers due to the additional chiral centres in the THP group. Bromination using NBS and HBr at room temperature proceeded with a yield of

43%. The NMR spectrum of the product **58** showed the disappearance of the alkene hydrogen and the appearance of a singlet at 4.38 ppm due to the H on the carbon bearing the Br. Moreover a much wider AB system from the benzylic methylene group is apparent (12 Hz) due to the nature of the bicyclic structure. In the final step following the Pfizer patent, the bicyclic intermediate **58** was refluxed in DMF for 16 hours in the presence of excess DBU. This caused elimination of HBr and subsequent aromatization to give 3-benzyloxy-5-hydroxy THP protected homo A-CD intermediate **59**. Unfortunately the yield of the final step was a disappointing 28%. The presence of the tri-substituted aromatic ring A in **59** was easily visible from the ^{1}H NMR with the expected disappearance of the AB system from the benzylic group.



Scheme 2.24 Overall synthetic route to 5-OH **60** starting from benzylic enol ether **56**.

The original patent did not discuss the mechanism or any literature supporting this type of reaction; therefore we proposed a mechanism whereby the Br participates in the oxidation of the A ring with the help of the base (DBU). The arrow pushing explaining the mechanism can be seen in **Figure 2.18.**

The remaining steps to complete the synthesis were acid treatment with TsOH affording an orange oil at 74% yield. The final step was a simple hydrogenation in order to reveal the 3-OH group and saturate the double bonds in the ring C. Once again the hydrogenation afforded mostly the *R* isomer, obtaining only 10% of the desired *S* at C9. This accounts mostly for the low overall yield of the synthesis (**Scheme 2.24**). The hydride shift could have been attempted on the alkene mixture **59** in order to install the proper *S* configuration at C9. However this was going to lengthen the synthesis by adding an additional 4 steps, questioning the practicality of this route.

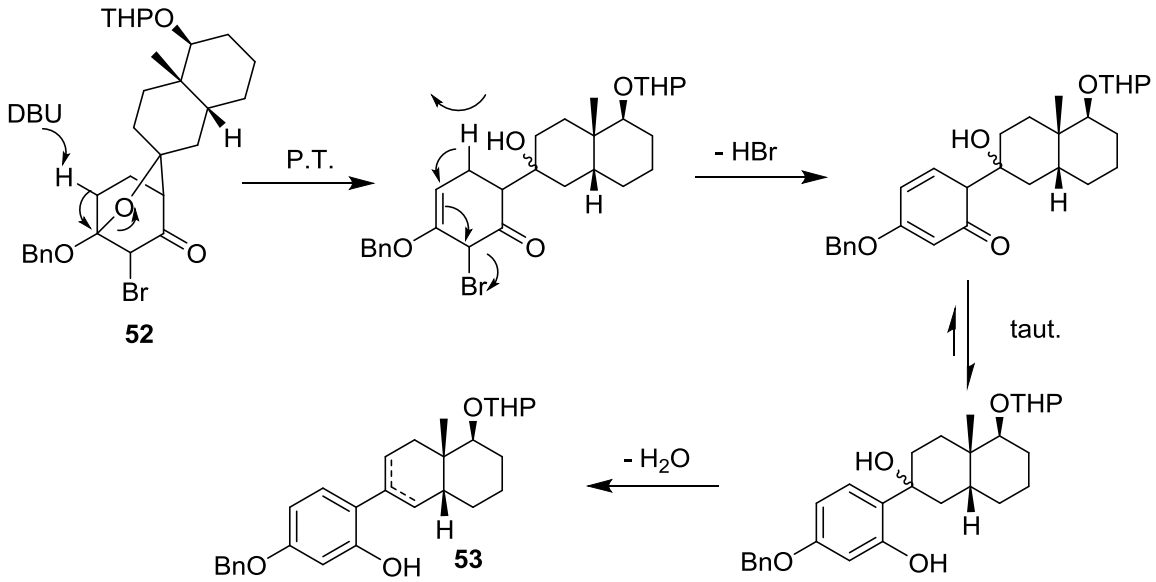


Figure 2.18 Mechanism of the aromatization of bicyclic **58** into **59** in the synthesis of 5-OH compound.

2.6 Qualitative study of the discovered 1,5-hydride shift resulting in C9 *S* configuration and ketone at C18

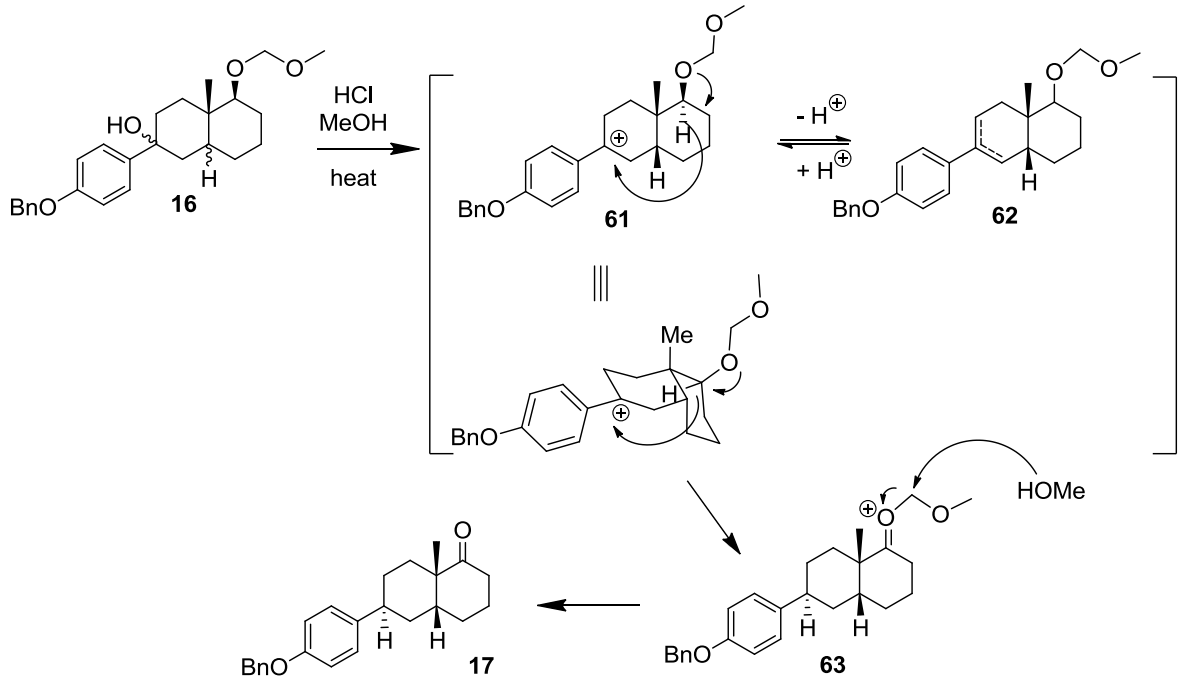
As previously mentioned in **Section 2.4.2**, acid treatment of the coupling product **16** resulted in the formation of a less polar compound, which was identified as ketone **17**.

The key feature of this compound was the installation of a C9 benzylic proton with the desired *S* configuration with concomitant loss of the MOM protecting group and formation of a carbonyl group at C18. This fortuitous discovery made way for stereospecific installation of the *S* stereochemistry at C9 thereby avoiding the hydrogenation as seen in the previous section which resulted in mixtures in which isomers with the undesired (9*R*) stereochemistry dominated in at least a 4:1 ratio. Furthermore these mixtures were very difficult to separate often requiring many cycles using the preparative recycling HPLC available in the group.

Surprisingly it proved impossible to repeat the formation of the rearrangement product under the same conditions i.e. conc. HCl in refluxing methanol. It was speculated that perhaps the excessive heat was required for the rearrangement reaction to proceed. Unfortunately, multiple attempts were carried out without success. Running the reaction using TsOH at room temperature in MeOH only yielded the dehydration product **56** even after stirring for two days.

Scheme 2.25 depicts the proposed mechanism for the conversion of **16** to **17**. The key steps are the protonation of C9 OH followed by the loss of H_2O to generate the carbocation **61**. This carbocation could also arise from the reprotonation of either the isomeric ring C alkenes formed by dehydration of **16**. The *cis* fusion of the C and D rings places the C18 in close proximity of the benzylic carbocation such that a hydride shift can take place. This is aided by the lone pair on the C18 oxygen subsituent to generate the intermediate oxonium ion **63**. Attack by the methanol solvent leads to the observed ketone. It is easily recognised that this rearrangement is only possible if the C and D ring rings are *cis* fused. When these rings are *trans* fused, the hydrogen at C18 is too far from

C9 carbocation and no hydride transfer is possible. A literature example of the transfer of a hydride transannularly in a 9 membered ring was shown earlier in this chapter **Figure 2.5**.

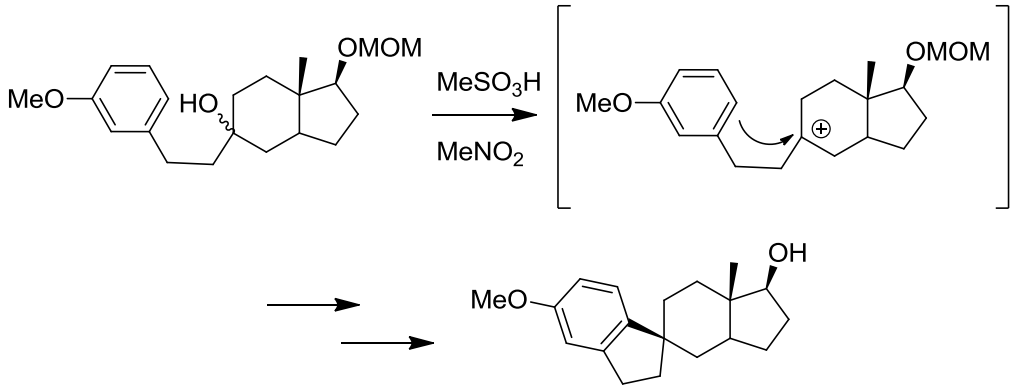


Scheme 2.25 Synthesis of ketone **17** with proposed mechanism for rearrangement reaction.

To find conditions favourable to the desired rearrangement we altered the reaction conditions, acid catalyst, and solvents. In one series, we used refluxing toluene with TsOH as the acid catalyst. It was thought that moving away from a protic solvent would destabilize the C9 carbocation and make it less susceptible to the hydride shift. After one hour reaction time the rearrangement product became visible on TLC, however other products, possibly dehydration of the C18 alcohol, were also forming and the rearrangement product was not the major compound. This result lead to further

experimentation with refluxing toluene as solvent and HCl as the catalyst. However this combination resulted in only in the formation of C ring alkenes.

The conditions - refluxing MeOH with TsOH as acid catalyst - yielded the dehydration product **62** as confirmed by proton NMR. At this time we recalled a reaction previously conducted by the group in synthesis of spiro compounds related to the A-CD project. The reaction shown below used $MeSO_3H$ as the acid with $MeNO_2$ as the solvent and was completed after a few seconds.[27] This reaction, like our rearrangement requires formation of a carbocation at C9 either directly from the tertiary alcohol or via reportonation of an alkene.



Scheme 2.26 Cyclization reaction using methane sulfonic acid in previously published work by our group[27]

To this effect, the ring C alkenes product **62** was redissolved in methanol and a couple of drops of methanesulfonic acid were added. After stirring the mixture at room temperature for a few minutes the rearrangement product appeared on TLC. Chromatographic isolation ensued and ^1H NMR confirmed the structure using the spectral data of **17** as reference.

The next step was to attempt the reaction on a larger scale for synthetic purposes. In fact, the rearrangement was attempted on coupling product **16** on both a 600mg and 800mg scale; however disappointing yields were obtained, ranging between 16 to 24%. Pushing the reaction beyond 4 hours was not favourable and numerous by products started appearing on TLC. For purposes of synthesis of parent **3** the combined products sufficed to push through the remaining steps until obtaining the final compound. However further studies were conducted in order to better understand the hydride shift and improve the yield and decrease the reaction time.

As abovementioned in the early trials of the rearrangement reaction, toluene proved to help in the formation of the desired product, and was therefore used in combination with the newly favourable acid $MeSO_3H$. Unfortunately the reaction conditions proved to be too harsh and a streak of formed compounds appeared TLC. As means to test the flexibility of this reaction, coupled compound 5-F **65** was also reacted with MeOH and $MeSO_3H$ with the hope of forming the ketone product. However this did not occur and simply the deportection and dehydration were seen in effect. Even when taking the latter product **30** and submitting it again to the same reaction, no change was seen after 2 hours. On the other hand changing the solvent to toluene yielded a small amount of the desired C18 ketone. It remained unclear why toluene would favour the rearrangement over methanol when intuitively a protic solvent favoured carbocation formation.

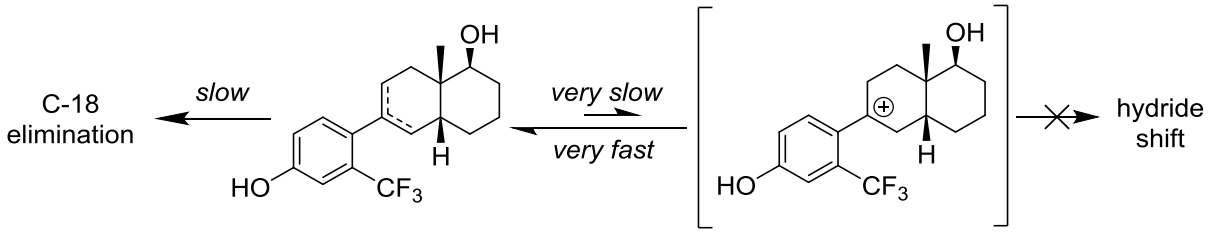
Following these attempts, there was thought given to both the acid and the solvent used and how to improve this reaction. In fact, nitromethane was a good candidate for solvent due to its history of use for carbocation formation. Moreover, the idea came to use a stronger acid in order to help form the carbocation and therefore allow for the hydride to

transfer. The acid chosen, triflic acid, was similar to $MeSO_3H$ in terms of properties and qualified as a superacid with a pK_a of -12. Superacids are known to be very good at creating positive charges and this is a property that was thought to be favourable for the intended use. As a result, the first attempt with CF_3SO_3H and $MeNO_2$ was conducted with 5-Me olefin **32** on a small scale at 100 ^oC (reflux) and the reaction was complete after 20 minutes. Changing the acid to TsOH while maintaining the same conditions did yield product but after one hour of refluxing. $MeSO_3H$ on the other hand afforded the ketone product in the same time span with secondary by-product. The use of HCl as the acid gave little to no product.

In an attempt to test the effect of A ring substituents on the rearrangement, triflic acid and $MeNO_2$ were used with 5-F alkenes **30**. The ketone product was obtained but required 1 hour to go to completion instead of 20 minutes. This was expected since Me is a donating group which should help stabilize the carbocation at C9 while the opposite would be true for a EWG such as F. Testing the latter compound on a larger scale (0.376g) afforded a respectable yield of 73%. Attempting the same reaction on both Me and F compounds at room temperature required longer reaction time. Rearrangement of the methyl compound was complete overnight while with the 5-F some starting material was still present during the same time frame. The combination of AcOH and sulfuric acid did achieve the hydride shift after 5 hours at room temperature when using the 5-F alkene **30** as substrate.

As mentioned in **Section 2.5.2** synthesis of 5-CF_3 with the (9*S*) stereochemistry proved to be very problematic since the hydrogenation of the olefin isomers strongly disfavoured the C9 *S* product. All attempts at the rearrangement failed to give the (9*S*) 18 ketone in this series. These included the same reaction conditions discussed above, with triflic acid

and nitromethane considered the best candidates. In most cases no product was seen to form at room temperature while refluxing the reaction mixture for several hours in an attempt to push product formation only afforded what seemed to be elimination of C18 OH.



Scheme 2.27 Pathway to C-9 carbocation and C-17 elimination for 5-CF_3 homo A-CD.

Explanation for this observation lies in the nature of the CF_3 group itself; a strong electron withdrawing group. As was seen in the difference in reactivity in the presence of F, groups that deactivate or decrease electron density in the aromatic ring give way a destabilized benzylic carbocation. As a result, the C9 carbocation's "life time" is too short in order for the hydride to transfer over from C18 and therefore a carbocation at the latter position becomes more favoured, explaining the elimination.

Table 2.2 Reaction summary of the hydride shift attempts on different compounds.

Compound	Catalyst	Solvent	Reaction Time	Temperature	Product Observed
16	HCl	MeOH	3 hrs	Reflux	None
16	TsOH	MeOH	2 days	RT	Dehydration C ring
16	TsOH	Toluene	1 hr	Reflux	Rearrangement + by products
16	HCl	Toluene	2-4 hrs	Reflux	Dehydration

					C ring
62	$MeSO_3H$	MeOH	5 min	RT	Rearrangement
62	$MeSO_3H$	Toluene	Mins - 4 hrs	RT-reflux	By products
65	$MeSO_3H$	MeOH	2 hrs	Reflux	Dehydration C ring
65	$MeSO_3H$	Toluene	2 hrs	Reflux	Rearrangement
32	CF_3SO_3H	$MeNO_2$	20 min	Reflux	Rearrangement
32	TsOH	$MeNO_2$	1 hr	Reflux	Rearrangement
32	$MeSO_3H$	$MeNO_2$	1 hr	Reflux	Rearrangement
32	HCl	$MeNO_2$	2 hrs	Reflux	None
30	CF_3SO_3H	$MeNO_2$	1 hr	Reflux	Rearrangement
30	CF_3SO_3H	$MeNO_2$	Overnight	RT	Rearrangement + S.M.
32	CF_3SO_3H	$MeNO_2$	Overnight	RT	Rearrangement
30	H_2SO_4	AcOH	5 hrs	RT	Rearrangement
71	CF_3SO_3H	$MeNO_2$	5 hrs	RT	None
71	CF_3SO_3H	$MeNO_2$	5 hrs	Reflux	Dehydration D ring

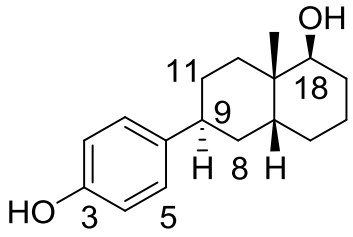
2.7 Relative Binding Affinity (RBA) results of bioassays for homo A-CD estrogens

Eight homo ring D compounds belonging to the series in which the parent ring was unsubstituted were sent for RBA affinity determination by the Katzenellenbogen group at the University of Illinois. This group has carried out close to 150 similar determinations for our group since the beginning of our estrogens receptor project. The assays were performed on purified full-length human ERα and ERβ estrogen receptors and affinities were calculated by a competitive radiometric binding assay using [^{3}H]estradiol as tracer. Hydroxyapatite was used to absorb the ligand-receptor complexes and free ligand was

washed away. The results of these determinations together with those of an additional nine compounds with F, CH_3, CF_3, and OH substituents at C5 are shown and discussed in this section.

The Relative Binding Affinity (RBA) results were disappointing based on the expectations expressed at the beginning of this chapter not so much with respect to the strength of the binding but more so with respect of the β/α selectivity.

Table 2.3 RBA values for ERα and ERβ with β/α ratio of synthesised compounds from the parent series with standard error. Two trials were conducted for each test.



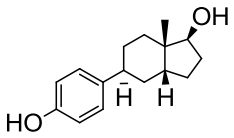
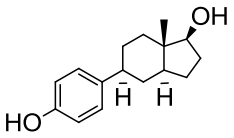
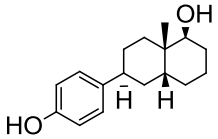
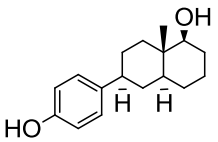
Compound	ERα	ERβ	β/α
3	0.64 ± 0.17	3.26 ± 0.98	5.1
14 (*trans*)	0.54 ± 0.15	0.78 ± 0.05	1.4
C-9 *R*	0.21 ± 0.05	0.56 ± 0.14	2.7
21 (C-18 *α*)	0.45 ± 0.14	1.86 ± 0.4	4.2
20 (ketone)	0.019 ± 0.004	0.153 ± 0.009	8.1
24 (9-8 ene)	0.18 ± 0.05	0.28 ± 0.08	1.5
25 (9-11 ene*)	0.60 ± 0.03	1.29 ± 0.09	2.2
26 (9-11 ene *trans*)	2.64 ± 0.7	3.95 ± 0.59	1.5
Diene	1.20 ± 0.28	1.43 ± 0.13	1.2

*contained 10% *trans*

The above **Table 2.3** displays the RBA results of the synthesised compounds in the parent series. The anticipated results predicted by calculation models were not obtained and this new 6-6 series gives lower binding affinities with somewhat comparable selectivity compared to the original 6-5 A-CDs.

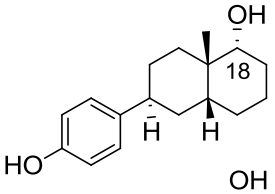
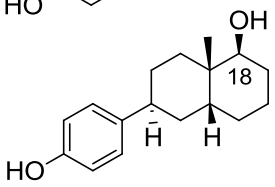
Table 2.4 gives the data for the parent *cis* **3** and *trans* **14** fused A-CD compounds for both the original and the homo series. The binding of the homo compound is reduced relative to the original series; the reduction is relatively modest, typically less than a factor of 10. Unfortunately the reduction for the β receptor is more significant than for the α, contrary to our hopes with the β/α receptor selectivity 14.6 and 4.6 respectively, for the *cis* and *trans* CD fused A-CD series and only 5.1 and 1.4 for the corresponding homo A-CD compounds. Interestingly in both sets the *cis* fused CD ring compounds showed both stronger binding to both receptors and a greater ERβ selectivity than the corresponding *trans* fused isomers.

Table 2.4 RBA values for ERα and ERβ with β/α ratio of synthesised homo parent compounds compared with original parent A-CD series with standard error.

	RBAα	RBAβ	β//α
	1.47 ± 0.26	21.6 ± 4.6	14.6
	2.38 ± 0.19	10.0 ± 1.3	4.6
	0.64 ± 0.17	3.26 ± 0.98	5.1
	0.54 ± 0.15	0.78 ± 0.05	1.4

Changing the stereochemistry at C18 from the natural α or *S* to β or *R* reduces the binding to both receptors by a surprisingly small amount, less than a factor of 1.5; the β/α selective is almost unchanged. This suggests that both receptors can accommodate either stereochemistry at C18 essentially equally well.

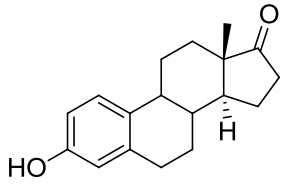
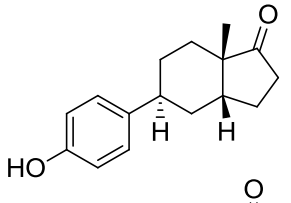
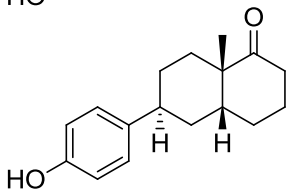
Table 2.5 RBA values for ERα and ERβ with β/α ratio of synthesised homo parent compounds with α and β C18 OH with standard error.

	RBAα	RBAβ	β//α
	0.64 ± 0.17	3.26 ± 0.98	5.1
	0.45 ± 0.14	1.86 ± 0.4	4.2

The RBAs of estrone has been shown to be approximately 4% of those of estradiol[12] indicating the importance of the 17-OH group in these molecules in the binding affinity to the ERs. This is further confirmed but with a more important difference when comparing the parent A-CD to its C17 ketone derivative where the latter has shown less than 1% of the affinity of the former. Differences between the C18 OH and the ketone in the homo series are similar to that observed between estradiol and estrone when speaking of affinity (approximately 5% of the affinity). Surprisingly the β/α selectivity is very similar for both the parent A-CD and its C17 ketone version (β/α values around 14). As for the new homo series, it seems that the C18 ketone is more selective than the parent version (8.1 compared to 5.1) and also about 50% more potent. Admittedly the potency of these ketones is at least 200 fold less for ER α and 20-30 times less for ER β compared

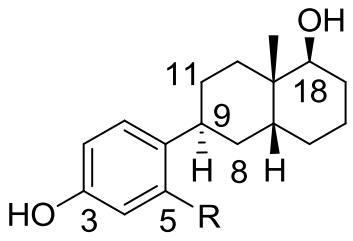
to estrone. The extent of the reduction in the binding of the *cis* fused 17-keto A-CD compound is similar to that observed in going estradiol to estrone.

Table 2.6 RBA values for ERα and ERβ with β/α ratio of synthesised homo parent C18 ketone compound compared with original parent A-CD analog and estrone with standard error.

	RBAα	RBAβ	β//α
	4.50 ± 1.0	3.8 ± 0.4	0.84
	0.008 ± 0.001	0.11 ± 0.01	14
	0.019 ± 0.004	0.153 ± 0.009	8.1

The binding affinity of the homo A-CD compounds having the CD *cis* ring junction bearing substituents at C5 to both estrogen receptors were typically significantly larger with the greater increase being seen for the α receptor; this lowers the β/α selectivity of these compounds relative to the parent A-CD compound. The effect was particularly strong for the series CH_3, F, CF_3, and OH (see **Table 2.7**). From the results obtained, the highest selectivity was surprisingly obtained by the "non-natural" 5-F compound at 8.6, followed by the parent ketone **20** with 8.1. All compounds displayed higher activity in ERβ compared to ERα, with the exception of "non-natural" 5-CH_3 which yielded a β/α ratio of 0.7.

Table 2.7 RBA values for ERα and ERβ with β/α ratio of synthesised compounds from substituted A ring series with standard error. Two trials were conducted for each test.



Compound	ERα	ERβ	β/α
33 (F)	9.11 ± 2.7	68.24 ± 9	7.5
34 (F 9 *R*)	0.11 ± 0.03	0.94 ± 0.1	8.6
37 (F ketone)	0.26 ± 0.03	1.61 ± 0.45	6.1
30 (F 8,9 ene)	4.87 ± 0.78	23.80 ± 0.16	4.9
35 (CH_3)	3.26 ± 0.79	8.70 ± 0.6	2.7
36 (CH_3 9 *R*)	0.043 ± 0.007	0.030 ± 0.008	0.70
43 (CF_3 *trans*)	1.68 ± 0.49	1.69 ± 0.1	1.0
46 (CF_3 8,9 ene)	210 ± 16	245 ± 38	1.2
60 (OH)	0.22 ± 0.02	0.37 ± 0.07	1.7

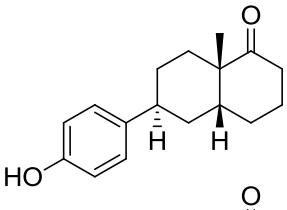
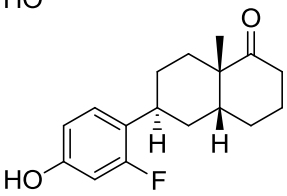
Comparison of the relative binding affinity data where both pairs of compounds were available gives a confusing picture. The 5-F derivative in the A-CD series has RBAα and β equal to 27 and 135, respectively with the β/α ratio = 5. The corresponding 5-F homo A-CD compound **33** also showed strong binding with RBAα = 9.1 and RBAβ = 68.2. The β/α selectivity of 7.5 for the homo compound is 50% greater than that in the parent series. In contrast for the 5-Me compounds the parent A-CD compound showed somewhat

higher binding affinities and a higher β/α selectivity ratio than the homo A-CD analog. This was arguably the largest discrepancy between the original and the homo series. Although binding to ERα was similar, with both showing values around 3, a greater difference was observed for RBAβ. The parent series for the 5-Me compound gave an RBAβ of 34 while the homo version **35** only resulted in 8.7, explaining the large difference in selectivity (12 compared to 2.7). The 5-CF_3 compounds in the A-CD series were the most potent in terms of binding to the estrogen receptors but with very little β/α selectivity. Unfortunately, as explained above, we have not yet been able to prepare the 5-CF_3, (9*S)* isomer, and thus no comparison can be made for the saturated compounds. The RBA of the C ring 8,9 unsaturated compound **46** bearing a 5-CF_3 group continues to show exceptionally strong binding to both ERα (210) and ERβ (245). As in the A-CD series there is little to no β/α selectivity. The binding to the α-receptor for **46** is the strongest that we have observed with any of the A-CD estrogens that we have prepared. Suprisingly, the binding affinity for the 5-CF_3 (9*S*) compound having the CD *trans* fusion is less than 2% of that of estradiol with a β/α ration of 1. Compounds such as **46** in which the binding to both estrogen receptors is larger than for estradiol itself have been designated as "super estrogens" by our group.[18]

The 5-F ketone **37** showed good β/α selectivity (6.1) with much better affinity to both receptors when comparing to parent ketone **20** with 10 times stronger binding observed. This result further suggests the possible role of the ketone group as a means to achieve selectivity. An interesting compound to prepare would have been 5-CF_3 ketone which in theory should show strong activity, as it has always been the case with these sorts of compounds, combined with better selectivity due to the carbonyl at C18. Unfortunately

we were not able to pursue this idea due to the inability of synthesising a CF_3 compound bearing the configuration *S* at C9.

Table 2.8 RBA values for ERα and ERβ with β/α ratio of synthesised ketone compounds comparing the parent to the 5-F, reproduced from previous tables.

	RBAα	RBAβ	β//α
	0.019 ± 0.004	0.153 ± 0.009	8.1
	0.26 ± 0.03	1.61 ± 0.45	6.1

The RBA results for the 5-OH **60** in the homo series were quite disappointing especially considering that the 5-OH A-CD compound had promising RBA and RTA data combined with no discernible toxicity and high metabolic stability. The disappointment was not so much in the strength of the binding of the homo compound relative to its A-CD analog but in the decrease of the β/α selectivity from about 15 to less than 2. Once again, RBAα for both series were similar (0.26) as seen previous in the 5-Me compounds. The difference lies in the RBAβ where the original gave 4.0 while the new series bound 10 times less (0.4). In most cases, values for ERβ displayed greater differences than those of ERα when comparing to the original A-CD series. One can speculate that the size of the receptors is at the origin of this observation, since ERβ is known to be smaller than ERα. Therefore the increased ligand size due to the expansion of the D ring may not be accommodated as well in the β receptor.

2.8 Conclusions

Having said that, the results obtained did not meet the expectations of the group despite the promising results from the calculations obtained by Wright. On the contrary most of the homo A-CD compounds synthesised proved to be less promising in terms of the desired β/α selectivity. One may argue that the smaller active site volume of ERβ compared to ERα plays a key role in limiting the size of the ligand binding into the ERβ pocket, which could explain the decreased selectivity observed. However this does not account for the very high potency of the 5-CF_3 alkene **41**, which was similar to the same analogs in the original A-CD series.

One may conclude that the ERβ can accommodate a variety of moieties and that thus far it is difficult to predict how well a given ligand would bind to the receptor. More studies need to be performed in order to better understand the binding pocket of the ERβ and therefore be able to predetermine binding interactions with a compound. If this project were to be pursued, exploring different substituents (CF_3 more specifically) on ketone compounds from the original series may be of interest due to the selectivity displayed.

3.0 EXPERIMENTAL SECTION

3.1 General Methods

All moisture-sensitive reactions were purged using nitrogen or argon. Thin Layer Chromatography was performed with 0.25mm silica gel 60F plates with 254nm fluorescent indicator from Merck. In order to visualise the plates, ultraviolet light was used and acidic ceric ammonium nitrate was used to stain, followed by gentle heating using a heat gun. Silica gel 60 (40-60um) was purchased from Aldrich and used for column chromatography. All spectra were recorded using Bruker Avance 300 and 400. Preparative and recycle HPLC was used to purify final compounds using reverse phase C-18 column (10μm particle size, 21.2 x 250 mm). The CD ring was prepared following the procedure of Hajos and Parrish.

Method A

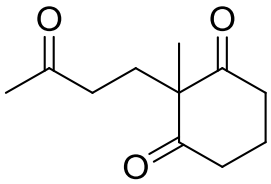
This general method was used when coupling protected A rings to CD rings. The A ring compound was placed in the reaction flask which was then purged with dry N_2. Dry THF was added and the mixture was stirred until fully dissolved. The flask was then placed in a dry ice bath of -78 ^{o}C and left to stir for 3 min. *n*BuLi was added dropwise and the solution was stirred for an additional 15 min. Then CD ring moiety, dissolved in 3mL of dry THF, was then added drop wise to the reaction mixture. The reaction was allowed to run for an additional 30 min at the low temperature before quenching with 10mL NH_4Cl in most cases. The mixture was removed from the bath to warm to room temperature.

Typical Workup

This method was employed when working up a reaction in order to obtain a crude product, which in most cases was purified by silica gel column chromatography. The reaction mixture was poured into a separatory funnel and extracted with specified solvent (2x). The combined organic phase was dried with $MgSO_4$, filtered and concentrated under vacuum using rotatory evaporation.

