MICROWAVE SYNTHESIS AND MOLECULAR RE-ARRANGEMENT OF A GRISADIENONE AND ITS DERIVATIVES

Submitted in fulfilment of the requirements for the degree of Master of Technology, Organic Chemistry, in the Faculty of Applied Science at Durban University of Technology

DURBAN UNIVERSITY of TECHNOLOGY

By

Thandekile Sithembile Ngcobo

BTech (Chemistry)

March 2011

PROMOTER: Dr. R.M Gengan CO-PROMOTER: Prof. F.O Shode

DURBAN UNIVERSITY OF TECHNOLOGY

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DECLARATION

The work stated in this thesis was done by the author under the supervision of Doctor R.M. Gengan at Durban University of Technology, Durban and Professor F.O. Shode at University of KwaZulu–Natal, Westville campus, Durban, South Africa from 2009 - 2010. The study presents original work by the author and has not been submitted in any form to another tertiary institution. Where use was made of the work of others, it has been duly acknowledged in the text.

Signed : Date

Thandekile Sithembile Ngcobo

Signed:

Doctor R.M. Gengan (Promoter) Date

Signed:

Professor F.O. Shode (Co-Promoter) Date

DEDICATION

I dedicate this work to the loving memories of my son and daughter. May their souls find joy in the Lamb of God – My Lord Jesus Christ.

ACKNOWLEDGEMENTS

I would like to express my gratiude to my Lord Jesus Christ for strength , support and his wisdom for me to be able to complete this project.

My sincere gratitude to the National Research Foundation (South Africa) and Durban University of Technology Award for funding my project.

I would also like to express my respect and deep gratitude to Dr R.M Gengan for introducing me to Organic Chemistry field and encouragement during the period of the research work.

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I would like to express my gratitude to Dr Pitchai for giving me the background knowledge in organic reaction mechanisms.

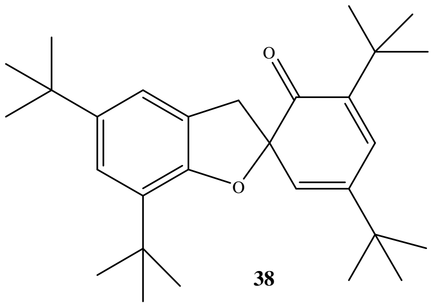
To my freinds and colleauges, I owe you many thanks from the bottom of my heart, Mr Damien Tshabangu, Mr Dilip Jagjivan And Miss Joyce J.Kiplimo for helping in NMR. Mr Talent Makhanya, Mrs Hlengiwe Ndaba, Mrs Nombewu Shange , Miss Liketso Qholosha for their moral support , DUT lab. Technician especially Miss N.P Sithole, Pastor Maduna and Pastor Slaughter for their spiritual support.

To my mom , Miss Thobekile Mbatha, thank you for your love that made everything possible; my brother Mr Bongani Mbatha for his encouragements and caring and all my family members.

Lastly to my husband, Mr Sibongiseni Ngcobo, for his support, encourangement, and understanding, thank you, my love.

ABSTRACT

ortho-Deoxygrisan (**38**), a spirodienone was synthesised from bisphenol (**42**) using both conventional and microwave assisted methods. The bisphenol (**42**) was synthesised from phenol (**52**) by conventional and microwave assisted methods. Benzophenone (**43**) was synthesised from compound (**49**) which in turn was synthesised from compound (**53**) by chromic acid oxidation in acetic anhydride or acetic acid. Compound (**53)** was synthesised from bisphenol (**42**) by mono-acetylation method.



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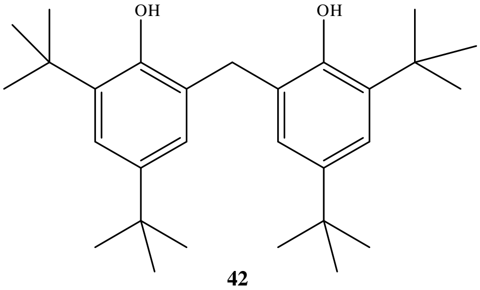

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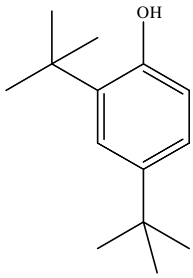

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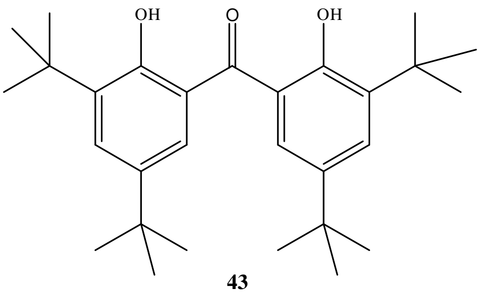

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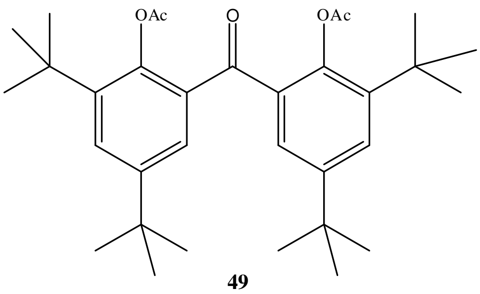

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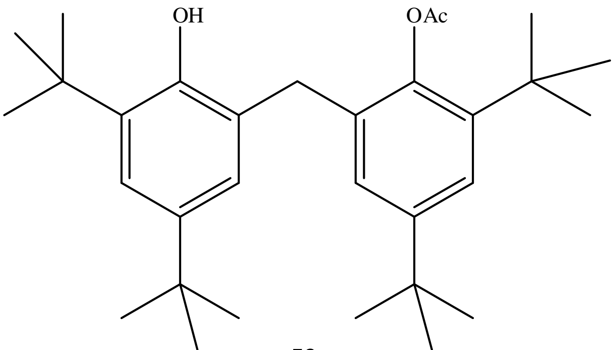

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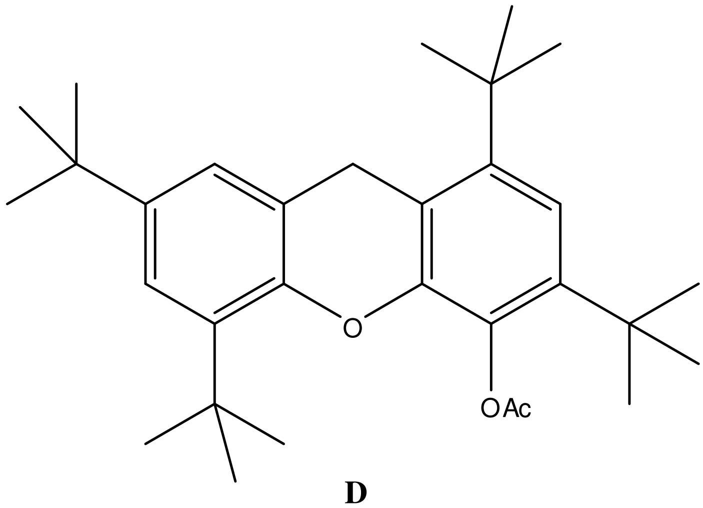
Acid-catalysed rearrangement of *ortho*-deoxygrisan (**38**) in the absence of light was investigated. Chromatography of the reaction mixture afforded compound (**D**) as a major component.



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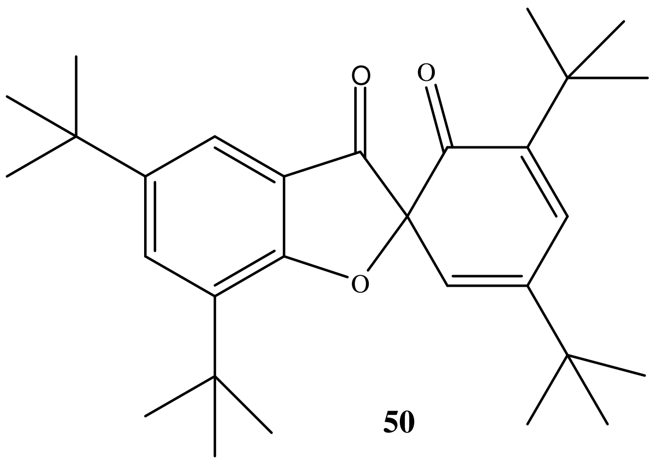
Attempts to synthesise *ortho*-grisan (**50**) from benzophenone (**43**) were unsuccessful.



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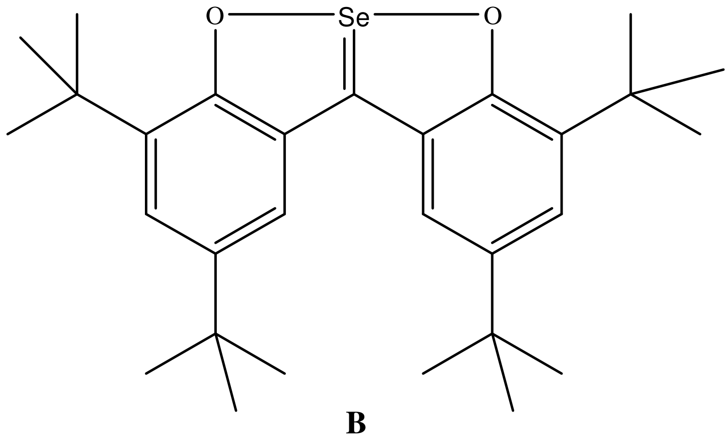
Microwave assisted selenium dioxide oxidation of compound (**53**) gave a yellow compound C. The spectra of this compound were very similar to the spectra of *ortho*-deoxygrisan (**38**). However, selenium dioxide was reacted with compound (**53**) in the absence of microwave to give a yellow solid B. The ^{1}H NMR spectral data of this compound led to the proposed structure B for it.



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List of Abbreviations

AcOH	acetic acid
Ac_2O	acetic anyhdride
Ag_2O	silver oxide
Ar-H	aromatic proton
Bu^t	tert-butyl
CCl_4	carbon tetrachloride
d	doublet
DCM	dichloromethane
CrO_3	chromium trioxide
CH_3I	iodomethane
DMAP	4-dimethyaminopyridine
HCl	hydrochloric acid
H_2CO	formaldehyde
H_2SO_4	sulphuric acid
hr	hour/s
H^+	acid
Hz	Hertz
H	proton
J	coupling constant
$Ke_3Fe(CN)_6$	potassium ferricyanide
K_2CO_3	potassium carbonate

MeOH	methanol
MW	microwave
min	minutes
NaOH	sodium hydroxide
Ox.	oxidation
pyr	pyridine
rt	room temperature
SeO_2	selenium dioxide
s	singlet
TLC	thin layer chromatography

Chapter 1

Introduction

1.1 Microwave technology in organic chemistry – A historical perspective

Microwave-assisted organic synthesis has become an essential tool to chemists for rapid organic synthesis. A large number of research articles[1-8] have been published over the last two decades to support the above statement.The application of microwave technology in chemistry involves the use of microwave irradiation to conduct chemical reactions or synthesis.[9-11] In classical chemical reactions, heating is achieved by using electric plate heater, oil bath, or heating mantle. This heating process is inefficient because it takes a long time to transport heat energy into the reaction medium since its mechanism depends on the convection currents and the thermal conductivity of the different types of materials that must be penetrated. Consequently, the final temperature of the reaction vessel is always higher than that of the reaction mixture and as a result, a temperature gradient develops within the sample.[12] Furthermore, the local overheating can lead to product, substrate, or reagent decomposition.

In microvawe technology, microwave dielectric heating utilises the ability of some liquids and solids to change an electromagnetic radiation into heat to conduct the chemical reactions.This method of heating has been utilised in the rapid heating of foodstuffs for many years. Microwave technology has opened up new opportunities to the synthetic chemists to perform new reactions that are impossible to perform when utilising the conventional heating method. This is because microwave technology improves reaction yields, decreased reaction times and even allows solvent–free reaction conditions.[13]

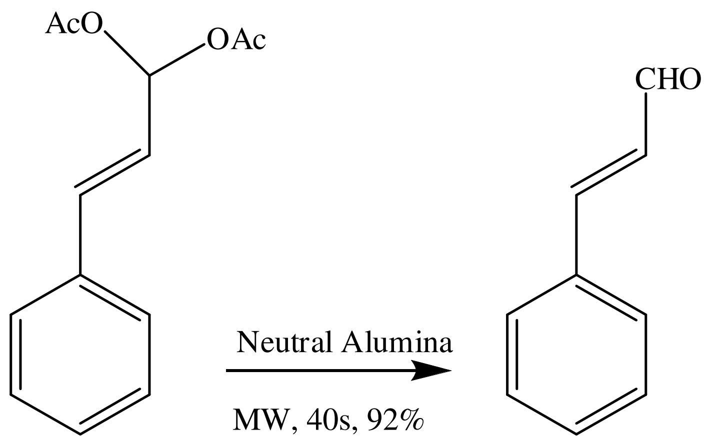
The fundamental theory of microwave technology has been well discussed in many recent reviews and publications.[14-17]

1.2 Some Applications of Microwave Technology in Organic Chemistry

In this section, some examples of the application of microwave technology will be presented to highlight the potential of this relatively new technology in contemporary organic chemistry. The use of microwave in organic reactions is gaining the attention of many chemists as the drive to make chemistry a “green” discipline is gaining momentum.

1.2.1 Deacylation of benzaldehyde diacetates

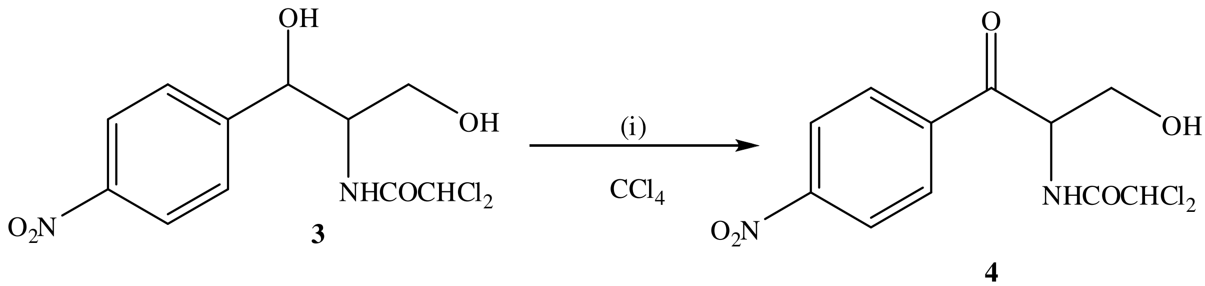
Two examples of deacylation of benzaldehyde diacetates has been reported. They involve using reagents like boron triiodide-N,N-diethylaniline complex[18] and ceric ammonium nitrate on silica gel[19]. The yield of the former method was between 60 – 65%. The latter method requires the presence of protic solvents that cause undesirable quinones. In order to overcome these problems, the microwave heating procedure was developed in which neutral alumina of chromatography grade was used and the regeneration of benzadehydes completed in less than one minute**.** For example, compound (**1**) was deacetylated to give compound (**2**) in 40 seconds and the yield was very good, 92 % yield.[20]



1 **2**

1.2.2 Oxidation of alcohols to carbonyl compounds

Oxidation of alcohols is a common reaction in many synthetic reactions. In conducting these reactions, excess solvents, strong oxidants, such as acids, peracids, peroxides, halogens, transition metals or their salts are used. These reagents have negative impact on the enviroment because of pollution. In order to overcome this problem, many chemists have been exploring selective methods to reduce the negative environmental impact of these reactions.[21] For example, Varma and Dahiya [22] and Varma [23] reported the microwave-assisted oxidation of alcohols under solvent-free conditions in the presence of clayfen to carbonyl compounds. Specifically, using benzimidazolium dichromate in carbon tetrachloride, compound (**3**) was oxidised to compound (**4**) in microwave environment.[24]

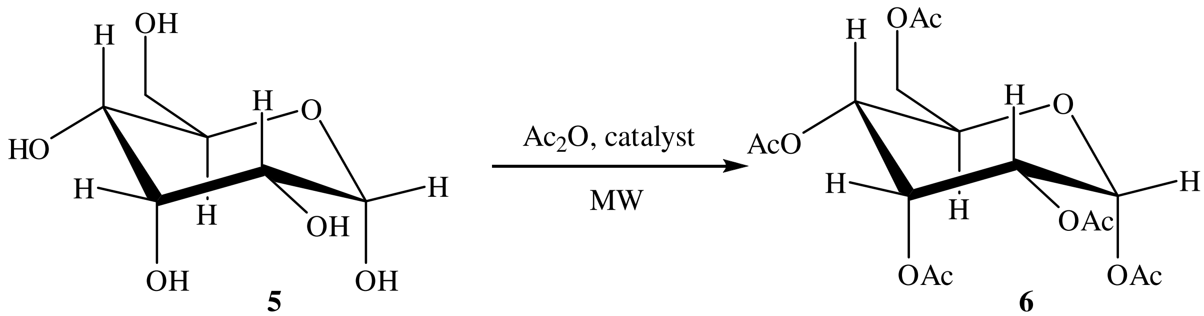


3 **4**

(i) = Benzimidazolium dichromate

1.2.3 Peracetylation of D-glucose

D-glucose (**5**) was converted into penta-acetate derivative (**6**) by using slightly excess acetic anhydride in the presence of a catalytic amount of either anydrous potassium or sodium acetate or zinc chloride in less then 15 minutes in a microwave environment.[25]

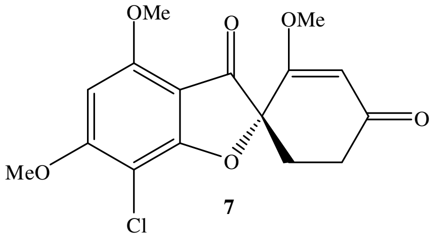


5 **6**

Many reviews and books have been published on the application of microwave heating in many other organic reactions namely cyloaddition, polymer chemistry, heterocyclic chemistry, and green chemistry.[9]

1.3 Motivation for the present study

The chemistry of griseofulvin (**7**) has attracted considerable attention since its isolation from *Pencillium griseofulvum*, a parasitic fungus, in 1939.[26-30] Griseofulvin (**7**) is a potent antimycotic agent still in clinical use today.[31] Several workers [32-36] have carried out various studies on its biosynthesis, synthesis, semi-synthesis, and rearrangement. These studies led to the development of the chemistry of spiro-compounds of the general types (**8**), (**9**), (**10**), and (**11**) in the 70s and 80s. Furthermore, the chemistry of bis(spirodienones) (**12**) and their precursors (calix[4]arenes)[37] has attracted our interest and constitute a part of the motivation for the investigation of microwave application in the synthesis and rearrangement of spiro-compounds of the types (**8**) (grisans) and (**10**) (deoxygrisans) as a prelude to the investigation of microwave assisted synthesis of calixarenes and bis(spirodienones).



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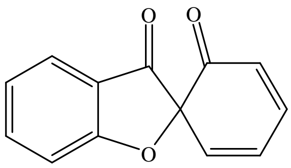

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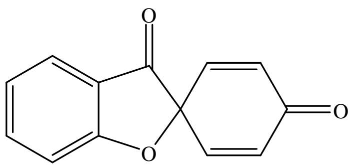

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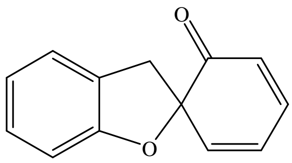

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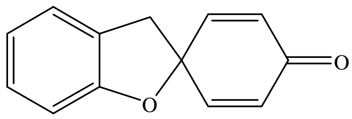

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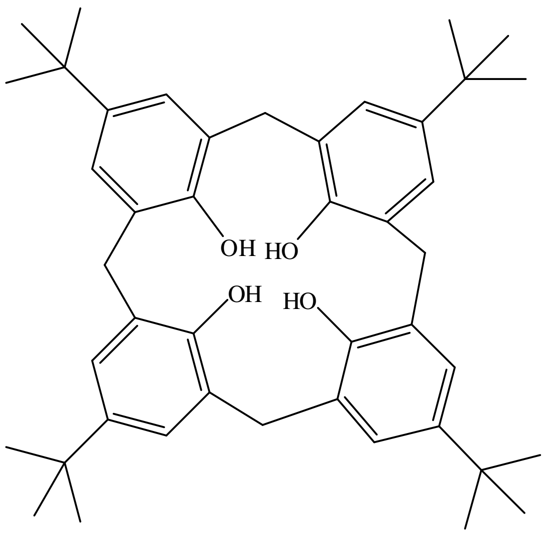
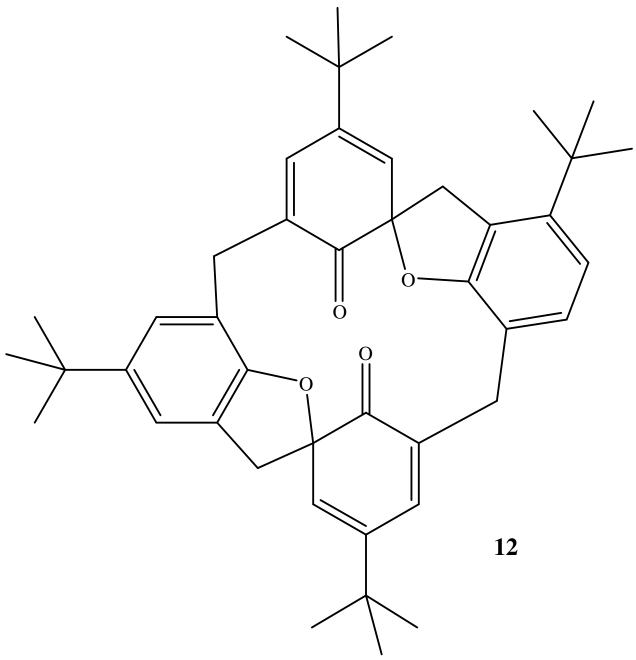


Calix[4]arenes



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Chapter 2

Literature Review, Research Aims and Objectives

2.1 Grisans (Grisadienediones)

2.1.1 Synthesis

2.1.2 Molecular Rearrangements

2.2 Deoxygrisans (Grisandienones)

2.2.1 Synthesis

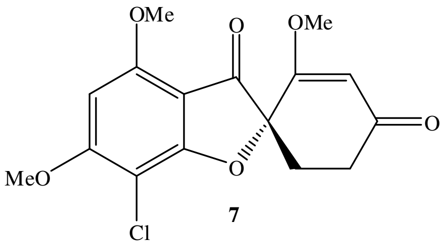
2.2.2 Molecular Rearrangements

2.3 Aims and objectives of research

2.4 References

2.1 Grisans or Grisadienediones

Grisans or grisadienediones are spirobenzofuranones of the general types (**8**) and (**9**). They are referred to as grisans because of their structural resemblance to griseofulvin (**7**), and other naturally occurring polyketide mould metabolites such as geodine (**12**), erdine (**13**), dehydrogriseofulvin (**14**), dihydrogriseofulvin (**15**), gillusdine (**16**), and thelerine (**17**). Compounds of the type (**8**) are trivially referred to *ortho*-grisans and compounds of type (**9**) are trivially referred to as *para*-grisans.[1]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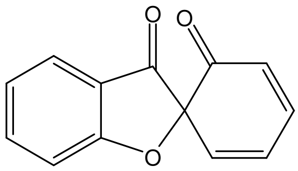
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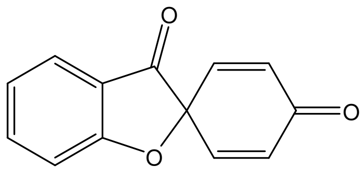
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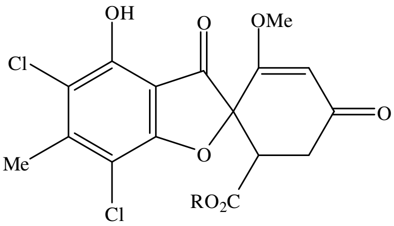
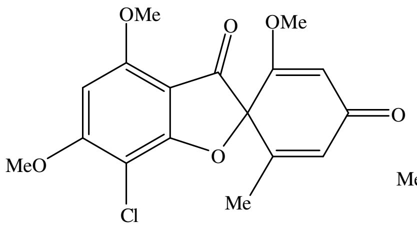

R = Me: **12**

R = H: **13**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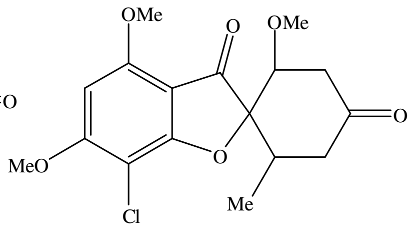
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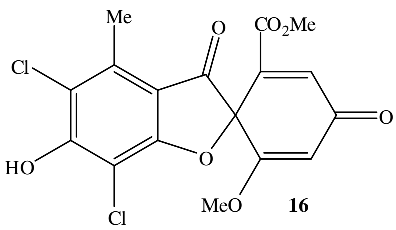
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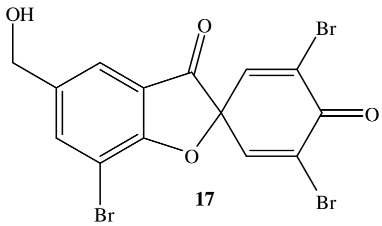
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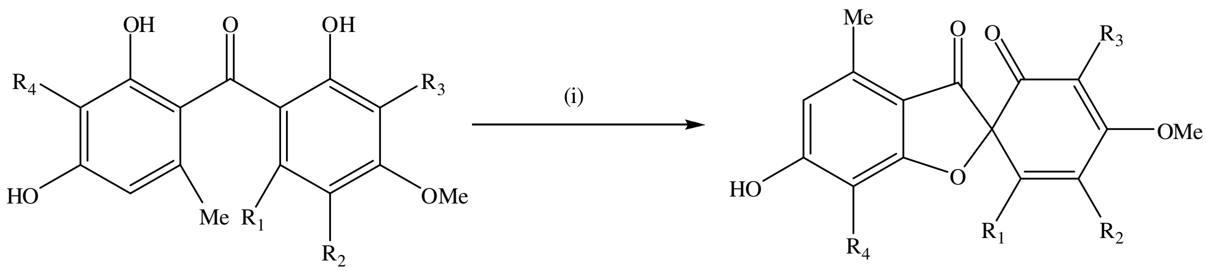
2.1.1 Synthesis

