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THE DESIGN AND SYNTHESIS

OF

NOVEL INHIBITORS

OF

TUBULIN POLYMERISATION.

by

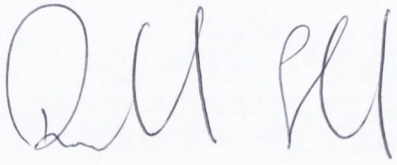
RICHARD SHAH

A thesis presented to the University of Dublin for the degree of Doctor of Philosophy.

Department of Pharmacognosy,
Trinity College,
University of Dublin,
Oct 2002.

DECLARATION

This thesis has not been submitted as an exercise for a degree at any other University. The work described is entirely my own work except where duly acknowledged. I agree that the library of Trinity College may lend or copy this thesis upon request.



Richard Shah.

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SUMMARY

This thesis is introduced with a review on the principles of tubulin polymerisation and how this process is necessary for cellular replication. This leads on to discussion of the structure-activity relationships of known natural occurring tubulin inhibitors that bind to specific sites on tubulin. The reported biological activity of natural tubulin inhibitors prompted the design and synthesis of several series of novel tubulin inhibitors, the details of which are set out in subsequent chapters.

Chapter 2 reports on the design and synthesis of the first series of novel biaryl compounds. This involved the synthesis of an aromatic A-ring fused to an aliphatic B-ring as the cyclic intermediate. The final step in the synthesis of this intermediate involved the novel use of pentafluorophenol to activate the acid functionality of the precursor prior to its cyclisation. Accordingly, this discovery was applied to the synthesis of fifteen benzocycloalkanones. This chapter closes with a description of the method used to couple various aromatic units to four of these benzocycloalkanones, to yield the first series of novel biaryl compounds.

Chapter 3 describes investigations of the aliphatic B-ring, which led to the evolution of a series of C-7 functionalised derivatives as potent tubulin inhibitors. Attempts to oxidise the allylic C-7 position of a biaryl compound are initially set out. Following this, functionalising the C-7 position prior to the addition of the second aromatic ring is detailed. This chapter continues by outlining the addition of the second aromatic unit in the presence of the C-7 hydroxyl group and the tubulin binding activity of the resultant compounds are discussed.

In an attempt to improve inhibition of tubulin polymerisation, manipulation of the A-ring by rotating the three methoxy substituents from the 2,3,4-positions to the 1,2,3 positions on the A-ring was investigated. Chapter 4 outlines the synthesis of biaryl compounds of this nature. The consequence of saturating the double bond of these compounds is also discussed. Details of these modifications and their influence on tubulin binding activity are presented.

Chapter 5 focuses on the possibility of increasing tubulin inhibitory activity by increasing the electronic character of the A-ring by the isosteric replacement of the benzylic methylene group from the B-ring with an oxygen atom resulting in an ether linkage at that position. The design, synthesis and tubulin binding activity of analogues of three compounds described in chapter 3, are discussed in detail.

ABBREVIATIONS

aq.	Aqueous
C.B.S.	Colchicine-binding site
CDI	Cyclin dependent kinase inhibitor
CDK	Cyclin dependent kinase
DCC	*N,N*-dicyclohexylcarbodiimide
DCM	Dichloromethane
DEPT	Distortionless enhancement transfer polarization
DMF	*N,N*-dimethylformamide
DMSO	Dimethylsulphoxide
DNA	Deoxyribonuceic acid
EtOAc	Ethyl acetate
EtOH	Ethanol
E-site	Exchangeable site
GDP	Guanosine diphosphate
GTP	Guanosine triphosphate
^{1}H-^{1}H COSY	^{1}H-^{1}H correlation spectroscopy
HMBC	Heteromultiple bond correlation
HMQC	Heteronuclear multiple-quantum correlation
HSV	Herpes simplex virus
IC_{50}	Concentration requiring 50% inhibition
ITP	Inhibition of tubulin polymerization
Kda	Kilodalton
$KOBu^t$	Potassium *tert*-butoxide
LDA	Lithium di-isopropylamide
M	Molar
MAPs	Microtubule-associated proteins
*m*CPBA	*meta*-chloroperoxybenzoic acid
MDR	Multidrug resistance
MeOH	Methanol
MRP	Multidrug resistance protein
n-BuLi	*n*-Butyl lithium

NBS	*N*-bromosuccinimide
NOE	Nuclear Overhauser effect
nM	Nanomolar
N-site	Non-exchangeable site
PCC	Pyridinium chlorochromate
P-gp	P-glycoprotein
PFP	Pentafluorophenol
ppm	Parts per million
PPA	Polyphosphoric acid
R_f	Retention factor; In TLC, ratio of distance travelled by compound to distance traveled by solvent front.
RNA	Ribonucleic acid
SAR	Structure-activity relationship
TBAF	*Tetra*-butyl ammonium fluoride
*t*BDMS	*tert*-butyldimethylsilyl
*t*BDPS	*tert*-butyldiphenylsilyl
t-BuOH	*tert*-butanol
THF	Tetrahydrofuran
TLC	Thin layer chromatography
UV	Ultra-Violet
γTuRC	γ-tubulin ring complex
μM	Micromolar
2°	Secondary

CHAPTER 1

INTRODUCTION

1.0 Introduction

1.1 Incidence of cancer

In Ireland, approximately 21,000 new cases of cancer are recorded annually and it is estimated that one-in-three of the Irish population is likely to develop cancer at some point during their lifetime[1]. While in the United States, it is estimated that approximately 1.2 million new cases will be diagnosed in 2002[2]. Globally, the incidence of cancer is staggering with an estimated 10 million new cases diagnosed in 2000 and mortality rates being recorded at 6.2 million deaths[3].

1.2 Nature of the disease

Cancer is a generic name used to describe about 200 different diseases, all of which are characterised by cells that have lost normal cellular control and maturation mechanisms, which regulate replication. Whereas normal eukaryotic cells only divide approximately fifty times[4], cancer cells multiply relentlessly, forming tumours that can compress and crowd out healthy tissue. As the tumour mass increases in size (usually 2-3 mm in diameter)[5], the nutrients and oxygen it obtained by simple diffusion from nearby capillaries are no longer sufficient[6]. This activates the developing tumour to switch from an avascular state to one, which promotes the dense formation of microvessels in a process known as *angiogenesis*[7]. The resulting neovasculaturisation of the tumour may then potentiate the dissemination of cells to remote sites of the body *via* the bloodstream, where they establish themselves and proliferate as secondary tumours[5]. This phenomenon is known as metastasis.

1.3 Cell cycle[8]

The growth and differentiation of cells to form tissues is under genetic control. However, errors in the control of such process may lead to changes in the cell cycle, which in turn may lead to the formation of cancerous cell growth. These cells are usually characterised by their ability to proliferate in an uncontrolled and disorganised fashion. Whereas normal eukaryotic cells grow in an orderly manner, cancer cells enter the cell cycle repeatedly and never differentiate. Investigation of the cell cycle has

shown that this process can be divided into five phases (G_0, G_1, S, G_2, M) with each phase driven by the sequential activation of cyclin-dependent kinase (CDK)/cyclin complexes. These enzyme complexes are themselves activated *via* phosphorylation by other kinases and are regulated by specific CDK inhibitors (CDI) (Figure 1.1).

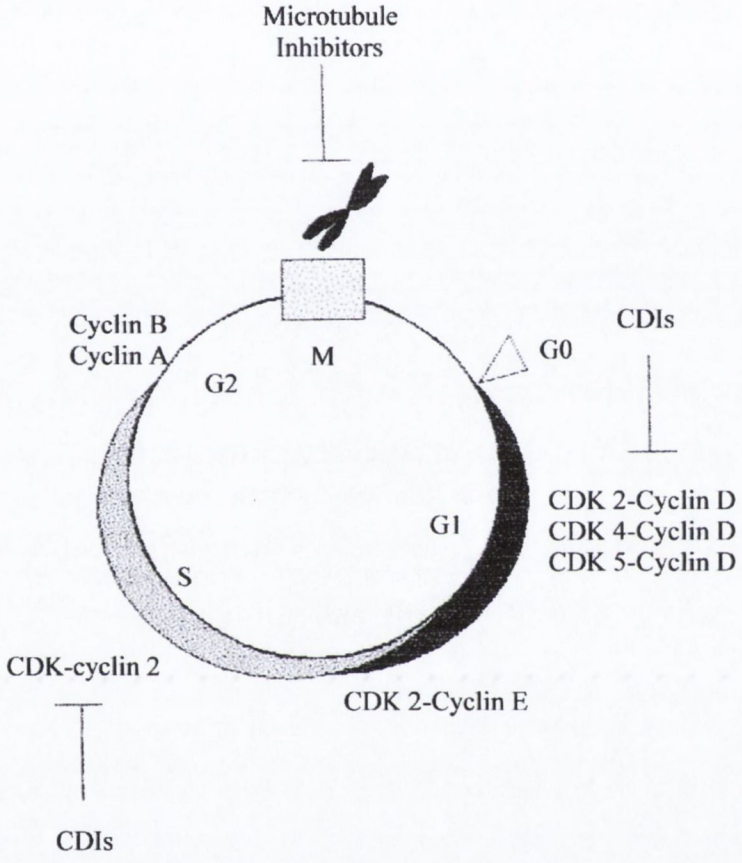


Figure 1.1. Cell cycle.

The cell cycle begins at the G_0 phase or resting state, where the cells continue to use energy but do not synthesise DNA or divide.

G_0 to G_1 stage

From the G_0 phase, the cell progresses to the G_1 (Gap 1) phase having been activated by a series of CDK/cyclin-D complexes. This is a period of gene expression and results in the increased production of cell organelles.

G_1 to S stage

The cell advances to the S phase and this phase requires the activation of two enzyme complexes, CDK2/cyclin-E and CDK2/cyclin-A, resulting in DNA synthesis and

duplication of the cell genome. This stage of the cell cycle is also known as the restriction step. Cells can return to the G_0 resting state from the G_1/S phase if it detects certain stress signals, however, once they have passed through this point then the cycle must be completed, as failure to do so will result in apoptosis or programmed cell death.

S to G_2 stage

The next phase is G_2 (Gap 2). During this phase many proteins are synthesised that are involved in replication such as the microtubule-associated proteins (MAPs). Collectively, these phases of the cell cycle (G_0, G_1, S, G_2) are known as interphase.

G_2 to M stage

This inevitably leads to the mitotic or M phase. During this phase the division of the eukaryotic nucleus occurs such that the daughter cells' nuclei acquire the same 23 pairs of chromosomes present in the parent cell. The M phase can be further subdivided into 4 sub-phases: prophase, metaphase, anaphase and telophase.

- Prophase is often recognised by the presence of condensed chromosomes that have no particular orientation. The nucleolus disappears in concurrence with the appearance of the spindle fibres.
- During metaphase, the spindle apparatus is fully formed with the chromosomes occupying the equatorial regions of the cell.
- Anaphase results in the splitting of the sister chromatids (duplicated chromosomes) into daughter chromosomes that migrate towards the poles of the cell.
- In the final phase, telophase, these daughter chromosomes begin to be surrounded by the formation of a new nucleolus in each daughter nuclei. Cytokinesis, or cytoplasmic cleavage now begins, causing the cell to split into two new cells.

The multistage nature of the cell cycle presents several targets for potential therapeutic intervention, and various compounds targeting specific events during cell division are used clinically (Table 1.1).

Antineoplastic agent	Stage of cell cycle arrest
Cisplatin	Cell cycle non-specific[9]
Cytarabine	S phase[10]
Colchicine	M phase
Etoposide	Late S and early G_2[11]
Mitomycin	Late G_1 and early S phase[12]
Mitozantrone Hydrochloride	Late S phase[13]

Table 1.1. Anti-cancer compounds that specifically target stages of the cell cycle.

1.4 Function of tubulin-binding agents in cancer chemotherapy

In the field of anti-neoplastic chemotherapy, a group of structurally diverse compounds, known as the tubulin-binding agents, have attracted intense interest. These molecules are unique among anti-cancer drugs in that their cytotoxicity is related to their ability to target the mitotic spindle rather than DNA (deoxyribonucleic acid). By interfering with the development of the mitotic spindle, the proliferating cell is blocked at the metaphase/anaphase junction[14] resulting in apoptosis[15, 16].

Inhibitors of tubulin polymerisation directly impair endothelial cell functioning and proliferation in tumour vasculature and angiogenesis respectively resulting in tumour vascular shutdown and apoptosis in proliferating endothelial cells[17, 18]. The ability of these agents to cause rapid shut-down of the capillary network is thought to be a consequence of the effects these agents have on endothelium cell shape. The net effect of change in endothelial cell morphology is increased vascular permeability and a significant rise in the interstitial fluid pressure around the tumour[19] resulting in necrosis of the surrounding cells[20]. Disabling this process not only prevents the tumour from receiving the essential nutrients and oxygen required for efficient growth but also reduces the possibility of disseminated tumour cells entering the bloodstream.

1.5 Microtubules; function and structure

Microtubules are sub-cellular organelles found in most eukaryotic cells and are involved in many cellular functions, such as secretion, cell movement, mitosis and intracellular movement. These microtubules are assembled from repeating units of tubulin hetero-dimers (molecular weight ~55 kDa). As illustrated in Figure 1.2 each dimer is composed of two peptides known as α- and β-tubulin. A third less abundant peptide, γ-tubulin, is localised in the microtubule organising centre known as the centrosomes[21]. Structurally, the α,β-heterodimers are thought to be packed head-to-tail to form a linear protofilament and about thirteen protofilaments associate to form the microtubule wall. Each tubulin dimer binds one molecule of Guanosine triphosphate (GTP) strongly in a specific site in the α-subunit, known as the non-exchangeable site (N-site) while a second molecule of GTP is bound more loosely, in the β-subunit, at a site known as the exchangeable site (E-site). The resulting polymer has a defined polarity denoted simply by the minus-end and the plus-end. The two-ends have different tubulin surfaces exposed and although both ends can grow or shorten, net growing occurs at the plus-end and net shortening at the minus end[22]. When both actions occur simultaneously a phenomenon known as *treadmilling*[21] occurs and results in the microtubule attaining a constant length enabling it to complete its required function in the cell.

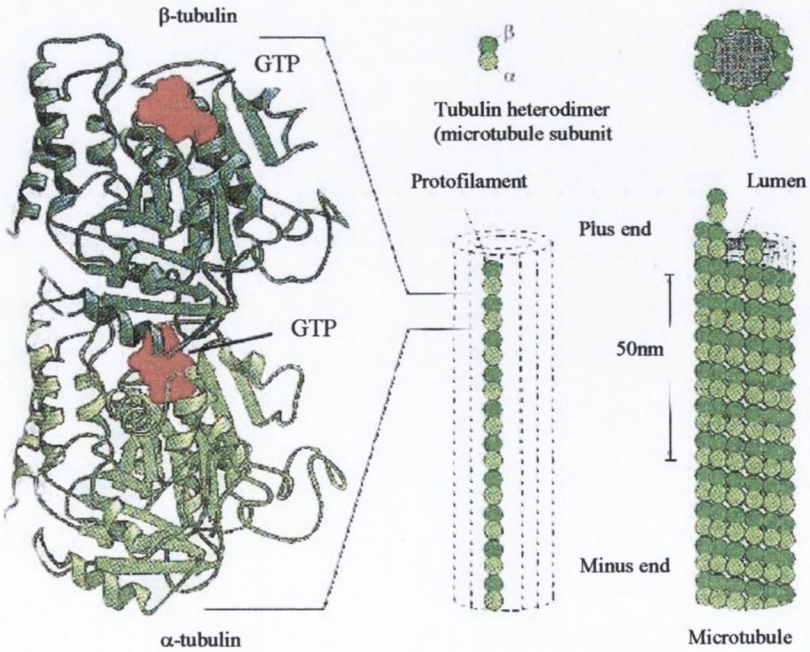


Figure 1.2. The structure of a microtubule and its tubulin heterodimer subunit[23].

During metaphase stage of the cell cycle, microtubule assembly results in the formation of the mitotic spindle. Microtubules themselves are formed by the reversible polymerisation of tubulin. They display *dynamic instability* by switching stochastically between continual cycles of assembly and disassembly. This entire process is fuelled by the hydrolysis of GTP and requires the assistance of microtubule-associated proteins (MAPs), such as MIP90, MAP2, MAP4, tau and STOP, whose function is to regulate microtubule growth[14].

The formation of the mitotic spindle occurs in three phases[21] (Figure 1.3):

(i) Nucleation – this entails the formation of short microtubule seeds with the growth of the microtubule beginning after the formation of a γ-tubulin ring complex (γTuRC) at the centrosome.

(ii) Elongation - addition of either tubulin α,β-dimers or short tubulin oligomers to the growing microtubule chain.

(iii) Steady state - a dynamic equilibrium involving no net change in microtubule length i.e. the rate of tubulin loss at the disassembly end is equal to the rate of addition at the assembly end.

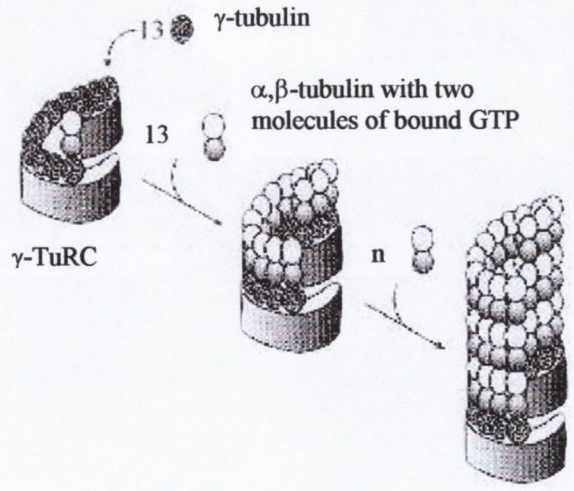


Figure 1.3. Assembly of the microtubule from the centrosome.

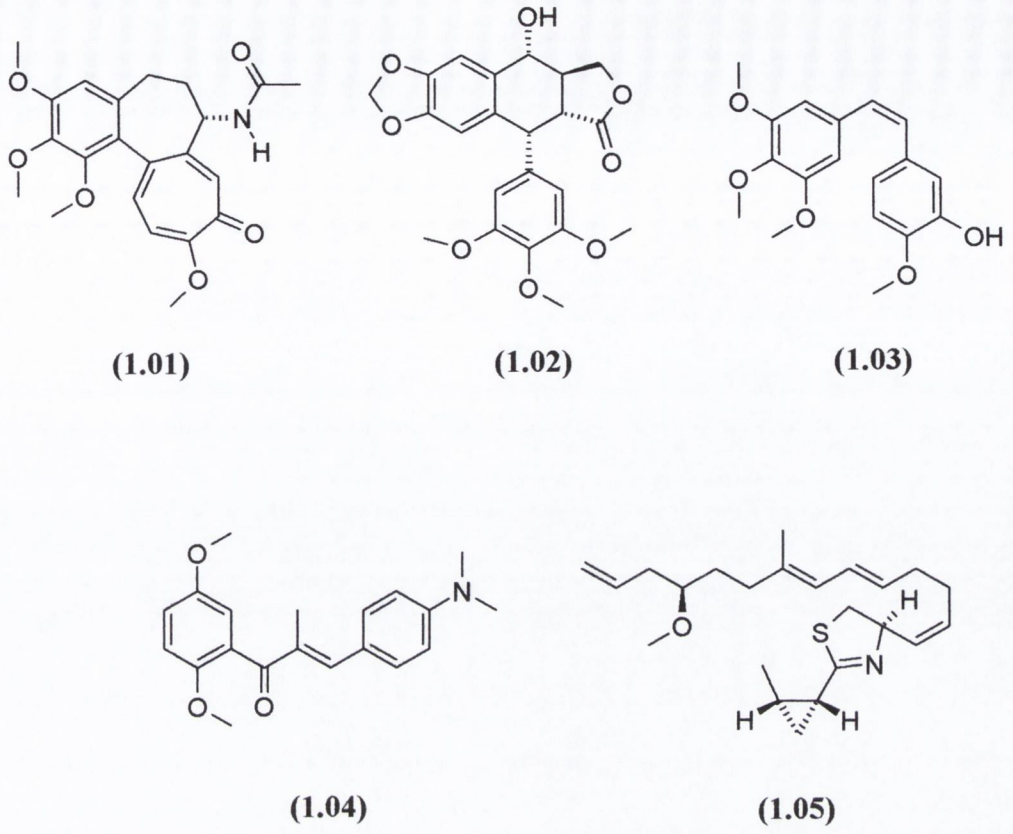
Anti-mitotic agents that bind to tubulin can affect both the microtubular structure and the normal functioning of the cell by inhibition or stabilisation of microtubule assembly.

More precisely, these compounds bind to a specific region on tubulin distorting its secondary structure and preventing the attachment of additional tubulin monomers, which ultimately stops microtubule growth. The consequence of this action is termination of the cell cycle[24], resulting in the expression of apoptotic gene products such as *bcl-2*[15] and *bcl-x*[25] and ultimately ending in death of the neoplastic cell.

Anti-mitotic agents, and in particular those which interfere with microtubule assembly, are classified according to the binding domain on tubulin to which they interact. To date, three different classes of tubulin inhibitors have been identified; those which interact with the (i) *colchicine*-binding domain, (ii) *vinca*-binding domain and (iii) the *taxoid*-binding domain.

(i) Drugs that interact with the ***colchicine*-binding** domain.

Examples include colchicine[26]**(1.01)** isolated from *Colchicum autumnale*, podophyllotoxin[27]**(1.02)** isolated from *Podophyllum peltatum* and combretastatin A-4[28] **(1.03)** isolated from *Combretum caffrum*. Each of these natural products possesses a trimethoxyphenyl ring, which is a component necessary for tubulin binding. However, a number of structurally unrelated compounds have also been discovered as *colchicine*-binding domain inhibitors. Examples include MDL 27048[29] **(1.04)** and curacin A[30] **(1.05)** isolated from a marine microorganism known as *Cyanobacterral matural* (Figure 1.4).



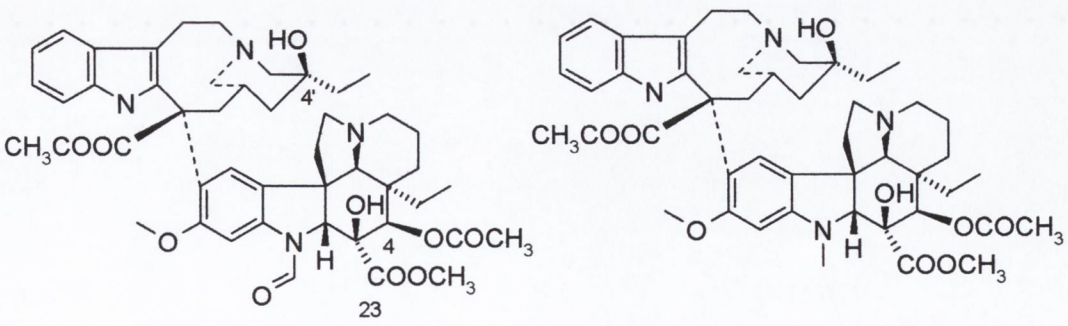
(1.01) **(1.02)** **(1.03)**

(1.04) **(1.05)**

Figure 1.4. Colchicine-binding agents

(ii) Drugs that interact with ***vinca*-alkaloid binding** domain.

These include the natural products vincristine **(1.06)** and vinblastine **(1.07)**, which were isolated from *Catharanthus roseus*[31] (Figure 1.5).

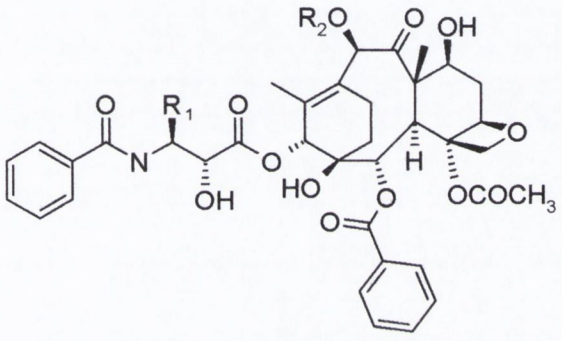


(1.06) **(1.07)**

Figure 1.5. Vinca alkaloids.

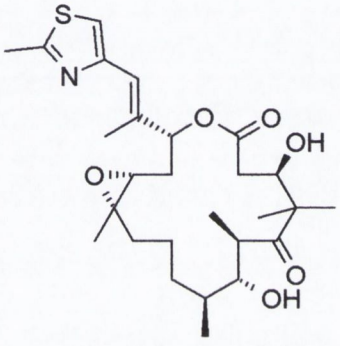
(iii) Drugs interacting with the ***taxoid*-binding** domain.

Compounds that bind to this region on tubulin exert a unique effect by stabilizing microtubule formation and in effect, prevent depolymerisation back to tubulin. Examples include paclitaxel[32] **(1.08)** isolated from *Taxus brevifolia*, its semi-synthetic analogue, taxotere **(1.09)** and epithilone B[33] **(1.10)** isolated from the myxobacterium, *Sorangium cellulosum* (Figure 1.6).



R_1 = Ph, R_2 = Ac; **(1.08)**

R_1 = *t*-BuO, R_2 = H; **(1.09)**



(1.10)

Figure 1.6. Taxoid-binding agents.

As the aim of this project was to design and synthesise novel C.B.S tubulin inhibitors, the concluding part of the introduction will concentrate on a detailed discussion of three well known natural products and their derivatives that bind to this receptor site of tubulin.

1.6 *Colchicine*-binding domain inhibitors

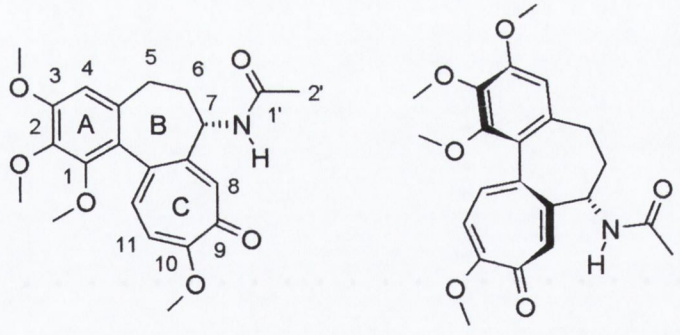
1.6.1 Colchicine

Colchicine occurs principally in the corm, seeds and flowers of the meadow saffron, *Colchicum autumnale* and in a related species *Gloriosa superba*[34].

It was first isolated in 1820 but its anti-mitotic activity was not linked with binding to tubulin until the 1960's[25]. Today it is used to treat severe cases of Gout, Familial Mediterranean fever, Schlerodermia, Behcet's disease, amyloidosis and liver cirrhosis[35]. Colchicine has shown potential experimental anti-tumoural properties against granulocytic leukaemia[36] and Hodgkin's lymphoma[37], however, its clinical use is limited due to its extreme toxicity and more recently due to the discovery of more effective chemotherapeutic agents in the treatment of advanced lymphomas and Hodgkin's disease[11].

1.6.1.1 Structure

Colchicine's structure (Figure 1.7) can be subdivided into four distinct parts: the trimethoxybenzene A-ring, the aliphatic B-ring, the pseudo-aromatic tropolone C-ring and the C-7 side chain. This natural product exists in the aS,7S (Cahn-Ingold-Prelog rules) conformation in which the C-7 acetamido-group causes the tropolone C-ring to adopt an axial configuration with respect to the A-ring. This causes the molecule to become warped in a non-coplanar orientation with a dihedral angle of about 53°[38].



(1.01)

Figure 1.7. Structure of colchicine **(1.01)**.

1.6.1.2 Binding to tubulin

The binding of colchicine to tubulin results in the inhibition of microtubule assembly. This process is a relatively slow one (in comparison to podophyllotoxin and the combretastatins) and is often incorrectly described as 'irreversible'[39]. Upon binding, GTP hydrolysis occurs at the E-site and a conformational change in the secondary

structure of tubulin takes place. This results in the weakening of the lateral bonds of the microtubule preventing the further addition of tubulin molecules[24]. Accordingly, microtubule spindle growth ceases and disassembly at the M-phase of mitosis begins[40].

Although the identity of this binding domain is still not understood recent evidence suggests that colchicine and its related analogues may interact at two potential binding sites in the tubulin dimer. One site is occupied entirely at the β-subunit while the location of the second site appears to be at the α-β-interface[41]. The first site is believed to include the amino acid residues 1-36 and 214-241 with the trimethoxybenzene A-ring occupying a 9Å cleft between Cys-354 and Cys-239[42].

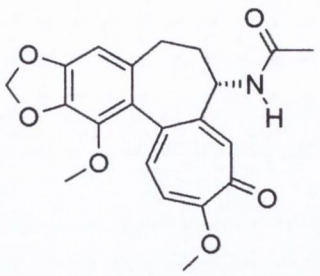
1.6.1.3 Structure-activity relationships

Experimentally, several colchinoid derivatives have shown potent *in vivo* activity against Hodgkins lymphoma, granulocytic leukaemia, melanoma and prostate cancer[37]. However, a narrow therapeutic window and a capacity to induce expression of the multi-drug resistant (MDR) phenotype in tumours have resulted in their infrequent use in cancer chemotherapy. In fact, multi-drug resistance is a major problem in the treatment of cancer. In tumour cells, resistance to these agents, and indeed to anti-mitotic agents in general, can be accomplished in several ways; by increased acetylation of tubulin[43], altering MAPs[44], increased metabolism, activation of enzymes[45] and by altering the intracellular drug concentration. The latter process is the most common exhibited by MDR resistant cancer cells. This is associated with the genetic expression of cell-membrane drug efflux pumps such as P-glycoprotein (P-gp) and multi-drug resistance protein (MRP)[45]. These pumps actively remove these anti-neoplastic agents from the cell thereby reducing the drugs exposure to nuclear targets[46]. Thus, in an effort to discover agents that are less toxic *in vivo* and are less susceptible to MDR, a large number of synthetic analogues have been developed[40].

A-ring

As a general rule all three methoxy groups are essential for tubulin binding activity as they act as a hydrophobic anchor to certain sites of tubulin. An exception is the natural plant product cornigerine **(1.11)**, which was isolated from *Colchicum cornigerum*[47].

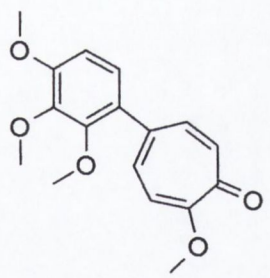
This compound contains a methylenedioxy-group in place of two of the methoxy substituents and is considered to be a more potent inhibitor of tubulin polymerisation[48].



(1.11)

B-ring

The role of the B-ring is less clear but is still considered an important contributor to the observed activity of the molecule. Although it appears to have no function regarding binding interactions at the colchicine-binding site (C.B.S), it does make an entropic contribution to binding by suppressing the free rotation about the biaryl bond and thus preventing isomerisation to its inactive aR isomer[49]. Its removal results in derivatives e.g. **(1.12)** with reduced tubulin binding affinity (IC_{50} = 6.9±2.0 μM)[50, 51].

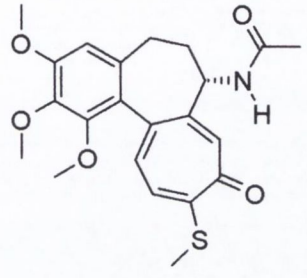


(1.12)

C-ring

The C-ring is an important contributor to the overall tubulin binding activity displayed by colchicine as chemical modification to this position resulted in derivatives displaying significantly different activity to that displayed by colchicine. Substitution of the C-10 methoxy group with a thiomethyl moiety resulted in a two-fold increase in potency[40] **(1.13)** (IC_{50} = 0.73μM), while exchanging the methoxy group and the carbonyl group to position 9 and 10 respectively resulted in an inactive compound (IC_{50} >100μM). The

natural product, allocolchicine[52] **(1.14)**, isolated from *C. cornigerum* and *C. autumnale*[35] and its semi-synthetic derivative, *N*-acetylcolchinol O-methylether[53] **(1.15)** both possessing a benzenoid C-ring and are known to be potent inhibitors of tubulin polymerisation ($IC_{50} = 0.73\mu M$ and $IC_{50} = 2.0\mu M$.



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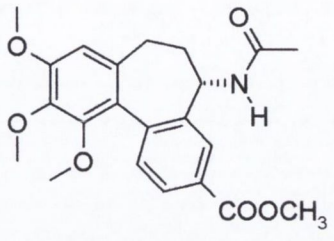

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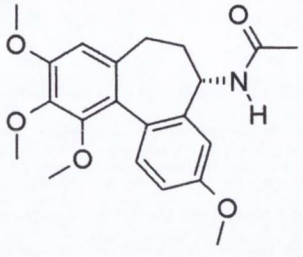
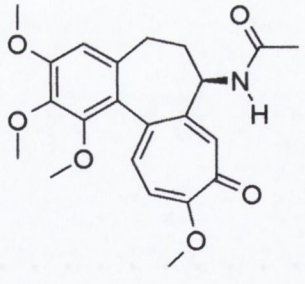


(1.15)

C-7 substituent

The observed binding activity of colchicine is partly due to the stereochemical positioning of the acetamide-group as studies, where this substituent is in the R-configuration, have shown that the resulting molecule **(1.16)** is virtually inactive, exhibiting only 1% of the anti-mitotic potency of natural (-)colchicine[52].



(1.16)

When the acetamide-group of colchicine was replaced with a ketonic functionality **(1.18)**, potent tubulin-binding activity was observed and more significantly, this compound was effective against both MDR negative and MDR positive tumours (Figure 1.8).

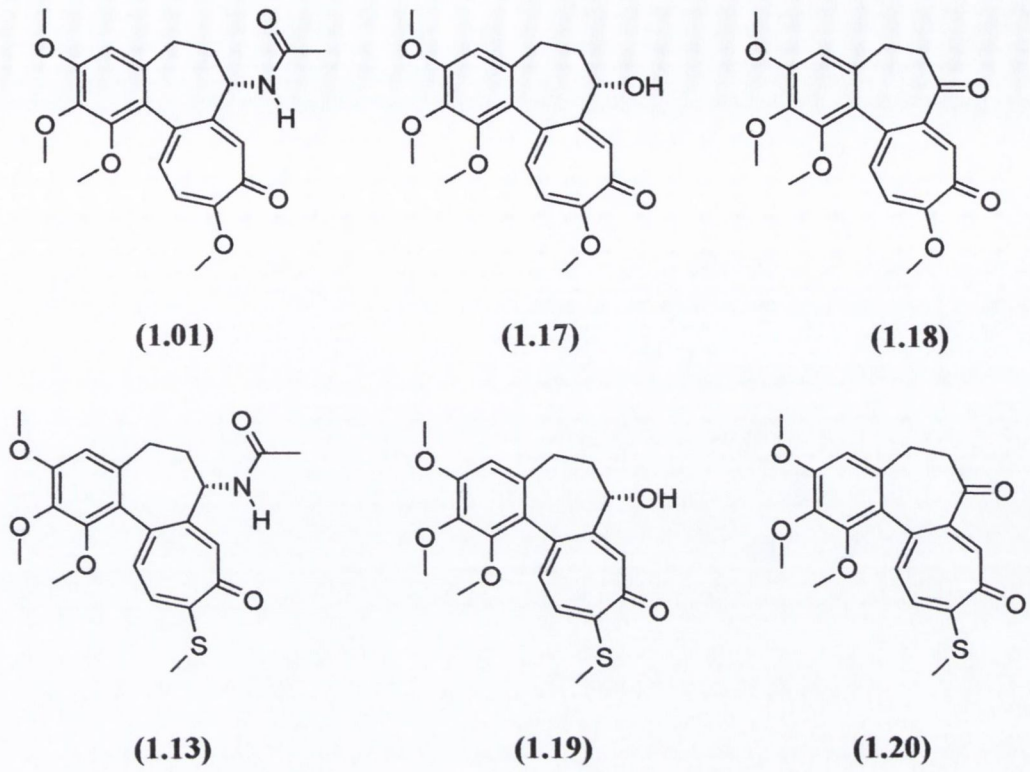


Figure 1.8. C-7 and C-10 derivatives of colchicine.

Several other derivatives of colchicine have been synthesised (Figure 1.8) and their tubulin binding activity as well as their cellular toxicity activity against a number of cancer cell lines have been reported (Table 1.2)

Compound	C-7 Substituent	ITP IC_{50} (μM)[a]	Cytotoxicity IC_{50} (nM)[b]	Cytotoxicity IC_{50} (nM)[c]
Colchicine **(1.01)**	$NHCOCH_3$	1.5	0.05	12000
Colchinol **(1.17)**	OH	-	-	-
Colchicone **(1.18)**	=O	-	11	50
Thiocolchicine **(1.13)**	$NHCOCH_3$	0.65	0.02	400
Thiocolchinol **(1.19)**	OH	0.75	2.8	-
Thiocolchicone **(1.20)**	=O	0.76	3.3	14

[a] Concentration requiring 50% inhibition of tubulin polymerization (ITP).

[b] Concentration requiring 50% inhibition of the breast cancer cell line MCF-7 WT.

[c] Concentration requiring 50% inhibition of the MDR breast cancer cell line MCF-7 ADRr.

Table 1.2. Biological activity exhibited by colchicine and thiocolchicine derivatives.

It is thought that by changing carbon-7 from an sp^3 to an sp^2-hybridised carbon results in a reduction in the conformational rigidity of the B-ring and as a result increases the flexibility of the bi-aryl system allowing an easier 'fit' in to the C.B.S[40]. De Vicenzo postulated that for high MDR positive activity the nitrogen atom at C-7 position is quaternized to a cation. This allows the P-gp pump to remove the compound from the cell. However, the presence of an oxygen atom avoids the formation of this cation and so the compound is prevented from being extruded from the cell[54].

1.6.2 Podophyllotoxin

Podophyllotoxin is the principle active compound isolated from the rhizome and dried roots of *Podophyllum peltatum, P. hexandrum* and *P. emodi*[34]. Podophyllotoxin has also been found in several species of juniper[55]. The *podophyllum* genus also produces several other podophyllotoxin derivatives namely deoxypodophyllotoxin, 4'-demethyl analogues and the peltatins[56].

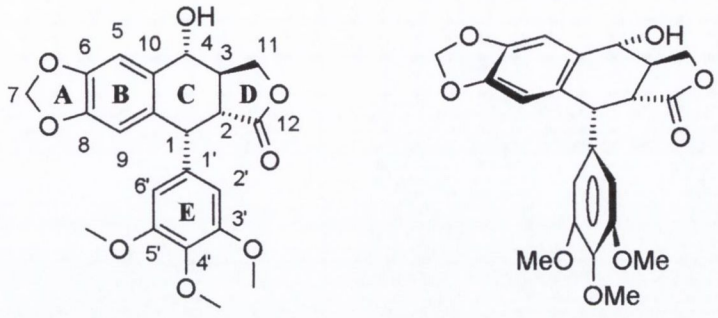
Historically, extracts from these plants have been used to treat a variety of maladies. In the first century A.D., Dioscorides recommended their use for "unhealthy granulations". *The Leech Book of Bald*, written in 900-950 A.D. described using the roots of wild chervil, *Anthriscus sylvestris*, and juniper needles as a treatment for cancer[57]. Native North Americans used the *P. peltatum* root as a purgative, anthelminthic, antirheumatic and laxative while Himalayan natives used the *podophyllum* root as a healing agent[58].

1.6.2.1 Structure

Podophyllotoxin belongs to a class of lignans containing the 2,3-dibenzylbutane skeleton. These are further classified into aryltetralin lactones and arylnaphthalene lactone lignans[58].

Structurally, podophyllotoxin is composed of a tetrahydronaphthalene moiety (B- and C-rings) with the methylenedioxy A-ring and lactone D-ring forming a pseudoplanar four ring grouping to which is attached at the C-1 position of the C-ring a nearly perpendicular aryl group, the trimethoxyphenyl E-ring. The twist in the C-ring of

podophyllotoxin causes the lactone ring to be positioned into an equatorial arrangement allowing the E-ring to rotate freely in its axial configuration[57] (Figure 1.9).



(1.02)

Figure 1.9. Structure of podophyllotoxin **(1.02)**.

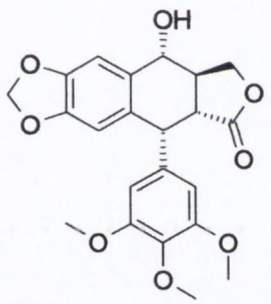
1.6.2.2 Binding to tubulin

It has been demonstrated that podophyllotoxin not only binds competitively at the C.B.S but also does so in a reversible manner and at a much faster rate than colchicine[59]. Computer modelling experiments performed by ter Haar *et al* have demonstrated that the A- and B-rings of podophyllotoxin and part of the B-ring of colchicine share the same binding site on tubulin. However, the trimethoxyphenyl-rings of podophyllotoxin (E-ring) and colchicine (A-ring) occupy different regions of the binding site, pointing away from the hydrophobic core that is occupied by the overlapping biophores[51].

The binding of podophyllotoxin to tubulin causes spindle growth cessation and is believed to occur as follows; podophyllotoxin binds quickly to dimeric tubulin, which lowers the concentration of polymerisable dimeric tubulin. This results in a rapid disassembly of polymer dimers to maintain a critical concentration of free dimers. These freed dimers also bind to podophyllotoxin, and so the tubulin-podophyllotoxin complex builds up until the concentration is sufficiently high that the complex starts to bind to the assembly (+) end of the microtubule. This prevents the addition of any further tubulin dimers and in effect "caps" the microtubule, preventing it from growing. During this process disassembly from the (-) end continues to maintain the tubulin dimers to microtubule equilibrium. Eventually, this process leads to total microtubule disassembly and a cessation of mitosis[60].

1.6.2.3 Biological activity

Podophyllotoxin and its analogues have a wide array of effects on biological systems, including toxicity, cell division arrest at metaphase and G_2, effects on membrane transport and viral replication[58]. Podophyllotoxin and its analogues are toxic to a wide range of organisms, though the dose and analogue specificity vary widely. Toxicity to mammals is mainly due to serious gastrointestinal irritation. In addition to their inhibitory effects on tubulin polymerisation, podophyllotoxin and its derivatives can also inhibit the transport of nucleosides in mammalian cells, thus influencing DNA and RNA synthesis[61]. This transport can be inhibited by podophyllotoxin and its analogues; however, higher concentrations of these agents are required than for inhibition of tubulin polymerisation (Table 1.3).



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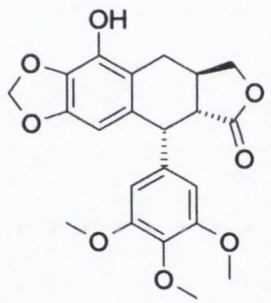

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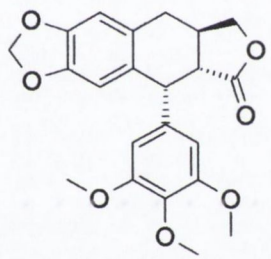

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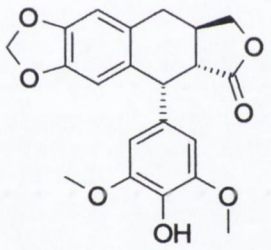


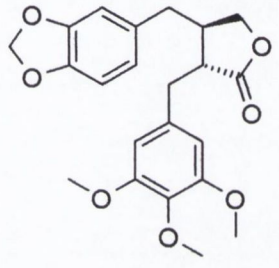
(1.23)

Compound	Inhibition of thymidine transport[a] (IC_{50}) μM	ITP (IC_{50}) μM
Podophyllotoxin **(1.02)**	9.0[57]	0.6[67]
β-peltatin **(1.21)**	10.0[57]	0.7[57]
Deoxypodophyllotoxin **(1.22)**	0.7[57]	0.5[67]
4'-Demethylpodophyllotoxin **(1.23)**	40.0[57]	0.5[57]

[a] Inhibition of nucleoside transport in HeLa cells.

Table 1.3. Nucleoside transport and inhibition of tubulin polymerisation data.

Podophyllotoxin (in the form of the alcoholic extract, podophyllin) is also effective at preventing viral replication; and is currently used in treating *condylomata acuminata*, a skin disease manifesting itself as a species-specific wart caused by the human papilloma virus[62]. Inhibition of viral replication by derivatives of podophyllotoxin has also been demonstrated in a number of viruses such as measles and herpes simplex I and II viruses (HSV I and II)[63]. Podophyllotoxin was shown to be the most potent anti-viral agent in treating HSV I and II, followed by β-peltatin **(1.21)** and deoxypodophyllotoxin **(1.22)**[64]. In contrast, C-ring opened analogues e.g. deoxypodorhizol **(1.24)** were ineffective against HSV replication implying that the presence of the C-ring may be necessary for antiviral activity[65].



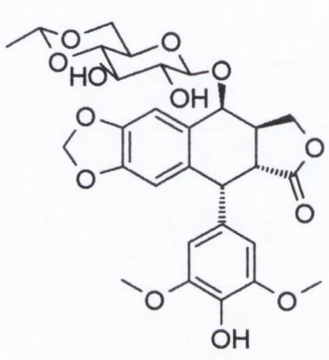
(1.24)

In an effort to determine the anti-viral mode of action of these compounds, experiments were conducted by, Markkanen *et al,* on deoxypodophyllotoxin **(1.22)**-treated cells. They concluded that **(1.22)** blocks transport of the viral nuclear capsid (a protective sheath that contains the virus RNA) to the nucleus by binding to the tubulin-based cytoskeleton in the cytoplasm[66]. It has also been suggested that some podophyllotoxin derivatives may interfere with nucleic acid metabolism and thereby prevent viral replication[58].

1.6.2.4 Structure-activity relationship

The recent discoveries of two powerful anti-mitotic derivatives of podophyllotoxin, namely; etoposide **(1.25)** and teniposide **(1.26)**, have led to the resurgence of interest in the synthesis of new molecules based on podophyllotoxin. Interestingly, the observed anti-mitotic effect of both **(1.25)** and **(1.26)** is based solely on their inhibitory effect on the enzyme, topoisomerase II, and not on tubulin binding[67]. Structure-activity studies[68]

have shown that its anti-tubulin activity is much more sensitive to alterations at certain regions of the molecule than at other positions. For example, tubulin-binding activity is not adversely affected by the presence or absence of a hydroxyl group at carbon -5 (B-ring), but the hydroxyl substituent on carbon-4 (C-ring) must be in the (R)-configuration, as activity is reduced by reversal of configuration. Demethylation at C-4' (E-ring) does not appear to have any great impact on activity, however, reversing the stereochemistry at C-1 (C-ring) results in an inactive compound.



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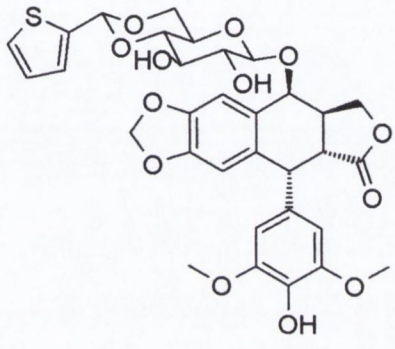
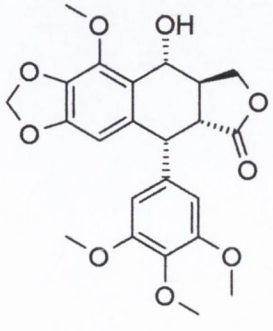


(1.26)

B-ring

Substituents on the B-ring, in particular C-5 of podophyllotoxin, are well tolerated, although large groups like glycosides reduce cytotoxicity significantly[69]. The C-5 substituted methyl ether **(1.27)** displayed potent cytotoxicity against HeLa tumour cells comparable to that of podophyllotoxin[70]. Interestingly, replacing the methylenedioxy-moiety with methoxy groups produced the derivative **(1.28)**, which is about ten-fold less cytotoxic than podophyllotoxin[71].