3.2 Procedures and Spectral Data

Preparation of 2-methyl-2-(3-oxobutyl)cyclohexane-1,3-dione

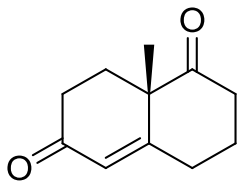


Chemical Formula: $C_{11}H_{16}O_3$
Molecular Weight: 196.24

A mixture of 10 drops of glacial AcOH were added with 10.6mL (128.4 mmol) of methylvinyl ketone was added to a solution of 8.1g (64.2 mmol) of 2-methyl-1,3-cyclohexan-di-one in 50mL of H_2O.. The mixture was stirred with a magnetic stirrer and was heated to 75^oC for 3 hours. Upon completion, the reaction was allowed to cool to room temperature before the addition of NaCl until saturation. The typical workup was employed using 35mL of EtOAc. Column chromatography was performed on the crude to obtain 9.7g of yellow oil as the product, representing 80% yield. The NMR data of this material matched that in the literature.[28]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 2.75-2.57 (m, 4H), 2.33 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 3H), 2.07-1.97 (m, 3H), 1.95-1.83 (m, 1H), 1.23 (s, 3H)

Preparation of (S)-8a-methyl-3,4,8,8a-tetrahydronaphthalene-1,6(2H,7H)-dione

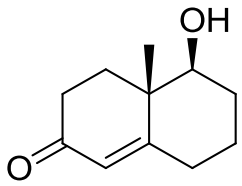


Chemical Formula: $C_{11}H_{14}O_2$
Molecular Weight: 178.23

2-(4-Butanone)-2-methyl-1,3-cyclohexan-di-one, 9.7g (49.4 mmol), was dissolved in 20mL of DMF in a 100mL round-bottom flask. To this was added 0.569g (4.94 mmol) of L-proline and the reaction mixture was stirred for 2 days. The typical workup was employed using 20mL each of ether and water. Column chromatography afforded 3g of the Wieland-Miescher ketone (yellow oil) at 34% yield. The NMR data of this material matched that of the literature.[28]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 5.83 (d, *J* = 1.82 Hz, 1H), 2.76-2.64 (m, 2H), 2.53-2.40 (m, 4H), 2.17-2.04 (m, 3H), 1.68 (qt, *J* = 13.34, 4.39 Hz, 1H), 1.43 (s, 1H)

Preparation of (4aS,5S)-5-hydroxy-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (7)



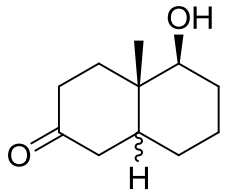
Chemical Formula: $C_{11}H_{16}O_2$
Molecular Weight: 180.24

The Wieland-Miescher ketone ,1.6g (8.98 mmol), was added to 10mL of a 50:50 solution of MeOH and DCM in a 50mL round bottom flask and the mixture was stirred to complete the dissolution. The flask was placed an acetone and dry ice bath of -78^{o}C. $NaBH_4$ (4.56 mmol) was then added in 3 portions and the reaction was stirred for 2 hours. After the addition of 5mL of acetone to quench the reaction, the mixture was allowed to warm to room temperature. 1M NaOH (5mL) was added and the typical workup was employed using 10mL of DCM. The product was purified by column chromatography to obtain 1.5 g of thick yellow oil (94%). The NMR data of this material matched that in the literature.[29]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 5.77 (d, *J* = 1.88 Hz, 1H), 3.41 (dd, *J* = 11.60, 4.32 Hz, 1H), 2.43-2.38 (m, 2H), 2.34-2.28 (m, 1H), 2.23-2.13 (m, 2H), 1.91-1.77 (m, 3H), 1.75-1.63 (m, 1H), 1.47-1.32 (m, 1H), 1.18 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$) δ ppm 199.8, 168.8, 125.3, 78.1, 41.6, 34.2, 33.6, 32.0, 30.2, 23.1, 15.2

Preparation of (4aS,5S)-5-hydroxy-4a-methyloctahydronaphthalen-2(1H)-one (**8**)

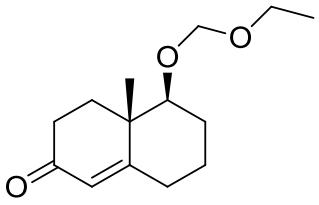


Chemical Formula: $C_{11}H_{18}O_2$
Molecular Weight: 182.26

To a mixture of 3.54g (19.64 mmol) of compound **7**, 40mL of MeOH, 20mL of AcOH and 0.98mL of 10% HCl was added 0.5g of Pd/C (10%). The mixture was stirred under H_2 atmosphere over night. The reaction mixture was filtered through Celite, washed with EtOAc and concentrated *in vacuo*. The crude was purified by flash chromatography to obtain 3.0g of compound **8** in 84% yield. The NMR data shows a 3 to 1 *cis* to *trans* mixture, based on the integration of the methyl and C18 signals. Also matched that in the literature.[30]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 3.80 (dd, *J* = 6.75, 3.46 Hz, 1H [C18 of *cis*]), 3.26 (dd, *J* = 11.44, 4.35 Hz, 1H [C18 of *trans*]), 2.44-2.26 (m, 3H), 2.25-2.16 (m, 1H), 2.05-1.97 (m, 2H), 1.84-1.74 (m, 1H), 1.72-1.47 (m, 4H), 1.44-1.14 (m, 3H), 1.13 (s, 3H [CH_3 of *cis*]), 1.01 (s, 3H [CH_3 of *trans*]).

Preparation of (4aS,5S)-5-(ethoxymethoxy)-4a-methyl-4,4a,5,6,7,8-hexahydronaphthalen-2(3H)-one (**9**)

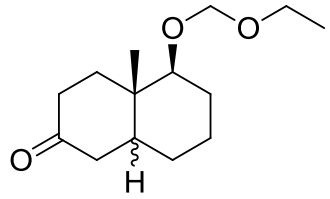


Chemical Formula: $C_{14}H_{22}O_3$
Molecular Weight: 238.32

CDring moitey **7**, 0.7g (3.9 mmol), was dissolved in 6mL of DCM. The flask was purged with N_2 and placed in an ice bath. DIPEA (1.35mL, 7.8 mmol) was added followed by dropwise addition of 0.72mL (7.8 mmol) of chloromethylethyl ethe. The reaction mixture was allowed to stir overnight while reaching room temperature. The mixture was quenched with brine (7mL) and the typical workup was employed using 7ml of DCM. The product was purified by column chromatography to obtain 0.8g of yellow oil (86%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 5.76 (d, *J* = 1.87 Hz, 1H), 4.76 (d, *J* = 7.2 Hz, 1H), 4.64 (d, *J* = 7.2 Hz, 1H), 3.65-3.56 (m, 2H), 3.29 (dd, *J* = 11.68, 4.32 Hz, 1H), 2.48-2.27 (m, 3H), 2.24-2.12 (m, 2H), 2.0-1.93 (m, 1H), 1.92-1.75 (m, 2H), 1.68-1.56 (m, 1H), 1.42-1.28 (m, 1H), 1.19 (s, 3H), 1.18 (t, *J* = 7.2 Hz, 3H)

Preparation of (4aS,5S)-5-(ethoxymethoxy)-4a-methyloctahydronaphthalen-2(1H)-one (**10**)

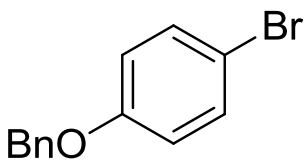


Chemical Formula: $C_{14}H_{24}O_3$
Molecular Weight: 240.34

CD ring moiety **8**, 3.0g (16.5 mmol), was dissolved in 35mL of DCM. The flask was purged with N_2 and placed in an ice bath. DIPEA (5.7mL, 33 mmol) was added followed by the dropwise addition of 2.5mL (33 mmol) of chloromethylethyl ether. The reaction mixture was allowed to stir overnight while reaching room temperature. The mixture was quenched with brine (15mL) and the typical workup was employed using 10mL of DCM. The product was purified by column chromatography to obtain 3.45g of yellow oil (93%).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 4.78 (d, *J* = 7.2 Hz, 1H), 4.63 (d, *J* = 7.2 Hz, 1H), 3.72 (bs, 1H), 3.70-3.53 (m, 2H), 1.19 (t, *J* = 7.2 Hz, 3H), 1.13 (s, 3H). The remaining peaks were difficult to interpret due to the presence of the *trans* isomer.

Preparation of 1-(benzyloxy)-4-bromobenzene (**11**)

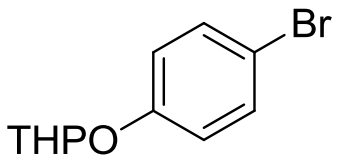


Chemical Formula: $C_{13}H_{11}BrO$
Molecular Weight: 263.13

4-bromophenol, 1.5g (8.67 mmol), was dissolved in 12mL of acetone. The solution was stirred and 1.32g (9.53 mmol) of K_2CO_3 was added followed by 1.13mL (9.53 mmol) of BnBr. The mixture was refluxed for 2 hours. Following the completion of the reaction, the mixture was allowed to cool to room temperature and filtered. The crude was evaporated under vacuum and purified by silica gel chromatography to afford 2.2g of white crystals, representing 88% yield. The NMR data of this material was consistent with the one previously obtained by the group.[12]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.43-7.30 (m, 7H), 6.85 (d, *J* = 8.8 Hz, 2H), 5.04 (s, 1H)

Preparation of 2-(4-bromophenoxy)tetrahydro-2H-pyran (**64**)

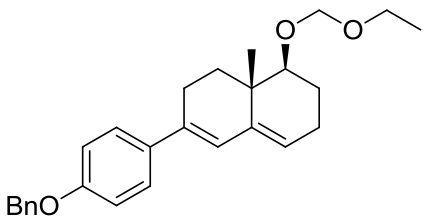


Chemical Formula: $C_{11}H_{13}BrO_2$
Molecular Weight: 257.12

The dissolution of 2.0g (11.6 mmol) of 4-bromophenol in 10mL of DCM was followed by the addition of 1.37mL (15.0 mmol) of 3,4-dihydro-*2H*-pyran. Then a few crystals of pTSA (0.05g) were added. The reaction was stirred at room temperature for 2 hours followed by evaporation of the solvent and column chromatography. The final product, a white solid, weighed 2.0g corresponding to 67% yield

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.37 (d, *J* = 9.04 Hz, 2H), 6.94 (d, *J* = 9.04 Hz, 2H), 5.37 (t, *J* = 3.21, 3.21 Hz, 1H), 3.87 (ddd, *J* = 11.45, 9.68, 3.15 Hz, 1H), 3.60 (dtd, *J* = 11.34, 4.19, 4.14, 1.41 Hz, 1H), 2.05-1.92 (m, 1H), 1.88-1.82 (m,2H), 1.72-1.57 (m, 3H)

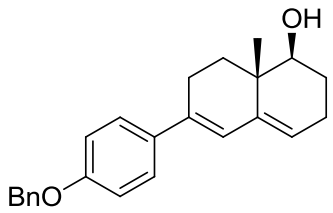
Preparation of (1S,8aS)-6-(4-(benzyloxy)phenyl)-1-(ethoxymethoxy)-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalene (**12**)



Chemical Formula: $C_{27}H_{32}O_3$
Molecular Weight: 404.54

Using Method A, 1.15g (4.36 mmol) of compound **11** was placed in a 50mL round-bottom flask with 20mL of dry THF. nBuLi (2.28mL, 3.86mmol) was added dropwise. Then 0.8g (3.37 mmol) of compound **9** dissolved in 3mL of dry THF was added drop wise to the reaction mixture. The reaction was quenched with 10mL NH_4Cl. The typical workup was employed with 20mL of EtOAc. The product was isolated by column chromatography to yield 0.9g (66%) of a viscous yellow oil. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

Preparation of (1S,8aS)-6-(4-(benzyloxy)phenyl)-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalen-1-ol (**13**)

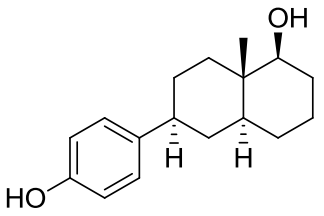


Chemical Formula: $C_{24}H_{26}O_2$
Molecular Weight: 346.46

Compound **12**, 0.9g (2.2 mmol), was dissolved in 6mL of MeOH. 3 drops of concentrated HCl were added and the mixture was refluxed until completion. The reaction mixture was evaporated under vacuum and purified using silica gel column. The final product was isolated at a yellow oil of 0.35g with a yield of 45%.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.45-7.32 (m,7H), 6.95 (d, *J* = 8.8 Hz, 2H), 6.39 (s, 1H), 5.49 (t, *J* = 3.83 Hz, 1H), 5.08 (s, 2H), 3.60 (dd, *J* = 11.30, 4.86 Hz, 1H), 2.62-2.52 (m, 2H), 2.35-2.30 (m, 2H), 2.17-2.10 (m, 1H), 1.91-1.81 (m, 2H), 1.45-1.36 (m, 1H), 1.03 (s, 3H)

Preparation of (1S,4aS,6S,8aS)-6-(4-hydroxyphenyl)-8a-methyldecahydronaphthalen-1-ol (**14**)



Chemical Formula: $C_{17}H_{24}O_2$
Molecular Weight: 260.37

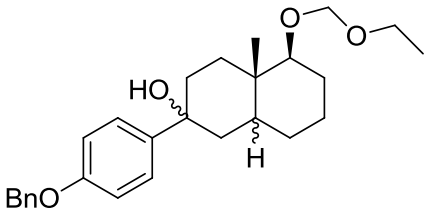
Compound **13**, 0.34g (0.98 mmol), was dissolved in10mL of pyridine. The addition of 0.2g of Pd/C followed and the mixture was stirred under H_2 atmosphere over night. The reaction mixture was filtered through Celite and concentrated *in vacuo*. The crude was recrystallized in EtOH to obtain 0.15g of compound **14** in 60% yield. The X-ray structure of this compound is given in **Figure 2.5**. Details of the X-Ray data are presented in the Appendix.

^{1}H NMR (400MHz, MeOD) δ ppm 6.97 (d, *J* = 8.8 Hz, 2H), 6.64 (d, *J* = 8.8 Hz, 2H), 3.16 (dd, *J* = 11.28, 4.61 Hz, 1H), 2.46-2.37 (m, 1H), 1.94 (td, *J* = 6.49, 3.49, 3.49 Hz, 1H), 1.73-1.67 (m, 1H), 1.69 (dd, *J* = 12.18, 2.36 Hz, 1H), 1.65-1.59 (m, 2H), 1.58-1.47 (m, 2H), 1.42-1.38 (m, 2H), 1.24-1.08 (m, 4H), 0.86 (s, 3H)

^{13}C NMR (100MHz,MeOD) δ ppm 10.5, 25.7, 29.3, 31.2, 31.4, 37.3, 39.0, 40.0, 45.6, 45.8, 80.4, 116.0, 128.6, 139.9, 156.4

HRMS: calculated for $C_{17}H_{24}O_2$ = 260.1776, found = 260.1763

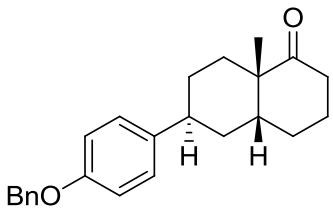
Preparation of (4aS,5S)-2-(4-(benzyloxy)phenyl)-5-(ethoxymethoxy)-4a-methyldecahydronaphthalen-2-ol (**16**)



Chemical Formula: $C_{27}H_{36}O_4$
Molecular Weight: 424.57

Method A was used with 2.8g (10.7mmol) of compound **11** dissolved in 10mL of dry THF. nBuLi (3.76mL, 9.4mmol) was added followed by 1.86g (8.21mmol) of compound **10**. The reaction was quenched with 5mL of NH_4Cl and allowed to warm to room temperature. The typical workup was employed with 10mL of EtOAc and the resulting crude was run through a silica gel column to yield 2.6g of the colourless oil, 77% yield. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

Preparation of (4aR,6S,8aS)-6-(4-(benzyloxy)phenyl)-8a-methyloctahydronaphthalen-1(2H)-one (**17**)



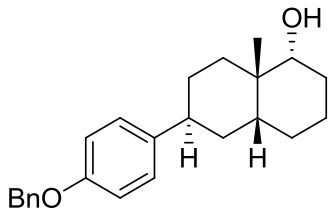
Chemical Formula: $C_{24}H_{28}O_2$
Molecular Weight: 348.48

Compound **16**, 0.48g (1.13 mmol), was dissolved in 4mL of MeOH. Three drops of conc. HCl were added and the mixture was refluxed and monitored by TLC. After 12 hours, the mixture was concentrated under vacuum and purified with flash chromatography. The pure compound obtained was a white solid weighing 0.1g (26% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.45-7.30 (m, 5H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 1H), 2.85 (ddd, *J* = 16.45, 8.32, 4.18 Hz, 1H), 2.61 (ddd, *J* = 14.64, 13.56, 6.02 Hz, 1H), 2.36-2.28 (m, 1H), 2.19-2.02 (m, 3H), 1.98-1.84 (m, 2H), 1.83-1.74 (m, 1H), 1.73-1.67 (m, 1H), 1.62-1.57 (m, 3H), 1.36-1.30 (m, 1H), 1.27 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$) δ ppm 20.0, 25.3, 27.4, 29.1, 31.0, 35.1, 37.1, 37.9, 42.9, 48.6, 70.0, 114.7, 127.5, 127.7, 127.9, 128.6, 137.2, 139.1, 157.1, 216.4

Preparation of (1R,4aR,6S,8aS)-6-(4-(benzyloxy)phenyl)-8a-methyldecahydronaphthalen-1-ol (**19**)

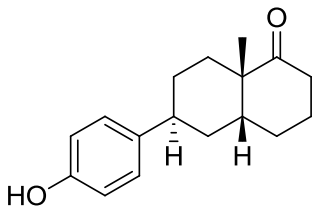


Chemical Formula: $C_{24}H_{30}O_2$
Molecular Weight: 350.49

Compound **17**, 0.1g (0.29 mmol), was dissolved in 3mL of 3:1 DCM:MeOH. The solution was placed in a – 20^{o}C bath and 0.005g (0.14 mmol) of $NaBH_4$ was added in small portions over 30min. After 2 hours, the reaction was quenched by adding 2mL of acetone followed by warming to room temperature. Another 3mL of 1M NaOH was added before the typical workup was performed with 7mL of DCM. The crude was purified by column chromatography to afford 0.1g of a white solid, representing a yield of 99%.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.46-7.29 (m, 1H), 7.13 (d, *J* = 8.8 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 1H), 5.04 (s, 1H), 3.38 (dd, *J* = 11.65, 4.47 Hz, 1H), 2.80-2.70 (m, 1H), 1.98 (dt, *J* = 13.69, 13.62, 4.92 Hz, 1H), 1.23 (s, 3H). The peaks representing the remaining aliphatic carbons were not recorded due to the difficulty in interpreting them.

Preparation of (4aR,6S,8aS)-6-(4-hydroxyphenyl)-8a-methyloctahydronaphthalen-1(2H)-one (**20**)



Chemical Formula: $C_{17}H_{22}O_2$
Molecular Weight: 258.36

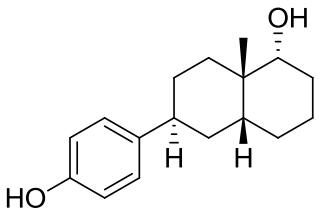
Compound **17**, 0.06g (0.17 mmol), was dissolved in 2mL of a mixture of EtOAc and DCM. Pd/C (0.01g) was added and the flask was placed under H_2 gas and allowed to stir overnight. The mixture was filtered through Celite and silica and washed with EtOAc. Upon concentration under vacuum, the crude was further purified by column chromatography to obtain 0.030g of a white solid (68% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.10 (d, *J* = 8.36 Hz, 2H), 6.80 (d, *J* = 8.36 Hz, 2H), 2.84 (tt, *J* = 12.26, 4.01 Hz, 1H), 2.61 (ddd, *J* = 14.66, 13.58, 6.05 Hz, 1H), 2.38-2.29 (m, 1H), 2.20-2.02 (m, 3H), 1.97-1.83 (m, 2H), 1.80-1.61 (m, 6H), 1.33 (td, *J* = 13.32, 3.08 Hz, 1H), 1.28 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$) δ ppm 216.4, 157.1, 139.1, 128.6, 114.7, 48.6, 42.9, 37.9, 37.1, 35.1, 31.0, 29.1, 27.4, 25.3, 20.2

HRMS: calculated for $C_{17}H_{22}O_2$ = 258.1620, found 258.1612

Preparation of (1R,4aR,6S,8aS)-6-(4-hydroxyphenyl)-8a-methyldecahydronaphthalen-1-ol (**21**)



Chemical Formula: $C_{17}H_{24}O_2$
Molecular Weight: 260.37

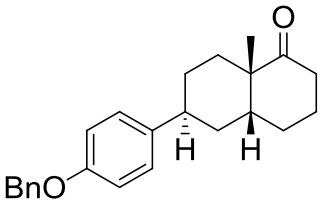
Compound **19**, 0.1g (0.29 mmol), was dissolved in 3mL of MeOH. A scoop (0.05g) of Pd/C was added and the mixture was placed under H_2 atmosphere and left to stir overnight. The reaction mixture was filtered through Celite and washed with MeOH. Upon concentration under vacuum, the crude was further purified by column chromatography, resulting in 0.045g of a white solid as the desired product (61% yield).

^{1}H NMR (400MHz, MeOD) δ ppm 6.99 (d, *J* = 8.8 Hz, 1H), 6.65 (d, *J* = 8.8 Hz, 1H), 3.26 (dd, *J* = 11.65, 4.47 Hz, 1H), 2.72-2.62 (m, 1H), 1.99-1.90 (m, 1H), 1.81-1.70 (m, 3H), 1.64-1.59 (m, 3H), 1.58-1.49 (m, 1H), 1.43-1.33 (m, 3H), 1.33-1.24 (m, 2H), 1.18 (s, 3H)

^{13}C NMR (100MHz, MeOD) δ ppm 157.3, 140.3, 129.5, 116.9, 76.1, 39.1, 38.5, 38.2, 37.3, 31.9, 31.7, 31.2, 29.3, 23.8, 19.1

HRMS: calculated for $C_{17}H_{24}O_2$ = 260.1776, found 260.1753

Preparation of (4aR,6S,8aS)-6-(4-(benzyloxy)phenyl)-8a-methyloctahydronaphthalen-1(2H)-one (**17**)



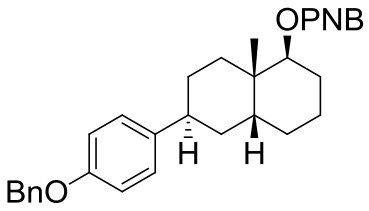
Chemical Formula: $C_{24}H_{28}O_2$
Molecular Weight: 348.48

Compound **16**, 0.6g (1.4 mmol), was dissolved in 5mL of MeOH. Three drops of $MeSO_4H$ were added and the reaction was refluxed for 4 hours. The reaction mixture was then concentrated under vacuum and the product was isolated by column chromatography. The reaction yield was of 49%, giving a white solid weighing 0.24g.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.45-7.30 (m, 5H), 7.15 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 1H), 2.85 (ddd, *J* = 16.45, 8.32, 4.18 Hz, 1H), 2.61 (ddd, *J* = 14.64, 13.56, 6.02 Hz, 1H), 2.36-2.28 (m, 1H), 2.19-2.02 (m, 3H), 1.98-1.84 (m, 2H), 1.83-1.74 (m, 1H), 1.73-1.67 (m, 1H), 1.62-1.57 (m, 3H), 1.36-1.30 (m, 1H), 1.27 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$) δ ppm 20.0, 25.3, 27.4, 29.1, 31.0, 35.1, 37.1, 37.9, 42.9, 48.6, 70.0, 114.7, 127.5, 127.7, 127.9, 128.6, 137.2, 139.1, 157.1, 216.4

Preparation of (1S,4aR,6S,8aS)-6-(4-(benzyloxy)phenyl)-8a-methyldecahydronaphthalen-1-yl 4-nitrobenzoate (**22**)

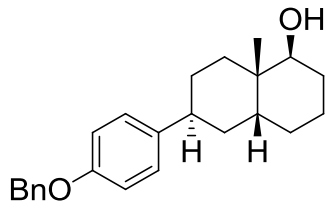


Chemical Formula: $C_{31}H_{33}NO_5$
Molecular Weight: 499.60

Compound **19**, 0.24g (0.68 mmol), was added with 0.359g (1.37 mmol) of PPh_3 and 0.229g (1.37 mmol) of PNBA into a 25mL round bottom flask. The flask was placed under N_2 atmosphere and 5mL of anhydrous THF was added. The solution was placed at 0^oC and 0.22mL (1.37 mmol) of DEAD was added. The reaction was stirred overnight allowing it to reach room temperature. 4mL of NH_4Cl was added to quench. The typical workup was employed using 7mL of DCM. The crude was purified by column chromatography to yield a yellow solid weighing 0.08g, representing a yield of 24%.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.31 (d, *J* = 9.2 Hz, 2H), 8.24 (d, *J* = 9.2 Hz, 2H), 7.45-7.29 (m, 5H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 2H), 5.00-4.97 (m, 1H), 2.88-2.78 (m, 1H), 1.14 (s, 3H). The remaining peaks representing the aliphatic carbon protons were not recorded due to the difficulty in interpreting them.

Preparation of (1S,4aR,6S,8aS)-6-(4-(benzyloxy)phenyl)-8a-methyldecahydronaphthalen-1-ol (**23**)

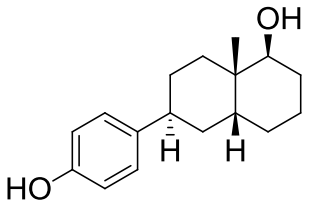


Chemical Formula: $C_{24}H_{30}O_2$
Molecular Weight: 350.49

Compound **22**, 0.08g (0.16 mmol), was dissolved in 2mL of MeOH/THF. Excess K_2CO_3 was added and the mixture was stirred overnight. Following the completion of the reaction, the solvent was evaporated and the crude run through a silica gel column to yield 0.04g of a white solid (71% yield).

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.46-7.30 (m, 5H), 7.16 (d, *J* = 8.8 Hz, 2H), 6.93 (d, *J* = 8.8 Hz, 2H), 5.05 (s, 2H), 3.43 (s, 1H), 2.83-2.75 (m, 1H), 1.17 (s, 3H), 1.09 (td, *J* = 12.76, 3.32, 3.32 Hz, 1H). The remaining peaks representing the aliphatic carbon protons were not recorded due to the difficulty in interpreting them.

Preparation of (1S,4aR,6S,8aS)-6-(4-hydroxyphenyl)-8a-methyldecahydronaphthalen-1-ol (**3**)



Chemical Formula: $C_{17}H_{24}O_2$
Molecular Weight: 260.37

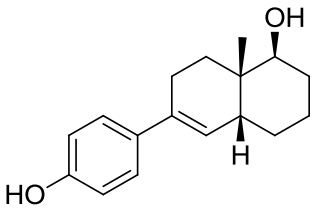
Compound **23**, 0.04g (0.11 mmol), was dissolved in 3mL of MeOH. A scoop (0.05g) of Pd/C was added and the reaction vessel was placed under H_2 gas overnight. The mixture was then filtered through Celite and silica and washed with MeOH. Following evaporation of the solvent, the product was further purified by preparative HPLC using 2:3 AcN to H_2O to yield 0.02g of a white solid, at 67% yield.

^{1}H NMR (400MHz, Acetone-d_6) δ ppm 8.07 (bs, 1H),7.07 (d, *J* = 8.8 Hz, 2H), 6.74 (d, *J* = 8.8 Hz, 2H), 3.36-3.34 (m, 1H), 2.82-2.72 (m, 1H), 1.95-1.86 (m, 2H), 1.82-1.79 (m, 4H), 1.76-1.69 (m, 1H), 1.68-1.56 (m, 2H), 1.48-1.30 (m, 3H), 1.16 (s, 3H), 1.03 (td, *J* = 13.10, 3.55, 3.55 Hz, 1H)

^{13}C NMR (100MHz, Acetone-d_6) δ ppm 157.3, 140.3, 129.5, 116.9, 76.1, 39.1, 38.5, 38.2, 37.3, 31.9, 31.7, 31.2, 29.3, 23.8, 21.8

HRMS: calculated for $C_{17}H_{24}O_2$ = 260.1776, found 260.1760

Preparation of (8aS)-6-(4-hydroxyphenyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (**24**)



Chemical Formula: $C_{17}H_{22}O_2$
Molecular Weight: 258.36

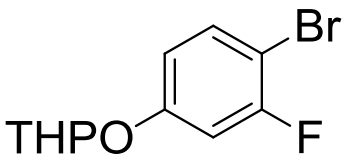
Compound **62**, 0.5g (1.18 mmol), was dissolved in 5mL of MeOH. A few drops of $MeSO_3H$ were added and the reaction was refluxed for 3 hours. The mixture was then evaporated under vacuum and run through a silica gel column to obtain a white solid weighing 0.23g, 82% yield. The isomer was isolated by preparative HPLC using 2:3 AcN to H_2O.

^{1}H NMR (400MHz, Acetone-d_6) δ ppm 8.25 (s, 1H), 7.27 (d, *J* = 8.71 Hz, 2H), 6.77 (d, *J* = 8.71 Hz, 2H), 5.72 (d, *J* = 0.80 Hz, 1H), 3.66-3.60 (m, 1H), 2.53-2.41 (m, 1H), 2.37-2.22 (m, 2H), 2.14 (ddd, *J* = 13.16, 6.00, 2.54 Hz, 1H), 1.80 (m 1H), 1.66-1.51 (m, 2H), 1.50-1.43 (m, 2H), 1.37-1.24 (m, 2H), 1.00 (s, 3H)

^{13}C NMR (100MHz, Acetone-d_6) δ ppm 158.3, 137.6, 135.2, 128.7, 127.7, 116.8, 69.9, 44.3, 37.8, 34.2, 32.5, 30.0, 26.1, 23.3, 21.6

HRMS: calculated for $C_{17}H_{22}O_2$ = 258.1620, found 260.1601

Preparation of 2-(4-bromo-3-fluorophenoxy)tetrahydro-2H-pyran (**27**)

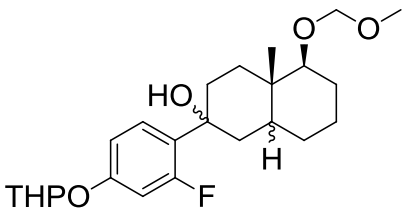


Chemical Formula: $C_{11}H_{12}BrFO_2$
Molecular Weight: 275.11

The dissolution of 3.0g (15.7 mmol) of 4-bromo-3-fluorophenol in 12mL of DCM was followed by the addition of 2.15mL (23.6 mmol) of 3,4-dihydro-2H-pyran. Then a few crystals of pTSA (0.05g) were added. The reaction was stirred at room temperature for 40 minfollowed by evaporation of the solvent and column chromatography. The final product, a colourless oil, weighed 3.0g corresponding to 70% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.39 (dd, *J* = 8.79, 8.11 Hz, 1H), 6.88 (dd, *J* = 10.48, 2.73 Hz, 1H), 6.75 (ddd, *J* = 8.87, 2.73, 1.09 Hz, 1H), 5.37 (t, *J* = 3.13, 3.13 Hz, 1H), 3.84 (ddd, *J* = 11.30, 9.98, 3.11 Hz, 1H), 3.61 (dtd, *J* = 11.35, 4.14, 4.06, 1.37 Hz, 1H), 2.05-1.91 (m, 1H), 1.89-1.81 (m, 2H), 1.73-1.56 (m, 3H)

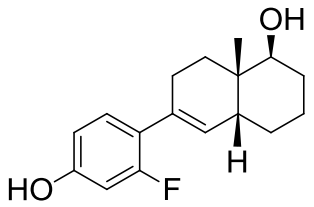
Preparation of (4aS,5S)-2-(2-fluoro-4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)-5-(methoxymethoxy)-4a-methyldecahydronaphthalen-2-ol (**65**)



Chemical Formula: $C_{24}H_{35}FO_5$
Molecular Weight: 422.53

Compound **27**, 3.0g (10.9 mmol), was placed in a 50mL round bottom flask. Method A was used with 10mL of THF and 3.8mL (8.4 mmol) of nBuLi. 1.15g (7.3 mmol) of compound **10** was dissolved in 3mL of dry THF and added to the reaction. Then 10mL of NH_4Cl was added to quench. The typical workup was employed using 15mL of EtOAc and the crude was purified by column chromatography. The product was a thick oil weighing 2.52g, 82% yield. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

Preparation of (1S,4aR,8aS)-6-(2-fluoro-4-hydroxyphenyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (**30**)



Chemical Formula: $C_{17}H_{21}FO_2$
Molecular Weight: 276.35

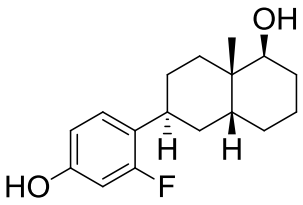
Compound **65**, 1.7g (4.02 mmol), was dissolved in 10mL of MeOH. A few drops of $MeSO_3H$ were added and the reaction was refluxed for 3 hours. The mixture was then evaporated under vacuum and run through a silica gel column to obtain a white solid weighing 1.2g, 98% yield. The isomer was isolated by preparative HPLC using 2:3 AcN to H_2O.

