ISOLATION, CHARACTERISATION AND SYNTHESIS OF INSECTICIDAL NATURAL PRODUCTS OF THE MYRTACEAE FAMILY

by

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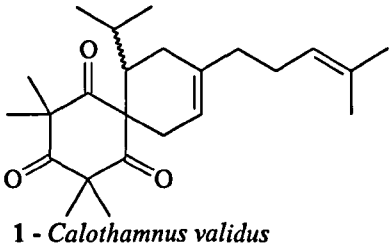
ABSTRACT

New insecticidal natural products are required to find compounds with higher intrinsic activities to lower field application rates, and with novel modes of action to combat insect pest species which have developed resistance to current commercial insecticides.

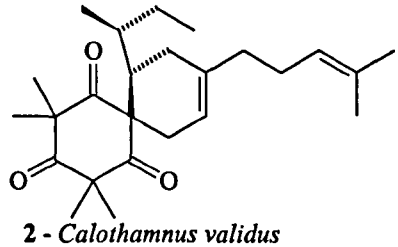
Using a taxanomic approach, studies on plants of the Myrtaceae family led to the isolation and characterisation of a range of insecticidal natural products **1 - 9** (figure 1). These compounds are all structually related as they contain a tetramethylcyclohexenedione group, attached to either a terpene or a phloroglucinol moiety. Seven of the nine compounds **(1 - 6, 9)** are novel. For compounds **7** and **8**, no synthesis had been previously reported.

The compounds are active against a range of insect species, although in general they are less active than commercial natural products. Further tests show some of the compounds are potent antifeedants.

Synthesis of seven of the nine natural products **(1 - 5, 7, 8)** by short, convergent, stereospecific and high yielding routes was achieved. The synthetic routes were devised to mimic the postulated biosynthesis of the compounds. Reaction of syncarpic acid, an aldehyde and pyrrollidine formed a Mannich base, which on elimination gave a key alkylidene intermediate. This key intermediate was reacted, with either terpenes in Diels-Alder reactions or with phloroglucinols in aromatic alkylation reactions, to synthesise seven of the natural products.



1 - *Calothamnus validus*



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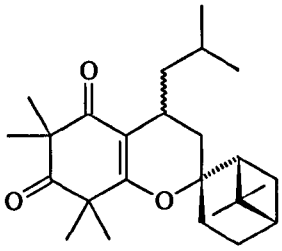
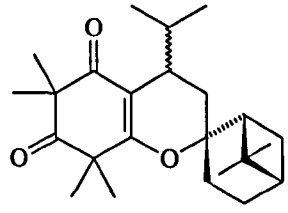
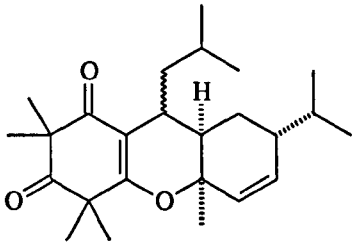


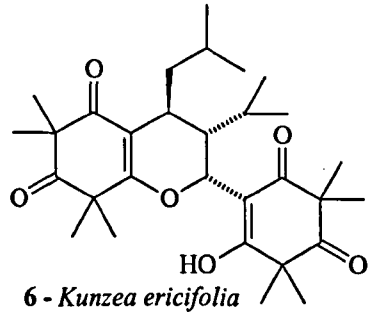
3 - *Eucalyptus ficifolia*
Kunzea ericoides



4 - *Calothamnus validus*



5 - *Callistemon viminalis*



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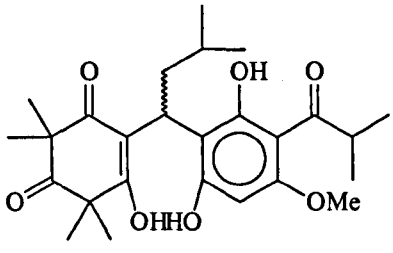
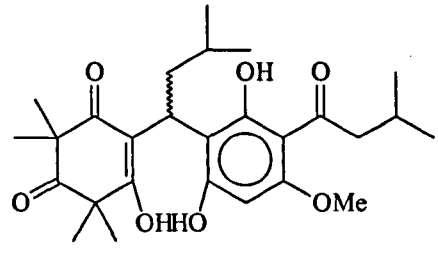
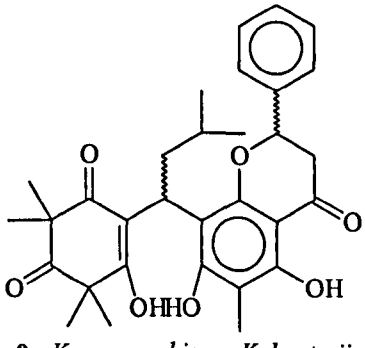


7 - *Kunzea aff. micromera, K. baxterii*
K. ericoides, K. sinclairii



8 - *Kunzea aff. micromera, K. baxterii*
K. ericoides, K. sinclairii



9 - *Kunzea ambigua, K. baxterii*

Figure 1 - Natural products isolated from plants of the Myrtaceae family

ACKNOWLEDGEMENTS

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I would also like to express my gratitude to Monique Simmonds and colleagues at the Royal Botanical Gardens, Kew, for their taxonomic knowledge in providing plant material and their expertise in antifeedant and insecticidal bioassays.

Finally, I would like to thank the British Technology Group for funding this work.

TABLE OF CONTENTS

ABBREVIATIONS

Ac -	Acetyl
COSY -	Correlation spectroscopy
DEAD -	Diethylazodicarboxylate
DEPT -	Depolarisation transfer
DMSO -	Dimethylsulfoxide
IR -	Infrared
LD_{50} -	Lethal dose which kills 50% of a population
LDA -	Lithium diisopropylamide
LICA -	Lithium n-cyclohexylisopropylamide
LTMSA -	Lithium bis-trimethylsilylamide
p-TSA -	Para-toluenesulfonic acid
TFA -	Trifluoroacetic acid
TFAA -	Trifluoroacetic anhydride
TMS -	Tetramethylsilane
UV -	Ultraviolet

CHAPTER 1

THE MODE OF ACTION OF INSECTICIDAL PHYTOCHEMICALS

1.1 INTRODUCTION

Throughout history, man has utilized plants not only as a source of nourishment, but also as a raw material providing a rich source of useful substances. These have included primary plant metabolites such as oils, resins, waxes, fibres and carbohydrates, and a large number of specific plant secondary metabolites. The classical view of these secondary constituents was that they were waste products of metabolism, which accumulated in tissues as they could not be excreted. Subsequent research, with over 10,000 secondary plant metabolites now chemically defined, indicated that many of these chemicals were beneficial to the producer. It is thought that plant taxa may have evolved these secondary metabolites as a highly sophisticated defense system against animals, insects, pathogens, microorganisms and even weeds. For thousands of years,[1] many of these chemicals have been exploited by man.

The need to protect our food supply from a range of pests is a major worldwide problem. Despite an enormous expenditure on agrochemicals, for instance $7,500 million is currently spent annually on insect control, approximately one third of the global food production is reportedly destroyed each year by pests.[2]

Many of the earliest ways to protect crops from insects were based on plant extracts,[3] and these were used both in the field and for crop storage after harvest. The first discovery of the value of plants as insecticides is not known, although it is documented that the Romans used two species of hellebore as rat and mouse poisons, as well as insecticides, whilst the Chinese discovered

the insecticidal properties of Derris.[4] To date, over 2000 plant species have shown pesticidal properties[2] and several hundred insecticidal compounds have been isolated and characterised.[5]

From 1940 onwards, with the advent of synthetic chemicals, the use of botanical insecticides diminished greatly. Only five botanical pesticides are currently registered for use in the USA (see table 1.1), and the United Kingdom Pesticide Manual[6] recognises only pyrethrum, rotenone and nicotine as important for practical insect control.

Table 1.1 - Botanical pesticides used in the USA.

Plant	Insecticidal Constituent	% A.I in concentrate	Cost - US $/Kg
Pyrethrum	Pyrethrins	25	75
Rotenone	Rotenoids	73	3
Ryania	Ryanodine alkaloids	0.1	3
Sabadilla	Veratrum alkaloids	0.8	8
Neem	Azadirachtin	25	37

Natural products have in general been superseded by a range of synthetic compounds belonging to three classes; pyrethroids, carbamates and organophosphates. These show greater intrinsic insect toxicities and improved physical properties over their natural counterparts.

There is a continuing search for new botanical insecticides for three main reasons:-

i) A need for more potent insecticides requiring lower field application rates.

ii) An increasing public assumption that natural products are safer than synthetic insecticides. This has led not only to a large increase in 'green' insecticides for garden use, but also in increasing pressure for farmers to produce food free from synthetic pesticides. A good example of the weakness of this assumption relates to pyrethroids. In fact the natural pyrethrins show a much greater mammalian toxicity than the related synthetic compounds, and moreover because of their lower intrinsic activities, the natural pyrethrins have overall a much lower safety factor. Furthermore some of the most toxic compounds known to man are natural, and so correlations between natural products and human safety should not be made without attention to the particular case in question.

iii) The third and most important factor is that with many years of continued use of synthetic insecticides, over five hundred insect species[7] have developed resistance. This has caused the three main classes of insecticides to become less effective, and in some cases totally ineffective, in the control of certain pest insect populations.

There are three ways in which insects are resistant to insecticides. Increased cuticle thickness reduces the amount of insecticide that can enter the insect, increased metabolism of the insecticide before it reaches the site of action and target site insensitivity which is caused by a mutation that affects

the insecticides site of action. For instance with pyrethroid insecticides two well defined strains of *kdr* and *super-kdr* houseflies (*Musca domestica* L.) have been shown to contain different modifications to the binding sites of pyrethroids. These modifications can confer over 500 fold resistance for certain compounds.[8]

To kill these resistant populations with modified sites of action, insecticides with alternative modes of action are required. Hence, there has been a resurgence of interest in novel insecticidal natural products with new modes of action, which can be incorporated into an integrated pest management strategy.[9]

Of the many hundreds of insecticidal natural products already isolated and characterised, some offer hope of development as botanical insecticides. This potential, and the factors that affect suitability will be discussed in this chapter.

Bioassay data are clearly vital, but extensive insecticidal data against a range of insect species are rarely reported, making analysis of potential difficult to assess.

The site of action is highly relevant, but may be similar in both insects and man, and hence many natural compounds reported to have insecticidal activity also have high mammalian toxicity and general biocidal effects. For instance cocaine has been reported to show insecticidal effects.[10]

1.2 THE MODE OF ACTION OF BOTANICAL INSECTICIDES

The site of action of many insecticidal natural products has been elucidated, and can be categorised into the following groups.

1.2.1 Natural Products Acting on the Nervous System

The ability of natural products to disrupt the functioning of the insect nervous system is one of the most important modes of action and accounts for two of the three main classes of synthetic insecticides along with a host of natural products.[11] Within the nervous system a range of active sites have been elucidated.

1.2.1a The Sodium Channel

The voltage sensitive sodium channel mediates the sodium permeability of the cell membrane and has been shown to possess multiple binding domains, some of which are targets for insecticides.

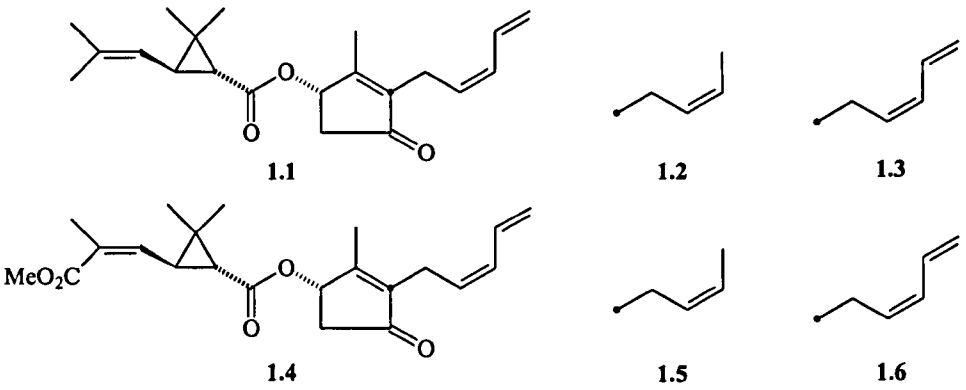
i) Pyrethrins from *Tanacetum cinerariaefolium*

The pyrethrins **1.1 - 1.6** (figure 1.1), which are currently the most economically important group of natural plant insecticides, are found in the pyrethrum plant *Tanacetum cinerariaefolium.* Early discovery of their use may well have been accidental,[12] but commercial use originated in Persia in the

early 1800's although secrecy about its production makes this difficult to pin point accurately. By 1828 pyrethrum was processed as a commercial insect control agent, and reached a peak in the late 1930's, with countries such as Japan growing 72 000 acres annually. Currently 25 000 tons of pyrethrum flowers are grown each year in countries such as Kenya, Tanzania and Ecuador.[13]

From 1910 to 1916, Staudinger and Ruzicka[14,15] extensively investigated the active principles of pyrethrum and published a series of papers in 1924 reporting the separation and partial identification of the two primary active principles of pyrethrum, pyrethrin I **1.1** and pyrethrin II **1.4**. Gnadinger, using the previous work as a basis, continued the study and after improving the assay methodology, wrote three important texts[16,17,18] on pyrethrum totalling almost 1000 pages.

In total six insecticidal compounds **1.1** - **1.6** from *Tanacetum cinerariaefolium* have been isolated and fully characterised.[19,20] Studies with related members of the family Compositae yielded no other significant source. The six compounds isolated are esters of two acids with three alcohols. Esters of chrysanthemic acid are called pyrethrin I **1.1**, cinerin I **1.2** and jasmolin I **1.3** and the esters of pyrethric acid are called pyrethrin II **1.4**, cinerin II **1.5** and jasmolin II **1.6**.



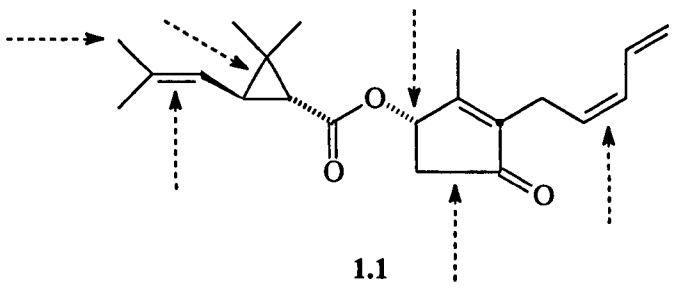
1.1 1.2 1.3

1.4 1.5 1.6

Figure 1.1 - Naturally occurring pyrethrins.

Although all six compounds are insecticidal, pyrethrin I **1.1** is the most effective for killing insects whilst pyrethrin II **1.4** provides much of the rapid knock-down action against flying insects.[21] The ratio of the six compounds was shown to vary slightly between different parts of the plant and where the plant is grown, but in general the two pyrethrins each account for approximately one third of the mixture, the cinerins each about one tenth and the jasmolins one twentieth.

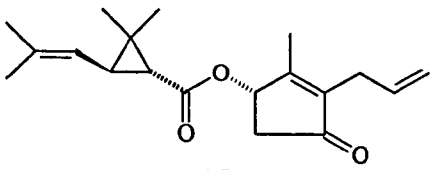
The natural pyrethrins show good insecticidal activity and low mammalian toxicity, but in general are too unstable to control pests of agricultural crops. This is due to six photolabile centres[22] (figure 1.2) which result in lifetimes on crops of only a few hours.



1.1

Figure 1.2 - Photolabile centres of pyrethrin I.

In 1949 Schechter *et al*[23] announced the synthesis of allethrin **1.7** (figure 1.3). The insecticidal activity of this compound excited great interest as it acted more rapidly and with greater efficacy against houseflies, than the natural pyrethrins. Structure activity relationships culminated in the synthesis of compounds such as deltamethrin **1.8**[22] in 1977. These are some of the most powerful commercial insecticides against a wide range of insect species, having activities more than a thousand times greater than pyrethrin I **1.1**, a useful lifetime on crops of 15 - 30 days and application rates lower than 50 g ha^{-1}. Since then almost every part of the molecule has been replaced by a unit of analogous structure without losing activity, and in many cases increasing it.



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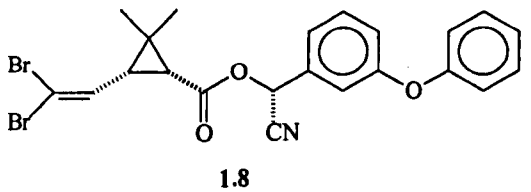

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Figure 1.3 - Structures of synthetic pyrethroids.

Information on the mode of action of the natural pyrethrins is limited.[24] An early study[25] investigated the action potentials in the giant-nerve pathway of the cockroach *Blatta orientalis*. Preparations were treated with pyrethrum extract and induced bursts of action potentials in the giant fibre pathway followed by a total blockade to cercal stimulation. Further studies with arthropods and crustaceans showed that bursts of action potentials in nerve and muscle preparations were produced.

Major studies on the mode of action of the synthetic pyrethroids have given us a much greater understanding of the bioactive sites. In summary, experimental data suggested that the primary insecticidal activity arises from interaction with the neuronal voltage-sensitive sodium channel. This action causes slow inactivation of the gating kinetics giving prolonged sodium currents during membrane depolarisations. Although the site of action has not been fully characterised, it is thought to be a unique site on the channel that is coupled allosterically to three well-characterised neurotoxin recognition sites. Within the site it is unclear if there is one or two binding domains;[26] generalities about the size and shape of the binding pocket have been drawn from analysis of structure activity relationships and from molecular modelling studies.

Further information on the site has been gathered from studies with insect strains with defined resistance mechanism, which has enabled analysis of mutations with modified sites of action.[27]

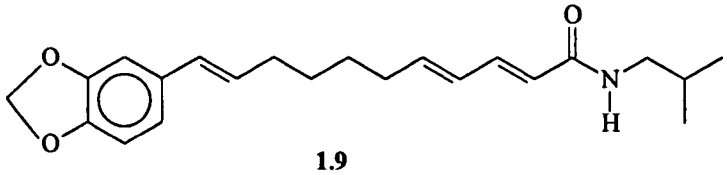
The low toxicity of pyrethrins to mammals has enabled them to be used safely throughout the world. This favourable toxicity profile is due to the

compound's ability to penetrate rapidly and to interact with sites of action within insects, but in mammals the compounds are degraded oxidatively and hydrolytically to polar metabolites and subsequently excreted.

The pyrethrins will continue to have widespread agrochemical use, especially in third world countries, although resistant insect populations will become an increasing problem.

ii) Isobutylamides from *Piper nigrum*

A group of naturally occurring isobutylamides from plants of the Rutaceae and Compositeae families, have shown good insecticidal and knockdown activities. These compounds, such as pipericide **1.9** from *Piper nigrum*, black pepper, and affinin **1.10** from *Heliopsis longipes* (figure 1.4) have had limited use, although a range of synthetic analogues to study structure activity relationships have been synthesised.[28]



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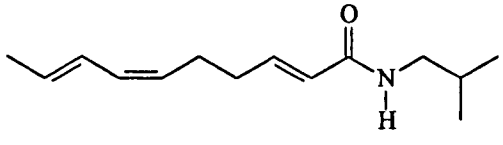


1.10

Figure 1.4 - Structure of two N-alkylamides.

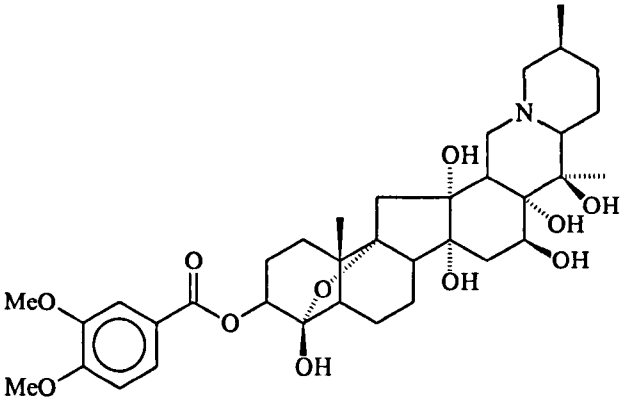
Experimental data have shown that N-alkylamides act on the sodium

channel, but *in vivo* and *in vitro* studies with pyrethroid resistant American cockroaches (*Periplaneta americana*) have shown no cross resistance to N-alkylamides, suggesting a different site of action. Subsequent studies[29,30] have indicated that N-alkylamides exert an effect at the activator recognition site (site 2, based on the classification of Catterall) which has been previously characterised by alkaloids such as veratridine **1.11** (see below).

An important feature of N-alkylamides is that they have selective potency against *super-kdr* pyrethroid resistant housefly (*Musca domestica* L.) strains[31] and hence may become important as control agents against certain resistant insect species.

iii) Veratrum alkaloids from *Schoenocaulon officinale* (Liliaceae)

The powdered seeds of *Schoenocaulon officinale*[32] have had limited use as a botanical insecticide, and contain alkaloids such as veratridine **1.11.**



1.11

Figure 1.5 - A veratrum alkaloid.

As mentioned previously, the mode of action of veratridine **1.11** is at site 2 of the sodium channel, identical to the isobutylamides.

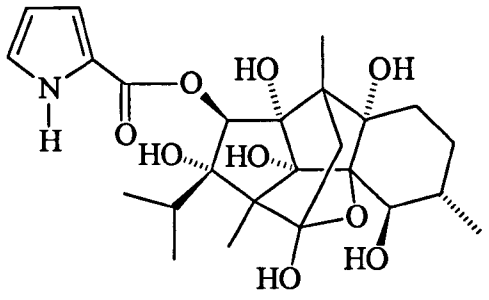
These alkaloids are toxic to mammals with a LD_{50} of 12.5 mg/kg. Because of this, their use as botanical insecticides has diminished greatly over recent years and their future looks limited.

1.2.1b The Calcium Channel

The calcium channel mediates calcium release in the excitation-contraction (EC) coupling of striated muscle. The EC coupling occurs at the triad junction of the transverse tubule membrane and the sarcoplasmic reticulum.

Ryanodine from *Ryania speciosa*

Ryania speciosa is a member of the Flacourtiaceae family and is found in tropical America. The leaves, stems and roots of this small tree contain the insecticide ryanodine **1.12**. This work represented the first example of screening plant extracts for insecticidal activity to give a commercially successful natural product. Ryanodine **1.12**[33] is a complex bridged diterpene heptol (figure 1.6), and is an ester of ryanodol.[34] Multi-step synthesis of this complex molecule was achieved by Deslongchamps *et al*[35] although large scale synthesis is not a viable commercial proposition. The natural product **1.12** was patented in 1946 by Merck & Co under the tradenames 'Ryanex' and 'Ryanicide' although its use was limited due to shortages of material.



1.12

Figure 1.6 - Structure of ryanodine.

Extensive mode of action studies have shown that ryanodine **1.12** influences EC coupling at the calcium release channel.[36,37] The ryanodine receptor of rabbit skeletal muscle has been investigated, by cloning and sequencing the complementary DNA to obtain the complete 5037 amino acid sequence.[38]

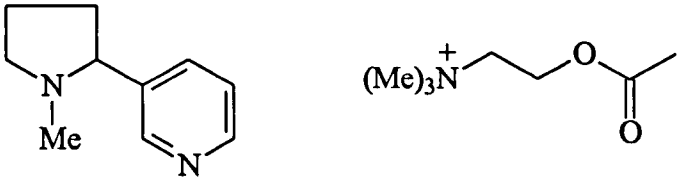
This natural product has in general been superseded by other more easily obtained botanicals with higher insect toxicities.

1.2.1c Acetylcholine Receptors

Acetycholine **1.14** is a neurotransmitter which transports signals between nerves, by releasing and binding to acetylcholine receptors.

i) Nicotine 1.13 from *Nicotiana rustica* L.

Over the centuries, some of the most important natural alkaloids used in insect control were nicotine **1.13** (figure 1.7) and related nicotinoids. Many *Nicotiana* species contain these compounds, including the familiar tobacco plant *Nicotiana tabacum* L., and *Nicotiana rustica* L. which contains between 2 - 8 percent in the leaves. The use of these plants as insecticides dates back over 300 years, and parts of Europe were cultivated solely for their nicotine content.



1.13 **1.14**

Figure 1.7 - Structure of nicotine **1.13** and acetylcholine **1.14**.

Their mode of action involves binding at acetylcholine receptors[39] in the nervous system, but as this occurs in both mammals and insects they are relatively toxic to man. Studies have shown that nicotine is a good mimic of acetylcholine **1.14** as it possesses a highly basic nitrogen protonated at physiological pH, and the pyridine nitrogen hydrogen bonds to the receptor in a similar way as the carbonyl oxygen of acetylcholine. The spacing between the nitrogen atoms is also similar to that between the nitrogen atom and the carbonyl oxygen in acetylcholine.

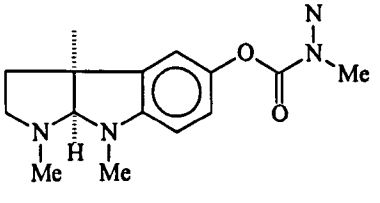
Nicotine **1.13** is lethal to most insects except the tobacco hornworm,

which as a specialist feeds on doses which are fatal to man. Because of its high toxicity along with high production costs and relatively poor insecticidal activity, use diminished greatly from its peak in the mid 1900's when over 500,000 Kg of nicotine sulfate were used in insect control.

Other compounds acting on the same receptor include methyllycaconitine from *Delphinium brownii*[40] which shows high mammalian toxicity, and imidacloprid[41] a synthetic compound which has recently been introduced into the insecticide market and has excellent potential.

ii) Physostigmine from *Physostigma venenosum*

The natural product physostigmine **1.15**, extracted from the calabar bean *Physostigma venenosum*, is insecticidal, although it is unsuitable for use in practice as it cannot penetrate the insect cuticle. Lipid soluble analogues with activity have subsequently been developed, such as Carbaryl **1.16** and Temik **1.17** (figure 1.8). These compounds inhibit acetylcholine esterase, which is important as the breakdown of acetylcholine is suppressed, and repetitive firing in the synapses occurs preventing the transmission of succeeding messages.



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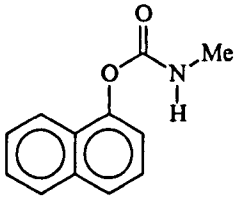

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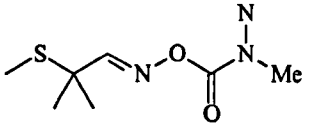


1.17

Figure 1.8 - Natural and synthetic carbamates.

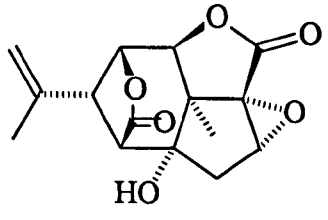
1.2.1d GABA Receptors

γ-Aminobutyric acid (GABA) is the main neurotransmitter in neuromuscular junctions and the central nervous system of insects. GABA receptors are ligand-gated ion channels containing a chloride channel.

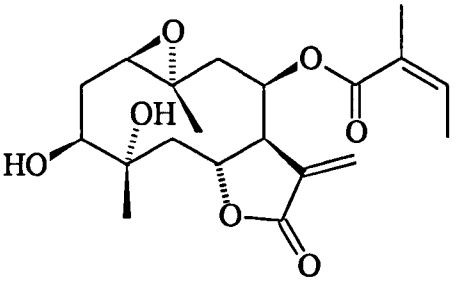
Two insecticide binding sites on the receptor are known.[42] One site interacts with GABA-gated chloride channel activators such as the avermectins. The second site is a noncompetitive blocker site where a limited number of natural products are known to act.

PTX from *Anamirta cocculus* and argophyllin A from *Helianthus annuus*

PTX **1.18**[43] and argophyllin **1.19**[44] (figure 1.9) have been shown to be noncompetitive blockers of GABA receptors. This is a novel site of action for insecticides. Unfortunately, they have too high mammalian toxicities for botanical use.



1.18



1.19

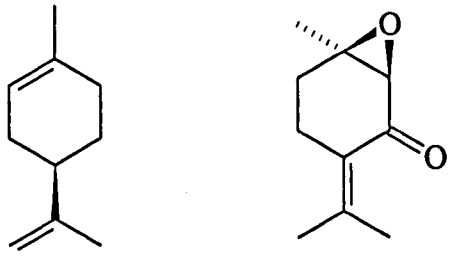
Figure 1.9 - GABA active natural products.

1.2.1e Neurotoxic Compounds with Unknown Modes of Action

Specific neurotoxic modes of action have been elucidated for a range of secondary metabolites. Further to these, various other compounds exhibit neurotoxic effects, but their sites of action have not been elucidated.

Monoterpenoids

A range of monoterpenoids have shown modest insecticidal activities.[45] They include (R)-(+)-limonene **1.20**[46] found in citrus oils, and pugelone-1,2-epoxide **1.21** (figure 1.10). Studies with pugelone-1,2-epoxide have suggested acetylcholine esterase inhibition,[47] whilst other studies have investigated electrophysiology in earthworms.[48] In general these compounds are too volatile for insecticidal use, although they have been used as greenhouse fumigants.

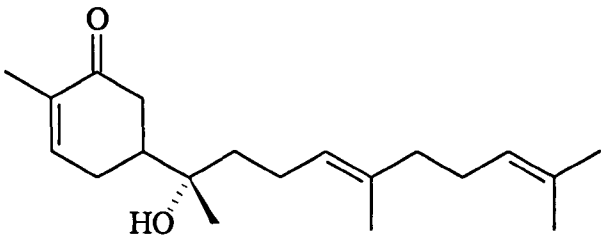


1.20 **1.21**

Figure 1.10 - Insecticidal monoterpenoids.

Diterpenoids

Information on diterpenes with neurotoxic activity is limited to a natural product **1.22** isolated from *Croton linearis*.[49]



1.22

Figure 1.11 - A diterpene from *Croton linearis.*

The behaviour of treated insects indicates neurotoxic effects such as antennal cleaning and sporadic bursts of running. By 24 hours, their legs became stiffened and was followed by paralysis, narcosis and death. Limited bioassay data precludes determination of future botanical use.

1.2.2 Natural Products Acting as Respiration Inhibitors

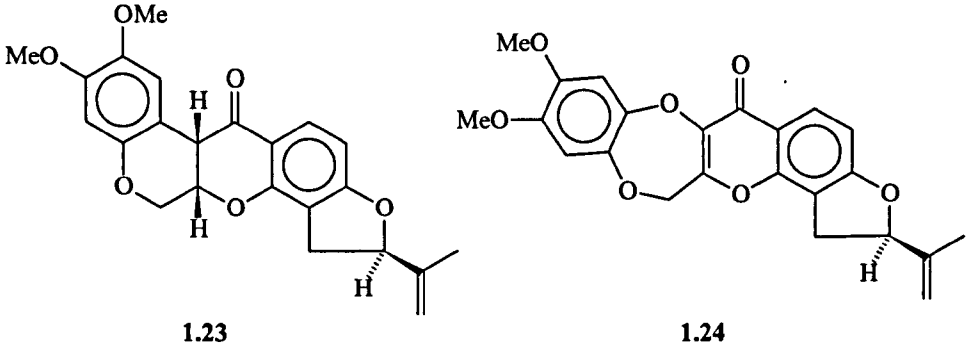
The respiration pathway in the mitochondria of cells has been extensively studied. There are three sites of energy conservation within the respiratory chain and these three regions have been named Site 1, 2 and 3. Given the complexity of these regions, for instance the enzyme complex of site 1 consists of at least seven subunits and has a molecular weight of 800,000 daltons, sites of insecticide action cannot be localised with high resolution.

1.2.2a Site 1 Mitochondrial Inhibitors

Rotenoids from *Derris elliptica*

Rotenone **1.23**[50] (figure 1.12), the main constituent of 'Derris powder' is a well known botanical insecticide and is still popular with gardeners today as a 'green' insecticide. It has been isolated from the roots of various Leguminosae including *Derris*, *Lonchocarpus* and *Tephrosia* species. The original use of these plants are as fish poisons, when they were dragged through the water to disable fish before capture, and in the East Indies in 1848 insecticidal use was reported. Until the advent of DDT, rotenone was one of the most widely used insecticides.

Isolation of related natural products is currently under investigation, for instance novel oxa-dehydrorotenoids **1.24** have recently been found,[51] although none has yet shown increased insecticidal properties.

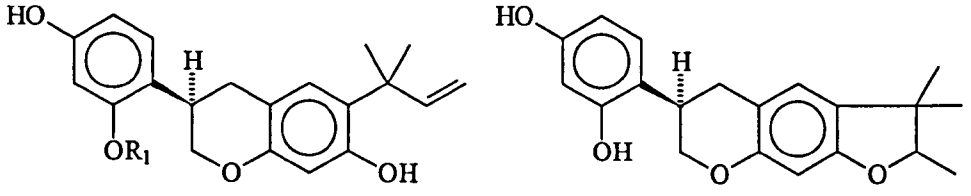


1.23 **1.24**

Figure 1.12 - Structure of rotenoids.

The A, B, C, D rings of rotenoids were thought to be necessary for insecticidal activity although isoflavans **1.25 - 1.27** isolated from *Milletia*

racemosa (figure 1.13) have shown promising insecticidal activities.[52] These compounds have clear structural similarities to rotenone **1.23**.



R_1 = H **1.25**
R_1 = Me **1.26**

1.27

Figure 1.13 - Structure of isoflavans from *Milletia racemosa.*

The mode of action of rotenone **1.23** has been established as a site 1 respiratory NADH / ubiquinone oxidoreductase inhibitor.[53,54]

Unfortunately, rotenone **1.23** does exhibit some human toxicity and large doses cause numbness, nausea, vomiting, muscle tremors and tachypnea.

The complex structure of rotenoids has precluded extensive structure activity relationships, although a short and versatile synthetic route involving a radical coupling[55,56] has enabled the core structure of the rotenoid skeleton to be made in good yield.

Rotenoids will continue to have an important role in the botanical insecticides market.

Acetogenins from *Annona squamosa*

A range of biological activities has been reported for *Annona squamosa*, thought until recently to be due to only one compound annonaine **1.28**, a benzoisoquinoline alkaloid. Subsequent research on various *Annona*

species has yielded a series of polar insecticidal compounds called acetogenins (figure 1.14).[57]

In total, over 90 acetogenins have been isolated from the genera *Annona*, *Asimina*, *Goniothalmus*, *Rolliniana* and *Uvaria* and these have been subgrouped into three structural types:

i) Compounds with adjacent bis-tetrahydrofuran rings - These structures include uvaricin **1.29**, the first acetogenin to be isolated, annonin 1 **1.30** and bullatacin **1.31**.[58]

ii) Compounds with a single tetrahydrofuran ring - e.g. annonacin **1.32**.

iii) Compounds with non-adjacent bis-tetrahydrofuran rings - a small subgroup comprising of three compounds of unknown stereochemistry e.g. gigantecin **1.33**.

The mode of action has been extensively studied. Pharmacological screening at Glaxo investigated over 30 bioassay systems. The results showed only one mode of action, inhibition of mitochondrial NADH dehydrogenase at complex 1. Further studies have confirmed this result.[59,60]

Acetogenins have been patented for insecticidal use, although the cytotoxic potencies of these compounds limits their widespread agricultural use.

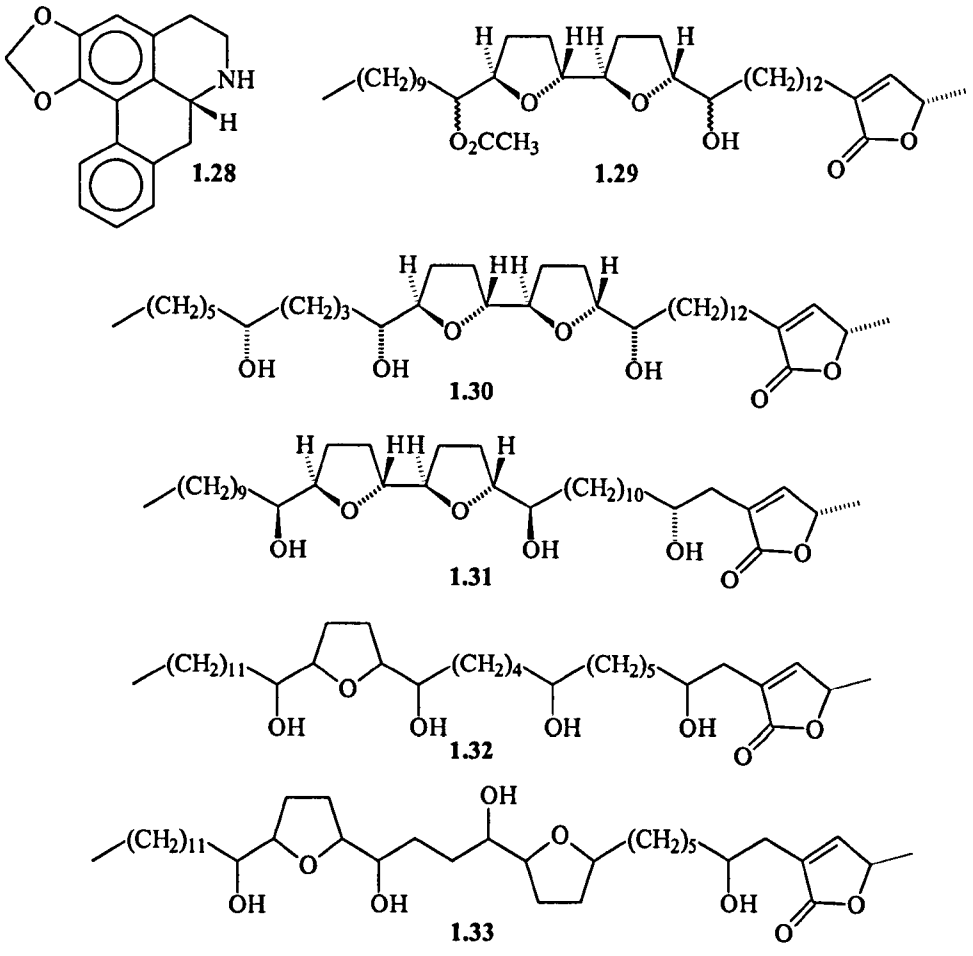


Figure 1.14 - Structure of annonaine **1.28** and various acetogenins.

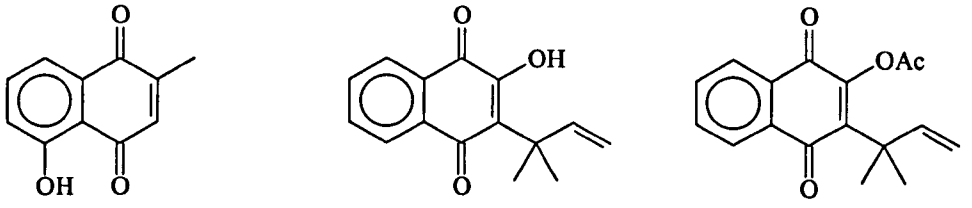
1.2.2b Site 3 Mitochondrial Inhibitors

Naphthoquinones

The general cytotoxic nature of naphthoquinones has long been recognised. For instance plumbagin **1.34** exhibits various biological activities including insecticidal and antifeedant.[61]

Recently hydroxynaphthoquinones **1.35, 1.36** have been isolated from

the plant *Calceolaria andina* (figure 1.15).[62,63] These compounds **1.35, 1.36** exhibit high insecticidal activity against a range of insect species, and low mammalian toxicity. For instance, activities against sucking pests such as whiteflies *Bemisia tabaci* and mites *Tetranychus urticae* are considerably greater than the pyrethrins and are comparable to those of commercial synthetic insecticides.



1.34 **1.35** **1.36**

Figure 1.15 - Structure of insecticidal naphthoquinones.

The mode of action of various synthetic hydroxy-naphthoquinones has been established as they act as inhibitors of mitochondria at complex 3.[64] Ongoing studies have indicated that there may in fact be more than one mode of action.[65]

Overall these natural products, with insecticidal activities comparable to those of commercial synthetic compounds, have excellent prospects as botanical insecticides; patents on natural products[66] and synthetic analogues[67] have been filed recently.

1.2.3 Photoactivated Insecticides

Over the last twenty years, many studies[68,69] have investigated the importance of light in promoting insecticidal activity. Initial work was with synthetic dyes, and this was continued by analysis of the light activation of a range of plant secondary metabolites.

The mode of action of photosensitizers from plants[70] occurs by one of three mechanisms:-

i) Photo-oxidation yielding singlet oxygen - This occurs by light excitation of the sensitiser from the ground state to the first excited state which by crossing leads to the formation of an excited triplet state.

$$S_0 \rightarrow {}^1S \rightarrow {}^3S$$

The excited triplet state transfers its excitation energy to oxygen leading to the production of singlet oxygen. The sensitiser returns to its ground state.

$${}^3S + {}^3O_2 \rightarrow {}^1S + {}^1O_2$$

This activated form of oxygen has been shown to cause biological damage by oxidation of compounds such as lipids, carbohydrates and proteins.

ii) Photo-oxidations yielding superoxide radicals - This less common mechanism occurs by a light adsorption series of electron transfer processes giving superoxide radicals $O_2^{\cdot-}$ which subsequently cause biological damage.

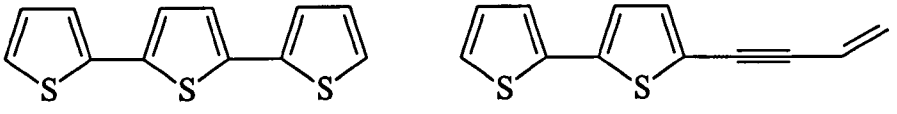
iii) Intercalation with DNA - A double bond of the sensitizer aligns with pyrimidine double bonds and under light activation, the excited state sensitiser undergoes cycloaddition reactions, forming mono- or di-functional adducts by interstrand cross linking. This can cause cell death by disruption of DNA

duplication and transcription.

Phototoxins can be grouped into the following classes:

i) Thiophenes

This class of natural products[69] is exemplified by the compound α-T **1.37** isolated from the roots of the African marigold *Tagetes erecta* (figure 1.16). It is a relatively stable crystalline compound and acts by photo-production of singlet oxygen. α-T **1.37** and related compounds **1.38** have been isolated from genera of the Asteraceae including *Adenophyllum, Chrysactinia, Dyssodia, Eclipta, Flaveria, Nicolletia* and *Tagetes.*



1.37 **1.38**

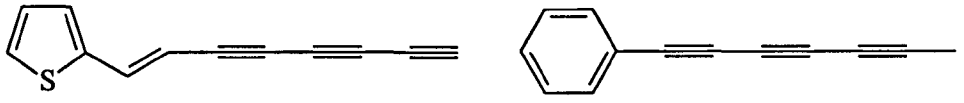
Figure 1.16 - Terthienyl natural products.

The synthesis of α-T **1.37** has been achieved in good yield by Friedel-Crafts formation of a diacyl bridge between two thiophenes, and reaction with Lawesson's reagent to form the central thiophene.[71] Related natural compounds have been synthesised by palladium-catalysed reaction of iodothiophenes and acetylenes.[72]

ii) Polyacetylenes

Over 20 photoactivated polyacetylenes e.g. compound **1.39** (figure

1.17), isolated from the Asteraceae family, have shown insecticidal activity. They show many inter-relations with the thiophenes, although there are indications that some polyacetylenes **1.40** may have an oxygen independent mode of action.[73]

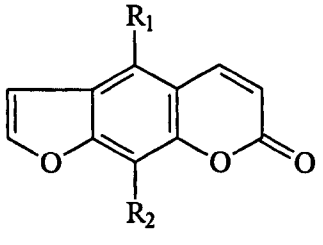


1.39 **1.40**

Figure 1.17 - Various polyacetylenes.

iii) Furanocoumarins

The mechanism of action of phototoxic furanocoumarins **1.41 - 1.44** has been elucidated as intercalation with DNA (mechanism iii)



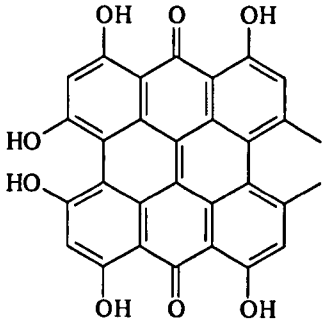
$R_1 = OCH_3, R_2 = H$	**1.41**
$R_1 = H, R_2 = OCH_3$	**1.42**
$R_1 = R_2 = H$	**1.43**
$R_1 = R_2 = OCH_3$	**1.44**

Figure 1.18 - Structures of phototoxic furanocoumarins.

Not all insecticidal furanocoumarins are phototoxic,[74] as some are active in the dark and have shown inhibition of insect cytochrome P_{450}'s.[75]

iv) Extended Quinones

Many quinones, exemplified by hypericin **1.45**,[76] found predominantly in the Hypericaceae, are photodynamic compounds.



1.45

Figure 1.19 - Structure of hypericin.

An important factor for natural phototoxins is the wavelengths of light needed to confer activity. For hypericin **1.45**, wavelenghts in the visible region (500 - 600 nm) are required, whereas for α-T **1.37** ultraviolet wavelenghts (320 - 400 nm) are needed.

These unique modes of action are useful against resistant strains of insects but although some phototoxins are patented, in general they are too biocidal and also in some cases too unstable as insecticides.

1.2.4 Insect Growth Regulators

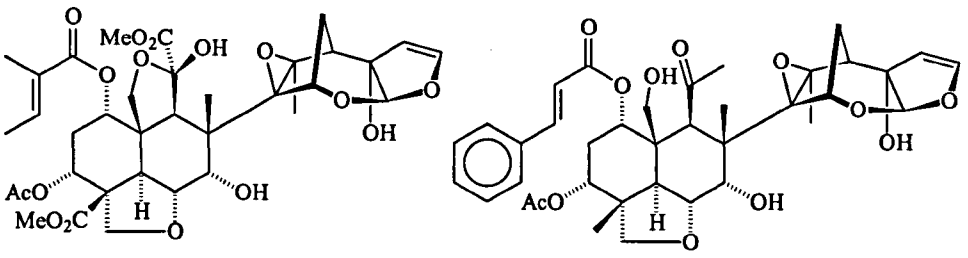
Insect growth regulators have the advantage of an insect specific mode of action. There are two main groups: Chitin synthesis inhibitors which disrupt moulting, and juvenile hormone analogues which interfere with metamorphic changes and reproduction.

A large variety of higher terpenoids show growth disruption, moulting inhibition and antifeedant effects.[77] The most interesting and well studied of these compounds is azadirachtin **1.46**.

***Azadirachta indica* and related species**

The insecticidal properties of extracts of the Meliaceae family have been well established, and active tetranortriterpenoids have been isolated (figure 1.20) from plants such as *Azadirachta indica, Melia azedarach, Melia dubia, Melia toosendan* and *Khaya nyasica.*[78]

The Neem tree *Azadirachta indica* has been used, for many hundreds of years, as a natural insecticide in India, and contains an insect antifeedant azadirachtin **1.46**. It was first isolated in pure form in 1968, but the structure was not fully elucidated until 1985. Related structures such as compound **1.47** have also been elucidated.[79] Synthesis of azadirachtin **1.46** has yet to be achieved, and the complex structure with many chiral centres, makes it an interesting synthetic challenge.[80]



1.46 1.47

Figure 1.20 - Azadirachtin and related compound.

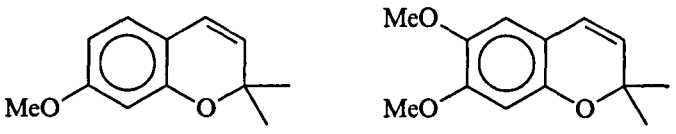
The mode of action has been investigated[81,82] and this work suggests that they antagonize the ecdysteroid function and / or affect the juvenile hormone titre. The structural similarity to the insect moulting hormone ecdysterone has been pointed out.[83]

Although the use of Neem is increasing, the slow acting nature and its limited insecticidal activity is likely to restrict use to selected applications.

Other Insect Growth Regulators

Chromenes of the *Asteraceae*

Chromenes have been shown to have various insecticidal modes of action[84,85] and although most are not insect growth regulators, Precocenes I **1.48** and II **1.49** (figure 1.21) have been shown to act as anti-juvenile hormones.[86]

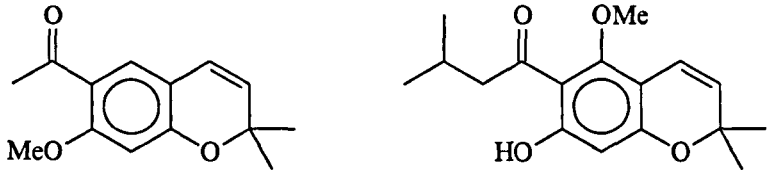


1.48 **1.49**

Figure 1.21 - Structure of precocenes.

They are thought to undergo oxidative activation within the *corpora allata*, the glands which synthesise juvenile hormone, resulting in cytotoxic effects.

Many structurally related chromenes[87,88] are active, but have unknown modes of action. For instance the encecalins **1.50, 1.51** (figure 1.22) are phototoxic to fungi and bacteria but show no phototoxicity to insects.



1.50 **1.51**

Figure 1.22 - Structure of chromenes with unknown mode of actions.

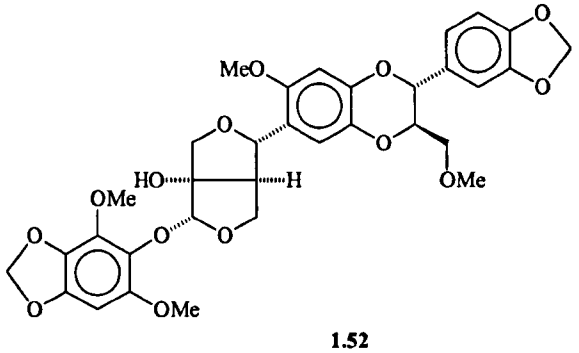
In general, the insecticidal activities of chromenes are too low for them to be considered as insecticidal natural products.

1.2.5 Natural Products of Unknown Mode of Action

There are many natural products with unknown modes of action although most of these have either been isolated recently so little work has been undertaken, or they have poor commercial prospects.

Lignans from *Phryma leptostachya*

Although most lignans are non-insecticidal, haedoxans A **1.52** isolated from *Phryma leptostachya*[89] (figure 1.23) show potent activities against houseflies and certain Lepidoptera. Synthetic studies[90] on the natural products and related analogues[91,92] confirmed the structural importance of the 3,4-methylenedioxy groups for insecticidal activity.



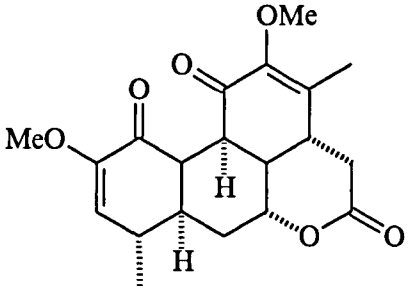
1.52

Figure 1.23 - Structure of haedoxan A.

The mode of action of these compounds is not known although symptoms, such as cessation of feeding and muscle relaxation[93] have indicated possible similarities to ryanodine **1.12** (see section 1.3.1b)

Quassinoids from *Quassia amara*

The wood from the tropical tree *Quassia amara*, a member of the Simarubaceae family, contains Quassin **1.53** a weakly insecticidal compound.[94] Aqueous extracts were used as insecticides between 1800 - 1950, and also boxes of the wood were reported to protect their contents from insects.



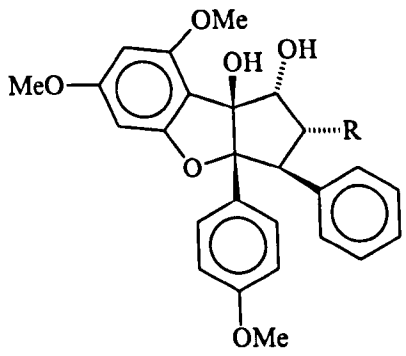
1.53

Figure 1.24 - Insecticidal compound from *Quassia amara.*

Quassin **1.53** acts as a contact, stomach and systemic poison to insects and is quite selective with no recorded toxic effects on vertebrates, although its limited activity precludes its widespread use as a botanical insecticide.

Rocaglamides from *Aglaia odorata*

Rocaglamide **1.54**[95] and related compounds **1.55-1.57**[96] (figure 1.25) have been isolated from *Aglaia odorata* and show inhibition of larval growth and insecticidal activity[97] against the variegated cutworm, *Peridroma saucia.* They also have pharmaceutical interest as they exhibit antileukemic activity.[98]

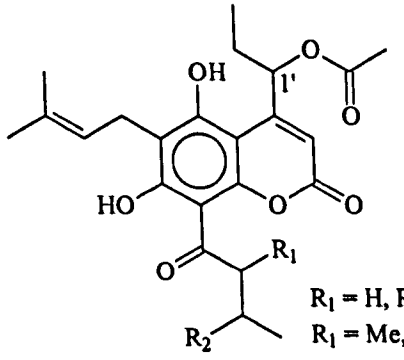


R = $CONMe_2$ **1.54**
CONHMe **1.55**
COOMe **1.56**
H **1.57**

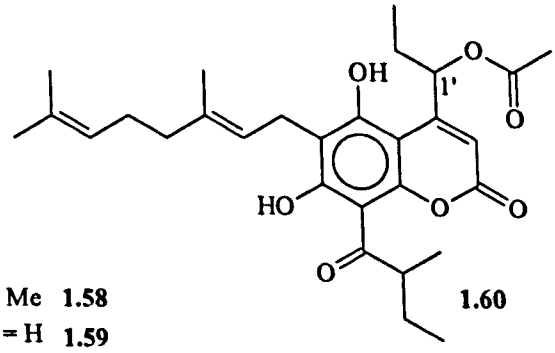
Figure 1.25 - Insecticidal benzofurans.

Mammeins from *Mammea americana*

Various coumarins have been isolated from *Mammea* species.[99] Although most were non-insecticidal, compounds with a 1' acetoxy group **1.58-1.60** (figure 1.26) show good activities.



R_1 = H, R_2 = Me **1.58**
R_1 = Me, R_2 = H **1.59**



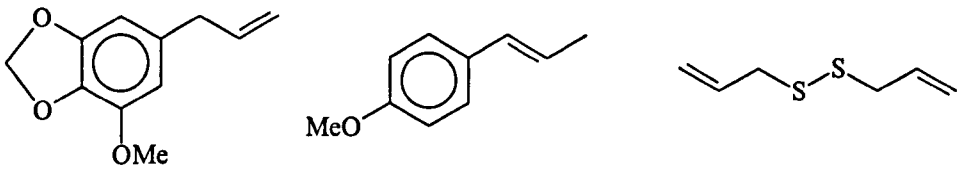
1.60

Figure 1.26 - Insecticidal mammeins.

Limited bioassay data makes it difficult to predict the future botanical use of these compounds.

Insecticidal Natural Products in Common Foodstuffs

Some compounds found in common foodstuffs have limited insecticidal activity, for instance myristicin **1.61** occurs in parsnips[100], trans-anethole **1.62** is found in anise[101] and allicin **1.63** has been isolated from garlic[102] (figure 1.27).



1.61 **1.62** **1.63**

Figure 1.27 - Insecticidal compounds found in common foodstuffs.

1.3 CONCLUSIONS

This survey has shown that there is a wide variety of insecticidal natural product. The range of modes of action of these compounds, may enable their use on resistant insect populations and be incorporated into an integrated pest management strategy. Although in general natural products have lower insecticidal activities than their synthetic counterparts, their public perception as being more benign, may give them a wider share of the agrochemical market.

Currently the natural products most suited for insect control are the pyrethrins **1.1-1.4** and rotenone **1.23**. New compounds which may challenge them include the hydroxy-naphthoquinones **1.35**, **1.36** which have excellent prospects for natural insect control as they possess high insecticidal activities and low mammalian toxicities.

Overall, the future for botanical insecticides looks promising and there is clearly a need for continued research in this area.

CHAPTER 2

ISOLATION AND CHARACTERISATION OF NEW INSECTICIDAL NATURAL PRODUCTS OF THE MYRTACEAE FAMILY

2.1 INTRODUCTION

During the search for insecticidal compounds in plants, interest in the family Myrtaceae was aroused by the discovery of insecticidal activity in extracts of *Kunzea sinclairii.* The active structures **7** and **8** had previously been reported by Bloor *et al*[103] as occuring in *Kunzea ericoides* but without recognition of their insecticidal activity. The present work constitutes a study to investigate insecticidal compounds in related plant species of the Myrtaceae family which occur mainly in Australia and New Zealand.

2.2 ISOLATION AND CHARACTERISATION OF NEW INSECTICIDAL NATURAL PRODUCTS

Extraction of the natural products was achieved with hexane as solvent at room temperature using dried and ground plant material. Purification was achieved by various bioassay guided chromatographic steps (See experimental section for full details).

Characterisation was achieved using infrared, NMR and mass spectral data (see experimental section, and appendix 1 for selected NMR spectra) and was aided by analogy to related natural compounds including various phloroglucinol compounds. In some cases the structures were confirmed by total synthesis (see chapter 3).

2.2.1 Compounds 1 and 2 from *Calothamnus validus*

The shrub *Calothamnus validus* shrub, called the net bush, is found in Western Australia. The hexane extract showed insecticidal activity and subsequent bioassay guided fractionation led to the isolation of an insecticidal mixture of compounds **1** and **2** (figure 2.1) in a 3 : 1 ratio, as a colourless oil in 0.063% yield. Separation of these two compounds by HPLC was difficult and limited by lack of material.

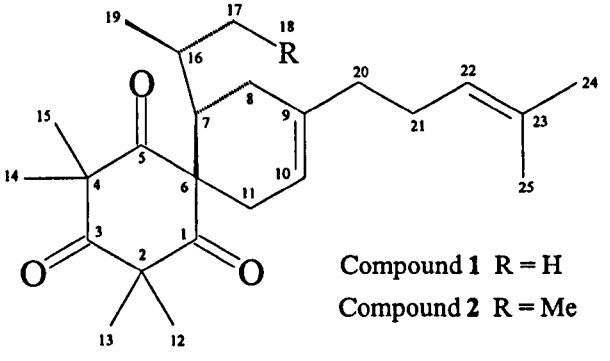


Figure 2.1 - Structure of compounds **1** and **2**.

Structural Elucidation of Compound 1

The molecular formula of the major component **1**, was established as $C_{24}H_{36}O_3$ by high resolution mass spectroscopy exhibiting a molecular ion peak at *m/z* 372.26733 (calc. 372.26644).

The infrared spectrum of the mixture of compounds **1** and **2** showed a strong absorbance at 1701 cm^{-1} which suggested the presence of carbonyl

groups.

The ^{1}H NMR spectrum of the major component exhibited two 1H peaks at δ 5.05 and 5.27 corresponding to olefinic protons. All other signals were within the range δ 0.85 to 2.49, corresponding to thirty four hydrogens and including eight methyl peaks, six singlets at δ 1.35, 1.39, 1.40, 1.42, 1.60 and 1.67 and two doublets at δ 0.85 and 0.90. The remaining protons were attributed to two 2H multiplets at δ 1.96 and 2.07 and six 1H multiplets at δ 1.67, 1.98, 2.19, 2.20, 2.25 and 2.49.

Analysis of the ^{13}C NMR data in conjunction with information from the DEPT spectra, showed three carbonyl peaks at δ 212.9, 208.6 and 208.5 and a further five quaternary carbon peaks at δ 138.0, 131.4, 67.0, 56.6 and 56.3. The remaining sixteen carbon peaks consisted of eight CH_3's at δ 26.2, 26.0, 25.0, 24.8, 25.7, 24.1, 19.1 and 17.7, four CH_2's at δ 37.1, 31.0, 27.7 and 26.1 and four CH's at δ 124.1, 115.4, 41.1 and 30.0.

^{1}H-^{1}H COSY (figure 2.2) gave correlations between various proton signals which enabled partial structures to be assigned. These included a CH_2CH_2CH= unit, an isolated CH_2CH= unit and a $CH(CH_3)_2$ unit. Further to these, weak allylic couplings were seen between the proton at H-10 and the protons at H-8 and H-20, and the proton at H-22 with protons at H-24 and H-25. Analysis of further correlations was hampered by severe overlapping in the high field region of the ^{1}H spectrum.

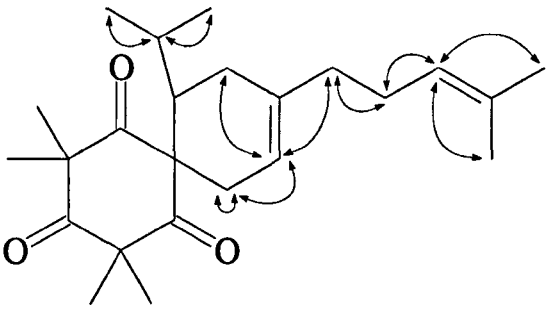


Figure 2.2 - Correlations observed in ^{1}H-^{1}H COSY spectrum of **1**.

Long range ^{1}H-^{13}C COSY (figure 2.3) provided the information necessary to connect these subunits enabling all carbons, except for those on the tetramethylcyclohexanetrione, to be unambiguously assigned (table 2.1). Correlations between the three ketone carbons C-1, C-3 and C-5 and the two quaternary carbons C-2 and C-4, with the protons at H-12 to H-15 were apparent, but individual correlations could not be analyzed due to similarity in shift values.

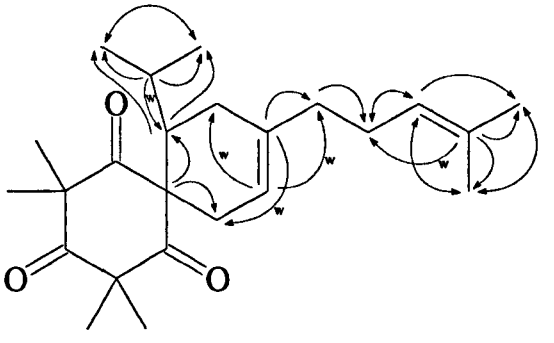


Figure 2.3 - Correlations observed in ^{1}H-^{13}C long range spectrum of **1**.

As the natural products **1** and **2** were isolated as a mixture, the chirality at C-7 could not be assigned unambigously. However the mixture showed zero

optical rotation suggesting that both compounds were racemic.

Table 2.1 - ^{1}H and ^{13}C NMR data for compound **1** in $CDCl_3$.

Position	^{1}H (*J*)	^{13}C	Position	^{1}H (*J*)	^{13}C
1a		208.5	13c	1.39, s	24.8
2b		56.3	14c	1.42, s	26.2
3		212.9	15c	1.40, s	25.0
4b		56.6	16	1.67, m	30.0
5a		208.6	17	0.90, d, (6.8)	24.1
6		67.0	18	-	-
7	2.20, m	41.1	19	0.85, d, (6.6)	19.1
8	1.98, 2.25, m	27.7	20	1.96, t, (7.7)	37.1
9		138.0	21	2.07, m	26.1
10	5.27, s	115.4	22	5.05, tt, (6.9, 1.5)	124.1
11	2.19, dd, (6.3, 3.1)	31.0	23		131.4
	2.49, dd, (17.6, 3.0)		24	1.67, s	25.7
12c	1.35, s	26.0	25	1.60, s	17.7

Chemical shift values are in ppm. Coupling constants (*J* values) in parentheses are in Hz.
a,b,c - Denotes assignments may be interchanged.

Structural Elucidation of Compound 2

The molecular formula of the minor component **2** (figure 3.1) was established as $C_{25}H_{38}O_3$ by high resolution mass spectroscopy exhibiting a molecular ion peak at *m/z* 386.28241 (calc. 386.28210) which suggested a CH_2 homologue of compound **1**. The minor component peaks in the spectrum of the mixture of compound **1** and **2**, where separate from those of compound **1**, were all doubled suggesting a 1 : 1 mixture. Unfortunately due to lack of sample

and overlapping of NMR peaks, complete structure elucidation of the natural product **2** was not possible. However, most peak shifts were comparable to those of compound **1**. The compound was assigned as a CH_2 homologue of compound **1** with the isobutyl group replaced by a *sec*-butyl group. Proof of structure was obtained by total synthesis (section 3.2).