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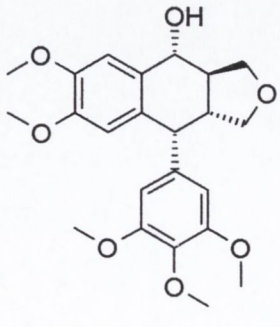
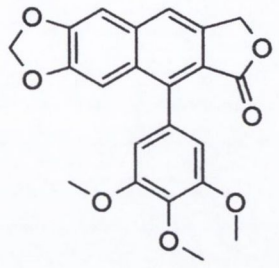


(1.28)

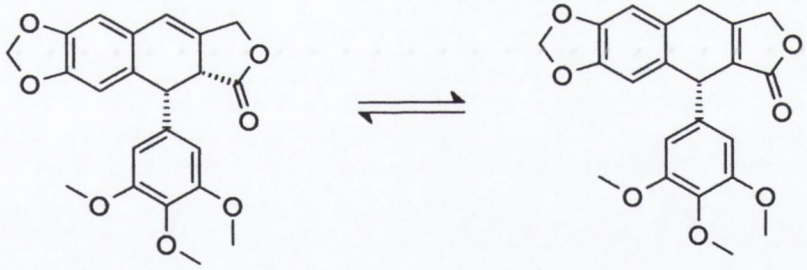
C-ring

Aromatising the C-ring **(1.29)** results in a significant loss of cytotoxicity since it causes the pseudo-axial E-ring to reorganise into a more planar conformation, thereby preventing its insertion into the C.B.S[72].



(1.29)

Dehydration of podophyllotoxin yields α-apopicropodophyllotoxin **(1.30)**, which can isomerise to β-apopicropodophyllotoxin **(1.31)** (Figure 1.10). The latter compound has been shown to have equivalent cytotoxicity to that of podophyllotoxin[67].



(1.30) **(1.31)**

Figure 1.10. Equilibriation of α-apopicropodophyllotoxin and β-apopicropodophyllotoxin

D-ring

For potent anti-neoplastic activity to exist it has long been known that the lactone D-ring must be in the *trans*-configuration as the *cis*-isomer is nearly inactive[73]. Many open-chain analogues have also been synthesised, often producing compounds with reduced anti-tubulin activity. It has been suggested that the presence of the lactone ring may permit nucleophilic attack by a thiol, amine or hydroxyl group present in the

C.B.S. to the methylene C-11 moiety and as a result increase its binding affinity to tubulin[74, 75] (Figure 1.11).

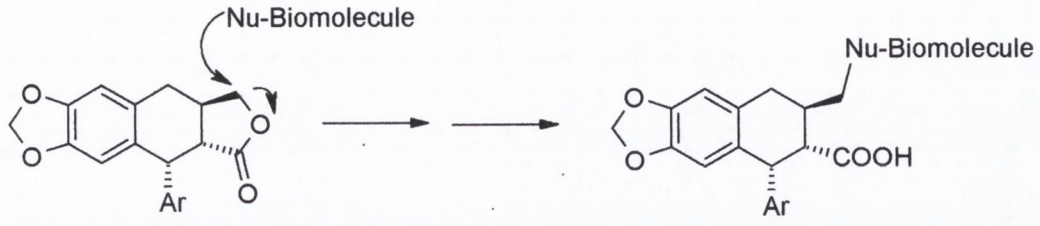
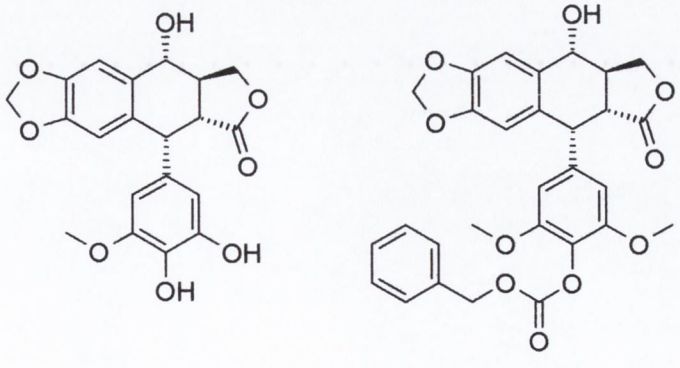


Figure 1.11. Proposed mechanism of the cytotoxic activity of the podophyllotoxin derivatives. Nu = SH, NH_2, OH.

E-ring

The E-ring must occupy a pseudo-axial conformation for potent tubulin binding. Demethylation of the 4'-methoxy group (4'-demethylpodophyllotoxin) **(1.23)** increases its activity against topoisomerase II but has a negligible effect on tubulin polymerisation activity. Demethylation of the 3'- and 4'-methoxy groups **(1.32)** reduces the anti-microtubule activity even further[76] with the addition of bulky groups on the 4'-oxygen (such as 4'-carbobenzoxy- **(1.33)** and the 4'-glucosides) resulting in total loss of tubulin-binding activity[60, 73](Table 1.4).



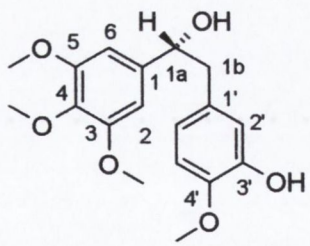
(1.32) **(1.33)**

Compound	position-4'	position-3'	ITP IC_{50} (μM)
4'-demethylpodophyllotoxin **(1.23)**	-OH	$-OCH_3$	2.0
3', 4'-didemethylpodophyllotoxin **(1.32)**	-OH	-OH	4.0
4'-carbobenzoxypodophyllotoxin **(1.33)**	$-COOCH_2Ph$	$-OCH_3$	>100

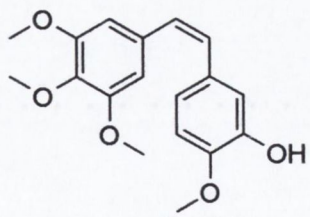
Table 1.4. Inhibition of microtubule assembly by podophyllotoxin derivatives modified in E-ring.

1.6.3 Combretastatins

The combretastatins are a group of bi-benzyl anti-neoplastic agents obtained from the South African tree *Combretum caffrum* also known as the bushwillow[77]. Traditionally, these trees have been used by natives of Africa and India to treat a variety of ailments[78] including abdominal pain, leprosy and infertility in women. Recently, extracts taken from the bushwillow were found to have excellent cytotoxic activity against P388 lymphocytic leukaemia[78]. The first active component isolated from the extract was combretastatin **(1.34)** and since then a large number of structurally similar compounds have been identified, the most potent being combretastatin A-4 **(1.03)**.



(1.34)



(1.03)

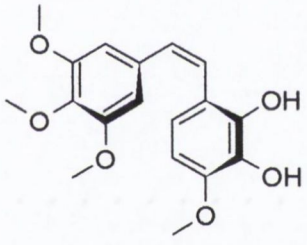
1.6.3.1 Structural features of combretastatin A-4

Combretastatin A-4 is composed of two substituted benzene rings connected by a two-carbon bridge. This relatively simple structure bears similarity to colchicine and

podophyllotoxin. Like colchicine, the A-ring of combretastatin has three-methoxy substituents. The 'B-ring' of combretastatin is "similar" to the C-ring of colchicine with the vicinal methoxy and hydroxyl groups in place of the vicinal methoxy and carbonyl groups. The two carbon bridge occupies a *cis*-configuration with the dihedral angle of the two aryl units being at an angle between 50°-60°. Since the discovery of combretastatin a-4, a large number of structurally-related compounds have been isolated from *C. caffrum*. Depending on the structural type, these compounds are now classified as belonging to the combretastatin A[79], B[80], C[81, 82] or D[83] family of compounds.

Classification of the combretastatins

- Combretastatin A derivatives are stilbenes. Examples of compounds in this category include combretastatin A-1 **(1.35)** and combretastatin A-2 **(1.36)**.



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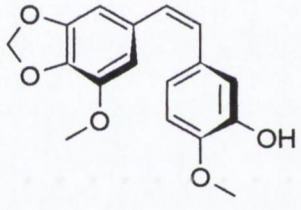
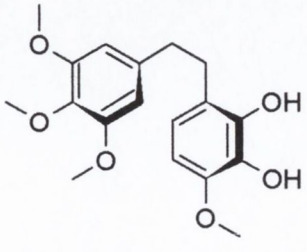


(1.36)

- The combretastatin B family are structurally similar except the two phenyl rings are separated by a saturated two-carbon bridge. These include combretastatin B-1 **(1.37)** and combretastatin B-4 **(1.38).**



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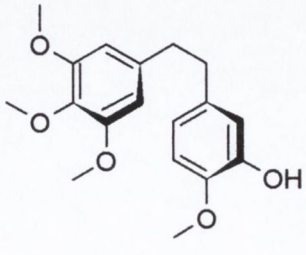
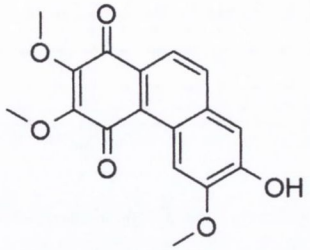


(1.38)

- Derivatives of the combretastatin C family have fused A, B and C rings that form a series of tri-cyclic structures known as the phenanthrenes.



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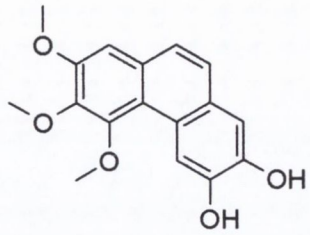
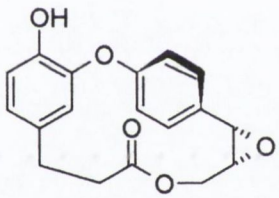


(1.40)

- Combretastatin D derivatives are identified as macrocyclic lactones. Examples of compounds in this family include combretastatin D-1 **(1.41)** and combretastatin D-2 **(1.42)**.



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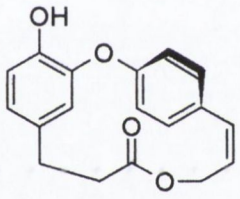
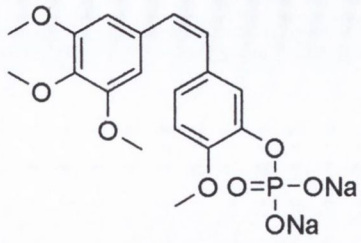


(1.42)

1.6.3.2 Binding to tubulin

The combretastatin family of compounds have all been shown to interact with tubulin resulting in the disruption of microtubular function and hence, cell cycle arrest. However, their modes of action differ depending on the class to which they belong.

Combretastatin A and B derivatives are known to competitively bind to the C.B.S. of tubulin *in vitro* with subsequent hydrolysis of GTP[84]. As stated previously, the most potent of these derivatives is combretastatin A-4[85], but unfortunately, its low aqueous solubility limit its use *in vivo*. This limitation has been partially resolved by its conversion to the phosphate derivative[86] **(1.43)**. This derivative is currently undergoing phase I/II clinical trial evaluation[87].



(1.43)

The combretastatin D series of compounds are also potent anti-mitotic agents, however, these compounds exert their anti-mitotic effect by stabilising microtubule assembly suggesting that they bind to tubulin at a site remote from the C.B.S[88].

1.6.3.3 Biological activity

Extracts taken from the combretaceae family have revealed a multitude of biological properties including anti-microbial, anti-inflammatory and potent anti-neoplastic activity[89].

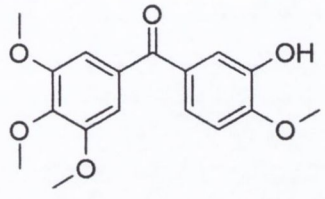
1.6.3.4 Structure-activity relationships based on the structure of combretastatin A-4

A-ring

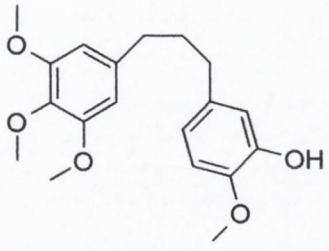
Most compounds synthesised based on the combretastatin structure utilise combretastatin A-4 as the model compound due to its high cytotoxicity, high activity against MDR cell lines and its simple structure. A structural feature common to most colchicine binding site inhibitors is the presence of a trimethoxyphenyl moiety. Substituting a methylenedioxy group at C-2 and C-3 for two of these methoxy substituents results in only a small reduction in potency[90]. However, rotation of the three-methoxy substituents from C-1, -2 and -3 to C-2, -3 and -4 results in a 10,000-fold reduction in cytotoxicity[91].

Bridge

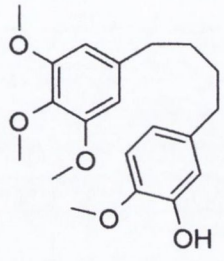
In general modifying the length of the ethylene bridge, C=C, results in compounds with lower activity against tubulin polymerisation. However, insertion of a carbonyl unit, phenstatin **(1.44),** in place of the ethylene bridge resulted in a potent inhibitor of tubulin polymerization (IC_{50} = 1μM)[92], but lengthening the bridge by the successive addition of methylene groups as in compounds **(1.45)** and **(1.46)** resulted in a progressive loss of activity against tubulin polymerization[89].



(1.44)

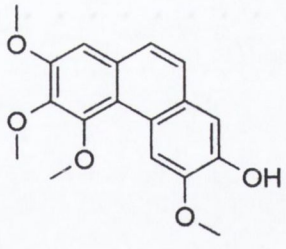


(1.45)



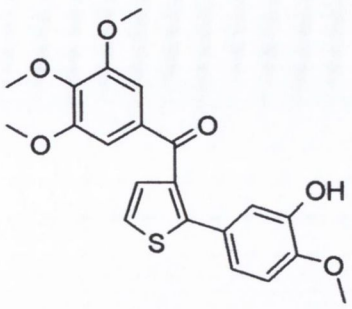
(1.46)

Increasing the rigidity by conversion of the ethylene bridge to a fused phenanthrene ring **(1.40)** adjusts the molecule into a pseudo-planar arrangement resulting in loss of activity[93] (Table 1.16).

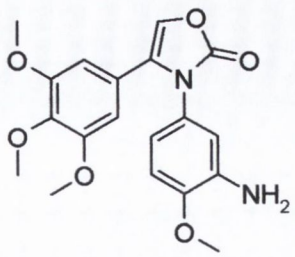


(1.40)

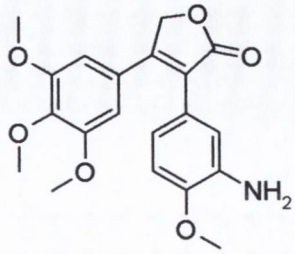
A number of novel bridging components have been inserted between the two phenyl rings with the resulting molecules demonstrating equivalent to, or better tubulin-binding and cytotoxic activity in comparison to combretastatin A-4. These include ketothiophene[94] **(1.47)**, oxazolone[95] **(1.48)**, furanone[96] **(1.49)**, (R,R)-1,3-dioxolane[97] **(1.50)** and sulphonate bridges[98] **(1.51)**. These compounds demonstrate excellent in vitro cellular toxicity against a number of different cancer cell lines, because their bridging components influence the spatial arrangement between the A- and B-rings permitting efficient binding to the C.B.S (Table 1.6).



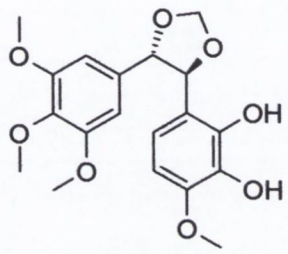
(1.47)



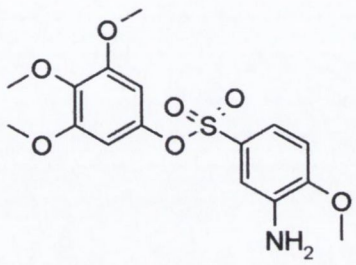
(1.48)



(1.49)



(1.50)



(1.51)

Compound	Bridge	ITP IC_{50}[a] (μM)	Cell line IC_{50} (nM)
(1.03)	C=C	1.2[97]	3.0[b]
(1.44)	C=O	1.0	5.7[b]
(1.38)	$(CH_2)_2$	4-5	200[d]
(1.45)	$(CH_2)_3$	10-15	1000[d]
(1.46)	$(CH_2)_4$	40-50	3000[d]
(1.40)	Phenanthrene	100	1000[d]
(1.47)	Ketothiophene	1.0	300±400[c]
(1.48)	Oxazolone	-	1.8[c]
(1.49)	Furanone	-	4.7[c]
(1.50)	Dioxolane	0.59	3.2[b]
(1.51)	Sulphonate	6.7	2.7[b]

[a] Concentration required to inhibit tubulin polymerisation 50%.

[b] NCI H460; non-small cell lung cancer cell line.

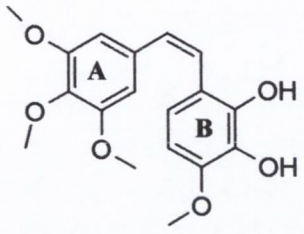
[c] MCF-7; human breast cancer cell line.

[d] L1210; murine leukaemia cell line.

Table 1.5. Biological data of combretastatin A-4 derivatives modified in bridge.

B-ring

Many structural B-ring variants have been discovered or recently synthesised in an effort to increase its tubulin-binding activity[93]. With the exception of **(1.52)**, **(1.53)** and **(1.54)**, few derivatives have demonstrated equivalent potency to combretastatin A-4 against tubulin polymerisation (Table 1.6).



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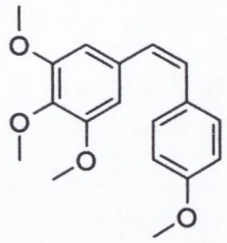

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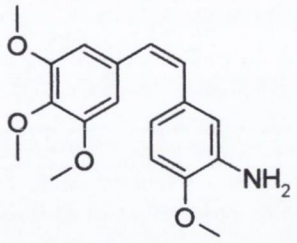
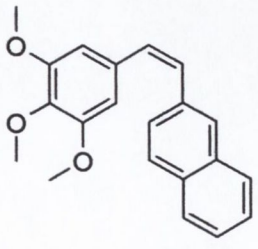


(1.53)

Compound	ITP IC_{50} (μM)
(1.03)	1.2[97]
(1.35)	4[83]
(1.52)	2.2[91]
(1.53)	4.0[90]

Table 1.6. Inhibition of tubulin polymerisation by combretastatin derivatives modified in B-ring.

In summary, high tubulin-binding activity is maintained by having small electron donating groups at the *meta*- or *para*-positions on the B-ring. Some anomalies do exist, as incorporation of a naphthalene ring **(1.54)** in place of the "necessary" 3-hydroxy-4-methoxyphenyl ring resulted in a potent inhibitor of tubulin polymerisation[99].



(1.54)

Based on the structure of combretastatin A-4 and its derivatives, a pharmacophore ideal for binding at the colchicine-binding domain of tubulin has been designed (Figure 1.12).

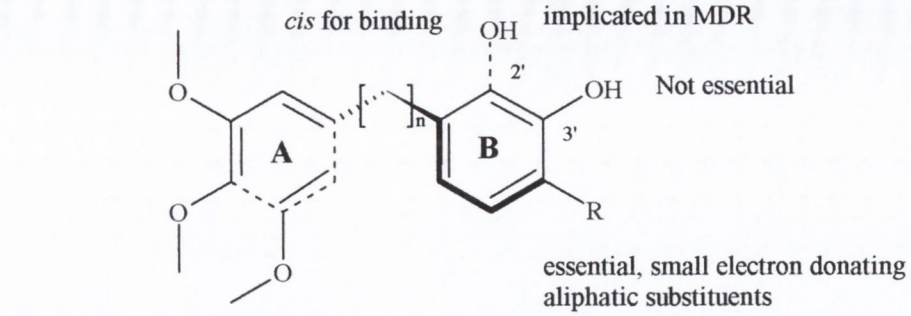


Figure 1.12. Suggested pharmacophore for tubulin binding.

Structural features of this model

(i) The non-coplanar spatial arrangement between the two aromatic rings is paramount for maintaining tubulin-binding activity, as these planar rings must be tilted with respect to each other at the correct dihedral angle[98].

(ii) The trimethoxybenzene A-ring, which is common to a number of other tubulin-binding agents, is considered to be essential for activity.

(iii) The 2-OH' group is believed to be responsible for MDR[100]. It has also been demonstrated that while tubulin inhibitory activity is very good, its cytotoxicity against various *in vitro* cancer cell lines is quite weak[97].

(iv) The 3'-OH group has a minimal effect on binding to tubulin.

(v) The 4'-OCH_3 moiety can be replaced with small hydrophobic groups (methyl, ethyl) while retaining significant activity.

(vi) The carbon linker, *n*, can be one or two carbon units long.

(vii) The two-aryl rings must be in a *cis*-configuration to retain maximum cytotoxic activity.

1.7 Summary of tubulin binding agents used clinically

Although a vast array of antineoplastic agents have been synthesised over the last forty years, many scientists still consider the design of a selective anticancer agent as the Holy Grail of medicinal chemistry. Interestingly, those that interfere with microtubular function have proved to be most effective in cancer chemotherapy. To date, only drugs that are known to interact with the *vinca*- and *taxoid*-binding domains of tubulin are in clinical use. These include vincristine, vinblastine (tubulin inhibitors) and taxol (tubulin stabiliser). Until recently, molecules that interact at the *colchicine*-binding site were considered too toxic for the treatment of neoplasia. However, the discovery of combretastatin A-4 has renewed interest in C.B.S agents as potential anti-neoplastic agents, as this compound not only inhibits tumour cell proliferation but also has remarkable anti-angiogenic activity.

1.8 Aims of the project

Of those compounds that bind to the colchicine binding site only combretastatin A-4 shows clinical promise. However, its continued development is limited as the unrestrained double bond is prone to photochemical isomerisation resulting in the inactive *trans*-analogue being formed. Altering the positioning of the two aromatic rings relative to one another is difficult, thereby reducing the possibility of actually producing a more potent and less toxic derivative. A further disadvantage of this compound lies in the fact that its phenolic functional group, important for bioactivity, is deactivated in the water-soluble prodrug form, which is necessary for *in vivo* administration. There is therefore considerable interest in, and a need for development of novel tubulin inhibitors with similar activity and selectivity to combretastatin A-4, but with better chemical stability.

Thus, the aim of this project was to create potent tubulin inhibitors based upon the molecular design shown in Figure 1.13. It was decided in the first instance to concentrate on the synthesis of compounds where the three methoxy substituents are positioned on carbons 1, 2 and 3 of the **A**-ring, where X = CH_2, Y = H and R_1, R_2, R_3 is any combination from H, OH, OMe or NH_2. The synthesis of these compounds is

discussed in Chapter 2, as well as a select number of compounds where the size of the B-ring was reduced.

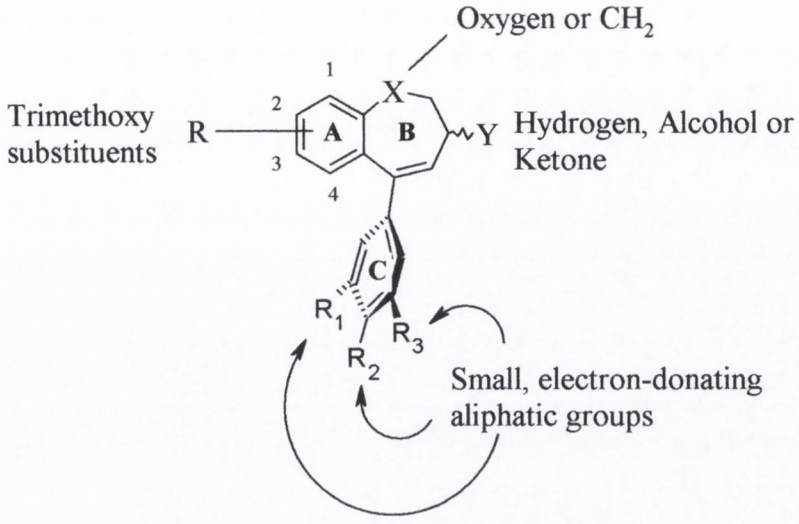


Figure 1.13. Molecular structure on which the novel compounds is to be based on.

The aim of the work described in chapter 3 was to synthesise a similar series of molecules to those described in chapter 2, but with one important difference, alcohol and keto-functionalities should be incorporated into the molecules where Y was originally hydrogen.

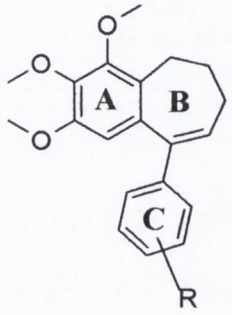
The aim of the work described in chapter 4 was to investigate the effect on tubulin binding activity of rotating the three methoxy substituents on positions 1,2, and 3 to positions 2,3,4 on the **A**-ring.

The aim of the work described in chapter 5 was to investigate the synthesis of compounds analogous to three of the compounds described in chapter 3. The essential difference between these compounds and those described in chapter 3 is the inclusion of an oxygen atom in place of a CH_2 at position X.

CHAPTER 2

2.0 Introduction

It was anticipated that a series of novel tubulin inhibitors could be synthesised by forming a biaryl system in which the biaryl moiety (A- and C-ring) is connected to an aliphatic B-ring (Figure 2.1). It was believed that if these compounds were to inhibit tubulin polymerisation then it was essential that both aromatic units should be in a spatially close non-coplanar arrangement allowing the molecule to possess a suitable dihedral angle necessary to permit optimal binding to the C.B.S of tubulin.



R = small electron-donating groups

Figure 2.1. Generalised structure of compounds synthesised in this chapter.

2.1 Synthetic strategy

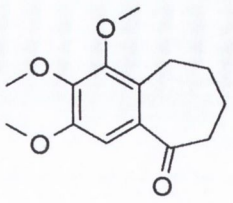
Two key stages were involved in the synthesis of these compounds, namely:

(i) The formation of trimethoxy- and methylenedioxybenzocycloalkanones with varying ring sizes.

(ii) The attachment of an additional aryl unit to these benzocycloalkanones.

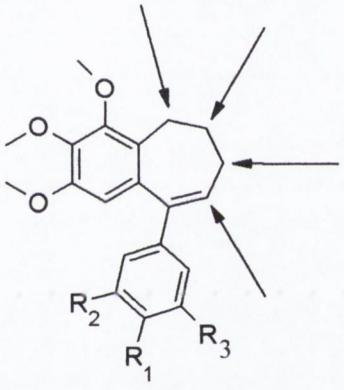
2.2 Synthesis of benzocycloalkanones

The initial strategy targeted the synthesis of 1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **(2.01)** since it was felt that this intermediate, when incorporated into the final structure, (Figure 2.2) would offer several positions for possible manipulation later on in our synthetic program.



(2.01)

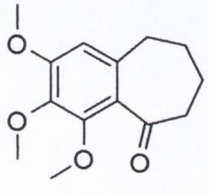
In particular, it was believed that functionalisation of the carbons indicated by the arrows (Figure 2.2), would result in additional compounds with greater potency than their unsubstituted analogues as these positions can be used to direct the spatial orientation of the two aryl rings. Additionally, judicious functionalisation of these positions should also influence the electron density within the overall molecule.



R_1, R_2, R_3 = small electron-donating substiuents

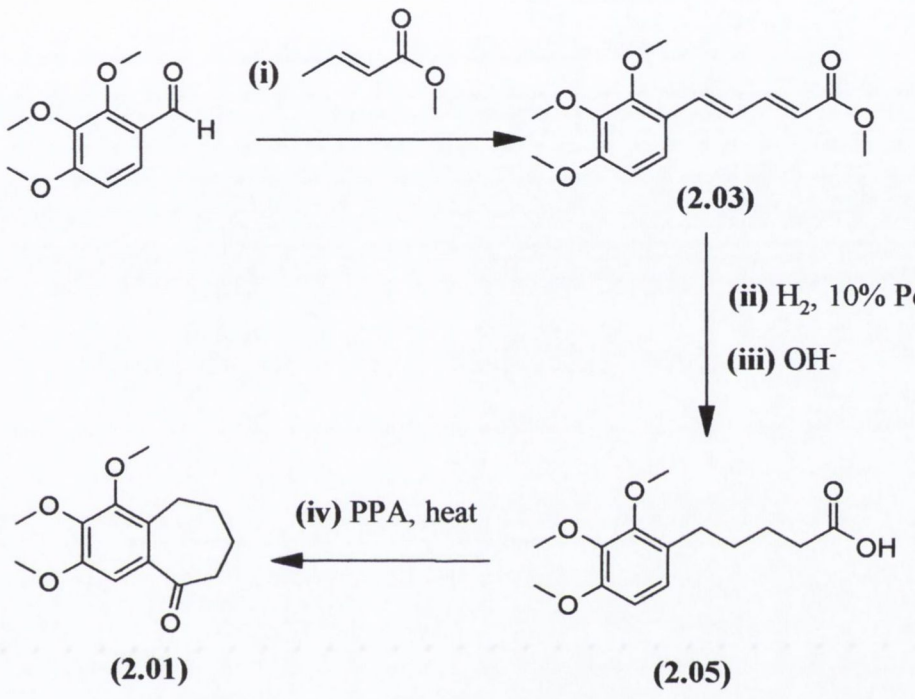
Figure 2.2. Positions available for functionalisation.

The synthesis of compound **(2.01)** was investigated by applying a method designed by Banwell *et al*[101] for the synthesis of its related regioisomer, 2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **(2.02)**. Although this method was used initially, the yield of the desired compound obtained was very low, typically only 2-5%.



(2.02)

This method involved the base-initiated condensation of 2,3,4-trimethoxybenzaldehyde with methyl crotonate. Base hydrolysis of the resulting coupled compound **(2.03)** was followed by hydrogenation. The resulting pentanoic acid **(2.05)** underwent direct cyclisation[102] in hot polyphosphoric acid (PPA) to afford the desired cyclic product **(2.01)** (Scheme 2.1).

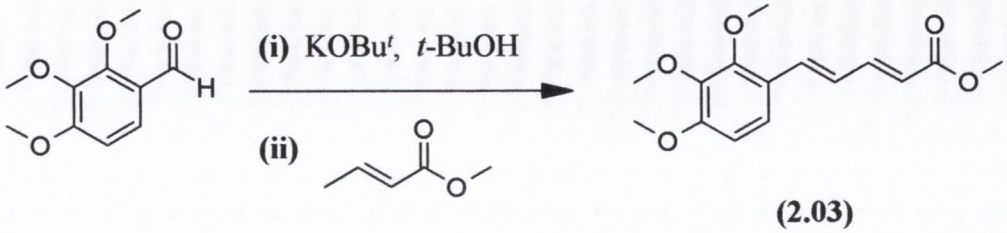


Scheme 2.1. Generalised reaction scheme for the synthesis of **(2.01)**.

After using this procedure, several side-products were noted including the formation of large quantities of trimethoxybenzoic acid in the first step and tarry by-products in the cyclisation step. To circumvent these problems the first step was carried out in the absence of light, the methyl ester was then hydrolysed before the hydrogenation step and the acid intermediate was activated prior to cyclisation.

2.2.1 Aldol condensation reaction

The major side product formed in this step of the reaction was trimethoxybenzoic acid. However, the formation of this compound was prevented by carrying out the reaction under an atmosphere of nitrogen and in the absence of light.

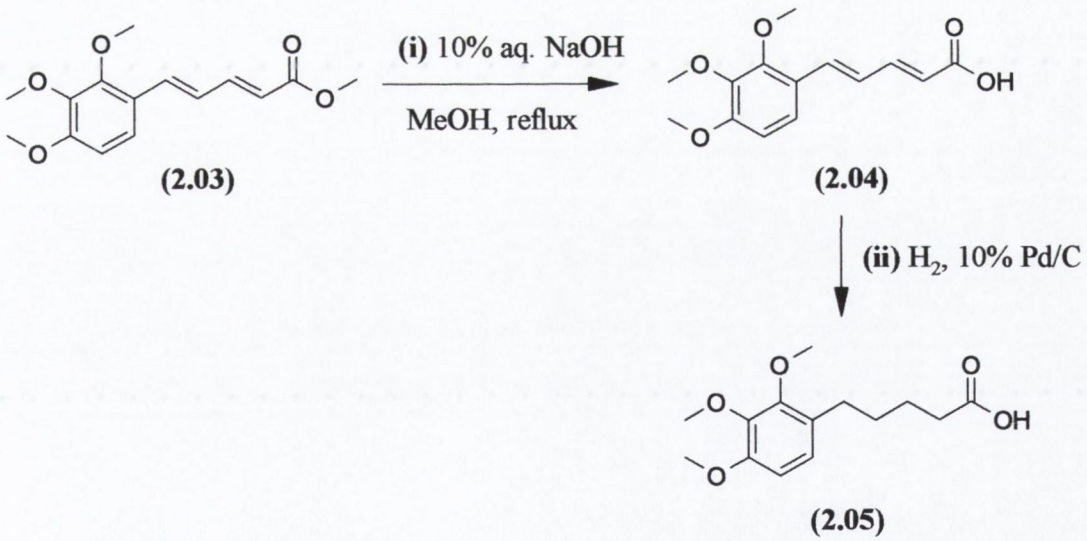


(2.03)

Scheme 2.2.

2.2.2 Base hydrolysis and hydrogenation steps

The methyl ester **(2.03)** was not purified extensively before the hydrolysis step, as under the basic conditions employed in the aldol reaction, partial hydrolysis of this ester had occurred. Therefore, the crude mixture was completely hydrolysed using 2.5M aq. NaOH. The resulting diene acid **(2.04)** was dissolved in a 1:1 mixture of ethanol/ethyl acetate and hydrogenated using 10% Pd/C as catalyst (Scheme 2.3). This approach also permitted the removal of any unreacted trimethoxybenzaldehyde after the hydrolysis step.



(2.03) **(2.04)** **(2.05)**

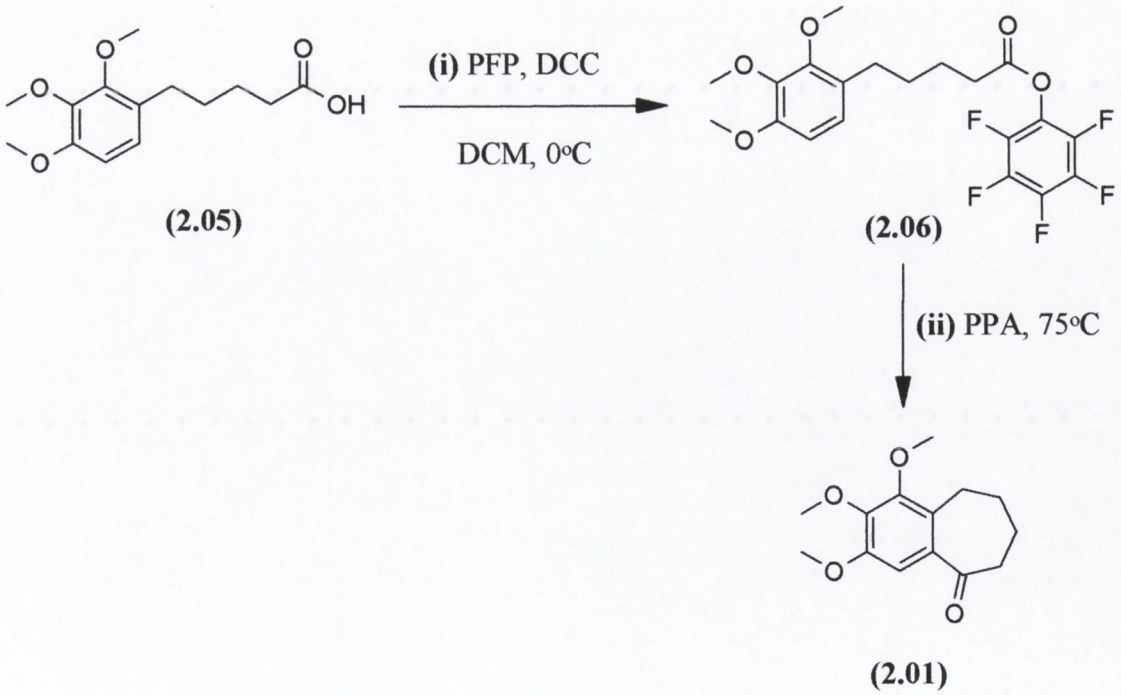
Scheme 2.3.

2.2.3 Cyclisation step

A significant problem with the cyclisation of **(2.05)** was the presence of butanoic acid as an impurity. Several attempts were made to purify the acid **(2.05)** prior to cyclisation including distillation under high vacuum. However, this approach resulted in

significant decomposition products being produced. A method was therefore sought to activate the acid **(2.05)** and subsequently purify, prior to cyclisation by flash column chromatography. This immediately ruled out the possibility of forming the corresponding acid chloride due to its sensitivity to atmospheric moisture and instability to silica gel.

Activation of acids by formation of pentafluorophenyl esters is a commonly employed procedure in peptide synthesis and this was also the preferred method of acid activation[103]. The synthesis of the pentafluorophenyl ester **(2.06)** was achieved by treating the acid **(2.05)** with dicyclohexylcarbodiimide (DCC) and pentafluorophenol (PFP), using anhydrous dichloromethane (DCM) as solvent, whilst maintaining the temperature of the reaction at 0°C. This intermediate was easily purified by flash column chromatography. Its cyclisation was effected using a large excess of polyphosphoric acid (PPA) and heating the reaction to 75°C (Scheme 2.4).



(2.05) **(2.06)** **(2.01)**

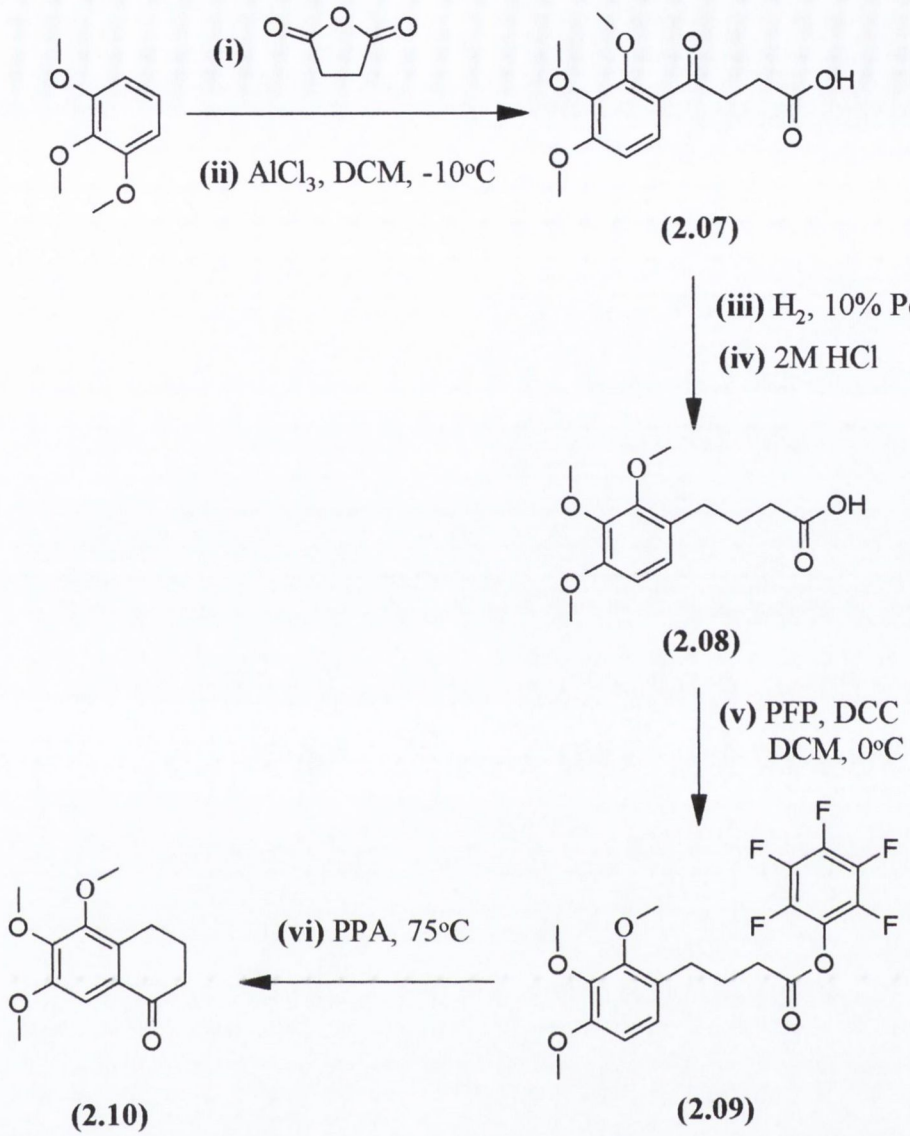
Scheme 2.4.

2.3 Synthesis of 6- and 5-membered B-ring trimethoxy- and methylenedioxy A-ring analogues

Due to the success of the cyclisation reaction, the synthesis of several indanone and tetralone derivatives was initiated. The A-ring of these compounds included trimethoxy- and methylenedioxy-substituents and hence resembled components of several known anti-mitotic natural products.

2.3.1 Synthesis of the tetralone analogues

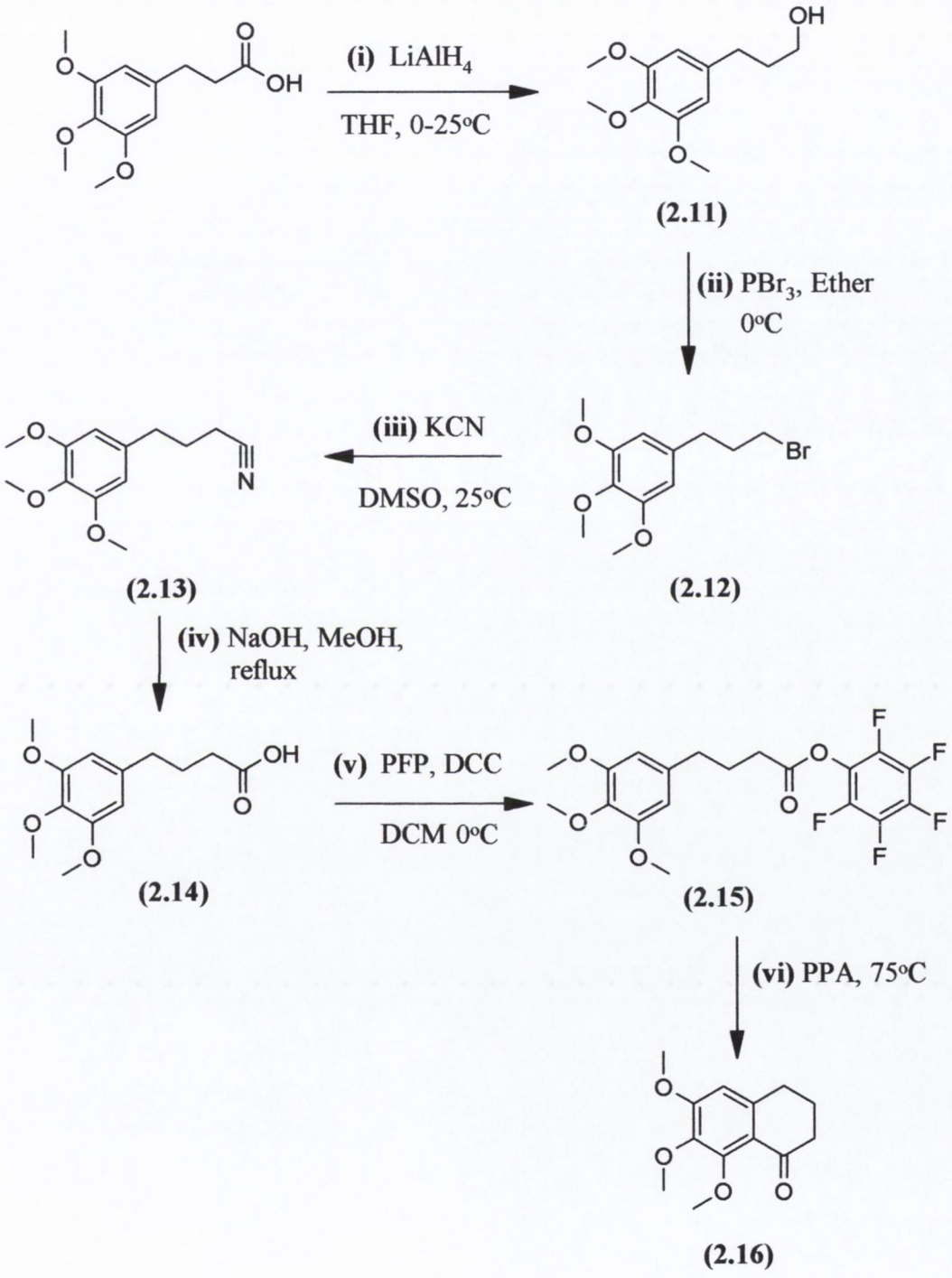
The tetralone analogues were synthesised using two different methods. The first approach employed the well-established Haworth reaction[104]. This reaction was instrumental in the formation of 5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-naphthalenone **(2.10)**. It involved the Friedel-Crafts addition of succinic anhydride to trimethoxybenzene using aluminium trichloride ($AlCl_3$) as Lewis acid catalyst and DCM as solvent. The resulting α,δ-keto-acid **(2.07)** was subsequently reduced *via* catalytic hydrogenation under acidic conditions (2M aq. HCl in ethanol) and activated to its pentafluorophenyl ester derivative **(2.09)** using PFP, DCC and DCM as solvent. Treatment of the ester with PPA and heating the mixture to 75°C afforded the desired tetralone **(2.10)** in an overall yield of 28% (Scheme 2.5).



Scheme 2.5.

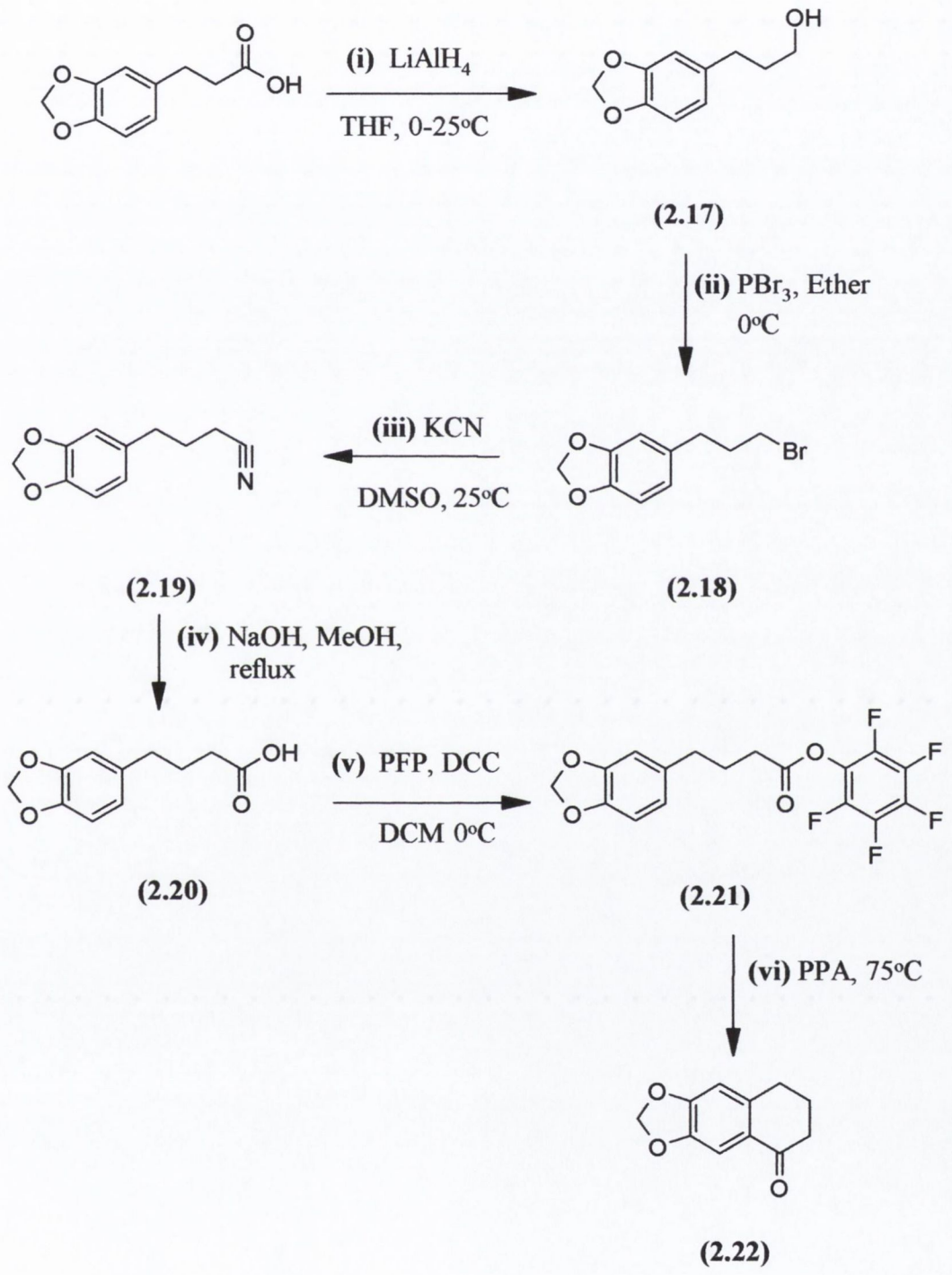
Regarding the synthesis of the tetralone derivative, 6,7,8-trimethoxy-1,2,3,4-tetrahydronaphthalone **(2.16)**, the reaction conditions employed in the initial Friedel-Crafts acylation step, the key intemediate, 3-(3,4,5-trimethoxyphenyl)butanoic acid **(2.14)**, could not be synthesised. An alternative synthesis of **(2.16)** was developed, which involved using the commercially available reagent 3-(3,4,5-trimethoxyphenyl)propanoic acid as the starting material. Reduction of this carboxylic acid to the alcohol **(2.11)** was accomplished using $LiAlH_4$[105]. Functional group interconversion of the alcohol using PBr_3 led to formation of the bromide **(2.12)**[106], which was subsequently converted to the nitrile **(2.13)** in high yields by using potassium cyanide (KCN) in dimethylsulphoxide (DMSO)[107]. The nitrile was then hydrolysed

using a methanolic solution of 10M aq. NaOH[108], and the resulting acid **(2.14)** activated to its pentafluorophenyl ester **(2.15)** and cyclised in PPA to afford the tetralone **(2.16)** (Scheme 2.6).