Several *ortho*-grisans have been synthesised from their corresponding benzophenones by oxidative coupling reactions.[2] For example, *ortho*-grisans (**19**), (**21**), and (**23**) were synthesised from their corresponding benzophenones (**18**), (**20**), and (**22**), respectively.[2]



18: $R_1 = R_3 = R_4 = Me$, $R_2 = Cl$

20: $R_1 = CH(Me)CH_2Me$, $R_2 = Br$, R_3 Me, $R_4 = H$

22: $R_1 = R_3 = Me$, $R_2 = Cl$, $R_4 = H$

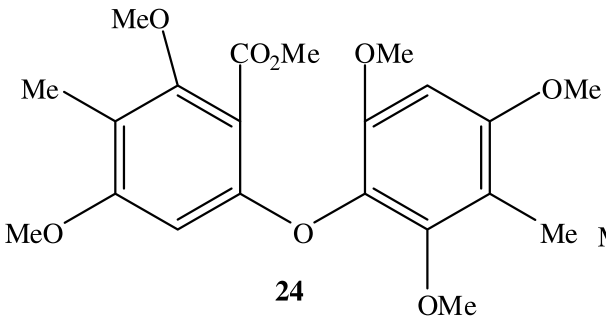
(i): $K_3Fe(CN)_6$, K_2CO_3aq, 30-120s

19: $R_1 = R_3 = R_4 = Me$, $R_2 = Cl$

21: $R_1 = CH(Me)CH_2Me$, $R_2 = Br$, R_3 Me, $R_4 = H$

23: $R_1 = R_3 = Me$, $R_2 = Cl$, $R_4 = H$

Furthermore, certain *para*-grisans can be readily synthesised from *o*-phenoxybenzoic esters by intramolecular *ipso*-acylation.[3] For example, *para*-grisans (**25**) and (**27**) were prepared from *o*-phenoxybenzoic esters (**24**) and (**26**), respectively.[3]



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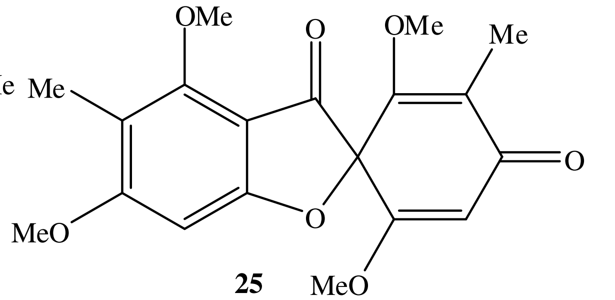

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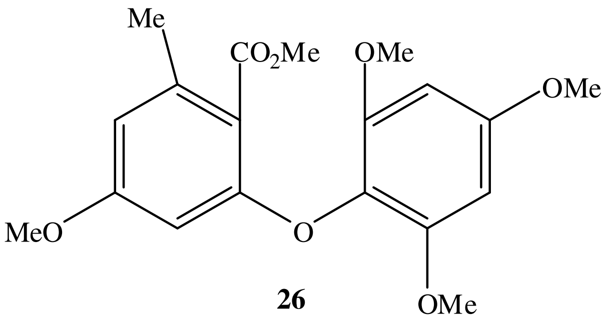

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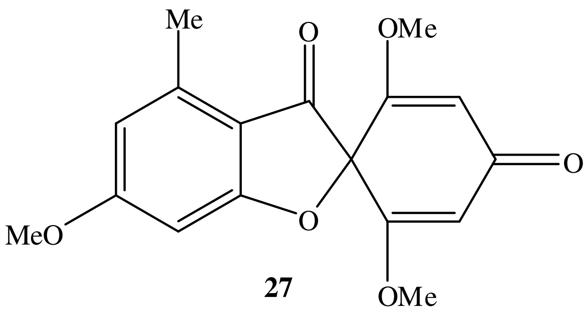

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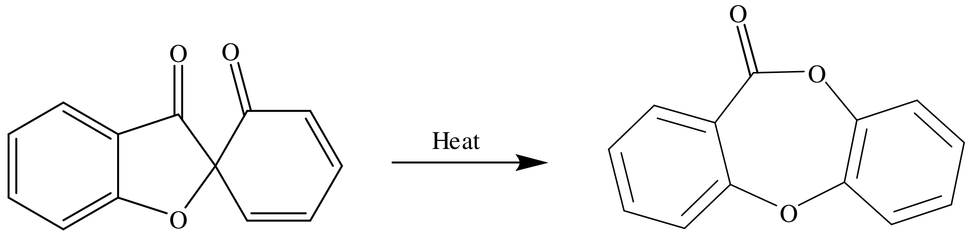
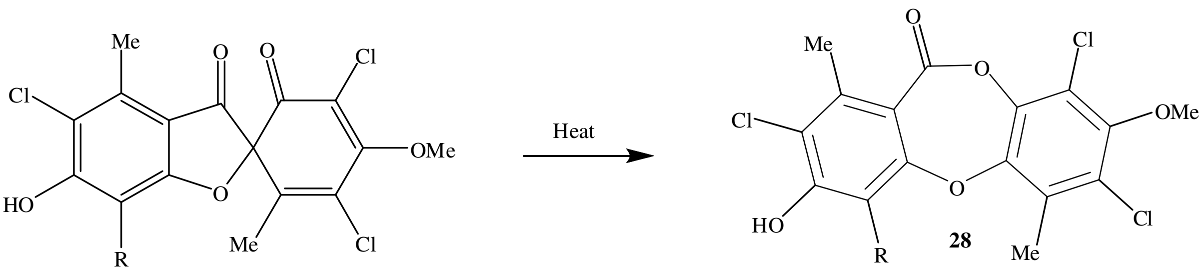
2.1.2 Molecular Rearrangements

2.1.2.1 Thermal Rearrangement

ortho-Grisans (**8**), on heating at temperatures above their melting points, undergo smooth transformations into depsidones (**28**). For example, *ortho*-grisan (**29**) was converted into the depsidone (**30**) on heating at 140° for 35 minutes.[2] Under similar conditions, the *ortho*-grisan (**31**) was transformed into diploicin (**32**)[2], a naturally occurring depsidone.



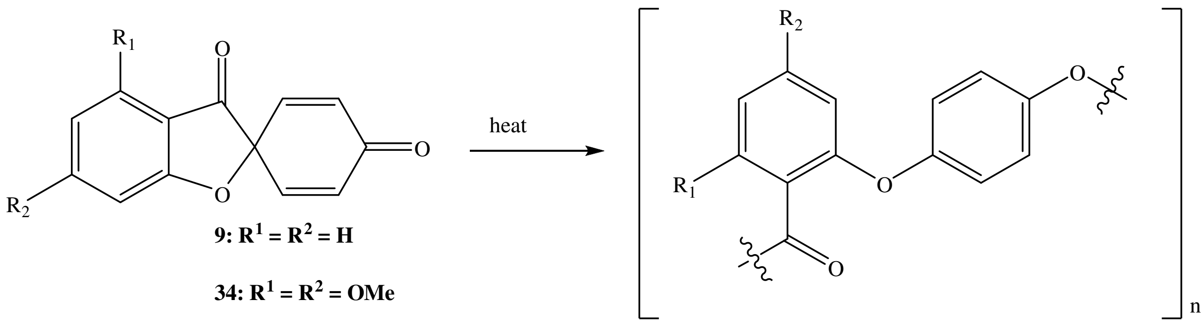
8 **28**



29: R = H
31: R = Cl

30: R = H
32: R = Cl

para-Grisans (**9**), on heating at temperatures near their melting points, are generally transformed into polymers (**33**).[4] Thus, thermolysis of *para*-grisan (**34**) at 160 – 170° for 4 hours resulted in an almost quantitative yield of the benzoate oligomer (**35**).[5]



9: $R^1 = R^2 = H$

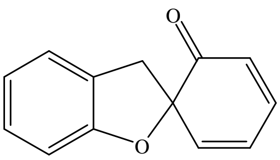
34: $R^1 = R^2 = OMe$

33: $R^1 = R^2 = H$, n = 7

35: $R^1 = R^2 = OMe$, n = 7

2.2 Deoxygrisans (Grisadienones)

Compounds of the general types (**36**) and (**37**) are referred to as *ortho*-deoxygrisans and *para*-deoxygrisans, respectively.[6] Few *ortho*-deoxygrisans and *para*-deoxygrisans are known today.[6] An active investigation of the chemistry of *ortho*-deoxygrisans commenced in 1977[6] with the synthesis of *ortho*-deoxygrisan (**38**) which was first synthesised in 1961 by Muller *et al.*[7]



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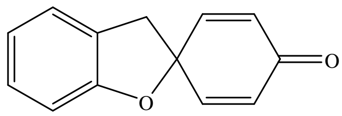

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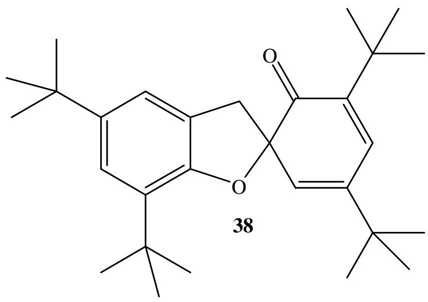
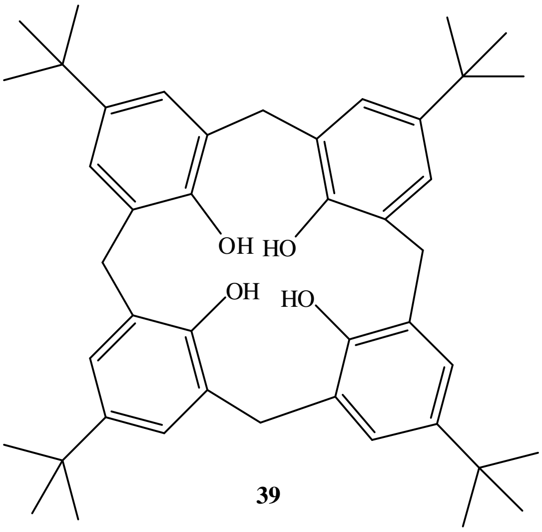


38

Bis(spirodienones) of the type (**12**) which are synthesised from calix[4]arenes (**39**) are new generations of *ortho*-deoxygrisans that were first made in the 1990s.Their chemistry has generated a revival of the chemistry of deoxygrisans.[8] Since the main focus of this work is on grisans and deoxygrisans, the chemistry of bis(spirodienones) will not be reviewed further.



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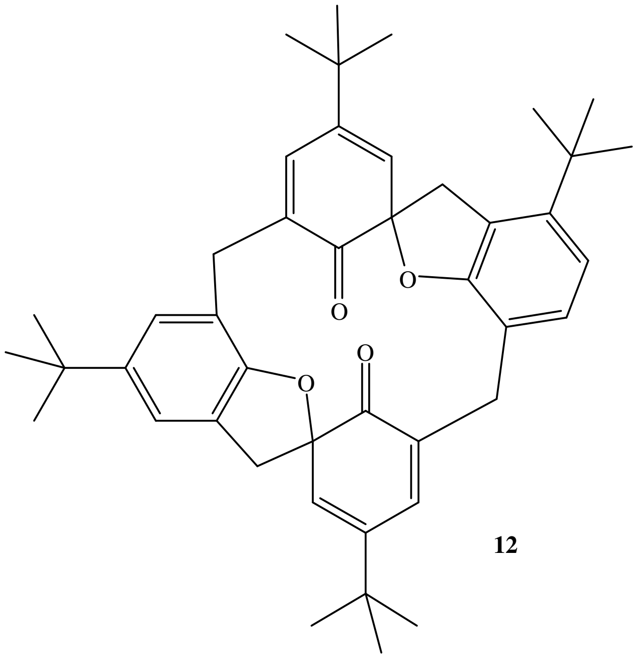
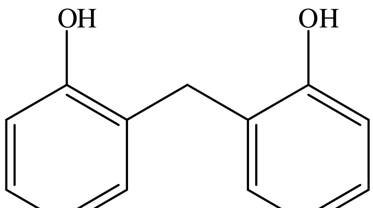


12

2.2.1 Synthesis

ortho-Deoxygrisans (**36**) and *para*-deoxygrisans (**37**) are synthesised from their corresponding bisphenol (**40**) and (**41**), respectively.[7] Thus, *ortho*-deoxygrisan (**38)** was synthesised from bisphenol (**42**) in good yield.[7]



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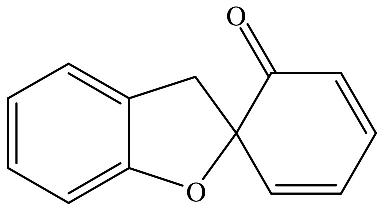

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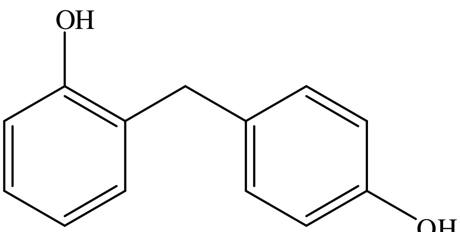

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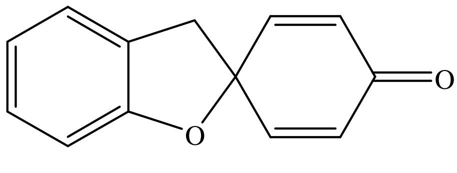

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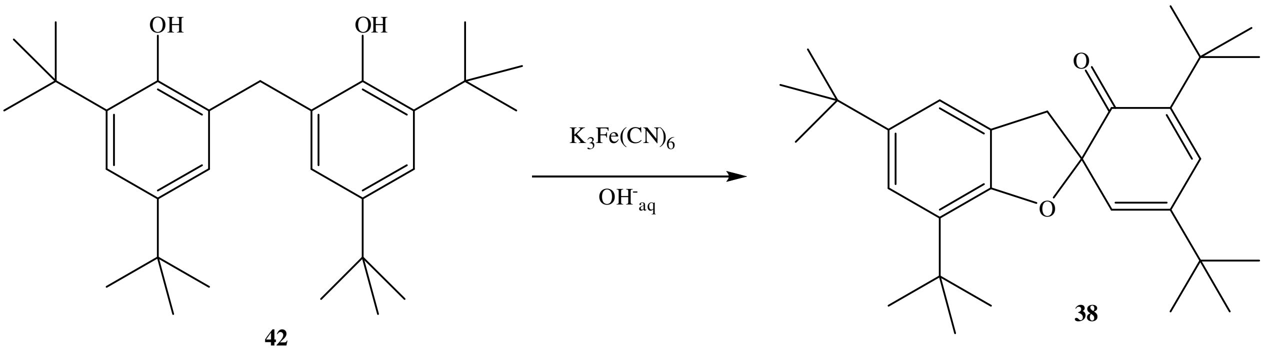
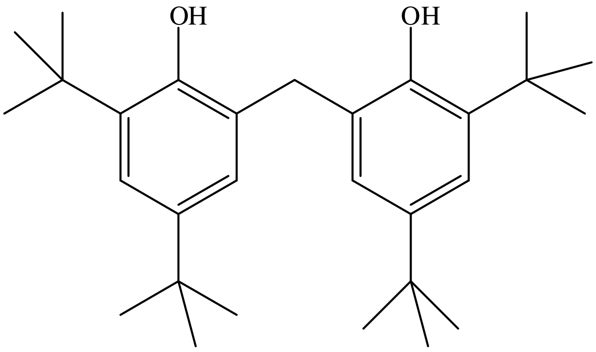


42 **38**

2.2.2 Molecular Rearrangement

2.2.2.1 Thermal Rearrangement

Shode[6] reported the thermal rearrangement of *ortho*-deoxygrisan (**38**). Thus, *ortho*-deoxygrisan (**38**), upon heating at 190°, produced a mixture of compounds . Chromatography of the mixture led to the isolation of bisphenol (**42**), dihydroxybenzophenone (**43**), xanthone (**44**), benzofuranotropone (**45**), and bisxanthyl (**46**) as major components.[6]



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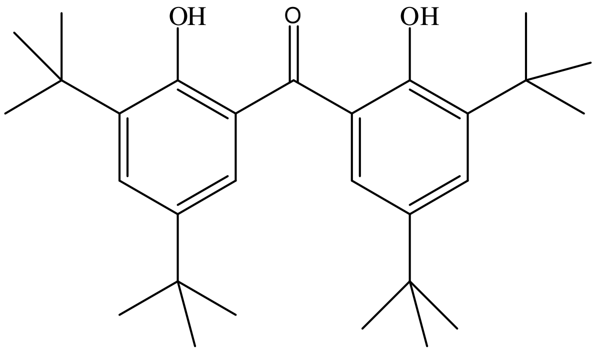

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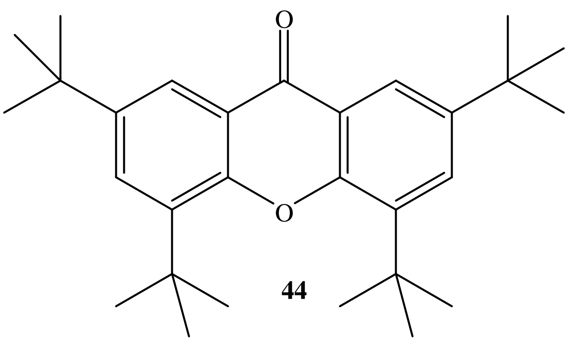

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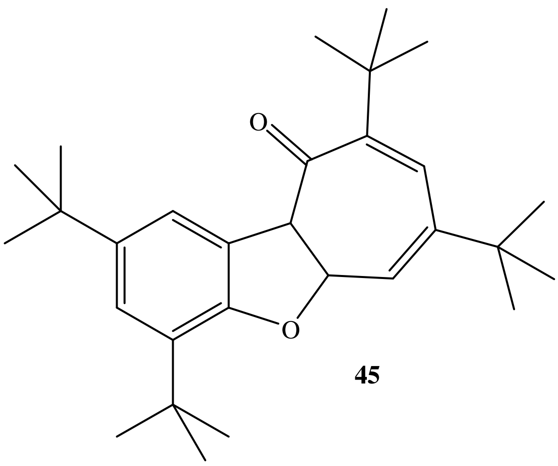

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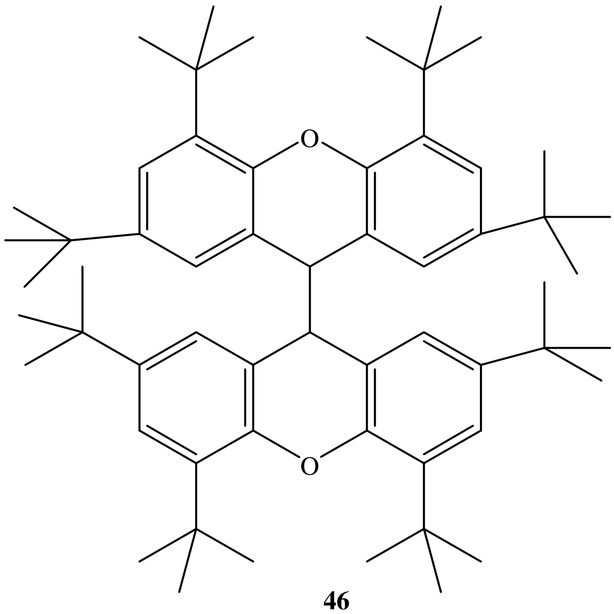

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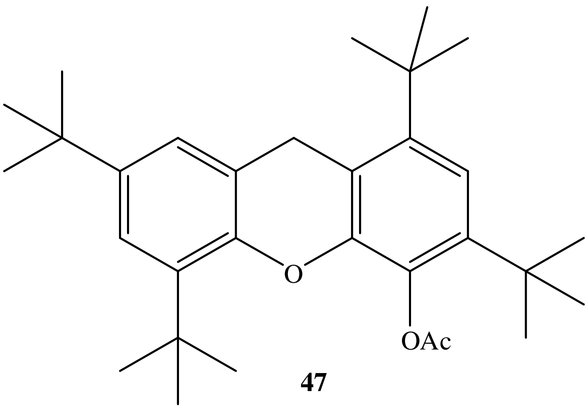
2.2.2.2 Acid-catalysed Rearrangement

The acid catalysed rearrangement of *ortho*-deoxygrisan (**38**) in acetic anhydride in the presence of few drops of concentrated H_2SO_4 has been reported.[6] Earlier investigator [6] observed that *ortho*-deoxygrisan (**38**) produced two acetoxyxanthenes (**47**) and (**48**) in 54% and 9%, respectively.



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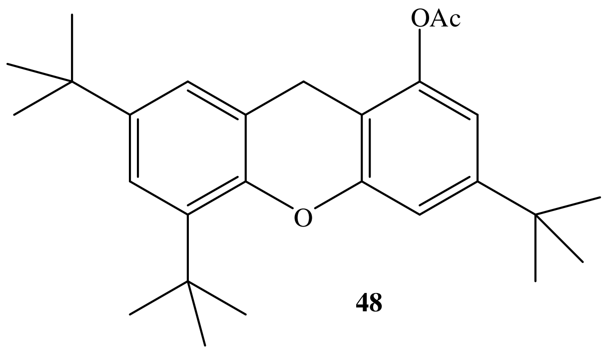

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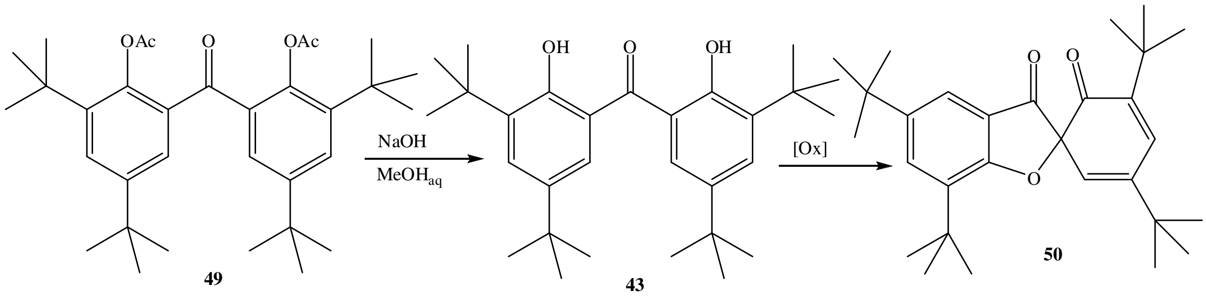
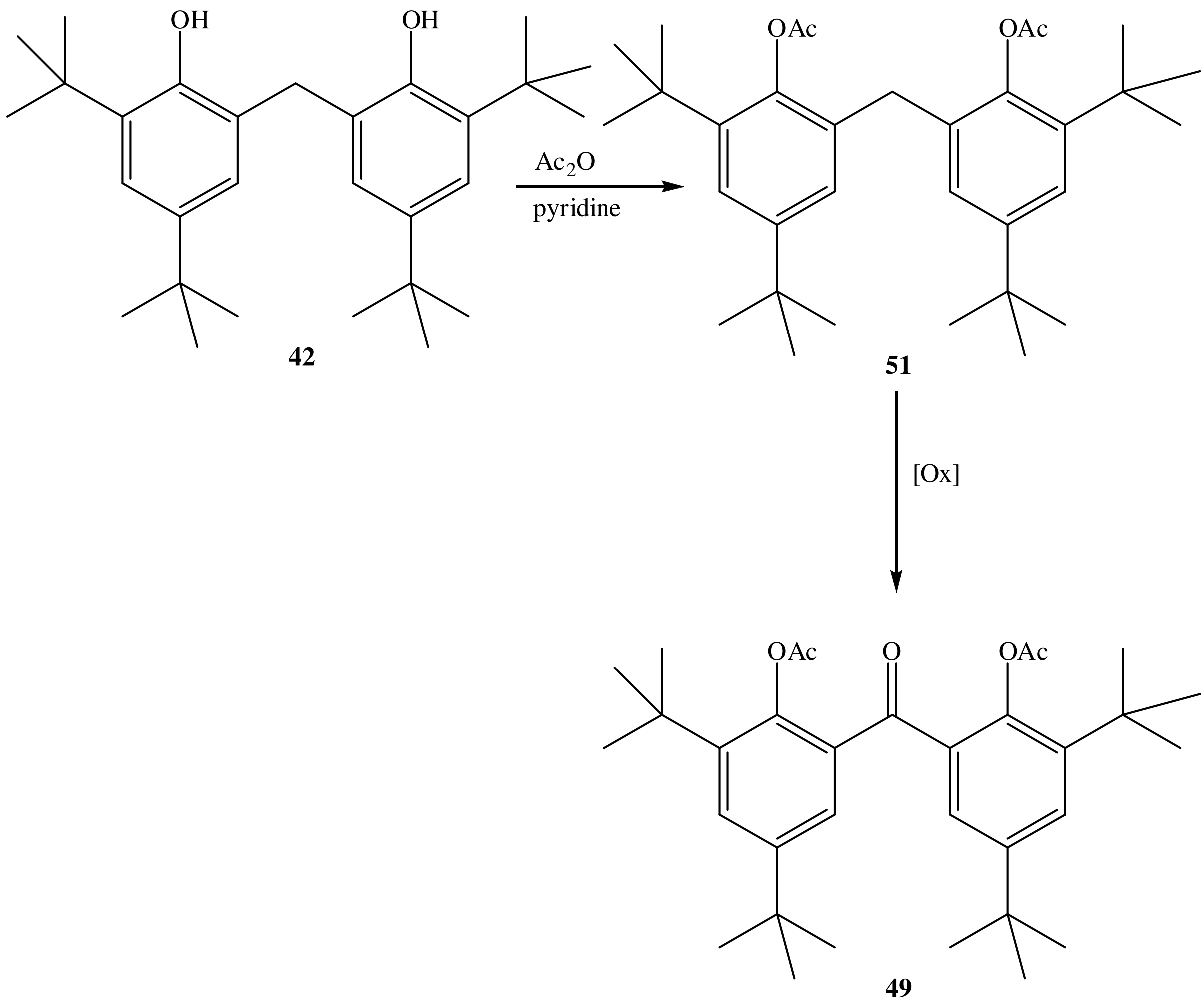
2.3 Aims and objectives of research

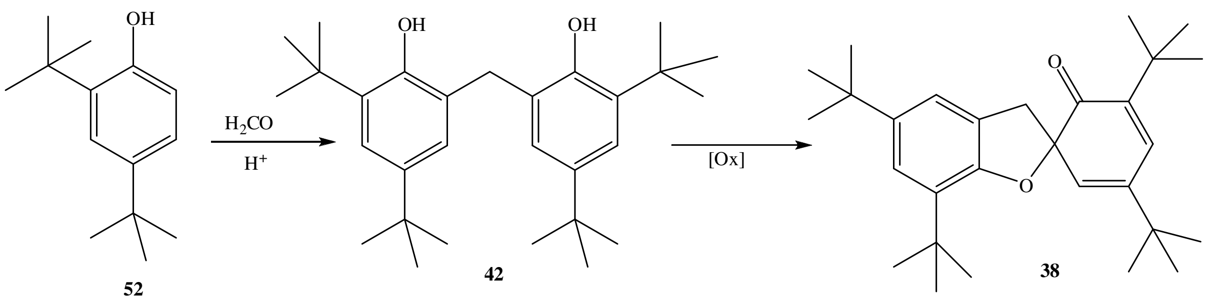
The aims and objectives of the present study were to synthesise *ortho*-grisan (**50**) from dihydroxybenzophenone (**43**) which in turn would be synthesised from diacetoxybenzophenone (**49**) (Scheme 1). Diacetoxybenzophenone (**49**) would be synthesised from diacetoxy-diphenylmethane (**51**) which in turn would be synthesised from bisphenol (**42**) (Scheme 2). These reactions would be carried out using both microwave irradiation and conventional methods. The third objective was to synthesise *ortho*-deoxygrisan (**38**) form bisphenol (**42**) which in turn would be synthesised from 2,4-di-*tert*-butylphenol (**52**) using both microwave irradiation and conventional methods (Scheme 3).