The ^{13}C NMR peaks for the natural product **2** visible in the mixture of compounds **1** and **2**, are given in table 2.2 (values in **bold**), along with the full assignment obtained from synthetic material.

The ^{1}H and ^{13}C NMR spectra for the naturally derived material, compound **2**, indicate a mixture of two diastereomers **2a** and **2b** due to chiral centres at C-7 and C-16. The synthetic compound **2** was separated by flash chromatography into diastereomers **2a** and **2b** and each was assigned unambiguously.

Table 2.2 - ^{1}H and ^{13}C NMR data for compound **2** in $CDCl_3$.

	Diastereomer **a**		Diastereomer **b**	
Position	^{1}H (*J*)	^{13}C	^{1}H (*J*)	^{13}C
1a		**208.4**		208.6
2b		**56.7**		56.6
3		**212.7**		212.8
4b		**56.7**		**56.8**
5a		**208.9**		209.1
6		**66.7**		**66.2**
7	2.27, m	**40.5**	2.27, m	**41.3**
8	1.26,d,(7.1),1.37,m	**30.7**	2.06, 2.28, m	**29.1**
9		**137.9**		**139.1**
10	5.28, m	**115.5**	5.28, d, (1.4)	**114.6**
11	2.14, m	**31.1**	2.14, d, (19.8)	**32.6**
	2.50, m		2.50, d, (15.7)	
12c	1.34, s	**25.9**	1.35, s	**25.5**
13c	1.39, s	24.8	1.39, s	**24.7**
14c	1.42, s	26.2	1.42, s	**26.4**
15c	1.39, s	**24.6**	1.39, s	**25.3**
16	1.33, m	**36.4**	1.43, m	**37.6**
17	1.24, m	**27.2**	1.05, dq, (6.3, 1.6)	**25.5**
	1.40, m		1.52, dq, (10.1, 7.1)	
18	0.85, t, (7.2)	**12.1**	0.83, d, (6.9)	**12.3**
19	0.80, d, (6.6)	**15.3**	0.84, d, (6.6)	**19.7**
20	1.96, t, (7.0)	**37.1**	1.96, t, (7.4)	**37.1**
21	2.07, t, (6.0)	26.2	2.05, m	26.2
22	5.06, t, (6.8)	**124.1**	5.05, td, (6.0, 1.4)	**124.1**
23		131.5		131.5
24	1.68, s	25.7	1.67, s	25.7
25	1.60, s	17.7	1.60, s	17.7

Chemical shift values are in ppm. Coupling constants (*J* values) in parentheses are in Hz.
a, b, c - Assignments may be interchanged.
Bold values denote ^{13}C peaks visible in natural product spectrum.

Correlations in the H-H COSY spectra (figure 2.4) for synthetic compounds **2a** and **2b** provided information to assign the *sec* butyl subunit fully.

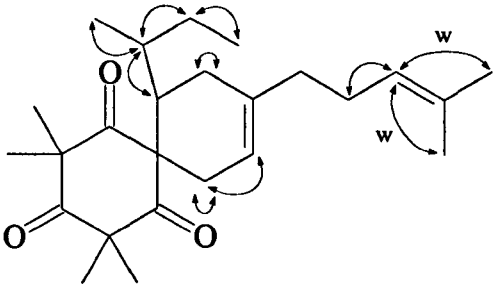


Figure 2.4 - Correlations observed in ^{1}H-^{1}H COSY spectra of **2a** and **2b**.

Long range ^{1}H-^{13}C COSY (figure 2.5) gave further information to confirm the proposed structures for compounds **2a** and **2b**.

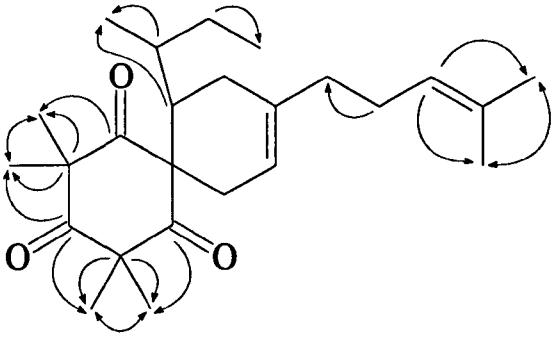


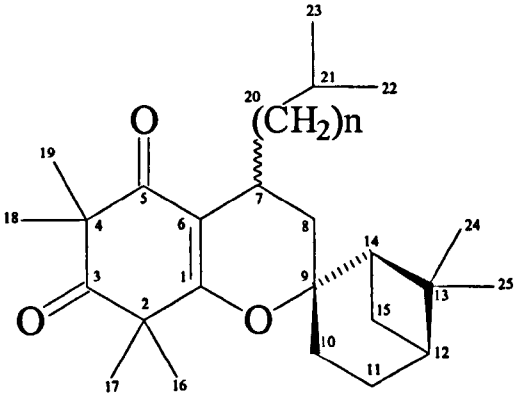
Figure 2.5 - Correlations observed in long range ^{1}H-^{13}C spectra of **2a** and **2b**.

These compounds **1** and **2** represent the first natural products to contain a spiro system connected to a tetramethylcyclohexanetrione unit, so discussion of their biosynthesis is particularly pertinent (section 2.3). In this respect, the presence of the *sec* butyl group, the mixture of diastereomers and the uniqueness of the spiro centre are all significant features.

2.2.2 Compound 3 from *Eucalyptus ficifolia* and *Kunzea ericoides* and Compound 4 from *Calothamnus validus*.

Bioassay guided fractionation on the hexane extracts of three species of Myrtaceae gave two novel homologous natural products. Compound **3** was isolated as a colourless oil from the Australian tree *Eucalyptus ficifolia* (red flowering gum) in 0.006% yield and from the Australian shrub *Kunzea ericoides* in 0.00025% yield. Compound **4** was isolated from the Australian shrub *Calothamnus validus* (net bush) as a colourless oil in 0.022% yield.

The establishment of their structures (figure 2.6) followed from spectroscopic data, by analogy to related compounds[104,105] and was confimed by total synthesis (section 3.3).



Compound **3** n = 1
Compound **4** n = 0

Figure 2.6 - Molecular structure of compounds **3** and **4**.

Structural Elucidation of Compound 3

The infrared spectrum of compound **3** showed a strong absorbance at 1710 cm^{-1} which suggested the presence of carbonyls.

The molecular formula was established as $C_{25}H_{38}O_3$ by high resolution mass spectroscopy exhibiting a molecular ion peak at *m/z* 386.28122 (calc. 386.28210).

Consideration of the ^{13}C NMR spectrum in conjunction with information from the DEPT spectra indicated the presence of a tetramethylcyclohexenedione unit, with three carbonyl resonances, one as an enol, at δ 213.5, 197.9, and 168.9, a further three quaternary carbon peaks at δ 112.9, 55.4 and 48.0 and four methyl peaks at δ 22.3, 24.3, 25.5 and 26.3. The presence of a peak at δ 84.2 indicated that the enol oxygen of the syncarpic acid was bonded to carbon through an ether link. The remaining fifteen carbon peaks consisted of four CH_3's at δ 27.3, 24.1, 23.4 and 20.8, five CH_2's at δ 42.2, 39.6, 27.9, 26.9 and 24.9 and four CH's at δ 51.2, 40.4, 25.6 and 25.6.

In the ^1H NMR spectrum all peaks were in the high field region. Within the range δ 0.90 to 2.75 corresponding to thirty eight hydrogens, in conjunction with ^1H-^{13}C COSY information, eight methyl peaks six singlets at δ 1.02, 1.30, 1.31, 1.33, 1.34 and 1.36 and two doublets at δ 0.90 and 0.98 were observed; the remaining protons were attributed to two 2H multiplets at δ 1.70 and 1.94 and ten 1H multiplets at δ 0.99, 1.46, 1.61, 1.73, 1.93, 1.99, 2.13, 2.14, 2.27 and 2.75.

Analysis of the ^{1}H-^{1}H COSY spectrum (figure 2.7) gave correlations between various protons enabling partial structures to be assigned, but analysis of further correlations was hampered by the complexity of the ^{1}H spectrum in the high field region.

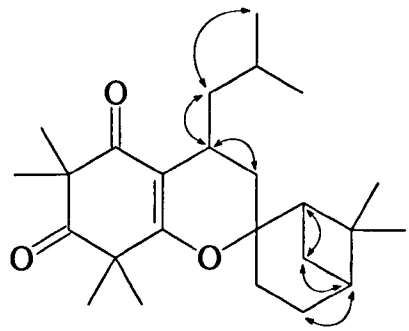


Figure 2.7 - Correlations observed in ^{1}H-^{1}H COSY spectrum of pinane **3**.

Long range ^{1}H-^{13}C COSY (figure 2.8) showed significant correlations from the carbon at C-6 with protons at H-7, H-8 and H-20 and from the carbon at C-1 with the proton at H-7. Other correlations enabled an isobutyl group partial structure to be assigned.

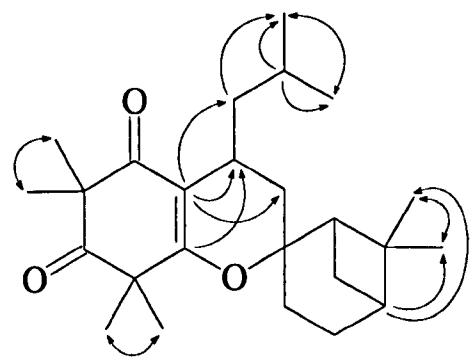


Figure 2.8 - Correlations observed in ^{1}H-^{13}C COSY spectrum of pinane **3**.

The full structural assignment (table 2.3) was confirmed by analogy with robustadials A and B, isolated from *Eucalyptus robusta*.

Table 2.3 - ^{1}H and ^{13}C NMR data for pinanes **3** and **4** in $CDCl_3$.

	Compound **3**		Compound **4**	
Position	^{1}H (*J*)	^{13}C	^{1}H (*J*)	^{13}C
1		168.9		171.1
2		48.0		48.3
3		213.5		213.8
4		55.4		55.2
5		197.9		198.0
6		112.9		111.3
7	2.73, dddd, (10.3, 8.8, 6.7, 3.5)	25.6	2.63, m	25.9
8	1.46, dd, (14.0, 8.8) 2.13, dd, (14.0, 6.6)	39.6	1.60, m 2.11, dd, (8.0, 7.0)	32.2
9		84.2		85.0
10	1.70, m	27.9	1.88, dt, (12.8, 5.8)	30.7
11	1.94, m	24.9	1.40, m	24.6
12	1.99, m	40.4	1.95, m	40.6
13		38.2		38.2
14	2.14, m	51.2	2.18, m	45.4
15	1.61, 2.27, m	26.9	1.45, 2.20, m	26.0
16a	1.34, s	25.5	1.26, s	26.2
17a	1.36, s	24.3	1.40, s	24.2
18a	1.33, s	26.3	1.30, s	25.7
19a	1.31, s	22.3	1.32, s	23.3
20	0.96, ddd, (13.1, 10.2, 3.9) 1.73, ddd, (13.1, 10.1, 3.4)	42.2	-	-
21	1.93, m	25.6	2.63, m	33.8
22	0.90, d, (6.3)	24.1	0.94, d, (6.5)	20.7
23	0.98, d, (6.3)	20.8	0.62, d, (6.9)	15.6
24	1.30, s	27.3	1.23, s	27.5
25	1.02, s	23.4	0.96, s	23.0

Chemical shift values are in ppm. Coupling constants (*J* values) in parentheses are in Hz.
a - Assignments (for pinane **3**) may be interchanged.

The structures of the robustadials were originally misassigned,[106,107] but were reevaluated by Cheng *et al*[105] using, in particular, 2D relayed coherence transfer and XCORFE pulse sequence NMR techniques.

Compound **3** has four chiral centres and an optical rotation of +35.9 ($CHCl_3$, c 0.92). The absolute stereochemistry was studied using NOESY experiments and analysis of coupling constants but was inconclusive. A stereoselective synthesis was devised (section 3.3) which enabled the stereochemistry at C-9, C-12 and C-14 to be defined.

Structural Elucidation of Compound 4

The molecular formula of compound **4** (figure 2.6) was established as $C_{24}H_{36}O_3$ by high resolution mass spectroscopy exhibiting a molecular ion peak at *m/z* 372.26724 (calc. 372.26641). the compound had an optical rotation of +40.9 ($CHCl_3$, c 0.44).

The infrared spectrum was comparable to that of compound **3** with a strong carbonyl absorbance.

^{13}C NMR spectral data was consistent with a nor-analogue of compound **3** with minor expected differences at C-14 and C-21 to 23.

The ^{1}H NMR spectrum, in conjunction with ^{1}H-^{13}C COSY data exhibited similar chemical shifts to compound **3** (see table 2.3), except for different shift values for H-11 and H-21 to H-23.

^{1}H-^{1}H COSY (figure 2.9) gave limited correlations between protons enabling partial structures to be assigned. Analysis of further correlations was again hampered by the complexity of the ^{1}H spectrum in the high field region.

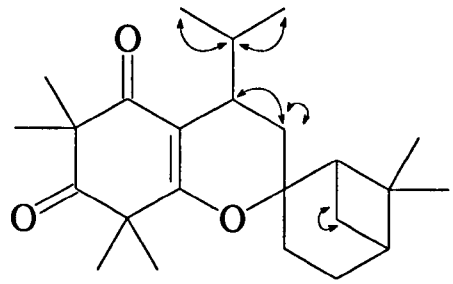


Figure 2.9 - Correlations observed in ^{1}H-^{1}H COSY spectrum of pinane **4**.

Long range ^{1}H-^{13}C COSY (figure 2.10) enabled all carbons of the syncarpic acid moiety to be assigned unambiguously.

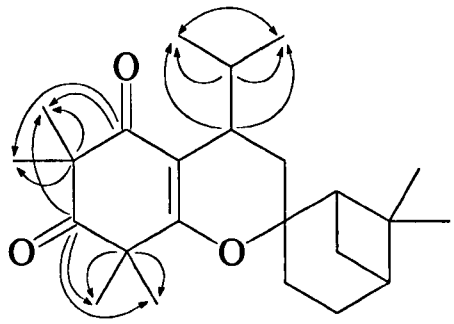


Figure 2.10 - Correlations observed in LORCH spectrum of pinane **4**.

The absolute stereochemistry could not be assigned by NMR techniques, and again was determined by total synthesis.

These pinane compounds have clear similarities to the robustadials

isolated from *Eucalyptus robusta* and phloroglucinols from *Baeckea frutescens*[104] and hence may be important in chemotaxonomic studies in Myrtaceae species and in the discussion of the biosynthesis of such phytochemicals.

2.2.3 Compound 5 from *Callistemon viminalis*

Examination of the weeping bottlebrush *Callistemon viminalis*, a shrub or small tree from Australia, showed that the hexane extract contains two previously unknown epimers **5a** and **5b** (figure 2.11). They were each isolated by bioassay guided chromatography as pale yellow oils in 0.01% yield.

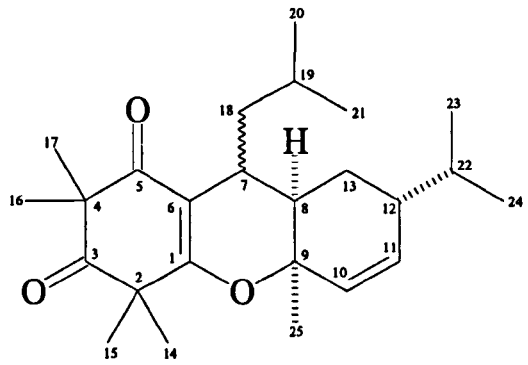


Figure 2.11 - Molecular structure of phellandrenes **5**.

The molecular formulas of **5a** and **5b** were established as $C_{25}H_{38}O_3$ by high resolution mass spectroscopy exhibiting molecular ion peaks at *m/z* 386.28113 and 386.28189 respectively (calc. 386.28210).. The optical rotation of compound **5a** was +120.6 ($CHCl_3$, c 0.96) and of compound **5b** was -25.5 ($CHCl_3$, c 1.32).

The infrared spectra of compounds **5a** and **5b** were similar and showed strong absorbances at 1713 and 1718 cm^{-1}, indicating the presence of carbonyl groups.

The ^{13}C NMR data for compound **5a** disclosed, by analogy to related structures, the presence of a tetramethylcyclohexenedione unit, with three

carbonyl peaks, one as an enol-ether, at δ 213.3, 198.5 and 166.9, a further three quaternary carbon peaks at δ 110.2, 55.8 and 47.9 and four methyl peaks at δ 26.8, 25.8, 23.8 and 23.5. The presence of a peak at δ 76.2 indicated that the enol oxygen of the tetramethylcyclohexenedione was bonded to carbon through an enol-ether link. Two peaks at δ 135.2 and 130.8 corresponded to a disubstituted double bond. The remaining twelve carbon peaks consisted of five CH_3's at δ 24.2, 21.6, 21.5, 21.0 and 20.8, two CH_2's at δ 35.2 and 20.7 and five CH's at δ 41.2, 33.6, 31.5, 28.2 and 24.6.

The ^1H NMR spectrum for compound **5a**, in conjunction with ^1H-^{13}C COSY, showed peaks at δ 5.75 and 5.99, and within the range δ 0.95 to 2.98, corresponding to thirty six hydrogens, nine methyl peaks, five singlets at δ 1.27, 1.29, 1.29, 1.32 and 1.36 and four doublets at δ 0.95, 0.96, 0.98 and 1.00 were observed. The remaining protons were attributed to nine 1H multiplets at δ 1.11, 1.30, 1.63, 1.67, 1.70, 1.87, 1.94, 1.97 and 2.98.

Analysis of the ^1H-^1H COSY spectrum gave a range of correlations summarised in figure 2.12 which enabled the majority of the alicyclic skeleton to be assigned.

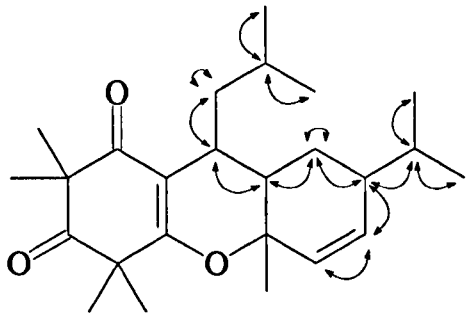


Figure 2.12 - Correlations observed in ^1H-^1H COSY spectrum of **5a**.

Unequivocal conformation of structure came from ^{1}H-^{13}C long range COSY (figure 2.13) which enabled all atoms, except the syncarpic acid fragment, to be assigned (table 2.4). Further proof came from comparison with related natural products.

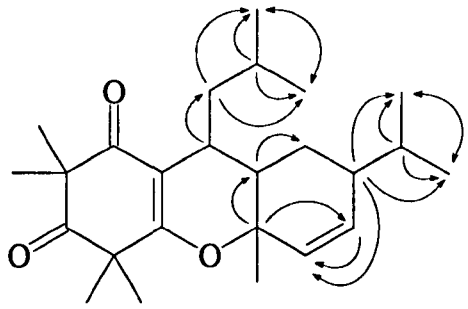


Figure 2.13 - Correlations observed in ^{1}H-^{13}C COSY spectrum of phellandrene **5a**.

The NMR spectral data for compound **5b** (table 2.4) was essentially identical to epimer **5a** and 2-D correlations confirmed compound **5b** was an isomer differing only in relative stereochemistry between the four chiral centres. Analysis of coupling constants and NOESY for the two epimers to assign absolute stereochemistry was inconclusive. Partial stereochemistry of the two epimers was assigned by comparison with synthesised isomers (section 3.4).

Table 2.4 - ^{1}H and ^{13}C NMR data for compounds **5a** and **5b** in $CDCl_3$.

	Compound **5a**		Compound **5b**	
Position	^{1}H (*J*)	^{13}C	^{1}H (*J*)	^{13}C
1		166.9		168.6
2		47.9		47.5
3		213.3		213.5
4		55.8		55.6
5		198.5		198.1
6		110.2		113.0
7	2.98, ddd, (11.6,6.3,3.5)	28.2	2.56, dt, (9.9, 3.3)	31.7
8	1.87, ddd, (15.2,6.5,3.0)	33.6	2.01, m	38.3
9		76.2		77.7
10	5.75, dd, (10.0, 1.8)	130.8	5.50, dd, (10.2, 2.2)	131.0
11	5.99, dd, (10.1, 3.7)	135.2	5.84, dd, (10.2, 3.9)	134.6
12	1.94, m	41.2	2.01, m	39.5
13	1.30, 1.70, m	20.7	1.57, m	29.1
14a	1.27, s	23.8	1.38, s	24.6
15a	1.29, s	25.8	1.33, s	25.3
16a	1.29, s	26.8	1.33, s	23.5
17a	1.36, s	23.5	1.33, s	25.4
18	1.11, td, (11.5, 2.5)	35.2	1.35, m	43.9
	1.97, m		1.45, m	
19	1.63, m	24.6	1.76, m	26.1
20	0.95, d, (6.7)	24.2	0.91, d, (6.3)	24.0
21	1.00, d, (6.4)	20.8	1.00, d, (6.6)	21.5
22	1.67, m	31.5	1.66, m	31.6
23	0.98, d, (6.4)	21.0	0.92, d, (6.6)	20.4
24	0.96, d, (6.7)	21.5	0.95, d, (6.6)	20.4
25	1.32, s	21.6	1.46, s	27.4

Chemical shift values are in ppm. Coupling constants (*J* values) in parentheses are in Hz.
a - Assignments may be interchanged.

2.2.4 Compound 6 from *Kunzea ericifolia*

Examination of the shrub *Kunzea ericifolia*, found in New Zealand, showed that the hexane extract contained a previously unknown natural product **6** (figure 2.14). It was isolated, by bioassay guided fractionation using the test insect species *Phaedon cochliariae*, as a colourless oil in 0.04% yield.

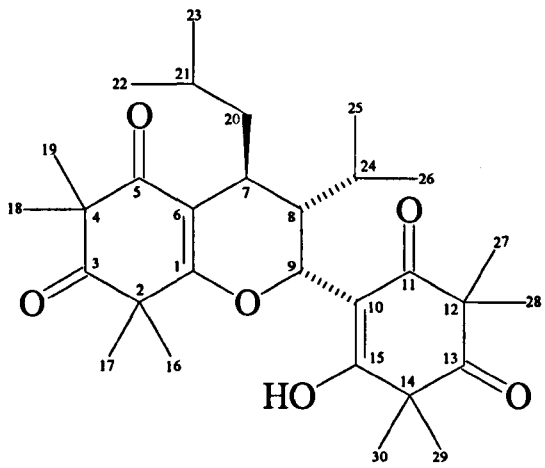


Figure 2.14 - Molecular structure of dimer **6**.

The molecular formula was established as $C_{30}H_{44}O_6$ by high resolution mass spectroscopy exhibiting a molecular ion peak at *m/z* 500.31512.

A strong infrared absorbance of 1706 cm^{-1} indicated the presence of carbonyl groups.

The ^{13}C NMR data, including information from DEPT spectra, disclosed the presence of two non-equivalent tetramethylcyclohexenedione units, with six carbonyl resonances, two as enols, at δ 212.0, 211.4, 197.8, 196.9, 175.0, and

167.4, a further six quaternary carbon peaks at δ 116.7, 107.1, 56.2, 55.2, 48.6 and 47.3 and eight methyl peaks at δ 26.7, 25.4, 25.1, 25.0, 24.9, 24.5, 23.7 and 21.3. The presence of a peak at δ 79.4 indicated that the enol oxygen of one syncarpic acid was bonded to carbon through an enol ether link, whilst the other syncarpic acid fragment was as a free enol. The remaining nine carbon peaks consisted of four CH_3's at δ 24.3, 23.8, 21.0 and 19.6, one CH_2 at δ 44.7 and four CH's at δ 41.4, 27.2, 26.7 and 25.3.

The ^1H NMR spectrum exhibited the majority of peaks in the high field region with only a 1H broad singlet at δ 9.01 attributed to a hydroxyl group, and a one-proton signal at δ 5.55 as the only peaks in the low field region. Within the range δ 0.75 to 2.81, in conjunction with ^1H-^{13}C COSY, twelve methyl peaks were observed, eight singlets at δ 1.34, 1.35, 1.39, 1.39, 1.40, 1.44, 1.52 and 1.52 and four doublets at δ 0.75, 0.95, 0.99 and 1.07. The remaining protons were attributed to six 1H multiplets at δ 1.35, 1.40, 1.74, 1.87, 1.87 and 2.81.

Analysis by ^1H-^1H COSY (figure 2.15) gave correlations between protons at H-7 with H-20 and between the proton at H-21 with protons at H-20, H-22 and H-23. This enabled an isobutyl sub-structure to be assigned. Further ^1H-^1H correlations between protons at H-8 and H-9 and between protons at H-24, H-25 and H-26 enabled other partial structures to be deduced.

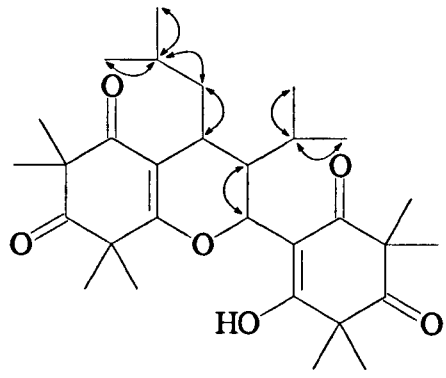


Figure 2.15 - Correlations observed in ^{1}H-^{1}H COSY spectrum of dimer **6**.

Long range ^{1}H-^{13}C COSY (figure 2.16) enabled all ring carbons and six of the eight methyl carbons of the two syncarpic acid moieties to be assigned unambiguously. Correlations between the enol proton at H-15 with carbons at C-10, C-14 and C-15 were especially useful. Unfortunately the proton signals were too complex to allow the position of the remaining two methyls of the tetramethylcyclohexenediones to be assigned conclusively and hence then could only be assigned by analogy with other tetramethylcyclohexenedione containing analogues.

Other significant long range correlations between the proton at H-9 and the carbon at C-10, the proton at H-7 and the carbon at C-6 and the proton at H-25 and the carbon at C-8 enabled all partial structures to be connected. Hence compound **6** was deduced to be a new tetramethylcyclohexenedione-isobutyl dimer.

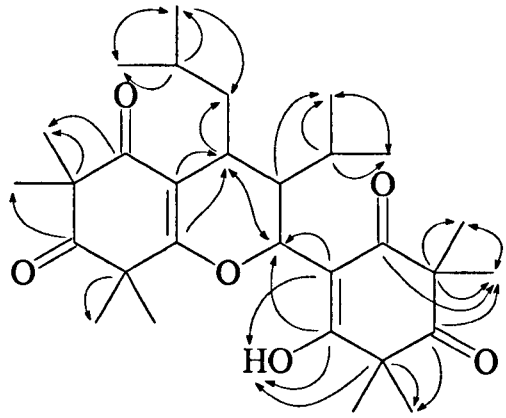


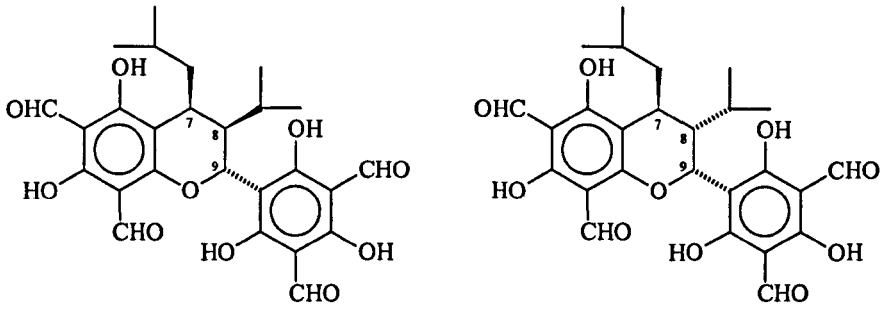
Figure 2.16 - Correlations observed in ^{1}H-^{13}C LORCH spectrum of **6**.

Table 2.5 - ^{1}H and ^{13}C NMR data for compound **6** in $CDCl_3$.

Position	^{1}H (*J*)	^{13}C	Position	^{1}H (*J*)	^{13}C
1		167.4	16a	1.34, s	21.3
2		47.3	17	1.44, s	25.4
3		212.0	18	1.52, s	25.0
4		55.2	19	1.39, s	24.5
5		197.8	20	1.35, 1.40, m	44.7
6		116.7	21	1.74, m	25.3
7	2.81, dd, (8.3, 1.4)	27.2	22	0.99, d, (6.8)	24.3
8	1.87, m	41.4	23	1.07, d, (6.4)	21.0
9	5.55, d, (2.5)	79.4	24	1.87, m	26.7
10		107.1	25	0.95, d, (6.8)	23.8
11		196.9	26	0.75, d, (6.8)	19.6
12		56.2	27	1.35, s	24.9
13		211.4	28	1.40, s	26.7
14		48.6	29	1.52, s	25.1
15		175.0	30a	1.39, s	23.7

Chemical shift values are in ppm. Coupling constants (*J* values) in parentheses are in Hz.
a - Assignments may be interchanged.

The dimer **6** contains three chiral centres and has an optical activity of -35.6 ($CHCl_3$, c 0.16). Comparison with the NMR data for the related sideroxylonals A **2.1** and B **2.2**[108] (figure 2.17) supports the proposed structure with only small differences for the central region due to the changes from the aromatic to tetramethylcyclohexenedione systems.



2.1 **2.2**

Figure 2.17 - Structure of related sideroxylonals A and B

In addition, it allows conclusions as to the relative stereochemistry at the three chiral centres, as this has been established in the aromatic analogues. Thus significant variations in the stereochemistry were observed when the stereochemistry at C-8 was inverted in the sideroxylonals. The coupling constants (table 2.6) for compound **6** suggests that it has the same relative stereochemistry as sideroxylonal B.

Table 2.6 - Comparison of ^1H signals for compound **6** and the sideroxylonals A and B in $CDCl_3$.

Position	Compound **6**	Sideroxylonal A	Sideroxylonal B
7	2.81, dd, (8.3, 1.4)	3.38, dt, (6.6, 3.7)	2.98, dd, (10.3, 1.5)
8	1.87, m	2.40, ddd, (11.7, 8.8, 3.7)	2.02, dd, (2.2, 1.5)
9	5.55, d, (2.5)	5.95, d, (11.7)	5.92, d, (1.5)

J values in parenthesis

2.2.5 Compounds 7 and 8 from *Kunzea aff. micromera*, *Kunzea baxterii*, *Kunzea ericoides* and *Kunzea sinclairii*

Two insecticidally active compounds **7** and **8** (figure 2.18) were isolated from the New Zealand and Australian shrubs *Kunzea aff. micromera*, *Kunzea baxterii*, *Kunzea ericoides* and *Kunzea sinclairii* as white crystals. These compounds had previously been isolated by Bloor *et al*[103] from *Kunzea ericoides* and shown to have antiviral activity, although no insecticidal activity was reported.

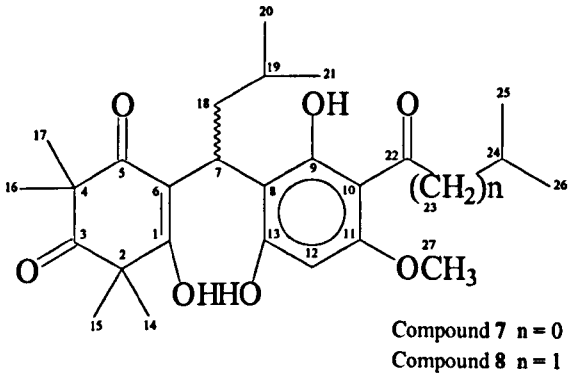


Figure 2.18 - Compounds **7** and **8** isolated from various *Kunzea* species.

The natural products **7** and **8** were isolated from the *Kunzea* species in varying ratios and yields (table 2.7).

Table 2.7 - Percentages (based on dry weight of plant material) of the natural products in various *Kunzea* species.

Kunzea species	Compound **7**	Compound **8**
aff. micromera	0.22%	0.28%
baxterii	0.25%	0.12%
ericoides	0.33%	0.17%
sinclairii	0.023%	0.023%

Natural product **7** was derivatised using excess diazomethane at 0°C to yield a single compound **2.3**. The structure was deduced by NMR spectroscopy (table 2.8), as the product of mono-methylation at the 13-OH (figure 2.19).

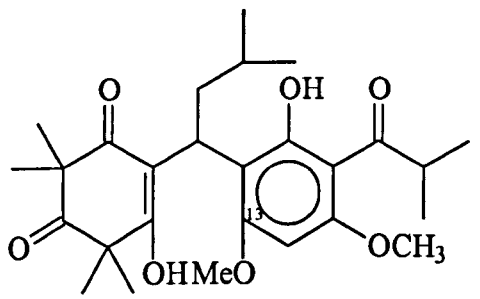


Figure 2.19 - Methylated derivative **2.3**.

It was concluded that the 9-OH hydrogen-bonds to the ketone at C-22 and hence did not react under the reaction conditions. No conformers, which were apparent in the natural products, were seen due to the loss of the intramolecular hydrogen bonding between H-13 and either O-1 or O-5. The additional steric bulk of the methyl ether was exemplified by significant

differences in shift values for certain ^{13}C resonances. For instance the C-6 resonance for derivative **2.3** was nearly 10 ppm greater than for the natural product **7**.

Table 2.8 - ^{1}H and ^{13}C NMR data for monomethylated compound **2.3**

Position	^{1}H (*J*)	^{13}C
1	10.50, s	178.4
2		50.5
3		211.1
4		55.3
5		206.4
6		124.4
7	4.92, m	29.1
8		109.0
9	14.91, s	163.4
10		104.1
11		161.4
12	5.94, s	92.7
13		166.5
14	1.43, s	23.3
15	1.28, s	23.8
16	1.39, s	26.2
17	1.35, s	26.6
18	2.21, m	40.0
19	1.40, m	26.0
20	0.84, d, (6.3)	21.9
21	0.89, d, (6.5)	22.4
22		210.3
23	-	-
24	3.76, sept, (6.8)	39.4
25	1.14, d, (6.3)	19.4
26	1.16, d, (6.3)	19.4
27	3.83, s	55.3
OMe	4.03	56.1

Chemical shift values are in ppm. Coupling constants (*J* values) in parentheses are in Hz.

2.2.6 Compound 9 from *Kunzea ambigua* and *Kunzea baxterii*

Compound **9** (figure 2.20) was isolated from two shrubs from New Zealand and Australia, *Kunzea ambigua* in 0.04% yield and *Kunzea baxterii* in 0.084% yield, as a colourless oil.

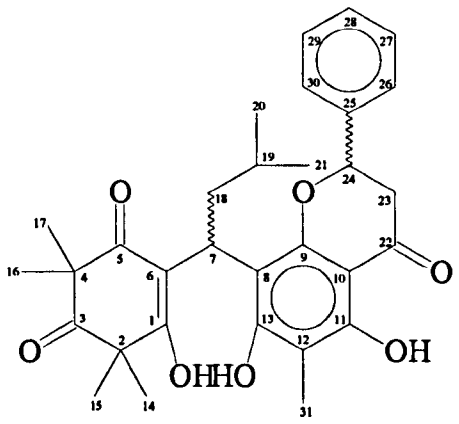


Figure 2.20 - Structure of compound **9**.

The molecular formula was established as $C_{31}H_{36}O_7$ by high resolution mass spectroscopy exhibiting a molecular ion peak at *m/z* 520.24609 (calc. 520.24610).

A strong infrared absorbance at 1710 cm^{-1} corresponded to a carbonyl group.

The ^1H NMR and ^{13}C NMR spectra (tables 2.9, 2.10) indicated a mixture of four compounds in a 10 : 5 : 4 : 3 ratio. The ^1H NMR spectrum for the major component **9a**, assigned in conjunction with ^1H-^{13}C COSY and DEPT data, exhibited three 1H broad singlet at δ 13.97, 11.77 and 9.91

attributed to three acidic hydroxyl groups. Peaks corresponding to five protons in the aromatic region δ 7.41 - 7.47 were observed along with seven methyl peaks with five as singlets at δ 2.07, 1.50, 1.41, 1.35 and two doublets at δ 0.87 and 0.86, and seven multiplets at δ 5.43, 4.33, 3.03, 2.89, 2.07, 1.80 and 1.41.

The ^{13}C NMR data for the major component **9a** disclosed the presence of a tetramethylcyclohexenedione unit, with three carbonyl peaks, one as an enol, at δ 212.0, 203.3 and 176.1 a further three quaternary carbon peaks at δ 114.5, 55.2 and 48.6 and four methyl peaks at δ 27.1, 26.2, 24.2 and 22.1. Peaks at δ 38.1, 27.6, 26.8, 22.6 and 22.3 corresponded to an iso-butyl moiety (c.f. compounds **3** and **5 - 8**) and confirmed by two-dimensional experiments (figures 2.21 and 2.22). Aromatic peaks at δ 164.9, 158.7, 156.7, 108.6, 106.8 and 101.5 corresponded to a trialkylated phloroglucinol moiety and peaks at δ 138.8, 128.8, 128.6 and 125.8 corresponded to a phenyl ring. The remaining peaks at δ 196.5, 78.5, 42.9 and 7.9 along with two-dimensional NMR techniques (figures 2.21, 2.22) enabled the flavanone (strobopinin)[109] partial structure to be assigned, and this was confirmed by analogy to previously reported flavanones.[110,111,112]

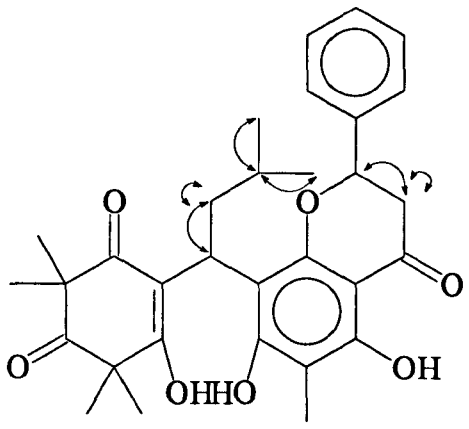


Figure 2.21 - ^{1}H-^{1}H COSY for compound **9**

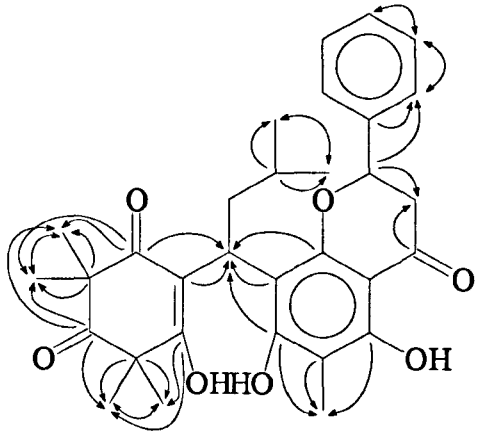


Figure 2.22 - Long range ^{1}H-^{13}C COSY for compound **9.**

It can be seen that the other compounds **9b, 9c, 9d** in the mixture have very similar ^{13}C spectra to that of compound **9a** (table 2.10), so they appear to be isomeric forms of compound **9a.** the situation is similar to that for compounds **7** and **8** which exist as conformers due to restricted rotation about the 6 - 7 and 7 - 8 bonds. In addition compounds **9a - 9d** contain two chiral centres at C-7 and C-24 and the mixture has an optical rotation of -55.4

($CHCl_3$, c 3.24), so appears to contain diastereomers arising from chirality at these centres. Hence the mixture may comprise two diastereomers each existing as two conformers as suggested for a related compound.[113] Separation of the diastereomers by HPLC was unsuccessful.

Table 2.9 - ^1H NMR data for compound **9a** in $CDCl_3$.

Position	^1H (*J*)	Position	^1H (*J*)
1	13.97, s	17	1.34, s
2		18	1.80, 2.07, m
3		19	1.41, m
4		20	0.86, d, (5.9)
5		21	0.87, d, (6.3)
6		22	
7	4.33, t, (7.6)	23	2.89, dd, (17.6, 3.4)
8			3.03, dd, (17.1, 12.7)
9	9.91, s	24	5.43, dd, (12.9, 10.0)
10		25	
11		26	7.44, m
12		27	7.45, m
13	11.77, s	28	7.42, m
14	1.50, s	29	7.45, m
15	1.35, s	30	7.44, m
16	1.41, s	31	2.07, s

Chemical shift values are in ppm. Coupling constants (*J* values) in parentheses are in Hz.

Table 2.10 - ^{13}C NMR data for compound **9** in $CDCl_3$.

Position	**9a** (10)	**9b** (5)	**9c** (4)	**9d** (3)
1	176.1	176.0	176.7	176.8
2	48.6	49.0	obs	obs
3	212.0	212.4	obs	obs
4	55.2	54.3	obs	obs
5	203.3	203.2	203.4	obs
6	114.5	114.6	114.7	114.7
7	27.6	29.7	27.5	29.3
8	108.6	108.7	obs	obs
9	156.7	157.6	obs	obs
10	101.5	101.6	102.1	101.9
11	158.7	158.6	obs	obs
12	106.8	107.1	107.0	106.6
13	164.9	164.7	164.2	164.5
14	26.2	26.1	26.0	25.9
15	24.2	24.3	23.8	24.0
16	22.1	obs	obs	obs
17	27.1	27.2	27.0	27.0
18	38.1	37.9	39.0	38.8
19	26.8	obs	obs	obs
20	22.6	obs	obs	obs
21	22.3	obs	obs	obs
22	196.5	196.6	197.1	197.0
23	42.9	42.9	42.9	42.9
24	78.5	78.6	obs	obs
25	138.8	138.7	138.7	138.6
26	128.8	obs	obs	obs
27	125.8	obs	obs	obs
28	128.6	obs	obs	obs
29	125.8	obs	obs	obs
30	128.8	obs	obs	obs
31	7.9	8.0	8.3	8.2

Chemical shift values are in ppm.
obs - Denotes peak obscured.

The absolute stereochemistry at C-24 was not elucidated, although flavanones have been isolated[114] from a Myrtaceae species *Leptospermum scoparium* with S stereochemistry at C-24. In general most natural flavanones of this type possess S stereochemistry.[115]

2.3 SUMMARY OF NATURAL PRODUCTS ISOLATED

In summary the following nine insecticidal natural products have been isolated and characterised (figure 2.23).

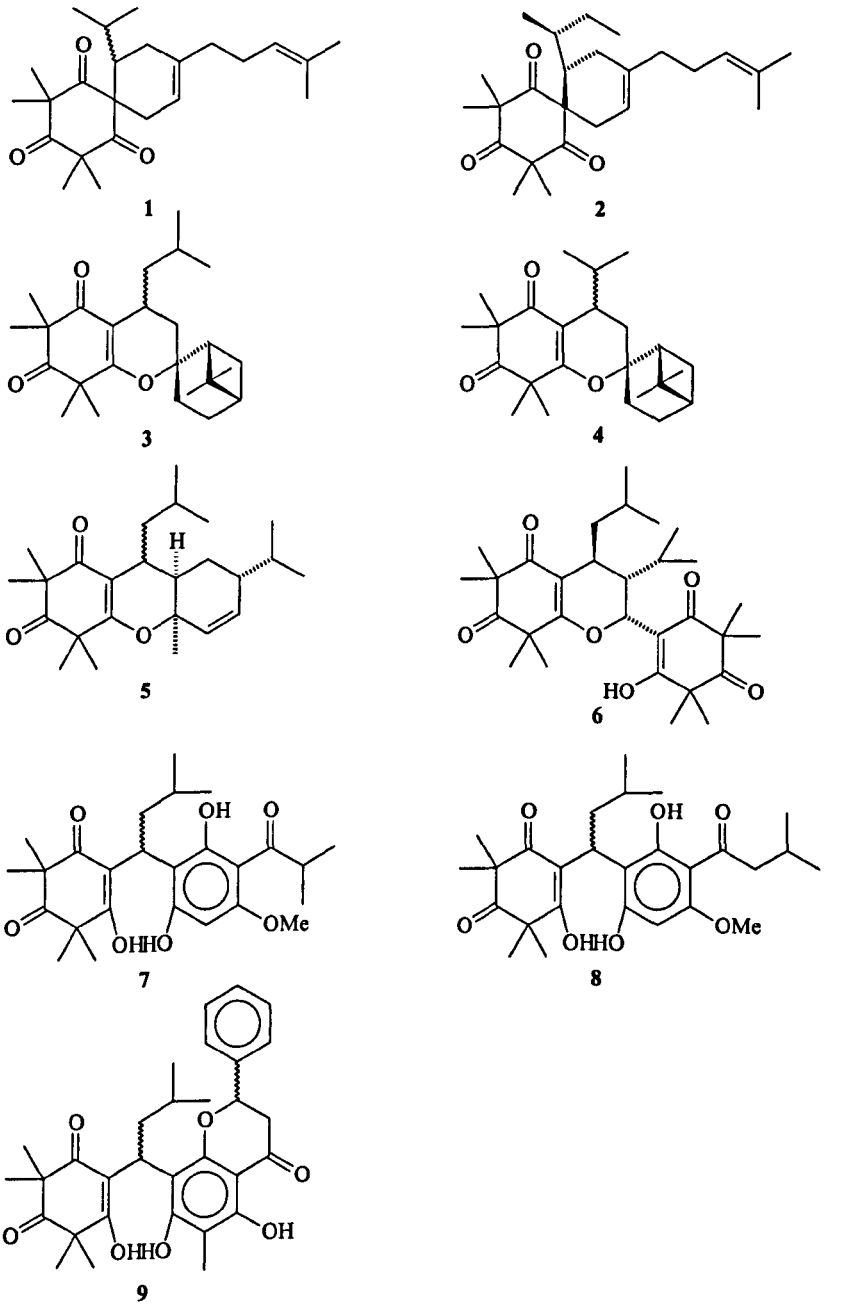


Figure 2.23 - Natural products isolated from the Myrtaceae family.

Few tetramethylcyclohexenedione natural products have been previously isolated (figure 2.24). These include myrtucommulone A **2.4**, from *Myrtus communis L.* (Myrtaceae)[116,117] and emorydone **2.5**, vafzelin **2.6** and uvafzelin **2.7** from *Uvaria afzelii* (Annonaceae).[118] Other simple tetramethylcyclohexenedione natural products, including syncarpic acid, have been synthesised (figure 3.1).

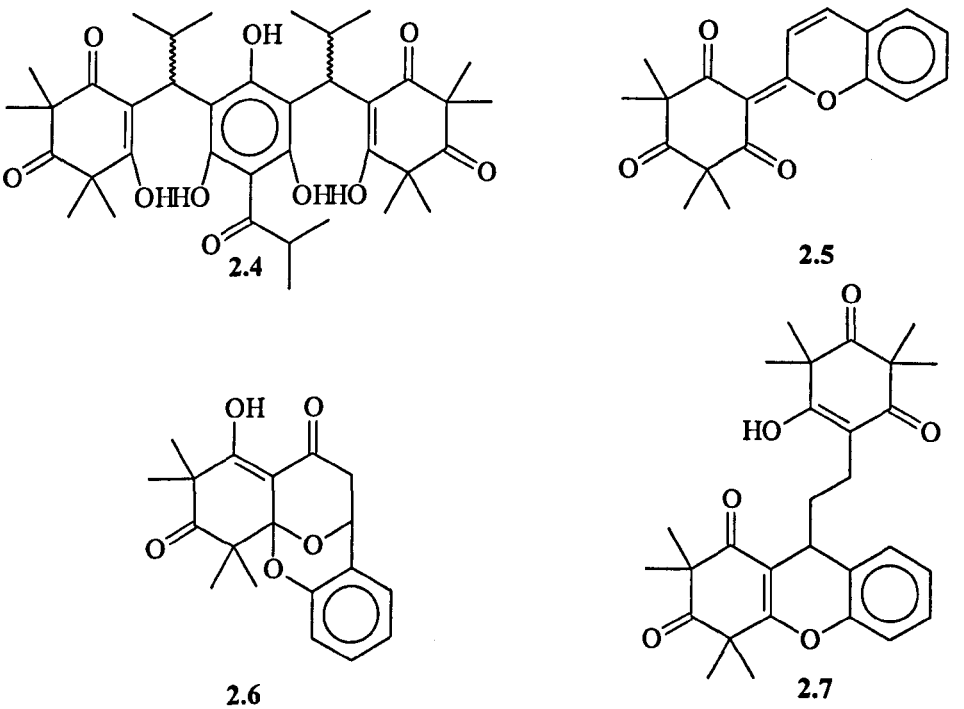
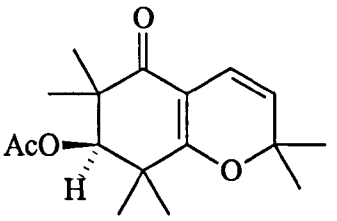
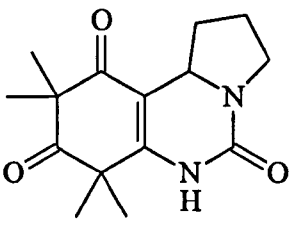


Figure 2.24 - Other syncarpic acid containing natural products.

Natural products clearly related to syncarpic acid (figure 2.25) include hillyl acetate **2.8** from *Syncarpia hillii* (Myrtaceae)[119] and a further compound from *Uvaria afzelli*, syncarpurea **2.9**.[120]



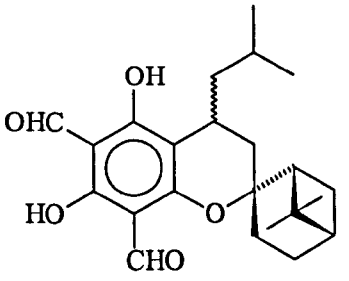
2.8



2.9

Figure 2.25 - Compounds related to syncarpic acid.

Many phloroglucinol based compounds for example compounds **2.10 - 2.13** (figure 2.26), stucturally related to compounds **3 - 9**, have been found in plants of the Myrtaceae family.[113,121,122] A recent paper on phloroglucinols[123] from *Eucalyptus* species reviews much of this work.



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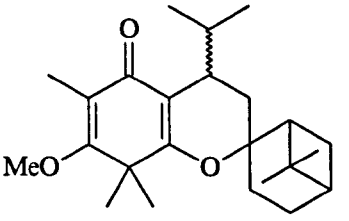

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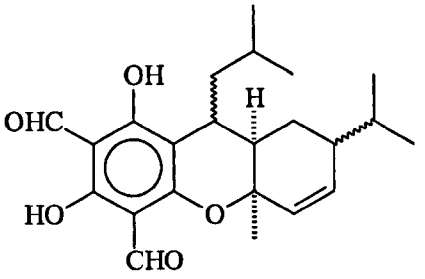

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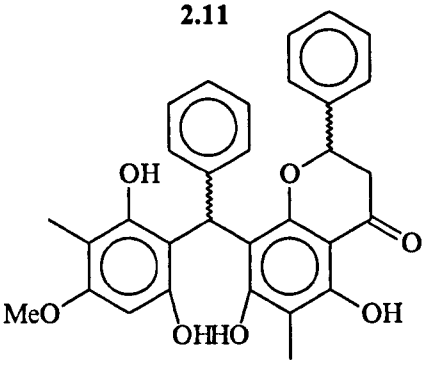


2.13

Figure 2.26 - Examples of related phloroglucinol compounds.

The relationship between the compounds isolated in this study and other

compounds previously isolated, can give us information as to the possible biosynthetic pathway of these types of natural products. This is discussed further in the following section.

2.4 POSTULATED BIOSYNTHESIS OF COMPOUNDS 1 TO 9.

No investigations into the biosynthesis of the natural products **1** to **9** were attempted, but postulation about the routes involved is possible. Information from biosynthetic routes can often be used to aid in the synthesis of the natural products (see chapter 3). It can be seen that compounds **1 - 9** are clearly related to the acylphloroglucinols from *Eucalyptus* species where biogenetic routes have been considered.[123]

Interestingly, the only natural product in this area that has been subject to biosynthetic studies is tasmone. This molecule is of historical importance as this and related studies were the first to recognise biological C-methylation.[124] ^{14}C methyl groups were introduced by feeding labelled methionine into cut shoots of *Eucalyptus camfieldii* and the subsequent labelled tasmone was isolated and analysed by degradation studies.

The biogenetic steps leading to tetramethylcyclohexenedione analogues (figure 2.27) involve a polyketide derived from an alkanoyl coenzyme A starter unit, which is extended by three malonyl CoA units. Claisen type cyclisation gives a phloroglucinol structure which is methylated at the doubly activated carbons with S-adenosylmethionine.

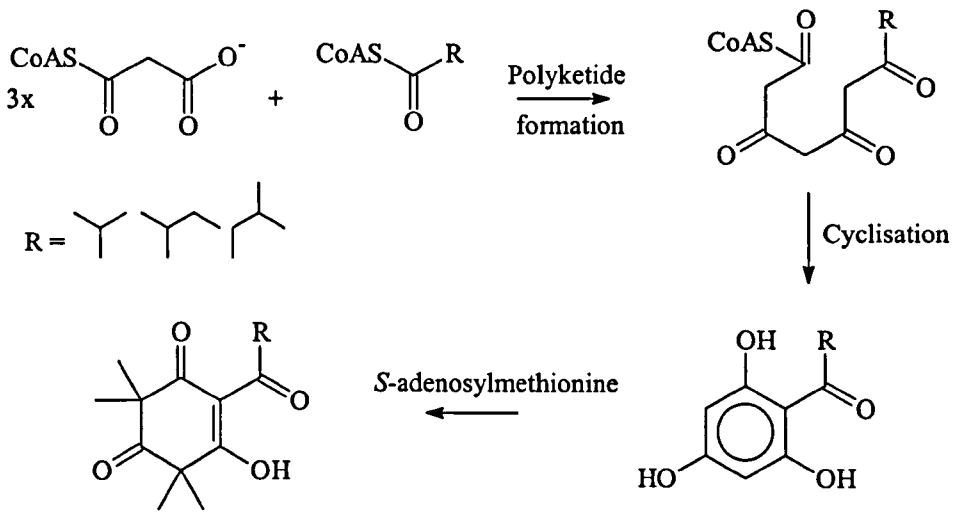


Figure 2.27 - Biosynthesis of acyl-syncarpic acid.

The biosynthesis of the phloroglucinol and flavanone molecules is also known to involve an alkanoyl coenzyme A (from phenylalanine for the flavanone) and three malonyl coenzyme A units, that are subsequently O- or C-methylated with *S*-adenosylmethionine.

Reduction and subsequent dehydration of the acyl-syncarpic acids would lead to key putative precursors (figure 2.28) from which all of the natural products **1** to **9**, could be derived.

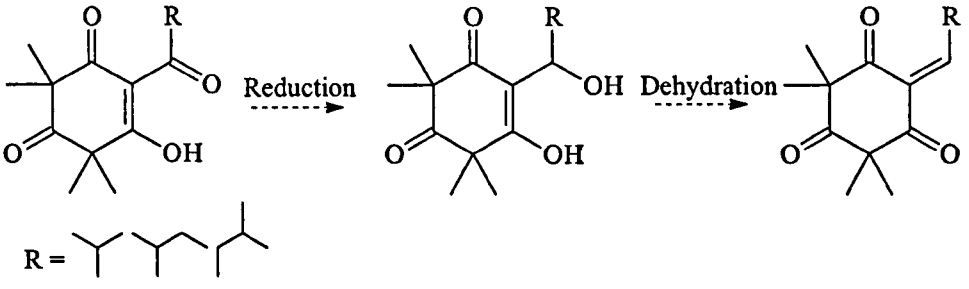


Figure 2.28 - Postulated key intermediates in biosynthesis.

These key intermediates could undergo Diels-Alder type cycloadditions with the terpenes myrcene to give the natural products **1** and **2**, β-pinene to give the natural products **3** and **4**, and α-phellandrene to give the natural product **5** (figure 2.29). It could also form the natural product **6** via a [4 + 2] cycloaddition with a syncarpic acid derivative formed from exo-dehydration.

It is interesting to note that the key intermediates appear to be capable of acting both as dienophiles for compounds **1** and **2** and as dienes for compounds **3 - 6**.

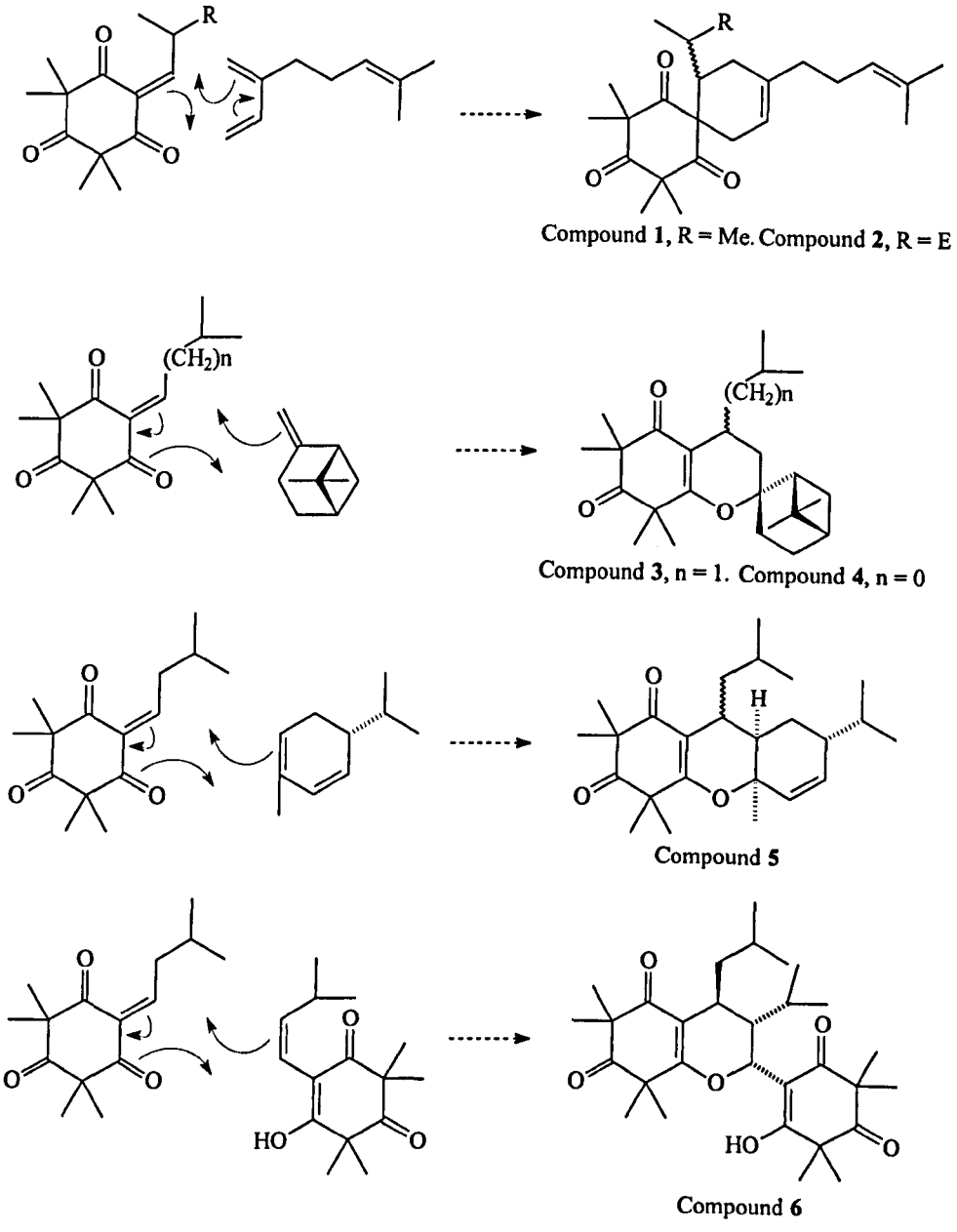


Figure 2.29 - Postulated biosynthesis via Diels-Alder addition.

The number of natural products postulated to be constructed via Diels - Alder reactions has increased noticeably in the recent literature.[125] Moreover, various studies have examined the possibility of a Diels-Alderase enzyme, and

limited evidence[126,127] has shown increased reaction rates and unexpected stereochemistry, suggesting enzyme catalysis.

The natural products **7** to **9** could also be derived from the key putative precursor (figure 2.30) via aromatic electrophilic substitution either to a phloroglucinol moiety or a flavanone.

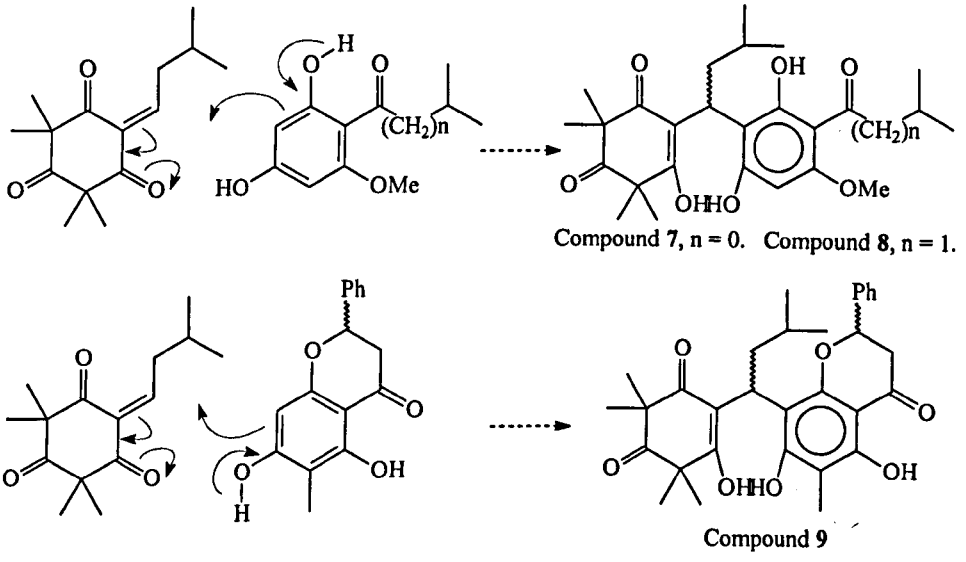


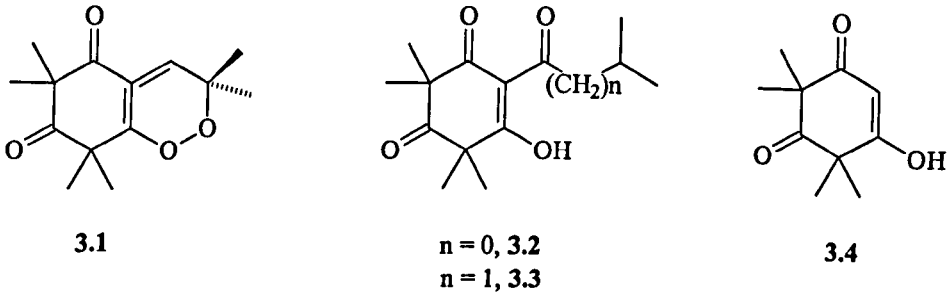
Figure 2.30 - Postulated biosynthesis of natural products **7** to **9**.

CHAPTER 3

STUDIES ON THE SYNTHESIS OF THE INSECTICIDAL NATURAL PRODUCTS ISOLATED

3.1 INTRODUCTION

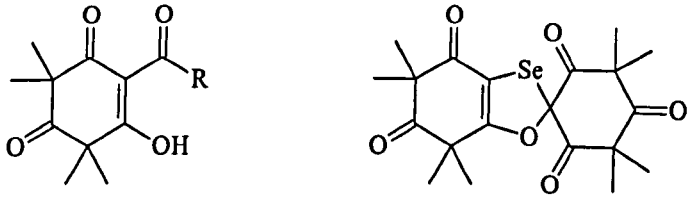
The synthesis of natural products containing a tetramethylcyclohexenedione moiety (figure 3.1) has been limited to G-regulators **3.1**,[128] simple acyl derivatives such as flavesone **3.2**[129] or leptospermone **3.3**[130,131] and syncarpic acid **3.4** itself.[132,133,134]



3.1 | **n = 0, 3.2**
n = 1, 3.3 | **3.4**

Figure 3.1 - Synthesised natural products containing syncarpic acid

Simple C-acyl derivatives **3.5** have been extensively synthesised (figure 3.2) and widely patented[135] as they possess pre-emergence and post-emergence herbicidal activity. Other studies with tetramethylcyclohexenediones have shown interesting oxidation reactions with selenium dioxide,[136] which gave various selenides, e.g. compound **3.6**, on rearrangement.