Scheme 2.6.

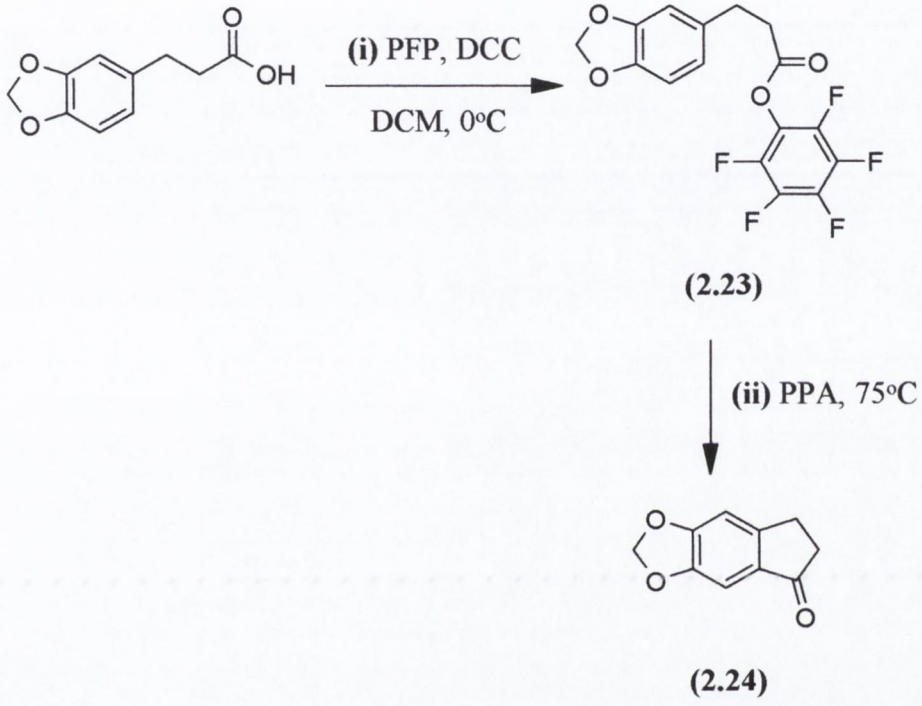
As similar regioselectivity problems were also encountered during the synthesis of 5,6,7,8-tetrahydronaphtho[2,3-d][1,3]dioxol-5-one **(2.22)** the conditions used were analogous to those employed for the preparation of **(2.16)** (Scheme 2.7).



Scheme 2.7.

2.3.2 Synthesis of the indanone analogues

The synthesis of 6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one **(2.24)** began by using 3-(1,3-benzodioxol-5-yl)propanoic acid as the starting material. This acid was converted to its corresponding pentafluorophenyl ester **(2.23)** and subsequently cyclised using polyphosphoric acid (Scheme 2.8).

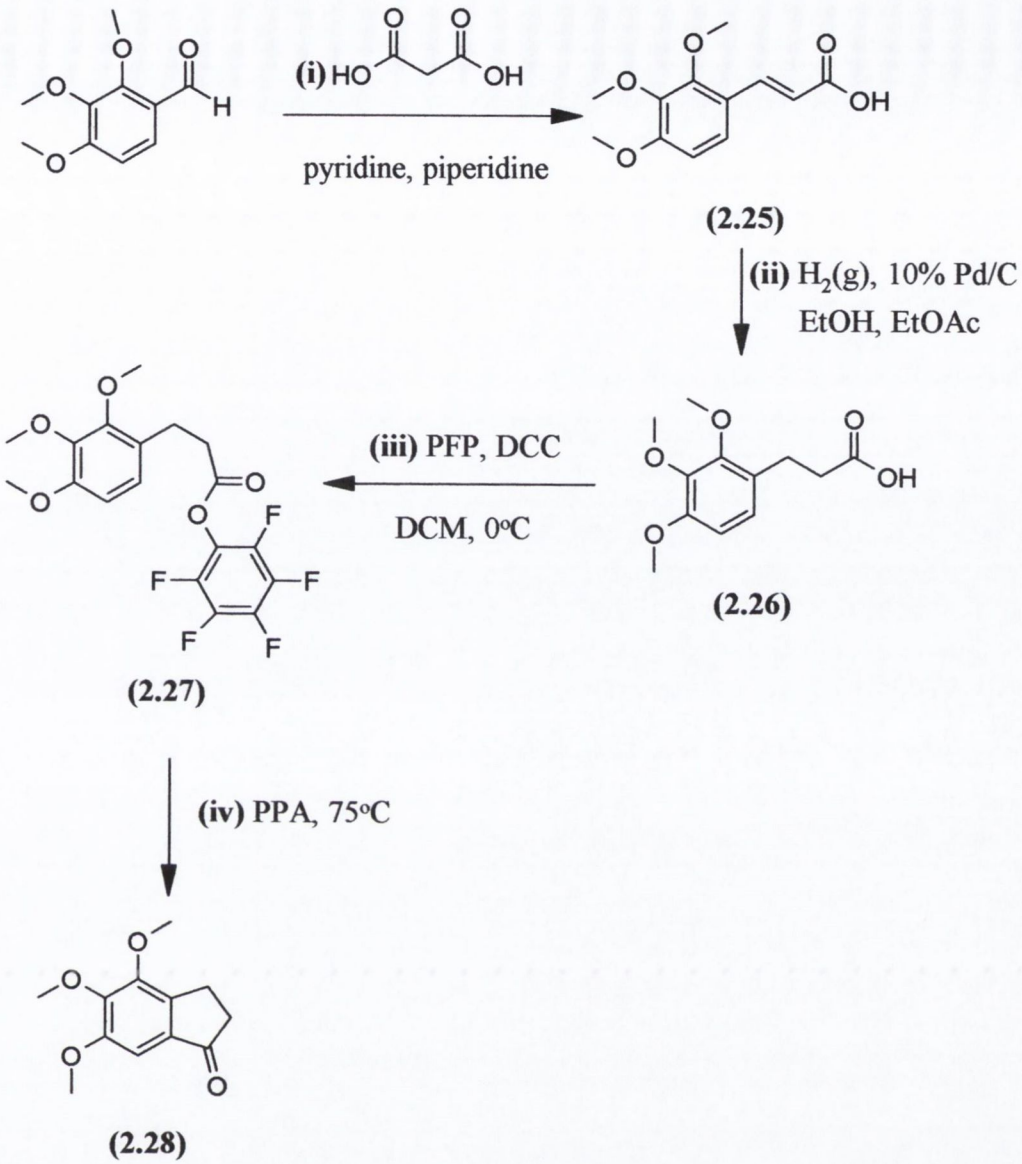


(2.23)

(2.24)

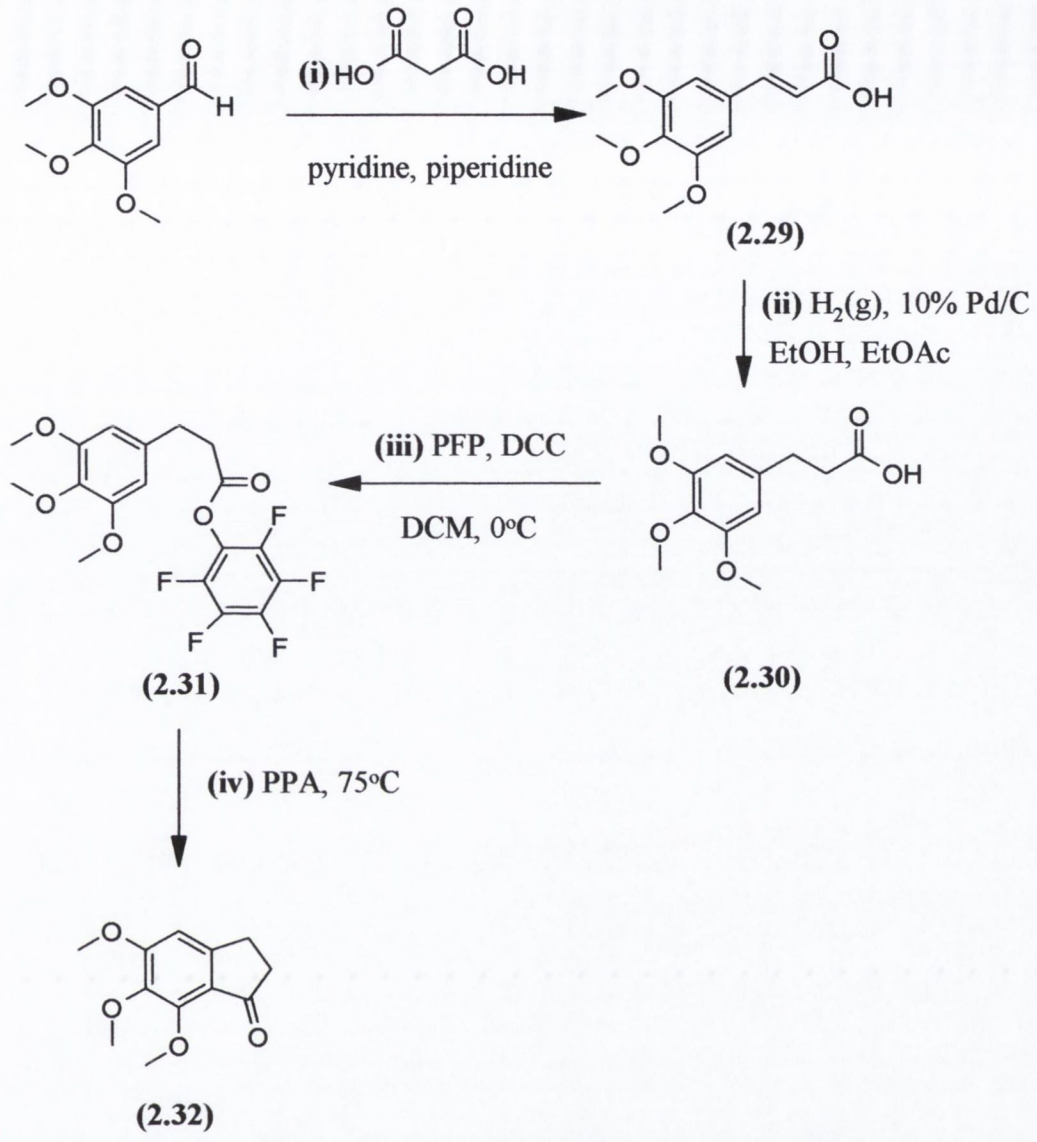
Scheme 2.8.

As 3-(2,3,4-trimethoxyphenyl)propanoic acid is not commercially available, the preparation of 4,5,6-trimethoxyindanone **(2.28)** began with the synthesis of 3-(2,3,4-trimethoxyphenyl)-2-propenoic acid **(2.25)**. This was achieved by a Perkin condensation reaction between malonic acid and 2,3,4-trimethoxybenzaldehyde. In this reaction a mixture of pyridine and piperidine was used as base and solvent respectively[109]. The resulting cinnamic acid **(2.25)** thus formed was reduced under catalytic hydrogenation conditions to afford 3-(2,3,4-trimethoxyphenyl)propanoic acid **(2.26)**. Activation of the saturated acid to its pentafluorophenyl ester **(2.27)** and cyclisation using PPA, afforded 4,5,6-trimethoxyindanone **(2.28)** as a white powder (overall yield was 78% from 2,3,4-trimethoxybenzaldehyde) (Scheme 2.9).



Scheme 2.9.

The formation of 5,6,7-trimethoxy-1-indanone **(2.32)** was accomplished under analogous conditions utilised for the synthesis of indanone **(2.28)** (Scheme 2.10).



Scheme 2.10.

2.4 Cyclisation of the non-activated benzocycloalkanones

To determine the scope of this new Friedel-Crafts acylation reaction, the cyclisation of a number of non-activated benzocycloalkanone derivatives from their pentafluorophenyl ester precursors **(2.33)-(2.38)** was investigated (Figure 2.3). Their cyclisation rates and yields were then compared with respect to their corresponding activated 5-, 6- and 7-membered analogues (Table 2.1). As expected, the cyclisation of aryl-activated pentafluorophenyl ester precursors proceeded at a much faster rate and with better yields than their corresponding non-activated analogues.

Cyclised product	Time (mins)	Temperature (°C)	Yield (%)[a]
(2.32)	150	75-80	98 (91)[110]
(2.28)	150	75-80	96 (36)[111]
(2.24)	160	75-80	89 (92)[112]
(2.10)	75	75-80	92 (94)[113]
(2.16)	60	75-80	85 (68)[114]
(2.22)	120	75-80	78 (30)[115]
(2.01)	45	75-80	89 (91)[116]
(2.02)	30	75-80	94 (64)[101]
(2.39)	300	75-80	72 (87)[117]
(2.40)	280	75-80	80 (68)[118]
(2.41)	360	75-80	70 (93)[119]
(2.42)	360	75-80	48 (90)[116]
(2.43)	420	75-80	71 (58)[120]

[a] The values quoted in parentheses are yields obtained from alternative methods of cyclisation.

Table 2.1. Cyclisation conditions using PFP methodology.

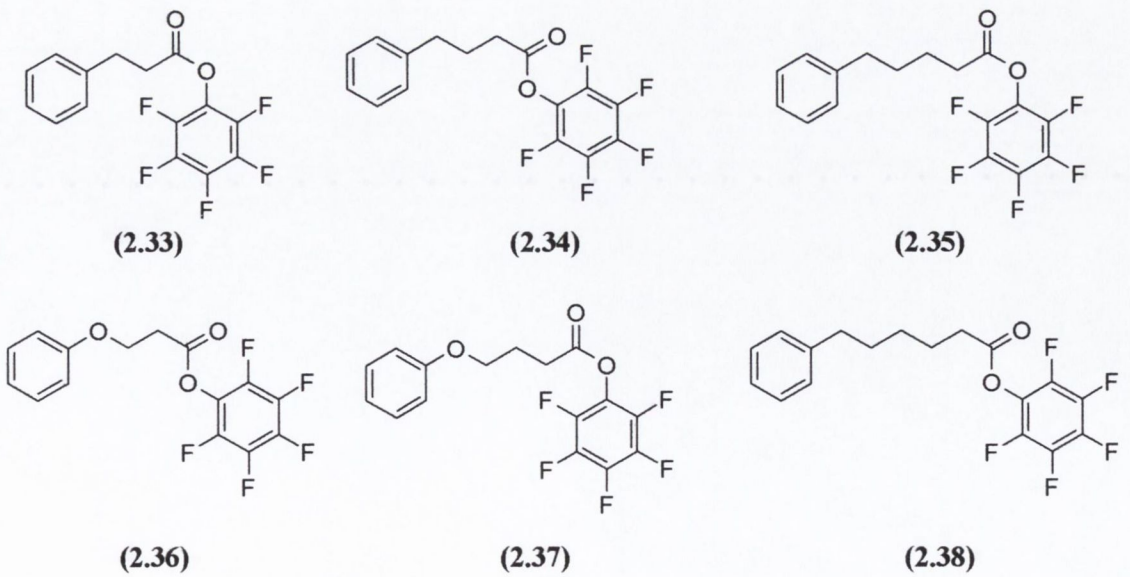
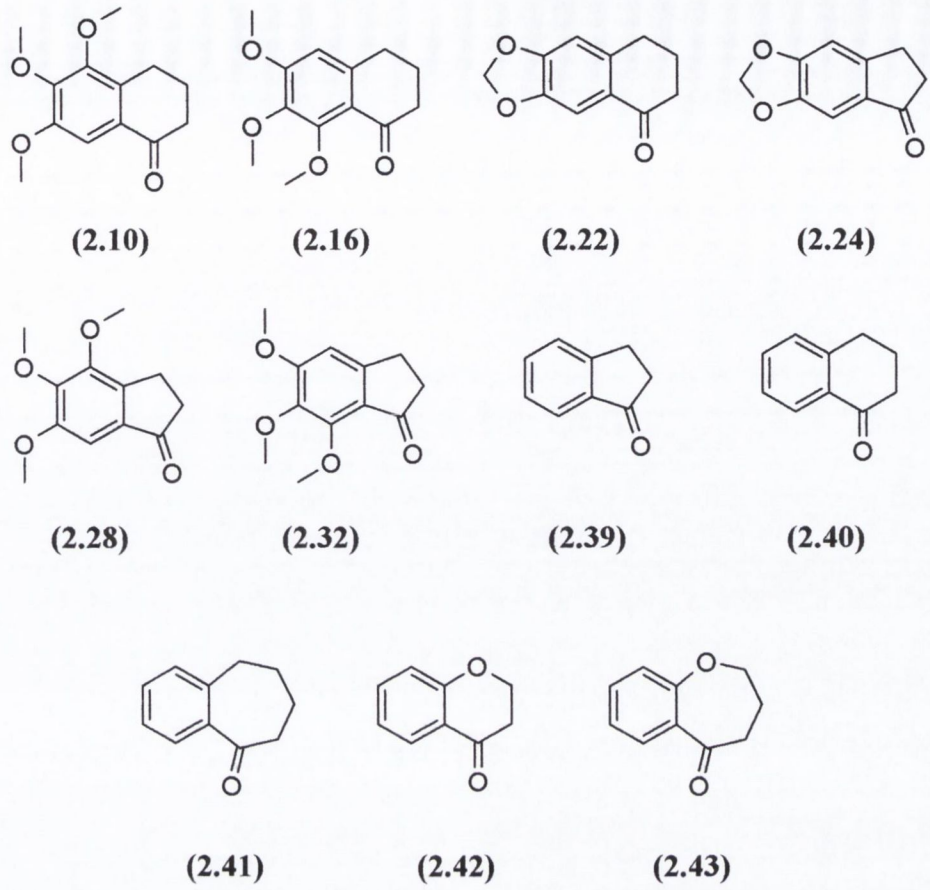


Figure 2.3. PFP ester precursors of the non-activated benzocycloalkanones.



(2.10) **(2.16)** **(2.22)** **(2.24)**

(2.28) **(2.32)** **(2.39)** **(2.40)**

(2.41) **(2.42)** **(2.43)**

Figure 2.4. Cyclised compounds using PFP methodology.

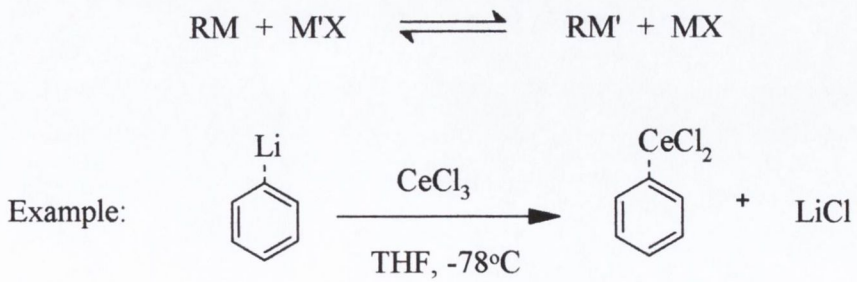
These reaction conditions are superior to other alternative ring-closure methods as it eliminates the use of pyrophoric reagents (e.g. PCl_5, $AlCl_3$, $SnCl_4$ and P_2O_5) and highly toxic solvents such as benzene and CS_2. In many cases, the yields and reaction rates obtained for these benzocycloalkanones were better than or comparable to well-established cyclisation procedures.

This was further illustrated by the successful synthesis of 3,4-dihydro-1(2*H*)-benzooxepin-5-one **(2.43)** as the presence of the ether linkage in this compound, restricts intramolecular cyclization, resulting in low yield of product **(2.43)**. Previous reports have stated that the maximum yield obtained for the cyclisation step was 58% from its acyl halide precursor or 55% by direct cyclisation of the carboxylic acid[120]. However, using the PFP methodology, the yield obtained was 71%.

2.5 Formation of aryl-substituted benzocycloalkenes

According to the SAR studies described in section 1.6.3.4, for optimal binding of the targeted compounds to tubulin, it was deemed necessary to attach an additional aryl unit at the ketonic centre of the benzocycloalkanone intermediates. In addition, it was also felt that the *meta*- and *para*-positions of this aryl unit would require substituents for potent binding to tubulin with a combination of methoxy, hydroxy and amino groups being preferred. Organometallic reactions represent an efficient method by which nucleophillic addition to carbonyl-containing compounds may be carried out. In particular, the formation of the corresponding Grignard or organolithium reagent of the respective aryl units should prove to be an effective approach by which this transformation may be achieved.

Although it was decided to focus on the formation and use of organolithium and Grignard reagents when attempting carbon-carbon bond formations, a large number of other metals can be utilised to generate the corresponding carbanion species; with aluminium[121], copper[122], titanium[123], chromium[124], zinc[125], cadmium[125], mercury[126], cerium[127] and the alkali earth metals[128] with the latter metals finding prominence for this type of transformation. Their formation is usually achieved through transmetallation (Scheme 2.11), metal-halide exchange (e.g. organolithium reagents) or metallation (e.g. Grignard reagents). Transmetallation is only successful if the metal (M') is lower in the electromotive series. As a result, this has become a powerful tool for forming organometallic complexes containing the more electropositive metals.



Scheme 2.11.

The application of a specific organometallic reagent in carbon-carbon bond formation is strongly dependent on the nature of the electrophile present and the occurrence of other functional groups within the molecule. Strongly basic organometallic compounds such as organolithium and Grignard reagents are powerful nucleophiles since the carbanion is heavily polarized due to the electropositive effect of the metal. These reagents usually produce high yields of carbon-carbon bond adducts. However, as a result of their high reactivity, they are quite unstable and can react with a number of other functional groups such as carbonyls, alcohols, amines, amides, thiols, nitro and nitriles if not suitably protected. Generally, non-activated alkenes, ethers and acetals may be present within the molecule when attempting carbon-carbon bond formations.

Alternatively, the use of protecting groups can be avoided by attenuating the basicity, and hence the nucleophilicity, of the carbanion. This can be achieved by using a less electropositive metal to generate this species. As a result, a number of functional groups may be present within the molecule and carbon-carbon bond formation need not only involve a carbonyl group. For example, the formation and reaction of a lithium organocuprate (Gilman reagent) can be carried out in the presence of carbonyl-based functional groups (such as amides and carboxylic acids). Regarding its addition to α,β-unsaturated carbonyl-containing compounds, carbon-carbon bond formation usually occurs at the 1,4-position (double bond) rather than at the 1,2-position (carbonyl group). In contrast, organocerium reagents will only react at the ketonic centre of an enone[129]. Even weaker organometallic compounds (such as organotitanium and organozirconium reagents) can be used to exhibit chemoselectivity over aldehydes, rather than ketones, when the reaction is carried out between -70°C and 0°C[130].

2.6 Synthesis of the mono-methoxyphenyl substituted benzocycloalkenes and their saturated analogues

Previous reports by Cushman[91] have described the synthesis and biological evaluation of two derivatives of the combretastatin family containing a single methoxy substituent on the *meta*- and *para*-positions of the B-ring (Figure 2.5). These compounds were shown to be potent inhibitors of tubulin polymerisation (IC_{50} 8.8 μM and 2.2 μM respectively).

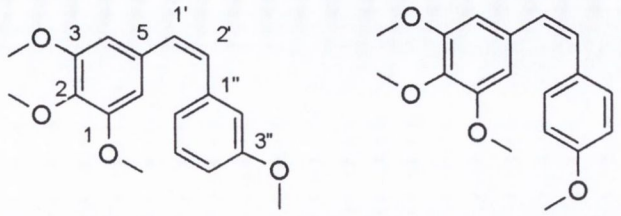
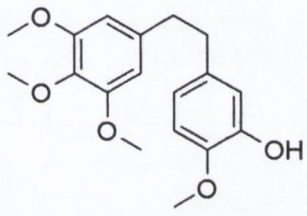


Figure 2.5. Combretastatin derivatives modified in B-ring.

In addition to those derivatives, other workers have shown that dihydrocombretastatin A-4 **(1.38)** is also a potent inhibitor of tubulin polymerisation (IC_{50} = 3.3 μM)[91].

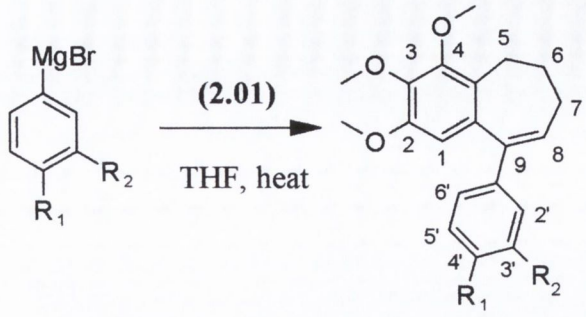


(1.38)

Based on these observations, the synthesis of four novel bi-aryl compounds **(2.44-2.47)** containing a single methoxy substituent on the *meta*- and *para*-positions of the second aromatic ring was investigated.

2.6.1 Synthesis of the 2,3,4-trimethoxy-9-(methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cycloheptene derivatives

The synthesis of these compounds were simplified somewhat, as both aryl precursors, 3-methoxyphenyl magnesium bromide and 4-methoxyphenyl magnesium bromide were commercially available from Aldrich™. Nucleophillic addition of these Grignard reagents to **(2.01)** under anhydrous conditions, afforded in each case, a tertiary alcohol adduct, which was dehydrated *in situ* by treatment with 2M aq. HCl to afford compounds **(2.44)** (55% yield) and **(2.45)** (66% yield) as viscous oils (Scheme 2.12).



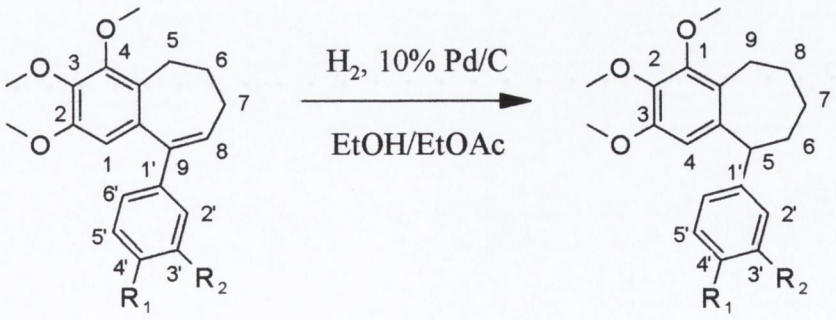
$R_1 = OCH_3, R_2 = H$ **(2.44)**

$R_1 = H, R_2 = OCH_3$ **(2.45)**

Scheme 2.12.

2.6.2 Synthesis of the 1,2,3-trimethoxy-5-(methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene derivatives

To optimise the binding affinity potential of these molecules to tubulin, it was believed that reduction of the double bond in compounds **(2.44)** and **(2.45)** would create derivatives with greater flexibility and thus allow these molecules to induce a conformation better suited to the profile of the C.B.S in tubulin. This reductive step was accomplished *via* catalytic hydrogenation using 10% Pd/C as the catalyst to afford the saturated derivatives, **(2.46)** and **(2.47)**, in quantitative yield (Scheme 2.13).



$R_1 = OCH_3, R_2 = H$ **(2.44)**

$R_1 = H, R_2 = OCH_3$ **(2.45)**

$R_1 = OCH_3, R_2 = H$ **(2.46)**

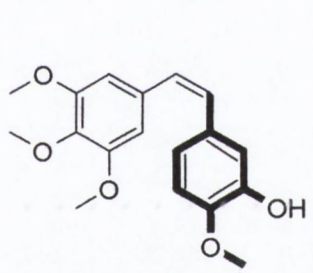
$R_1 = H, R_2 = OCH_3$ **(2.47)**

Scheme 2.13.

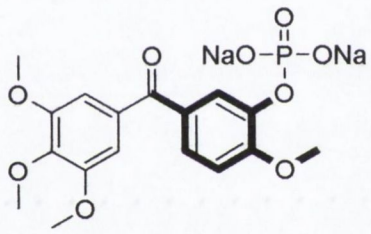
2.7 Formation of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)phenol (2.52)

Since the isolation of combretastatin **(1.33)** from the bark of the South African tree, *Combretum caffrum*[78], a large number of other derivatives have been discovered or synthesized that possess potent anti-mitotic activity. Most notable of these compounds is combretastatin A-4 **(1.03)**, a potent tubulin inhibitor, showing high oncolytic activity against a wide variety of human cancer cell lines including MDR cancer cell lines[131].

Therefore, to synthesise compounds within the proposed model with equivalent potency to combretastatin A-4, it was deemed necessary that the second aryl unit should contain a hydroxy substituent *ortho* to the methoxy substituent in **(2.45)**. This approach was used previously by Pettit *et al*[92] which led to the development of phenstatin phosphate (Figure 2.6).



(1.03)



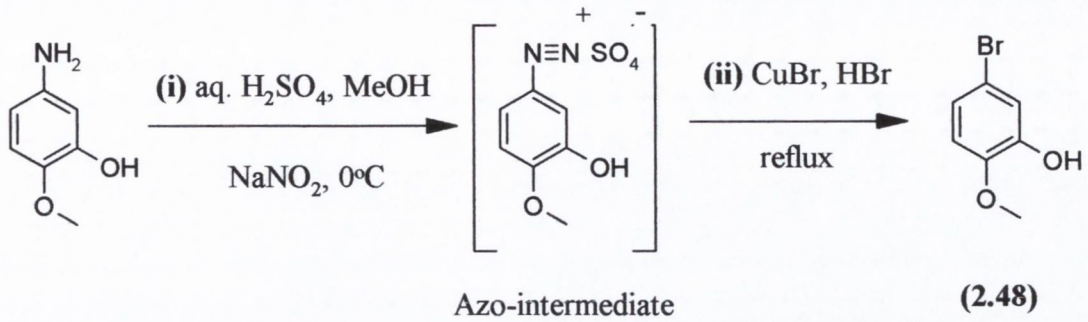
Phenstatin phosphate

Figure 2.6. The structures highlighted in bold represent the methoxyphenol unit.

2.7.1 Synthesis of the intermediate, (5-bromo-2-methoxyphenoxy)(*tert*-butyl)dimethylsilane (2.50)

During the synthesis of 5-bromo-2-methoxyphenol **(2.48)** two different methods were explored. The first procedure began with 5-amino-2-methoxyphenol and involved conversion of the amino-functionality to a bromide. This was accomplished by the Sandmeyer reaction[132], which involved treating the aniline with a sulphuric acid/methanol solution together with the slow addition of sodium nitrite to afford the azo-intermediate. This intermediate was subsequently converted to the bromo compound by refluxing the azo-intermediate in hydrobromic acid and cuprous bromide[133]. When the reaction was complete, the product, 5-bromo-2-methoxyphenol

(2.48) was extracted with diethyl ether and purified by flash column chromatography. Unfortunately, the best yield obtained using this method was only 15% (Scheme 2.14).

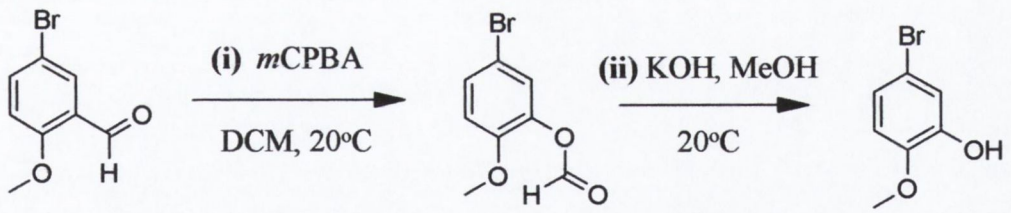


Azo-intermediate

(2.48)

Scheme 2.14.

Due to this unsatisfactory yield and the large expense of 5-amino-2-methoxyphenol, an alternative procedure was undertaken. This new approach involved the conversion of 5-bromo-2-methoxybenzaldehyde to 5-bromo-2-methoxyphenyl formate **(2.49)** *via* Baeyer-Villager oxidation[134]. This reaction required the use of *meta*-chloroperoxybenzoic acid (*m*CPBA) as the oxidizing agent. Following conversion to the formate ester **(2.49)**, subsequent hydrolysis using methanolic KOH solution resulted in the formation of the phenol **(2.48)** in high yields (90%) (Scheme 2.15).

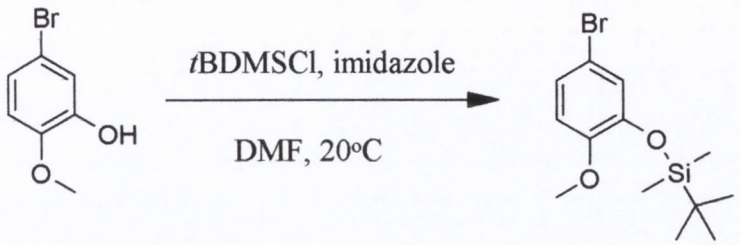


(2.49) **(2.48)**

Scheme 2.15.

The phenol **(2.48)** was protected as a *tert*-butyldimethylsilyl ether[135] (*t*BDMS) **(2.50)** as this protecting group is stable to the conditions employed when forming its organometallic derivative and furthermore, cleavage back to the phenol is straightforward, only requiring the use of *tetra*-butylammonium fluoride (TBAF). The silyl derivative **(2.50)** was prepared by dissolving the phenol **(2.48)** in DMF, followed by the addition of *tert*-butyldimethylchlorosilane (2.0 molar equivalents) and imidazole

(2.5 molar equivalents). The reaction was allowed to proceed at ambient temperatures for four hours and after work-up, the protected phenol **(2.50)** was isolated in 96% yield (Scheme 2.16).

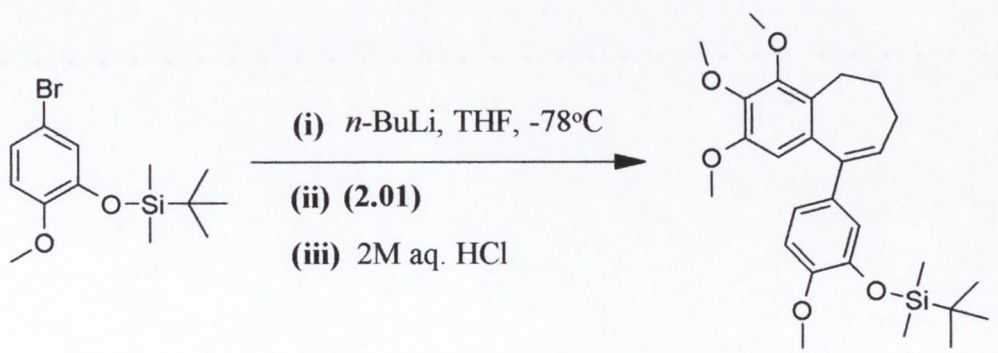


(2.48) **(2.50)**

Scheme 2.16.

2.7.2 Organometallic addition of (2.50) to (2.01)

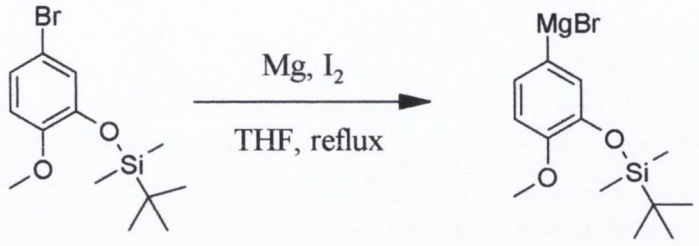
The aryl bromide **(2.50)** was then converted to its corresponding organolithium derivative by metal-halide exchange using *n*-BuLi in tetrahydrofuran (THF) at -78°C. This was then coupled *in situ* to the ketone **(2.01)** at -78°C, under an atmosphere of nitrogen. This afforded the carbinol intermediate, which was dehydrated *in situ* following the addition of 2M aq. HCl. After work-up and purification by flash column chromatography, the biaryl product **(2.51)** was isolated as a mobile oil in 58% yield (Scheme 2.17).



(2.50) **(2.51)**

Scheme 2.17.

In addition to forming the organolithium derivative of **(2.50)**, the coupling of **(2.50)** to **(2.06)** was also carried out by forming the Grignard derivative of **(2.50)**. This intermediate was formed by adding **(2.50)** to a mixture of iodine-activated magnesium turnings in THF and gently refluxing the reaction[136] (Scheme 2.18).



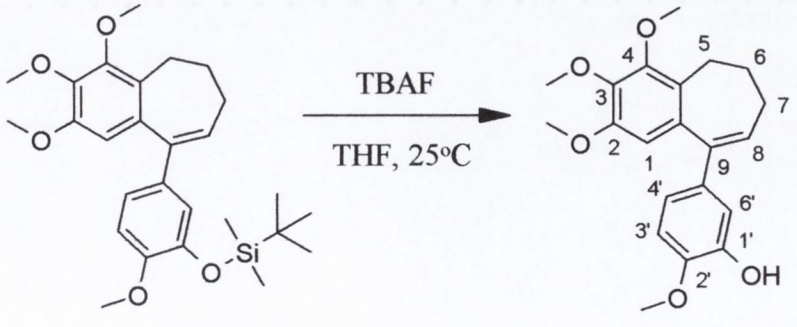
(2.50)

Scheme 2.18.

Upon formation of the Grignard reagent, the ketone **(2.06)** was added at room temperature to the mixture before refluxing the solution for several hours. However, after acidic work-up and purification by flash column chromatography the maximum yield of **(2.51)** obtained using this procedure was only 23%.

2.7.3 *t*BDMS deprotection of (2.51) to 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)phenol (2.52)

The silyl intermediate **(2.51)** was converted in quantitative yield to the phenol **(2.52)** using TBAF. The reagents were dissolved in THF and the conversion to the phenol proceeded smoothly at room temperature[137] (Scheme 2.19).



(2.51) **(2.52)**

Scheme 2.19.

2.7.4 Structural elucidation of (2.52)

The ^{1}H NMR spectrum of **(2.52)** revealed that the geminally-related methylene protons on the aliphatic B-ring resonated at different frequencies. The three multiplets for each of these methylene groups resonated at 1.95 ppm, 2.12 ppm and 2.65 ppm. Analysis of the ^{1}H-^{1}H COSY spectrum (Figure 2.7) revealed the methylene H-7 protons (1.95 ppm) coupling strongly to the alkenyl H-8 proton (6.34 ppm). A correlation contour was also observed between these protons and the quintet at 2.12 ppm representing coupling to the methylene protons on carbon-6. In addition, the ^{1}H-^{1}H COSY spectrum also revealed strong coupling between the methylene H-6 protons and a triplet resonating at 2.65 ppm, and so was assigned as the benzylic H-5 protons. The methyl protons of the methoxy substituents resonated as sharp singlets at 3.70 ppm, 3.90 ppm, 3.91 ppm and 3.94 ppm. The broad singlet at 5.57 ppm was assigned as the phenolic proton. The shielded aromatic proton (H-1) resonated as a singlet at 6.40 ppm. A complex multiplet, integrating for two protons resonated between 6.77 ppm and 6.82 ppm and was attributed to both H-3' and H-4'. From the ^{1}H-^{1}H-COSY spectrum, this showed correlation to the doublet (J = 1.5Hz) at 6.91ppm. This doublet was probably split by the weak *meta*-coupling to the H-4' proton and was assigned as the H-6' proton.

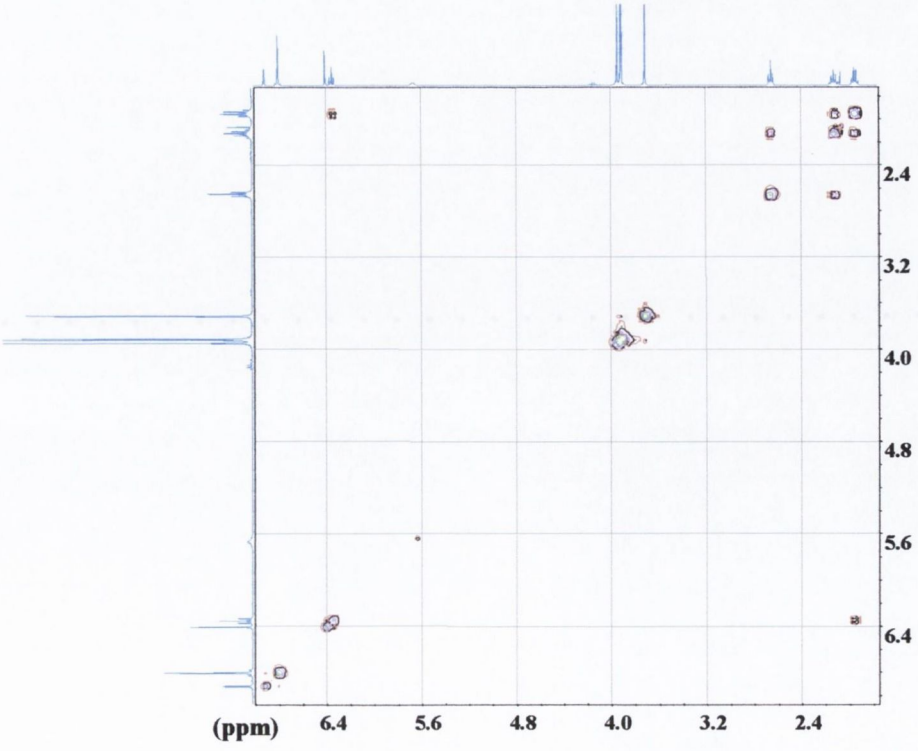


Figure 2.7. ^{1}H-^{1}H COSY spectrum of **(2.52)**.

The ^{13}C NMR spectrum of **(2.51)** identified three methylene carbons resonating at 23.08 ppm, 25.02 ppm and 34.46 ppm. Upon close inspection of the HMQC spectrum (Figure 2.8) these resonances displayed coupling to H-5, H-7 and H-6 and so were assigned as the methylene carbons-5, -7 and -6 carbons respectively. The methoxy carbons resonated at 55.55 ppm, 55.57 ppm, 60.38 ppm and 61.06 ppm. By inspection of both DEPT 90 and HMQC spectra, the five-methine carbons resonated at 108.50 ppm (C-1), 113.74 ppm (C-6'), and 126.76 ppm (C-8) while the signals resonating at 109.86 ppm and 119.21 ppm were assigned as C-3' and C-4' respectively. The nine quaternary carbons in the molecule were observed in the ^{13}C NMR spectrum resonating between 123.29 ppm and 150.50 ppm.

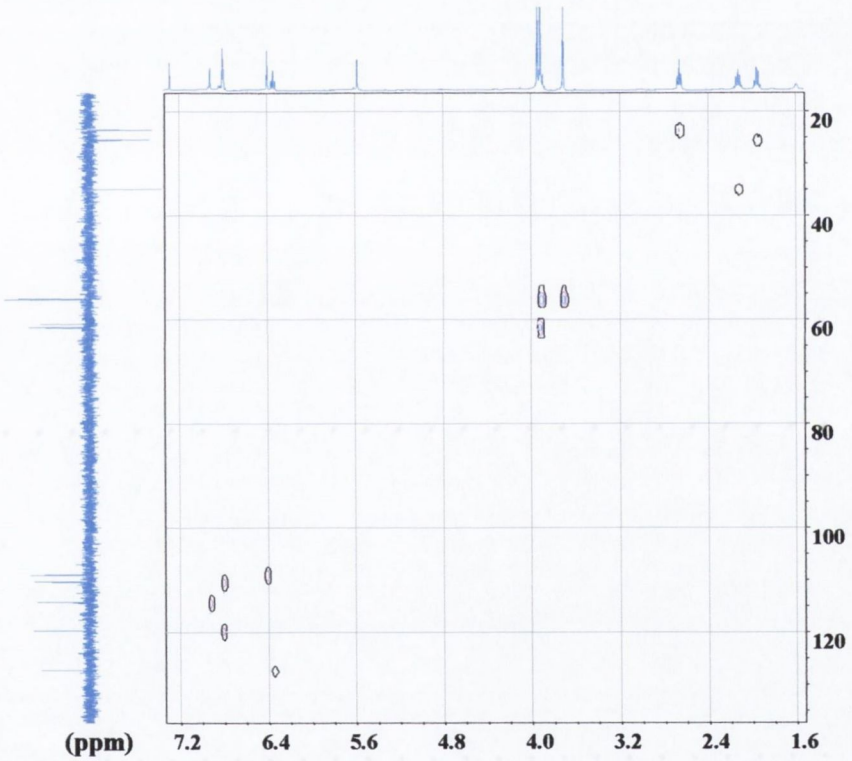


Figure 2.8. HMQC spectrum of **(2.52)**.

In an attempt to identify the orientation of the C-ring hydroxy substituent with respect to the trimethoxy-substituents on the A-ring, a number of NOE experiments were performed on **(2.52)**.

A reciprocated positive NOE effect was observed for H-8 (6.34 ppm) after irradiation of H-6' (6.91 ppm) (Figure 2.10). From this, one can conclude that the alkenyl H-8 proton interacts through space with the H-6' proton on the C-ring. Further experiments also

revealed NOE interactions between the H-4' proton (6.79 ppm) and H-8. From these results, it would appear that at ambient temperature, the aromatic C-ring rotates rapidly about the C(5')-C(9) bond as illustrated in Figure 2.9.

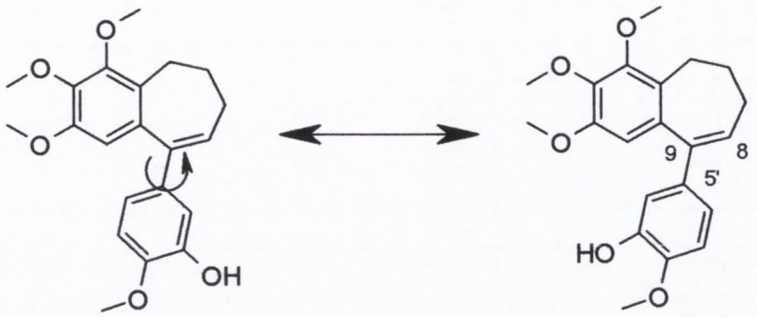


Figure 2.9. Illustrates rotation around the C-5'-C-9 bond.

