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Abbreviations and Symbols

Ac	acetyl
$AlCl_3$	aluminum chloride
Al_2O_3	aluminum oxide
nBuLi	n butyllithium
BPO	piperonyl butoxide
br	broad
Bu_3N	tri-n-butylamine
°C	degrees Celsius
Calc.	calculated
CH_2Br_2	dibromomethane
CH_2ClBr	bromochloromethane
CH_2Cl_2	methylene chloride
$CHCl_3$	chloroform
CH_3I	methyl iodide
CH_2I_2	diiodomethane
cm^{-1}	wave number
^{13}C NMR	carbon-13 nuclear magnetic resonance
CYP3A4	human cytochrome P450 enzyme
d	doublet
DCC	1,3-dicyclohexylcarbodiimide
dd	doublet of doublets

ddt	doublets of doublets of triplets
DMAP	N,N-dimethylaminopyridine
DMF	N,N-dimethylformamide
DMG	direct metallating group
DoM	directed ortho metallation
EI	electron impact
eq.	equivalents
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram
h	hour
HCl	hydrochloric acid
^1H NMR	proton nuclear magnetic resonance
H_2O	water
H_2O_2	hydrogen peroxide
HPLC	high performance liquid chromatography
HRMS	high resolution liquid chromatography
Hz	hertz
IC_{50}	concentration to inhibit growth by 50%
IR	infrared
IUPAC	International Union of Pure and Applied Chemistry
J	coupling constant
K_2CO_3	potassium carbonate

KF	potassium fluoride
KOH	potassium hydroxide
LiCuMe2	lithium dimethylcuprate
LDA	lithium diisopropylamide
$LiN(TMS)_2$	lithium hexamethyldisilazide
m	multiplet
M	molar
m/z	mass to charge ratio
mCPBA	meta-chloroperbenzoic acid
MDP	methylenedioxyphenyl
Me	methyl
Me_2SO_4	magnesium sulfate
MeI	methyl iodide
mfo	mixed-function oxidase
mg	milligram
min	minutes
ml	milliliter
mM	millimolar
mmol	millimoles
mol	moles
MOM	methoxymethyl
MOMCl	methoxymethyl chloride
MnO_2	manganese dioxide

MP	melting point
MS	low resolution mass spectroscopy
N	normal
Na_2CO_3	sodium carbonate
NaI	sodium iodide
NaOH	sodium hydroxide
NH_4Cl	ammonium chloride
$POCl_3$	phosphorus oxychloride
ppm	parts per million
q	quartet
RT	room temperature
s	singlet
SeO_2	selenium oxide
$SnCl_4$	tin tetrachloride
t	triplet
α-T	alpha terthienyl
TBHP	*tert*-butylhydroperoxide
THF	tetrahydrofuran
tlc	thin layer chromatography
TsOH	*p*-toluenesulfonic acid
μM	micromolar

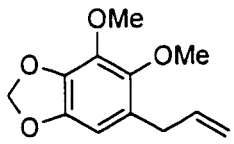
ABSTRACT

Part A

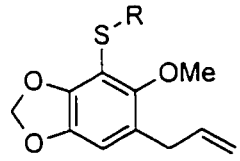
This thesis describes a new route for the synthesis of dillapiol, a natural synergist, starting with the commercially available sessamol. It has potential for significant scale-up reactions. A key step in our synthesis is the introduction of an oxygen substituent at the C-4 position via an ortho metallation –DMF sequence on suitably protected sessamol followed by a Baeyer Villiger oxidation. The new route allowed us to prepare the first 4-thio, 4-sulfinyl and 4-sulfonyl derivatives of dillapiol.

The 4-thio derivatives have been screened for their ability to synergize the light-activated pesticide, α-T. Some of the 4-thio derivatives were more active than dillapiol; the 4-sulfinyl and the 4-sulfonyl compounds showed lower synergism with α-T than dillapiol.

The ability of these compounds to act as drug sparing agents by inhibiting CYP3A4 has also been briefly investigated. In this case the 4-sulfonyl derivatives were found to be potent in inhibiting CYP3A4 with IC_{50} values in micro molar range.



Dillapiol

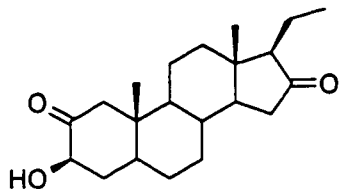


4-Thio derivative

Part B

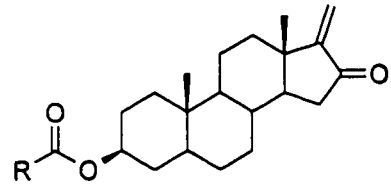
The synthesis of trichiliasterone B was completed starting from an androsterone intermediate (16-ethylenedioxypregnan-3-one) prepared earlier by Hantos. It involved converting the 3-keto functionality of the Hantos intermediate into a 2-keto-3β-hydoxy

arrangement. This was accomplished via preparation and thermolysis of 3β-acetoxy-2α,3α-epoxy-16-ethylenedioxypregnane followed by treatment with basic alumina.



Trichiliasterone B

Four ester derivatives of 3β-hydroxyandrost-17(20)-en-16-one were prepared and sent for screening as potential anti-cancer agents based on the concept that the α,β-unsaturated ketone should act as a potential Michael acceptor. Promising activity was found towards *in vitro* tests against the human leukemia cell line.



Ester derivative

Part A: The Syntheses of Dillapiol and its 4 - Thio Derivatives

Chapter 1

Introduction

1.1 Pesticide chemistry

Insecticide resistance is a dynamic, multidimensional phenomenon dependent on genetic, physiological, biochemical and ecological factors.[1] All these vary with species, population and geographic location. Resistant strains develop through the survival and reproduction of individuals carrying a genome altered by one or more of many possible mechanisms that allow survival after the exposure to an insecticide.[1]

Insects have developed resistance to all major classes of insecticides such as DDT, cyanide, lindane, organophosphate, carbamates and pyrethroids. This is not surprising when viewed in ecological and evolutionary perspectives. Herbivorous insects have coexisted with higher plants for 250-million years.[1] Plants produce many allelochemicals, such as alkaloids, terpenes and phenols, for defense against insects and pathogens. These chemicals are often appreciably toxic and have favored the evolution of counter adaptations, modified physiological processes and biochemical mechanisms. Insects often rely on complex defensive enzymes to overcome the potential toxicity of the plants they eat and thus adapt to the toxic allelochemicals.[1]

Insecticide resistance is predominantly associated with an improved capacity to metabolically detoxify insecticides as well as decreased sensitivity due to modification in target sites.[1] Lipophilic insecticides are primarily detoxified by microsomal oxidases, in particular cytochrome P-450, carboxyesterases (E.C 3.1.1.1 and E.C 3.1.1.2) and

gluthathione transferases (E.C 2.5.1.18). They convert lipophilic foreign compounds to polar metabolites that can be excreted.[2] In contrast to the slow evolution of resistance towards natural insecticides, resistance to synthetic insecticides has developed much more rapidly, perhaps because of the intense selection pressure created by highly toxic synthetics.[3] One strategy for managing resistance or slowing it down is the use of pesticide synergists.

1.2 Pesticides synergists

Pesticides synergists are compounds that are either non-toxic or of negligible toxicity. They enhance the toxicity of a pesticide when combined with it.[4] The development of synergists for the use in pest control stems from the premise that the individual chemicals or combinations can be found to be selective and preferentially control pests without harm to man and useful species.

The methylenedioxyphenyl (MDP) compounds, such as sesamolin **1**, sesamin **2**, piperonal butoxide **3**, safrole **4**, sulfoxide **6** and dillapiol **7**, are the most important synergists from the stand point of historical development and current use.[4] Synergistic activity with the insecticide chemicals is not restricted to MDP compounds because other materials are sometimes as, or even more active. Other groups of synergists include: N-alkyl compounds, such as SKF 525A and MGK 264, O- (2-propynyl) ethers and esters, such as RO 5-8019 and naphthyl propynl ether as shown in Figure 1.1.

Sesame oil was one of the first MDP compounds used as a synergist commercially. It is active because it contains sesamin and more potent sesamolin.[4] The planar MDP group appears to bind preferentially to the heme of cytochrome P-450 in the mixed-function oxidase (mfo), forming relatively stable adducts. Thus, they act as inhibitors by serving as an

alternate substrate for the mfo system, sparing the insecticide chemical from detoxification.[2,3,4]

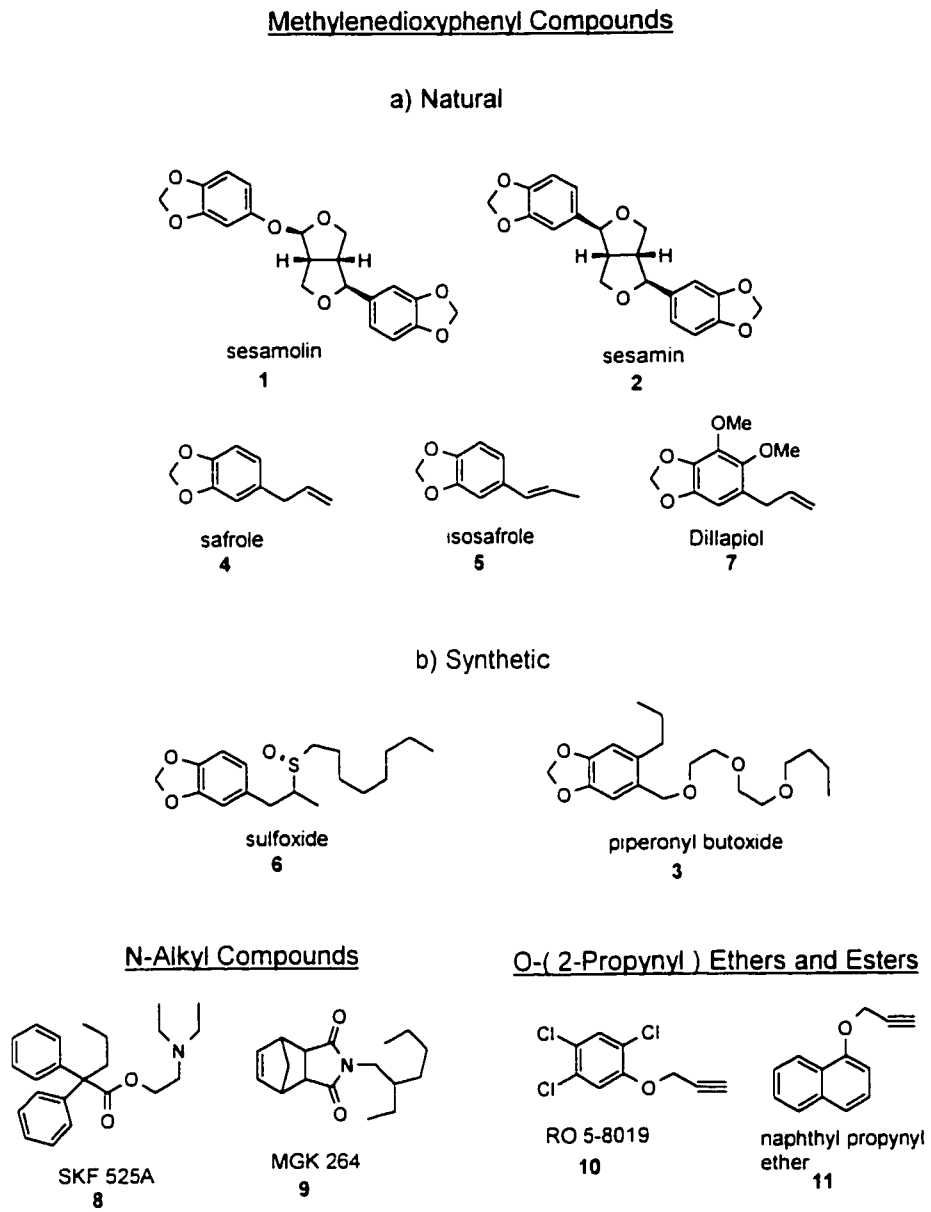


Figure 1.1 : Structures of selected synergists for insecticides
Reference: Casida, J.E, 1970

Currently most widely used synthetic synergists such as piperonyl butoxide **3** and the sulfoxide **6** are prepared from the natural product safrole. N-Alkyl and O-(-2-propynyl) ethers and esters compounds (Figure 1.1) are also inhibitors of microsomal oxidation in the similar manner as MDP compounds.[5,6]

Piperonyl butoxide **3**, a commonly used pyrethrum synergist, presently dominates the market but is under toxicological review and may be deregistered.[3] Dillapiol **7**, a major constituent (35%) of Indian dill (*Anethum Sowa* Roxb.) seed oil was also found to have synergistic action [3,7,8] and is potentially a safe alternative to piperonyl butoxide. Dillapiol offers several advantages over piperonyl butoxide, the most significant being its natural origin in food plants thereby suggesting non-toxicity to humans and other mammals. The synergistic activity of dillapiol towards insecticides has been shown in many instance to surpass that of piperonyl butoxide.[3] Several new derivatives of dillapiol have shown good synergism of pyrethrum against flour beetles (*Tribolium castaneum* Herbst.). [7,8] Dillapiol, being a natural compound, is also limited in supply and it would be desirable to enhance its value by preparing more potent derivatives from it. With such an objective in mind, the synthesis of a number of derivatives of it has been investigated.

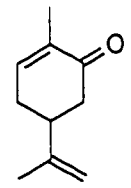
1.3 Sources of dillapiol

1.3.1 Natural sources

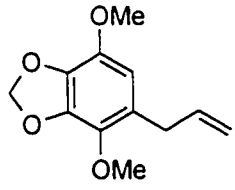
1.3.1.1 *Anethum graveolens* (Apiaceae)

Dill, *Anethum graveolens*, is a common yellow-flowered annual herb, from the same family as carrot or other aromatic herbs such as corriander, fennel or parsley.[9] Its popularity is due to culinary and medicinal properties mainly of its seeds, from which oil is extracted. The

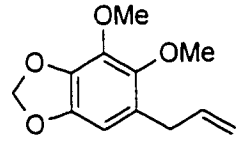
main constitute in dill seed oil in all *Anethum graveolens* sub species is carvone. Carvone, is the main odorant component of dill seeds[10] and is well known for its anticarcinogenic[9] and toxic properties.[11] Other important constituents are phenolic compounds such as apiol and myristicin, an important odorant component of dill herb[10] and insecticidal synergist.[11] Dillapiol, an isomer of apiol, is known to co-occur in various dill subspecies out not in all. It is in highest amount in Indian dill, *Anethum Sowa* Roxb[7,12,13] in about 27-35%. Majerus investigated the content of dillapiol in *Anethum Sowa* Roxb. and showed that the oil was mainly composed of carvone and dillapiol in a 7:1 ratio and the yield of dillapiol was 2%.[3] Apiol and dillapiol being isomers were difficult to separate by distillation or chromatography. In contrast she also found that Canadian dill seed showed no trace of dillapiol.



Carvone



Apiol



Dillapiol

1.3.1.2 *Piper aduncum* (Piperaceae)

Piper aduncum is a tropical shrub coming from the family of Piperaceae.[9] Humans have used *Piper aduncum* for various medicinal purposes such as a tonic, a diuretic, a digestive stimulant and homeostatic agents. *Piper aduncum* from different areas of the world was found to contain dillapiol as main constituent: the essential oil of piper plants from Fiji contained 58% dillapiol [14]; two varieties from Brazil were found to contain dillapiol in 74.5%

and 88.4% [9]and a variety from Panama contained 90% dillapiol.[9] In 1994, fruits, leaves and wood chips/sawdust from *Piper aduncum* plant were collected from Costa Rica and later steam distilled by members of our research group.[3] The seeds of the fruits contained 0.3% of dillapiol, a smaller amount (0.03%) in wood chips/sawdust and only a trace in leaves. The major advantage of *Piper aduncum* as a source of dillapiol is that the product of steam distillation is dillapiol of >95% purity and no apiol was found in the *Piper aduncum* extracts. The most recent study[15] was a general evaluation of the chemistry of *Piper aduncum* found in Costa Rica. Essential oils in leaves of *Piper aduncum* were examined in two Costa Rican locations by the gas-chromatography / mass spectrometry method. The result showed the occurance of fifty-three compounds among which dillapiol is in 32.9% in one population and 61.5% in other, hence *Piper aduncum* is a significant natural source of dillapiol.

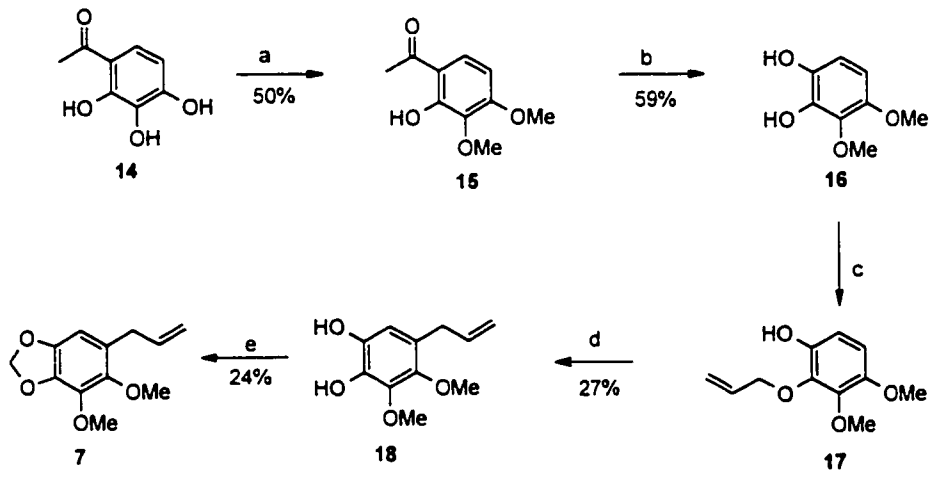
1.3.2 Synthetic sources

Four syntheses of dillapiol have been reported. Despite the simplicity of this molecule which contains no chiral centers or unstable functional groups, all of these syntheses suffer from either low overall yield[16,17,18] or reaction conditions which are not amenable to large scale synthesis.[3] Thus a viable synthetic route to dillapiol would be valuable. Also, a new route may make the synthesis of potentially new, more potent analogs more efficient.

1.3.2.1 Baker's synthesis

Baker et al[16] were the first to synthesize dillapiol in 1934. Their synthesis consists of 5-steps, starting from gallacetophenone **14**, which is now commercially available.

Gallacetophenone was treated with dimethyl sulfate and potassium carbonate to give the o-hydroxy acetophenone **15** in 50% yield. Oxidation of this acetyl function of **15** under Dakin Reaction conditions afforded **16** in 59% yield. The Dakin Reaction involves the initial attack of peroxide anion on the carbonyl carbon. Formation of an ester intermediate via phenyl migration is then followed by hydrolysis to give the desired catechol. Treatment of **16** with allyl bromide and potassium carbonate yielded monoallyl ether **17**, which underwent Claisen rearrangement on heating to give **18** in 27% yield. The structure of **18** was based on the knowledge that the migration of allyl group yields either ortho or para hydroxyallyl benzenes.[16,19] Methylenation of **18** yielded dillapiol **7** in 24% yield. The overall yield of dillapiol via this synthesis is 2%, which limits its usefulness in large-scale synthesis.



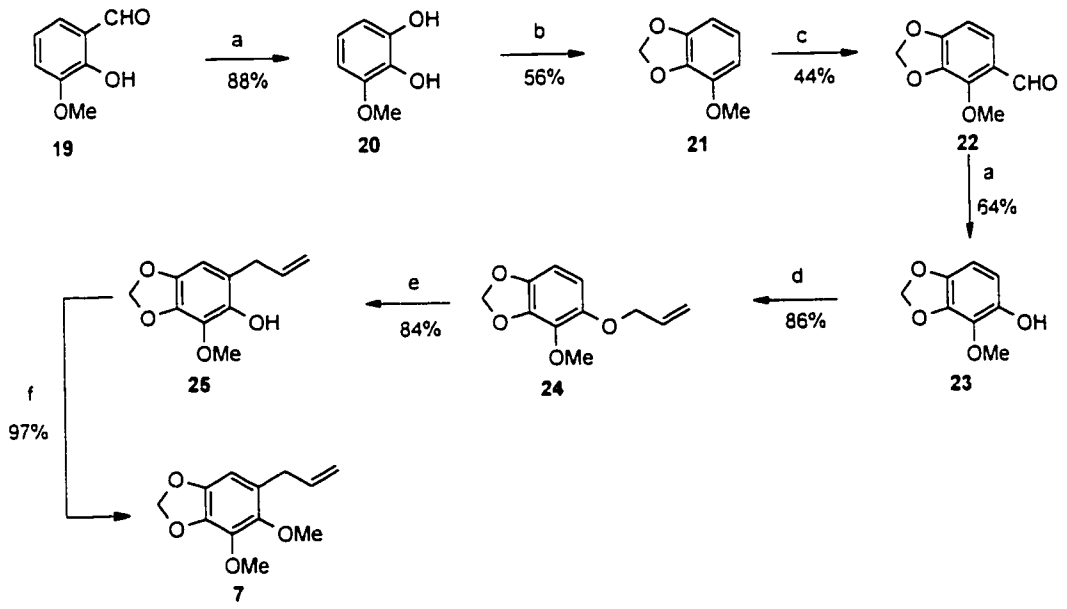
Reagents: (a) Me_2SO_4, K_2CO_3; (b) NaOH, 30% H_2O_2; (c) allyl bromide, K_2CO_3; (d) heat; (e) CH_2I_2, K_2CO_3

Scheme 1.1- Baker's Synthesis of Dillapiol **7**

1.3.2.2 Dallacker's synthesis

Dallacker synthesis was developed in 1969.[17] It started with the tri-substituted benzene, 2-hydroxy-3-methoxy-benzaldehyde (o-vanillin) **19**, which was converted to **20** via Dakin oxidation. Compound **20** was treated with bromochloromethane under basic condition to give **21** in 56% yield. Formylation of **21** under Vilsmeir-Haack Reaction conditions afforded **22** in 44% yield. Oxidation of **22** under Dakin oxidation conditions gave phenol **23** in 64% yield. Compound **23** was treated with allyl bromide and potassium carbonate to give allyl ether **24**, followed by Claisen rearrangement which afforded **25** in 72%. Treatment of **25** with dimethyl sulfate and potassium carbonate resulted in dillapiol 7. The overall yield of dillapiol via this sequence is 10%.

The Dallacker's synthesis is 2-steps longer than Baker's synthesis and despite this, it



Reagents: (a) NaOH, 30% H_2O_2; (b) CH_2ClBr, Na_2CO_3; (c) $POCl_3$, DMF; (d) allyl bromide, K_2CO_3; (e) 190°C; (f) Me_2SO_4, K_2CO_3

Scheme 1.2 - Dallacker's Synthesis of Dillapiol **7**

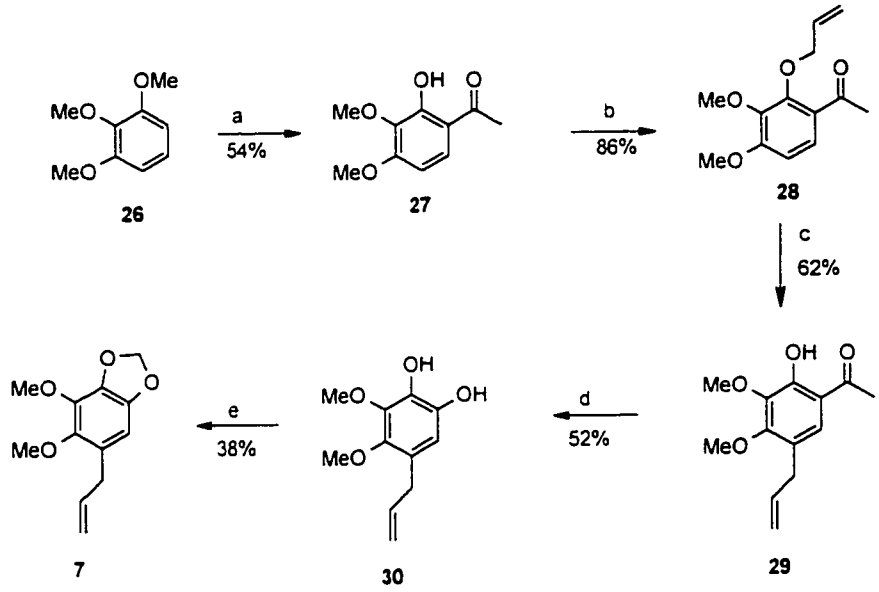
gave higher yield than Baker's. Both the formations of methylenedioxy ring and Vilsmeir-Haack Reaction occur in relatively low yield.

1.3.2.3 Cannon's synthesis

Cannon's synthesis was reported in 1980.[18] It commenced with 1,2,3-trimethoxy benzene **26**. Treatment of **26** with acetyl chloride/$AlCl_3$ afforded **27** in 54% yield. Treatment of **27** with allyl bromide and potassium carbonate yielded allyl ether **28** which underwent Claisen rearrangement to give phenolic ketone **29** in 53% overall yield from **27**. Compound **29** underwent Dakin oxidation affording a mixture of the desired compound **30** and unreacted starting material. Attempts to separate this mixture were not rewarding and as a result the reaction mixture was treated directly with dibromomethane and potassium flouride giving dillapiol **7** in 38% yield from **30** and 6% overall yield. This low overall yield is once again mainly due to the difficulties encountered in the formation of methylenedioxy ring. A synthesis, which avoids this ring closure, could significantly improve the overall yield of dillapiol.

1.3.2.4 Majerus' synthesis

Majerus' synthesis was developed in 1997.[3] It started with sesamol **31**, which had the advantage of avoiding low yield associated with the formation of methylenedioxy ring. Sesamol was treated with allyl bromide and potassium carbonate to form allyl ether **32** in >99% yield. The allyl ether was subjected to Claisen rearrangement condition to give **33** in 81% yield. Formylation of **33** with tin tetrachloride, tri-n-butylamine and paraformaldehyde

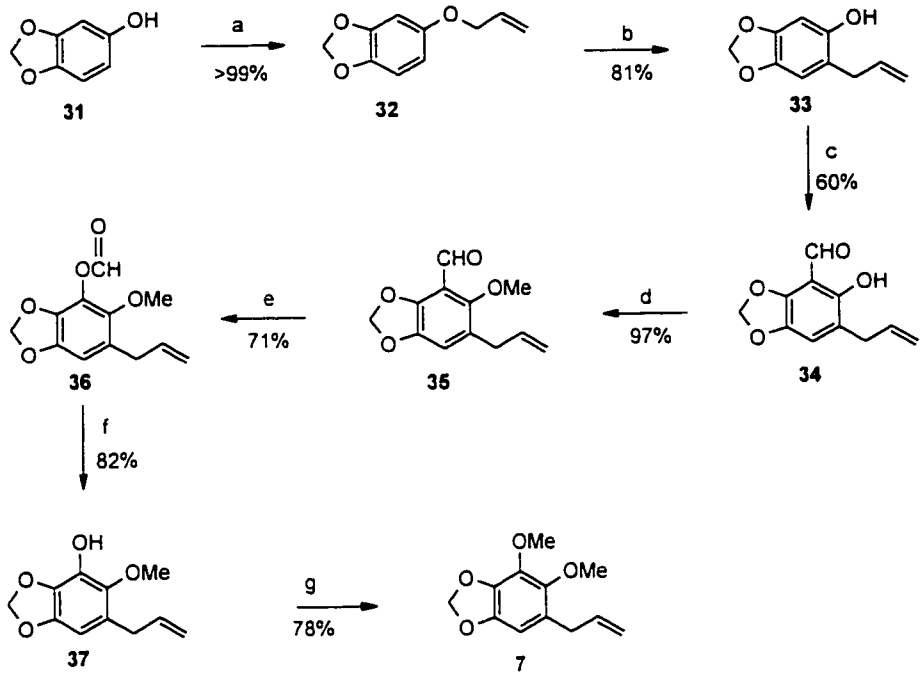


Reagents: (a) AcCl, $AlCl_3$; (b) allyl bromide, K_2CO_3; (c) heat;
(d) 5% NaOH, 30% H_2O_2; (e) CH_2Br_2, KF

Scheme 1.3 - Cannon's Synthesis of Dillapiol **7**

gave **34** in 60% yield. Methylation of **34** with MeI in presence of potassium carbonate gave **35** in 97% yield. Baeyer-Villiger oxidation was carried out on **35** to give **36** in 71% yield, which was then hydrolyzed using 3N NaOH to give **37** in 82% yield. The final transformation involves methylation of phenol **37** with MeI and potassium carbonate to give dillapiol **7** in 78% yield. The overall yield of this synthesis is approximately 21%.

This synthesis has an advantage over the previously reported syntheses due to a substantially higher overall yield. It has one low yielding step, the introduction of formyl group with tin tetrachloride and paraformaldehyde and one tricky step, the Baeyer Villiger oxidation of **35**. This reaction needed to be done carefully to avoid epoxidation of the allyl group. It is particularly difficult to carry out these steps on a multi gram scale.



Reageants: (a) allyl bromide, K_2CO_3; (b) 190°C; (c) $SnCl_4$, Bu_3N, paraformaldehyde; (d) CH_3I, K_2CO_3;(e) mCPBA; (f) 3N NaOH; (g) CH_3I, K_2CO_3

Scheme 1.4 - Majerus' Synthesis of Dillapiol **7**

Results and Discussion

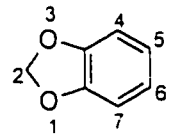
Chapter 2

A new synthesis of dillapiol and its 4-thio derivatives

2.1 Introduction

The synergistic activity of dillapiol and a large number of its derivatives towards pyrethrum have been reported earlier.[7,8,20,21] These compounds owe their activity to the presence of a benzo-1,3-dioxole (MDP) group. Baker's, Dallacker's and Cannon's syntheses all had the disadvantage of low overall yield due to the problem during the formation of the methylenedioxy ring. Majerus' synthesis, although with a much improved overall yield, required careful manipulation to avoid the epoxidation of the allyl group during a Baeyer Villiger oxidation. Her synthesis was not suitable for the preparation of multi gram quantities of dillapiol. Thus a new synthesis of dillapiol that overcame these shortcomings was developed.

The nomenclature of the dillapiol and its derivatives in this thesis conforms to IUPAC regulation. Figure 2.1 illustrates the numbering system of the rings.

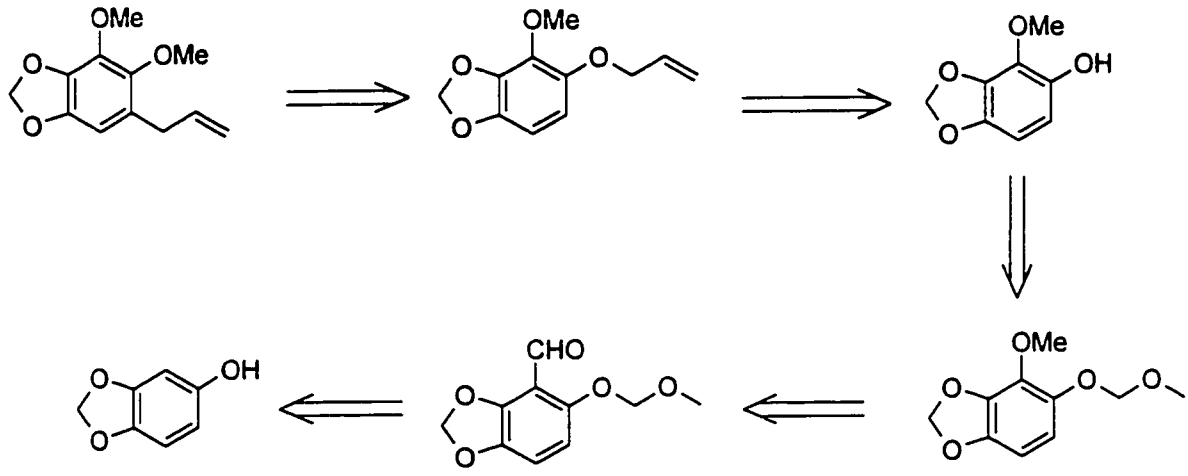


1,3-benzodioxole

Figure 2.1- IUPAC numbering system of dillapiol skeleton

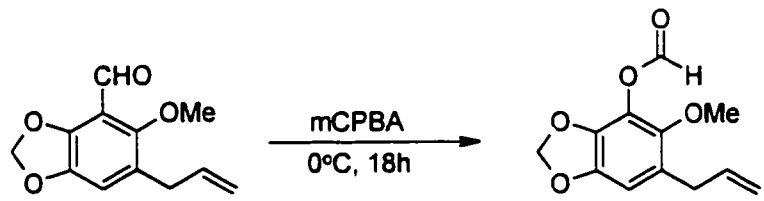
2.2 A new synthesis of dillapiol 7

This synthesis uses commercially available sessamol **31**, as starting material. It also avoids the reported low yielding steps associated with the formation of the methylenedioxy ring. A retrosynthetic approach is shown in Scheme 2.1. The new synthesis is essentially a



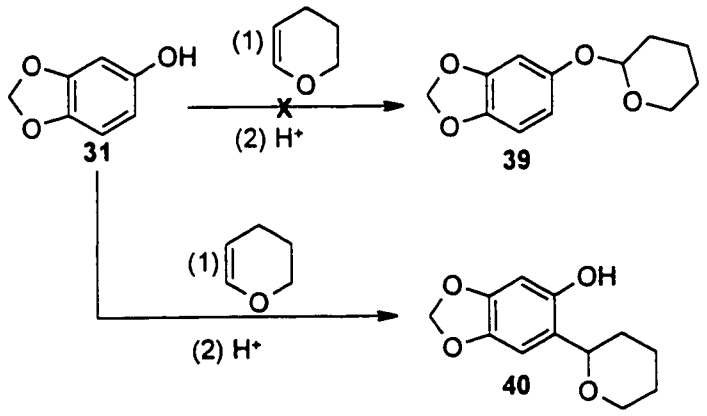
Scheme 2.1- A Retrosynthetic Scheme for the Formation of Dillapiol

variation of that carried out by Majerus. It alters the sequence of the introduction of the 4-methoxy and 6-allyl groups and thereby avoids the care needed to carry out the peracid induced Baeyer Villiger rearrangement in the presence of the 6-allyl group as shown below.