^{1}H NMR (400MHz, Acetone-d_6) δ ppm 8.69 (s, 1H), 7.12 (t, *J* = 8.79, 8.79 Hz, 1H), 6.62 (dd, *J* = 8.37, 2.34 Hz, 1H), 6.55 (dd, *J* = 12.72, 2.42 Hz, 1H), 5.54 (s, 1H), 3.75-3.69 (m, 1H), 2.54-2.42 (m, 1H), 2.32-2.23 (m, 1H), 2.13-2.08 (m, 1H), 1.84-1.80 (m, 1H), 1.67-1.63 (m, 1H), 1.59-1.54 (m, 1H), 1.36-1.23 (m, 1H), 1.51-1.37 (m, 2H), 1.34-1.25 (m, 2H), 1.01 (s, 3H)

^{13}C NMR (100MHz, Acetone-d_6) δ ppm 163.5, 161.1, 159.5, 159.4, 134.9, 133.4, 133.3, 131.7, 131.6, 123.9, 123.7, 113.1, 113.0, 104.8, 104.6, 69.8, 44.1, 37.6, 32.3, 29.6, 27.4, 27.3, 23.0, 21.3. The peaks representing the aromatic carbons are doubled due to carbon-fluorine coupling.

HRMS: calculated for $C_{17}H_{21}FO_2$ = 276,1526, found 276.1501

Preparation of (1S,4aR,6S,8aS)-6-(2-fluoro-4-hydroxyphenyl)-8a-methyldecahydronaphthalen-1-ol (**33**)



Chemical Formula: $C_{17}H_{23}FO_2$
Molecular Weight: 278.36

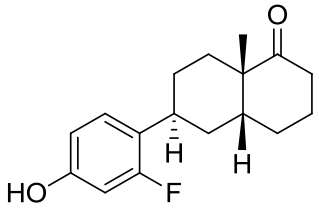
Compound **30**, 0.53g (1.92 mmol), was dissolved in 4mL of MeOH. A scoop (0.1g) of Pd/C was added and the reaction vessel was placed under H_2 gas overnight. The reaction mixture was then filtered through Celite and silica before washing with MeOH. The solvent was evaporated under vacuum and the isomer was isolated by careful column chromatography using 5% EtOAc in hexanes as eluent. The final product was a white solid weighing 0.05g, representing a 9% yield.

^{1}H NMR (400MHz, MeOD) δ ppm 7.04 (t, *J* = 8.67, 8.67 Hz, 1H), 6.49 (dd, *J* = 8.38, 2.18 Hz, 1H), 6.39 (dd, *J* = 12.36, 2.39 Hz, 1H), 3.30 (s, 1H), 3.07-2.99 (m, 1H), 1.97-1.84 (m, 2H), 1.81-1.76 (m, 3H), 1.74-1.63 (m, 1H), 1.60-1.57 (m, 2H), 1.51-1.46 (m, 1H), 1.36-1.27 (m, 2H), 1.12 (s, 1H), 1.01 (d, *J* = 12.80 Hz, 1H)

^{13}C NMR (100MHz, MeOD) δ ppm 163.7, 161.3, 158.0, 157.8, 129.3, 129.2, 125.8, 125.7, 112.2, 112.1, 103.7, 103.4, 76.5, 37.9, 37.8, 35.1, 32.1, 31.4, 30.2, 29.4, 28.5, 22.9, 21.2. The peaks representing the aromatic carbons are doubled due to carbon-fluorine coupling.

HRMS: calculated for $C_{17}H_{23}FO_2$ = 278.1682, found 278.1671

Preparation of (4aR,6S,8aS)-6-(2-fluoro-4-hydroxyphenyl)-8a-methyloctahydronaphthalen-1(2H)-one (**37**)



Chemical Formula: $C_{17}H_{21}FO_2$
Molecular Weight: 276.35

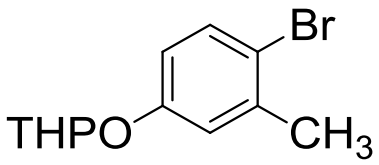
Compound **30**, 0.376g (1.4 mmol), was dissolved in 5mL of $MeNO_2$. Three drops of CF_3SO_4H were added and the reaction was refluxed for 40 min. The reaction mixture was then concentrated under vacuum and the product was isolated by column chromatography. The reaction yield was of 73%, giving a white solid weighing 0.24g.

^{1}H NMR (400MHz, Acetone-d_6) δ ppm 8.59 (bs, 1H), 7.17 (t, *J* = 8.69, 8.69 Hz, 1H), 6.63 (dd, *J* = 8.44, 2.41 Hz, 1H), 6.54 (dd, *J* = 12.36, 2.46 Hz, 1H), 3.18 (tt, *J* = 12.55, 12.55, 4.02, 4.02 Hz, 1H), 2.69 (dt, *J* = 14.15, 14.08, 6.04 Hz, 1H), 2.31-2.22 (m, 1H), 2.22-2.14 (m, 2H), 2.03-1.96 (m, 1H), 1.90-1.83 (m, 1H), 1.82-1.74 (m, 1H), 1.73-1.64 (m, 2H), 1.63-1.60 (m, 1H), 1.59-1.57 (m, 1H), 1.56-1.54 (m, 1H), 1.25-1.20 (m, 1H), 1.23 (s, 3H)

^{13}C NMR (100MHz, Acetone-d_6) δ ppm 215.9, 164.1, 1661.7, 158.8, 158.7, 130.2, 130.1, 125.9, 125.8, 113.2, 113.1, 104.6, 104.3, 50.1, 44.9, 39.3, 35.6, 32.6, 32.3, 29.6, 29.0, 27.1, 21.3. The peaks representing the aromatic carbons are doubled due to carbon-fluorine coupling.

HRMS: calculated for $C_{17}H_{21}FO_2$ = 276.1526, found = 276.1535

Preparation of 2-(4-bromo-3-methylphenoxy)tetrahydro-2H-pyran (**28**)

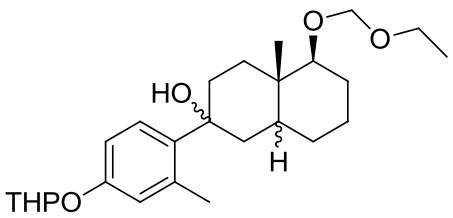


Chemical Formula: $C_{12}H_{15}BrO_2$
Molecular Weight: 271.15

The dissolution of4-bromo-3-methylphenol, 3.0g (16.0 mmol), in 12mL of DCM was followed by the addition of 1.90mL (20.9 mmol) of 3,4-dihydro-2H-pyran. Then a few crystals (0.1g) of pTSA were added. The reaction was stirred at room temperature for 40 min followed by evaporation of the solvent and column chromatography. The final product, a colourless oil, weighed 2.7g corresponding to 63% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.39 (d, *J* = 8.73 Hz, 1H), 6.95 (d, *J* = 2.57 Hz, 1H), 6.77 (dd, *J* = 8.73, 2.59 Hz, 1H), 5.37 (t, *J* = 3.19, 3.19 Hz, 1H), 3.87 (ddd, *J* = 11.42, 9.76, 3.12 Hz, 1H), 3.60 (dtd, *J* = 11.34, 4.18, 4.12, 1.44 Hz, 1H), 2.36 (s, 3H), 2.04-1.93 (m, 1H), 1.87-1.81 (m, 2H), 1.72-1.57 (m, 3H)

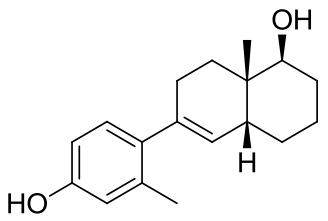
Preparation of (4aS,5S)-5-(ethoxymethoxy)-4a-methyl-2-(2-methyl-4-((tetrahydro-2H-pyran-2-yl)oxy)phenyl)decahydronaphthalen-2-ol (**66**)



Chemical Formula: $C_{26}H_{40}O_5$
Molecular Weight: 432.59

Compound **28**, 1.66g (6.1 mmol), was dissolved with 10mL of THF using Method A followed by the addition of 2.2mL (5.4 mmol) of nBuLi. Compound **10**, 1.13g (4.7 mmol), was dissolved in 3mL of dry THF and added to the reaction. Then 10mL of NH_4Cl was added to quench. The typical workup was employed using 15mL of EtOAc and the crude was purified by column chromatography. The product was a thick oil weighing 1.48g, 73% yield. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

Preparation of (1S,4aR,8aS)-6-(4-hydroxy-2-methylphenyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (**32**)



Chemical Formula: $C_{18}H_{24}O_2$
Molecular Weight: 272.38

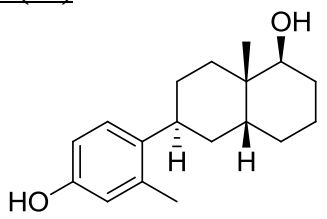
Compound **66**, 0.7g (1.62 mmol), was dissolved in 5mL of MeOH. Three drops of $MeSO_3H$ were added and the reaction was refluxed for 2 hours. The mixture was then evaporated under vacuum and the product isolated via a silica gel column. The product was a white solid weighing 0.22g, 50% yield. The isomer was isolated by preparative HPLC using 2:3 AcN to H_2O.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 6.90 (d, *J* = 8.11 Hz, 1H), 6.64 (d, *J* = 2.56 Hz, 1H), 6.60 (dd, *J* = 8.11, 2.67 Hz, 1H), 5.38 (m, 1H), 3.56 (t, *J* = 3.22 Hz, 1H), 2.47-2.30 (m, 2H), 2.23 (s, 3H), 1.88-1.83 (m, 3H), 1.71-1.62 (m, 2H), 1.61-1.54 (m, 2H), 1.49-1.44 (m, 2H), 1.10 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$) δ ppm 157.3, 138.2, 138.0, 128.1, 127.7, 118.8, 116.8, 114.7, 69.9, 44.3, 37.8, 34.2, 32.5, 30.0, 26.1, 23.3, 21.6, 20.7

HRMS: calculated for $C_{18}H_{24}O_2$ = 272.1776, found 272.1751

Preparation of (1S,4aR,6S,8aS)-6-(4-hydroxy-2-methylphenyl)-8a-methyldecahydronaphthalen-1-ol (**34**)



Chemical Formula: $C_{18}H_{26}O_2$
Molecular Weight: 274.40

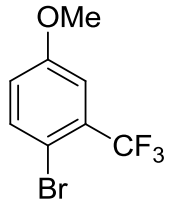
Compound **32**, 0.53g (1.92 mmol), was dissolved in 4mL of MeOH. A scoop of (0.05g) Pd/C was added and the reaction vessel was placed under H_2 gas overnight. The reaction mixture was then filtered through Celite and silica before washing with MeOH. The solvent was evaporated under vacuum and the isomer was isolated by careful column chromatography using 5% EtOAc in hexanes. The final product was a white solid weighing 0.05g, representing a 9% yield.

^{1}H NMR (400MHz, Acetone-d_6) δ ppm 7.91 (bs, 1H), 7.09 (d, *J* = 8.09 Hz, 1H), 6.64-6.59 (m, 2H), 3.32 (s, 1H), 3.07-2.97 (m, 1H), 2.23 (s, 3H), 1.98-1.85 (m, 2H), 1.85-1.72 (m, 5H), 1.63-1.53 (m, 2H), 1.47-1.44 (m, 1H), 1.38-1.24 (m, 2H), 1.19 (s, 3H), 1.05 (td, *J* = 12.80, 3.17, 3.17 Hz, 1H)

^{13}C NMR (100MHz, Acetone-d_6) δ ppm 156.8, 138.2, 138.0, 128.1, 118.8, 114.7, 76.4, 38.6, 38.4, 36.9, 34.6, 32.3, 30.5, 30.3, 29.2, 24.0, 21.8, 20.4.

HRMS calculated for $C_{18}H_{26}O_2$ = 274.1933, found 274.1909

Preparation of 1-bromo-4-methoxy-2-(trifluoromethyl)benzene (**39**)

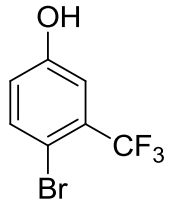


Chemical Formula: $C_8H_6BrF_3O$
Molecular Weight: 255.03

The dissolution of 1-methoxy-3-(trifluoromethyl)benzene **38**, 1.0mL (6.91 mmol), in 10mL of AcOH was followed by the dropwise addition of a mixture of 0.53mL(10.4 mmol) of Br_2 in 5mL of AcOH using a dropping funnel. The reaction mixture was stirred overnight. The typical workup was employed using 15mL each of ether and H_2O before performing a column chromatography for purification. This yielded 1.1g of colourless oil (62% yield). The NMR data of this material matched the one previously obtained by the group.[18]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.58 (d, *J* = 8.80 Hz, 1H), 7.21 (d, *J* = 3.02 Hz, 1H), 6.91 (dd, *J* = 8.80, 3.02 Hz, 1H), 3.83 (s, 1H)

Preparation of 4-bromo-3-(trifluoromethyl)phenol (**40**)

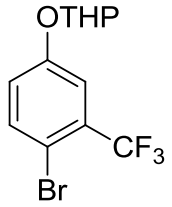


Chemical Formula: $C_7H_4BrF_3O$
Molecular Weight: 241.01

Compound **39**, 3.2g (12.5 mmol), was placed in a flask purged with dry N_2 and 15mL of dry DCM was added. The resulting solution was placed in a -30^oC bath and 1.79mL (18.8mmol) of BBr_3 was added dropwise. The reaction mixture was stirred for 2 hours. To quench the reaction, 10mL of MeOH was added slowly followed by 10mL of brine. The typical workup was employed using 10mL of DCM. Column chromatography yielded 1.9g of amber-coloured oil, representing 63% yield. The NMR data of this material matched the one previously obtained by the group.[18]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.54 (d, *J* = 8.65 Hz, 1H), 7.18 (d, *J* = 3.00 Hz, 1H), 6.87 (dd, *J* = 8.65, 3.00 Hz, 1H)

Preparation of 2-(4-bromo-3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran (**41**)

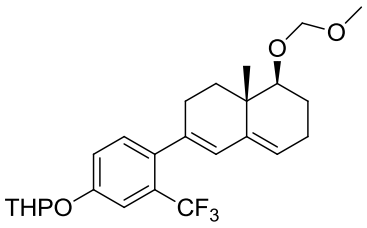


Chemical Formula: $C_{12}H_{12}BrF_3O_2$
Molecular Weight: 325.12

Compound **40**, 1.9g (7.88 mmol), was dissolved in 15mL of DCM and 0.94mL (10.2 mmol) of 3,4-dihydro-2H-pyran was added followed by a few crystals (0.1g) of pTSA. The reaction mixture was stirred at room temperature for one hour followed by evaporation of the solvent and column chromatography. The final product, a light green oil, weighed 1.7g corresponding to 68% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.57 (d, *J* = 8.80 Hz, 1H), 7.38 (d, *J* = 2.92 Hz, 1H), 7.09 (dd, *J* = 8.77, 2.82 Hz, 1H), 5.43 (t, *J* = 3.02, 3.02 Hz, 1H), 3.82 (ddd, *J* = 11.00, 10.28, 3.08 Hz, 1H), 3.62 (dtd, *J* = 11.36, 4.15, 4.03, 1.45 Hz, 1H), 2.05-1.90 (m, 1H), 1.90-1.84 (m, 2H), 1.76-1.67 (m, 2H), 1.64-1.57 (m, 1H)

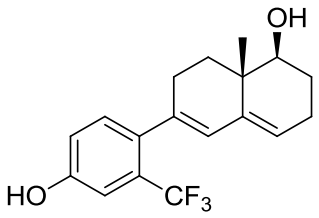
Preparation of 2-(4-((4aS,5S)-5-(methoxymethoxy)-4a-methyl-3,4,4a,5,6,7-hexahydronaphthalen-2-yl)-3-(trifluoromethyl)phenoxy)tetrahydro-2H-pyran (**37**)



Chemical Formula: $C_{25}H_{31}F_3O_4$
Molecular Weight: 452.51

Method A was used to prepare compound **42** using 0.75g (2.3 mmol) of compound **41** with 10mL of THF and 1.0mL (2.0 mmol) of nBuLi. Compound **9**, 0.40g (1.8 mmol), was dissolved in 3mL of dry THF and added to the reaction. Then 5mL of NH_4Cl was added to quench. The typical workup was employed using 10mL of EtOAc and the crude was purified by column chromatography. The product was a thick oil weighing 0.55g, 67% yield. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

Preparation of (1S,8aS)-6-(4-hydroxy-2-(trifluoromethyl)phenyl)-8a-methyl-1,2,3,7,8,8a-hexahydronaphthalen-1-ol (**67**)

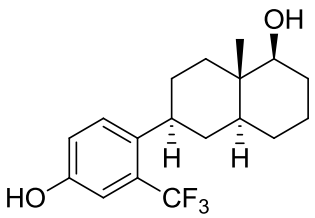


Chemical Formula: $C_{18}H_{19}F_3O_2$
Molecular Weight: 324.34

Compound **42**, 0.55g (1.22 mmol), was dissolved in 5mL of MeOH. Three drops of $MeSO_3H$ were added and the reaction was refluxed for 1 hour. The mixture was then evaporated under vacuum and the product isolated via a silica gel column. The product was a white solid weighing 0.29g, 74% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.12-7.09 (m, 2H), 6.95 (dd, *J* = 8.38, 2.61 Hz, 1H), 5.90-5.88 (m, 1H), 5.42 (t, *J* = 3.76, 3.76 Hz, 1H), 3.60 (dd, *J* = 11.35, 4.77 Hz, 1H), 2.56-2.45 (m, 1H), 2.32-2.24 (m, 3H), 2.09-2.04 (m, 1H), 1.91-1.83 (m, 2H), 1.43 (dt, *J* = 12.75, 12.57, 5.49 Hz, 1H), 1.08 (s, 3H)

Preparation of (1S,4aS,6S,8aS)-6-(4-hydroxy-2-(trifluoromethyl)phenyl)-8a-methyldecahydronaphthalen-1-ol (**43**)



Chemical Formula: $C_{18}H_{23}F_3O_2$
Molecular Weight: 328.37

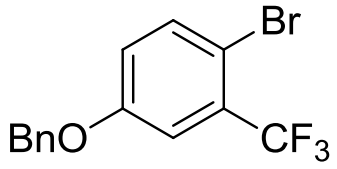
Compound **67**, 0.29g (0.89 mmol), was dissolved in 4mL of MeOH. A scoop of (0.05g) Pd/C was added and the reaction vessel was placed under H_2 gas overnight. The reaction mixture was then filtered through Celite and silica before washing with MeOH. The solvent was evaporated under vacuum and the isomer was isolated by column chromatography. The final product was a white solid weighing 0.25g, representing 86% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.33 (d, *J* = 8.54 Hz, 1H), 7.06 (d, *J* = 2.74 Hz, 1H), 6.96 (dd, *J* = 8.52, 2.75 Hz, 1H), 3.31 (dd, *J* = 11.37, 4.26 Hz, 1H), 2.96-2.86 (m, 1H), 1.97 (td, *J* = 13.04, 3.29, 3.29 Hz, 1H), 1.78-1.64 (m, 4H), 1.63-1.48 (m, 4H), 1.36-1.42 (m, 1H)1.23-1.16 (m, 3H), 0.95 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$) δ ppm 82.6, 48.8, 46.6, 41.0, 39.2, 37.3, 31.4, 41.2, 29.3, 25.7, 10.9

HRMS: calculated for $C_{18}H_{23}F_3O_2$ = 328.1650, found 328.1633

Preparation of 4-(benzyloxy)-1-bromo-2-(trifluoromethyl)benzene (**68**)

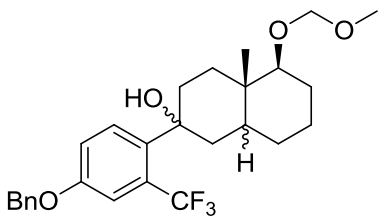


Chemical Formula: $C_{14}H_{10}BrF_3O$
Molecular Weight: 331.13

Compound **40**, 0.45g (1.87 mmol), was dissolved in 5mL of acetone. The solution was stirred and 0.28g (2.05 mmol) of K_2CO_3 was added followed by 0.24mL (2.05 mmol) of BnBr. The mixture was refluxed for 2 hours. Following the completion of the reaction, the mixture was allowed to cool to room temperature and filtered. The crude was evaporated under vacuum and purified by silica gel chromatography to afford 0.58g of white solid, representing 94% yield.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.46-7.32 (m, 5H), 7.25-7.17 (m, 2H), 7.16-7.09 (m, 1H), 5.10 (s, 2H)

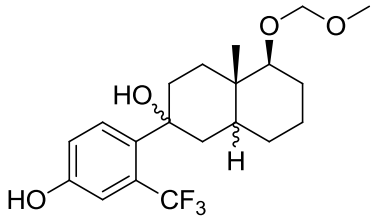
Preparation of (4aS,5S)-2-(4-(benzyloxy)-2-(trifluoromethyl)phenyl)-5-(methoxymethoxy)-4a-methyldecahydronaphthalen-2-ol (**69**)



Chemical Formula: $C_{27}H_{33}F_3O_4$
Molecular Weight: 478.54

Compound **68**, 0.90g (2.72 mmol), was dissolved with 10mL of THF using Method A. Then 1.32mL (2.61 mmol) of nBuLi were added followed by 0.47g (2.09 mmol) of compound **10** which was dissolved in 3mL of dry THF. Then 5mL of NH_4Cl was added to quench. The typical workup was employed using 10mL of EtOAc and the crude was purified by column chromatography. The product was a thick oil weighing 0.60g, 60% yield. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

Preparation of (4aS,5S)-2-(4-hydroxy-2-(trifluoromethyl)phenyl)-5-(methoxymethoxy)-4a-methyldecahydronaphthalen-2-ol (**70**)



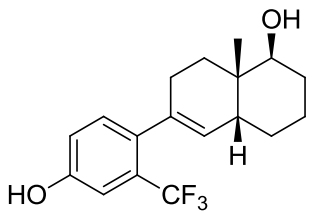
Chemical Formula: $C_{20}H_{27}F_3O_4$
Molecular Weight: 388.42

Compound **69**, 0.36g (0.75 mmol), was dissolved in 4mL of EtOAc. A scoop of (0.05g) $Pd/CaCO_3$ was added and the reaction vessel was placed under H_2 gas overnight. The reaction mixture was then filtered through Celite and silica before washing with EtOAc. The solvent was evaporated under vacuum and the isomer was isolated by column chromatography. The final product was a white solid weighing 0.16g, representing 55% yield.

^{1}H NMR (400MHz, MeOD) δ ppm 7.54 (d, *J* = 8.91 Hz, 1H), 7.16 (d, *J* = 2.70 Hz, 1H), 6.94 (dd, *J* = 8.91, 2.70 Hz, 1H), 4.77 (d, *J* = 6.92 Hz, 1H), 4.57 (d, *J* = 6.92 Hz, 1H), 3.98-3.94 (m, 1H), 3.37 (s, 3H), 2.20-2.08 (m, 3H), 1.94-1.85 (m, 3H), 1.70-1.45 (m, 6H), 1.16-1.09 (m, 1H), 1.04 (s, 3H)

^{13}C NMR (100MHz, MeOD) δ ppm 130.5, 125.0, 119.1, 116.0, 115.9, 96.4, 75.7, 74.7, 55.9, 40.8, 39.7, 37.7, 34.7, 31.7, 28.7, 27.6, 22.2, 21.6.

Preparation of (1S,4aR,8aS)-6-(4-hydroxy-2-(trifluoromethyl)phenyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (**71**)



Chemical Formula: $C_{18}H_{21}F_3O_2$
Molecular Weight: 326.35

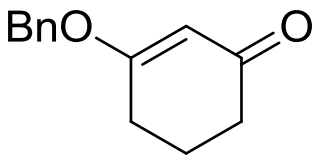
Compound **70**, 0.16g (0.41 mmol), was dissolved in 5mL of MeOH. Three drops of conc. HCl were added and the reaction mixture was refluxed for 2 hours. The mixture was then evaporated under vacuum and the product isolated via a silica gel column. The product was a white solid weighing 0.13g, 97% yield. The isomer was isolated by preparative HPLC using 2:3 AcN to H_2O.

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 8.97-8.78 (m, 1H), 7.14 (d, *J* = 8.36 Hz, 1H), 7.11 (d, *J* = 2.47 Hz, 1H), 7.03 (dd, *J* = 8.36, 2.47 Hz, 1H), 5.25 (s, 1H), 3.84-3.70 (m, 1H), 2.45-2.29 (m, 1H), 2.27-2.06 (m, 3H), 1.82-1.75 (m, 1H), 1.72-1.64 (m, 1H), 1.61-1.43 (m, 2H), 1.43-1.25 (m, 3H), 1.02 (s, 3H)

^{13}C NMR (100MHz, $CDCl_3$) δ ppm 75.3, 44.1, 37.6, 32.3, 29.6, 27.4, 27.3, 23.0, 21.3.

HRMS: calculated for $C_{18}H_{21}F_3O_2$ = 326.1494, found 326.1472

Preparation of 3-(benzyloxy)cyclohex-2-enone (**56**)

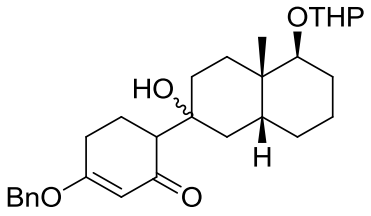


Chemical Formula: $C_{13}H_{14}O_2$
Molecular Weight: 202.25

The dissolution of 0.10g (0.89 mmol) of 1,3-cyclohexan-di-one in 5mL of $CHCl_3$ was followed by the slow addition of 0.14mL (1.16 mmol) of BnBr. Then 0.27g (1.16 mmol) of Ag_2O was added to the solution. The reaction mixture was refluxed for two hours. The mixture was then filtered and concentrated under vacuum. The crude product was purified by column chromatography yielding 0.15g of white solid, representing 80% yield. The NMR data of this material matched that in the literature.[26]

^{1}H NMR (400MHz, $CDCl_3$) δ ppm 7.42-7.31 (m, 1H), 5.48 (s, 1H), 4.89 (s, 2H), 2.47 (t, *J* = 6.27, 2H), 2.00 (t, *J* = 6.27, 2H), 2.39-2.34 (quint, *J* = 6, 12.8 Hz, 2H)

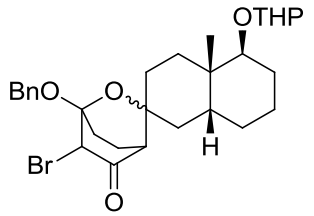
Preparation of 3-(benzyloxy)-6-((4aS,5S,8aR)-2-hydroxy-4a-methyl-5-((tetrahydro-2H-pyran-2-yl)oxy)decahydronaphthalen-2-yl)cyclohex-2-enone (**57**)



Chemical Formula: $C_{29}H_{40}O_5$
Molecular Weight: 468.62

Preparation of this material required Method A starting with 0.80g (3.96 mmol) of compound **56** with 10mL of THF and 1.75mL (3.50 mmol) of LDA. Then 0.81g (3.04 mmol) of compound **10** was dissolved in 3mL of dry THF and added to the reaction mixture. Then 5mL of NH_4Cl was added to quench. The typical workup was employed using 10mL of EtOAc and the crude was purified by column chromatography. The product was a white solid weighing 1.63g, 74% yield. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

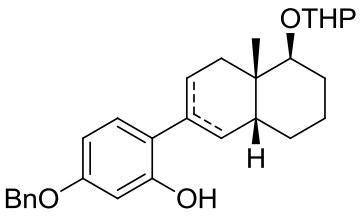
Preparation of (4a'S,5'S,8a'R)-1-(benzyloxy)-6-bromo-4a'-methyl-5'-((tetrahydro-2H-pyran-2-yl)oxy)octahydro-1'H-2-oxaspiro[bicyclo[2.2.2]octane-3,2'-naphthalen]-5-one (**58**)



Chemical Formula: $C_{29}H_{39}BrO_5$
Molecular Weight: 547.52

Compound **57**, 0.90g (1.92 mmol) was dissolved in 6mL of DCM. The solution was placed in an ice bath followed by the addition of 0.36g (2.02 mmol) of NBS and three drops of 10% HBr. The reaction ran for two hours before employing the typical workup using 5mL each of aqueous sodium metabisulfite and DCM. The crude product was purified by flash chromatography affording 0.44g of fluffy white solid (42%). The NMR data of this material appeared to be consistent with the desired structure. and was used directly without full characterization in the next step. Characterization was rendered difficult due to the presence of multiple chiral centres.

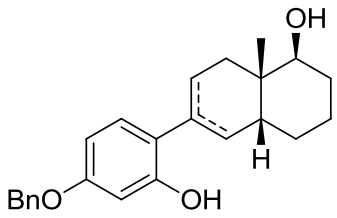
Preparation of 5-(benzyloxy)-2-((4aS,5S,8aR)-4a-methyl-5-((tetrahydro-2H-pyran-2-yl)oxy)-3,4,4a,5,6,7,8,8a-octahydronaphthalen-2-yl)phenol (**59**)



Chemical Formula: $C_{29}H_{35}O_4$
Molecular Weight: 447.59

Compound **58**, 0.44g (0.80 mmol), was dissolved in 6mL of DMF. Then 0.25mL (1.69 mmol) of DBU was added and the reaction mixture was refluxed at 140^{o}C for 16 hours. The reaction was allowed to cool to ambient temperature and the typical workup was employed using 5mL each of EtOAc and H_2O. The crude product was purified by flash chromatography affording 0.10g of greenish sticky oil (28%). The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step. Aromatization was confirmed with the desired peaks and patterns apparent in the spectrum.

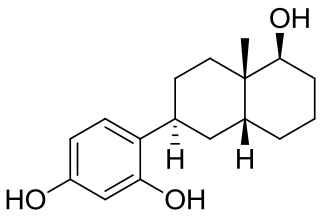
Preparation of (1S,4aR,8aS)-6-(4-(benzyloxy)-2-hydroxyphenyl)-8a-methyl-1,2,3,4,4a,7,8,8a-octahydronaphthalen-1-ol (**72**)



Chemical Formula: $C_{24}H_{27}O_3$
Molecular Weight: 363.47

Compound **59**, 0.10g (0.22 mmol), was dissolved in 5mL of MeOH. A few crystals (0.01g) of pTSA were added and the reaction mixture was refluxed for 1 hour. The mixture was then evaporated under vacuum and the product isolated via a silica gel column. The product was an orange oil weighing 0.06g, 74% yield. The NMR data of this material appeared to be consistent with the desired structure and was used directly without full characterization in the next step.

Preparation of 4-((2S,4aS,5S,8aR)-5-hydroxy-4a-methyldecahydronaphthalen-2-yl)benzene-1,3-diol (**60**)



Chemical Formula: $C_{17}H_{24}O_3$
Molecular Weight: 276.37

Compound **72**, 0.06g (0.17 mmol), was dissolved in 4mL of MeOH. A scoop of (0.01g) Pd/C was added and the reaction vessel was placed under H_2 gas overnight. The reaction mixture was then filtered through Celite and silica before washing with MeOH. The solvent was evaporated under vacuum and the isomer was isolated by preparative HPLC using 2:3 AcN to H_2O.The final product **60** was a white solid weighing 0.005g, representing 11% yield.