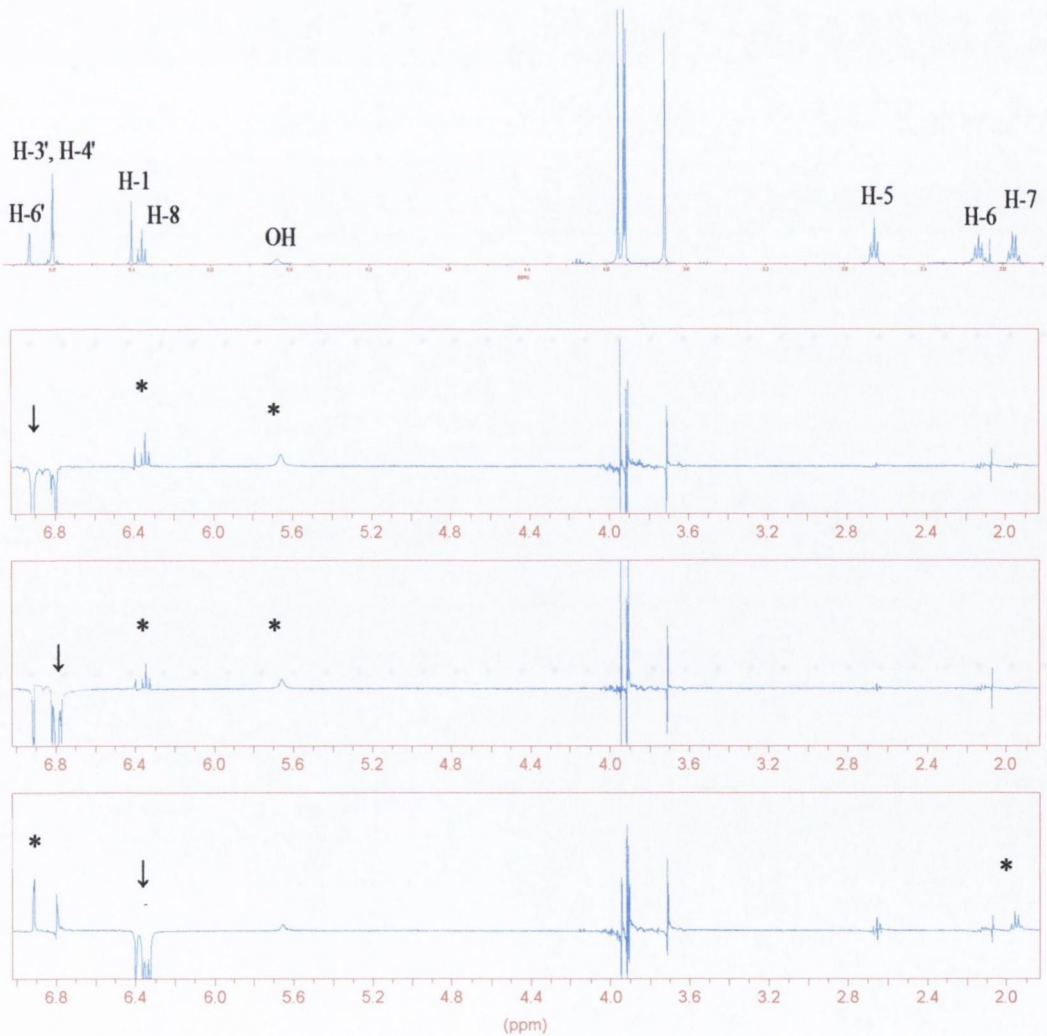


Figure 2.10. NOE experiments demonstrated the interactions between H-6' and H-8 and the weaker interaction between H-4 and H-8. The irradiated peaks are denoted by ↓ and the positive NOE interaction is denoted by *.

Additionally, it was also possible to see a spatial interaction between the H-8 proton and the methylene H-7, H-6 and H-5 protons. Presumably, these interactions occur due to the flexible B-ring occupying many conformational states in solution thereby permitting each methylene proton to interact with the H-8 proton during the NMR timescale (Figure 2.11). Structurally, it was concluded that in solution and at ambient temperature, **(2.52)** exists as a highly flexible compound which also allows for rotation about the C(5')-C(9) bond.

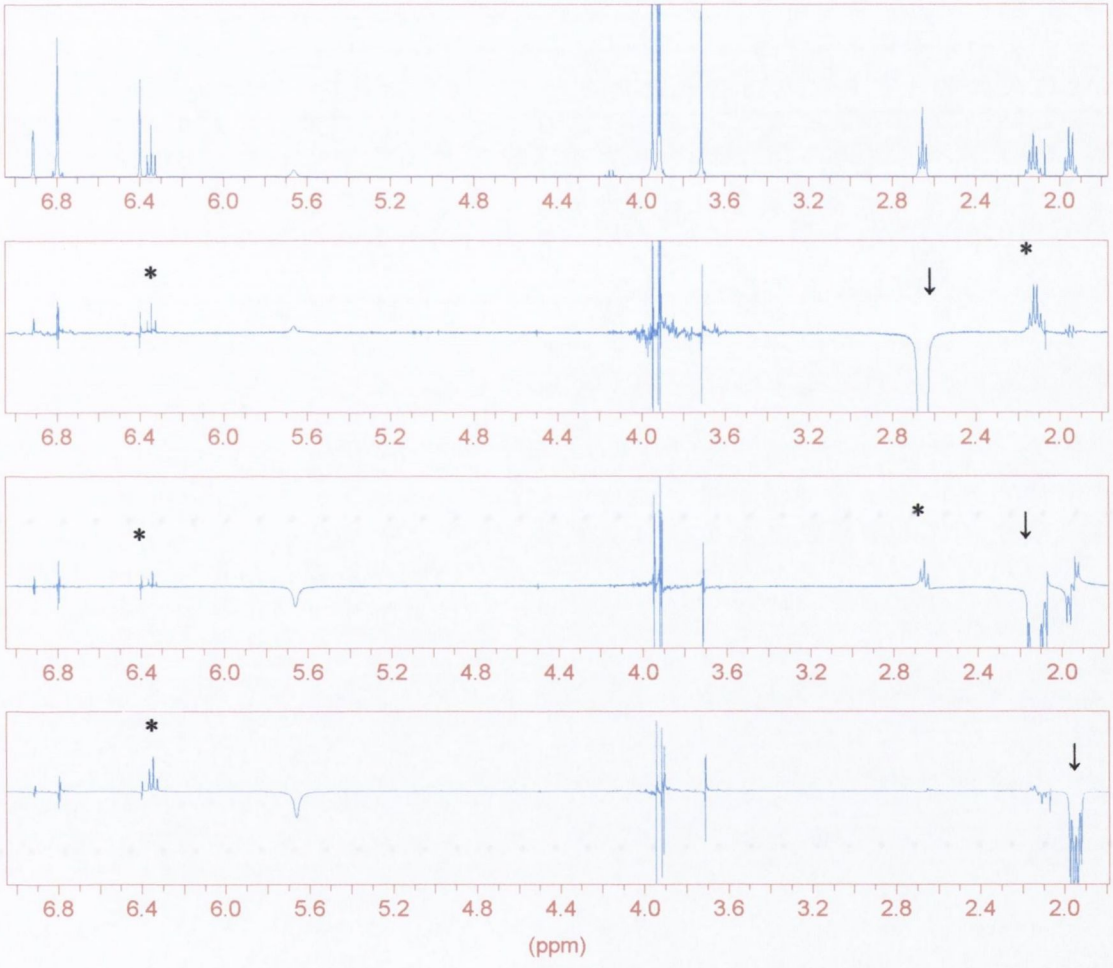
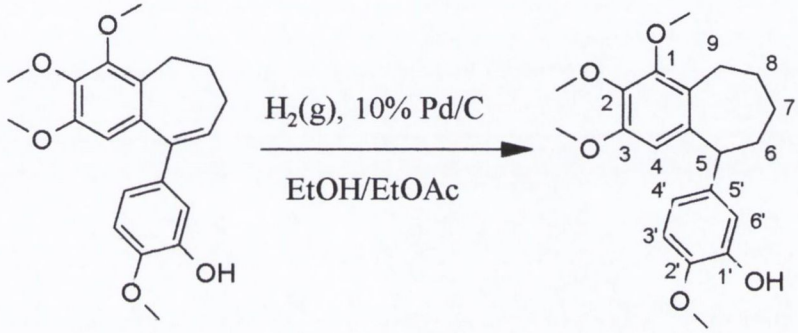


Figure 2.11. NOE experiments showing spatial interactions between the methylene protons and the alkenyl H-8 proton. The irradiated peaks are denoted by ↓ and the positive NOE interactions are denoted by *.

2.8 Synthesis of 2-methoxy-5-(1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-yl)phenol (2.53)

Saturation of the double bond of **(2.52)** involved its solubilisation in a solution of EtOH/EtOAc containing 10% Pd/C as catalyst and hydrogenating the mixture for 48 hours. Removal of the catalyst by filtration and evaporation of the solvent afforded **(2.53)** as a colourless oil in quantitative yield (Scheme 2.20).



(2.52) **(2.53)**

Scheme 2.20.

2.9 Formation of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-1,3-benzenediol (2.57)

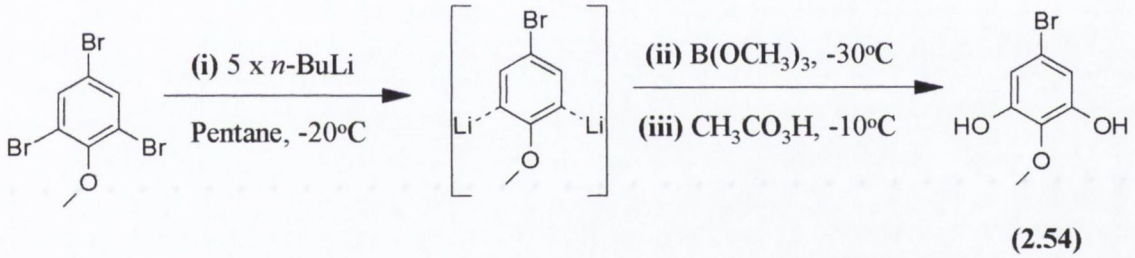
Having tentatively established that compound **(2.52)** exists as a rotamer, it was decided to explore the effect on tubulin binding of introducing another hydroxyl group *ortho* to the 2'-methoxy group in **(2.52)**. It was felt that this additional functionality would add an element of symmetry to this aryl unit and thereby increase the probability of finding a suitable orientation that was appropriate to the profile of the C.B.S.

2.9.1 Synthesis of (5-bromo-3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-2-methoxyphenoxy)(*tert*-butyl)dimethylsilane (2.55)

It was anticipated that the attachment of this second hydroxyl substituent would require the initial synthesis of 5-bromo-2-methoxy-1,3-benzendiol **(2.54)**. A previously reported synthesis of **(2.54)** involved methylation of pyrogallol (1,2,3-

trihydroxybenzene (a natural product isolated from the twigs of *Quercus infectoria*) with subsequent separation of all the methylated products[138]. The overall yield obtained after separation was very poor, amounting to a maximum yield of only 1%.

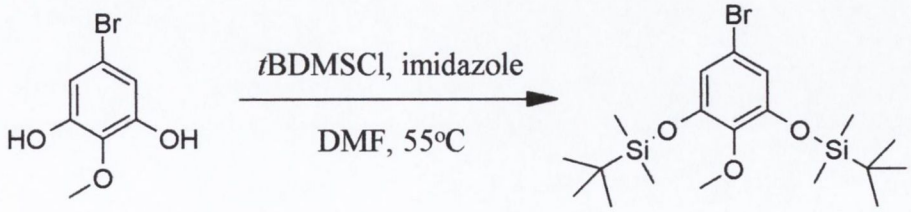
The method used followed a more recently published synthesis of **(2.54)**[139], which reported yields of 91%. It involved *ortho*-lithiation of 2,4,6-tribromoanisole with 5 equivalents of *n*-BuLi dissolved in pentane. This produced a di-lithiated intermediate, which was quenched with trimethylborate and 40% peracetic acid/acetic acid solution to yield the di-phenol **(2.54)**. In this reaction, *ortho*-lithiation occurs as the methoxy group has a directing effect on the *ortho*-bromides whilst leaving the *para*-bromide unaffected (Scheme 2.21). The yield obtained was satisfactory (63%) but not as high as previously quoted. This was probably due to the thick suspension that formed during the lithiation stage, which prevented adequate mixing with a magnetic stirrer.



(2.54)

Scheme 2.21.

The di-phenol **(2.54)** was subsequently protected as a *t*BDMS ether **(2.55)** by the usual method except the reaction temperature was increased to 55°C (Scheme 2.22).

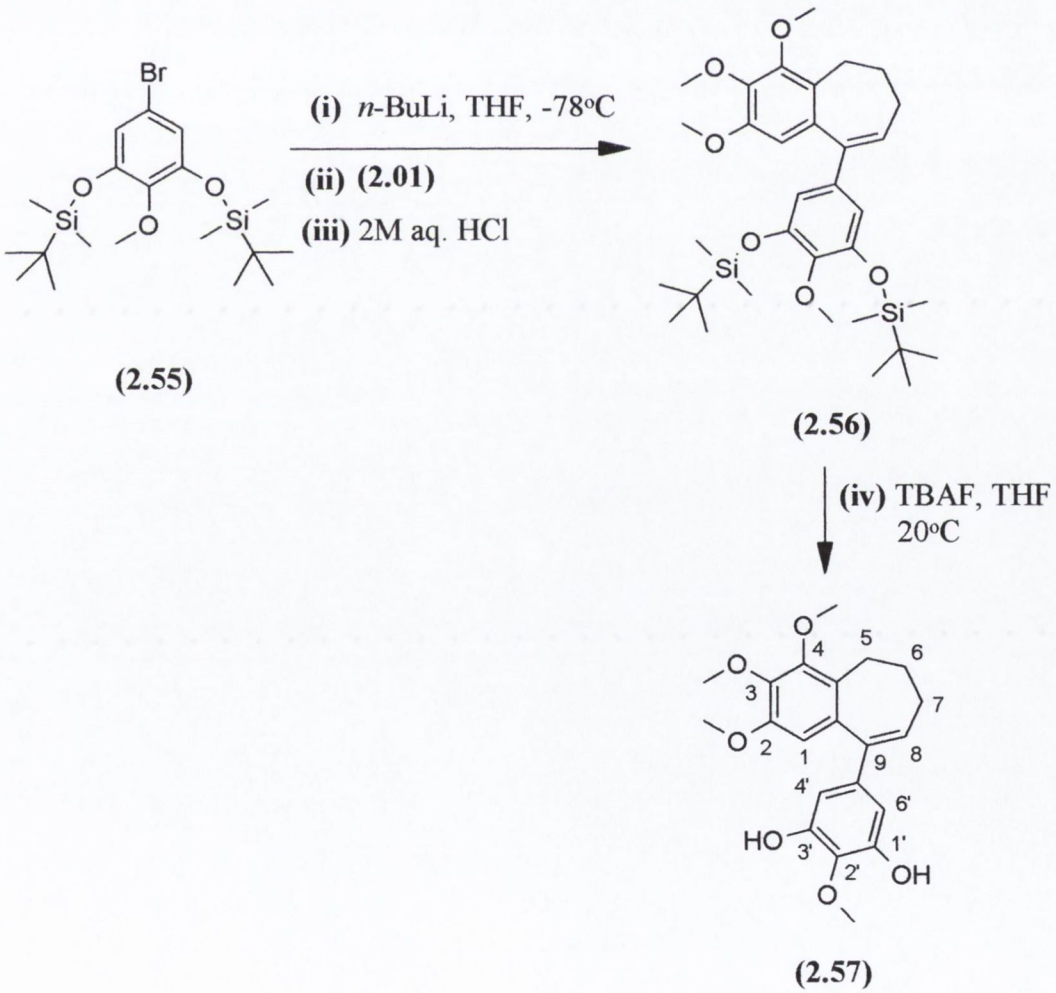


(2.54) **(2.55)**

Scheme 2.22.

2.9.2 Coupling of (2.55) to (2.01) with subsequent silyl deprotection

The aryl bromide **(2.55)** was converted to its organolithium derivative after treatment with *n*-BuLi (refer to section 2.7.2). This reactive intermediate was immediately added to a solution of **(2.01)** in THF at -78°C. The temperature of the reaction was maintained at -78°C for 2 hours, before allowing it to rise slowly to 0°C over a period of 6 hours. After stirring the reaction for an additional 6 hours, the reaction was quenched by the addition of 2M aq. HCl. The crude product **(2.56)** was isolated after extracting the reaction mixture with ether and purifying by flash column chromatography. The desired di-hydroxy compound **(2.57)** was attained in 25% yield after reacting **(2.56)** with 2.5 molar equivalents of 1M TBAF in THF at room temperature (Scheme 2.23).



(2.55)

(2.56)

(2.57)

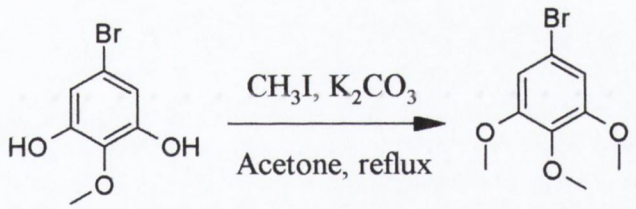
Scheme 2.23.

2.10 Formation of 2,3,4-trimethoxy-9-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cycloheptene (2.59)

The presence of a trimethoxyphenyl group (E-ring) on podophyllotoxin is known to be an essential component responsible for potent inhibition of tubulin polymerisation[57]. It was believed that in our molecular model, similar substituents on the C-ring would also have a positive influence in effecting inhibition of tubulin polymerisation.

2.10.1 Synthesis of the intermediate, 5-bromo-1,2,3-trimethoxybenzene (2.58)

Synthesis of this aryl intermediate involved methylation of the aforementioned 5-bromo-2-methoxy-1,3-benzendiol **(2.54)**. This transformation involved refluxing the phenol for 2 hours in acetone containing excess iodomethane (CH_3I) and potassium carbonate (K_2CO_3)[140]. The alkylated compound **(2.58)** was isolated in 94% yield following purification by flash column chromatography (Scheme 2.24).

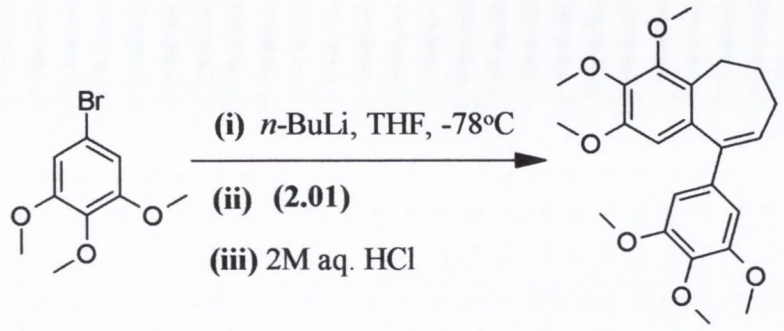


(2.54) **(2.58)**

Scheme 2.24.

2.10.2 Organolithium formation and addition of (2.58) to (2.01)

In an analogous manner to the method employed in the synthesis of **(2.56)**, the aryl bromide **(2.58)** was converted to its organolithium derivative after treatment with *n*-BuLi. The intermediate thus formed was immediately added to a solution of **(2.01)** in THF at -78°C. Following on with the same steps as those employed for the formation of **(2.56)**, **(2.59)** was isolated as an oil in 44% yield (Scheme 2.25).

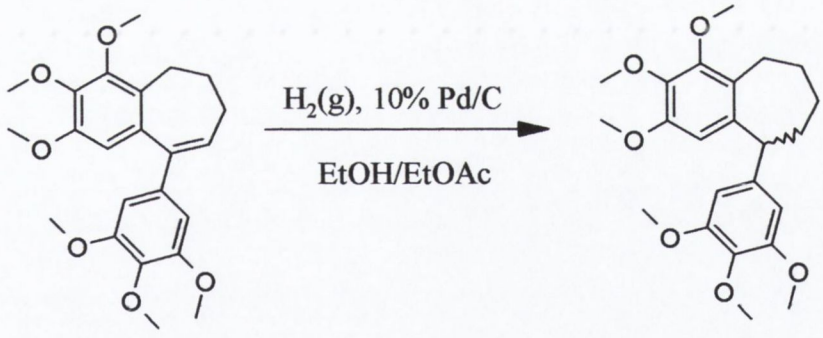


(2.58) **(2.59)**

Scheme 2.25.

2.11 Synthesis of 1,2,3-trimethoxy-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene (2.60)

Catalytic hydrogenation of **(2.59)** using 10% Pd/C as catalyst afforded the alkane **(2.60)** as an oil in quantitative yields (Scheme 2.26).



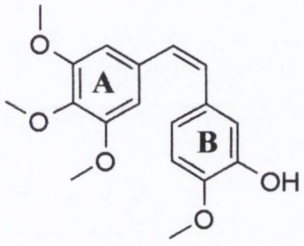
(2.59) **(2.60)**

Scheme 2.26.

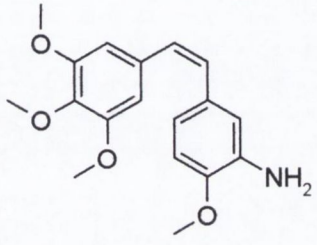
The ^{1}H NMR spectrum of **(2.60)** identified the presence of the benzylic methine signal at 4.17 ppm; this was reinforced by the disappearance of the vinylic proton (6.40 ppm) in **(2.59)**. Analysis of the ^{13}C DEPT 135 spectrum also revealed the occurrence of an additional methylene group at 30.54 ppm.

2.12 Formation of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)aniline (2.65)

Throughout the last decade a large number of B-ring analogues of combretastatin A-4 have been synthesised. One such potent analogue synthesised (IC_{50} = 4 μM)[90], involved substituting the hydroxyl group in combretastatin A-4 **(1.03)** with an amino substituent **(1.54)**.



(1.03)



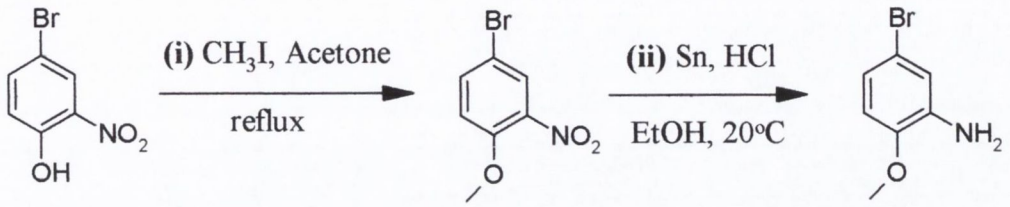
(1.54)

An additional feature of this compound is the ease by which its aqueous solubility can be improved upon by simple conversion to its hydrochloride, sulphate or oxalate salt, facilitating pharmaceutical formulation. In an analogous fashion it was decided to embark on the synthesis of the amino derivative of **(2.52)**.

2.12.1 Synthesis of the intermediate, 5-bromo-2-methoxyaniline (2.62)

It was anticipated that the synthesis of **(2.65)** could be achieved by the organometallic addition of a suitably protected anilino intermediate to **(2.06)**. Therefore, preparation of 5-bromo-2-methoxyaniline **(2.62)** was essential and its synthesis began from 4-bromo-2-nitrophenol. The hydroxy functionality of 4-bromo-2-nitrophenol was methylated using CH_3I and K_2CO_3 as base in refluxing acetone[140], before reducing the aromatic nitro group to the aniline. Common reducing agents such as $LiAlH_4$ and $NaBH_4$ are not suitable for the reduction of aromatic nitro compounds as treatment with $LiAlH_4$ may result in the formation of azo-derivatives[141], although this intermediate can be subsequently reduced to the aniline by treatment with zinc in refluxing mineral acid (e.g. HCl). In the case of $NaBH_4$, the aromatic ring is usually exhaustively reduced to

cyclohexane either with the nitro group intact or cleaved from the ring[142]. The reagent of choice for the reduction of aromatic nitro groups to aromatic amines is tin powder[143] in ethanol and concentrated HCl. Using this method, the aniline **(2.62)** was afforded as a white solid in 93% yield (Scheme 2.27).



(2.61) **(2.62)**

Scheme 2.27.

2.12.2 Amine protection: synthesis of 1-(5-bromo-2-methoxyphenyl)-2,5-dimethyl-1*H*-pyrrole (2.63)

A suitable amino protecting group was sought for the amine, which would be stable to the strongly basic conditions employed in the formation of the organolithium reagent prior to its addition to **(2.06)**. Due to the strongly basic conditions employed in organolithium formation, only a select number of protecting groups may be considered. These include protecting the amine as *N,N*-allyl[144] or benzyl amines[145] but these groups are so stable that their removal would require very harsh conditions. Alternatively, the use of a "stabase"[146] (Figure 2.12) provides only a temporary solution as this protecting group is quite labile and is easily removed during the acidic work-up or purification using flash column chromatography.

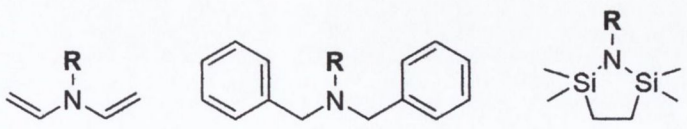
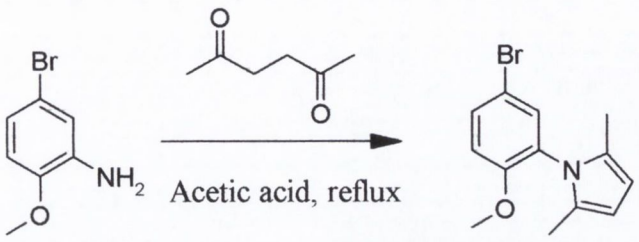


Figure 2.12. *N,N*-allyl, *N,N*-dibenzyl and stabase protecting groups.

It was decided to protect the amine group by transforming it into a 2,5-dimethylpyrrole ring **(2.63)**. Its formation involved treatment of the aniline **(2.62)** in refluxing acetic

acid with hexane-2,5-dione[147] (Scheme 2.28). This protecting group was ideal as it exhibited stability in the presence of strongly basic reagents e.g. *n*-BuLi and to the acidic work-up conditions employed.

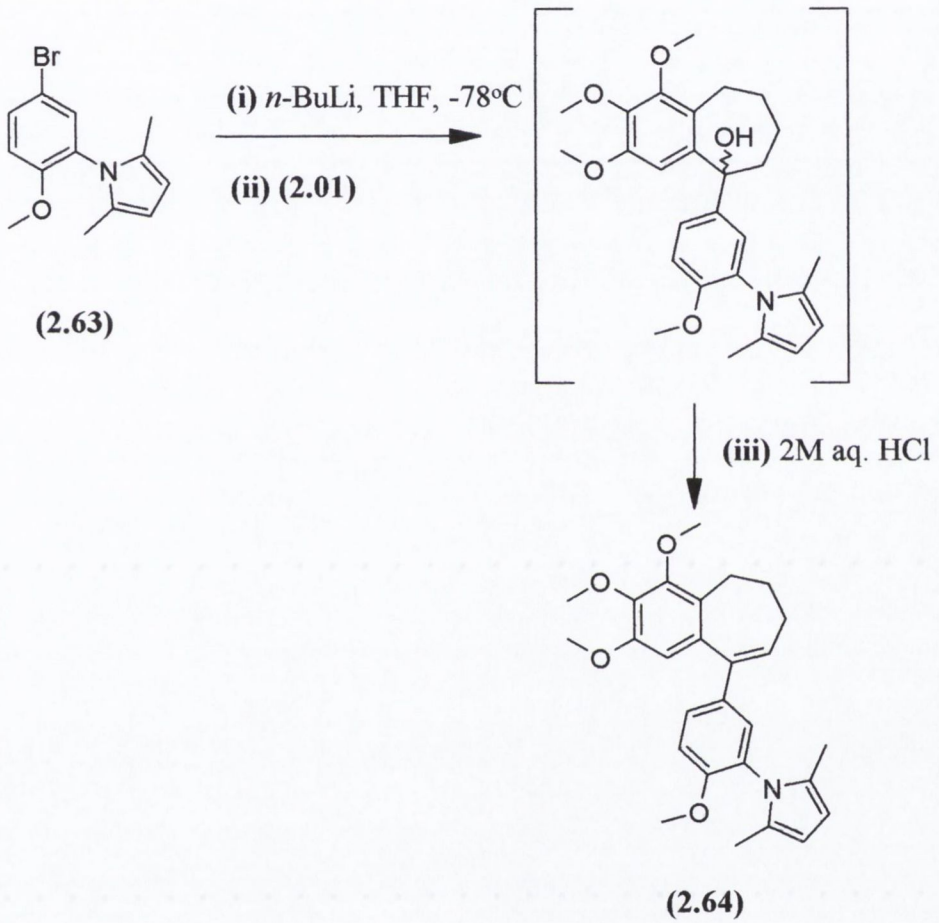


(2.62) **(2.63)**

Scheme 2.28.

2.12.3 Organolithium addition (2.63) to (2.01)

The bromide **(2.63)** was lithiated and coupled to **(2.01)** using the same conditions as those employed for the synthesis of **(2.56)**. The resulting tertiary alcohol was dehydrated *in situ* by the addition of 2M aq. HCl to afford, after isolation and purification by flash column chromatography, **(2.64)** as an oil in 46% yield (Scheme 2.29).



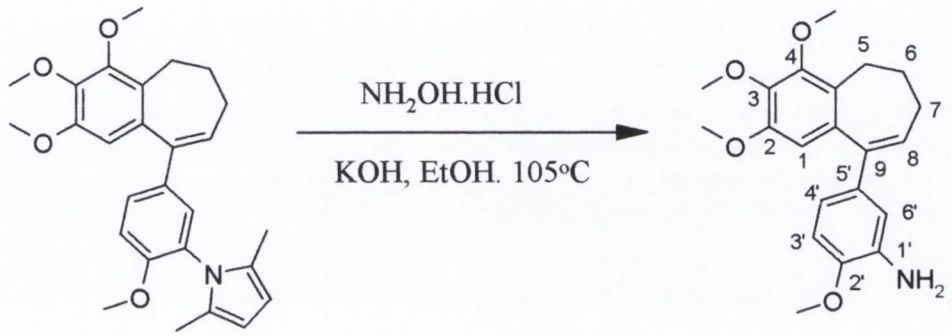
(2.63)

(2.64)

Scheme 2.29.

2.12.4 Amine deprotection step

Deprotection of **(2.64)** was accomplished by refluxing an ethanolic solution of this compound with KOH and hydroxylamine hydrochloride ($NH_2OH.HCl$)[147] (Scheme 2.30). This afforded the aniline **(2.65)**, after purification by flash column chromatography, as an off-white solid in 49% yield.



(2.64) **(2.65)**

Scheme 2.30.

2.13 Reduction of the aliphatic B-ring size

From SAR studies, it has been noted that compounds that bind to the C.B.S in tubulin are subject to stringent steric requirements. In particular, the biaryl system must occupy a specific orientation such that for optimal binding to the C.B.S the dihedral angle should be within an ideal range[148].

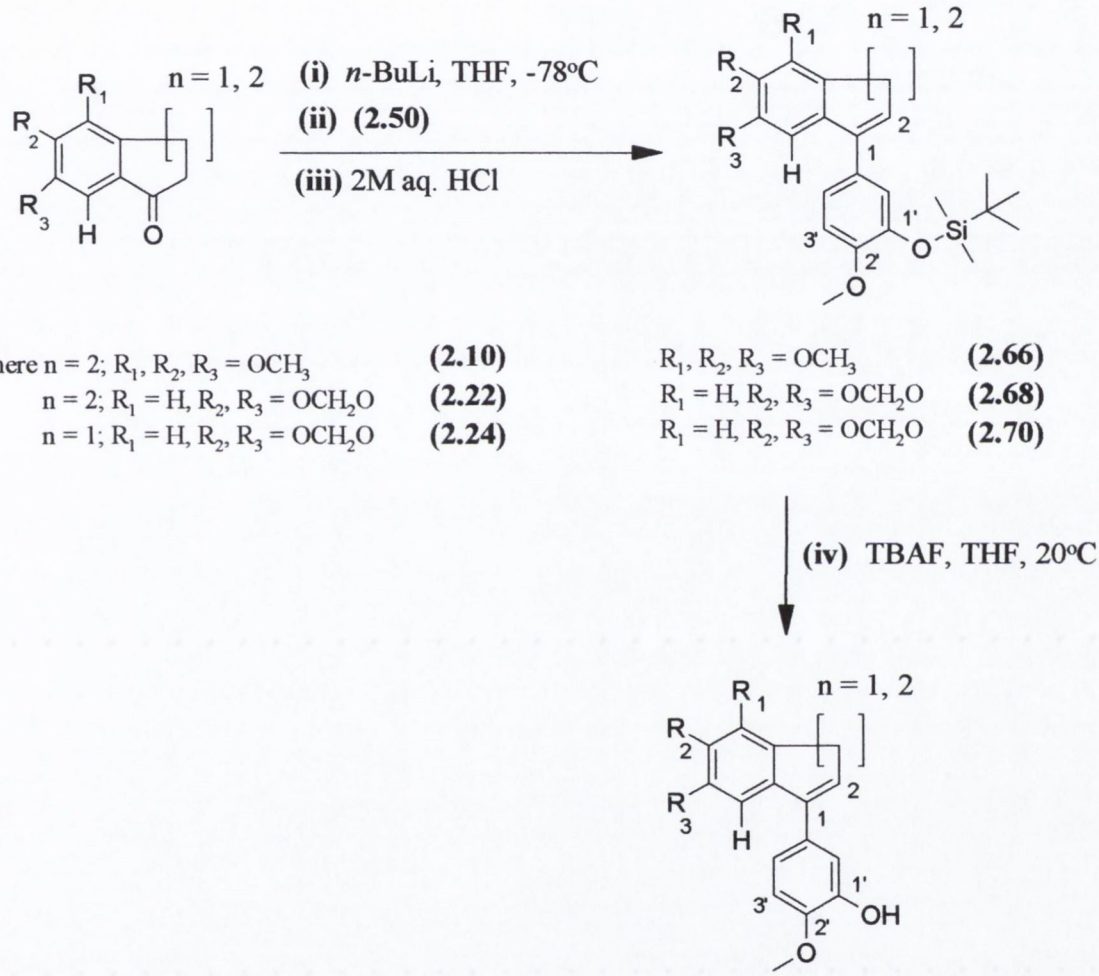
It was decided to investigate the synthesis of compounds where the dihedral angle between the two-aryl units could be adjusted upon alteration of the size of the B-ring.

2.13.1 Arylation of the tetralone and indanone intermediates

The six-carbon B-ring analogues were synthesized in an analogous fashion to **(2.52)** by coupling the organolithium derivative of **(2.50)** to two tetralone analogues, 5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-naphthalenone **(2.10)** and 5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxol-5-one) **(2.22)** (Scheme 2.31). The yields obtained,

after deprotection of the silyl ether, were 53% and 91% for compounds **(2.67)**, and **(2.69)** respectively.

Using the same sequence of steps, the five-carbon B-ring derivative **(2.71)** was also synthesised in 51% yield from its parent indanone **(2.24)** (Scheme 2.31).



Where n = 2; R_1, R_2, R_3 = OCH_3 **(2.10)**
n = 2; R_1 = H, R_2, R_3 = OCH_2O **(2.22)**
n = 1; R_1 = H, R_2, R_3 = OCH_2O **(2.24)**

R_1, R_2, R_3 = OCH_3 **(2.66)**
R_1 = H, R_2, R_3 = OCH_2O **(2.68)**
R_1 = H, R_2, R_3 = OCH_2O **(2.70)**

Where n = 2; R_1, R_2, R_3 = OCH_3 **(2.67)**
n = 2; R_1 = H, R_2, R_3 = OCH_2O **(2.69)**
n = 1; R_1 = H, R_2, R_3 = OCH_2O **(2.71)**

Scheme 2.31. Generalised reaction sequence for the ring-contracted analogues.

2.14 Tubulin binding data

Each compound synthesised was evaluated as a potential inhibitor of tubulin polymerisation[149]. The results are summarised in Table 2.2. Of the thirteen compounds evaluated, only four demonstrated the ability to inhibit tubulin polymerisation. Common to all of these compounds is the presence of a small electron donating substituent *ortho* to the methoxy group on the C-ring. An additional point worthy of discussion is that the presence of the double bond within the molecular design appears to be essential for activity. This was observed in **(2.52)** (IC_{50} = 6.7 μM) whereas **(2.53)** shows poor activity against tubulin polymerisation (IC_{50} = 18.6 μM).

Compound	ITP IC_{50} (μM)	R^2 Values
(2.44)	Inactive	-
(2.45)	Inactive	-
(2.46)	Inactive	-
(2.47)	Inactive	-
(2.52)	6.7	0.923
(2.53)	18.6	-
(2.57)	Inactive	-
(2.59)	Inactive	-
(2.60)	Inactive	-
(2.65)	4.05	0.979
(2.67)	Inactive	-
(2.69)	Inactive	-
(2.71)	11.51	0.958
Combretastatin A-4	1.45	0.999

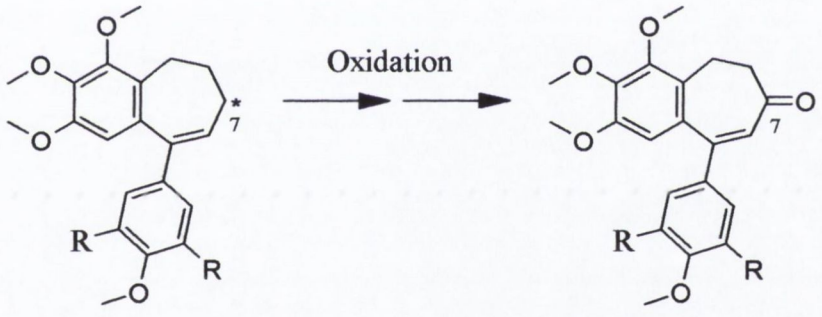
Table 2.2. IC_{50} values obtained from inhibition of tubulin polymerisation (ITP).

It was demonstrated that while the seven-carbon B-ring derivative **(2.52)** exhibited good activity (IC_{50} = 6.7 μM), reducing the ring size to six carbons, as in **(2.67)** and **(2.69)**, rendered these compounds inactive. However, further reduction of the ring size to five carbons units, **(2.71)**, partially restored its inhibitory activity against tubulin polymerisation (IC_{50} = 11.5 μM). On the basis of the promising tubulin binding data obtained on two of the above compounds, it was decided to pursue the synthesis of an analogous series of compounds where position seven of the B ring contains either hydroxy or carbonyl functionality.

CHAPTER 3

3.0 Introduction

In accordance with the tubulin binding data obtained by Emmet M^{c}Cormack[149], it is apparent that only those compounds, of the form discussed in Chapter 2, with a *para*-methoxy and *meta*-amino or *meta*-hydroxy substituent on the second aryl unit will inhibit tubulin polymerisation. It was postulated that judicious functionalisation at position seven would result in derivatives with even greater potency than that observed to date. In particular, it was felt that a ketonic functionality would affect, both the conformation, and the electronic properties of the molecule (Figure 3.1). A carbonyl substituent would also allow for the inclusion of other substituents at this position, including oximo, imino and amino derivatives. Furthermore, direct reduction of the carbonyl unit to the alcohol would lead to the generation of enantiomers, whose individual inhibitory effects could be evaluated.



R = Small electron donating groups

Figure 3.1. Functionalisation of C-7.

3.1 Synthetic strategy

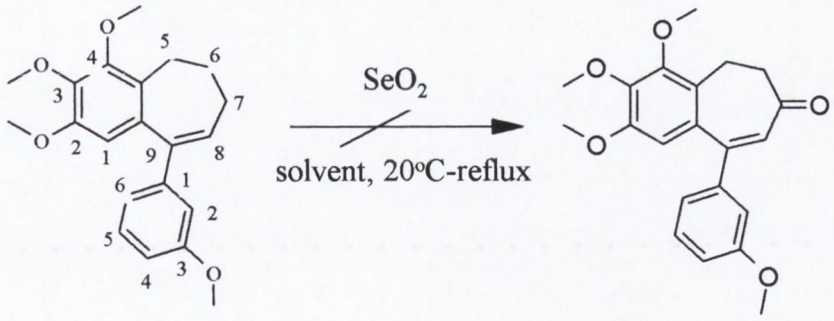
The work described in this chapter involved the development of the aliphatic B-ring in creating phenyl-substituted benzocyclohepten-7-ones as potential tubulin inhibitors. Preparation of these compounds was initially attempted *via* allylic oxofunctionalisation of **(2.45)** using selenium dioxide or chromium-based oxidizing agents.

3.2 Model studies on allylic oxidation

The use of powerful oxidizing agents can been used to functionalise activated methylene fragments adjacent to π-bonds (allylic, benzylic and carbonyl groups). However, it is an established fact that allylic oxidation of cyclic double bonds is a notoriously difficult transformation as potential side reactions may take place such as epoxidation, double-bond isomerisation, oligomerisation and other non-related reactions[150]. While a number of oxidising agents can be used to effect this transformation, it was decided to concentrate our efforts on the utilisation of cheap and easily available reagents such as selenium dioxide, Jones' reagent and potassium dichromate

3.2.1 Attempted allylic oxidation using SeO_2

The first approach involved the use of selenium dioxide (SeO_2), which is the reagent of choice for this type of transformation. As illustrated in Table 3.1, several different reaction conditions were used, without success, in an attempt to oxidise the C-7 position of **(2.45)** (Scheme 3.1).



(2.45)

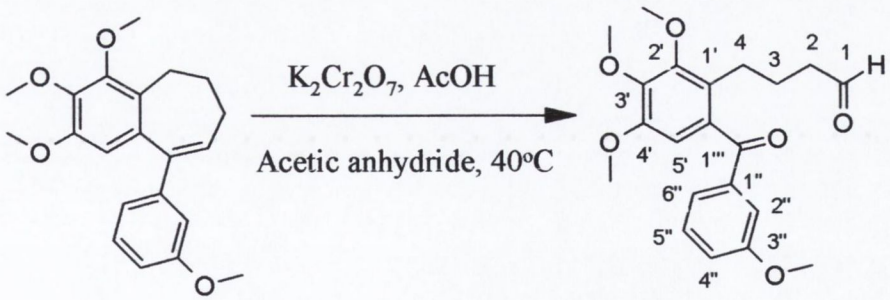
Scheme 3.1.

Reagent used	Solvent used	Reaction conditions	Product
SeO_2	(i) Dioxane[151] (ii) *t*-BuOH (iii) EtOH[152] (iv) DCM	25°C and reflux	Starting material

Table 3.1. Conditions used for attempted SeO_2 allylic oxidations.

3.2.2 Attempted allylic oxidation with chromium-based reagents

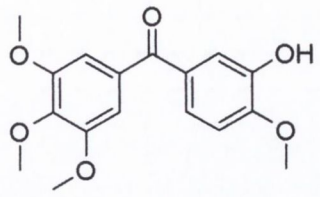
Jones reagent[153] ($Na_2Cr_2O_7$ dissolved in sulphuric acid and water) is considered a stronger oxidizing agent than SeO_2. For example, with Jones reagent, oxidation of the benzylic position of **(2.45)** is also possible, but this is avoidable by careful consideration to the reaction conditions used. The reaction conditions employed dissolving **(2.45)** in acetone at 0°C and subsequently adding Jones reagent drop-wise to the reaction over a period of 15 min. Unfortunately, analysis of the reaction mixture by TLC indicated the formation of a large number of by-products and therefore, the reaction was discontinued. An attempt was made to oxidise the C-7 position of **(2.45)**, by using potassium dichromate in acetic anhydride and acetic acid[154] (Scheme 3.2). However, contrary to the anticipated transformation, this reagent oxidatively cleaved the double bond of **(2.45)**, resulting in the formation of the keto-aldehyde **(3.01)**.



(2.45) **(3.01)**

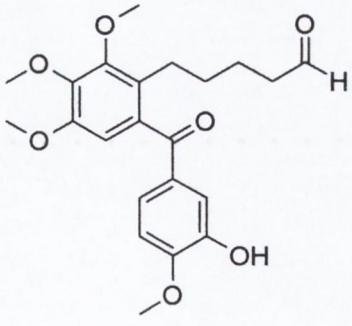
Scheme 3.2. Oxidative cleavage using $K_2Cr_2O_7$.

This compound is an interesting by-product, as its structure resembled a known tubulin inhibitor, phenstatin **(1.44)**.



(1.44)

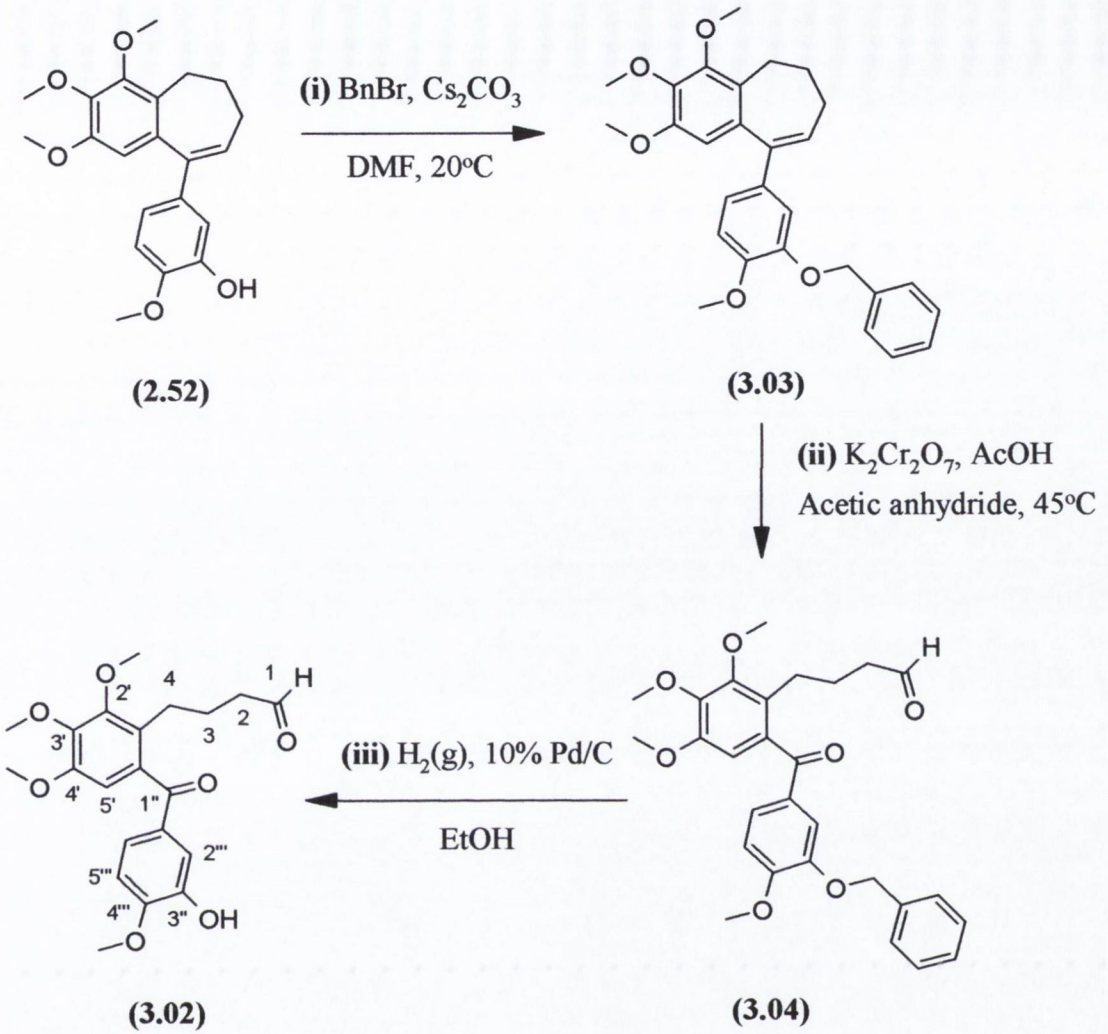
Although **(1.44)** is a potent tubulin inhibitor, its lack of aqueous solubility is a significant problem. This difficulty has been partially resolved by converting the phenolic hydroxyl to a phosphate salt[92] enabling solubility in aqueous solutions. However, due to the abundance of phosphatases in human serum this functionality will only remain attached *in vivo* for a short period. Excluding the fact that **(3.01)** does not contain substituents at the correct positions on the lower aryl ring, the only difference between it and **(1.43)** is the presence of the butanal side chain at C-1'. If compounds of this type, bearing the correct aryl substituents, did inhibit tubulin polymerisation then it may be possible to use this side chain to attach water-soluble groups to aid in the selective delivery of these cytotoxic agents to the tumour site. On this basis, it was decided to pursue the synthesis of the aldehyde **(3.02)**.