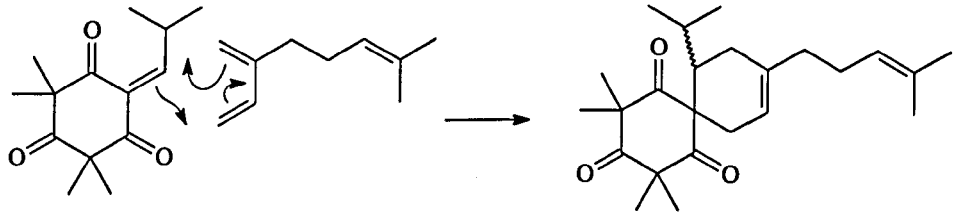


R = Alkyl, 3.5 | **3.6**

Figure 3.2 - Synthetic compounds containing tetramethylcyclohexenediones.

3.2 SYNTHESIS OF SPIRO COMPOUNDS 1 AND 2

Biosynthetically, compound **1** can be considered to be an adduct arising from the combination of alkyl-syncarpic acid and monoterpene residues (see section 2.3), giving rise to an unusual spiro centre at the ring junction of syncarpic acid. Using this postulated biosynthetic route, a biomimetic synthesis was designed (scheme 3.1), envisaging a Diels-Alder reaction, between an alkylidene unit **3.7** and myrcene **3.8**, as the key step.



3.7 **3.8** **1**

Scheme 3.1 - Key step in synthesis of **1**.

Myrcene **3.8** is a commercially available compound, and precursor **3.7** was thought to be derivable from C-alkylation of syncarpic acid.

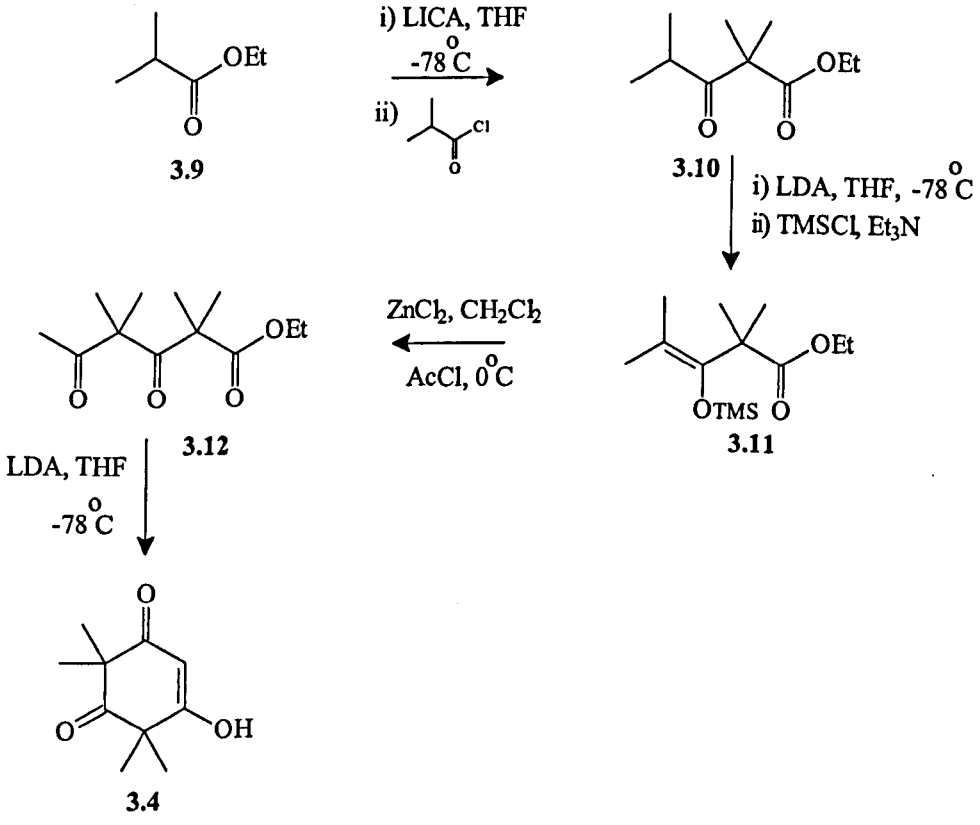
Synthesis of syncarpic acid 3.4

The synthesis of 1-hydroxy-4,4,6,6-tetramethylcyclohexen-3,5-dione (syncarpic acid) **3.4** was achieved by modifications to two published routes, each with overall yields of 40%.

Route 1 - Synthesis by intra-molecular cyclisation[132] (scheme 3.2)

Claisen condensation of ethyl isobutyrate **3.9** and isobutyryl chloride,

using lithium n-cyclohexylisopropylamide (LICA) as base, gave the β-ketoester **3.10** in 95% yield. The TMS enol ether **3.11**, formed by trapping with TMS chloride the anion of the β-ketoester **3.10**, underwent selective C-acylation with acetyl chloride to give the β,δ-diketoester **3.12**. Further deprotonation with LDA caused intramolecular cyclisation to yield syncarpic acid **3.4** in 40% overall yield.

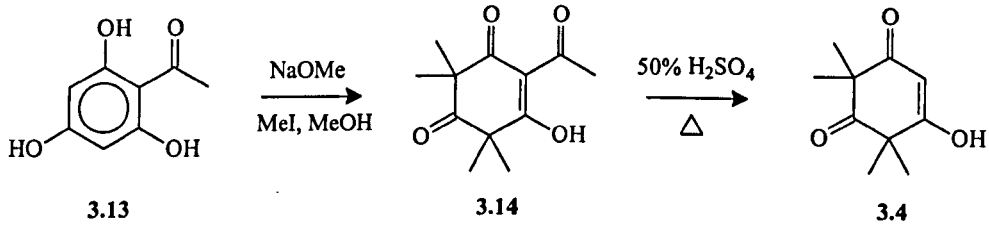


Scheme 3.2 - Synthesis of syncarpic acid **3.4** via intramolecular cyclisation.

Route 2 - Synthesis from trihydroxyacetophenone **3.13**[133] (scheme 3.3)

Syncarpic acid **3.4** was synthesised in two steps starting from 2,4,6-trihydroxyacetophenone **3.13**. Reaction with sodium methoxide and excess methyl iodide gave the tetramethylated product **3.14** in quantitative yield. Deacylation under the reported conditions[134] using 2M hydrochloric acid was

unsuccessful and gave low yields of syncarpic acid **3.4** along with unreacted starting material. Under the conditions of refluxing 50% sulfuric acid, deacetylation was achieved to give syncarpic acid **3.4** in good yield.



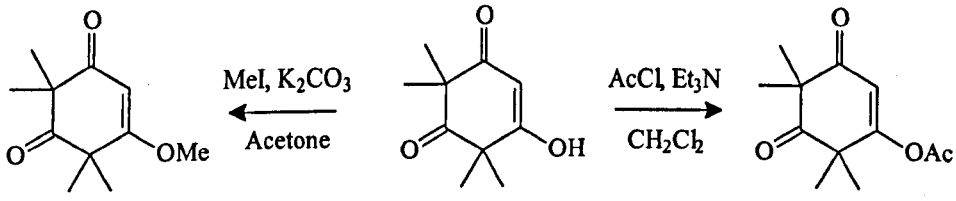
3.13 **3.14** **3.4**

Scheme 3.3 - Synthesis of syncarpic acid **3.4** via per-methylation.

Alkylation of syncarpic acid 3.4

For the subsequent studies, route 2 (scheme 3.3) was preferred to synthesise syncarpic acid **3.4** in large amounts.

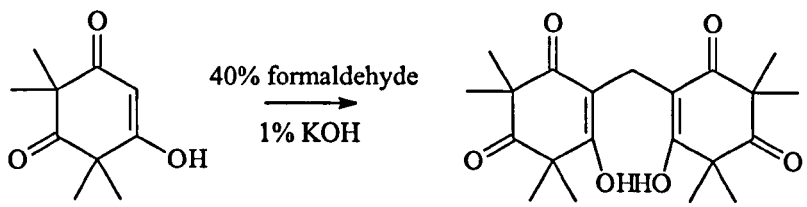
Alkylation reactions of β-diketones such as dimedone (5,5-dimethyl-1,3-cyclohexanedione) and 1,3-cyclohexanedione have been extensively studied[137,138,139,140] to define conditions that direct the alkylation onto the carbon or the oxygen atom. O-Alkylation of syncarpic acid **3.4** was achieved with methyl iodide and potassium carbonate to give the methyl ether **3.15**, and O-acylation by esterification of syncarpic acid **3.4** with acetyl chloride to give compound **3.16** (scheme 3.4).



3.15 **3.4** **3.16**

Scheme 3.4 - O-alkylation and O-acylation of syncarpic acid **3.4**

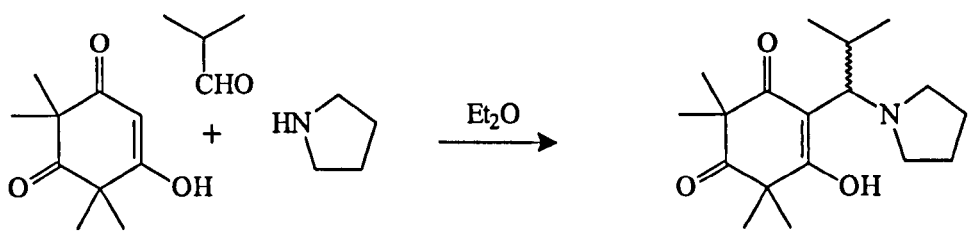
It has been reported[141] that aldehydes react with cyclohexanediones to give bis-products and this has been exploited in the identification and characterisation of aldehydes by analysis of the melting points of derivatives. Using this methodology, reaction of syncarpic acid **3.4** with 40% formaldehyde solution in 1% potassium hydroxide gave the bis-compound **3.17** (scheme 3.5) in quantitative yield.



3.4 **3.17**

Scheme 3.5 - Formation of bis-compound.

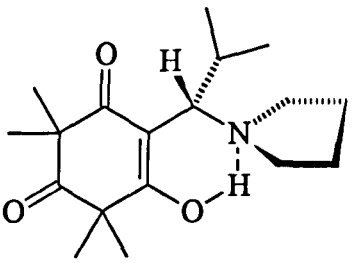
To suppress dimer formation, syncarpic acid **3.4** was reacted with an aldehyde in the presence of a base such as pyrrolidine, to give a pyrrolidine complex via the Mannich reaction.[142,143,144] Hence reaction of syncarpic acid **3.4**, isobutyraldehyde and pyrrolidine yielded the crystalline Mannich base **3.18** (scheme 3.6). No bis-products were isolated.



3.4 **3.18**

Scheme 3.6 - Formation of Mannich base.

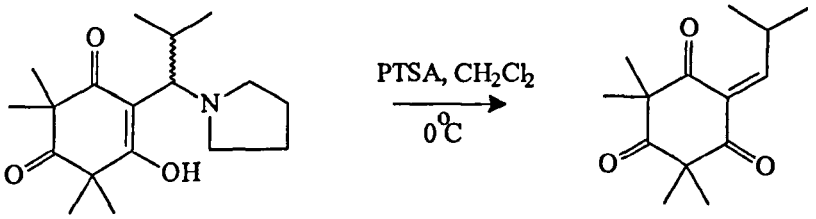
Interestingly, the NMR of the Mannich base **3.18** indicated that all eight protons of the pyrrolidine ring were non-equivalent. These observations were rationalised by hydrogen bonding[128] between the enol hydrogen and the nitrogen atom (figure 3.3), leaving the pyrrolidine ring in a conformation perpendicular to the syncarpic acid.



3.18

Figure 3.3 - Conformation of Mannich base.

The Mannich base **3.18** (scheme 3.7) underwent acid catalysed elimination to give the required alkylidene precursor **3.7.**

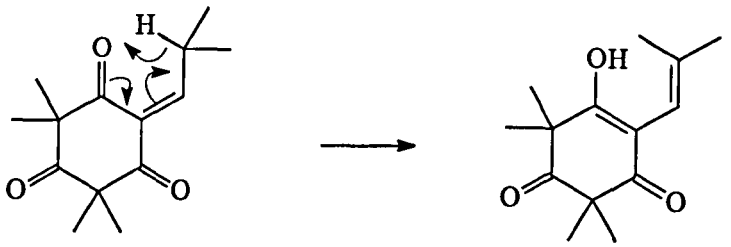


3.18 **3.7**

Scheme 3.7 - Elimination of Mannich base.

The alkylidene **3.7** was stable under neutral conditions, but in strong acidic or basic media, rearrangement occurred (scheme 3.8) which gave the

thermodynamically more stable conjugated enol structure **3.19**.

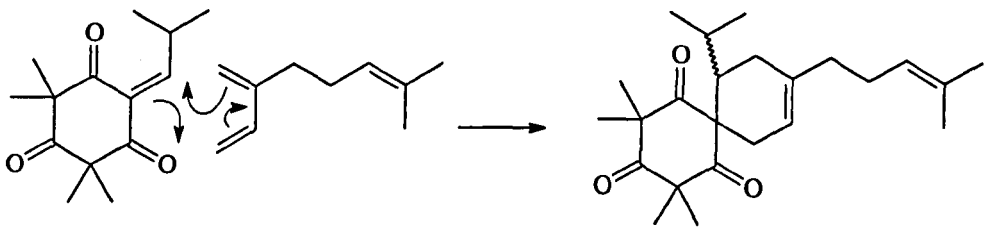


3.7 **3.19**

Scheme 3.8 - Rearrangement of the alkylidene **3.7**.

Diels-Alder biomimetic synthesis

Diels-Alder reaction of the alkylidene **3.7** and myrcene **3.8** in refluxing benzene (scheme 3.9) gave the required spiro compound **1** in low yields of 10 - 20 %. The major byproduct of the reaction was the rearranged alkylidene **3.19**. This work demonstrated the feasibility of this methodology to synthesise natural product **1**, although the low yield of the reaction required improvement.

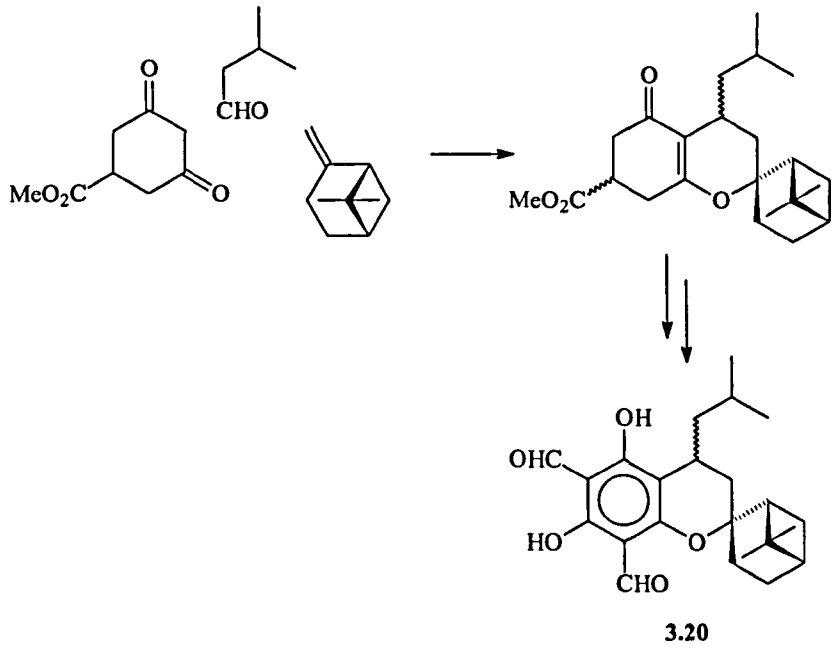


3.7 **3.8** **1**

Scheme 3.9 - Diels-Alder reaction.

Addition of Lewis acids such as $Et_2O.BF_3$ was studied, but gave exclusive rearrangement of the alkylidene **3.7** (scheme 3.8) and no Diels-Alder products were detected.

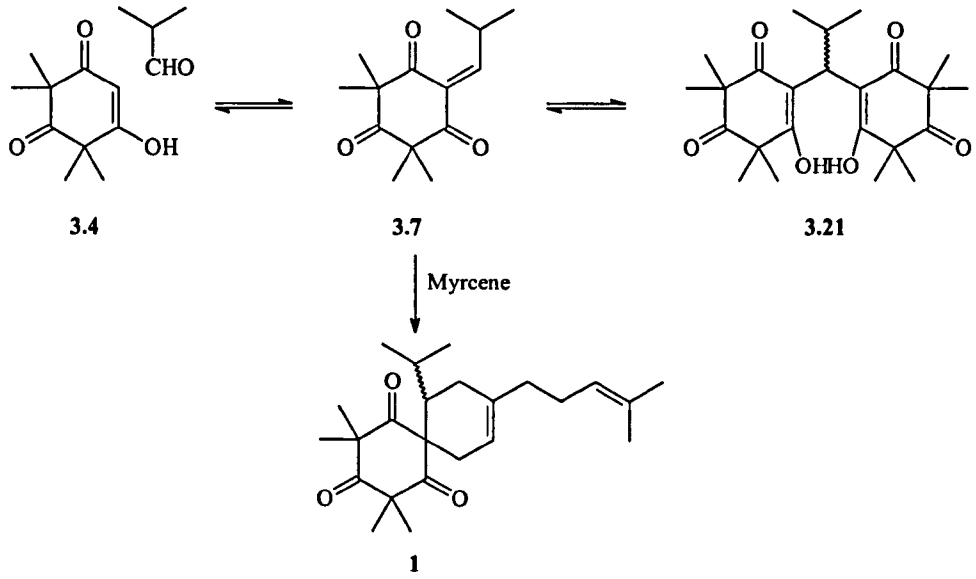
An alternative possible improvement was explored using the methodology of Koser[145] in the synthesis of intermediates of the robustadials **3.20** (scheme 3.10) where in one pot, alkylidenes were formed *in situ* and subsequently reacted with β-pinene in a Diels-Alder reaction.



3.20

Scheme 3.10 - Synthesis by Koser of intermediates of robustadials **3.20.**

The reaction conditions were anticipated to set up an equilibrium, equivalent to that proposed by Koser, between syncarpic acid **3.4**, the cyclohexanetrione **3.7** and the bis compound **3.21** (scheme 3.11) so that the cyclohexanetrione **3.7** was continually available for reaction with myrcene **3.8.**



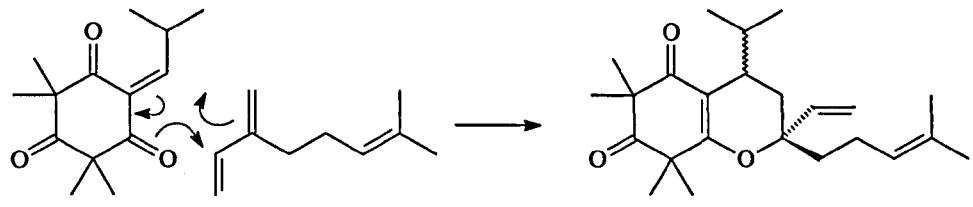
Scheme 3.11 - Equilibria during reaction

Reaction of syncarpic acid **3.4**, isobutyraldehyde and myrcene **3.8** in refluxing acetic acid using this methodology did indeed give the spiro natural product **1** in 43% yield. NMR and mass spectral data of natural and synthetic compounds were identical.

The Diels-Alder reaction of myrcene **3.8**, an electron rich diene, and the electron poor dienophile **3.7** (scheme 3.9) as expected proceeded favourably and gave a regiospecific product. This regioselectivity has been explained by molecular-orbital considerations of analogous reactions.[146,147,148]

A minor by-product of the reaction, due to a hetero Diels-Alder reaction (scheme 3.12) between the cyclohexanetrione **3.7** acting as diene and myrcene **3.8** acting as a dienophile, gave the compound **3.22** as a mixture of diastereomers in 4% yield. Full characterisation was achieved using NMR spectroscopy. In particular, long range C-H correlations between the quaternary carbon at C-9 and adjacent protons at H-8, H-10 and H-23 were useful in

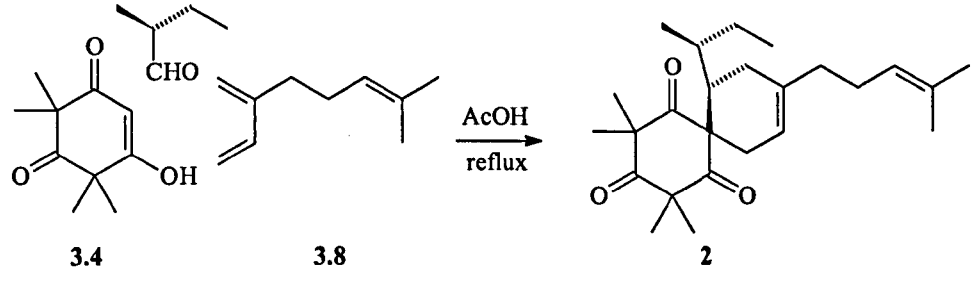
elucidation of the structure.



3.7 3.8 3.22

Scheme 3.12 - Hetero Diels-Alder by-product of reaction.

The spiro natural product **2** was synthesised using identical methodology (scheme 3.13) and a 58% yield was obtained for the Diels-Alder reaction. As before, a small amount of hetero Diels-Alder product was also obtained.



3.4 3.8 2

Scheme 3.13 - Synthesis of spiro natural product **2**.

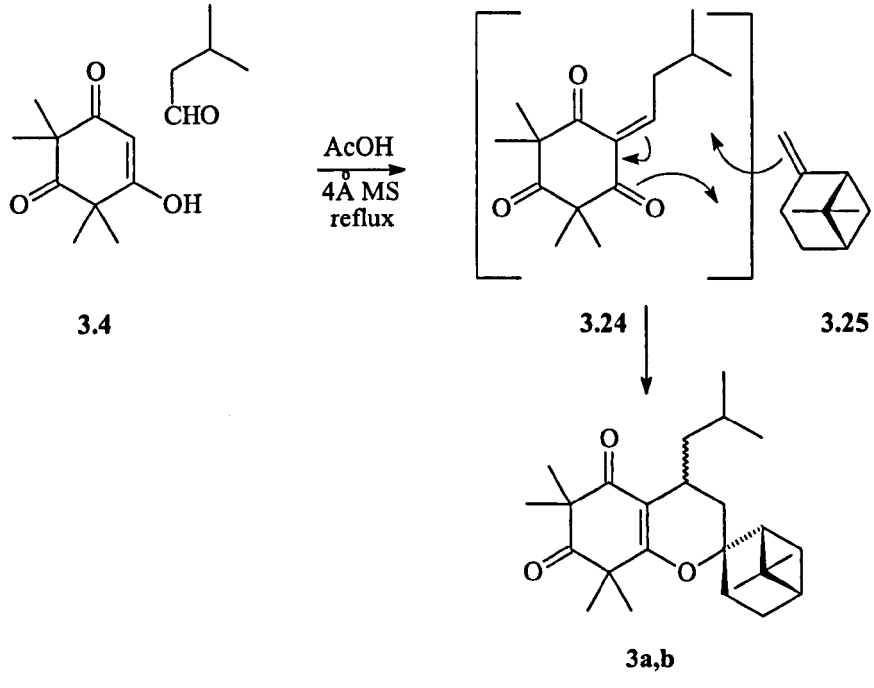
The reaction was performed using racemic 2-methylbutyraldehyde and gave a mixture of stereoisomers which were separated by chromatography into two diastereomers **2a** and **2b**. The natural product **2** was also as a mixture of stereoisomers and natural and synthetic samples were identical by NMR spectroscopy.

A further synthetic isobutyl analogue **3.23** was successfully synthesised (using isovaleraldehyde) to confirm the versatility of this reaction. It is

therefore envisaged that the synthetic strategy could be extrapolated to a range of aldehydes and dienes to give a variety of analogues.

3.3 SYNTHESIS OF PINANE COMPOUNDS 3 AND 4

The pinane natural product **3** was synthesised as outlined in scheme 3.14. Knoevenagel condensation of syncarpic acid **3.4** and isovaleraldehyde formed *in situ* the cyclohexanetrione **3.24** as described previously. The cyclohexanetrione **3.24** then underwent a hetero Diels-Alder reaction with (S)-(-)-β-pinene **3.25** to give a mixture of two epimeric compounds **3a** and **3b** in 53% yield. These two epimers were separable by flash chromatography, with the less polar epimer identical to the natural product by NMR and α_D.

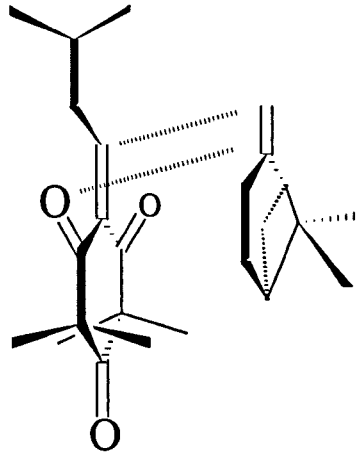


Scheme 3.14 - Synthesis of pinane natural product.

The electron deficient cyclohexanetrione **3.24** participates preferentially with the electron rich dienophile **3.25** in an inverse electron demand Diels-Alder reaction.[149,150,151] The electron withdrawing β-keto group lowers the

$LUMO_{diene}$ energy level and enhances the rate of reaction.

In general, cycloaddition reactions of oxabutadienes exhibit predictable regioselectivity,[152] the only exceptions being reactions of electron deficient oxabutadienes with electron deficient dienophiles.[153] In the synthesis of pinane **3**, the 'well matched' Diels-Alder reaction showed regioselectivity from preferred endo approach of reactants (figure 3.4) with the oxygen of the oxabutadiene attacking the more substituted end of the pinene double bond. These cycloaddition reactions are believed to be concerted but nonsynchronous with carbon-carbon bond formation more advanced than carbon-oxygen bond formation.



3.24 **3.25**

Figure 3.4 - Attack of oxabutadiene to double bond.

Moreover, the reaction is thought to be stereoselective[145] with respect to the spirocentre, as the oxabutadiene **3.24** approaches the π-face of the double bond, not only in an endo manner, but also away from the dimethyl bridge of the pinene **3.25**.

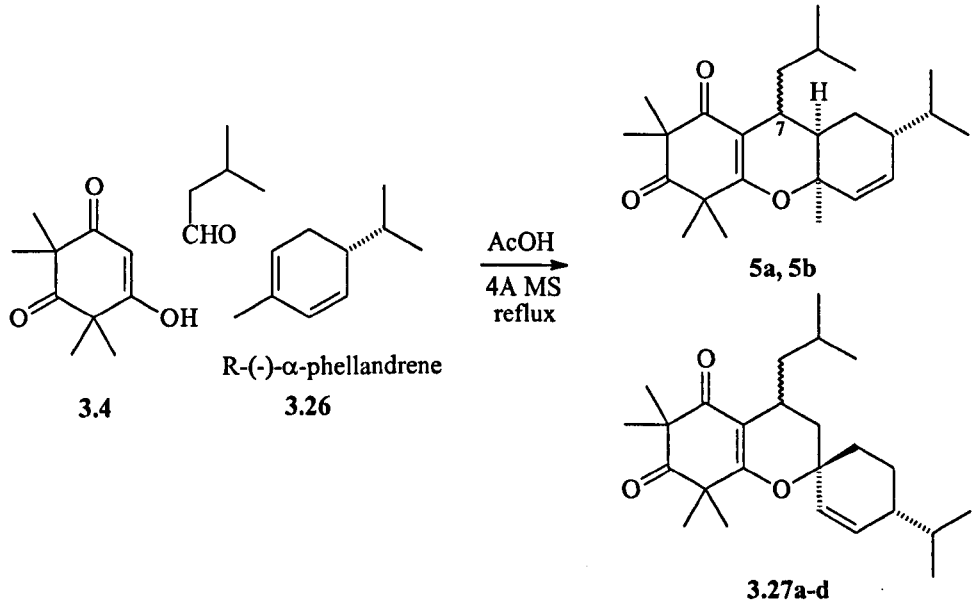
The remaining stereocentre, containing the isobutyl moiety, was undefined by the reaction and two epimers **3a** and **3b** were formed in equal amounts and separated by column chromatography.

The homologous natural product **4** isolated from *Calothamnus validus* was synthesised using identical conditions to the natural product **3** (scheme 3.14), using isovaleraldehyde in place of isobutyraldehyde. Yields and stereochemistry of products were comparable.

3.4 SYNTHESIS OF PHELLANDRENE COMPOUNDS 5a AND 5b

Using similar methodology to that used in the synthesis of the pinane natural products (section 3.2), reaction of syncarpic acid **3.4**, 1R-(α)-phellandrene **3.26** and isovaleraldehyde in refluxing acetic acid gave a mixture of six compounds (scheme 3.15). These compounds were separated by flash chromatography and silica gel HPLC.

By NMR and α_D, two of the compounds were identical to the natural products **5a** and **5b** and were assigned as epimers at C-7.

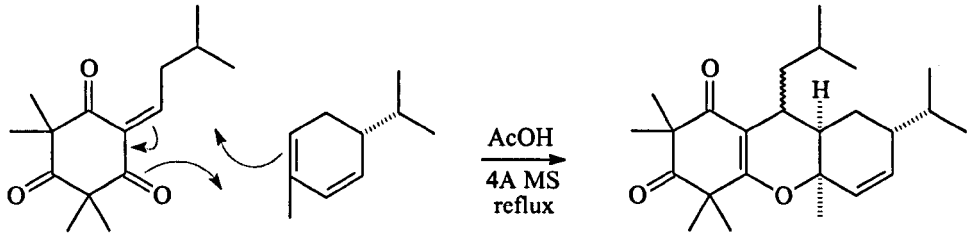


3.4 **3.26** **3.27a-d**

Scheme 3.15 - Synthesis of the phellandrene natural products **5a** and **5b**.

The success of this synthesis suggests that, as for the earlier syntheses, a hetero Diels-Alder reaction (scheme 3.16) is occurring. Again the cycloaddition reaction was regioselective with the oxygen of the cyclohexanetrione attacking the more substituted end of the trisubstituted

double bond through *endo* approach and giving *cis* fusion at the ring junctions. By analogy with the pinane cycloaddition, the oxabutadiene may approach the phellandrene double bond on the π-face away from the isopropyl group hence forming the ring junction stereospecifically, with the hydrogen and methyl at the ring junctions and the isopropyl group all *cis* to each other.



3.24 **3.26** **5a, 5b**

Scheme 3.16 - Hetero Diels-Alder reaction with α-phellandrene.

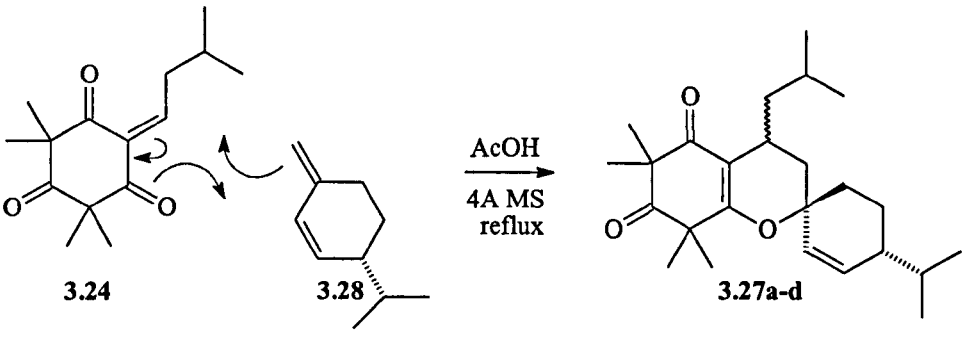
The remaining four compounds **3.27a-d** were assigned as four spiro stereoisomers and their full NMR assignments given in table 3.1. The structural elucidation of compounds **3.27a-d** was assisted by long range C - H correlations. Information about the relative stereochemistry of compounds **3.27a-d** was obtained from NOESY. Correlations between H-7 and H-10 were present for compounds **3.27a,b** but absent for **3.27c,d**. Unfortunately absolute stereochemical assignments were not possible as correlations from the defined R stereochemistry at C-12 were not conclusive.

Table 3.1 - ^{1}H and ^{13}C NMR data for compounds **3.27a-d**

	3.27a		**3.27b**		**3.27c**		**3.27d**	
	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C	^{1}H	^{13}C
1		169.2		169.1		169.1		169.3
2		47.9		47.9		48.0		47.8
3		213.6		213.5		213.5		213.5
4		55.4		55.4		55.5		55.5
5		198.1		198.0		198.1		198.0
6		112.3		113.0		112.5		112.5
7	2.87	25.7	2.75	25.8	2.74	25.4	2.74	25.7
8	1.00	42.8	1.00	42.4	0.93	42.4	1.04	42.3
	1.60		1.89		1.83		1.68	
9		75.1		76.7		75.7		77.9
10	5.71	126.6	5.63	127.4	5.63	129.6	5.64	130.6
11	5.84	137.1	5.75	134.4	5.92	136.6	5.77	133.5
12	1.99	42.2	2.03	41.6	1.94	42.1	2.06	41.7
13	1.61	20.6	1.38	38.6	1.52	20.7	1.77	22.1
14	1.95	38.4	1.57	22.1	1.33	31.1	1.69	31.8
	2.04		2.14		1.99		1.91	
15	1.38	24.0	1.38	23.8	1.39	24.2	1.39	24.1
16	1.26	25.3	1.33	25.0	1.31	26.1	1.32	25.4
17	1.31	26.1	1.32	26.2	1.32	26.2	1.32	26.3
18	1.33	22.6	1.34	22.3	1.34	22.3	1.33	22.2
19	1.64	35.4	1.54	34.5	1.56	39.3	1.71	36.6
	1.99		1.92		1.92		1.94	
20	1.75	25.5	1.40	25.4	1.68	25.3	1.72	25.7
21	0.97	20.7	1.02	20.7	0.95	20.7	0.97	20.8
22	0.89	24.2	0.90	24.2	0.89	24.2	0.88	24.2
23	1.7	31.7	1.66	31.6	1.68	31.6	1.70	31.6
24	0.89	19.0	0.89	19.4	0.91	19.1	0.91	19.3
25	0.92	19.5	0.90	19.8	0.93	19.5	0.92	19.6

Chemical shift values are in ppm. For coupling constants see experimental section.

These compounds were presumably formed by hetero Diels-Alder reaction with β-phellandrene **3.28** (scheme 3.17) or an equivalent complexed form.

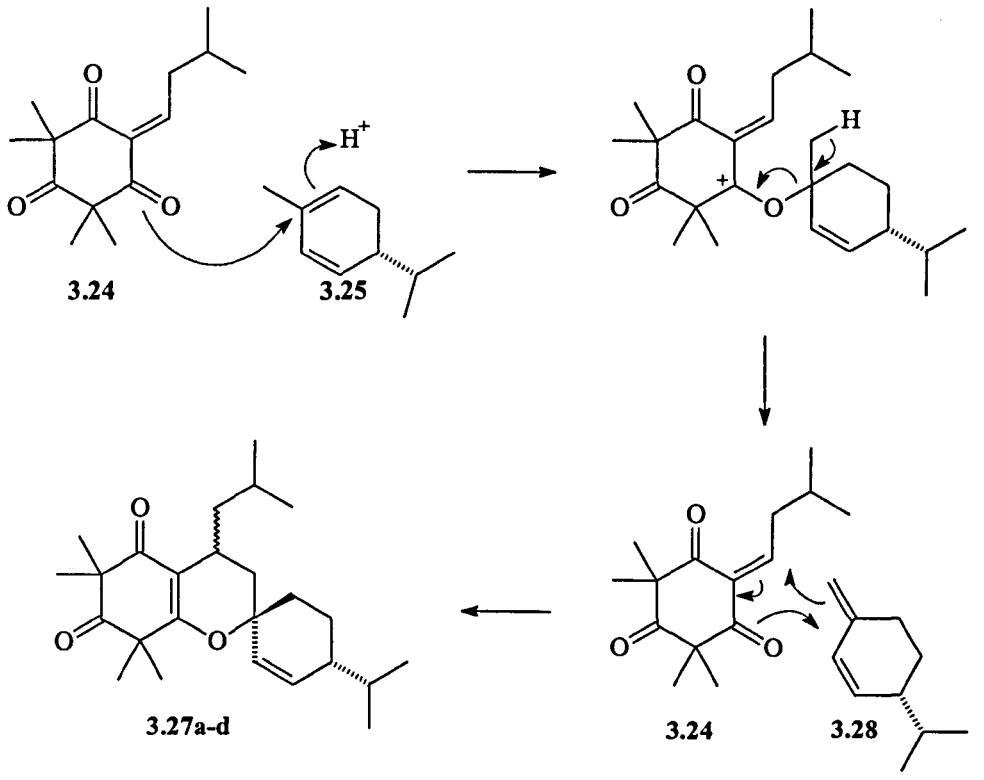


3.24 **3.28** **3.27a-d**

Scheme 3.17 - Postulated hetero Diels-Alder reaction with β-phellandrene.

It is unclear if β-phellandrene was formed under the reaction conditions and attempts to study this have been inconclusive. The four spiro compounds constituted 44% of the reaction products and if an α ⇌ β equilibrium was set up and a small proportion of β was formed, the Diels - Alder reaction with β-phellandrene might have proceeded faster to produce more spiro products.

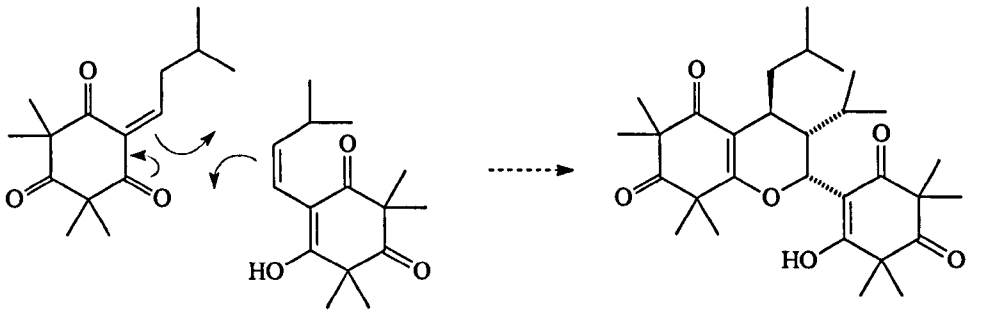
One possible explanation is the participation of the alkylidene **3.24** in isomerisation of α-phellandrene **3.25** (scheme 3.18), which would give β-phellandrene in close proximity to the diene and hence undergo a Diels - Alder reaction.



Scheme 3.18 - Possible route to spiro compounds 3.27a-d.

3.5 ATTEMPTED SYNTHESIS OF DIMERIC COMPOUND 6

The synthesis of the dimeric natural product **6** was attempted by hetero-Diels-Alder reaction of cyclohexanetrione **3.24** and conjugated alkene **3.29.** Under a variety of conditions the reaction failed to give any required product (scheme 3.19). This may have been due to the poorly matched [4 + 2] reaction of an electron-deficient oxabutadiene with an electron-deficient dienophile.



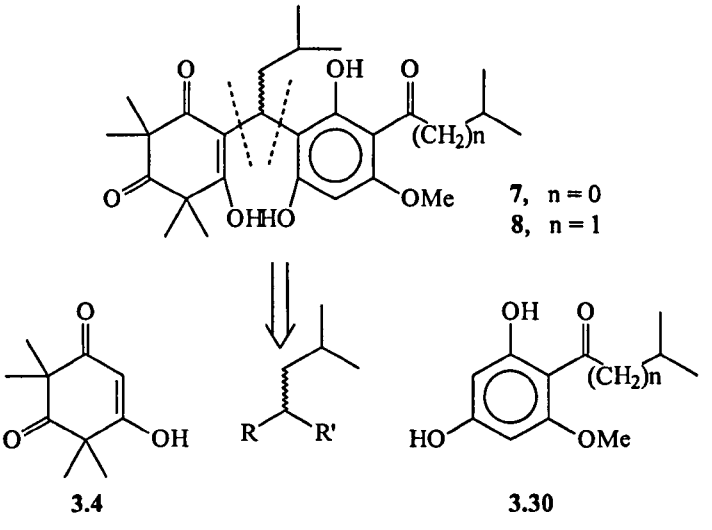
3.24 **3.29** **6**

Scheme 3.19 - Proposed synthesis of dimeric compound **6.**

It is hoped that optimisation of the Diels-Alder reaction conditions may produce the required compound.

3.6 SYNTHESIS OF PHLOROGLUCINOL COMPOUNDS 7 AND 8

For the synthesis of compound **7**, it was planned to couple syncarpic acid **3.4**, an isovaleryl moiety and a phloroglucinol fragment **3.30** (scheme 3.20).



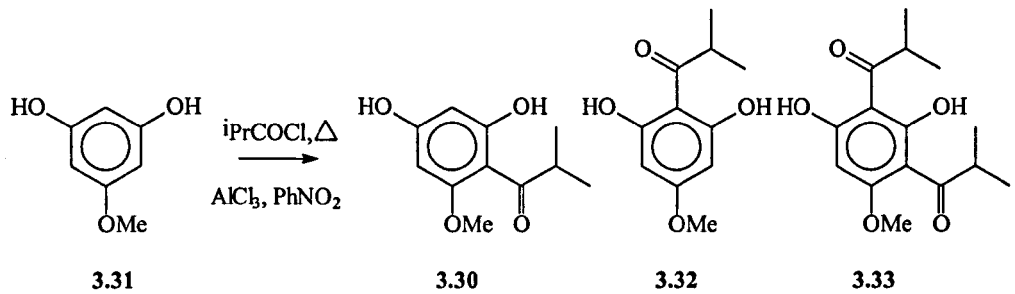
Scheme 3.20 - Retrosynthetic analysis of natural products **7** and **8**

Coupling of alkyl groups to syncarpic acid **3.4** via aldehydes had been achieved (scheme 3.6) so initially for this approach, synthesis of the phloroglucinol moiety **3.30** was required.

Synthesis of 4,6-dihydroxy-2-methoxyisobutyrophenone 3.30

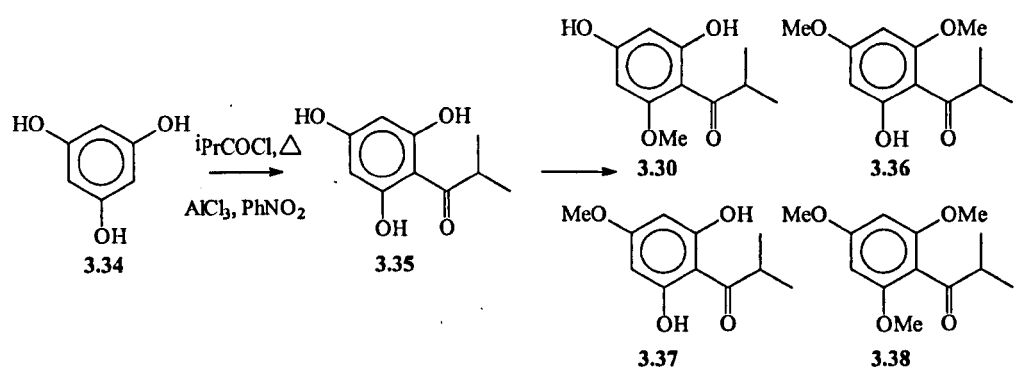
Synthesis of 4,6-dihydroxy-2-methoxyisobutyrophenone **3.30** was achieved in modest yield by acylation of 5-methoxyresorcinol **3.31** with isobutyryl chloride under standard Friedel-Crafts conditions (scheme 3.21). As expected, the reaction gave mixtures of the monoacylated **3.30, 3.32** and the

diacylated products **3.33** which required extensive separation and purification.



Scheme 3.21 - Acylation of 5-methoxyresorcinol **3.31.**

Acylation of phloroglucinol **3.34** with isobutyryl chloride (scheme 3.22) gave the mono-acylated product **3.35** in 70% yield, but selective monomethylation under a variety of conditions gave mixtures of mono-, di- and tri-methylated products **3.30, 3.36, 3.37** and **3.38** which proved difficult to separate.

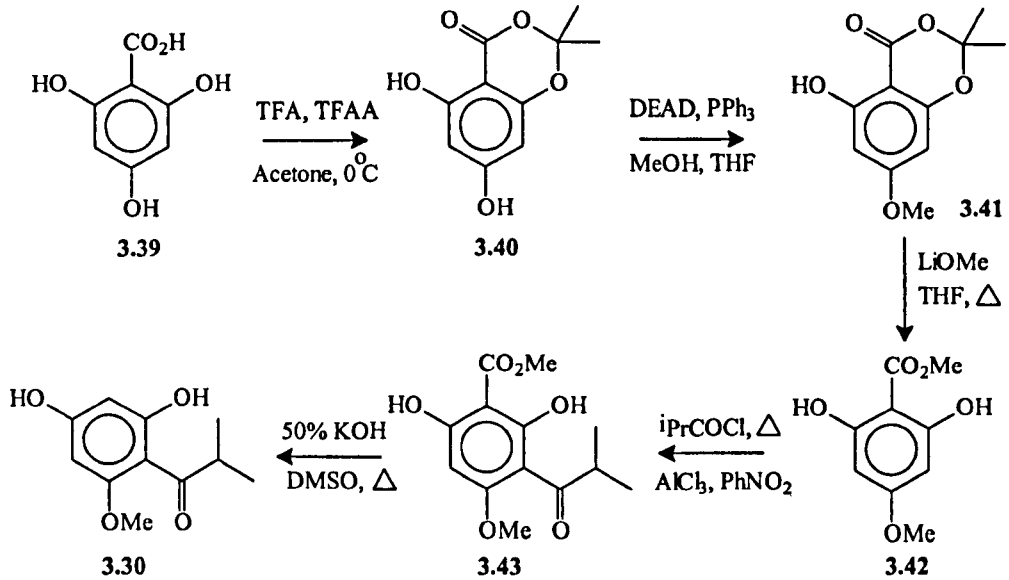


Scheme 3.22 - Synthesis of compound **3.30** from phloroglucinol.

For the synthesis of substantial amounts of compound **3.30,** a regioselective route was devised (scheme 3.23) which selectively gave the required compound in good overall yield, and used the cheap and readily

available starting material 2,4,6-trihydroxybenzoic acid **3.39**.

Reaction of acetone with 2,4,6-trihydroxybenzoic acid **3.39** in the presence of trifluoroacetic anhydride and trifluoroacetic acid gave the 1,3-benzodioxin **3.40**.[154] Regioselective monomethylation of the 4-hydroxyl group under Mitsunobu conditions was achieved in excellent yield to give the methylether **3.41**. Methylation of the 6-hydroxyl was less favoured due to strong hydrogen bonding with the carbonyl of the benzodioxin. Treatment of the benzodioxin **3.41** with lithium methoxide afforded the methyl ester **3.42** which was acylated with isobutyryl chloride under standard Friedel-Crafts conditions. Subsequent saponification and decarboxylation of the ester **3.43** with potassium hydroxide in DMSO gave the required product **3.30** in 46% overall yield.



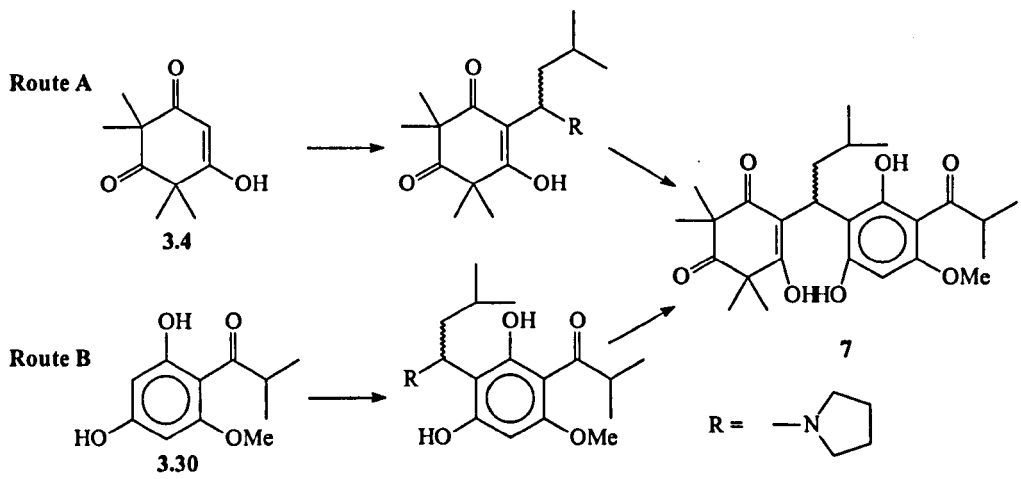
Scheme 3.23 - Regioselective synthesis of compound **3.30**

Coupling procedures

The coupling of syncarpic acid **3.4**, an aldehyde and a phloroglucinol **3.30** was achieved by two routes (scheme 3.24):-

Route A) - Mannich reaction between syncarpic acid **3.4** and isovaleraldehyde followed by subsequent coupling to the phloroglucinol derivative **3.30**.

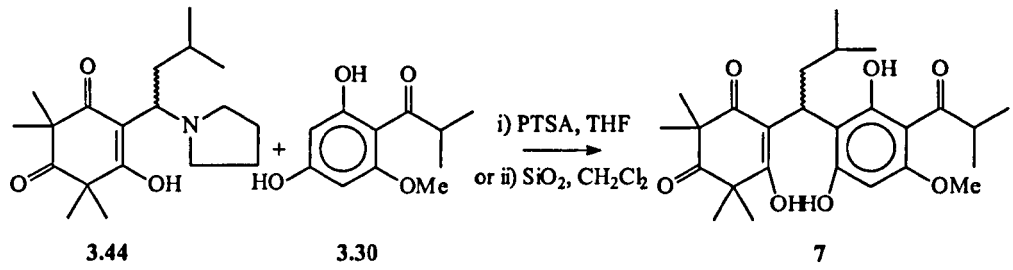
Route B) - Coupling between the phloroglucinol derivative **3.30** and isovaleraldehyde followed by coupling to syncarpic acid **3.4**.



Scheme 3.24 - Coupling routes to natural product **7**.

Synthesis of natural product **7** by route A:-

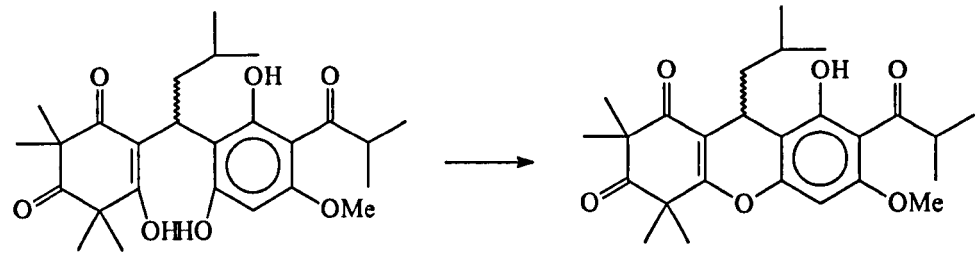
The pyrrolidine complex **3.44**, formed as previously described (scheme 3.6), and the required phloroglucinol moiety **3.30** were reacted under acidic conditions (scheme 3.25) and gave compound **7** in variable yields of 5 - 20%. NMR data for the synthetic compound **7** were identical to those for the natural product and showed a 3 : 1 mixture of conformers in $CDCl_3$.



3.44 3.30 7

Scheme 3.25 - Synthesis of natural product **7**.

The use of p-toluenesulfonic acid as catalyst gave as a major byproduct (scheme 3.26) the dehydrated compound **3.45** formed by cyclisation of compound **7**.



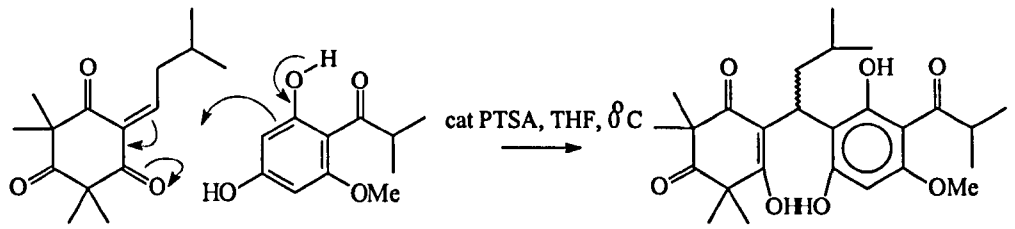
7 3.45

Scheme 3.26 - Dehydration of natural product **7**.

In order to prevent this side reaction, milder catalysis was employed using the mildly acidic silica gel 60 (Fluka). Improved yields in the range 20 - 50% were observed.

All reactions were regioselective, with coupling occurring at the 5-position of the phloroglucinol ring between the two hydroxyl groups. Coupling in the 3-position between hydroxy and methoxy groups did not occur. This regioselectivity was rationalised by electronic factors causing the 5-position more susceptible to nucleophilic substitution.

Finally, reaction of the alkylidene **3.24** formed by elimination of the Mannich base (scheme 3.7) with the phloroglucinol **3.30** using a catalytic amount of p-toluenesulfonic acid in THF (scheme 3.27) gave compound **7** in high yields (80 - 90%).



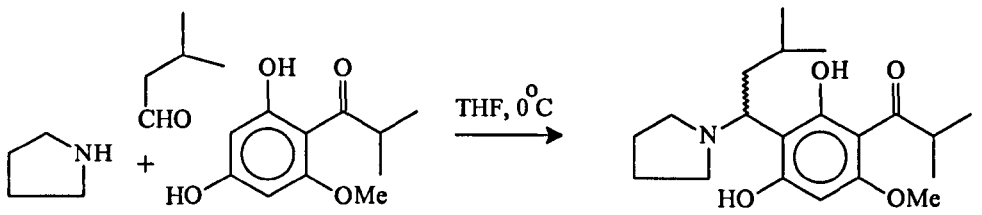
3.24 **3.30** **7**

Scheme 3.27 - Coupling of alkylidene **3.24**.

Route B

Condensation between phenols and aldehydes occurs readily. Bakelite, a phenol-formaldehyde copolymer, is among the oldest commercial plastics and is made by condensation of phenol and formaldehyde under basic conditions and at elevated temperatures.

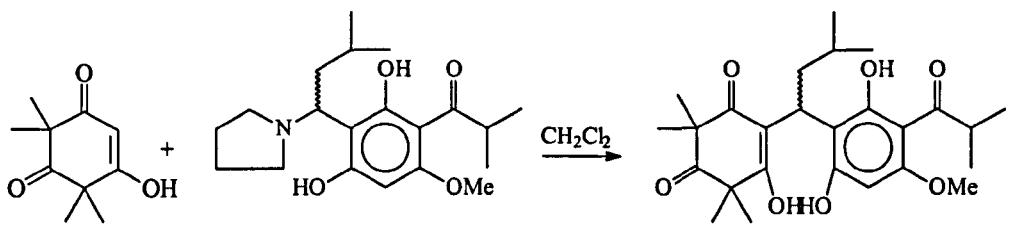
It was therefore envisaged that using similar methodology, phloroglucinol moieties could be reacted with aldehydes and pyrrolidine to give Mannich bases. This was indeed the case (scheme 3.28), and highest yields were obtained by reaction of the phloroglucinol **3.30** with excess pyrrolidine, causing the ketone group of the acyl side chain to form an enamine intermediate which was subsequently hydrolysed on work up.



3.30 3.46

Scheme 3.28 - Formation of Mannich base **3.46**

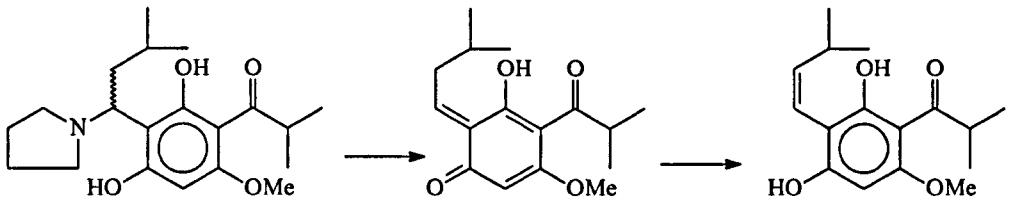
On stirring in dichloromethane, syncarpic acid **3.4** and Mannich base **3.46** were coupled (scheme 3.29) without catalysis, to give compound **7** in high yield.



3.4 3.46 7

Scheme 3.29 - Coupling reaction.

Elimination of the Mannich base **3.46** under acid conditions to give an o-quinone methide **3.47** (scheme 4.30) was not suitable for the coupling reaction due to its rapid rearrangement to give compound **3.48.**



3.46 3.47 3.48

Scheme 3.30 - Formation of the o-quinonemethide **3.47.**

The natural product **8** was synthesised by reaction of the alkylidene **3.24** and the required phloroglucinol **3.49** using the methodology of scheme 3.27 in good yield.

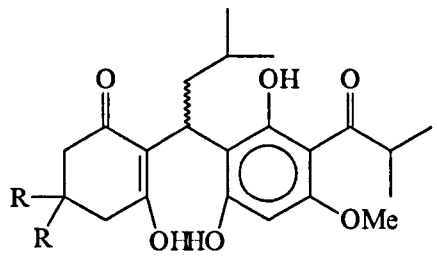
Scope and Limitations for Routes A and B

The insecticidal activities of the natural products **7** and **8** prompted structure activity relationship studies, so synthetic routes that give analogues are particularly valuable. Hence the possibility of variation in each of the regions is now discussed.

1) Syncarpic acid moiety

During the previously described reactions, syncarpic acid behaved as a 1,3-β-diketone and hence it was not surprising that reactions with other diketones such as 1,3-cyclohexanedione and dimedone proceeded in high yields. For instance, dimedone reacted with isovaleraldehyde and pyrrolidine

to form the Mannich base **3.50** (as scheme 3.6), which was then eliminated to form the alkylidene **3.51** (as scheme 3.7). Both dimedone and 1,3-cyclohexanedione were coupled to the Mannich base **3.46** to give analogues of the natural product **3.52** and **3.53** respectively (fig 3.5). Although not further exemplified, the scope for this reaction with more complicated systems appears extensive.



R = H, **3.52**

R = Me, **3.53**

Figure 3.5 - Syncarpic acid analogues of natural product **7.**

2) Aldehyde moiety (see table 3.2)

The Mannich reaction of syncarpic acid **3.4** and pyrrolidine proceeded with a variety of aldehydes. Simple straight chain aldehydes such as paraformaldehyde and butanal gave good yields of the Mannich bases **3.54** and **3.55** which were subsequently reacted to give analogues **3.56** and **3.57.**

Branched alkyl chains 2-methylpropanal, 2,2-dimethylbutanal 2-methylbutanal and 2-ethylbutanal gave the Mannich bases **3.58, 3.59, 3.60** and **3.61** respectively, although reaction with 2,2-dimethylpropanal failed due to increased steric constraints. The Mannich bases **3.58** and **3.59** were reacted as for scheme 3.25 to give coupled products **3.62** and **3.63,** whilst the pyrrolidine complexes **3.60** and **3.61** were reacted as for scheme 3.27 via the alkylidenes

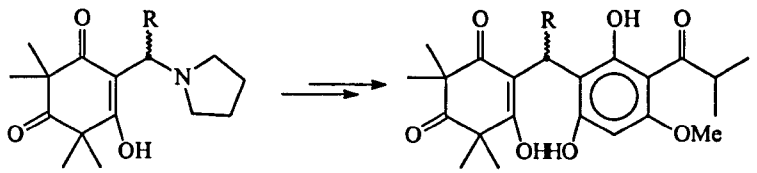
3.64 and **3.65** to give analogues **3.66** and **3.67.**

A halogen containing Mannich base **3.68** from trifluoroacetaldehyde ethylhemiacetal was obtained in 77% yield (*in situ* formation of aldehyde), but Mannich base **3.68** or its eliminated form **3.69** failed to give any coupled products.

Aromatic aldehydes such as phenylacetaldehyde and p-methoxy benzaldehyde again gave good yields of Mannich bases **3.70** and **3.71,** but although the phenylacetaldehyde complex coupled in 45% yield to give analogue **3.72,** coupling of the eliminated p-methoxyphenyl alkylidene **3.73** gave exclusively the dehydrated cyclised product **3.74.**

All attempted reactions with ketones failed to give any pyrrolidine complexes under a variety of conditions. This was not surprising as very few ketones have been successfully used in Mannich reactions.[142]

Table 3.2 - Analogues of the natural product **7**



R =	Mannich base	Product	Yield
H	**3.54**	**3.56**	16%
	3.55	**3.57**	19%
	3.58	**3.62**	99%
	3.59	**3.63**	45%
	3.60	**3.66***	13%
	3.61	**3.67***	22%
Ph	**3.70**	**3.72**	29%

* denotes synthesis via alkylidene

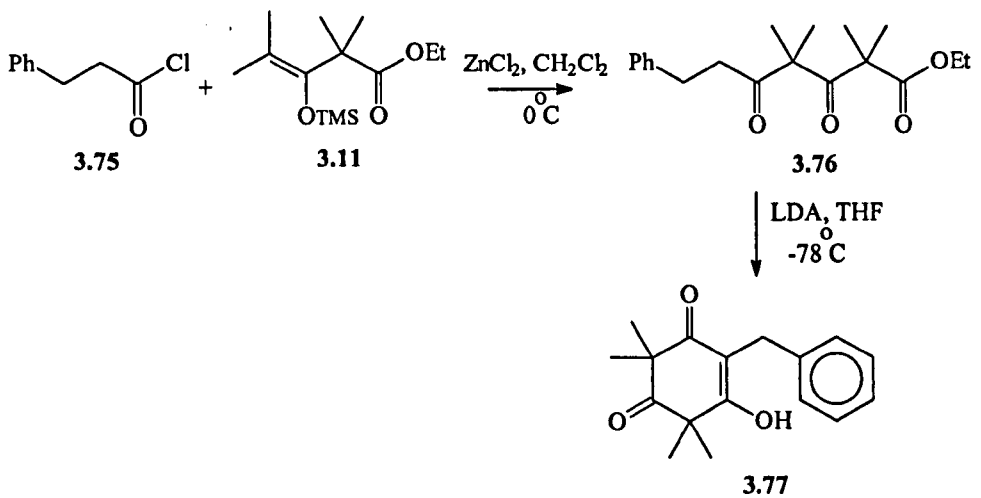
3) Phloroglucinol Moiety

Variations in this section of the molecule were unsuccessful. Although it is unclear why this was the case, it had been observed in the synthesis of the natural product **7** that the coupling reaction proceeded regioselectively at a position between the two hydroxyls. This suggests that the reaction was electronically sensitive to changes in the phloroglucinol ring, e.g. that it

requires an aromatic ring that is strongly activated by oxy-substituents for electrophilic substitution.