Scheme 1. Proposed synthesis of *ortho*-grisan (**50**)



Scheme 2. Proposed synthesis diacetoxybenzophenone (**49**).



Scheme 3. Synthesis of *ortho*-deoxygrisan (**38**)

Finally, the acid catalysed rearrangement of *ortho*-grisan (**50**) and *ortho*-deoxygrisan (**38**) would be investigated.

2.4 References

1. Sharp, R. *PhD Thesis,* **1972**, Sheffield University.
2. Sala, T.S.; Sargent, M.V. *J.C.S. Chem. Comm.* **1978**, 1043-1044.
3. Sargent, M.V. *J.C.S. Perkin I.* **1982**, 403-411.
4. Mahandru, M.M.; Tajbakhsh, A. *Journal of the Chemical Society, Perkin Transactions 1: Organic and Bio-Organic Chemistry*. **1983** (2), 413-416.
5. Rey, M. *MSc Thesis.* **1973**, Sheffield University.
6. Shode, F.O. *PhD Thesis*, **1981**, Sheffield University.
7. Müller, von E.; Mayer, R., Narr, B.; Rieker, A.; Scheffler, K. *Ann.* **1961**, 645, 25-?
8. Litwak, A.M.; Grynazpan, F.; Aleksiuk, O.; Cohen, S.; Biali, S.E. *J. Org. Chem.* **1993**, 58, 393-402.

Chapter 3

Materials and methods

3.6.4 Method D

3.7 Preparation of *ortho*-deoxygrisan (38)

3.7.1 Method A

3.7.2 Method B

3.7.3 Method C

3.7.4 Method D

3.7.5 Method E

3.7.6 Method F

3.8 Acid–catalysed rearrangement of *ortho*-deoxygrisan (38)

3.8.1 Method A

3.9 Reactions of 2-hydroxy-2’- acetoxy-3, 3’, 5, 5’-tetra-*tert*-butyldiphenylmethane (53) with selenium dioxide

3.9.1 Method A

3.9.2 Method B

3.1 General experimental procedures

Melting points were determined with Electro thermal 9100 melting point, Raychem, instrument and are uncorrected. Thin layer chromatography was operated on pre-coated silica gel plates (F254 Merck). Chromatography was done using silica gel (SRL 100-200 mesh).The products were visualized either with ultra-violet light or in an iodine chamber.

Infra-red spectra were recorded on a Perkin Elmer FT-IR 1600 spectrophometer. ^{1}H and ^{13}C NMR spectra were obtained on a Bruker Avance III 400 MHz spectrometer, using tetramethysilane as the internal standard. Chemical shifts (δ) were reported in part per million (ppm) and coupling constants (J) in Hertz (Hz).

In the description of ^{1}H NMR the following abbreviations have been utilized: s = singlet, bs = broad singlet, d = doublet, t = triplet, q = quartet, and m = multiplet. Microwave (CEM) instrument was used for microwave irradiation experiments. For Gas-Chromatography-MassSpectrometry measurements, Agilent Technology 6890 Series GC system, 5973 Mass Selective Detector and Library: NIST98L was used.

3.2 Preparation of 2, 2'–dihydroxy-3,3', 5, 5'-tetra-*tert*-butyldiphenylmethane (42)

3.2.1 Method A: Conventional method

A mixture of 2,4-di-*tert*-butylphenol (**52**) (10 .0 g, 0.485mol), concentrated hydrochloric acid (32%, 10mL), and formaldehyde (37-40% , 4mL) in a 100ml round bottom flask was stirred at room temperature for three days during which a light brown solid mass was formed over a liquid. The solid mass was broken and the liquid was decanted and discarded.The solid was washed with water (10mL x 3) and then recrystallised from acetic acid to give white crystals of bisphenol (**42**) (7.8 g, 78%). Its structure was confirmed as follows: M.p 147-148 ^{o}C (Lit [35].142-143^{o} C), (found: M^{+} 424. $C_{29}H_{44}O_2$ requires M 424) ; IR: 3528 and 2953cm^{-1}; δ_H ($CDCl_3$) 7.17 (2H, d, *J* = 2.5 Hz, 2 x ArH), 7.17 (2H , d, *J* = 2.4 Hz, 2 x ArH) 5.56 (2H, s, dissappeared after D_2O shake , 2-OH), 3.59 (2H, s , $-CH_2-$) and 1.48 and 1.24 (36 H , s , 4 x Bu^t). δ_C ($CDCl_3$) 146 (C), 143 (C), 136 (C), 126 (C), 125 (CH), 122 (CH), 34 (2 x C), 32 (CH_2).

3.2.2 Method B: Conventional method

A mixture of 2,4-di-*tert*-butylphenol (**52**) (6.8 g, 0.485 mol), concentrated hydrochloric acid (32%, 6.8 ml), and formaldehyde (37-40%, 3 ml) was refluxed for 30 minutes. The reaction mixture was allowed to cool. During the cooling, a light brown solid was formed.[2, 3] The solid was washed with water (10mL x 3) and then recrystallised from acetic acid to give white crystals of bisphenol (**42**) (5.34 g, 79%), m.p 147.5 – 148°C.

3.2.3 Method C: Microwave method

A mixture of 2,4-di-tertbutylphenol (**52**) (10 .0 g, 0.485mol), concentrated hydrochloric acid (32% ,10mL), and formaldehyde (37-40%, 4mL) was microwave irradiated under the following conditions were : power = 300W; temperature = 50 °C; and reaction time = 20 minutes. The reaction mixture was allowed to cool during which a solid mass was formed. The solid was washed with water (3 x 10mL) and recrystallised from acetic acid to give white crystals of bisphenol (**42**) (4.51 g, 44%).

3.2.4 Method D: Microwave method

A mixture of 2,4-di-*tert*-butylphenol (**52**) (10 .0 g, 0.485mol), concentrated hydrochloric acid (32%, 10ml), and formaldehyde (37-40% , 4.5 mL) was microwave irradiated under the following conditions: power =300 W, temperature = 50°C , and reaction time = 20 minutes. The reaction mixture was allowed to cool during which a solid was formed. [2-3] The solid was washed with water (3 x 10mL) and recrystallised from acetic acid to give white crystals of bisphenol (**42**) (8.0 g, 80%).

3.3 Preparation of 2-hydroxy-2'-acetoxy-3,3', 5, 5′-tetra-*tert*-butyl-diphenylmethane (53)

3.3.1 Method A: Microwave method

A mixture of 2,2'_ dihydroxy-3,3′ 5,5′-tetra-*tert*-butyldiphenylmethane (**42**) (1.1 g, 2.3 mmol), acetic anhydride (10 mL), pyridine (50 mL), and 4-dimethypyridine (0.2 g) was microwave irradiated under the following conditions: power = 150 W, temperature = 150 °C, and reaction time = 10 minutes.[4] The reaction mixture was allowed to cool and poured into a beaker containing crushed ice-water. The cold mixture was stirred for half an hour, filtered under vacuum and the obtained solid was recrystallized from methanol to give white powder of 2-hydroxy-2'-acetoxy-3,3′,5,5′-tetra-*tert*- butyldiphenylmethane (**53**) (1.0 g, 90%). M.p. 157 ^oC, (found: M^+ 281. $C_{17}H_{45}O_3$ requires M 297); IR: 1759 cm^{-1} and 1212 cm^{-1} ; δ_H ($CDCl_3$): 7.26 (1H, d, *J* = 2.36 Hz, ArH), 7.22 (1H, d, *J* = 2.44 Hz, ArH), 6.97 (1H, d , J = 2.36 Hz , ArH) , 6.73 (1H, d , J = 2.32 Hz , ArH), 3.68 (2H, s ,-CH_2-), 2.35 (3H, s,$OCOC\underline{H_3}$),1.35 (9H –Bu^t, s),1.32 (9H, s, Bu^t),1.28 (9H, s, Bu^t,) and 1.20 (9H, s, Bu^t).

3.3.2 Method B: Conventional method

A mixture of 2,2'‗ dihydroxy-3, 3′, 5, 5′-tetra-*tert*-butyldiphenylmethane (**42**) (1 g, 2.3 mmol), acetic anhydride (10 mL), pyridine (10 mL), and 4-dimethypyridine (0.2 g) was stirred at room temperature for 24 hours. [5-11] The reaction mixture was poured into crushed ice-water, stirred for half an hour, and filtered under vacuum. The crude solid obtained was recrystallized from methanol to give 2-hydroxy-2'-acetoxy-3,3′,5,5′-tetra-*tert*-butyl-diphenylmethane (**53**) (1.0 g, 90%).

3.3.3 Method C: Microwave method

A mixture of 2,2'- dihydroxy-3,3',5, 5'-tetra-*tert*-butyldiphenylmethane (**42**) (1.1 g, 2.3mmol), acetic anhydride (79 mL), and *p*-toluenesulfonic acid (0.03 g) was microwave irradiated under the following conditions: power = 300 W, temperatures = 150 ^oC, and reaction time = 5 minutes. [12] The reaction mixture was allowed to cool before pouring into a beaker containing crushed ice-water and the mixture stirred for half an hour. The solid formed was filtered under vacuum and recrystallized from methanol to give white powder of 2-hydroxy-2'-acetoxy-3,3′,5,5′ -tetra-*tert*-butyldiphenylmethane (**53**) (1.01 g, 91%).

3.3.4 Method D: Conventional method

A mixture of 2, 2'‗ dihydroxy-3,3′,5,5′-tetra-*tert*-butydiphenylmethane (**42**) (1.1 g , 2.3mmol), acetic anhydride (3 mL), and iodine (0.05 g) was stirred at room temperature for 10 minutes. The iodine was destroyed by adding saturated sodium thiosulphate (5mL) followed by ether (10mL). Organic layer was separated and then washed with sodium bicarbonate solution (2x5 mL), brine, and dried with sodium sulphate anhydrous. Removal of the organic solvent followed by recrystallisation from methanol gave 2-hydroxy-2'-acetoxy-3,3′,5,5′-tetra-*tert*-butyldiphenylmethane (**53**) (0.86 g, 78 %). [13-15]

3.3.5 Method E: Microwave method

A mixture of 2,2'-dihydroxy-3,3′5,5′-tetra-*tert*-butyldiphenylmethane (**42**) (1.1 g, 2.3mmol), acetic anhydride (10 ml), and pyridine was microwave irradiated under the following conditions: power = 150 W, temperature =170 ^{o}C, reaction time = 12 minutes.[16] The reaction mixture was allowed to cool and poured into a beaker containing crushed ice-water. It was stirred for half an hour and the obtained solid was filtered under vacuum before recrystallization from methanol to give white powder of 2-hydroxy-2'-acetoxy-3,3',5,5'-tetra- *tert*-butyldiphenylmethane (**53**)(0.93 g, 84%)

3.4 Preparation of 2,2 –diacetoxy-3,3′,5,5′-tetra-*tert*-butylbenzophenone (49)

3.4.1 Method A: Conventional method

A mixture of 2-hydroxy-2'-acetoxy-3,3',5,5'-tetra- *tert*-butyldiphenylmethane (**53**) (1.07 g 3.6 mmol), acetic anhydride (55ml), and chromium trioxide (0.94g) was stirred at room temperature for 3 hours and refluxed for 5 minutes.[17-19] The reaction mixture was allowed to cool before pouring into a beaker of water, stirred for an hour and the solid that was formed was filtered under vacuum.The product was crystallized from methanol to give white crystals of 2,2'–diacetoxy-3, 3', 5, 5'- tetra-*tert*-butylbenzophenone (**49**) (0.35 g, 33 %). M.p 138 - 139^{o}C (Lit [36].136-138^{o}C) , found : M^+ 480.$C_{33}H_{46}O_5$ requires M = 522) ,IR :1759 cm^{-1} and 1655 cm^{-1}; δ_H ($CDCl_3$) 7.55 (2H , d, J = 2.72 Hz, 2 x ArH), 7.49 (2H, d, J = 2.36 Hz, 2 x ArH), 1.94 (3H, s , -$OCOCH_3$), 1.34 and 1.27 (36H, s, 4 x Bu^t).

3.4.2 Method B: Conventional method

A mixture of 2- hydroxy-2'-acetoxy-3, 3′, 5, 5′,-tetra-*tert*-butyldiphenylmethane (**53**) (0.1 g, 0.19mmol), glacial acetic acid (2.5mL), and chromium trioxide (0.1 g) was stirred at room temperature overnight. [20-22] The reaction mixture was poured into a beaker containing ice water, stirred, and filtered under vacuum . The obtained solid was dried and recrystallised from methanol or purified by column chromography (SiO_2; hexane: 100%) to give 2, 2'–diacetoxy-3, 3', 5, 5'-tetra-*tert*-butylbenzophenone (**49**) (0.03 g, 30 %).

3.4.3 Method C: Conventional method

A mixture of 2-hydroxy-2'- acetoxy-3,3',5,5'-tetra- *tert*- butyldiphenylmethane (**53**) (0.25 g, 0.49 mmol), acetic acid (0.6mL), acetic anhydride (1.25mL), and chromium trioxide (0.1 g) was stirred in a water bath at < 20^{o}C for an hour and continued stirring at room temperature for another hour.[23] Water (75mL) was added to the reaction in a separating funnel, the mixture was shaken, then extracted with ether (3 x 50 mL). The organic layer was separated, dried with sodium sulphate anhydrous and filtered.The organic layer was concentrated under reduced pressure. The crude product was recrystallised from methanol to give 2,2'–diacetoxy-3, 3', 5, 5'-tetra-*tert*-butylbenzophenone (**49**) (0.08 g, 32%).

3.4.4 Method D: Conventional method

A mixture of 2-hydroxy-2'- acetoxy-3,3',5,5'-tetra- *tert*- butyldiphenylmethane (**53**) (0.25 g, 8.4 x 10^{-4} mol) and freshly prepared Jones reagent[24] was stirred in a cold water bath (< 20^{o}C) for 1hour and at room temperature for 4 hours. The reaction mixture was poured into water, extracted with ethyl acetate, dried over sodium sulphate anhydrous, filtered, and the filtrate evaporated in *vacuo*. The residue was recrystallised from methanol to give white crystals of 2,2–diacetoxy-3,3′,5,5′-tetra-*tert*-butylbenzo-phenone (**49**).

3.5 Preparation of 2,2'–dihydroxy-3, 3 ′, 5, 5'-tetra-*tert*-butylbenzophenone (43)

3.5.1 Method A: Conventional method

A mixture of 2,2'–diacetoxy-3,3′,5,5′ tetra-tert-butyl benzophenone (**49**) (0.07g, 1.34mmol), 10 % sodium hydroxide (5.6 mL), and methanol (11.4 mL) was refluxed for 30-45 minutes, acidified with hydrochloric acid (5.6 mL) and methanol (3.22 mL) for 5-10 minutes.[25] The reaction mixture was cooled to room temperature, poured into water, stirred, filtered and rinsed with water three times before recrystallisation from methanol. The yellow solid of 2,2'–dihydroxy-3,3′,5,5′-tetra-*tert*-butylbenzophenone (**43)** was obtained (0.05 g. 71%). M.p 203-205 ^{o}C (Lit [36] 202-204 ^{o}C) found : (M^{+} 438 $C_{29}H_{42}O_3$, requires M = 438) IR : 1692 cm^{-1} and 1200 cm^{-1}; δ_H ($CDCl_3$) 7.53 (2H, d, J = 2.10 Hz, 2 x ArH), 7.34 (2H, d, J = 2.28 Hz, 2 x ArH) , 11.15 (-OH, s, 2 x-OH), 1.43 and 1.25 (36H , s , 4 x Bu^t).

3.5.2 Method B: Convectional method

A mixture of 2,2’–diacetoxy-3,3′,5,5′-tetra-*tert*-butylbenzophenone (**49**) (0.1g, 0.22 mmol), 10 % sodium hydroxide (4 mL), and methanol (15 mL) was stirred at room temperature for 24 hours, then acidified with hydrochloric acid until pH (1-2).[26-28] The reaction mixture was poured into water and extracted with ethyl acetate. The organic layer was separated, dried over sodium sulphate anhydrous and the organic solvent was removed under reduced pressure and the residue was recrystallised methanol to give 2, 2’–dihydroxy-3,3’,5,5′ -tetra-*tert*-butylbenzophenone (**43)** (0.70g ,70%).

3.5.3 Method C: Microwave method

A mixture of 2, 2 –diacetoxy-3, 3′, 5, 5′ tetra-*tert*-butylbenzophenone (**49**) (0.0 2 g, 0.038 mmol), 10 % sodium hydroxide (3.26mL), and methanol (1.6mL) was microwave irradiated under the following conditions: power = 300 W, temperature = 200^{o}C, and time = 15 minutes. The reaction mixture was acidified with hydrochloric acid (5ml).[29 -30] The solution was cooled to room temperature, poured into water, stirred, filtered, and rinsed with water (3 x 10 mL) before recrystallisation from methanol to give yellow crystals of 2, 2’–dihydroxy-3, 3′, 5, 5′-tetra-*tert*-butylbenzophenone (**43)** (0.015 g. 75%).

3.6 Attempted preparation of *ortho*-grisan (50)

3.6.1 Method A: Conventional method

A solution of 2,2’-dihydroxy-3,3′,5,5′ tetra-*tert*-butylbenzophenone (**43)** (0.05g,1.1 x10^{-4} mol) in toluene (20 mL) was added dropwise into a solution of potassium hexaferricyanate (0.1g) in water of 6.2 mL and potassium carbonate (0.4 g) in water (12.5 mL) while stirring. The reaction mixture was then stirred for 2 hours.[31-34] The yellow reaction mixture was separated and the organic layer was washed with water (3 x 20 mL), dried over sodium carbonate anhydrous, filtered, and the organic solvent removed under reduced pressure. The residue was recrystallised with methanol. The starting material was recovered unreacted.

3.6.2 Method B: Conventional method

A solution of 2,2’-dihydroxy-3,3′ ,5,5′-tetra-tert-butylbenzophenone (**43)** (0.02 g, 1.1 x10^{-4} mol) in toluene (20mL) was added over 1hour to a stirred solution of potassium hexaferricyanate (0.44 g) and sodium hydroxide (0.05g) in water (4 ml), in the presence or absence of nitrogen gas at room temperature. The reaction was then stirred for 2 hours after the addition of (**43**).[35] The reaction mixture was extracted with ethyl acetate and the organic layer dried over sodium sulphate anhydrous, filtered, and the filtrate concentrated under reduced pressure. The yellow solid obtained was the unreacted 2,2'-dihydroxy-3, 3′, 5, 5′ -tetra-*tert*-butylbenzophenone (**43)**

3.6.3 Method C: Conventional method

A mixture of 2,2'-di-hydroxy-3,3′,5,5′-tetra-*tert*-butylbenzophenone (**43)** (0.1 g, 2.2×10^{-4} mol), iodo-methane (5mL) and silver oxide (0.5 g) was stirred at room tempeature for three hours.[36] The starting compound (**43**) was recovered unchanged.

3.6.4 Method D: Conventional method

A mixture of 2,2'-di-hydroxy-3,3′ 5,5′-tetra-*tert*-butylbenzophenone (**43)** (0.02 g, 4.4×10^{-5} mol), benzene (8mL) and silver oxide (0.04 g) was stirred at room temperature for 3 hours.[37] The starting compound (**43**) was recovered unchanged.

3.7 Preparation of *ortho*-deoxygrisan (38)

3.7.1 Method A

A mixture of 2,2'–dihydroxy-3, 3', 5,5′- tetra-*tert*-butyldiphenylmethane (**42**) (0.4 g ,9.3×10^{-4} mol), acetic anhydride (20mL), and chromium trioxide (0.32 g) was stirred at room temperature for 3 hours and then refluxed for 10 minutes.[43] The reaction mixture was cooled, poured into water, stirred half an hour, and filtered. The crude solid obtained was purified by column chromatography with hexane as eluent (100%). Recrystallization of the yellow solid obtained from the column chromatography gave *ortho*-deoxygrisan (**38**) (0.33g, 82 %).

M.p. 155-157^{o} (Lit[1]. 153-155^{o}C) found M^+ 422. $C_{29}H_{42}O$ requires M = 422). IR: 1654cm^{-1} and 1008 cm^{-1}. δ_H ($CDCl_3$) 7.01 (1H, s), 6.96 (1H, s), 6.82 (2H, d, *J* = 2.4Hz), 6.14, (2H, d, *J* = 2.4Hz), 2.99 (2H, s), 1.47 (9H, s), 1.38 (9H, s), 1.27 (9H, s) and 1.18, (9H, s);

3.7.2 Method B: Microwave method

A mixture of 2, 2'–dihydroxy-3, 3', 5, 5′-tetra-*tert*-butyl diphenylmethane (**42**) (0.4 g, $9.3x10^{-4}$ mol), acetic anhydride (18 mL), and chromium trioxide (0.38 g) was microwave irradiated under the following conditions: power =300W, temperature = 200 ^{o}C and time = 9 min.The reaction mixture was allowed to cool before purification of the product by column chromatography followed by recrystallization from methanol to yield *ortho*-deoxygrisan (**38**) (0.32 g, 80 %)

3.7.3 Method C: Conventional method

A mixture of 2,2'–dihydroxy-3.3', 5, 5′ tetra-*tert*-butyldiphenylmethane (**42**) (0.3 g, 7.0 $x10^{-4}$ mol), dichloromethane (6 mL), and silver oxide (1.26 g) was stirred at room temperature for 10 minutes. The reaction mixture was filtered and the spent silver oxide washed with dichloromethane. The filtrate was concentrated under vacuum and the crude product was recrystallised from methanol to give *ortho*-deoxygrisan (**38**) (0.29 g, 96 %).

3.7.4 Method D: Conventional method

A mixture of 2,2'–Dihydroxy-3,3',5,5′ -tetra-*tert*-butyldiphenylmethane (**42**) (5.8 $x10^{-4}$ mol), freshly prepared Jones reagent (1.1 mL) and acetone 15 mL was stirred at 20 ^{o}C for 3 hours.[24] The reaction mixture was poured into water, stirred for half an hour, and filtered under vacuum. The crude product was purified by column chromatography over SiO_2 with hexane and ethyl acetate mixture as eluent (9.5:0.2). The expected *ortho*-deoxygrisan (**38**) was obtained in 30% yield.

3.7.5 Method E : Convectional method

A solution of 2,2'–dihydroxy-3,3', 5,5′-tetra-*tert*-butyl diphenylmethane (**42**) (1.5g, 3.5 $x10^{-3}$ mol) in toluene (5 ml) was added over an hour to a solution of potassium hexaferricyanate (III) (3.3 g) and sodium hydroxide (0.4 g) in water (30 ml).[35] The reaction mixture was further stirred at room temperature for 3 hours.The reaction mixture was extracted with petroleum ether (2 x 50 mL). The organic layer was washed with water, dried over sodium sulphate anhydrous, and filtered.The filtrate was evaporated under vacuum pressure and the residue was recrystallised from methanol to give *ortho*-deoxygrisan (**38**) (1.2 g, 80 %).