(3.02)

3.2.2.1 Synthesis of 4-[6-(3-hydroxy-4-methoxybenzoyl)-2,3,4-trimethoxyphenyl]butanal (3.02)

To test this hypothesis, the synthesis of **(3.02)** began with **(2.52)** as the starting material. This compound was used, as its A-ring and C-ring substituents are identical to that of phenstatin. To prevent potential oxidation to the quinone, it was decided to convert the phenol to a benzyl ether derivative. In addition, this protecting group was expected to display good stability in the acidic conditions employed later in the synthesis. This transformation required treatment of **(2.52)** with Cs_2CO_3 and benzyl bromide at ambient temperature to afford **(3.03)** in quantitative yield. Once formed, oxidative cleavage of **(3.03)** was achieved by the addition of $K_2Cr_2O_7$ in an acetic anhydride/acetic acid solution to yield the di-carbonyl compound **(3.04)**. Deprotection of the phenol was achieved *via* catalytic hydrogenolysis of the benzyl group using H_2 and 10% Pd/C as catalyst. As aryl ketones can also be reduced to methylene groups under these conditions, careful consideration to the reaction conditions was required. This transformation was effected by dissolving **(3.04)** in ethanol. This deprotection step was complete after 15 minutes to afford **(3.02)** as a mobile oil in an overall yield of 37% from **(2.52)** (Scheme 3.3).



Scheme 3.3.

Analysis of the ^{1}H NMR spectrum of **(3.02)** identified three multiplets resonating at 1.83 ppm, 2.36 ppm and 2.58 ppm; these were attributed to the three-methylene groups on the butanal side chain. The protons on the four-methoxy groups were found resonating as three singlet peaks at 3.81 ppm, 3.94 ppm (2 x OCH_3) and 3.99 ppm. The phenolic proton was identified as a broad singlet resonating at 5.69 ppm, while other features of the spectrum included a singlet at 6.60 ppm which was assigned as the lone aromatic proton, H-5'. The doublet (J = 8Hz) at 6.91 pm and the complex multiplet at 7.41 ppm represented the protons on the 'C-ring' but due to the complex splitting pattern, the individual protons could not be assigned. The remaining signal at 9.69 ppm confirmed the presence of the aldehyde.

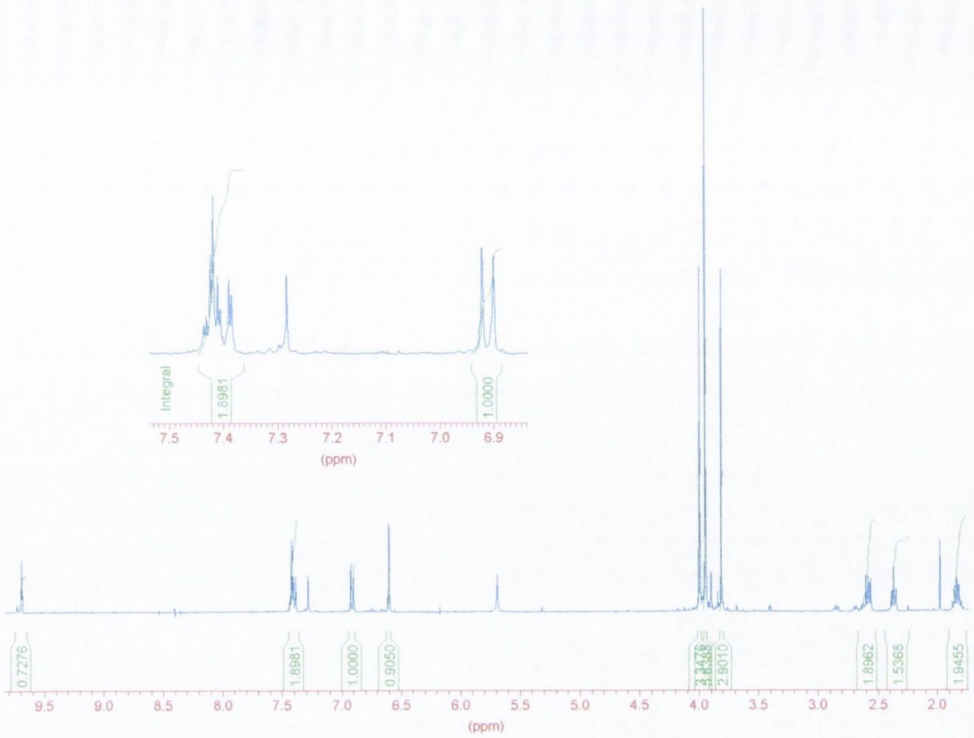


Figure 3.2. ^{1}H NMR spectrum of **(3.02)**.

In the DEPT 135 spectrum of **(3.02)** (Figure 3.3), the methylene carbons were easily identifiable resonating at 23.14 ppm, 25.93 ppm and 42.94 ppm. Two methoxy carbons occurred as an enhanced peak at 55.67 ppm while the remaining methoxy groups resonated at 60.30 ppm and 60.56 ppm. The methine signal at 106.96 ppm was assigned as the A-ring carbon, C-5'. The 'C-ring' methine carbons were also identified in this region, resonating at 109.38 ppm, 115.57 ppm and 123.59 ppm. From the ^{13}C NMR spectrum (Figure 3.3), all the aromatic quaternary carbons were accounted for, resonating between 126.13 ppm to 151.94 ppm. Both carbonyl groups at C-1 and C-1" degenerated to a single resonant peak at 201.07 ppm. This was confirmed in the IR spectrum of **(3.02)** which identified the two carbonyl groups as strong intensity stretching peaks at 1721.6 cm^{-1} (C-1) and 1654.2 cm^{-1} (C-1"). Also identifiable from this spectrum was a broad peak at 3403.8 cm^{-1}, which was indicative of the presence of a hydroxyl group.

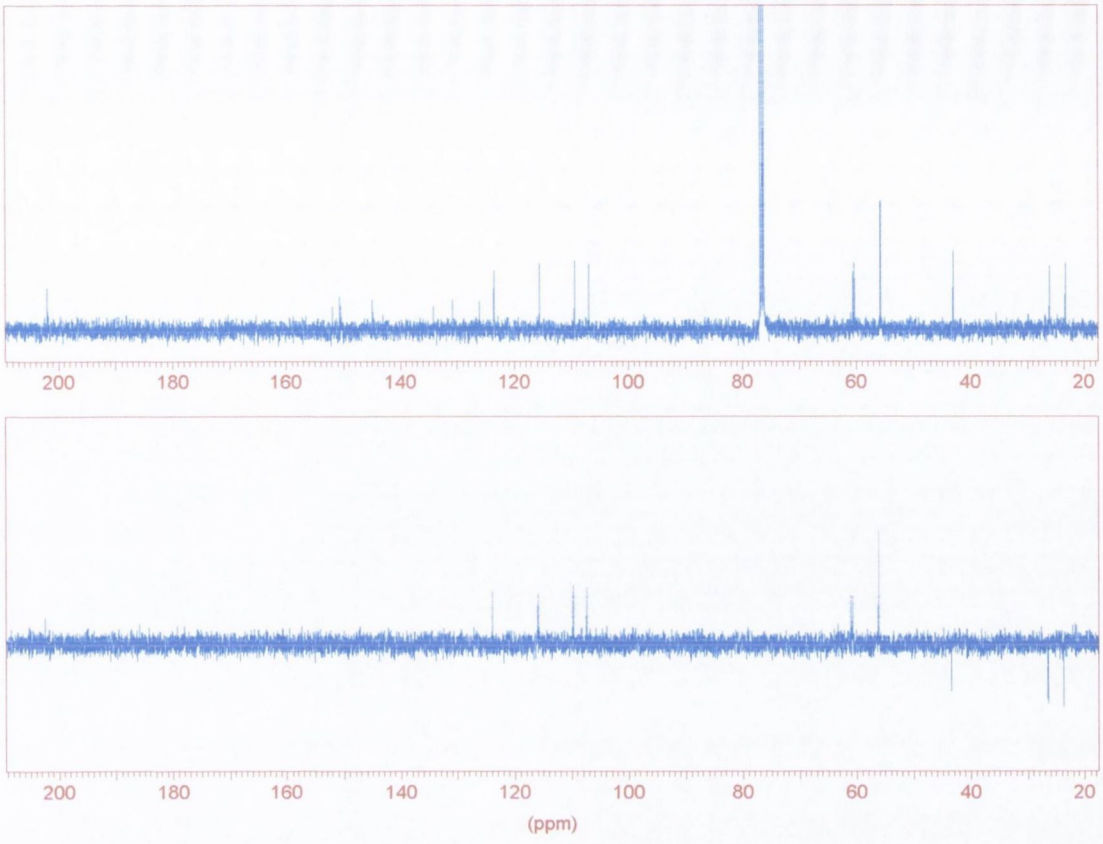
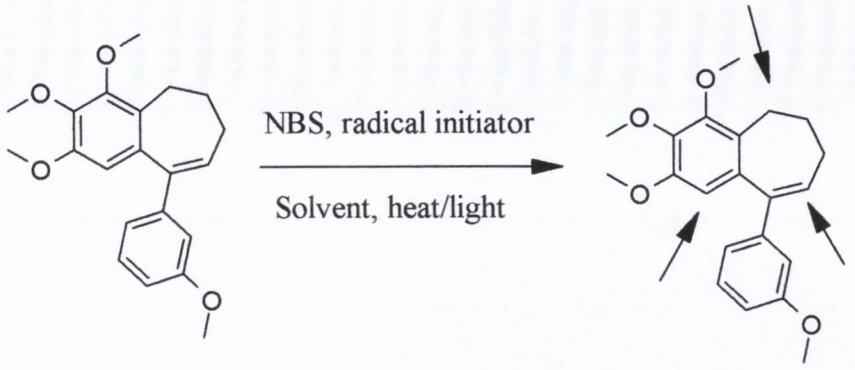


Figure 3.3. ^{13}C NMR and DEPT 135 spectra of **(3.02)**.

Although the keto-aldehyde **(3.02)** did inhibit tubulin polymerisation (IC_{50} = 9.85 μM), its activity was less than its cyclic precursor **(2.52)** (IC_{50} = 6.7 μM).

3.2.3 Attempted allylic bromination

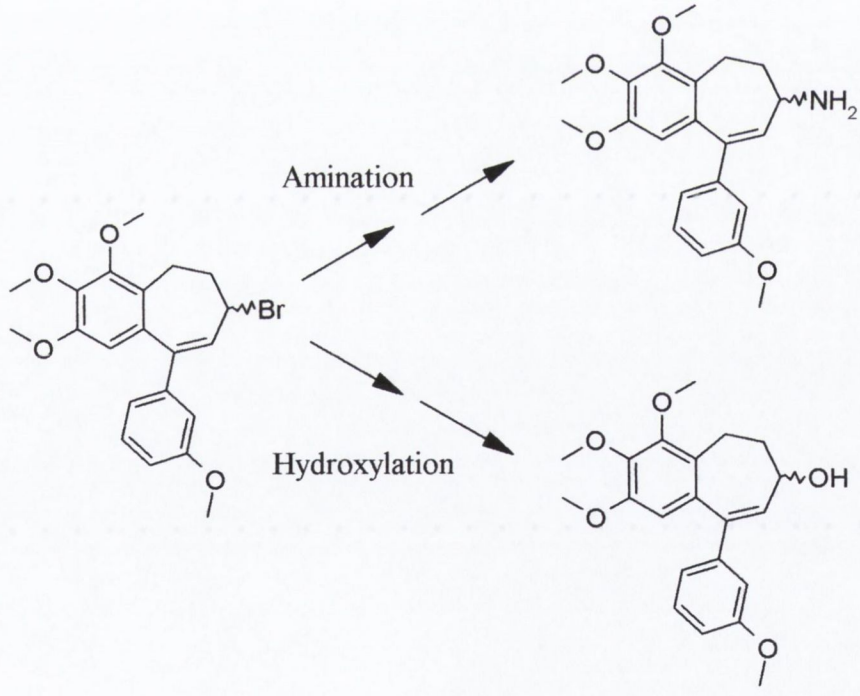
As all attempts at allylic oxidation were still unsuccessful, it was decided that the next approach should involve the bromination of the allylic position of **(2.45)**, by using N-bromosuccinimide[155,156]. This is a particularly sensitive transformation as benzylic bromination and aromatic bromination of **(2.45)** are also competing reactions (Scheme 3.4).



(2.45)

Scheme 3.4. Potential unwanted bromination sites.

It was felt that if bromination at the C-7 position was successful then its displacement by nucleophillic reagents could allow for the insertion of hydroxyl or amino functionality (Scheme 3.5).



Scheme 3.5.

Because of structural similarities of these molecules to colchicine, the first bromination reaction that was attempted utilized the exact conditions described in the literature for bromination of colchicine[157]. However, inspection of the reaction by TLC analysis

revealed the formation of large numbers of by-products that were too difficult to separate by column chromatography.

In an attempt to effect allylic bromination of **(2.45)**, the solvent, temperature and the radical initiator used in the reaction was varied (Table 3.2). However, all of the conditions employed failed to give any of the desired allylic bromide.

Radical initiator	Reagent	Solvent	Reaction conditions	Product
Dibenzoylperoxide	NBS	CCl_4	UV light	Multiple Products
Dibenzoylperoxide	NBS	CCl_4	Reflux	Multiple Products
Dibenzoylperoxide	NBS	CCl_4	UV light and reflux	Multiple Products
Azobis(cyclohexane-carbonitrile)	NBS	α,α,α-trifluorotoluene	UV light	Multiple Products

Table 3.2. Conditions used in attempted allylic bromination.

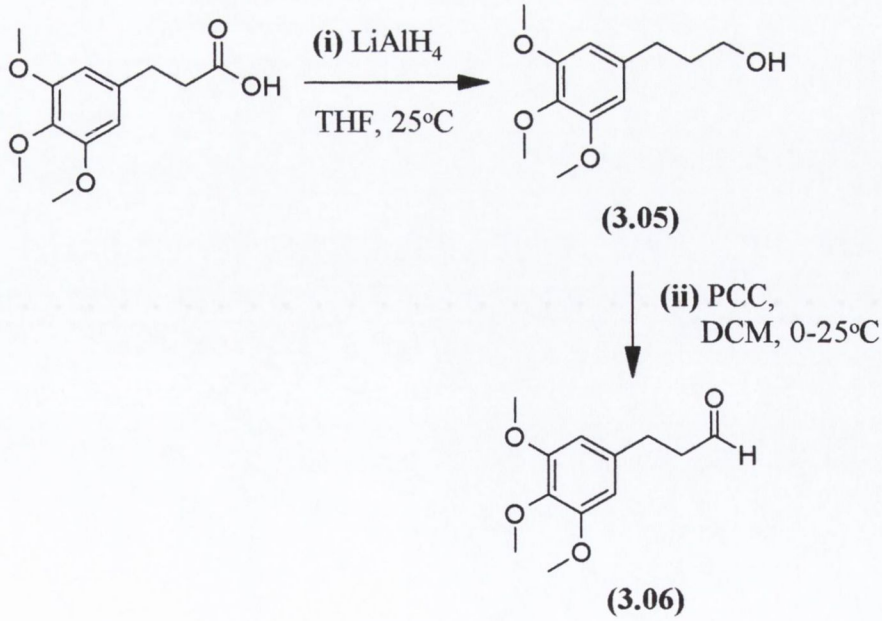
3.3 Incorporation of C-7 functionality prior to C-ring addition

As selective oxidation at the allylic position of **(2.45)** proved to be an ineffective procedure, a synthetic route was devised that would permit the presence of the necessary carbonyl or hydroxyl group at the C-7 position of 1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **(2.01)**. It was felt that subsequent protection of the C-7 substituent would permit nucleophillic attack of an organometallic reagent at the C-5 ketonic centre to afford the desired compounds.

3.4 Model reactions on 3-(3,4,5-trimethoxyphenyl)propanal (3.06)

Clearly, the use of this precursor would ultimately result in a cyclised compound with one of its methoxy substituents in position 4, rather than the position 1 as desired. However, in the model reactions that follow, it was decided to use precursors with this methoxy-substituted pattern on the aromatic ring, as some of these precursors were commercially available, and in addition the resultant cyclised intermediate, would be used to synthesise the compounds described in Chapter 4.

As a five-carbon chain was required to form a seven-membered ring, the formation of 3-(3,4,5-trimethoxyphenyl)propanal **(3.06)** was necessary to allow the addition of a two-carbon unit whilst creating an oxygenated substituent at the required position prior to cyclization. As a result, **(3.06)** was synthesised by the initial reduction of 3-(3,4,5-trimethoxyphenylpropionic acid to 3-(3,4,5-trimethoxyphenyl)propanol[143] **(3.05)** using three molar equivalents of $LiAlH_4$ at room temperature. The alcohol was isolated and selectively oxidised to the aldehyde, using pyridinium chlorochromate (PCC) in DCM at ambient temperature[158] (Scheme 3.6).



Scheme 3.6.

3.4.1 Addition of Grignard reagents to (3.06)

Grignard reagents represent a very convenient means by which carbon-carbon bond formation may be carried out. In this synthesis, the addition of a two-carbon unit to 3-(3,4,5-trimethoxyphenyl)propanal **(3.06)** was required, with one of the carbon's suitably masked with functionality to allow for the ready conversion to its corresponding acid later in the synthetic sequence (Table 3.3).

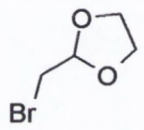
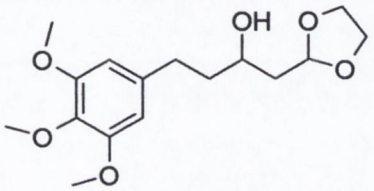
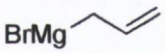
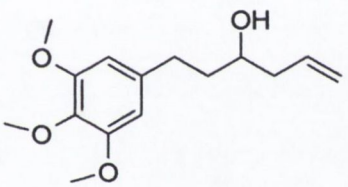
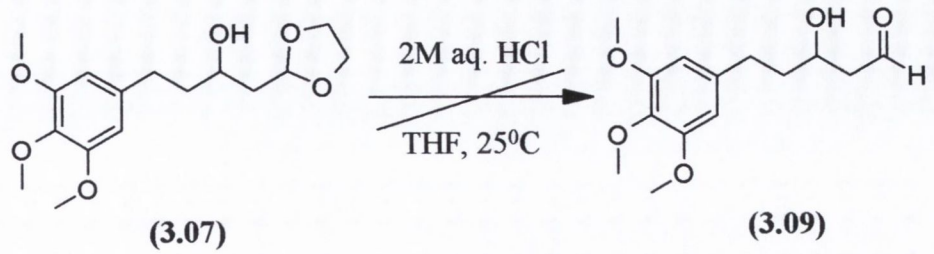
Reactant used	Adduct formed	Yield (%)
	 **(3.07)**	24
	 **(3.08)**	88

Table 3.3. Grignard addition products with associated yields.

3.4.1.1 Addition of 2-methyl-1,3-dioxolane magnesium bromide to (3.06)

Although this reaction resulted in reasonable yields (24%) of the adduct **(3.07)**, its optimisation was not pursued as the subsequent deprotection step failed to give any of the desired hydroxy-aldehyde **(3.09)** (Scheme 3.7).

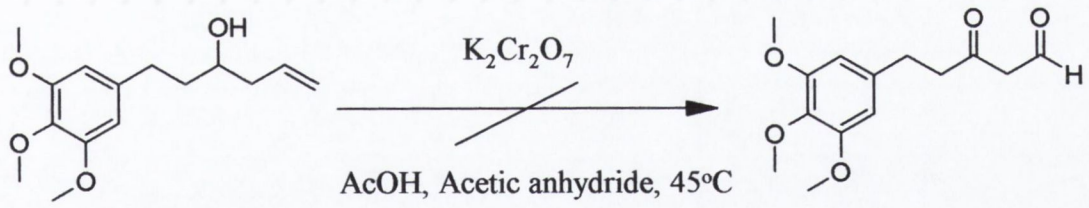


(3.07) (3.09)

Scheme 3.7. Attempted synthesis of the hydroxy-aldehyde (**3.09**).

3.4.1.2 Addition of vinyl magnesium bromide to (3.06)

The addition of vinyl magnesium bromide to the aldehyde **(3.06)** was investigated as it was felt that the resultant hydroxy-alkene **(3.08)** could be readily transformed to the corresponding keto-aldehyde **(3.11)** using $K_2Cr_2O_7$ in an acetic anhydride/acetic acid solution (Scheme 3.8), conditions similar to those used in the formation of **(3.01)** and **(3.04)** (refer to section 3.2.2). The oxidative cleavage reaction was monitored by TLC but was discontinued due to the formation of large numbers of side-products.

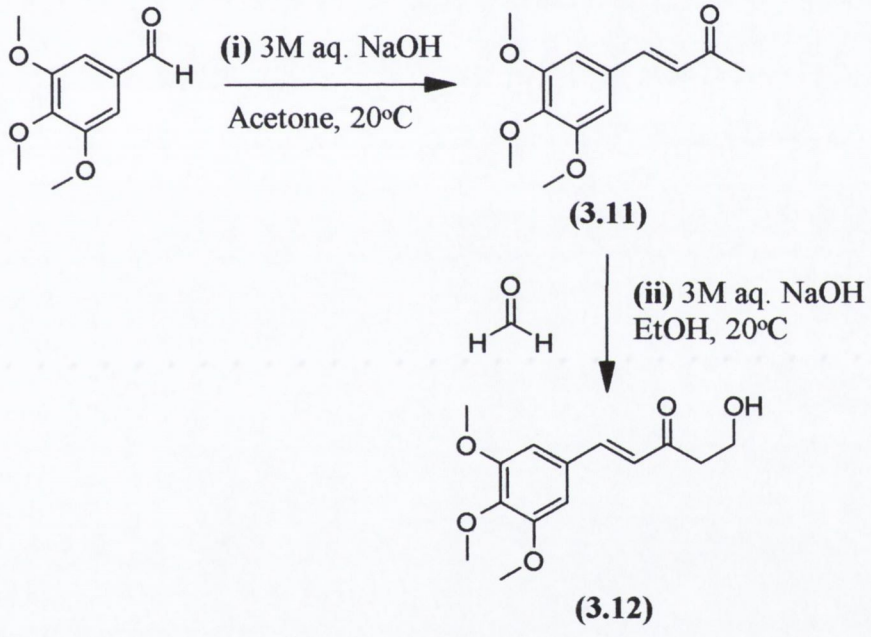


(3.08) (3.10)

Scheme 3.8. Attempted synthesis of the keto aldehyde (**3.10**).

3.5 Claisen-Schmidt condensation reaction

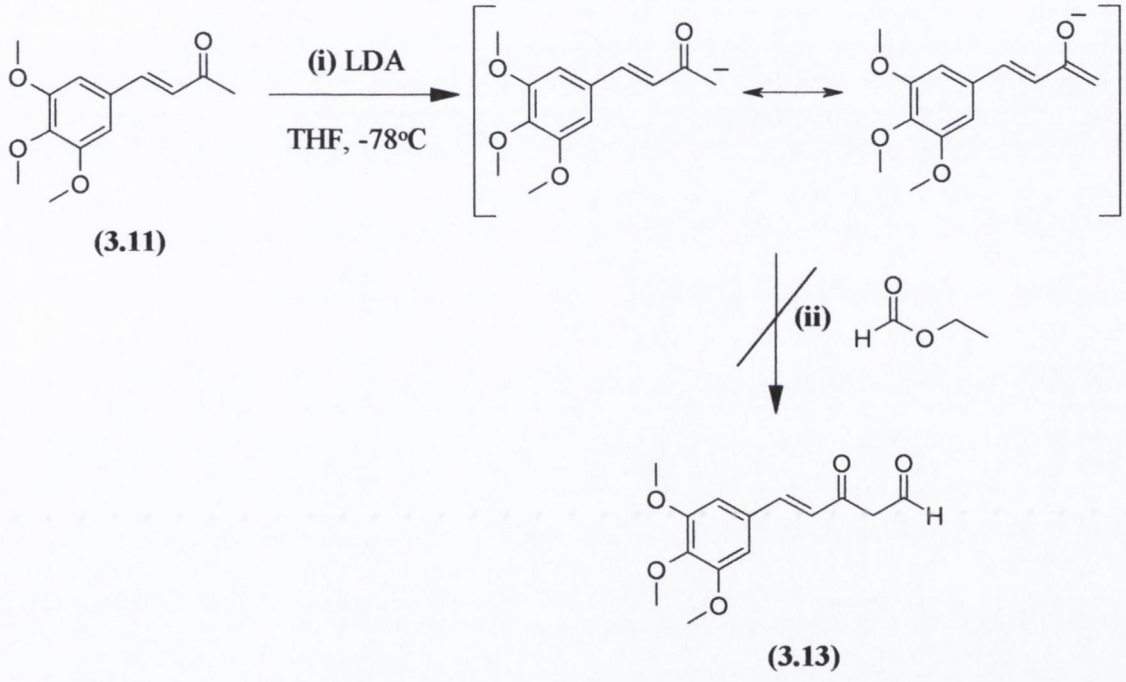
As all attempts to generate the desired acid derivative had failed, a new route to the acid, which involved a Claisen-Schmidt condensation step[159] between acetone and 3,4,5-trimethoxybenzaldehyde was devised. This transformation was successful in producing the enone **(3.11)** in high yield as a yellow solid. The next step involved treating the enone **(3.11)**, under thermodynamic conditions, with a solution of 3M aq. NaOH in ethanol followed by the subsequent addition of paraformaldehyde (Scheme 3.9). However, this reaction was not pursued as analysis of the reaction mixture by TLC indicated the presence of several unknown compounds.



Scheme 3.9. Expected reaction between the α,β-unsaturated ketone **(3.11)** and formaldehyde.

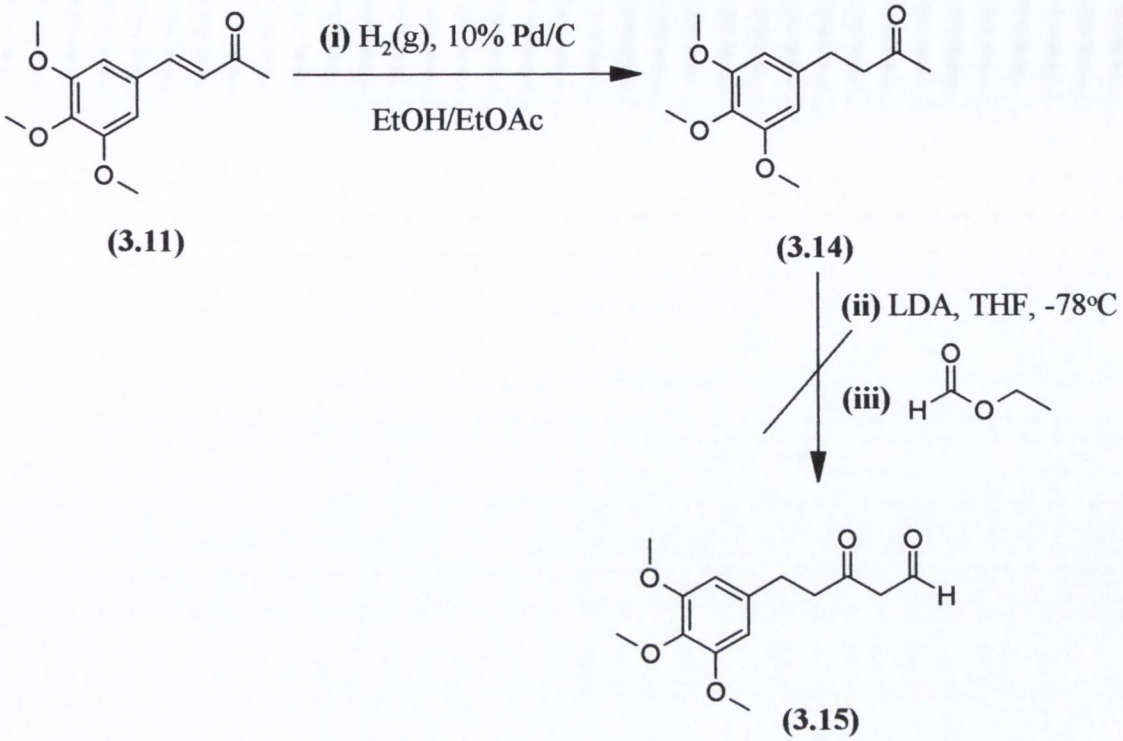
To ensure complete deprotonation took place and therefore eliminate any possibility of potential by-products from occurring a very strong base was utilised to produce the anion of **(3.11)**. Lithium di-isopropylamide (LDA) was selected as the base to use under these conditions. LDA is a very strong base capable of extracting the weakly acidic hydrogen adjacent to a carbonyl but being sufficiently bulky as to be non-nucleophillic. This bulkiness also ensures that in unsymmetrical ketones, where the possibility of deprotonation on either side of the carbonyl group could occur, the more sterically accessible proton is removed faster (kinetic deprotonation) to form the kinetic enolate.

The reaction between LDA and **(3.11)** was carried out at -78°C in anhydrous THF. After enolate formation, a solution of ethyl formate in THF was subsequently added to the reaction (Scheme 3.10). From TLC analysis, the reaction produced a compound with a lower R_f than the starting material but after the work up, which involved the partitioning the mixture between aqueous acid/ether and purification by flash column chromatography only the enone **(3.11)** was isolated.



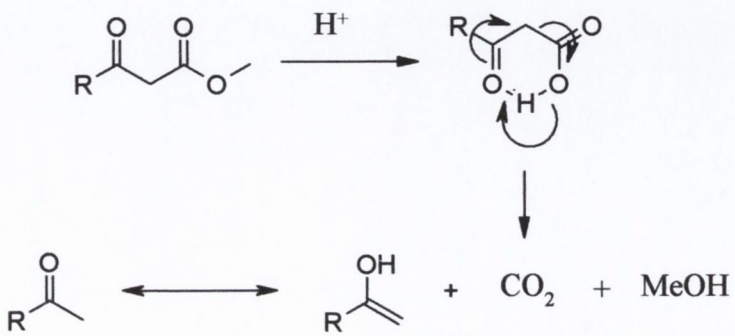
Scheme 3.10. Attempted synthesis of the keto-aldehyde **(3.13)**.

These reaction conditions were employed again but on this occasion, the saturated ketone **(3.14)** was used (Scheme 3.11). However, the only compound isolated, was the "unreacted" starting material **(3.14)**.



Scheme 3.11. Attempted synthesis of the β-ketoaldehyde (**3.15**).

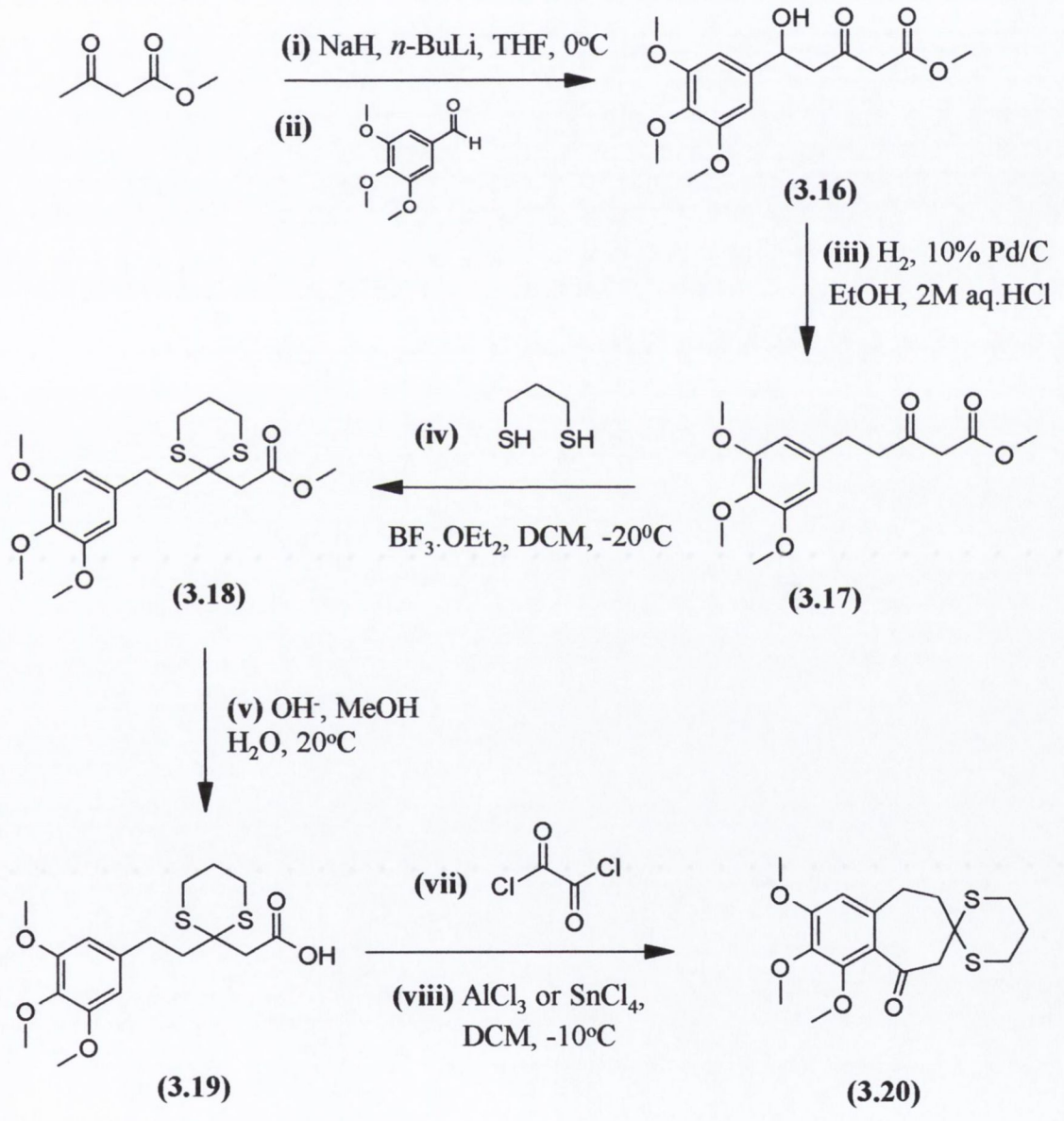
Although TLC analysis of these reactions indicated that a lower R_f compound was formed, the only compound isolated, after work-up and purification, was the starting material. It is now presumed that this lower R_f compound was indeed the product, but the acidic conditions employed in during the work-up procedure resulted in it being decarboxylated. The acid that was used to neutralise the base protonates the di-carbonyl moiety producing a six-membered cyclic transition state which then readily undergoes a reversed Oxy-Cope rearrangement[160] to form carbon dioxide and the methyl ketone (Scheme 3.12).



Scheme 3.12. Mechanism of decarboxylation *via* a reversed Oxy-Cope rearrangement.

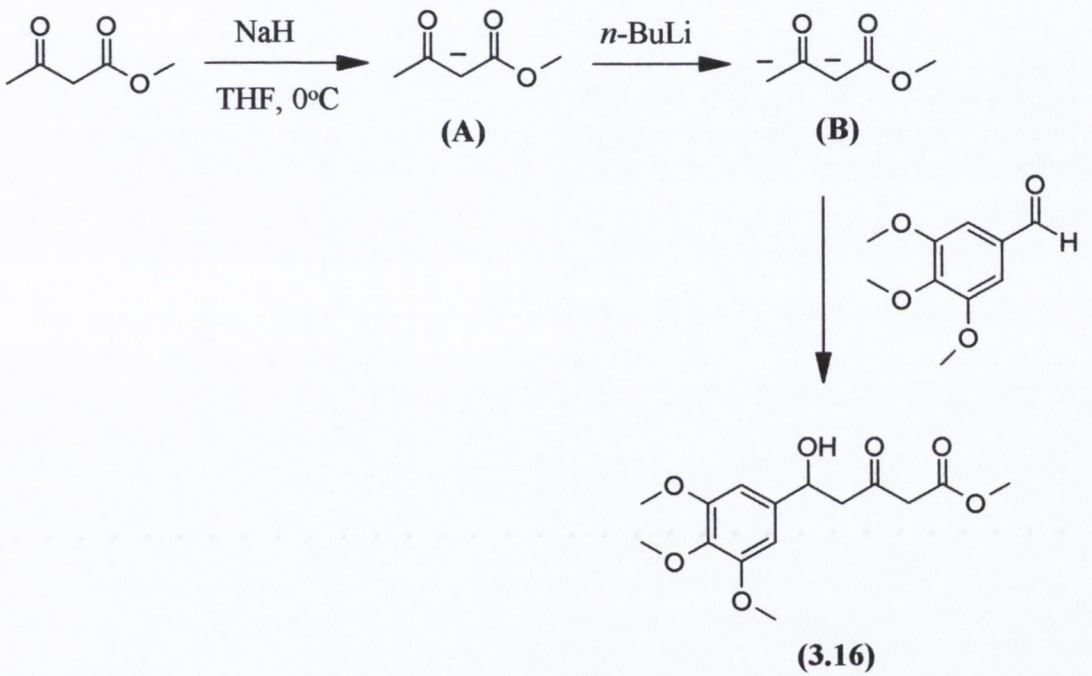
3.6 Condensation of methyl acetoacetate with 3,4,5-trimethoxybenzaldehyde

As illustrated in Scheme 3.13, a new synthetic strategy was devised that would permit functionalisation at the required C-7 and C-9 positions when forming the aliphatic B-ring. This approach utilized 2,3,4-trimethoxybenzaldehyde and methyl crotonate as the chief building blocks.



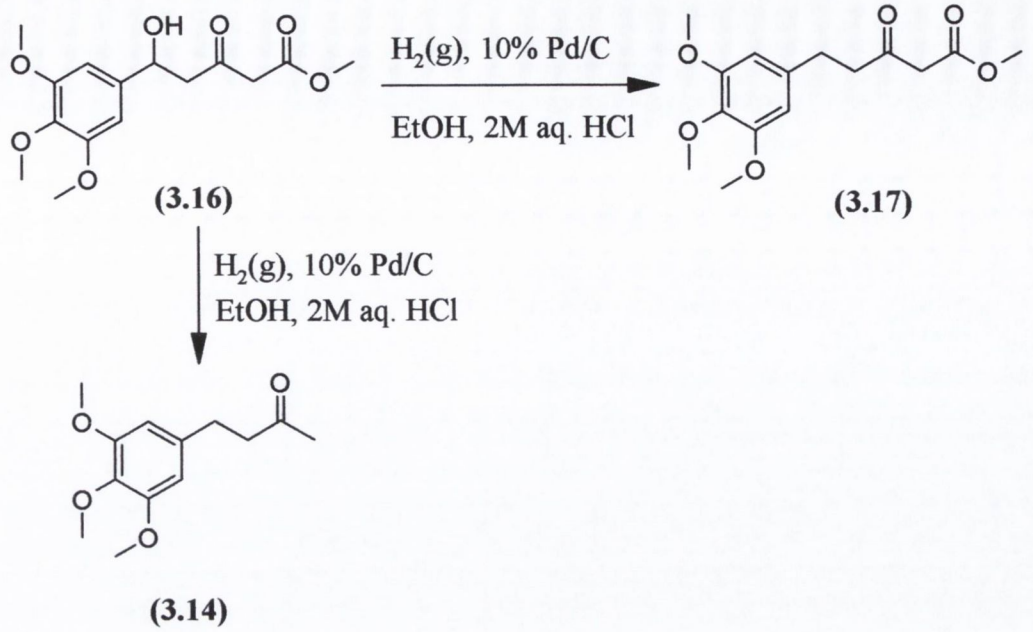
Scheme 3.13.

Thus, the initial step of the synthesis involved the preparation of the dianion of methyl acetoacetate[161]. This was prepared by the addition of methyl acetoacetate to NaH, to form the enolate anion **(A)** between the two-keto groups. *n*-BuLi was then added to the reaction mixture to form the dianion **(B)**. Subsequent addition to 3,4,5-trimethoxybenzaldehyde to the solution afforded the aldol product **(3.16)** (Scheme 3.14).



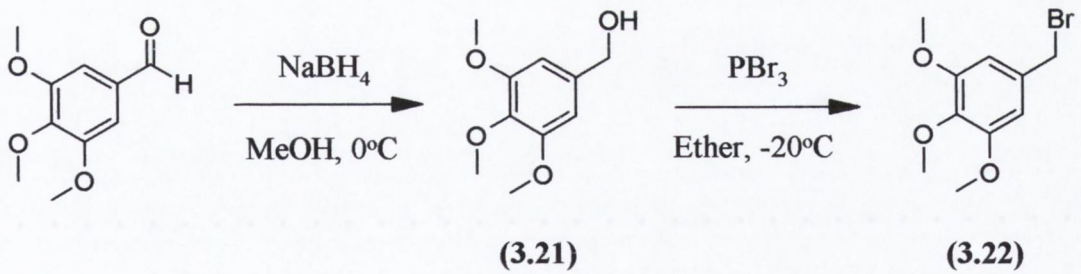
Scheme 3.14.

The hydroxyl group on **(3.16)** was then removed *via* catalytic hydrogenation under acidic conditions[162]. As might have been predicted from the attempted synthesis of **(3.12)**, **(3.13)** and **(3.15)**, this reaction proved to be very inefficient as although it would reduce the hydroxyl group to a methylene group, the mild acidic conditions used were strong enough to decarboxylate the molecule and form 4-(3,4,5-trimethoxyphenyl)-2-butanone **(3.14)** as a significant side product (Scheme 3.15).



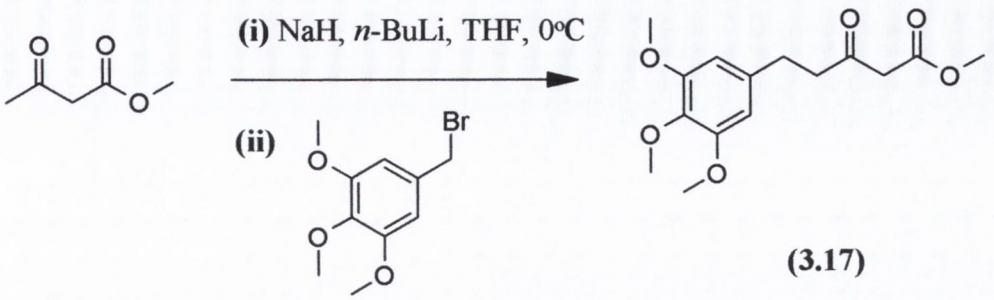
Scheme 3.15.

This problem was circumvented, by changing the electrophile from an aldehyde to a bromide. This was accomplished by reducing 3,4,5-trimethoxybenzaldehyde with $NaBH_4$ to form the benzyl alcohol[163] **(3.21)**, followed by treatment with PBr_3 to produce trimethoxybenzyl bromide[106] **(3.22)** (Scheme 3.16).



Scheme 3.16.

The bromide **(3.22)** was then added to the dianion of methyl acetoacetate, to afford **(3.17)**, in 60% yield (Scheme 3.17).



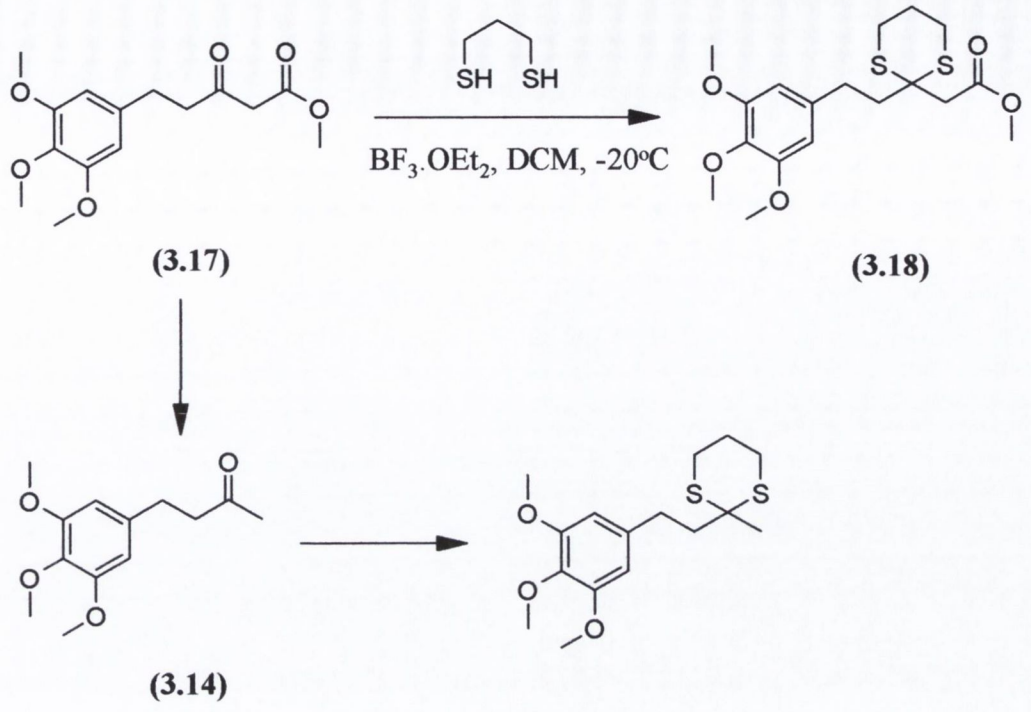
(3.22)

(3.17)

Scheme 3.17.

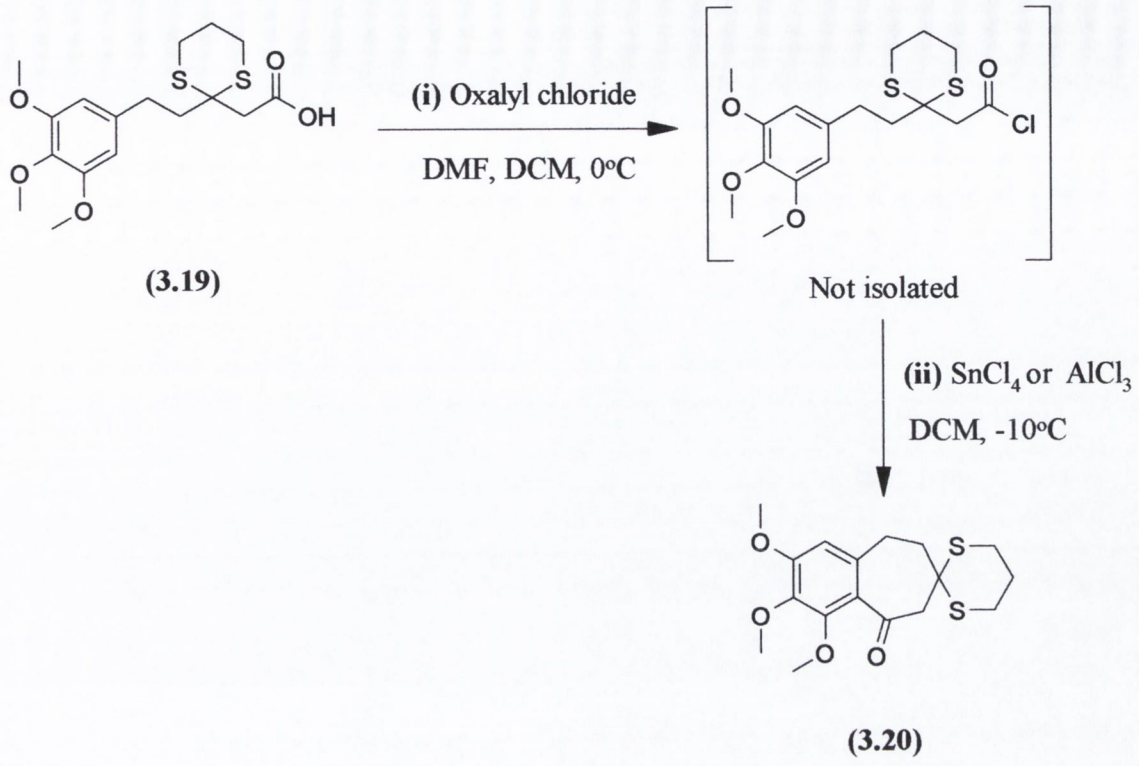
3.6.1 Synthesis of the cyclic precursor (3.20)

Having established a very efficient means of synthesising the β-keto-ester **(3.17)**, the next milestone towards the targeted compound **(3.32)** was the synthesis of the benzosuberone intermediate **(3.20)**. As β-keto-acids are prone to decarboxylation under both acidic and basic conditions, it was essential that the keto group should be suitably protected to prevent the possibility of decarboxylation occurring during the hydrolysis of the methyl ester. Dithiane protection is a commonly employed means of protecting carbonyl groups being stable to Lewis acids, basic hydrolysis and organometallic reagents, conditions that will be employed later in the synthesis of the targeted compound. Dithiane protection[164] of the β-keto-ester **(3.17)** was carried out using propan-1,3-dithiol. The keto-ester and thiol were dissolved in anhydrous DCM at -20°C and the catalyst, boron trifluoride ($BF_3.OEt_2$), was added drop-wise to the resulting solution. Due to the acidic nature of this catalyst, partial decarboxylation of **(3.17)** did occur together with the concomitant protection of the resulting methyl ketone **(3.14)** as illustrated in Scheme 3.18. Careful consideration to the concentrations of the reactants and rates of addition were required to optimise the formation of compound **(3.18)**.