Synthesis of Model Compounds via Intramolecular Cyclisation Reactions

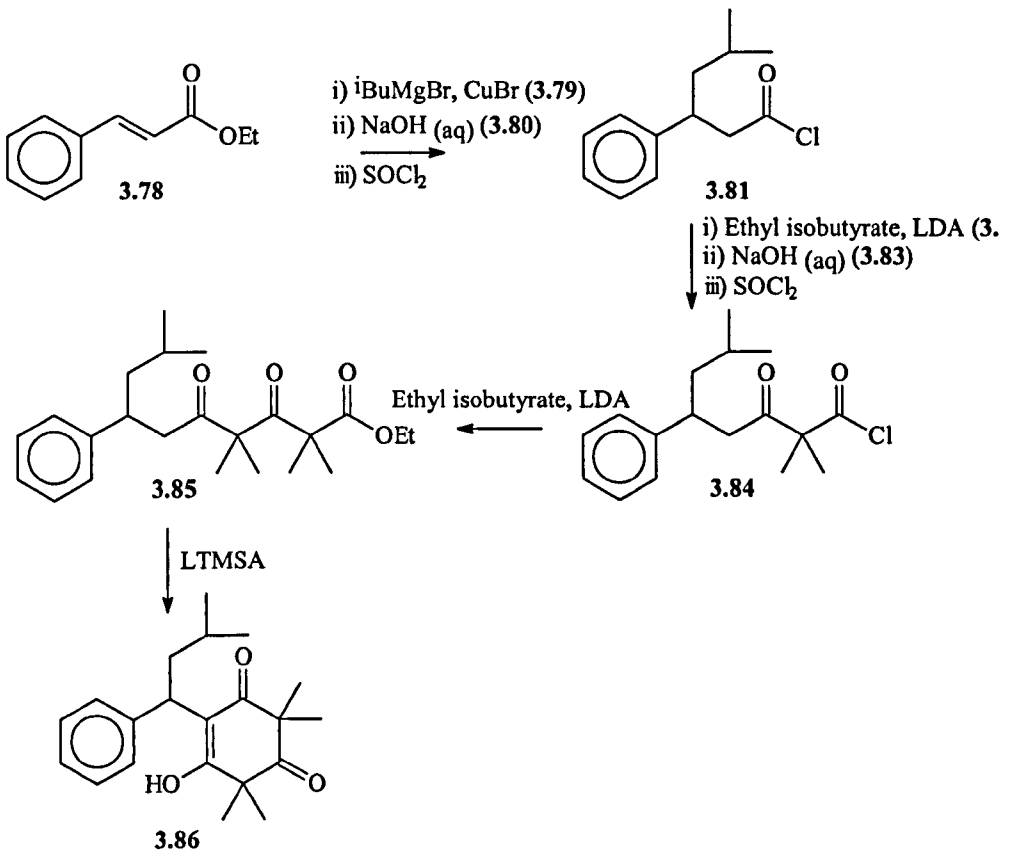
The intramolecular cyclisation route (scheme 3.2) for synthesis of syncarpic acid **3.4** was adapted for the synthesis of model compounds. The trimethylsilylenol ether **3.11** was reacted with dihydrocinnamoyl chloride **3.75** under Lewis acid conditions to give the β,δ-diketoester **3.76**. This was cyclised to the syncarpic acid analogue **3.77** using LDA (scheme 3.31).



Scheme 3.31 - Synthesis of model compound by intramolecular cyclisation.

A further model compound was synthesised containing an isobutyl side chain (scheme 3.32). This was achieved by 1,4-addition of the cuprate derived from isobutylmagnesium bromide, to ethyl cinnamate **3.78**. Saponification of the subsequent ester **3.79** gave the acid **3.80** and reaction with thionyl chloride

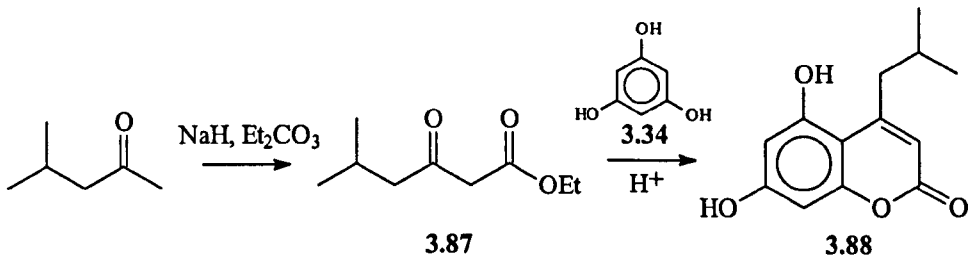
gave the acid chloride **3.81** which underwent a Claisen condensation with ethyl isobutyrate anion to give the β-ketoester **3.82** which was converted, via the acid **3.83** to the acid chloride **3.84**. Condensation of the anion derived from ethyl isobutyrate with the acid chloride **3.84** gave the β,δ-diketoester **3.85** which was cyclised with lithium bistrimethylsilylamide to give analogue **3.86**.



Scheme 3.32 - Synthesis of model compound.

This methodology was continued in an attempt to synthesise the natural product **7**. This required the synthesis of precursors such as analogues of compound **3.81** with the correct aromatic substitution. In order to obtain large amounts of these precursors a coumarin route was devised.

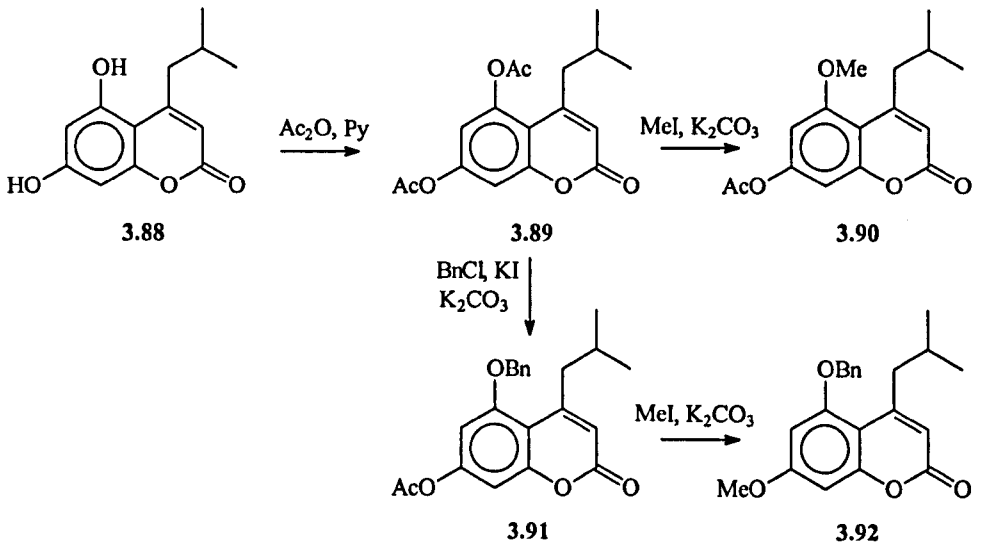
Reaction of diethyl carbonate to the anion of 4-methylpentanone gave the β-ketoester **3.87** (scheme 3.33) which was reacted with phloroglucinol under acidic conditions to give the coumarin **3.88.**



3.87 **3.88**

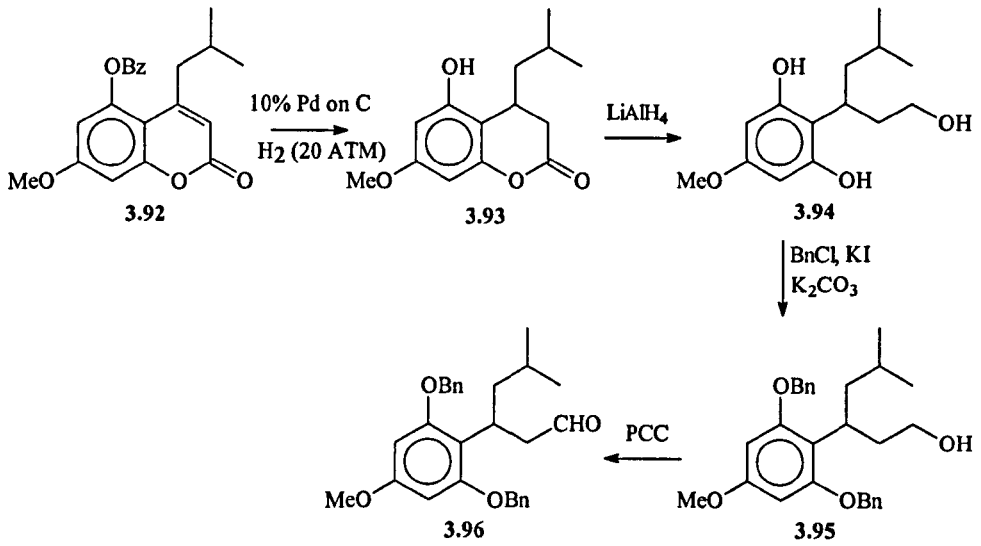
Scheme 3.33 - Synthesis of coumarin **3.88**

The selective O-alkylation of 5,7-dihydroxycoumarins has been reported by Ahluwalia *et al*[155,156] where diacylated coumarins gave selective methylation at the 7-position. Acetylation of coumarin **3.88** to give compound **3.89** was achieved in quantitative yields, but methylation under the reported conditions gave exclusively the 5-methoxy compound **3.90** (scheme 3.34). The structure was confirmed by reductive opening of the coumarin, which gave a non-symmetrical product. As the 7-methoxy compound was required, the diacetoxycoumarin **3.89** was benzylated at the 5-position to give the coumarin **3.91** and then methylated to give the 7-methoxy compound **3.92.**



Scheme 3.34 - Selective methylation of 5,7-diacetoxycoumarin **3.89**.

Reduction of the double bond of the coumarin **3.92** proved difficult, but was eventually achieved using 10% Pd on C as catalyst at 80°C under 20 ATM of hydrogen (scheme 3.35). The resultant dihydrocoumarin **3.93** was reductively cleaved and the resultant triol **3.94** dibenzylated to give compound **3.95**. This compound was oxidised to the aldehyde **3.96** but subsequent reactions using this intermediate were unsuccessful.

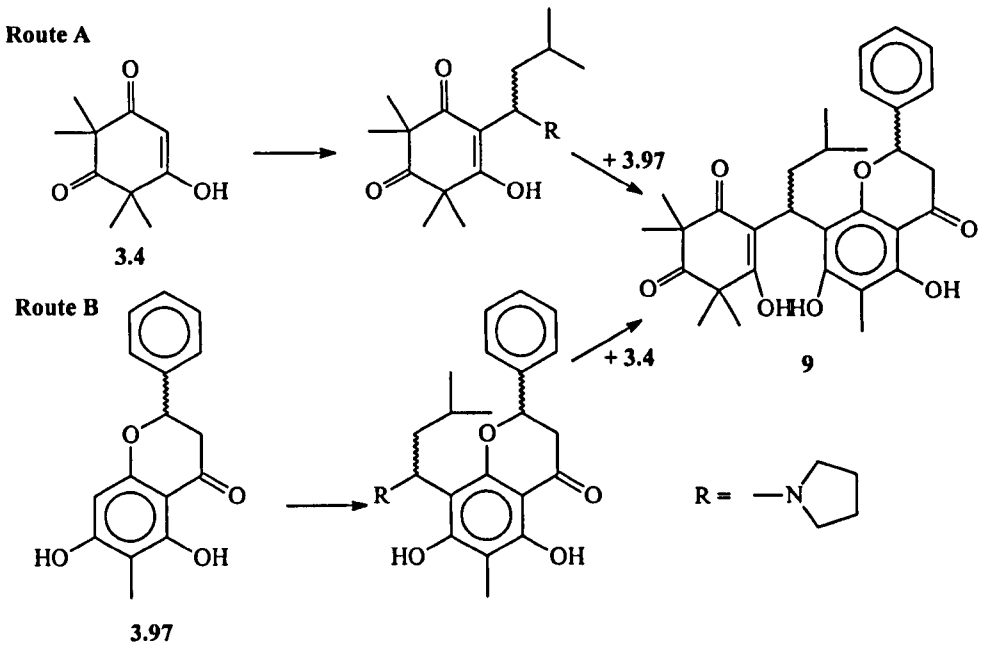


Scheme 3.35 - Synthesis of aldehyde precursor **3.96**

Further studies on this route were curtailed in preference to the successful routes previously described, where extensive protection procedures were not required.

3.7 ATTEMPTED SYNTHESIS OF FLAVANONE COMPOUND 9

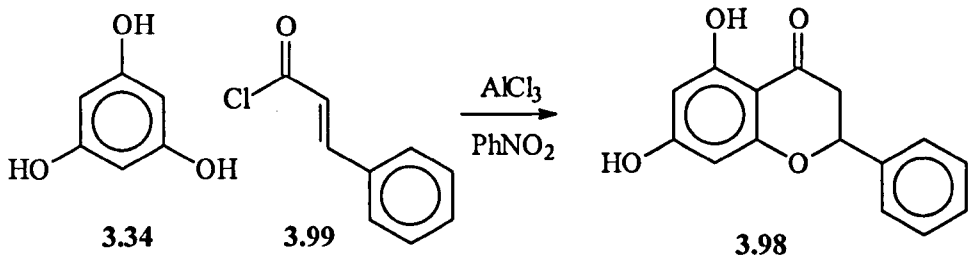
Because of the similarity of this compound to the previously synthesised natural products **7** and **8**, a similar synthetic strategy (scheme 3.36) was envisaged by coupling syncarpic acid **3.4** with an aldehyde and a flavanone **3.97.**



Scheme 3.36 - Routes to the natural product **9.**

Synthesis of flavanone

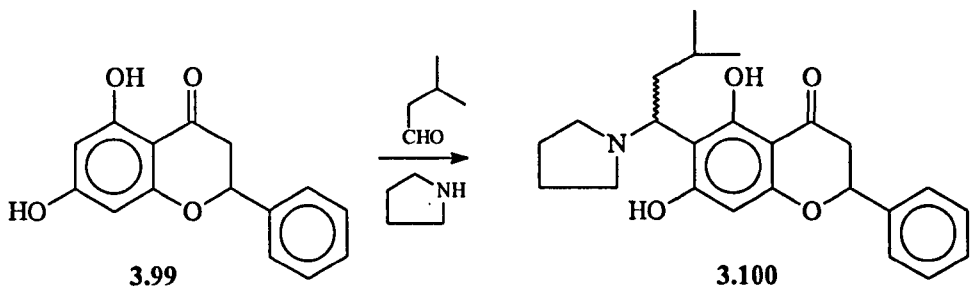
For model studies, 2,3-dihydro-5,7-dihydroxy-2-phenyl-4*H*-1-benzopyran-4-one **3.98** was synthesised by Friedel-Crafts reaction of phloroglucinol **3.34**, cinnamoyl chloride **3.99** and aluminium chloride in nitrobenzene (scheme 3.37).



3.34 3.99 3.98

Scheme 3.37 - Synthesis of model flavanone.

The flavanone **3.98** was reacted with isovaleraleraldehyde and pyrrolidine (scheme 3.38). Unfortunately the Mannich reaction occurred at the 6-position of the flavanone, to give the Mannich base **3.100.**



3.99 3.100

Scheme 3.38 - Synthesis of pyrrolidine flavanone complex **3.100.**

Coupling, using the previously described procedures for the natural products **7** and **8**, of either the flavanone **3.99** or the pyrrolidine complex **3.100** with suitable precursors failed to give any coupled product.

Until successful conditions for this model reaction are found, there is little hope for extending it to the flavanone with a methyl at C-6.

3.8 CONCLUSIONS

Knowledge of possible biosynthetic routes provides invaluable information to aid in the synthesis of complex natural products. This has been exemplified by the synthesis of seven of the nine insecticidal natural products isolated from plants of the Myrtaceae family. The synthesis of compounds **6** and **9** requires further investigation although I feel the general schemes outlined in this chapter, with modified reaction conditions, would lead to a successful outcome.

CHAPTER 4

INSECTICIDAL AND ANTIFEEDANT ACTIVITIES OF THE NATURAL AND SYNTHETIC COMPOUNDS

4.1 INTRODUCTION

Accurate and reproducible bioassay data are vital to assess the potential of a botanical pesticide. Practical and financial considerations often limit the number of routine tests possible, but ideally data on both pest and beneficial insects are required. In general, tests based on contact activity such as topical application are the most sensitive and reproducible, although residual assays are often employed as they are cheaper and less time consuming.

The bioassays in this chapter were carried out by colleagues at IACR-Rothamsted and RBG-Kew who have considerable experience of insecticidal bioassays for a range of insect species.[28,157]

No insecticidal natural products from plants of the Myrtaceae family had previously been isolated and characterised, although there is substantial literature on insecticidal extracts and essential oils especially from *Eucalyptus* species.[5] Essential oils from Myrtaceae species have also shown other bioactivities.[158,159]

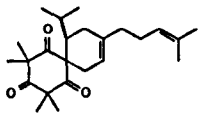
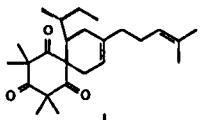
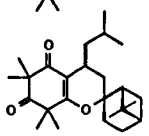
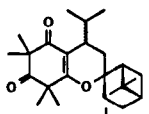
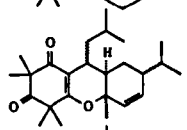
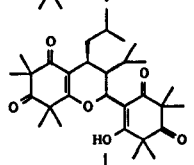
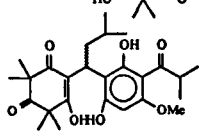
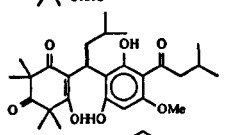
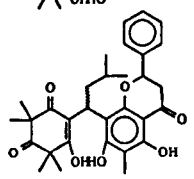
There are few examples of insecticidal compounds, similar to the natural products **1** - **9**. The only diones considered commercially for insecticidal properties were various 1,3-indandiones in the 1950's,[160] but their activities were too low for widespread use.

4.2 INSECTICIDAL ACTIVITIES OF THE NATURAL PRODUCTS 1-9

The natural products were initially screened against three insect species (table 4.1): Houseflies (*Musca domestica* L.), mustard beetles (*Phaedon cochliariae*) and plutella larvae (*Plutella xylostella*).

The results show that six of the natural products **4 - 9** are active against houseflies. The most active compound **7**, has an LD_{50} (lethal dose to kill 50% of a population of insects) of ca 0.2 μg/insect, an activity comparable to the pyrethrins (0.3 μg/insect) and rotenone (0.6 μg/insect). With the exception of compound **3**, the natural products are active against mustard beetles, although their activities are less than the pyrethrins (0.01 μg/insect) or rotenone (0.02 μg/insect). No significant activity against plutella larvae is observed.

Table 4.1 - Insecticidal activities of the natural products **1 - 9.**

Natural product		LD50 (μg per insect) *Musca domestica*	*Phaedon cochliariae*	*Plutella xylostella*
1		NT	c6.0	NT
2		-	c2.0	2.5μg = 25%*
3		NT	NT	-
4		c19	c12	NT
5a		1.85	-	-
5b		10μg = 60%*	-	-
6		10μg = 97%*	1.39	-
7		0.2μg = 56%*	0.55	NT
8		3.5	2.0	NT
9		10μg = 83%*	1.0	-

* - Denotes percentage kill at single dose

NT - Non toxic

The natural products are moderately active at 100ppm against two species of mosquito (*Aedes aegypti* and *Culex quinquefasciatus*) and the western flower thrip (*Frankliniella occidentalis*) (table 4.2).

Table 4.2 - Insecticidal activities of the natural products **1 - 9.**

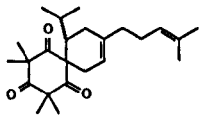
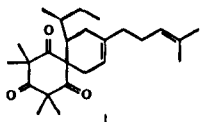
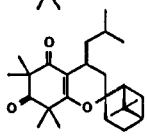
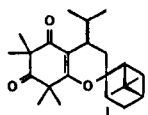
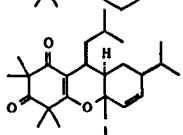
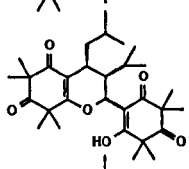
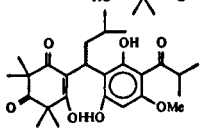
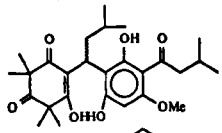
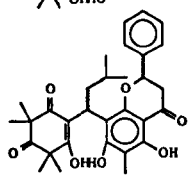
Natural product		Mortality (% kill at 100ppm)		
		Aedes aegypti	*Culex quinquefasciatus*	*Frankliniella occidentalis*
1		30	34	30
2		-	-	-
3		48	30	26
4		46	48	20
5a		18	26	10
6		20	26	12
7		-	-	-
8		-	-	-
9		NT	10	NT

Table 4.3 - Insecticidal activities of compound **1**.

	LD_{50} µg / insect over 72 h			
	Spodoptera litura	*Spodoptera frugiperda*	*Pieris rapae*	*Pieris brassicae*
Cpd **1**	45	27	56	34
Cypermethrin	24	18	29	38

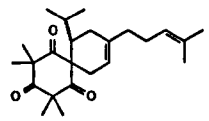
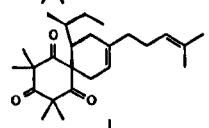
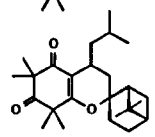
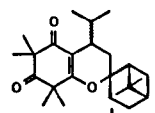
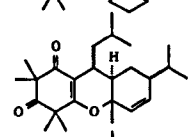
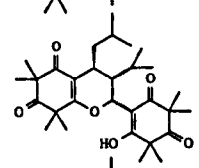
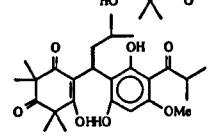
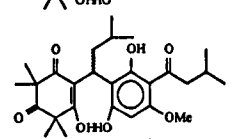
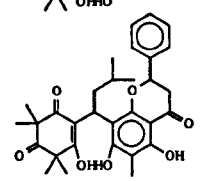
N.b 3rd stadium larvae

Further bioassays with the natural product **1** against a range of insect species (table 4.3), gave LD_{50}'s ranging from 30 µg/insect to 60 µg/insect. It is interesting to note, that the LD_{50} of compound **1** against the caterpillar of the large white butterfly (*Pieris brassicae*) is comparable to that of the synthetic pyrethroid cypermethrin.

4.3 ANTIFEEDANT ACTIVITIES OF THE NATURAL PRODUCTS

Compounds **1, 3, 4** and **8** exhibit significant antifeedant activities against the African leafworm *Spodoptera littoralis* and the western cotton rootworm *Diabrotica virgifera.*

Table 4.4 - Antifeedant activities (%) of the natural compounds.

		Antifeedant activity (%)	
		10 ppm	100 ppm
	Natural product	*Spodoptera littoralis*	*Diabrotica virgifera*
1		37	66
2		-	-
3		45	50
4		53	64
5a		-31	-
6		0	20
7		7	-
8		47	-
9		NT	-

Further studies with compound **1** show it has potent antifeedant activities against many insect species (table 4.5), with results comparable to the potent antifeedant azadirachtin.

Table 4.5 - Antifeedant activity (%) of compound **1** at 10 ppm.

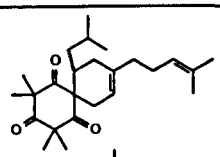
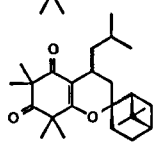
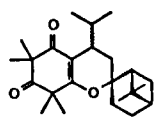
	Spodoptera littoralis	*Spodoptera frugiperda*	*Spodoptera exempta*	*Heliosis virescens*	*Pieris rapae*	*Pieris brassicae*
Compound **1**	37	79	100	76	100	100
Azadirachtin	99	89	100	87	98	98

	Diabrotica virgifera	*Thrips tabaci*	*Blatta orientalis*	*Lice*	*Phormia regina*
Compound **1**	66	34	67	65	23
Azadirachtin	78	56	45	54	54

4.4 INSECTICIDAL ACTIVITIES OF SYNTHETIC ANALOGUES

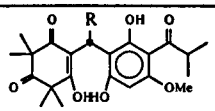
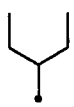
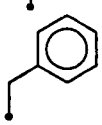
To enable structure activity relationships to be studied, various synthetic analogues of the natural compounds were tested. The data for these compounds (Table 4.6) shows that minor structural variations (e.g. compound **3.23**) results in loss of activity. Also, as with many natural products, the absolute stereochemistry of the compound (e.g. compounds **3b** and **4b**) is important for activity.

Table 4.6 - Insecticidal activity of various synthetic compounds.

		Percentage mortality		
Compound	Structure	*Musca domestica*	*Phaedon cochliariae*	*Plutella xylostella*
3.23		NT	10 μg = 35%	5 μg = 25%
3b		NT	NT	-
4b		NT	20 μg = 28%	NT

A study on compounds with variations to the central alkyl chain of natural product **7** (table 4.7) results in complete loss of housefly activity for all analogues. For mustard beetles, minor variations results in only small losses of activity. Interestingly the benzyl analogue exhibits reasonable activity suggesting that a large lipophilic central group is favoured.

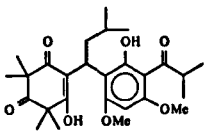
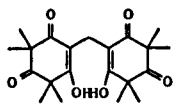
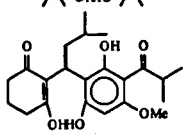
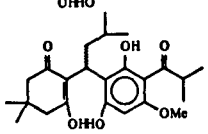
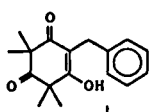
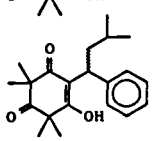
Table 4.7 - Insecticidal activity of compounds with variations in the central alkyl chain of compound **7**.

Compound		Insecticidal activity μg / insect	
		Musca domestica	*Phaedon cochliariae*
3.56		NT	NT
3.57		NT	1.0
3.62		NT	c4.0
3.63		NT	20 μg = 40%*
3.66		NT	0.48
3.67		NT	2.37
3.72		NT	c2.0

* - Denotes percentage mortality at a single dose

Modifications to the phloroglucinol fragment of compounds **7** and **8** (e.g. compound **3.86**) results in loss of activity (table 4.8), but replacement of the syncarpic acid fragment with dimedone (compound **3.53**) does not affect mustard beetle activity.

Table 4.8 - Insecticidal activity of compounds with modifications to the natural products **7** and **8**.

Compound	Structure	Insecticidal activity μg / insect	
		Musca domestica	*Phaedon cochliariae*
2.3		NT	c6.0
3.17		NT	NT
3.52		NT	NT
3.53		NT	1.0
3.77		NT	NT
3.86		NT	NT

4.5 CONCLUSIONS

The natural products **1 - 9** are insecticidal against a range of insect species. In general, their activities are too low and the spectrum of activities too small for commercial consideration. The antifeedant activities of compound **1** are very promising and require further investigations to ascertain any commercial possibilities.

The bioassay data on the natural compounds and certain synthetic compounds has enabled structure activity relationships to be studied. These have shown that small structual variations from the natural products results in large reductions of insecticidal activity. The absolute stereochemistry of the compounds was also shown to be important. Hence, the site of action is sensitive to the size, shape and electronic nature of the compounds.

CHAPTER 5

EXPERIMENTAL SECTION

5.1 GENERAL EXPERIMENTAL

^{1}H and ^{13}C NMR spectra were recorded on a JEOL GX400 spectrometer, operating at 400 and 100 MHz respectively. Deuteriochloroform was used as solvent, unless otherwise stated, and chemical shift values quoted in ppm downfield from tetramethylsilane. (See appendix 1 for selected NMR spectra). $^{a, b, c}$ denotes NMR assignments may be interchanged.

Accurate mass measurements were recorded on a VG Autospec mass spectrometer at 60 eV. Infrared spectra were recorded using a Nicolet Impact 410 FT-IR spectrometer with the compounds as a solution in chloroform. A Shimadzu UV-160A UV-Vis spectrophotometer was used to record ultraviolet spectra of compounds in chloroform. Optical rotations were recorded, using a known concentration of compound in chloroform, on a Thorn NPL143 polarimeter. Melting points were recorded using an electrothermal melting point apparatus and are uncorrected.

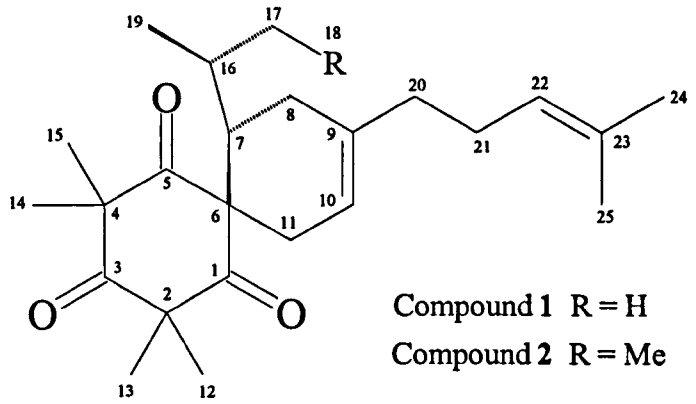
HPLC was performed using Gilson equipment and Dynamax 60A HPLC columns. Peaks were monitored using a diode array UV detector set at 210, 230, 254, 280 and 300 nm. Flash column chromatography was carried out using either 35-70 or 63-200 mesh silica gel or RP18 - Lichroprep (Merck) reverse phase silica gel. Preparative tlc used 1000 micron 20 x 20 cm silica gel 60 plates (Analtech) containing a fluorescent indicator and visualised by uv light (254 nm). Analytical tlc plates were visualised using uv light (254 nm), iodine vapour or anisaldehyde spray.

Diethyl ether and petrol ether 60 - 80°C were dried by storing over sodium wire prior to use. Tetrahydrofuran was distilled from sodium-benzophenone and stored under nitrogen. All other reagents were used as supplied or purified as required.[161]

Bioassay guided fractionation of the natural products was performed using mustard beetles *Phaedon cochleariae* as test insect species. The compounds were topically applied, to the thorax of the insect, in acetone solutions and mortality noted after 24h and 48h.

5.2 EXTRACTION AND ISOLATION PROCEDURES

5.2.1 Compounds 1 and 2 from *Calothamnus validus*



Compound **1** R = H
Compound **2** R = Me

Plant material

The leaves and stems of *Calothamnus validus* were collected from the Royal Botanical Gardens, Kew, London on the 8th February 1994. The plant was verified by E. Nielughadha.

Extraction and Isolation

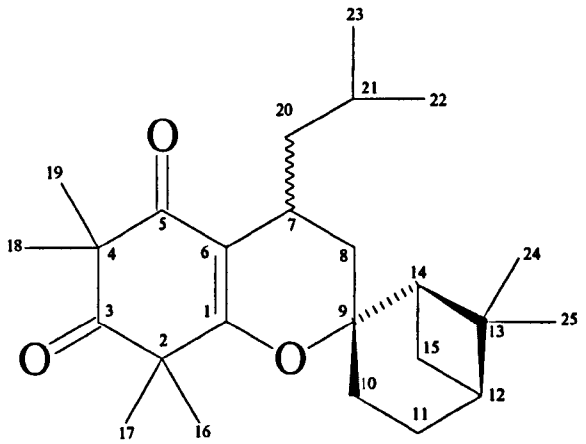
The ground, air-dried leaves and stems of *Calothamnus validus* (73 g) were extracted with hexane (3 x 300 ml) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (2 g).

The residue (1.93 g) was chromatographed on silica gel using petrol ether - diethyl ether (12 : 1) as eluent. The biologically active fraction (0.57 g) was rechromatographed on silica gel eluting with petrol ether - diethyl ether

(25 : 1). This gave two fractions exhibiting biological activity, the less polar of which, after evaporation of the solvent in vacuo, afford a 3 : 1 mixture of compounds **1** and **2** (46 mg, 0.063%) as a pale yellow oil; n_D 1.4425; $[\alpha]_D^{25}$ 0.0 (*c* 0.92 in $CDCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3034, 2961, 1701, 1695, 1466, 1382; λ_{max} ($CHCl_3$)/nm 267; **Compound 1**; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.6, H-19), 0.90 (3H, d, *J* 6.8, H-17), 1.35 (3H, s, H-12[c]), 1.39 (3H, s, H-13[c]), 1.40 (3H, s, H-15[c]), 1.42 (3H, s, H-14[c]), 1.60 (3H, s, H-25), 1.67 (3H, s, H-24), 1.67 (1H, m, H-16), 1.96 (2H, t, *J* 7.7, H-20), 1.98 (1H, m, H-8), 2.07 (2H, m, H-21), 2.19 (1H, dd, *J* 6.7, 3.1, H-11), 2.20 (1H, m, H-7), 2.25 (1H, m, H-8), 2.49 (1H, dd, *J* 17.6, 3.0, H-11), 5.05 (1H, t, *J* 6.9, H-22), 5.27 (1H, m, H-10); δ_C($CDCl_3$) 17.7 (C-25), 19.1 (C-19), 24.1 (C-17), 24.8 (C-13[c]), 25.0 (C-15[c]), 25.7 (C-23), 26.0 (C-12[c]), 26.1 (C-21), 26.2 (C-14[c]), 27.7 (C-8), 30.0 (C-16), 31.0 (C-11), 37.1 (C-20), 41.1 (C-7), 56.3 (C-2[b]), 56.6 (C-4[b]), 67.0 (C-6), 115.4 (C-10), 124.1 (C-22), 131.4 (C-23), 138.0 (C-9), 208.5 (C-1[a]), 208.6 (C-5[a]), 212.9 (C-3); m/z (Found: M+, 372.26733. $C_{24}H_{36}O_3$ requires M, 372.26644). **Compound 2** (see synthetic sample for full NMR data) as a mixture of two diastereomers **2a**; δ_H($CDCl_3$) all peaks obscured; δ_C($CDCl_3$) peaks obscured except 12.1 (C-18), 15.3 (C-19), 24.6 (C-15[c]), 25.9 (C-12[c]), 27.2 (C-17), 30.7 (C-8), 31.1 (C-11), 36.4 (C-16), 37.1 (C-20), 40.5 (C-7), 56.7 (C-2[b]), 56.7 (C-4[b]), 66.7 (C-6), 115.5 (C-10), 124.1 (C-22), 208.4 (C-1[a]), 208.9 (C-5[a]), 212.7 (C-3); **2b**; δ_H($CDCl_3$) all peaks obscured; δ_C($CDCl_3$) peaks obscured except 12.3 (C-18), 19.7 (C-19), 24.7 (C-13[c]), 25.3 (C-15[c]), 25.5 (C-12[c]), 25.5 (C-17), 26.4 (C-14[c]), 29.1 (C-8), 32.6 (C-11), 37.1 (C-20), 37.6 (C-16), 41.3 (C-7), 56.8 (C-4b), 66.2 (C-6), 114.6 (C-10), 124.1 (C-22); m/z (Found: M+, 386.28241. $C_{25}H_{38}O_3$

requires M, 386.28210).

5.2.2 Compound 3 from *Eucalyptus ficifolia*



Plant material

Leaves and stems of *Eucalyptus ficifolia* (Accession number 1980-2857) were collected from the Royal Botanical Gardens, Kew, London on the 16th December 1993. The plant was verified by E. Nielughadha.

Extraction and Isolation

Ground air-dried leaves and stems of *Eucalyptus ficifolia* (300 g) were extracted with hexane (3 x 1 l) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (11.1 g).

The residue (5.5 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (9 : 1). The biologically active fraction (1.47 g) was rechromatographed on silica gel eluting with petrol ether - diethyl ether (13 :

1). The biologically active fraction (0.67 g) was rechromatographed on silica gel eluting with petrol ether - diethyl ether (15 : 1) The resultant biologically active fraction (0.06 g) was rechromatographed by silica gel HPLC eluting with hexane - ethyl acetate (15 : 1) to afford compound **3** (18 mg, 0.006%) as colourless semi-solid; $[\alpha]_D^{25}$ +35.9 (*c* 0.92 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2958, 2870, 1710, 1644, 1604, 1472, 1384; λ_{max} ($CHCl_3$)/nm 266; δ_H($CDCl_3$) 0.90 (3H, d, *J* 6.3, H-22), 0.96 (1H, ddd, *J* 13.1, 10.2, 3.9, H-20), 0.98 (3H, d, *J* 6.3, H-23), 1.02 (3H, s, H-25), 1.30 (3H, s, H-24), 1.31 (3H, s, H-19[a]), 1.33 (3H, s, H-18[a]), 1.34 (3H, s, H-16[a]), 1.36 (3H, s, H-17[a]), 1.46 (1H, dd, *J* 14.0, 8.8, H-8), 1.61 (1H, m, H-15), 1.70 (2H, m, H-10), 1.73 (1H, ddd, *J* 13.1, 10.1, 3.4, H-20), 1.93 (1H, m, H-21), 1.94 (2H, m, H-11), 1.99 (1H, m, H-12), 2.13 (1H, dd, *J* 14.0, 6.8, H-8), 2.14 (1H, m, H-14), 2.27 (1H, m, H-15), 2.73 (1H, dddd, *J* 10.3, 8.8, 6.7, 3.5, H-7); δ_C($CDCl_3$) 20.8 (C-23), 22.3 (C-19[a]), 23.4 (C-25), 24.1 (C-22), 24.3 (C-17[a]), 24.9 (C-11), 25.5 (C-16[a]), 25.6 (C-7), 25.6 (C-21), 26.3 (C-18[a]), 26.9 (C-15), 27.3 (C-24), 27.9 (C-10), 38.2 (C-13), 39.6 (C-8), 40.4 (C-12), 42.2 (C-20), 48.0 (C-2), 51.2 (C-14), 55.4 (C-4), 84.2 (C-9), 112.9 (C-6), 168.9 (C-1), 197.9 (C-5), 213.5 (C-3); m/z (Found: M^+, 386.28122. $C_{25}H_{38}O_3$ requires M, 386.28210).

5.2.3 Compound 3 from *Kunzea ericoides*

Plant material

The leaves and stems of *Kunzea ericoides* (Accession number 1993-

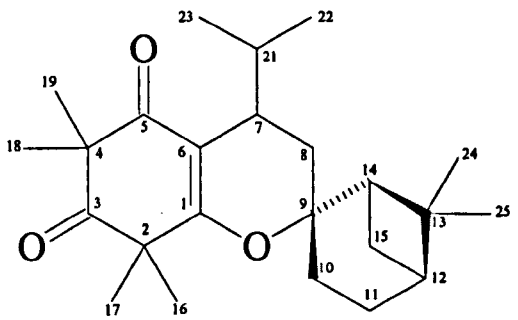
1871) were collected from the Royal Botanical Gardens, Kew, London on the 23rd August 1993. The plant was verified by E. Nielughadha.

Extraction and Isolation

The ground air-dried leaves and stems of *Kunzea ericoides* (50 g) were extracted with hexane (3 x 200 ml) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (1.15 g).

The residue (0.95 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (6 : 1). The less polar biologically active fraction (0.025 g) was a mixture of compounds containing 50% compound **3**.

5.2.4 Compound 4 from *Calothamnus validus*



Plant material

The leaves and stems of *Calothamnus validus* were collected from the Royal Botanical Gardens, Kew, London on the 8th February 1994. The plant

was verified by E. Nielughadha.

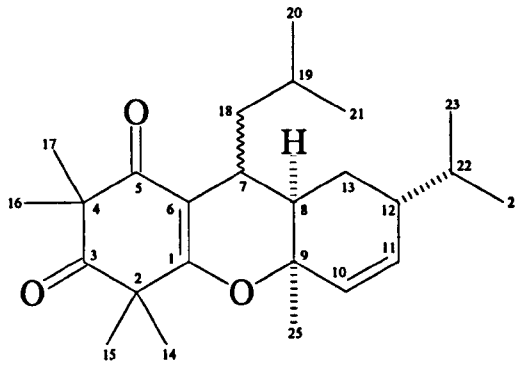
Extraction and Isolation

The ground air-dried leaves and stems of *Calothamnus validus* (73 g) were extracted with hexane (3 x 300 ml) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (2 g).

The residue (1.93 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (12 : 1). The biologically active fraction (0.57 g) was rechromatographed on silica gel eluting with petrol ether - diethyl ether (25 : 1). This gave two fractions exhibiting biological activity, the more polar of which (0.21 g) was purified further on silica gel eluting with petrol ether - diethyl ether (12 : 1). The resultant biologically active fraction (0.09 g) was rechromatographed by silica gel HPLC eluting with hexane - ethyl acetate (15 : 1) to afford compound **4** (16 mg, 0.022%) a pale yellow semi-solid; $[\alpha]_D^{25}$ +40.9 (*c* 0.44 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2958, 2926, 2872, 1710, 1642, 1599, 1467, 1381; λ_{max} ($CHCl_3$)/nm 268; δ_H($CDCl_3$) 0.62 (3H, d, *J* 6.9, H-23), 0.94 (3H, d, *J* 6.5, H-22), 0.96 (3H, s, H-25), 1.23 (3H, s, H-24), 1.26 (3H, s, H-16), 1.30 (3H, s, H-18), 1.32 (3H, s, H-19), 1.40 (3H, s, H-17), 1.40 (2H, m, H-11), 1.45 (1H, m, H-15), 1.60 (1H, m, H-8), 1.88 (2H, dt, *J* 12.8, 5.8, H-10), 1.95 (1H, m, H-12), 2.10 (1H, dd, *J* 8.0, 7.0, H-8), 2.18 (1H, m, H-14), 2.20 (1H, m, H-15), 2.63 (1H, m, H-21), 2.63 (1H, m, H-7); δ_C($CDCl_3$) 15.6 (C-23), 20.7 (C-22), 23.0 (C-25), 23.3 (C-19), 24.2 (C-17), 24.6 (C-11), 25.7 (C-18), 25.9 (C-7), 26.0 (C-15), 26.2 (C-16), 27.5 (C-24), 30.7 (C-10), 32.2 (C-8), 33.8 (C-21), 38.2 (C-13), 40.6 (C-12), 45.4 (C-14), 48.3 (C-2), 55.2 (C-

4), 85.0 (C-9), 111.3 (C-6), 171.1 (C-1), 198.0 (C-5), 213.8 (C-3); m/z (Found: M+, 372.2672. $C_{24}H_{36}O_3$ requires M, 372.2664).

5.2.5 Compound 5 from *Callistemon viminalis*



Plant material

The leaves and stems of *Callistemon viminalis* (Accesssion number 1987-1503) were collected from the Royal Botanical Gardens, Kew, London on the 6th April 1995. The plant was verified by E. Nielughadha.

Extraction and Isolation

The ground air-dried leaves and stems of *Callistemon viminalis* (1.2 kg) were extracted with hexane (4 x 1.5 l) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (12.7 g).

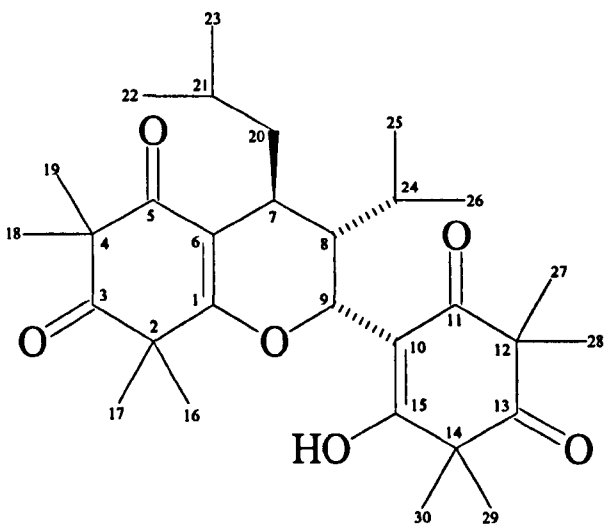
The residue (12.6 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (9 : 1). The biologically active fraction (1.07 g) was

rechromatographed on silica gel eluting with hexane - diethyl ether (19 : 1). This gave two fractions exhibiting biological activity, the more polar of which (0.24 g) was further purified by flash column chromatography on silica gel using petrol ether - diethyl ether (24 : 1). The resultant insecticidal fraction, after evaporation of the solvent in vacuo, afford compound **5a** (0.12 g, 0.01%) as a pale yellow oil, n_D 1.4437; $[\alpha]_D^{25}$ +120.3 (*c* 0.96 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3019, 2958, 2933, 2872, 1713, 1642, 1606, 1467, 1385; λ_{max} ($CHCl_3$)/nm 262; δ_H($CDCl_3$) 0.95 (3H, d, *J* 6.7, H-20), 0.96 (3H, d, *J* 6.7, H-24), 0.98 (3H, d, *J* 6.4, H-23), 1.00 (3H, d, *J* 6.4, H-21), 1.11 (1H, td, *J* 11.5, 2.5, H-18), 1.27 (3H, s, H-14[a]), 1.29 (3H, s, H-15[a]), 1.29 (3H, s, H-16[a]), 1.30 (1H, m, H-13), 1.32 (3H, s, H-25), 1.36 (3H, s, H-17[a]), 1.63 (1H, m, H-19), 1.67 (1H, m, H-22), 1.70 (1H, m, H-13), 1.87 (1H, ddd, *J* 15.2, 6.5, 3.0, H-8), 1.94 (1H, m, H-12), 1.97 (1H, m, H-18), 2.98 (1H, ddd, *J* 11.6, 6.3, 3.5, H-7), 5.75 (1H, dd, *J* 10.0, 1.8 H-10), 5.99 (1H, dd, *J* 10.1, 3.7, H-11); δ_C($CDCl_3$) 20.7 (C-13), 20.8 (C-21), 21.0 (C-23), 21.5 (C-24), 21.6 (C-25), 23.5 (C-17[a]), 23.8 (C-14[a]), 24.2 (C-20), 24.6 (C-19), 25.8 (C-15[a]), 26.8 (C-16[a]), 28.2 (C-7), 31.5 (C-22), 33.6 (C-8), 35.2 (C-18), 41.2 (C-12), 47.9 (C-2), 55.8 (C-4), 76.2 (C-9), 110.2 (C-6), 130.8 (C-10), 135.2 (C-11), 166.9 (C-1), 198.5 (C-5), 213.3 (C-3); m/z (Found: M+, 386.28113. $C_{25}H_{38}O_3$ requires M, 386.28210).

The less polar biologically active fraction (0.28 g) was rechromatographed on silica gel eluting with petrol ether - diethyl ether (24 : 1). The resultant insecticidal fraction, after evaporation of the solvent in vacuo, afford compound **5b** (0.027 g, 0.0023%) as a pale yellow semi-solid; $[\alpha]_D^{25}$ -25.5 (*c* 1.32 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3031, 2965, 2937, 2871, 1718, 1612, 1471,

1389; λ_{max} ($CHCl_3$)/nm 269; δ_H($CDCl_3$) 0.91 (3H, d, *J* 6.3, H-20), 0.92 (3H, d, *J* 6.6, H-23), 0.95 (3H, d, *J* 6.6, H-24), 1.00 (3H, d, *J* 6.6, H-21), 1.33 (3H, s, H-15[a]), 1.33 (3H, s, H-16[a]), 1.33 (3H, s, H-17[a]), 1.35 (1H, m, H-18), 1.38 (3H, s, H-14[a]), 1.45 (1H, m, H-18), 1.46 (3H, s, H-25), 1.57 (2H, m, H-13), 1.66 (1H, m, H-22), 1.76 (1H, m, H-19), 2.01 (1H, m, H-12), 2.01 (1H, m, H-8), 2.56 (1H, dt, *J* 9.9, 3.3, H-7), 5.50 (1H, dd, *J* 10.2, 2.2 H-10), 5.84 (1H, dd, *J* 10.2, 3.9, H-11); δ_C($CDCl_3$) 20.4 (C-23), 20.4 (C-24), 21.5 (C-21), 23.5 (C-16[a]), 24.0 (C-20), 24.6 (C-14[a]), 25.3 (C-15[a]), 25.4 (C-17[a]), 26.1 (C-19), 27.4 (C-25), 29.1 (C-13), 31.6 (C-22), 31.7 (C-7), 38.3 (C-8), 39.5 (C-12), 43.9 (C-18), 47.5 (C-2), 55.6 (C-4), 77.7 (C-9), 113.0 (C-6), 131.0 (C-10), 134.6 (C-11), 168.6 (C-1), 198.1 (C-5), 213.5 (C-3); m/z (Found: M+, 386.28189. $C_{25}H_{38}O_3$ requires M, 386.28210).

5.2.6 Compound 6 from *Kunzea ericifolia.*



Plant material

The leaves and stems of *Kunzea ericifolia* (Accession number 1993-1871))were collected from the Royal Botanical Gardens, Kew, London on the 10th July 1995. The plant was verified by E. Nielughadha.

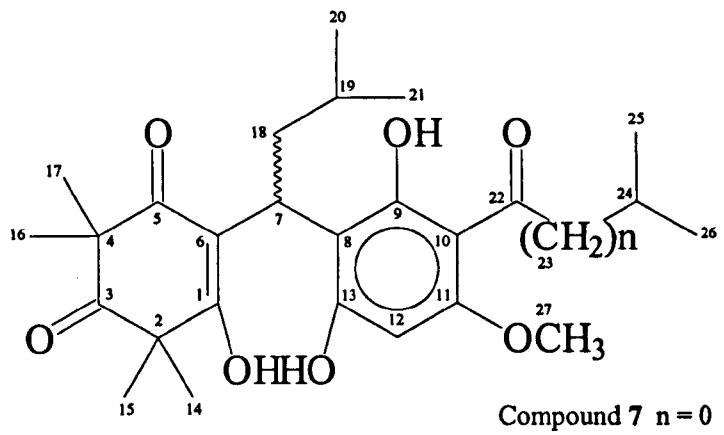
Extraction and Isolation

The ground air-dried leaves and stems of *Kunzea ericifolia* (100 g) were extracted with hexane (3 x 1 l) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (1.1 g).

The residue (1.1 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (9 : 1). The biologically active fraction (0.15 g) was rechromatographed by silica gel HPLC eluting with hexane - ethyl acetate (9 : 1) to afford compound **6** (0.04 g, 0.04%) as a colourless oil; $[\alpha]_D^{25}$ -35.6 (*c* 0.16 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3029, 2962, 2928, 2872, 1706, 1628, 1466, 1382; λ_{max} ($CHCl_3$)/nm 259; δ_H($CDCl_3$) 0.75 (3H, d, *J* 6.8, H-26), 0.95 (3H, d, *J* 6.8, H-25), 0.99 (3H, d, *J* 6.8, H-22), 1.07 (3H, d, *J* 6.4, H-23), 1.34 (3H, s, H-16[a]), 1.35 (1H, m, H-20), 1.35 (3H, s, H-27), 1.39 (3H, s, H-19), 1.39 (3H, s, H-30[a]), 1.40 (1H, m, H-20), 1.40 (3H, s, H-28), 1.44 (3H, s, H-17), 1.52 (3H, s, H-18), 1.52 (3H, s, H-29), 1.74 (1H, m, H-21), 1.87 (1H, m, H-8), 1.87 (1H, m, H-24), 2.81 (1H, dd, *J* 8.3, 1.4, H-7), 5.55 (1H, d, *J* 2.5, H-9), 9.01 (1H, s, OH); δ_C($CDCl_3$) 19.6 (C-26), 21.0 (C-23), 21.3 (C-16[a]), 23.7 (C-30[a]), 23.8 (C-25), 24.3 (C-22), 24.5 (C-19), 24.9 (C-27), 25.0 (C-18), 25.1 (C-29), 25.3 (C-21), 25.4 (C-17), 26.7 (C-24), 26.7 (C-28), 27.2 (C-7), 41.4 (C-8), 44.7 (C-20), 47.3 (C-2), 48.6 (C-14), 55.2 (C-4), 56.2 (C-12), 79.4 (C-9), 107.1

(C-10), 116.7 (C-6), 167.4 (C-1), 175.0 (C-15), 196.9 (C-11), 197.8 (C-5), 211.4 (C-13), 212.0 (C-3); m/z (Found: M+, 500.31512. $C_{30}H_{44}O_6$ requires M, 500.31379).

5.2.7 Compounds 7 and 8 from *Kunzea aff. micromera*



Compound **7** n = 0
Compound **8** n = 1

Plant material

The leaves and stems of *Kunzea aff. micromera* were collected from the Royal Botanical Gardens, Kew, London on the 10th August 1993.

Extraction and Isolation

Ground air-dried leaves and stems of *Kunzea aff. micromera* (18 g) were extracted with hexane (3 x 100 ml) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (1.4 g).

The residue (1.4 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (4 : 1). The biologically active fraction (0.19 g) was

rechromatographed on silica gel eluting with hexane - diethyl ether (4 : 1). This gave a fraction containing pure compound **8** (26 mg) and a fraction containing a mixture of compounds **7** and **8** (0.14 g) which was further purified by silica gel thin layer chromatography using petrol ether - diethyl ether (4 : 1), eluting each plate three times. The resultant fractions, after evaporation of the solvent in vacuo, afford compound **7** (0.04 g, 0.22%) as pale yellow crystals, m.p. 123 - 124 °C; $[\alpha]_D^{25}$ 0 (*c* 1.12 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3105, 3028, 2959, 2871, 1714, 1622, 1588, 1470, 1387; λ_{max} ($CHCl_3$)/nm 243, 292; **Conformer 1**; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.4, H-20), 0.86 (3H, d, *J* 6.8, H-21), 1.17 (3H, d, *J* 6.3, H-25), 1.19 (3H, d, *J* 6.3, H-26), 1.33 (3H, s, H-15), 1.34 (1H, s, H-17), 1.40 (1H, m, H-19), 1.40 (3H, s, H-16), 1.49 (1H, s, H-14), 1.78 (1H, dt, *J* 7.3, 6.8, H-18), 2.11 (1H, dt, *J* 7.3, 6.8, H-18), 3.81 (1H, sept, *J* 6.8, H-24), 3.86 (3H, s, H-27), 4.38 (1H, t, *J* 6.8, H-7), 6.04 (1H, s, H-12), 10.40 (1H, s, OH-1), 11.63 (1H, s, OH-13), 17.11 (1H, s, OH-9); δ_C($CDCl_3$) 19.3 (C-25), 19.3 (C-26), 22.3 (C-20), 22.4 (C-15), 22.6 (C-21), 24.3 (C-14), 26.1 (C-17), 26.8 (C-19), 27.0 (C-16), 27.9 (C-7), 38.1 (C-18), 39.2 (C-24), 48.6 (C-2), 55.1 (C-4), 55.6 (C-27), 94.0 (C-12), 103.6 (C-10), 109.0 (C-8), 114.9 (C-6), 161.8 (C11), 163.9 (C-9), 164.6 (C-13), 176.6 (C-1), 203.1 (C-5), 210.8 (C-22), 212.3 (C-3). **Conformer 2**; δ_H($CDCl_3$) all peaks obscured except 0.88 (3H, m, H-21), 1.13 (3H, m, H-25), 1.21 (3H, m, H-26), 1.33 (3H, s, H-15), 1.36 (1H, s, H-17), 1.38 (3H, s, H-16), 1.48 (1H, s, H-14), 3.86 (3H, s, H-27), 6.09 (1H, s, H-12), 10.62 (1H, s, OH-1), 11.28 (1H, s, OH-13), 16.91 (1H, s, OH-9); δ_C($CDCl_3$) 19.2 (C-25), 19.3 (C-26), 22.3 (C-20), 22.4 (C-15), 22.6 (C-21), 24.3 (C-14), 26.1 (C-17), 26.8 (C-19), 27.0

(C-16), 29.1 (C-7), 38.7 (C-18), 39.1 (C-24), 49.0 (C-2), 54.2 (C-4), 55.7 (C-27), 93.6 (C-12), 104.0 (C-10), 108.9 (C-8), 114.7 (C-6), 161.8 (C-11), 164.2 (C-9), 164.9 (C-13), 177.4 (C-1), 203.2 (C-5), 211.3 (C-22), 212.8 (C-3); *m/z* (Found: M^+, 460.24872. $C_{26}H_{36}O_7$ requires M, 460.24610); and further pure compound **8** (0.05 g, 0.28%) as pale yellow crystals, m.p. 124 - 125 °C; $[\alpha]_D^{25}$ 0 (*c* 1.23 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3122, 3029, 2959, 1714, 1618, 1591; λ_{max} ($CHCl_3$)/nm 242, 291; **Conformer 1**; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.3, H-20), 0.86 (3H, d, *J* 6.3, H-21), 0.99 (2 x 3H, d, *J* 6.3, H-25,26), 1.33 (3H, s, H-15), 1.34 (1H, s, H-17), 1.40 (1H, m, H-19), 1.40 (3H, s, H-16), 1.49 (1H, s, H-14), 1.79 (1H, t, *J* 6.9, H-18), 2.12 (1H, t, *J* 6.9, H-18), 2.22 (1H, m, H-24), 2.89 (2H, d, *J* 6.9, H-23), 3.86 (3H, s, H-27), 4.38 (1H, t, *J* 7.7, H-7), 6.02 (1H, s, H-12), 10.39 (1H, s, OH-1), 11.66 (1H, s, OH-13), 16.88 (1H, s, OH-9); δ_C($CDCl_3$) 22.3 (C-20), 22.4 (C-15), 22.6 (C-21), 22.9 (2 x C-25,26), 24.2 (C-14), 25.4 (C-24), 26.1 (C-17), 26.8 (C-19), 27.0 (C-16), 27.9 (C-7), 38.1 (C-18), 48.6 (C-2), 52.5 (C-23), 55.1 (C-4), 55.5 (C-27), 93.9 (C-12), 104.5 (C-10), 108.9 (C-8), 114.7 (C-6), 162.0 (C-11), 163.6 (C-9), 164.6 (C-13), 176.6 (C-1), 203.1 (C-5), 206.0 (C-22), 212.3 (C-3). **Conformer 2**; δ_H($CDCl_3$) all peaks obscured except 6.08 (1H, s, H-12), 10.63 (1H, s, OH-1), 11.27 (1H, s, OH-13), 17.07 (1H, s, OH-9); δ_C($CDCl_3$) all peaks obscured except 24.3 (C-14), 27.1 (C-16), 29.1 (C-7), 38.7 (C-18), 49.0 (C-2), 54.2 (C-4), 55.6 (C-27), 93.5 (C-12), 104.9 (C-10), 114.9 (C-6), 164.3 (C-13), 177.3 (C-1), 203.2 (C-5), 206.5 (C-22), 212.7 (C-3); *m/z* (Found: M^+, 474.26236. $C_{27}H_{38}O_7$ requires M, 474.26175).

5.2.8 Compounds 7 and 8 from *Kunzea baxterii*

Plant material

The leaves and stems of *Kunzea baxterii* were collected from the Royal Botanical Gardens, Kew, London on the 10th July 1995.

Extraction and Isolation

The ground air-dried leaves and stems of *Kunzea baxterii* (215 g) were extracted with hexane (3 x 1 l) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (4 g).

The residue (3.9 g) was chromatographed on silica gel by gradient elution with petrol ether - diethyl ether (7 : 3 to 3 : 1). This gave two biologically active fractions, the less polar of which (1.2 g) was rechromatographed on silica gel eluting with petrol ether - diethyl ether (9 : 1). The resultant insecticidal fraction, after evaporation of the solvent in vacuo, afford compounds **7** and **8** (0.18 g, 0.25% and 0.12%) in a 2 : 1 ratio.

5.2.9 Compounds 7 and 8 from *Kunzea ericoides*

Plant material

The leaves and stems of *Kunzea ericoides* were collected from the Royal Botanical Gardens, Kew, London on the 23rd August 1994.

Extraction and Isolation

The ground air-dried leaves and stems of *Kunzea ericoides* (50 g) were extracted with hexane (3 x 200 ml) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (1.2 g).

The residue (0.95 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (6 : 1). The more polar biologically active fraction contained a mixture of compounds **7** and **8** (0.25 g, 0.33% and 0.17%) in a 2 : 1 ratio.

5.2.10 Compounds 7 and 8 from *Kunzea sinclairii*

Plant material

The leaves and stems of *Kunzea sinclairii* were collected from New Zealand.

Extraction and Isolation (Procedure 1)

The ground air-dried leaves and stems of *Kunzea sinclairii* (65 g) were extracted with diethyl ether (3 x 1 l) using a soxlet extractor. The combined extracts were evaporated in vacuo to give a dark green residue (5 g). The residue (5 g) was back extracted with hexane (3 x 150 ml) and the combined extracts evaporated in vacuo to give a green brown residue (3 g).

The residue (0.6 g) was chromatographed on reverse phase silica gel eluting with ethanol to give a biologically active fraction (0.4 g). This fraction

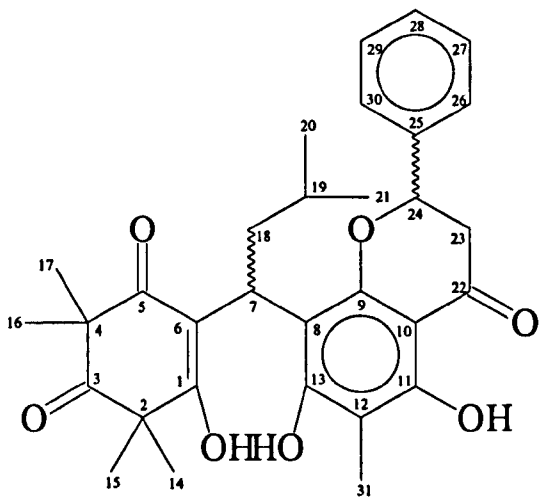
(0.16 g) was dissolved in diethyl ether (20 ml) and extracted with 1M aquoeus sodium hydroxide (2 x 10 ml). The combined aquoeus phases were acidified to pH 5 with 1M HCl (ca 20 ml) and extracted with diethyl ether (3 x 10 ml). After evaporation of the combined ethereal extracts, the thick oily residue (0.09 g) was dissolved in the minimum amount of hexane and cooled to 0 ^{0}C. The resultant non-insecticidal crystals were removed by filtration and the filtrate evaporated. The residue (0.07 g) was chromatographed on a nitrile HPLC column by gradient elution with hexane - methanol (1 : 0 to 9 : 1). This gave a fraction containing a mixture of compounds **7** and **8** (30 mg, 0.046%) in a 1 : 1 ratio.

Extraction and Isolation (Procedure 2)

The ground, air-dried leaves and stems of *Kunzea sinclairii* (65 g) were extracted with diethyl ether (3 x 1 l) using a soxlet extractor. The combined extracts were evaporated in vacuo to give a dark green residue (5 g). The residue (5 g) was back extracted with hexane (3 x 150 ml) and the combined extracts evaporated in vacuo to give a green brown residue (3 g).

The residue (0.6 g) was chromatographed on reverse phase silica gel eluting with ethanol to give a biologically active fraction (0.4 g). This fraction (0.075 g) was chromatographed by reverse phase C4 HPLC eluting with methanol water (9 : 1). The biologically active fraction (0.025 g) was chromatographed on a nitrile HPLC column by gradient elution with hexane - methanol (1 : 0 to 9 : 1). This gave a fraction containing a mixture of compounds **7** and **8** (10 mg) in a 1 : 1 ratio.

5.2.11 Compound 9 from *Kunzea ambigua*



Plant material

The leaves and stems of *Kunzea ambigua* were collected from the Royal Botanical Gardens, Kew, London on the 26th May 1993 and the 10th August 1993. The plant was verified by E. Nielughadha.

Extraction and Isolation

The ground air-dried leaves and stems of *Kunzea ambigua* (36 g) were extracted with hexane (3 x 500 ml) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (0.77 g).

The residue (0.74 g) was chromatographed on silica gel eluting with petrol ether - diethyl ether (7 : 3). The biologically active fraction (0.12 g) was rechromatographed on silica gel preparative thin layer chromatography plates eluting with petrol ether - diethyl ether (1 : 1). This gave a fraction exhibiting biological activity (20 mg) which was further purified by flash column

chromatography on silica gel using petrol ether - diethyl ether (1 : 1). The resultant insecticidal fraction, after evaporation of the solvent in vacuo, afforded compound **9** (16 mg, 0.044%) as a light brown semi-solid and as a mixture of diastereomers and conformers in a 10 : 5 : 4 : 3 ratio; $[\alpha]_D^{25}$ -55.4 (*c* 3.24 in $CDCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 3029, 2981, 2654, 2870, 1710, 1627, 1468, 1384; λ_{max} ($CHCl_3$)/nm 242, 299; **diastereomer 9a** δ_H($CDCl_3$) 0.86 (3H, d, *J* 5.9, H-20), 0.87 (3H, d, *J* 6.3, H-21), 1.34 (3H, s, H-17), 1.35 (3H, s, H-15), 1.41 (3H, s, H-16), 1.41 (1H, m, H-19), 1.50 (3H, s, H-14), 1.80 (1H, m, H-18), 2.07 (1H, m, H-18), 2.07 (3H, s, H-31), 2.89 (1H, dd, *J* 17.6, 3.4, H-23), 3.03 (1H, dd, *J* 17.1, 12.7, H-23), 4.33 (1H, t, *J* 7.6, H-7), 5.43 (1H, dd, *J* 12.9, 10.0, H-24), 7.42 (1H, s, H-28), 7.44 (2 x 1H, s, H-26,30), 7.45 (2 x 1H, s, H-27,29), 9.91 (1H, s, OH-9), 11.77 (1H, s, OH-13), 13.97 (1H, s, OH-1); δ_C($CDCl_3$) 7.9 (C-31), 22.1 (C-16), 22.3 (C-21), 22.6 (C-20), 24.2 (C-15), 26.2 (C-14), 26.8 (C-19), 27.1 (C-17), 27.6 (C-7), 38.1 (C-18), 42.9 (C-23), 48.6 (C-2), 55.2 (C-4), 78.5 (C-24), 101.6 (C-10), 106.8 (C-12), 108.6 (C-8), 114.5 (C-6), 125.8 (2 x C-27,29), 128.6 (C-28), 128.8 (2 x C-26,30), 138.8 (C-25), 156.7 (C-9), 158.7 (C-11), 164.9 (C-13), 176.1 (C-1), 196.5 (C-22), 203.3 (C-5), 212.0 (C-3); **diastereomers b,c,d** for nmr see table 2.12; *m/z* (Found: M^+, 520.24609. $C_{31}H_{36}O_7$ requires M, 520.24610).