3.8 Acid –catalyzed rearrangement of deoxygrisan (38)

3.8.1 Method A

A mixture of *ortho*-deoxygrisan (**38**) (1.03g, 3.4 x10^{-4}mol), acetic anhydride (4ml) and few drops of concentrated sulphuric acid was stirred in the dark overnight. [35] The reaction mixture was poured into water (50 mL), stirred for an hour and filtered. TLC of the crude product showed that it was a mixture of two components, one was major and the other one was minor. The major product was isolated as a solid (compound **D**).

3.9 Reaction of 2-hydroxy- 2'-acetoxy-3, 3′, 5, 5′-tetra-*tert*-butyldiphenylmethane (53) selenium dioxide

3.9.1 Method A: Conventional method

A mixture of 2-hydroxy-2'- acetoxy-3, 3′, 5, 5′-tetra-*tert*- butyldiphenylmethane (**53**) (0.12 g, 4.0 x10^{-4} mol) and selenium dioxide (0.2 g) was heated in an oil bath at 200 °C for 30 min. [41-42] The reaction mixture was allowed to cool and extracted with dichloromethane. The organic extract was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, hexane as eluent) to give a yellow solid (compound **B**).

3.9.2 Method B: Microwave method

A mixture of 2-hydroxy-2'-acetoxy-3,3′,5,5′-tetra-*tert*-butyldiphenylmethane (**53**) (0.12 g, 4.0 x10^{-4} mol) and selenium dioxide (0.2 g) was microwave irradiated under the following conditions: power = 300W, temperature = 150°C, and time = 9 minutes. [41-42] The reaction mixture was allowed to cool and extracted with dichloromethane. The organic extract was concentrated under vacuum and the residue was purified by column chromatography (SiO_2, hexane as eluent) to give a yellow solid (compound **C**).

3.10 References

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Chapter 4

Results

4.0 Introduction

4.1 Synthesis of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenylmethane (42)

4.2 Synthesis of 2-hydroxy- 2'-acetoxy-3, 3', 5, 5'-tetra-*tert*–butyldiphenylmethane (53)

4.3 Sythesis of 2,2'–diacetoxy-3,3',5,5'-tetra-*tert*-butylbenzophenone (49)

4.4 Sythesis of 2,2' –dihydroxy-3,3' 5,5' tetra-*tert*-butylbenzophenone (43)

4.5 Attempted synthesis of *ortho*-grisan (50)

4.6 Synthesis of *ortho*-deoxygrisan (38)

4.7 Acid-catalysed rearrangement of *ortho*-deoxygrisan (38)

4.8 Reactions of 2-hydroxy-2'- acetoxy-3, 3', 5, 5'-tetra-*tert*-butyldiphenylmethane (53) with selenium dioxide

4.9 References

No references

4.0 Introduction

In this Chapter, I will present the results of the experiments that were carried out during the project.

4.1 Synthesis of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenylmethane (42)

A total of four methods were used to synthesise compound (**42**). Two conventional methods and two microwave-assisted methods (see Table 1). The structure of (**42**) was confirmed by spectroscopic analysis.

Table 1. Summary of the synthesis of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyl-diphenyl-methane (**42**)

Method	Reaction conditions	Reagents	Product yield
A Conventional	Ambient conditions, 72 h	2,4-Di-*tert*-butylphenol (**52**), formalin (4 mL), conc. HCl	78%
B Conventional	Reflux for 30 min.	2,4-Di-*tert*-butylphenol (**52**), formalin, (3 mL), conc. HCl	79%
C Microwave irradiation	MW; 300 W, 50^{o}C, 20 min.	2,4-Di-*tert*-butylphenol (**52**), formalin (4 mL), conc. HCl	44%
D Microwave irradiation	MW; 300 W, 50^{o}C, 20 min.	2,4-Di-*tert*-butylphenol (**52**), formalin (4.5 mL), conc. HCl	80%

4.2 Synthesis of 2-hydroxy-2'-acetoxy-3, 3', 5, 5'-tetra-*tert*–butyldiphenylmethane (53)

Five methods were used for the synthesis of 2-hydroxy-2'-acetoxy-3, 3', 5, 5'-tetra-*tert*-butyldiphenylmethane (**53**). A summary of these methods are presented in Table 2.

Table 2. Summary of the synthesis of 2-hydroxy-2'-acetoxy-3, 3', 5, 5'-tetra-*tert*-butyl-diphenylmethane (**53**).

Method	Conditions	Reagents	Product Yield
A Microwave irradiation	MW; 150W; 150°C; 10 min.	Compound (**42**); Ac_2O; pyr. ; 4-DMAP.	90%
B Conventional	Stirring at rt for 24h.	Compound (**42**); Ac_2O; pyr.; 4-DMAP.	90%
C Microwave irradiation	MW; 300W; 150°C; 5 min.	Compound (**42**); Ac_2O; *p*-toluene-sulphonic acid.	91%
D Conventional	Stirring at rt for 10 min.	Compound (**42**); Ac_2O; iodine.	90%
E Microwave irradiation	MW; 150W; 170°C; 12 min.	Compound (**42**); Ac_2O; pyr.	84%

4.3 Synthesis of 2,2'–diacetoxy-3,3',5,5'-tetra-*tert*-butylbenzophenone (49)

Four methods were used for the synthesis of 2,2'–diacetoxy-3,3',5,5'-tetra-*tert*-butylbenzophenone (**49**). These methods are summarised in Table 3.

Table 3. Summary of the synthesis of 2,2'–diacetoxy-3,3',5,5'-tetra-*tert*-butylbenzophenone (**49**).

Method	Conditions	Reagents	Product Yield
A Conventional	Stirring at rt for 3h; refluxed for 5 min.	Compound (**53**); Ac_2O; CrO_3.	33%
B Conventional	Stirring at rt overnight	Compound (**53**); AcOH; CrO_3.	30%
C Conventional	Stirring at < 20^{o}C for 1h; stirring at rt for 1h.	Compound (**53**); AcOH; CrO_3.	32%
D Conventional	Stirring at < 20^{o}C for 1h; stirring at rt for 4h.	Compound (**53**); Jone's reagent.	60%

4.4 Synthesis of 2,2' –dihydroxy-3,3' 5,5'-tetra-*tert*-butylbenzophenone (43)

The synthesis of 2,2' –dihydroxy-3,3' 5,5' tetra-*tert*-butylbenzophenone (**43**) was carried out using three methods (see Table 4).

Table 4. Summary of the synthesis of 2,2'–dihydroxy-3,3' 5,5'-tetra-*tert*-butylbenzophenone (**43**).

Method	Conditions	Reagents	Product yield
A Conventional	Refluxed for 45 min.	Compound (**49**); 10% $NaOH_{aq}$; MeOH	71%
B Conventional	Stirring at rt overnight	Compound (**49**); 10% $NaOH_{aq}$; MeOH	70%
C Microwave irradiation	MW; 300 W; 200oC; 15 min.	Compound (**49**); 10% $NaOH_{aq}$; MeOH	75%

4.5 Attempted synthesis of *ortho*-grisan (50)

Four attempts to synthesis *ortho*-grisan (**50**) were unsuccessful. These methods are presented in Table 5.

Table 5. Summary of attempted synthesis of *ortho*-grisan (**50**).

Method	Conditions	Reagents	Product yield
A Conventional	Stirring at rt for 2h.	Compound (**43**); $K_3Fe(CN)_6$; K_2CO_3.	0%
B Conventional	Stirring at rt for 2h.	Compound (**43**); $K_3Fe(CN)_6$; NaOH; inert atmosphere (N_2 gas)	0%
C Conventional	Stirring at rt for 3h.	Compound (**43**); $K_3Fe(CN)_6$; CH_3I; Ag_2O.	0%
D Conventional	Stirring at rt for 3h.	Compound (**43**); Benzene; Ag_2O.	0%

4.6 Synthesis of *ortho*-deoxygrisan (38)

Five methods were used in the synthesis of *ortho*-deoxygrisan (**38**). The five methods are presented in Table 6.

Table 6. Summary of the synthesis of *ortho*-deoxygrisan (**38**).

Method	Conditions	Reagents	Product yield
A Conventional	Stirring at rt for 3h; reflux for 10 min.	Compound (**42**); Ac_2O; CrO_3.	82%
B Microwave	MW; 300 W; 200^{o}C; 9 min.	Compound (**42**); Ac_2O; CrO_3	80%
C Conventional	Stirring at rt, 10 min.	Compound (**42**); DCM; Ag_2O.	96%
D Conventional	Stirring at 20^{o}C, for 3h.	Compound (**42**); Jones reagent	30%
E Conventional	Stirring at rt, 4h.	Compound (**42**); $K_3Fe(CN)_6$	80%

4.7 Acid-catalysed rearrangement of *ortho*-deoxygrisan (38)

The acid-catalysed rearrangement of *ortho*-deoxygrisan (**38**) produced a mixture of products from which one solid product (compound **D**), the major product, was isolated by chromatography.

4.8 Reactions of 2-hydroxy-2'- acetoxy-3, 3', 5, 5'-tetra-*tert*-butyldiphenylmethane (53) with selenium dioxide

The reaction of 2-hydroxy-2'- acetoxy-3, 3', 5, 5'-tetra-*tert*-butyldiphenylmethane (**53**) with selenium dioxide without microwave irradiation produced a yellow solid (**B**). The reaction of 2-hydroxy-2'- acetoxy-3,3',5, 5'-tetra-*tert*-butyldiphenylmethane (**53**) with selenium dioxide in the presence of microwave irradiation produced a yellow solid (**C**). The spectral properties of these compounds will be presented in chapter 5.

4.9 References

No references

Chapter 5

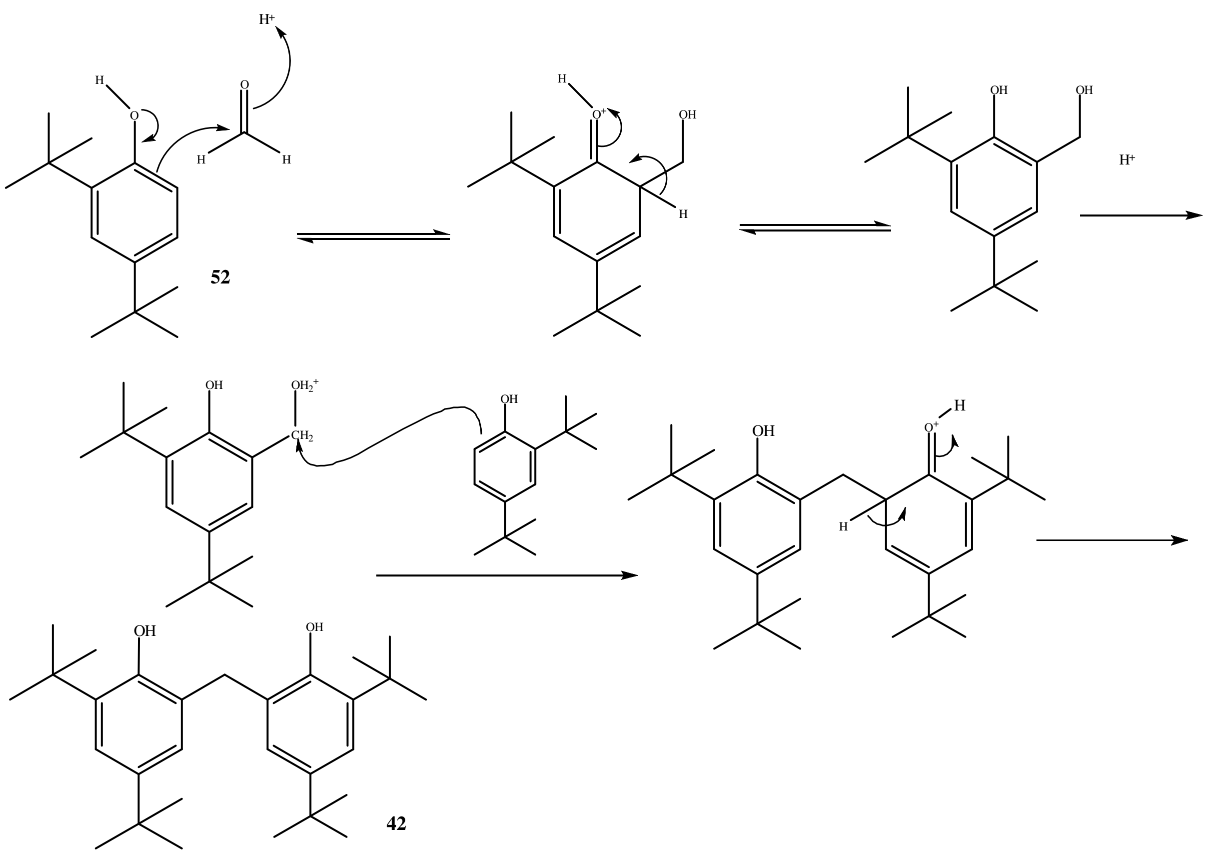
Discussion

5.0 Introduction

In this chapter, the results presented in chapter 4 will now be discussed.

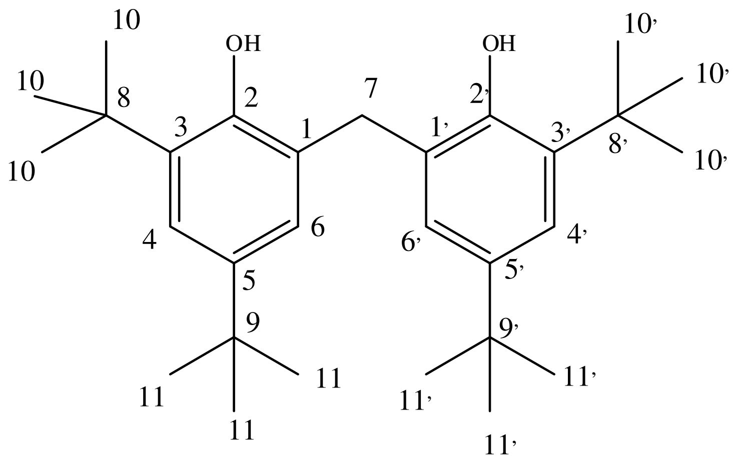
5.1 Synthesis of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenylmethane (42)

2, 2'–Dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenylmethane (**42**) was synthesised successfully by both microwave and conventional methods (see Table 1). The yields varied from 44% to 80%. However, it is pertinent to note that in method C the yield was the lowest at 44%. This was due to the insuficient amount of the formalin. This conclusion is supported by the result obtained in method D where sufficient amount of formalin was used and the yield was 80%. The plausible mechanism of the conversion of phenol (**52**) to bisphenol (**42**) is depicted in Scheme 1.



Scheme 4. Plausible mechanism for the conversion of phenol (**52**) to bisphenol (**42**).

The structure of compound (**42**) was confirmed by spectroscopic analysis (Table 7). The spectra of compound (**42**) are contained in Appendix A.



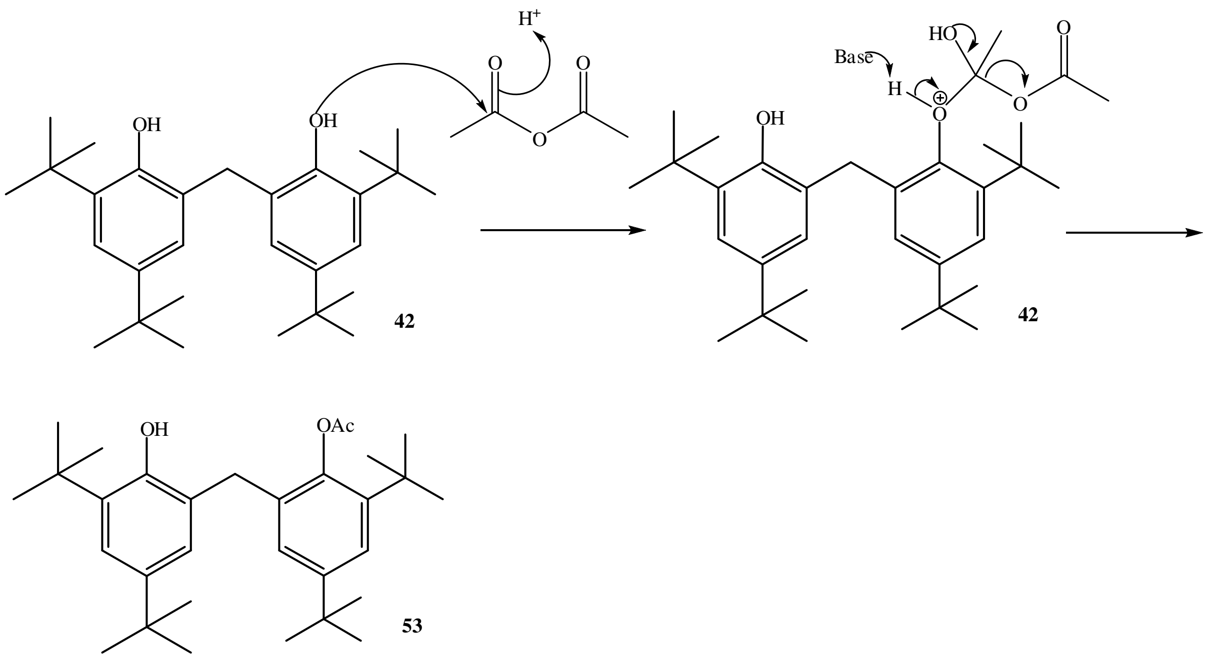
42

Table 7. ^{1}H and ^{13}C NMR spectral data of compound (**42**)

Carbon Position	δ_C	Multiplicity [DEPT]	δ_H
1, 1'	135.5	2 x C	-
2, 2'	149.9	2 x C	-
3, 3'	143.0	2 x C	
4, 4'	122.6	2 x CH	7.17 (2H, d, *J* = 2.5 Hz)
5, 5'	126.1	2 x C	-
6, 6'	125.2	2 x CH	7.17 (2H, d, *J* = 2.4 Hz)
7	33.1	CH_2	3.59 (2H, s)
8, 8'	35.0	2 x C	-
9, 9'	35.0	2 x C	-
10, 10'	31.0	6 x CH_3	1.48 (18H, s)
11, 11'	32.0	6 x CH_3	1.24 (18H. S)
2 x OH	-	3.5 (2H,s)	

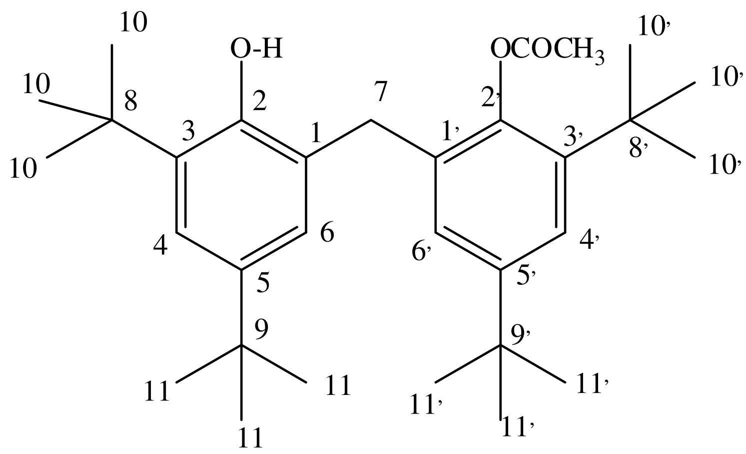
5.2 Synthesis of 2-hydroxy-2’-acetoxy-3, 3’, 5, 5’-tetra-*tert*–butyldiphenylmethane (53)

2-Hydroxy-2’-acetoxy-3,3’,5,5’-tetra-*tert*–butyldiphenylmethane (**53**) was synthsised successfully by both microwave and conventional methods (see Table 2) and the reaction yields varied from 84% to 91%. The microwave method C gave the highest yield of 91%. The catalyst used in method C was p-toluenesulphonic acid. The plausible mechanism for this reaction is summarised in Scheme 2.



Scheme 5. Plausible mechanism for the mono-acetylation of bisphenol (**42**).

The structure of compound (53) was confirmed by its spectra data (Table 8). The spectra of compound (**53**) are included in Appendix B.



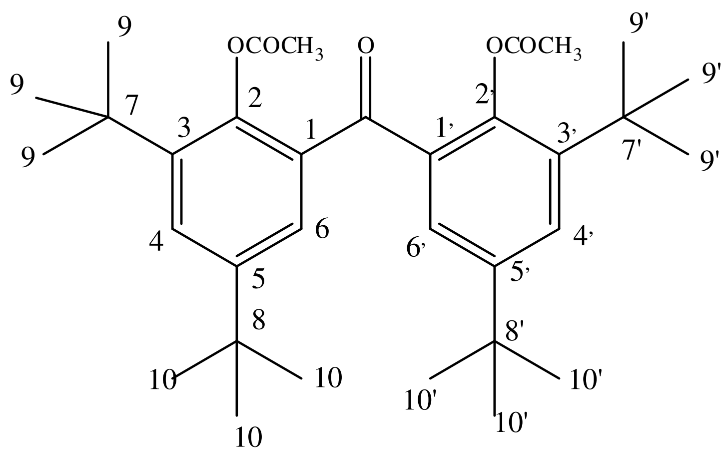
53

Table 8. ^{1}H NMR spectral data of compound (**53**)

Carbon Position	δ_H
1, 1’	-
2, 2’	-
3, 3’	-
4	7.26 (1H, d, *J* = 2.36 Hz, Ar-H)
4’	6.97 (1H, d, *J* = 2.36 Hz, Ar-H)
5, 5’	-
6	7.22 (1H, d, *J* = 2.44 Hz, Ar-H)
6’	6.73 (1H, d, *J* = 2.32 Hz, Ar-H)
7	3.68 (2H, s, $-CH_2-$)
8, 8’	-
9, 9’	-
10	1.34 (9H, s, Bu^t)
10’	1.28 (9H, s, Bu^t)
11	1.32 (9H, s, Bu^t)
11’	1.20 (9H, s, Bu^t)
-OH	Not so obvious
$-OCOCH_3$	2.35 (3H, s)

5.3 Synthesis of 2,2'–diacetoxy-3,3',5,5'-tetra-*tert*-butylbenzophenone (49)

2,2'–Diacetoxy-3,3',5,5'-tetra-*tert*-butylbenzophenone (**49**) was synthesised from 2-hydroxy-2'-acetoxy-3, 3', 5, 5'-tetra-*tert*–butyldiphenylmethane (**53**) by four conventional methods (Table 3). The yields varied from 30% to 60%. Method D (Table 3) gave the highest yield of 60%. This method was very successful when compared to methods A – C which gave 30% - 33% of compound (**49**). The success of method D could be attributed to the effectiveness of Jones reagent in oxidation reactions. The acetylation of the second phenolic hydroxyl group during the oxidation came as a surprise because it was unexpected. The spectral data of compound (**49**) are presented in Table 9 and the spectra are included in Appendix C.



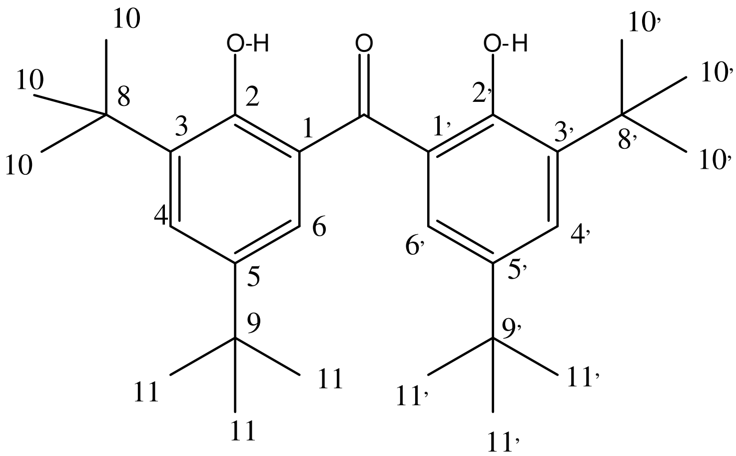
49

Table 9. ^{1}H NMR spectral data of compound (**49**)

Carbon Position	δ_H
1, 1'	-
2, 2'	-
3, 3'	-
4, 4'	7.55 (2H, d, *J* = 2.7 Hz, 2 x Ar-H)
5, 5'	-
6, 6'	7.49 (2H, d, *J* = 2.36 Hz, 2 x Ar-H)
7, 7'	-
8, 8'	-
9, 9'	-
10, 10'	1.34 (18H, s, 2 x Bu^t)
11, 11'	1.27 (18H, s, 2 x Bu^t)
2 x $OCOCH_3$	1.94 (6H, s)

5.4 Synthesis of 2,2'–dihydroxy-3,3' 5,5' tetra-*tert*-butylbenzophenone (43)

2,2'–Dihydroxy-3,3' 5,5' tetra-*tert*-butylbenzophenone (**43**) was synthesised from compound (**49**) by alkaline deacetylation using both conventional and microwave methods (Table 4). The reaction yields varied from 71% to 75%. The MW method C gave the highest yield of 75%. The spectral data of compound (**43**) are presented in Table 10 and the spectra are included in Appendix D.