^{1}H NMR (400MHz, Acetone-d_6) δ ppm 7.99 (s, 1H), 7.88 (s, 1H), 6.98 (d, *J* = 8.30 Hz, 1H), 6.36 (d, *J* = 2.42 Hz, 1H), 6.29 (dd, *J* = 8.29, 2.44 Hz, 1H), 3.32 (bs, 1H), 3.19 (tt, *J* = 12.55, 3.99 Hz, 1H),1.99-1.86 (m, 3H), 1.85-1.79 (m, 3H), 1.77-1.70 (m, 1H), 1.66-1.56 (m, 2H), 1.46-1.42 (m, 1H), 1.38-1.29 (m, 2H), 1.17 (s, 3H), 1.01 (dt, *J* = 12.89, 3.21 Hz, 1H)

^{13}C NMR (100MHz, Acetone-d_6) δ ppm 157.9, 157.2, 129.1, 126.6, 108.4, 104.4, 76.4, 38.7, 38.4, 35.5, 32.3, 32.2, 31.3, 31.1, 29.3, 24.0, 21.9

HRMS: calculated for $C_{17}H_{24}O_3$ = 276.1725, found 276.1711

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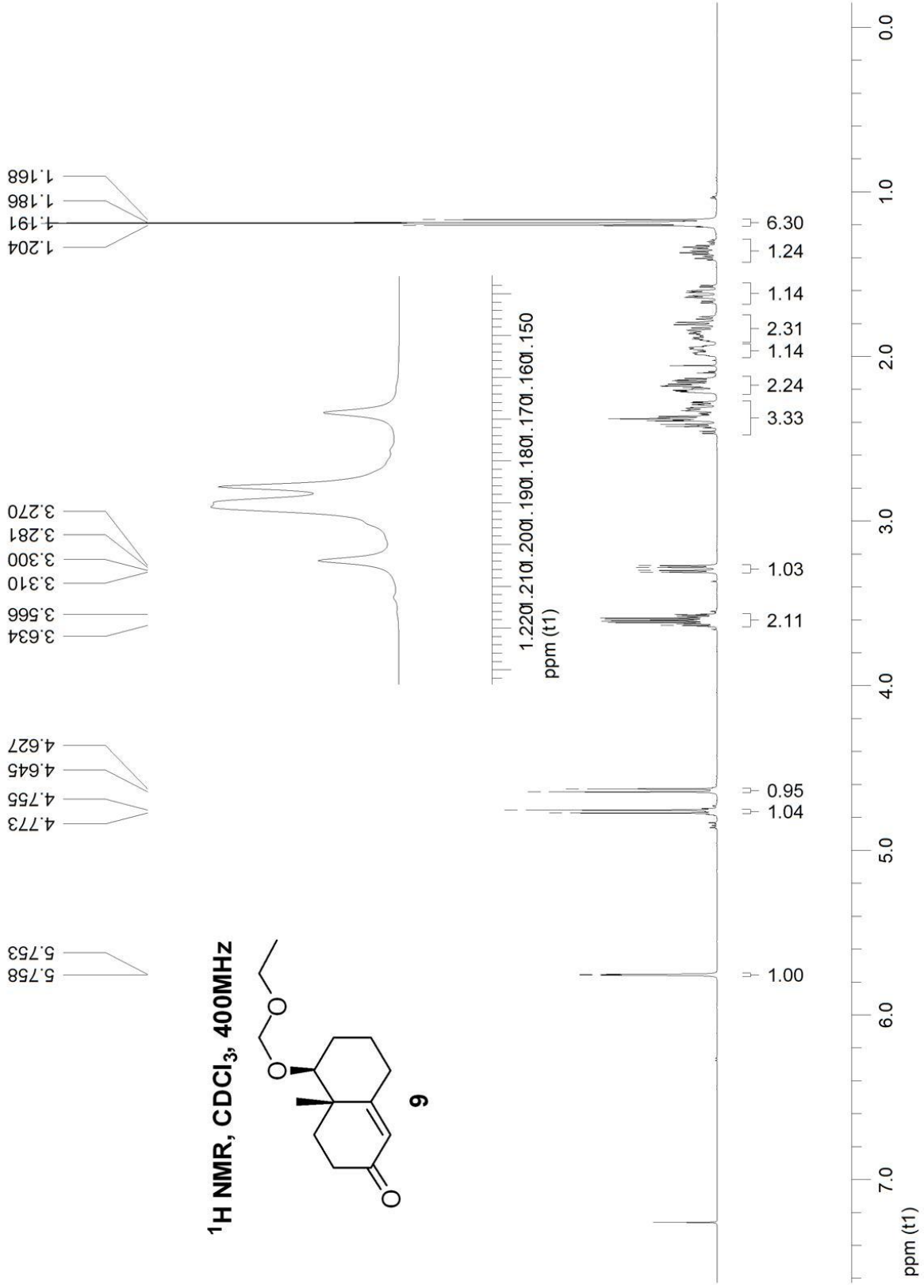
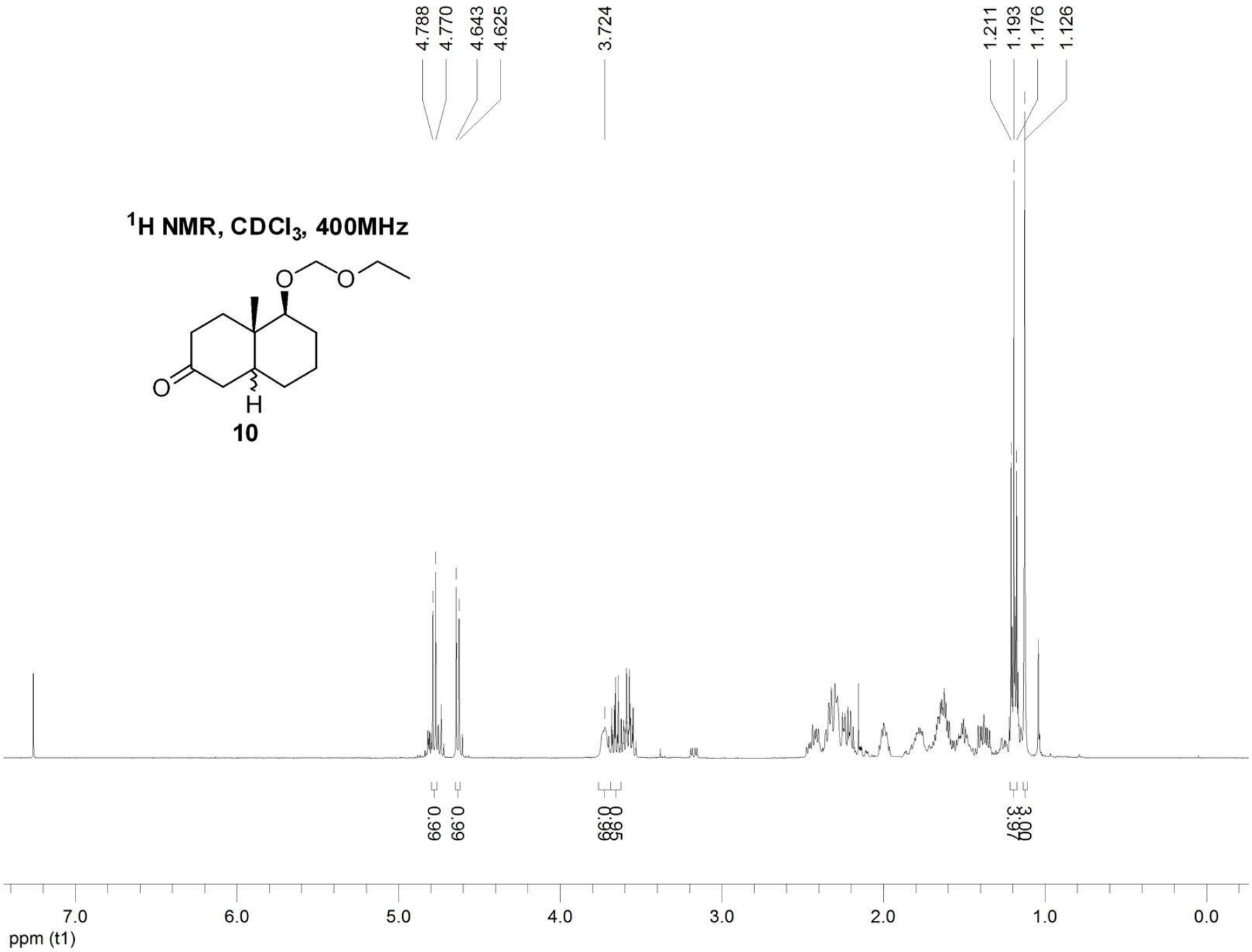
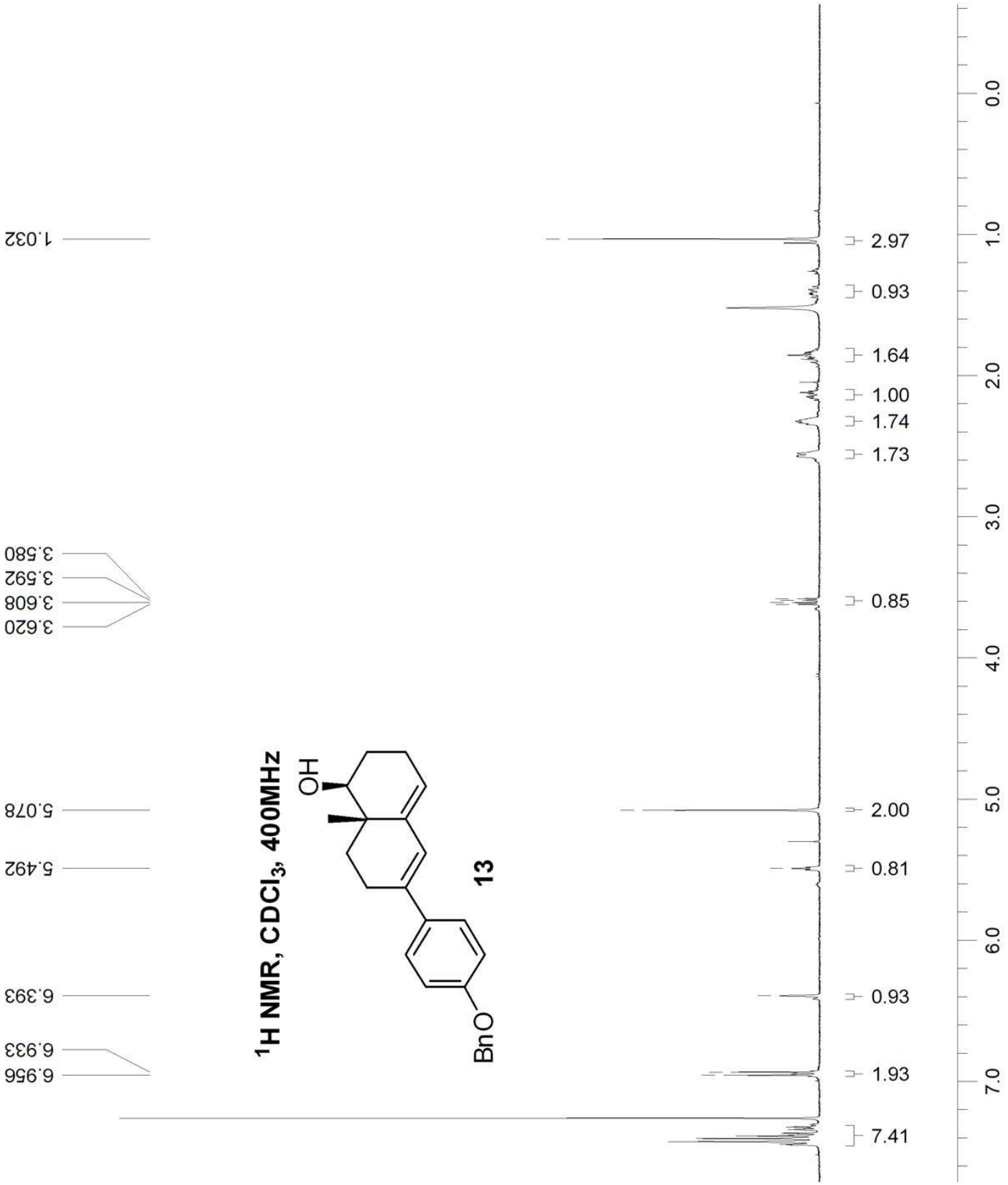
APPENDIX I – NMR SPECTRA

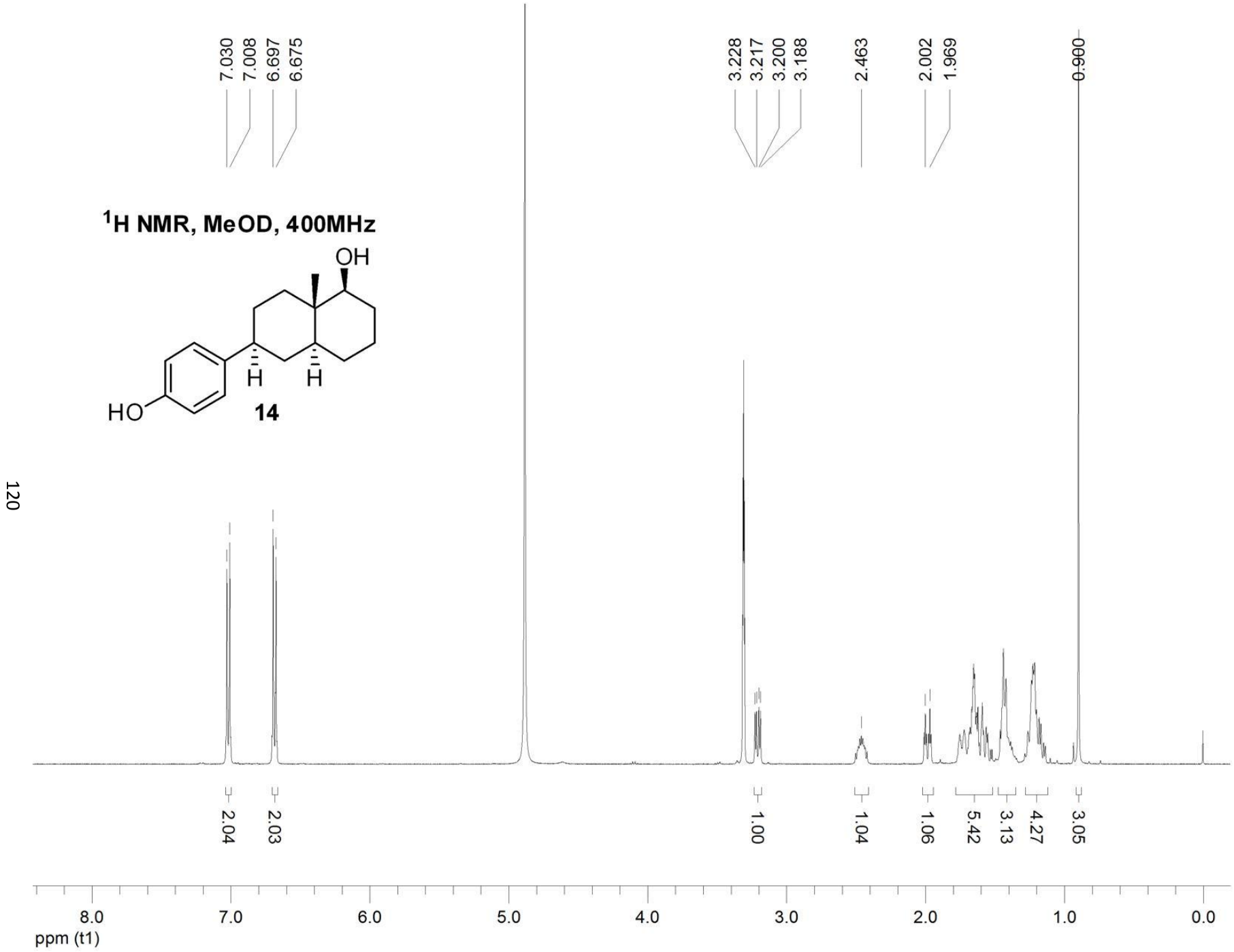


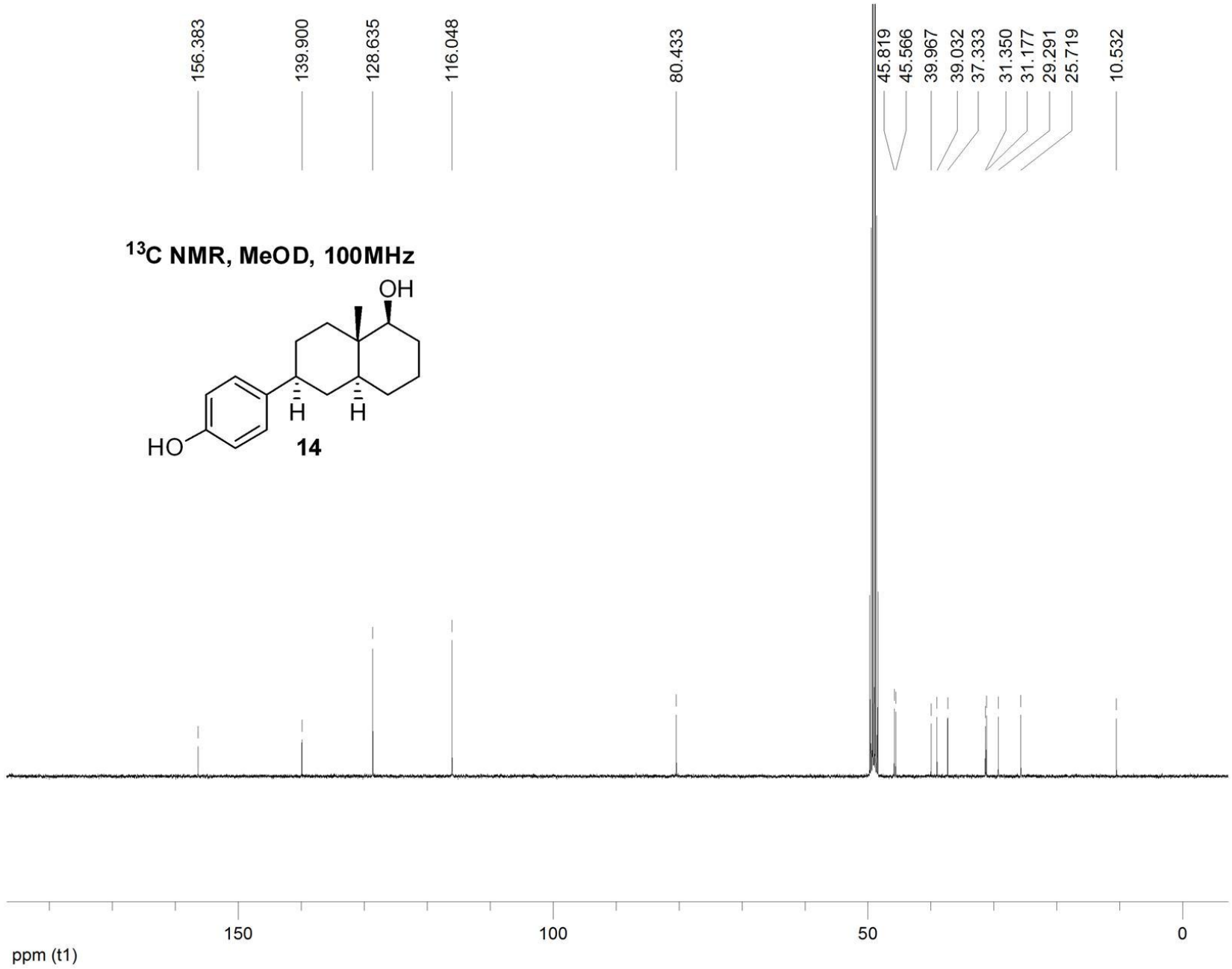


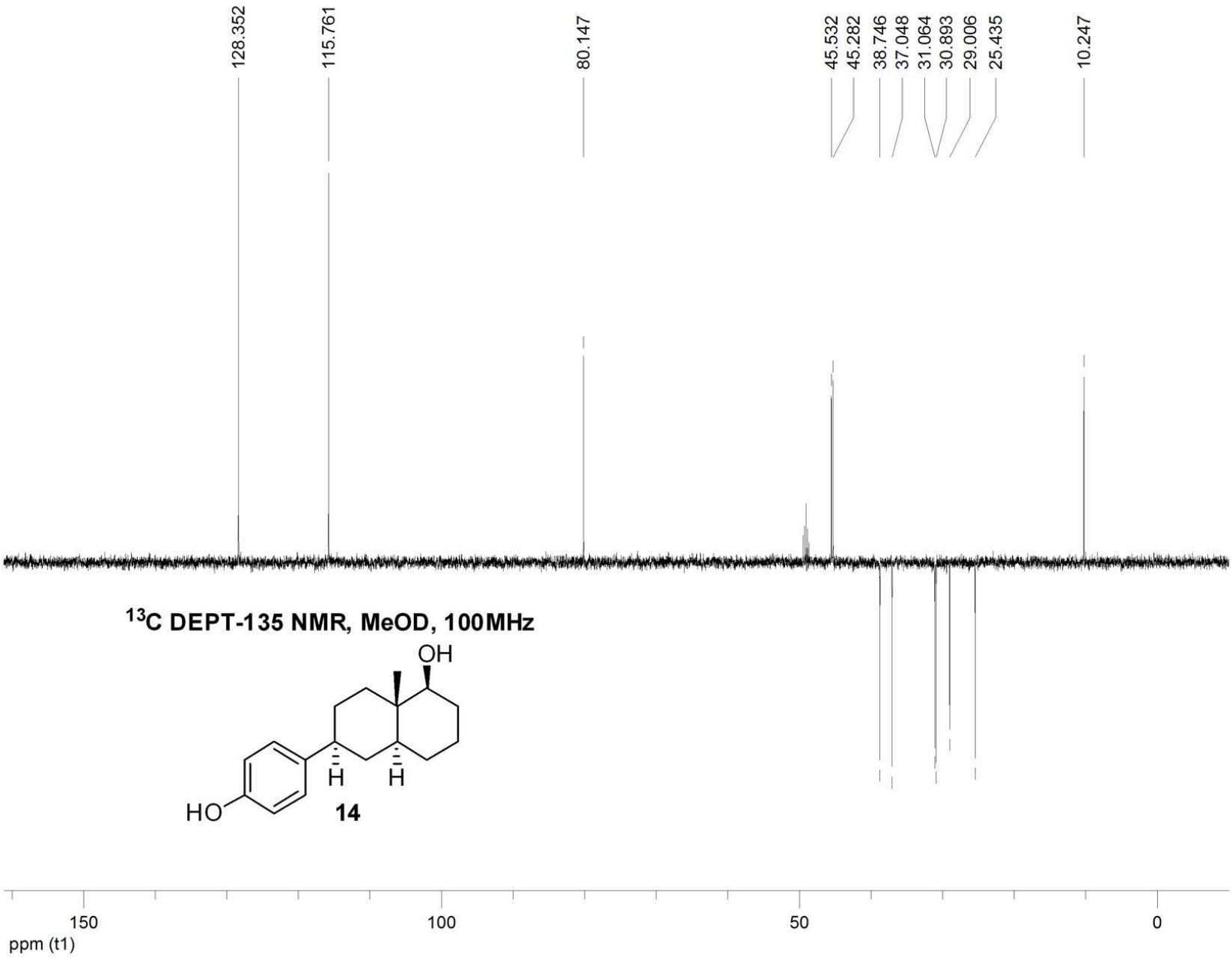
^{1}H NMR, $CDCl_3$, 400MHz

10


1.032
3.620
3.608
3.592
3.580
5.078
5.492
6.393
6.933
6.956
2.97
0.93
1.64
1.00
1.74
1.73
0.85
2.00
0.81
0.93
1.93
7.41
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
^{1}H NMR, CDCl$_3$, 400MHz
OH
BnO
13

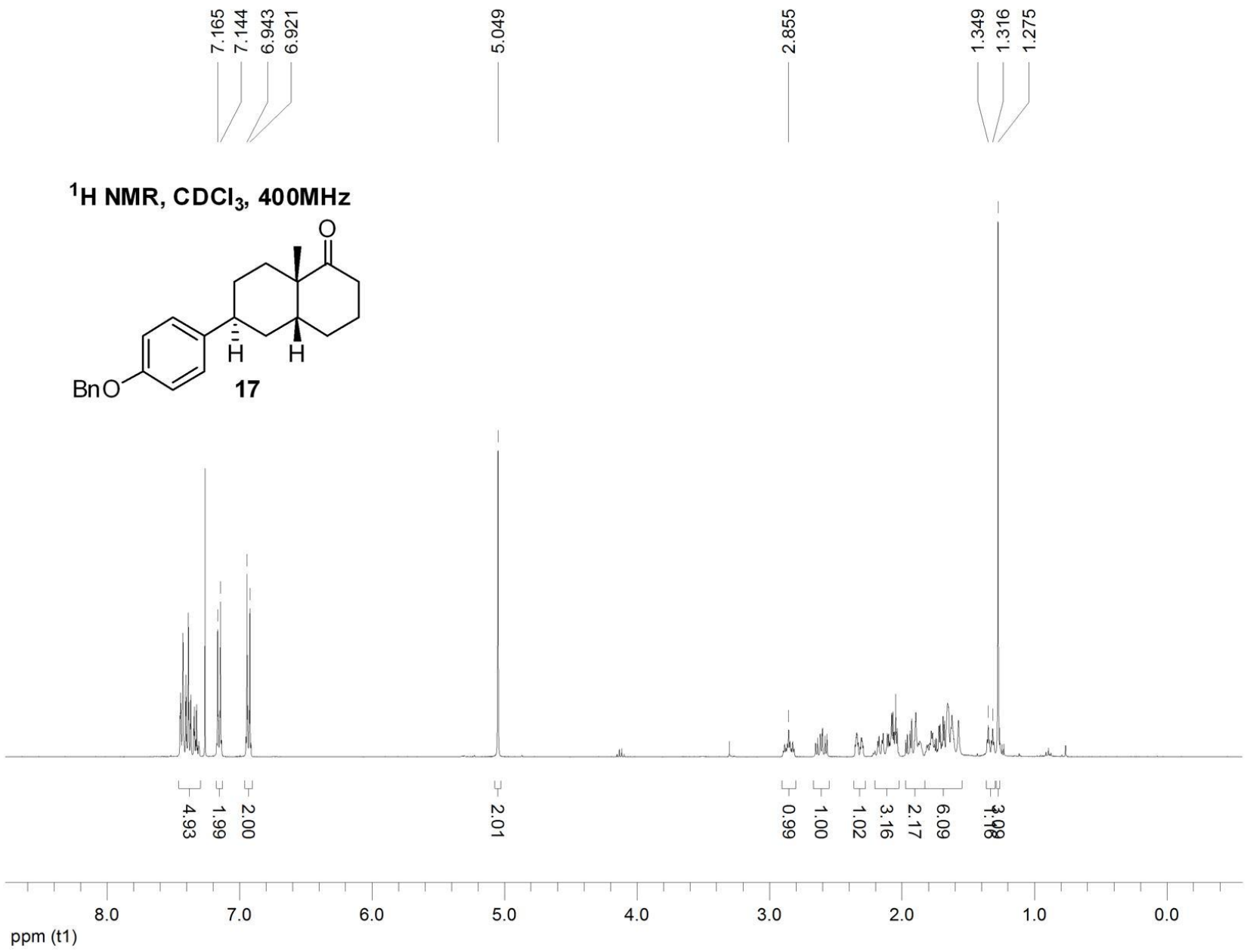

7.030
7.008
6.697
6.675
3.228
3.217
3.200
3.188
2.463
2.002
1.969
0.900
^{1}H NMR, MeOD, 400MHz
OH
HO
14
120
2.04
2.03
1.00
1.04
1.06
5.42
3.13
4.27
3.05
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

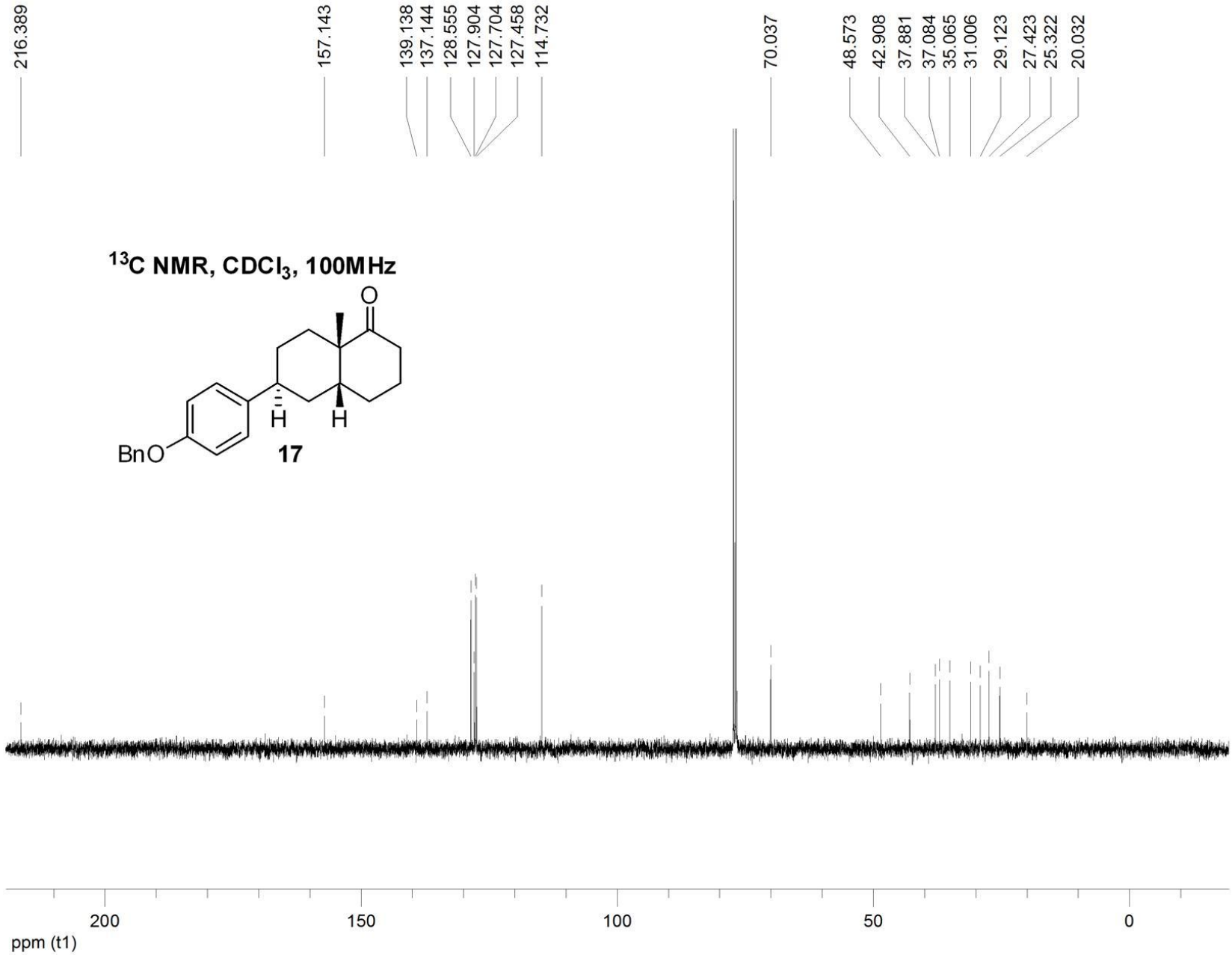

156.383
139.900
128.635
116.048
80.433
45.819
45.566
39.967
39.032
37.333
31.350
31.177
29.291
25.719
10.532
^{13}C NMR, MeOD, 100MHz
OH
H
H
HO
14
150
100
50
0
ppm (t1)