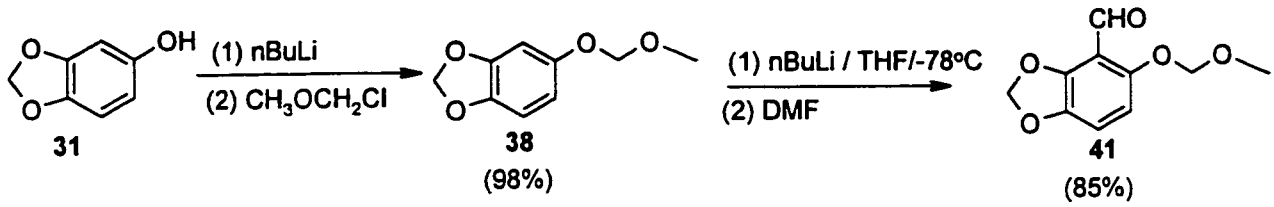
Sessamol was treated with 2.2N nBuLi and MOM-chloride to give **38** in quantitative yield after purification by flash column chromatography (Scheme 2.3). Confirmation of this

transformation was obtained from both the ^{1}H NMR and ^{13}C NMR spectra. The appearance of three sharp singlets at 3.47 ppm, 5.08 ppm and 5.91 ppm in the ^{1}H NMR corresponds to the methyl group, methylene group in the side chain and benzo-1,3-dioxole group respectively. The ^{13}C NMR spectrum also accounted for the ether functionality by the appearance of peaks at 55.9 ppm, 95.5 ppm and 99.7 ppm. It was our initial goal to use the less expensive dihydropyran and protect the hydroxyl group as THP. This group, like the MOM group, is known to be effective in directing an ortho metallation.[22] Unfortunately reaction of **31** with dihydropyran in the presence of catalytic amount of TsOH afforded the product **40** rather than the desired product **39** (Scheme 2.2).



Scheme 2.2 - Electrophilic Substitution of Dihydropyran on **31**

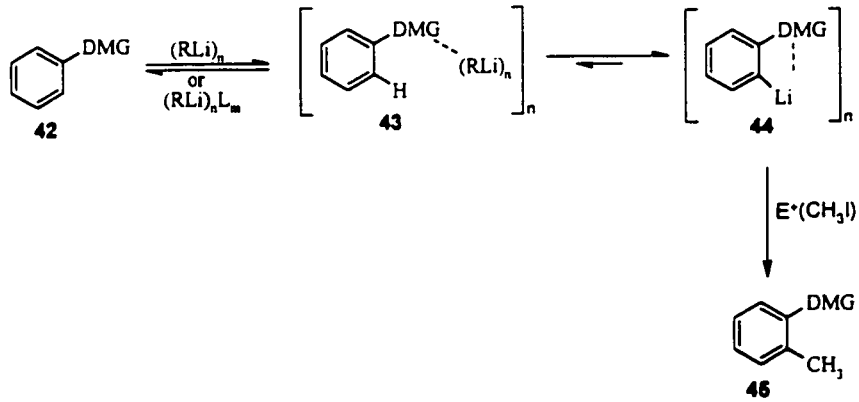
The product **38**, when reacted with 2.2N nBuLi and DMF, underwent a directed ortho-metallation (DoM) reaction to give **41** in 85% yield (Scheme 2.3) as shown by both the ^{1}H NMR and ^{13}C NMR spectra (Figures 2.2 and 2.3 respectively). The appearance of a singlet at 10.35 ppm in the ^{1}H NMR spectrum, the signal at 188.0 ppm in the ^{13}C NMR spectrum and the 1683 cm^{-1} stretching vibration in the infrared spectrum confirmed the aldehyde functionality.



Scheme 2.3 - Preparation of 4-Formyl-5-Methoxymethoxy-1,3-Benzodioxole **41**

The experimental procedure used for this transformation was based on Snieckus' review article.[22] The DoM reaction (Scheme 2.4) involves the deprotonation of a site ortho to a heteroatom-containing metal chelating group, in our case the methoxy methyl ether, by a strong base, normally an alkyllithium reagent, leading to an ortho-lithiated species **44**. This species upon treatment with electrophilic reagents yields 1,2 disubstituted products, for example **45**.

For a successful deprotonation to occur, the DMG group must exhibit a good coordination site for the alkyllithium and a poor electrophilic site for attack by this strong base. A heteroatom is therefore an obligatory component of the DMG. Inductive effects also have been shown to play a major role in an ortho deprotonation of fluorobenzene and benzonitrile since neither can achieve normal coordination stabilized ortho-lithio intermediates. Snieckus has compiled a list of substituents and their relative ability to direct



Scheme 2.4- The Directed Ortho Metallation Reaction (DoM)

Figure 2.2 – ^{1}H NMR spectrum of 4-formyl-5-methoxymethoxy-1,3-benzodioxole (41)

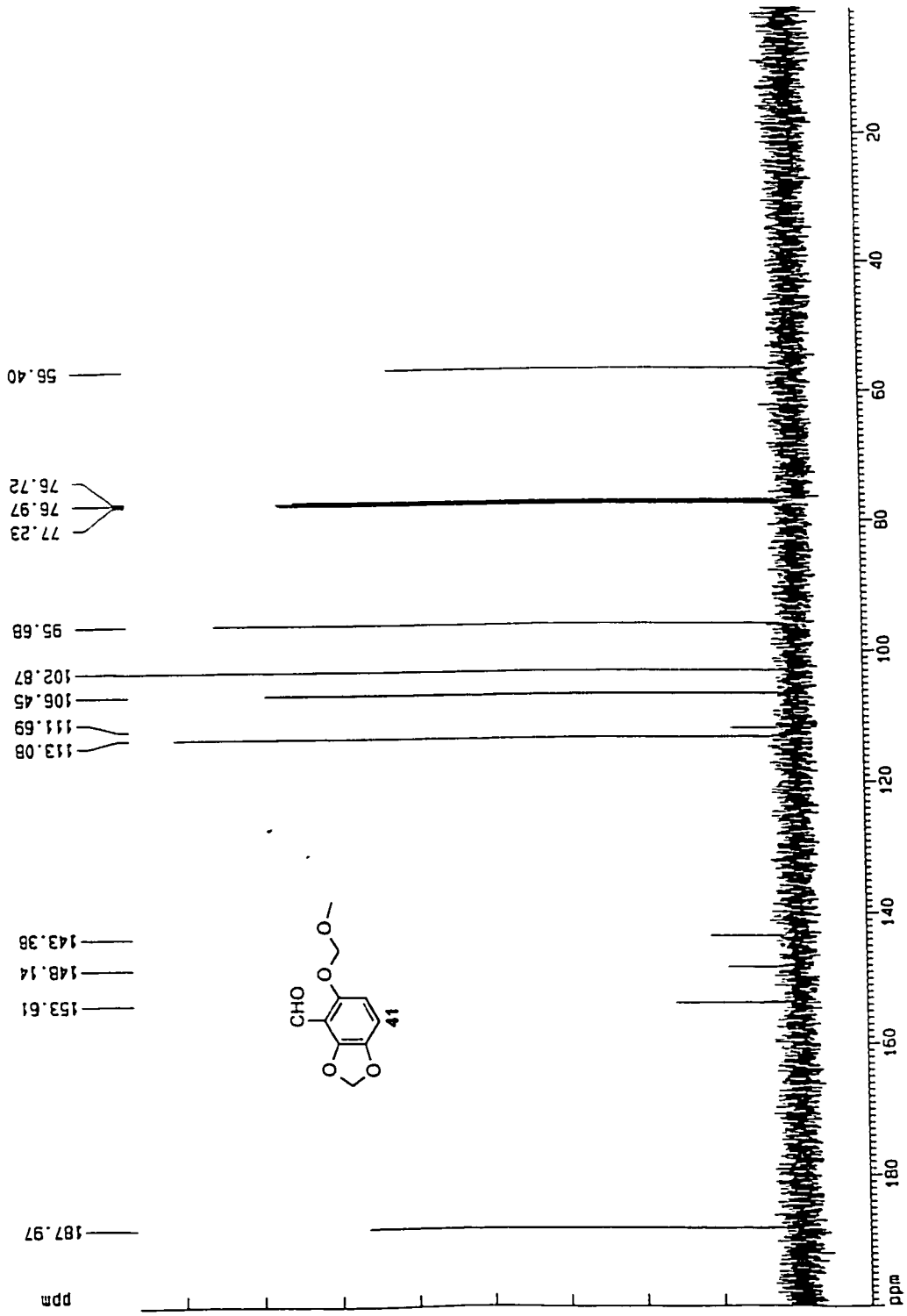
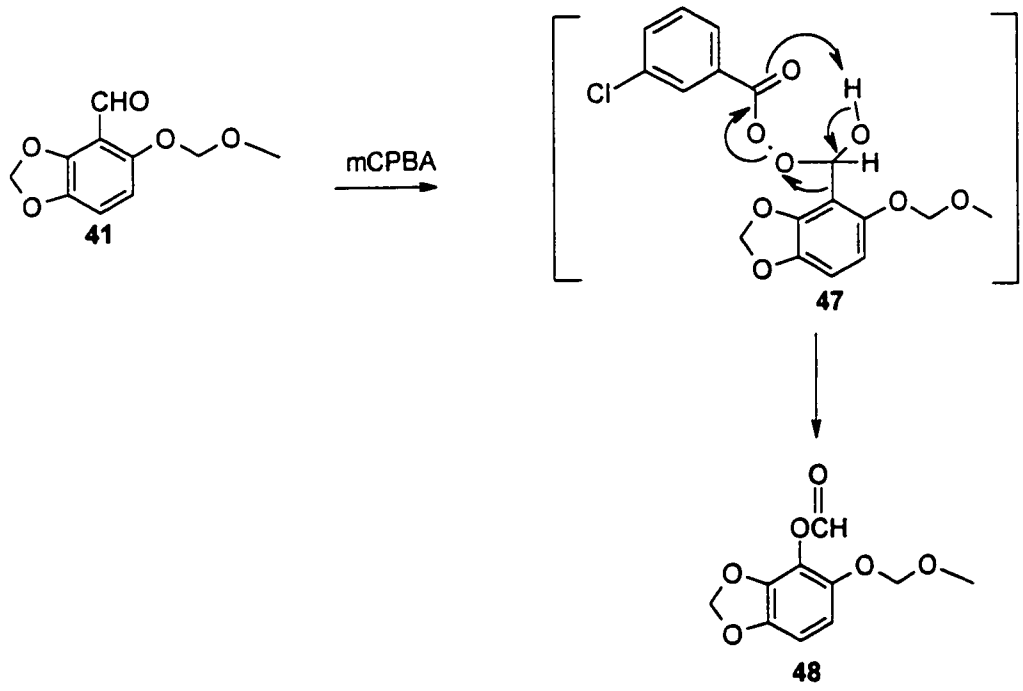


Figure 2.3 – ^{13}C NMR spectrum of 4-formyl-5-methoxymethoxy-1,3-benzodioxole (41)

ortho metallation via internal competition experiments. In this list the methoxy methyl (MOM) group is of average ability, better than OCH_3 but much weaker than groups such as N,N-diethylcarboamide($C(O)N(Et)_2$) or the carbamate group ($O\text{-}CONEt_2$).

Baeyer Villiger oxidation was then performed on **41**. This reaction, which was carried out at 0°C, afforded the product as a pale yellow liquid **48** in 91% yield. The presence of the formyl group is identified by the appearance of a singlet at 8.24 ppm in the ^1H NMR spectrum for the formyl hydrogen and a signal at 157.7 ppm in the ^{13}C NMR spectrum for the carbonyl carbon. The carbonyl group also has a characteristic peak in the infrared spectrum at 1752 cm^{-1}.

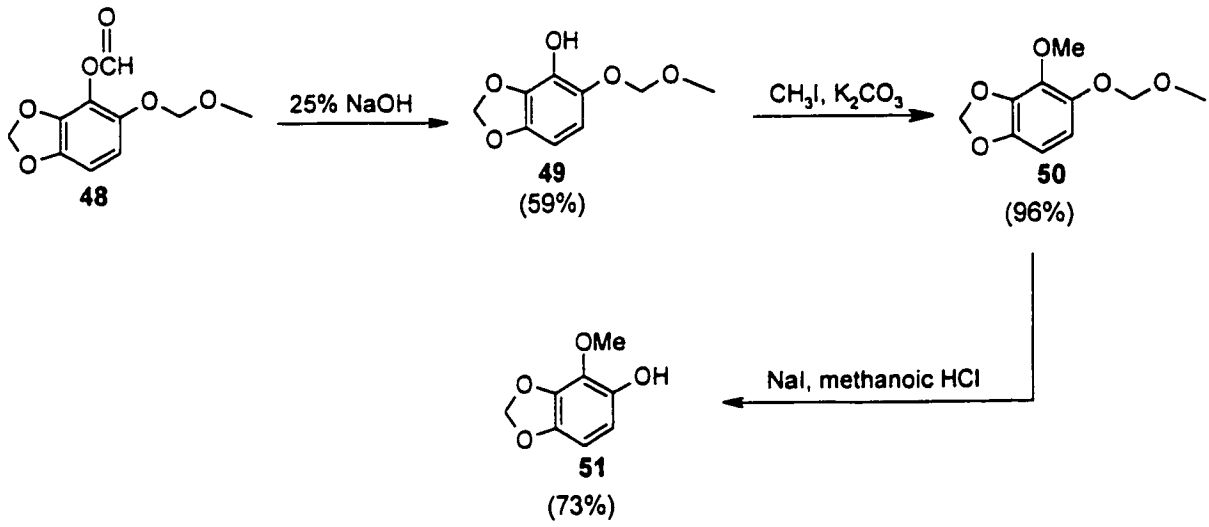
The mechanism is essentially similar to the Dakin Reaction. It first involves the addition of the peracid to the carbonyl carbon [19,23] (Scheme 2.5) to give **47** as the intermediate, which then collapses to give an ester **48**.



Scheme 2.5 - Mechanism of the Baeyer-Villiger Oxidation

Hydrolysis of the ester **48** was carried out with 25% NaOH solution for 4 h at RT, affording the phenol **49** in 59% yield after acid work up. Methylation of phenol **49** with methyl iodide in the presence of potassium carbonate proceeded for 48 h at RT to give **50** in 96% yield as a pale yellow liquid. The ^{1}H NMR spectrum showed an additional 3H singlet at 3.99 ppm corresponding to the methyl proton in the OMe functionality at the C-4 position.

Removal of the MOM group from **50** using NaI and 3N methanoic HCl after 4 h gave **51** as pale orange crystals in 73% yield. Lack of the methyl proton signals from OCH_2 and OCH_3 in the ^{1}H NMR spectrum and the appearance of a 1H singlet at 5.43 ppm corresponding to the phenolic proton and an IR peak at 3541 cm^{-1} confirmed the presence of **51**.

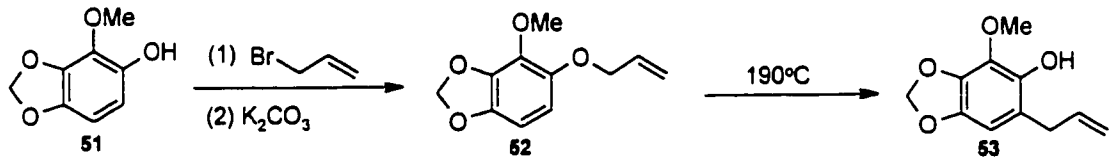


Scheme 2.6 - Preparation of 5-Hydroxy-4-Methoxy-1,3-Benzodioxole **51**

Allylation of **51** using allyl bromide and potassium carbonate formed allyl ether **52** in 86% yield as a yellow liquid after purification by flash column chromatography (Scheme 2.7). Confirmation of this transformation was obtained from both the ^{1}H NMR and ^{13}C NMR

spectra. The appearance of two doublets of triplets patterns at 5.22 ppm and 5.35 ppm and a multiplet in the region of 6.00-6.06 ppm in the ^{1}H NMR spectrum corresponds to the vinylic hydrogens. The ^{13}C NMR spectrum showed signals at 117.5 ppm, 133.6 ppm and 71.2 ppm corresponding to the two vinylic carbons and the carbon in the OCH_2 group respectively.

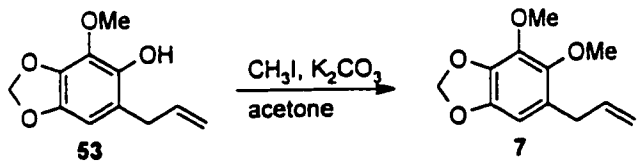
The allyl ether **52** underwent Claisen rearrangement to afford **53** in 87% yield as a pale yellow liquid. The lack of a proton signal for the OCH_2 group in the ^{1}H NMR spectrum and the appearance of a 1H singlet at 4.03 ppm corresponding to the phenolic hydrogen confirmed the transformation. The appearance of a peak at 3538 cm^{-1} in the infrared spectrum confirms the presence of the hydroxyl group.



51 52 53

Scheme 2.7 - Preparation of 5-Hydroxy-4-Methoxy-6-(2-propenyl)-1,3-benzodioxole **53**

The final transformation involved the methylation of phenol **53** with methyl iodide and potassium carbonate in acetone at RT for 36 h to give the desired product, dillapiol 7, as a pale yellow liquid in 80% yield. The spectroscopic properties (Figures 2.4 and 2.5) of the synthetic material were identical to those cited in literature.[16,17,18] The overall yield of dillapiol starting with sessamol **31** is 19%. This is comparable to that of 21% obtained by Majerus. Our new synthesis has one relatively low yielding step, surprisingly the hydrolysis



53 7

Scheme 2.8 - Methylation of **53** to afford Dillapiol **7**

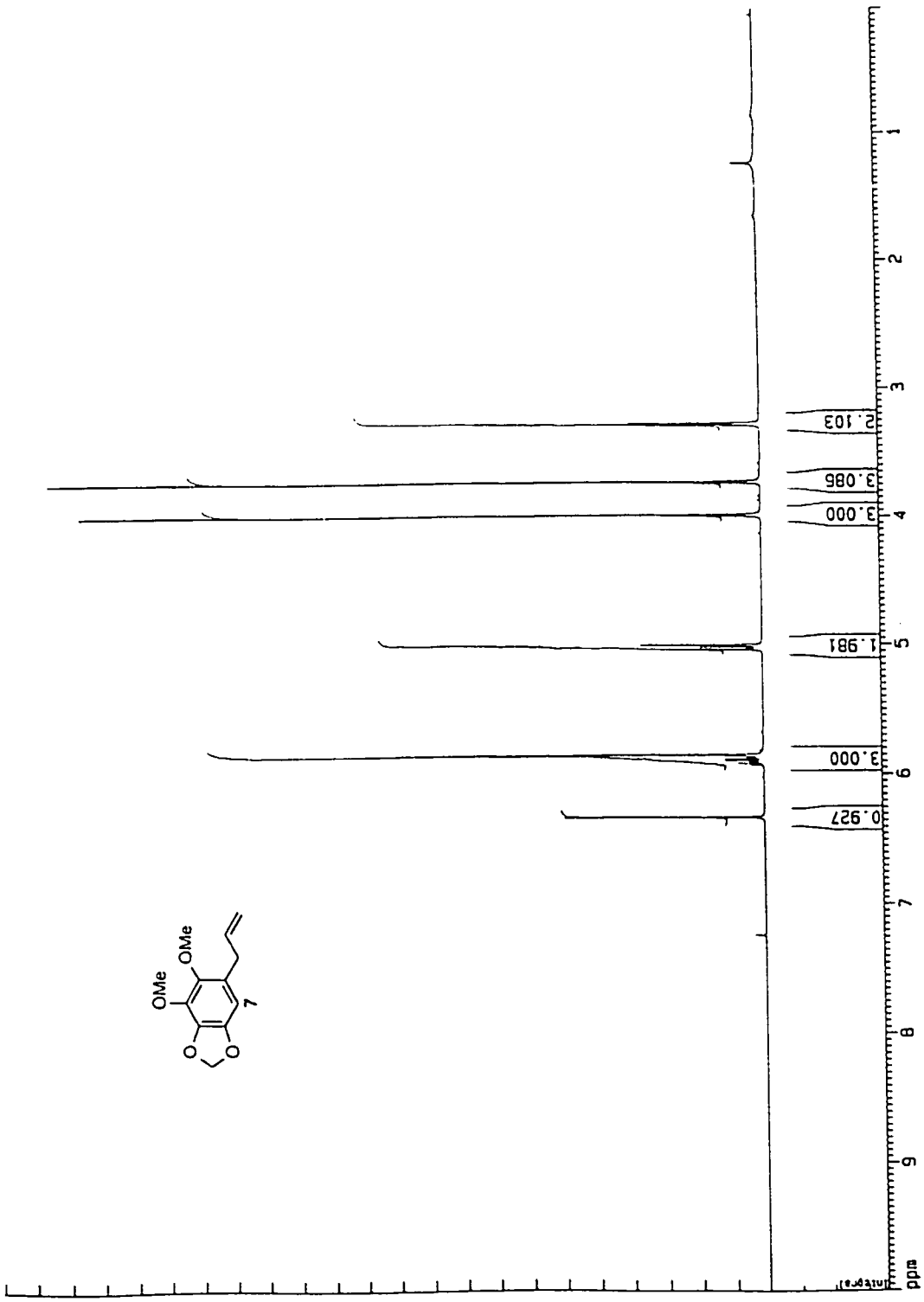


Figure 2.4 – ^{1}H NMR spectrum of dillapiol (7)

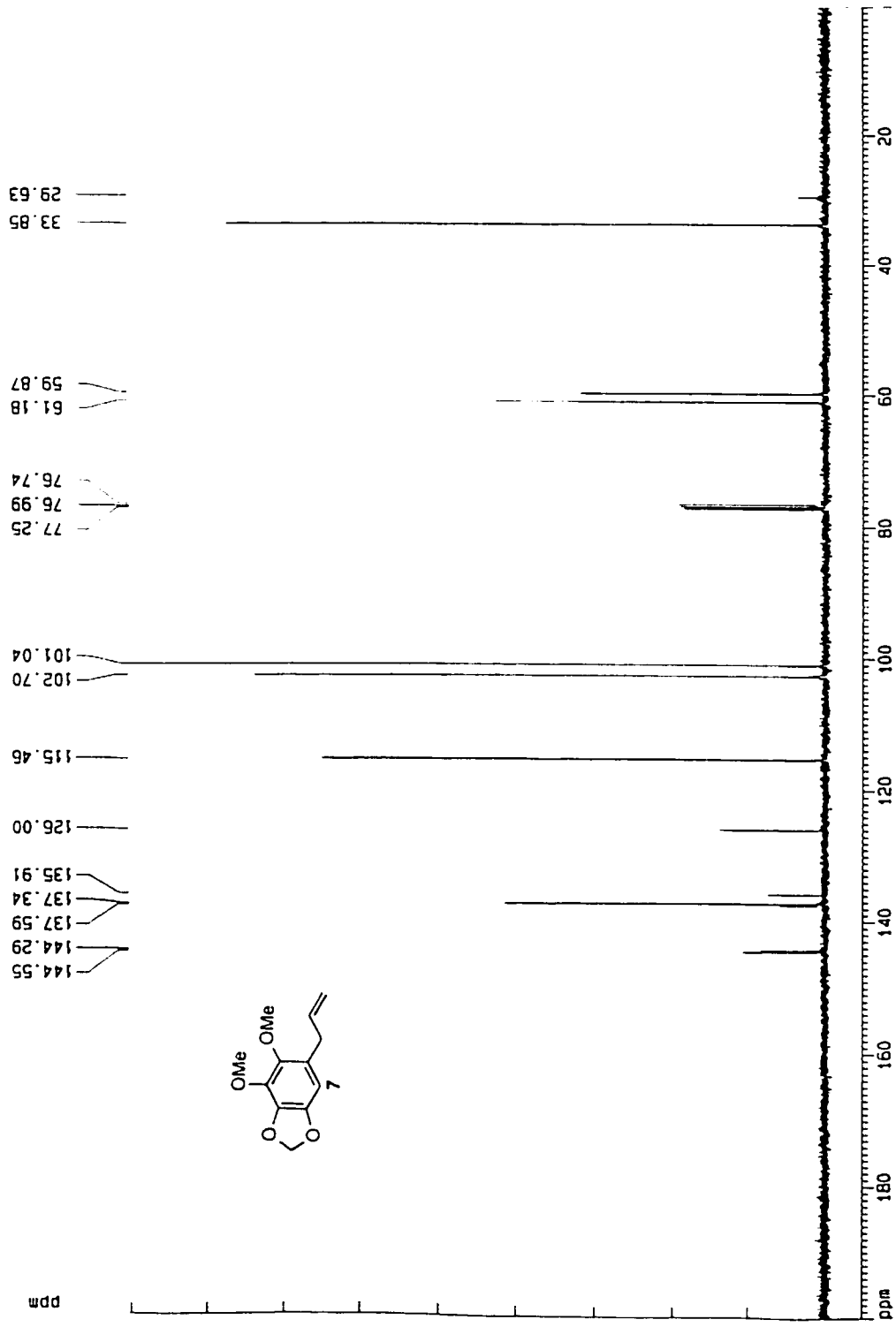
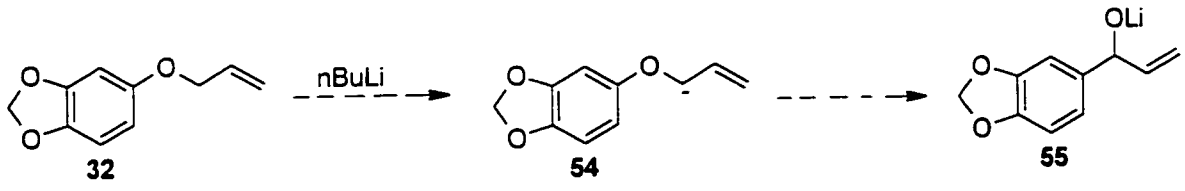


Figure 2.5 – ^{13}C NMR spectrum of dillapiol (7)

of the formate ester **48**. It is suspected that the 59% yield is due to the isolation problem rather than the inefficiency of the hydrolysis. The fact that the removal of the MOM group from **50** to **51** also occurred in only 73% yield gives credance to the above suggestion. If the recovery of each of the phenols (**49** and **51**) could be improved to at least 80%, the overall yield of dillapiol 7 via this route would be around 27%. No attempts were made to optimize the isolation of the phenols **49** and **51**.

Although the current overall yield in the new synthesis has not improved over that of the Majerus process, the synthesis offers the advantage of simpler reaction conditions which should be amenable to scale up. If a large scale synthesis of dillapiol was contemplated via this route, it would be worthwhile to consider carrying out the methylations of the phenols **49**, **51** and **53** on the crude reaction products, probably using the less expensive dimethyl sulfate in place of methyl iodide. The use of basic hydrogen peroxide rather than mCPBA as the reagent for the Baeyer Villiger reaction should also be considered. Finally, the use of a less expensive alternative to the phenol protecting MOM group should be investigated. The ideal would be the allyl group itself since its use would save two steps in this synthesis. Unfortunately, metallation of **32** is likely to result in lateral metallation followed by 1,2-Wittig rearrangement to afford **55** rather than an ortho metallation (Scheme 2.9). However, see Section 2.6 at the end of this chapter.

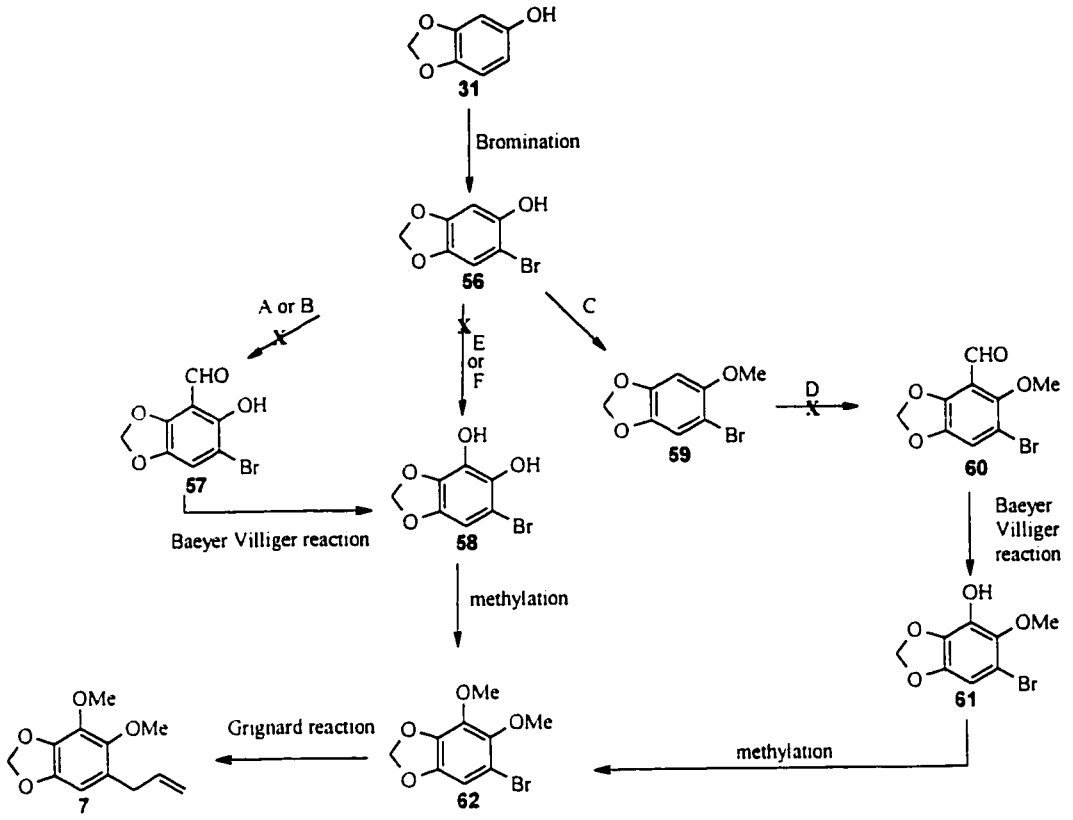


Scheme 2.9 - Potential 1,2 Wittig Rearrangement of Allyl Ether **32** to **55**

2.3 Attempted synthesis of dillapiol 7 via alternate routes

During the development of the above synthesis, a number of alternative routes to dillapiol were investigated with the hope of developing a simpler, cost-efficient approach. The allylation of aromatic Grignard reagents to give allyl benzene has been reported.[24] Thus it appeared that **62** could be a penultimate intermediate to dillapiol. Possible approaches to **62** were investigated. These are outlined in Scheme 2.10. The ideal route from sessamol, **31**, to **62** would involve bromination of sessamol to **56**, followed by introduction of a second hydroxyl group and methylation of both the phenolic groups. If successful, this would constitute a four step conversion of sessamol, **31**, to dillapiol, 7. Other somewhat longer routes from **56** to **62** were contemplated in case the most desirable one was unsuccessful.

The ortho bromination of sessamol **31** to give **56** was carried out using the procedure by Alexander et al.[25] The ^{1}H NMR and ^{13}C NMR spectra were identical to those found in literature.[25] 6-Bromo-5-hydroxy-1, 3-benzodioxole **56** was used as the intermediate material for several different approaches to introduce the fifth substituent at the C-4 carbon. The introduction of the fifth substituent was the greatest obstacle in this synthetic route. The different approaches investigated include: Vilsmeier-Haack Reaction conditions, Casiraghi Reaction conditions, enzymatic hydroxylation and copper catalyzed hydroxylation using molecular oxygen.