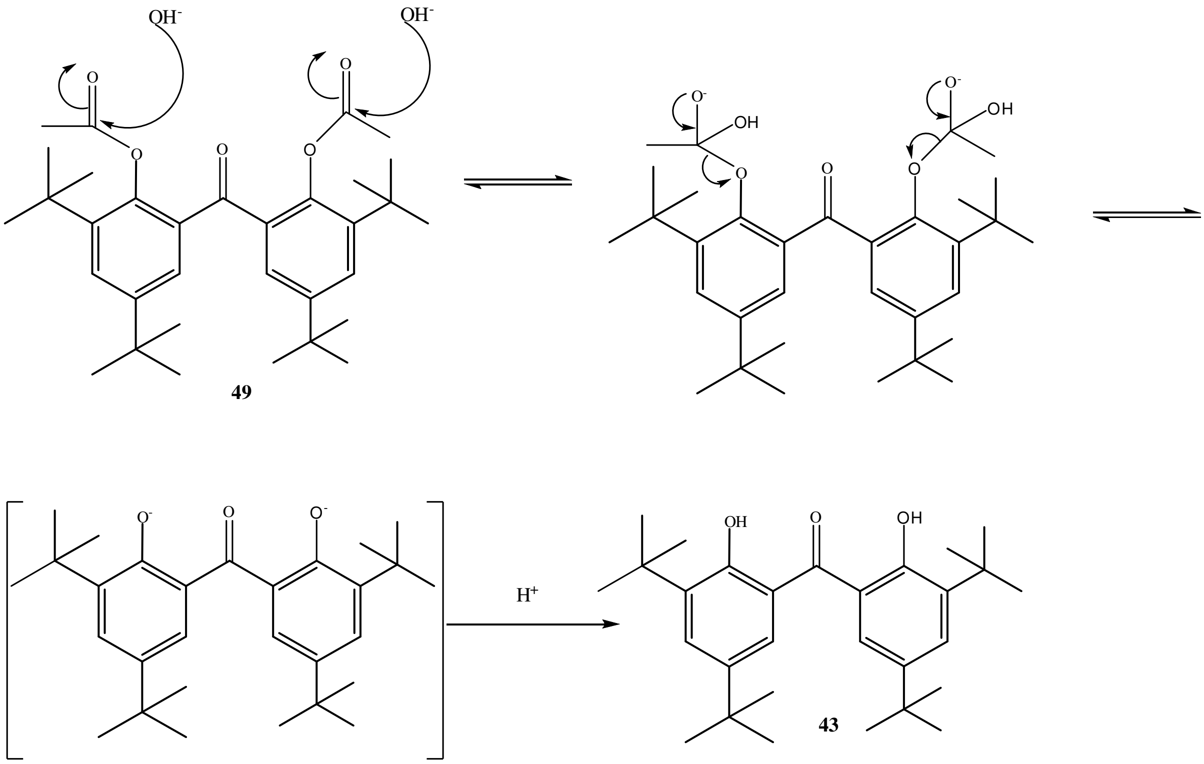


43

Table 10. [1]H and [13]C NMR spectral data of compound (**43**).

Carbon Position	δ_C	Multiplicity [DEPT]	δ_H
1, 1’	119.6	C	-
2, 2’	158.9	C	-
3, 3’	139.8	C	-
4, 4’	130.5	CH	7.52 (2H, d, J = 2.1 Hz, 2 x Ar-H)
5, 5’	137.8	C	-
6, 6’	127.6	CH	7.34 (2H, d, J = 2.25 Hz, 2 x Ar-H)
7, 7’	204.7	C	-
8, 8’	35.3	C	-
9, 9’	34.4	C	-
10, 10’	31.5	CH_3	1.43 (18H, s, 2 x Bu^t)
11, 11’	29.5	CH_3	1.25 (18H, s, 2 x Bu^t)
2 x –OH			11.15 (2H, s)

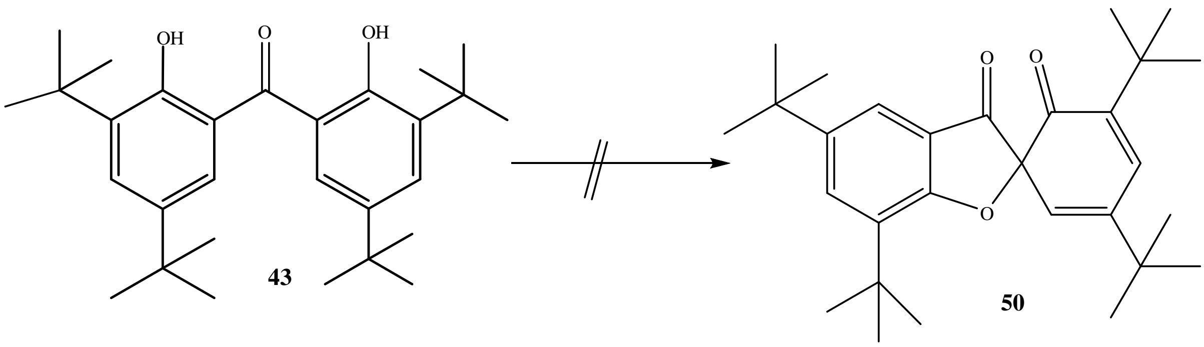
The plausible mechanism for the de-esterification of compound (**49**) is shown in Scheme 6.



Scheme 6. Plausible mechanism for the de-esterification of compound (**49**).

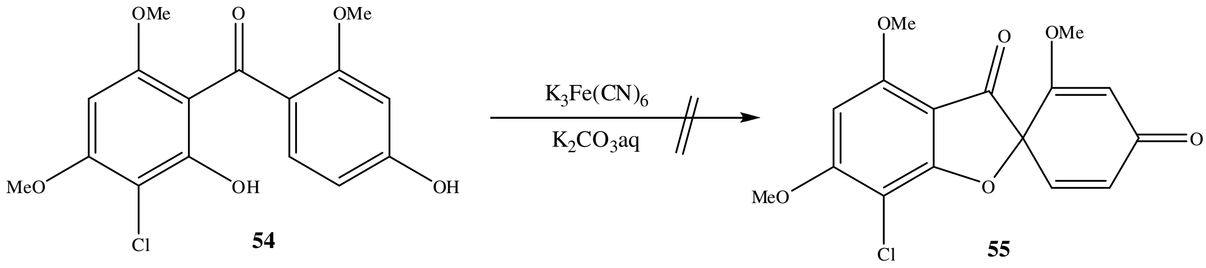
5.5 Attempted synthesis of *ortho*-grisan (50)

The synthesis of *ortho*-grisan (**50**) from compound (**43**) was attempted using four conventional methods (see Table 5) and were unsuccessful.



Our frustration from the various attempts to synthesise *ortho*-grisan (**50**) encouraged us to search the literature for clues and new ideas. Taub *et al.*[1] have reported their inability to synthesise *para*-grisan (**55**) from benzophenone (**54**) using potassium ferricyanide method.

The synthesis of the desired *ortho*-grisan (**50**) was discontinued for future project.



5.6 Synthesis of *ortho*-deoxygrisan (38)

ortho-Deoxygrisan (**38**) was successfully synthesised in 30% to 96% yields using methods A – E which are summarised in Table 6 (Chapter 4). Methods A, B, C, and D are reported for the first time as methods for synthesising compound (**38**). Method C (Ag_2O/DCM) gave the highest yield of 96%. The MW method B gave 80% yield. The structure of the synthesised compound (**38**) was confirmed by spectroscopic methods and comparison with literature values (see Table 11).[2] The spectra of compound (38) are included in Appendix E. A plausible mechanism for the formation of compound (**38**) from compound (**42**) is presented in Scheme 7.

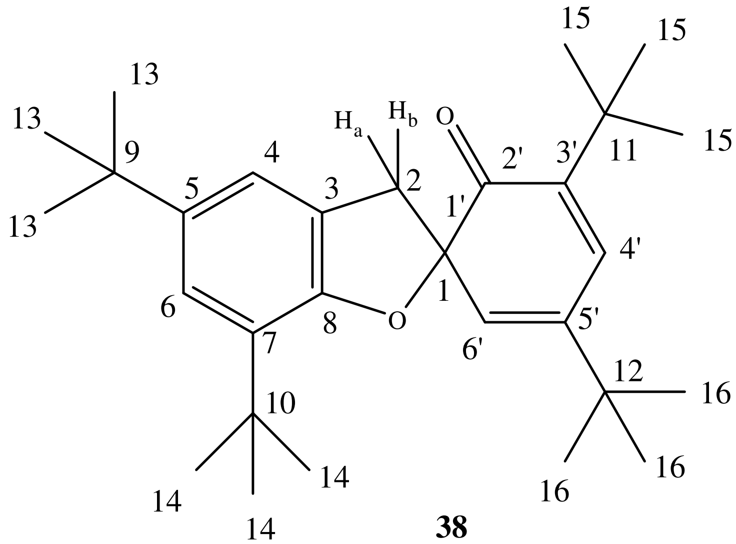


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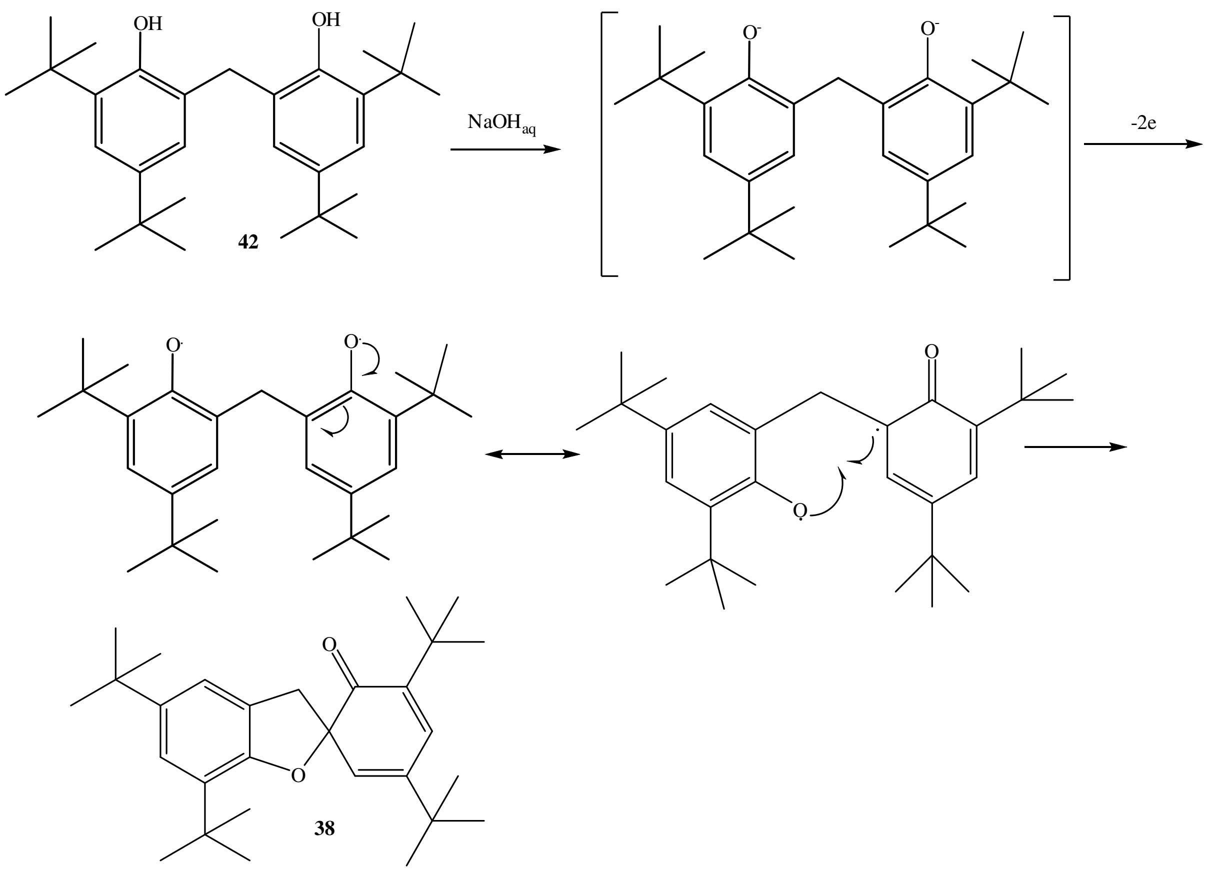
Table 11. ^{1}H and ^{13}C NMR spectral data of compound (**38**).

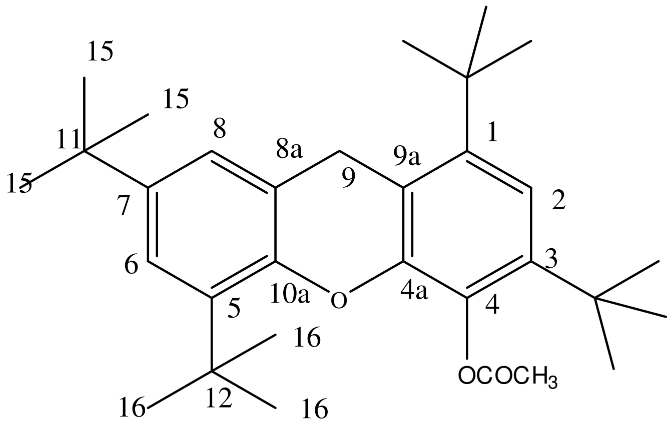
Position	δ_C	Multiplicity [DEPT]	δH
1,1’	88.6	C	-
2	39.6	CH_2	2.96 (H_a, d, J = 15.6 Hz) 3.42 (H_b, d, J = 15.6 Hz)
2’	199.9	C	-
3	124.1	C	-
3’	143.6	C	-
4	124.1	CH	7.09 (1H, bs, Ar-H)
4’	131.9	CH	6.14 (1H, d, J = 2.4 Hz)
5	141.8	C	-
6	122.1	CH	7.0 (1H, bs, Ar-H)
6’	119.6	CH	6.31 (1H, d, J = 2.4 Hz)
7	130.9	C	-
8	155.3	C	-
9	34.5	C	-
10	34.4	C	-
11	34.3	C	-
12	34.2	C	-
13	31.8	3 x CH_3	1.55 (9H, s, Bu^t)
14	29.3	3 x CH_3	1.33 (9H, s, Bu^t)
15	29.3	3 x CH_3	1.30 (9H, s, Bu^t)
16	28.9	3 x CH_3	1.23 (9H, s, Bu^t)



Scheme 7. Plausible mechanism for the formation of compound (**38**) from compound (**42**) by oxidative phenolic coupling.

5.7 Acid-catalysed rearrangement of *ortho*-deoxygrisan (38)

The acid-catalysed rearrangement of *ortho*-deoxygrisan (**38**) was carried out in the presence of acetic anhydride without sunlight as described in section 3.8 (Chapter 3). The column chromatography of the reaction mixture led to the isolation of a solid compound D (section 4.8 (Chapter 4) as the major product. The ^{1}H and ^{13}C NMR spectral data of compound D are presented in Table 12. The spectra of compound D are included in Appendix F. On the basis of its spectroscopic properties, structure D1 (Figure 1) is proposed for compound D. This assignment is motivated by the work of Shode[2] who had investigated the acid-catalysed rearrangement of compound (**38**) in 1980. Further chemical characterisation is required to confirm the proposed structure D especially the observation of the diastereotopicity of the bridge methylene group in compound D.



D

Figure 1. Proposed structure for compound D.

Table 12. ^{1}H and ^{13}C NMR spectral data of compound D.

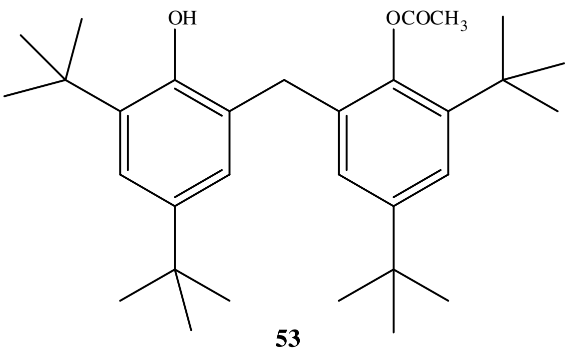
Position	δ_C	Multiplicity [DEPT]	δ_H
1	146.5	C	
2	118.6	CH	7.13 (1H, s, Ar-H)
3	135.9	C	
4	145.4	C	
4a	149.4	C	
5	136.0	C	
6	121.5	CH	7.20 (1H, d, *J* = 2.24 Hz)
7	143.7	C	
8	122.8	CH	7.05 (1H, d, *J* = 2.12 Hz)
8a	138.7	C	
9a	122.9	C	
9	36.1	CH_2	4.33 (1H, d, *J* = 17.2 Hz) 3.91 (1H, d, *J* = 17.1 Hz)
10a	138.7	C	
11	34.94	C	
12	34.68	C	

Table 12. Continued

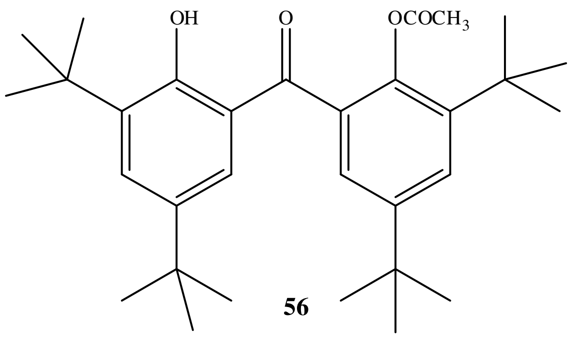
Position	δ_C	Multiplicity [DEPT]	δ_H
13	34.44	C	
14	34.68	C	
15	30.43	3 x CH_3	1.47 (9H, s)
16	31.11	3 x CH_3	1.45 (9H, s)
17	29.86	3 x CH_3	1.33 (9H, s)
18	31.59	3 x CH_3	1.30 (9H, s)
-$OCOCH_3$	22.01		2.42 (3H, s)

5.8 Reactions of 2-hydroxy-2'- acetoxy-3, 3', 5, 5'-tetra-*tert*-butyldiphenylmethane (53) with selenium dioxide

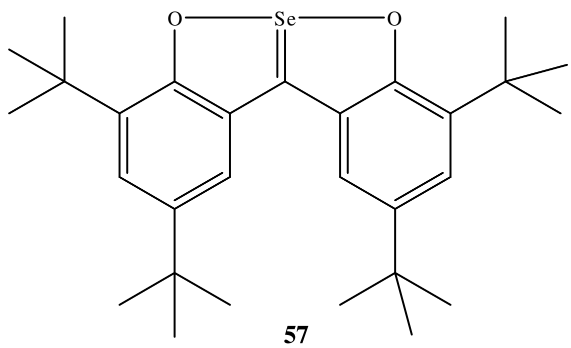
In an attempt to synthesise compound (**56**), compound (**53**) was reacted with SeO_2 at high temperature without microwave radiation. Chromatographic separation of the reaction mixture led to the isolation of a yellow solid (compound B). The ^{1}H NMR spectrum of compound B contained two meta-coupled aromatic protons at δ 8.45 (1H, d, *J* = 2.16 Hz) and δ 7.64 (1H, d, *J* = 2.0 Hz). There were also two singlets at δ 1.54 and δ 1.45 attributable to four *tert*-butyl groups. These spectral data are in agreement with the spectral data of compound (**57**) which was proposed for the oxidation product of bisphenol (**42**) with SeO_2.[2] To the best of our knowledge, this is the first report on the formation of compound (**57**) from compound (**53**).



53

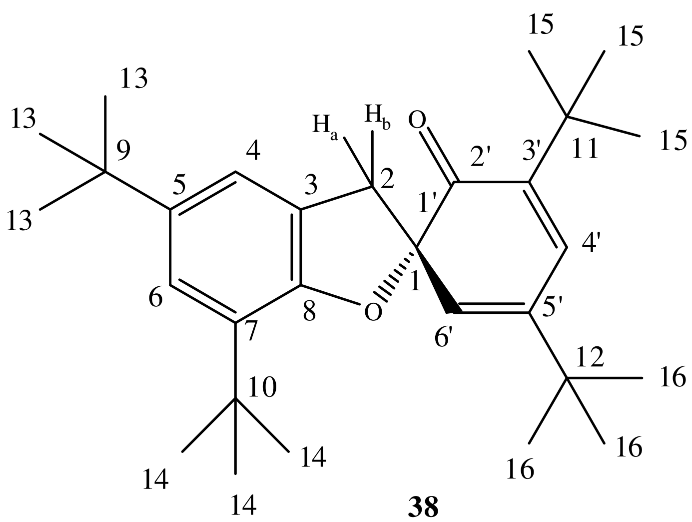


56



57

In a similar reaction, a mixture of compound **53** and selenium dioxide was irradiated by microwave. Chromatography of the reaction products gave a yellow solid, compound C. The ^{1}H NMR spectrum of compound C contained three aromatic doublets at δ 7.10 (1H, d, *J* = 1.9 Hz), δ 6.83 (1H, d, *J* = 2.5 Hz), δ 6.14 (1H, d, *J* = 2.5 Hz), one broad aromatic singlet at δ 6.96 (1H, bs), two doublets at δ 3.43 (1H, d, *J* = 15.6 Hz), δ 3.01 (1H, d, *J* = 15.6 Hz), and four *tert*-butyl groups at δ 1.38, 1.26, 1.22, and 1.12. These spectral data are very similar to the spectral data of *ortho*-deoxygrisan (**38**). On this basis, we concluded that compound C has structure **38**.



38

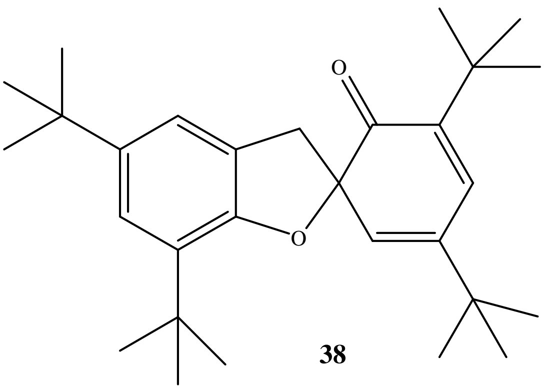
5.9 References

1. Daub, D.; Kuo, C.H.; Wendler, N.L. *Journal of Organic Chemistry*, **1963,** 28(12), 3344-8.
2. Shode, F.O.; PhD. Thesis. **1980**

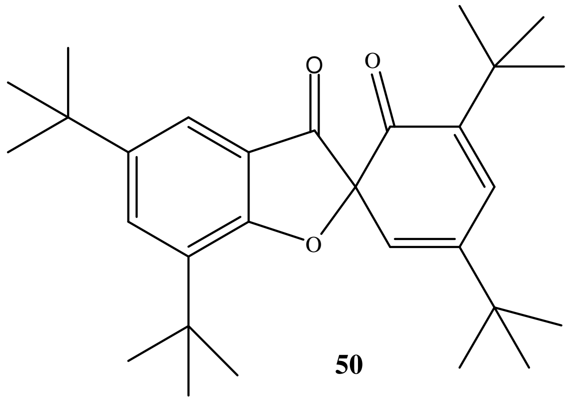
Chapter 6

Conclusions

In conclusion, the main objectives of this project were to synthesise *ortho*-grisan (**50**) and *ortho*-deoxygrisan (**38**) using both conventional and microwave methods and investigate their acid-catalysed rearrangement.

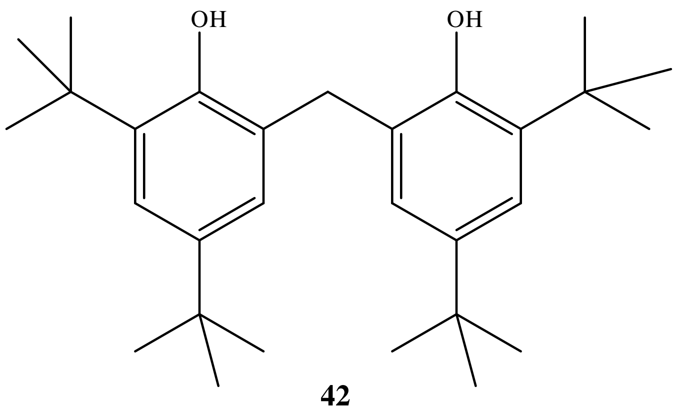


38



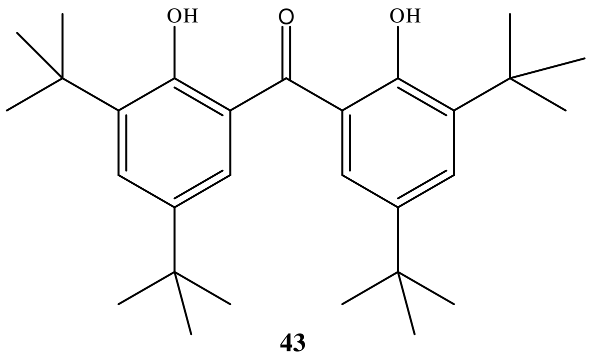
50

ortho-Deoxygrisan (**38**) was successfully synthesised from bisphenol (**42**) using both conventional and microwave methods. The highest yield (96%) was obtained by the reaction of compound (**42**) with Ag_2O in DCM at ambient conditions for 10 minutes.This was a novel discovery. Furthermore, the microwave method (compound (**42**) plus acetic anhydride plus chromic trioxide plus microwave radiation at 300W, 200^{o}C, 9 min.) gave 80% yield of compound (**38**).

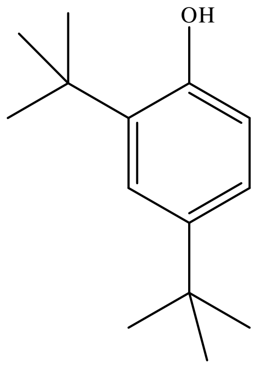


42

The five conventional methods used to synthesise *ortho*-grisan (**50**) from dihydroxy-benzophenone (**43**) failed in our hands. Compound (**43**) was synthesised from compound (**42**) which in turn was synthesised from phenol (**52**).