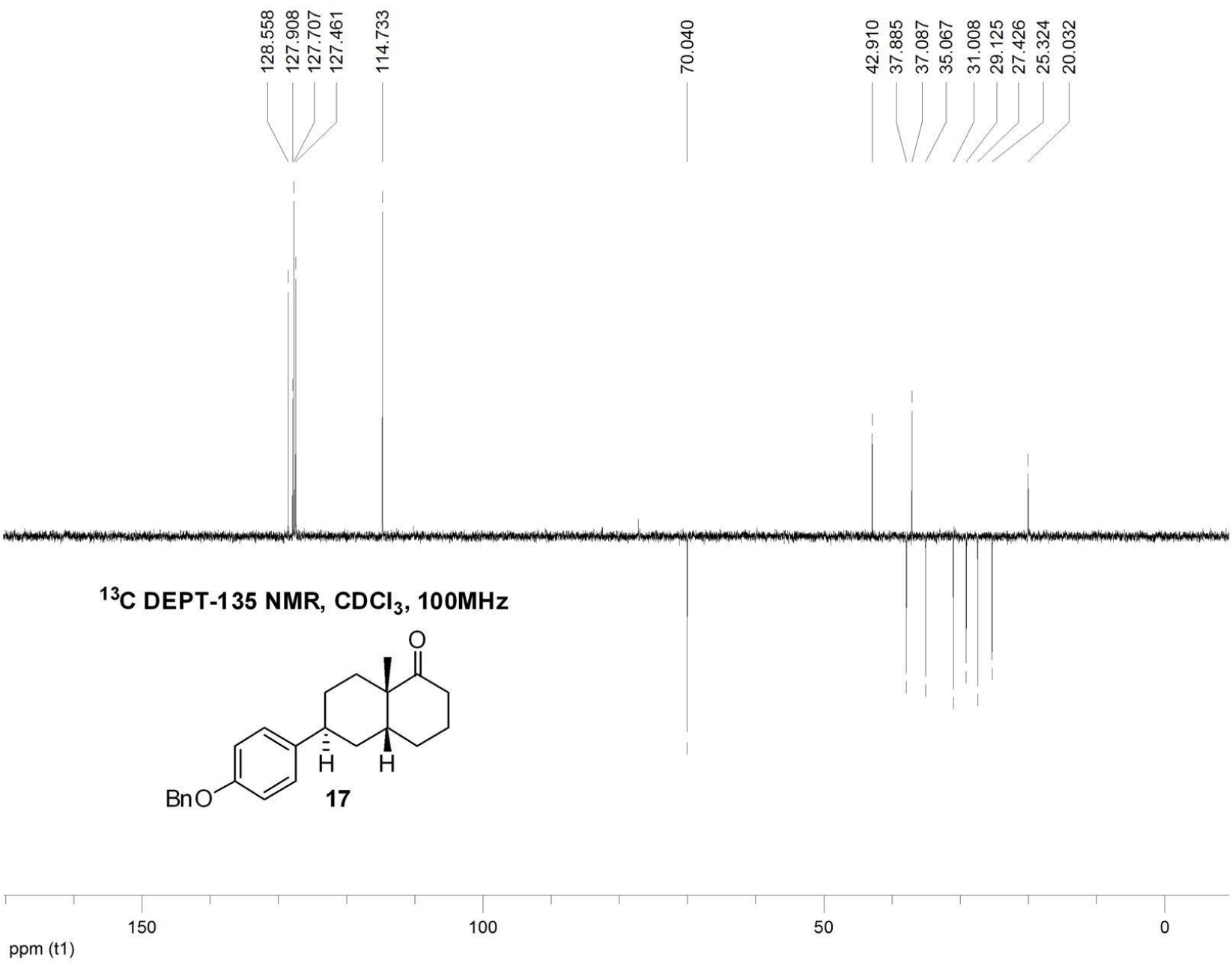


^{13}C DEPT-135 NMR, MeOD, 100MHz

14

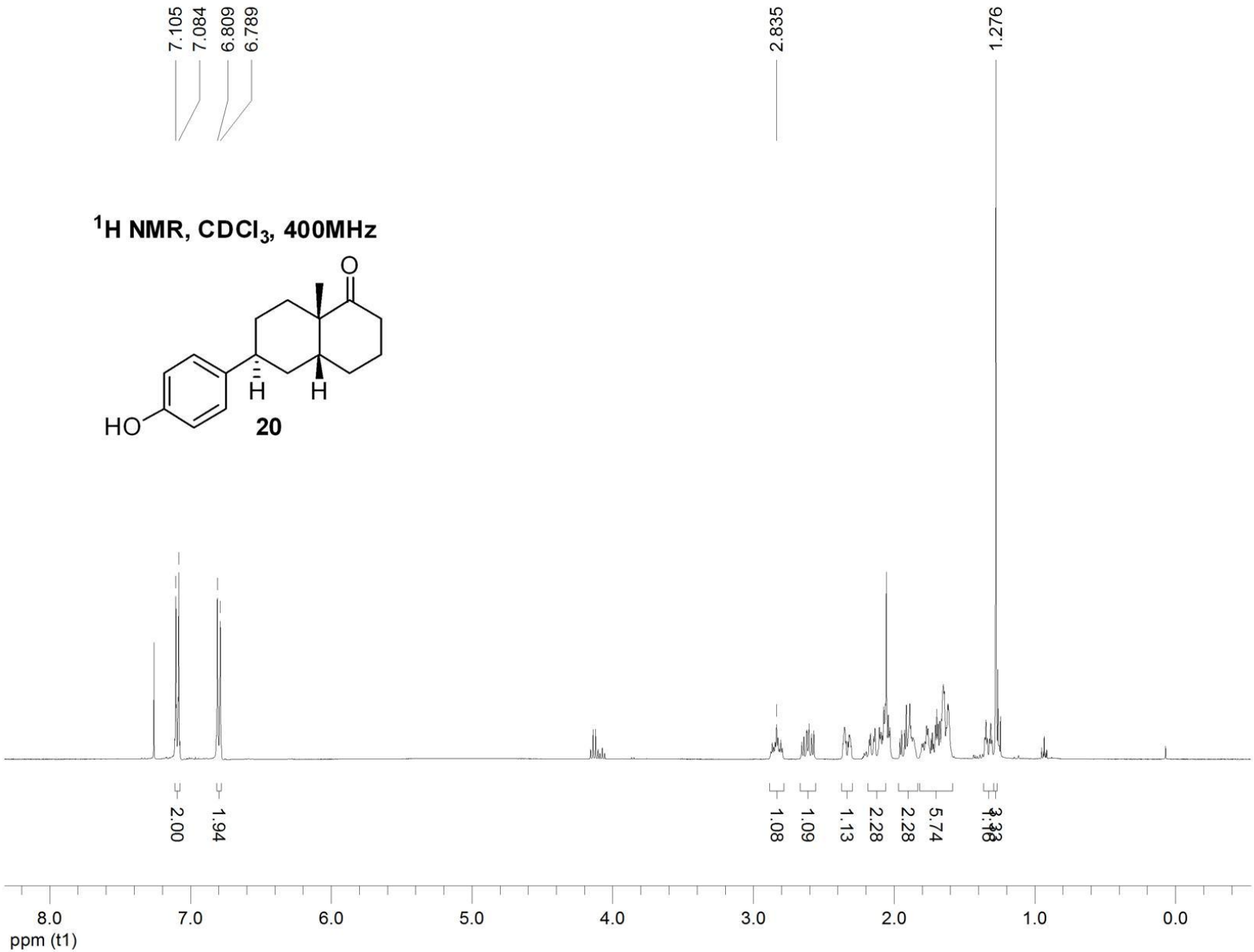

7.165
7.144
6.943
6.921
5.049
2.855
1.349
1.316
1.275
^{1}H NMR, CDCl$_3$, 400MHz
O
H
H
BnO
17
4.93
1.99
2.00
2.01
0.99
1.00
1.02
3.16
2.17
6.09
3.18
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

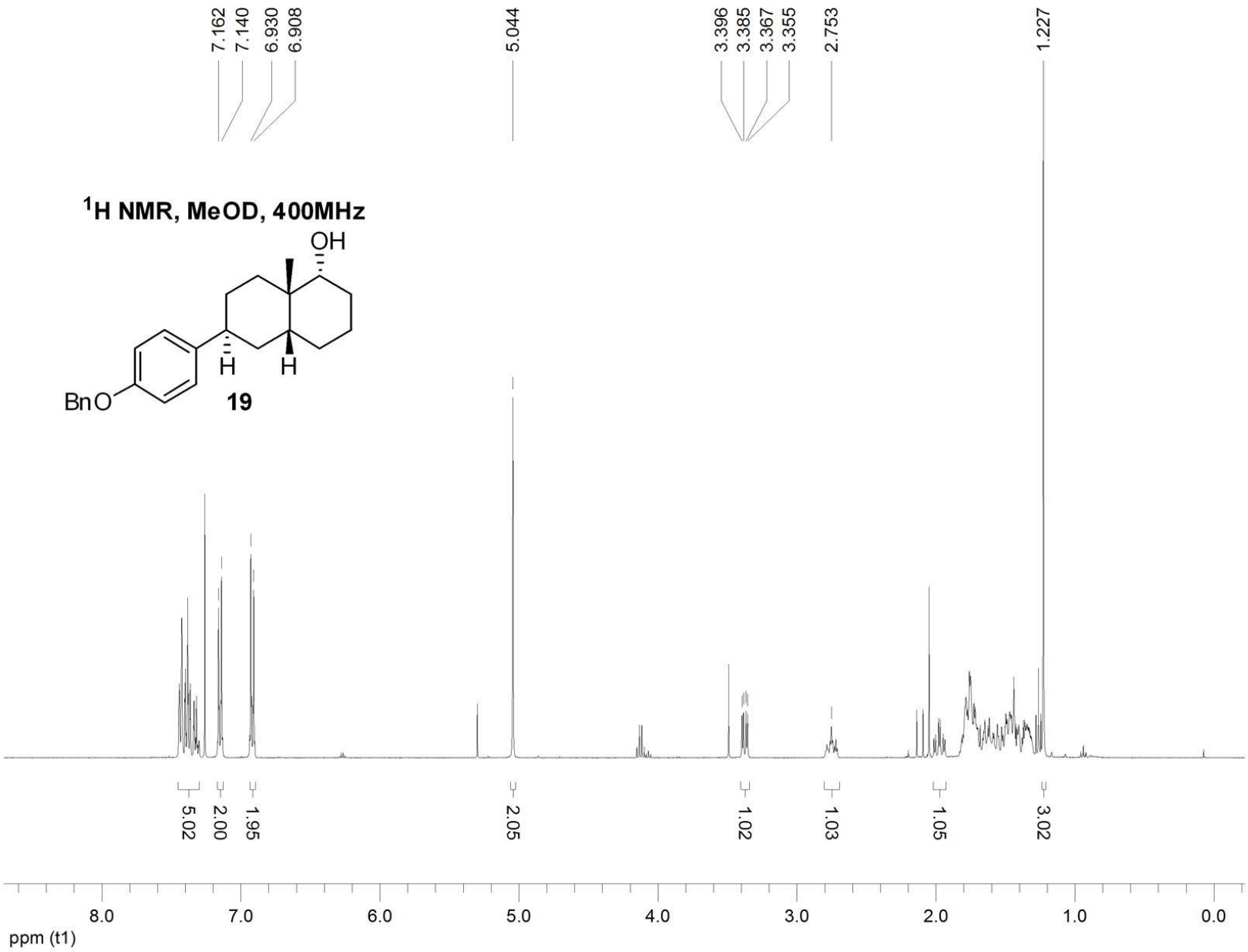

216.389
157.143
139.138
137.144
128.555
127.904
127.704
127.458
114.732
70.037
48.573
42.908
37.881
37.084
35.065
31.006
29.123
27.423
25.322
20.032
^{13}C NMR, CDCl$_3$, 100MHz
O
H
H
BnO
17
200
150
100
50
0
ppm (t1)

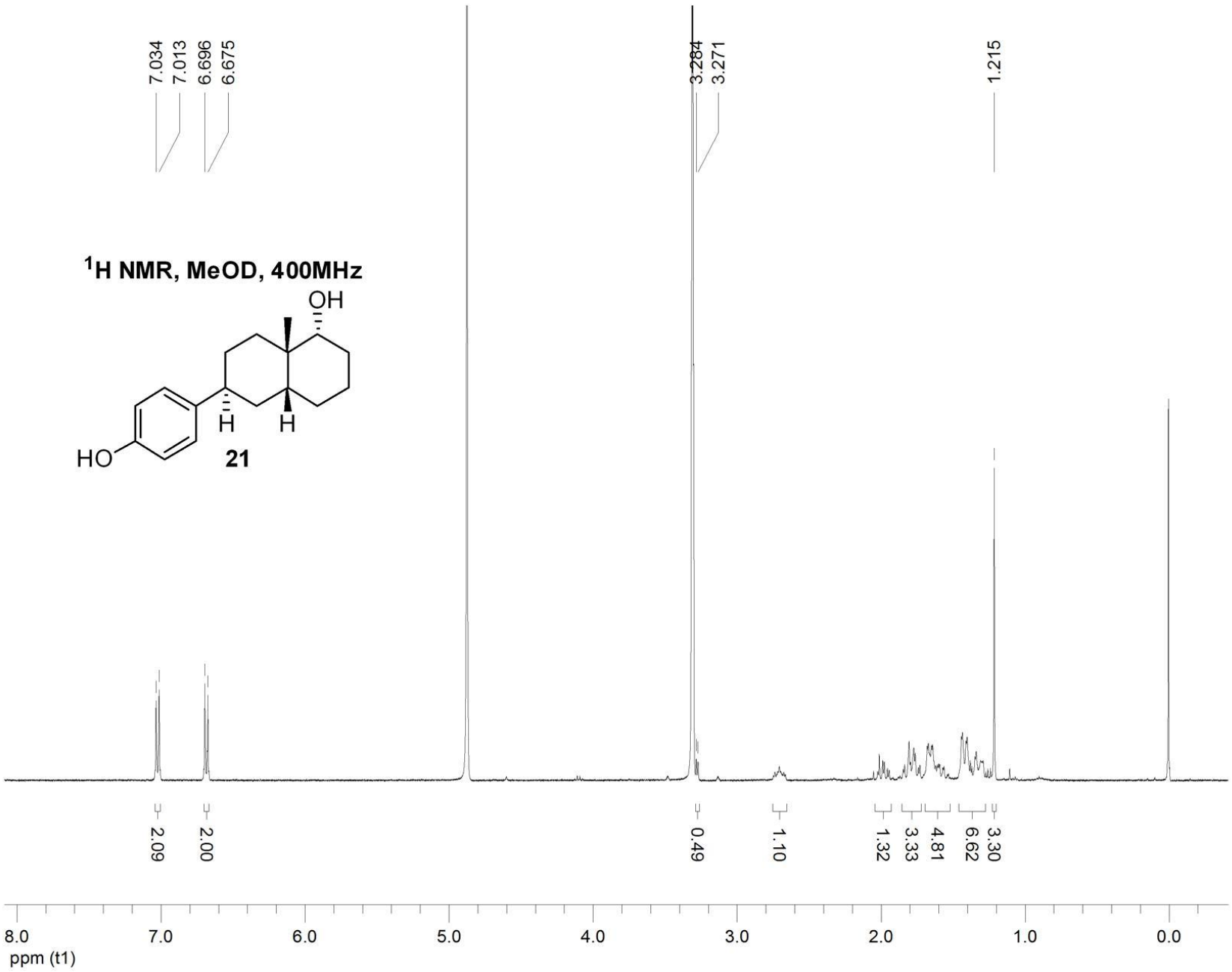


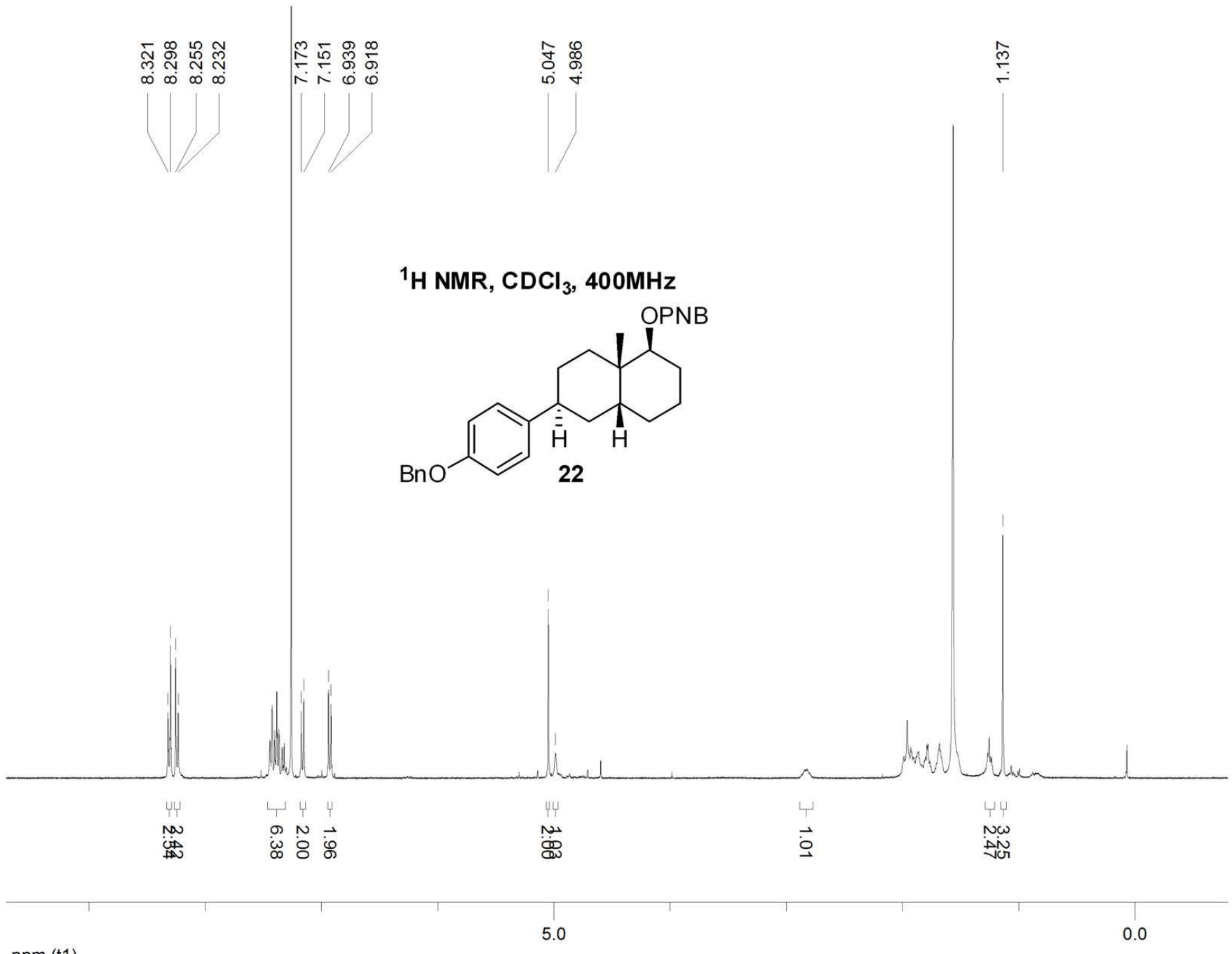
^{13}C DEPT-135 NMR, $CDCl_3$, 100MHz

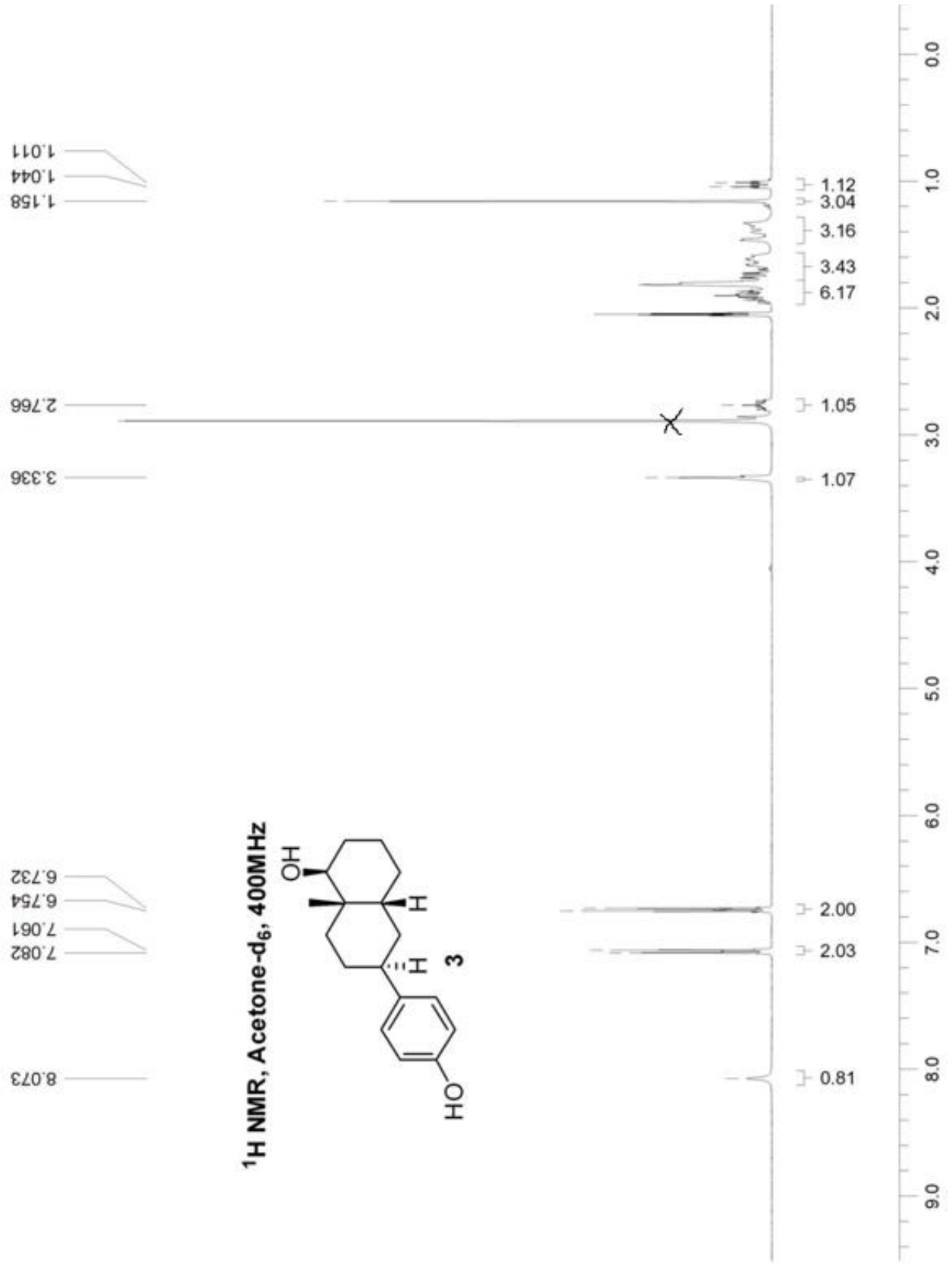
17

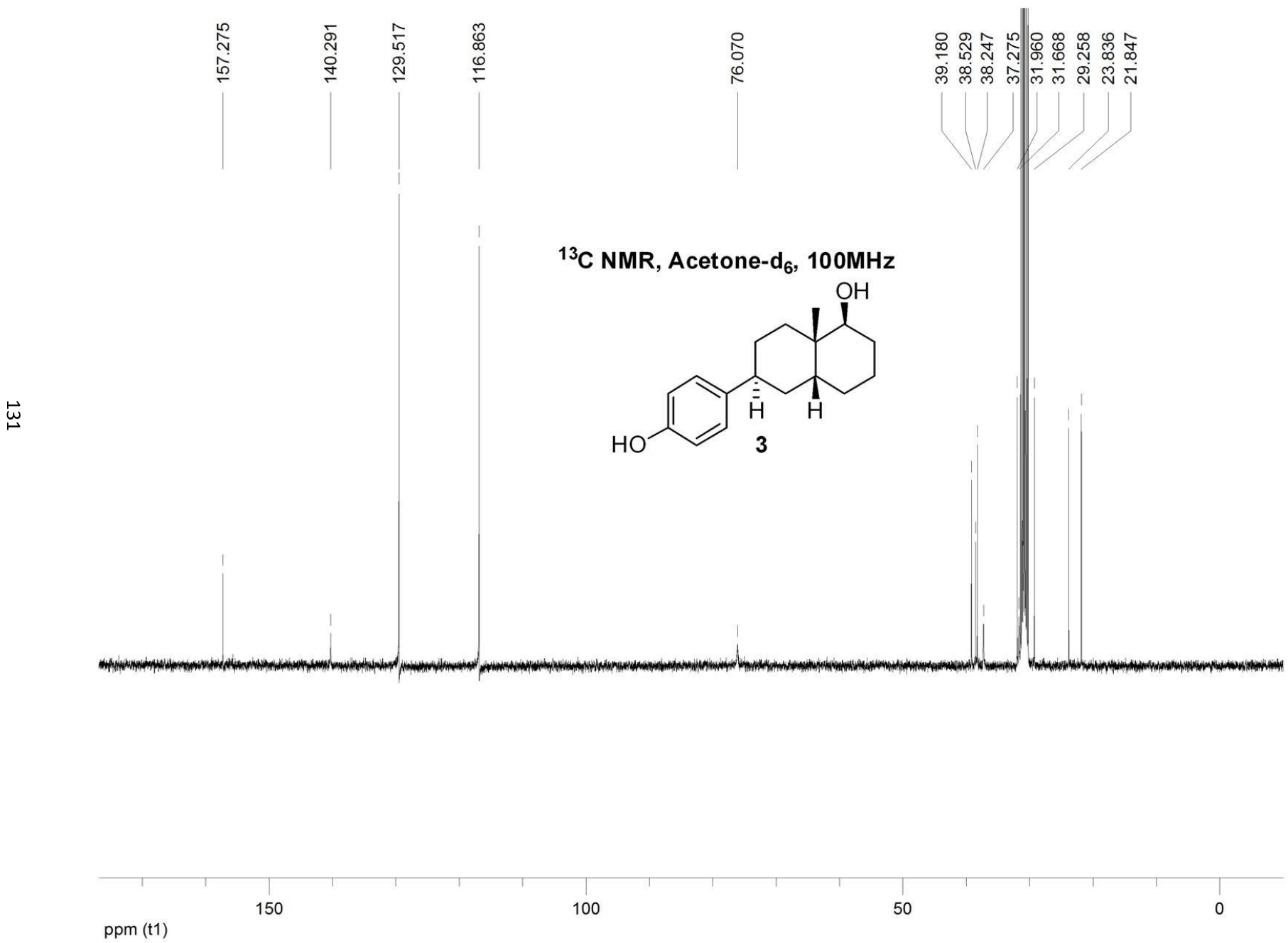

7.105
7.084
6.809
6.789
2.835
1.279
^{1}H NMR, CDCl$_3$, 400MHz
O
H
H
HO
20
2.00
1.94
1.08
1.09
1.13
2.28
2.28
5.74
3.32
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

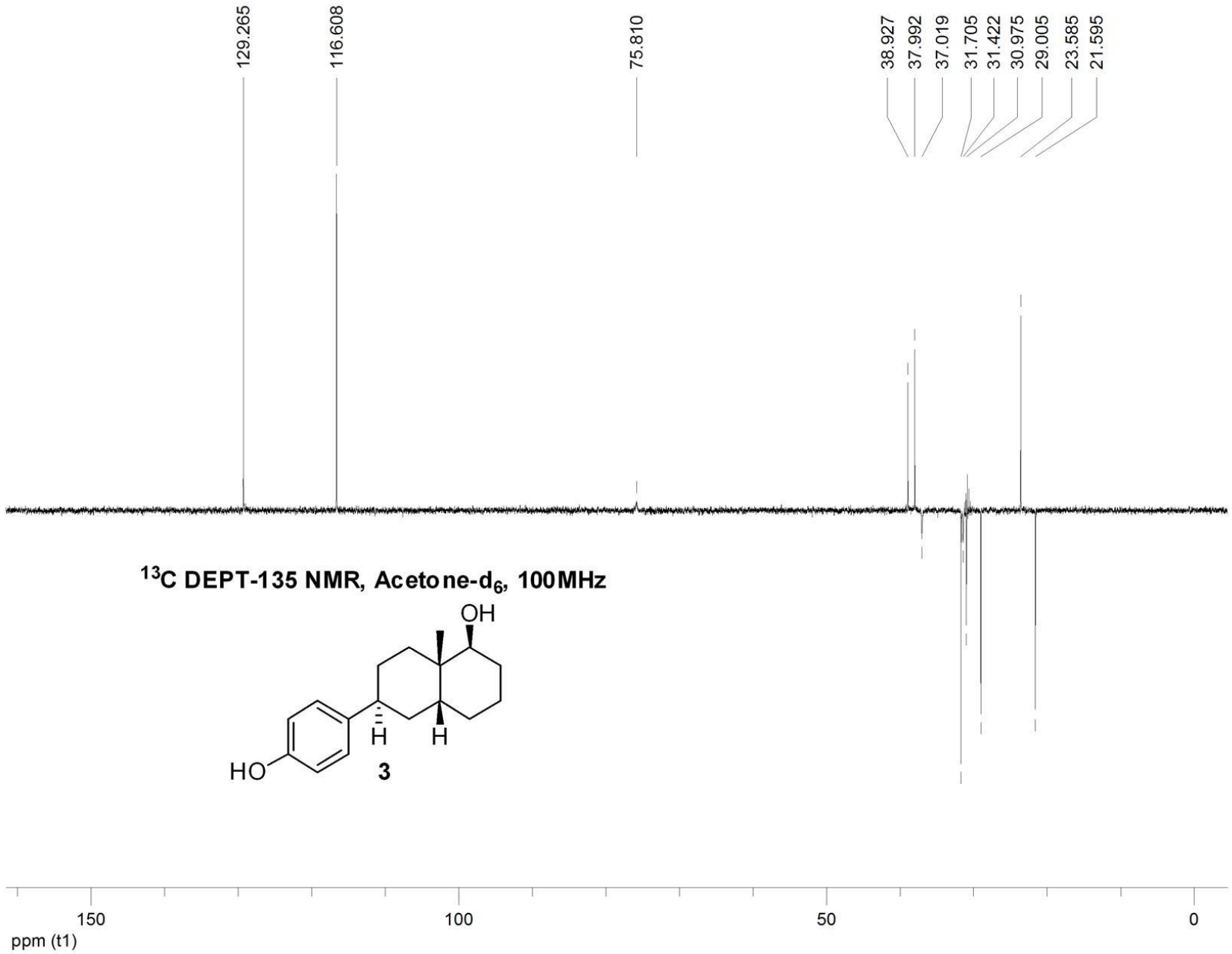

7.162
7.140
6.930
6.908
5.044
3.396
3.385
3.367
3.355
2.753
1.227
¹H NMR, MeOD, 400MHz
OH
H
H
BnO
19
5.02
2.00
1.95
2.05
1.02
1.03
1.05
3.02
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


7.034
7.013
6.696
6.675
3.284
3.271
1.215
^{1}H NMR, MeOD, 400MHz
OH
H
H
HO
21
2.09
2.00
0.49
1.10
1.32
3.33
4.81
6.62
3.30
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


8.321
8.298
8.255
8.232
7.173
7.151
6.939
6.918
5.047
4.986
1.137
^{1}H NMR, CDCl$_3$, 400MHz
OPNB
H
H
BnO
22
2.54
2.42
6.38
2.00
1.96
2.00
1.01
2.47
3.25
5.0
0.0
ppm (t1)

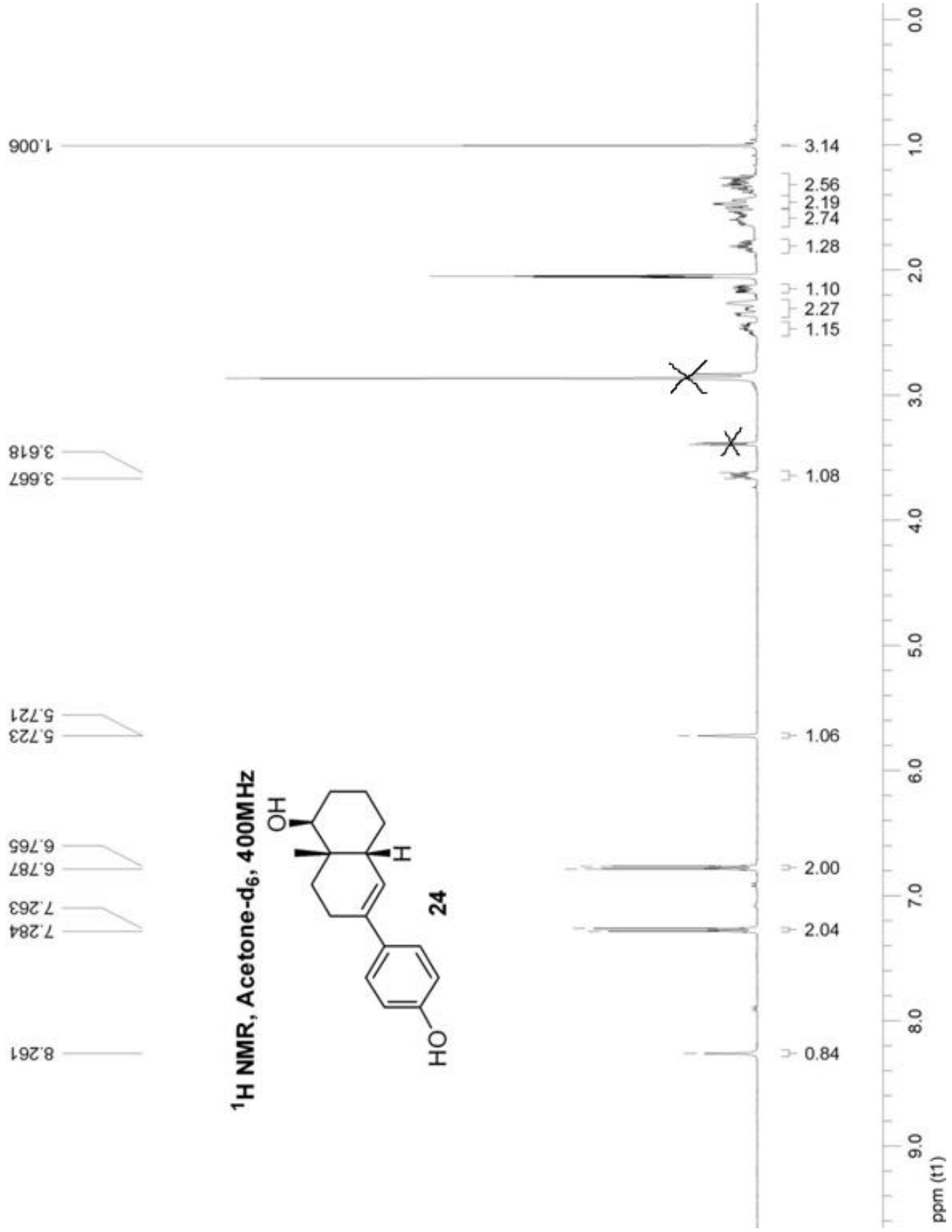

1.011
1.044
1.158
2.766
3.336
6.732
6.754
7.061
7.082
8.073
1.12
3.04
3.16
3.43
6.17
1.05
1.07
2.00
2.03
0.81
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
^{1}H NMR, Acetone-d_6, 400MHz
OH
H
H
HO
3