5.2.12 Compound 9 from *Kunzea baxterii*

Plant material

Leaves and stems of *Kunzea baxterii* were collected from the Royal Botanical Gardens, Kew, London on the 10th July 1995. The plant was verified by E. Nielughadha.

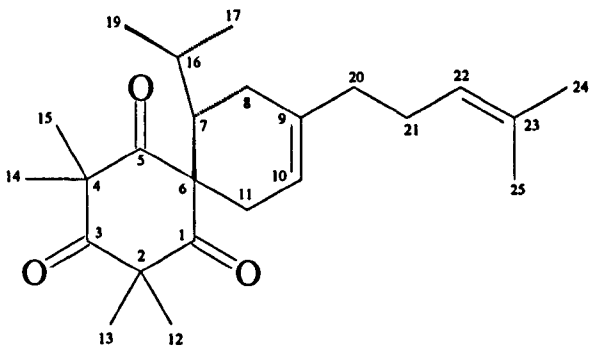
Extraction and Isolation

Ground air-dried leaves and stems of *Kunzea baxterii* (215 g) were extracted with hexane (3 x 1 l) at room temperature. The combined extracts were evaporated in vacuo to give a dark green residue (4 g).

The residue (3.9 g) was chromatographed on silica gel by gradient elution with petrol ether - diethyl ether (7 : 3 to 3 : 1). This gave two biologically active fractions, the more polar of which (1.4 g) was rechromatographed on silica gel eluting with petrol ether - diethyl ether (7 : 3). The resultant insecticidal fraction, after evaporation of the solvent in vacuo, afford compound **9** (0.18 g, 0.084%).

5.3 EXPERIMENTAL PROCEDURES

2,2-[2-(1-methylethyl)-4-(4-methylpent-3-enyl)cyclohex-4-ene]-4,4,6,6-tetramethylcyclohexan-1,3,5-trione 1 (Method 1)



The trione **3.7** (0.1 g, 0.42 mmol) and myrcene **3.8** (0.058 g, 0.42 mmol) were refluxed in dry benzene (3 ml) for 6 h. On cooling, the solvent was removed under reduced pressure and the crude product purified by column chromatography using 10 % diethyl ether / petrol ether as eluant to afford the title compound **1** (0.02 g, 13%) as a pale yellow oil, n_D 1.4431; υ_{max} ($CHCl_3$)/cm^{-1} 3029, 2972, 2927, 1701, 1467, 1392; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.6, H-19), 0.90 (3H, d, *J* 6.7, H-17), 1.35 (3H, s, H-12[c]), 1.39 (3H, s, H-13[c]), 1.40 (3H, s, H-15[c]), 1.42 (3H, s, H-14[c]), 1.60 (3H, s, H-25), 1.68 (3H, s, H-24), 1.67 (1H, m, H-16), 1.96 (2H, t, *J* 7.5, H-20), 1.98 (1H, m, H-8), 2.07 (2H, m, H-21), 2.19 (1H, dd, *J* 6.7, 3.1, H-11), 2.20 (1H, m, H-7), 2.25 (1H, m, H-8), 2.49 (1H, dd, *J* 17.3, 2.8, H-11), 5.05 (1H, t, *J* 6.9, H-22), 5.27 (1H, m, H-10); δ_C($CDCl_3$) 17.7 (C-25), 19.1 (C-19), 24.1 (C-17), 24.9 (C-13[c]), 25.0

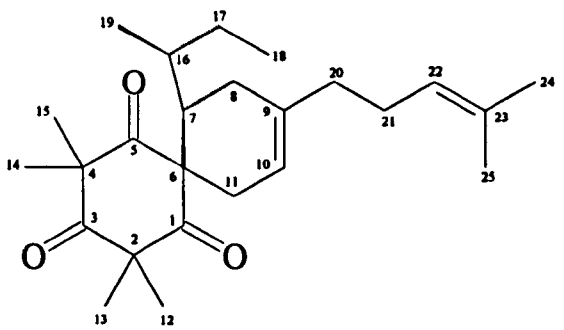
(C-15[c]), 25.7 (C-23), 26.0 (C-12[c]), 26.1 (C-21), 26.2 (C-14[c]), 27.7 (C-8), 30.0 (C-16), 31.0 (C-11), 37.1 (C-20), 41.1 (C-7), 56.3 (C-2[b]), 56.6 (C-4[b]), 67.0 (C-6), 115.4 (C-10), 124.1 (C-22), 131.4 (C-23), 138.0 (C-9), 208.5 (C-1[a]), 208.7 (C-5[a]), 212.9 (C-3); m/z (Found: M+, 372.26691. $C_{24}H_{36}O_3$ requires M, 372.26644). This data closely parallels those measured for the natural product **1**.

2,2-[2-(1-methylethyl)-4-(4-methylpent-3-enyl)cyclohex-4-ene]-4,4,6,6-tetramethylcyclohexen-1,3,5-trione 1 (Method 2)

A solution of syncarpic acid **3.4** (0.4 g, 2.2 mmol), isobutyraldehyde (0.32 g, 2.4 mmol), myrcene **3.8** (1.2 g, 8.8 mmol), potassium acetate (0.022 g, 0.22 mmol) and 4A molecular sieves (1 g) in acetic acid (10 ml) was refluxed for 6 h. On cooling the solvent was removed under reduced pressure and the crude product purified by column chromatography using 5 % diethyl ether / petrol ether as eluant to afford the title compound **1** (0.3 g, 38%) and as a minor impurity compound **3.22** (0.03 g, 4%) as a colourless oil; $\delta_H(CDCl_3)$ 0.66 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.92 (3H, d, *J* 7.0, $CH(CH_3)_2$), 1.33 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.48 (3H, s, CH_3), 1.54 (1H, m, $CHCH_2$), 1.56 (3H, s, CH_3), 1.60 (2H, m, CH_2), 1.66 (3H, s, CH_3), 1.85 (2H, m, CH_2), 2.01 (1H, m, $CHCH_2$), 2.62 (1H, m, $CH(CH_3)_2$), 2.71 (1H, m, CH_2CH), 5.01 (1H, t, *J* 9.0, C=CH), 5.22 (1H, dd, *J* 11.0, 1.2, $CH=CH_2$), 5.32 (1H, dd, *J* 17.4, 1.2, $CH=CH_2$), 5.93 (1H, dd, *J* 17.4, 11.0, $CH=CH_2$);

$\delta_C(CDCl_3)$ 16.2 (CH_3), 17.7 (CH_3), 20.7 (CH_3), 22.3 (CH_2), 23.0 (CH_3), 24.6 (CH_3), 25.6 (CH_3), 26.0 (CH_3), 26.1 (CH_3), 26.4 (CH), 30.4 (CH_2), 33.1 (CH), 48.4 (C_q), 55.4 (C_q), 81.0 (C_q), 111.7 (C_q), 113.6 (CH_2), 123.4 (CH), 132.1 (C_q), 140.6 (CH), 169.7 (C_q), 198.0 (C_q), 213.4 (C_q).

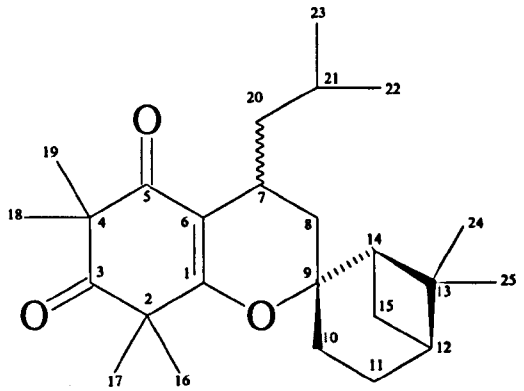
2,2-[2-(1-methylpropyl)-4-(4-methylpent-3-enyl)cyclohex-4-ene]-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 2



A solution of syncarpic acid **3.4** (0.4 g, 2.2 mmol), 2-methylbutanal (0.38g, 4.4 mmol), myrcene **3.8** (1.2 g, 8.8 mmol), potassium acetate (0.22 g, 0.22 mmol) and 4A molecular sieves (1 g) in acetic acid (10 ml) was refluxed for 6 h. On cooling the solvent was removed under reduced pressure and the crude product purified by column chromatography using 10 % diethyl ether / petrol ether as eluant to afford the title compound as a mixture of diastereomers **2** (0.24 g, 28 %). The two diastereomers were separated by column chromatography to give **2a** and **2b** as pale yellow semi-solids; υ_{max} ($CHCl_3$)/cm^{-1} 2969, 2937, 2856, 1704, 1465, 1388; Diastereomer **2a** $\delta_H(CDCl_3)$

0.80 (3H, d, *J* 6.6, H-19), 0.85 (3H, t, *J* 7.2, H-18), 1.24 (1H, m, H-17), 1.26 (1H, d, *J* 7.1, H-8), 1.33 (1H, m, H-16), 1.34 (3H, s, H-12c), 1.37 (1H, m, H-8), 1.39 (3H, s, H-13c), 1.39 (3H, s, H-15c), 1.40 (1H, m, H-17), 1.42 (3H, s, H-14c), 1.60 (3H, s, H-25), 1.68 (3H, s, H-24), 1.96 (2H, t, *J* 7.0, H-20), 2.07 (2H, t, *J* 6.0, H-21), 2.14 (1H, m, H-11), 2.27 (1H, m, H-7), 2.50 (1H, m, H-11), 5.06 (1H, t, *J* 6.8, H-22), 5.28 (1H, m, H-10); δ_C($CDCl_3$) 12.1 (C-18), 15.3 (C-19), 17.7 (C-25), 24.6 (C-15c), 24.8 (C-13c), 25.7 (C-24), 25.9 (C-12c), 26.2 (C-14c), 26.2 (C-21), 27.2 (C-17), 30.7 (C-8), 31.1 (C-11), 36.4 (C-16), 37.1 (C-20), 40.5 (C-7), 56.7 (C-2b), 56.7 (C-4b), 66.7 (C-6), 115.5 (C-10), 124.1 (C-22), 131.5 (C-23), 137.9 (C-9), 208.4 (C-1a), 208.9 (C-5a), 212.7 (C-3); Diastereomer **2b** δ_H($CDCl_3$) 0.83 (3H, d, *J* 6.9, H-18), 0.84 (3H, t, *J* 6.6, H-19), 1.05 (1H, dq, *J* 6.3, 1.6, H-17), 1.35 (3H, s, H-12c), 1.39 (3H, s, H-13c), 1.39 (3H, s, H-15c), 1.42 (3H, s, H-14c), 1.43 (1H, m, H-16), 1.52 (1H, dq, 10.1, 7.1, H-17), 1.60 (3H, s, H-25), 1.67 (3H, s, H-24), 2.05 (2H, m, H-21), 2.06 (1H, m, H-8), 2.14 (1H, d, *J* 19.8, H-11), 2.27 (1H, m, H-7), 2.28 (1H, m, H-8), 2.50 (1H, d, *J* 15.7, H-11), 5.05 (1H, td, *J* 6.0, 1.4, H-22), 5.28 (1H, d, *J* 1.4, H-10); δ_C($CDCl_3$) 12.3 (C-18), 17.7 (C-25), 19.7 (C-19), 24.7 (C-13c), 25.3 (C-15c), 25.5 (C-12c), 25.5 (C-17), 25.7 (C-24), 26.2 (C-21), 26.4 (C-14c), 29.1 (C-8), 32.6 (C-11), 37.1 (C-20), 37.6 (C-16), 41.3 (C-7), 56.6 (C-2b), 56.8 (C-4b), 66.2 (C-6), 114.6 (C-10), 124.1 (C-22), 131.5 (C-23), 139.1 (C-9), 208.6 (C-1a), 209.1 (C-5a), 212.8 (C-3); m/z (Found: M+, 386.28241. $C_{25}H_{38}O_3$ requires M, 386.28210). This data closely parallels those measured for the natural product **2**.

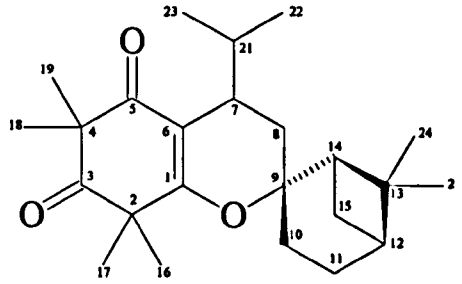
Natural Product 3



Syncarpic acid **3.4** (0.2 g, 1.1 mmol), isovaleraldehyde (0.19 g, 2.2 mmol), (1S)-(-)-β-pinene **3.25** (0.6 g, 4.4 mmol), potassium acetate (0.011 g, 0.11 mmol) and 4A molecular sieves (1 g) in acetic acid (4 ml) was refluxed for 6h. On cooling the solvent was removed under reduced pressure, dichloromethane (10 ml) added and the resultant solution filtered. The filtrate was washed with water (10 ml) and evaporated under reduced pressure. The resultant crude product was purified by column chromatography using 9 % diethyl ether / petrol ether as eluant to afford two fractions each containing epimers of the title compound **3**. Epimer **3a** (0.12 g, 28 %) as a colourless oil, n_D 1.5035; $[\alpha]_D^{25}$ +64.2 (*c* 1.81 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2971, 1720, 1644, 1630, 1472, 1294; δ_H($CDCl_3$) 0.91 (3H, d, *J* 6.4, H-22), 0.96 (1H, ddd, *J* 13.0, 10.4, 3.9, H-20), 0.98 (3H, d, *J* 6.3, H-23), 1.02 (3H, s, H-25), 1.29 (3H, s, H-24), 1.31 (3H, s, H-19[a]), 1.33 (3H, s, H-18[a]), 1.34 (3H, s, H-16[a]), 1.36 (3H, s, H-17[a]), 1.46 (1H, dd, *J* 14.0, 8.8, H-8), 1.61 (1H, m, H-15), 1.70 (2H, m, H-10), 1.73 (1H, ddd, *J* 13.1, 10.1, 3.4, H-20), 1.93 (1H, m, H-21), 1.94 (2H, m, H-11), 1.99 (1H, m, H-12), 2.13 (1H, dd, *J* 14.0, 6.8, H-8), 2.14 (1H, m, H-14), 2.27 (1H, m, H-15), 2.73 (1H, dddd, *J* 10.3, 8.8, 6.8, 3.4, H-7); δ_C($CDCl_3$)

20.8 (C-23), 22.3 (C-19[a]), 23.4 (C-25), 24.2 (C-22), 24.3 (C-17[a]), 24.9 (C-11), 25.5 (C-16[a]), 25.6 (C-7), 25.6 (C-21), 26.3 (C-18[a]), 26.9 (C-15), 27.3 (C-24), 27.9 (C-10), 38.2 (C-13), 39.6 (C-8), 40.4 (C-12), 42.3 (C-20), 48.0 (C-2), 51.2 (C-14), 55.5 (C-4), 84.2 (C-9), 112.9 (C-6), 168.9 (C-1), 197.9 (C-5), 213.5 (C-3). This data closely parallels those measured for the natural product **3**. Epimer **3b** (0.11 g, 26 %) as a colourless oil, n_D 1.5052; $[\alpha]_D^{25}$ -103.4 (*c* 2.08 in $CHCl_3$); $\delta_H(CDCl_3)$ 0.90 (3H, d, *J* 6.6, H-22), 0.93 (1H, m, H-20), 0.96 (3H, d, *J* 6.3, H-23), 0.99 (3H, s, H-25), 1.25 (3H, s, H-24), 1.27 (3H, s, H-19[a]), 1.29 (3H, s, H-18[a]), 1.32 (3H, s, H-16[a]), 1.39 (3H, s, H-17[a]), 1.53 (1H, m, H-15), 1.58 (1H, dd, *J* 14.3, 10.4, H-8), 1.71 (1H, dsept, *J* 6.4, 4.1, H-21), 1.77 (1H, ddd, *J* 11.0, 10.6, 3.3, H-20), 1.91 (1H, m, H-10), 1.91 (2H, m, H-11), 1.97 (1H, m, H-12), 2.10 (1H, m, H-10), 2.12 (1H, m, H-15), 2.15 (1H, d, *J* 4.7, H-14), 2.27 (1H, dd, *J* 14.3, 6.6, H-8), 2.66 (1H, dddd, *J* 10.4, 10.1, 6.6, 3.3, H-7); $\delta_C(CDCl_3)$ 20.7 (C-23), 22.7 (C-19[a]), 23.2 (C-25), 23.9 (C-17[a]), 24.2 (C-22), 24.2 (C-21), 24.7 (C-11), 25.3 (C-16[a]), 26.1 (C-15), 26.2 (C-18[a]), 26.3 (C-7), 27.5 (C-24), 30.4 (C-10), 38.1 (C-13), 39.1 (C-8), 40.5 (C-12), 42.1 (C-20), 46.7 (C-14), 48.1 (C-2), 55.2 (C-4), 84.8 (C-9), 112.3 (C-6), 168.6 (C-1), 198.0 (C-5), 213.6 (C-3).

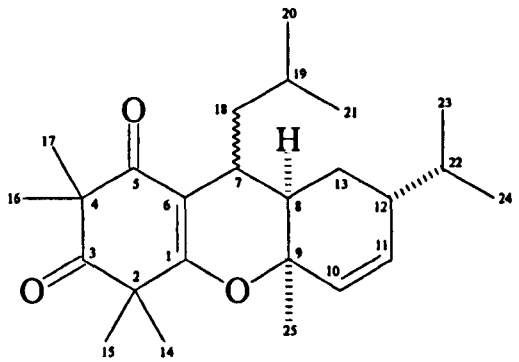
Natural product 4



A solution of syncarpic acid **3.4** (0.2 g, 1.1 mmol), isobutyraldehyde (0.16 g, 2.2 mmol), (1S)-(-)-β-pinene **3.25** (0.6 g, 4.4 mmol), potassium acetate (0.011 g, 0.11 mmol) and 4A molecular sieves (1 g) in acetic acid (4 ml) was refluxed for 6 h. On cooling the solvent was removed under reduced pressure, dichloromethane (10 ml) added and the resultant solution filtered. The filtrate was washed with water (10 ml) and evaporated under reduced pressure. The resultant crude product was purified by column chromatography using 9 % diethyl ether / petrol ether as eluant to afford two fractions of the title compound **4** as two separated epimers. Epimer **4a** (0.07 g, 17%) as a pale yellow semi-solid; $[\alpha]_D^{25}$ +66.9 (*c* 1.24 in $CHCl_3$); υ_{max} ($CHCl_3$)/cm^{-1} 2971, 2863, 1712, 1651, 1599, 1381; λ_{max} ($CHCl_3$)/nm 270; δ_H($CDCl_3$) 0.63 (3H, d, *J* 6.7, H-23), 0.94 (3H, d, *J* 6.6, H-22), 0.96 (3H, s, H-25), 1.23 (3H, s, H-24), 1.26 (3H, s, H-16), 1.30 (3H, s, H-18), 1.32 (3H, s, H-19), 1.40 (3H, s, H-17), 1.42 (2H, m, H-11), 1.46 (1H, m, H-15), 1.61 (1H, m, H-8), 1.88 (2H, dt, *J* 12.6, 5.9, H-10), 1.95 (1H, m, H-12), 2.09 (1H, dd, *J* 8.1, 6.9, H-8), 2.18 (1H, m, H-14), 2.20 (1H, m, H-15), 2.62 (1H, m, H-21), 2.65 (1H, m, H-7); δ_C($CDCl_3$) 15.6 (C-23), 20.7 (C-22), 23.0 (C-25), 23.3 (C-19), 24.2 (C-17),

24.6 (C-11), 25.7 (C-18), 25.9 (C-7), 26.0 (C-15), 26.2 (C-16), 27.5 (C-24), 30.7 (C-10), 32.2 (C-8), 33.8 (C-21), 38.2 (C-13), 40.6 (C-12), 45.4 (C-14), 48.3 (C-2), 55.2 (C-4), 85.0 (C-9), 111.3 (C-6), 171.1 (C-1), 198.1 (C-5), 213.8 (C-3); Epimer **4b** (0.052 g, 13 %) white crystals, m.pt. 95 - 96 °C; $\delta_H(CDCl_3)$ 0.61 (3H, d, *J* 6.8, H-23), 0.94 (3H, d, *J* 6.9, H-22), 1.00 (3H, s, H-25), 1.32 (3H, s, H-24), 1.32 (3H, s, H-16), 1.33 (3H, s, H-18), 1.34 (3H, s, H-19), 1.36 (2H, m, H-11), 1.38 (3H, s, H-17), 1.42 (1H, m, H-15), 1.64 (1H, m, H-8), 1.87 (2H, dt, *J* 11.6, 6.0, H-10), 1.94 (1H, m, H-12), 1.99 (1H, m, H-8), 2.05 (1H, m, H-14), 2.31 (1H, m, H-15), 2.73 (1H, m, H-21), 2.75 (1H, m, H-7); $\delta_C(CDCl_3)$ 15.5 (C-23), 20.6 (C-22), 23.1 (C-25), 23.4 (C-19), 24.5 (C-17), 24.9 (C-11), 25.4 (C-18), 25.9 (C-7), 25.9 (C-15), 26.9 (C-16), 27.0 (C-24), 27.5 (C-10), 32.5 (C-8), 33.4 (C-21), 38.2 (C-13), 40.4 (C-12), 48.2 (C-14), 42.9 (C-2), 55.4 (C-4), 84.3 (C-9), 112.5 (C-6), 170.1 (C-1), 197.8 (C-5), 213.7 (C-3). This data closely parallels those measured for the natural product **4**.

Compound 5



Syncarpic acid **3.4** (0.4 g, 2.2 mmol), isovaleraldehyde (0.32 g, 4.4

mmol), (1R)-α-phellandrene **3.26** (0.4 g, 2.9 mmol), potassium acetate (0.022 g, 0.22 mmol) and 4A molecular sieves (1 g) in acetic acid (10 ml) was refluxed for 6h. On cooling the solvent was removed under reduced pressure, dichloromethane (10 ml) added and the resultant solution filtered. The filtrate was washed with water (10 ml) and evaporated under reduced pressure. The resultant crude product was purified by column chromatography using 10 % diethyl ether / petrol ether as eluant to afford a crude mixture of products (0.63 g). This crude mixture (0.2 g) was further purified by HPLC using 5% ethyl acetate / hexane to give five fractions. The fifth fraction afforded the title compound **5a** (0.04 g, 15%) as a pale yellow oil, n_D 1.4378; $[\alpha]_D^{25}$ +107.5 (*c* 1.20 in $CHCl_3$); $\delta_H(CDCl_3)$ 0.94 (3H, d, *J* 6.8, H-20), 0.96 (3H, d, *J* 6.7, H-24), 0.98 (3H, d, *J* 6.4, H-23), 1.00 (3H, d, *J* 6.4, H-21), 1.12 (1H, td, *J* 11.7, 2.8, H-18), 1.27 (3H, s, H-14[a]), 1.29 (3H, s, H-15[a]), 1.29 (3H, s, H-16[a]), 1.30 (1H, m, H-13), 1.32 (3H, s, H-25), 1.36 (3H, s, H-17[a]), 1.63 (1H, m, H-19), 1.67 (1H, m, H-22), 1.70 (1H, m, H-13), 1.89 (1H, ddd, *J* 14.8, 6.6, 3.2, H-8), 1.94 (1H, m, H-12), 1.97 (1H, m, H-18), 2.97 (1H, ddd, *J* 11.4, 6.4, 3.4, H-7), 5.75 (1H, dd, *J* 10.0, 1.8 H-10), 6.00 (1H, dd, *J* 10.0, 3.7, H-11); $\delta_C(CDCl_3)$ 20.7 (C-13), 20.8 (C-21), 21.0 (C-23), 21.5 (C-24), 21.6 (C-25), 23.5 (C-17[a]), 23.8 (C-14[a]), 24.2 (C-20), 24.6 (C-19), 25.8 (C-15[a]), 26.8 (C-16[a]), 28.2 (C-7), 31.5 (C-22), 33.6 (C-8), 35.2 (C-18), 41.2 (C-12), 47.9 (C-2), 55.8 (C-4), 76.2 (C-9), 110.2 (C-6), 130.8 (C-10), 135.2 (C-11), 166.9 (C-1), 198.5 (C-5), 213.3 (C-3). This data closely parallels those measured for the natural product **5a**. The second fraction contained a mixture of two compounds **5b** and **3.27b** as a pale yellow liquid in a 7 : 3 ratio; $[\alpha]_D^{25}$ -45.6 (*c* 2.04 in $CHCl_3$); Compound

5b (0.035 g, 13%); $\delta_H(CDCl_3)$ 0.91 (3H, d, *J* 6.3, H-20), 0.92 (3H, d, *J* 6.6, H-23), 0.95 (3H, d, *J* 6.6, H-24), 1.00 (3H, d, *J* 6.6, H-21), 1.33 (3H, s, H-15[a]), 1.33 (3H, s, H-16[a]), 1.33 (3H, s, H-17[a]), 1.35 (1H, m, H-18), 1.39 (3H, s, H-14[a]), 1.45 (1H, m, H-18), 1.46 (3H, s, H-25), 1.57 (2H, m, H-13), 1.66 (1H, m, H-22), 1.76 (1H, m, H-19), 2.00 (1H, m, H-12), 2.02 (1H, m, H-8), 2.56 (1H, dt, *J* 9.9, 3.2, H-7), 5.50 (1H, dd, *J* 10.2, 2.2 H-10), 5.84 (1H, dd, *J* 10.2, 3.9, H-11); $\delta_C(CDCl_3)$ 20.4 (C-23), 20.4 (C-24), 21.5 (C-21), 23.5 (C-16[a]), 24.0 (C-20), 24.6 (C-14[a]), 25.3 (C-15[a]), 25.4 (C-17[a]), 26.1 (C-19), 27.4 (C-25), 29.1 (C-13), 31.6 (C-22), 31.8 (C-7), 38.3 (C-8), 39.5 (C-12), 43.9 (C-18), 47.5 (C-2), 55.6 (C-4), 77.7 (C-9), 113.0 (C-6), 131.0 (C-10), 134.6 (C-11), 168.6 (C-1), 198.1 (C-5), 213.5 (C-3). This data closely parallels those measured for the natural product **5b**.

The least polar fraction 1 afforded compound **3.27a** (0.015 g, 6%) as a white solid; $[\alpha]_D^{25}$ +48.2 (*c* 0.48 in $CHCl_3$); $\delta_H(CDCl_3)$ 0.89 (3H, d, *J* 6.3, H-22), 0.89 (3H, d, *J* 6.9, H-24), 0.92 (3H, d, *J* 6.9, H-25), 0.97 (3H, d, *J* 6.0, H-21), 1.00 (1H, m, H-8), 1.26 (3H, s, H-16), 1.31 (3H, s, H-17), 1.33 (3H, s, H-18), 1.38 (3H, s, H-15), 1.60 (1H, m, H-8), 1.61 (1H, m, H-13), 1.64 (1H, m, H-19), 1.70 (1H, m, H-23), 1.75 (1H, m, H-20), 1.95 (1H, m, H-14), 1.99 (1H, m, H-12), 1.99 (1H, m, H-19), 2.04 (1H, m, H-14), 2.87 (1H, ddt, *J* 8.5, 8.5, 2.9, H-7), 5.71 (1H, d, *J* 9.8, H-10), 5.84 (1H, dd, *J* 10.0, 1.8, H-11); $\delta_C(CDCl_3)$ 19.0 (C-24), 19.5 (C-25), 20.6 (C-13), 20.7 (C-21), 22.6 (C-18), 24.0 (C-15), 24.2 (C-22), 25.3 (C-16), 25.5 (C-20), 25.7 (C-7), 26.1 (C-17), 31.7 (C-23), 35.4 (C-19), 38.4 (C-14), 42.2 (C-12), 42.8 (C-8), 47.9 (C-2), 55.4 (C-4), 75.1 (C-9), 112.3 (C-6), 126.6 (C-10), 137.1 (C-11), 169.2 (C-1), 198.1

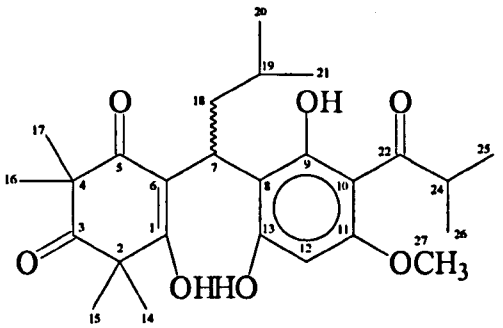
(C-5), 213.6 (C-3); m/z (Found: M+, 386.27930. $C_{25}H_{38}O_3$ requires M, 386.28210).

Fraction 2 afforded compound **3.27b** (0.015 g, 6%); $\delta_H(CDCl_3)$ 0.89 (3H, d, *J* 6.3, H-24), 0.90 (3H, d, *J* 6.9, H-25), 0.90 (3H, d, *J* 6.6, H-22), 1.00 (3H, m, H-21), 1.00 (1H, m, H-8), 1.32 (3H, s, H-17), 1.33 (3H, s, H-16), 1.34 (3H, s, H-18), 1.38 (3H, s, H-15), 1.38 (1H, m, H-13), 1.40 (1H, m, H-20), 1.54 (1H, m, H-19), 1.57 (1H, d, *J* 6.9, H-14), 1.66 (1H, m, H-23), 1.89 (1H, m, H-8), 1.92 (1H, m, H-19), 2.03 (1H, m, H-12), 2.14 (1H, d, *J* 6.9, H-14), 2.75 (1H, m, H-7), 5.63 (1H, dd, *J* 10.4, 2.2, H-10), 5.75 (1H, dd, *J* 10.4, 2.6, H-11); $\delta_C(CDCl_3)$ 19.4 (C-24), 19.8 (C-25), 20.7 (C-21), 22.1 (C-13), 22.3 (C-18), 23.8 (C-15), 24.2 (C-22), 25.0 (C-16), 25.4 (C-20), 25.8 (C-7), 26.2 (C-17), 31.6 (C-23), 34.5 (C-19), 38.6 (C-14), 41.6 (C-12), 42.4 (C-8), 47.9 (C-2), 55.4 (C-4), 76.7 (C-9), 113.0 (C-6), 127.4 (C-10), 134.4 (C-11), 169.1 (C-1), 198.0 (C-5), 213.5 (C-3).

Fraction 3 afforded compound **3.27c** (0.021 g, 8%) as a colourless semi-solid; $[\alpha]_D^{25}$ +79.0 (*c* 0.76 in $CHCl_3$); $\delta_H(CDCl_3)$ 0.89 (3H, d, *J* 6.9, H-22), 0.91 (3H, d, *J* 7.7, H-24), 0.93 (1H, m, H-8), 0.93 (3H, d, *J* 6.9, H-25), 0.95 (3H, d, *J* 6.6, H-21), 1.31 (3H, s, H-16), 1.32 (3H, s, H-17), 1.33 (1H, m, H-14), 1.34 (3H, s, H-18), 1.39 (3H, s, H-15), 1.52 (1H, m, H-13), 1.56 (1H, m, H-19), 1.68 (1H, m, H-20), 1.68 (1H, m, H-23), 1.83 (1H, td, *J* 10.2, 3.0, H-8), 1.92 (1H, t, *J* 6.9, H-19), 1.94 (1H, m, H-12), 1.99 (1H, m, H-14), 2.74 (1H, m, H-7), 5.63 (1H, d, *J* 10.2, H-10), 5.92 (1H, d, *J* 10.2, H-11); $\delta_C(CDCl_3)$ 19.1 (C-24), 19.5 (C-25), 20.7 (C-21), 20.7 (C-13), 22.3 (C-18), 24.2 (C-15), 24.2 (C-22), 25.3 (C-20), 25.4 (C-7), 26.1 (C-16), 26.2 (C-17), 31.1 (C-14), 31.6 (C-

23), 39.3 (C-19), 42.1 (C-12), 42.4 (C-8), 48.0 (C-2), 55.5 (C-4), 75.7 (C-9), 112.5 (C-6), 129.6 (C-10), 136.6 (C-11), 169.1 (C-1), 198.1 (C-5), 213.5 (C-3). Fraction 4 afforded compound **3.27d** (0.01 g, 4%) as a colourless semi-solid; $[\alpha]_D^{25}$ -29.7 (*c* 0.36 in $CHCl_3$); $\delta_H(CDCl_3)$ 0.88 (3H, d, *J* 5.8, H-22), 0.91 (3H, d, *J* 6.0, H-24), 0.92 (3H, d, *J* 6.6, H-25), 0.97 (3H, d, *J* 5.8, H-21), 1.04 (1H, t, *J* 10.0, H-8), 1.32 (3H, s, H-16), 1.32 (3H, s, H-17), 1.33 (1H, s, H-18), 1.39 (3H, s, H-15), 1.68 (1H, m, H-8), 1.69 (3H, m, H-14), 1.70 (1H, m, H-23), 1.71 (1H, m, H-19), 1.72 (1H, m, H-20), 1.77 (1H, m, H-13), 1.91 (1H, m, H-14), 1.94 (1H, dd, *J* 7.4, 6.9, H-19), 2.06 (1H, ddd, *J* 6.0, 5.7, 5.7, H-12), 2.74 (1H, m, H-7), 5.64 (1H, d, *J* 9.5, H-10), 5.77 (1H, dd, *J* 10.3, 2.3, H-11); $\delta_C(CDCl_3)$ 19.3 (C-24), 19.6 (C-25), 20.8 (C-21), 22.1 (C-13), 22.2 (C-18), 24.1 (C-15), 24.2 (C-22), 25.4 (C-16), 25.7 (C-7), 25.7 (C-7), 26.3 (C-17), 31.6 (C-23), 31.8 (C-14), 36.6 (C-19), 41.7 (C-12), 42.3 (C-8), 47.8 (C-2), 55.5 (C-4), 77.9 (C-9), 112.5 (C-6), 130.6 (C-10), 133.5 (C-11), 169.3 (C-1), 198.0 (C-5), 213.5 (C-3).

2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]-3-methyl-butyl-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 7 (Method 1)



The pyrrolidine complex **3.44** (0.04 g, 0.13 mmol) and the phloroglucinol **3.30** (0.026 g, 0.13 mmol) in dry THF (4 ml) were stirred at 0 ^{0}C and p-toluenesulfonic acid (0.024 g, 0.13 mmol) added. After warming to RT over 1 h, the THF was removed under reduced pressure, water (10 ml) added and the product extracted with diethyl ether (3 x 10 ml). The combined ethereal extracts were washed with water, dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 50% diethyl ether / petrol ether as eluant to afford the title compound **7** (0.011 g, 20%) as pale yellow crystals, m.p. 123 - 124 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3034, 2961, 1695, 1466, 1382; **Conformer 1**; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.4, H-20), 0.86 (3H, d, *J* 6.8, H-21), 1.17 (3H, d, *J* 6.3, H-25), 1.19 (3H, d, *J* 6.3, H-26), 1.33 (3H, s, H-15), 1.34 (1H, s, H-17), 1.40 (1H, m, H-19), 1.40 (3H, s, H-16), 1.49 (1H, s, H-14), 1.78 (1H, dt, *J* 7.3, 6.8, H-18), 2.11 (1H, dt, *J* 7.3, 6.8, H-18), 3.81 (1H, sept, *J* 6.8, H-24), 3.86 (3H, s, H-27), 4.38 (1H, t, *J* 6.8, H-7), 6.04 (1H, s, H-12), 10.40 (1H, s, OH-1), 11.63

(1H, s, OH-13), 17.11 (1H, s, OH-9); δ_C($CDCl_3$) 19.3 (C-25), 19.3 (C-26), 22.3 (C-20), 22.4 (C-15), 22.6 (C-21), 24.3 (C-14), 26.1 (C-17), 26.8 (C-19), 27.0 (C-16), 27.9 (C-7), 38.1 (C-18), 39.2 (C-24), 48.6 (C-2), 55.1 (C-4), 55.6 (C-27), 94.0 (C-12), 103.6 (C-10), 109.0 (C-8), 114.9 (C-6), 161.8 (C11), 163.9 (C-9), 164.6 (C-13), 176.6 (C-1), 203.1 (C-5), 210.8 (C-22), 212.3 (C-3). **Conformer 2**; δ_H($CDCl_3$) all peaks obscured except 0.88 (3H, m, H-21), 1.13 (3H, m, H-25), 1.21 (3H, m, H-26), 1.33 (3H, s, H-15), 1.36 (1H, s, H-17), 1.38 (3H, s, H-16), 1.48 (1H, s, H-14), 3.86 (3H, s, H-27), 6.09 (1H, s, H-12), 10.62 (1H, s, OH-1), 11.28 (1H, s, OH-13), 16.91 (1H, s, OH-9); δ_C($CDCl_3$) 19.2 (C-25), 19.3 (C-26), 22.3 (C-20), 22.4 (C-15), 22.6 (C-21), 24.3 (C-14), 26.1 (C-17), 26.8 (C-19), 27.0 (C-16), 29.1 (C-7), 38.7 (C-18), 39.1 (C-24), 49.0 (C-2), 54.2 (C-4), 55.7 (C-27), 93.6 (C-12), 104.0 (C-10), 108.9 (C-8), 114.7 (C-6), 161.8 (C-11), 164.2 (C-9), 164.9 (C-13), 177.4 (C-1), 203.2 (C-5), 211.3 (C-22), 212.8 (C-3). This data closely parallels those measured for the natural product **7**.

2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]-3-methyl-butyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 7 (Method 2)

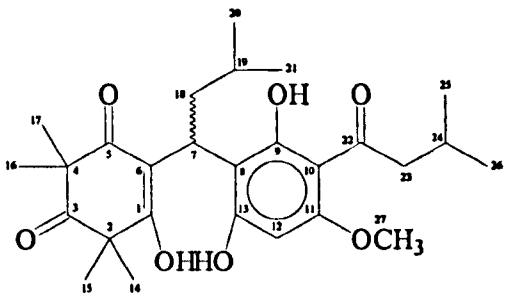
The pyrrolidine complex **3.46** (0.01 g, 0.029 mmol) and syncarpic acid **3.4** (0.01 g, 0.052 mmol) in dry CH_2Cl_2 (1 ml) were stirred at RT and p-toluenesulfonic acid (0.002 g, 0.01 mmol) added. After stirring at RT for 18 h, water (10 ml) was added and the product extracted with CH_2Cl_2 (3 x 2 ml).

The combined extracts were washed with water, dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 20% diethyl ether / petrol ether as eluant to afford the title compound **7** (0.001 g, 7%).

2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]-3-methyl-butyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 7 (Method 3)

The reaction was repeated as for method 2, except without addition of p-toluenesulfonic acid, to give the title compound (0.001 g, 7%).

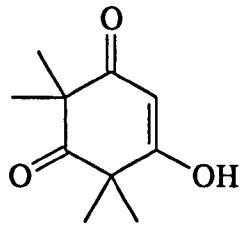
2-{1-[2,6-dihydroxy-4-methoxy-3-(3-methyl-1-oxobutyl)phenyl]-3-methyl-butyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 8



A solution of the alkylidene **3.24** (0.05 g, 0.2 mmol) and the phloroglucinol **3.49** (0.045 g, 0.2 mmol) in dry dichloromethane (5 ml) was stirred at 0°C and p-toluenesulfonic acid (0.002 g, 0.01 mmol) added. After

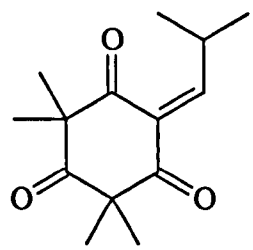
warming to RT over 1 h, 2N HCl (10 ml) was added and the product extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with water (10 ml), dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 20% diethyl ether / petrol ether as eluant to afford the title compound **8** (0.047 g, 50%) as pale yellow crystals, m.p. 124 - 125 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3201, 1710, 1603, 1581; λ_{max} ($CHCl_3$)/nm 242, 290; **Conformer 1**; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.3, H-20), 0.86 (3H, d, *J* 6.3, H-21), 0.99 (2 x 3H, d, *J* 6.3, H-25,26), 1.33 (3H, s, H-15), 1.34 (1H, s, H-17), 1.40 (1H, m, H-19), 1.40 (3H, s, H-16), 1.49 (1H, s, H-14), 1.79 (1H, t, *J* 6.9, H-18), 2.12 (1H, t, *J* 6.9, H-18), 2.22 (1H, m, H-24), 2.89 (2H, d, *J* 6.9, H-23), 3.86 (3H, s, H-27), 4.38 (1H, t, *J* 7.7, H-7), 6.02 (1H, s, H-12), 10.39 (1H, s, OH-1), 11.66 (1H, s, OH-13), 16.88 (1H, s, OH-9); δ_C($CDCl_3$) 22.3 (C-20), 22.4 (C-15), 22.6 (C-21), 22.9 (2 x C-25,26), 24.2 (C-14), 25.4 (C-24), 26.1 (C-17), 26.8 (C-19), 27.0 (C-16), 27.9 (C-7), 38.1 (C-18), 48.6 (C-2), 52.5 (C-23), 55.1 (C-4), 55.5 (C-27), 93.9 (C-12), 104.5 (C-10), 108.9 (C-8), 114.7 (C-6), 162.0 (C-11), 163.6 (C-9), 164.6 (C-13), 176.6 (C-1), 203.1 (C-5), 206.0 (C-22), 212.3 (C-3). **Conformer 2**; δ_H($CDCl_3$) all peaks obscured except 6.08 (1H, s, H-12), 10.63 (1H, s, OH-1), 11.27 (1H, s, OH-13), 17.07 (1H, s, OH-9); δ_C($CDCl_3$) all peaks obscured except 24.3 (C-14), 27.1 (C-16), 29.1 (C-7), 38.7 (C-18), 49.0 (C-2), 54.2 (C-4), 55.6 (C-27), 93.5 (C-12), 104.9 (C-10), 114.9 (C-6), 164.3 (C-13), 177.3 (C-1), 203.2 (C-5), 206.5 (C-22), 212.7 (C-3). This data closely parallels those measured for the natural product **8**.

1-Hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.4[134]



The trione **3.14** (12 g, 5.4 mmol) was dissolved in 50% sulfuric acid (120 ml) and the mixture refluxed for 24 h. On cooling, water (200 ml) was added and the product removed by filtration. Recrystallisation from diethyl ether afforded the title compound **3.4** (4.9 g, 48%) as off white crystals, m.p. 180 - 182 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3024, 2980, 2941, 1709, 1473, 1385; δ_H[$(CD_3)_2CO$] 1.33 (12H, s, 4 x CH_3), 5.50 (1H, s, CH=C); δ_C[$(CD_3)_2CO$] 24.9 (4 x CH_3), 51.7 (2 x C_q), 102.0 (C_q), 188.0 (2 x C_q), 214.0 (C_q).

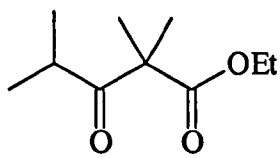
2-(2-Methylpropenyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 3.7[143]



The dione **3.18** (0.3 g, 1 mmol) in dichloromethane (10 ml) was stirred at 0 °C and p-TSA (0.17 g, 1 mmol) added. After 1 hour, water (10 ml) was added and the product extracted with dichloromethane (3 x 20 ml). The combined organic layers were washed copiously with water until neutral and evaporated to afford the title compound **3.7** (0.18 g, 78%) as white crystals,

m.p 161 - 162 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3028, 2981, 2935, 2873, 1726, 1695, 1641, 1591, 1471, 1381; δ_H($CDCl_3$) 1.12 (6H, d, *J* 6.6, $CH(CH_3)_2$), 1.32 (6H, s, 2 x CCH_3), 1.33 (6H, s, 2 x CCH_3), 1.37 (1H, dsept, *J* 6.6, 6.6, $CH(CH_3)_2$), 7.26 (1H, d, *J* 10.7, CH=C); δ_C($CDCl_3$) 21.8 (2 x CH_3), 21.9 (2 x CH_3), 22.3 (2 x CH_3), 28.6 (CH), 58.2 (C_q), 58.5 (C_q), 130.7 (C_q), 164.8 (CH), 196.6 (C_q), 199.8 (C_q), 208.8 (C_q).

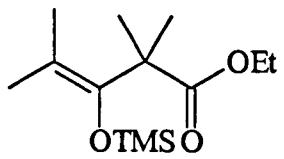
Ethyl 3-oxo-2,2,4-trimethylpentanoate 3.10[132]



2.5M n-BuLi (16 ml, 0.04 mol) was added dropwise to n-cyclohexylisopropylamine (5.6 g, 0.04 mol) in dry THF (20 ml) at -78 °C under N_2. After 10 mins, ethylisobutyrate **3.9** (4.6 g, 0.04 mol) in THF (10 ml) was added dropwise and after a further 10 mins isobutyryl chloride (3.1 g, 0.04 mol) was added and the mixture stirred at -78 °C for 1 h. On warming to room temperature, 1N HCl (20 ml) was added and the product extracted with dichloromethane (3 x 20 ml), the combined extracts washed with water (40 ml), dried and evaporated under reduced pressure to afford the title compound **3.10** (7.1 g, 95%) as a colourless oil; υ_{max} ($CHCl_3$)/cm^{-1} 3033, 2979, 2937, 2874, 1741, 1708, 1471, 1390; δ_H($CDCl_3$) 1.09 (6H, d, *J* 6.7, $CH(CH_3)_2$), 1.27 (3H, t, *J* 7.2, CH_2CH_3), 1.37 (6H, s, 2 x CH_3), 2.88 (1H, sept, *J* 6.8, CH), 4.19 (2H, q, *J* 7.3, CH_2); δ_C($CDCl_3$) 14.1 (CH_3), 20.4 (2 x CH_3), 21.8 (2 x

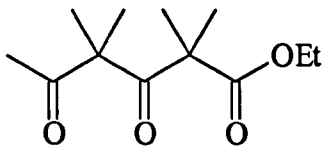
CH_3), 36.8 (CH), 56.1 (C_q), 61.3 (CH_2), 173.7 (C_q), 210.7 (C_q).

Ethyl 3-trimethylsilyloxo-2,2,4-trimethylpent-3-enoate 3.11[132]



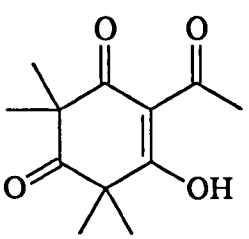
2.5M n-BuLi (14 ml, 0.035 mol) was added dropwise to diisopropylamine (4.9 ml, 0.035 mol) in dry THF (10 ml) at -78 °C under N_2. After 10 mins, the β-ketoester **3.10** (6.5 g, 0.035 mol) in THF (5 ml) was added dropwise and after a further 10 mins triethylamine (3.5 g, 0.035 mol) and trimethylsilylchloride (7.6 g, 0.07 mol) were added and the mixture stirred at -78 °C for 30 mins. On warming to room temperature, water (10 ml) and saturated sodium carbonate solution (10 ml) were addedand the product extracted with diethyl ether (3 x 20 ml), the combined extracts washed with water (20 ml), dried and evaporated under reduced pressure to afford the title compound **3.11** (7.4 g, 85%) as a light brown oil, n_D 1.4576; υ_{max} ($CHCl_3$)/cm^{-1} 3034, 2980, 2869, 1705, 1469, 1385, 1257; δ_H[$(CD_3)_2CO$] 0.03 (9H, s, $Si(CH_3)_3$), 0.99 (3H, t, *J* 7.2, CH_2CH_3), 1.03 (6H, s, $C(CH_3)_2$) 1.21 (3H, s, CH_3), 1.35 (3H, s, CH_3), 3.87 (2H, q, *J* 7.3, CH_2); δ_C[$(CD_3)_2CO$] -0.7 (3 x CH_3), 12.9 (CH_3), 16.9 (CH_3), 18.9 (CH_3), 24.3 (2 x CH_3), 45.7 (C_q), 59.3 (CH_2), 108.5 (C_q), 145.8 (C_q), 175.7 (C_q), 204.2 (C_q).

Ethyl 3,5-dioxo-2,2,4,4-tetramethylhexanoate 3.12[132]



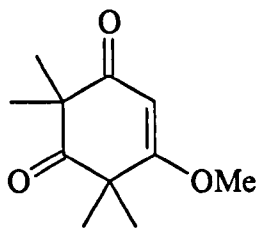
Acetylchloride (0.78 g, 10 mmol) was added dropwise to a stirred solution of zinc chloride (1.4 g, 10 mmol) in dichloromethane (10 ml) and diethyl ether (2 ml) at 0°C under nitrogen. After 5 mins, the tms-enol ether **3.11** (2.6 g, 10 mmol) was added dropwise and the mixture stirred at 0°C for 1h, and warmed to room temperature over a further 1h. Water (20 ml) was added and the product extracted with dichloromethane (3 x 20 ml), the combined extracts washed with water (40 ml), dried and evaporated under reduced pressure. The crude product was columned using 10% diethyl ether / petrol ether to afford the title compound **3.12** (1.1 g, 46%) as a colourless oil; $\delta_H(CDCl_3)$ 1.27 (3H, t, *J* 7.1, CH_2CH_3), 1.37 (6H, s, 2 x CH_3), 1.39 (6H, s, 2 x CH_3), 2.14 (3H, s, $COCH_3$), 4.15 (2H, q, *J* 7.1, CH_2); $\delta_C(CDCl_3)$ 13.9 (CH_3), 22.6 (2 x CH_3), 23.9 (2 x CH_3), 25.7 (CH_3), 55.2 (C_q), 61.5 (CH_2), 63.5 (C_q), 173.6 (C_q), 206.0 (C_q), 207.0 (C_q).

1-Hydroxy-2-oxoethyl-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.14[133]



Sodium (10 g, 0.43 mol) was added slowly to methanol (100 ml) with cooling until formation of sodium methoxide was complete. 2,4,6-Trihydroxyacetophenone **3.13** (10 g, 54 mmol) and iodomethane (34 ml, 54 mmol) were added successively and the mixture refluxed for 3 h. On cooling the solvent was removed by evaporation, and 2N HCl (100 ml) added. The resultant solid was filtered, dissolved in $NaHCO_3$ solution, acidified and filtered to afford the title compound **3** (12 g, 99%) as pale yellow crystals, m.p. 58 - 60 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3025, 2983, 2936, 2875, 1721, 1561, 1472; δ_H[$(CD_3)_2CO$] 1.41 (6H, s, 2 x CH_3), 1.46 (6H, s, 2 x CH_3), 2.61 (3H, s, $COCH_3$), 18.25 (1H, s, OH); δ_C[$(CD_3)_2CO$] 24.1 (2 x CH_3), 24.6 (2 x CH_3), 27.3 (CH_3), 52.5 (C_q), 57.3 (C_q), 110.4 (C_q), 201.7 (C_q), 205.9 (C_q), 206.3 (C_q), 210.2 (C_q).

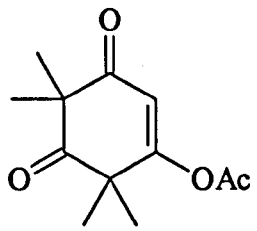
1-Methoxy-4,4,6,6-tetramethylcyclohexen-3,5-dione 3.15



A solution of syncarpic acid **3.4** (0.1 g, 0.55 mmol), methyl iodide (0.34 g, 5.5 mmol) and potassium carbonate (0.38 g, 2.8 mmol) in acetone (10 ml) was refluxed for 2 h. On cooling, diethyl ether (20 ml) was added and the product filtered. The filtrate was evaporated under reduced pressure and the

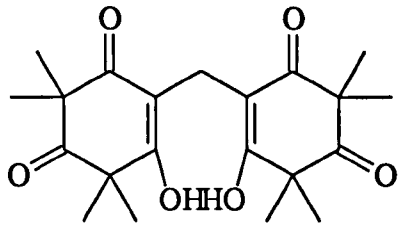
crude product purified by silica gel column chromatography eluting with 30% diethyl ether / petrol ether to afford the title compound **3.15** (0.05 g, %) as white crystals, m.p. 54 - 55 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2991, 2943, 1718, 1650, 1613, 1474, 1460, 1385, 1355; δ_H($CDCl_3$) 1.35 (3H, s, 2 x CH_3), 1.40 (3H, s, 2 x CH_3), 3.81 (3H, s, OCH_3), 5.52 (1H, s, CH=C); δ_C($CDCl_3$) 24.3 (2 x CH_3), 25.0 (2 x CH_3), 48.1 (C_q), 55.3 (C_q), 99.1 (CH), 178.4 (C_q), 199.3 (C_q), 213.3 (C_q).

1-Acetoxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.16



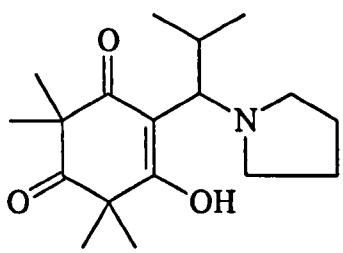
Acetylchloride (0.013 g, 0.14 mmol) was added dropwise to a stirred solution of syncarpic acid **3.4** (0.025 g, 0.14 mmol) and triethylamine (0.015 g, 0.14 mmol) in dichloromethane (10 ml). After stirring for 2 hours, water (10 ml) was added and the product extracted with dichloromethane (3 x 10 ml), the combined extracts washed with water (20 ml), dried and the solvent evaporated under reduced pressure to afford the title compound **3.16** (0.02 g, 65%) as a semi-solid; υ_{max} ($CHCl_3$)/cm^{-1} 3032, 2956, 2931, 2855, 1714, 1671, 1599, 1467; δ_H($CDCl_3$) 1.31 (6H, s, 2 x CH_3), 1.32 (6H, s, 2 x CH_3), 2.23 (3H, s, $COCH_3$), 6.10 (1H, s, CH); δ_C($CDCl_3$) 20.2 (CH_3), 22.8 (2 x CH_3), 23.5 (2 x CH_3), 46.9 (C_q), 55.7 (C_q), 114.0 (CH), 166.0 (C_q), 167.1 (C_q), 198.3 (C_q), 210.6 (C_q).

2, 2'-bis(1-Hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione)methyl 3.17



The dione **3.4** (0.85 g, 4.7 mmol) and 40% formaldehyde solution (0.22 ml) were stirred in 1% potassium hydroxide solution (30 ml) for 30 mins. On acidification with 2N HCl (20 ml), the resultant precipitate was filtered and recrystallised from methanol to afford the title compound **3.17** (0.4 g, 46%) as white crystals, m.p. 155 - 156 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2984, 2935, 2876, 1725, 1601, 1476, 1390, 1362; δ_H($CDCl_3$) 1.38 (12H, s, 4 x CH_3), 1.44 (12H, s, 4 x CH_3), 3.32 (2H, s, CH_2), 12.40 (2H, s, 2 x OH); δ_C($CDCl_3$) 19.4 (CH_2), 24.9 (4 x CH_3), 25.1 (4 x CH_3), 51.3 (2 x C_q), 110.8 (2 x C_q), 191.6 (4 x C_q), 212.5 (2 x C_q).

1-Hydroxy-2-[1-pyrrolidine-2-methylpropyl]-4,4,6,6-tetramethycyclohexene-3,5-dione 3.18[143]

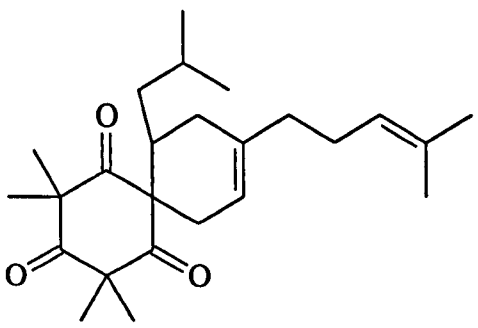


A solution of syncarpic acid **3.4** (0.5 g, 2.8 mmol) and pyrrolidine (0.21

g, 3.0 mmol) in dry diethyl ether (20 ml) was cooled to 0 °C and isobutyraldehyde (0.22 g, 3 mmol) added dropwise over 5 mins. After stirring for 1 h, the resultant solid was filtered, washed with cold diethyl ether and dried under reduced pressure to afford the title compound **3.18** (0.72 g, 86%) as white crystals, m.p 139 - 140 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2985, 2939, 1707, 1595, 1521, 1459, 1409; δ_H($CDCl_3$) 0.90 (3H, d, *J* 6.9, C*H*$_3$CH), 0.96 (3H, d, *J* 6.6, C*H*$_3$CH), 1.36 (6H, s, 2 x CH_3C), 1.38 (6H, s, 2 x CH_3C), 2.29 (1H, dsept, *J* 3.6, 6.6, C*H*(CH_3)$_2$), 2.91 br (4H, d, 2 x NCH_2CH_2), 3.37 br (2H, m, NCH_2), 3.49 br (2H, m, NCH_2), 4.41 (1H, d, *J* 3.3, NCH); δ_C($CDCl_3$) 17.3 (CH_3), 20.2 (CH_3), 22.4 (CH_2), 24.3 (CH_2), 25.0 (2 x CH_3), 25.4 (2 x CH_3), 31.8 (CH), 49.8 (CH_2), 52.0 br (2 x C_q), 53.9 (CH_2), 69.2 (CH), 98.4 (C_q), 192.1 br (2 x C_q), 216.8 (C_q).

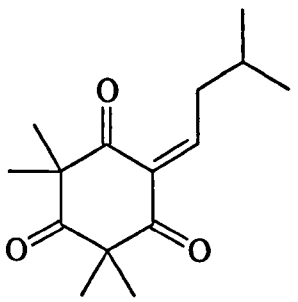
Compound 3.22 - See experimental for compound **1.**

2,2-[2-(2-methylpropyl)-4-(4-methylpent-3-enyl)cyclohex-4-ene]-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 3.23



The trione **3.4** (0.19 g, 0.76 mmol) and myrcene **3.8** (0.103 g, 0.76 mmol) were refluxed in dry benzene (5 ml) for 6 h. On cooling, the solvent was removed under reduced pressure and the crude product purified by column chromatography using 5% diethyl ether / petrol ether as eluant to afford the title compound **3.23** (0.035 g, 12%) as a colourless oil; υ_{max} ($CHCl_3$)/cm^{-1} 3033, 2961, 2926, 2868, 1695, 1613, 1466, 1380; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.3, CHC*H*$_3$), 0.87 (3H, d, *J* 6.3, CHC*H*$_3$), 1.34 (3H, s, CH_3), 1.36 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.59 (3H, s, CH_3), 1.63 (2H, m, CH_2), 1.67 (3H, s, CH_3), 1.94 (1H, m, C*H*(CH_2)$_2$), 1.94 (2H, m, CH_2), 2.01 (2H, m, CH_2), 2.04 (2H, d, *J* 7.7, CH_2), 2.15 (1H, m, C*H*(CH_3)$_2$), 2.29 (2H, m, CH_2), 5.03 (1H, m, CH=C), 5.31 (1H, m, CH=C); δ_C($CDCl_3$) 17.7 (CH_3), 20.9 (CH_3), 24.3 (CH_3), 24.3 (CH_3), 24.9 (CH_3), 25.4 (CH_2), 25.7 (CH_3), 25.9 (CH_2), 26.1 (CH_3), 26.3 (CH_3), 29.3 (CH), 30.5 (CH_2), 33.9 (CH_2), 37.1 (CH_2), 39.0 (CH), 56.1 (C_q), 56.7 (C_q), 67.6 (C_q), 115.9 (CH), 123.9 (CH), 131.6 (C_q), 136.5 (C_q), 208.1 (C_q), 208.2 (C_q), 213.0 (C_q); m/z (Found: M+, 386.28302. $C_{25}H_{38}O_3$ requires M, 386.28210).

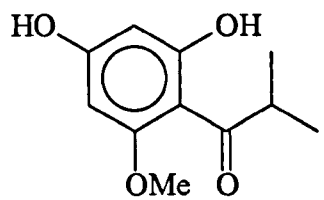
2-(3-Methylbutenyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 3.24



The dione **3.44** (0.3 g, 0.93 mmol) and p-TSA (0.19 g, 0.93 mmol) were reacted as for compound **3.7**, to afford the title compound **3.24** (0.23 g, 98%) as a colourless oil; $\delta_H(CDCl_3)$ 0.97 (3H, d, *J* 6.7, $CHCH_3$), 1.06 (3H, d, *J* 7.0, $CHCH_3$) 1.32 (6H, s, 2 x CCH_3), 1.33 (6H, s, 2 x CCH_3), 1.91 (1H, t, *J* 6.8, $CH(CH_3)_2$), 2.62 (2H, t, *J* 7.2, CH_2), 7.53 (1H, t, *J* 7.7, CH=C); $\delta_C(CDCl_3)$ 22.0 (2 x CH_3), 22.3 (2 x CH_3), 22.6 (2 x CH_3), 28.7 (CH), 38.9 (CH_2), 58.0 (C_q), 58.6 (C_q), 133.1 (C_q), 159.1 (C_q), 196.4 (C_q), 199.6 (C_q), 208.8 (C_q).

Compounds 3.27a - d - See experimental for compound **5**.

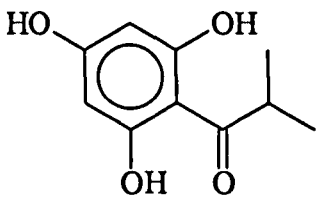
4,6-Dihydroxy-2-methoxyisobutyrophenone 3.30



The ester **3.43** (0.2 g, 1 mmol), 50% aqueous potassium hydroxide solution (3 ml) and DMSO (10 ml) were heated to 115 °C for 2 hours. On cooling, 2N hydrochloric acid (20 ml) was added and the product extracted with diethyl ether (3 x 50 ml). The combined extracts were washed with water (50 ml), dried and evaporated. The crude product was columned using 40%

diethyl ether / petrol ether to afford the title compound **3.30** (0.12 g, 77%) as white xtals, m.p 138 - 139 °C ; υ_{max} ($CHCl_3$)/cm^{-1} 3586, 2973, 2938, 2873, 1622, 1601, 1467, 1440; δ_H($CDCl_3$) 1.16 (6H, d, *J* 6.4, $(CH_3)_2CH$), 3.75 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 3.86 (3H, s, OCH_3), 5.85 (1H, s, OH), 5.93 (1H, d, *J* 2.0, Ar), 6.01 (1H, d, *J* 2.0, Ar), 14.09 (1H, s, OH); δ_C($CDCl_3$) 19.2 (2 x CH_3), 39.5 (CH), 55.7 (CH_3), 90.9 (CH), 96.7 (CH), 105.2 (C_q), 162.3 (C_q), 163.2 (C_q), 167.5 (C_q), 210.5 (C_q); m/z Found: M+, 210.08939. $C_{11}H_{14}O_4$ requires M, 210.08921).