43



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Appendix

APPENDIX

APPENDIX A: Spectra of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenylmethane (42)

Plate 1 IR spectrum of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenylmethane **(42)**

Plate 2 ^{1}H NMR spectrum of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenyl-methane **(42)**

Plate 3 ^{13}C NMR spectrum 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenyl-methane **(42)**

Plate 4 DEPT spectrum of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenyl-methane **(42)**

Plate 5 GC-MS spectrum of 2, 2'–dihydroxy-3, 3', 5, 5'– tetra-*tert*-butyldiphenyl-methane **(42)**

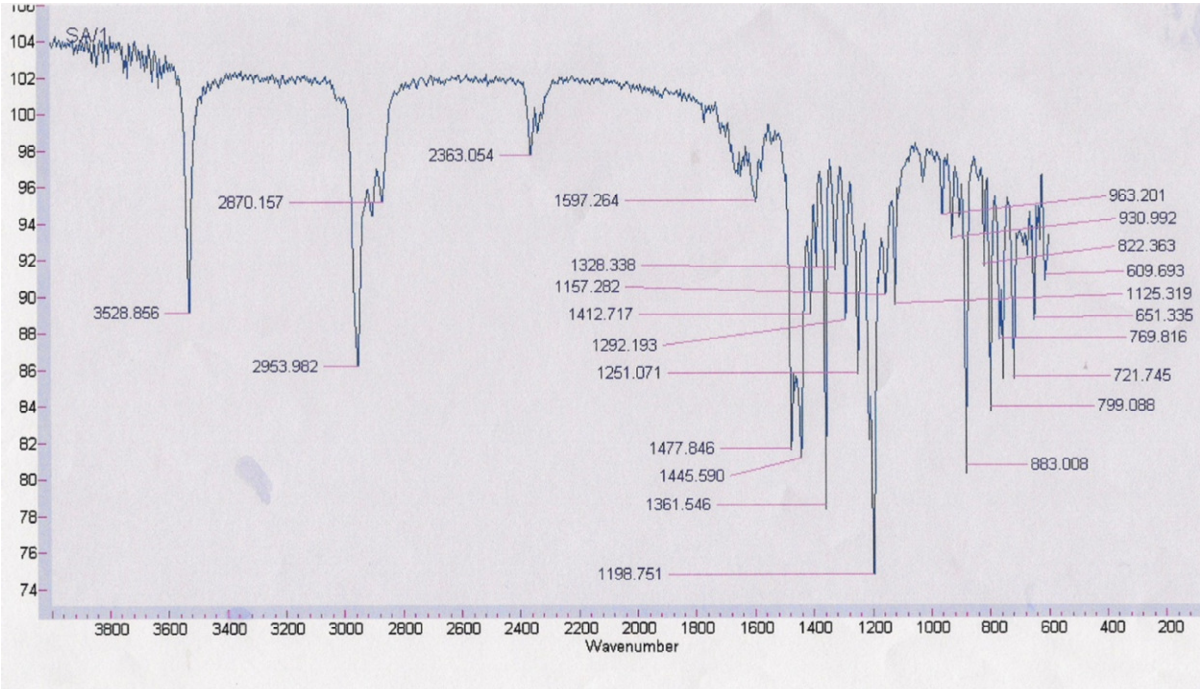
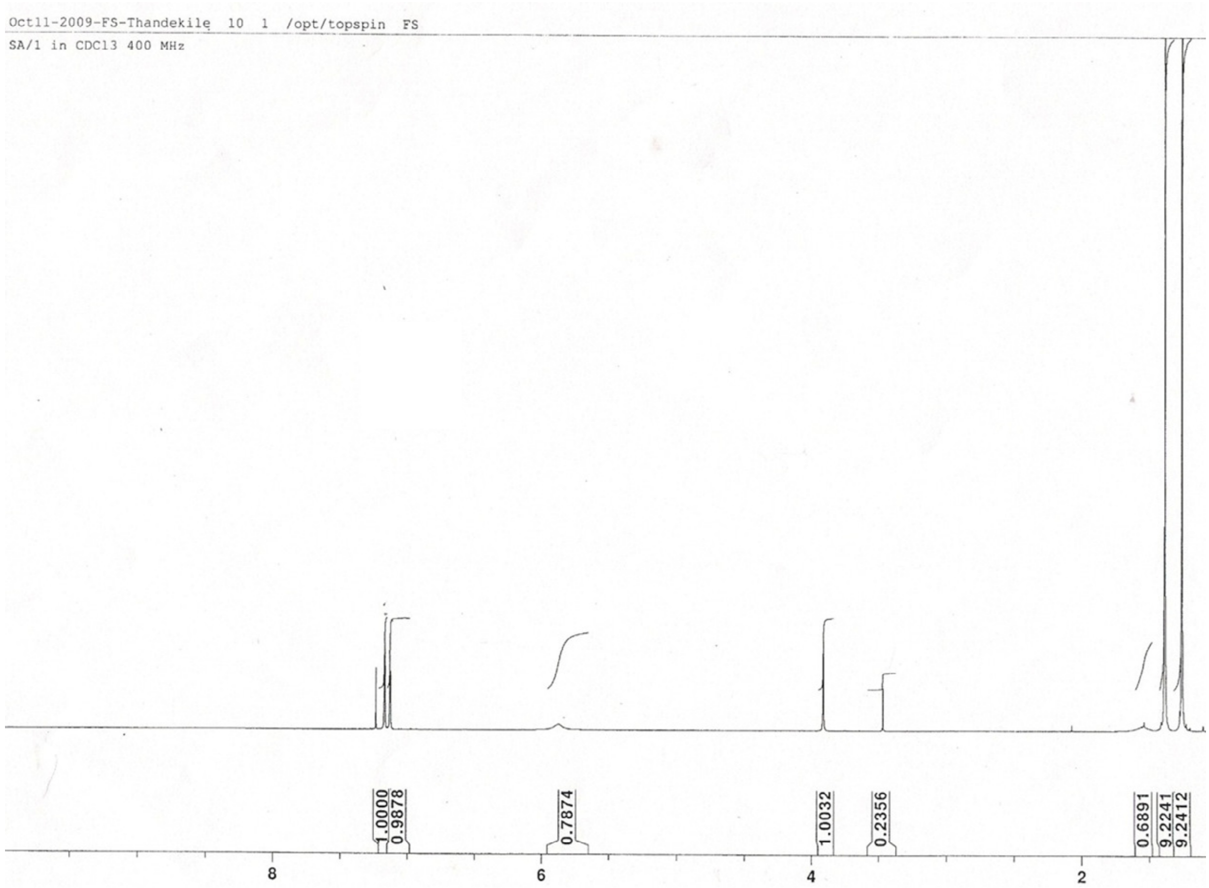
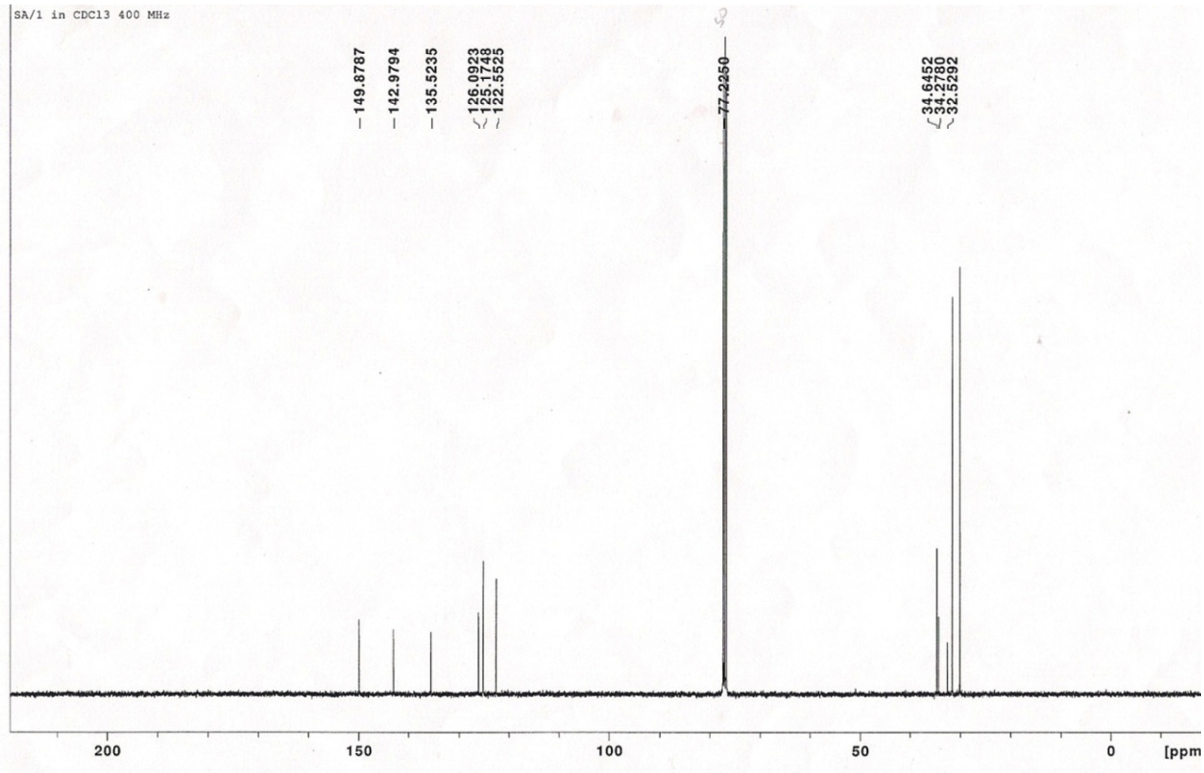


Plate 1. IR spectrum of compound (**42**).



Peak	ν(F1) [ppm]	ν(F1) [Hz]	Intensity [rel]	Annotation
1	7.2332	2894.8714	0.60	
2	7.1730	2870.7782	0.64	
3	7.1668	2868.2968	0.83	
4	7.1310	2853.9689	0.75	
5	7.1251	2851.6077	0.58	
6	5.8748	2351.2126	0.05	
7	3.9104	1565.0204	0.96	
8	3.4674	1387.7229	0.43	
9	2.0736	829.8962	0.05	
10	1.5410	616.7390	0.09	
11	1.4143	566.0312	0.09	
12	1.2739	509.8403	0.21	
13	1.2365	494.8721	0.06	
14	1.2268	490.9899	0.07	
15	1.1010	440.6422	0.06	

Plate 2. ^{1}H NMR spectrum of compound (**42**)



Peak	ν(F1) [ppm]	ν(F1) [Hz]	Intensity [rel]	Annotation
1	149.8787	15083.1028	1.72	
2	142.9794	14388.7890	1.56	
3	135.5235	13638.4615	1.50	
4	126.0923	12689.3489	1.89	
5	125.1748	12597.0159	3.02	
6	122.5525	12333.1197	2.67	
7	77.2250	7771.5687	0.58	
8	34.6452	3486.5335	3.30	
9	34.2780	3449.5802	1.87	
10	32.5292	3273.5890	1.21	

Plate 3. ^{13}C NMR spectrum of compound (**42**).

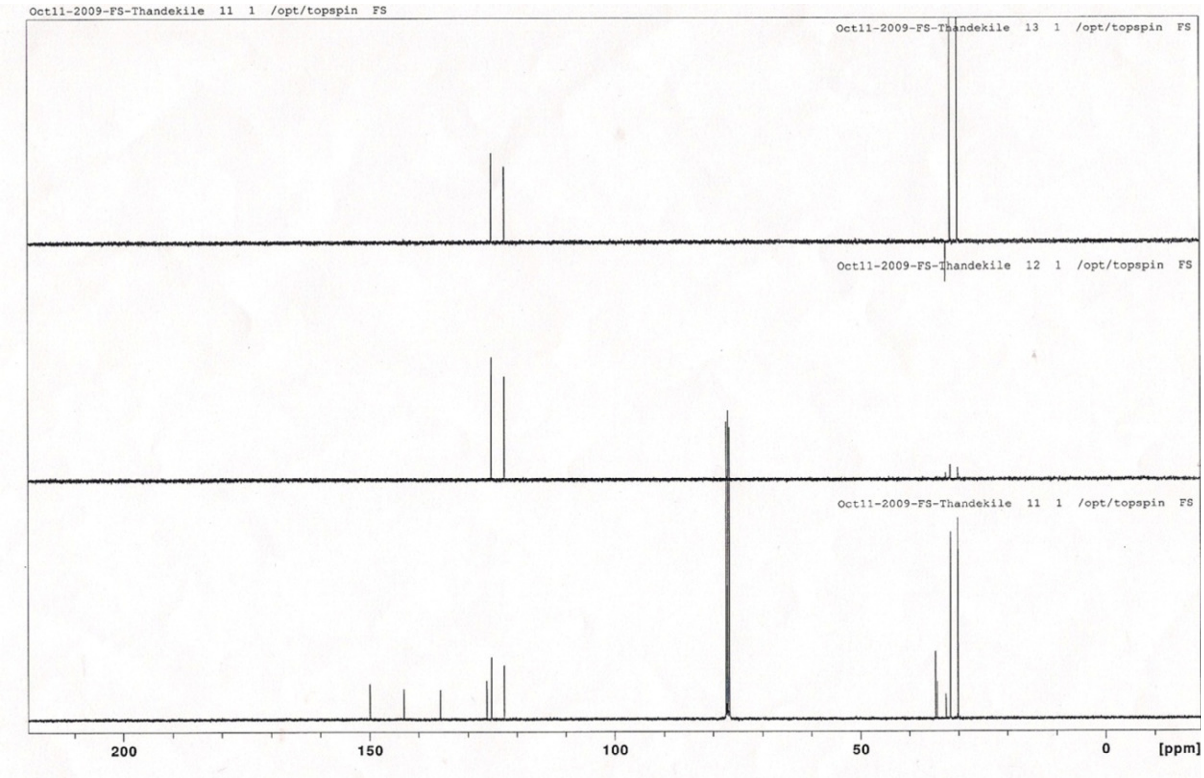


Plate 4. DEPT spectrum of compound (**42**).

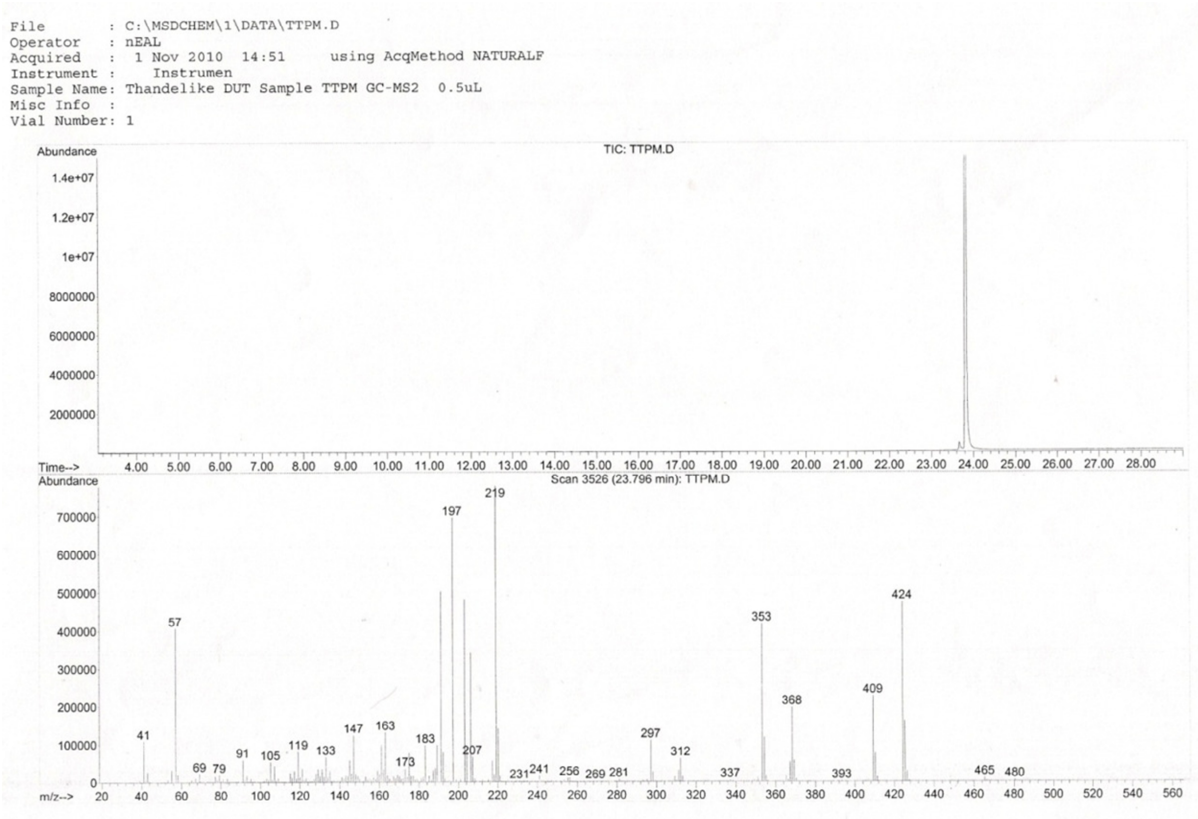


Plate 5. GC-MS spectrum of compound (**42**).

APPENDIX B: Spectra of 2-hydroxy-2'-acetoxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane (53)

Plate 6 IR of 2-hydroxy-2'-acetoxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane **(53)**

Plate 7 ^{1}H NMR of 2-hydroxy-2'-acetoxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane **(53)**

Plate 8 GC-MS spectrum of 2-hydroxy-2'-acetoxy-3,3',5,5'-tetra-*tert*-butyldiphenylmethane **(53)**

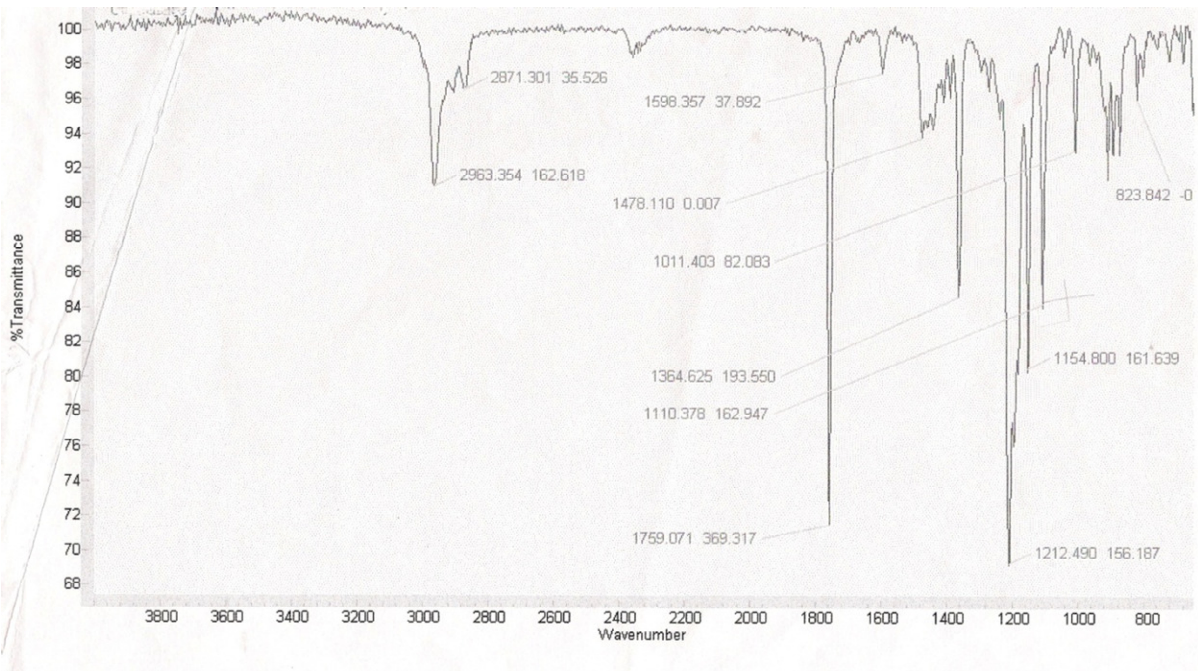
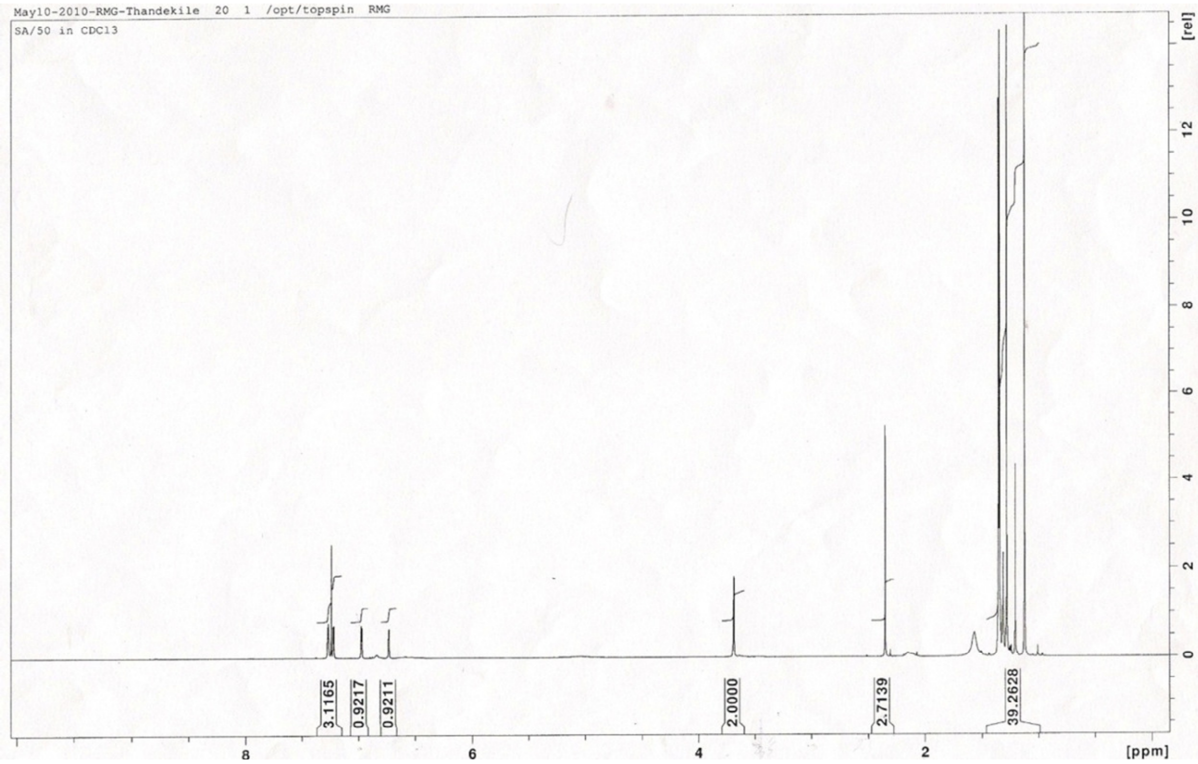


Plate 6. IR spectrum of compound (**53**).



1	7.2715	2910.1998	0.70
2	7.2656	2907.8385	0.79
3	7.2401	2897.6329	2.49
4	7.2243	2891.3095	0.72
5	7.2182	2888.8681	0.75
6	6.9781	2792.7753	0.73
7	6.9722	2790.4140	0.68
8	6.7367	2696.1622	0.64
9	6.7309	2693.8409	0.64
10	3.6887	1476.2916	1.80
11	2.3525	941.5176	5.17
12	1.5677	627.4249	0.54
13	1.3553	542.4182	12.67
14	1.3459	538.6561	14.27
15	1.3344	534.0536	0.77
16	1.3157	526.5695	2.29
17	1.2929	517.4445	0.70
18	1.2821	513.1221	14.70
19	1.2074	483.2256	4.29

Plate 7. ^{1}H NMR spectrum of compound (**53**).

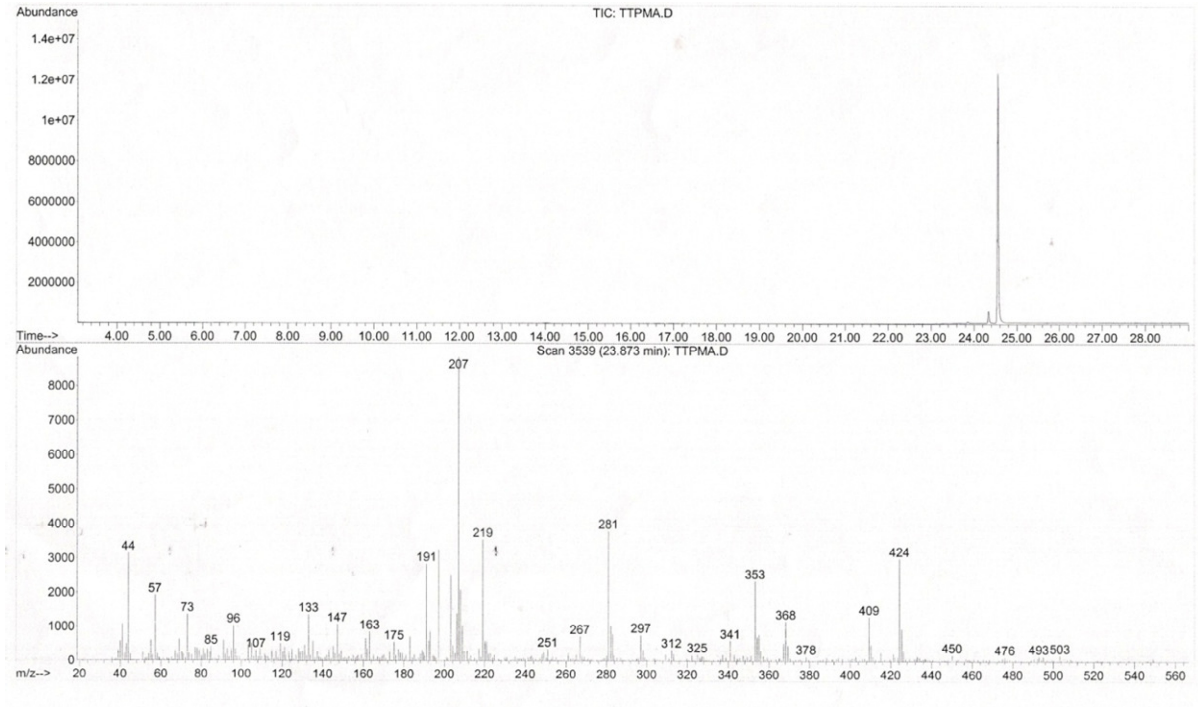


Plate 8. GC-MS spectrum of compound (53).