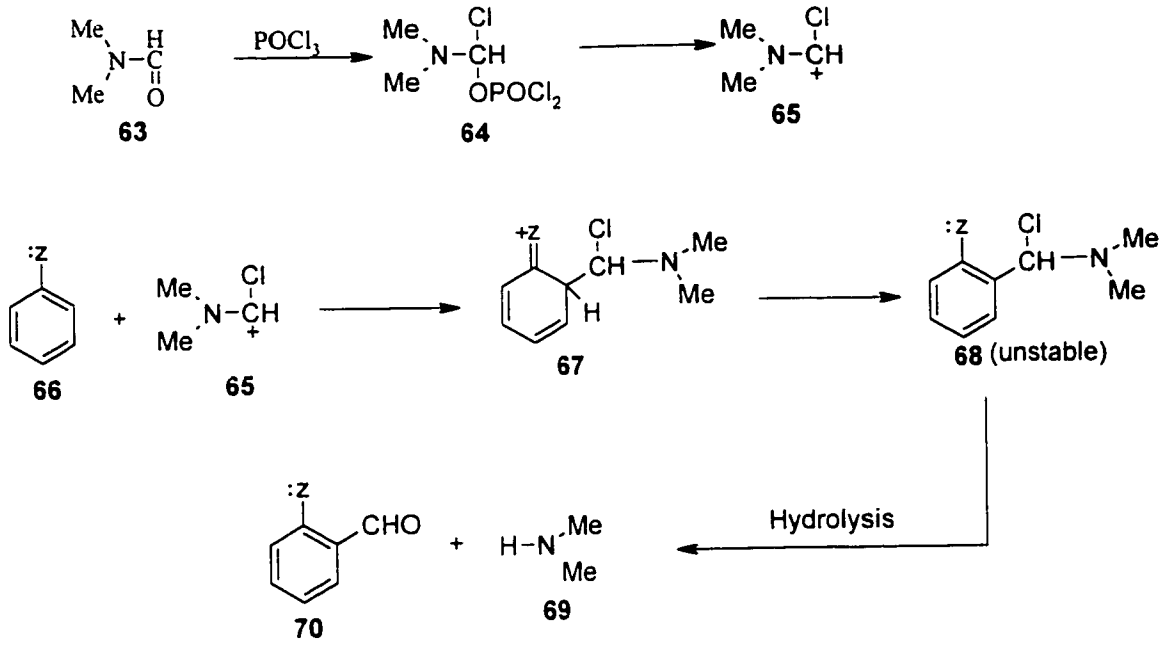
Approaches:
Ortho formylation of **56** via (A) Vilsmeier-Haack reaction conditions; (B) Casiraghi reaction conditions.
Ortho formylation of **59** via (D) Vilsmeier-Haack reaction conditions
Ortho hydroxylation of **56** via (E) Tyrosinase; (F) Copper catalyst using molecular oxygen.

Scheme 2.10 - General Overview of Various Schematic Routes Attempted to Synthesize Dillapiol **7**

2.3.1 Aromatic formylation

2.3.1.1 Ortho formylation of aromatic ring via Vilsmeier-Haack Reaction conditions

The adducts of dimethylformamide (DMF) with acyl halides are the key reagents in the Vilsmeier-Haack Reaction. The most common halide used for the formylation of aromatic rings is phosphorous oxychloride.[19,26] The mechanism of Vilsmeier-Haack Reaction is shown in Scheme 2.11, where the disubstituted formamide **63** reacts with

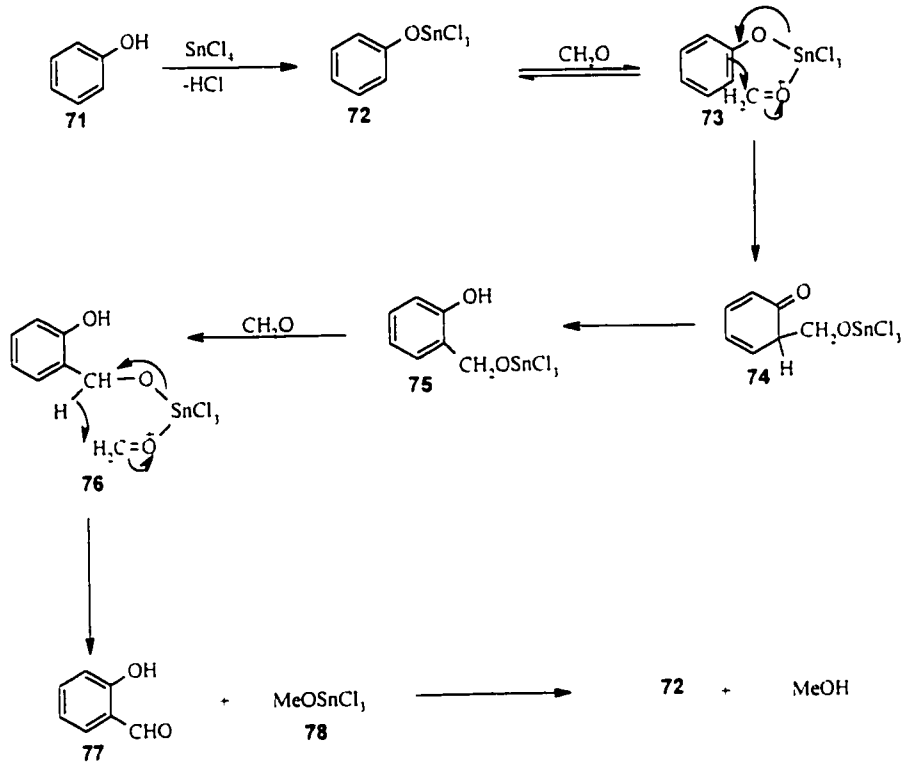


Scheme 2.11 - Mechanism of Vilsmeier-Haack Reaction

phosphorous oxychloride to give the reactive species **65**. This species then reacts with a phenol or amine, **66**, to give **68**, which is unstable and hydrolyzes to the final product **70**. When the phenol **56** was treated with these reagents under Vilsmeier-Haack Reaction conditions only starting material was recovered (Scheme 2.10, route A). Dallacker et al[17] have shown that the Vilsmeier-Haack Reaction worked on their system (Scheme 1.2) which is very similar to ours. The main difference is that they had a methoxy group ortho to the formylation site whereas in our case we have a hydroxyl group. In order to achieve similar structure to their system, phenol **56** was methylated to give **59** (Scheme 2.10, route C). The Vilsmeier-Haack reaction was attempted on **59** under the Dallacker conditions but was unsuccessful. A black solid, insoluble in any organic solvent, was obtained. No additional efforts were made in this direction.

2.3.1.2 Ortho formylation via Casiraghi Reaction conditions

Casiraghi et al[27] have developed an ortho formylation procedure for preparing salicylaldehyde from phenol, using tin tetrachloride, a base and paraformaldehyde. It was postulated that in the first stage of the reaction (Scheme 2.12), the phenol, **71**, reacts with tin tetrachloride to give the intermediate **72**. This intermediate is then believed to interact with paraformaldehyde giving a complex **73** in which the metal atom serves as a link between the two reacting species.



Scheme 2.12 - Mechanistic Pathway for the Casiraghi Reaction.

A base, such as amine, is needed to trap the hydrogen chloride generated in the first stage of the reaction. The base must have poor affinity for coordination with metal atoms in

order to have a high concentration of metal complex **73** otherwise it will lower the yield of this metal complex product by competing with paraformaldehyde.

The donating ability of the solvent also plays an important role in the formation of the complex **73**. Donor agents, such as DMF, can strongly solvate the phenolate metal counter-ion and hence retard the process, whereas solvents, which are poor donors, such as benzene or toluene, do not interfere in the formation of **73** are favored.

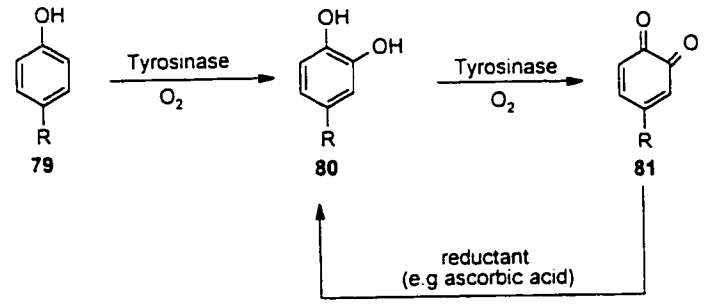
The subsequent intramolecular collapse of **73** leads to **75** via the dienone **74**. Reaction with a second equivalent of paraformaldehyde led to the formation of salicyladehyde **77** via a concerted hydride transfer. The last stage involved the alcoholysis of **71** with **78** leading to MeOH with re-formation of the active species **72**. Attempts were made to formylate **56** using the described reaction conditions (Scheme 2.10, route B). None of the desired product was isolated and only starting material was recovered.

2.3.2 Aromatic hydroxylation

2.3.2.1 Enzymatic ortho hydroxylation via the use of tyrosinases

Klibanov et al[28] have successfully developed a regioselective hydroxylation of phenols via tyrosinases. Tyrosinases are metallo-enzymes with an active site consisting of two neighboring copper atoms.[29] These enzymes catalyze the hydroxylation of phenols, such as **79**, with molecular oxygen to catechols **80** and subsequently dehydrogenation to *o*-quinones **81** (Scheme 2.13). This reaction is not feasible in water due to polymerization of quinone but is feasible only in chloroform. Chloroform also allows a 10-fold higher solubility of O_2 than water and a greater solubility to most phenols. The reactivity of this

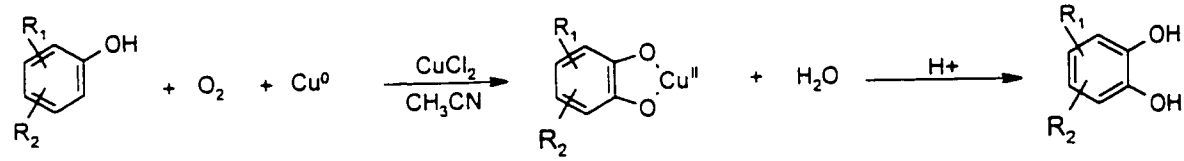
reaction depends on the R substituent; it decreases upon a transition of R from electron donating to electron withdrawing substituent. Attempts to hydroxylate the phenol **56** using Klibanov conditions were unsuccessful as only starting material was recovered.



Scheme 2.13 - Ortho Hydroxylation of Phenols via the Use of Molecular Oxygen by Tyrosinase

2.3.2.2 Copper catalyzed ortho hydroxylation via the activation of molecular oxygen

Capdevielle and Maumy developed an ortho hydroxylation method that mimics the oxidation of phenols by tyrosinases.[29] This method consists of the activation of molecular oxygen with cuprous salts which leads to exclusive formation of catechols. The oxidation of phenol is carried out in acetonitrile in the presence of a catalytic amount of cuprous chloride and consumes oxygen and elemental copper as indicated in Scheme 2.14. The most striking feature of this method is its total selectivity due to the stability of copper (II) catecholates

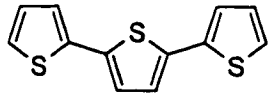


Scheme 2.14 - Copper Catalyzed Ortho Hydroxylation of Phenols via the Activation of Molecular Oxygen

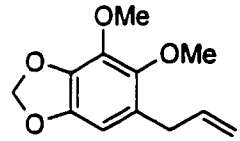
under the reaction conditions, conditions under which the free catechols are oxidized to quinones. Attempts to hydroxylate phenol **56** using these conditions were unsuccessful as only starting material was recovered.

2.4 Synthesis of dillapiol derivatives

Synergism plays an important role in the formulation of high-cost insecticides like pyrethrum[21] since addition of a relatively low cost synergist, such as the commercial piperonyl butoxide (BPO), can increase the activity of the insecticide by a factor of 2 to 4. The synergistic activity of dillapiol towards several classes of insecticides is comparable to or somewhat higher than piperonyl butoxide. Both of these compounds and a number of other naturally occuring synergists such as safrole **4** contain a benzo-1,3-dioxole group which binds to the heme of the mfos, the detoxification enzymes, to form adducts that are stable and not easily displayed by other ligands.[2,3] Several dillapiol derivatives such as **83**, **84** and **85** were synthesized previously in our laboratory and evaluated for their ability to synergize the insecticidal property of α-terthienyl (α-T), **82**.



82



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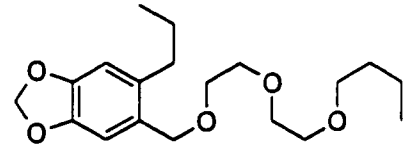

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α-T, **82,** is a light-activated insecticide which when exposed to light produces singlet oxygen which in turn causes the peroxidation of phospholipids and the oxidation of enzymes and other proteins. It is potent against mosquito larvae at a nano molar concentration.[30] The

synergism factors of these derivatives were found to be comparable to that of dillapiol (Table 2.1).

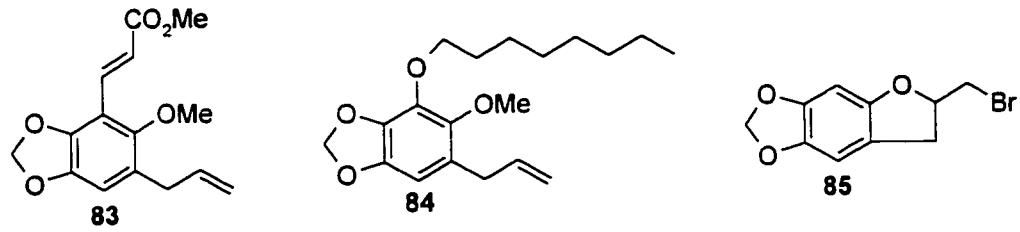


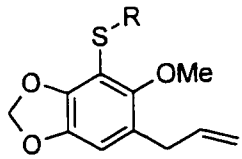
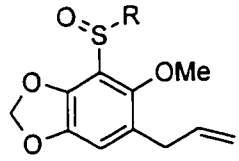
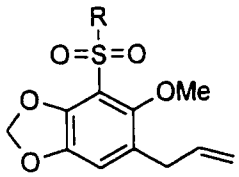
Figure 2.7 - Derivatives of dillapiol previously synthesized in our laboratory

Table 2.1- Synergism Factors of Dillapiol and its Derivatives on Mosquito Larvae

Compound	Synergism Factor
α-T + Dillapiol 7	1.89
α-T + **83**	2.40
α-T + **84**	1.78
α-T + **85**	1.73

There have been no reports on the preparation of thio analogs of dillapiol. The concept was to prepare analogs by replacing the alkoxy substituent at C-4 by a sulfur analog, either as the sulfide, sulfoxide or sulfone, and examine their activity as insecticide synergists. The availability of the three sulfur oxidation states would allow us also to probe the effect of electron donating vs electron withdrawing groups on the synergism factor. Four series of sulfides, sulfoxide and sulfone shown in Table 2.2 were prepared and evaluated as synergists.

Table 2.2- Synthetic Thio Derivatives of Dillapiol

sulfides	sulfoxides	sulfones
		

where R= methyl
= p-methoxy phenyl
= phenyl
= benzyl

These series were synthesized in a similar manner to dillapiol (Scheme 2.1); the only difference was in the variation of the structure of the sulfur electrophile. The major goal was to prepare a small library of derivatives for evaluation of biological activity; hence little notice was paid to yield optimization. The overall yield of these compounds from sessamol when compared to dillapiol is much higher and thus a dozen derivatives were readily obtained.

The first set of thio derivatives of dillapiol, namely the sulfide **90a**, the sulfoxide **91a** and the sulfone **92a**, were prepared starting from the protected sessamol **38** as outlined in Scheme 2.15. Thus reaction of **38** with nBuLi and dimethyl disulfide, afforded **86a** as a yellow liquid in 91% yield. Confirmation of this transformation was obtained from both the ^{1}H NMR and ^{13}C NMR spectra (Figures 2.7 and 2.8 respectively). The appearance of a 3H singlet at 2.41 ppm in the ^{1}H NMR spectrum corresponds to the methyl proton in SCH_3 and a peak at 16.9 ppm in the ^{13}C NMR spectrum corresponds to the carbon atom in SCH_3. HRMS confirmed the molecular formula.

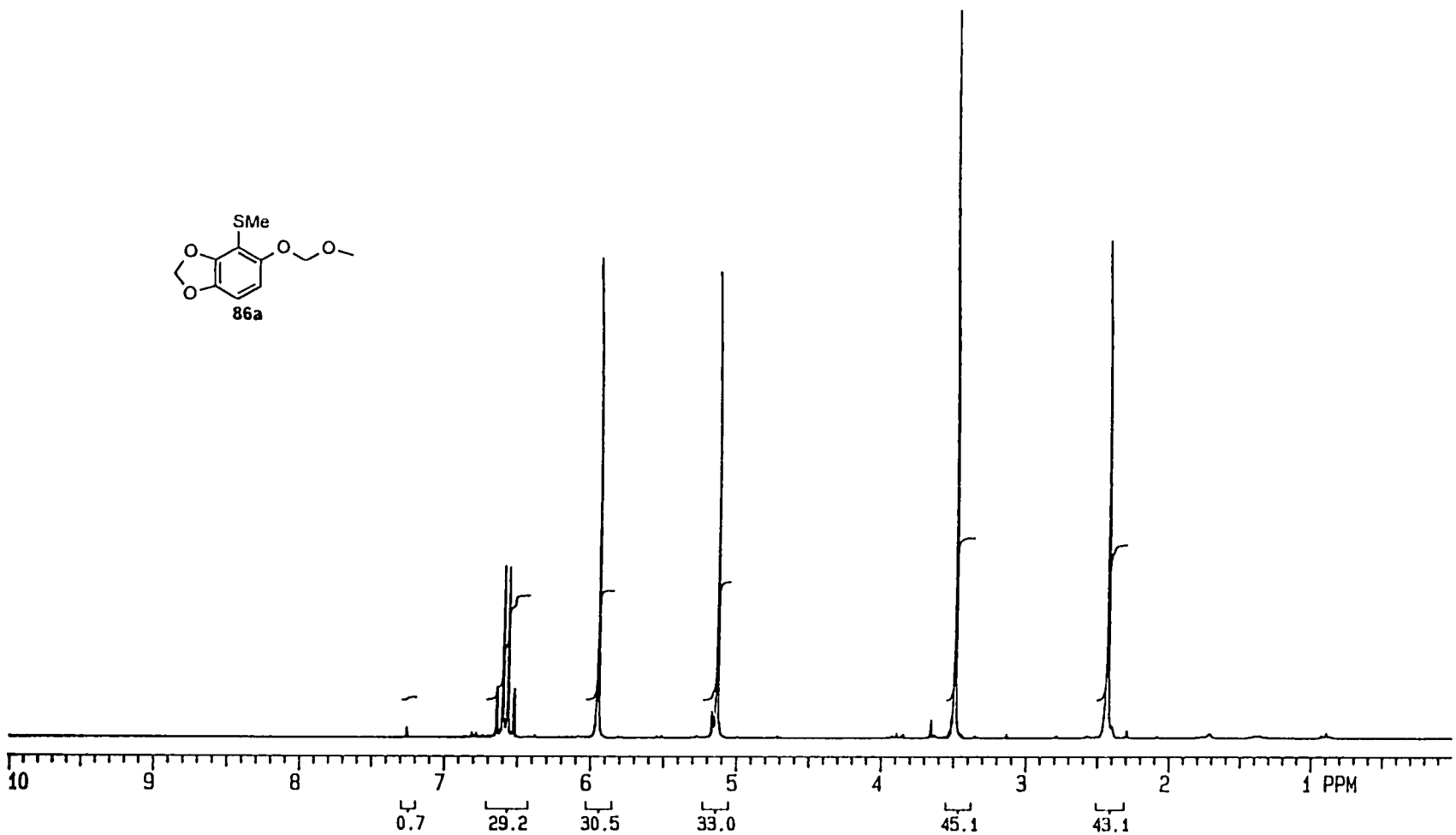


Figure 2.7 – ^{1}H NMR spectrum of 5-methoxymethoxy-4-thiomethyl-1,3-benzodioxole (86a)

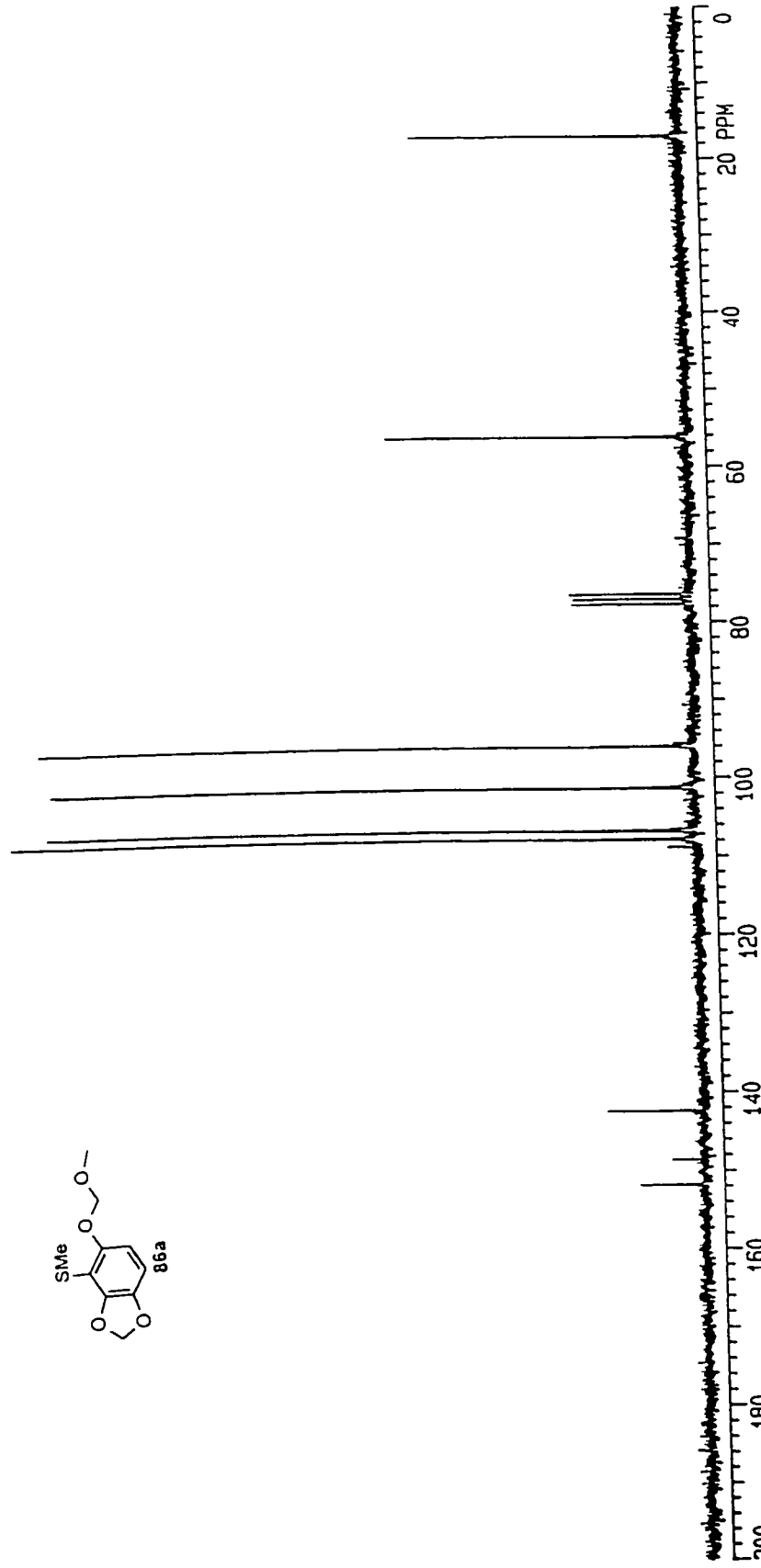
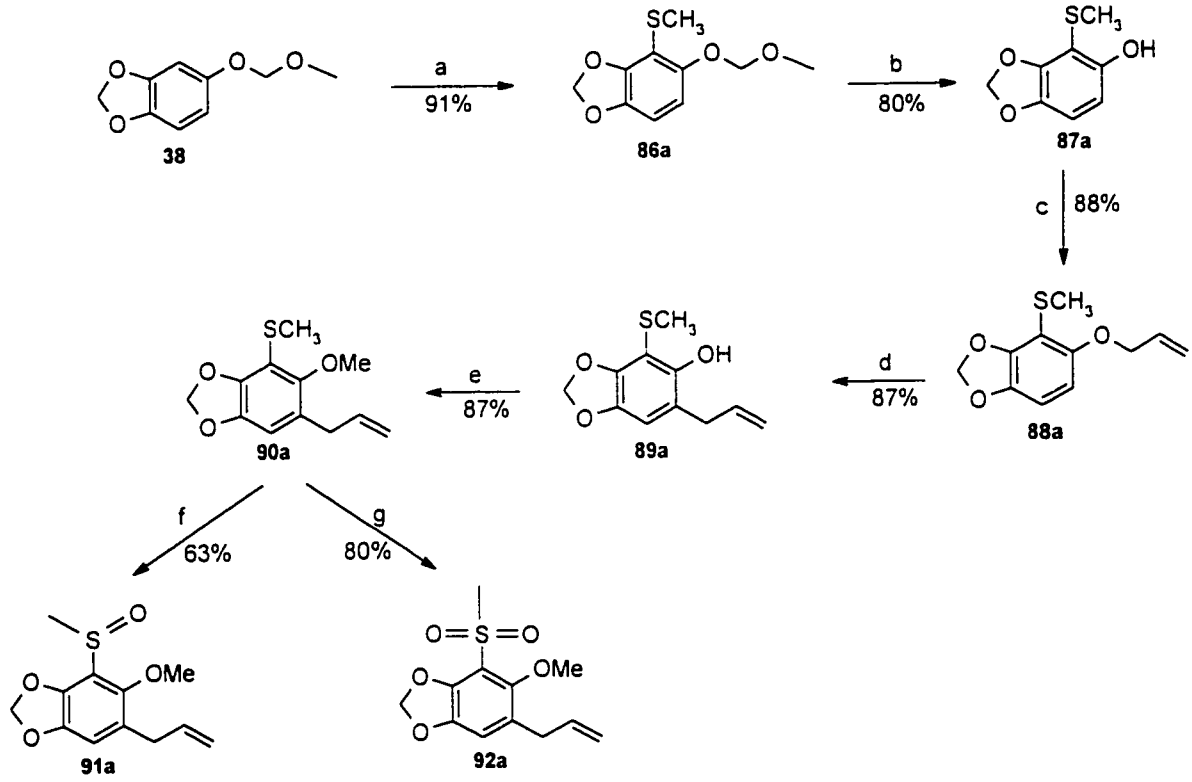


Figure 2.8 – ^{13}C NMR spectrum of 5-methoxymethoxy-4-thiomethyl-1,3-benzodioxole (86a)

Removal of the MOM group from **86a** using NaI and 3N methanoic HCl afforded **87a** as white powder in 80% yield. It is evidenced by the disappearance of the methyl signals from OCH_2 and OCH_3 from the ^1H NMR spectrum and the appearance of a singlet at 6.22 ppm belonging to the hydroxyl hydrogen confirming the transformation had taken place. The infrared spectrum showed the characteristic peak at 3428 cm^{-1} indicating the presence of the hydroxyl group.



Reagents: (a) BuLi, dimethyl disulfide; (b) NaI, methanoic HCl; (c) allyl bromide, K_2CO_3; (d) 190°C; (e) CH_3I, K_2CO_3; (f) 1.2eq mCPBA; (g) 4.0eq mCPBA

Scheme 2.15 - The Synthesis of the Thio Derivatives **89a**, **90a**, **91a** and **92a** of Dillapiol

Allylation of **87a** using allyl bromide and potassium carbonate afforded the allyl ether **88a** in 88% as a clear colorless liquid. As expected, the allyl ether **88a** underwent Claisen rearrangement when subjected to its reaction conditions to afford a pale yellow liquid **89a** in

87% yield upon purification by flash column chromatography. Confirmation of this transformation was obtained via both the ^{1}H NMR and ^{13}C NMR spectra (Figures 2.9 and 2.10 respectively).

Finally methylation of **89a** with methyl iodide and potassium carbonate afforded **90a**, the first sulfur derivative of dillapiol, in 87% yield after purification by flash column chromatography. The ^{1}H NMR and ^{13}C NMR spectra (Figures 2.11 and 2.12 respectively) closely resemble those of dillapiol, **7**, except that one of the OCH_3 groups (3.99 ppm) in dillapiol had been replaced by SCH_3 (2.45 ppm) in **90a**. The 4-thio analog **90a** of dillapiol was thus obtained in six steps from sessamol in 48% yield. It represents the first sulfur analog of dillapiol. It is of considerable interest to compare the biological properties, in particular the synergist factors, of **90a** with dillapiol. The availability of **90a** gives rapid access to the corresponding sulfoxide and sulfone and potential information concerning the effect on biological activity of changing an electron donor substituent, SCH_3, into the strongly electron withdrawing SO_2CH_3 group.