Scheme 3.18. Keto-protection step showing the formation of the dithianyl by-product.

The methyl ester **(3.18)** was hydrolysed using sodium methoxide, dissolved in methanol/water (4:1), to afford the acid **(3.19)**. This acid **(3.19)** was then converted to its corresponding acid halide by the addition of oxalyl chloride and a catalytic amount of dimethylformamide (DMF). This intermediate was used directly to form 2,3,4-trimethoxy-7,7-dithianyl-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **(3.20)** under Friedel-Crafts acylation conditions[165] (Scheme 3.19). Several different Lewis acids were used to promote the intramolecular cyclisation reaction (Table 3.4). The maximum yield achieved for the cyclisation step was 50% using $SnCl_4$ as Lewis acid catalyst. The only other catalyst that was shown to be effective was $AlCl_3$, but the yield using this reagent obtained was only 33%.



(3.19) **(3.20)**

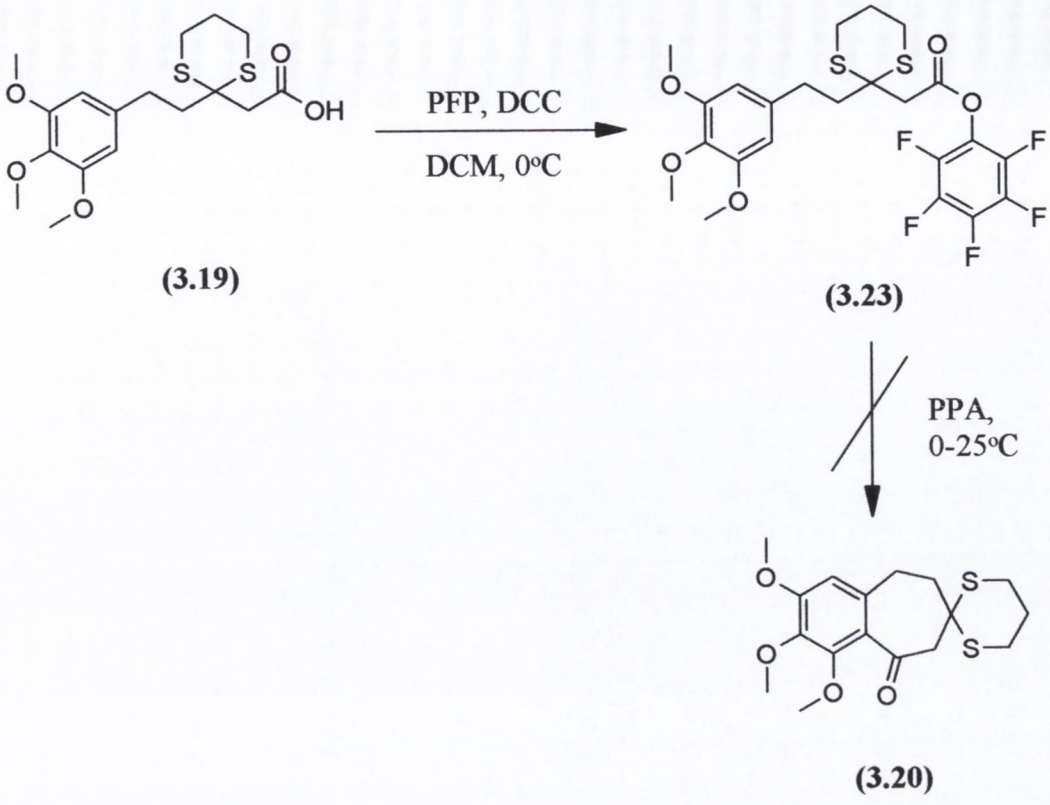
Scheme 3.19.

Lewis acid	Molar amounts	Reaction time (mins)	Temperature (°C)	Yield (%)
PPA	8 equiv.*	10	0-25	-
$BF_3.OEt_2$	1M	120	0-25	-
$AlCl_3$	2.0-0.3M	60	10	18-33%
$SnCl_4$	0.3M	15	0	30-50%

* 8 equivalents of PPA (polyphosphoric acid) by weight.

Table 3.4. Attempted cyclisations using different Lewis acids.

Initial attempts to form the ketone **(3.20)** involved activation of the acid **(3.19)** by formation of its pentafluorophenyl ester **(3.23)** and cyclisation using polyphosphoric acid (Scheme 3.20). However, this method of cyclisation was not pursued as deprotection of the dithiane group occurred rapidly under the acidic conditions employed.

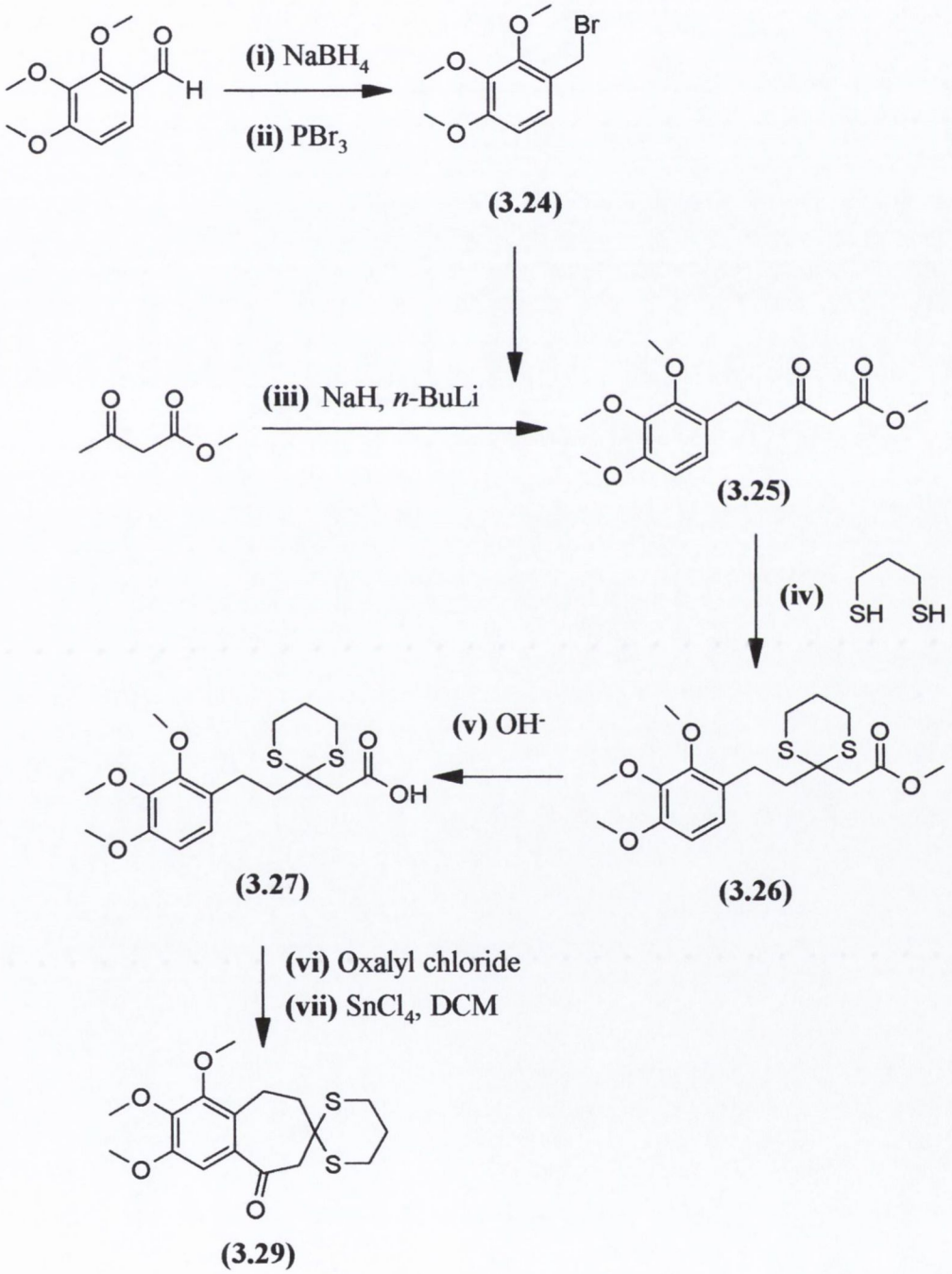


(3.19) **(3.23)** **(3.20)**

Scheme 3.20.

3.7 Synthesis of 7,7-dithianyl-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.29)

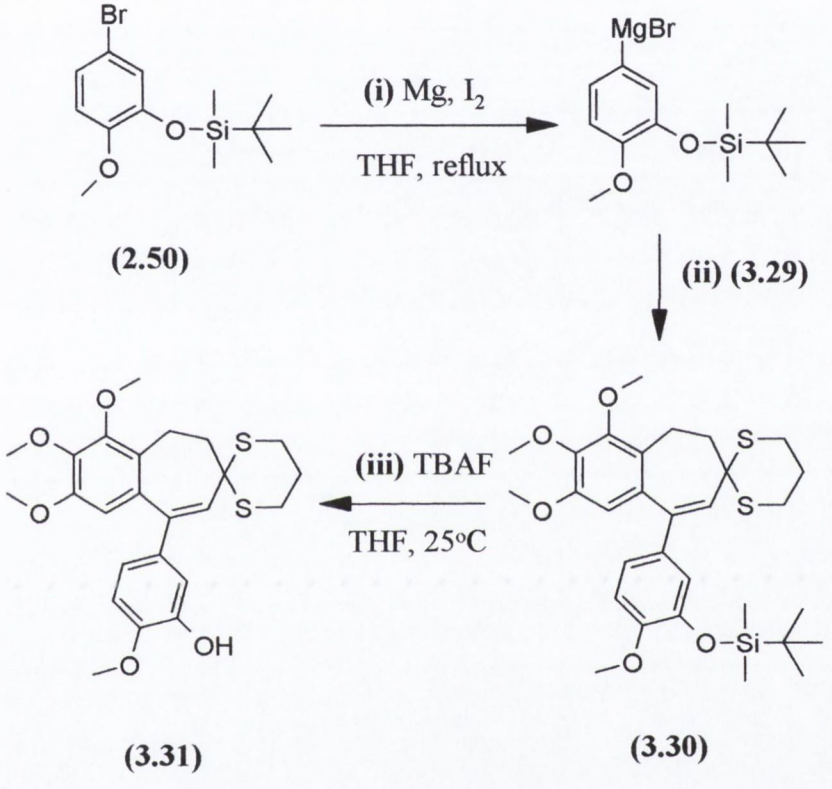
The synthesis of the cyclic intermediate **(3.29)** was accomplished using exactly the same conditions as that employed for its regioisomer, **(3.20)** (Scheme 3.21).



Scheme 3.21. Generalised reaction scheme involving the synthesis of **(3.29)**

3.8 Arylation of (3.29)

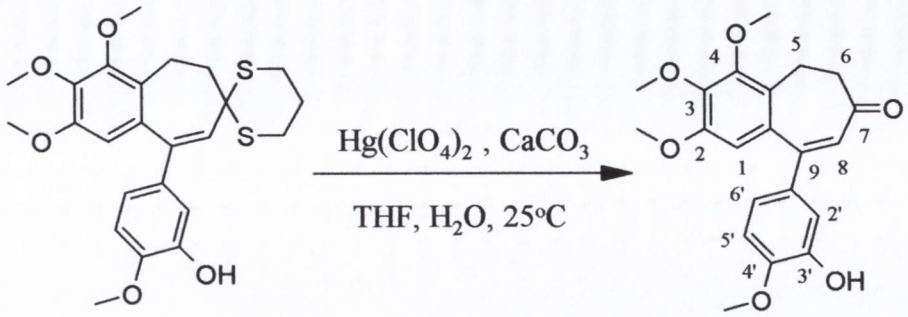
The organometallic addition of substituted aryl derivatives to **(3.29)** was carried out by the initial conversion of the aryl bromide **(2.50)** to its corresponding Grignard reagent. The coupled product **(3.30)** was then treated with TBAF to afford the phenol **(3.31)** as a yellow solid in an overall yield of 33% (Scheme 3.22).



Scheme 3.22.

3.8.1 Dithioacetal deprotection

Although protection of the ketonic group as a dithioacetal seemed apt at the time, its regeneration back to the ketone proved to be a difficult transformation. A number of different deprotecting agents were investigated (Table 3.5) with mercury perchlorate ($Hg(ClO_4)_2$, in the presence of $CaCO_3$, (Scheme 3.23) being the only method resulting in moderate yields of ketone (25%). Other reagents used, included treatment of **(3.31)** with NBS, silica gel, $Tl(NO_3)_2$ and CH_3I.



(3.31) **(3.32)**

Scheme 3.23.

Reagent used	Conditions	Product
NBS[166]	Acetonitrile or Acetone/H_2O (9:1)	No reaction
Silica gel	EtOAc, 60°C, 3 hours	No reaction
$Tl(NO_3)_2$[167]	MeOH, 25°C, 0.5 hour	By-products not characterised
$Hg(ClO_4)_2$[168]	THF, H_2O, $CaCO_3$, 25°C	**(3.32)**
CH_3I[169]	Acetonitrile, H_2O (9:1)	By-products not characterised

Table 3.5. Conditions used for dithiane deprotection.

3.8.2 Structural elucidation of (3.32)

As the synthesis of **(3.32)** was the primary focus of the work discussed in this chapter, its spectroscopic features are dealt with in detail in this following section. In addition to using both low and high resolution mass spectrometry **(3.32)** was also characterised through IR and multiple NMR spectroscopic methods. In the IR spectrum, the most distinguishing features were the broad peak at 3400.2 cm^{-1} representative of the phenolic hydroxyl group and the $C{=}O_{str}$ absorption peak at 1652.4 cm^{-1} indicative of enone functionality. The associated medium intensity $C{=}C_{str}$ peak at 1592.2 cm^{-1}

confirmed the presence of this functional group. The low resolution mass spectrum displayed the characteristic molecular ion peak of 370. Its high resolution mass spectrum revealed, as the base peak, its protonated molecular ion 371.1460 (MH^+).

Extensive HMBC, HMQC, and NOE experiments were used in the assignment of both the ^1H and ^{13}C signals of **(3.32)**. Two multiplets were observed at 2.71 ppm and 3.15 ppm and were assigned as the aliphatic protons on the B-ring. Further analysis of the HMBC spectrum displayed the methylene H-5 proton contour, coupling at 2.72 ppm to the signal representing C-6 (19.80 ppm). This also showed long range coupling to C-7 (203.54 ppm) and C-9a (128.66 ppm). The multiplet at 3.15 ppm was assigned as the methylene protons on C-6 and this was confirmed, with the aid of the HMBC spectrum, by correlation to C-8 (127.71 ppm). The four-methoxy proton signals resonated as a collection of three singlets at 3.64 ppm, 3.91 ppm and 3.95 ppm. The most upfield of these signals at 3.64 ppm was assigned as the C-2 methoxy group since a reciprocating NOE effect was observed with the aromatic H-1 (6.38 ppm). The methoxy signal at 3.95 ppm also showed a positive NOE effect with the aromatic C-ring protons and was assigned as the C-4' methoxy group (Figure 3.4). Unfortunately, the remaining C-3 and C-4 methoxy groups could not be differentiated. The phenolic proton was observed as a singlet resonating at 5.67 ppm. The singlet at 6.38 ppm, which integrated for two protons, was assigned as the two-overlapping signals from H-1 and H-8. The overlapping doublet at 6.92 ppm was allocated as H-2' since a positive NOE effect was observed after irradiation of the phenolic (5.67 ppm) signal. NOE experiments also permitted the assignment of H-5' at 6.86 ppm since a positive response was recorded when the C-4' methoxy group signal was irradiated. Finally, the doublet (J = 1.5Hz) resonating at 6.90 ppm was assigned as H-6'.

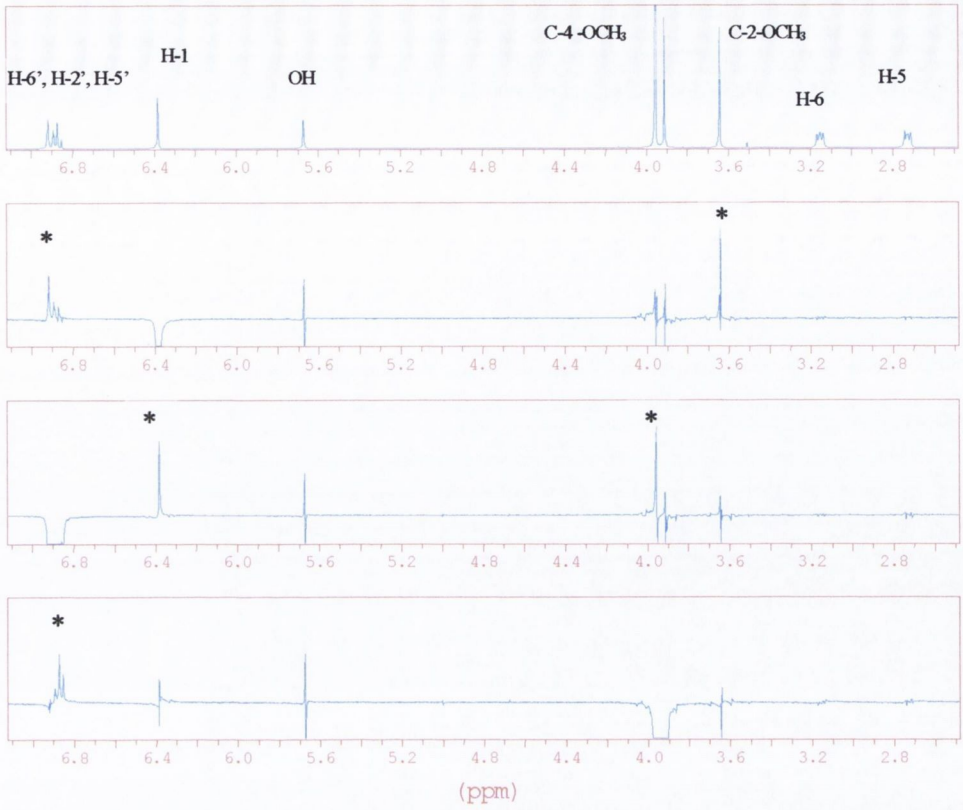


Figure 3.4. NOE spectra of **(3.32)** illustrating through space coupling. Positive NOE interaction is denoted by *.

The carbon assignments of **(3.32)** were made with the aid of DEPT 135, DEPT 90 and HMQC spectra (Figure 3.5). The aliphatic carbons, C-5 and C-6, were assigned by HMQC correlation from their corresponding proton resonance's to 45.22 ppm and 19.80 ppm respectively. The C-2 methoxy carbon resonated at 55.62 ppm whereas the C-4' methoxy carbon was observed at 55.54 ppm. The remaining two-methoxy carbons, at positions C-3 and C-4, were recorded at 60.43 ppm and 60.92 ppm. All five methine carbons were assigned from the HMQC. H-1 (6.38 ppm) correlated to the signal at 111.58 ppm (C-1) while C-8 was characteristically observed at 127.71 ppm. The aromatic C-ring carbons were also identified by HMQC with C-5', C-6' and C-2' resonating at 109.77 ppm, 120.68 ppm and 114.99 ppm respectively. From ^{13}C NMR, all nine quaternary carbons were recorded from 128.66 ppm to 151.77 ppm. Fortunately, a number of these carbons could be distinguished with the aid of HMBC analysis (Figure 3.6). The phenolic proton showed coupling to C-3' (144.84 ppm) while long-range coupling identified C-4' at 146.85 ppm. A correlation contour was also recorded from the C-2 methoxy protons to the quaternary C-2 at 150.65 ppm. The two

remaining quaternary carbons (C-3 and C-4) that were attached to methoxy groups were observed resonating at 149.51 ppm and 144.84 ppm.

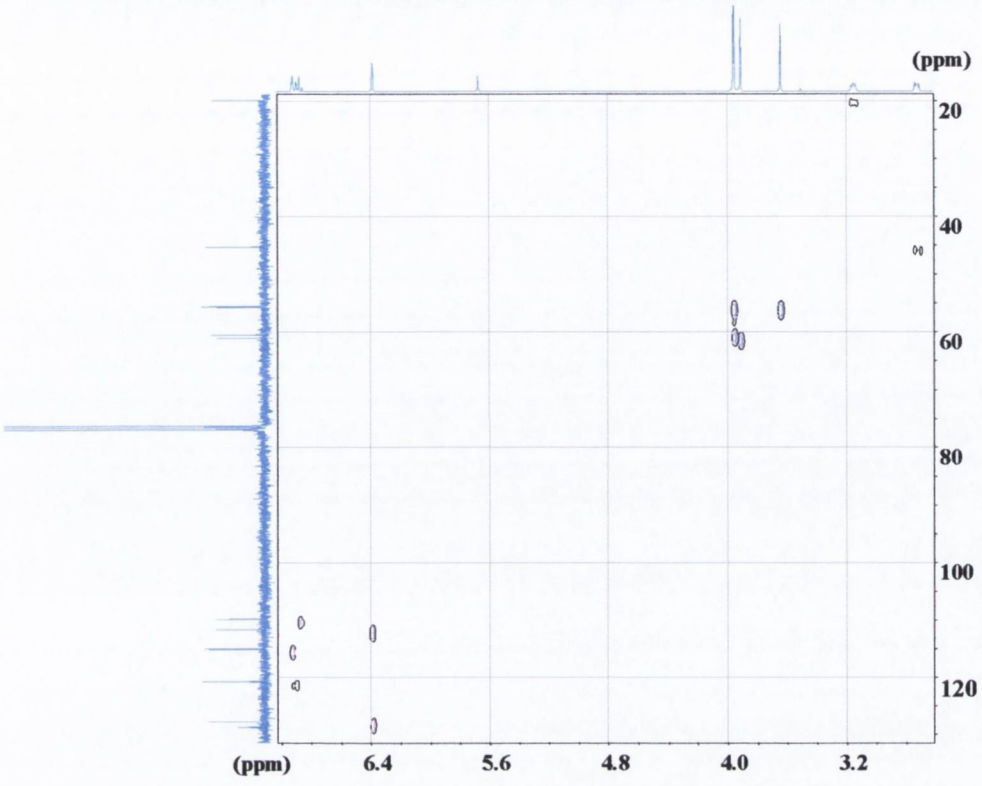


Figure 3.5. HMQC spectrum of **(3.32)**.

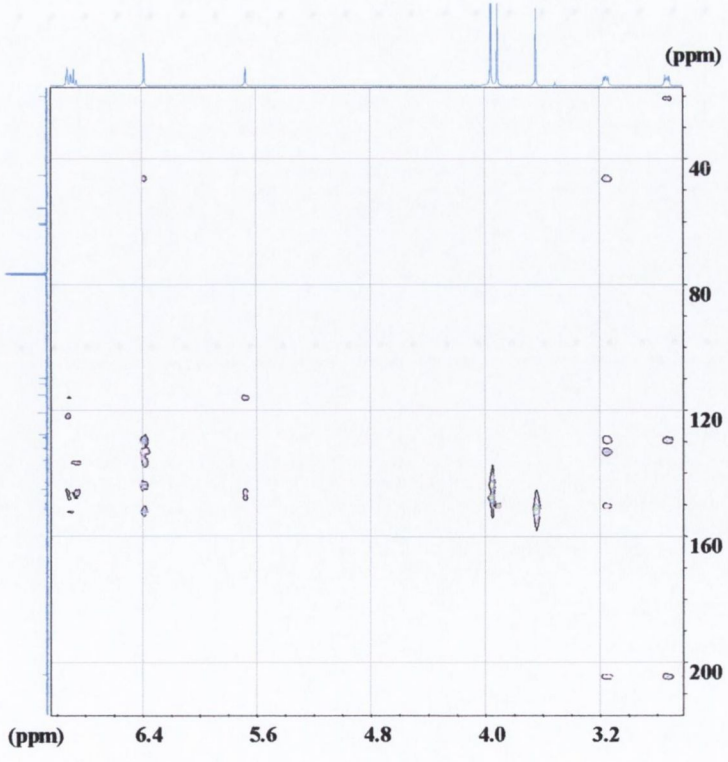
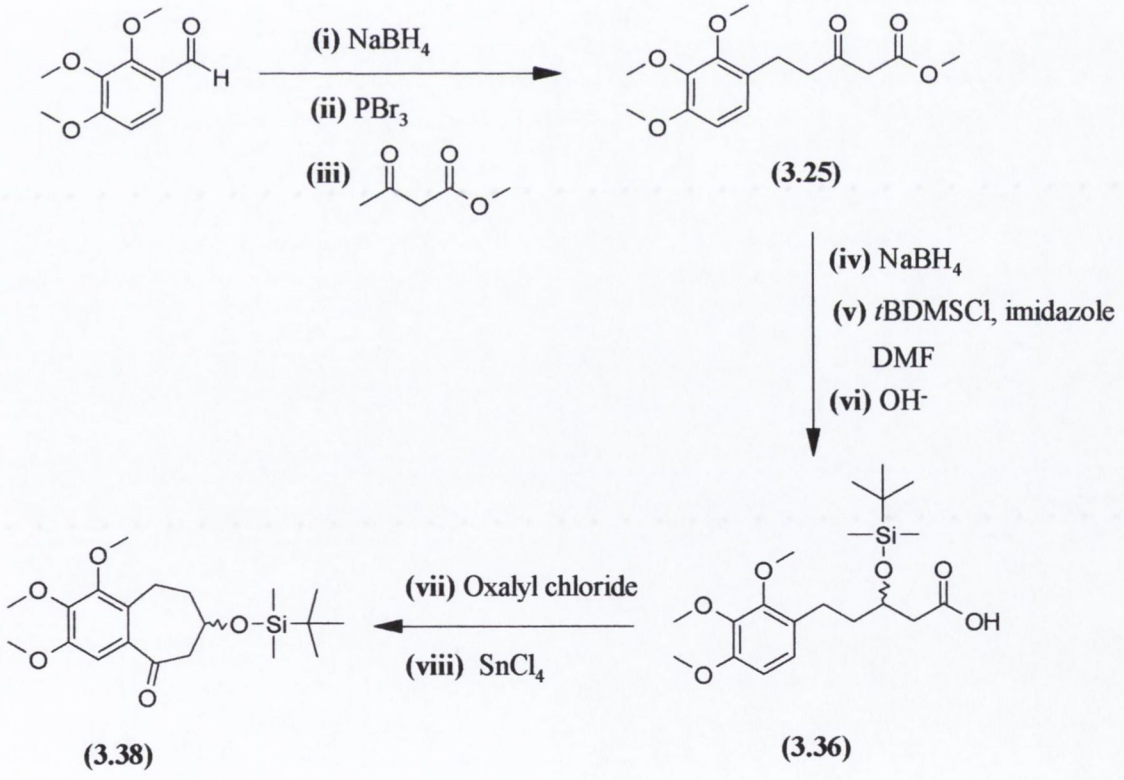


Figure 3.6. HMBC spectrum of **(3.32)**.

3.9 Improved synthesis of the cyclic intermediate

3.9.1 Synthesis of 7-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.38)

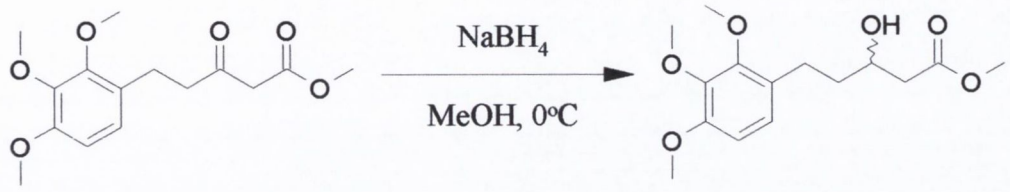
Although a means of synthesising **(3.32)** was established, it was somewhat disappointing that the dithiane-deprotection step proved to be quite a difficult transformation. An alternative synthetic method was sought that would allow for a higher yielding deprotection step. Instead of trying to protect the carbonyl group, it was decided to reduce it and protect the resulting alcohol as a *t*BDMS ether derivative. Previous experience with this protecting group has shown that its removal is easily accomplished with TBAF. Scheme 3.24 illustrates the proposed route to this cyclic intermediate **(3.38)**.



Scheme 3.24. Proposed synthetic route to **(3.38)**.

Reduction of the carbonyl group in **(3.25)** was accomplished using a methanolic solution of $NaBH_4$[170]. This required careful consideration to the reaction conditions as

an excess of the hydride reducing agent did result in the partial hydrolysis of the methyl ester. The transformation was optimised by the portion-wise addition of 0.33 molar equivalents of $NaBH_4$ to the keto-ester in methanol at 0°C to afford the β-hydroxy-ester **(3.33)** as an oil in 91% yield (Scheme 3.25).

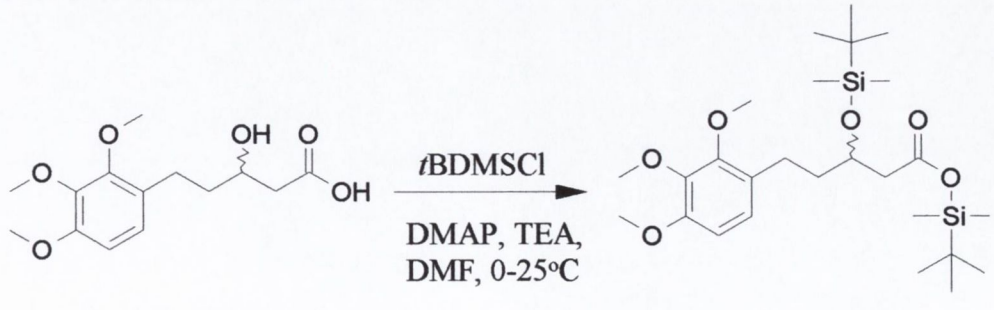


(3.25) **(3.33)**

Scheme 3.25.

The methyl ester **(3.33)** was hydrolysed following treatment with a cold ethanolic solution of aq. KOH, which afforded the hydroxy-acid **(3.34)**[171]. The reaction was carefully quenched by reducing the pH to 3.0 using cold 2M aq. HCl.

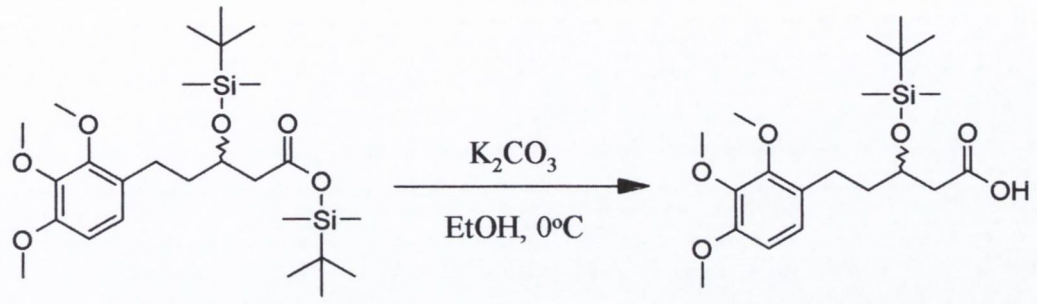
Protection of the hydroxyl group from the β-hydroxy-acid **(3.34)** was attempted using tert-butyldimethylsilyl chloride and imidazole in DMF at 0°C. It was felt that selective protection at the hydroxyl group would occur if *N,N*-dimethylaminopyridine (DMAP) and triethylamine (TEA) were used together as described by Seebach *et al*[171]. Isolation of the product by flash column chromatography however revealed the formation of the di-silylated product **(3.35)** (Scheme 3.26).



(3.34) **(3.35)**

Scheme 3.26.

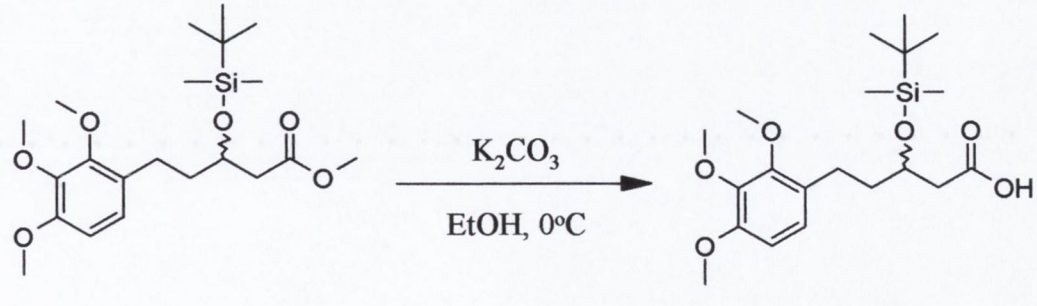
Compound **(3.35)** was used, as selective deprotection was possible with the ester being less stable than the ether. This was successfully achieved by using a methanolic solution of K_2CO_3 to generate the acid **(3.36)**[172] (Scheme 3.27).



(3.35) **(3.36)**

Scheme 3.27.

Although this was a successful reaction, it was considered a wasteful process since the methyl ester **(3.33)** was hydrolysed just to put on a silyl ester, which would then be hydrolysed again, in the following step. Instead, the *t*BDMS ether was introduced after reduction of the ketone in **(3.25)** to the secondary alcohol **(3.33)** in the usual manner[173] followed by basic hydrolysis of the methyl ester **(3.37)** using 1M aq. NaOH in methanol[173] afforded the acid as a white waxy-solid **(3.36)** in 85% yield (Scheme 3.28).

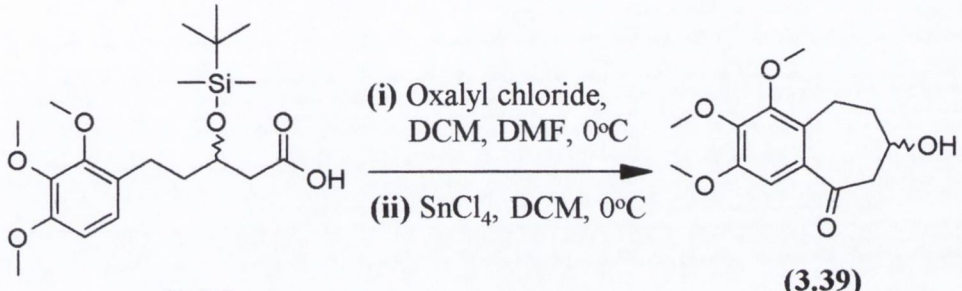


(3.37) **(3.36)**

Scheme 3.28.

The next step involved activation of the acid to the acid chloride under conditions previously described for the synthesis of **(3.29)**. The resulting acid chloride was then cyclised, *in situ*, using a mild Lewis acid. It was felt that $AlCl_3$ could not be used since

its acidity would result in deprotection of the silyl ether. Therefore, $SnCl_4$ was used at -10°C in anhydrous DCM. The reaction was monitored by TLC analysis. This reaction produced numerous side products, however, isolation of one of the by-products by flash column chromatography afforded 7-hydroxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **(3.39)** albeit in 8% yield (Scheme 3.29).



(3.36) **(3.39)**

Scheme 3.29.

The keto-alcohol **(3.39)** was identified by IR and NMR analysis. In the IR spectrum, the most distinguishing features were the broad peak at 3431.1 cm^{-1} representative of the phenolic hydroxyl group and the $C{=}O_{str}$ absorption peak at 1673.3 cm^{-1} indicative of a benzylic ketone.

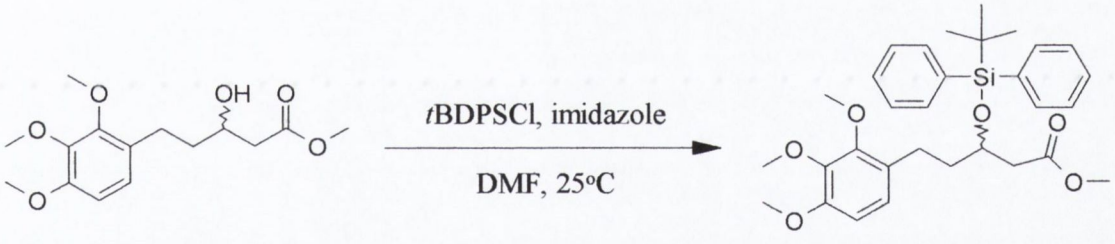
The ^1H NMR spectrum of **(3.39)** revealed one of methylene H-6 protons resonating as a multiplet at 1.89 ppm and the other at 2.19 ppm. This significant difference in chemical shift was attributed to their relative proximity to the adjacent carbonyl and hydroxyl substituents. The protons attached to C-8 and C–9 resonated at 3.09 ppm and 3.01 ppm respectively. The methoxy group protons resonated, as predicted, at 3.86 ppm, 3.89 ppm and 3.95 ppm. The quintet at 4.35 ppm (J = 6Hz) was assigned to the H-7 proton being split on either side by the two adjacent protons on C-6 and C-8. The remaining singlet at 7.18 ppm was assigned as the H-4 proton.

An inspection of the ^{13}C NMR and DEPT 135 spectra of **(3.39)** identified the methylene carbons resonating at 20.58 ppm, 35.51 ppm and 49.91 ppm. The three-methoxy carbons resonated at 55.53 ppm, 60.39 ppm and 60.65 ppm, while the methine signal resonating at 66.78 ppm was attributed to C-7. From the DEPT 135 spectrum, the peak at 107.08 ppm was identified as C-4. Aside from the aromatic quaternary signals, the

other significant unassigned resonance in the ^{13}C NMR was a peak at 198.94 ppm, attributable to the carbonyl carbon.

3.9.2 Formation of (3.39) *via* of 7-[1-(*tert*-butyl)-1,1-diphenylsilyl]oxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.43)

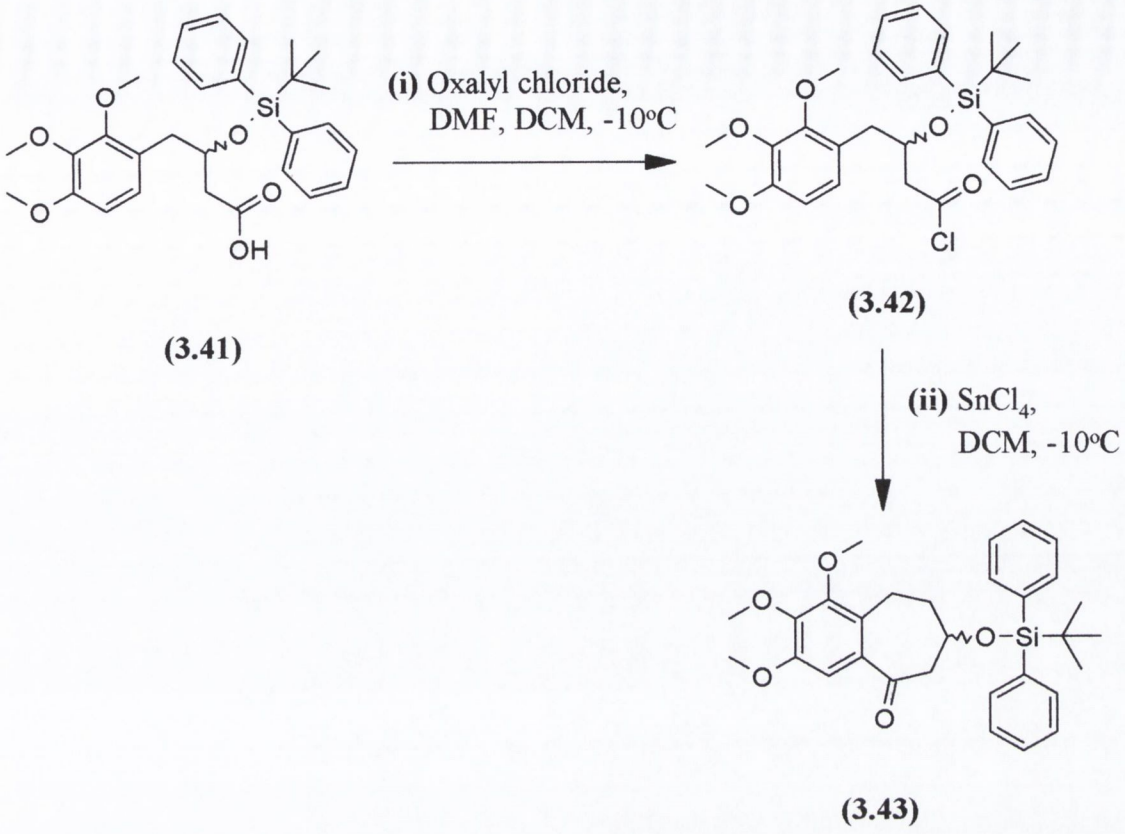
It was felt that protection of the C-7 alcohol functional group with a more robust silyl-protecting group would enhance the yield of the cyclization step. The use of *tert*-butyldiphenylsilyl ethers (*t*BDPS) as protecting groups is widespread in organic synthesis. This group is considerably more stable (~100 times) than *t*BDMS towards acidic hydrolysis[174] due to the steric encumbrance of the two-phenyl groups around the silicon atom. Introduction of the *t*BDPS group onto the β-hydroxy-ester **(3.33)** was achieved using the *t*BDPS chloride with imidazole and DMF as base and solvent respectively (Scheme 3.30). Upon completion, the product **(3.40)** was isolated by water/ether extraction and purified by flash column chromatography to yield the silyl ether as a clear oil in near quantitative yields.



(3.33) **(3.40)**

Scheme 3.30.

The conditions used for hydrolysis of the methyl ester **(3.40)** were identical to that used in the hydrolysis of **(3.37)**. The cyclisation of the acid **(3.41)** involved *in situ* formation of the acid halide **(3.42)** with subsequent intramolecular acylation using $SnCl_4$ (0.3 molar equivalents) to afford **(3.43)** as an orange oil in 79% yield (scheme 3.31).



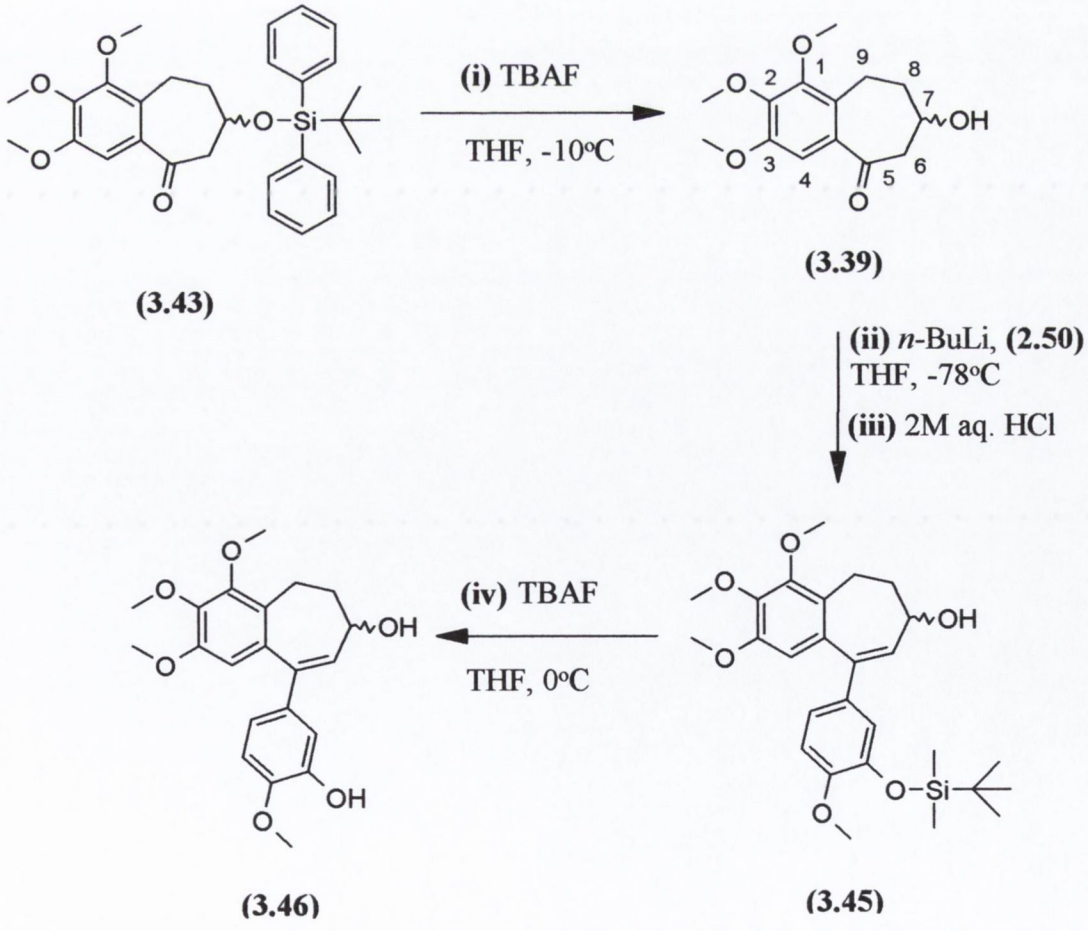
(3.41) **(3.42)** **(3.43)**

Scheme 3.31.

3.10 Formation of the biaryl systems

3.10.1 Addition of the C-ring to 7-hydroxy-1,2,3-trimethoxy-6,7,8,9 tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.39)

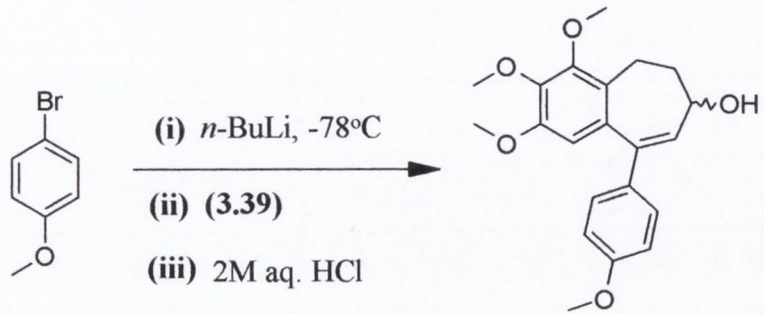
As described in Chapter 2, the attachment of the aryl substituents to the trimethoxybenzosuberone **(2.06)** involved their lithiation using *n*-BuLi at -78°C. In an analogous fashion, the attachment of lithiated **(2.50)** to **(3.43)** was attempted. However, nucleophillic addition of the organolithium reagent to **(3.43)** failed to take place possibly due to the steric bulk of the di-phenyl substituent. The protecting group was removed using TBAF to afford the keto-alcohol **(3.39),** taking into account inherent acidity of the resulting hydroxyl proton; the coupling of **(2.50)** to **(3.39)** was accomplished in high yields by using a three molar excess of the aryl bromide (Scheme 3.32).



Scheme 3.32.

3.10.2 Synthesis of 2,3,4-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.44)

Organolithium formation of *para*-bromoanisole with subsequent addition to 0.33 molar equivalents of **(3.39)** at -78°C in anhydrous THF led to the synthesis of **(3.44)** (Scheme 3.33).

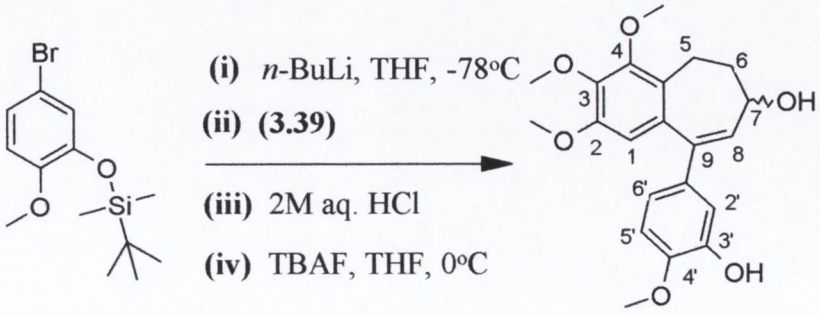


(3.44)

Scheme 3.33.