APPENDIX C: Spectra of 2,2'–diacetoxy-3,3',5,5'-tetra-*tert*-butylbenzophenone (49)

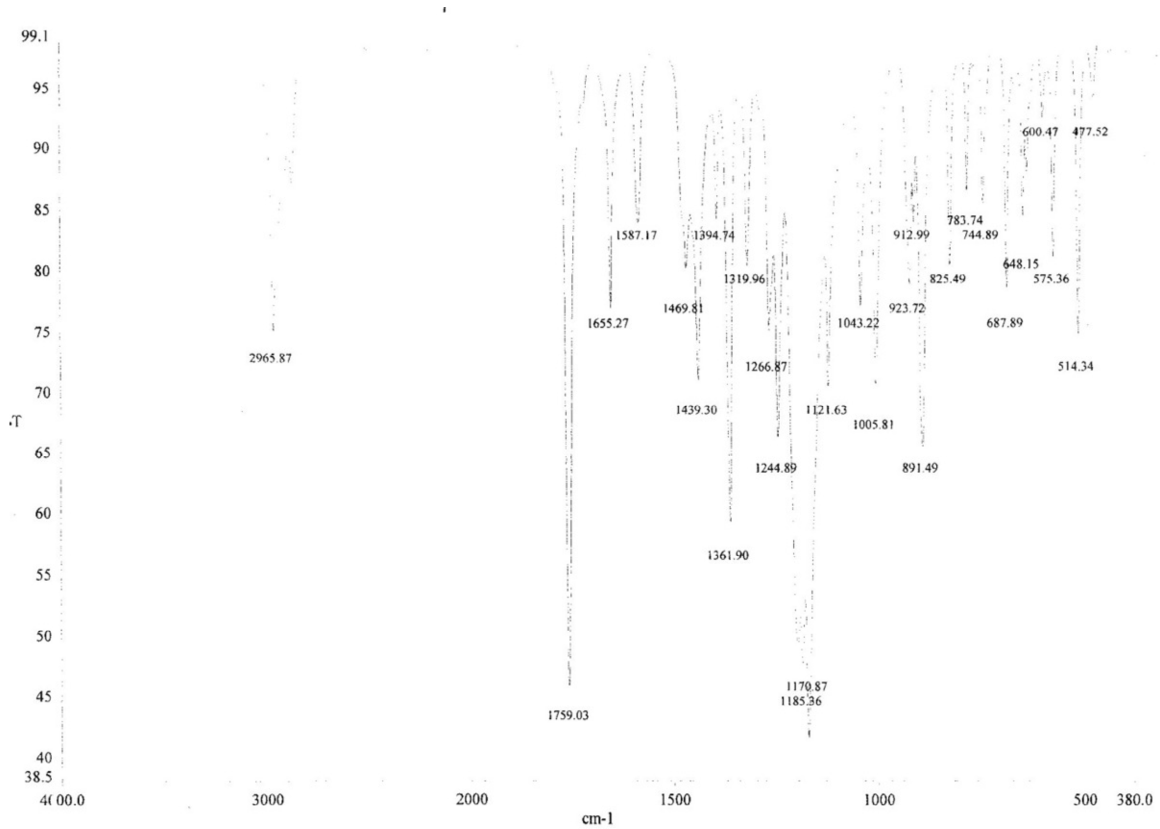


Plate 9. IR spectrum of compound (**49**).

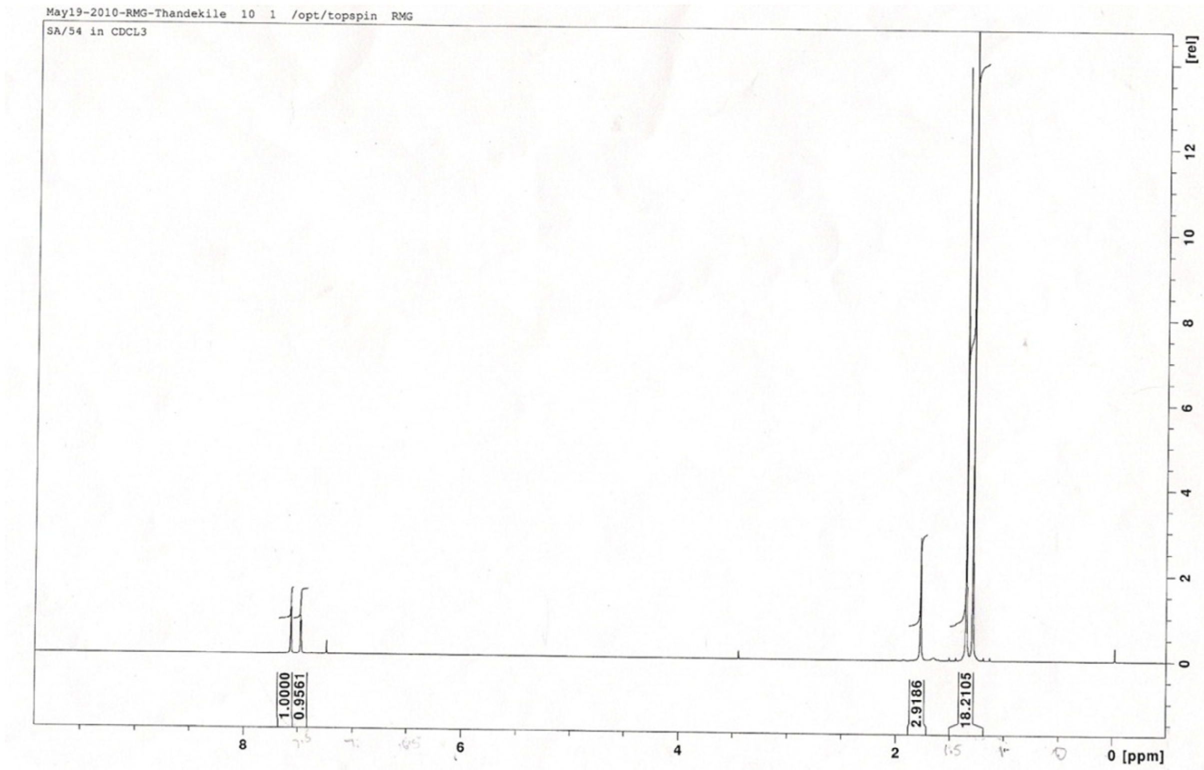


Plate 10. ^{1}H NMR of compound (**49**).

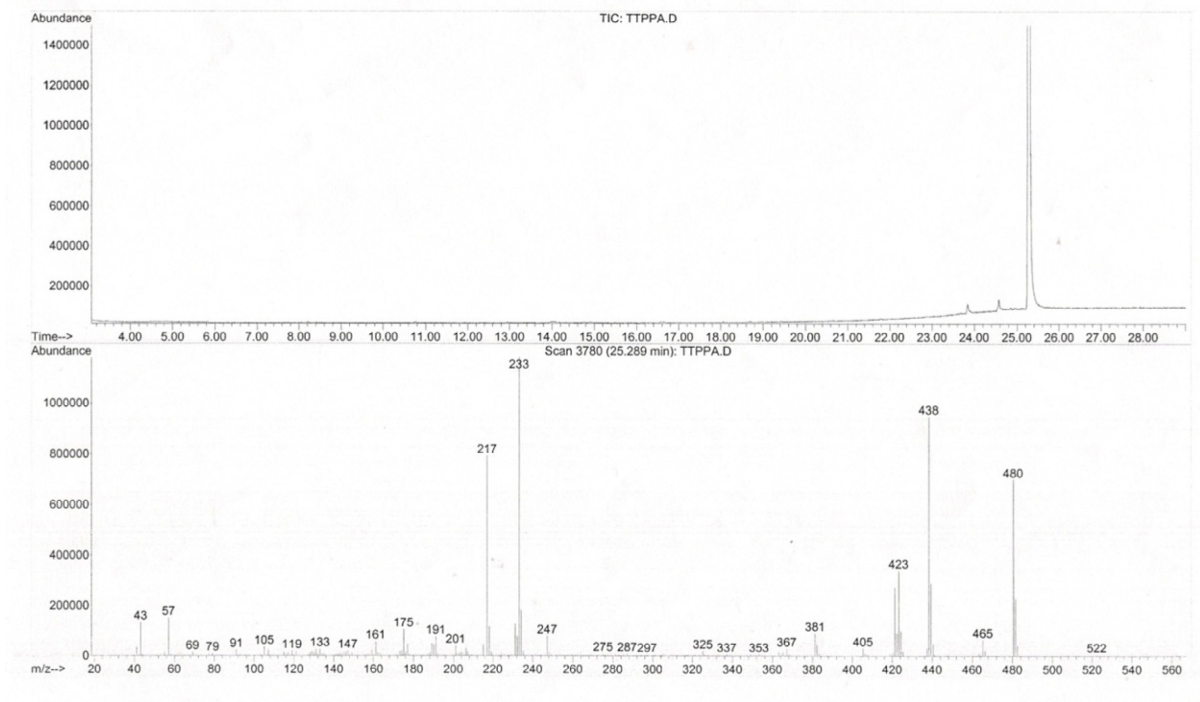


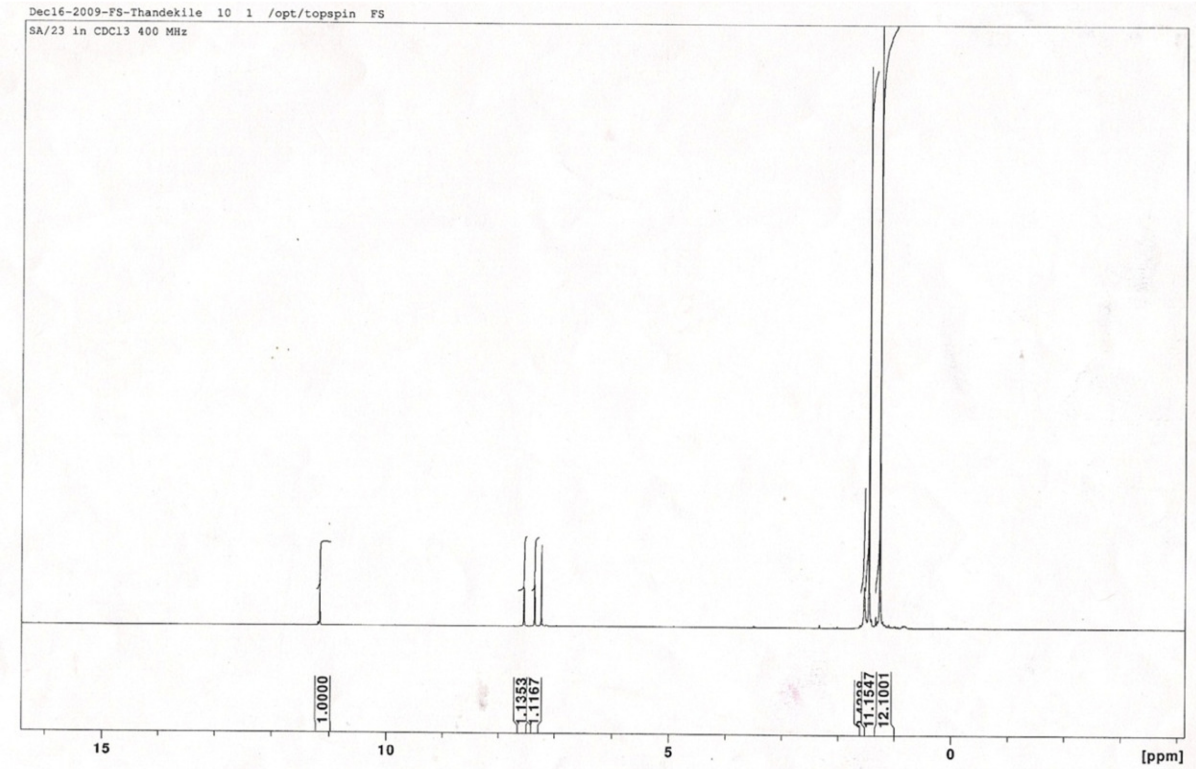
Plate 11. GC-MS spectrum of compound (**49**).

APPENDIX D: Spectra of 2,2 –dihydroxy-3,3’5,5’- tetra-*tert*-butyl benzophenone (43)

Plate 12 — ^{1}H NMR spectrum of 2,2’–dihydroxy-3,3’5,5’- tetra-*tert*-butyl benzophenone **(43)**

Plate 13 — ^{13}C NMR spectrum of 2,2’–dihydroxy-3,3’5,5’- tetra-*tert*-butylbenzophenone **(43)**

Plate 14 — GC-MS spectrum of 2,2’ –dihydroxy-3,3’5,5’- tetra-*tert*-butylbenzophenone **(43)**



Peak	v(F1) [ppm]	v(F1) [Hz]	Intensity [rel]	Annotation
1	11.1533	4463.7739	1.45	
2	7.5369	3016.4182	0.84	
3	7.5317	3014.3371	0.87	
4	7.3472	2940.4965	0.94	
5	7.3415	2938.2152	0.89	
6	7.2255	2891.7897	1.85	
7	1.5205	608.5345	0.93	
8	1.4382	575.5964	13.10	
9	1.2475	499.2745	15.00	

Plate 12. ^{1}H NMR spectrum of compound (**43**).

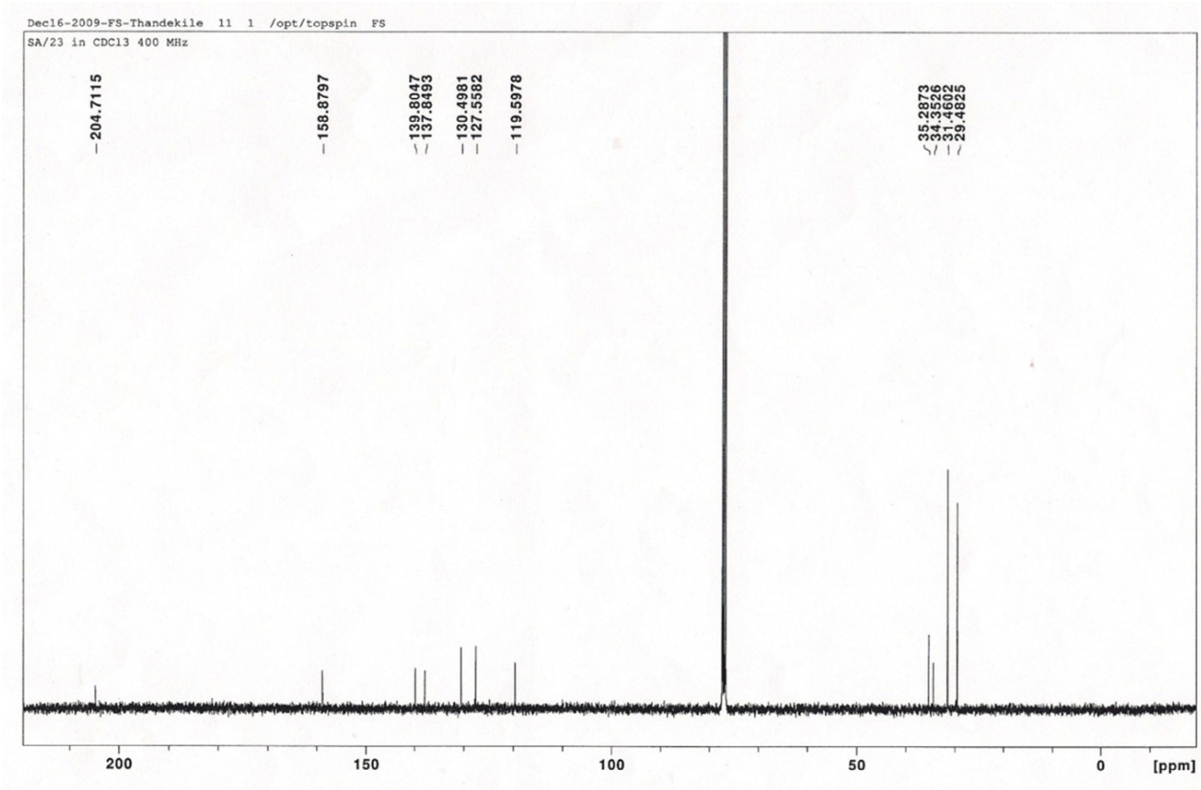


Plate 13. ^{13}C NMR of compound (**43**).

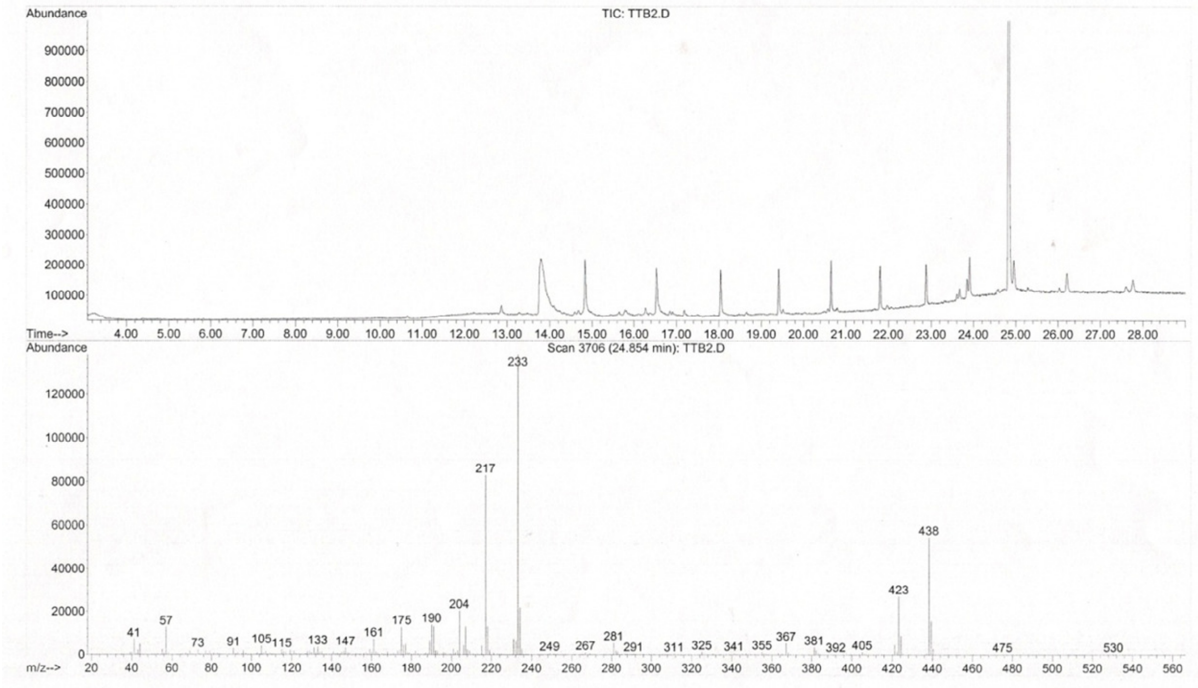


Plate 14. GC-MS spectrum of compound (**43**).

APPENDIX E: Spectra of *ortho*-deoxygrisan (38)

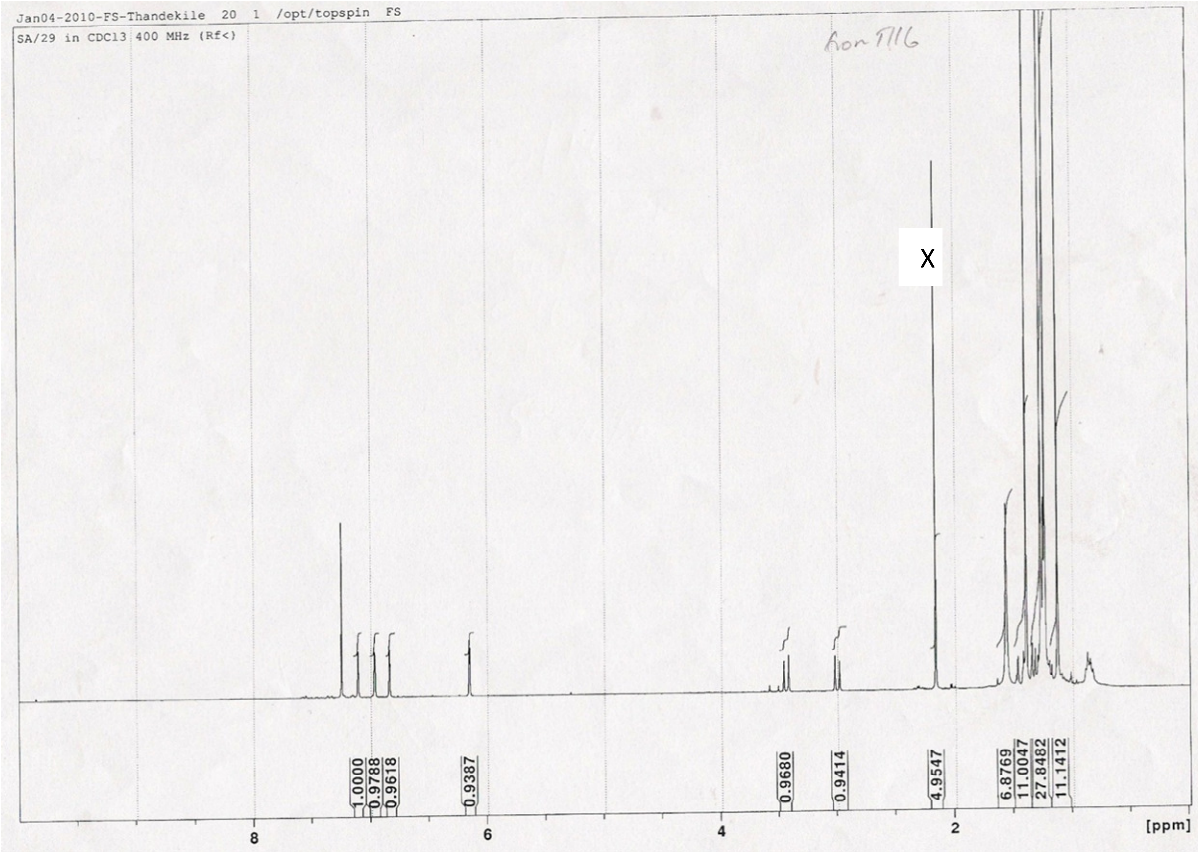


Plate 15. ^{1}H NMR spectrum of compound (**38**).

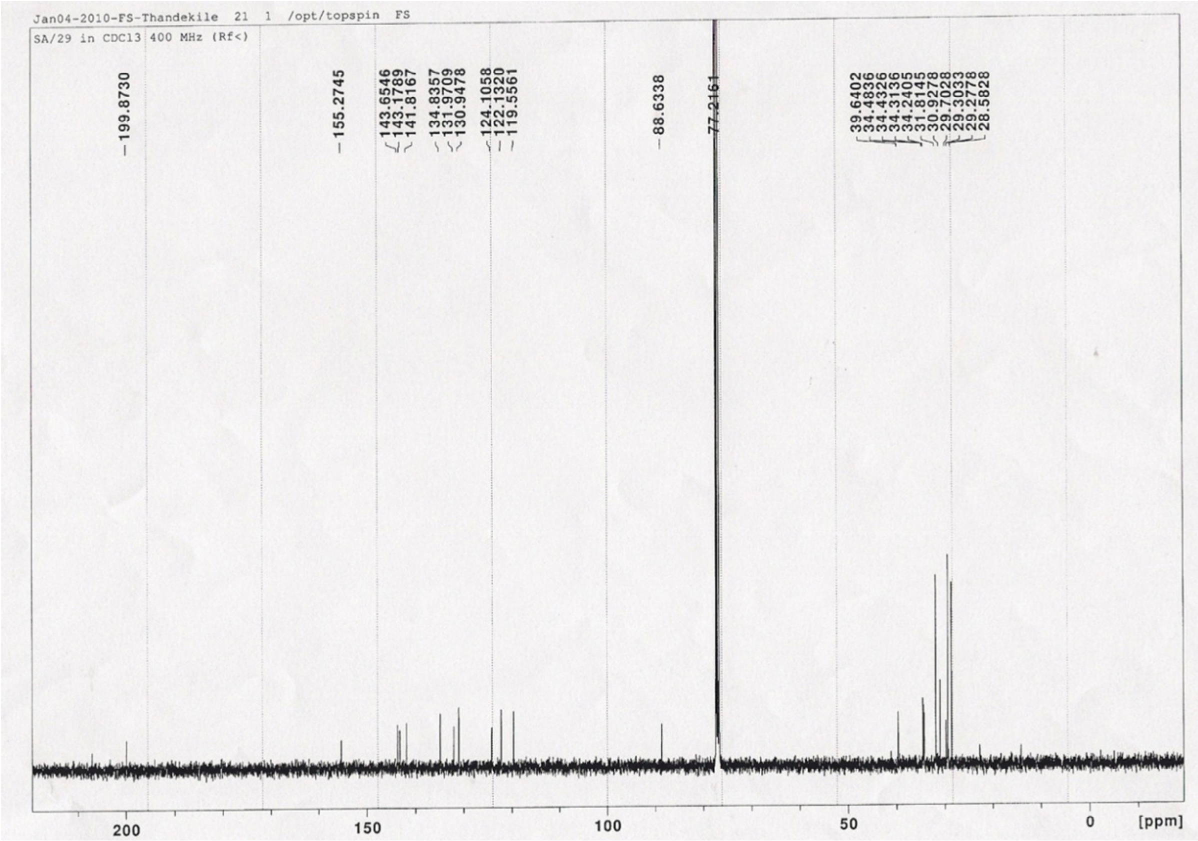


Plate 16. ^{13}C NMR spectrum of compound (**38**).