The sulfide **90a** was then transformed to the sulfoxide and sulfone using mCPBA. For the formation of sulfoxide **91a**, a solution of **90a** in ethyl acetate at -40°C was treated with 1.2e.q of mCPBA and then allowed to warm to RT. Workup after 24 h and purification by chromatography afforded the desired product as a pale yellow liquid in 63% yield. The ^{1}H NMR spectrum of **91a** closely resembles that of **90a** except that the methyl peak of SCH_3 in **91a** was shifted downfield to 3.01 ppm due to the electronegativity effects of the sulfoxide (Figure 2.13). The ^{13}C NMR spectrum indicated a peak at 39.7 ppm belonging to the carbon atom of $SOCH_3$. Furthermore the presence of the S=O stretch of sulfoxide at 1050 cm^{-1} was observed in the infrared spectrum. When **90a** was treated with 4e.q of mCPBA at RT for

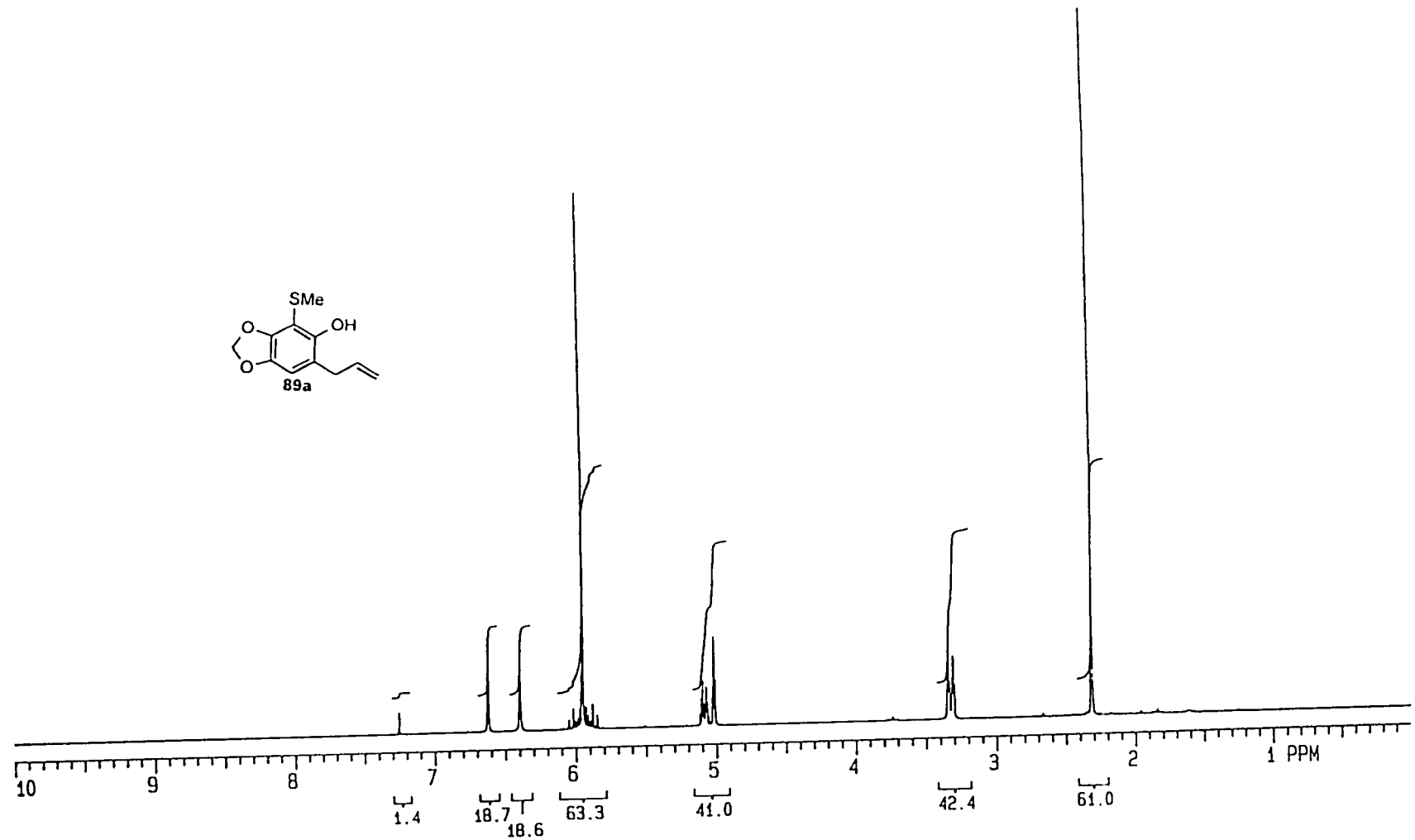


Figure 2.9 – ^{1}H NMR spectrum of 5-hydroxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole (89a)

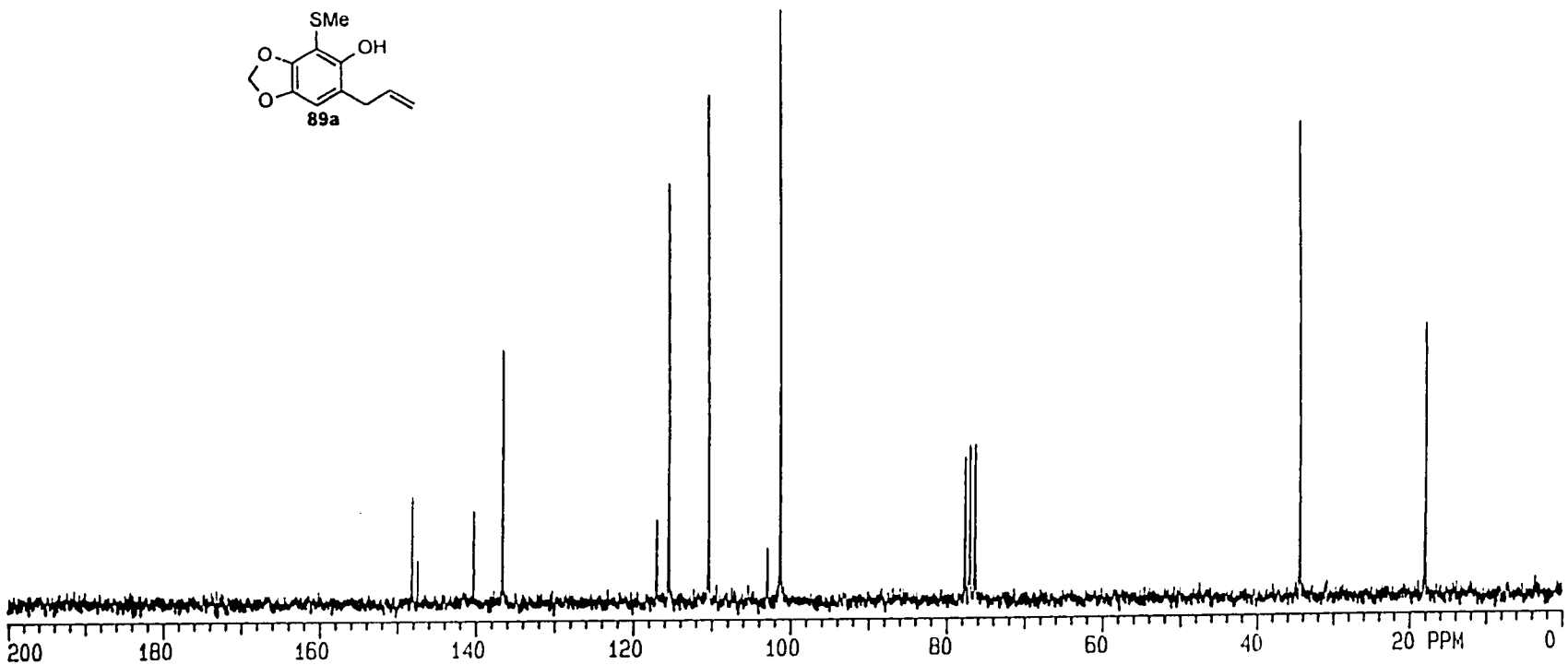


Figure 2.10 – ^{13}C NMR spectrum of 5-hyrdoxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole (89a)

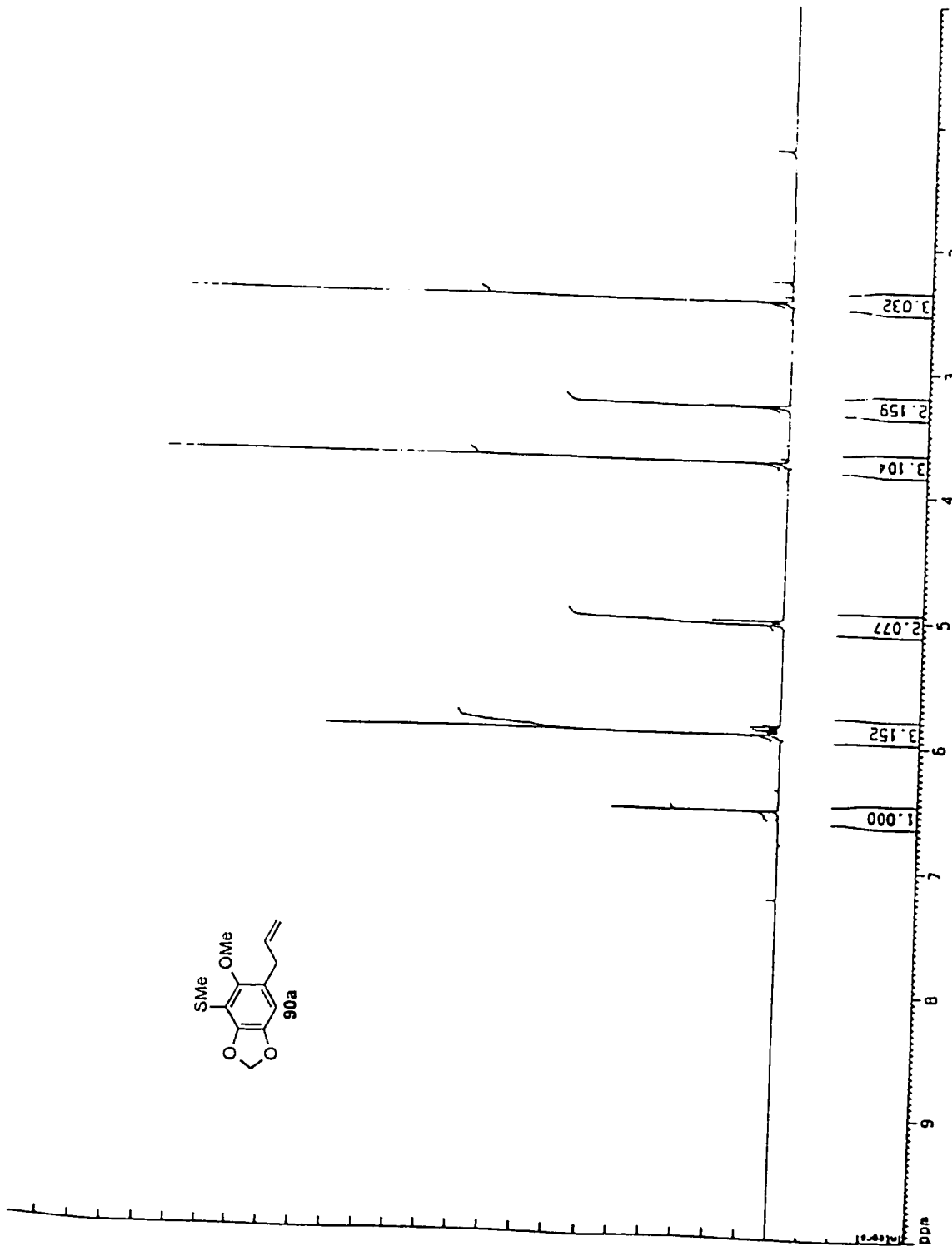


Figure 2.11 – ^{1}H NMR spectrum of 5-methoxy-6(2-propenyl)-4-thiomethyl-1,3-benzodioxole (90a)

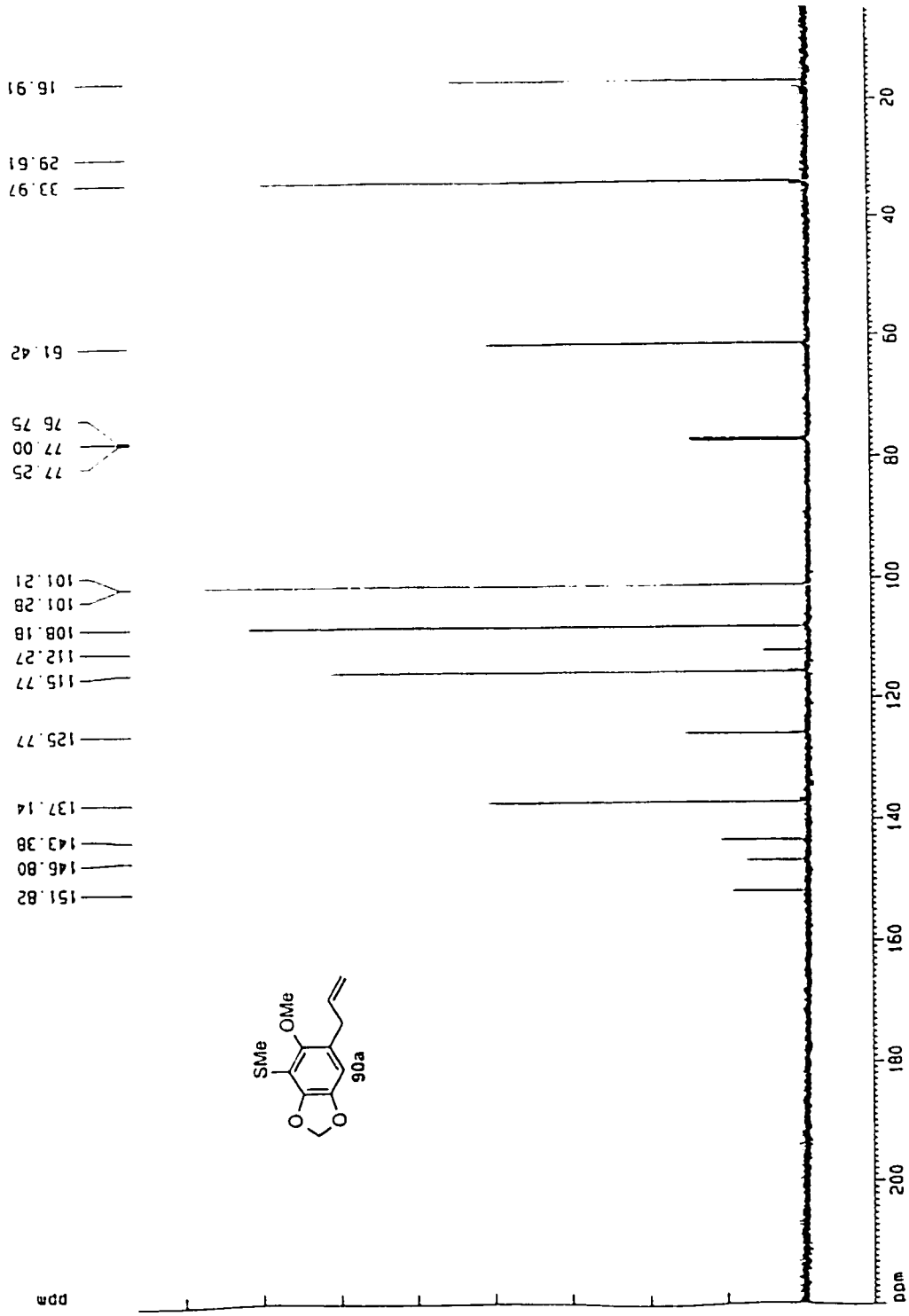


Figure 2.12 – ^{13}C NMR spectrum of 5-methoxy-6(2-propenyl)-4-thiomethyl-1,3-benzodioxole (90a)

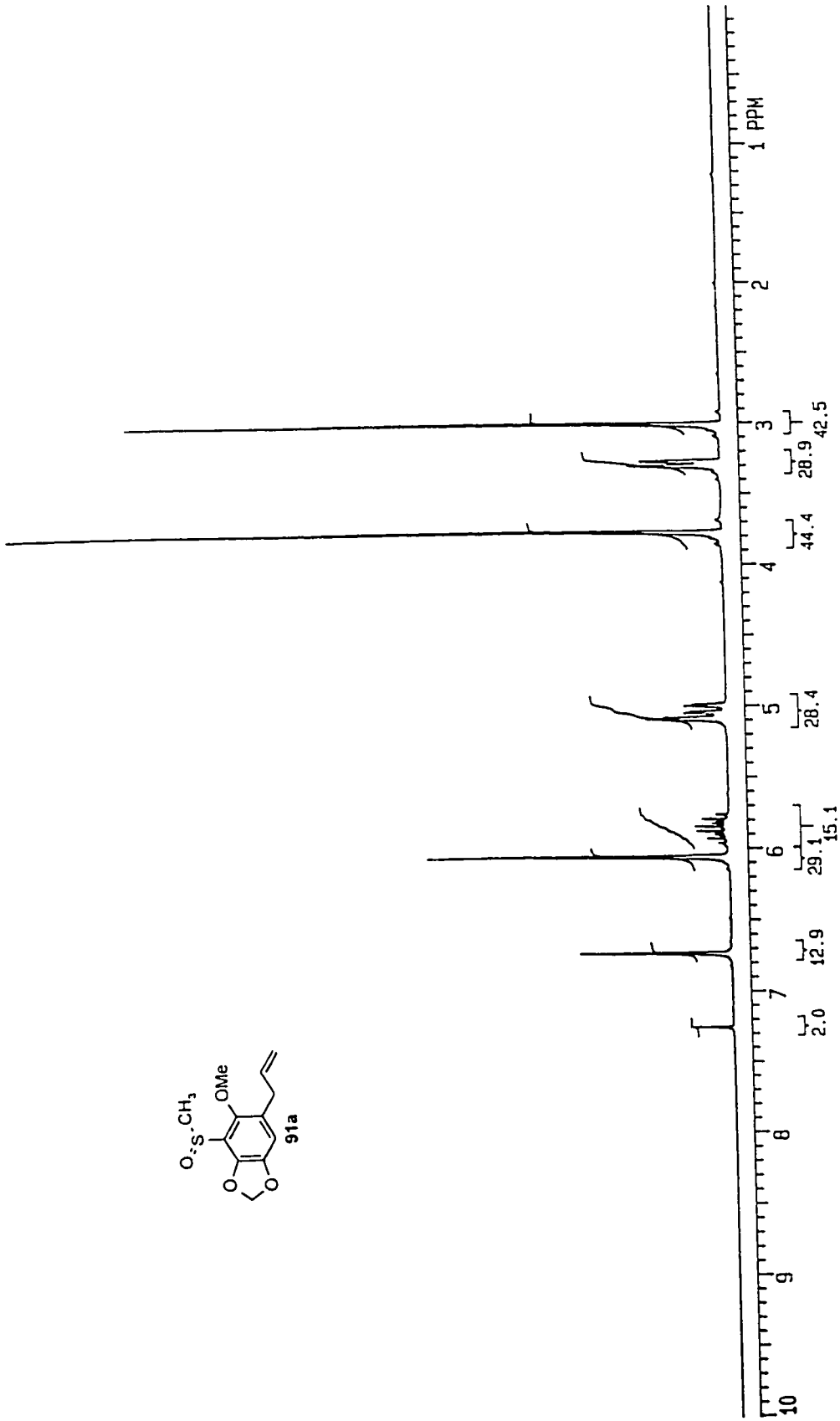
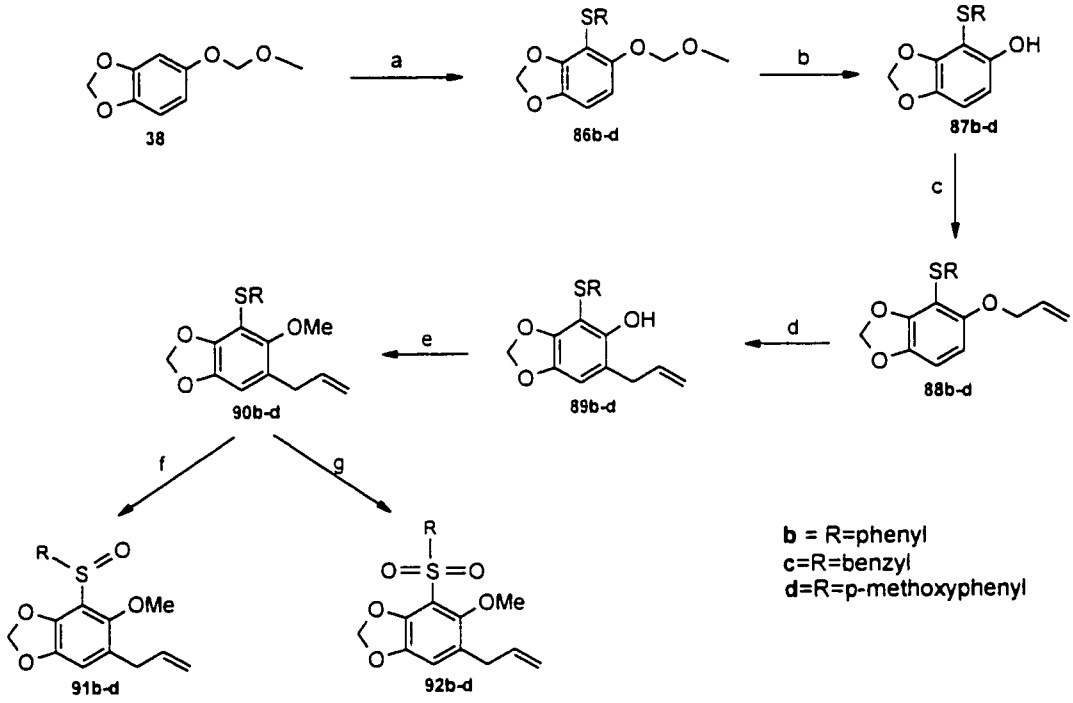


Figure 2.13 – ^{1}H NMR spectrum of 5-methoxy-4-methylsulfinyl-6-(2propenyl)-1,3-benzodioxole (91a)

24 h, it afforded **92a** as pale yellow crystals in 80% yield. The ^{1}H NMR and ^{13}C NMR spectra of **92a** are similar to those of **91a** except that the methyl peak in SO_2CH_3 is shifted further downfield to 3.26 ppm, as expected, once again due to the increased electron withdrawing effects of the sulfone relative to the sulfoxide. The infrared spectrum further confirmed the presence of the sulfone with its S=O symmetric stretch at 1136 cm^{-1} and the asymmetric stretch at 1316 cm^{-1}.



Reagents: (a) BuLi, R-disulfide; (b) NaI, methanoic HCl; (c) allyl bromide, K_2CO_3; (d) 190°C; (e) MeI, K_2CO_3; (f) 1.2eq mCPBA; (g) 4.0eq mCPBA

Scheme 2.16 - Preparations of the Thio Derivatives **89b-d**, **90b-d**, **91b-d** and **92b-d** of Dillapiol

In a similar manner (Scheme 2.16) three more sets of sulfide, sulfoxide and sulfone were synthesized from the readily available disulfides. The yields for each step in the synthesis of the sulfide, sulfoxide and sulfone from sessamol are shown in Table 2.3. The structures of

the products were confirmed via the ^{1}H NMR and ^{13}C NMR spectra and the HRMS. The ^{1}H NMR and ^{13}C NMR spectra of each intermediate and the target sulfide, corresponding sulfoxide and sulfone are as expected. For each of the series of sulfide, sulfoxide and sulfone, the peaks for the hydrogens on carbons α to the sulfur function showed the expected downfield shift due to the increased electron withdrawing effect (i.e. from SR to SO_2R). Detailed spectroscopic data are found in the experimental section. Currently these derivatives are being investigated as synergists and drug sparing agents.

Table 2.3 - Percentage Yield of Each of the Synthetic Intermediate and the Target Sulfide, Corresponding Sulfoxide and Sulfone.

	Yield %			
Compounds	**a**	**b**	**c**	**d**
86	91	30	58	40
87	80	>99	91	83
88	88	81	83	76
89	87	37	98	97
90	87	87	96	96
91	63	76	61	68
92	80	71	45	71

2.5 Biological activity

2.5.1 Synergists

α-T is a naturally occurring phototoxin active against the mosquito larvae. It is activated by light, producing singlet oxygen which causes peroxidation of phospholipids.[30] Previous work on this insecticide in collaboration with Dr. J. T. Arnason, University of Ottawa, have shown that dillapiol and several of its derivatives gave good synergism factors with α-T.[3,9] As a result of this success, an investigation of the thio analogs of dillapiol was carried out in the hope of enhancing the synergism factor with α-T.

Mireille Marcotte, a fourth year undergraduate student in Biology at the University of Ottawa, carried out preliminary investigation of the synergistic effect of thio analogs of dillapiol. The results of the investigation are shown in Table 2.4 which represents the synergism factors of thio analogs relative to dillapiol.

When compared with dillapiol, compounds **90a** and **90c** were the only ones that showed slightly higher synergism factors of 1.15 and 1.21 respectively. All the other analogs showed synergistic effects lower than dillapiol. With the exception of the sulfoxide **91d**, it appears that the better synergists are the sulfides. The various sulfoxides and sulfones have approximately half the synergist effect of dillapiol. However one must be careful in drawing firm conclusions since the investigation for the synergistic effect was carried out during the winter period when the growth and development of mosquito larvae is slow. Therefore these experiments need to be repeated. Due to the time constraints, this study was not repeated but will be investigated shortly by another researcher.

Table 2.4 - Synergism Factors of the Thio Derivatives of Dillapiol Relative to Dillapiol

Compound	Synergism factor relative to Dillapiol
Dillapiol **7**	1.00
89b	0.68
89c	0.54
90a	1.15
90b	0.79
90c	1.21
90d	0.81
91b	0.57
91c	0.57
91d	0.86
92b	0.55
92c	0.74
92d	0.52

2.5.2 Drug sparing agents

CYP3A4 is a human cytochrome P450 enzyme found in high amounts in the small intestine and the liver. It is a major contributor to the metabolism of foreign compounds following oral drug administration and acts by detoxification of a drug before it reaches the blood stream. CYP3A4 has an extremely wide range of substrate specificity and it has been suggested that it mediates the oxidation of approximately 40-50% of drugs administered to humans.[32]

Recently, many studies have shown that concomitant oral administration of grapefruit juice increases the bioavailabilty and /or prolongs the metabolic elimination of many drugs. Hence it significantly increases their plasma concentration by disrupting the detoxification pathway mediated by CYP3A4.[31] Because of this it has been suggested that other natural products may inhibit CYP3A4. Therefore when taken concomitantly with prescription drugs, such drugs may decrease the required dosage and financial cost of an expensive drug regime, by acting as drug sparing agents. A potential negative effect is that such products could also increase the duration and severity of side effects due to the increase in drug concentration in plasma because of a decrease in metabolic breakdown.

Jason Budzinski, a graduate student in Biology at the University of Ottawa, screened pure plant compounds along with commercially available plant extracts for their ability to inhibit CYP3A4 *in vitro* using a fluorometric microtitre plate assay.[31] Among the pure compounds studied was dillapiol. Dillapiol was found to be the most potent inhibitor of CYP3A4 with an IC_{50} value of 17 μM. As a result of this discovery, the thio analogs are currently being tested for inhibitory activity towards CYP3A4. Preliminary results indicate that compounds **90c**, **91c**, **92b** and **92d** showed IC_{50} values comparable to dillapiol for the inhibition of CYP3A4 (Figure 2.14) and thus can be considered to be potent inhibitors of CYP3A4. All the other compounds showed moderate inhibition of CYP3A4. With the exception of sulfide **90c** and sulfoxide **91c**, it appears sulfones are the better inhibitors of CYP3A4. Currently the investigation is ongoing and the determination of accurate IC_{50} values is in progress.

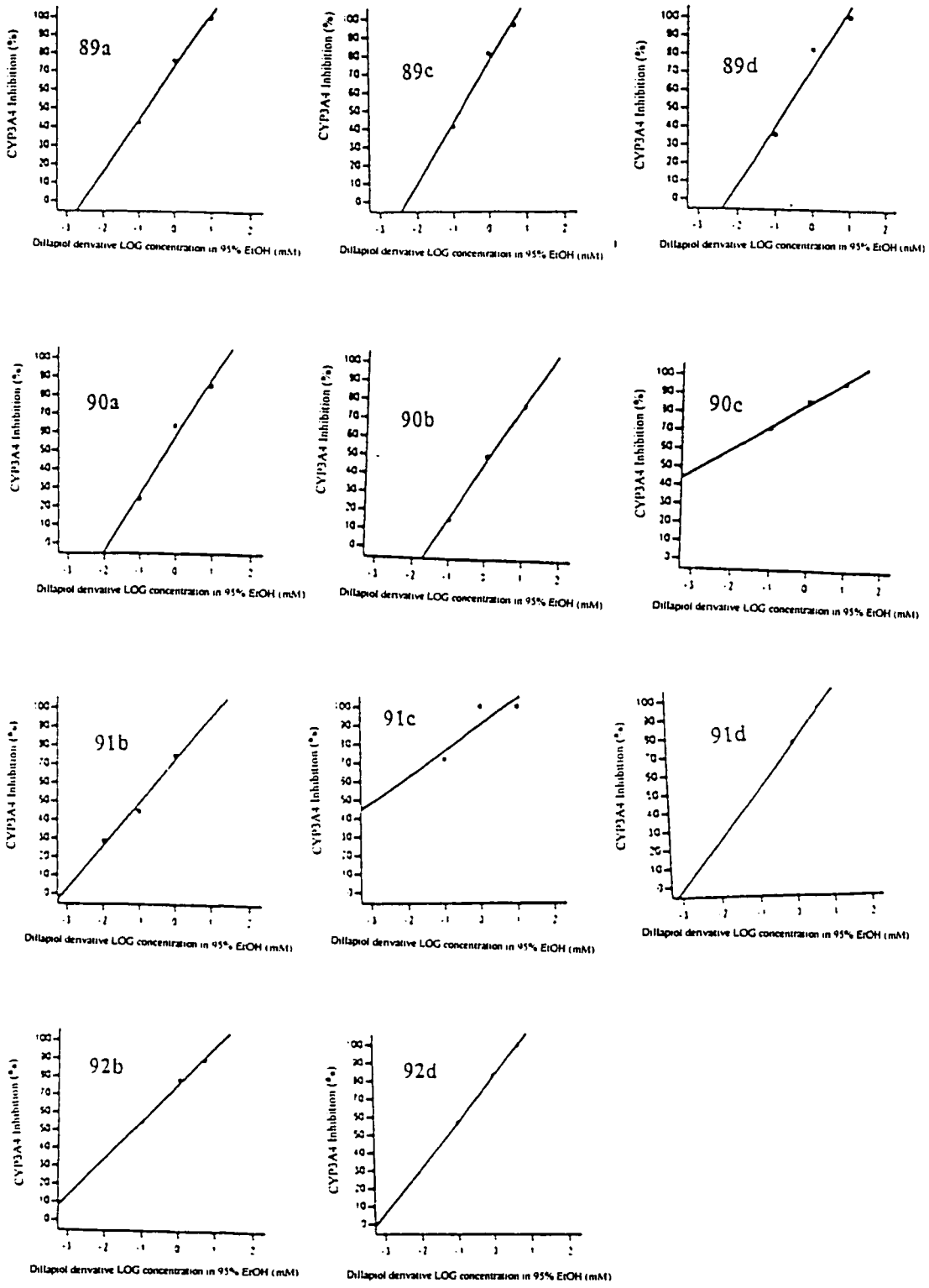
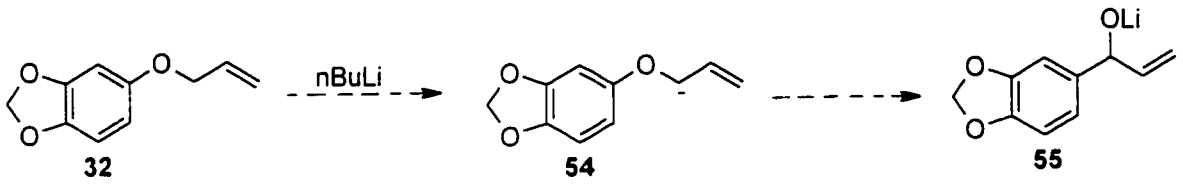


Figure 2.14 – Preliminary Results of the Inhibition of CYP3A4 by the Thio Derivatives of Dillapiol. The IC_{50} Values are Obtained by Interpolating the Graphs at 50% Inhibition Mark.

2.6 An improved route to dillapiol

As was mentioned in Section 2.2, we had considered the metallation of the allyl ether obtained from sessamol. After some thought it was decided that the 1,2-Wittig Rearrangement would be the most likely product upon treatment with nBuLi and this approach was not investigated.

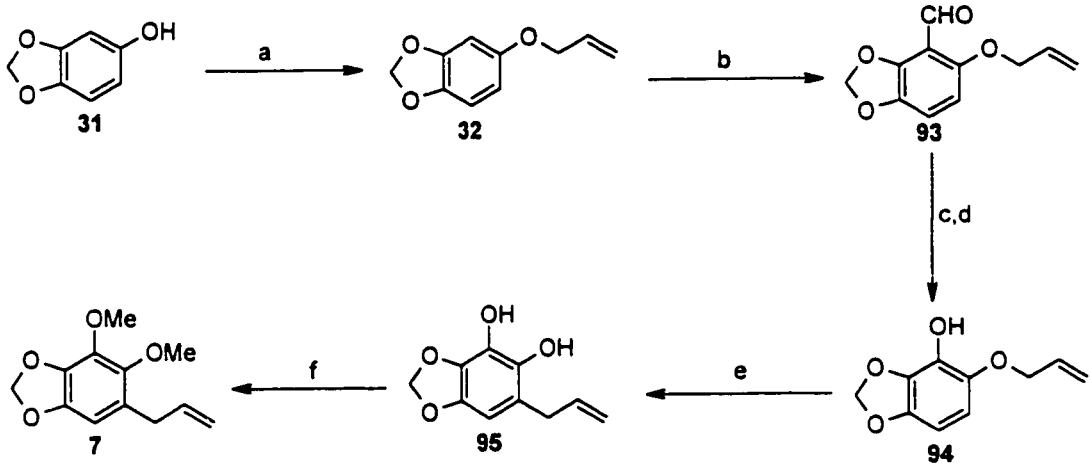


Cross reference: Scheme 2.9 - 1,2 Wittig Rearrangement of Allyl Ether **32** to afford **55**

During the preparation of this thesis reactivity of the allyl ether toward base was reconsidered. If the Wittig rearrangement could be avoided, then the route from sessamol to dillapiol described in this thesis would be shortened by two steps: (1) the protection of phenols by MOM ether and (2) subsequent deprotection. The other advantage would be avoiding the expensive MOMCl reagent. The proposed route is shown in Scheme 2.17.

Indeed as demonstrated by Dr. Sasmita Tripathy treatment of **32** with nBuLi followed by addition of DMF gave the aldehyde **93** in 89% yield. This yield was comparable to that for the ortho metallation of MOM ether **38** and its trapping with DMF. There was no evidence of the feared 1,2-Wittig rearrangement. Interestingly the reaction of mCPBA with **93** was highly chemoselective and gave only the Baeyer Villiger product with no trace of

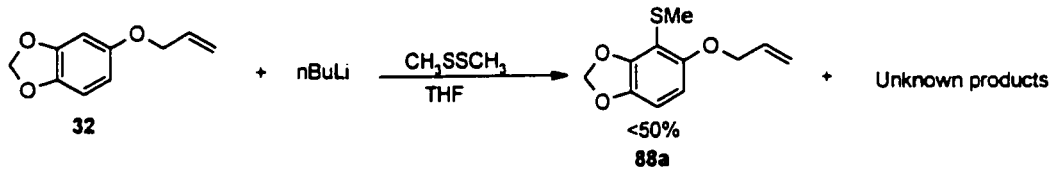
epoxidation of the allyl ether. The remaining steps of the synthesis were completed as planned and the overall unoptimized yield of dillapiol from sessamol was 40%.