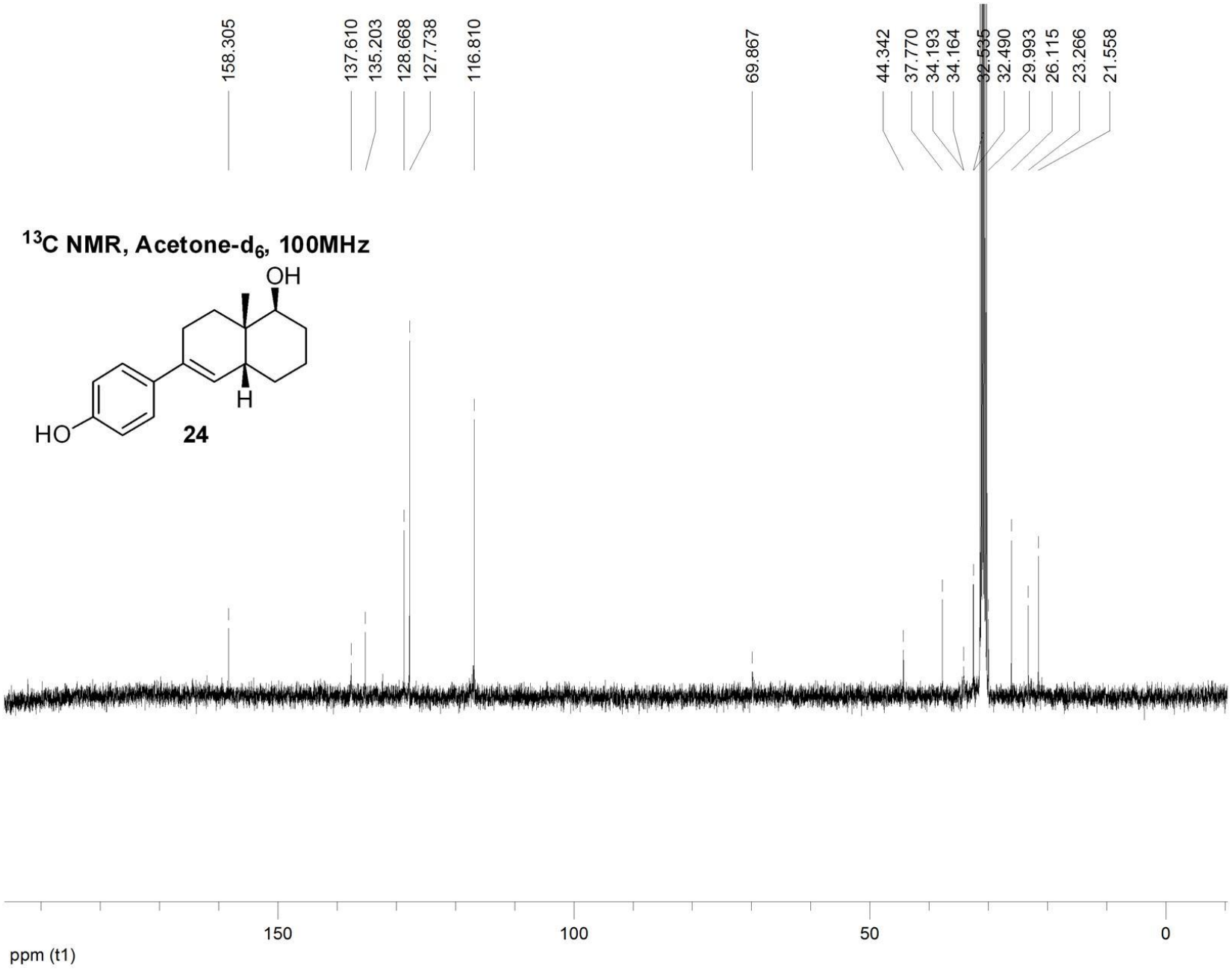

157.275
140.291
129.517
116.863
76.070
39.180
38.529
38.247
37.275
31.960
31.668
29.258
23.836
21.847
^{13}C NMR, Acetone-d$_6$, 100MHz
OH
H
H
HO
3
150
100
50
0
ppm (t1)

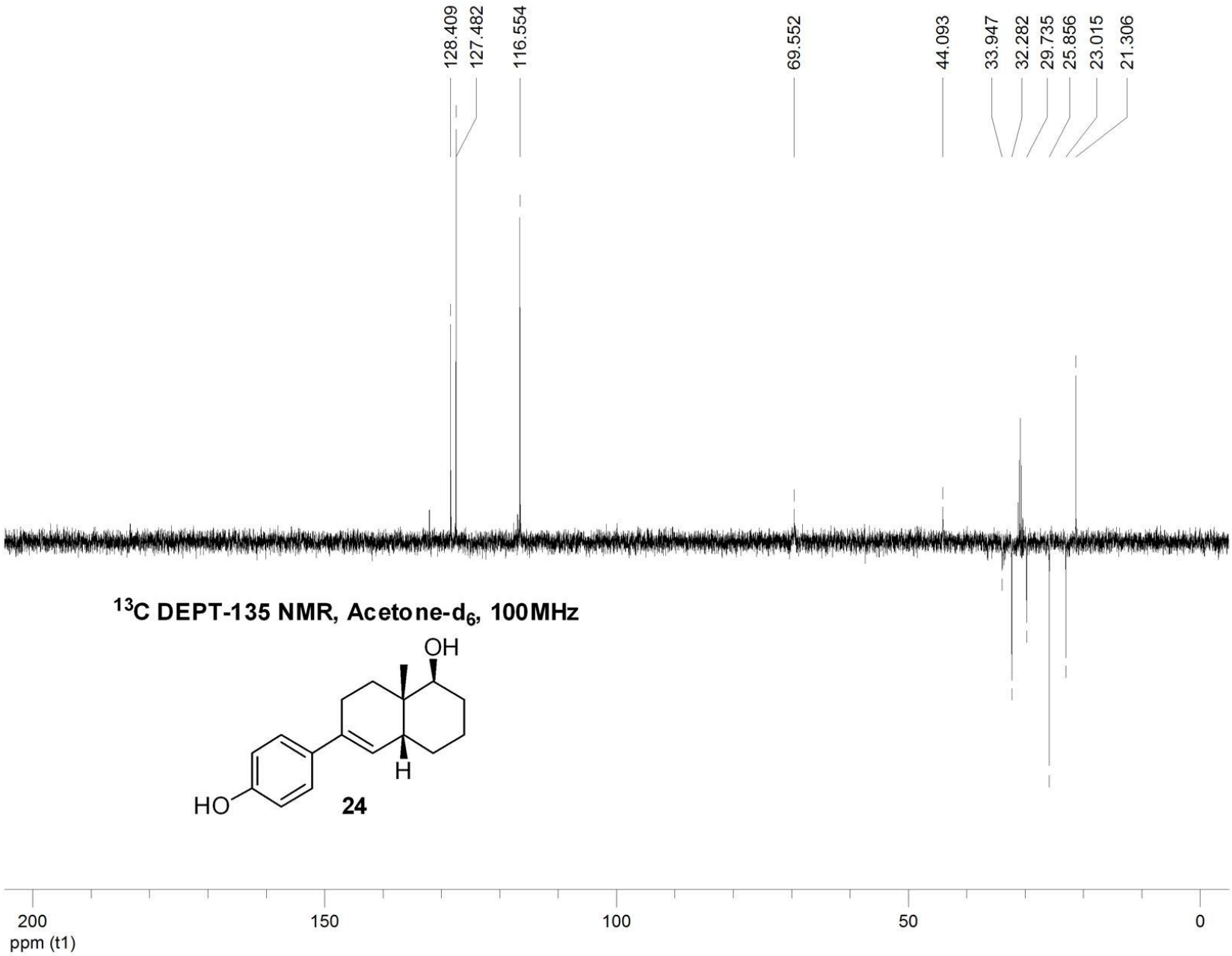


^{13}C DEPT-135 NMR, Acetone-d_6, 100MHz

3

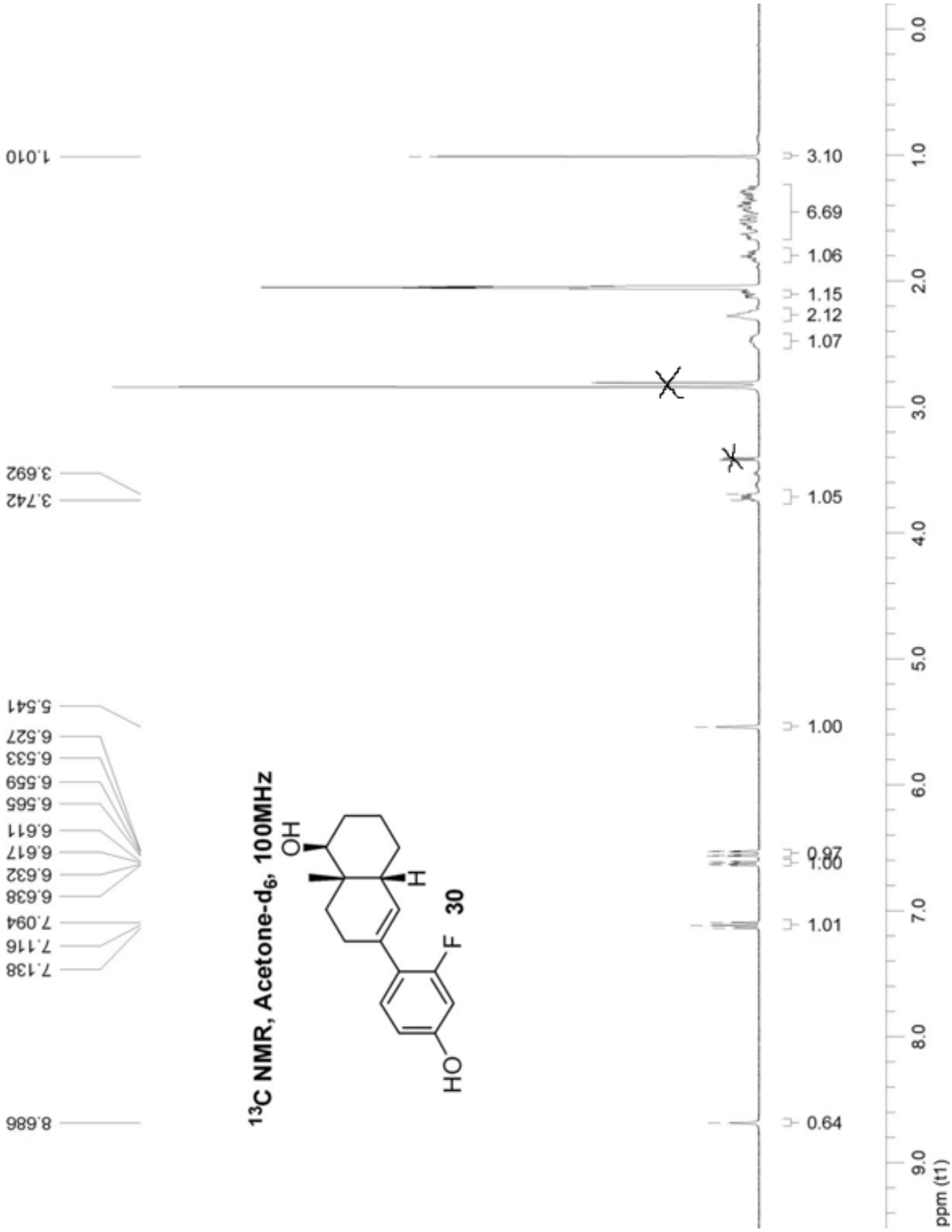

1.006
3.618
3.667
5.721
5.723
6.765
6.787
7.263
7.284
8.261
3.14
2.56
2.19
2.74
1.28
1.10
2.27
1.15
1.08
1.06
2.00
2.04
0.84
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
^{1}H NMR, Acetone-d$_6$, 400MHz
OH
H
HO
24

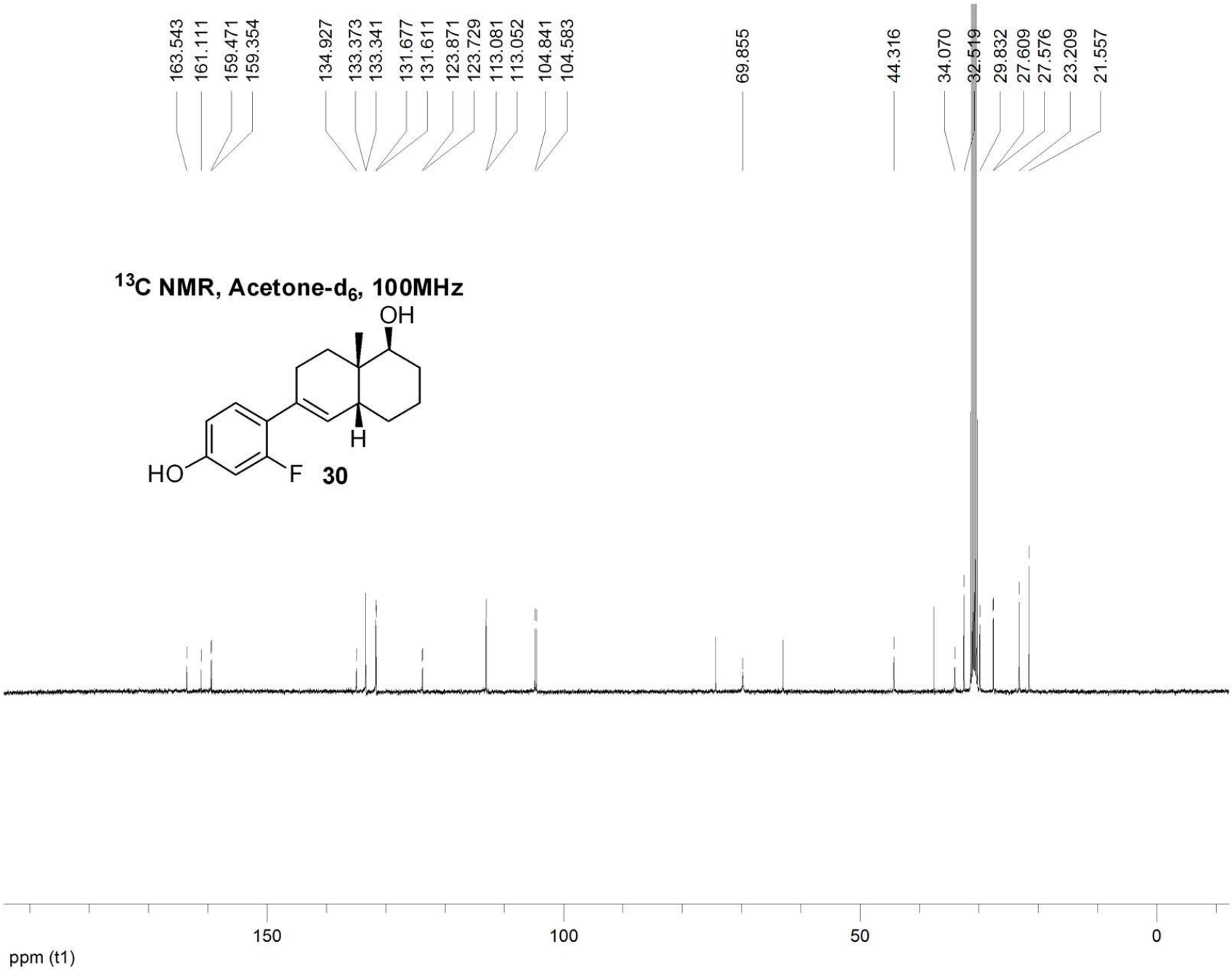

158.305
137.610
135.203
128.668
127.738
116.810
69.867
44.342
37.770
34.193
34.164
32.535
32.490
29.993
26.115
23.266
21.558
13C NMR, Acetone-d6, 100MHz
OH
HO
H
24
150
100
50
0
ppm (t1)

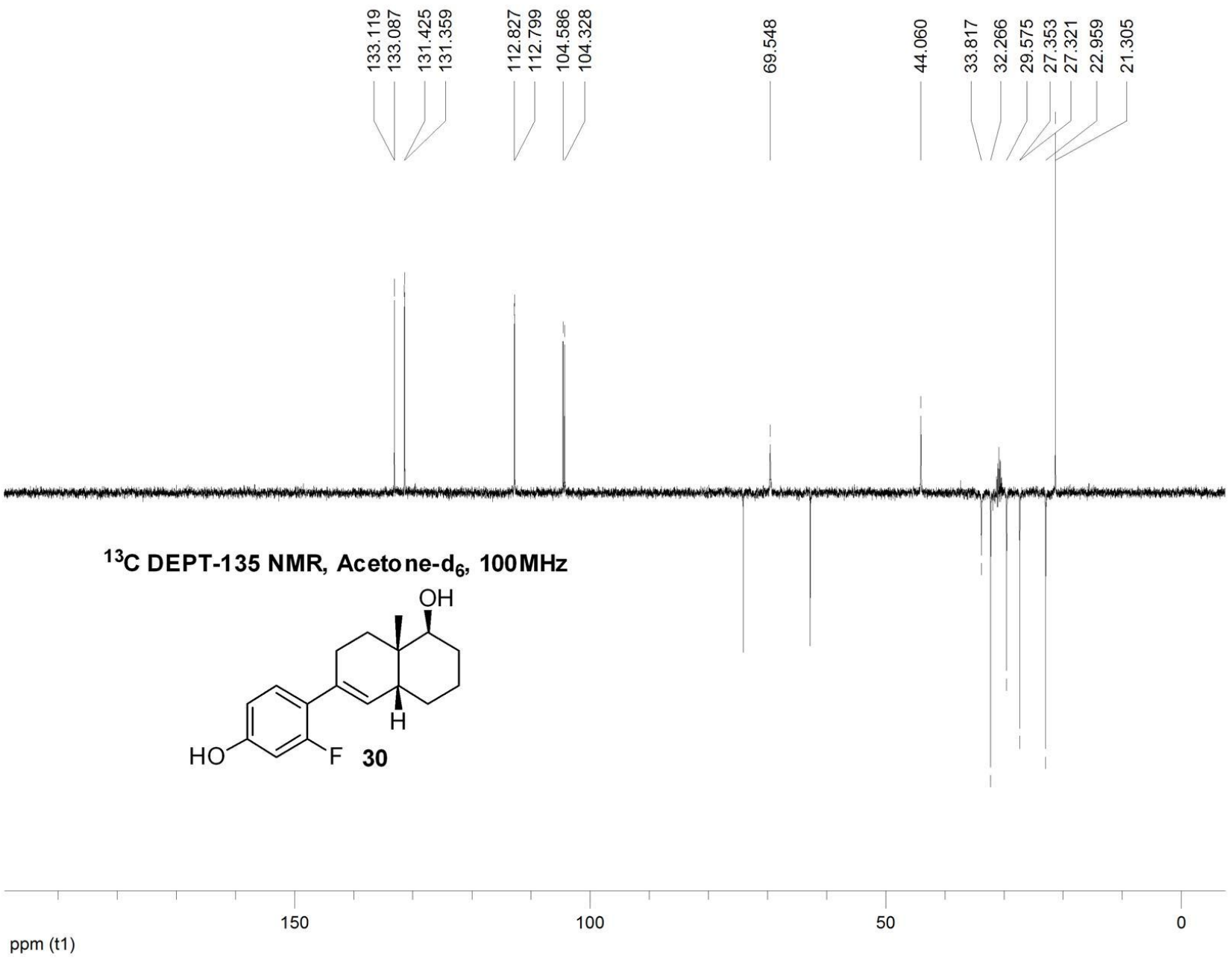


^{13}C DEPT-135 NMR, Acetone-d_6, 100MHz

24

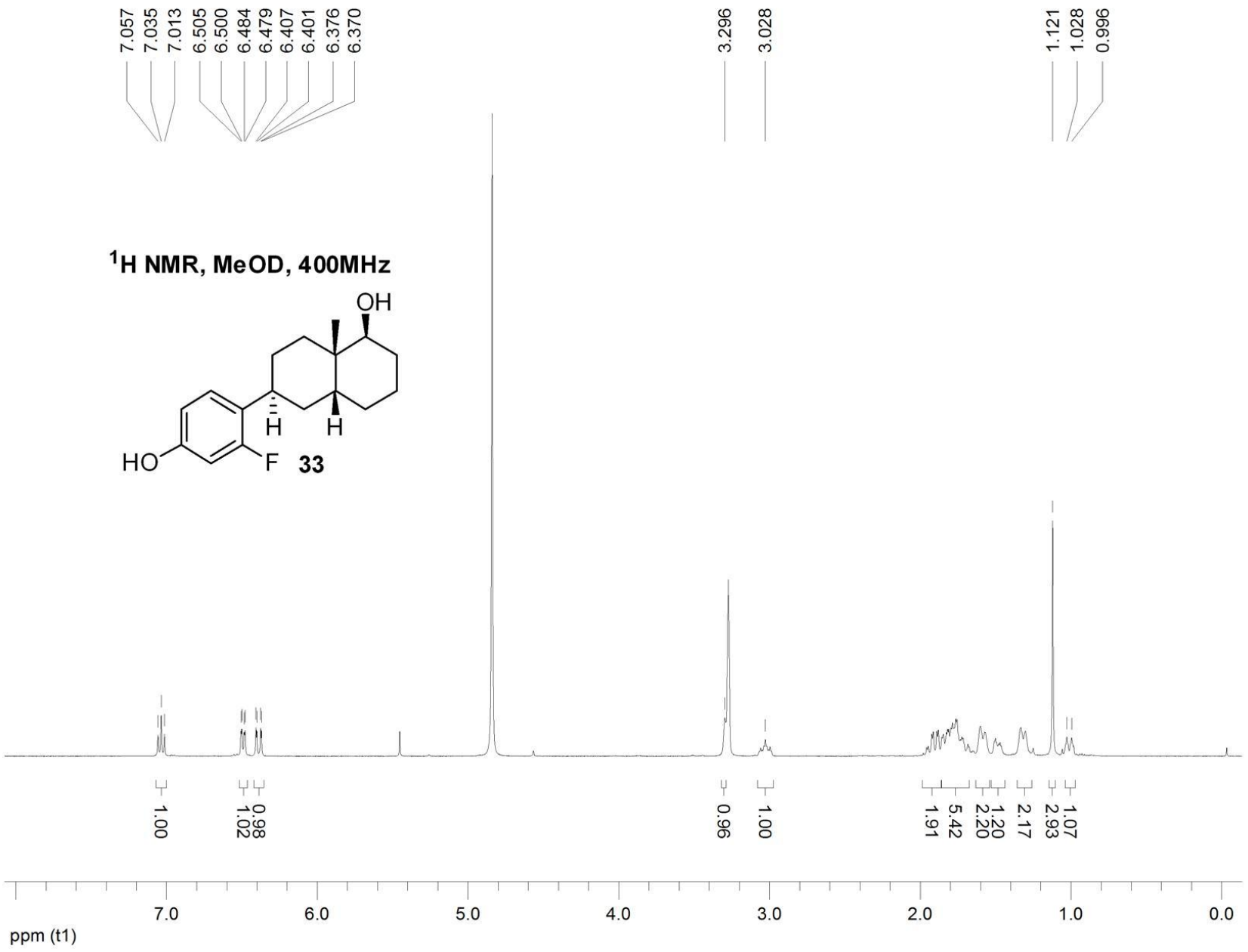

1.010
3.692
3.742
5.541
6.527
6.533
6.559
6.565
6.611
6.617
6.632
6.638
7.094
7.116
7.138
8.686
3.10
6.69
1.06
1.15
2.12
1.07
1.05
1.00
0.97
1.00
1.01
0.64
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
^{13}C NMR, Acetone-d$_6$, 100MHz
OH
H
F
HO
30

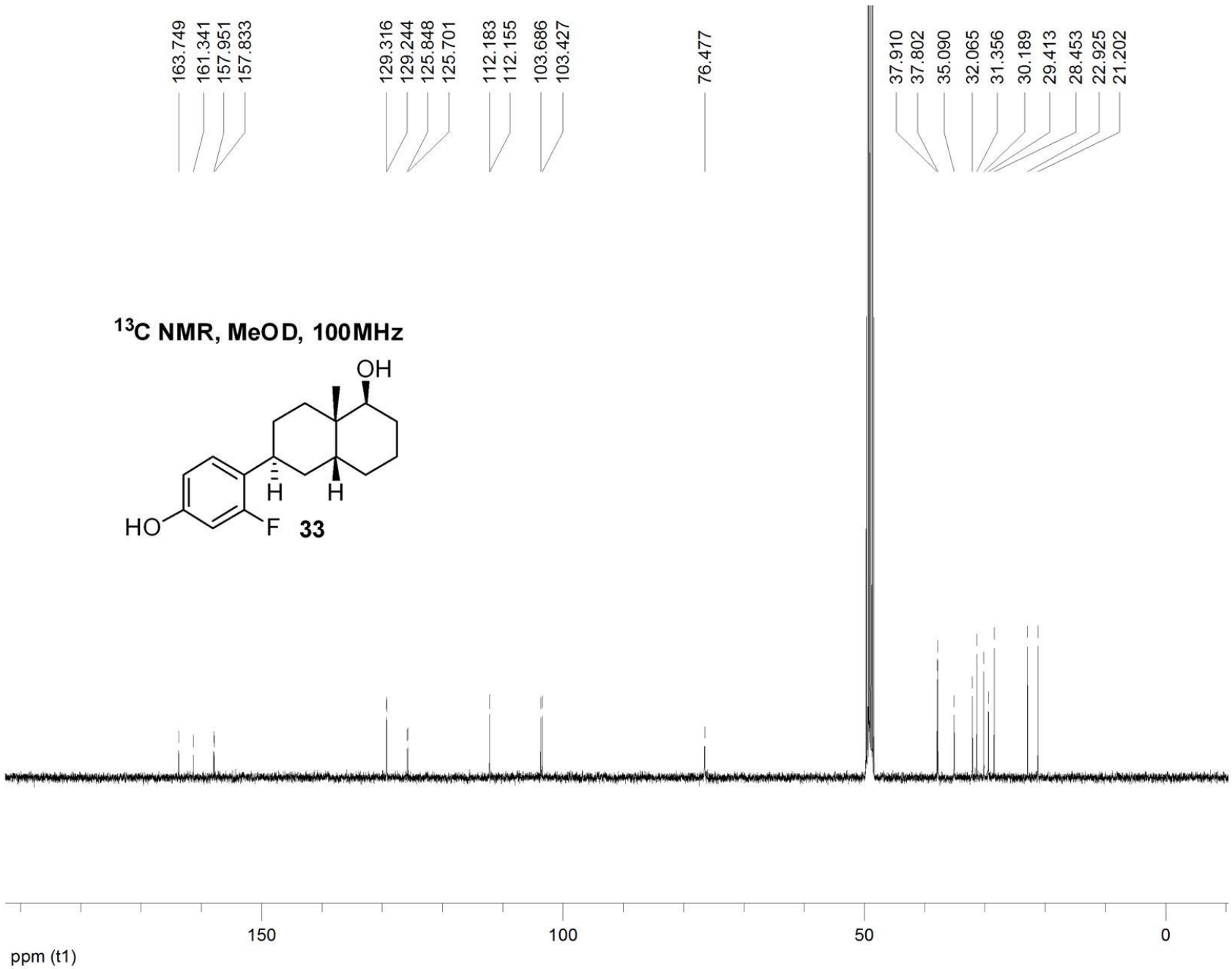

163.543
161.111
159.471
159.354
134.927
133.373
133.341
131.677
131.611
123.871
123.729
113.081
113.052
104.841
104.583
69.855
44.316
34.070
32.519
29.832
27.609
27.576
23.209
21.557
^{13}C NMR, Acetone-d$_6$, 100MHz
OH
H
HO
F
30
150
100
50
0
ppm (t1)