3.10.3 Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.46)

Compound **(3.46)** was prepared *via* the formation of the organolithium of **(2.50)** as described in section 2.7.1. Once prepared, 0.33 molar equivalents of **(3.39)** were added at -78°C. The reaction proceeded for 1 hour at this temperature. Dehydration, followed by treatment of the coupled product **(3.45)** with TBAF, afforded the allylic alcohol **(3.46)** (Scheme 3.34).



(2.50) **(3.46)**

Scheme 3.34.

Compound **(3.46)** was identified by IR, and NMR spectroscopy. IR analysis identified the presence of the hydroxyl groups as a broad peak at 3403.2 cm^{-1} whilst the $C{=}C_{str}$ was observed as a medium intensity peak at 1509.5 cm^{-1}.

Assignment of **(3.46)** was aided by ^1H NMR, ^1H-^1H COSY and HMQC spectral analysis. From ^1H NMR spectroscopy, it was clear that the methylene protons from the B-ring were non-equivalent, possibly because of the aliphatic ring being structurally rigid. This rigidity restricts rapid ring flipping allowing each proton to exist in its own magnetic environment during an NMR timescale. Hence, each methylene proton is recorded as a complex multiplet with the equatorial protons resonating about 0.5-0.6 ppm higher than the axial protons. This is probably attributed to anisotropic deshielding by the σ-electrons in the β-γ bond of the B-ring.

Analysis of HMQC spectrum revealed correlation contours between the peaks at 2.09 ppm and 2.51 ppm and the methylene carbon at 21.39 ppm. ^1H-^1H COSY analysis also displayed a coupling between these two multiplets and the multiplet at 4.00 ppm (H-7). Therefore, the signals at 2.09 ppm and 2.51 ppm were assigned as the equatorial and axial H-6 protons respectively. The two remaining multiplets at 2.35 ppm and 3.03 ppm were assigned as the equatorial and axial H-5 protons respectively. The four methoxy-group protons resonated as three singlet peaks at 3.66 ppm, 3.87 ppm and 3.89 ppm. The broad singlet peak at 5.66 ppm was assigned as the phenolic proton from the C-ring. The protons in the aromatic region of the spectrum were deciphered primarily by their splitting patterns. ^1H-^1H COSY spectral analysis (Figure 3.7) revealed a doublet (J=5Hz) at 6.22 ppm correlating to the adjacent H-7 proton. This was therefore assigned as the alkenyl H-8 proton. The singlet at 6.40 ppm was assigned as the H-1 proton from the A-ring. The double-doublet (J = 2Hz, 8.5Hz) at 6.74 ppm was assigned as the H-2' proton. The H-6' proton exhibited *meta*-coupling to H-2' and as a result was observed resonating as a doublet (2.0Hz) at 6.76 ppm, while the doublet (J=8Hz) at 6.88 ppm was assigned as the H-5' proton.

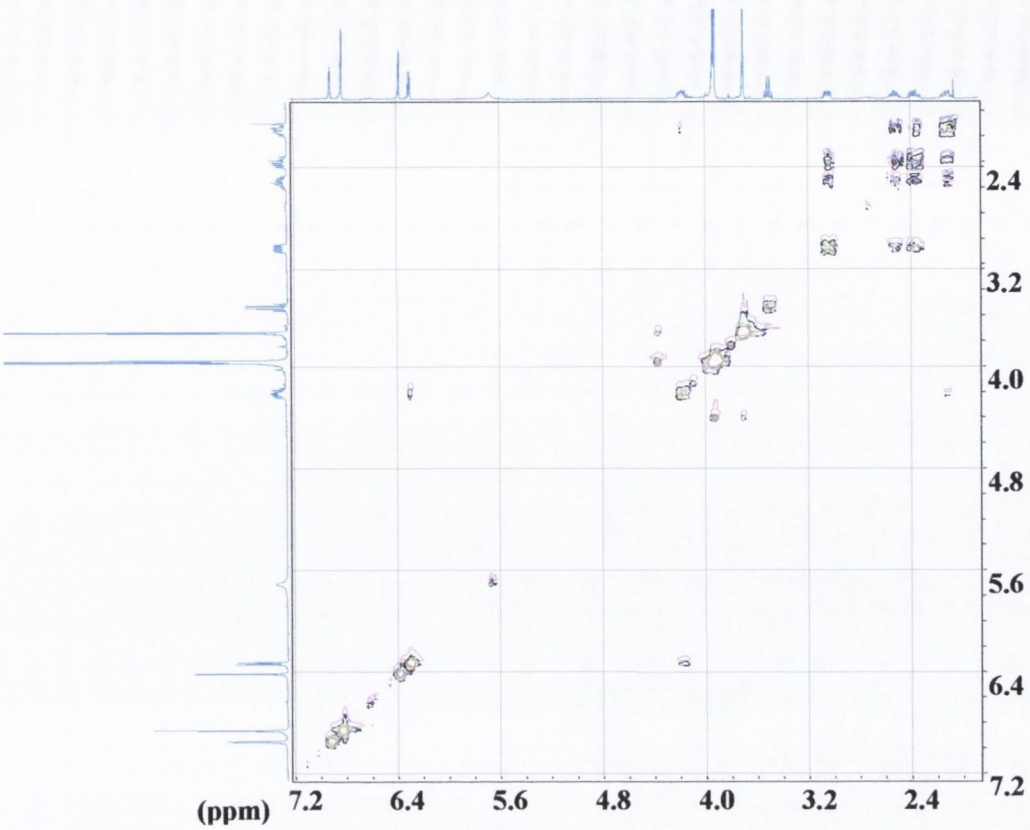


Figure 3.7. ^{1}H-^{1}H COSY spectrum of **(3.46)**.

The carbon framework of compound **(3.46)** was elucidated with the help of HMQC, DEPT 135 and DEPT 90 spectra. From the HMQC spectrum (Figure 3.8), the two H-6 proton multiplets at 2.09 ppm and 2.51 ppm coupled to the methylene carbon (C-6) at 21.39 ppm. The H-5 protons coupled to the carbon signal (C-5) at 42.28 ppm. The methoxy peaks resonated at 54.59 ppm, 54.61 ppm, 59.40 ppm and 60.21 ppm. A correlation contour was observed between H-7 (4.00 ppm) and the signal at 68.41 ppm. The C-1 signal characteristically appeared in the DEPT 135 at 108.78 ppm. The H-2' and H-6' protons were found to correlate to the carbon signals at 111.09 ppm (C-2') and 119.14 ppm (C-6') in the HMQC spectrum. Likewise, the signal at 114.59 ppm was assigned as the C-5 carbon while the signal at 131.19 ppm was assigned as the alkenyl C-8 carbon. The nine quaternary carbons were all observed in the ^{13}C NMR spectrum at 127.41 ppm, 133.92 ppm, 135.19 ppm, 138.12 ppm, 140.89 ppm, 145.48 ppm, 146.93 ppm, 150.14 ppm and 150.74 ppm.

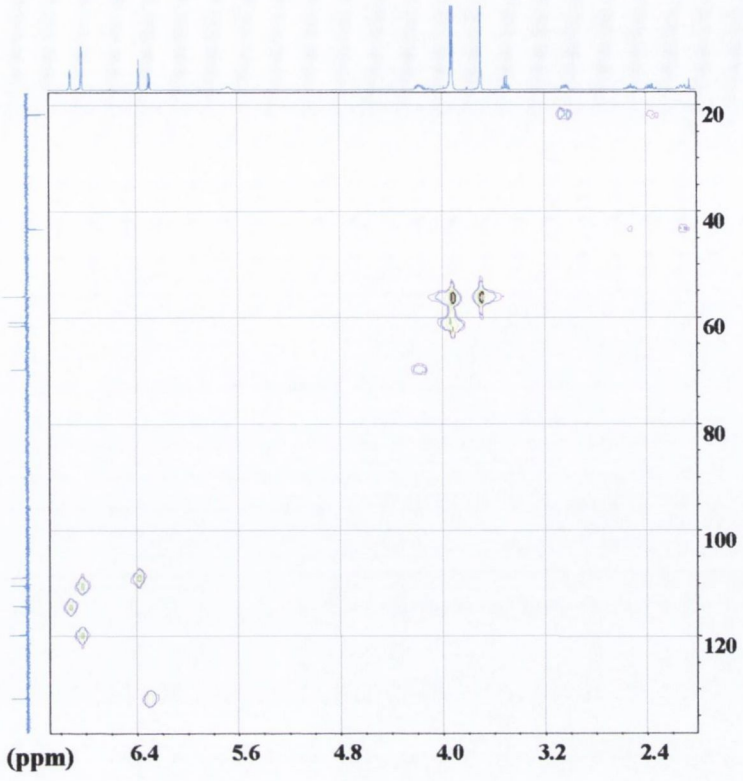
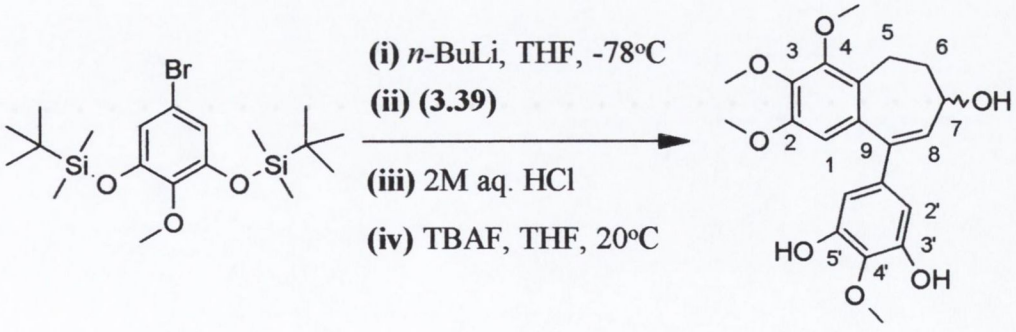


Figure 3.8. HMQC spectrum of **(3.46)**.

3.10.4 Synthesis of 5-(7-hydroxy-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-2-methoxy-1,3-benzenediol (3.48)

Compound **(3.48)** was similarly prepared as described in section 3.10.3 (Scheme 3.35).

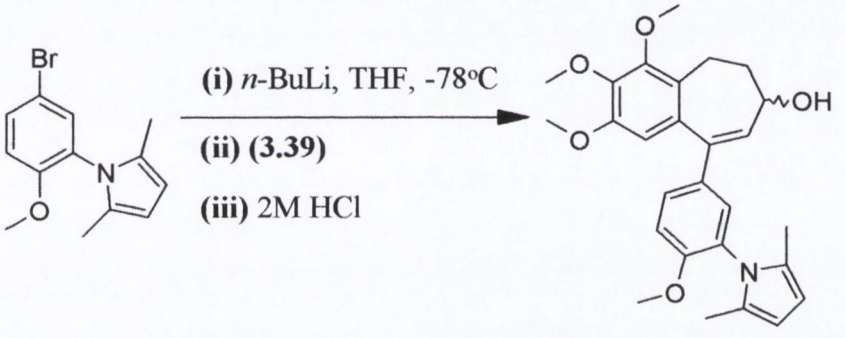


(2.55) **(3.48)**

Scheme 3.35.

3.10.5 Attempted synthesis of 9-(3-amino-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.50)

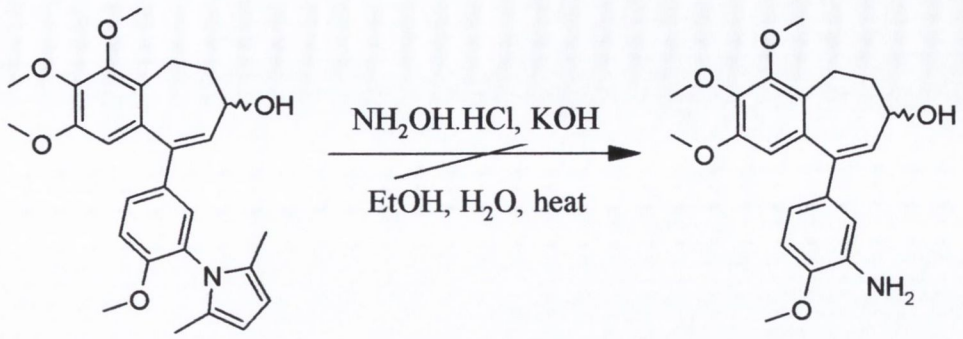
From previous work, the amino analogue **(2.65)** was identified as an effective inhibitor of tubulin polymerisation (section 2.14). Consequently, the formation of **(3.50)** was initiated *via* the lithiation of **(2.63)**. Nucleophillic addition to **(3.39)** gave, after addition of acid and purification by column chromatography, 9-[3-(2,5-dimethyl-1*H*-1-pyrrolyl)-4-methoxyphenyl]-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol **(3.49)** in 60% yield (Scheme 3.36).



(2.63) **(3.49)**

Scheme 3.36.

Regeneration of the amino group from the pyrrole ring **(3.49)** was attempted using $NH_2OH.HCl$ in ethanol (Scheme 3.37). However, due to the aggressive conditions employed, this reaction was ineffective resulting in the formation of a large number of unknown by-products when analysed by TLC. Varying the reaction conditions and the concentrations of the reagents had no effect and so the formation of **(3.50)** was abandoned (Table 3.6).



(3.49) **(3.50)**

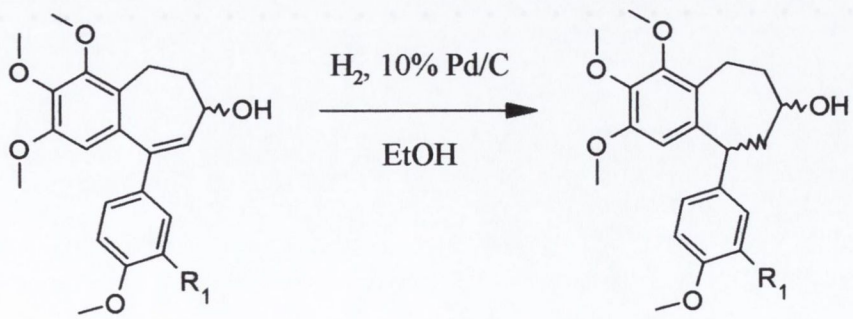
Scheme 3.37.

KOH (Molar amounts)	$NH_2OH.HCl$ (Molar amounts)	Temperature (°C)	Product (TLC)
3	5	25	No reaction
6	10	25	No reaction
3	5	Reflux	By-Products
1	5	Reflux	By-Products

Table 3.6. Conditions used in the attempted deprotection of the pyrrole ring.

3.11 Saturation of the double bond

Catalytic hydrogenation of the α,β-unsaturated alcohols, **(3.44)** and **(3.46)**, using as catalyst, 10% Pd/C, afforded the saturated products in quantitative yield (Scheme 3.38).



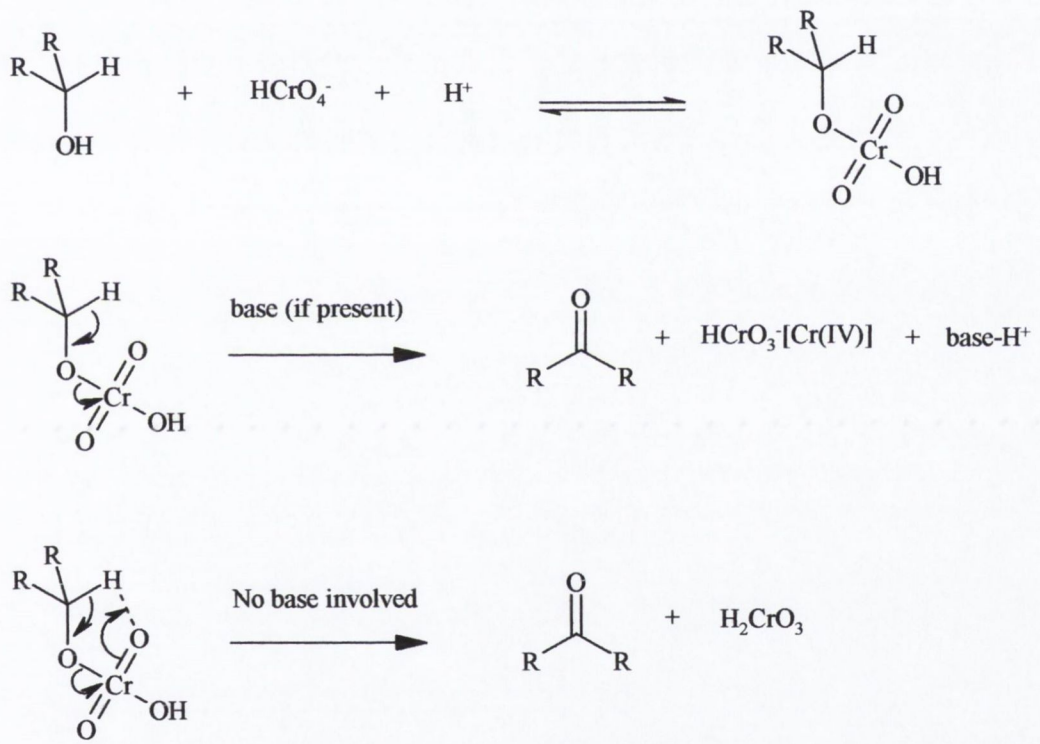
$R_1 = H$ **(3.44)**
$R_1 = OH$ **(3.46)**

$R_1 = H$ **(3.51)**
$R_1 = OH$ **(3.52)**

Scheme 3.38.

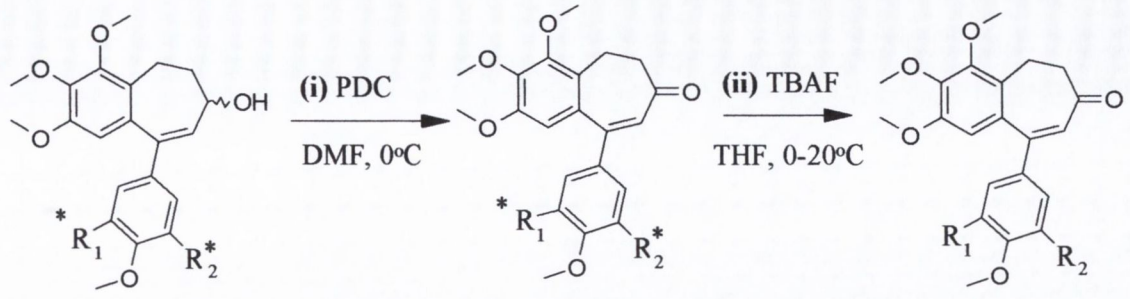
3.12 Oxidation of the C-7 hydroxyl group

Many reagents have been employed in oxidizing allylic alcohols to α,β-unsaturated ketones. Some of these include manganese dioxide (MnO_2)[175], Jones reagent[176] and CrO_3[177]. In all cases, the formation of the inorganic ester is the critical step in the reaction, which ultimately is cleaved, *via* a β-elimination pathway to yield the ketone. The base in the second step may be water, though it may be possible that in some cases no external base is involved and that the proton is transferred directly to one of the CrO_3H oxygen atoms[178] (Scheme 3.39).



Scheme 3.39.

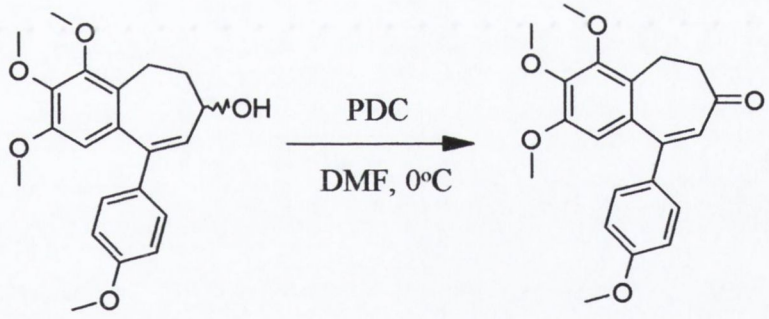
Dissolving the allylic alcohol in DMF and reacting with PDC at 0°C achieved oxidation to an enone moiety (Scheme 3.40). Mild conditions were necessary since benzylic oxidation and oxidative cleavage were both possible side-reactions. This step also required the continued protection of the phenol as the *t*BDMS ether since these conditions were strong enough to potentially oxidise the phenol to the quinone. The subsequent deprotection step-using TBAF managed to afford the product in satisfactory yields.



Scheme 3.40. Generalised reaction scheme for the oxidation of the secondary alcohol to the ketone.

3.12.1 Synthesis of 2,3,4-trimethoxy-9-(4-methoxyphenyl)-6,7- dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.53)

Oxidation of **(3.44)** to the enone **(3.53)** was accomplished by treating **(3.44)** with PDC (1.5 molar equivalents) in DMF for 12 hours. The product **(3.53)** was extracted in diethyl ether and purified by flash column chromatography to afford the enone in 60% yield (Scheme 3.41).



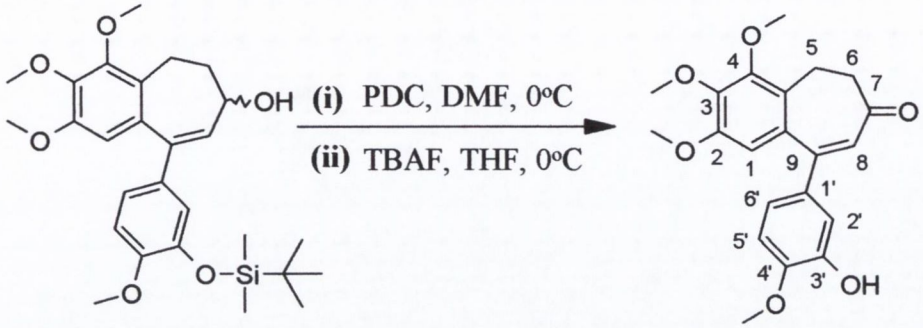
(3.44) **(3.53)**

Scheme 3.41.

3.12.2 Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.32)

Oxidation of **(3.45)** using two molar equivalents of PDC in DMF afforded **(3.32)**. The enone was extracted in diethyl ether and purified by flash column chromatography. The addition of TBAF in THF resulted in the deprotection of the *t*BDMS ether to afford the

product **(3.32)** as a yellow solid, which was recrystallised from hot methanol to afford pale yellow crystals in an overall yield of 51% (Scheme 3.42).

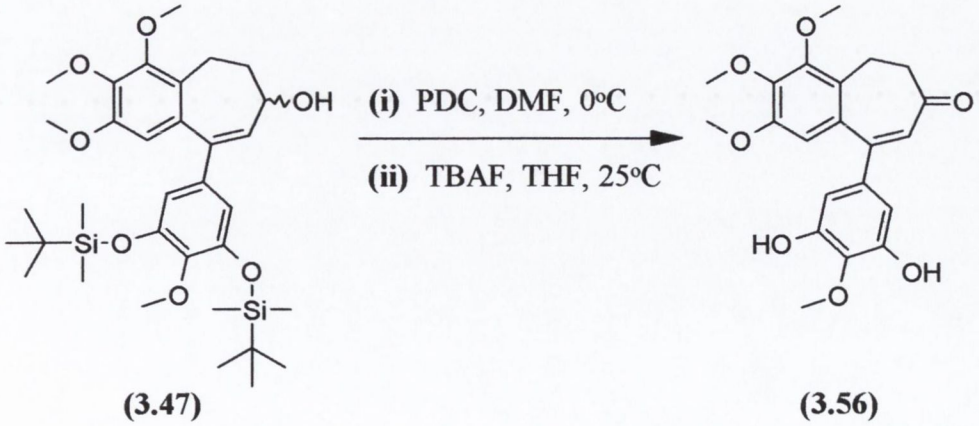


(3.45) **(3.32)**

Scheme 3.42.

3.12.3 Synthesis of 9-(3,5-dihydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.56)

Oxidation of the allylic alcohol **(3.47)** using PDC with subsequent removal of the di-silyl ethers with TBAF afforded, after isolation and purification by flash column chromatography, the enone **(3.56)** in 48% yield (Scheme 3.43).

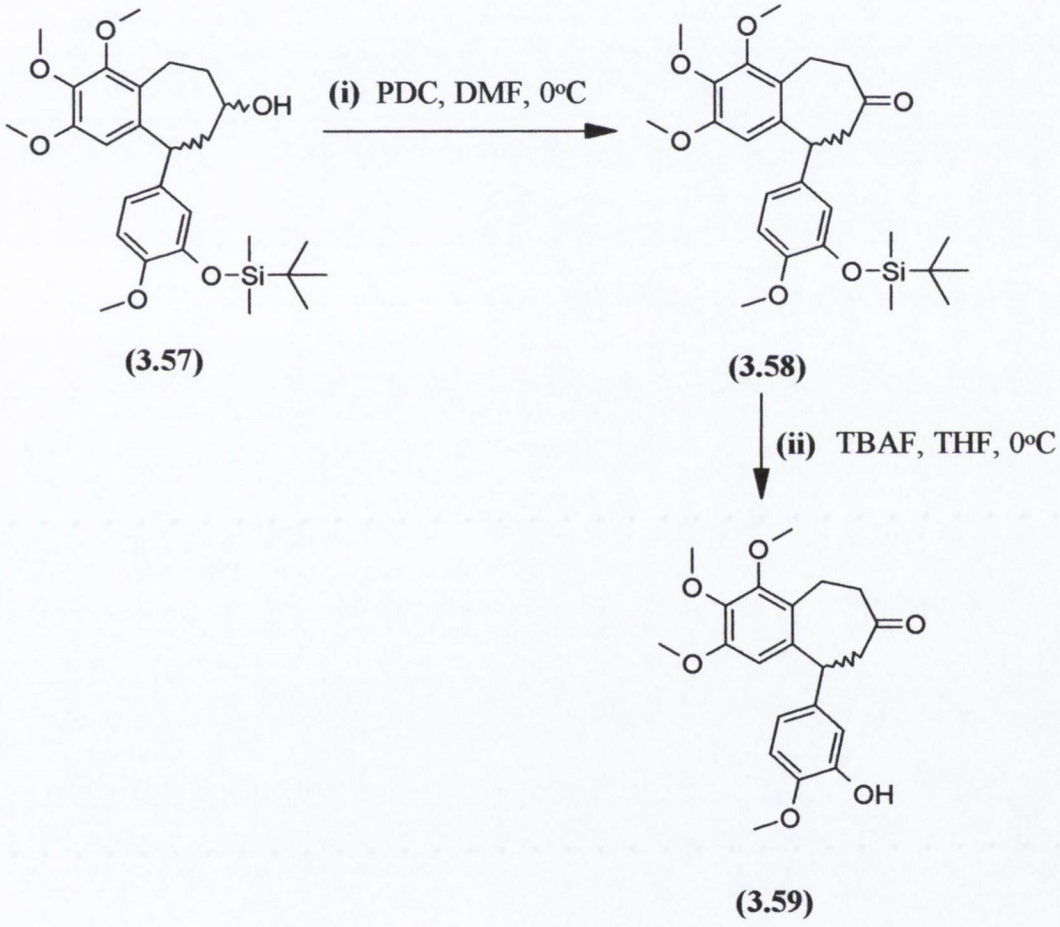


(3.47) **(3.56)**

Scheme 3.43.

3.12.4 Synthesis of 5-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-one (3.59)

Synthesis of **(3.59)** involved the initial reduction of **(3.47)** *via* catalytic hydrogenation to afford **(3.57)**. This was subsequently oxidised to **(3.58)** using PDC in DMF at 0°C for 48 hours. The final product **(3.59)** was afforded by deprotection with TBAF and purified by flash column chromatography as a white solid (Scheme 3.44).



Scheme 3.44.

3.13 Tubulin binding data

Eleven of the novel B-ring functionalised biaryl compounds were evaluated as potential inhibitors of tubulin polymerisation[149]. It is clear from the data obtained, (Table 3.7) that insertion of oxygen-based functionality onto the B-ring had a pronounced effect on tubulin polymerisation in comparison to their unfunctionalised analogues. As an example, the mono-methoxy derivative **(2.44)** was inactive as a tubulin inhibitor, however, its corresponding C-7 hydroxy analogue **(3.44)** exhibited potent anti-tubulin activity (IC_{50} = 2.1 μM). Even higher inhibitory activity was observed when the C-ring was replaced with the hydroxy-anisole entity to afford **(3.46)**. This compound displayed excellent anti-tubulin activity (IC_{50} = 1.1 μM) and was even more active than combretastatin A-4 (IC_{50} = 1.45 μM). The addition of an extra hydroxyl group onto the C-ring **(3.48)** resulted in total loss of activity, as did saturation of the double bond to afford compounds **(3.51)** and **(3.52)**. Oxidation of the α,β-unsaturated alcohol **(3.46)** to the enone compound **(3.32)** resulted in increased tubulin binding activity. Compound **(3.32)** had the highest inhibitory activity (IC_{50} = 1.05 μM) reinforcing the concept that maximum activity was obtained only when the molecule contained the hydroxy-anisole C-ring in addition to the enone functionality on the B-ring. This was further emphasised with the synthesis of compound **(3.59)** as this compound without the double bond was inactive. Finally, compound **(3.56)** was found to exhibit potent anti-tubulin activity (IC_{50} = 1.72 μM) comparable to that of combretastatin A-4 (IC_{50} = 1.45 μM). This was an unexpected result as compound **(2.57)**, which also possessed the di-hydroxy-anisole C-ring moiety was inactive against tubulin polymerisation. On the basis of these very promising results, it was decided to pursue the synthesis of an analogous series of compounds (Chapter 4) where one of the methoxy substituents on the A-ring has been moved from position 1 to position 4.

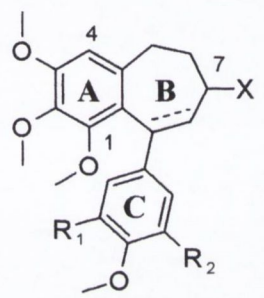
Compound	ITP IC_{50} (μM)	R^2 value
(3.02)	9.85	0.522
(3.31)	4.35	0.958
(3.32)	1.05	0.923
(3.44)	2.1	0.817
(3.46)	1.1	0.958
(3.48)	Inactive	-
(3.50)	Inactive	-
(3.51)	Inactive	-
(3.53)	2.76	0.990
(3.56)	1.72	0.958
(3.59)	Inactive	-
Combretastatin A-4	1.45	0.999

Table 3.7. Tubulin binding data obtained for C-7 modified compounds.

CHAPTER 4

4.0 Introduction

As the trimethoxy substituent on the A-ring of the compounds described in chapter 2 and 3 appears to be a necessary component for inhibition of tubulin polymerisation, it was decided to investigate the effect on tubulin binding activity of altering the positioning of one of these methoxy substituents. As illustrated in Figure 4.1, the methoxy substituent originally placed on carbon-4 of the previous compounds synthesised, has been relocated to carbon-1 within this new molecular structure.



Structural features include:

1. Hindered trimethoxybenzene A-ring

2. Aliphatic B-ring

3. C-7 substituent represented as X= H, -OH or =O

4. Absence or presence of the double bond

5. Substituents on R_1 and/or R_2

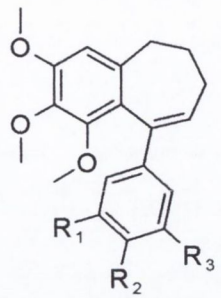
Figure 4.1. Generalised structure of compounds synthesised in this chapter.

It was anticipated that the C-1 methoxy group may play a role in controlling the spatial orientation of the C-ring in a way similar to the C-1 methoxy group of colchicine[179] **(1.01)** and in doing so place the second aromatic unit into a position suitable for efficient binding at the C.B.S. on tubulin. In addition to manipulating the A-ring, it was believed that B-ring substituents would, as in the series of compounds described in chapter 3, have a significant role in determining the ultimate conformation of the two-aryl units. Therefore, in the design strategy, a series of compounds should be synthesised with substituents on the C-7 position of this new molecular structure.

The compounds discussed in this chapter have been conveniently allotted into three groups.

Group 1

In this group of compounds, the synthesis of a series of novel biaryl compounds is discussed having as their key feature, the presence of the double bond to confer rigidity on the overall structure (Figure 4.2).

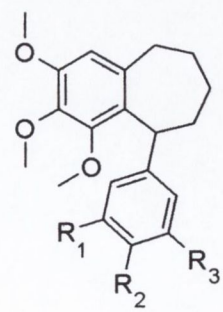


R_1, R_2, R_3 = small electron-donating groups

Figure 4.2. Generalised structure of Group 1 compounds.

Group 2

In this series of potential tubulin inhibitors the compounds discussed are those in which the double bond of the molecules described in the first group has been reduced (Figure 4.3). The concept behind this strategy was that if those compounds in Group 1 failed to inhibit tubulin polymerisation, then these less rigid molecules might be able to adopt an optimal conformation necessary for binding to tubulin. B-ring-contracted analogues of the type illustrated in Figure 4.3 have been have been previously synthesised[180, 181]. These compounds, depending on the nature of the substituents on the A- and C-rings displayed similar activity to the natural products, colchicine and podophyllotoxin.

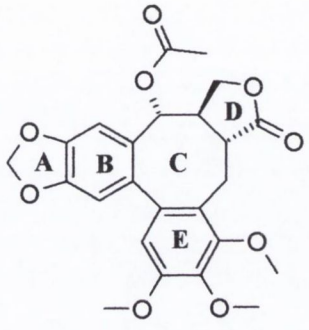


R_1, R_2, R_3 = small electron-donating groups

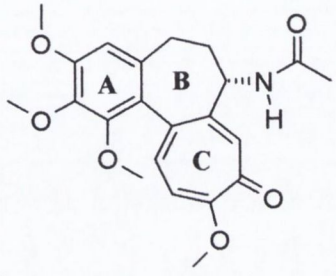
Figure 4.3. Generalised structure of Group 2 compounds.

Group 3

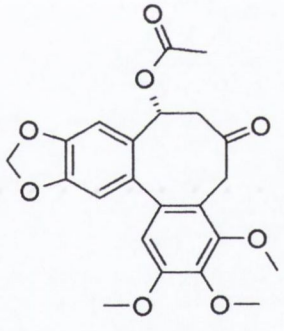
The third group of compounds discussed in this chapter were synthesised on the premise that with steganacin and colchicine, the replacement of the lactone and acetamido- functionalities with a carbonyl moiety (Figure 4.4) resulted in derivatives with greater potency[182, 51].



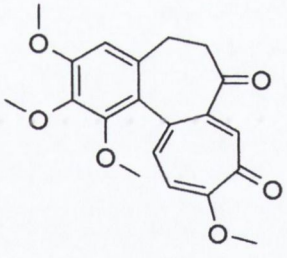
Steganacin



Colchicine



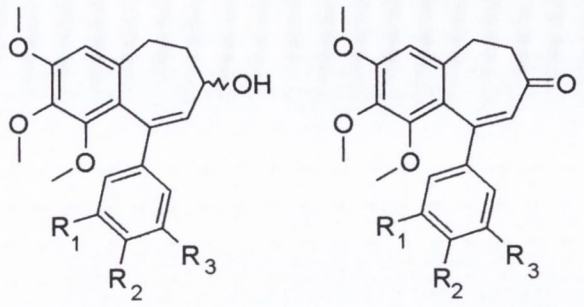
Steganone



Colchicone

Figure 4.4. Derivatives of C.B.S agents.

It was also evident from the tubulin binding data obtained for compounds described in Chapter 3 that oxofunctionalization of carbon-7 increased activity against tubulin polymerisation. It was felt, therefore, that insertion of a carbonyl group or hydroxyl group at the C-7 position on the B-ring might also produce compounds with similar potency (Figure 4.5).



R_1, R_2, R_3 = small electron donating groups

Figure 4.5. Generalised structures of compounds in Group 3.

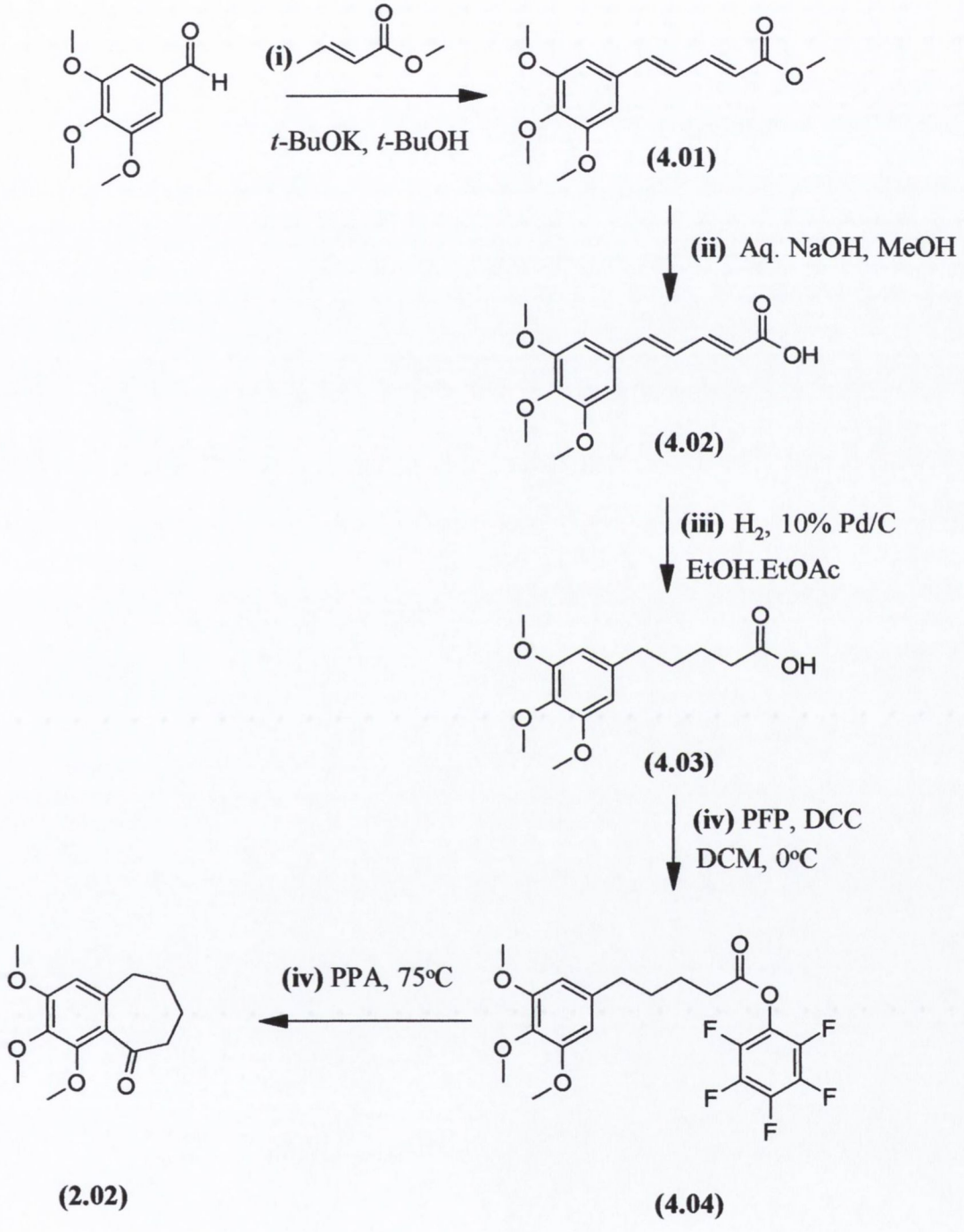
4.1 Synthesis of compounds in Group 1

4.1.1 Synthesis of 2,3,4-trimethoxy-6,7,8.9-tetrahydro-5*H*-benzo-[a]cyclohepten-5-one (2.02)

The design strategy involved the formation of the key intermediate 2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **(2.02)**. The synthetic method employed in the preparation of this molecule was identical to that used in making 1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one **(2.01)**.

Synthesis of **(2.02)** began with the aldol condensation reaction of methyl crotonate with 3,4,5-trimethoxybenzaldehyde using potassium *tert*-butoxide as base in *tert*-butanol. This reaction afforded the conjugated methyl ester **(4.01)** as two geometric isomers (*cis*- and *trans*-) in 83% yield, which was hydrolysed directly to the pentenoic acid **(4.02)**. This step was accomplished in 3 hours by refluxing the ester **(4.01)** in a methanolic solution of 10% aq. NaOH. The acid **(4.02)** was then dissolved in ethanol/ethyl acetate (1:1 mixture) and subjected to catalytic hydrogenation for one week using 10% Pd/C as catalyst. Isolation of the reduced acid **(4.03)** was followed by formation of its pentafluorophenyl ester **(4.04)** using DCC and PFP. Treatment of this ester with polyphosphoric acid at 75°C resulted in its efficient cyclisation to the ketone **(2.02)** (Scheme 4.1). After isolation, purification by flash column chromatography and

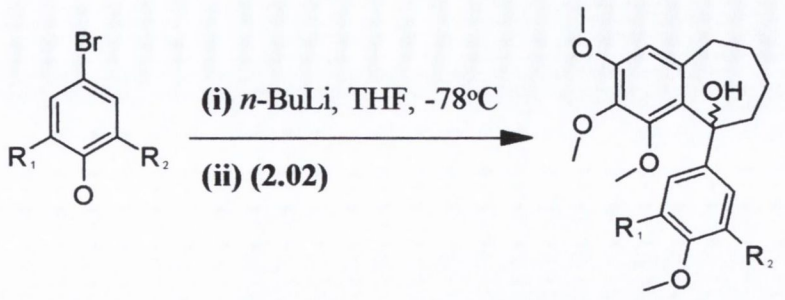
recystallisation from hot methanol, **(2.02)** was afforded as a white crystalline compound in an overall yield of 58%.



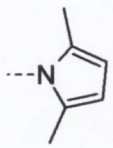
Scheme 4.1.

4.1.2 Arylation of (2.02)

Preparation of the biaryl analogues involved the initial synthesis of a series of aryl bromide derivatives that were then utilised as substrates for the coupling reaction to trimethoxybenzosuberone **(2.02)**. These synthetic precursors included the aryl bromides **(2.50)**, **(2.55)** and **(2.63)**, *para*-bromoanisole and *meta*-bromoanisole. The latter two bromides were commercially available as Grignard reagents and so were used directly as described in section 2.7.1 to form compounds **(4.06)** and **(4.07)** respectively. The bromides **(2.50)**, **(2.55)** and **(2.63)** were lithiated *via* metal-halogen exchange using 2.5M *n*-BuLi and coupled to **(2.02)** using the methodology described in section 2.8.2 to afford compounds **(4.08)**, **(4.10)** and **(4.12)**. After isolation and purification by flash column chromatography, the protecting groups attached to these compounds was subsequently removed using the appropriate deprotecting reagent (Table 4.1) to afford compounds **(4.09)**, **(4.11)** and **(4.13)**, Scheme 4.2.



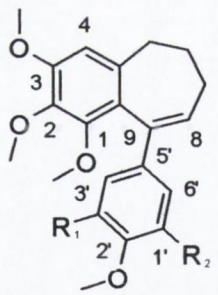
R_1 = H, R_2 = O-*t*BDMS **(4.08)**

R_1 = H, R_2 =  **(4.10)**

R_1 = O-*t*BDMS, R_2 = O-*t*BDMS **(4.12)**

(iii) H^+

(iv) Deprotection



R_1 = H, R_2 = OH **(4.09)**

R_1 = H, R_2 = NH_2 **(4.11)**

R_1 = OH, R_2 = OH **(4.13)**

Scheme 4.2.

Intermediate	Deprotecting agent	Product	% Yield
(4.08)	TBAF	**(4.09)**	99
(4.10)	$NH_2OH.HCl$	**(4.11)**	37
(4.12)	TBAF	**(4.13)**	42

Table 4.1. Illustrating the deprotecting reagent used for its corresponding intermediate.

In the ^1H NMR spectrum of **(4.09)**, the three multiplets for each of the methylene groups resonated at 1.95 ppm, 2.08 ppm and 2.55 ppm and were similar to the chemical shift values of the B-ring protons on its less-hindered isomer **(2.52)**. The methyl protons of the methoxy substituents resonated as sharp singlets at 3.44 ppm, 3.82 ppm, 3.89 ppm and 3.92 ppm. In comparison to **(2.52)**, these methoxy group signals were similar except for the methoxy peak at 3.44 ppm, which was shifted upfield from 3.70 ppm. As the only difference between these two molecules was the positioning of the methoxy substituents, the signal at 3.44 ppm was assigned as the relocated C-1 methoxy group. As expected, the phenolic proton was identified as a broad singlet at 5.52 ppm. The alkenyl H-8 proton was characteristically identified resonating at 6.35 ppm. The aromatic A-ring proton was shifted slightly downfield to 6.61 ppm when compared to the A-ring proton of **(2.52)**, which resonated at 6.40 ppm. The C-ring of **(4.09)** clearly showed that its protons; H-3', H-4' and H-6' existed as an ABX system. The doublet (J = 2Hz) at 6.87 ppm was identified as the H-6' proton as it displayed weak *meta*-coupling to H-4' (6.70 ppm). The H-3' proton resonated as a doublet (J = 8Hz) at 6.76 ppm due to *ortho*-coupling to H-4', with the H-4' proton resonating as double-doublet (J = 8Hz, 2Hz) at 6.70 ppm as a result of *ortho*- and *meta*-coupling to H-3' and H-6' respectively.

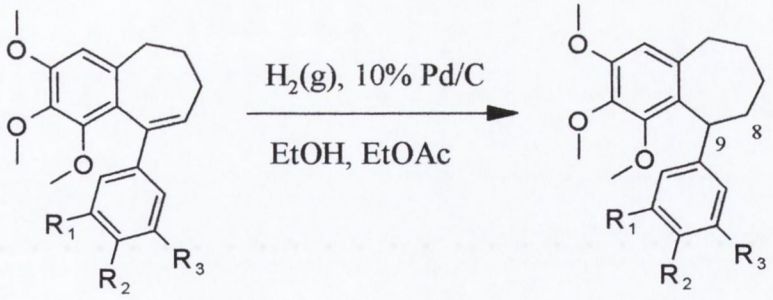
The ^{13}C NMR spectrum of **(4.09)** identified the three-methylene carbons resonating at 24.50 ppm, 31.81 ppm and 33.95 ppm. The four-methoxy carbons were recorded as three signals resonating at 55.51 ppm, 59.67 ppm (2 x OCH_3) and 60.35 ppm. The five-methine carbons resonated at 106.81 ppm, 109.78 ppm, 112.03 ppm, 117.34 ppm and 127.55 ppm, while the alkenyl and aromatic quaternary carbons resonated between 125.17 to 152.11 ppm.

As expected the ^{1}H NMR spectrum of **(4.11)** resembled that of **(4.09)**. A similar ABX pattern also existed for the C-ring protons of **(4.11)**, although, changing the C-1' substituent from the hydroxy to an amino-group resulted in the chemical shift of H-6' being moved slightly upfield from 6.87 ppm in **(4.09)** to 6.63 ppm.

As predicted from its structure, these splitting patterns disappeared for the C-ring protons of **(4.13)** as in this compound the H-3' proton is replaced by a hydroxy group resulting in a symmetrical aryl ring and thus, causing H-6' and H-4' protons to resonate together at 6.40 ppm. The two-phenolic protons were also identified, resonating together as a broad singlet at 5.35 ppm.

4.2 Formation of compounds in Group 2

This section of work describes the method used to reduce the double bond of those compounds in Group 1. Each compound, **(4.06)**, **(4.07)**, **(4.09)** and **(4.13)**, was dissolved in ethanol/ethyl acetate and hydrogenated using 10% Pd/C as catalyst, under a hydrogen atmosphere to afford the saturated analogues **(4.14)**, **(4.15)**, **(4.16)** and **(4.17)** in quantitative yields following purification by flash column chromatography (scheme 4.4).



$R_1 = H, R_2 = OCH_3, R_3 = H$ **(4.06)**

$R_1 = H, R_2 = H, R_3 = OCH_3$ **(4.07)**

$R_1 = H, R_2 = OCH_3, R_3 = OH$ **(4.09)**

$R_1 = OH, R_2 = OCH_3, R_3 = O$ **(4.13)**

$R_1 = H, R_2 = OCH_3, R_3 = H$ **(4.14)**

$R_1 = H, R_2 = H, R_3 = OCH_3$ **(4.15)**

$R_1 = H, R_2 = OCH_3, R_3 = OH$ **(4.16)**

$R_1 = OH, R_2 = OCH_3, R_3 = OH$ **(4.17)**

Scheme 4.3.