Reagents : (a) K_2CO_3, allyl Bromide; (b) nBuLi/THF/-78°C, DMF; (c) mCPBA,CH_2Cl_2; (d) NaOH
(e) 190°C; (f) CH_3I, acetone

Scheme 2.17- A New Improved Route to Dillapiol 7

Once the ortho metallation of the allyl ether had been demonstrated, the synthesis of the thio derivatives should also be shortened since the allyl ether **88a** might be prepared in two steps from sessamol rather than four. Surprisingly when this was attempted the formation of **88a** was accompanied by a significant amount of an, as yet, unidentified byproducts. These results indicate that this route is not practicable for the synthesis of thio derivatives of dillapiol.



Scheme 2.18 - Formation of **88a** via Treatment of **32** with nBuLi

Experimental Procedures

Chapter 3

Experimental

General procedure

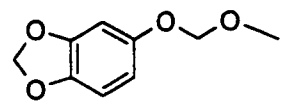
Melting points were determined by use of a Thomas Hoover Capillary melting point apparatus and are uncorrected. Infrared spectra were recorded with a Bomem-Michelson MB-100 FT-IR spectrometer by preparing thin methylene chloride films on potassium bromide plate. The ^{1}H and ^{13}C NMR spectra were obtained from either a Bruker AMX-500 spectrometer, Varian XL-300 or a Varian Gemini-200 spectrometer. The samples were run in spectroscopic grade deuterated chloroform. Chemical shifts are in parts per million relative to tetramethyl silane. The multiplicities of the NMR signals are reported as s, singlet; d, doublet; dd, doublet of doublets; ddd, doublet of doublet of doublets; dt, doublet of triplets; t, triplet; q, quartet and m, multiplet. Mass spectrum analyses and high resolution mass spectra were performed by the analytical services available at University of Ottawa. Low resolution mass spectra were performed using electron impact ionization. High resolution mass spectroscopy was performed on a Kratos Concept-IIA mass spectrometer. Unstable compounds of high molecular weight were examined by FABH (Fast Atom Bombardment) accurate mass experiments.

Solvents used for reactions and chromatographic purifications were routinely distilled prior to use. Reactions were monitored by thin layer chromatography (tlc) using silica gel on alumina sheets, 60 F_{254}. Individual compounds were seen either by ultraviolet light or by staining. The stain that was used was a 5% solution of ammonium

molybdate in 10% aqueous H_2SO_4. The tlc plates were developed by dipping the plates into the stain and then heating the plates with heat gun. Silica gel 270-400 mesh was used for flash chromatography.

All reactions were performed under nitrogen unless otherwise stated. The glassware that was used for moisture sensitive reactions was either dried overnight in an oven or flame dried with a propane torch. Oven dried syringes were used to transfer chemical and solvents. "Drying" refers to removing the water from the organic mixture with anhydrous magnesium sulfate if it is not stated. " Concentrated" refers to the removal of solvent by roto-evaporation.

5 - Methoxymethoxy - 1, 3 - benzodioxole 38



38

To a cooled (0 °C) solution of sesamol **31** (5 g, 36.2 mmol) in dry THF (20 ml) was added 1 eq of nBuLi (16.5 ml, 2.2 M). The reaction mixture was stirred for 30 min and then 1.5eq of methoxymethyl chloride (4.4 g, 4.1 ml) was added. The resulting mixture was stirred at room temperature and was monitored using thin layer chromatography (tlc), eluting with 3:1 hexane / ethyl acetate, and was found to be almost completed after 24 h. The reaction mixture was quenched using saturated NH_4Cl solution (10 ml) and the aqueous phase extracted with Et_2O (3 x 20 ml). The organic phase was then washed with NaOH solution (3 x 10 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide compound **38** as colorless liquid (6.5 g, 98%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.47 (s, 3H), 5.08 (s, 2H), 5.91 (s, 2H), 6.49 (dd, 1H, J=8.4Hz, 2.4Hz), 6.62 (d,1H, J=2.2 Hz), 6.70 (d, 1H, J=8.4Hz).

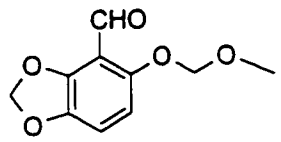
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 55.9, 95.5, 99.7, 101.2, 108.0, 108.4, 142.5, 148.1, 152.5

EI-MS (m/z, %): 182 (M^+, 100), 152 (75), 137 (30)

HRMS: Calc. for $C_9H_{10}O_4$: 182.0579; Found: 182.05830

IR (cm^{-1}): 1042, 1215

4-Formyl- 5 - methoxymethoxy - 1, 3 – benzodioxole 46



41

To a cooled (0 °C) solution of **38** (5 g, 27.5 mmol) in dry THF (20 ml) was added 1eq of nBuLi (12.5 ml, 2.2 M). The reaction mixture was stirred for 30 min and then 1.5eq of DMF (3 g, 3.18 ml) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 3:1 hexane / ethyl acetate. It was completed after 4 h. The reaction mixture was quenched using NH_4Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacou to provide orange powder, which upon purification by flash column chromatography (3:1 hexane / ethyl acetate) gave compound **41** as pale yellow crystals (4.9 g, 85%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.48 (s, 3H), 5.17 (s, 2H), 6.09 (s, 2H), 6.58 (d, 1H, J=8.6 Hz), 6.86 (d, 1H, 8.6Hz), 10.35 (s, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 56.4, 95.7, 102.9, 106.4,111.7, 113.1, 143.4, 148.1, 153.6, 188.0

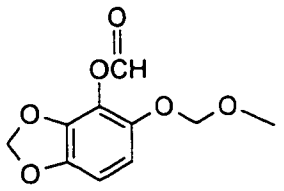
EI-MS (m/z, %): 210 (M^+, 92), 178 (53), 164 (82)

HRMS: Calc. for $C_{10}H_{10}O_5$: 210.0528; Found: 210.05317

IR (cm^{-1}): 1218, 1683

MP: 85-87 °C

4 - Formyloxy - 5 - methoxymethoxy -1, 3 –benzodioxole 48



48

To a cooled (0 °C) solution of aldehyde **41** (3 g, 14.3 mmol) in dry $CHCl_3$ (25 ml) was added 2eq of mCPBA (5.30 g, 30.7 mmol) in one portion. The reaction mixture was warmed up to room temperature and stirred for 24 h after which the reaction mixture was washed with sodium sulfite solution (sat., 2 x 15 ml), sodium bicarbonate (sat., 2 x 20 ml) and water (2 x 20 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (5:1 hexane / ethyl acetate) affording compound **48** as a pale yellow liquid (2.76 g, 91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.45 (s, 3H), 5.06 (s, 2H), 5.96 (s, 2H), 6.64 (d, 1H, J=8.6 Hz), 6.62 (d, 1H, J=8.6 Hz), 8.24 (s, 1H)

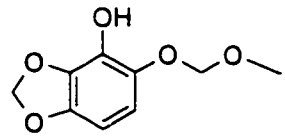
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 56.2, 96.2, 102.3, 105.5, 108.5, 124.1, 139.8, 143.9, 144.6, 157.7

EI-MS (m/z, %): 226 (M+, 6), 45 (100)

HRMS: Calc. for $C_{11}H_{10}O_6$: 226.077; Found: 226.04806

IR (cm^{-1}): 1216, 1752

4 - Hydroxy - 5 - methoxymethoxy - 1, 3 benzodioxole 49



49

To a solution of **48** (20 mg, 0.094 mmol) in THF (5 ml) was added 25% NaOH solution (2 ml). The reaction mixture was stirred for 4 h at room temperature and extracted with water (4 x 5 ml). The aqueous phase was then acidified with conc. HCl and extracted with CH_2Cl_2 (3 x 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide an oily residue. The resulting oily residue was purified using flash chromatography (9:1 hexane / ethyl acetate) affording phenol, **49**, as a pale yellow liquid (1.1 mg, 59%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.51 (s, 3H), 5.07 (s, 2H), 5.92 (s, 1H), 6.20 (s, 1H), 6.30 (d, 1H, J=8.4 Hz), 6.54 (d, 1H, J=8.4 Hz).

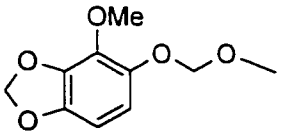
^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 56.5, 97.6, 99.2, 101.7, 109.4, 132.23, 134.5, 141.5,144.5

EI-MS (m/z, %): 198 (M^+, 100), 166 (29), 153 (33)

HRMS: Calc. for $C_9H_{10}O_5$: 198.0528; Found: 198.05296

IR (cm^{-1}): 1049, 1217, 3540

4 - Methoxy - 5- methoxymethoxy - 1, 3 – benzodioxole 50



50

To a solution of phenol **49** (4.9 g, 24.7 mmol) in acetone (20 ml) was added K_2CO_3 (5.13g, 37.1 mmol) and stirred for 30 min, after which CH_3I (15.5 ml, 247 mmol) was added and the resulting reaction mixture stirred at room temperature for 48 h. The solvent was then concentrated in vacuo and the crude residue was dissolved in water (10 ml) and 10% NaOH solution (25 ml). The aqueous phase was extracted with Et_2O (3 x 20 ml) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated affording, after flash chromatography (9:1 hexane / ethyl acetate), compound **50** as a pale yellow liquid (5.05 g, 96%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.49 (s, 3H), 3.99 (s, 3H), 5.08 (s, 2H), 5.88 (s, 2H), 6.41 (d, 1H, J=8.4 Hz), 6.57 (d, 1H, J=8.6 Hz).

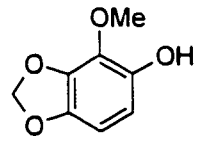
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 56.1, 60.1, 96.6, 101.2, 101.4, 110.1, 135.4, 137.7, 144.1, 144.2

EI-MS (m/z, %): 212 (M^+, 100), 182 (89), 167 (69)

HRMS: Calc. for $C_{10}H_{12}O_5$: 212.06846; Found: 212.07089

IR (cm^{-1}): 1056, 1155

5 - Hydroxy - 4 - methoxy - 1, 3 – benzodioxole 51



51

To a solution of **50** (4.86 g, 22.9 mmol) in acetone (15 ml) was added NaI (5.15 g, 34.3 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 40 ml) was added and the resulting reaction mixture stirred for 4 h. The solvent was concentrated and the crude residue dissolved in water (10 ml). The aqueous phase was extracted with Et_2O (3 x 15 ml) and the combined organic extracts were then washed with 10% NaOH solution (3 x 15 ml). The combined aqueous phase were acidified using conc. HCl and extracted with Et_2O (3 x 20 ml), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide compound **51** as a pale orange crystals (2.81 g, 73%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 4.02 (s, 3H), 5.43 (s, 1H), 5.87 (s, 2H), 6.39 (s, 2H).

^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 59.9, 101.1, 101.8, 105.9, 131.4, 136.2, 142.1, 142.7

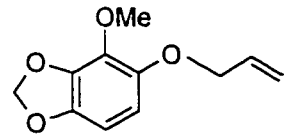
EI-MS (m/z, %): 168 (M^+, 100), 153 (76)

HRMS: Calc. for $C_8H_8O_4$: 168.04224; Found: 168.04076

IR (cm^{-1}): 1056, 1215, 3541

MP: 53-55 °C

4 - Methoxy - 5 - (2 - propenyloxy) -1, 3 – benzodioxole 52



52

To a solution of **51** (2.55 g, 15.2 mmol) in acetone (15 ml) was added anhydrous K_2CO_3 (3.15 g, 23.0 mmol) and allyl bromide (2 ml, 23.0 mmol). The resulting mixture was stirred and refluxes for 30 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo and the crude residue was dissolved in water (20 ml) and 10% NaOH solution (10 ml). The aqueous phase extracted with Et_2O (3 x 20 ml) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to give the compound **52** as a yellow liquid (2.72 g, 86%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.97 (s, 3H), 4.47 (dt, 2H, J=5.4 Hz, 1.4 Hz), 5.22 (ddt, 1H, J=10.5 Hz, 1.6 Hz, 1.4 Hz), 5.35 (ddt, 1H, J=17.3 Hz, 1.6 Hz, 1.6 Hz), 5.86 (s, 1H), 6.00-6.06 (m, 1H), 6.32 (d, 1H, J=8.5 Hz), 6.38 (d, 1H, J=8.5 Hz).

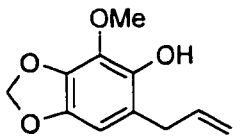
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 60.2, 71.2, 101.1, 101.2, 107.2, 117.5, 133.6, 134.9, 138.1, 143.4, 146.2

EI-MS (m/z, %): 208 (M^+, 39), 167 (100)

HRMS: Calc. for $C_{11}H_{12}O_4$: 208.07356; Found: 208.07554

IR (cm^{-1}): 977, 929, 1247

5 -Hydroxy - 4 - methoxy - 6 - (2 - propenyl)- 1, 3 - benzodioxole 53



53

A solution of allyl ether **52** (0.46 g, 20 mmol) in N, N-dimethylaniline (5 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with Et_2O (7 ml) and washed several times with 10% NaOH solution. The alkaline extract was acidified with conc. HCl and extracted with Et_2O (3 x 15 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give compound **53** as a pale yellowish liquid (0.40g, 87%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.30 (d, 2H, J=6.6 Hz), 4.03 (s, 3H), 5.00-5.11 (m, 2H), 5.43 (s, 1H), 5.84 (s, 2H), 5.85-6.02 (m, 1H), 6.33 (s, 1H).

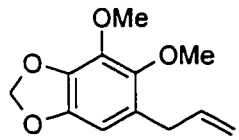
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 33.7, 59.9, 100.9, 102.8, 115.4, 117.5, 131.1, 143.2, 136.7, 139.9, 141.6

EI-MS (m/z, %): 208 (M^+, 100)

HRMS: Calc. for $C_{11}H_{12}O_4$: 208.07356; Found: 208.07308

IR (cm^{-1}): 926, 987, 1054, 1215

4, 5 - Dimethoxy - 6 - (2 - propenyl) -1, 3 - benzodioxole 7



7

To a stirred solution of phenol **53** (0.14 g, 0.70 mmol) in acetone (5 ml) was added K_2CO_3 (0.14 g, 1.0 mmol) and stirred for 30 min, after which CH_3I (0.5 ml, 8.0 mmol) was added and the resulting mixture was stirred at room temperature for 118 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et_2O (3 x 10 ml) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to provide compound **7** as a pale yellowish liquid (0.13 g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.28 (dt, 2H, J=6.5 Hz, 1.4 Hz), 3.73 (s, 3H), 3.99 (s, 3H), 5.00-5.04 (m, 2H), 5.85 (s, 2H), 5.86-5.92 (m, 1H), 6.33 (s, 1H).

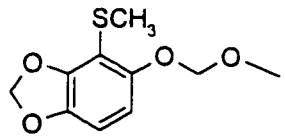
^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 33.9, 59.9, 61.2, 101.0, 102.7, 115.5, 126.0, 135.9, 137.3, 137.6, 144.3, 144.6

EI-MS (m/z, %): 222 (M^+, 100), 177 (22)

HRMS: Calc. for $C_{12}H_{14}O_4$: 222.08922; Found: 222.08817

IR (cm^{-1}): 923, 998, 1063, 1215

5 - Methoxymethoxy - 4 - thiomethyl - 1, 3 - benzodioxole 86a



86a

To a cooled (0 °C) solution of **38** (5 g, 27.5 mmol) in dry THF was added 1eq of nBuLi (12.5 ml, 2.2 M). The reaction mixture was stirred for 30 min and then 1.5eq of dimethyl disulfide (4 ml, 41.2 mmol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 3:1 hexane / ethyl acetate, and was found to be completed after 3 h. The reaction mixture was quenched using NH_4Cl solution (sat., 10 ml) and then the aqueous phase extracted with Et_2O (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacou to provide compound **86a** as a pale yellow liquid (5.7 g, 91%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 2.41 (s, 3H), 3.47 (s, 3H), 5.92 (s, 2H), 5.11 (s, 2H), 5.92 (s, 2H), 6.52 (d, 1H, J=8.6 Hz), 6.59 (d, 1H, J=8.6 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 16.9, 56.1, 95.9, 101.2, 106.7, 107.8, 108.8, 142.3, 148.5, 151.7

EI-MS (m/z, %): 228 (M^+, 100), 198 (63), 182 (17)

HRMS: Calc. for $C_{10}H_{12}O_4S$: 228.04563; Found: 228.04679

IR (cm^{-1}): 1044, 1240

5 -Hydroxy - 4 - thiomethyl - 1, 3 - benzodioxole 87a

87a

To a solution of **86a** (4 g, 18 mmol) in acetone (15 ml) was added NaI (3.94 g, 26 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 40 ml) was added and the resulting reaction mixture stirred for 4 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with Et_2O (3 x 15 ml) and the combine organic extracts were then washed with 10% NaOH solution (3 x 15 ml). The combined alkaline phase was acidified using conc. HCl and extracted with Et_2O (3 x 20 ml), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide phenol, **87a**, as white powder (2.65g, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 2.31 (s, 3H), 5.98 (s, 2H), 6.22 (s, 1H), 6.42 (d, 1H, J=8.4 Hz), 6.69 (d, 1H, J=8.4 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 18.0, 101.6, 103.4, 105.4, 109.4, 140.7, 149.3, 151.2

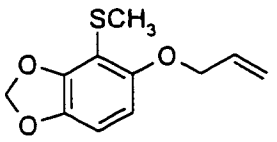
EI-MS (m/z, %): 184 (M^+, 100), 169 (30)

HRMS: Calc. for $C_8H_8O_3S$: 184.01941; Found: 184.01633

IR (cm^{-1}): 3428

MP: 51-53 °C

5 - (2 - Propenyloxy) - 4 - thiomethyl - 1, 3 - benzodioxole 88a



88a

To a solution of **87a** (1.89 g, 10.3 mmol) and in acetone (15 ml) was added anhydrous K_2CO_3 (2.13 g, 15.0 mmol) and stirred for 30 min, after which allyl bromide (0.9 ml, 10.3 mmol) was added and the resulting mixture was stirred and refluxed for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **88a** as a clear liquid (2.03g, 88%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 2.46 (s, 1H), 4.53 (dt, 2H, J=5.1 Hz, 1.4 Hz), 5.28 (dd, 1H, J=10.5 Hz, 1.5 Hz), 5.44 (dd, 1H, J=17.0 Hz, 1.6 Hz), 5.97 (s, 2H), 6.00-6.09 (m, 1H), 6.31 (d, 1H, J=8.5Hz), 6.63 (d, 1H, J=8.5 Hz).

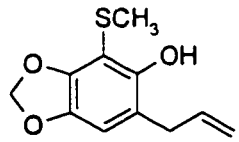
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 16.9, 70.3, 101.2, 104.5, 106.4, 117.4, 133.1, 133.8, 141.5, 148.7, 153.3

EI-MS (m/z, %): 224.1 (M^+, 100), 184 (13), 137 (98)

HRMS: Calc. for $C_{11}H_{12}O_3S$: 224.05073; Found: 224.05332

IR (cm^{-1}): 929, 953, 1448, 1606

5 - Hydroxy - 6 -(2 -propenyl) - 4 -thiomethyl - 1, 3 - benzodioxole 89a



89a

A solution of allyl ether **88a** (1.0g, 4.0 mmol) in N, N-dimethylaniline (5 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with Et_2O (7 ml) and washed several times with 10% NaOH solution. The alkaline extract was acidified with conc. HCl and extracted with Et_2O (3 x 15 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give the compound **89a** as a pale yellowish liquid (0.87 g, 87%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 2.31 (s, 3H), 3.32 (dt, 2H, J=6.8 Hz, 1.4 Hz), 5.01-5.11 (m, 2H), 5.95 (s, 2H), 5.88-6.02 (m, 1H), 6.40 (s, 1H), 6.62 (s, 1H).

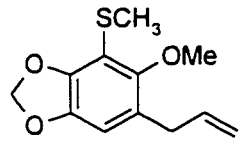
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 18.0, 34.4, 101.3, 102.9, 110.4, 115.5, 117.1, 136.6, 140.3, 147.5, 148.2

EI-MS (m/z, %): 224 (M^+, 100), 197 (9), 176 (18)

HRMS: Calc. for $C_{11}H_{12}O_3S$: 224.05073; Found: 224.04925

IR (cm^{-1}): 927, 953, 3425

5 - Methoxy - 6 -(2 - propenyl) - 4 -thiomethyl - 1, 3 - benzodioxole 90a



90a

To a stirred solution of phenol **89a** (0.4 g, 1.8 mmol) in acetone (5 ml) was added K_2CO_3 (0.37 g, 3.0 mmol) and stirred for 30 min, after which CH_3I (1.1 ml, 18.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et_2O (3 x 10 ml) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to provide compound **90a** as a pale yellowish liquid (0.37 g, 87%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 2.45 (s, 3H), 3.30 (dt, 2H, J=6.5 Hz, 1.4 Hz), 3.75 (s, 3H), 5.01-5.05 (m, 2H), 5.93 (s, 2H), 5.84-5.92 (m, 1H), 6.53 (s, 1H).

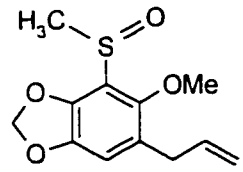
^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 16.9, 34.0, 61.4, 101.3, 108.2, 112.3, 115.7, 125.8, 137.1, 143.4, 146.8, 151.8

EI-MS (m/z, %): 238 (M^+, 100), 223 (13), 176 (41)

HRMS: Calc. for $C_{12}H_{14}O_3S$: 238.06639: Found: 238.06815

IR (cm^{-1}): 949, 996, 1054

5 - Methoxy – 4 - methylsulfinyl - 6 - (2 -propenyl) - 1, 3 - benzodioxole 91a



91a

To a cooled (-40°C) solution of **90a** (100 mg, 42.0 mmol) in ethyl acetate (6 ml) was added 1.2eq of mCPBA (80 mg, 0.5 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x10 ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The resulting oily was residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) affording compound **91a** as a pale yellow liquid (6.7mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.01 (s, 3H), 3.16 (dd, 2H, J=6.4 Hz, 1.5 Hz), 3.78 (s, 3H), 5.03-5.09 (m, 2H), 5.84-5.89 (m, 1H), 6.06 (s, 2H), 6.74 (s, 1H).

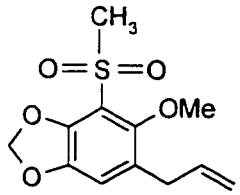
^{13}C NMR (50MHz, $CDCl_3$): δ ppm 33.1, 39.7, 63.4, 102.7, 112.3, 116.5, 120.8, 126.1, 136.3, 145.0, 145.5, 149.1

EI-MS (m/z, %): 254 (M^+, 83), 237 (100)

HRMS: Calc. for $C_{12}H_{14}O_4S$: 254.06129; Found: 254.06070

IR (cm^{-1}): 942, 994, 1050

5 - Methoxy - 4 - methylsulfonyl - 6 - (2 - propenyl) - 1, 3 - benzodioxole 92a



92a

To a solution of **90a** (50 mg, 0.21 mmol) in ethyl acetate (6 ml) was added 4eq of mCPBA (144 mg, 8.40 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness, purified by flash column chromatography (9:1 hexane / ethyl acetate) to provide compound **92a** as pale yellow crystals (45 mg, 80%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.26 (s, 3H), 3.54 (d, 2H, J=6.5 Hz), 3.84 (s, 3H), 5.06-5.13 (m, 2H), 5.84-5.92 (m, 1H), 6.05 (s, 2H), 6.83 (s, 1H).

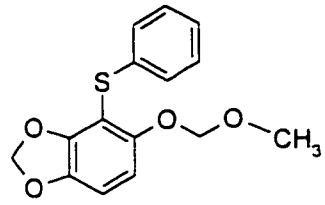
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 32.1, 44.8, 63.8, 102.8, 113.9, 117.0, 118.1, 127.0, 135.9, 145.0, 145.2, 149.2

EI-MS (m/z, %): 270 (M^+, 100)

HRMS: Calc. for $C_{12}H_{14}O_5S$: 270.05619; Found: 270.05406

IR (cm^{-1}): 950, 993, 1136, 1316

5 - Methoxymethoxy - 4 - thiophenyl - 1, 3 - benzodioxole 86b



86b

To a cooled (0 °C) solution of **38** (1.5g, 8.0 mmol) in dry THF was added 1eq of nBuLi (3.3 ml, 2.5 M). The reaction mixture was stirred for 30 min and then 1eq of phenyl disulfide (1.8 g, 8.0 mmol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 9:1 hexane / ethyl acetate. It was completed after 16 h. The reaction mixture was quenched using NH_4Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide compound **86b,** as white crystals (0.67 g, 30%)

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.33 (s, 3H), 5.05 (s, 2H), 5.93 (s, 2H), 6.63 (d, 1H, J=8.5 Hz), 6.77 (d, 1H, J=8.5 Hz), 7.08-7.20 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 56.1, 95.7, 101.6, 104.2, 107.8, 108.8, 125.5, 127.1, 128.7, 136.2, 142.5, 150.4, 152.7

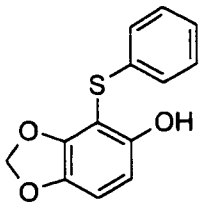
EI-MS (m/z, %): 290 (M^+, 51), 260 (25), 91 (50)

HRMS: Calc. for $C_{15}H_{14}O_4S$: 290.06129; Found: 290.06001

IR: 689, 1050, 1225, 1452, 1478

MP: 67-69 °C

5 - Hydroxy - 4 -thiophenyl - 1, 3 - benzodioxole 87b



87b

To a solution of **86b** (0.67g, 2.30 mmol) in acetone (10 ml) was added NaI (0.52 g, 3.50 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 8 ml) was added and the resulting reaction mixture stirred for 1 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with EtOAc (3 x 15 ml), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo, purified by flash column chromatography (9: 1 hexane / ethyl acetate) to provide phenol, **87b**, as white powder (0.60g, >99%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 5.96 (s, 2H), 6.18 (s, 1H), 6.52 (d, 1H, J=8.5 Hz), 6.81 (d, 1H, J=8.6 Hz), 7.12-7.26 (m, 5H).

^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 99.5, 101.9, 105.9, 110.8, 126.5, 127.0, 129.3, 134.2, 141.0, 150.1, 151.9

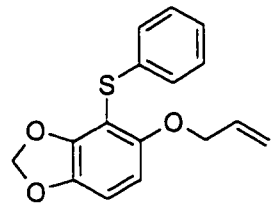
EI-MS (m/z, %): 246 (M^+, 100), 162 (23), 140 (49)

HRMS: Calc. for $C_{13}H_{10}O_3S$: 246.03507; Found: 246.03335

IR (cm^{-1}): 1050, 1453, 1478, 3441

MP: 119 - 122 °C

5 - (2 -Propenyloxy) - 4 - thiophenyl -1, 3 - benzodioxole 88b



88b

To a solution of **87b** (1.62g, 6.60 mmol) and in acetone (15 ml) was added anhydrous K_2CO_3 (1.10 g, 8.0 mmol) and stirred for 30 min, after which allyl bromide (0.63 ml, 7.0 mmol) was added and the resulting mixture was stirred and refluxes for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **88b** as yellow oil (1.52 g, 81%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 4.44 (dt, 2H, J=5.0 Hz, 1.6 Hz), 5.15 (ddt, 1H, J=10.5 Hz, 1.6 Hz, 1.5 Hz), 5.25 (ddt, 1H, J=17.0 Hz, 1.7 Hz, 1.6 Hz), 5.76-5.95 (m, 1H), 5.93 (s, 2H), 6.35 (d, 1H, J=8.5 Hz), 6.75 (d, 1H, J=8.5 Hz), 7.07-7.22 (m, 5H).

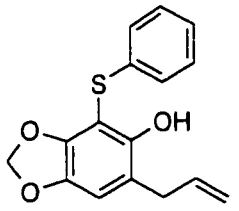
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 70.3, 101.6, 103.5, 104.9, 108.4, 117.2, 125.4, 127.3, 128.6, 132.8, 136.2, 141.7, 150.5, 145.1

EI-MS (m/z, %): 268 (M^+, 52), 245 (52), 91 (100)

HRMS: Calc. for $C_{16}H_{14}O_3S$: 286.06639; Found: 286.06491

IR (cm^{-1}): 943, 996, 1059, 1234, 1684, 2893

5 -Hydroxy - 6 - (2 - propenyl) - 4 -thiophenyl - 1, 3 - benzodioxole 89b



89b

A solution of allyl ether **88b** (1.50 g, 5.20 mmol) in N, N-dimethylaniline (5 ml) was heated at 190 °C for 3.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with Et_2O (10 ml) and washed several times with 25% NaOH solution. The alkaline extract was acidified with conc. HCl and extracted with Et_2O (3x 15 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane /ethyl acetate) to give the compound **89b** as a pale yellow oil (0.55 g, 37%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.35 (dt, 2H, J=6.4 Hz, 1.4 Hz), 5.05-5.09 (m, 2H), 5.92 (s, 2H), 5.93-5.99 (m, 1H), 6.31 (s, 1H), 6.73 (s, 1H), 7.13-7.23 (m, 5H).

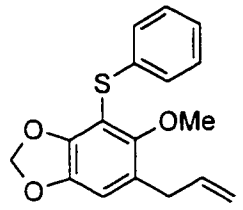
^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 34.4, 99.0, 101.5, 111.9, 115.7, 117.6, 126.5, 127.0, 129.3, 134.3, 136.5, 140.6, 148.3, 148.9

EI-MS (m/z, %): 286 (M^+, 100), 162 (8)

HRMS: Calc. for $C_{16}H_{14}O_3S$: 286.06639; Found: 286.06414

IR (cm^{-1}): 953, 997, 1050, 1638, 2897, 3443

4 - Methoxy - 6 - (2 - propenyl) - 4 - thiophenyl - 1, 3 - benzodioxole 90b



90b

To a stirred solution of phenol **89b** (0.55g, 1.9 mmol) in acetone (15 ml) was added K_2CO_3 (0.32 g, 2.0 mmol) and stirred for 30 min, after which CH_3I (1.21 ml, 13.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et_2O (3 x 10 ml) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to provide compound **90b** as pale yellow oil (0.50 g, 87 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.35 (dt, 2H, J=6.4 Hz, 1.4Hz), 3.73 (s, 3H), 5.02-5.11 (m, 2H), 5.91 (s, 2H), 5.86-6.05 (m, 1H), 6.71 (s, 1H), 7.10-7.22 (m, 5H).

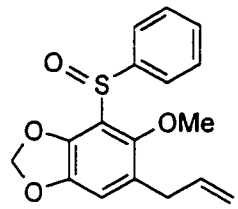
^{13}C NMR (50 MHz, $CDCl_3$): δ pmm 34.2, 62.2, 101.6, 107.6, 110.4, 116.0, 125.6, 126.2, 127.1, 128.9, 136.2, 137.1, 143.7, 148.6, 153.2

EI-MS (m/z, %): 300 (M^+, 100), 176 (48), 162 (15)

HRMS: Calc. for $C_{17}H_{16}O_3S$: 300.08205; Found: 300.08021

IR (cm^{-1}): 948, 995, 1055, 1210, 1639

5 - Methoxy - 4 - phenylsulfinyl - 6 - (2 -propenyl) - 1, 3 - benzodioxole 91b



91b

To a cooled (-40°C) solution of **90b** (0.10g, 0.03 mmol) in ethyl acetate (6 ml) was added 1.2eq of mCPBA (0.07g, 0.40 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x 10ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The resulting oily was residue was purified by flash column chromatography (3:1 hexane / ethyl acetate) affording compound **91b** as white solid (0.08g, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.29 (d, 2H, J=6.4 Hz), 3.85 (s, 3H), 5.00-5.07 (m, 2H), 5.82 (s, 1H), 5.82-5.88 (m, 1H), 5.97 (s, 1H), 6.68 (s, 1H), 7.24-7.71 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 33.0, 63.2, 102.6, 112.4, 116.5, 124.3, 125.8, 128.8, 130.3, 136.2, 143.8, 145.4

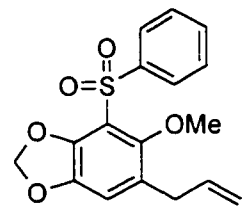
EI-MS (m/z, %): 316 (M^+, 39), 299 (100), 190 (59)

HRMS: Calc. for $C_{17}H_{16}O_4S$: 316.07695; Found: 316.07656

IR (cm^{-1}): 948, 994, 1054, 1218, 1639

MP: 83-87 °C

5 - Methoxy - 4 - phenylsulfonyl - 6 - (2 -propenyl) - 1, 3 - benzodioxole 92b



92b

To a solution of **90b** (90mg, 0.21 mmol) in ethyl acetate (6 ml) was added 2eq of mCPBA (90 mg, 0.50 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness, purified by flash column chromatography (3:1 hexane /ethyl acetate) to provide compound **92b** as white solid (70 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.23 (dt, 2H, J=6.4 Hz, 1.5 Hz), 3.80 (s, 3H), 5.03-5.07 (m, 2H), 5.77-5.82 (m, 1H), 6.08 (s, 2H), 6.78 (s, 1H), 7.41-7.57 (m, 5H).