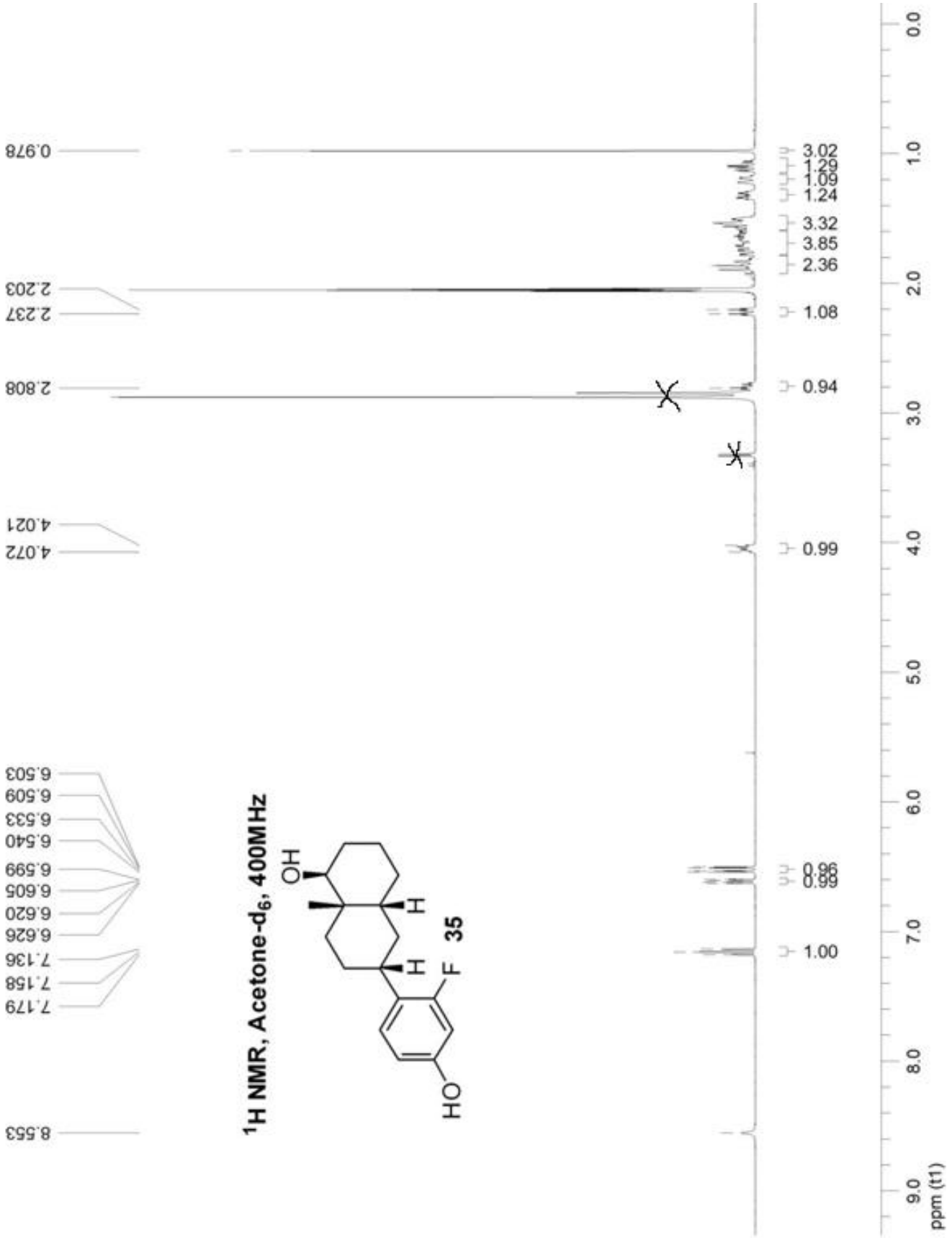


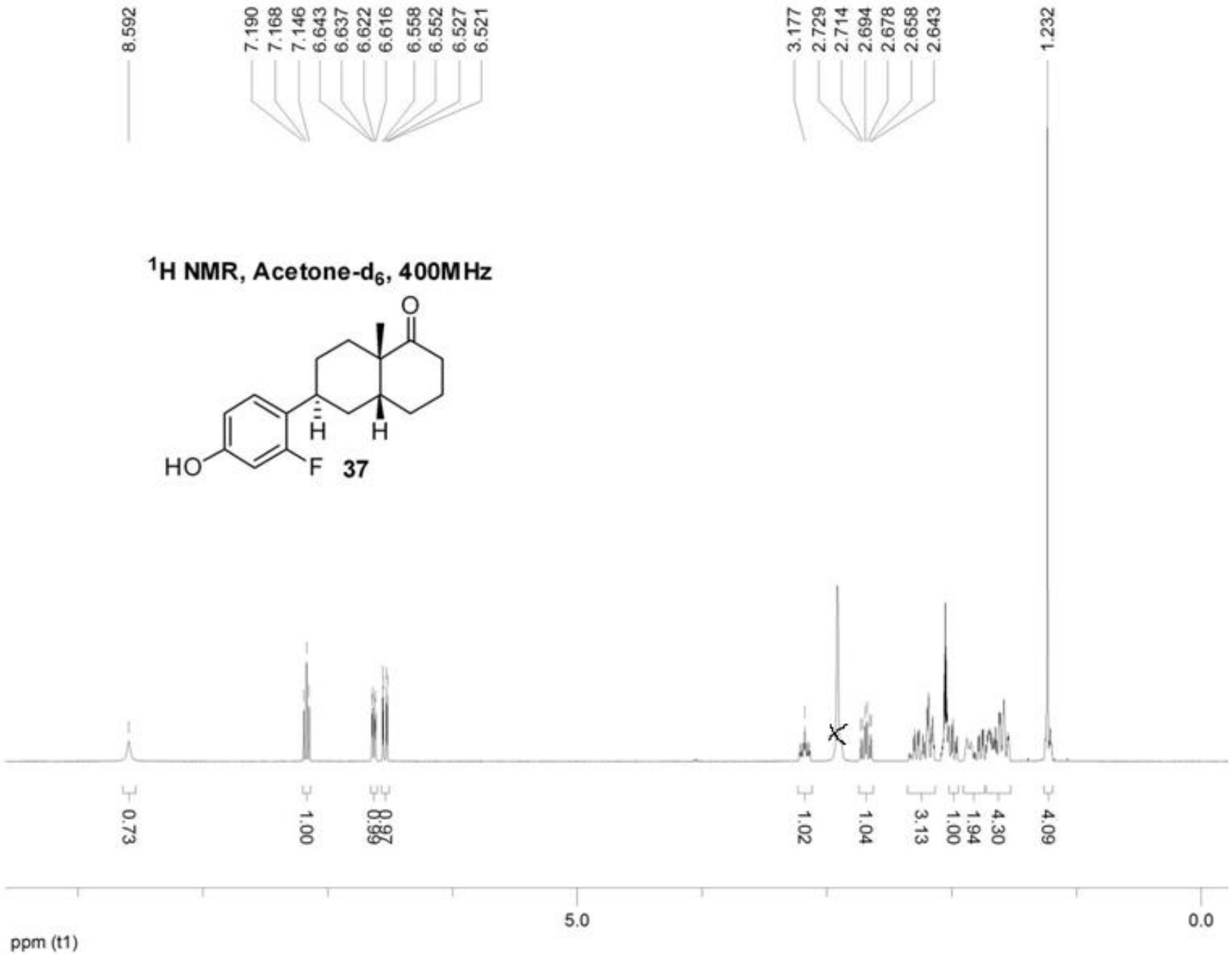
^{13}C DEPT-135 NMR, Acetone-d_6, 100MHz

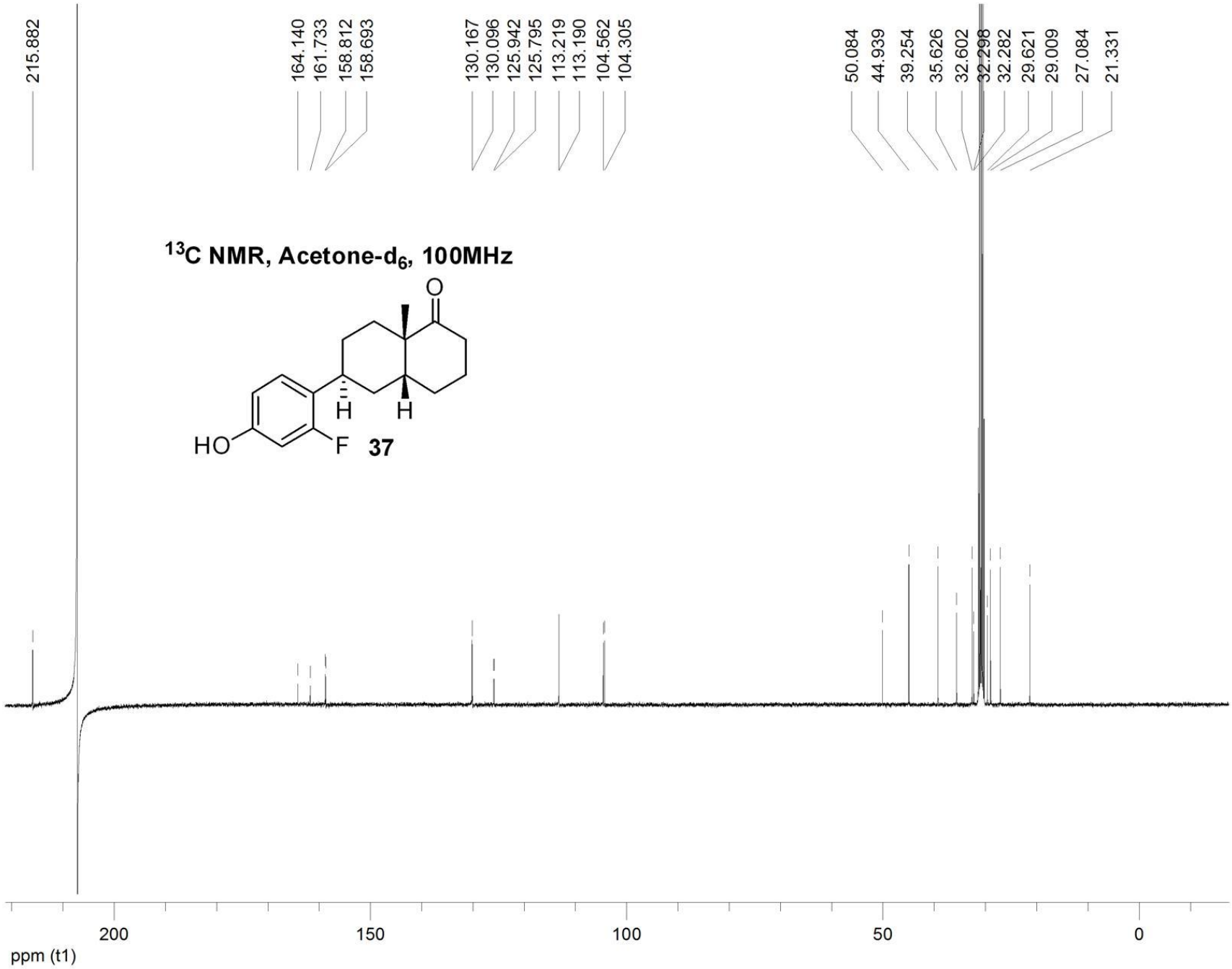
30

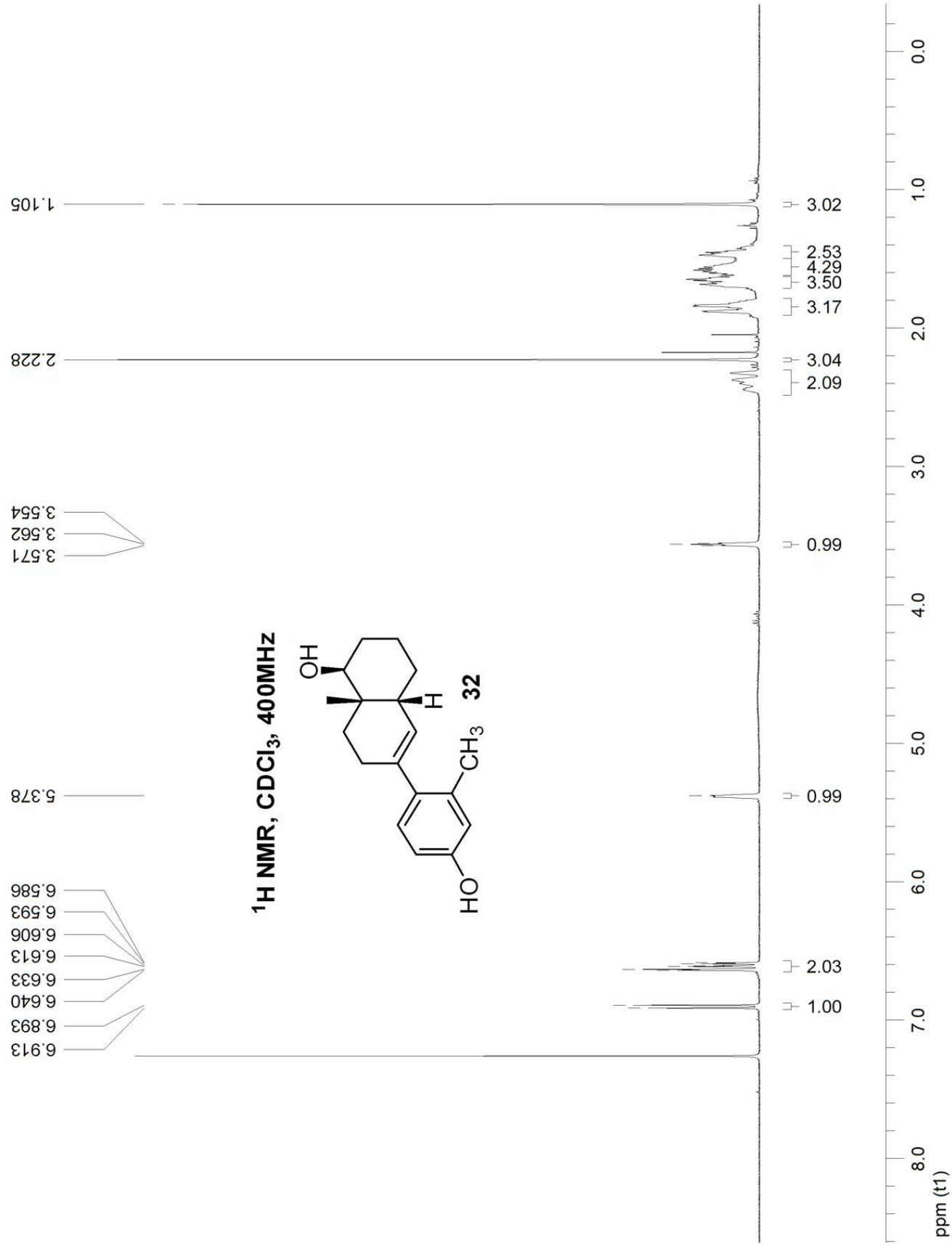

7.057
7.035
7.013
6.505
6.500
6.484
6.479
6.407
6.401
6.376
6.370
3.296
3.028
1.121
1.028
0.996
1H NMR, MeOD, 400MHz
OH
H
H
HO
F
33
1.00
1.02
0.68
0.96
1.00
1.91
5.42
2.20
1.20
2.17
2.93
1.07
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)

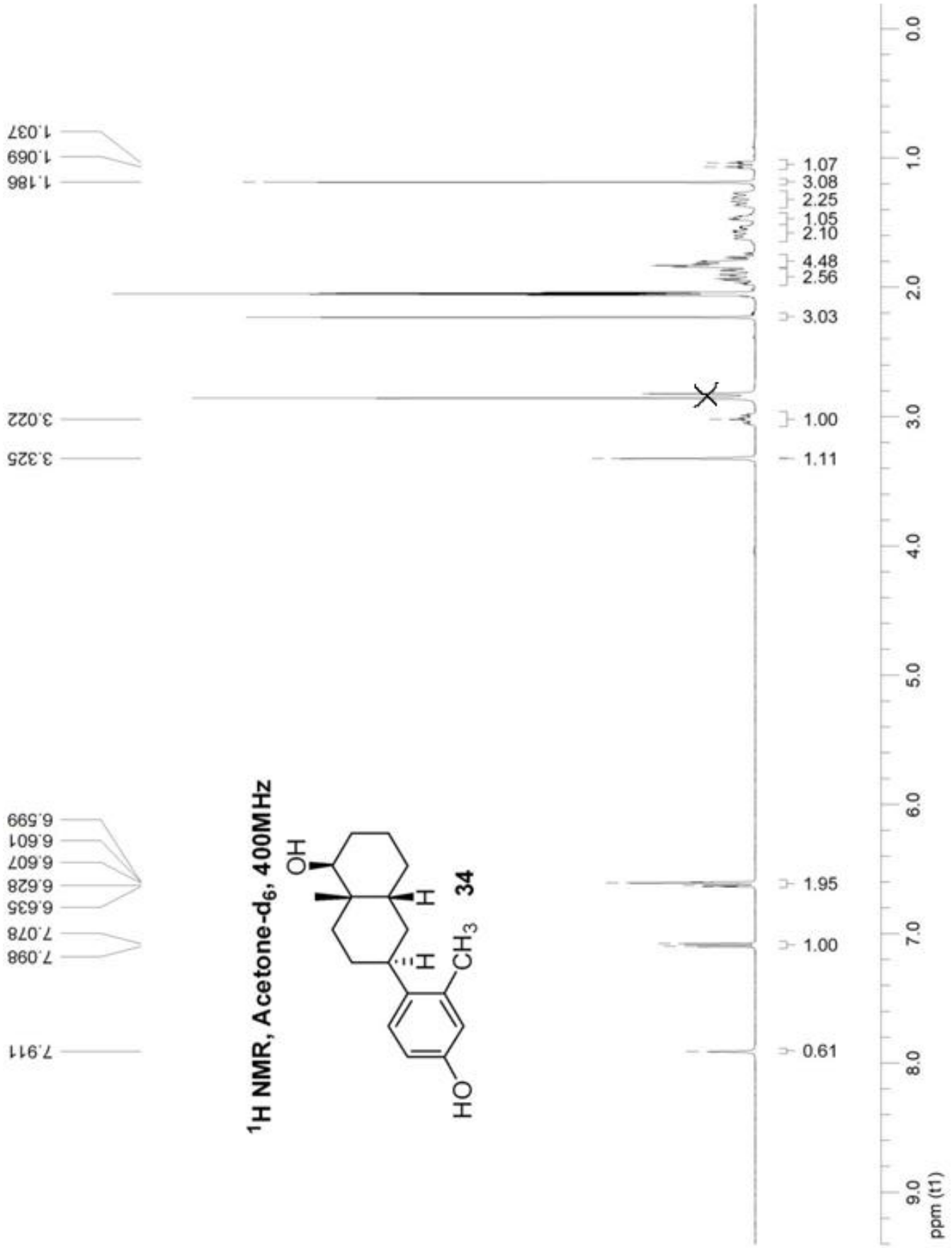

163.749
161.341
157.951
157.833
129.316
129.244
125.848
125.701
112.183
112.155
103.686
103.427
76.477
37.910
37.802
35.090
32.065
31.356
30.189
29.413
28.453
22.925
21.202
^{13}C NMR, MeOD, 100MHz
OH
H
H
HO
F
33
150
100
50
0
ppm (t1)

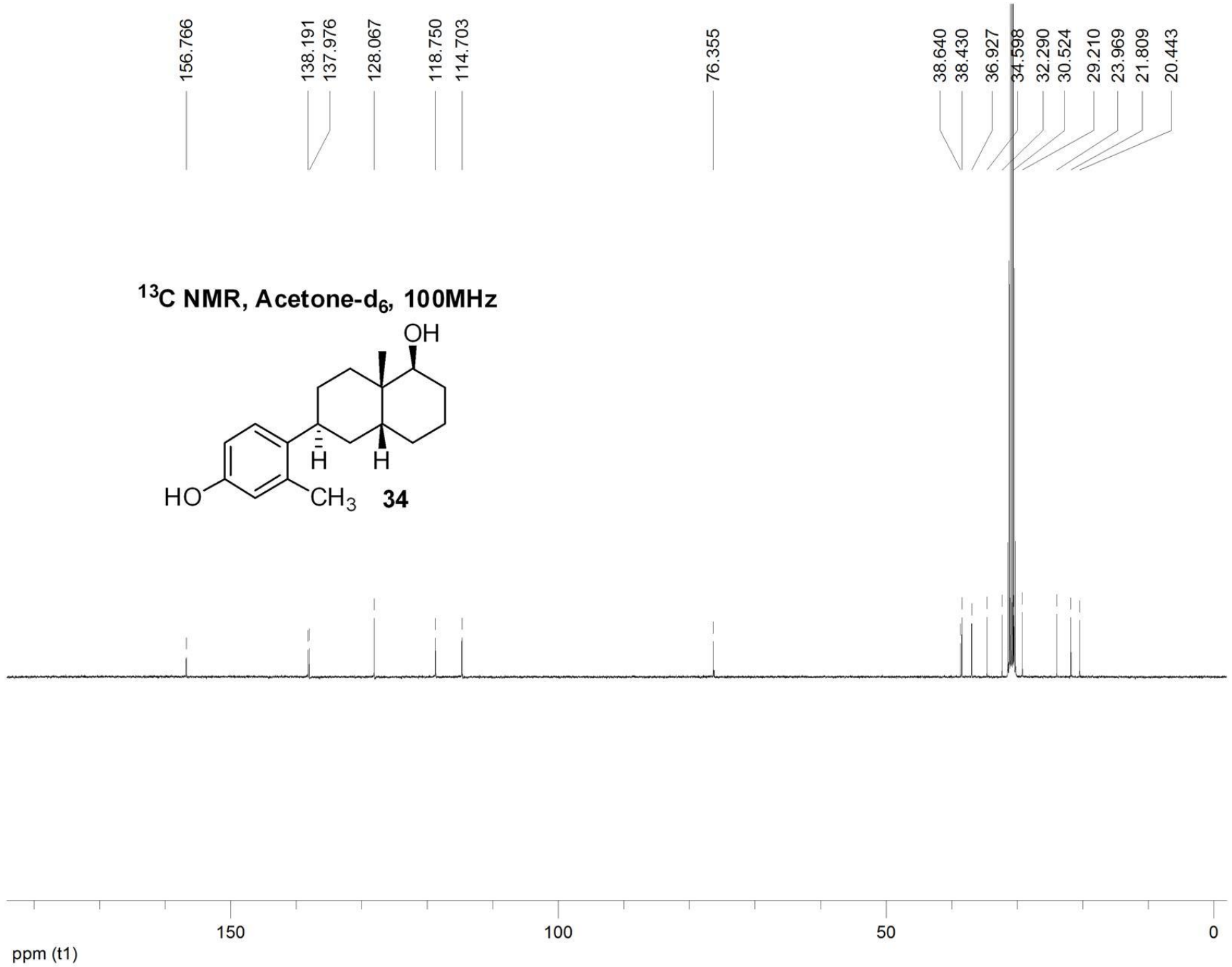

0.978
2.203
2.237
2.808
4.021
4.072
6.503
6.509
6.533
6.540
6.599
6.605
6.620
6.626
7.136
7.158
7.179
8.553
3.02
1.29
1.09
1.24
3.32
3.85
2.36
1.08
0.94
0.99
0.96
0.99
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
^{1}H NMR, Acetone-d_6, 400MHz
OH
H
H
F
HO
35

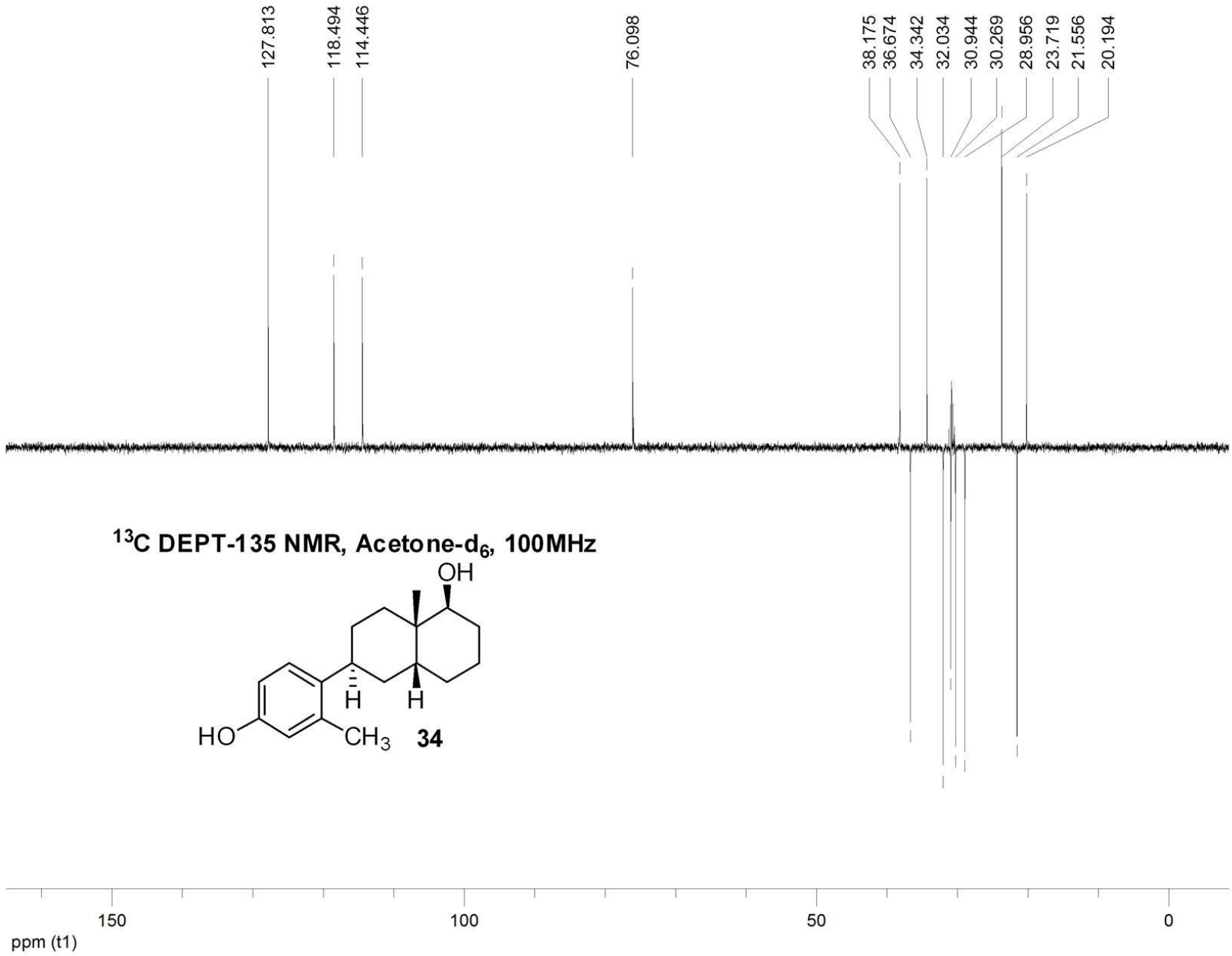

8.592
7.190
7.168
7.146
6.643
6.637
6.622
6.616
6.558
6.552
6.527
6.521
3.177
2.729
2.714
2.694
2.678
2.658
2.643
1.232
1H NMR, Acetone-d6, 400MHz
O
H
H
HO
F
37
0.73
1.00
0.99
0.97
1.02
1.04
3.13
1.00
1.94
4.30
4.09
5.0
0.0
ppm (t1)


215.882
164.140
161.733
158.812
158.693
130.167
130.096
125.942
125.795
113.219
113.190
104.562
104.305
50.084
44.939
39.254
35.626
32.602
32.298
32.282
29.621
29.009
27.084
21.331
13C NMR, Acetone-d6, 100MHz
O
H
H
HO
F
37
200
150
100
50
0
ppm (t1)


1.105
2.228
3.554
3.562
3.571
5.378
6.586
6.593
6.606
6.613
6.633
6.640
6.893
6.913
3.02
2.53
4.29
3.50
3.17
3.04
2.09
0.99
0.99
2.03
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
^{1}H NMR, CDCl$_3$, 400MHz
OH
H
CH$_3$
HO
32

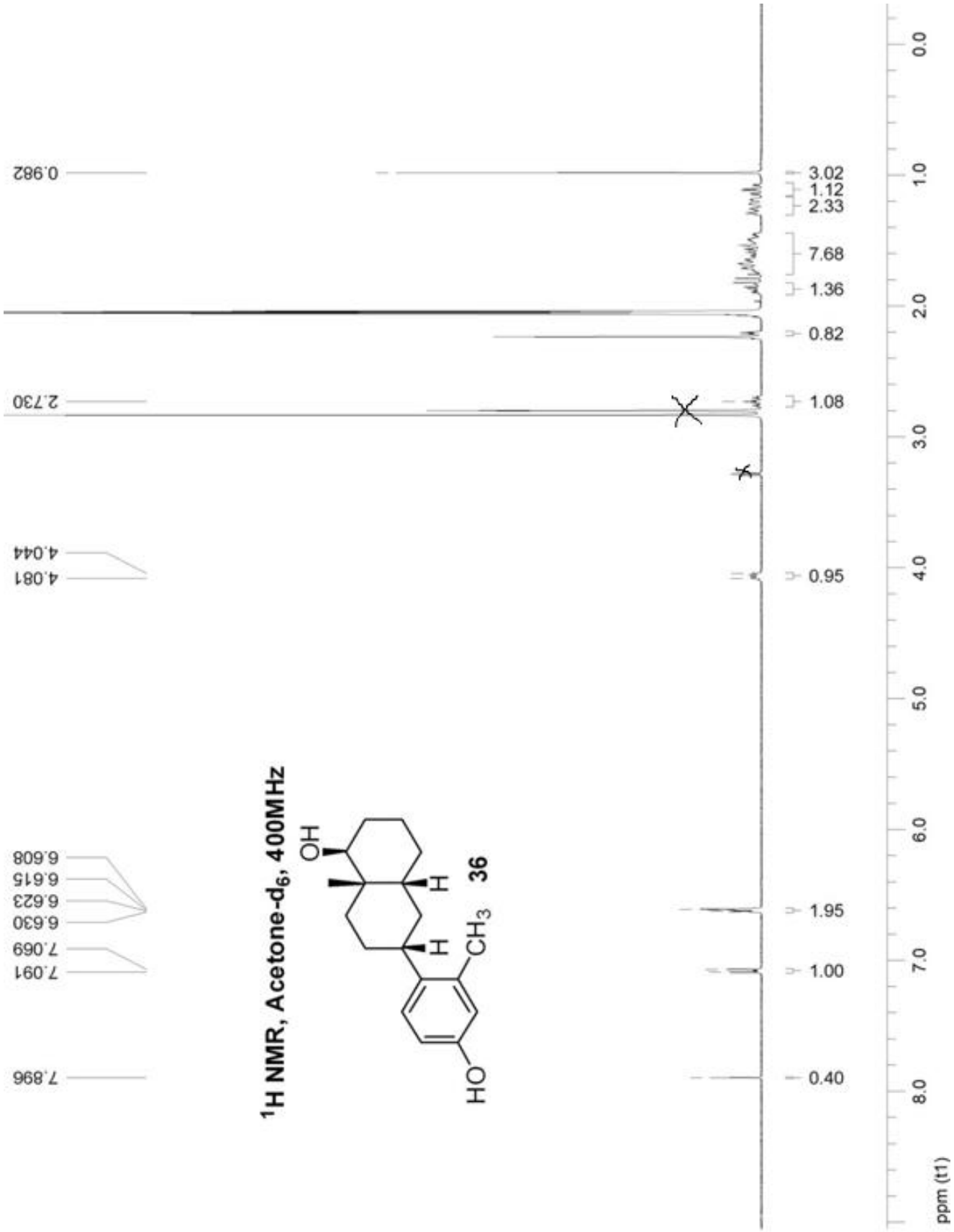

1.037
1.069
1.186
3.022
3.325
6.599
6.601
6.607
6.628
6.635
7.078
7.098
7.911
1.07
3.08
2.25
1.05
2.10
4.48
2.56
3.03
1.00
1.11
1.95
1.00
0.61
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
9.0
ppm (t1)
^{1}H NMR, Acetone-d_6, 400MHz
OH
H
H
CH_3
HO
34


156.766
138.191
137.976
128.067
118.750
114.703
76.355
38.640
38.430
36.927
34.598
32.290
30.524
29.210
23.969
21.809
20.443
^{13}C NMR, Acetone-d$_6$, 100MHz
OH
H
H
HO
CH$_3$
34
150
100
50
0
ppm (t1)