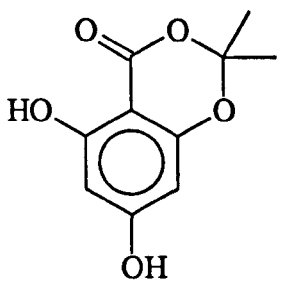
2,4,6-Trihydroxyisobutyrophenone 3.35



Isobutyrylchloride (4.2 g, 0.04 mol) was added dropwise to a stirred solution of phloroglucinol **3.34** (5 g, 0.04 mol), and aluminium chloride (15.9 g, 0.12 mol) in nitrobenzene at 0°C under nitrogen. After 10 mins, the solution was refluxed for 1 h. On cooling, 2N hydrochloric acid was added and the product extracted with diethyl ether (3 x 50 ml). The combined extracts were washed with water, dried and evaporated. The crude product was columned using 50% diethyl ether / petrol ether to afford the title compound **3.35** (3.1 g, 40%) as white xtals; υ_{max} ($CHCl_3$)/cm^{-1} 3321, 3030, 2982, 1711, 1630, 1604,

1527, 1453; $\delta_H[(CD_3)_2CO]$ 1.17 (6H, d, *J* 6.7, $(CH_3)_2CH$), 3.47 (1H, s, OH), 4.00 (1H, sept, *J* 6.7, $CH(CH_3)_2$), 4.47 (1H, s, OH), 5.99 (2H, s, 2 x Ar), 6.01 (1H, d, *J* 2.0, Ar), 6.01 (1H, d, *J* 2.4, Ar), 9.25 (1H, s, OH); $\delta_C[(CD_3)_2CO]$ 19.6 (2 x CH_3), 39.5 (CH), 95.9 (2 x CH), 104.2 (C_q), 165.0 (C_q), 165.3 (2 x C_q), 208.2 (C_q).

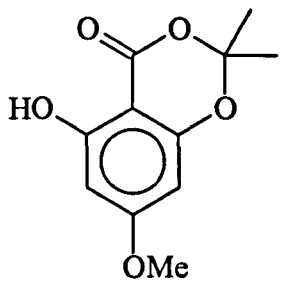
5,7-Dihydroxy-2,2-dimethyl-4*H*-1,3-benzodioxin-4-one 3.40[154]



Trifluoroacetic anhydride (70 ml) was added to a suspension of 2,4,6-trihydroxybenzoic acid monohydrate **3.39** (11 g, 0.065 mol) in trifluoroacetic acid (100 ml) at 0 °C. The mixture was warmed to room temperature over 24 h and concentrated under reduced pressure. The product was poured into saturated aqueous $NaHCO_3$ and extracted with diethyl ether (3 x 20 ml). The combined extracts were washed with water, dried and evaporated. The crude product was recrystallised from diethyl ether to afford the title compound **3.40** (5.6 g, 41%) as white crystals, m.p 184-186°C; υ_{max} $(CHCl_3)/cm^{-1}$ 3583, 3023, 1687, 1643, 1597; $\delta_H[(CD_3)_2CO]$ 1.72 (6H, s, 2 x CH_3), 6.01 (1H, d, *J* 2.4, Ar), 6.08 (1H, d, *J* 2.5, Ar), 9.74 br (1H, s, OH), 10.46 (1H, s, OH); $\delta_C[(CD_3)_2CO]$ 25.6 (2 x CH_3), 93.0 (C_q), 97.9 (CH), 98.0 (CH), 107.6 (C_q),

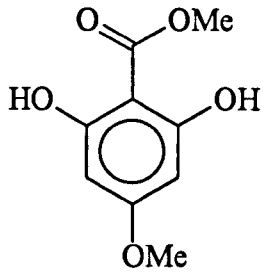
158.1 (C_q), 164.0 (C_q), 165.8 (C_q), 167.2 (C_q).

7-Methoxy-2,2-dimethyl-5-hydroxy-4*H*-1,3-benzodioxin-4-one 3.41[154]



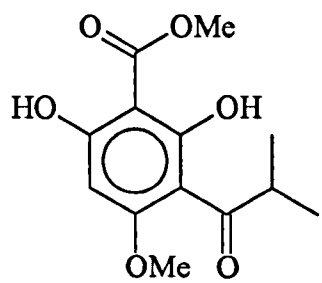
A solution of the phenol **3.40** (5.5 g, 26 mmol) in a mixture of methanol (1.2 ml, 28 mmol) and THF (100 ml) was stirred at 0 °C. Triphenylphosphine (7.3 g, 27 mmol) and DEAD (5.5 ml, 27 mmol) were added successively. The mixture was warmed to room temperature over 3 h, and diluted with diethyl ether (300 ml). The resultant solution was washed with water (3 x 100 ml), dried and the solvent evaporated. The crude product was purified by column chromatography using 10% diethyl ether / petrol ether as eluant to afford the title compound **3.41** (4.0 g, 68%) as white crystals, m.p 102 - 103 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3200, 3027, 2999, 2943, 1685, 1638, 1583, 1512, 1358; δ_H($CDCl_3$) 1.73 (6H, s, 2 x CH_3), 3.82 (3H, s, OCH_3), 6.00 (1H, d, *J* 2.4, Ar), 6.14 (1H, d, *J* 2.1, Ar), 10.44 (1H, s, OH); δ_C($CDCl_3$) 25.6 (2 x CH_3), 55.7 (CH_3), 93.1 (C_q), 94.6 (CH), 95.7 (CH), 106.9 (C_q), 156.9 (C_q), 163.1 (C_q), 165.2 (C_q), 167.7 (C_q).

Methyl 2,6-dihydroxy-4-methoxy-benzoate 3.42



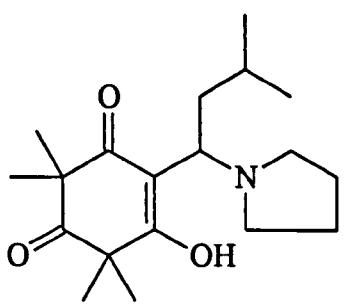
To a solution of the benzodioxin **3.41** (3.9 g, 17 mmol) in THF (100 ml) was added lithium methoxide (3.3 g, 85 mmol) and the mixture heated under reflux for 4 h. On cooling, water was added and the product extracted with diethyl ether (3 x 100 ml), washed with water, dried and evaporated. The crude product was columned using 10% diethyl ether / petrol ether as eluant to afford the title compound **3.42** (3.3 g, 95%) as off white crystals, m.p 102 - 104 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3440, 3030, 2956, 2849, 1677, 1641, 1582, 1307; δ_H($CDCl_3$) 3.80 (3H, s, OCH_3), 4.04 (3H, s, CO_2CH_3), 6.04 (2H, s, 2 x Ar), 10.01 (2H, br s, 2 x OH); δ_C($CDCl_3$) 52.5 (CH_3), 55.5 (CH_3), 93.9 (C_q), 94.5 (2 x CH), 162.2 (2 x C_q), 166.5 (C_q), 169.8 (C_q).

Methyl 2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)benzoate 3.43



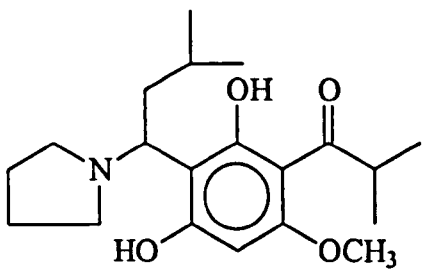
To a solution of the ester **3.42** (0.8 g, 4 mmol) and aluminium trichloride (0.59 g, 4.4 mmol) in dry nitrobenzene (80 ml) was added isobutyryl chloride (0.45 g, 4.2 mmol). After 20 minutes, the mixture was refluxed for 4 hours. On cooling, 2N hydrochloric acid (50 ml) was added and the product extracted with diethyl ether (3 x 100 ml). The combined organic layers were back-extracted with 4N sodium hydroxide solution (3 x 100 ml), acidified and extracted with diethyl ether (3 x 100 ml). The combined organic layers were washed with water, dried and evaporated. The crude product was columned using 15% diethyl ether / petrol ether as eluant to afford the title compound **3.43** (0.69 g, 64%) as white crystals, m.p 91 - 93 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3436, 3023, 2979, 2873, 1653, 1595, 1449, 1343; δ_H($CDCl_3$) 1.15 (6H, d, *J* 6.8, $(CH_3)_2CH$), 3.66 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 3.91 (3H, s, OCH_3), 3.99 (3H, s, CO_2CH_3), 6.00 (2H, s, 2 x Ar), 12.54 (1H, s, OH), 15.45 (1H, s, OH); δ_C($CDCl_3$) 19.1 (2 x CH_3), 39.9 (CH), 52.6 (CH_3), 55.9 (CH_3), 91.4 (CH), 95.9 (C_q), 104.7 (C_q), 165.9 (C_q), 169.4 (C_q), 171.6 (C_q), 183.5 (C_q), 210.3 (C_q).

1-Hydroxy-2-[1-pyrrolidine-3-methylbutyl]-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.44



A solution of the dione **3.4** (0.5 g, 2.8 mmol) and pyrrolidine (0.21 g, 3.0 mmol) in dry diethyl ether (20 ml) was cooled to 0 °C and isovaleraldehyde (0.26 g, 3.0 mmol) added dropwise over 5 mins. After stirring for 1 h, the resultant solid was filtered, washed with cold diethyl ether and dried under reduced pressure to afford the title compound **3.44** (0.62 g, 70%) as white crytals, m.p. 52 - 54 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2981, 2930, 1702, 1586, 1522, 1466, 1405; δ_H($CDCl_3$) 0.88 (3H, d, *J* 6.3, C*H*$_3$CH), 0.96 (3H, d, *J* 6.0, C*H*$_3$CH), 1.35 (6H, s, 2 x CCH_3), 1.35 (6H, s, 2 x CCH_3), 1.46 (1H, m, C*H*(CH_3)$_2$), 2.07 (2H, m, CH_2), 2.86 (2H, dd, *J* 9.6 and 18.1, NCH_2CH_2), 3.02 (2H, dd, *J* 8.3 and 11.9, NCH_2CH_2), 3.34 (2H, m, NCH_2), 3.57 (2H, m, NCH_2), 4.46 (1H, dd, *J* 3.5 and 11.5, NCH); δ_C($CDCl_3$) 22.2 (CH_3), 22.8 (CH_3), 24.2 (CH_2), 24.6 (CH_2), 25.0 (2 x CH_3), 25.1 (2 x CH_3), 25.7 (CH), 40.3 (CH_2), 50.9 (2 x C_q), 52.8 (CH_2), 52.9 (CH_2), 64.5 (CH), 102.4 (C_q), 192.1 (2 x C_q), 216.9 (C_q).

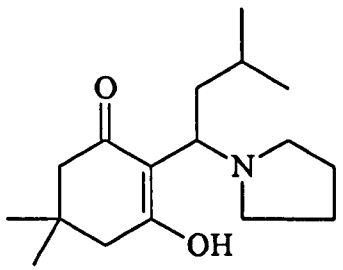
4,6-Dihydroxy-2-methoxy-5-[1-pyrrolidine-3-methylbutyl]-isobutyrophenone 3.46



A solution of the isobuytrophenone **3.30** (0.05 g, 0.24 mmol) and pyrrolidine (0.051 g, 0.72 mmol) in dry diethyl ether (10 ml) was cooled to 0

°C and isovaleraldehyde (0.12 g, 0.72 mmol) added dropwise over 5 mins. After stirring for 1 h, methanol (5 ml) was added and the solvent evaporated to afford the title compound **3.46** (0.08 g, 96 %) as a light brown semi-solid; υ_{max} ($CHCl_3$)/cm^{-1} 2956, 2868, 1614, 1469, 1389; δ_H($CDCl_3$) 0.81 (3H, d, *J* 6.7, CH_3CH), 0.99 (3H, d, *J* 6.1, CH_3CH), 1.15 (3H, d, *J* 6.8, CH_3CH), 1.16 (3H, d, *J* 6.7, CH_3CH), 1.42 (1H, sept, *J* 6.7, $CH(CH_3)_2$), 1.60 (1H, m, CH_2), 1.77 (1H, m, CH_2), 1.84 (4H, m, 2 x NCH_2CH_2), 2.95 (4H, m, 2 x NCH_2), 3.76 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 3.82 (3H, s, OCH_3), 4.03 (1H, dd, *J* 3.7, 10.7, NCH), 5.84 (1H, s, Ar); δ_C($CDCl_3$) 19.3 (CH_3), 19.6 (CH_3), 22.6 (CH_3), 23.4 (2 x CH_2), 24.4 (CH_3), 25.1 (CH), 39.2 (CH), 42.8 (CH_2), 52.0 (2 x C_q), 55.3 (CH_3), 60.7 (CH), 92.0 (CH), 102.8 (C_q), 106.2 (C_q), 162.3 (C_q), 164.7 (C_q), 167.4 (C_q), 209.5 (C_q).

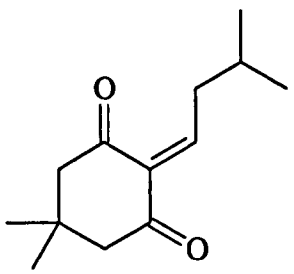
1-Hydroxy-2-[1-pyrrolidine-3-methylbutyl]-5,5-dimethylcyclohexene-3-one 3.50



Dimedone (1.0 g, 7.1 mmol), isovaleraldehyde (0.65 g, 7.4 mmol) and pyrrolidine (0.56 g, 7.4 mmol) were reacted as for compound **3.18** to afford the title compound **3.50** (0.97 g, 49%) as white crystals, m.p 116 - 117 °C;

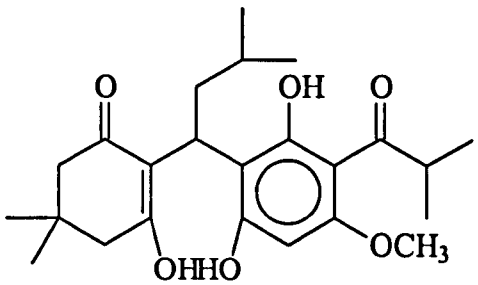
υ_{max} ($CHCl_3$)/cm^{-1} 2968, 2870, 1578, 1506, 1419, 1260; δ_H($CDCl_3$) 0.87 (3H, d, *J* 6.6, C*H*$_3$CH), 0.97 (3H, d, *J* 6.3, C*H*$_3$CH), 1.05 (6H, s, 2 x CCH_3), 1.55 (1H, m, C*H*(CH_3)$_2$), 1.97 (4H, m, $CH_2CH_2CH_2$), 2.09 (2H, m, CH_2), 2.19 (4H, s, 2 x CH_2CO), 2.80 (1H, m, NCH_2), 2.93 (1H, m, NCH_2), 3.38 (1H, m, NCH_2), 3.59 (1H, m, NCH_2), 4.36 (1H, dd, *J* 11.6, 3.6, CH); δ_C($CDCl_3$) 22.1 (2 x CH_3), 24.2 (2 x CH_3), 25.6 (CH), 28.9 (2 x CH_3), 32.0 (CH_q), 40.5 (CH_2), 49.7 (2 x CH_2), 51.0 (CH_2), 52.9 (CH_2), 63.6 (CH), 105.4 (C_q), 191.5 (2 x C_q).

2-(3-Methylbutenyl)-5,5-dimethylcyclohexane-1,3-dione 3.51



The pyrrolidine complex **3.50** (0.3 g, 0.71 mmol) and p-TSA (0.13 g, 0.74 mmol) were reacted as for compound **3.7** to afford the title compound **3.51** (0.14 g, 94%) as off white crystals, m.p. 77 - 78 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2963, 2937, 2868, 1596, 1389, 1371; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.6, CH(C*H*$_3$)$_2$), 0.96 (3H, d, *J* 6.9, CH(C*H*$_3$)$_2$), 1.06 (6H, s, 2 x CH_3), 1.38 (1H, dsept, m, C*H*(CH_3)$_2$), 2.28 (2H, s, CH_2CO), 2.29 (2H, s, CH_2CO), 2.70 (2H, m, CH_2), 5.31 (1H, ??, *J* ???, CH=C); δ_C($CDCl_3$) 22.4 (CH_3), 22.6 (CH_3), 28.5 (C_q), 29.9 (CH), 31.1 (2 x CH_3), 37.7 (CH_2), 46.2 (CH_2), 47.0 (CH_2), 116.6 (CH), 160.1 (C_q), 189.8 (C_q), 189.9 (C_q).

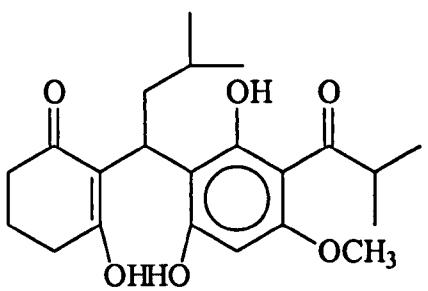
2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]3-methylbutyl}-1-hydroxy-5,5-dimethylcyclohexene-3-one 3.52



A solution of the pyrrolidine complex **3.46** (0.05 g, 0.14 mmol) and dimedone (0.02 g, 0.14 mmol) in dry CH_2Cl_2 (5 ml) was stirred at RT for 18 h. Water (10 ml) was added and the product extracted with CH_2Cl_2 (3 x 2 ml). The combined extracts were washed with water, dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 20% diethyl ether / petrol ether as eluant to afford the title compound **3.52** (0.016 g, 27%) as a 2 : 1 mixture of conformers as off white crystals, m.p. 135 - 136 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3024, 2976, 2931, 2880, 1622, 1600, 1473, 1432; **Conformer 1**; δ_H($CDCl_3$) 0.85 (3H, d, *J* 6.4, CHC*H*$_3$), 0.86 (3H, d, *J* 6.4, CHC*H*$_3$), 1.04 (3H, s, CH_3), 1.09 (3H, s, CH_3), 1.15 (3H, d, *J* 6.8, CHC*H*$_3$), 1.17 (3H, d, *J* 6.7, CHC*H*$_3$), 1.35 (1H, sept, *J* 6.7, C*H*(CH_3)$_2$), 1.98 (1H, m, CH_2), 2.04 (1H, m, CH_2), 2.33 (4H, s, 2 x CH_2), 3.79 (1H, sept, *J* 6.8, C*H*(CH_3)$_2$), 3.84 (3H, s, OCH_3), 4.33 (1H, t, *J* 6.8, CH), 6.01 (1H, s, Ar), 9.89 (1H, s, OH), 11.56 (1H, s, OH), 16.60 (1H, s, OH); δ_C($CDCl_3$) 19.2 (CH_3), 19.4 (CH_3), 22.3 (CH_3), 22.5 (CH_3), 26.7 (CH_3), 26.8 (CH_3), 27.0 (CH), 29.6 (CH), 31.3 (C_q), 38.2 (CH_2), 39.1 (CH), 43.0 (CH_2),

50.5 (CH_2), 55.5 (CH_3), 93.9 (CH), 103.6 (C_q), 109.7 (C_q), 116.6 (C_q), 161.6 (C_q), 163.7 (C_q), 164.5 (C_q), 175.9 (C_q), 202.5 (C_q), 210.7 (C_q). **Conformer 2**; all peaks obscured except $\delta_H(CDCl_3)$ 1.07 (3H, s, CH_3), 1.20 (3H, d, *J* 6.8, $CHCH_3$), 2.32 (4H, s, 2 x CH_2), 4.38 (1H, m, CH), 6.06 (1H, s, Ar), 10.56 (1H, s, OH), 10.66 (1H, s, OH), 16.78 (1H, s, OH); $\delta_C(CDCl_3)$ 19.3 (CH_3), 19.4 (CH_3), 22.6 (CH_3), 22.7 (CH_3), 26.5 (CH_3), 26.9 (CH_3), 27.5 (CH), 29.8 (CH), 31.1 (C_q), 38.5 (CH_2), 39.2 (CH), 43.7 (CH_2), 49.5 (CH_2), 55.6 (CH_3), 93.5 (CH), 103.6 (C_q), 109.6 (C_q), 116.6 (C_q), 161.6 (C_q), 164.0 (C_q), 164.6 (C_q), 175.5 (C_q), 202.4 (C_q), 211.1 (C_q); m/z (Found: M+ 418.23544. $C_{24}H_{34}O_6$ requires M, 418.23554).

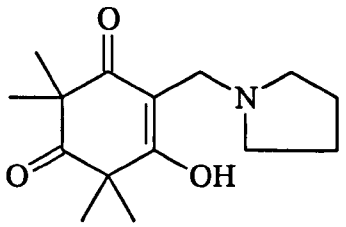
2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]3-methylbutyl}-1-hydroxycyclohexene-3-one 3.53



The pyrrolidine complex **3.46** (0.05 g, 0.14 mmol) and cyclohexane-1,3-dione (0.016 g, 0.14 mmol) in dry CH_2Cl_2 (5 ml) were stirred at RT for 18 h. Water (10 ml) was added and the product extracted with CH_2Cl_2 (3 x 2 ml). The combined extracts were washed with water, dried and the solvent

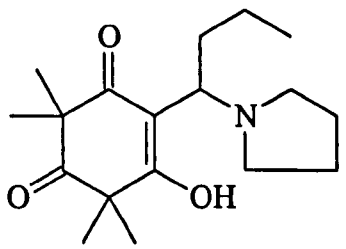
evaporated under reduced pressure. The crude product was purified by column chromatography using 20% diethyl ether / petrol ether as eluant to afford the title compound **3.53** (0.016 g, 27 %) as a 2 : 1 mixture of conformers; **Conformer 1**; $\delta_H(CDCl_3)$ 0.85 (3H, d, *J* 7.4, CHC*H*$_3$), 0.86 (3H, d, *J* 7.3, CHC*H*$_3$), 1.15 (3H, d, *J* 6.9, CHC*H*$_3$), 1.17 (3H, d, *J* 6.9, CHC*H*$_3$), 1.25 (2H, m, CH_2), 1.35 (1H, sept, *J* 6.8, C*H*$(CH_3)_2$), 1.88 (2H, m, CH_2), 2.26 (2H, m, CH_2), 2.52 (2H, m, CH_2), 3.79 (1H, sept, *J* 6.8, C*H*$(CH_3)_2$), 3.84 (3H, s, OCH_3), 4.30 (1H, t, *J* 7.3, CH), 6.01 (1H, s, Ar), 10.07 (1H, s, OH), 11.72 (1H, s, OH), 16.67 (1H, s, OH); $\delta_C(CDCl_3)$ 19.1 (CH_3), 19.4 (CH_3), 20.0 (CH_2), 22.3 (CH_3), 22.7 (CH_3), 26.9 (CH), 27.3 (CH), 29.5 (CH_2), 36.8 (CH_2), 38.3 (CH_2), 39.1 (CH), 55.6 (CH_3), 94.0 (CH), 103.5 (C_q), 109.6 (C_q), 118.0 (C_q), 161.6 (C_q), 163.8 (C_q), 164.6 (C_q), 178.1 (C_q), 202.8 (C_q), 210.7 (C_q). **Conformer 2**; all peaks obscured except $\delta_H(CDCl_3)$ 0.84 (3H, d, *J* 7.3, CHC*H*$_3$), 0.87 (3H, d, *J* 7.3, CHC*H*$_3$), 1.18 (3H, d, *J* 6.8, CHC*H*$_3$), 3.48 (1H, s, CH_3), 4.38 (1H, m, CH), 6.02 (1H, s, Ar), 10.76 (1H, s, OH), 10.82 (1H, s, OH), 16.84 (1H, s, OH); $\delta_C(CDCl_3)$ 19.2 (CH_3), 19.4 (CH_3), 20.0 (CH_2), 22.1 (CH_3), 22.7 (CH_3), 27.0 (CH), 27.7 (CH), 31.9 (CH_2), 35.8 (CH_2), 38.6 (CH_2), 39.2 (CH), 55.6 (CH_3), 93.6 (CH), 103.9 (C_q), 109.5 (C_q), 118.4 (C_q), 161.6 (C_q), 162.6 (C_q), 164.2 (C_q), 177.7 (C_q), 202.9 (C_q), 211.1 (C_q).

1-Hydroxy-2-[1-pyrrolidinemethyl]-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.54



Syncarpic acid **3.4** (0.2 g, 1.1 mmol), paraformaldehyde (0.41 g, 1.4 mmol) and pyrrolidine (0.094 g, 1.3 mmol) were reacted as for compound **3.18** to afford the title compound **3.54** (0.26 g, 90%) as white crystals, m.p 139 - 140 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2985, 2935, 1703, 1587, 1517; δ_H($CDCl_3$) 1.32 (12H, s, 4 x CCH_3), 2.07 br (2H, m, NCH_2CH_2), 2.15 br (2H, m, NCH_2CH_2), 3.09 br (2H, m, NCH_2), 3.47 br (2H, m, NCH_2), 4.12 (2H, s, CH_2); δ_C($CDCl_3$) 23.6 (2 x CH_2), 25.1 (4 x CH_3), 52.6 (CH_2), 52.9 (2 x CH_2), 53.4 (2 x C_q), 98.5 (C_q), 193.0 br (2 x C_q), 216.9 (C_q).

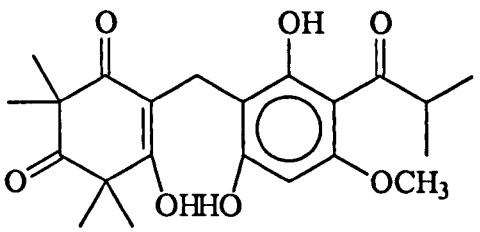
1-Hydroxy-2-[1-pyrrolidine-3-butyl]-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.55



Syncarpic acid **3.4** (0.2 g, 1.1 mmol), butyraldehyde (0.1 g, 1.4 mmol)

and pyrrolidine (0.21 g, 3 mmol) were reacted as for compound **3.18** to afford the title compound **3.55** (0.3 g, 89%) as white crystals, m.p 139 - 140 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2981, 2935, 2876, 1703, 1587, 1521, 1459, 1405; δ_H($CDCl_3$) 0.90 (3H, t, *J* 7.4, CH_3CH_2), 1.32 (2H, m, CH_2CH_2), 1.35 (6H, s, 2 x CH_3C), 1.36 (6H, s, 2 x CH_3C), 1.71 (2H, m, CH_2CH), 2.00 br (3H, m, 1.5 x NCH_2CH_2), 2.18 br (1H, m, NCH_2CH_2), 2.88 br (1H, m, NCH_2), 2.99 br (1H, m, NCH_2), 3.34 br (1H, m, NCH_2), 3.56 br (1H, m, NCH_2), 4.43 (1H, dd, *J* 10.6, 3.8, NCH); δ_C($CDCl_3$) 14.2 (CH_3), 19.2 (CH_3), 22.7 (CH_2), 24.4 (CH_2), 25.0 (2 x CH_3), 25.1 (2 x CH_3), 33.4 (CH), 50.5 br (2 x C_q), 52.7 (CH_2), 53.1 (CH_2), 65.2 (CH), 102.0 (C_q), 192.1 br (2 x C_q), 216.8 (C_q).

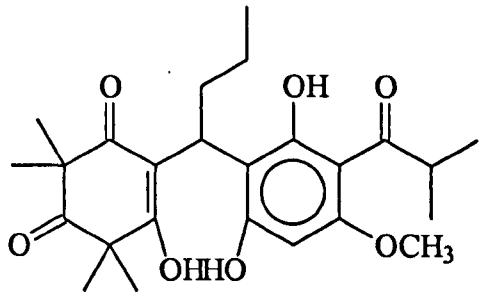
2-{[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]methyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.56



A solution of the pyrrolidine complex **3.54** (0.05 g, 0.19 mmol), the phloroglucinol **3.30** (0.04 g, 0.19 mmol) and silica gel 60H (0.05 g) in dry dichloromethane (3 ml) was stirred at RT for 16 h. After filtration, the filtrate was evaporated to dryness under reduced pressure and the crude product purified by column chromatography using 50% diethyl ether / petrol ether as

eluant. The semi-pure product was further purified by column chromatography using 40% diethyl ether / petrol ether as eluant to afford the title compound **3.56** (0.012 g, 16%) as a pale yellow semi-solid; $\delta_H(CDCl_3)$ 1.18 (6H, d, *J* 6.8, $CH(CH_3)_2$), 1.36 (6H, s, 2 x CH_3), 1.44 (6H, s, 2 x CH_3), 3.52 (2H, s, CH_2), 3.80 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 3.86 (3H, s, OCH_3), 6.08 (1H, s, Ar), 10.60 (1H, s, OH), 10.76 (1H, s, OH), 16.70 (1H, s, OH); $\delta_C(CDCl_3)$ 17.4 (CH_2), 19.2 (2 x CH_3), 25.1 br (4 x CH_3), 39.2 (CH), 48.4 (C_q), 54.1 (C_q), 55.7 (CH_3), 93.1 (CH), 103.8 (C_q), 106.1 (C_q), 111.3 (C_q), 162.0 (C_q), 163.7 (C_q), 163.9 (C_q), 177.1 (C_q), 203.0 (C_q), 210.9 (C_q), 212.7 (C_q).

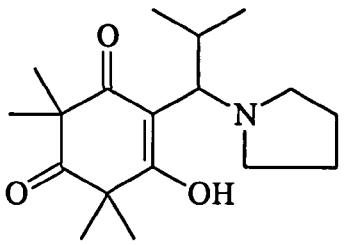
2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]butyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.57



The pyrrolidine complex **3.55** (0.037 g, 0.18 mmol) and silica gel 60H (0.05 g) in dry THF (5 ml) were stirred at 0 °C under nitrogen and the phloroglucinol **3.30** (0.054 g, 0.18 mmol) added over 10 mins. After warming to RT over 1h, the THF was removed under reduced pressure, water (10 ml) added and the product extracted with diethyl ether (3 x 10 ml). The combined ethereal extracts were washed with water (10 ml), dried and the solvent

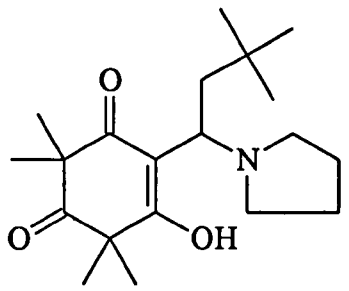
evaporated under reduced pressure. The crude product was purified by preparative thin layer chromatography using 50% diethyl ether / petrol ether as eluant to afford the title compound **3.57** (0.015 g, 19%) as a mixture of conformers in a 2 : 1 ratio as white crystals, m.p. 126 - 128 °C; **Conformer 1**; $\delta_H(CDCl_3)$ 0.87 (3H, t, *J* 7.3, CH_2CH_3), 1.17 (3H, d, *J* 6.8, $CHCH_3$), 1.19 (3H, d, *J* 6.8, $CHCH_3$), 1.33 (6H, s, 2 x CH_3), 1.40 (3H, s, CH_3), 1.46 (2H, m, CH_2), 1.49 (3H, s, CH_3), 1.93 (1H, m, CH_2), 2.16 (1H, m, CH_2), 3.80 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 3.86 (3H, s, OCH_3), 4.29 (1H, t, *J* 7.8, CH), 6.04 (1H, s, Ar), 10.32 (1H, s, OH), 11.59 (1H, s, OH), 16.75 (1H, s, OH); $\delta_C(CDCl_3)$ 13.8 (CH_3), 19.3 (2 x CH_3), 21.9 (CH_2), 22.3 (CH_3), 24.3 (CH_3), 26.2 (CH_3), 27.1 (CH_3), 30.1 (CH_2), 31.5 (CH), 39.2 (CH), 48.6 (C_q), 55.1 (C_q), 55.6 (CH_3), 94.0 (CH), 103.6 (C_q), 108.9 (C_q), 114.5 (C_q), 161.8 (C_q), 164.0 (C_q), 164.4 (C_q), 176.7 (C_q), 203.1 (C_q), 210.8 (C_q), 212.3 (C_q). **Conformer 2**; $\delta_H(CDCl_3)$ all peaks obscured except 6.09 (1H, s, Ar), 10.32 (1H, s, OH), 11.21 (1H, s, OH), 17.18 (1H, s, OH); $\delta_C(CDCl_3)$ 13.8 (CH_3), 19.2 (2 x CH_3), 21.2 (CH_2), 22.1 (CH_3), 24.2 (CH_3), 25.6 (CH_3), 25.8 (CH_3), 29.7 (CH_2), 31.4 (CH), 39.2 (CH), 49.0 (C_q), 54.2 (C_q), 55.7 (CH_3), 93.6 (CH), 104.0 (C_q), 108.9 (C_q), 114.6 (C_q), 161.8 (C_q), 164.3 (C_q), 164.8 (C_q), 177.1 (C_q), 203.3 (C_q), 211.3 (C_q), 212.3 (C_q).

1-Hydroxy-2-[1-pyrrolidine-2-methylpropyl]-4,4,6,6-tetramethyl-cyclohexene-3,5-dione 3.58[143]



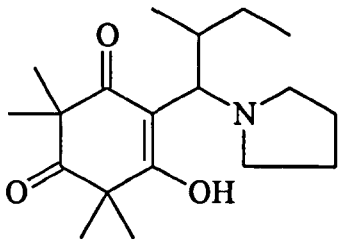
A solution of syncarpic acid **3.4** (0.5 g, 2.8 mmol) and pyrrolidine (0.21 g, 3.0 mmol) in dry diethyl ether (20 ml) was cooled to 0 °C and isobutyraldehyde (0.22 g, 3 mmol) added dropwise over 5 mins. After stirring for 1 h, the resultant solid was filtered, washed with cold diethyl ether and dried under reduced pressure to afford the title compound **3.58** (0.72 g, 86%) as white crystals, m.p 139 - 140 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2985, 2939, 1707, 1595, 1521, 1459, 1409; δ_H($CDCl_3$) 0.90 (3H, d, *J* 6.9, C*H*$_3$CH), 0.96 (3H, d, *J* 6.6, C*H*$_3$CH), 1.36 (6H, s, 2 x CH_3C), 1.38 (6H, s, 2 x CH_3C), 2.29 (1H, dsept, *J* 3.6, 6.6, C*H*(CH_3)$_2$), 2.91 br (4H, d, 2 x NCH_2CH_2), 3.37 br (2H, m, NCH_2), 3.49 br (2H, m, NCH_2), 4.41 (1H, d, *J* 3.3, NCH); δ_C($CDCl_3$) 17.3 (CH_3), 20.2 (CH_3), 22.4 (CH_2), 24.3 (CH_2), 25.0 (2 x CH_3), 25.4 (2 x CH_3), 31.8 (CH), 49.8 (CH_2), 52.0 br (2 x C_q), 53.9 (CH_2), 69.2 (CH), 98.4 (C_q), 192.1 br (2 x C_q), 216.8 (C_q).

1-Hydroxy-2-(1-pyrrolidine-3,3-dimethylbutyl)-4,4,6,6-tetramethyl-cyclohexene-3,5-dione 3.59



Syncarpic acid **3.4** (0.2 g, 1.1 mmol), 3,3-dimethylbutyraldehyde (0.14 g, 1.4 mmol) and pyrrolidine (0.094 g, 1.3 mmol) were reacted as for compound **3.18** to afford the title compound **3.59** (0.34 g, 97%) as white crystals, m.p 179 - 180 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2995, 1705, 1582, 1515, 1473, 1407; δ_H($CDCl_3$) 0.92 (9H, s, C(CH_3)$_3$), 1.33 (6H, s, 2 x CCH_3), 1.35 (6H, s, 2 x CCH_3), 1.64 (1H, d, *J* 13.5, CH_2CH), 2.03 br (3H, m, 1.5 x NCH_2CH_2), 2.14 (1H, d, *J* 10.5, CH_2CH), 2.16 br (1H, m, 0.5 x NCH_2CH_2), 2.91 br (1H, m, NCH_2), 3.06 br (1H, m, NCH_2), 3.29 br (1H, m, NCH_2), 3.62 br (1H, m, NCH_2), 4.51 (1H, dd, *J* 10.4, 1.4, CH); δ_C($CDCl_3$) 23.2 (CH_2), 24.4 (CH_2), 24.7 (2 x CH_3), 25.2 (2 x CH_3), 29.8 (CH_3), 30.6 (2 x CH_3), 44.7 (CH_2), 51.9 (2 x C_q), 52.5 (CH_2), 52.6 (CH_2), 64.2 (CH), 105.5 (C_q), 191.6 (2 x C_q), 217.2 (C_q).

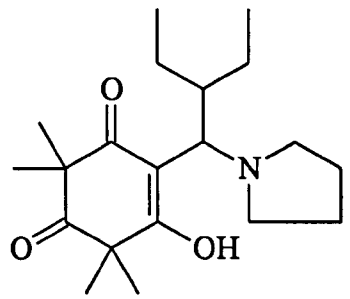
1-Hydroxy-2-[1-pyrrolidine-2-methylbutyl]-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.60



A solution of the dione **3.4** (0.5 g, 2.8 mmol) and pyrrolidine (0.21 g, 3.0 mmol) in dry diethyl ether (20 ml) was cooled to 0 °C and 2-methylbutyraldehyde (0.26 g, 3.0 mmol) added dropwise over 5 mins. After stirring for 1 h, the resultant solid was filtered, washed with cold diethyl ether and dried under reduced pressure to afford the title compound **3.60** (0.78 g, 88%) as white xtals, m.p. 140 - 141 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2977, 2935, 1699, 1587, 1529, 1459, 1405; **Diastereomer 1**, δ_H($CDCl_3$) 0.89 (3H, t, *J* 7.0, C*H*$_3$CH$_2$), 0.94 (2H, m, C*H*$_2$CH$_3$), 0.95 (3H, d, *J* 6.9, C*H*$_3$CH), 1.35 (6H, s, 2 x CH_3C), 1.36 (3H, s, CH_3C), 1.37 (3H, s, CH_3C), 2.00 (4H, m, 2 x NCH_2), 2.18 (1H, m, C*H*CH$_3$), 2.91 (2H, m, NCH_2), 3.36 (2H, m, NCH_2), 4.44 (1H, d, *J* 17.3, NCH); δ_C($CDCl_3$) 12.1 (CH_3), 14.3 (CH_3), 22.4 (CH_2), 24.2 (2 x CH_3), 25.0 (2 x CH_3), 25.4 (2 x CH_2), 39.3 (CH), 49.8 (CH_2), 53.0 br (2 x C_q), 53.8 (CH_2), 68.7 (CH), 98.9 (C_q), 192.1 br (2 x C_q), 216.7 (C_q). **Diastereomer 2**, δ_H($CDCl_3$) 0.91 (3H, t, *J* 6.3, C*H*$_3$CH$_2$), 0.94 (2H, m, C*H*$_2$CH$_3$), 0.96 (3H, d, *J* 6.6, C*H*$_3$CH), 1.35 (6H, s, 2 x CH_3C), 1.36 (3H, s, CH_3C), 1.37 (3H, s, CH_3C), 2.00 (4H, m, 2 x NCH_2), 2.18 (1H, m, C*H*CH$_3$), 2.91 (2H, m, NCH_2), 3.49 (2H, m, NCH_2), 4.44 (1H, d, *J* 17.3, NCH); δ_C($CDCl_3$) 12.4 (CH_3), 15.9 (CH_3), 23.7 (CH_2), 24.2 (2 x CH_3), 25.0 (2 x CH_3), 26.7 (2 x CH_2), 39.4 (CH),

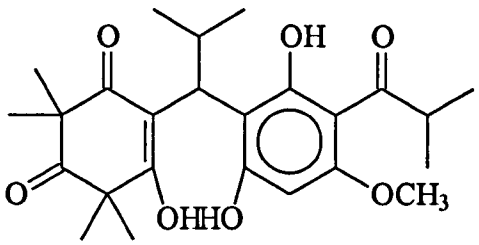
49.8 (CH_2), 53.0 br (2 x C_q), 53.8 (CH_2), 69.4 (CH), 99.1 (C_q), 192.1 br (2 x C_q), 216.7 (C_q).

1-Hydroxy-2-[1-pyrrolidine-2-ethylbutyl]-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.61



Syncarpic acid **3.4** (0.5 g, 2.7 mmol), 2-ethylbutyraldehyde (0.3 g, 3 mmol) and pyrrolidine (0.22 g, 3 mmol) were reacted as for compound **3.18** to afford the title compound **47** (0.57 g, 62%) as white crystals, m.p. 138 - 139 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2987, 2936, 2874, 1708, 1587, 1524, 1458, 1399; δ_H($CDCl_3$) 0.91 (3H, t, *J* 7.4, CH_3CH_2), 1.04 (3H, t, *J* 7.1, CH_3CH_2), 1.35 (6H, s, 2 x CCH_3), 1.36 (6H, s, 2 x CCH_3), 1.62 (1H, m, CH_2CH_3), 1.78 (1H, m, CH_2CH_3), 2.01 (2H, m, CH_2CH_3), 2.91 br (4H, m, 2 x NCH_2CH_2), 3.21 br (4H, m, NCH_2), 4.53 (1H, m, NCH); δ_C($CDCl_3$) 12.4 (CH_3), 13.2 (CH_3), 22.1 (CH_2), 22.3 (CH_2), 22.5 (2 x CH_2), 24.3 (CH_3), 24.9 (2 x CH_3), 25.5 (CH_3), 47.0 (CH), 50.0 (CH_2), 53.0 br (2 x C_q), 54.0 (CH_2), 67.3 (CH), 99.5 (C_q), 192.0 (2 x C_q), 216.8 (C_q).

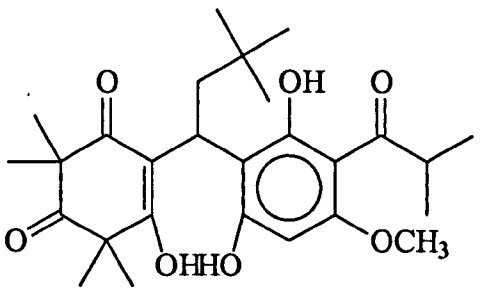
2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]-3-methylpropyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.62



A solution of the alkylidene **3.7** (0.06 g, 0.25 mmol) and the phloroglucinol **3.30** (0.054 g, 0.25 mmol) in dry dichloromethane (5 ml) were stirred at 0 °C and p-toluenesulfonic acid (0.002 g, 0.01 mmol) added. After warming to RT over 1 h, 2N HCl (10 ml) was added and the product extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with water (10 ml), dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 20% diethyl ether / petrol ether as eluant to afford the title compound **3.62** (0.11 g, 99%) as a 2 : 1 mixture of conformers and as white crystals, m.p. 150 - 151 °C; **Conformer 1**; δ_H($CDCl_3$) 0.77 (3H, d, *J* 6.3, $CHCH_3$), 0.86 (3H, d, *J* 5.3, $CHCH_3$), 1.18 (3H, d, *J* 6.8, $CHCH_3$), 1.19 (3H, d, *J* 7.8, $CHCH_3$), 1.33 (3H, s, CH_3), 1.35 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.50 (3H, s, CH_3), 1.65 (1H, m, $CH(CH_3)_2$), 3.02 (1H, dd, *J* 10.8, 6.4, $CHCH(CH_3)_2$), 3.79 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 3.87 (3H, s, OCH_3), 6.04 (1H, s, Ar), 10.42 (1H, s, OH), 11.57 (1H, s, OH), 16.88 (1H, s, OH); δ_C($CDCl_3$) 19.3 (CH_3), 19.3 (CH_3), 21.8 (CH_3), 22.0 (CH_3), 23.4 (CH_3), 24.8 (CH_3), 25.9 (CH), 25.9 (CH_3), 26.5 (CH_3), 39.1 (CH), 39.1 (CH), 48.7 (C_q), 54.9 (C_q), 55.6 (CH_3), 93.9 (CH), 103.6 (C_q),

108.9 (C_q), 114.2 (C_q), 161.8 (C_q), 164.2 (C_q), 164.3 (C_q), 178.1 (C_q), 202.9 (C_q), 210.8 (C_q), 212.5 (C_q). **Conformer 2** all peaks obscured except; $\delta_H(CDCl_3)$ 0.80 (3H, d, *J* 6.3, CHC*H*$_3$), 0.88 (3H, d, *J* 6.8, CHC*H*$_3$), 1.12 (3H, d, *J* 6.8, CHC*H*$_3$), 1.36 (3H, s, CH_3), 1.39 (3H, s, CH_3), 1.73 (1H, m, C*H*$(CH_3)_2$), 3.05 (1H, m, C*H*CH$(CH_3)_2$), 3.87 (3H, s, OCH_3), 6.10 (1H, s, Ar), 10.58 (1H, s, OH), 11.26 (1H, s, OH), 17.14 (1H, s, OH); $\delta_C(CDCl_3)$ 19.3 (CH_3), 19.3 (CH_3), 22.0 (CH_3), 22.0 (CH_3), 24.0 (CH_3), 24.7 (CH_3), 25.5 (CH), 26.1 (CH_3), 26.6 (CH_3), 39.2 (CH), 40.3 (CH), 49.0 (C_q), 54.3 (C_q), 55.6 (CH_3), 93.7 (CH), 103.8 (C_q), 108.6 (C_q), 114.2 (C_q), 161.8 (C_q), 164.4 (C_q), 164.7 (C_q), 176.6 (C_q), 203.5 (C_q), 211.3 (C_q), 212.8 (C_q).

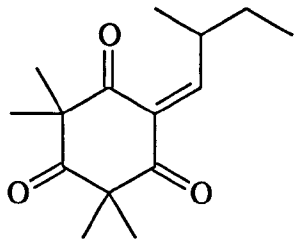
2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]-3,3-dimethylbutyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.63



A solution of the pyrrolidine complex **3.59** (0.062 g, 0.19 mmol), the phloroglucinol **3.30** (0.04 g, 0.19 mmol) and silica gel 60H (0.2 g) in dry dichloromethane (5 ml) was stirred at RT under nitrogen for 1 h. The solvent was allowed to evaporate over 1 h. Thin layer chromatography indicated the reaction was incomplete, so further pyrrolidine complex **3.59** (0.02 g, 0.06

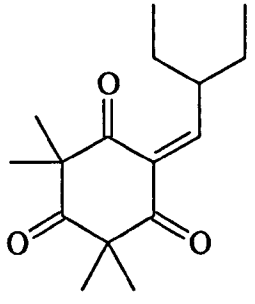
mmol) and dichloromethane (5 ml) were added and the solvent allowed to evaporate over 1 h. The crude product was purified by column chromatography using 10% diethyl ether / petrol ether as eluent to afford the title compound **3.63** (0.04 g, 45%) as a mixture of conformers in a 2 : 1 ratio and as white crystals, m.p. 185 - 186 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3104, 2957, 2874, 1728, 1618, 1588, 1467, 1433, 1380; **Conformer 1**; δ_H($CDCl_3$) 0.83 (9H, s, C(CH_3)$_3$), 1.17 (3H, d, *J* 6.8, CHCH_3), 1.19 (3H, d, *J* 6.8, CHCH_3), 1.33 (6H, s, CH_3), 1.34 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.47 (3H, s, CH_3), 1.77 (1H, dd, *J* 14.2, 4.4, CH_2), 2.19 (1H, dd, *J* 14.4, 5.6, CH_2), 3.81 (1H, sept, *J* 6.9, C*H*(CH_3)$_2$), 3.86 (3H, s, OCH_3), 4.38 (1H, m, CH), 6.04 (1H, s, Ar), 10.54 (1H, s, OH), 11.69 (1H, s, OH), 16.99 (1H, s, OH); δ_C($CDCl_3$) 19.2 (CH_3), 19.3 (CH_3), 22.9 (CH_3), 24.2 (CH_3), 26.0 (CH_3), 26.3 (CH_3), 27.2 (C_q), 29.2 (3 x CH_3), 32.0 (CH_2), 39.1 (CH), 44.9 (CH), 48.6 (C_q), 54.9 (C_q), 55.6 (CH_3), 94.2 (CH), 103.5 (C_q), 111.2 (C_q), 117.0 (C_q), 161.8 (C_q), 163.2 (C_q), 164.3 (C_q), 176.2 (C_q), 202.8 (C_q), 210.8 (C_q), 212.4 (C_q). **Conformer 2**; δ_H($CDCl_3$) all peaks obscured except 1.68 (1H, m, CH_2), 2.05 (1H, m, CH_2), 6.09 (1H, s, Ar), 10.75 (1H, s, OH), 11.43 (1H, s, OH), 17.19 (1H, s, OH); δ_C($CDCl_3$) 19.2 (CH_3), 19.3 (CH_3), 24.6 (CH_3), 24.8 (CH_3), 25.1 (CH_3), 25.6 (CH_3), 27.2 (C_q), 29.2 (3 x CH_3), 32.0 (CH_2), 39.2 (CH), 44.4 (CH), 49.0 (C_q), 53.9 (C_q), 55.7 (CH_3), 93.6 (CH), 104.2 (C_q), 111.4 (C_q), 117.2 (C_q), 161.7 (C_q), 163.6 (C_q), 164.5 (C_q), 177.3 (C_q), 202.8 (C_q), 211.2 (C_q), 212.9 (C_q); m/z (Found: M+, 474.26114. $C_{27}H_{38}O_7$ requires M, 474.26175).

2-(2-Methylbutenyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 3.64



The dione **3.60** (0.2 g, 0.62 mmol) and p-TSA (0.13 g, 0.62 mmol) were reacted as for compound **3.7** to afford the title compound **3.64** (0.15 g, 99%) as white crystals; m.p. 98 - 100 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3028, 2977, 2939, 2873, 1718, 1591, 1467, 1389, 1351; δ_H($CDCl_3$) 0.87 (3H, t, *J* 7.5, CH_2CH_3), 1.10 (3H, d, *J* 6.7, $CHCH_3$) 1.32 (6H, s, 2 x CCH_3), 1.34 (6H, s, 2 x CCH_3), 1.43 (2H, m, CH_2), 3.18 (1H, m, CH), 7.26 (1H, d, *J* 10.7, CH=C); δ_C($CDCl_3$) 11.9 (CH_3), 19.4 (CH_3), 21.4 (CH_3), 22.0 (CH_3), 22.3 (CH_3), 22.6 (CH_3) 29.5 (CH_2), 35.3 (CH), 58.0 (C_q), 58.4 (C_q), 131.7 (C_q), 164.3 (C_q), 196.3 (C_q), 199.7 (C_q), 208.7 (C_q).

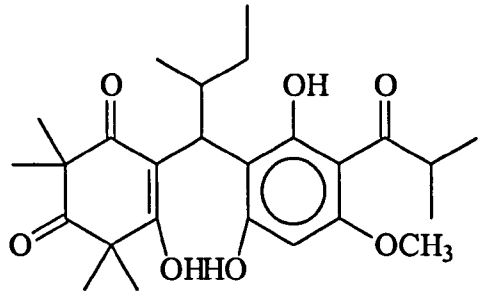
2-(2-Ethylbutenyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 3.65



The dione **3.61** (0.2 g, 0.6 mmol) and p-TSA (0.12 g, 0.6 mmol) were reacted as for compound **3.7** to afford the title compound **3.65** (0.15 g, 95%)

as off white crystals, m.p. 76 - 77 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3034, 2987, 2942, 2880, 1727, 1690, 1639, 1587, 1466, 1387; δ_H($CDCl_3$) 0.78 (6H, t, *J* 7.4, 2 x CH_2CH_3), 1.25 (12H, s, 4 x CCH_3), 1.54 (4H, m, 2 x CH_2), 3.02 (1H, dpent, *J* 11.2, 6.0, CH), 7.17 (1H, d, *J* 11.3, CH=C); δ_C($CDCl_3$) 12.0 (2 x CH_3), 21.9 (2 x CH_3), 22.4 (2 x CH_3), 27.6 (2 x CH_2), 42.3 (CH), 58.0 (C_q), 58.5 (C_q), 133.2 (C_q), 164.0 (CH), 196.2 (C_q), 199.7 (C_q), 208.8 (C_q).

2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]-2-methylbutyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.66

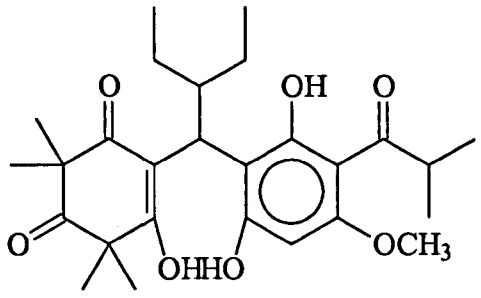


A solution of the alkylidene **3.64** (0.05 g, 0.2 mmol) and the phloroglucinol **3.30** (0.042 g, 0.2 mmol) in dry dichloromethane (5 ml) was stirred at 0°C and p-toluenesulfonic acid (0.005 g, 0.02 mmol) added. After warming to RT over 18h, water (10 ml) was added and the product extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with water, dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 10% diethyl ether / petrol ether as eluant and the resultant semi pure compound purified by silica

gel HPLC using 20% ethyl acetate / hexane as eluant to afford the title compound **3.66** (0.012 g, 13 %) as a mixture of conformers in a 2 : 1 ratio with each conformer as a mixture of two diastereomers; υ_{max} ($CHCl_3$)/cm^{-1} 3108, 2971, 2934, 2874, 1722, 1622, 1589, 1470, 1437, 1385; **Conformer 1** (major) n.b. assignments between the diastereomers **3.66a** and **3.66b** are interchangeable; **Diastereomer 3.66a** δ_H($CDCl_3$) 0.73 (3H, m, CH_2CH_3), 0.80 (3H, m, $CHCH_3$), 0.97 (2H, m, CH_2CH_3), 1.17 (3H, d, *J* 7.3, $CHCH_3$), 1.19 (3H, d, *J* 7.3, $CHCH_3$), 1.32 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.83 (1H, m, $CHCH_2CH_3$), 3.81 (1H, m, $CH(CH_3)_2$), 3.86 (3H, s, OCH_3), 3.92 (1H, d, *J* 6.8, CHCH), 6.03 (1H, s, Ar), 10.44 (1H, s, OH), 11.60 (1H, s, OH), 16.88 (1H, s, OH); δ_C($CDCl_3$) 10.4 (CH_3), 17.4 (CH_3), 19.2 (CH_3), 19.3 (CH_3), 23.3 (CH_3), 24.8 (CH_3), 25.9 (CH_3), 26.5 (CH_3), 27.7 (CH_2), 31.6 (CH), 36.5 (CH), 39.1 (CH), 48.7 (C_q), 54.9 (C_q), 55.6 (CH_3), 93.9 (CH), 103.6 (C_q), 108.7 (C_q), 113.9 (C_q), 161.8 (C_q), 164.2 (C_q), 164.3 (C_q), 177.9 (C_q), 203.0 (C_q), 210.8 (C_q), 212.6 (C_q). **Diastereomer 3.66b** δ_H($CDCl_3$) 0.73 (3H, m, CH_2CH_3), 0.80 (3H, m, $CHCH_3$), 0.97 (2H, m, CH_2CH_3), 1.17 (3H, d, *J* 7.3, $CHCH_3$), 1.19 (3H, d, *J* 7.3, $CHCH_3$), 1.32 (3H, s, CH_3), 1.34 (3H, s, CH_3), 1.41 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.83 (1H, m, $CHCH_2CH_3$), 3.81 (1H, m, $CH(CH_3)_2$), 3.86 (3H, s, OCH_3), 3.92 (1H, d, *J* 6.8, CHCH), 6.03 (1H, s, Ar), 10.43 (1H, s, OH), 11.58 (1H, s, OH), 16.87 (1H, s, OH); δ_C($CDCl_3$) 10.6 (CH_3), 17.7 (CH_3), 19.2 (CH_3), 19.3 (CH_3), 23.5 (CH_3), 24.7 (CH_3), 25.9 (CH_3), 26.5 (CH_3), 27.4 (CH_2), 31.6 (CH), 37.0 (CH), 39.1 (CH), 48.7 (C_q), 54.9 (C_q), 55.6 (CH_3), 93.8 (CH), 103.6 (C_q), 108.6 (C_q), 114.2 (C_q), 161.8 (C_q), 164.3 (C_q), 164.5 (C_q), 178.2 (C_q), 203.0 (C_q), 210.8

(C_q), 212.6 (C_q). **Conformer 2** (minor) n.b. assignments between the diastereomers **3.66c** and **3.66d** are interchangeable; **Diastereomer 3.66c** $\delta_H(CDCl_3)$ 0.74 (3H, m, CH_2CH_3), 0.84 (3H, m, $CHCH_3$), 0.97 (2H, m, CH_2CH_3), 1.17 (3H, d, *J* 7.3, $CHCH_3$), 1.19 (3H, d, *J* 7.3, $CHCH_3$), 1.35 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.84 (1H, m, $CHCH_2CH_3$), 3.81 (1H, m, $CH(CH_3)_2$), 3.86 (3H, s, OCH_3), 3.94 (1H, d, *J* 6.8, $CHCH$), 6.09 (1H, s, Ar), 10.61 (1H, s, OH), 11.30 (1H, s, OH), 17.14 (1H, s, OH); $\delta_C(CDCl_3)$ 10.5 (CH_3), 17.8 (CH_3), 19.2 (CH_3), 19.2 (CH_3), 24.2 (CH_3), 24.8 (CH_3), 25.5 (CH_3), 26.1 (CH_3), 27.7 (CH_2), 32.3 (CH), 37.7 (CH), 39.2 (CH), 49.0 (C_q), 54.3 (C_q), 55.7 (CH_3), 93.7 (CH), 103.8 (C_q), 108.6 (C_q), 114.2 (C_q), 161.7 (C_q), 164.2 (C_q), 164.6 (C_q), 176.7 (C_q), 203.6 (C_q), 211.3 (C_q), 212.9 (C_q); **Diastereomer 3.66d** $\delta_H(CDCl_3)$ 0.74 (3H, m, CH_2CH_3), 0.84 (3H, m, $CHCH_3$), 0.97 (2H, m, CH_2CH_3), 1.17 (3H, d, *J* 7.3, $CHCH_3$), 1.19 (3H, d, *J* 7.3, $CHCH_3$), 1.35 (3H, s, CH_3), 1.38 (3H, s, CH_3), 1.43 (3H, s, CH_3), 1.50 (3H, s, CH_3), 2.84 (1H, m, $CHCH_2CH_3$), 3.81 (1H, m, $CH(CH_3)_2$), 3.86 (3H, s, OCH_3), 3.94 (1H, d, *J* 6.8, $CHCH$), 6.09 (1H, s, Ar), 10.60 (1H, s, OH), 11.25 (1H, s, OH), 17.10 (1H, s, OH); $\delta_C(CDCl_3)$ 10.5 (CH_3), 17.8 (CH_3), 19.2 (CH_3), 19.2 (CH_3), 24.0 (CH_3), 24.7 (CH_3), 25.5 (CH_3), 26.1 (CH_3), 27.7 (CH_2), 32.1 (CH), 38.0 (CH), 39.2 (CH), 49.0 (C_q), 54.2 (C_q), 55.7 (CH_3), 93.8 (CH), 103.8 (C_q), 108.3 (C_q), 113.9 (C_q), 161.7 (C_q), 164.2 (C_q), 164.8 (C_q), 176.9 (C_q), 203.6 (C_q), 211.3 (C_q), 212.9 (C_q); m/z (Found: M+, 460.24722. $C_{26}H_{36}O_7$ requires M, 460.24610).

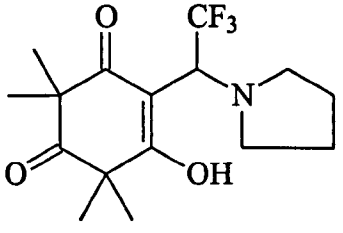
2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]-2-ethylbutyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.67



A solution of the alkylidene **3.65** (0.08 g, 0.31 mmol) and the phloroglucinol **3.30** (0.064 g, 0.31 mmol) in dry dichloromethane (10 ml) was stirred at 0 °C and p-toluenesulfonic acid (0.005 g, 0.02 mmol) added. After warming to RT over 24 h, thin layer chromatography indicated incomplete reaction, so further alkylidene **3.65** (0.08 g, 0.31 mmol) was added. After 4h, 2N HCl (10 ml) was added and the product extracted with dichloromethane (3 x 10 ml). The combined extracts were washed with water, dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 10% diethyl ether / petrol ether as eluant to afford the title compound **3.67** (0.032 g, 22 %) as a 2 : 1 mixture of conformers and as pale yellow crystals, m.p. 174 - 175 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3107, 2973, 2941, 2876, 1719, 1624, 1589, 1473, 1436, 1386; **Conformer 1**; δ_H($CDCl_3$) 0.72 (3H, t, *J* 7.5, CH_2CH_3), 0.78 (3H, t, *J* 7.2, CH_2CH_3), 1.18 (3H, d, *J* 7.8, $CHCH_3$), 1.20 (3H, d, *J* 6.9, $CHCH_3$), 1.32 (3H, s, CH_3), 1.32 - 1.49 (4H, m, 2 x CH_2), 1.35 (3H, s, CH_3), 1.42 (3H, s, CH_3), 1.49 (3H, s, CH_3), 2.82 (1H, m, $CH(CH_2CH_3)_2$), 3.81 (1H, sept, *J* 6.8, $CH(CH_3)_2$), 3.86 (3H, s,

OCH_3), 4.07 (1H, d, *J* 11.2, CH), 6.03 (1H, s, Ar), 10.51 (1H, s, OH), 11.63 (1H, s, OH), 16.92 (1H, s, OH); $\delta_C(CDCl_3)$ 8.9 (CH_3), 9.6 (CH_3), 19.4 (2 x CH_3), 21.8 (CH_3), 21.9 (CH_3), 23.6 (CH_3), 24.8 (CH_3), 25.8 (CH_3), 26.3 (CH_3), 33.3 (CH), 35.9 (CH), 39.1 (CH), 48.7 (C_q), 54.9 (C_q), 55.6 (CH_3), 93.9 (CH), 103.6 (C_q), 108.5 (C_q), 114.0 (C_q), 161.8 (C_q), 164.3 (C_q), 164.5 (C_q), 178.1 (C_q), 203.1 (C_q), 210.8 (C_q), 212.6 (C_q). **Conformer 2**; $\delta_H(CDCl_3)$ all peaks obscured except 4.11 (1H, d, *J* 11.7, CH), 6.09 (1H, s, Ar), 10.67 (1H, s, OH), 11.33 (1H, s, OH), 17.14 (1H, s, OH); $\delta_C(CDCl_3)$ 9.4 (CH_3), 9.4 (CH_3), 19.2 (2 x CH_3), 22.0 (CH_3), 22.0 (CH_3), 24.0 (CH_3), 24.7 (CH_3), 25.6 (CH_3), 26.1 (CH_3), 34.4 (CH), 36.6 (CH), 39.1 (CH), 49.1 (C_q), 54.2 (C_q), 55.7 (CH_3), 93.8 (CH), 103.7 (C_q), 108.4 (C_q), 113.9 (C_q), 161.7 (C_q), 164.7 (C_q), 164.8 (C_q), 177.1 (C_q), 203.5 (C_q), 211.3 (C_q), 212.8 (C_q).

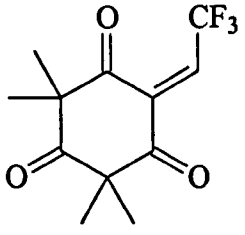
1-Hydroxy-2-(1-pyrrolidine-2,2,2-trifluoromethyl)-4,4,6,6-tetramethyl-cyclohexene-3,5-dione 3.68



A solution of the dione **3.4** (0.2 g, 1.1 mmol) and pyrrolidine (0.16 g, 2.2 mmol) in dry diethyl ether (5 ml) was cooled to 0 °C and trifluoroacetaldehyde ethylhemiacetal (0.16 g, 1.1 mmol) added dropwise over

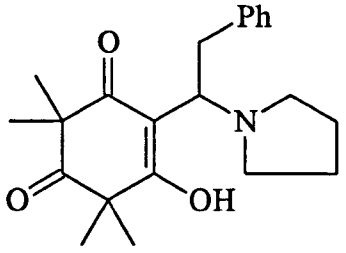
5 mins. After stirring for 1 h, the solvent was removed under reduced pressure, the resultant solid was filtered, washed with 50% cold diethyl ether / petrol ether (10 ml) and dried under reduced pressure to afford the title compound **3.68** (0.28 g, 77%) as white xtals, m.p. 136 - 137 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3028, 2984, 2933, 2754, 1709, 1523; δ_H($CDCl_3$) 1.29 (6H, s, 2 x CCH_3), 1.30 (6H, s, 2 x CCH_3), 2.07 (4H, m, 2 x CH_2CH_2N), 3.30 (4H, m, 2 x NCH_2), 5.13 (1H, q, *J* 8.0, $CHCF_3$), 8.20 br (1H, s, OH); δ_C($CDCl_3$) 24.3 (2 x CH_2), 25.1 (2 x CH_3), 25.2 (2 x CH_3), 45.7 (2 x C_q), 52.7 (2 x CH_2), 68.9 (q, *J* 31.8, CH), 100.7 (C_q), 126.6 (q, *J* 285, CF_3), 194.3 (2 x C_q), 215.9 (C_q).