^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 33.0, 63.6, 102.8, 114.0, 116.9, 118.7, 126.9, 127.5, 128.7, 133.2, 136.0, 142.6, 145.0, 145.4, 149.3

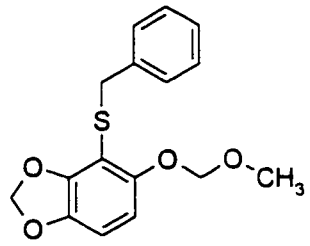
EI-MS (m/z, %): 332 (M^+, 100), 176 (34)

HRMS: Calc. for $C_{17}H_{16}O_5S$: 332.07185; Found: 332.06986

IR (cm^{-1}): 992, 953, 1148, 1319, 1701

MP: 86-88 °C

5 - Methoxymethoxy - 4 - thiomethylphenyl - 1, 3 - benzodioxole 86c



86c

To a cooled (0 °C) solution of **38** (3.0 g, 16.0 mmol) in dry THF was added 1eq of nBuLi (7.0 ml, 2.5 M). The reaction mixture was stirred for 30 min and then 1.2 eq of benzyl disulfide (5.35, 0.022mol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 9:1 hexane / ethyl acetate. It was completed after 16 h. The reaction mixture was quenched using NH_4Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide compound **86c** as a yellow oil (2.37 g, 58%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.45 (s, 3H), 4.07 (s, 2H), 5.03 (s, 2H), 5.85 (s, 2H), 6.54 (d, 1H, J=8.5 Hz), 6.63 (d, 1H, J=8.5 Hz), 7.20 (s, 5H).

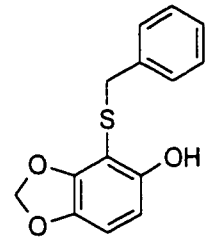
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 38.0, 56.1, 96.0, 101.2, 106.5, 107.4, 107.9, 126.9, 128.1, 128.8, 138.0, 142.2, 149.5, 152.5

EI-MS (m/z, %): 304 (M^+, 29), 259 (18), 182 (26), 91 (100)

HRMS: Calc. for $C_{16}H_{16}O_4S$: 304.07919; Found: 304.07584

IR: 1041, 1226, 1496, 1601

5 - Hydroxy - 4 - thiomethylphenyl - 1, 3 - benzodioxole 87c



87c

To a solution of **86c** (2.51g, 8.20 mmol) in acetone (10 ml) was added NaI (1.86 g, 12.0 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 40 ml) was added and the resulting reaction mixture stirred for 1 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with EtOAc (3 x 15 ml), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo, purified by flash column chromatography (9: 1 hexane / ethyl acetate) to provide phenol, **87c**, as yellow oil (1.68 g, 91%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.87 (s, 2H), 5.85 (s, 2H), 6.03 (s, 1H), 6.35 (d, 1H, J=8.4 Hz), 6.68 (d, 1H, J=8.4 Hz), 7.10-7.25 (m, 5H).

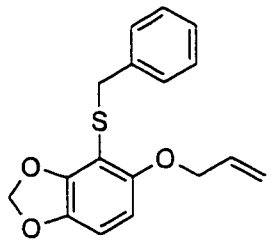
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 39.3, 101.0, 101.5, 105.3, 109.8, 127.4, 128.4, 128.7, 137.2, 140.4, 149.8, 151.7

EI-MS (m/z, %): 260 (M^+, 36), 169 (8.2), 91 (100)

HRMS: Calc. for $C_{14}H_{12}O_3S$: 260.0507; Found: 260.05124

IR (cm^{-1}): 1050, 1206, 1496, 1601, 3434

5 - (2 -Propenyloxy) - 4 - thiomethylphenyl - 1, 3 - benzodioxole 88c



88c

To a solution of **87c** (1.68g, 6.50 mmol) and in acetone (15 ml) was added anhydrous K_2CO_3 (1.10 g, 8.0 mmol) and stirred for 30 min, after which allyl bromide (0.63 ml, 7.0 mmol) was added and the resulting mixture was stirred and refluxed for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **88c** as white oil (1.39 g, 83%).

^{1}H NMR ($CDCl_3$): δ ppm 4.09 (s, 2H), 4.46 (d, 2H, J=5.1 Hz), 5.27 (dd, 1H, J=10.5 Hz, 1.5 Hz), 5.43 (dd, 1H, J=15.6 Hz, 1.6 Hz), 5.84 (s, 2H), 5.95-6.11 (m, 1H), 6.30 (d, 1H, J=8.4 Hz), 6.62 (d, 1H, J=9.2 Hz), 7.21 (s, 5H).

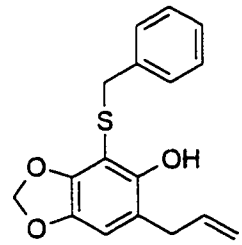
^{13}C NMR ($CDCl_3$): δ ppm 37.9, 70.3, 101.1, 104.6, 105.5, 107.1, 117.3, 126.8, 128.1, 128.8, 133.1, 138.0, 141.3, 149.7, 153.9

EI-MS (m/z, %): 300 (M^+, 30), 259 (38), 91 (100)

HRMS: Calc. for $C_{17}H_{16}O_3S$: 300.08205; Found: 300.08198

IR (cm^{-1}): 953, 995, 1060, 1234, 1448, 1495, 1602

5 -Hydroxy - 6 - (2 - propenyl) - 4- thiomethylphenyl - 1, 3 - benzodioxole 89c



89c

A sclution of allyl ether **88c** (0.43 g, 1.40 mmol) in N, N-dimethylaniline (4 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with EtOAc (10 ml) and conc. HCl (3 ml) was added. The solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give the compound **34** as a pale yellow oil (0.42g, 98%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.25 (d, 2H, J=6.4 Hz), 3.87 (s, 2H), 4.93-5.04 (m, 2H), 5.82-5.96 (m, 1H), 5.83 (s, 2H), 6.18 (s, 1H), 6.61 (s, 1H), 7.08-7.25 (m, 5H).

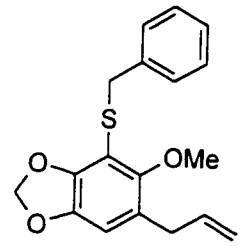
^{13}C NMR (75 MHz, $CDCl_3$): δ ppm 34.4, 39.4, 100.6, 101.2, 110.9, 115.3, 116.9, 127.4, 128.5, 128.7, 136.6, 137.2, 140.1, 148.0, 148.8

EI-MS (m/z, %): 300 (M^+, 48), 224 (91), 209 (28), 176 (48)

HRMS: Calc. for $C_{17}H_{16}O_3S$: 300.08205; Found: 300.08239

IR: 954, 997, 1051, 1215, 1497, 1602, 1638, 3429

5 - Methoxy - 6 - (2 - propenyl) - 4 - thiomethylphenyl - 1, 3 - benzodioxole 90c



90c

To a stirred solution of phenol **89c** (0.42 g, 1.40 mmol) in acetone (15 ml) was added K_2CO_3 (0.23 g, 1.70 mmol) and stirred for 30 min, after which CH_3I (0.88 ml, 14.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et_2O (3 x 10 ml) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to provide compound **90c** as a pale yellow oil (0.42 g, 96 %).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.30 (dt, 2H, J=6.4 Hz, 1.5 Hz), 3.65 (s, 3H), 4.12 (s, 2H), 4.96-5.07 (m, 2H), 5.88 (s, 2H), 5.83-5.95 (m, 1H), 6.55 (s, 1H), 7.17-7.24 (m, 5H).

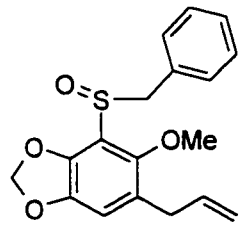
^{13}C NMR ($CDCl_3$): δ ppm 34.0, 37.9, 61.6, 101.3, 108.9, 109.9, 115.7, 125.7, 127.0, 128.3, 128.9, 137.2, 138.0, 143.2, 147.6, 152.5

EI-MS (m/z, %): 314 (M^+, 72), 223 (11), 91 (100)

HRMS: Calc. for $C_{18}H_{18}O_3S$: 314.09771; Found: 314.09530

IR (cm^{-1}): 950, 994, 1054, 1213, 1457, 1601, 1638

5 - Methoxy - 4 -(phenylmethane)sulfinyl - 6 -(2 - propenyl) - 1, 3 - benzodioxole 91c



91c

To a cooled (-40°C) solution of **90c** (0.11 g, 0.40 mmol) in ethyl acetate (10 ml) was added 1.2eq of mCPBA (0.07g, 0.40 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x 10ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The resulting oily was residue was purified by flash column chromatography (3:1 hexane / ethyl acetate) affording compound **91c** as a pale yellow oil (0.07g, 61%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.24 (d, 2H, J=6.3 Hz), 3.56 (s, 3H), 4.34 (d, 1H, J=12.5 Hz), 4.45 (d, 1H, J=12.5 Hz), 5.00-5.06 (m, 2H), 5.82 (d, 1H, J=1.34), 5.90 (d, 1H, J=1.4 Hz), 5.81-5.87 (m, 1H), 6.67 (s, 1H), 7.10-7.24 (m, 5H).

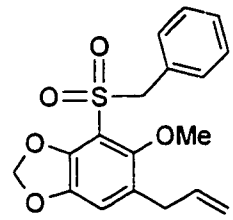
^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 33.0, 59.2, 63.0, 102.6, 112.3, 116.3, 118.6, 125.8, 128.1, 128.4, 130.2, 130.3, 136.4, 145.2, 145.8, 149.4

EI-MS (m/z, %): 330 (M^+, 21), 283 (47), 91 (100)

HRMS: Calc. for $C_{18}H_{18}O_4S$: 330.09261; Found: 330.09099

IR (cm^{-1}): 951, 992, 1049, 1071, 1215, 1462

5 - Methoxy - 4 -(phenylmethane)sulfonyl - 6 -(2 - propenyl) - 1, 3 - benzodioxole 92c



92c

To a solution of **90c** (80 mg, 0.25 mmol) in ethyl acetate (6 ml) was added 2eq of mCPBA (90 mg, 0.50 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness, purified by flash column chromatography (3:1 hexane / ethyl acetate) to provide compound **92c** as a white solid (40 mg, 45%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.35 (d, 2H, J=6.4 Hz), 3.88 (s, 3H), 4.57 (s, 2H), 5.05-5.15 (m, 2H), 5.82 (s, 2H), 5.88-5.93 (m, 1H), 6.77 (s, 1H), 7.20-7.24 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 33.2, 62.2, 63.9, 102.6, 114.1, 116.8, 126.7, 128.1, 128.3, 128.5, 130.9, 133.9, 144.9, 146.3, 149.4

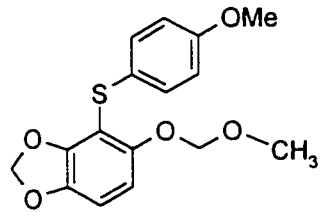
EI-MS (m/z, %): 346 (M^+, 34), 139 (16), 91 (100)

HRMS: Calc. for $C_{18}H_{18}O_5S$: 346.08751; Found: 346.08519

IR (cm^{-1}): 1052, 1149, 1215, 1320, 1462

MP: 133-136 °C

5 - Methoxymethoxy - 4 - thio (4-methoxyphenyl) - 1, 3 - benzodioxole 86d



86d

To a cooled (0 °C) solution of **38** (420mg, 2.0 mmol) in dry THF was added 1eq of nBuLi (0.92 ml, 2.5 M). The reaction mixture was stirred for 30 min and then 1eq of p-methoxy disulfide (0.53 g, 2.0 mmol) was added. The resulting mixture was stirred at room temperature and was monitored using tlc, eluting with 9:1 hexane / ethyl acetate. It was completed after 16 h. The reaction mixture was quenched using NH_4Cl solution (sat., 10 ml) and then the aqueous phase extracted with EtOAc (3 x 20 ml). The organic phase was then washed with water (3 x 15 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide compound **86d** as white crystals (250 mg, 40%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.34 (s, 3H), 3.69 (s, 3H), 5.03 (s, 2H), 5.88 (s, 2H), 6.56 (d, 1H, J=8.5 Hz), 6.68 (d, 1H, J=8.5 Hz), 6.74 (d, 2H, J=8.9 Hz), 7.22 (d, 2H, J=8.9 Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 55.0, 55.9, 95.7, 101.4, 106.3, 107.7, 108.1, 114.2, 126.2, 130.7, 142.3, 149.8, 152.3, 158.3

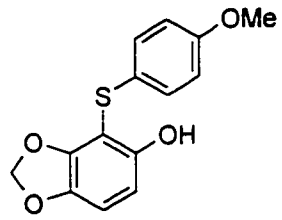
EI-MS (m/z, %): 320 (M^+, 8.6), 278 (46), 139 (100)

HRMS: Calc. for $C_{16}H_{16}O_5S$: 320.07182; Found: 320.07059

IR: 1050, 1286, 1493, 1593

MP: 82-84°C

5 - Hydroxy - 4 - thio (4-methoxyphenyl) -1, 3 - benzodioxole 87d



87d

To a solution of **86d** (0.25 g, 0.78 mmol) in acetone (10 ml) was added NaI (0.18 g, 1.20 mmol) and stirred for 30 min, after which 3N methanoic HCl (3:1 methanol / HCl, 8 ml) was added and the resulting reaction mixture stirred for 2 h. The solvent was concentrated and the crude residue was dissolved in water (10 ml). The aqueous phase was extracted with EtOAc (3 x 15 ml), dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo, purified by flash column chromatography (9: 1 hexane / ethyl acetate) to provide phenol, **87d**, as white powder (0.18 g, 83%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.74 (s, 3H), 5.94 (s, 2H), 6.31 (s, 1H), 6.47 (d, 1H, J=8.5 Hz), 6.75 (d, 1H, J=8.4 Hz), 6.79 (d, 1H, J=6.9 Hz), 7.20 (d, 1H, J=7.6Hz).

^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 55.3, 101.5, 101.7, 105.8, 110.4, 114.9, 124.5,130.4, 140.9, 149.8, 151.6, 159.0

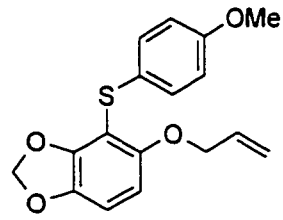
EI-MS (m/z, %): 276 (M^+, 100), 162 (18), 140 (44)

HRMS: Calc. for $C_{14}H_{12}O_4S$: 276.04563; Found: 276.04656

IR (cm^{-1}): 1047, 1246, 1494, 1593, 3443

MP: 82-83 °C

5 - (2 -Propenyloxy) - 4 - thio (4-methoxyphenyl) - 1, 3 - benzodioxole 88d



88d

To a solution of **87d** (1.10 g, 4.0 mmol) and in acetone (15 ml) was added anhydrous K_2CO_3 (0.83 g, 6.0 mmol) and stirred for 30 min, after which allyl bromide (0.41 ml, 5.0 mmol) was added and the resulting mixture was stirred and refluxed for 23 h. After cooling the reaction mixture to room temperature, the solvent was concentrated in vacuo. The crude residue was dissolved in water (5 ml) and 10% NaOH solution (10 ml) and the aqueous phase extracted with Et_2O (3 x 10 ml). The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **88d** as clear oil (0.96 g, 76%).

^{1}H NMR (200 MHz, $CDCl_3$): δ ppm 3.72 (s, 3H), 4.43 (dt, 2H, J=5.1 Hz, 1.5 Hz), 5.18 (ddt, 1H, J=12 Hz, 1.6 Hz, 1.5 Hz), 5.31 (ddt, 1H, J=18 Hz, 1.7 Hz, 1.6 Hz), 5.90 (s, 2H), 5.83-5.97 (m, 1H), 6.30 (d, 1H, J=8.5 Hz), 6.67 (d, 1H, J=8.5 Hz), 6.75 (d, 2H, J=9.0 Hz), 7.26 (d, 2H, J=9.0 Hz).

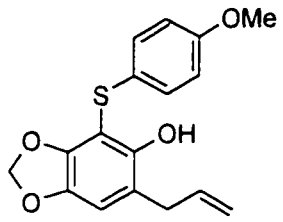
^{13}C NMR (50 MHz, $CDCl_3$): δ ppm 55.1, 70.3, 101.4, 104.8, 105.6, 107.8, 114.2, 117.2, 126.3, 131.0, 132.9, 141.6, 149.9, 153.7, 158.4.

EI-MS (m/z, %): 316 (M^+, 32), 275 (30), 149 (100)

HRMS: Calc. for $C_{17}H_{16}O_4S$: 316.07696; Found: 316.07664

IR (cm^{-1}): 931, 953, 1059, 1227, 1449, 1493, 1593

5 - Hydroxy - 6 - (2 - propenyl) - 4 - thio (4-methoxyphenyl) - 1, 3 - benzodioxole 89d



89d

A solution of allyl ether **88d** (0.30 g, 0.90 mmol) in N, N-dimethylaniline (3 ml) was heated at 190 °C for 2.5 h by means of oil bath and then cooled to room temperature. The solution was diluted with EtOAc (10 ml) and conc. HCl (3 ml) was added. The solution was extracted with EtOAc. The combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo. The crude residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) to give the compound **89d** as a pale yellow oil (0.29g, 97%).

^{1}H NMR (500 MHz, CDCl3): δ ppm 3.32 (d, 2H, J=6.5 Hz), 3.74 (s, 3H), 5.02 (s, 1H), 5.05 (d, 2H, J=6 Hz), 5.91 (s, 2H), 5.89-5.97 (m, 1H), 6.42 (s, 3H), 6.67 (s, 1H), 6.78 (d, 2H, J=8.7 Hz), 7.19 (d, 2H, J=8.7 Hz).

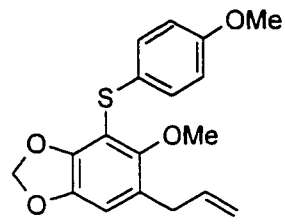
^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 34.5, 55.4, 101.1, 101.5, 111.5, 114.9, 115.6, 117.5, 124.7, 130.4, 136.6, 140.6, 148.0, 148.7, 159.0

EI-MS (m/z, %): 316 (M^+, 100), 208 (22), 180 (47)

HRMS: Calc. for $C_{17}H_{16}O_4S$: 316.07695; Found: 316.07487

IR (cm^{-1}): 949, 995, 1051, 1244, 1493, 1593, 1638, 3440

5 - Hydroxy - 6 - (2 - propenyl) - 4 - thio (4-methoxyphenyl) - 1, 3 - benzodioxole 90d



90d

To a stirred solution of phenol **89d** (0.17 g, 0.50 mmol) in acetone (5 ml) was added K_2CO_3 (0.09g, 0.60 mmol) and stirred for 30 min, after which CH_3I (0.34 ml, 10.0 mmol) was added and the resulting mixture was stirred at room temperature for 77 h. The solvent was concentrated and the crude residue dissolved in water (5 ml) and 10% NaOH solution (10 ml). The aqueous phase was extracted with Et_2O (3 x 10 ml) and the combined organic extracts were dried over anhydrous $MgSO_4$, filtered and concentrated to provide compound **90d** as pale yellow oil (0.17 g, 96 %).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.34 (dt, 2H, J=6.5 Hz, 1.5 Hz), 3.73 (s, 3H), 3.75 (s, 3H), 5.03-5.07 (m, 2H), 5.87 (s, 2H), 5.88-5.94 (m, 1H), 6.63 (s, 1H), 6.77 (d, 2H, J=8.9 Hz), 7.24 (d, 2H, J=8.9 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 34.1, 55.2, 62.0, 101.5, 109.7, 109.8, 114.5, 115.9, 126.0, 126.3, 130.7, 137.1, 143.6, 148.1, 152.7, 158.5

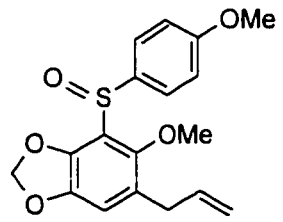
EI-MS (m/z, %): 330 (M^+, 100), 176 (21), 121 (68)

HRMS: Calc. for $C_{18}H_{18}O_4S$: 330.09261; Found: 330.09421

IR (cm^{-1}): 949, 995, 1050, 1244, 1493, 1593, 1638

5 - Methoxy - 4 - (4-methoxyphenyl)sulfinyl - 6 - (2- propenyl) - 1, 3 - benzodioxole

91d



91d

To a cooled (-40°C) solution of **90d** (0.14g, 0.42 mmol) in ethyl acetate (6 ml) was added 1.2eq of mCPBA (0.08 g, 0.50 mmol). The reaction was allowed to warm up to room temperature and stirred for 24 h. After 24 h, the reaction mixture was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 1 x 10 ml) and water (1 x 10 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The resulting oily was residue was purified by flash column chromatography (3:1 hexane / ethyl acetate) affording compound **91d** as a pale yellow oil (0.10 g, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.27 (dt, 2H, J=6.4 Hz, 1.4 Hz), 3.77 (s, 3H), 3.82 (s, 3H), 4.99-5.06 (m, 2H), 5.81-5.84 (m, 1H), 5.87 (s, 1H), 5.98 (s, 1H), 6.66 (s, 1H), 6.92 (d, 2H, J=8.9 Hz), 7.64 (d, 2H, J=8.9 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 33.1, 55.4, 63.2, 102.6, 112.1, 114.4, 116.5, 122.1, 125.9, 126.4, 135.4, 136.4, 144.7, 145.5, 149.2, 161.5

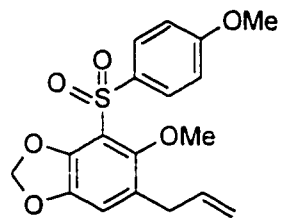
EI-MS (m/z, %): 330 (M^+, 60), 190 (28), 121 (100)

HRMS: Calc. for $C_{18}H_{18}O_5S$: 346.08751; Found: 346.08748

IR (cm^{-1}): 949, 993, 1228, 1044, 1085, 1495, 1594, 1639

5 - Methoxy - 4 - (4-methoxyphenyl)sulfonyl - 6 - (2- propenyl) - 1, 3 - benzodioxole

92d



92d

To a solution of **90d** (90mg, 0.21 mmol) in ethyl acetate (6 ml) was added 2eq of mCPBA (0.09g, 0.50 mmol). The reaction was stirred at room temperature for 24 h, after which it was washed with sodium sulfite (sat., 2 x 10 ml), sodium bicarbonate (sat., 2 x 10 ml) and water (4 x 10 ml). The extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness, purified by flash column chromatography (3:1 hexane / ethyl acetate) to provide compound **92d** as a white solid (70 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 3.22 (dt, 2H, J=6.4 Hz, 1.4 Hz), 3.80 (s, 3H), 3.81 (s, 3H), 4.99-5.07 (m, 2H), 5.75-5.83 (m, 1H), 6.05 (s, 2H), 6.92 (s, 1H), 6.84 (d, 2H, J=8.9Hz), 7.93 (d, 2H, J=8.9 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 33.1, 55.5, 63.6, 102.7, 113.7, 113.9, 116.9, 126.9, 129.8, 134.4, 136.0, 144.9, 145.1, 149.2, 163.4

EI-MS (m/z, %): 362 (M^+, 38), 300 (100), 176 (52)

HRMS: Calc. for $C_{18}H_{18}O_6S$: 362.08241; Found: 362.08209

IR (cm^{-1}): 953, 992, 1145, 1315, 1499, 1596

MP: 82-85 °C

Part B: The Synthesis of Trichiliasterone B

Chapter 4

The total synthesis of 3β - hydroxypregnan - 2,16 - dione 96

4.1 Introduction

Maliaceae is a family of woody tropical plants. Plants in this family are a rich source of limonoids and have attracted considerable attention due to a wide range of biological activity, including bacterial, anti-viral, anti-fungal and also as insect anti-feedant and growth inhibitory activity.[33] Limonoids, also referred to as tetranortriterpenoids, consist of 26 carbons with the basic skeleton shown in Figure 4.1.

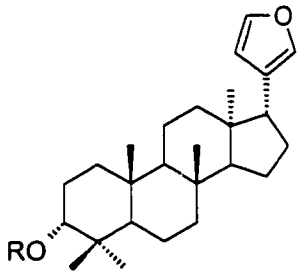
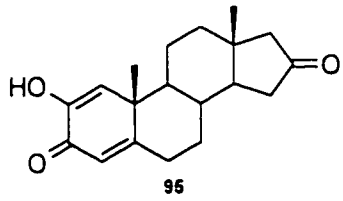


Figure 4.1 - The basic skeleton of tetranortriterpenoids

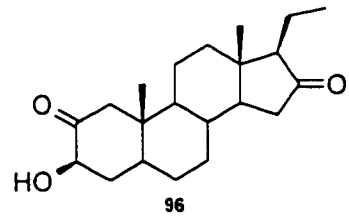
Several years ago, members of our research group screened various Maliaceae species in Central America for natural insecticidal activity.[33] Ethanol extracts of *Trichilia hirta*, a Costa Rican tree, showed the most inhibitory growth pattern on larvae of *Ostrinia nubilalis* (European corn borer) and *Peridroma saucia* (the neonate variegated cutworm). The active extracts were further fractionalized in methylene chloride and other organic solvents in order

to identify the compounds responsible for observed activity. The methylene chloride fraction showed the highest growth inhibition of the insects. Two pure compounds, 2-hydroxyandrosta-1,4-diene-3,16-dione (**95**) and 3β-hydroxypregnan-2,16-dione (**96**), were isolated from the methylene chloride fraction via repeated column chromatography and preparatory reverse phase HPLC. Both of these compounds lacked the resonance for the furan ring in the ^{1}H NMR spectrum, thus they did not belong to the limonoid family. These compounds were eventually assigned the structures **95** and **96** [33] and given the trivial name trichiliasterone A and trichiliasterone B respectively.[34]



95

2-hydroxyandrosta-1,4-diene-3,16-dione
Trichiliasterone A



96

3 β-hydroxypregnan-2,16-dione
Trichiliasterone B

The nomenclature of the steroids conforms to IUPAC regulation.

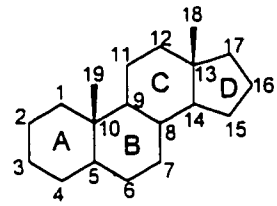


Figure 4.2 - IUPAC numbering system of the steroid skeleton

There are relatively few examples of plant steroids with 16-keto functionality. Plant steroids having this functionality are lanisterone E and Z (**97a** and **97b**) from *Lansium*

anamallayanum Bedd, which like *Trichilia hirta* belongs to the Maliaceae family[35]; Z and E guggulsterone (**99a** and **99b**) from *Commiphora mukul* in India[36]; **100** from the roots of *Solanum hainanense* Hance, a Vietnamese plant[37]; and more recently three more of these 16-keto steroids have been isolated from *Melia volkensii*, a plant also belonging to Maliaceae family.[38] These compounds include E and Z volkendousin (**98a** and **98b**) and meliavosin **101**.

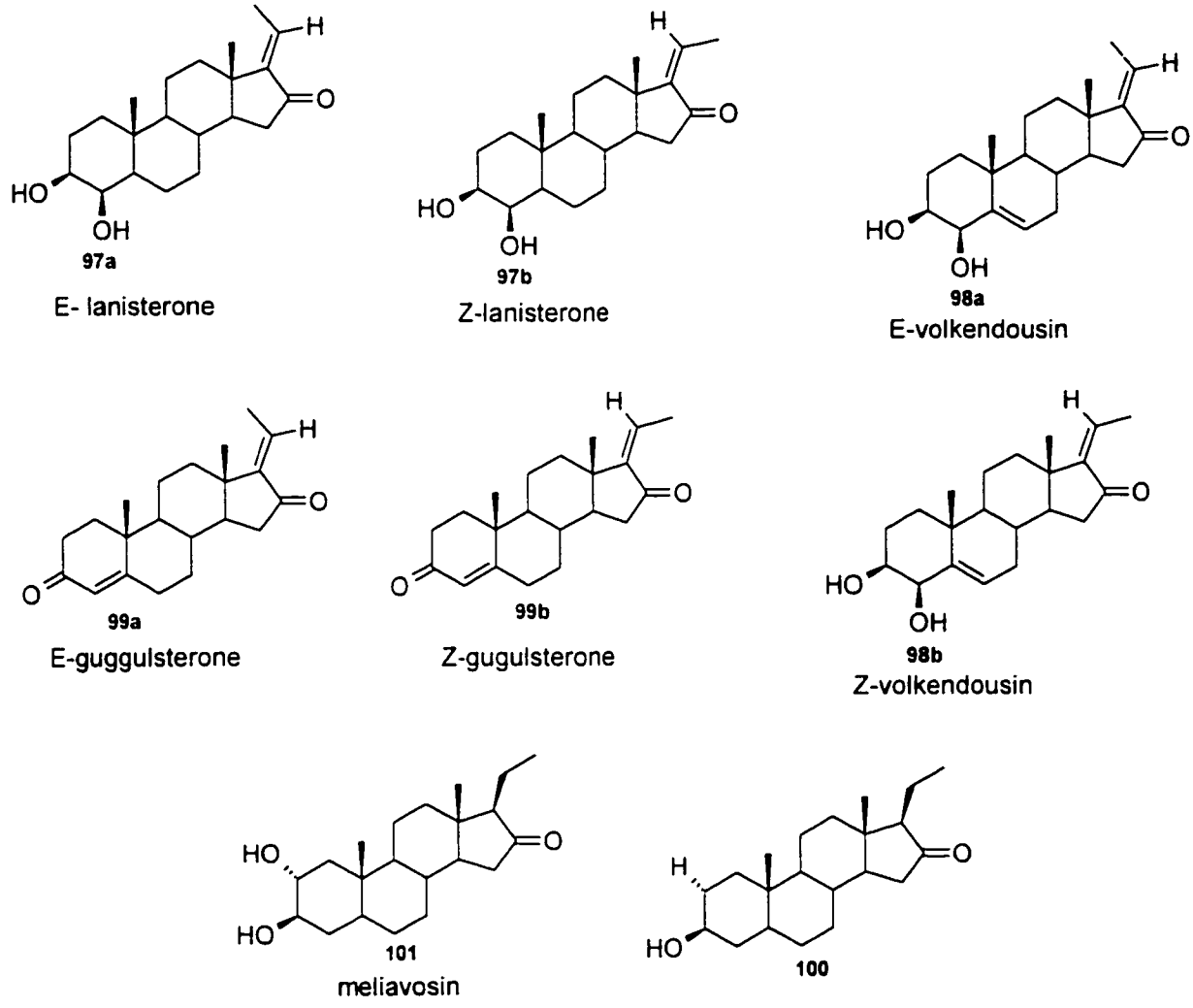


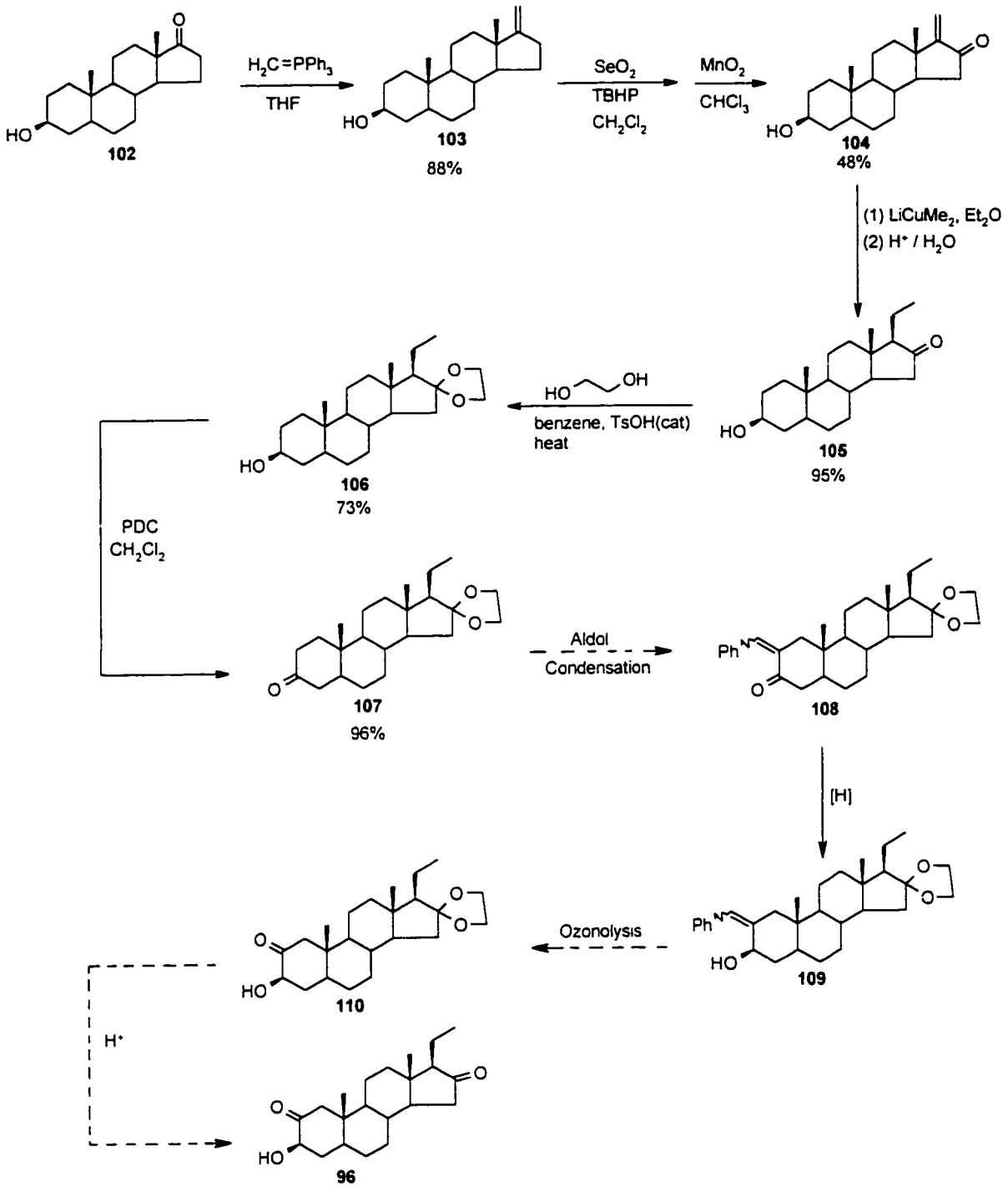
Figure 4.3 - Plant steroids with 16-keto functionality

Trichiliasterone A and B were isolated in small quantity, 0.001% of each component based on dry sawdust. Thus to investigate biological activity, synthesis of trichiliasterone A and B were undertaken by our laboratory. The synthesis of trichiliasterone A, starting with testosterone acetate, was completed in our laboratory by Hantos.[34] She also initiated work on the synthesis of trichiliasterone B but was unable to complete it. The completion of the synthesis of trichiliasterone B is described in the next section of this thesis.