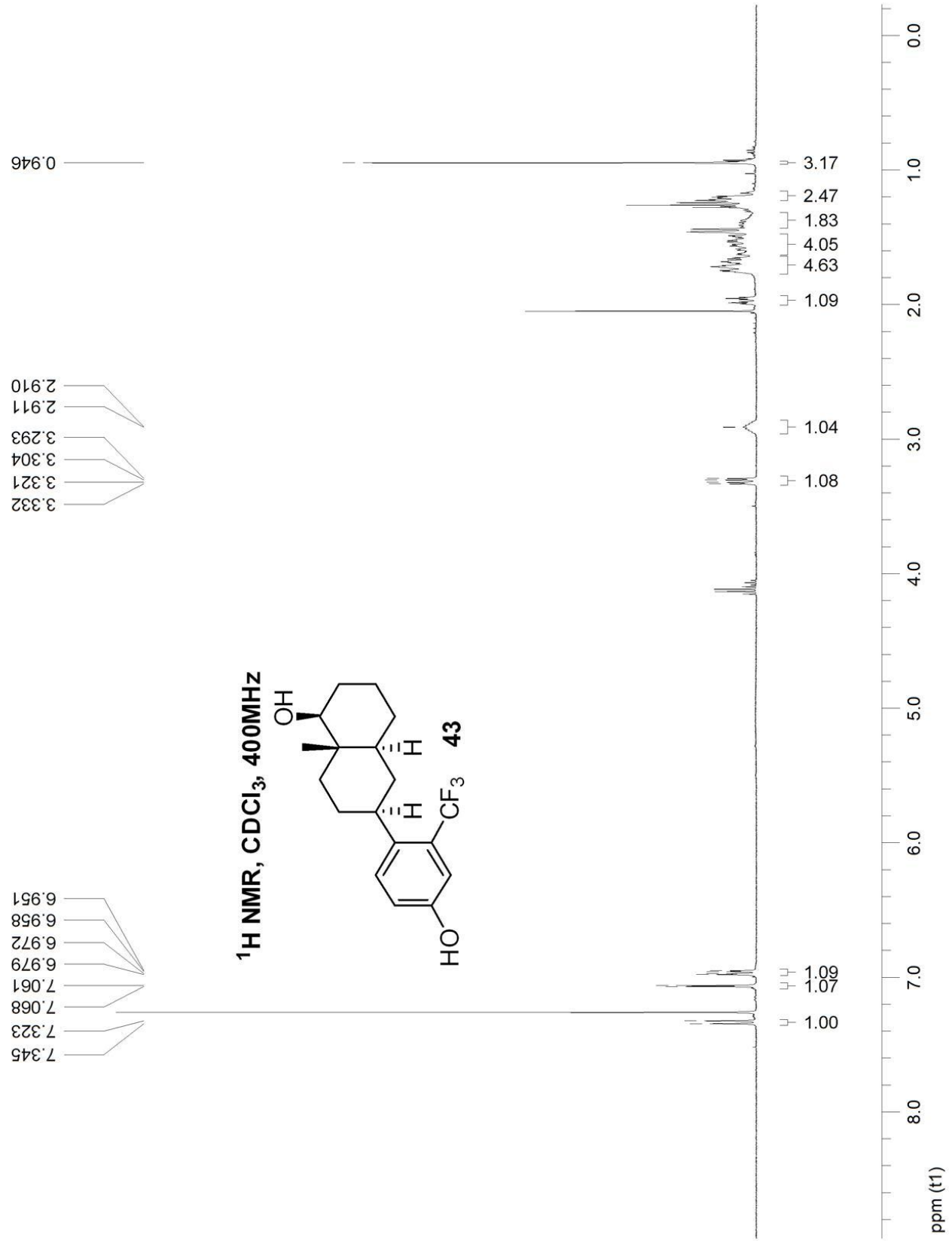


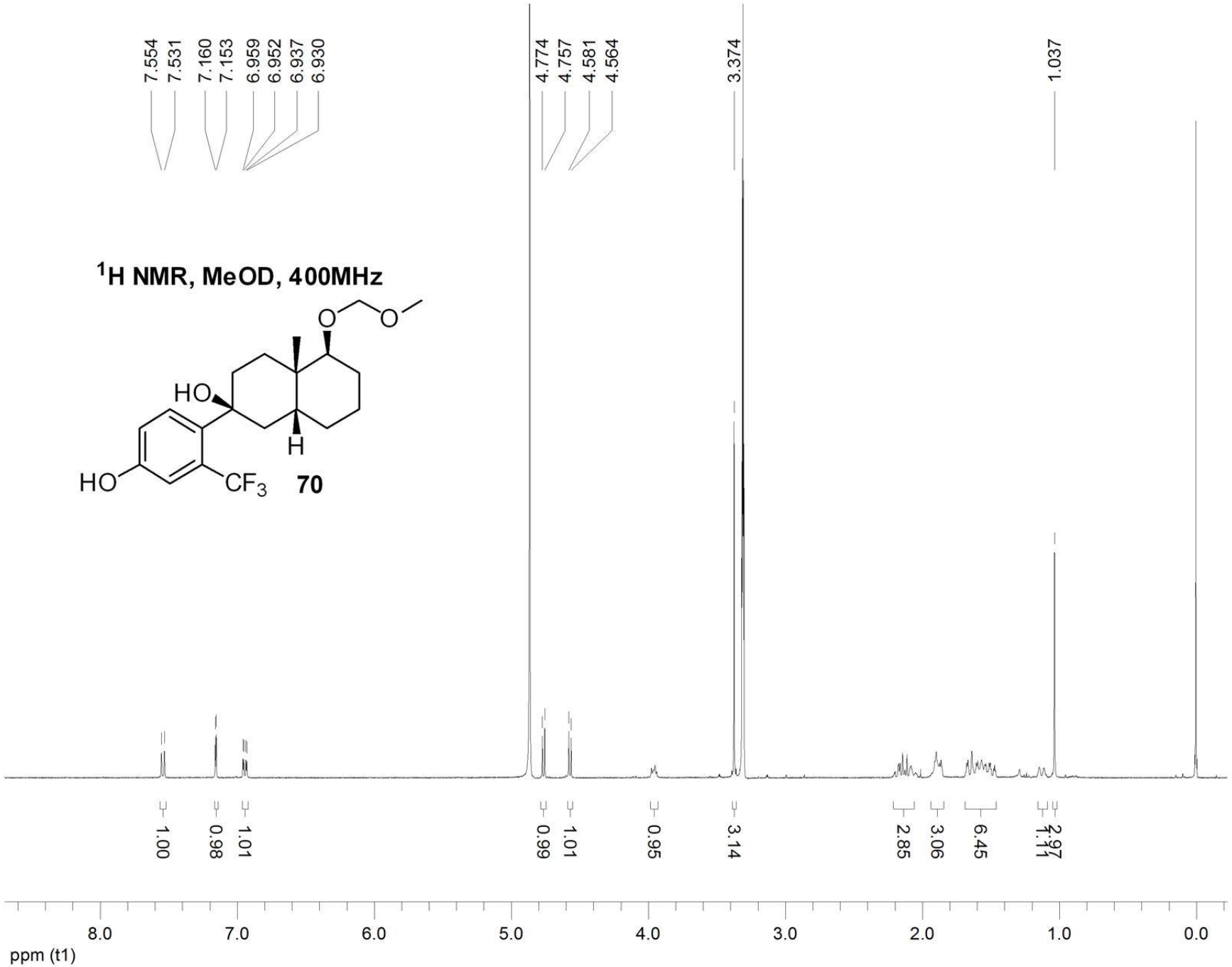
^{13}C DEPT-135 NMR, Acetone-d_6, 100MHz

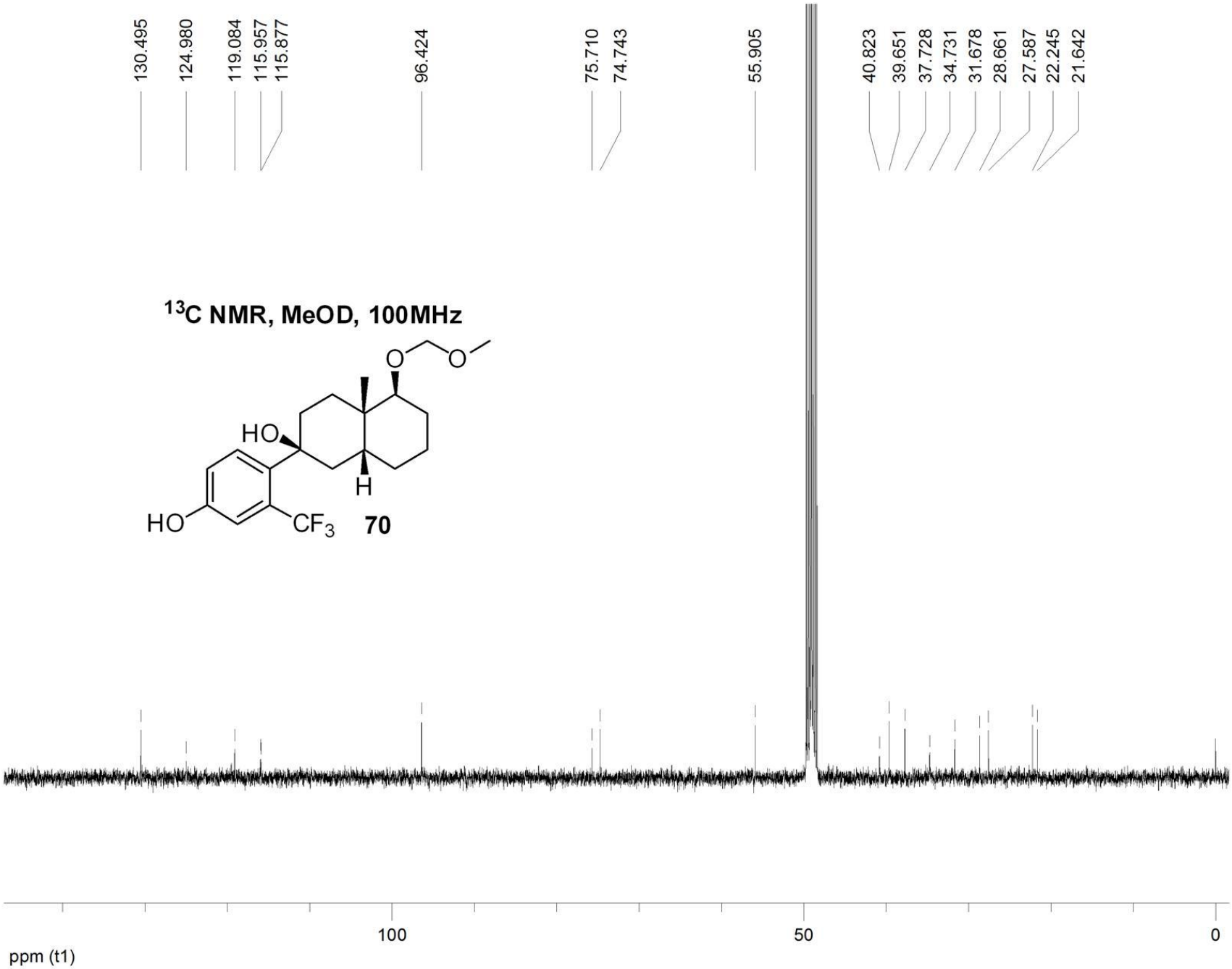
34

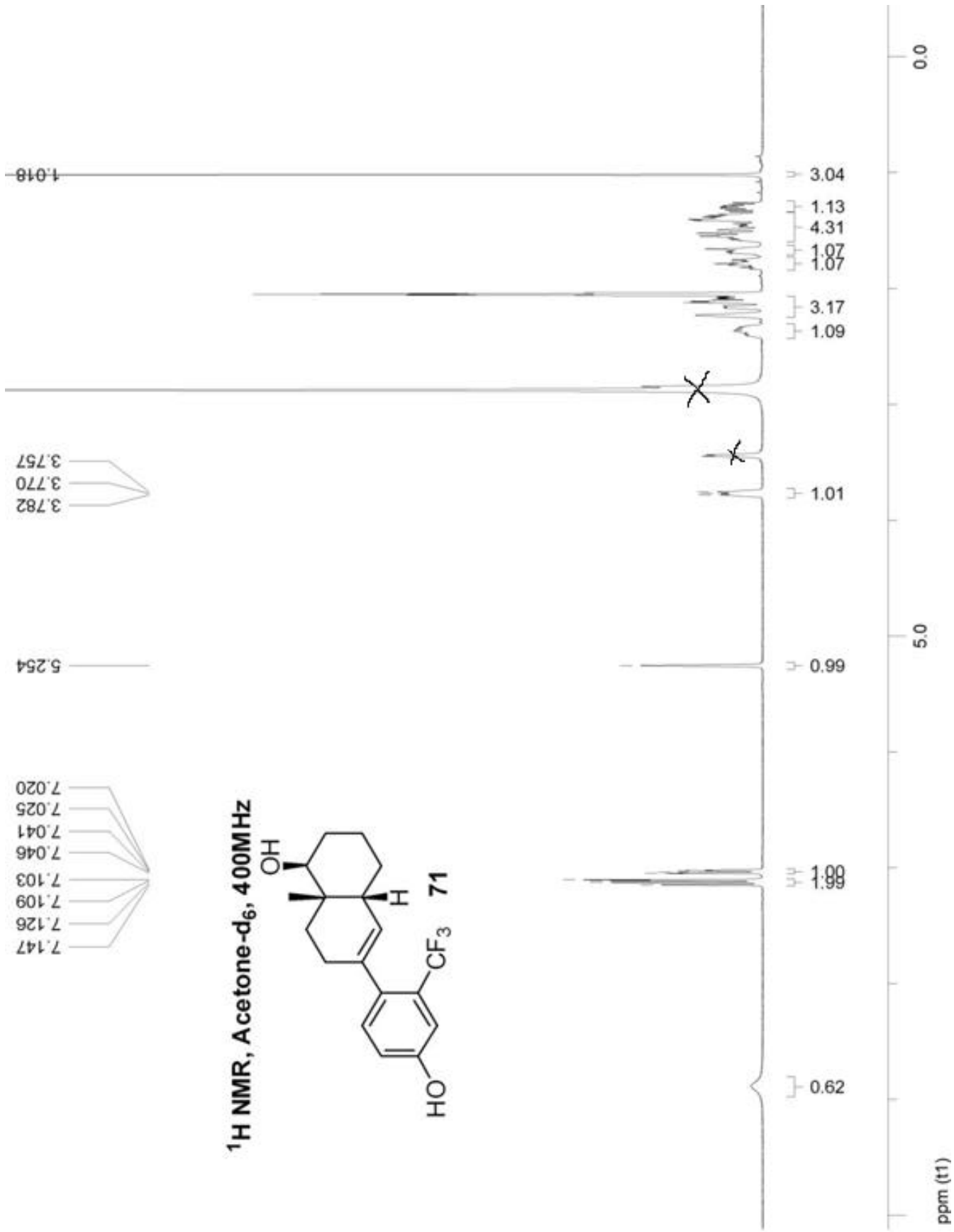


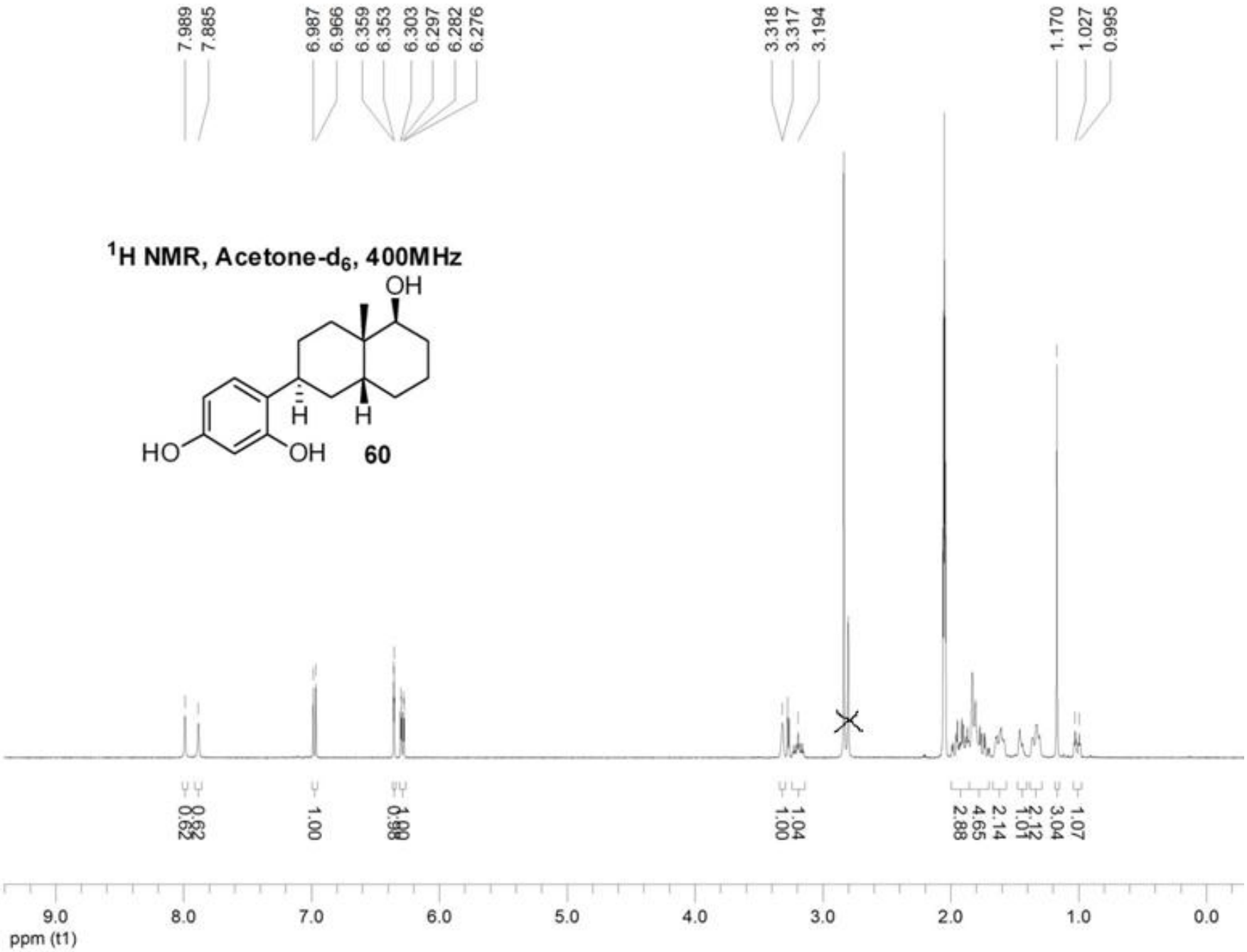
^{1}H NMR, Acetone-d_6, 400MHz

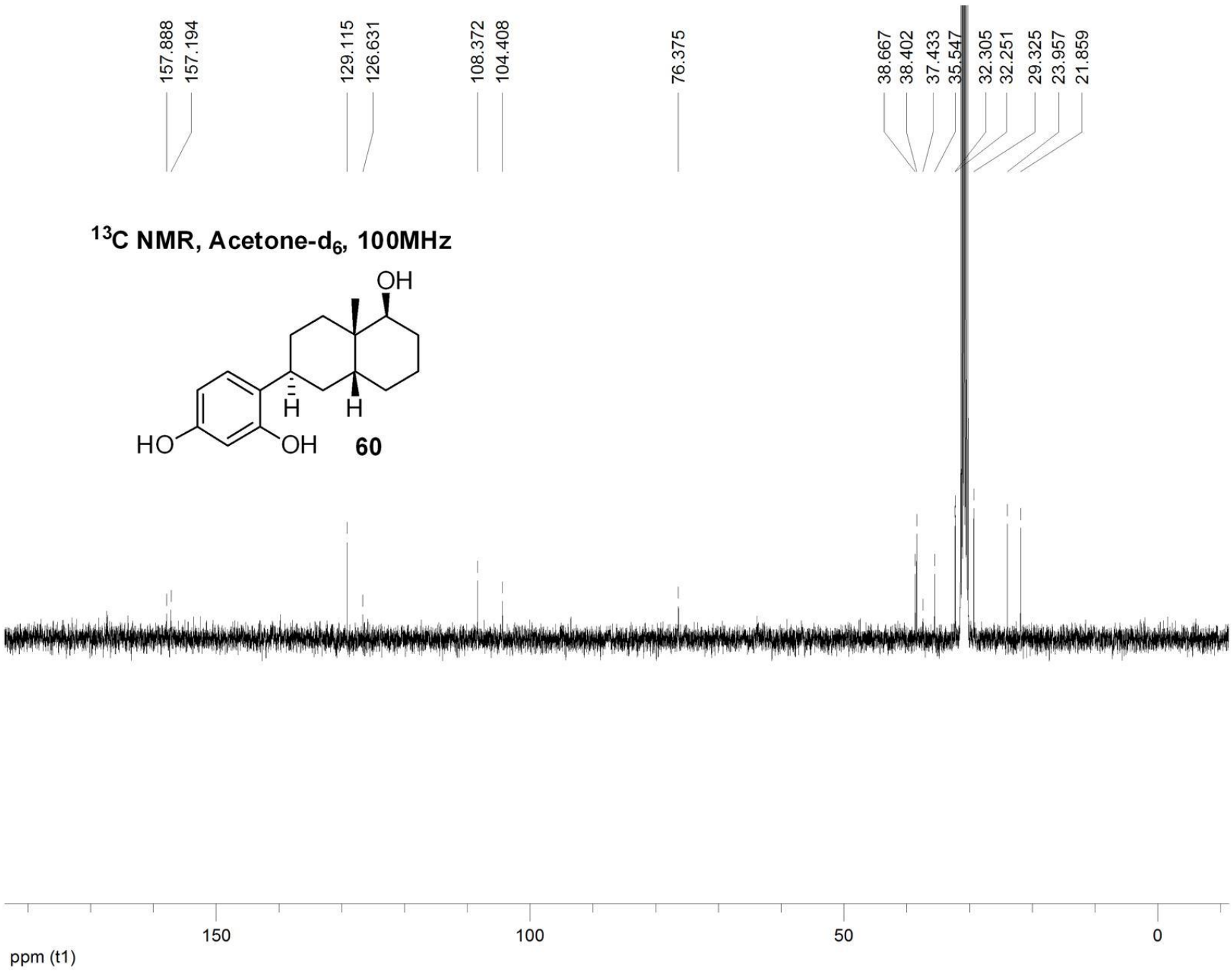

0.946
2.910
2.911
3.293
3.304
3.321
3.332
6.951
6.958
6.972
6.979
7.061
7.068
7.323
7.345
3.17
2.47
1.83
4.05
4.63
1.09
1.04
1.08
1.09
1.07
1.00
0.0
1.0
2.0
3.0
4.0
5.0
6.0
7.0
8.0
ppm (t1)
^{1}H NMR, CDCl$_3$, 400MHz
OH
H
H
CF$_3$
HO
43


7.554
7.531
7.160
7.153
6.959
6.952
6.937
6.930
4.774
4.757
4.581
4.564
3.374
1.037
1H NMR, MeOD, 400MHz
HO
H
HO
CF3
70
1.00
0.98
1.01
0.99
1.01
0.95
3.14
2.85
3.06
6.45
2.97
1.11
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


130.495
124.980
119.084
115.957
115.877
96.424
75.710
74.743
55.905
40.823
39.651
37.728
34.731
31.678
28.661
27.587
22.245
21.642
^{13}C NMR, MeOD, 100MHz
O
O
HO
H
HO
CF_3
70
100
50
0
ppm (t1)


1.018
3.782
3.770
3.757
5.254
7.020
7.025
7.041
7.046
7.103
7.109
7.126
7.147
3.04
1.13
4.31
1.07
1.07
3.17
1.09
1.01
0.99
1.00
1.99
0.62
0.0
5.0
ppm (t1)
OH
H
CF3
HO
71
1H NMR, Acetone-d6, 400MHz


7.989
7.885
6.987
6.966
6.359
6.353
6.303
6.297
6.282
6.276
3.318
3.317
3.194
1.170
1.027
0.995
^{1}H NMR, Acetone-d$_6$, 400MHz
OH
H
H
HO
OH
60
0.92
0.92
1.00
1.00
1.00
1.04
4.65
2.14
2.12
1.01
3.04
1.07
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
ppm (t1)


157.888
157.194
129.115
126.631
108.372
104.408
76.375
38.667
38.402
37.433
35.547
32.305
32.251
29.325
23.957
21.859
^{13}C NMR, Acetone-d$_6$, 100MHz
OH
H
H
HO
OH
60
150
100
50
0
ppm (t1)

APPENDIX II – X-RAY DATA

Table 1. Crystal data and structure refinement for td012.

Identification code	td012
Empirical formula	C17 H25 O2.50
Formula weight	269.37
Temperature	200(2) K
Wavelength	0.71073 A
Crystal system, space group	Monoclinic, C2/c
Unit cell dimensions	a = 20.135(3) A alpha = 90 deg. b = 6.0120(7) A beta = 92.844(2) deg. c = 24.588(3) A gamma = 90 deg.
Volume	2972.7(6) A^3
Z, Calculated density	8, 1.204 Mg/m^3
Absorption coefficient	0.079 mm^-1
F(000)	1176
Crystal size	0.15 x 0.10 x 0.07 mm
Theta range for data collection	1.66 to 24.72 deg.
Limiting indices	-23<=h<=23, -7<=k<=7, -28<=l<=28
Reflections collected / unique	15918 / 2501 [R(int) = 0.0372]
Completeness to theta = 24.72	98.5 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9945 and 0.9883
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	2501 / 0 / 177
Goodness-of-fit on F^2	1.023
Final R indices [I>2sigma(I)]	R1 = 0.0496, wR2 = 0.1213
R indices (all data)	R1 = 0.0715, wR2 = 0.1336
Largest diff. peak and hole	0.337 and -0.441 e.A^-3

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for td012.
U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	4070(1)	4641(3)	7378(1)	38(1)
O(2)	4324(1)	2028(3)	3055(1)	36(1)
O(3)	5000	1239(4)	7500	36(1)
C(1)	3755(1)	3062(4)	5284(1)	33(1)
C(2)	4390(1)	3655(4)	5619(1)	33(1)
C(3)	4282(1)	3534(4)	6228(1)	30(1)
C(4)	3699(1)	4962(3)	6406(1)	27(1)
C(5)	3529(1)	4336(4)	6988(1)	32(1)
C(6)	2941(1)	5634(4)	7184(1)	39(1)
C(7)	2330(1)	5313(5)	6801(1)	44(1)
C(8)	2472(1)	5775(4)	6208(1)	39(1)
C(9)	3076(1)	4458(4)	6039(1)	30(1)
C(10)	3201(1)	4640(4)	5432(1)	32(1)
C(11)	3885(1)	2884(4)	4684(1)	31(1)
C(12)	4190(1)	986(4)	4495(1)	32(1)
C(13)	4333(1)	715(4)	3956(1)	32(1)
C(14)	4175(1)	2396(4)	3586(1)	28(1)
C(15)	3876(1)	4314(4)	3759(1)	34(1)
C(16)	3733(1)	4543(4)	4302(1)	36(1)
C(17)	3908(1)	7425(4)	6383(1)	36(1)

Table 3. Bond lengths [A] and angles [deg] for td012.

O(1)-C(5)	1.428(2)
O(2)-C(14)	1.371(2)
C(1)-C(11)	1.515(3)
C(1)-C(10)	1.522(3)
C(1)-C(2)	1.529(3)
C(2)-C(3)	1.525(3)
C(3)-C(4)	1.534(3)
C(4)-C(5)	1.536(3)
C(4)-C(9)	1.538(3)
C(4)-C(17)	1.541(3)
C(5)-C(6)	1.517(3)
C(6)-C(7)	1.525(3)
C(7)-C(8)	1.525(3)
C(8)-C(9)	1.526(3)
C(9)-C(10)	1.531(3)
C(11)-C(12)	1.387(3)
C(11)-C(16)	1.392(3)
C(12)-C(13)	1.380(3)
C(13)-C(14)	1.386(3)
C(14)-C(15)	1.378(3)
C(15)-C(16)	1.388(3)
C(11)-C(1)-C(10)	116.17(17)
C(11)-C(1)-C(2)	111.24(18)
C(10)-C(1)-C(2)	109.12(17)
C(3)-C(2)-C(1)	111.26(18)
C(2)-C(3)-C(4)	113.61(17)
C(5)-C(4)-C(9)	106.50(16)
C(5)-C(4)-C(3)	109.70(16)
C(9)-C(4)-C(3)	109.66(16)
C(5)-C(4)-C(17)	110.09(17)
C(9)-C(4)-C(17)	112.60(17)
C(3)-C(4)-C(17)	108.26(17)
O(1)-C(5)-C(6)	107.55(17)
O(1)-C(5)-C(4)	113.37(17)
C(6)-C(5)-C(4)	112.64(18)
C(5)-C(6)-C(7)	110.89(18)
C(8)-C(7)-C(6)	112.61(19)
C(7)-C(8)-C(9)	110.82(19)
C(10)-C(9)-C(8)	113.60(17)
C(10)-C(9)-C(4)	112.82(17)
C(8)-C(9)-C(4)	112.15(17)
C(9)-C(10)-C(1)	110.32(17)
C(12)-C(11)-C(16)	116.73(19)
C(12)-C(11)-C(1)	119.00(18)
C(16)-C(11)-C(1)	124.24(19)
C(11)-C(12)-C(13)	122.42(19)
C(14)-C(13)-C(12)	119.4(2)
O(2)-C(14)-C(15)	123.27(18)
O(2)-C(14)-C(13)	116.88(19)
C(15)-C(14)-C(13)	119.85(18)
C(14)-C(15)-C(16)	119.65(19)
C(15)-C(16)-C(11)	121.9(2)

Table 4. Anisotropic displacement parameters (A^2 x 10^3) for td012.
The anisotropic displacement factor exponent takes the form:
-2 pi^2 [h^2 a*^2 U11 + ... + 2 h k a* b* U12]

	U11	U22	U33	U23	U13	U12
O(1)	43(1)	44(1)	28(1)	-10(1)	-7(1)	11(1)
O(2)	45(1)	42(1)	22(1)	6(1)	4(1)	11(1)
O(3)	41(1)	33(1)	33(1)	0	-6(1)	0
C(1)	39(1)	32(1)	26(1)	0(1)	-2(1)	3(1)
C(2)	31(1)	42(1)	26(1)	-1(1)	0(1)	8(1)
C(3)	30(1)	34(1)	25(1)	-1(1)	-3(1)	5(1)
C(4)	28(1)	28(1)	26(1)	-1(1)	-1(1)	0(1)
C(5)	33(1)	36(1)	26(1)	-3(1)	-3(1)	-1(1)
C(6)	38(1)	46(1)	33(1)	-4(1)	4(1)	1(1)
C(7)	31(1)	61(2)	39(1)	-5(1)	6(1)	2(1)
C(8)	27(1)	53(2)	35(1)	-3(1)	-1(1)	3(1)
C(9)	31(1)	31(1)	27(1)	-2(1)	-2(1)	-2(1)
C(10)	30(1)	40(1)	26(1)	0(1)	-6(1)	2(1)
C(11)	32(1)	34(1)	25(1)	0(1)	-3(1)	2(1)
C(12)	36(1)	34(1)	24(1)	5(1)	-1(1)	8(1)
C(13)	32(1)	33(1)	30(1)	2(1)	3(1)	8(1)
C(14)	25(1)	36(1)	22(1)	2(1)	-2(1)	-1(1)
C(15)	42(1)	32(1)	27(1)	5(1)	-4(1)	4(1)
C(16)	45(1)	32(1)	30(1)	-2(1)	-4(1)	9(1)
C(17)	36(1)	30(1)	42(1)	-3(1)	0(1)	-4(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for td012.

	x	y	z	U(eq)
H(1B)	4362	3674	7330	46
H(2C)	4212	3141	2866	44
H(3C)	5320	272	7634	54
H(1A)	3620	1545	5403	39
H(2A)	4749	2615	5529	40
H(2B)	4532	5178	5525	40
H(3A)	4693	4024	6431	36
H(3B)	4200	1967	6328	36
H(5A)	3407	2723	6988	38
H(6A)	3055	7234	7205	47
H(6B)	2840	5126	7554	47
H(7A)	2168	3766	6834	52
H(7B)	1972	6321	6912	52
H(8A)	2554	7384	6159	46
H(8B)	2079	5359	5971	46
H(9A)	2968	2859	6104	36
H(10A)	3327	6187	5344	39
H(10B)	2789	4270	5215	39
H(12A)	4304	-171	4745	38
H(13A)	4539	-613	3839	38
H(15A)	3768	5473	3507	41
H(16A)	3527	5871	4418	43
H(17A)	4305	7661	6623	54
H(17B)	3545	8364	6502	54
H(17C)	4008	7815	6009	54

Table 6. Torsion angles [deg] for td012.

C(11)-C(1)-C(2)-C(3)	-172.50(18)
C(10)-C(1)-C(2)-C(3)	58.0(2)
C(1)-C(2)-C(3)-C(4)	-54.9(2)
C(2)-C(3)-C(4)-C(5)	167.20(18)
C(2)-C(3)-C(4)-C(9)	50.6(2)
C(2)-C(3)-C(4)-C(17)	-72.6(2)
C(9)-C(4)-C(5)-O(1)	178.04(17)
C(3)-C(4)-C(5)-O(1)	59.4(2)
C(17)-C(4)-C(5)-O(1)	-59.6(2)
C(9)-C(4)-C(5)-C(6)	-59.5(2)
C(3)-C(4)-C(5)-C(6)	-178.15(18)
C(17)-C(4)-C(5)-C(6)	62.8(2)
O(1)-C(5)-C(6)-C(7)	-177.57(18)
C(4)-C(5)-C(6)-C(7)	56.8(2)
C(5)-C(6)-C(7)-C(8)	-51.7(3)
C(6)-C(7)-C(8)-C(9)	51.9(3)
C(7)-C(8)-C(9)-C(10)	173.61(19)
C(7)-C(8)-C(9)-C(4)	-57.0(2)
C(5)-C(4)-C(9)-C(10)	-170.74(17)
C(3)-C(4)-C(9)-C(10)	-52.1(2)
C(17)-C(4)-C(9)-C(10)	68.5(2)
C(5)-C(4)-C(9)-C(8)	59.5(2)
C(3)-C(4)-C(9)-C(8)	178.08(18)
C(17)-C(4)-C(9)-C(8)	-61.3(2)
C(8)-C(9)-C(10)-C(1)	-172.90(18)
C(4)-C(9)-C(10)-C(1)	58.0(2)
C(11)-C(1)-C(10)-C(9)	173.81(18)
C(2)-C(1)-C(10)-C(9)	-59.5(2)
C(10)-C(1)-C(11)-C(12)	-156.7(2)
C(2)-C(1)-C(11)-C(12)	77.6(2)
C(10)-C(1)-C(11)-C(16)	25.0(3)
C(2)-C(1)-C(11)-C(16)	-100.6(2)
C(16)-C(11)-C(12)-C(13)	-0.7(3)
C(1)-C(11)-C(12)-C(13)	-179.0(2)
C(11)-C(12)-C(13)-C(14)	0.6(3)
C(12)-C(13)-C(14)-O(2)	-179.51(18)
C(12)-C(13)-C(14)-C(15)	-0.1(3)
O(2)-C(14)-C(15)-C(16)	179.15(19)
C(13)-C(14)-C(15)-C(16)	-0.2(3)
C(14)-C(15)-C(16)-C(11)	0.1(3)
C(12)-C(11)-C(16)-C(15)	0.4(3)
C(1)-C(11)-C(16)-C(15)	178.6(2)

Symmetry transformations used to generate equivalent atoms:

Table 7. Hydrogen bonds for td012 [A and deg.].

D-H...A	d(D-H)	d(H...A)	d(D...A)	<(DHA)

CLAIMS TO ORIGINAL RESEARCH

1. The synthesis of more than a dozen of homo A-CD estrogens with evaluation of their RBA data
2. The asymmetric synthesis of 9 (*S*) A-CD compounds using a 1,5-hydride shift
3. The synthesis of ketone A-CD compounds using a 1,5-hydride shift
4. The synthesis of **TD81** and homo analog **60** starting from 1,3-cyclohexan-di-one