2-(2,2,2-trifluoroethenyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 3.69



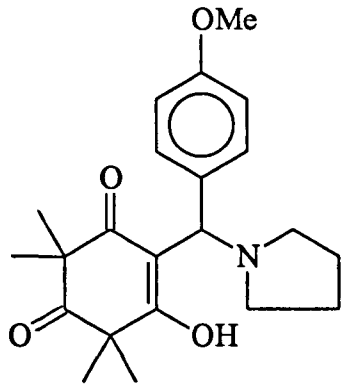
The dione **3.68** (0.1 g, 0.3 mmol) and p-TSA (0.055 g, 0.33 mmol) were reacted as for compound **3.7** to afford the title compound **3.69** (0.04 g, 51%) as a colourless oil; δ_H($CDCl_3$) 1.40 (6H, s, 2 x CCH_3), 1.42 (6H, s, 2 x CCH_3), 5.58 (1H, q, *J* 7.0, CH); δ_C($CDCl_3$) 23.8 (2 x CH_3), 25.2 (2 x CH_3), 52.0 br (2 x C_q), 68.0 (q, *J* 33, CH), 103.8 (C_q), 124.6 (q, *J* 284, C_q), 189 br (2 x C_q), 211.9 (C_q).

1-Hydroxy-2-[1-pyrrolidine-3-phenylethyl]-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.70



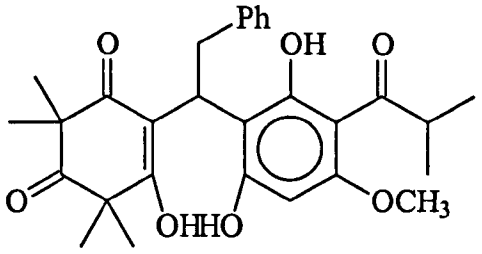
Syncarpic acid **3.4** (0.2 g, 1.1 mmol), phenylacetaldehyde (0.17 g, 1.4 mmol) and pyrrolidine (0.094 g, 1.3 mmol) were reacted as for compound **3.18** to afford the title compound **3.70** (0.29 g, 76%) as a semi-solid; υ_{max} ($CHCl_3$)/cm^{-1} 2993, 2935, 2873, 1703, 1587, 1517; δ_H($CDCl_3$) 1.10 (6H, s, 2 x CCH_3), 1.28 (6H, s, 2 x CCH_3), 2.00 br (4H, m, 2 x NCH_2CH_2), 2.87 br (1H, m, NCH_2), 3.03 br (1H, m, NCH_2), 3.24 (2H, d, *J* 7.4, CH_2Ph), 3.34 br (1H, m, NCH_2), 3.60 br (1H, m, NCH_2), 4.82 (1H, t, *J* 7.5, NCH), 7.15 - 7.27 (5H, m, Ar); δ_C($CDCl_3$) 22.6 (CH_2), 24.3 (2 x CH_3), 24.6 (CH_2), 25.2 (2 x CH_3), 37.3 (CH_2), 51.0 (CH_2), 52.4 (2 x C_q), 53.7 (CH_2), 65.2 (CH), 102.4 (C_q), 126.7 (CH), 128.2 (2 x CH), 129.3 (2 x CH), 136.7 (C_q), 191.3 (2 x C_q), 217.0 (C_q).

1-Hydroxy-2-[1-pyrrolidine-1-(4-methoxyphenyl)methyl]-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.71



Syncarpic acid **3.4** (0.2 g, 1.1 mmol), p-anisaldehyde (0.15 g, 1.1 mmol) and pyrrolidine (0.094 g, 1.3 mmol) were reacted as for compound **3.18** to afford the title compound **3.71** (0.32 g, 78%) as white crystals, m.p 156 - 158 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3030, 2983, 2937, 1706, 1588, 1513, 1459, 1401, 1359; δ_H($CDCl_3$) 1.33 (6H, s, 2 x CH_3C), 1.36 (6H, s, 2 x CH_3C), 1.95 br (2H, m, 2 x NCH_2CH_2), 2.07 br (2H, m, 2 x NCH_2CH_2), 2.76 br (1H, m, NCH_2), 2.98 br (1H, m, NCH_2), 3.16 br (1H, m, NCH_2), 3.48 br (1H, m, NCH_2), 3.78 (3H, s, OCH_3), 5.24 (1H, s, NCH), 6.38 (2H, d, *J* 8.8, Ar), 7.52 (2H, d, *J* 8.8, Ar); δ_C($CDCl_3$) 23.3 (CH_2), 23.8 (CH_2), 24.9 (2 x CH_3), 24.9 (2 x CH_3), 51.4 (CH_2), 52.3 (C_q), 52.6 (C_q), 53.6 (CH_2), 55.3 (CH_3), 69.4 (CH), 104.3 (C_q), 114.2 (2 x CH), 129.7 (2 x CH), 130.6 (C_q), 159.7 (C_q), 191.3 (C_q), 195.3 (C_q), 216.3 (C_q).

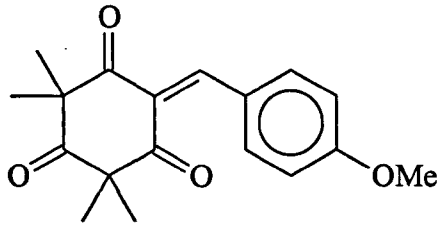
2-{1-[2,6-dihydroxy-4-methoxy-3-(2-methyl-1-oxopropyl)phenyl]2-phenylethyl}-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.72



A solution of the pyrrolidine complex **3.70** (0.087 g, 0.24 mmol), the phloroglucinol **3.30** (0.05 g, 0.24 mmol) and silica gel 60H (0.2 g) in dry dichloromethane (5 ml) was stirred at RT under nitrogen for 1 h and the solvent allowed to evaporate over 1 h. Thin layer chromatography indicated the reaction was incomplete, so further pyrrolidine complex **3.70** (0.05 g, 0.14 mmol) and dichloromethane (5 ml) were added and the solvent allowed to evaporate over 1 h. The crude product was purified by column chromatography using 10% diethyl ether / petrol ether as eluant to afford the title compound **3.72** (0.035 g, 29 %) as a mixture of conformers in a 2 : 1 ratio and as white crystals, m.p. 122 - 123 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3111, 2984, 2934, 1712, 1619, 1592, 1469, 1433, 1384; **Conformer 1**; δ_H($CDCl_3$) 0.86 (3H, d, *J* 6.8, CHC*H*$_3$), 0.87 (3H, d, *J* 6.8, CHC*H*$_3$), 1.17 (3H, s, CH_3), 1.19 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.25 (3H, s, CH_3), 3.13 (2H, m, CH_2), 3.81 (1H, m, C*H*(CH_3)$_2$), 3.87 (3H, s, OCH_3), 4.77 (1H, m, CH), 6.08 (1H, s, Ar), 7.19 (1H, m, Ar), 7.20 (2H, m, Ar), 7.26 (2H, m, Ar), 10.38 (1H, s, OH), 11.83 (1H, s, OH), 16.96 (1H, s, OH); δ_C($CDCl_3$) 19.3 (2 x CH_3), 23.0 (CH_3), 24.8 (CH_3), 25.3 (CH_3), 26.1 (CH_3), 31.4 (CH_2), 34.9 (CH), 39.2 (CH), 48.5 (C_q), 54.8 (C_q),

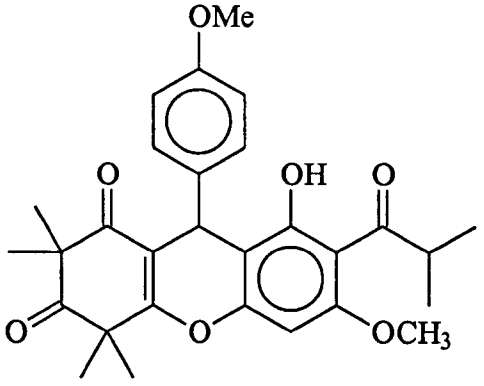
55.7 (CH_3), 94.2 (CH), 103.6 (C_q), 108.8 (C_q), 113.5 (C_q), 126.4 (CH), 128.3 (2 x CH), 128.8 (2 x CH), 139.5 (C_q), 162.0 (C_q), 164.0 (C_q), 164.6 (C_q), 178.0 (C_q), 203.1 (C_q), 210.8 (C_q), 212.3 (C_q). **Conformer 2**; $\delta_H(CDCl_3)$ all peaks obscured except 4.64 (1H, m, CH), 6.11 (1H, s, Ar), 10.81 (1H, s, OH), 11.35 (1H, s, OH), 17.31 (1H, s, OH); $\delta_C(CDCl_3)$ 19.2 (2 x CH_3), 22.3 (CH_3), 24.6 (CH_3), 25.5 (CH_3), 26.6 (CH_3), 31.9 (CH_2), 35.7 (CH), 39.2 (CH), 48.8 (C_q), 54.1 (C_q), 55.7 (CH_3), 93.7 (CH), 104.1 (C_q), 108.9 (C_q), 113.4 (C_q), 126.4 (CH), 128.3 (2 x CH), 128.8 (2 x CH), 140.3 (C_q), 162.0 (C_q), 164.2 (C_q), 165.0 (C_q), 176.5 (C_q), 203.9 (C_q), 211.4 (C_q), 216.6 (C_q); m/z (Found: M+, 494.23160. $C_{29}H_{34}O_7$ requires M, 494.23045).

2-(4-Methoxybenzyl)-4,4,6,6-tetramethylcyclohexane-1,3,5-trione 3.73



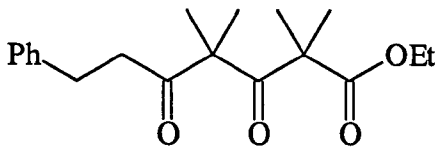
The dione **3.71** (0.1 g, 0.27 mmol) and p-TSA (0.05 g, 0.3 mmol) were reacted as for compound **3.7** to afford the title compound **3.73** (0.18 g, 78%) as a colourless oil; $\delta_H(CDCl_3)$ 1.29 (6H, s, 2 x CCH_3), 1.31 (6H, s, 2 x CCH_3), 3.80 (3H, s, OCH_3), 6.86 (2H, d, *J* 8.8, Ar), 7.88 (2H, d, *J* 8.9, Ar), 7.95 (1H, s, CH=C); $\delta_C(CDCl_3)$ 22.2 (2 x CH_3), 22.5 (2 x CH_3), 55.5 (CH_3), 58.4 (C_q), 58.7 (C_q), 114.3 (2 x CH), 125.5 (C_q), 127.7 (C_q), 135.8 (2 x CH), 150.6 (CH), 163.7 (C_q), 196.6 (C_q), 200.5 (C_q), 209.1 (C_q).

Compound 3.74



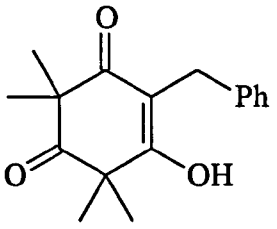
A solution of the trione **3.73** (0.06 g, 0.2 mmol), the phloroglucinol **3.30** (0.046 g, 0.2 mmol) and p-TSA (0.02 g, 0.1 mmol) were stirred in dichloromethane (5 ml). After 16 h, water (10 ml) was added and the product extracted with dichloromethane (3 x 5 ml). The combined extracts were washed with water (10 ml), dried and the solvent evaporated under reduced pressure. The crude product was purified by column chromatography using 50% diethyl ether / petrol ether as eluant to afford the title compound **3.74** (0.1 g, 99%) as a colourless oil; $\delta_H(CDCl_3)$ 0.86 (1H, d, *J* 7.4, $CH(CH_3)_2$), 0.87 (1H, d, *J* 7.3, $CH(CH_3)_2$), 1.20 (3H, s, CH_3), 1.23 (3H, s, CH_3), 1.27 (3H, s, CH_3), 1.31 (3H, s, CH_3), 3.18 (1h, sept, *J* 6.8, $CH(CH_3)_2$), 3.67 (3H, s, OCH_3), 3.72 (3H, s, OCH_3), 5.16 (1H, s, CH), 6.21 (1H, s, Ar), 6.74 (2H, d, *J* 8.8, Ar), 7.18 (2H, d, *J* 8.8, Ar); $\delta_C(CDCl_3)$ 18.0 (CH_3), 18.1 (CH_3), 23.3 (CH_3), 24.5 (CH_3), 24.7 (CH_3), 25.3 (CH_3), 31.6 (CH), 42.3 (CH), 47.4 (C_q), 55.2 (CH_3), 55.8 (CH_3), 56.3 (C_q), 96.3 (CH), 105.3 (C_q), 111.4 (C_q), 112.3 (C_q), 114.0 (2 x CH), 129.1 (2 x CH), 136.1 (C_q), 147.4 (C_q), 156.0 (C_q), 158.3 (C_q), 165.6 (C_q), 197.8 (C_q), 207.4 (C_q), 211.6 (C_q); m/z (Found: M+, 492.21564. $C_{29}H_{32}O_7$ requires M, 492.21480).

Ethyl 3,5-dioxo-7-phenyl-2,2,4,4-tetramethylheptanoate 3.76



Dihydrocinnamylchloride **3.75** (0.14 g, 0.8 mmol) was added to a stirred solution of anhydrous zinc chloride (0.11 g, 0.8 mmol) in dichloromethane (3 ml) at 0 °C. Silyl enol **3.11** (0.2 g, 0.8 mmol) was added dropwise and the mixture stirred at 0 °C for 1 h followed by warming to room temperature for 1 h. Water (10 ml) was added and the product extracted with dichloromethane (3 x 10 ml), the combined extracts washed with water (20 ml), dried and evaporated under reduced pressure. The crude product was columned using 10% diethyl ether / petrol ether to afford the title compound **3.76** (0.17 g, 67%) as a colourless oil; υ_{max} ($CHCl_3$)/cm^{-1} 3031, 2984, 2941, 1718, 1687, 1471, 1388, 1365; δ_H($CDCl_3$) 1.22 (3H, t, *J* 7.2, CH_2CH_3), 1.32 (6H, s, $C(CH_3)_2$), 1.33 (6H, s, $C(CH_3)_2$), 2.78 (2H, m, CH_2), 2.87 (2H, m, CH_2), 4.12 (2H, q, *J* 7.8, CH_2CH_3), 7.17 (2H, m, 2 x Ar), 7.18 (2H, m, 2 x Ar), 7.27 (1H, t, *J* 7.8, Ar); δ_C($CDCl_3$) 13.9 (CH_3), 22.6 (2 x CH_3), 23.8 (2 x CH_3), 29.9 (CH_2), 39.6 (CH_2), 55.2 (C_q), 61.4 (CH_2), 62.8 (C_q), 126.3 (CH), 128.4 (4 x CH), 141.0 (C_q), 173.7 (C_q), 207.2 (C_q), 207.9 (C_q).

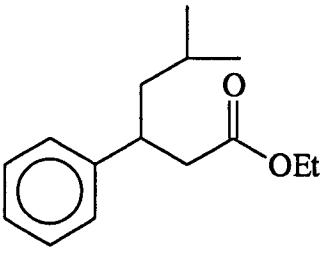
2-Benzyl-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.77



2.5 M n-Butyllithium (0.25 ml, 0.63 mmol) was added dropwise to a stirred solution of diisopropylamine (0.07 ml, 0.63 mmol) in anhydrous THF (10 ml) at -78 °C under N_2. A solution of diketoester **3.76** (0.2 g, 0.63 mmol) in anhydrous THF (2 ml) was added dropwise and the solution stirred for 1h. 2N HCl (10 ml) was added and the product extracted with dichloromethane (3 x 10 ml), the combined extracts washed with water (20 ml), dried and evaporated under reduced pressure. The crude product was columned using 50% diethyl ether / petrol ether to afford the title compound **3.77** (0.066 g, 39%) as a pale yellow crystals; υ_{max} ($CHCl_3$)/cm^{-1} 3028, 2964, 2934, 2873, 1711, 1473, 1386; Mix of triketone and diketoenol. **Triketone form** δ_H($CDCl_3$) 1.21 (6H, s, 2 x CH_3), 1.33 (6H, s, 2 x CH_3), 3.31 (2H, d, *J* 5.9, CH_2), 3.95 (1H, t, *J* 5.9, CH), 7.20 (2H, m, 2 x Ar), 7.24 (2H, m, 2 x Ar), 7.28 (1H, m, Ar); δ_C[$CDCl_3$] 22.2 (2 x CH_3), 22.8 (2 x CH_3), 28.9 (CH_2), 58.4 (2 x C_q), 63.2 (CH), 126.5 (CH), 128.4 (2 x CH), 129.1 (2 x CH), 139.0 (C_q), 204.3 (2 x C_q), 210.7 (C_q). **Diketoenol form** δ_H($CDCl_3$) 1.39 (12H, s, 4 x CH_3), 3.79 (2H, s, CH_2), 7.20 (2H, m, 2 x Ar), 7.24 (2H, m, 2 x Ar), 7.28 (1H, m, Ar); δ_C[$CDCl_3$] 24.7 (4 x CH_3), 28.5 (CH_2), 58.4 (2 x C_q), 111.8 (C_q), 126.7 (CH), 127.9 (2 x CH), 129.0 (2 x CH), 138.6 (C_q), 199.0 (2 x C_q), 212.8 (C_q); m/z

(Found: M+, 272.13983. $C_{17}H_{20}O_3$ requires M, 272.14124).

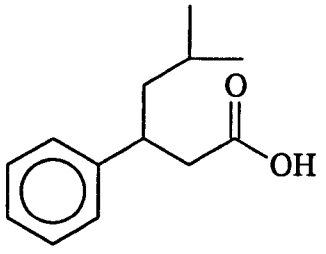
Ethyl 5-methyl-3-phenylhexanoate 3.79



Cuprous chloride (0.3 g, 2.8 mmol) was added to 2.0 M isobutylmagnesium chloride (21 ml) in diethyl ether at -78°C under nitrogen. The solution was allowed to warm to -30 °C for 15 mins before cooling to -78 °C and ethyl *trans*-cinnamate **3.78** (5 g, 28 mmol) in diethyl ether (20 ml) added dropwise. The solution was allowed to warm to 0 °C over 3 h, 2N HCl (50 ml) added the product extracted with diethyl ether (3 x 50 ml), the combined extracts washed with water (100 ml), dried and evaporated under reduced pressure. The crude product was columned using 10% diethyl ether / petrol ether to afford the title compound **3.79** (5.2 g, 78%) as a colourless oil, n_D 1.4928; υ_{max} ($CHCl_3$)/cm^{-1} 3022, 2980, 2926, 2903, 2874, 1728, 1456, 1366; δ_H($CDCl_3$) 0.82 (3H, d, *J* 6.4, $CH(CH_3)_2$), 0.88 (3H, d, *J* 6.4, $CH(CH_3)_2$), 1.11 (3H, t, *J* 7.0, CH_2CH_3), 1.33 (1H, m, $CH(CH_3)_2$), 1.41 (1H, m, CH_2), 1.60 (1H, m, CH_2), 2.54 (2H, t, *J* 7.0, CH_2), 3.19 (1H, m, CH), 4.00 (2H, q, *J* 7.1, CH_2), 7.17 (1H, t, *J* 7.9, Ar), 7.18 (2H, d, *J* 8.2, 2 x Ar), 7.26 (1H, t, *J* 7.2, 2 x Ar); δ_C($CDCl_3$) 14.0 (CH_3), 21.5 (CH_3), 23.4 (CH_3), 25.2 (CH), 39.9 (CH_2),

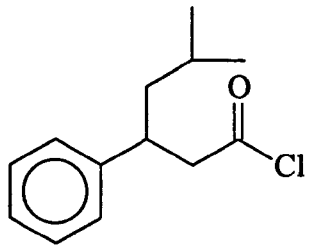
42.3 (CH_2), 45.3 (CH), 60.0 (CH_2), 126.2 (CH), 127.4 (2 x CH), 128.2 (2 x CH), 144.0 (C_q), 172.2 (C_q).

5-Methyl-3-phenylhexanoic acid 3.80



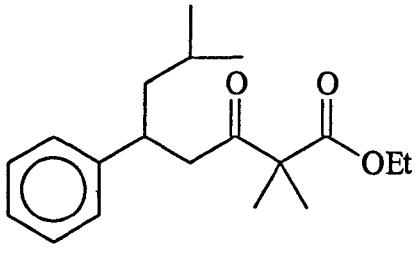
The ester **3.79** (2 g, 2.1 mmol) and potassium hydroxide (0.21 g, 3.8 mmol) were refluxed in ethanol (25 ml) for 3 h. On cooling, ethanol was removed under reduced pressure, water (20 ml) added and extracted with diethyl ether (3 x 20 ml). The aqueous layer was acidified with 2N HCl (20 ml) and extracted with diethyl ether (3 x 20 ml). The combined extracts were washed with water (100 ml), dried and evaporated under reduced pressure to afford the title compound **3.80** (1.5 g, 87%) as a colourless oil, n_D 1.4958; υ_{max} ($CHCl_3$)/cm^{-1} 3027, 2963, 2930, 2874, 1709, 1467, 1370; δ_H($CDCl_3$) 0.82 (3H, d, *J* 6.8, $CH(CH_3)_2$), 0.86 (3H, d, *J* 6.4, $CH(CH_3)_2$), 1.32 (1H, m, $CH(CH_3)_2$), 1.41 (1H, m, CH_2), 1.58 (1H, m, CH_2), 2.56 (1H, d, *J* 7.8, CH_2), 2.58 (1H, d, *J* 7.0, CH_2), 3.17 (1H, m, CH), 7.18 (2H, t, *J* 7.7, 2 x Ar), 7.19 (2H, d, *J* 8.0, 2 x Ar), 7.27 (1H, t, *J* 7.4, Ar); δ_C($CDCl_3$) 21.5 (CH_3), 23.4 (CH_3), 25.2 (CH), 39.1 (CH), 42.1 (CH_2), 45.3 (CH_2), 126.5 (CH), 127.4 (2 x CH), 128.6 (2 x CH), 143.8 (C_q), 179.1 (C_q).

5-Methyl-3-phenylhexanoyl chloride 3.81



The acid **3.80** (1.2 g, 5.8 mmol) in thionyl chloride (20 ml) was refluxed for 2 h. Excess thionyl chloride was removed by distillation and the crude product azeotroped with diethyl ether under reduced pressure to afford the title compound **3.81** (1.2 g, 92%) as a colourless oil; υ_{max} ($CHCl_3$)/cm^{-1} 3034, 2956, 2930, 1713, 1411, 1281.

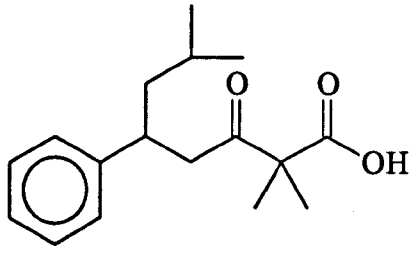
Ethyl 3-oxo-5-phenyl-2,2,7-trimethyloctanoate 3.82



2.5M n-BuLi (1.8 ml, 4.5 mmol) was added dropwise to n-cyclohexylisopropylamine (0.63 g, 4.5 mmol) in dry THF (20 ml) at -78 °C under N_2. After 10 mins, ethylisobutyrate (0.52 g, 4.5 mmol) in THF (10 ml) was added dropwise and after a further 10 mins the acid chloride **3.81** (1 g, 4.5 mmol) was added and the mixture stirred at -78 °C for 1 h. On warming to

room temperature, 1N HCl (20 ml) was added and the product extracted with dichloromethane (3 x 20 ml), the combined extracts washed with water (40 ml), dried and evaporated under reduced pressure. The crude product was columned using 4% diethyl ether / petrol ether to afford the title compound **3.82** (0.95 g, 70%) as a colourless oil, n_D 1.4843; υ_{max} ($CHCl_3$)/cm^{-1} 3031, 2961, 1718, 1471, 1393, 1369, 1275; δ_H($CDCl_3$) 0.83 (3H, d, *J* 6.4, $CH(CH_3)_2$), 0.88 (3H, d, *J* 6.4, $CH(CH_3)_2$), 1.14 (3H, s, CH_3), 1.18 (3H, t, *J* 7.2, CH_2CH_3), 1.28 (3H, s, CH_3), 1.33 (1H, m, $CH(CH_3)_2$), 1.37 (1H, m, CH_2), 1.55 (1H, m, CH_2), 2.70 (2H, dd, *J* 9.9, 6.8, CH_2), 3.33 (1H, m, CH), 4.05 (2H, q, *J* 7.1, CH_2CH_3), 7.13 - 7.27 (5H, m, Ar); δ_C($CDCl_3$) 13.9 (CH_3), 21.3 (CH_3), 21.3 (CH_3), 21.6 (CH_3), 23.5 (CH_3), 25.2 (CH), 38.1 (CH_2), 44.9 (CH_2), 46.0 (CH), 55.5 (C_q), 61.1 (CH_2), 126.1 (CH), 127.5 (2 x CH), 128.2 (2 x CH), 144.5 (C_q), 173.4 (C_q), 206.2 (C_q).

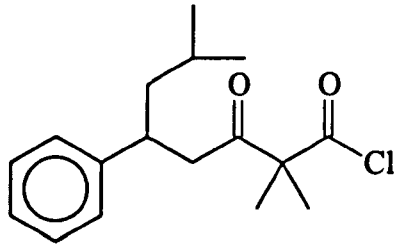
3-Oxo-5-phenyl-2,2,7-trimethyloctanoic acid 3.83



A solution of the ester **3.82** (0.16 g, 0.53 mmol) and sodium hydroxide (0.5 g, 13 mmol) in ethanol (10 ml) were refluxed for 2 h. On cooling, the ethanol was removed under reduced pressure, water (10 ml) added and

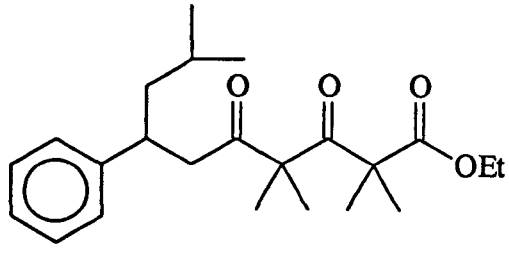
extracted with diethyl ether (3 x 10 ml). The aqueous layer was acidified with 2N HCl (10 ml) and extracted with diethyl ether (3 x 10 ml). The combined extracts were washed with water (20 ml), dried and evaporated under reduced pressure to afford the title compound **3.83** (0.13 g, 88%) as a semi-solid; υ_{max} ($CHCl_3$)/cm^{-1} 3027, 2959, 2926, 1709.

3-Oxo-5-phenyl-2,2,7-trimethyoctanoyl chloride 3.84



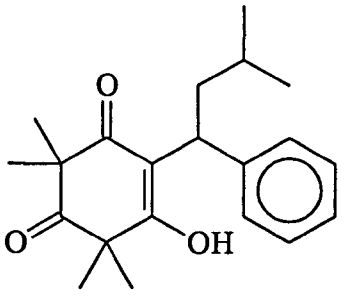
The acid **3.83** (0.11 g, 0.34 mmol) in thionyl chloride (10 ml) was refluxed for 2h. Excess thionyl chloride was removed by distillation and the crude product azeotroped with diethyl ether under reduced pressure to afford the title compound **3.84** (0.11 g, 94%) as a colourless oil.

Ethyl 3,3-dioxo-2,2,4,4,9-pentamethyl-7-phenyldecanoate 3.85



2.5M n-BuLi (0.16 ml, 0.41 mmol) was added dropwise to n-cyclohexylisopropylamine (0.057 g, 0.41 mmol) in dry THF (2 ml) at -78 °C under N_2. After 10 mins, ethyl isobutyrate (0.047 g, 0.41 mmol) in THF (1 ml) was added dropwise and after a further 10 mins the acid chloride **3.84** (0.12 g, 0.41 mmol) was added and the mixture stirred at -78 °C for 1 h. On warming to room temperature, 1N HCl (5 ml) was added and the product extracted with dichloromethane (3 x 5 ml), the combined extracts washed with water (20 ml), dried and evaporated under reduced pressure. The crude product was columned using 5% diethyl ether / petrol ether to afford the title compound **3.85** (0.028 g, 18%) as a colourless oil; $\delta_H(CDCl_3)$ 0.80 (3H, d, *J* 6.4, $CH(CH_3)_2$), 0.88 (3H, d, *J* 6.4, $CH(CH_3)_2$), 1.14 (3H, s, CH_3), 1.16 (3H, s, CH_3), 1.22 (3H, t, *J* 7.3, CH_2CH_3), 1.27 (6H, s, 2 x CH_3), 1.31 (1H, m, $CH(CH_3)_2$), 1.34 (1H, m, CH_2), 1.55 (1H, m, CH_2), 2.62 (1H, dd, *J* 15.8, 5.8, CH_2), 2.83 (1H, dd, *J* 18.3, 8.3, CH_2), 3.27 (1H, m, CH), 4.09 (2H, q, *J* 7.0, CH_2CH_3), 7.13 - 7.26 (5H, m, Ar); $\delta_C(CDCl_3)$ 13.9 (CH_3), 21.5 (CH_3), 22.0 (CH_3), 22.7 (CH_3), 23.2 (CH_3), 23.5 (CH_3), 23.9 (CH_3), 25.4 (CH), 38.2 (CH_2), 45.2 (CH_2), 45.4 (CH), 55.2 (C_q), 61.4 (CH_2), 62.9 (C_q), 126.2 (CH), 127.7 (2 x CH), 128.3 (2 x CH), 144.6 (C_q), 173.6 (C_q), 206.5 (C_q), 207.4 (C_q).

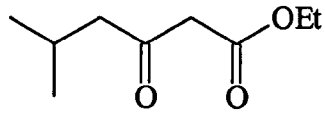
2-(1-Phenyl-3-methylbutyl)-1-hydroxy-4,4,6,6-tetramethylcyclohexene-3,5-dione 3.86



1.0M Lithium bistrimethylsilylamide (0.067 ml, 0.067 mmol) was added dropwise to the ester **3.85** (0.025 g, 0.067 mmol) in dry THF (1 ml) at -78 °C under N_2. Thin layer chromatography showed 30% completion, so further 1.0M lithium bistrimethylsilylamide (0.34 ml, 0.34 mmol) added and the reaction warmed to room temperature. 1N HCl (5 ml) was added and the product extracted with diethyl ether (3 x 5 ml), the combined extracts backextracted with 1N NaOH (3 x 10 ml), the combined aqueous layers acidified with 1N HCl (30 ml) and extracted with diethyl ether (3 x 10 ml). The combined extracts were washed with water (20 ml), dried and evaporated under reduced pressure to give the product **3.86** (0.018 g, 80%) as a pale yellow semi-solid; $\delta_H(CDCl_3)$ 0.96 (3H, d, *J* 6.3, $CH(CH_3)_2$), 0.98 (3H, d, *J* 6.3, $CH(CH_3)_2$), 1.27 (3H, s, CH_3), 1.37 (3H, s, CH_3), 1.37 (3H, CH_3), 1.41 (3H, s, CH_3), 1.66 (1H, ddd, *J* 13.7, 8.3, 5.9, CH_2), 1.96 (1H, ddd, *J* 13.2, 7.3, 6.8, CH_2), 4.66 (1H, t, *J* 7.8, CH), 5.95 (1H, s, OH), 7.15 - 7.40 (5H, m, Ar); $\delta_C(CDCl_3)$ 22.7 (CH_3), 23.1 (CH_3), 24.5 (CH_3), 24.6 (CH_3), 24.7 (CH_3), 24.8 (CH_3), 26.1 (CH), 35.8 (CH), 40.0 (CH_2), 48.0 (C_q), 55.4 (C_q), 1117.2 (C_q), 127.2 (CH), 127.2 (2 x CH), 129.5 (2 x CH), 142.4 (C_q), 171.2 (C_q), 198.1

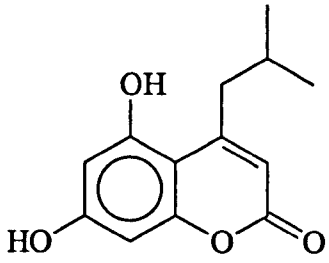
(C_q), 212.6 (C_q).

Ethyl 3-oxo-5-methylhexanoate 3.87



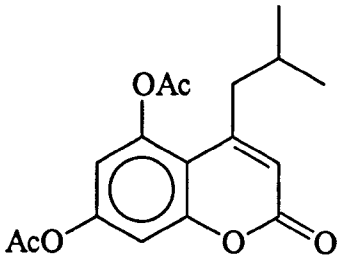
Diethylcarbonate (11.8 g, 0.1 mol) was added dropwise to a suspension of 60% sodium hydride (4 g, 0.1 mol) in dry diethyl ether (200 ml).After 30 mins, 4-methyl-2-pentanone (5 g, 0.05 mol) was added dropwise and the mixture refluxed for 6 h. On cooling to room temperature the solution was poured onto ice / water containing acetic acid (6 ml). The product was extracted with diethyl ether (3 x 100 ml), the combined extracts washed with water (200 ml), dried and evaporated under reduced pressure. The crude product was purified by column chromatography using 5% diethyl ether / petrol ether as eluant to afford the title compound **3.87** (7.8 g, 91%) as a colourless oil, n_D 1.4278; υ_{max} ($CHCl_3$)/cm^{-1} 3025, 2964, 2873, 1744, 1715, 1657, 1468, 1377; δ_H($CDCl_3$) 0.94 (6H, d, *J* 6.7, $CH(CH_3)_2$), 1.28 (3H, t, *J* 7.2, CH_2CH_3), 2.16 (1H, sept, *J* 6.7, CH), 2.42 (2H, d, *J* 7.0, CH_2CH), 3.41 (2H, s, CH_2), 4.19 (2H, q, *J* 7.3, CH_2); δ_C($CDCl_3$) 14.1 (CH_3), 22.4 (2 x CH_3), 24.3 (CH), 50.7 (CH_2), 51.9 (CH_2), 61.3 (CH_2), 167.2 (C_q), 202.5 (C_q).

5,7-Dihydroxy-4-(2-methylethyl)coumarin 3.88



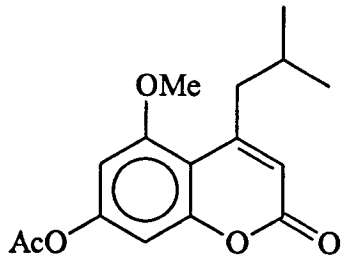
Conc. sulfuric acid (11 ml) was added dropwise to a solution of phloroglucinol **3.34** (5 g, 0.04 mol) and the β-ketoester **3.87** (6.8 g, 0.04 mol)in acetic acid (120 ml). After stirring at room temperature for 24 h, water (200 ml) was added and the product extracted with diethyl ether (3 x 100 ml), the combined extracts washed with water (200 ml), dried and evaporated under reduced pressure. The crude product was recrystallised from diethyl ether to afford the title compound **3.88** (8.4 g, 90%) as white crystals, m.p. 204 - 205 °C; υ_{max} ($CHCl_3$)/cm^{-1} 2956, 2869, 1659, 1603, 1460, 1352; δ_H[$(CD_3)_2CO$] 0.96 (6H, d, *J* 6.8, $CH(CH_3)_2$), 2.07 (1H, t sept, *J* 6.8, 6.4, $CH(CH_3)_2$), 2.82 (2H, d, *J* 6.8, CH_2), 5.82 (1H, s, CH=), 6.33 (1H, d, *J* 2.5, Ar), 6.41 (1H, d, *J* 2.4, Ar), 9.53 (2H, s, OH); δ_C[$(CD_3)_2CO$] 22.6 (2 x CH_3), 28.8 (CH), 45.7 (CH_2), 96.3 (CH), 100.3 (CH), 103.0 (C_q), 111.1 (CH), 158.0 (C_q), 158.4 (C_q), 161.1 (C_q), 161.7 (C_q).

5,7-Acetoxy-4-(2-methylethyl)coumarin 3.89



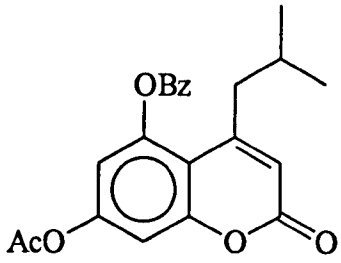
Acetic anhydride (8 ml) was added dropwise to a stirred solution of the coumarin **3.88** (4 g, 17 mmol) in pyridine (100 ml). After stirring at room temperature for 5 h, water (200 ml) was added and the product extracted with diethyl ether (3 x 100 ml), the combined extracts washed with water (200 ml), dried and evaporated under reduced pressure. The crude product was recrystallised from diethyl ether to afford the title compound **3.89** (5.2 g, 96%) as white crystals, m.p. 115 - 116 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3022, 2964, 1773, 1727, 1613, 1376; δ_H($CDCl_3$) 0.98 (6H, d, *J* 6.7, $CH(CH_3)_2$), 1.99 (1H, t sept, *J* 6.8, 6.6, $CH(CH_3)_2$), 2.33 (3H, s, $COCH_3$), 2.39 (3H, s, $COCH_3$), 2.66 (2H, d, *J* 7.1, CH_2), 6.17 (1H, s, CH=), 6.87 (1H, d, *J* 2.2, Ar), 7.07 (1H, d, *J* 2.5, Ar); δ_C($CDCl_3$) 21.1 (CH_3), 21.6 (CH_3), 22.5 (2 x CH_3), 27.2 (CH), 44.6 (CH_2), 108.7 (CH), 110.8 (C_q), 113.8 (CH), 116.4 (CH), 147.8 (C_q), 151.9 (C_q), 153.5 (C_q), 155.5 (C_q), 159.6 (C_q), 168.3 (C_q), 168.4 (C_q).

7-Acetoxy-5-methoxy-4-(2-methylethyl)coumarin 3.90



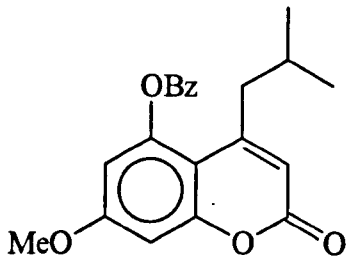
The coumarin **3.89** (1 g, 3.1 mmol), iodomethane (2.0 ml, 31 mmol) and potassium carbonate (1.2 g, 9.4 mmol) in dry acetone (30 ml) was refluxed for 4 h. On cooling,, the mixture was filtered and the filtrate evaporated under reduced pressure. The crude product was recrystallised from diethyl ether to afford the title compound **3.90** (0.17 g, 19%) as white crystals, m.p. 120 - 121 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3029, 2960, 1768, 1726, 1614, 1468, 1421, 1372; δ_H($CDCl_3$) 0.96 (6H, d, *J* 6.6, $CH(CH_3)_2$), 1.91 (1H, sept, *J* 6.6, $CH(CH_3)_2$), 2.34 (3H, s, CH_3CO), 2.74 (2H, d, *J* 6.6, CH_2), 3.90 (3H, s, OCH_3), 6.02 (1H, s, CH=), 6.54 (1H, d, *J* 2.2, Ar), 6.74 (1H, d, *J* 2.2, Ar); δ_C($CDCl_3$) 21.2 (CH_3), 22.4 (2 x CH_3), 28.1 (CH), 45.8 (CH_2), 56.2 (CH_3), 101.0 (CH), 103.6 (CH), 108.0 (C_q), 114.3 (CH), 153.1 (C_q), 156.2 (C_q), 158.3 (C_q), 160.7 (C_q), 168.7 (C_q).

7-Acetoxy-5-benzyloxy-4-(2-methylethyl)coumarin 3.91



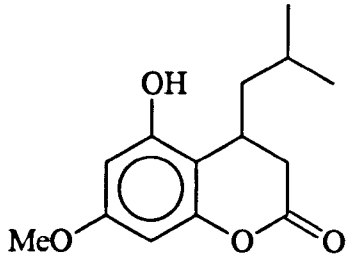
The coumarin **3.89** (3 g, 9.4 mmol), benzyl chloride (3.0 ml, 26 mmol) potassium iodide (3 g, 18 mmol) and potassium carbonate (9 g, 88 mmol) in dry acetone (100 ml) was refluxed for 3 h. On cooling,, the mixture was filtered and the filtrate evaporated under reduced pressure. The crude product was recrystallised from diethyl ether to afford the title compound **3.91** (3.4 g, 96%) as white crystals, m.p. 119 - 120 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3031, 2963, 2869, 1771, 1726, 1621, 1433, 1372; δ_H($CDCl_3$) 0.60 (6H, d, *J* 6.6, $CH(CH_3)_2$), 1.81 (1H, sept, *J* 6.7, $CH(CH_3)_2$), 2.34 (3H, s, CH_3CO), 2.62 (2H, d, *J* 6.8, CH_2), 5.05 (2H, s, CH_2), 6.00 (1H, s, CH=), 6.66 (1H, s, Ar), 6.76 (1H, s, Ar), 7.42 (5H, m, Ar); δ_C($CDCl_3$) 21.2 (CH_3), 21.8 (2 x CH_3), 27.6 (CH), 45.6 (CH_2), 71.9 (CH_2), 101.8 (CH), 103.8 (CH), 108.1 (C_q), 114.7 (CH), 128.5 (5 x CH), 134.8 (C_q), 153.0 (C_q), 156.2 (C_q), 156.3 (C_q), 157.5 (C_q), 160.3 (C_q), 168.7 (C_q).

5-Benzyloxy-7-methoxy-4-(2-methylethyl)coumarin 3.92



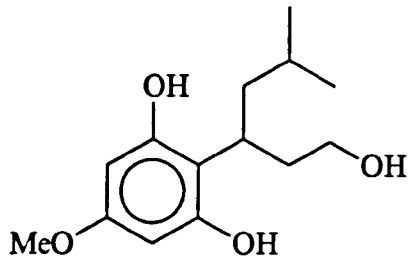
The coumarin **3.91** (0.9 g, 2.6 mmol), iodomethane (1.5 ml, 26 mmol) and potassium carbonate (3.5 g, 26 mmol) in dry acetone (10 ml) was refluxed for 24 h. On cooling, the mixture was filtered and the filtrate evaporated under reduced pressure. The crude product was columned using 20% diethyl ether / petrol ether to afford the title compound **3.92** (0.54 g, 65%) as white crystals, m.p. 146 - 147 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3016, 2960, 2873, 1715, 1624, 1606, 1376, 1354; δ_H($CDCl_3$) 0.63 (6H, d, *J* 6.6, $CH(CH_3)_2$), 1.82 (1H, sept, *J* 6.6, $CH(CH_3)_2$), 2.61 (2H, d, *J* 6.9, CH_2), 3.84 (3H, s, OCH_3), 5.05 (2H, s, CH_2), 5.89 (1H, s, CH=), 6.41 (1H, d, *J* 2.5, Ar), 6.48 (1H, d, *J* 2.5, Ar), 7.39 - 7.42 (5H, m, Ar); δ_C($CDCl_3$) 22.0 (2 x CH_3), 27.8 (CH), 45.5 (CH_2), 55.7 (CH_3), 71.6 (CH_2), 93.8 (CH), 96.5 (CH), 104.4 (C_q), 112.2 (CH), 128.6 (2 x CH), 128.7 (CH), 128.8 (2 x CH), 135.3 (C_q), 156.9 (C_q), 157.5 (C_q), 157.8 (C_q), 161.0 (C_q), 162.5 (C_q).

5-Hydroxy-7-methoxy-4-(2-methylethyl)-3,4-dihydrocoumarin 3.93



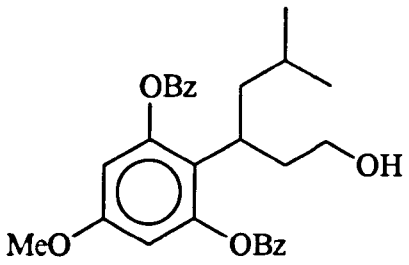
A solution of the coumarin **3.92** (0.6 g, 1.8 mmol) and 10% Pd on C (0.6 g) in ethanol (10 ml) was stirred at 80 °C under 20 ATM of hydrogen for 16 h. On cooling,, the mixture was filtered and the filtrate evaporated under reduced pressure to afford the title compound **3.93** (0.44 g, 99%) as white crystals, m.p. 94 - 95 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3024, 2972, 1772, 1630, 1604, 1515, 1444; δ_H[$(CD_3)_2CO$] 0.89 (3H, d, *J* 6.6, $CH(CH_3)_2$), 0.96 (3H, d, *J* 6.6, $CH(CH_3)_2$), 1.26 (1H, m, CH_2), 1.35 (1H, m, CH_2), 1.69 (1H, sept, *J* 6.6, $CH(CH_3)_2$), 2.71 (2H, m, CH_2), 3.40 (1H, m, CH), 3.70 (3H, s, OCH_3), 6.08 (1H, d, *J* 2.2, Ar), 6.37 (1H, d, *J* 2.4, Ar); δ_C[$(CD_3)_2CO$] 22.4 (CH_3), 23.5 (CH_3), 25.8 (CH), 27.6 (CH_2), 34.9 (CH), 44.3 (CH_2), 55.5 (CH_3), 94.1 (CH), 98.5 (CH), 108.2 (C_q), 153.7 (C_q), 156.5 (C_q), 160.5 (C_q), 168.9 (C_q).

3-(2,6-Dihydroxy-4-methoxyphenyl)-5-methylhexanol 3.94



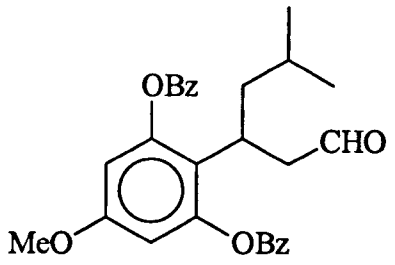
A solution of the dihydrocoumarin **3.93** (0.4 g, 1.6 mmol) in diethyl ether (10 ml) was added dropwise to a suspension of lithium aluminium hydride (0.18 g, 4.8 mmol) in diethyl ether (40 ml) at 0°C. After warming to room temperature over 2h, 2N hydrochloric acid (20 ml) was added and the product extracted with diethyl ether (3 x 50 ml). The combined extracts were washed with water (100 ml) dried and evaporated under reduced pressure to afford the title compound **3.94** (0.4 g, 98%) as a semi-solid; υ_{max} ($CHCl_3$)/cm^{-1} 3370, 3015, 2965, 1629, 1602, 1510, 1467, 1437; δ_H($CDCl_3$) 0.83 (3H, d, *J* 6.1, $CH(CH_3)_2$), 0.85 (3H, d, *J* 6.3, $CH(CH_3)_2$), 0.98 (1H, m, CH), 1.37 (2H, m, CH_2), 1.88 (2H, m, CH_2), 2.12 (1H, m, CH), 3.37 (2H, m, CH_2O), 3.71 (3H, s, OCH_3), 5.30 (2H, s, 2 x OH), 6.04 (2H, s, Ar); δ_C($CDCl_3$) 21.8 (CH_3), 23.6 (CH_3), 26.4 (CH_2), 29.1 (CH), 35.8 (CH), 42.8 (CH_2), 55.1 (CH_3), 61.4 (CH_2), 94.3 (2 x CH), 108.4 (C_q), 157.2 (2 x C_q), 158.8 (C_q).

3-(2,6-Dibenzyloxy-4-methoxyphenyl)-5-methylhexanol 3.95



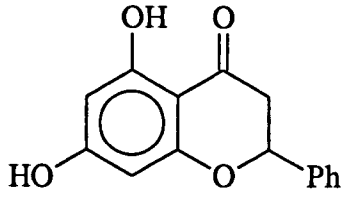
A solution of the alcohol **3.94** (0.39 g, 1.5 mmol), benzyl chloride (0.39 g, 3.8 mmol), potassium iodide (0.6 g, 3.8 mmol) and potassium carbonate (0.4 g, 3.8 mmol) in acetone (40 ml) was refluxed for 24h. On cooling, the mixture was filtered and the filtrate evaporated under reduced pressure. The crude product was purified by column chromatography using 30% diethyl ether / petrol ether as eluant to afford the title compound **3.95** (0.55 g, 85%) as white crystals, m.p. 57 - 59 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3009, 2956, 2876, 1608, 1467, 1383; δ_H($CDCl_3$) 0.80 (3H, d, *J* 6.3, $CH(CH_3)_2$), 0.87 (3H, d, *J* 6.3, $CH(CH_3)_2$), 1.20 (1H, m, CH), 1.26 (2H, m, CH_2), 1.75 (1H, m, CH), 2.00 (2H, m, CH_2), 3.47 (2H, m, CH_2O), 3.75 (3H, s, OCH_3), 5.02 (4H, s, 2 x CH_2Ph), 6.22 (2H, s, Ar), 7.33 - 7.43 (10H, m, Ar); δ_C($CDCl_3$) 22.0 (CH_3), 23.6 (CH_3), 26.3 (CH_2), 29.0 (CH), 36.8 (CH), 42.9 (CH_2), 55.2 (CH_3), 61.7 (CH_2), 70.2 (CH_2), 70.9 (CH_2), 91.8 (CH), 92.8 (CH), 112.1 (C_q), 127.4 (C_q), 127.4 (2 x CH), 127.5 (2 x CH), 127.9 (CH), 128.1 (C_q), 128.2 (CH), 128.5 (2 x CH), 128.7 (2 x CH), 158.9 (C_q), 159.1 (C_q).

3-(2,6-Dibenzyloxy-4-methoxyphenyl)-5-methylhexanal 3.96



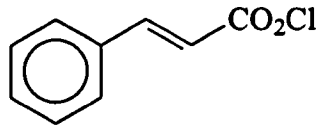
A solution of the alcohol **3.95** (0.15 g, 0.35 mmol) in dichloromethane (10 ml) was added dropwise to a suspension of pyridinium chlorochromate (0.15 g, 0.7 mmol) in dichloromethane (5 ml). After stirring for 1h, the solvent was evaporated under reduced pressure. The crude product was purified by column chromatography using 30% diethyl ether / petrol ether as eluant to afford the title compound **3.96** (0.097 g, 65%) as white crystals, m.p. 64 - 65 °C; υ_{max} ($CHCl_3$)/cm^{-1} 3035, 3013, 2959, 1721, 1611, 1501, 1467, 1383; δ_H($CDCl_3$) 0.79 (3H, d, *J* 6.3, $CH(CH_3)_2$), 0.84 (3H, d, *J* 6.0, $CH(CH_3)_2$), 1.32 (2H, m, CH_2), 1.96 (1H, m, CH), 2.58 (1H, m, CH_2), 2.80 (1H, m, CH_2), 3.72 (3H, s, OCH_3), 4.03 (1H, m, CH), 5.03 (4H, s, 2 x CH_2Ph), 6.18 (2H, s, Ar), 7.30 - 7.43 (10H, m, Ar), 9.56 (1H, t, *J* 2.8, CHO); δ_C($CDCl_3$) 22.1 (CH_3), 23.5 (CH_3), 26.1 (CH_2), 27.6 (CH), 42.8 (CH), 48.2 (CH_2), 55.2 (CH_3), 70.5 (2 x CH_2), 92.2 (2 x CH), 111.8 (C_q), 127.4 (C_q), 127.4 (4 x CH), 127.9 (4 x CH), 128.6 (2 x CH), 137.0 (2 x C_q), 159.0 (2 x C_q), 159.4 (C_q), 204.3 (CH).

5,7-Dihydroxy-2-phenylflavanone 3.98



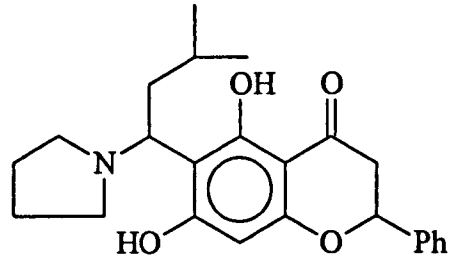
Cinnamoyl chloride **3.99** (2.7 g, 0.016 mol) was added dropwise to a stirred solution of phloroglucinol **3.34** (2 g, 0.016 mol) and aluminium trichloride (4.2 g, 0.032 mol) in dry nitrobenzene (50 ml). After stirring at RT for 1 h, the mixture was refluxed for 1 h. On cooling, 2N sodium hydroxide solution (50 ml) was added and the mixture washed with diethyl ether (3 x 50 ml). The aqueous layer was acidified and the product extracted with diethyl ether (3 x 50 ml). The combined extracts were washed with water, dried and evaporated. The crude product was columned using 30% diethyl ether / petrol ether as eluant to afford the title compound **3.98** (0.68 g, 17%) as white crystals; υ_{max} ($CHCl_3$)/cm^{-1} 2925, 1646, 1598, 1457; δ_H($CDCl_3$) 2.81 (1H, m, CH_2), 3.18 (1H, m, CH_2), 5.58 (1H, m, CH), 5.97 (1H, s, Ar), 6.01 (1H, s, Ar), 7.20 - 7.91 (5H, m, Ar), 9.71 (1H, s, OH), 12.17 (1H, s, OH); δ_C($CDCl_3$) 43.6 (CH_2), 80.0 (CH), 95.9 (CH), 96.9 (CH), 103.2 (C_q), 127.3 (2 x CH), 129.4 (CH), 129.5 (2 x CH), 140.1 (C_q), 164.2 (C_q), 165.3 (C_q), 167.4 (C_q), 196.9 (C_q).

Cinnamoyl chloride 3.99



Oxalyl chloride (13 g, 0.1 mol) was added dropwise to a stirred solution of cinnamic acid (10 g, 0.068 mol) in dry benzene (50 ml). Triethylamine (10 mg) was added and the mixture stirred at room temperature for 4 h. Evaporation under reduced pressure afforded the title compound **3.99** (11.2 g, 99%) as a colourless oil; υ_{max} ($CHCl_3$)/cm^{-1} 3027, 1687, 1633, 1448, 1417, 1310.

5,7-Dihydroxy-2-phenyl-6-[1-pyrrolidine-3-methylbutyl]-flavanone 3.100



Isovaleraldehyde (0.092 g, 9.8 mmol) in diethyl ether (5 ml) was added dropwise to a stirred solution of the flavanone **3.98** (0.1 g, 3.9 mmol) and pyrrolidine (0.069 g, 9.8 mmol) in diethyl ether (20 ml). After stirring at RT for 2 h, methanol (10 ml) was added and the solvent evaporated to afford the title compound **3.100** (0.1 g, 65%) as a mixture of diastereomers and as a light brown semi-solid; υ_{max} ($CHCl_3$)/cm^{-1} 2961, 2933, 2868, 1644, 1453, 1375,

1344; $\delta_H(CDCl_3)$ 0.89 (3H, d, *J* 6.3, CH_3) & 0.92 (3H, d, *J* 6.3, CH_3), 0.98 (3H, d, *J* 6.3, CH_3) & 1.04 (3H, d, *J* 6.3, CH_3), 1.4 (1H, m, CH), 1.64 (2H, m, CH_2), 1.91 (4H, m, 2 x CH_2), 2.81 (4H, m, CH_2), 3.08 (2H, m, CH_2), 4.07 (1H, t, *J* 7.3, CH), 5.42 (1H, m, CH), 5.95 (1H, s, CH) & 5.96 (1H, s, CH), 7.32 - 7.50 (5H, m, Ar), 11.7br (2H, s, 2 x OH); $\delta_C(CDCl_3)$ 22.3 & 22.4 (CH_3), 23br (2 x CH_2), 24.4 & 24.4 (CH_3), 25.1 & 25.2 (CH), 42.3 & 42.3 (CH_2), 43.2 & 43.5 (CH_2), 51br (2 x CH_2), 60.6 & 60.6 (CH), 78.8 & 78.8 (CH), 96.8 & 97.1 (CH), 100.6 & 100.7 (C_q), 106.0 & 106.1 (C_q), 126.1 & 126.1 (2 x CH), 128.6 & 128.8 (2 x CH), 128.7 (CH), 138.9 & 138.9 (C_q), 161.0 & 161.0 (C_q), 162.3 & 162.3 (C_q), 171.1 & 171.3 (C_q), 194.6 & 194.9 (C_q).