4.2 The synthesis of 3β - hydroxypregnan -2,16 - dione 96

As mentioned previously the synthesis of trichiliasterone B had been started in our laboratory by Hantos.[34] It started with wittig methylation of isoandrosterone **102** to afford **103** in 88% yield using 5 eq of methylene triphenyl phosphorane as shown in Scheme 4.1. Allylic oxidation at the C-16 position of **103** was then performed using SeO_2 and t-butyl hydroperoxide. This procedure gave a mixture of the desired enone **104** and also the C-16 allylic alcohol. The crude mixture was further oxidized using MnO_2 in dichloromethane to afford **104** in 48% yield. Reaction of **104** with lithium dimethylcuprate in diethyl ether at 0°C resulted in **105** in 95% yield. The 16-oxo functionality of **105** was protected as the ethylene ketal **106** using ethylene gylcol and catalytic amount of p-toluenesulfonic acid in benzene prior to modification of ring A. The 3-hydroxyl group of **106** was then oxidized to **107** in 96% yield using PDC in CH_2Cl_2. The final four steps planned for the completion of the synthesis of trichiliasterone B were aldol condensation of **107** with benzaldehyde to afford **108**, reduction of 3-oxo group of **108** to afford **109**, ozonolysis at the C-2 position of **109** to afford **110** and finally the hydrolysis of the C-16 ketal of **110** to afford the desired product **96**. Initial attempts at aldol condensation via the procedure by Barton et al[39] using 0.1M KOH in ethanol and benzaldehyde were unsuccessful. Due to time limitation Hantos did not continue with the synthesis.

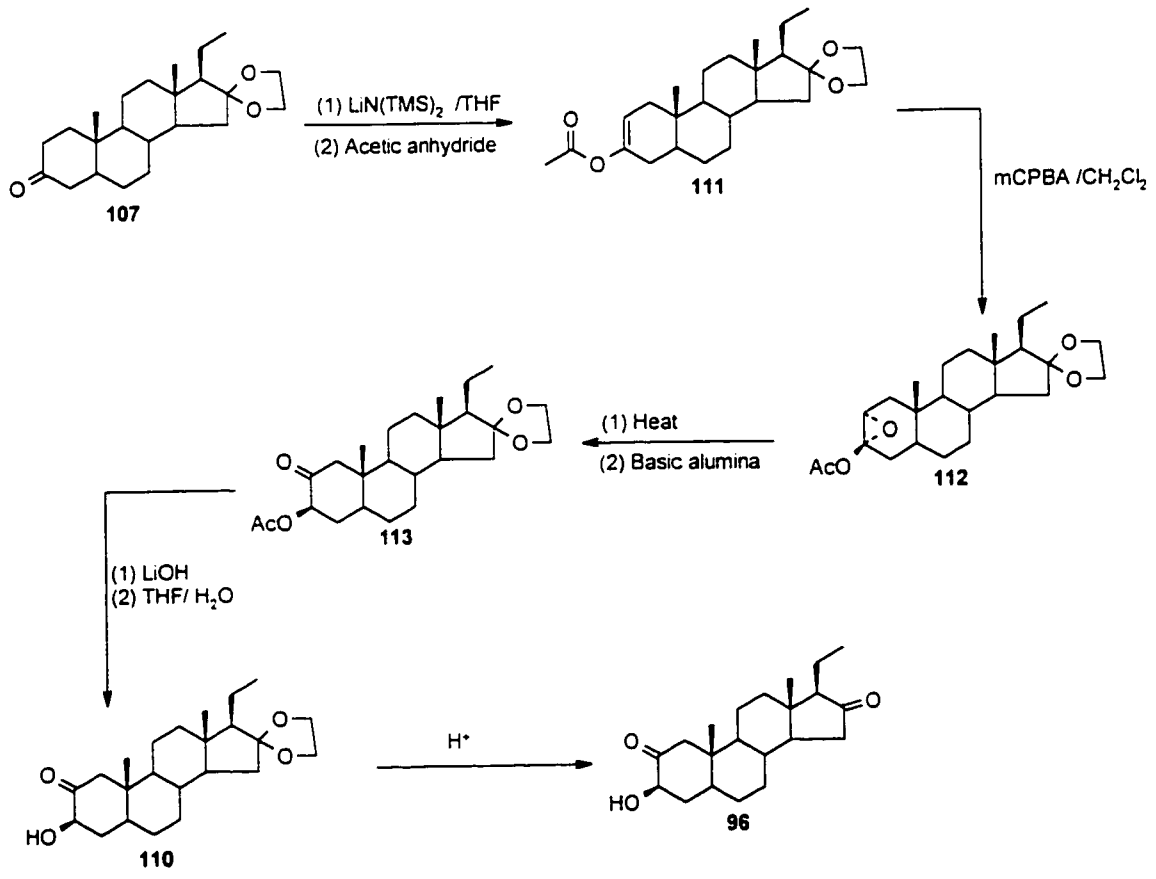
To explore the aldol condensation reaction further, we reacted **107** with lithium hexamethyldisilazide or LDA as base at -78°C for 1 h followed by benzaldehyde. The reaction mixture was quenched after 30 min with aqueous NH_4Cl. These conditions led to



Scheme 4.1 - Proposed Route for the Synthesis of Trichiliasterone B

complex product mixtures with little, if any, of the desired product **108**. Thus this route to trichiliasterone B was abandoned.

The route chosen to complete the synthesis of trichiliasterone B is shown in Scheme 4.2. Conceptually it involved introducing oxygen functionality at the C-2 position, initially in the form of an epoxide, specifically the epoxy acetate **112**. It has been reported[40] that thermal ring opening of α-epoxy acetate such as **114** can lead to a 3-keto-2-acetoxy product that under basic conditions[41] can be isomerized to afford mainly the 2-keto-3-acetoxy derivative. We therefore opted for this approach, recognizing that mixtures of 3α- and 2β-hydroxy ketones will arise. We anticipated that we would be able to separate these mixtures and thus complete the synthesis of trichiliasterone B.



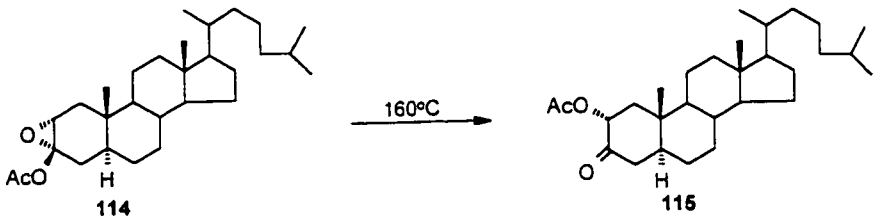
Scheme 4.2 - The Synthesis of Trichiliasterone B via Different Route

The 3-keto derivative **107** was treated with $LiN(TMS)_2$ and acetic anhydride to give the enol acetate **111** in 84% yield as white crystals, which melted at 100-104°C. The ^1H NMR spectrum showed a singlet at 2.07 ppm corresponding to the methyl group in the acetyl moiety and a double doublets at 5.23 ppm, coupling constant J=5.8 Hz and J=1.4 Hz, corresponding to the proton at the C-2 position. The ^{13}C NMR spectrum showed the signal at 147.0 ppm for the C-3 carbon in steroid **111** whereas in steroid **107** the signal for the C-3 carbon was at 211.8 ppm. The molecular ion was calculated to be 402.2771 and the HRMS of **111** showed a M^+ ion at *m/z* 402.2782.

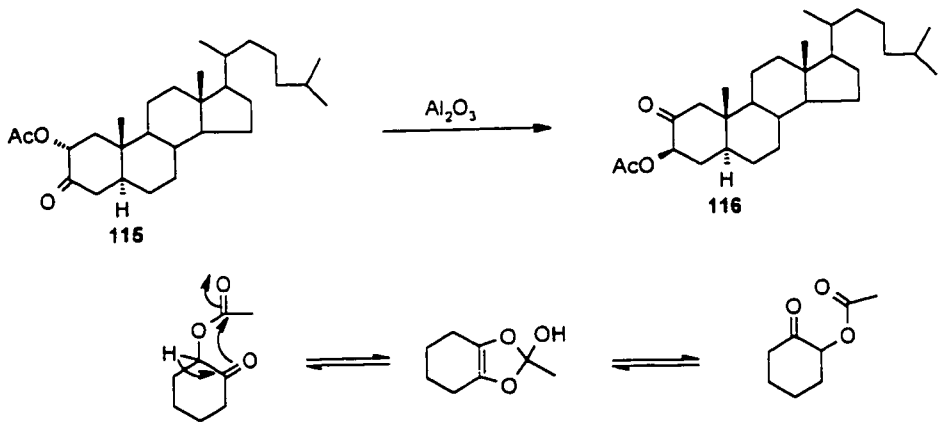
Oxidation of **111** using mCPBA in dichloromethane for 24 h afforded epoxy acetate **112** in 72% yield as white crystals that melted at 95-100°C. A wide range of melting point is observed, suggesting a mixture of stereoisomers but the ^1H NMR spectrum of **112** indicates the presence of only one product. Thus this wide range of melting point could be due to thermal decomposition of the product **112** since it has been reported that epoxy acetate can undergo thermal ring opening. The stereochemistry of **112** is based on the notion that the attack by mCPBA should occur from the less hindered α-face. The ^1H NMR spectrum showed a doublet at 3.29 ppm, with coupling constant J=5.6 Hz, corresponding to the proton signal at the C-2 position. The ^{13}C NMR spectrum showed the carbon signal of enol acetate **111** at the C-2 (112.5 ppm) and C-3 (147.0 ppm) positions to be replaced by the epoxy acetate signal at 58.3 ppm and 83.0 ppm respectively. The molecular ion was calculated to be 418.2720 and the HRMS of **112** showed a M^+ ion at *m/z* 418.2745.

It has been shown by Williamson et al[40] that the 2α,3α-oxido-3β-acetoxycholestane **114** smoothly rearranges to the acetoxy ketone **115** by simply heating to 160°C for 5 minutes

(Scheme 4.3) and Bowers et al[41] showed that acetoxy ketones like **115** may rearrange during chromatography on basic alumina to give more stable isomer **116** (Scheme 4.4). Thus the steroid **112** was heated at 160°C for 10 min and the product was mounted onto a basic alumina column and left there for 24 h, after which it was eluted with 3:1 hexane / ethyl acetate. A mixture of **113** and **117** in 68% yield was observed (Scheme 4.5).



Scheme 4.3 - Thermal Rearrangement of Epoxy Acetate **114**



Scheme 4.4 - Rearrangement of Acetoxy Ketones on Basic Alumina

The ^{1}H NMR spectrum (Figure 4.4) showed a multiplet at 5.17-5.31 ppm corresponding to the -CH attached to the acetate group and a singlet at 2.13 ppm corresponding to the methyl protons in the acetyl moiety for both the minor and major product. The methyl peaks at the C-18 and C-19 positions in the minor product **113** were at 0.69 ppm and 0.75 ppm whereas in

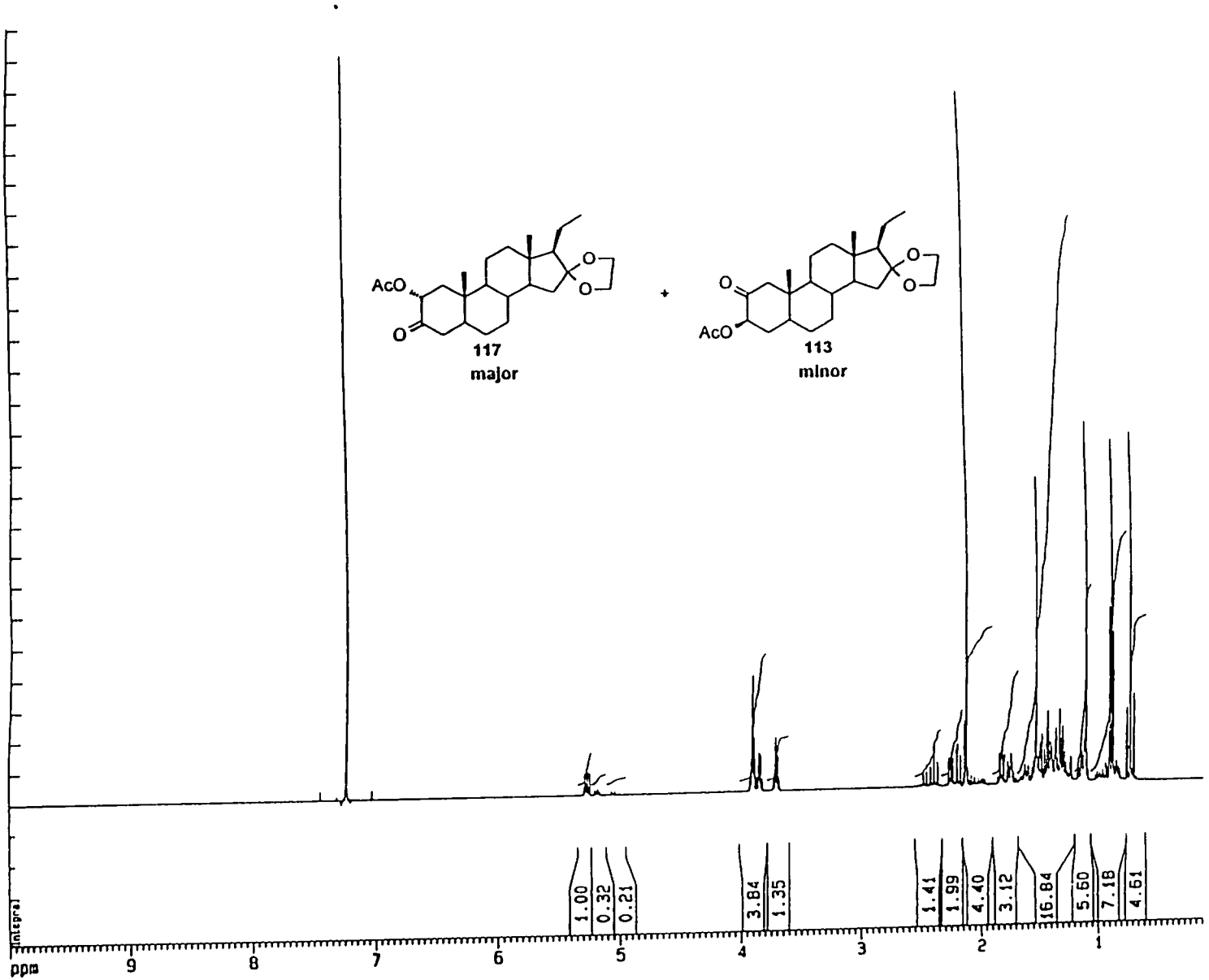
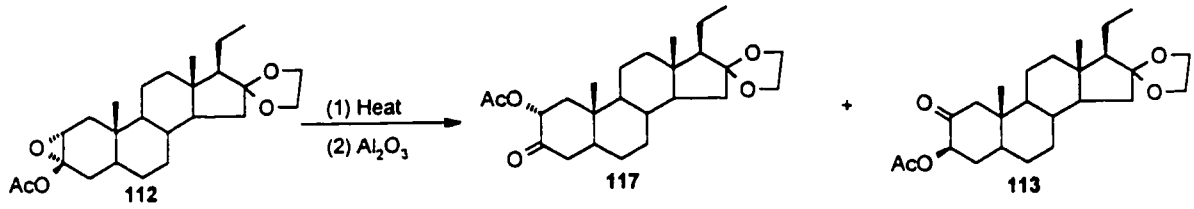


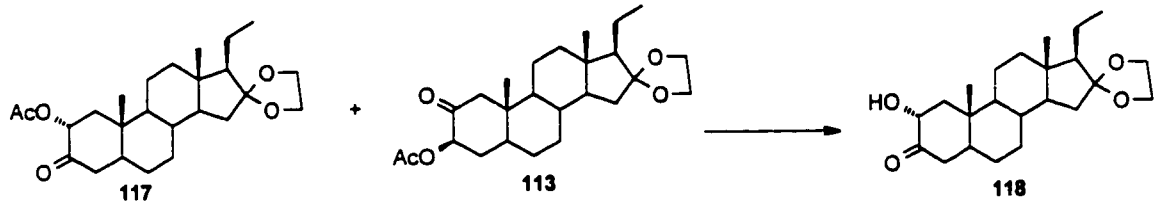
Figure 4.4 – ^{1}H NMR spectrum of 3β-acetoxy-16-ethylenedioxypregnan-2-one (113) and 2α-acetoxy-16-ethylenedioxypregnan-3-one (117)

the major product **117**, they were at 0.72 ppm and 1.10 ppm. The ratio of the minor **113** to the major product **117** was calculated to be 1:4. The mixture was difficult to separate, hence was subjected to hydrolysis of the acetate group.



Scheme 4.5 - Thermal Rearrangement of the Epoxy Acetate **112**

De-acetylation of the crude mixture of **113** and **117** using LiOH in THF/water mixture yielded **118** as a major product in 80% yield as white crystals, which melted at 126-130°C. The ^{1}H NMR spectrum (Figure 4.5) showed the disappearance of a singlet at 2.13 ppm corresponding to the methyl group in the acetyl moiety and the appearance of a doublet at 3.48 ppm, coupling constant J=3.3 Hz, corresponding to the hydroxyl proton and a multiplet at 4.23 ppm corresponding to the proton at the C-2 position. The IR spectrum showed the broad band at 3615 cm^{-1}, characteristic of the hydroxyl group. The molecular ion was calculated to be 376.2615 and the HRMS of **118** showed a M^+ ion at m/z 376.2592. Alternatively, epoxy acetate **112** was reacted with LiOH in THF/water mixture to yield steroid **118** in 30% yield.



Scheme 4.6 - De-acetylation of the Crude Mixture of Steroids **113** and **117** to afford the Steroid **118**

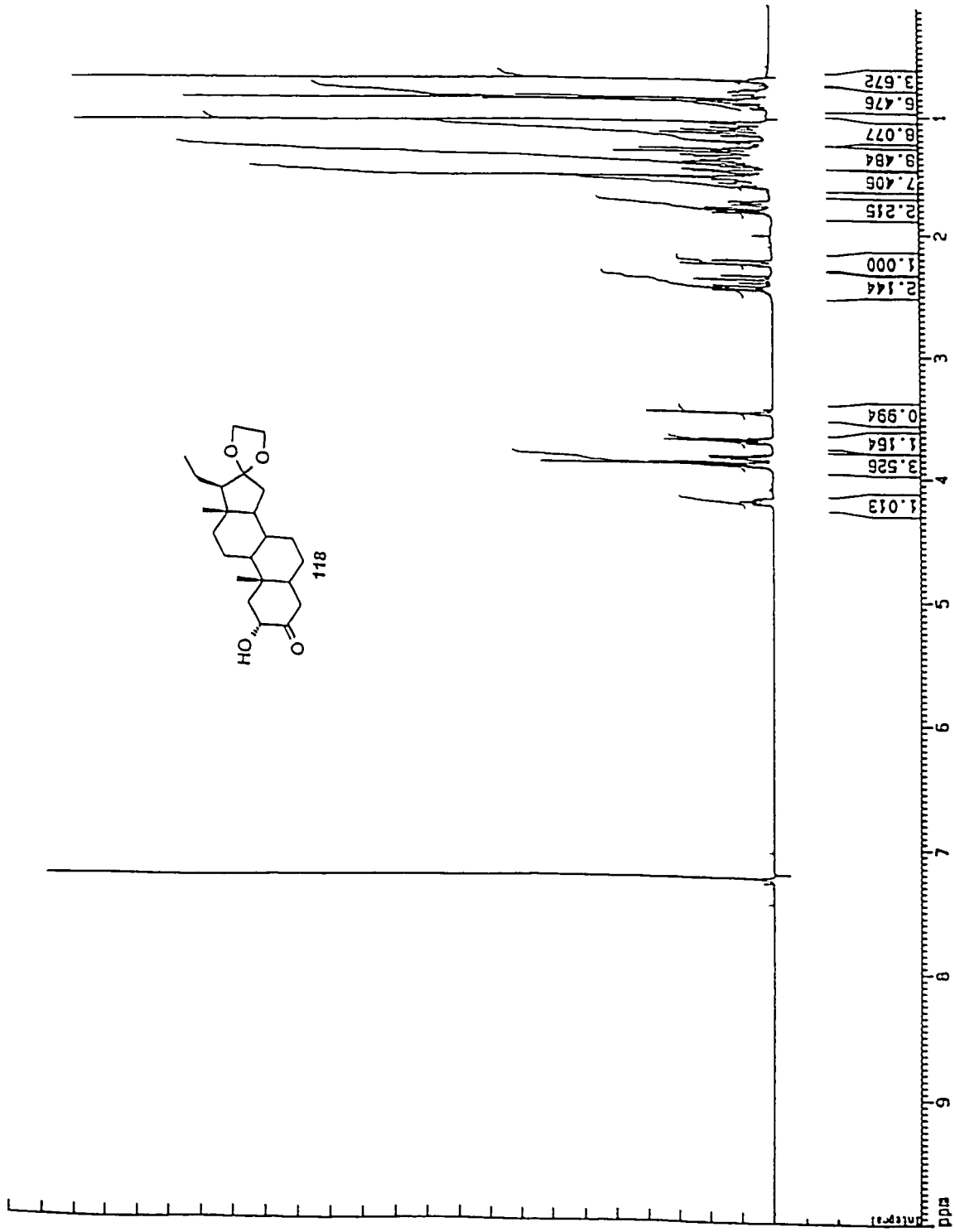
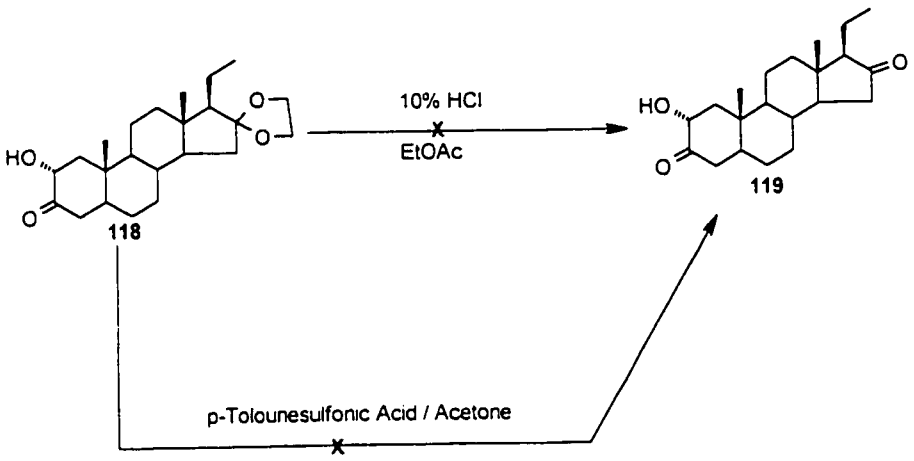


Figure 4.5 – ^{1}H NMR spectrum of 2α-hydroxy-16-ethylenedioxypregnan-3-one (118)

The final step was the hydrolysis of the ketal at the C-16 position. Steroid **118** was reacted with 10% HCl solution in ethyl acetate for 24 h. Work-up after 24 h led to a mixture of products, none of which was the desired product. Alternatively, we reacted the steroid **118** with p-toluenesulfonic acid in acetone for 24 h. Work up after 24 h led to a mixture of products, again none of which was the desired product (Scheme 4.7). Thus this route to the synthesis of trichiliasterone B was abandoned. A new route was suggested with the hope that

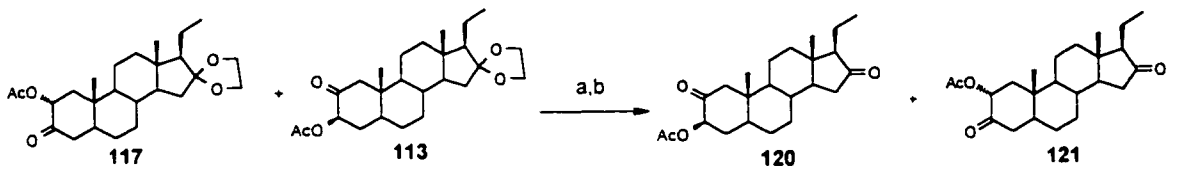


Scheme 4.7 - Hydrolysis of the Ketal Group at C-16 from the Steroid **118**

it will lead us to the desired product **96**. It involved the manipulation of the sequence of the removal of the ketal group at the C-16 position. Instead of the removal of the acetyl moiety first, we decided to remove the ketal group first, followed by the acetyl group.

With the help of Dr. Sasmita Tripathy in our group, the crude mixture of **113** and **117** was refluxed with pyridinium tosylate in acetone for 3 h after which the solvent was removed in vacou. The residue was extracted into ethyl acetate and washed with sodium bicarbonate and brine. The organic layer was separated and dried with anhydrous $MgSO_4$. It afforded the crude products **120** and **121** in 90% yield (Scheme 4.8). The crude ^1H NMR spectrum

showed the absence of the signal due to the ethylenedioxy group in the region of 3.81-3.90 ppm.



Reagents: a) pyridinium tosylate / acetone; b) reflux, 3 h

Scheme 4.8 - Hydrolysis of the Ketal Group at C-16 Position in Steroids **113** and **117**

The crude products **120** and **121** were not purified but de-acetylated using LiOH in THF/water mixture affording **96** as white crystals, which melted as 144-145°C, in 13% yield and **119** as white crystals, which melted at 136-137°C, in 43% yield. The ^{1}H NMR spectrum of the steroid **119** (Figure 4.6) showed a double doublets at 4.20 ppm, coupling constants J= 12.0 Hz and 7.1 Hz, for the proton at the C-2 position, a singlet at 3.50 ppm corresponding to the hydroxyl group and the methyl groups at the C-18 and C-19 positions at 0.68 ppm and 1.08 ppm. The molecular ion was calculated to be 332.2351 and the HRMS of **119** showed a M+ ion at *m/z* 332.2359. The stereochemistry of the hydroxyl group was assigned as equatorial from the coupling constant of the proton at the C-2 position. The coupling constant J=12.0 Hz is due to the coupling of the axial proton at the C-2 position with the axial proton at the C-1 position and the coupling constant J=7.0 Hz is due to coupling of the axial proton at the C-2 with the equatorial proton at the C-1 position. If the position of the hydroxyl group was axial, then the proton at the C-2 position would show two small couplings in the range 0 - 7 ppm. The spectroscopic data of steroid **119** were compared with the available spectrum of trichiliasterone B and were found to be different. Steroid **119** was found to be the 2α-hydroxy-3-keto isomer of the natural product, trichiliasterone B, and

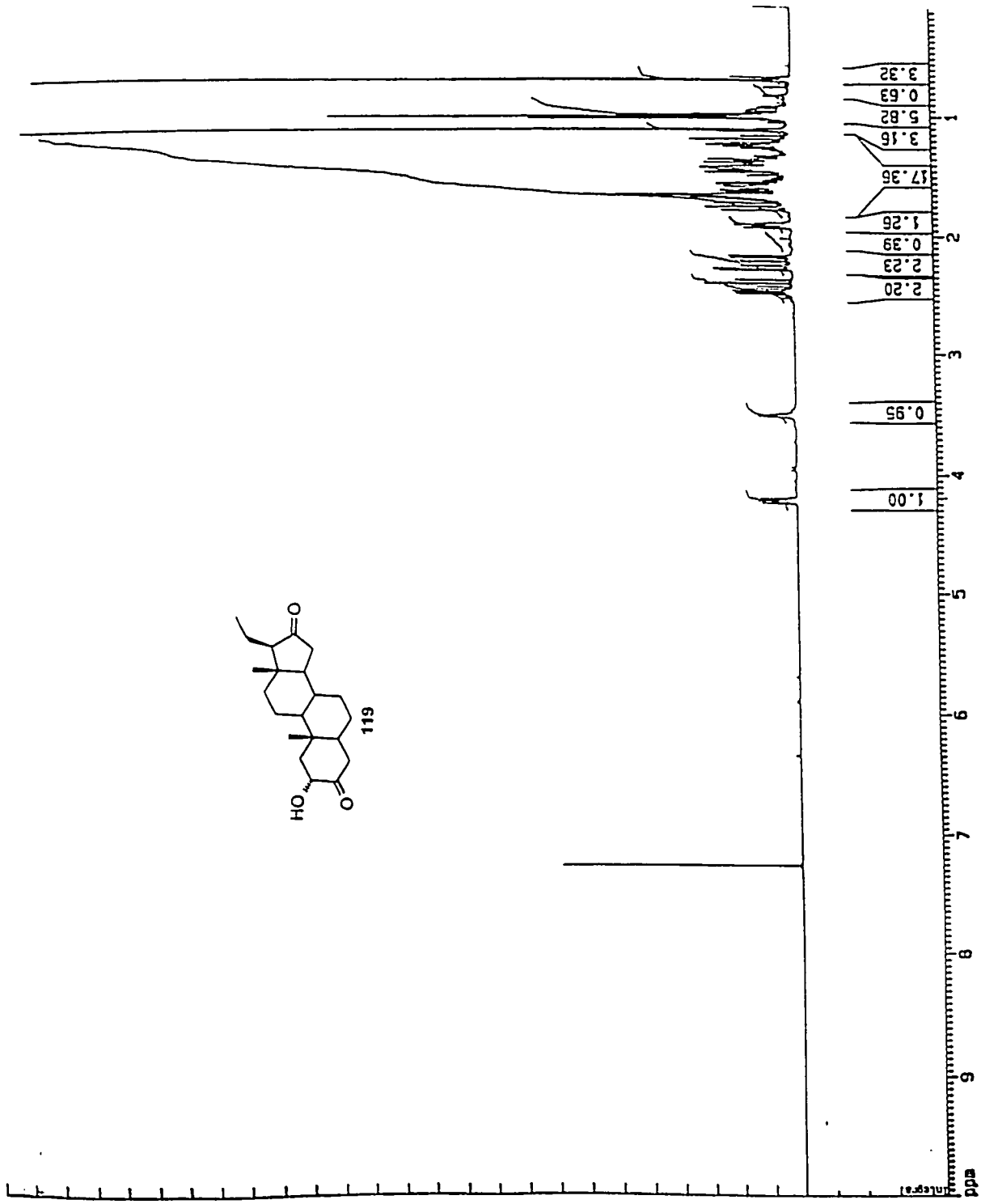


Figure 4.6 – ^{1}H NMR spectrum of 2α-hydroxypregnan-3,16-dione (119)

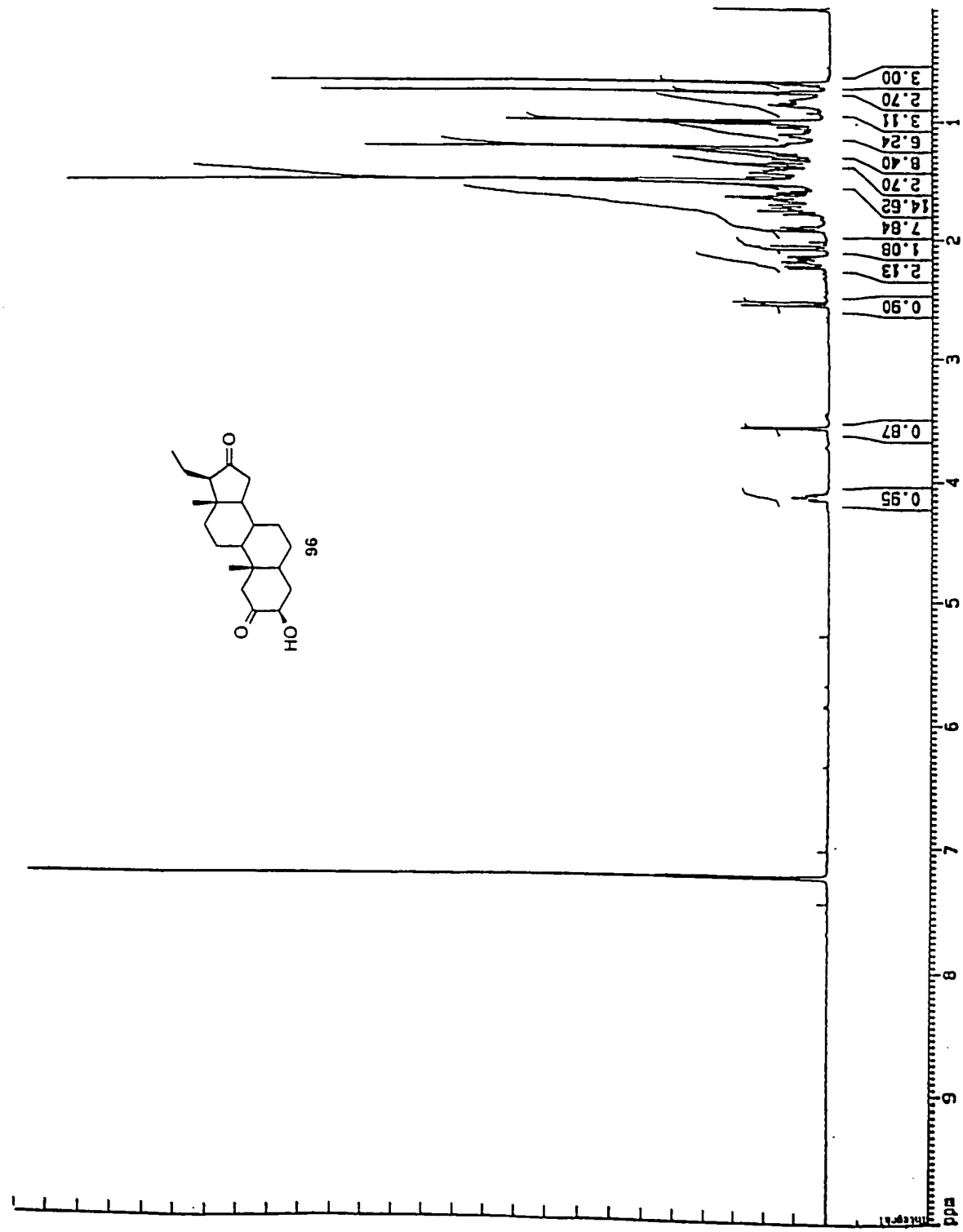
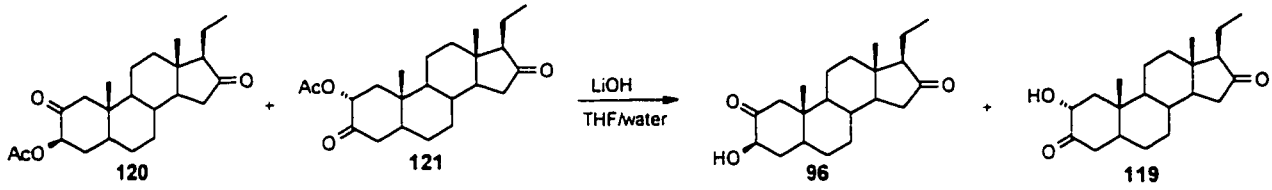


Figure 4.7 – ^{1}H NMR spectrum of 3β-hydroxypregnan-2,16-dione (96)

hence the intermediates were assigned the 2α-hydroxy-3-keto structures since the final product did not lead to the natural product.