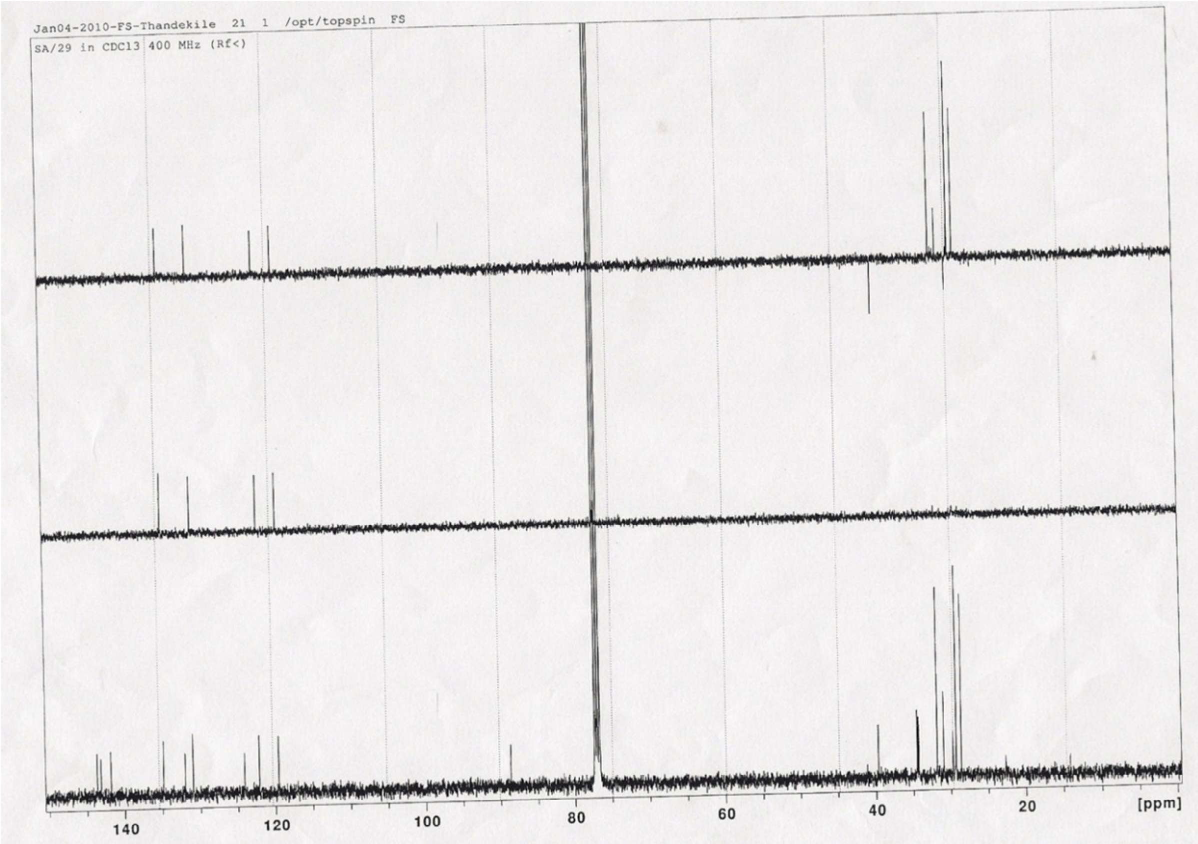


Plate 17. DEPT spectrum of compound (**38**).

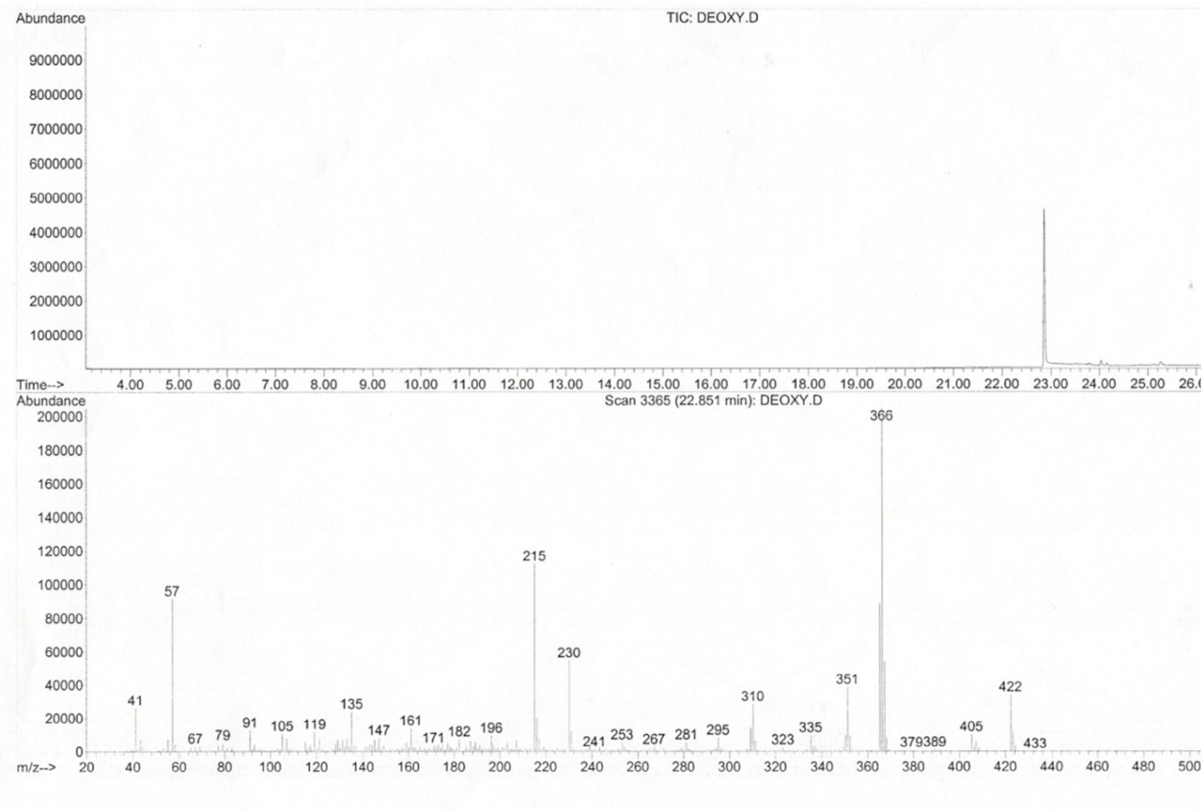


Plate 18. GC-MS spectrum of compound (**38**).

APPENDIX F: Spectra of compound D

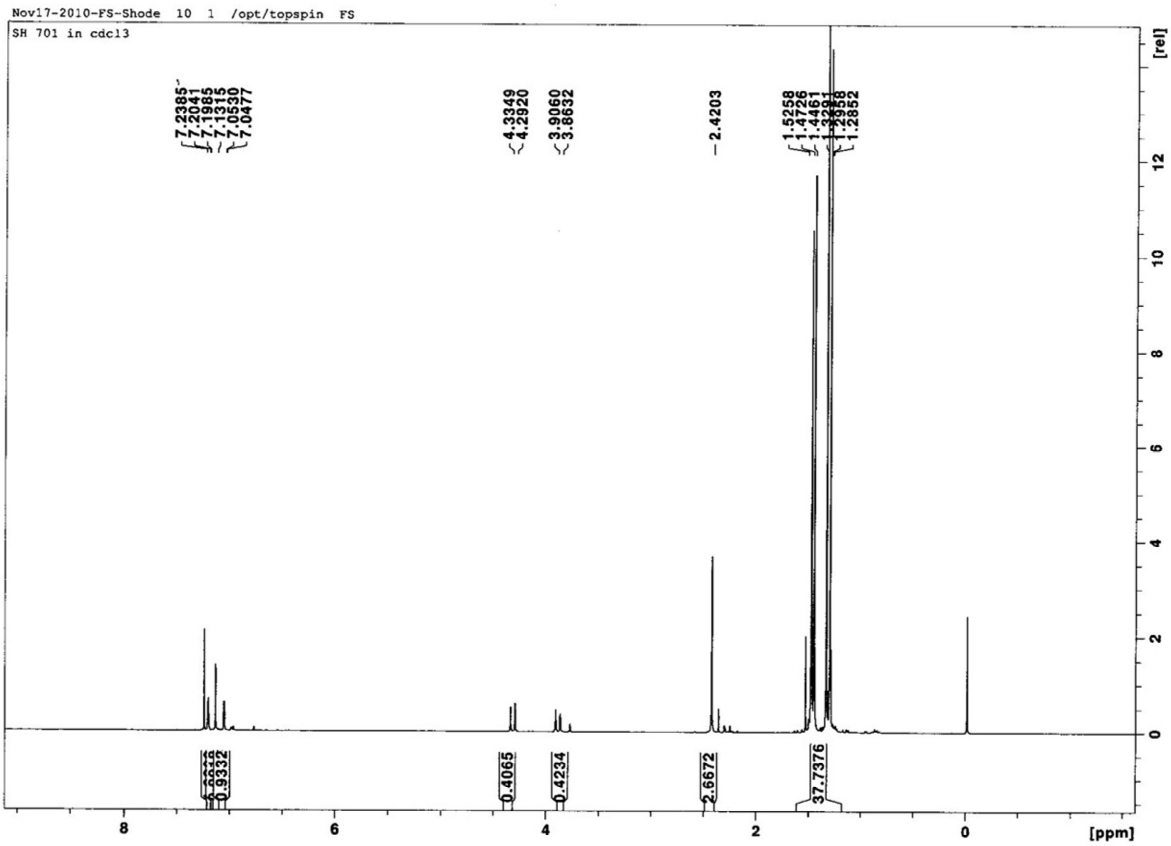


Plate 19. [1]H NMR of compound D

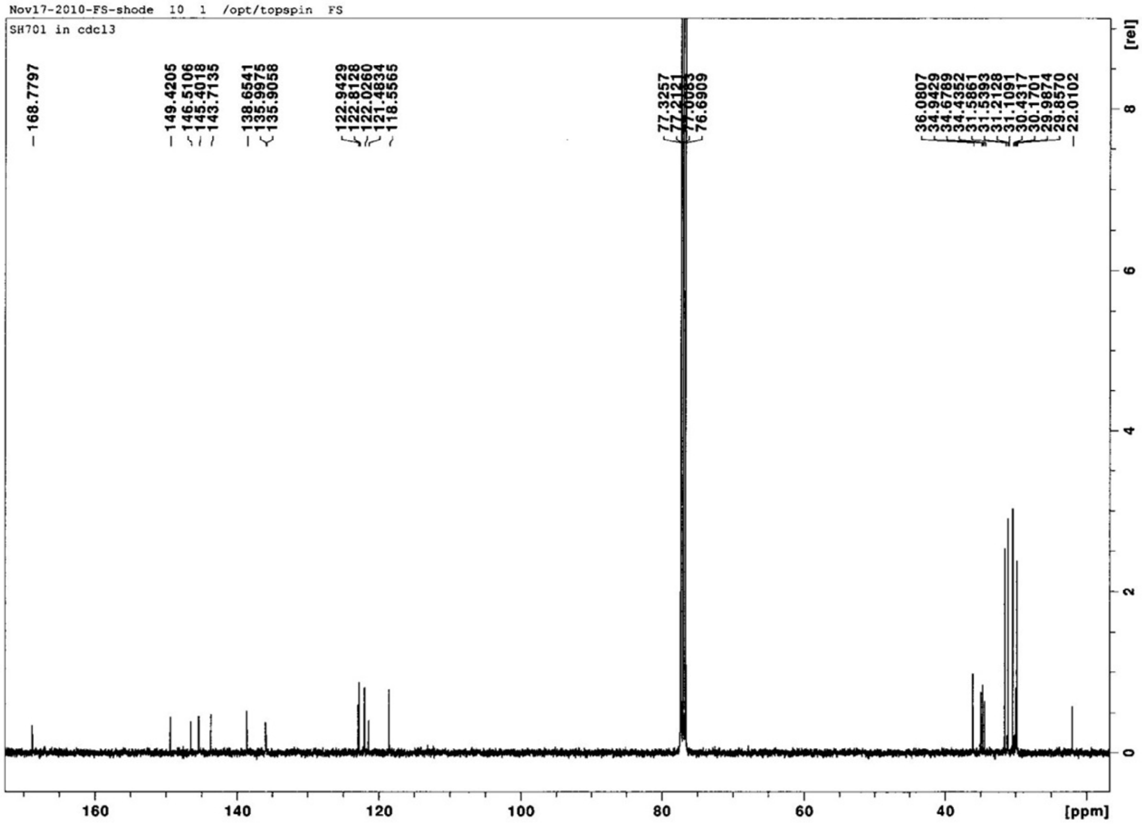


Plate 20. ^{13}C NMR spectrum of compound D

APPENDIX G: Spectra of compounds B and C

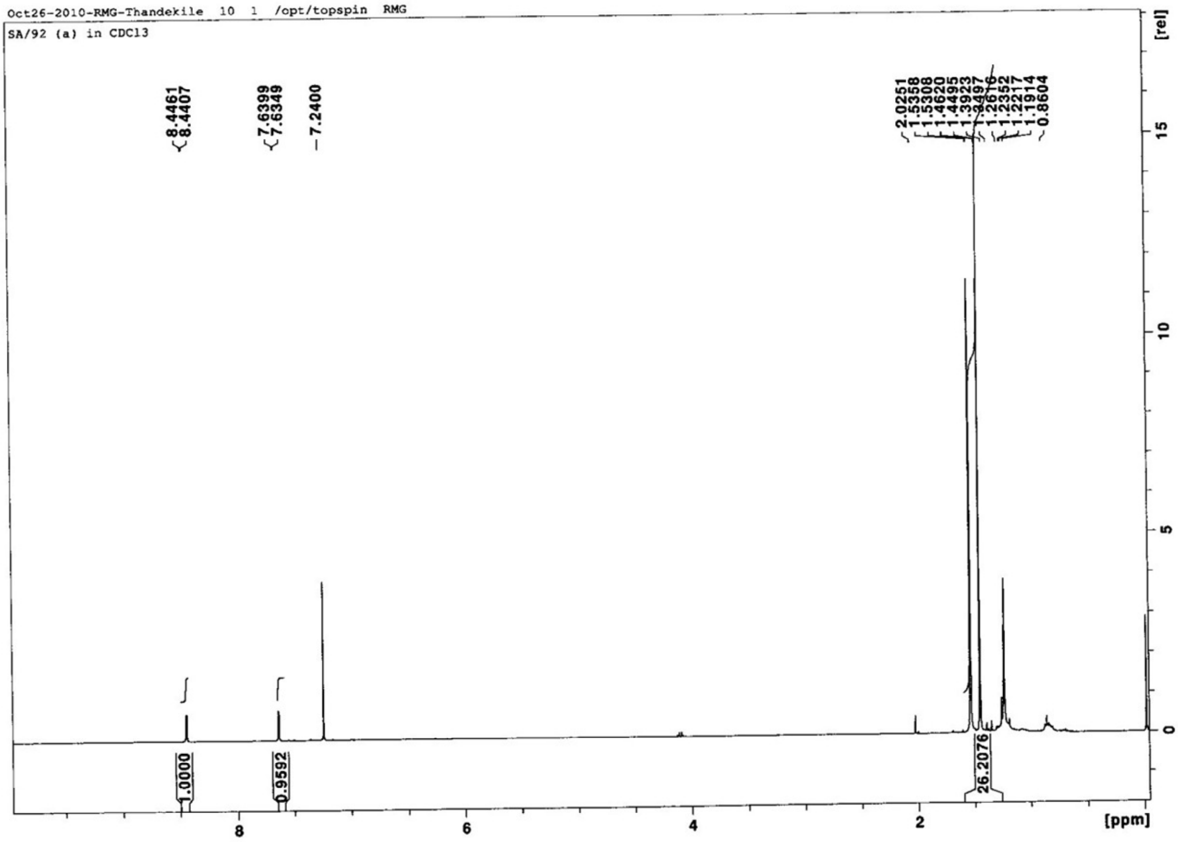


Plate 21. ^{1}H NMR spectrum of compound B

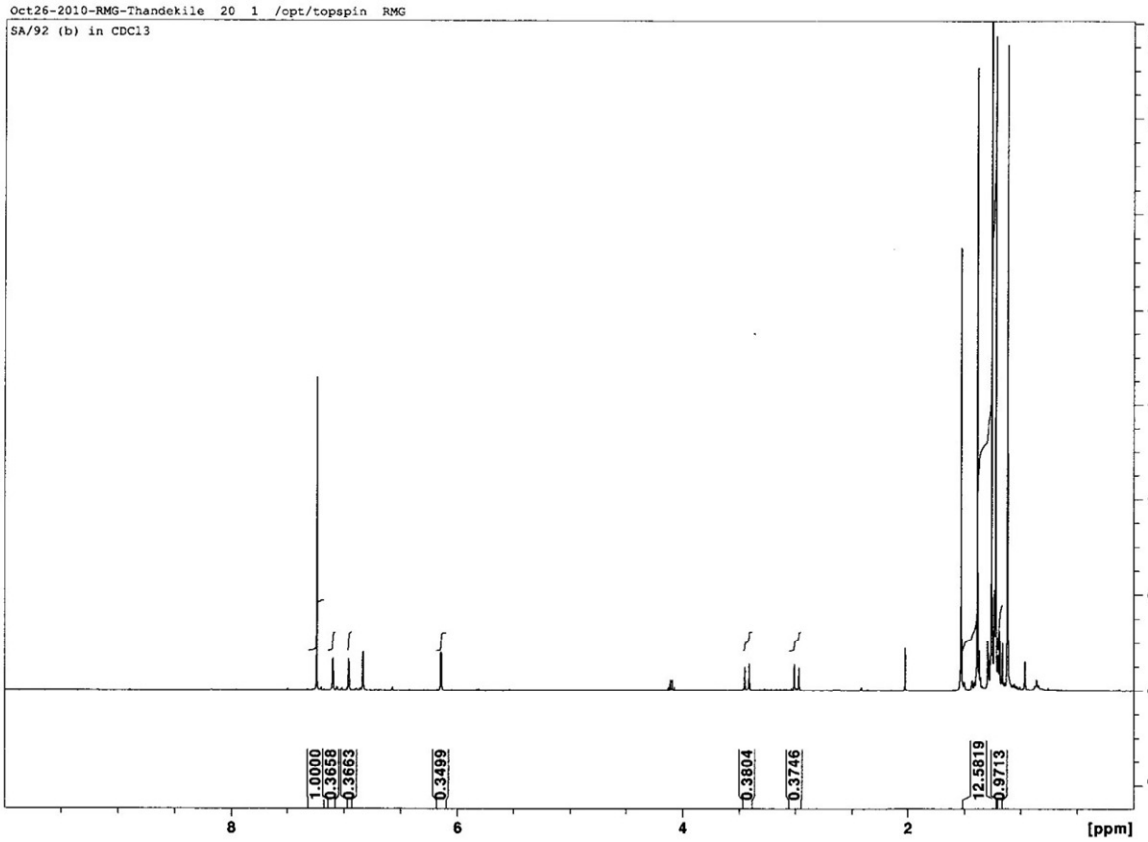


Plate 22. ^{1}H NMR spectrum of compound C.

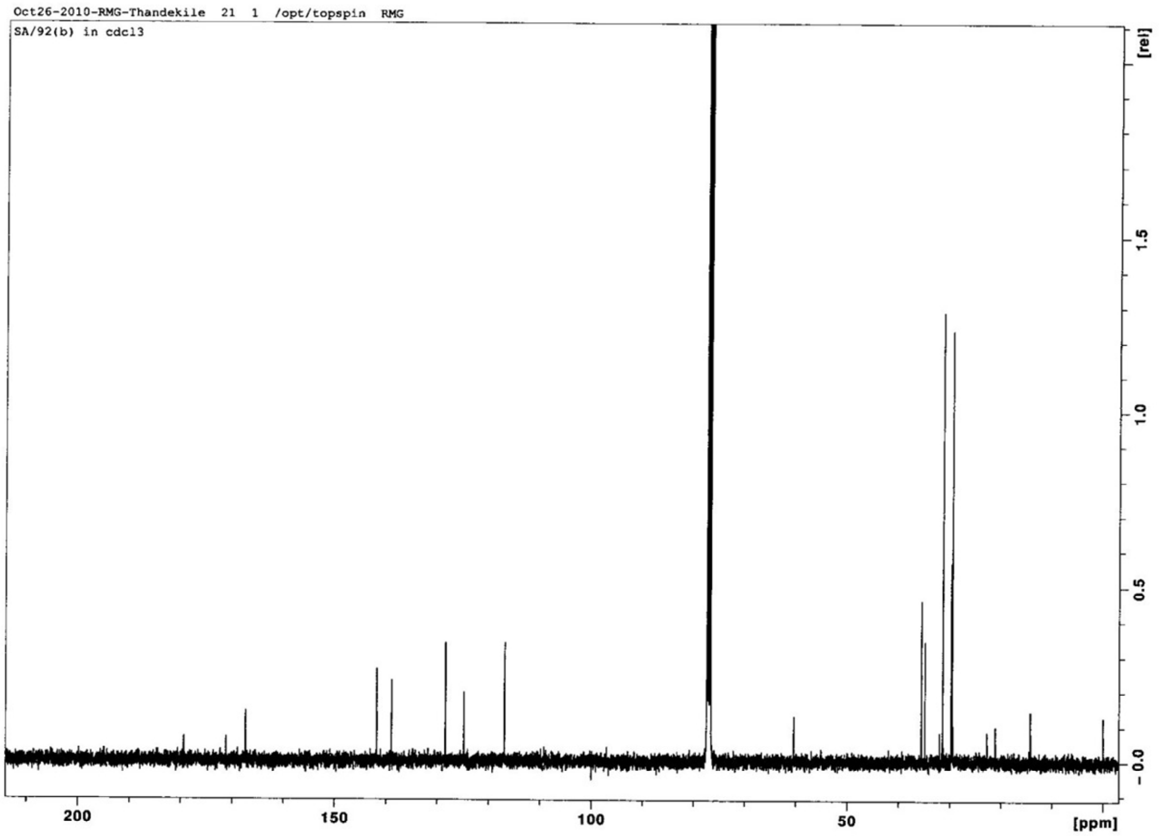


Plate 23. ^{13}C NMR spectrum of compound C.

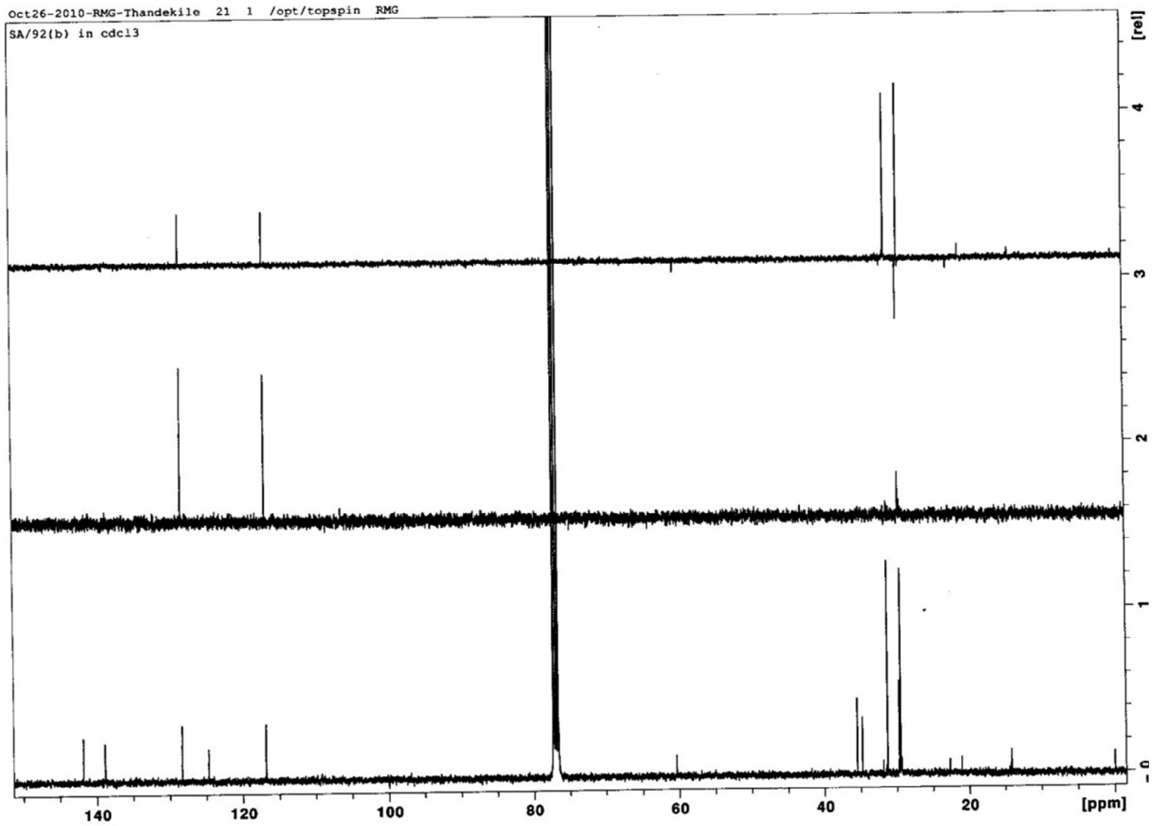


Plate 24. DEPT spectrum of compound C.