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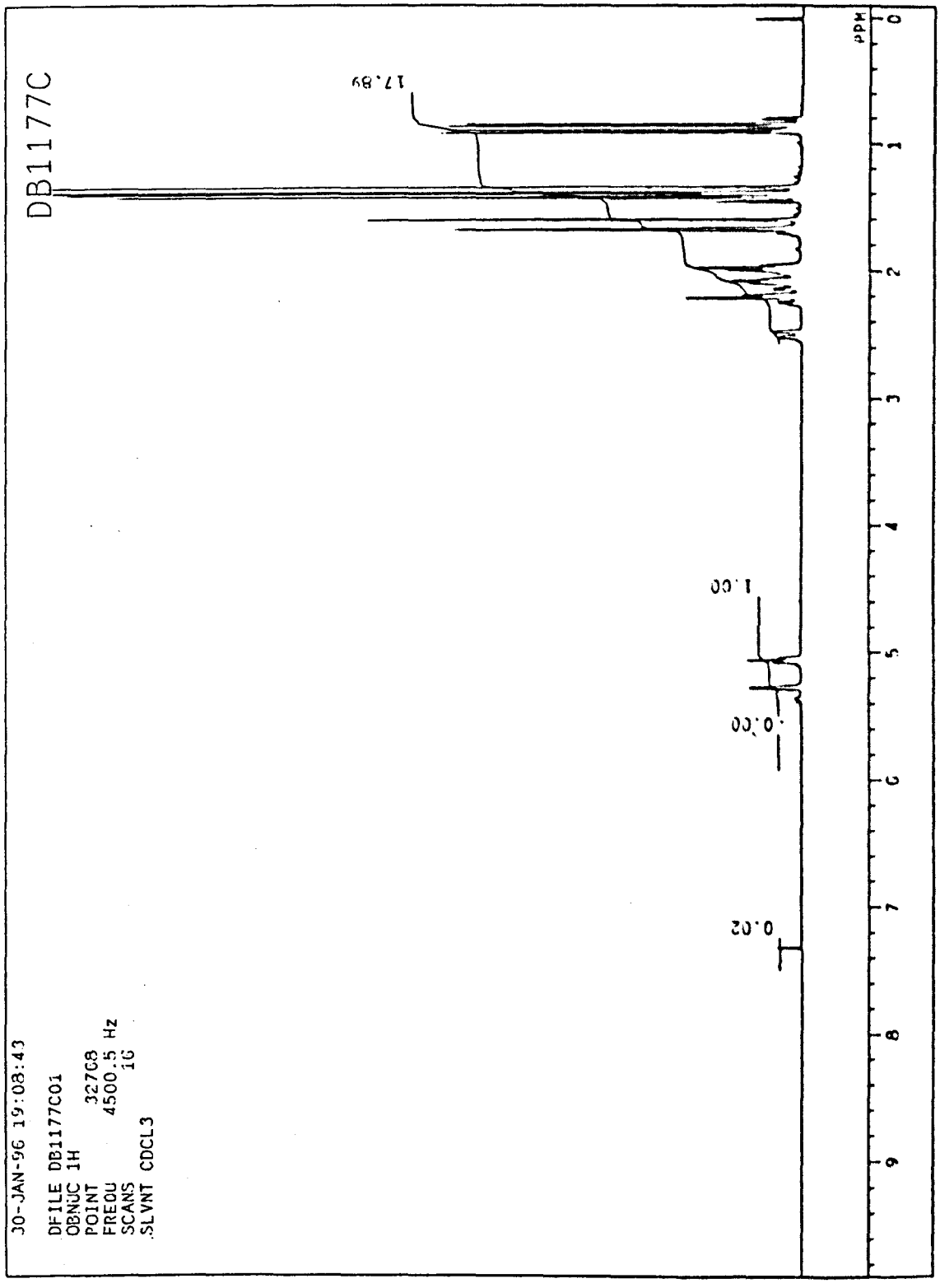
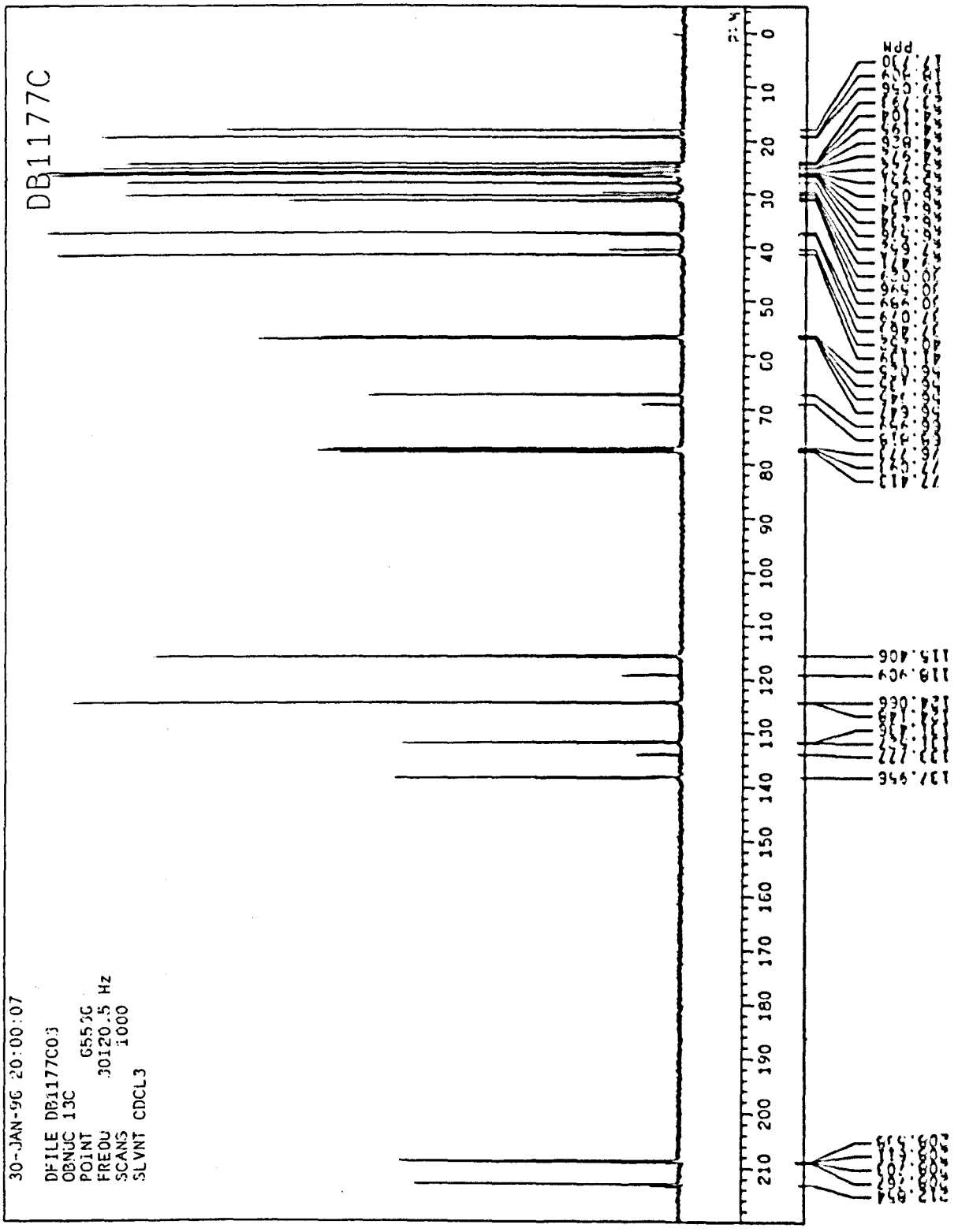
APPENDIX

^{1}H and ^{13}C NMR SPECTRA OF COMPOUNDS 1 TO 9

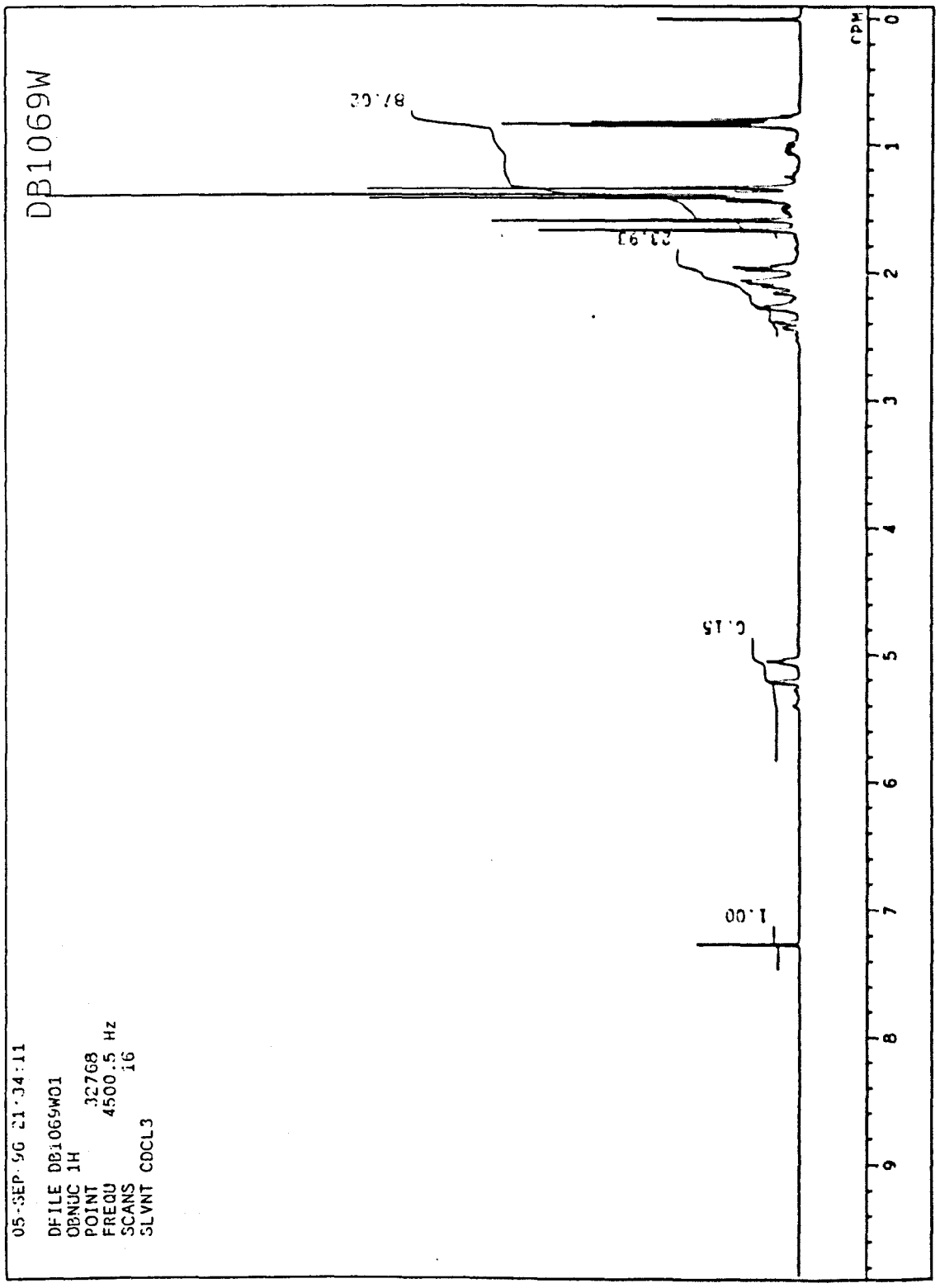
^{1}H NMR spectrum of compound 1



^{13}C NMR spectrum of compound 1



^{1}H NMR spectrum of compound 2a



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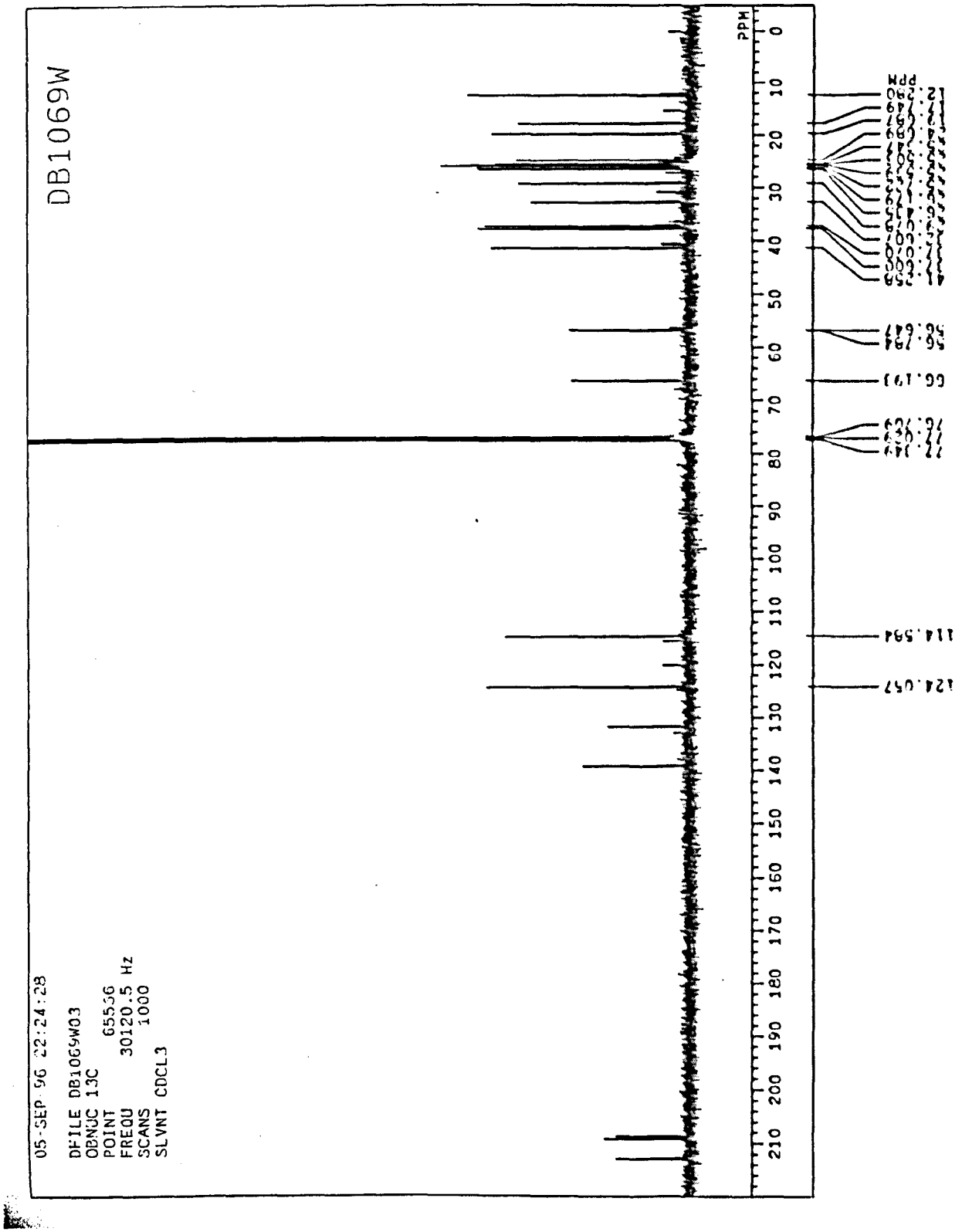
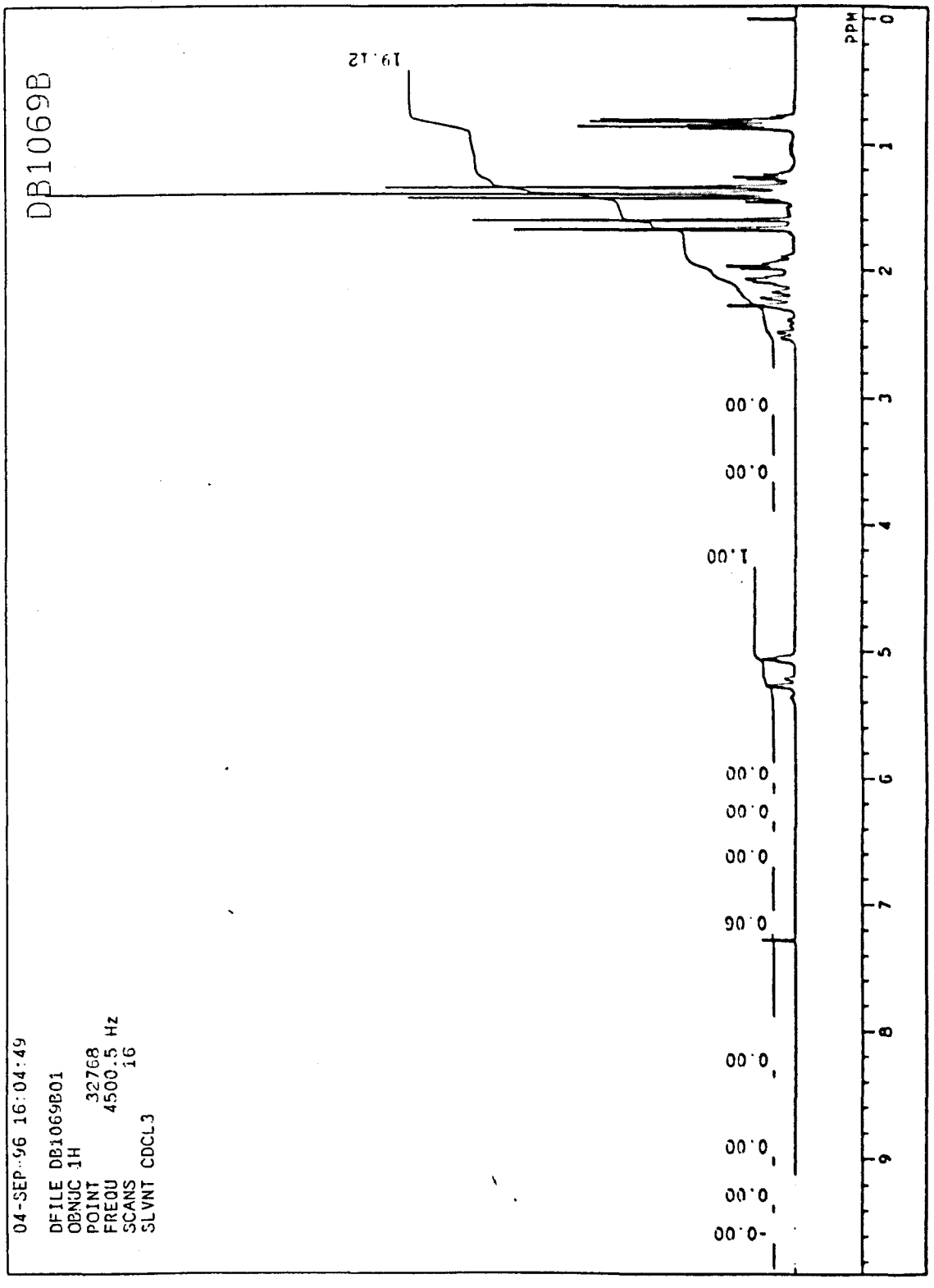
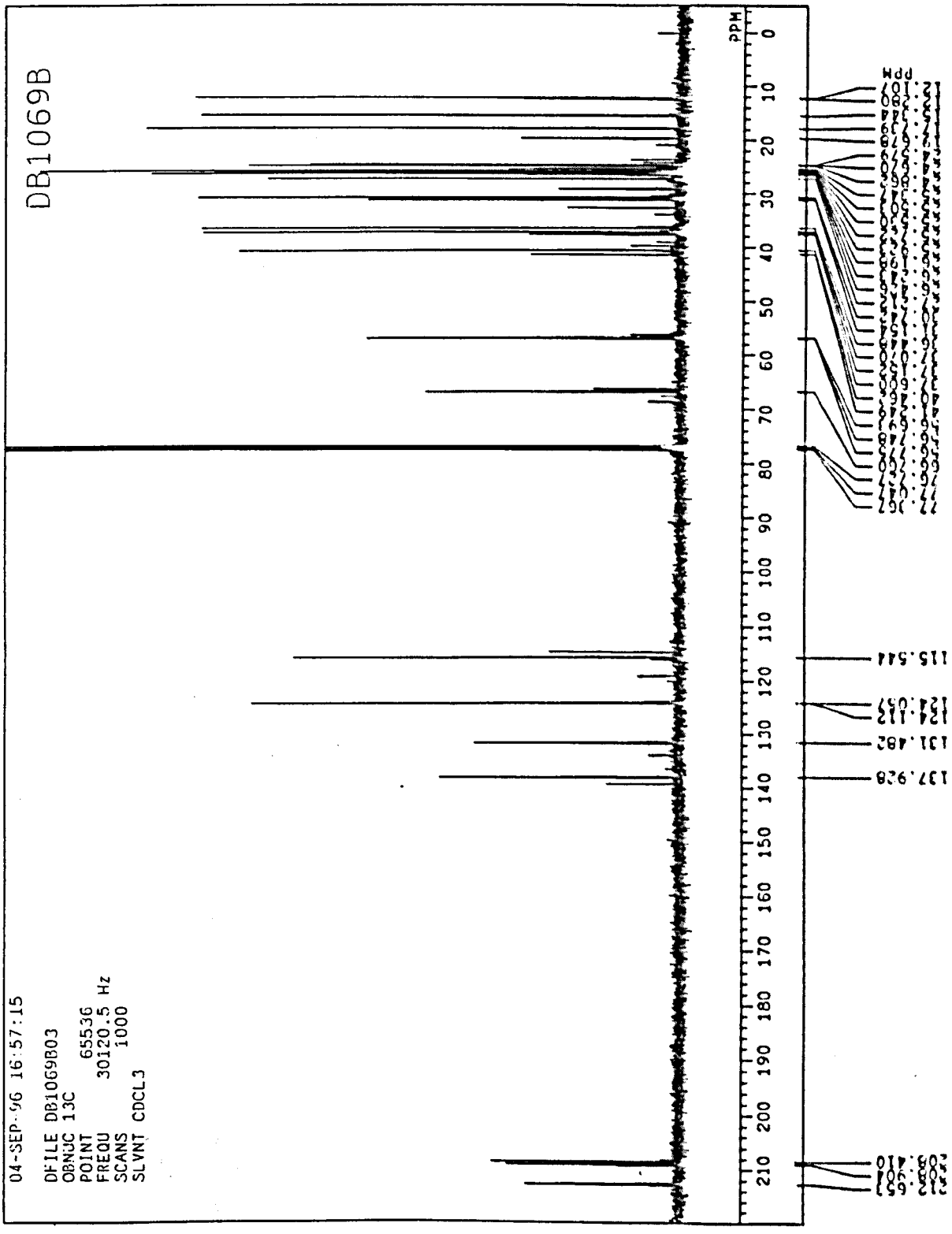


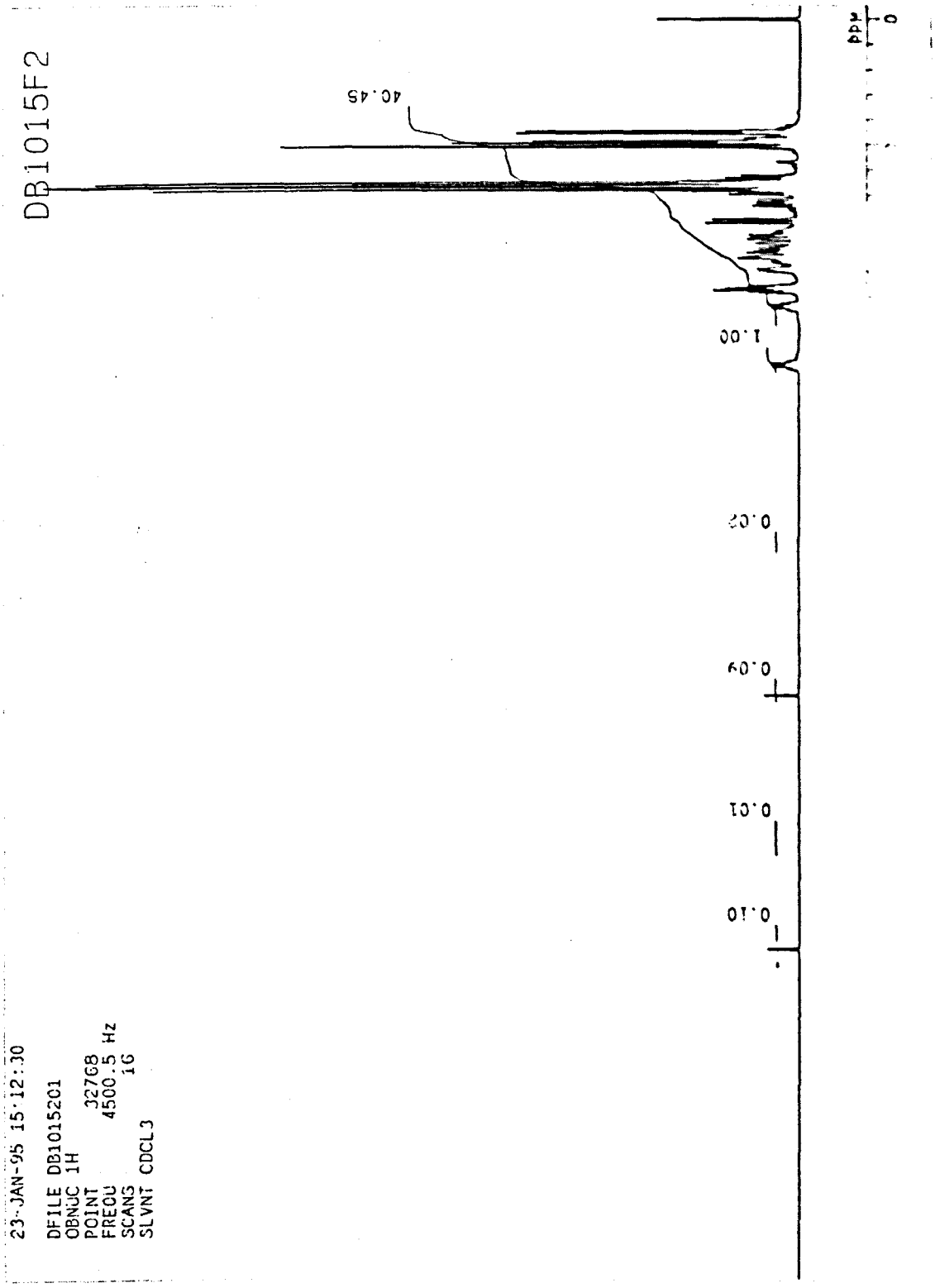
^{1}H NMR spectrum of compound 2b



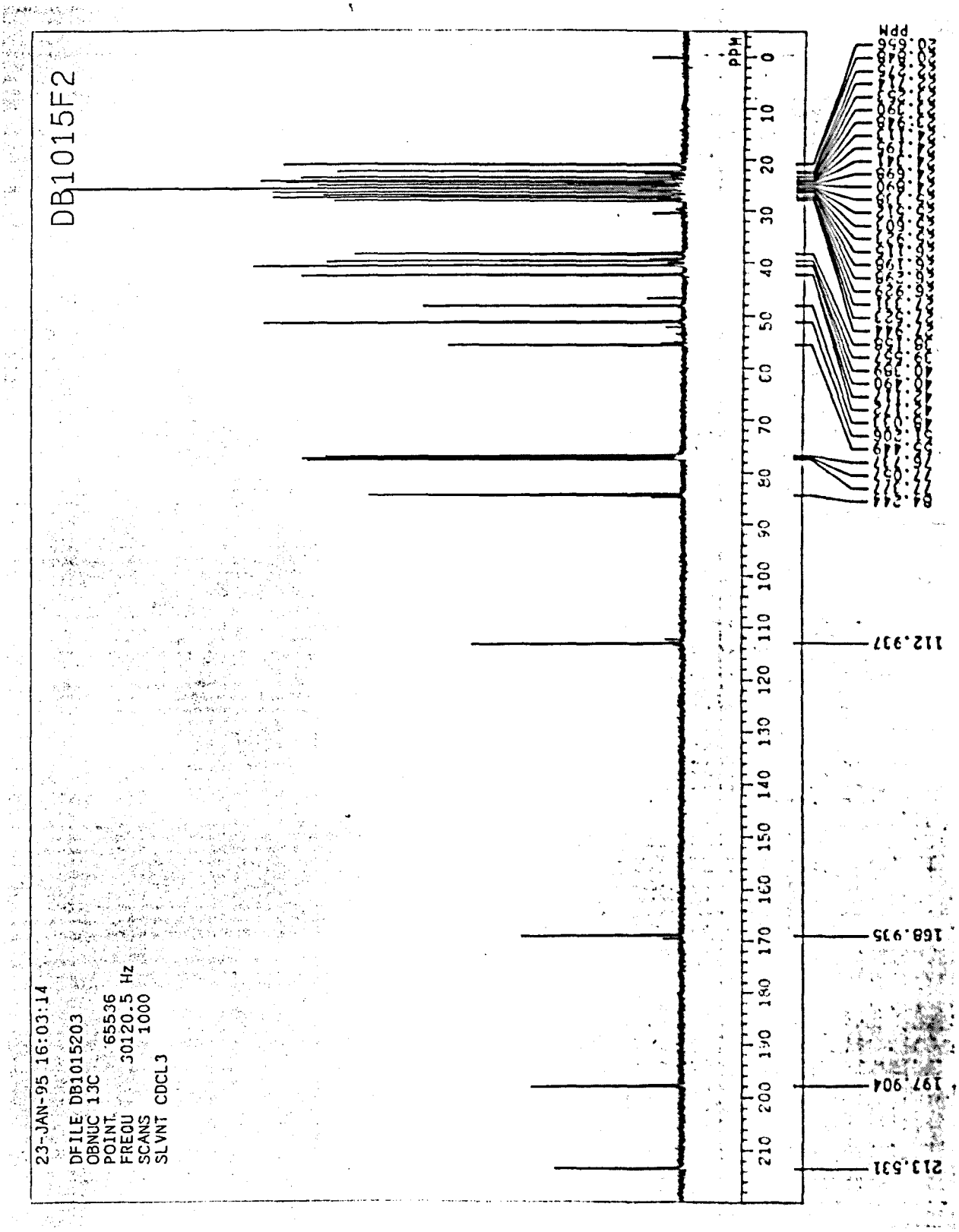
^{13}C NMR spectrum of compound 2b



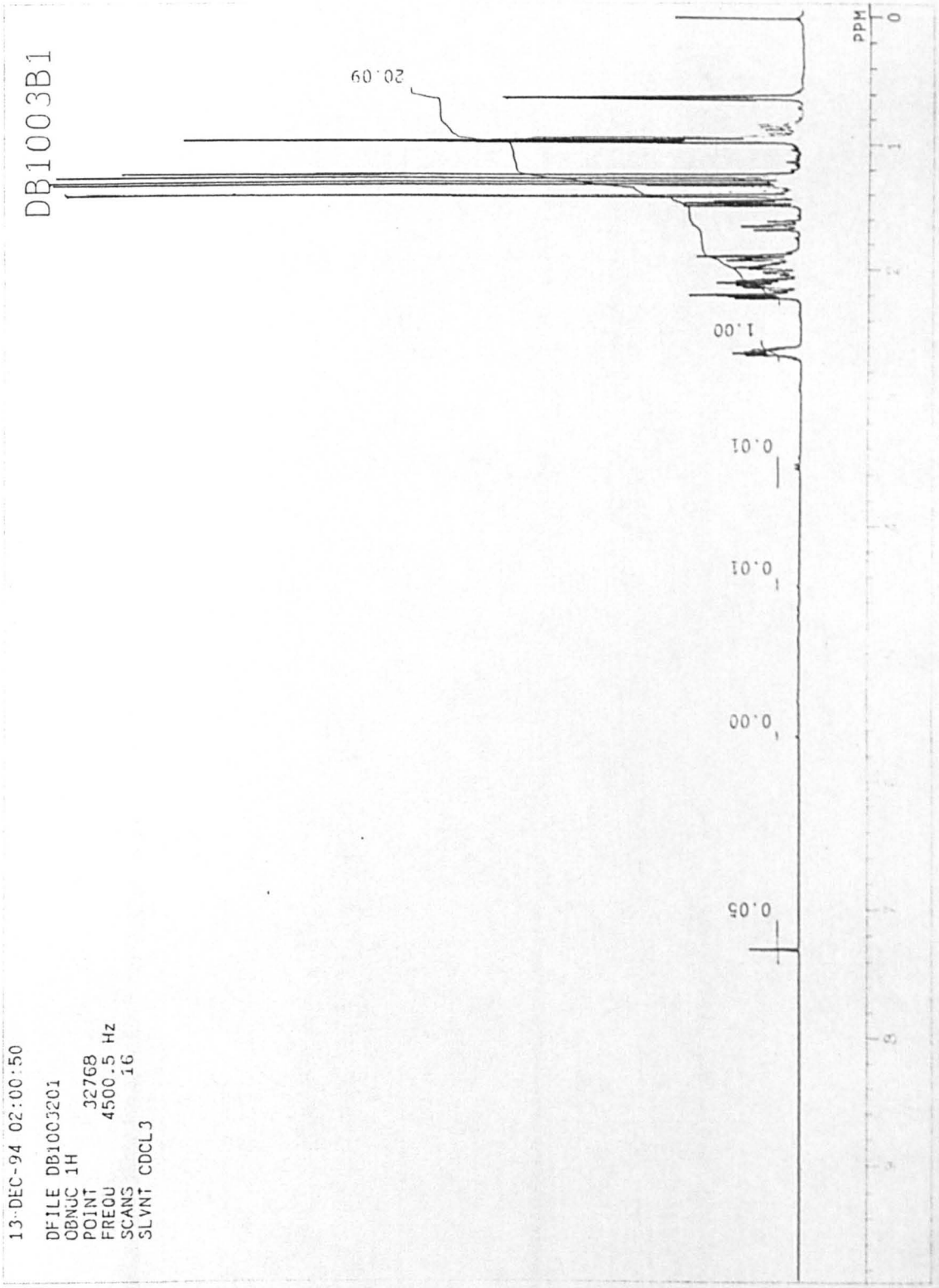
^{1}H NMR spectrum of compound 3



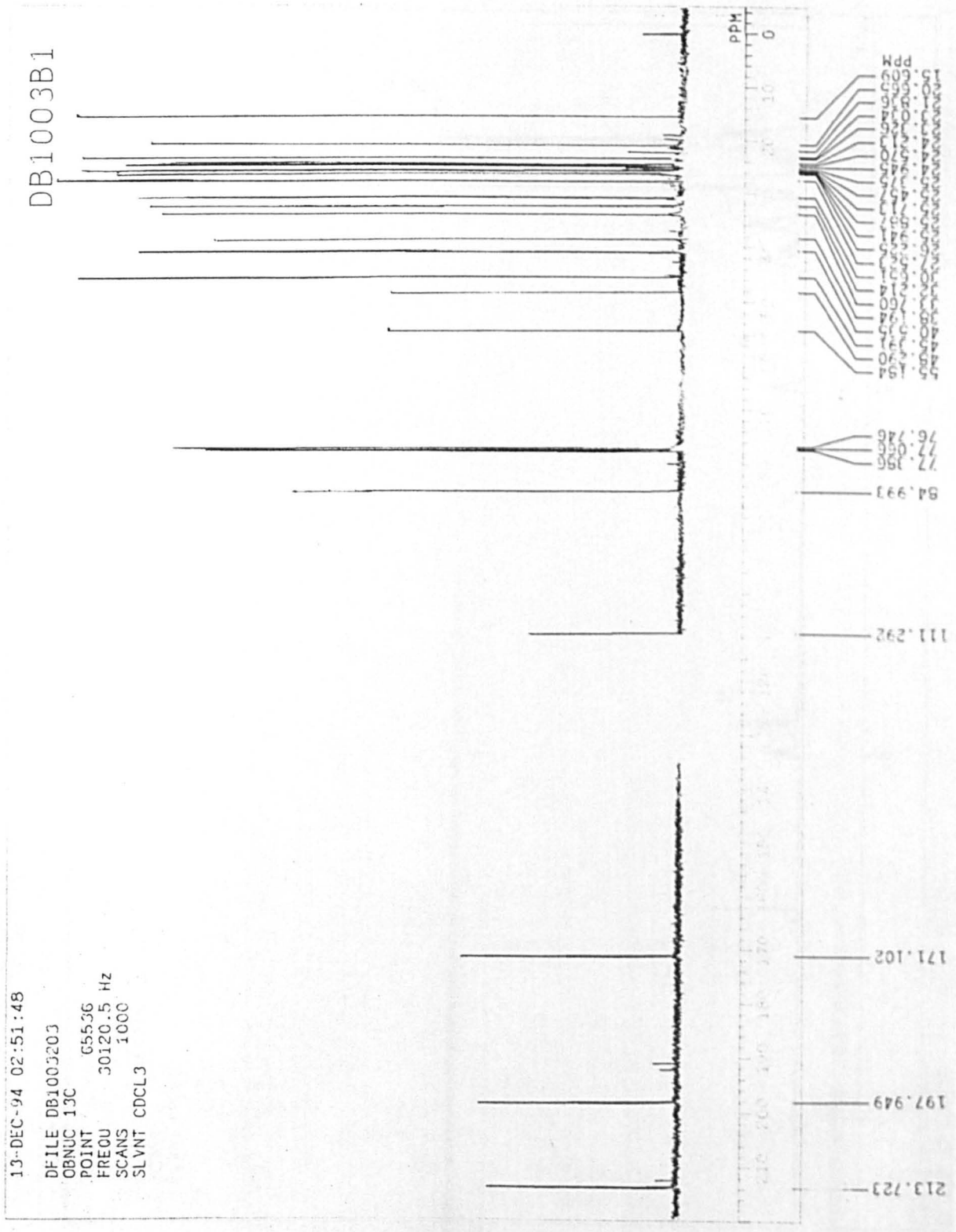
^{13}C NMR spectrum of compound 3



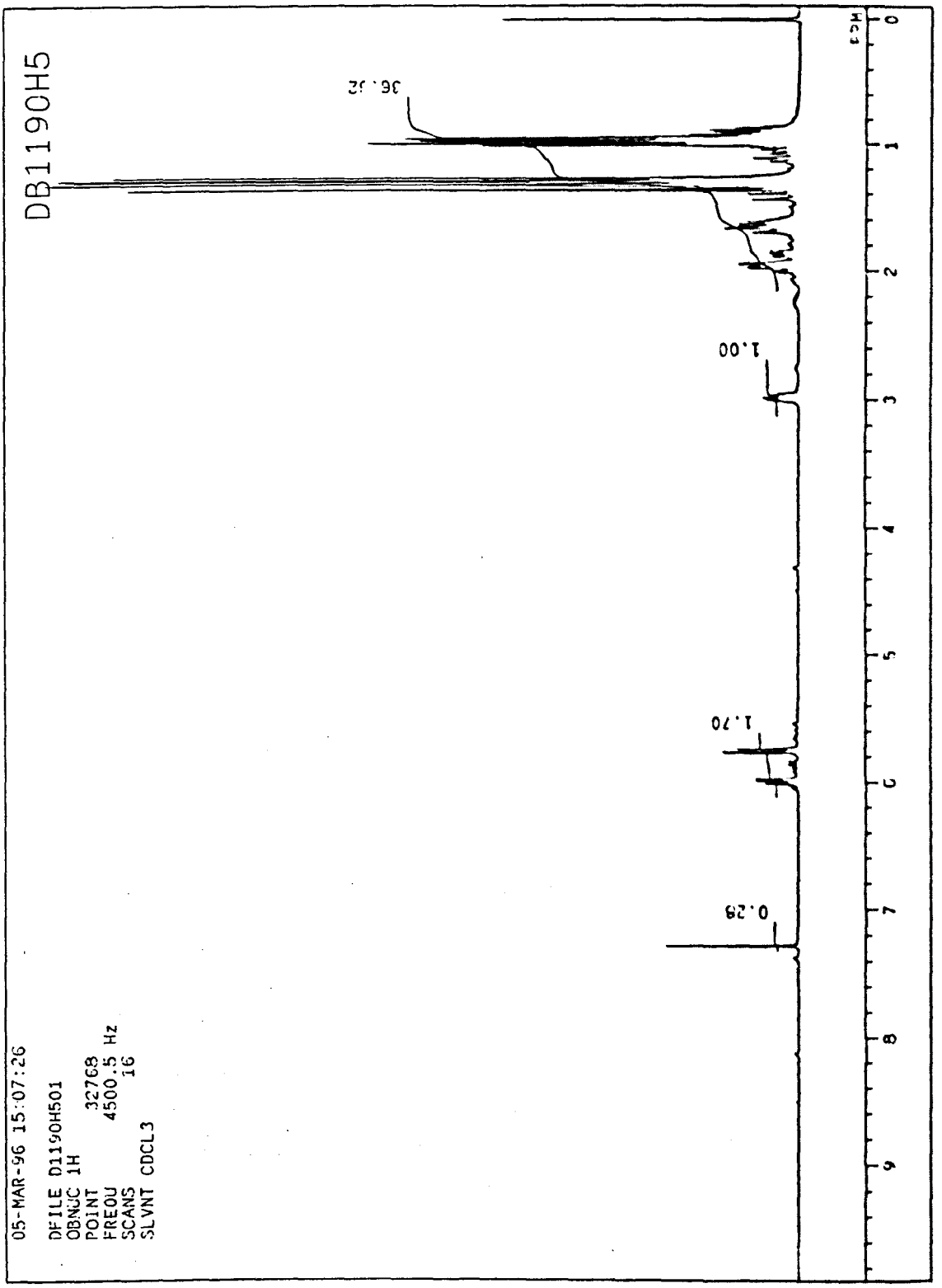
^{1}H NMR spectrum of compound 4



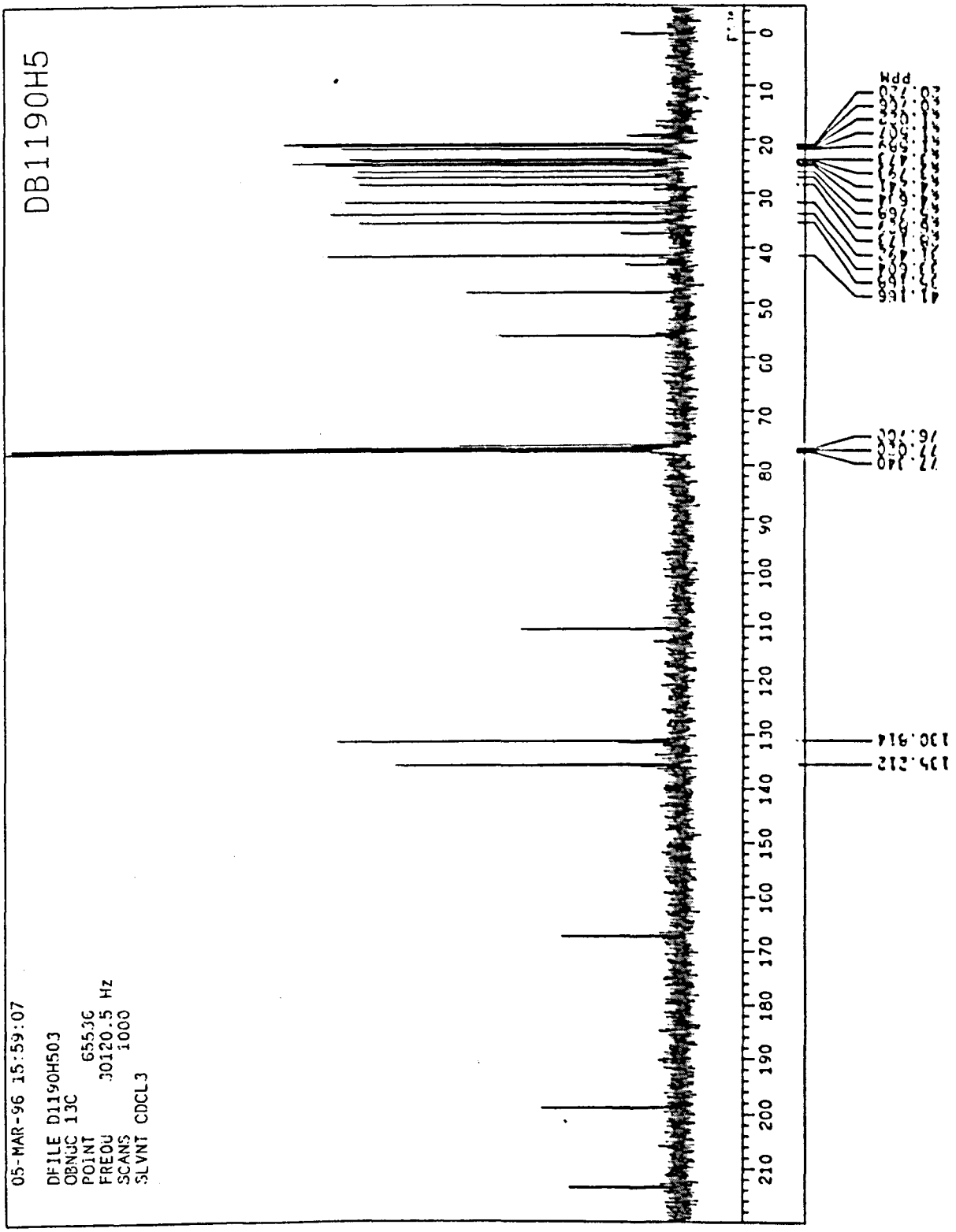
^{13}C NMR spectrum of compound 4



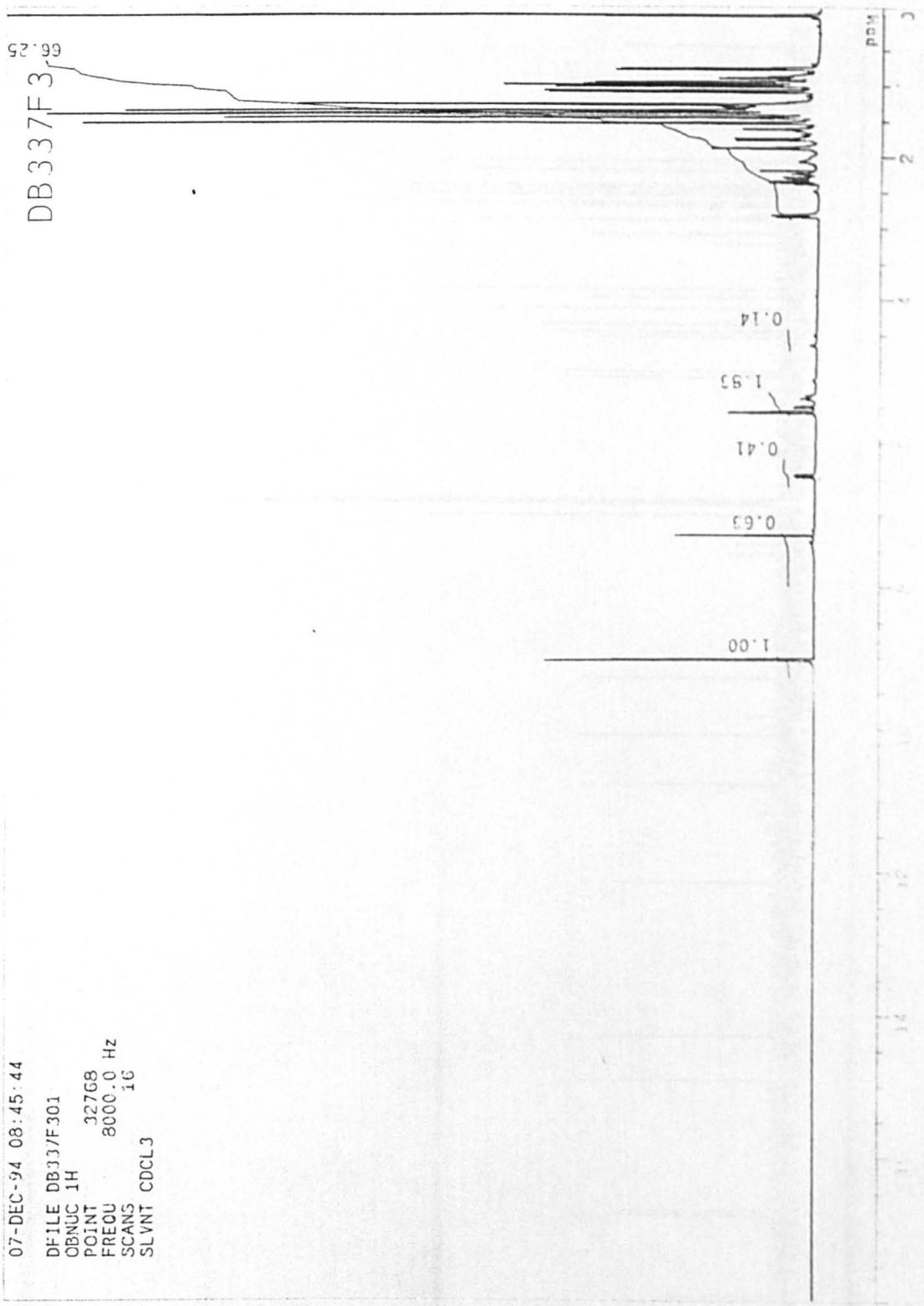
^{1}H NMR spectrum of compound 5a



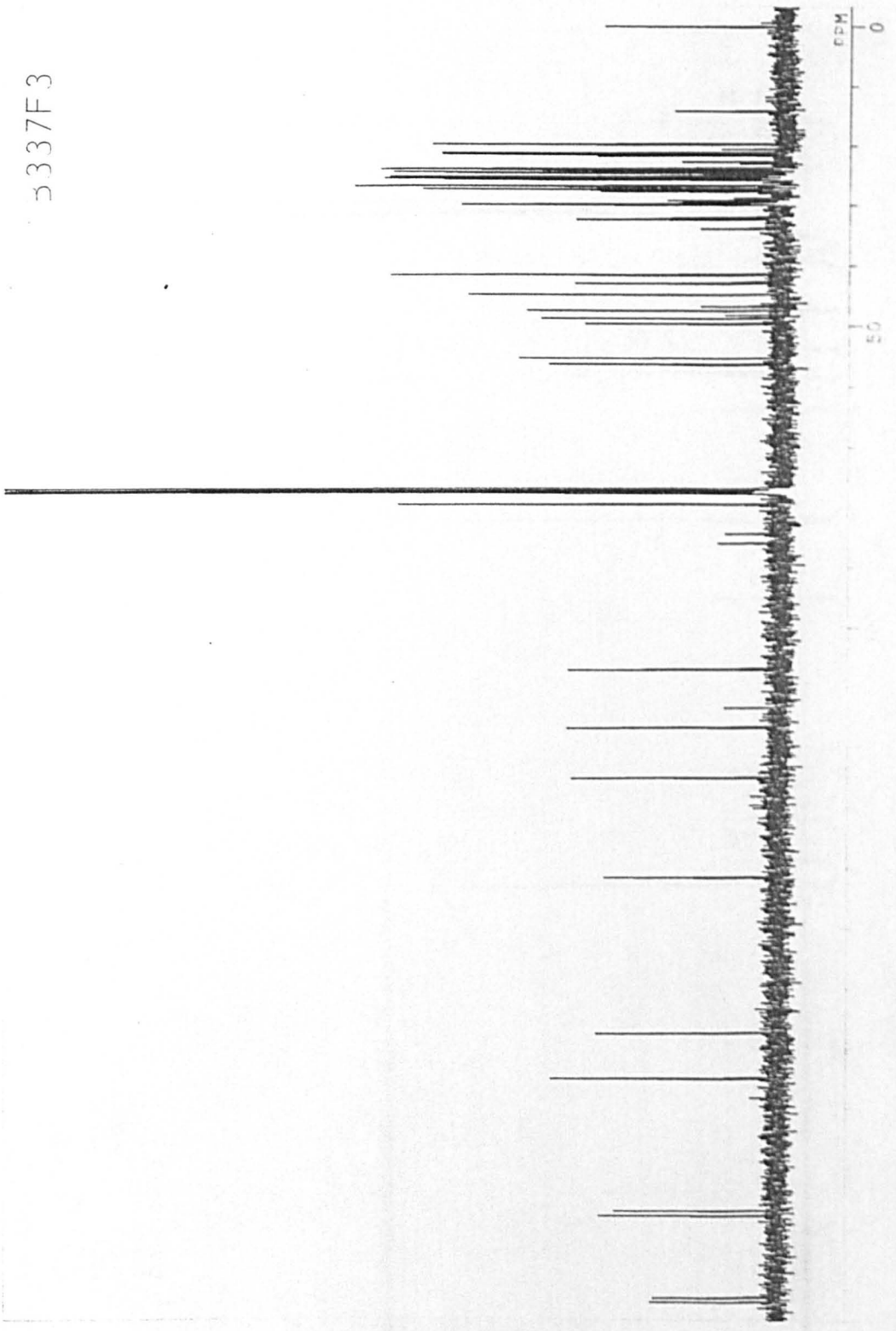
^{13}C NMR spectrum of compound 5a



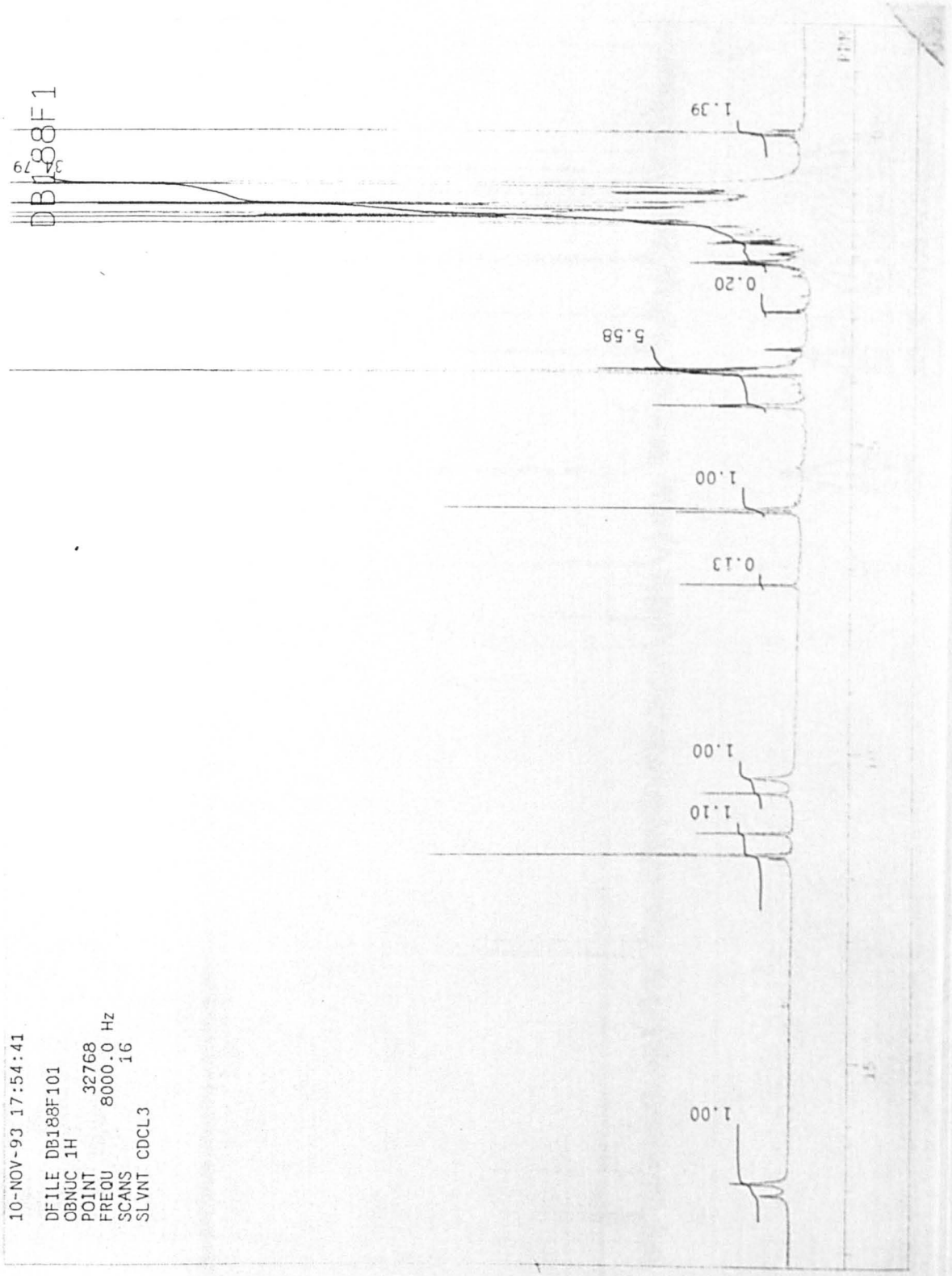
^{1}H NMR spectrum of compound 6



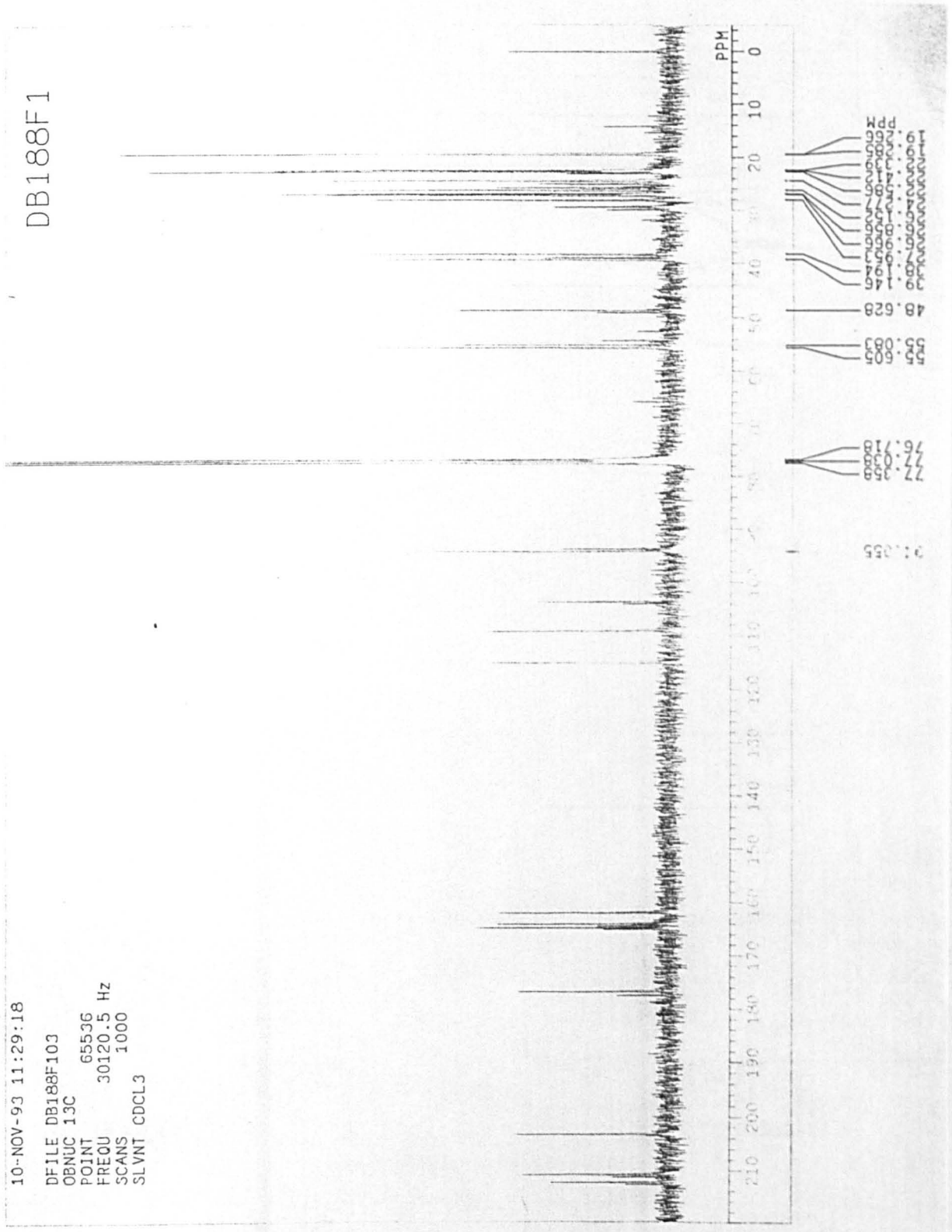
^{13}C NMR spectrum of compound 6



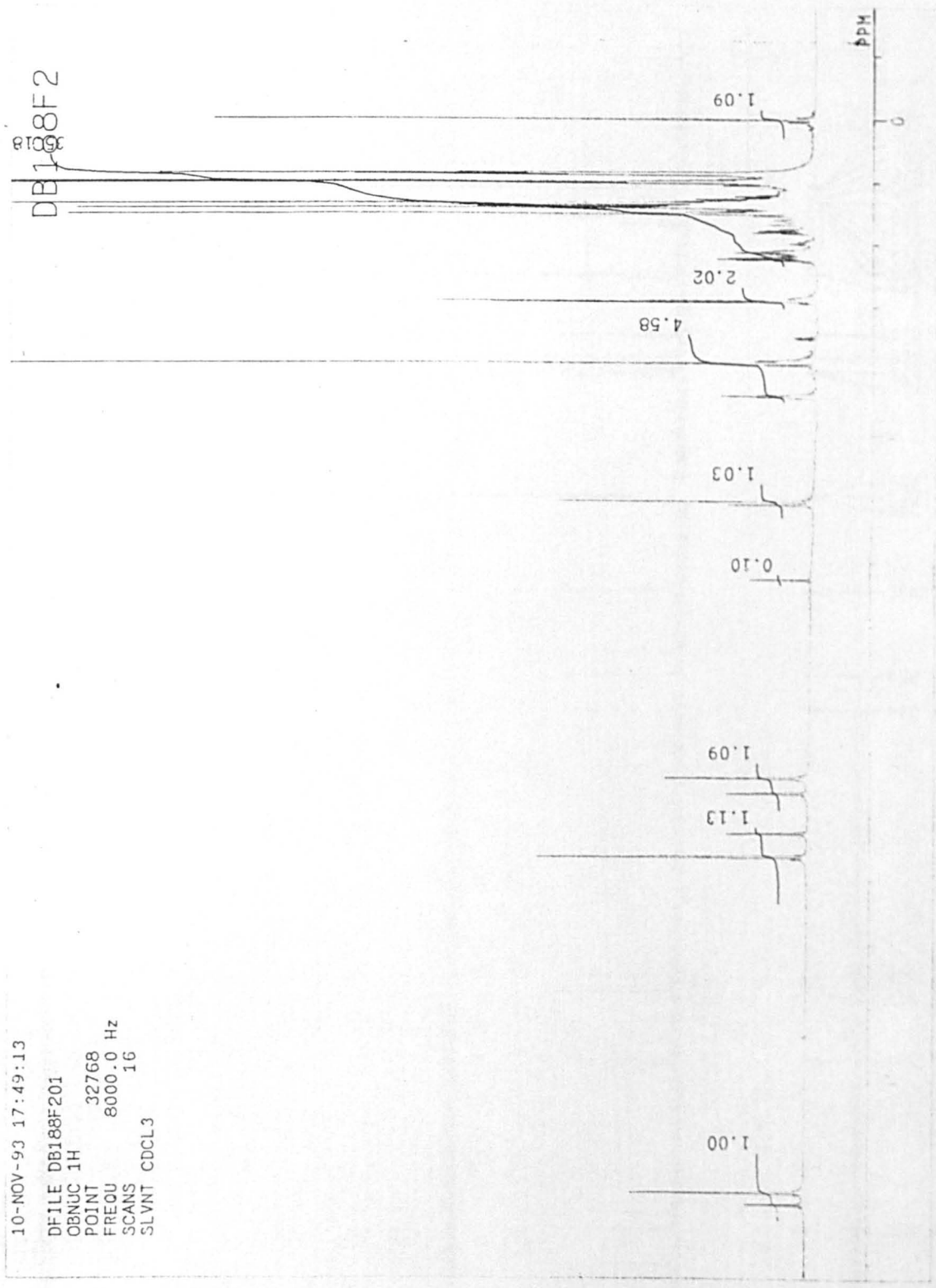
^{1}H NMR spectrum of compound 7



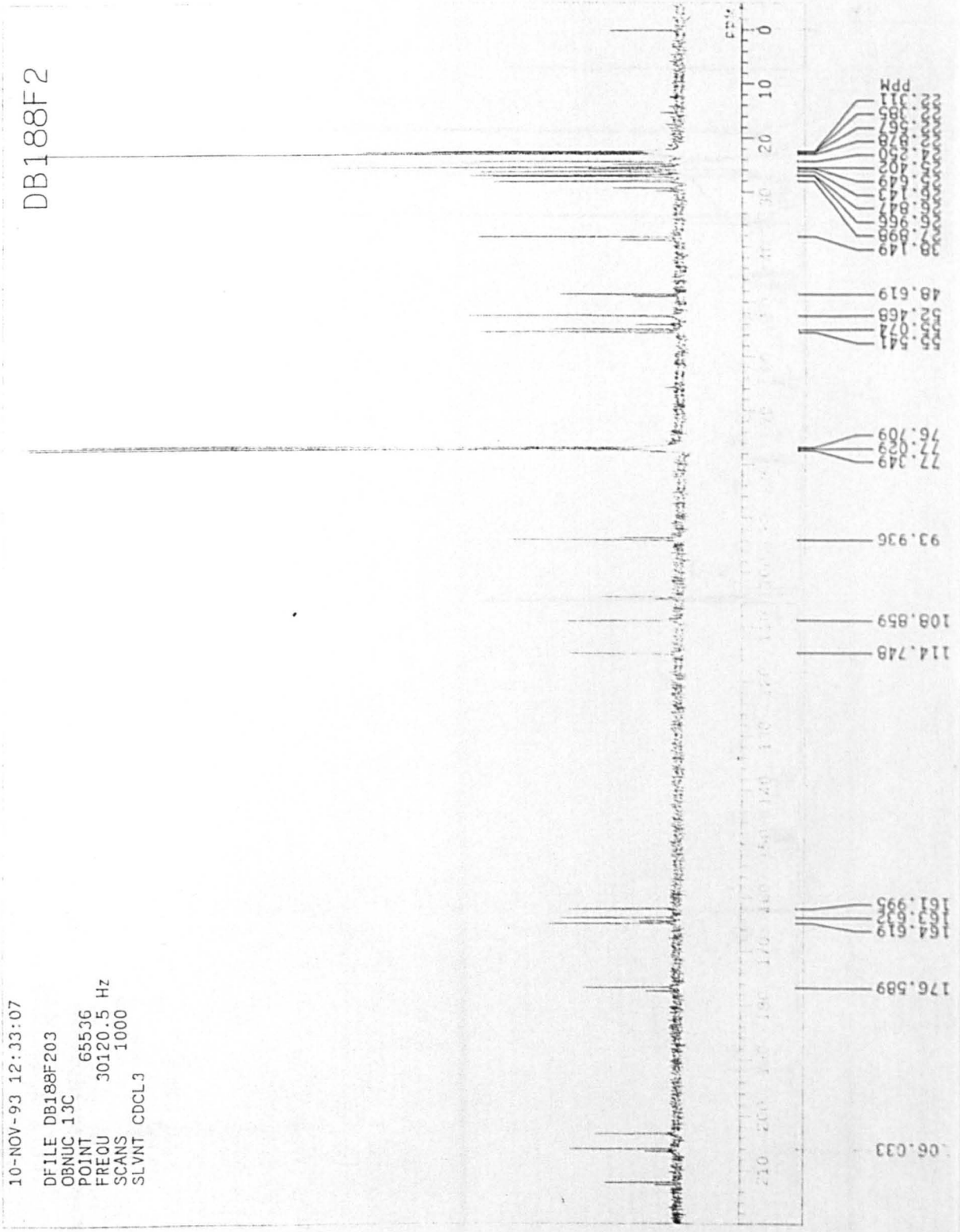
^{13}C NMR spectrum of compound 7



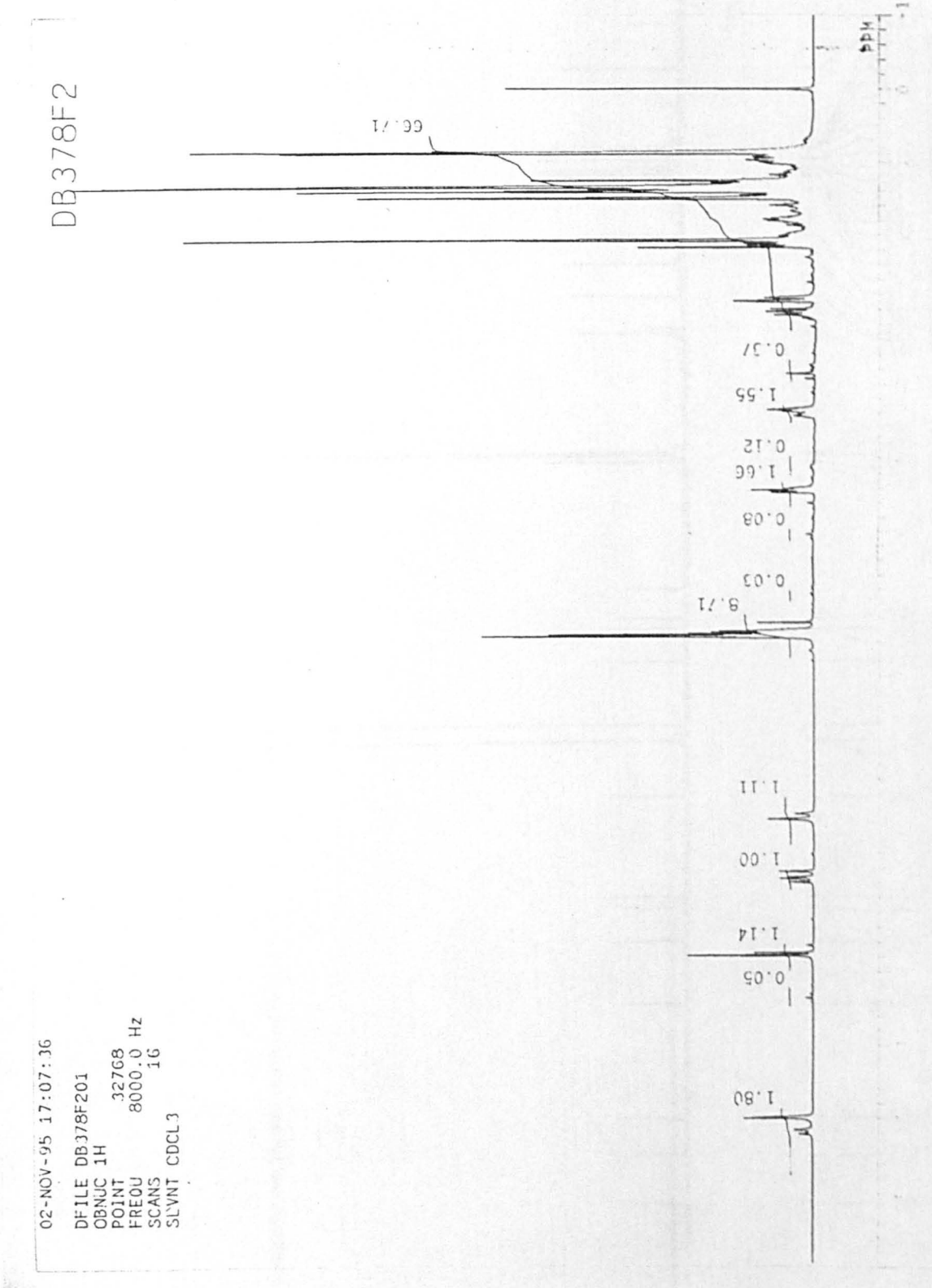
^{1}H NMR spectrum of compound 8



^{13}C NMR spectrum of compound 8



^{1}H NMR spectrum of compound 9



^{13}C NMR spectrum of compound 9