The spectroscopic data of the minor product matched those of the natural product, trichiliasterone B, cited by Chauret et al.[33] The molecular ion was calculated to be 332.2351 and the HRMS of **96** showed M^+ ion at *m/z* 332.2336. The major differences between the



Scheme 4.9 - Hydrolysis of the Acetyl Moiety in Steroids **120** and **121**

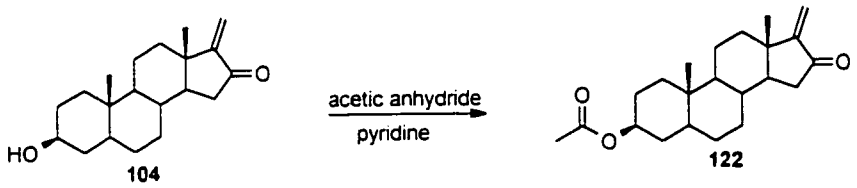
two isomers is the position of the methyl peaks at the C-18 and C-19 positions in the ^1H NMR spectrum (Figures 4.6 and 4.7). In steroid **119**, the methyl peaks are at 0.70 ppm and 1.08 ppm whereas in the natural product, **96**, the methyl peaks are at 0.67 ppm and 0.76 ppm.

4.3 Cytotoxicity of the steroid 104 and its derivatives

McLaughlin et al reported the isolation of **98a**, **98b** and **101** from the root bark of *Melia volkensii* which occurs in Kenya, Africa.[38] All three compounds showed biological activity and we speculate it could be due to the α, β unsaturated enone system in ring D being the excellent Michael receptor. The methylene ketone **104**, prepared during the synthesis of trichiliasterone B, should be as potent as the isolated steroids **98a**, **98b** and **101**

or even more potent, since it is sterically unhindered and contains no electron donating group on the β-carbon of the α, β unsaturated enone. Thus with this in mind some ester derivatives of **104** were synthesized and tested for anti-cancer activity along with **104**.

Steroid **104** was reacted with 1eq of acetic anhydride in pyridine to afford **122** as white crystals in 53% yield. The ^{1}H NMR spectrum showed the appearance of a singlet at 2.00 ppm corresponding to the methyl group in the acetyl moiety. The ^{13}C NMR spectrum



Scheme 4.10 - The synthesis of the steroid **122**

showed the carbonyl peak in the acetyl moiety at 170.6 ppm and the C-3 carbon peak at 73.4 ppm whereas in steroid **104** the C-3 carbon peak was at 71.2 ppm.

Other ester derivatives were prepared in a similar manner as steroid **122** and are tabulated in Table 4.1. The ^{1}H NMR and ^{13}C NMR spectra were as expected. They are summarized in the experimental section. Relatively little effort was made to optimize the yield. The major goal was to produce significant quantities of pure compounds for the biological screening.

All these five compounds show *in vitro* sub micromolar toxicity to most cell lines when tested by Biochem Pharma. The results of the tests are shown in Table 4.2. Dr. Gourdeau, who carried out the assays at Biochem Pharma, pointed out that these compounds showed best activity against the leukemia cell line. Since there are currently a number of viable treatments specifically for childhood leukemia, there is relatively little interest in the

anti-leukemia compounds, unless it can be proven that the compounds mode of action is novel. She recommended that we submit our compounds' to the US National Cancer Institute. They carry out screening against several human cancer cell lines and produce a detailed profile for each compound. This profile is compared with those of known anti-cancer compounds and the unusual effects are highlighted. Based on such an extensive screening, a decision might be made whether to initiate *in vitro* tests and possibly prepare additional analogs.

Table 4.1- The Synthetic Ester Derivatives of the Steroid **104**

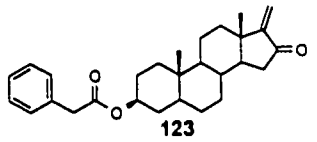
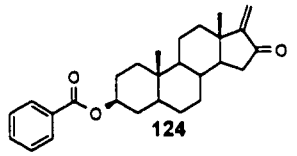
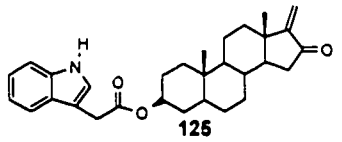
Derivatives of Steroid **104**	Yield
 **123**	45%
 **124**	58%
 **125**	53%

Table 4.2 - The IC_{50} Values, Expressed in Micro Molar Concentrations, of Compounds **104**, **122**, **123**, **124** and **125** Against Different Cancer Cell Lines Obtained by Biochem Pharma.

IC 50 also expressed in µM. conc. MTT, 3H THY= PRISM

Cell Lines		1		2		3		4		5	
		MTT	3H-Thy. Inc.	MTT	3H-Thy. Inc.	MTT	3H-Thy. Inc.	MTT	3H-Thy. Inc.	MTT	3H-Thy. Inc.
Hep G 2	(Liver epatho. carc.)	2.4	0.94	2.7	2.53	3	0.23	2.9	0.33	1.8	0.117
HL 60	(Leukemia)	0.17	0.177	0.14	0.093	0.027	0.035	0.088	0.096	0.18	0.182
HSF	(Normal Fibroblasts)	1.5	0.063	0.33	0.13	0.37	2.64	0.85	2.6	0.42	0.66
HT-1080	((Fibrosarcoma)	0.36	0.28	0.39	0.3	0.96	0.52	4.9	3.22	0.62	0.3
HT-29	(Colon Adenocarc.)	0.77	0.24	1.81	0.48	1.68	0.74	3.62	0.95	0.9	0.27
MCF-7	(Breast Adenocarc.)	0.42	0.25	0.16	0.35	0.24	0.3	0.51	0.032	0.36	0.19
PC-3	(Prostate Carc.)	0.38	0.27	0.7	0.33	0.62	0.35	1.6	0.69	0.58	0.42

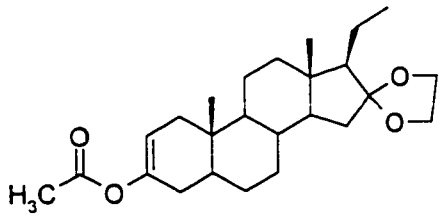
Legend

1 = compound **104**, 2 =compound **122**, 3 = compound **123**, 4 = compound **124** and 5 = compound **125**

4.4 Experimental

General procedure: See experimental section, Chapter 3, for general procedure.

3 β - Hydroxy - 16 - ethylenedioxypregnane 111



111

To a cooled solution (-78 °C) of steroid **107** (25 mg, 0.069 mmol) in dry THF was added 2eq of $LiN(TMS)_2$ (1 M, 0.13 ml). The reaction mixture was stirred for 1 h after which 3eq of acetic anhydride (0.02 ml) were added. The resulting mixture was stirred and monitored using thin layer chromatography (tlc), eluting with 12:1 toluene / acetone. It was completed after 30 min. The reaction mixture was quenched with water and extracted with EtOAc (3 x 10 ml). The organic phase was dried with anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide compound **111** as white crystals (23 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.71-1.01 (m, 4H), 0.88 (t, 3H, J=7.0 Hz), 0.80 (s, 3H), 0.70 (s, 3H), 1.10-1.61 (m, 11H), 1.81 (ddd, 2H, J=12.8 Hz, 7.0 Hz), 1.74 (dt, 1H, J=6.7 Hz, 3.7 Hz), 1.91-1.95 (m, 2H), 2.00 (dd, 1H, J = 17.0 Hz, 3.3 Hz), 2.07 (s, 3H), 3.67-3.72 (m, 1H, ketal), 3.81-3.86 (m, 1H, ketal), 3.87-3.92 (m, 2H, ketal), 5.23 (d, 1H, J = 5.8 Hz, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 11.7, 12.9, 13.5, 17.0, 20.7, 21.0, 28.3, 31.4, 31.6, 34.7, 38.1, 38.6, 40.0, 41.8, 42.1, 52.0, 53.7, 60.8, 62.9, 64.9, 112.5 (C-2), 117.5 (C-16), 147.0 (C-3), 169.5 (OAc)

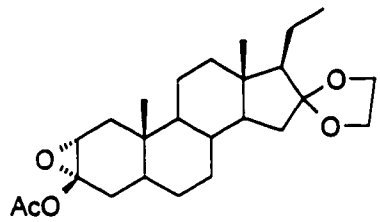
EI-MS (m/z, %): 402 (M^+, 9), 316 (30), 142 (50), 99 (100)

HRMS: Calc. for $C_{25}H_{38}O_4$: 402.2777; Found: 402.2782

MP: 100-104 °C

IR (cm^{-1}): 1030, 1046, 1333, 1424, 1602, 1745

3β - Acetoxy - 2α, 3α - epoxy - 16 - ethylenedioxypregnane 112



112

To a cooled (0 °C) solution of **111** (174 mg, 0.432 mmol) in dry CH_2Cl_2 (25ml) was added 2eq of mCPBA (149 mg, 0.863mmol) in one portion. The reaction mixture was warmed to room temperature and stirred for 24 h after which the reaction mixture was washed with sodium sulfite solution (sat., 2 x 5 ml), sodium bicarbonate (sat., 2 x 5 ml) and water (2 x 10 ml). The organic extract was dried over anhydrous $MgSO_4$, filtered and evaporated to dryness. The resulting oily residue was purified by flash column chromatography (9:1 hexane / ethyl acetate) affording compound **112** as white crystals (130 mg, 72%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.78-0.84 (m, 1H), 0.66-0.69 (m, 1H), 0.68 (s, 3H), 0.87 (t, 3H, J = 7.0 Hz), 0.93 (s, 3H), 0.95-1.54 (m, 14H), 1.72 (dt, 1H, J = 9.0 Hz, 3.0 Hz), 1.79 (dd, 1H, J=12.9 Hz, 7.0 Hz), 1.88 (dd, 1H, J = 14.0 Hz, 11.0 Hz), 1.97-2.07 (m, 2H), 2.02 (s, 3H), 3.29 (d, 1H, J = 5.6 Hz, H-2), 3.67-3.70 (m, 1H, ketal), 3.81-3.86 (m, 1H, ketal), 3.87-3.90 (m, 2H, ketal).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 12.7, 12.8, 13.4, 16.9, 20.5, 21.1, 27.9, 30.7, 31.5, 34.4, 34.6, 38.4, 38.6, 38.7, 39.9, 41.9, 51.9, 53.5, 58.3 (C-2), 60.7, 62.9, 64.8, 83.0 (C-3), 117.4 (C-16), 169.3

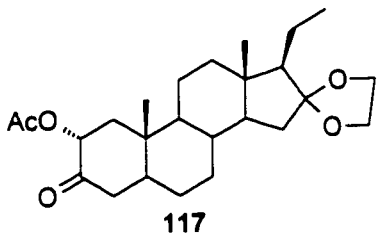
EI-MS (m/z, %): 418 (M^+, 16), 319 (34), 142 (59), 99 (100)

HRMS: Calc. for $C_{25}H_{38}O_5$: 418.27204; Found: 418.27447

MP: 95-100 °C

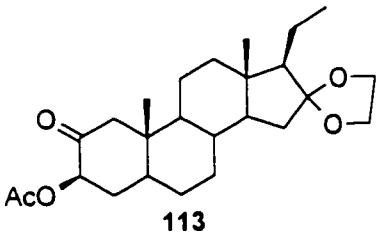
IR (cm^{-1}): 1046, 1333, 1476, 1601, 1745

3β - Acetoxy - 16 - ethylenedioxypregnan - 2 - one 113 and 2α - Acetoxy - 16 - ethylenedioxypregnan - 3 - one 117



117

major



113

minor

In a round bottom flask, compound **112** (25.5 mg, 0.061 mmol) was heated at 160 °C by means of oil bath for 15 min. The resulting yellow oily solution was mounted onto basic alumina column and left there for 24 h. After 24 h it was eluted using 3:1 hexane / ethyl

acetate. The resulting fractions were collected and concentrated in vacou to give a mixture of **117** and **113** as white crystals (17.3mg, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm **major:** 0.73 (s, 3H), 1.11 (s, 3H), 5.27 (dd, 1H, J=12.6 Hz, 7.0 Hz, H-2), **minor:** 0.69 (s, 3H), 0.75 (s, 3H), 5.18 (dd, 1H, J= 11 Hz, 7.2 Hz, H-3), **major + minor:** 0.81-1.11 (m, 4H), 0.89 (t, 3H, J=7.5 Hz), 1.12-1.17 (m, 2H), 1.22-1.69 (m, 8H), 1.70-1.79 (m, 2H), 1.82 (dd, 1H, J=12.9 Hz, 7.0 Hz), 2.13 (s, 3H), 1.99-2.15 (m, 1H), 2.19 (dd, 1H, J=14.0 Hz, 3.6 Hz), 2.25 (dd, 1H, J=12.4 Hz, 9.4 Hz), 2.34-2.48 (m, 1H), 3.68-3.74 (m, 1H), 3.82-3.83 (m, 1H).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm **major:** 74.4 (C-2), 204.0 (C-3), **minor:** 76.1 (C-3), 204.3 (C-2), **major + minor:** 12.8, 13.0, 13.5, 17.0, 20.8, 21.2, 28.3, 31.6, 33.9, 37.3, 38.4, 40.0, 42.2, 43.5, 44.7, 47.8, 51.8, 54.0, 60.7, 63.0, 64.9, 117.4, 170.1.

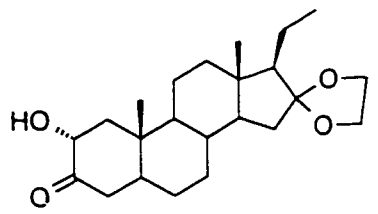
EI-MS (m/z, %): 418 (M^+, 9), 319 (20), 142 (44), 99 (100)

HRMS: Calc. for $C_{25}H_{38}O_5$: 418.27204; Found: 418.27247

MP: 178-184°C

IR (cm^{-1}): 1041, 1094, 1331, 1445, 1726, 1743, 2933, 2962

2α - Hydroxy - 16 - ethylenedioxypregnan - 3 - one <u>118</u>



118

To a crude solution of **117** and **113** (17.3 mg, 0.041 mmol) in 3:1 THF / water mixture at room temperature was added 2eq of LiOH. The resulting mixture was stirred overnight, after which it was diluted with EtOAc. The organic phase was washed with water (2 x10 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide whitish yellow powder, which upon purification by flash column chromatography (3:1 hexane / ethyl acetate) gave the major compound **118** as white crystals (12.4 mg, 80%).

Different route for the synthesis of **118**

To a solution of **112** (26.9 mg, 0.064 mmol) in 3:1 THF / water at room temperature was added 2eq of LiOH. The resulting mixture was stirred overnight, after which it was diluted with EtOAc. The organic phase was washed with water (2 x10 ml) and dried over anhydrous $MgSO_4$, filtered and concentrated in vacuo to provide whitish yellow powder, which upon purification by flash column chromatography (3:1 hexane / ethyl acetate) gave compound **118** as white crystals (8.1mg, 30%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.72 (s, 3H), 0.80-0.93 (m, 4H), 0.88 (t, 3H, J=7.5 Hz), 1.07 (s, 3H), 1.08-1.62 (m, 12H), 1.75 (dt, 1H, J=6.7 Hz, 3.0Hz), 1.81 (dd, 1H, J=12.9 Hz, 7.1 Hz), 2.24 (dd, 1H, J=14.1 Hz, 3.8 Hz), 2.38 (dt, 1H, J=14.0 Hz, 1.2 Hz), 2.45 (dd, 1H, J=12.6 Hz, 7.1 Hz), 3.48 (d, 1H, J=3.3 Hz, OH), 3.69-3.71 (m, 1H, ketal), 3.82-3.83 (m, 1H, ketal), 3.84-3.92 (m, 2H, ketal), 4.20-4.25 (m, 1H, H-2).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 12.8, 12.9, 13.4, 16.9, 21.1, 28.4, 31.6, 33.8, 37.1, 38.4, 39.9, 42.1, 42.3, 48.3, 51.7, 53.9, 60.7, 62.9, 64.9, 72.7 (C-2), 117.4 (C-16), 210.9 (C-3).

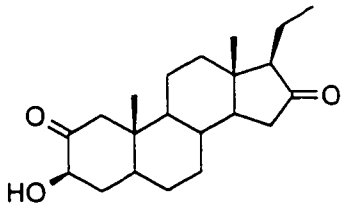
EI-MS (m/z, %): 376 (M^+, 9), 277 (17), 142 (57), 113 (100)

HRMS: Calc. for $C_{23}H_{36}O_4$: 376.26148; Found: 376.25920

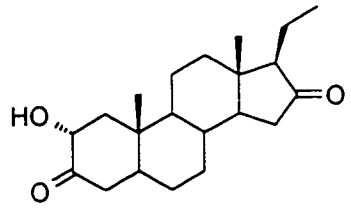
MP: 126-130 °C

IR: 1034, 1046, 1424, 1476, 1713, 3620

3β - Hydroxypregnan - 2, 16 - dione 96 and 2α - Hydroxypregnan - 3, 16 - dione 119



96



119

To a solution of **113** and **117** (132 mg, 0.32 mmol) in aqueous acetone (5 mL), pyridinium tosylate (23.0 mg, 0.095 mmol) was added. The resultant reaction mixture was allowed to reflux for 3 h. The solvent was removed in vacuo to get the residue, which was extracted into ethyl acetate and washed with aqueous solution of sodium bicarbonate and brine. The organic layer was separated, dried and concentrated to get the crude products (**120** and **121**), which were used for the next reaction without any further purification. The crude mixture of **120** and **121** were confirmed from the ^{1} H NMR spectrum, which showed the absence of signal due to ethelenedioxy group in the region of 3.81-3.90 ppm.

Subsequently to a solution of **120** and **121** (106 mg, 0.28 mmol) in a 3:1 THF / water mixture (5 mL) was added 2eq of LiOH (1 M solution, 0.6 mL) at 0°C and stirred for 2 h. After 2 h, the reaction mixture was extracted into ethyl acetate (10 mL) and washed with water (2 mL). The organic layer was separated, dried and concentrated to get the crude residue. The resulting crude mixture was purified by flash column chromatography (3:7

ethyl acetate / hexane) affording the corresponding products **96** (12.0 mg, 13.2 %) and **119** (40.0 mg, 43.2 %) as white solid.

3β - Hydroxypregnan - 2, 16 - dione **96**

The spectroscopic properties were identical with the reported data.

HRMS: Calc. for $C_{21}H_{32}O_3$: 332.2351; found: 332.2356.

MP: 144-145°C.

$[\alpha]_D$: -78° (c 0.47, MeOH).

2α - Hydroxypregnan - 3, 16 - dione **119**

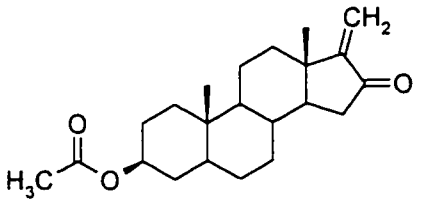
^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 4.20 (dd, J=7.1, 12.0 Hz, 1 H), 3.50 (bs, 1H, OH), 2.46 (dd, J=7.0, 12.5 Hz, I H), 2.39 (t, J=13.9 Hz, 1 H), 2.27 (dd, J=3.7, 14.1 Hz, 1 H), 2.19 (dd, J=7.6, 18.2 Hz, 1 H), 1.92 (dt, J=2.9, 12.5 Hz, 1H), 1.78-0.90 (m, 16 H), 1.08 (s, 3H), 0.97 (t, J=7.5 Hz, 3 H), 0.68 (s, 3 H).

^{13}C NMR (500 MHz, $CDCl_3$): δ ppm 12.8, 13.3, 13.5, 17.5, 21.1, 28.2, 31.8, 33.6, 37.2, 38.0, 38.3, 42.1, 42.2, 48.1, 48.2, 50.1, 53.7, 65.2, 72.6, 210.7, 218.2.

HRMS: Calc. for $C_{21}H_{32}O_3$: 332.2351; Found: 332.2359.

MP: 136-137°C

3β - Acetoxyandrost - 17 (20) - ene 122



122

To a solution of **104** (50 mg, 0.165 mmol) in pyridine (1 ml) was added 1eq of acetic anhydride (15 ml, 0.165 mmol). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with EtOAc then washed with water (3 x 10 ml), the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **122** as white crystals (30 mg, 53%).

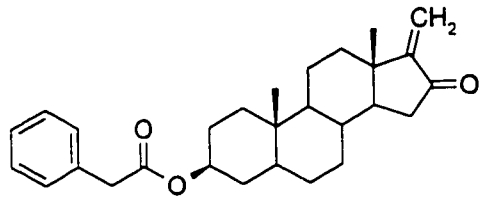
^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.81-0.83 (m, 1H), 0.85 (s, 3H), 0.92 (s, 3H), 0.96-1.03 (m, 1H), 1.18-1.75 (m, 14H), 1.79-1.83 (m, 1H), 1.85-1.95 (m, 1H), 1.97-2.00 (m, 1H), 2.00 (s, #H, OAc), 2.20 (dd, 1H, J=17.5 Hz, 6.9 Hz), 4.66 (m, 1H, H-3), 4.98 (s, 1H, $=CH_2$), 5.76 (s, 1H, $=CH_2$).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 12.2, 19.1, 20.6, 21.4, 27.3, 28.2, 31.8, 33.9, 34.4, 35.2, 35.7, 36.4, 37.9, 42.8, 44.6, 49.3, 54.2, 73.4 (C-3), 111.8 ($=CH_2$), 156.7 (C-17), 170.6 (C=O, OAc), 206.9 (C-16)

FAB (MH^+): Calc. for $C_{22}H_{32}O_3$: 345.2323; Found: 345.2353

MP: 125-127 °C

3β - [(Phenylacetyl)oxy]androst - 17 (20) -ene 123



123

To a solution of **104** (50 mg, 0.165 mmol) in CH_2Cl_2 (2 ml) was added 1.5eq of phenyl acetic acid (30 mg, 0.220 mmol), followed by DCC (34 mg, 0.202 mmol) and DMAP (1.3 mg,). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (5 ml) then washed with water (3x 10 ml), the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **123** as white crystals (30 mg, 45%).

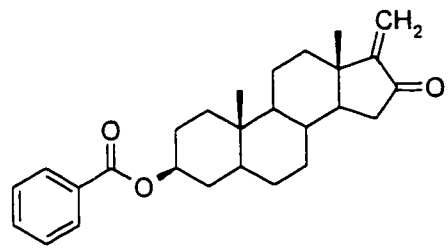
^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.80-0.82 (m, 1H), 0.85 (s, 3H), 0.92 (s, 3H), 0.95-1.02 (m, 2H), 1.23-1.75 (m, 13H), 1.76-1.85 (m, 1H), 1.90-2.00 (m, 1H), 2.00 (dd, 1H, J=17 Hz, 14 Hz), 2.20 (dd, 1H, J=17 Hz, 6.9 Hz), 3.56 (s, 2H, benzylic CH_2), 4.67-4.71 (m, 1H), 4.98 (s, 1H), 5.77 (s, 1H), 7.23-7.31 (m, 5H).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 12.2, 19.1, 20.7, 27.3, 28.2, 31.8, 33.8, 34.4, 35.2, 35.7, 36.4, 37.9, 41.7, 42.8, 44.6 (benzylic C), 49.3, 54.2, 73.9 (C-3), 111.9, 126.9, 128.5, 129.1, 134.3, 156.7 (C-17), 171.1, 206.9 (C-16)

FAB (MH^+): Calc. for $C_{28}H_{36}O_3$: 421.2666; Found: 421.3437

MP: 104-106 °C

3β - [(Benzoyl)oxy]androst - 17 (20) - ene 124



124

To a solution of **104** (50 mg, 0.165 mmol) in pyridine (1 ml) was added 2eq of benzoyl chloride (38 ml, 0.330 mmol). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with EtOAc then washed with water (3 x 10 ml), the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **124** as white crystals (40 mg, 58%).

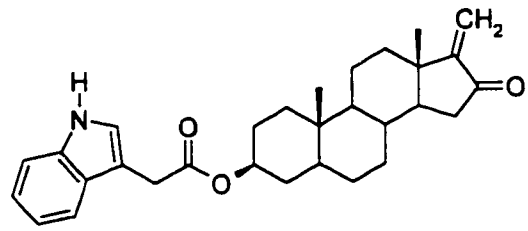
^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.87 (s, 3H), 0.93 (s, 3H), 0.78-1.05 (m, 1H), 1.10 (dt, 1H, J=13.5 Hz, 3.8 Hz), 1.21-1.81 (m, 14H), 1.89-2.04 (m, 3H), 2.21 (dd, 1H, J=17.5 Hz, 6.9 Hz), 4.89-4.96 (m, 1H, H-3), 4.98 (s, 1H), 5.77 (s, 1H), 7.38-8.02 (m, 5H, Ph).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 12.3, 19.1, 20.7, 27.5, 28.3, 31.9, 34.0, 34.4, 35.3, 35.8, 36.5, 37.9, 42.8, 44.7, 49.3, 54.3, 74.0 (C-3), 111.8, 128.2, 129.5, 130.8, 132.7, 156.8 (C-17), 166.0, 206.9 (C-16)

FAB (MH^+): Calc. for $C_{27}H_{34}O_3$: 407.25096; Found: 407.3182

MP: 206-209 °C

3β - [(2 - (3-indolyl)acetyl)oxy]androst -17 (20) -ene 125



125

To a solution of **104** (50 mg, 0.165 mmol) in CH_2Cl_2 (2 ml) was added 1.5eq of indole-3-acetic acid (29 mg, 0.248 mmol), followed by DCC (34 mg, 0.202 mmol) and DMAP (1.3 mg,). The resulting mixture was stirred at room temperature for 24 h. The mixture was diluted with CH_2Cl_2 (5 ml) then washed with water (3 x 10 ml), the organic phase was dried over anhydrous $MgSO_4$, filtered and concentrated to give compound **125** as white crystals (30 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$): δ ppm 0.78-0.86 (m, 1H), 0.85 (s, 3H), 0.92 (s, 3H), 0.94-1.05 (m, 2H), 1.16-1.74 (m, 15H), 1.81-1.84 (m, 1H), 1.89-1.92 (m, 1H), 2.01 (dd, 1H, J=17.5 Hz, 14 Hz), 2.21 (dd, 1H, J=17.5 Hz, 6.9 Hz), 3.72 (s, 2H,), 4.70-4.74 (m, 1H, H-3), 4.98 (s, 1H), 5.77 (s, 1H), 7.09-7.19 (m, 2H), 7.33 (d, 1H, J=8.0 Hz), 7.60 (d, 1H, J=7.9 Hz).

^{13}C NMR (125 MHz, $CDCl_3$): δ ppm 12.2, 19.1, 20.7, 27.3, 28.2, 29.6, 31.7, 31.8, 33.8, 35.2, 35.7, 36.4, 37.9, 42.8, 44.6, 49.3, 54.2, 73.9 (C-3), 108.7, 111.1, 111.9, 118.9, 119.5, 122.1, 122.9, 127.2, 136.1, 156.8 (C-17), 171.5, 207.0 (C-16)

EI-MS (m/z, %): 459 (M^+, 41), 130 (100)

HRMS: Calc. for $C_{30}H_{37}NO_3$: 459.277748; Found: 459.27937

MP: 226-228 °C

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Claims to original research

(1) A new synthesis of dillapiol, 7, starting from sessamol using an ortho directed metallation to introduce a substituent at the C-4 position.

(2) The first syntheses of 5-methoxy-6-(2-propenyl)-4-thiomethyl-1,3-benzodioxole **90a**, and the sulfinyl and sulfonyl analogs, **91a** and **92a**.

(3) The syntheses of three additional 4-thio-, 4-sulfinyl- and 4-sufonyl analogs of the compounds described in claim 2.

(4) The synthesis of trichiliasterone B by modifying Ring A of a previously synthesized intermediate.

(5) The preparation of esters of 3β-hydroxyandrost-17(20)-en-16-one for the purpose of evaluating their anti-cancer activity.