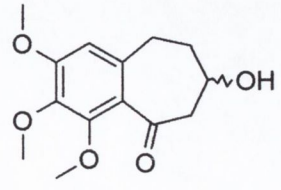
In the ^{1}H NMR spectrum of **(4.14)**, the absence of the alkenyl H-8 proton signal (6.35 ppm) confirmed the successful reduction of the double bond in addition to the appearance of the H-9 proton as a multiplet resonating at 4.94 ppm. Possibly as a result of the increased flexibility in the B-ring, the C-8 methylene protons could not be readily distinguished in the ^{1}H NMR spectrum, however, the DEPT 135 spectrum readily identified C-8 as a signal resonating at 27.52 ppm.

^{1}H NMR analysis of **(4.15)** also revealed the presence of a multiplet at 4.96 ppm, which was indicative of the H-9 proton along with its corresponding carbon signal found resonating at 39.16 ppm in the ^{13}C NMR. The presence of the C-8 methylene group was also identified in the ^{13}C NMR spectrum resonating at 27.42 ppm.

The successful synthesis of compounds **(4.16)** and **(4.17)** were readily identified by the presence of the methine H-9 signal at 4.87 ppm for **(4.16)** and 4.84 ppm for **(4.17)**. While, the C-9 carbon signals resonated at 38.60ppm and 38.73 ppm respectively. Additional confirmation of the successful synthesis of both compounds was made by the noted absence of the alkenyl H-8 proton.

4.3 Formation of compounds in Group 3

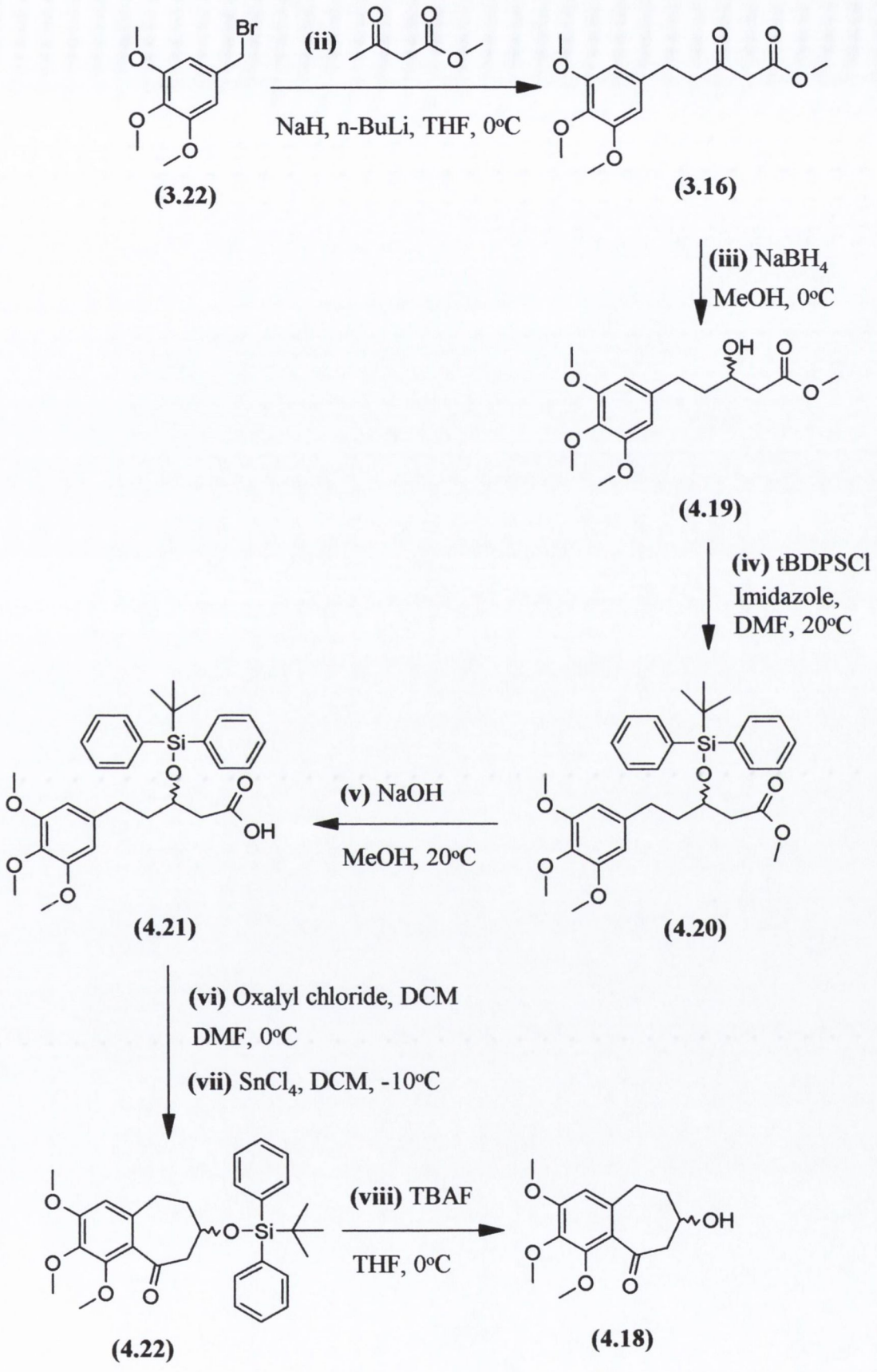
The construction of the C-7 oxygenated biaryl compounds discussed in this group required the initial synthesis of the keto alcohol **(4.18)**. The synthetic route employed in the preparation of this compound is outlined in Scheme 3.10 and involved similar methodology to that used for the preparation of its isomer 3.39. Two key steps were involved, namely; (i) the reaction of methyl acetoacetate to 3,4,5-trimethoxybenzyl bromide, and (ii) the cyclisation step, requiring the use of $SnCl_4$.



(4.18)

4.3.1 Synthesis of 7-hydroxy-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (4.18)

Thus, bromination of 3,4,5-trimethoxybenzyl alcohol **(3.21)** with PBr_3 was followed by the nucleophillic addition of the dianion of methyl acetoacetate to the resulting benzylic bromide **(3.22)** to afford methyl 3-oxo-5-(3,4,5-trimethoxyphenyl)pentanoate **(3.16)**. Careful reduction of the ketonic functionality of **(3.16)** with $NaBH_4$ resulted in the formation of the β-hydroxy-ester **(4.19)**, which was subsequently protected as a *tert*-butyldiphenylsilyl ether **(4.20)**. After alkaline hydrolysis of the methyl ester, the resulting acid **(4.21)** was obtained as a clear oil. Treatment of this acid with oxalyl chloride produced the acid chloride, which was not isolated but immediately subjected to $SnCl_4$ under anhydrous conditions. This resulted in the efficient formation of the intramolecular acylated product **(4.22)**, which after treatment with TBAF in THF afforded **(4.18)** in an overall yield of 11% (Scheme 4.4).


(ii)
NaH, n-BuLi, THF, 0°C
(3.22)
(3.16)
(iii) NaBH4
MeOH, 0°C
(4.19)
(iv) tBDPSCl
Imidazole,
DMF, 20°C
(v) NaOH
MeOH, 20°C
(4.21)
(4.20)
(vi) Oxalyl chloride, DCM
DMF, 0°C
(vii) SnCl4, DCM, -10°C
(viii) TBAF
THF, 0°C
(4.22)
(4.18)

Scheme 4.4.

The IR spectrum of **(4.18)**, displayed a broad peak at 3444.0 cm^{-1},which was attributed to the C-7 hydroxyl group and a sharp peak observed at 1673.6 cm^{-1} was assigned to the benzylic carbonyl group.

In the ^1H NMR spectrum of **(4.18)**, the aliphatic B-ring protons appeared as a complex collection of multiplets resonating between 1.88-3.55 ppm. ^1H-^1H COSY (Figure 4.6) and HMQC experiments (Figure 4.7) revealed that each proton on the aliphatic B-ring existed in its own unique chemical and magnetic environment. This could only occur if this molecule was prevented from occupying different conformations. The assignment of each set of methylene protons was made possible by inspection of the HMQC spectrum. From this two-dimensional spectrum, it was observed that the protons resonating at 1.92 ppm and 2.18 ppm were attached to the same carbon, which resonated at 35.17 ppm. The protons resonating at 2.65 ppm and 2.97 ppm correlated to the carbon signal at 29.79 ppm, while the multiplets at 2.89 ppm and 3.02 ppm correlated to the methylene carbon resonating at 52.30 ppm. From the ^1H-^1H COSY spectrum, the H-7 proton resonating at 4.20 ppm coupled to the protons resonating at 2.89 ppm and 3.02 ppm and these were assigned as the methylene H-6 protons, on the basis that they did not couple to any of the other aliphatic protons. The protons that resonated at 1.92 ppm/2.18 ppm and 2.65 ppm/2.97 ppm were assigned as the methylene H-9 and H-8 protons respectively. The singlets at 3.85 ppm and 3.88 ppm integrated for three and six protons respectively and were assigned as the three-methoxy group protons. The aromatic proton typically resonated as a singlet at 6.47 ppm.

The assignment of the carbon skeleton of this molecule was achieved by analysis of its HMQC spectrum. As stated previously, the methylene carbons, C-6, C-8 and C-9, resonated at 52.30 ppm, 35.17 ppm and 29.79 ppm respectively. The methoxy-group carbons resonated at 55.95 ppm, 60.81 ppm and 62.31 ppm. The signal at 68.07 ppm was attributable to C-7, while the C-1 carbon resonated at 108.44 ppm. The five aromatic quaternary carbons of **(4.18)** were all identified resonating between 127.98 ppm and 154.04 ppm. The existence of the carbonyl carbon was confirmed by the downfield signal at 200.64 ppm.

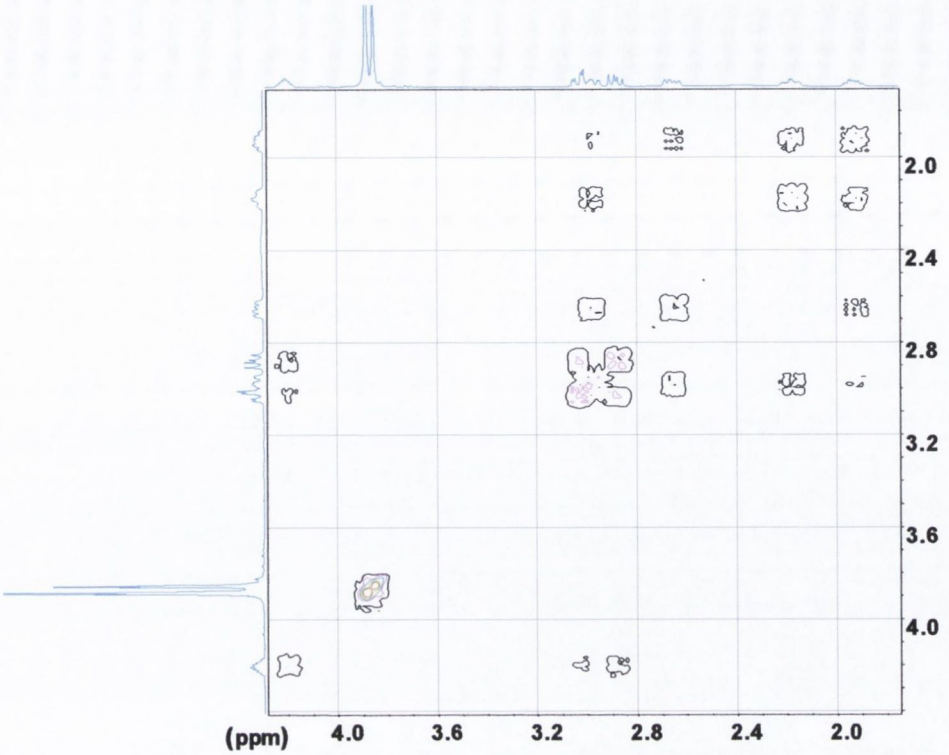


Figure 4.6. ^{1}H-^{1}H COSY spectrum of **(4.18)**.

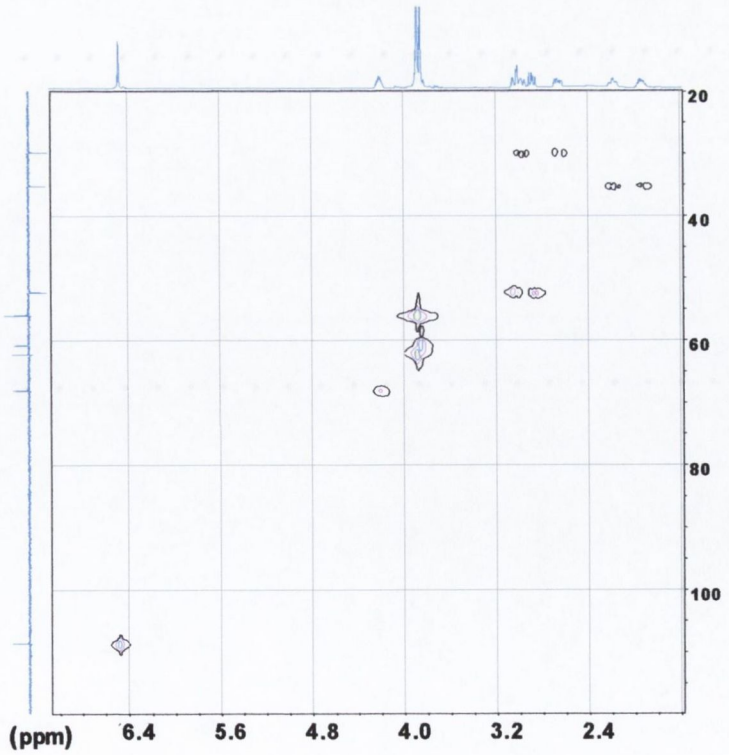
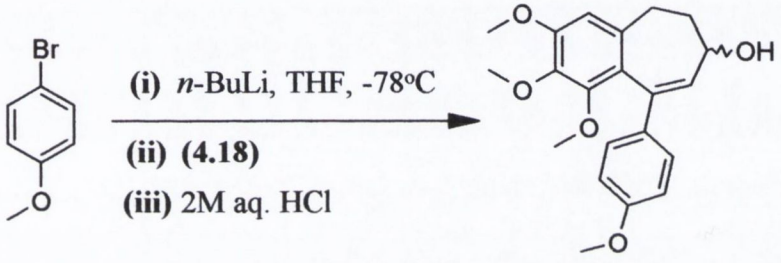


Figure 4.7. HMQC spectrum of **(4.18)**.

4.3.2. Synthesis of 1,2,3-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (4.23)

Arylation at the ketonic centre of **(4.18)**, was effected by the addition of three molar equivalents of the organolithium derivative of *para*-bromoanisole to (4.24) in THF at – 78°C. After 30 minutes the temperature was allowed to reach room temperature, before the addition of 2M aq. HCl, necessary to dehydrate the resulting coupled compound. After isolation and subsequent purification by flash column chromatography, the product **(4.23)** was isolated as a white solid in 83% yield (Scheme 4.5).



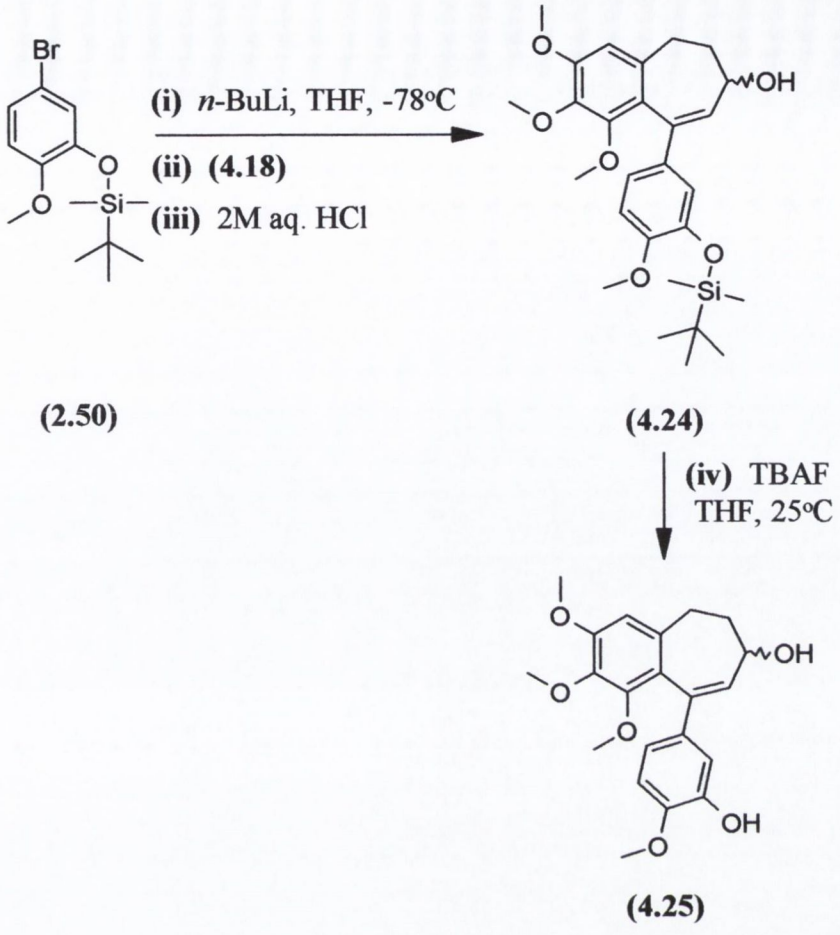
(4.23)

Scheme 4.5.

In the IR spectrum of **(4.23)**, the broad peak at 3422.4 cm^{-1} is indicative of hydroxy functionality. In the ^{1}H NMR spectrum of **(4.23)**, notable features included a multiplet resonating at 6.20 ppm attributed to the alkenyl H-8 proton and a singlet at 6.77 ppm, which was identified as the lone aromatic proton at C-4. The corresponding carbon signals for C-8 and C-4 were recorded in the ^{13}C NMR spectrum at 131.47 ppm and 107.05 ppm respectively.

4.3.3 Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (4.25)

Using the same methodology described for the synthesis of **(4.23)**, the allylic alcohol **(4.24)** was prepared. Removal of the silyl-protecting group was achieved through the use of TBAF in THF to afford **(4.25)** in an overall yield of 74% from **(4.23)** (Scheme 4.6).

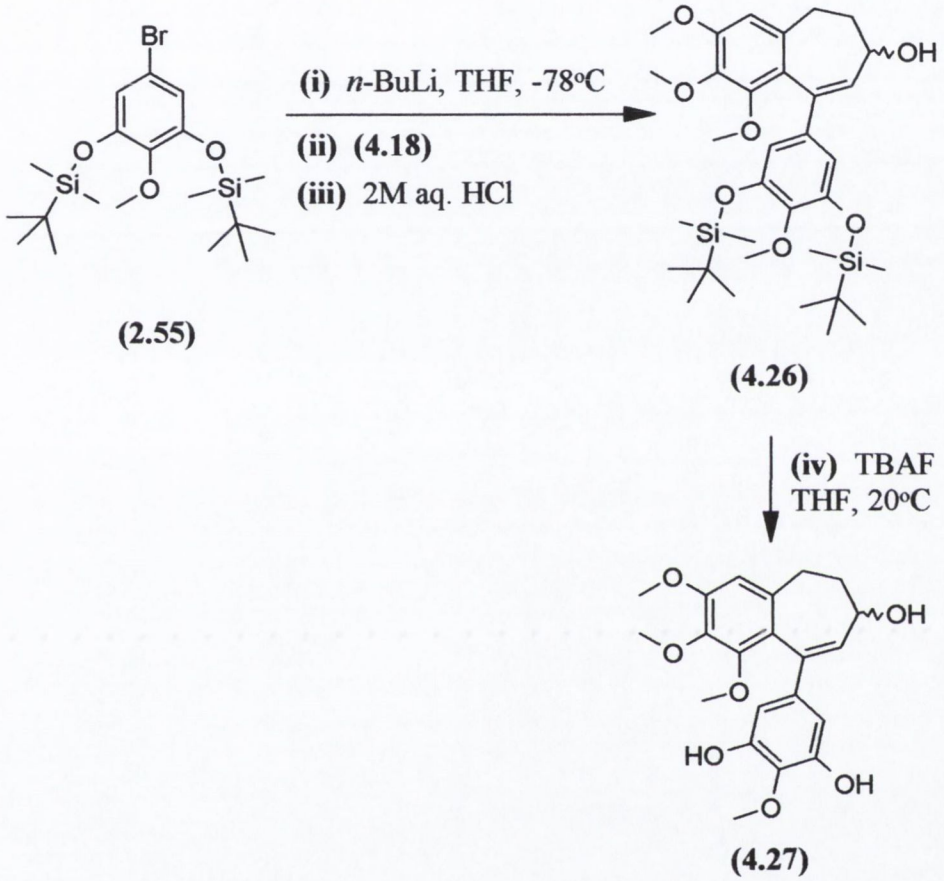


Scheme 4.6.

The ^{1}H NMR spectrum of **(4.25)** was similar to that of **(4.23)**. The only difference between the two compounds was the additional hydroxy substituent on the C-ring of **(4.25)**. The aromatic region of the ^{1}H NMR spectrum revealed signals at 6.67 ppm, 6.74 ppm and 6.81 ppm, which were attributable to the C-ring protons. The ^{13}C NMR spectrum supported the assigned structure, with the aforementioned C-ring methine signals resonating at 110.62 ppm, 112.67 ppm and 116.91 ppm.

4.3.4 Synthesis of 5-(7-hydroxy-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-2-methoxy-1,3-benzenediol (4.27)

The trihydroxy compound **(4.27)** was synthesised using the methodology described for the preparation of **(4.25)** (Scheme 4.7).



(2.55) **(4.26)** **(4.27)**

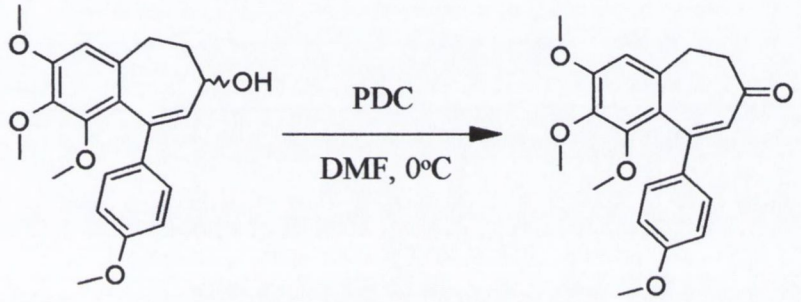
Scheme 4.7.

In the IR spectrum of **(4.27)**, the hydroxyl functionality was noted as a broad peak, at 3409.7 cm^{-1}. The ^1H NMR spectrum identified the aromatic C-ring protons resonating as a singlet at 6.39 ppm, while the alkenyl H-8 proton was characteristically found at 6.26 ppm.

4.4 Oxidation of the C-7 hydroxyl group to the ketone

4.4.1 Synthesis of 1,2,3-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (4.28)

The enone **(4.28)**, following oxidation of the parent enol **(4.23)** with PDC, was isolated as a white solid in 68% yield (Scheme 4.8).



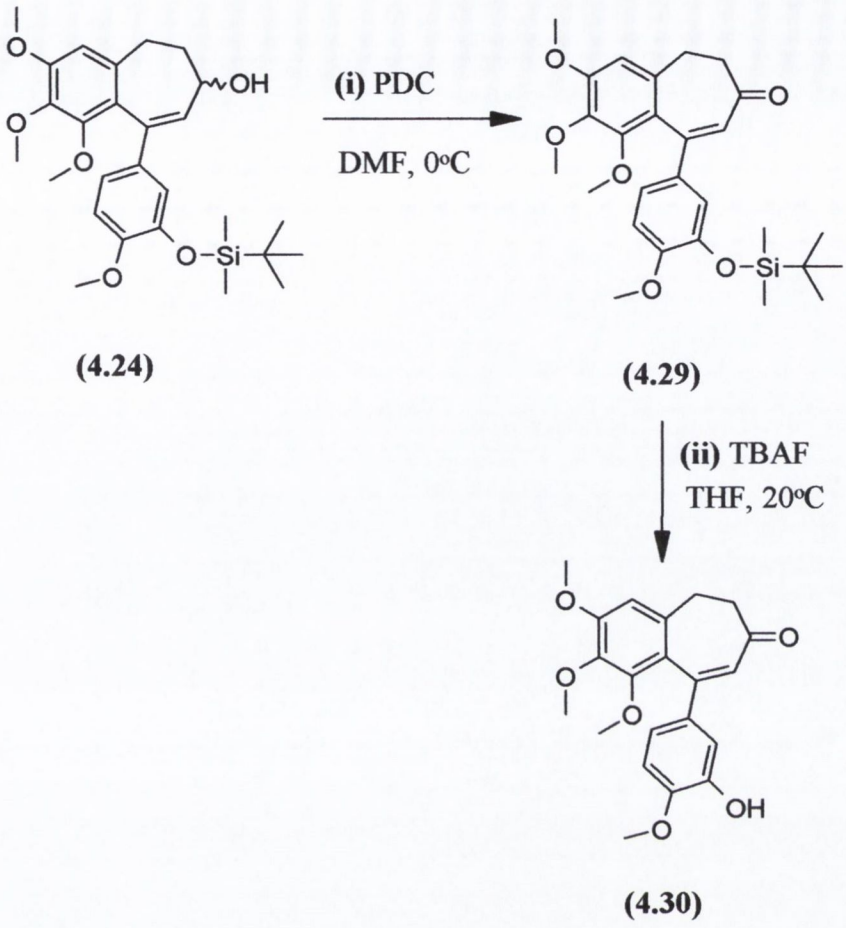
(4.23) **(4.28)**

Scheme 4.8.

Analysis of the IR spectrum of **(4.28)** revealed the presence of a sharp peak at 1659.8 cm^{-1}. This was indicative of the α,β-unsaturated ketone in the molecule. In the ^{1}H NMR spectrum, the disappearance of a methine signal at 4.06ppm was noted, while the ^{13}C NMR spectrum confirmed the presence of a keto-group resonating at 205.62 ppm.

4.4.2 Synthesis of 1,2,3-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (4.30)

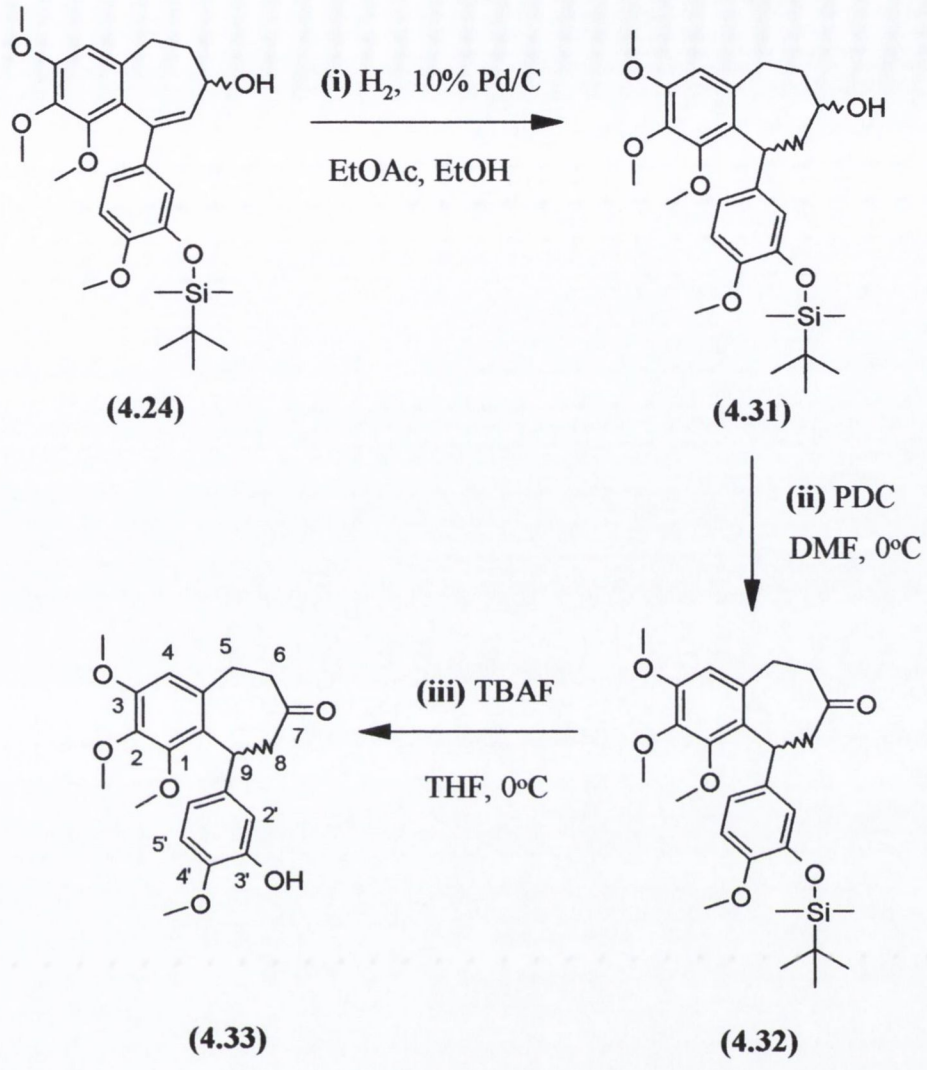
This oxidative transformation step was carried out in accordance with the method described for the synthesis of **(4.28)**. The silyl-protected intermediate **(4.29)** was dissolved in THF at 0°C and deprotected using 1M TBAF. After purification by flash column chromatography, **(4.30)**, was isolated as a white solid in 50% yield (Scheme 4.9).



Scheme 4.9.

4.4.3 Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-one (4.33)

To prepare the ketone **(4.33)**, the enol **(4.23)** was conveniently reduced using 10% Pd/C under hydrogen, to the alcohol **(4.31)**. Treatment of the alcohol with PDC in DMF led to the formation of the ketone **(4.32)**. The identity of this ketone was confirmed through IR analysis. The absence of a broad hydroxyl peak at ~ 3400 cm^{-1} and the presence of the carbonyl-stretching peak at 1701.6 cm^{-1} indicated that this reaction step was successful. The targeted compound **(4.33)** was afforded in 99% yield after treatment of **(4.32)** with 1M TBAF in THF (Scheme 4.10).



Scheme 4.10.

^{1}H NMR spectrum of **(4.33)** revealed four multiplet peaks in the aliphatic region of the spectrum. From the HMQC spectrum, it was observed that the H-8 protons resonated as two separate double doublets with one H-8 proton resonating at 2.87 ppm and the other at 3.37 ppm. From the ^{1}H-^{1}H COSY, these multiplets coupled to a coalesced double doublet (J = 6Hz) resonating at 4.95 ppm. This signal was assigned as the H-9 proton. From the HMQC spectrum, two separate multiplets resonated at 2.63 ppm and 2.94 ppm. These were found to correlate to a methylene carbon and as a result, were assigned as the H-5 protons. The two remaining multiplets at 2.46 ppm and 2.67 ppm coupled to the two H-5 multiplets in the ^{1}H-^{1}H COSY and were assigned as the H-6 protons. The methyl protons of the methoxy substituents resonated as sharp singlets at 3.69 ppm, 3.86 ppm, 3.88 ppm, and 3.89 ppm. The phenolic proton was

characteristically recognized as a broad singlet resonating at 5.53 ppm. The aromatic hydrogen at H-4 resonated as a singlet at 6.53 ppm. The C-ring H-2' proton was identified as a doublet (J = 2.0Hz) resonating at 6.62 ppm. Presumably, this resulted from a weak meta-coupling to the H-6' proton. The H-6' proton resonated as double-doublet (J = 8.5Hz, 2.0Hz) at 6.67 ppm as a result of *ortho*- and *meta*-coupling from H-5' and H-2' respectively. The remaining aromatic H-5' proton was observed as a doublet (J = 8.5Hz) at 6.76 ppm.

^{13}C NMR analysis of compound **(4.33)** revealed three methylene carbon signals resonating at 29.67 ppm, 43.85 ppm, and 47.55 ppm from the DEPT 135 spectrum. From the HMQC spectrum, these were found to correlate to H-5, H-6, and H-8 respectively and as such, were assigned as C-5, C-6 and C-8. The C-9 carbon was observed as at 37.04 ppm in the DEPT 90. The methoxy carbons resonated at 55.46 ppm, 55.50 ppm, 60.26 ppm, and 60.60 ppm. From the DEPT 90, four-aromatic CH carbons were observed at 109.01 ppm, 110.07 ppm, 112.98 ppm, and 118.02 ppm. These were subsequently assigned as C-4, C-2', C-6' and C-5' respectively as these signals were found to correlate to their respective proton signals in the HMQC spectrum. Seven quaternary carbon signals were identified in the region between 126.98 ppm and 151.79 ppm. The presence of the C-7 carbonyl group was confirmed by the presence of a signal resonating at 210.47 ppm.

4.5 Tubulin binding data

Rotation of the trimethoxy-substituent from the 2,3,4-position to the more hindered 1,2,3-position on the A-ring was synthetically investigated and the effects on tubulin polymerisation of fifteen novel compounds were evaluated[149]. The results are summarized in Table 4.2.

Compound	ITP IC_{50} (μM)	R^2 Value
(4.06)	Inactive	-
(4.07)	Inactive	-
(4.09)	Inactive	-
(4.11)	Inactive	-
(4.13)	Inactive	-
(4.14)	Inactive	-
(4.15)	Inactive	-
(4.16)	> 93	-
(4.17)	Inactive	-
(4.23)	Inactive	-
(4.25)	Inactive	-
(4.27)	Inactive	-
(4.28)	Inactive	-
(4.30)	Inactive	-
(4.33)	Inactive	-
Combretastatin A-4	1.45	0.999

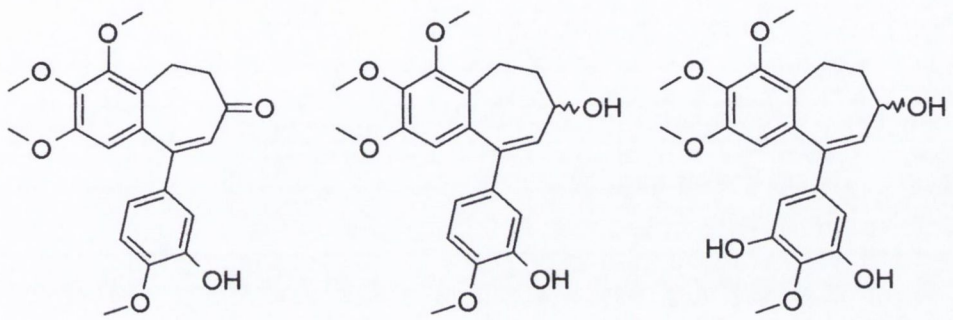
Table 4.2. Inhibition of tubulin polymerisation data.

From Table 4.1, it is evident that relocating the methoxy substituent from C-4 to C-1 results in a total loss of activity against tubulin polymerisation. Only compound **(4.16)** displayed very weak activity against tubulin polymerisation (IC_{50} >93 μM). On the basis of these disappointing results, it was decided to place further emphasis on modifying the B-ring in an attempt to create compounds with greater potency.

CHAPTER 5

5.0 Introduction

It was postulated that the potent tubulin binding activity of compounds **(3.32)** and **(3.46)** and the inactive compound **(3.48)** may be enhanced by isosteric atom replacement at the benzylic methylene group with an oxygen atom (Figure 5.1).



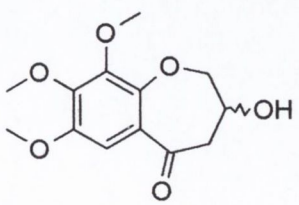
(3.32) **(3.46)** **(3.48)**

Figure 5.1. Potent tubulin inhibitors **(3.32)** and **(3.46)** and the inactive compound **(3.48)**.

Also as SAR studies on colchicine[36, 183] have shown that the hydrophobic, electron rich A-ring is essential for binding, therefore, the isosteric replacement of the benzylic methylene group with an oxygen atom would permit greater electronic density within the A-ring without adding additional bulk to the molecule.

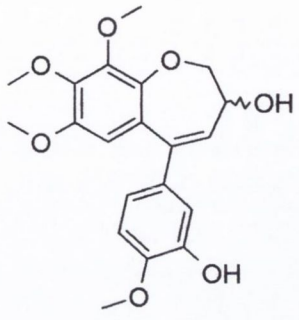
5.1 Synthetic strategy

The formation of the targeted phenyl-substituted benzoxepinols and benzoxepinones relied upon the viable preparation of the key intermediate, 3-hydroxy-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1-benzoxepin-5-one **(5.01)**.

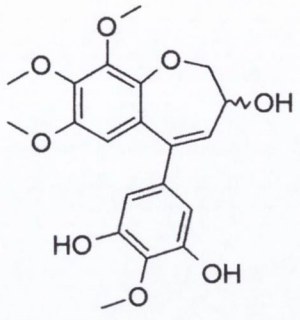


(5.01)

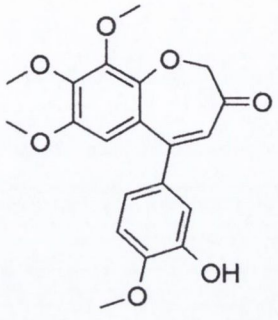
Once synthesized, the respective aryl units were attached to **(5.01)** *via* an organometallic reaction to afford two α,β-unsaturated alcohols **(5.02)**, **(5.03)**, and after allylic oxidation, one enone **(5.04)** (Figure 5.2).



(5.02)



(5.03)

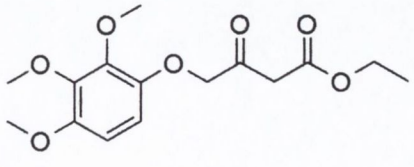


(5.04)

Figure 5.2. Potential tubulin inhibitors modified in B-ring.

5.2 Synthesis of 3-hydroxy-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1-benzoxepin-5-one (5.01)

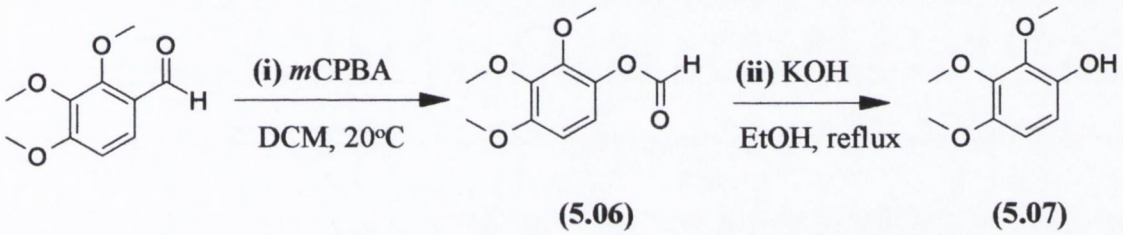
The formation of benzoxepinones is considered to be a difficult target in synthetic chemistry (see section 2.4). This difficulty is further compounded by the required presence of an oxygenated functionality *beta* to the ketonic centre. However, it was believed that this obstacle could be overcome by forming the key intermediate, ethyl-3-oxo-4-(2,3,4-trimethoxyphenoxy)butanoate **(5.05)**. Once synthesised, the keto-group could be selectively reduced to the alcohol and suitably protected. Formation of **(5.01)** would ensue by (i) hydrolysis of the ester to the acid, (ii) conversion to its corresponding acyl halide and (ii) cyclisation of the acyl halide under Friedel-Crafts conditions.



(5.05)

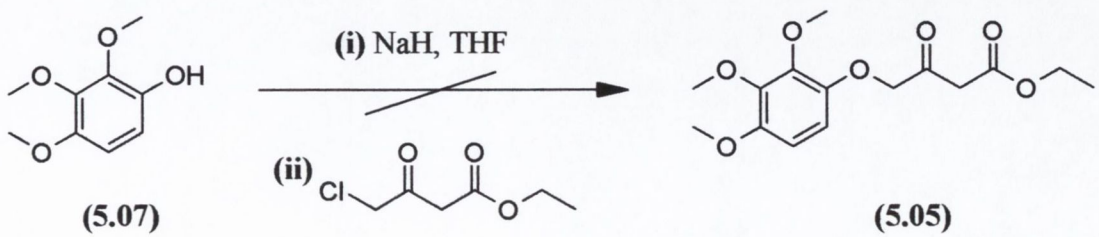
5.2.1 Attempted synthesis of ethyl 3-oxo-4-(2,3,4-trimethoxyphenoxy)butanoate (5.05)

It was anticipated that the synthesis of **(5.05)** could be achieved through the addition of trimethoxyphenol **(5.07)** to ethyl 4-chloro-3-oxobutanoate, using NaOH as base. The synthesis of 2,3,4-trimethoxyphenol[134] was accomplished *via* Baeyer-Villager oxidation of 2,3,4-trimethoxybenzaldehyde with *m*CPBA to afford the formate ester **(5.06)**. This ester was immediately hydrolysed *in situ* using methanolic NaOH to afford the phenol **(5.07)** as a white waxy solid in 79% yield, after purification by flash column chromatography (Scheme 5.1).



Scheme 5.1.

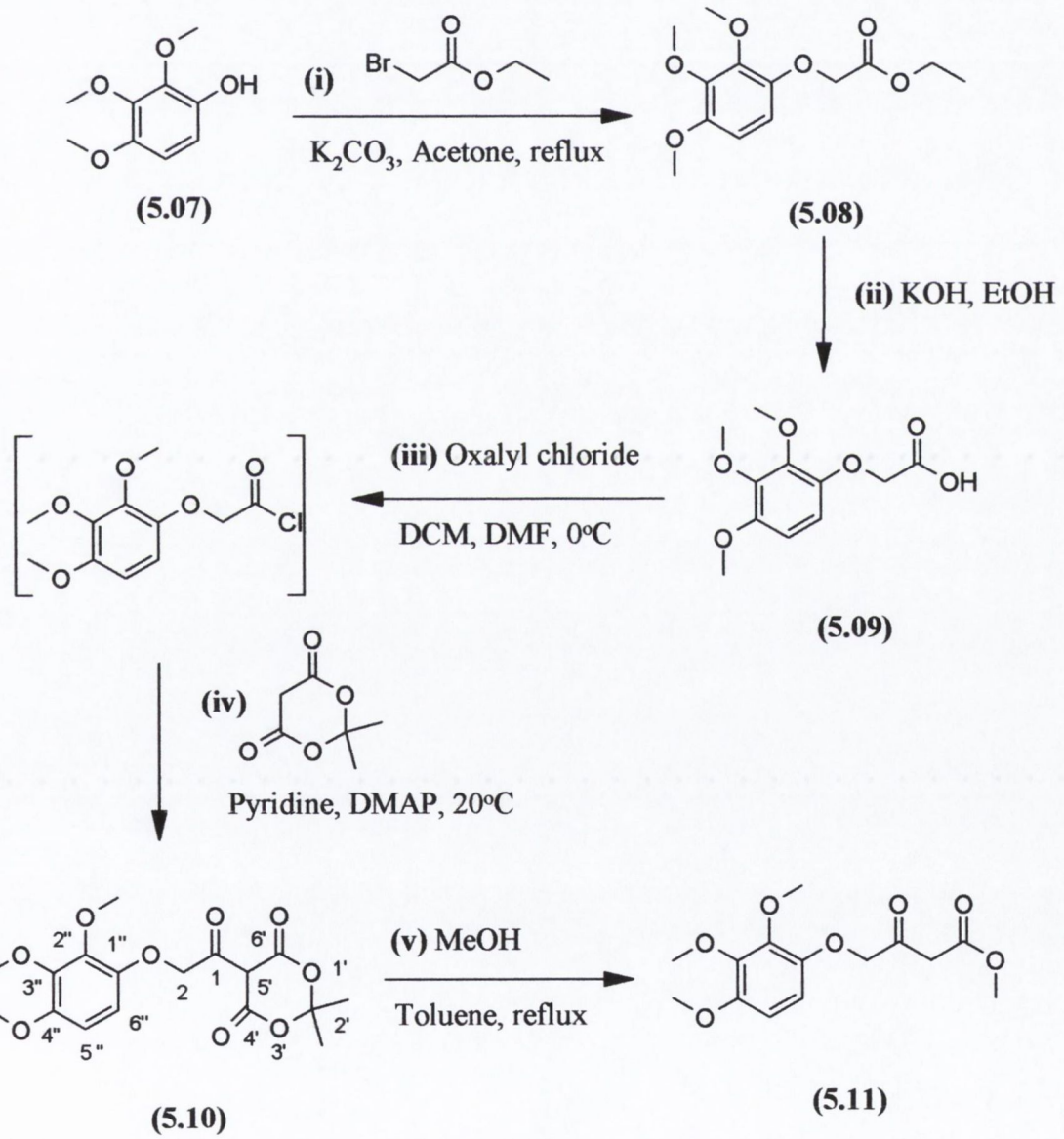
The phenol **(5.07)** was converted to its sodium phenoxide derivative and added to separate solutions of ethyl 4-chloro-3-oxobutanoate in DMSO and DMF as described by Kumazawa *et* al[184]. However, both these approaches failed to give the desired coupled compound **(5.05)**. The *in situ* formation of the phenoxide was also attempted by treating **(5.07)** with NaH followed by the addition of ethyl 4-chloro-3-oxobutanoate in anhydrous THF[185] (Scheme 5.2). However, as with the previous approaches, this method failed to produce any of the desired intermediate.



Scheme 5.2.

5.2.2 Preparation of (5.01) *via* the synthesis of methyl-3-oxo-4-(2,3,4-trimethoxyphenoxy)butanoate (5.11)

As all attempts to synthesise **(5.05)** failed, an alternative multi-step synthesis to **(5.01)** was devised. This synthesis involved the initial formation of ethyl 2-(2,3,4-trimethoxyphenoxy)acetic acid **(5.09)** with the subsequent addition of Meldrum's acid (2,2-dimethyl-1,3-dioxane-4,6-dione to it, followed by subsequent decarboxylation to afford **(5.11)** (Scheme 5.3).



Scheme 5.3.

The first step of the reaction was carried out through the addition of ethyl bromoacetate to a refluxing acetone solution of **(5.07)** in K_2CO_3[186]. This afforded the ester **(5.08)** as an oil which was subsequently hydrolysed by dissolving it in an ethanolic solution of 10% aq. NaOH to form the acid **(5.09)**. After drying the acid for several hours *in vacuo*, it was then converted to the acid chloride under the conditions described in section 3.6.1. The acid chloride in anhydrous DCM was then treated, without isolation, with Meldrum's acid and DMAP to afford 2,2-dimethyl-5-[2-(2,3,4-trimethoxyphenoxy)acetyl]-1,3-dioxane-4,6-dione[187] **(5.10)** in 62% yield after isolation and purification by flash column chromatography.

The ^{1}H NMR spectrum of **(5.10)** (Figure 5.3) revealed the two methyl groups resonating together as a singlet at 1.78 ppm. The characteristic singlets found at 3.84 ppm, 3.92 ppm and 3.96 ppm were assigned as the three-methoxy group substituents on the aromatic ring. A singlet integrating for two protons was observed resonating downfield at 5.46 ppm and was identified as the deshielded protons attached to C-2. The aromatic protons were observed as two-doublets (J = 7.0Hz) resonating at 6.57 and 6.65 ppm. Because of its acidic nature, the proton on C-5 was unaccounted for.

In the ^{13}C NMR spectrum of **(5.10)** (Figure 5.4), the two-methyl carbons resonated as a single peak at 26.90 ppm. The methoxy carbons were observed as three peaks resonating at 56.33 ppm, 60.17 ppm and 61.33 ppm. The resonance peak at 69.48 ppm was assigned as C-2 as this signal was present in the DEPT 135 spectrum. The aromatic C-5'' and C-6'' signals were observed at 106.49 and 109.92 ppm. A quaternary signal resonating at 105.98 ppm was assigned as C-2' whilst the remaining quaternary signals resonating at 145.92 ppm, 149.20 ppm, 159.91 ppm and 162.42 ppm were assigned as the aromatic carbons. The two-carboxyl groups, C-4' and C-6', resonated as a single peak at 169.91 ppm due to the two groups residing in similar chemical and magnetic environments, whilst the carbonyl group at C-1 resonated at 192.13 ppm.

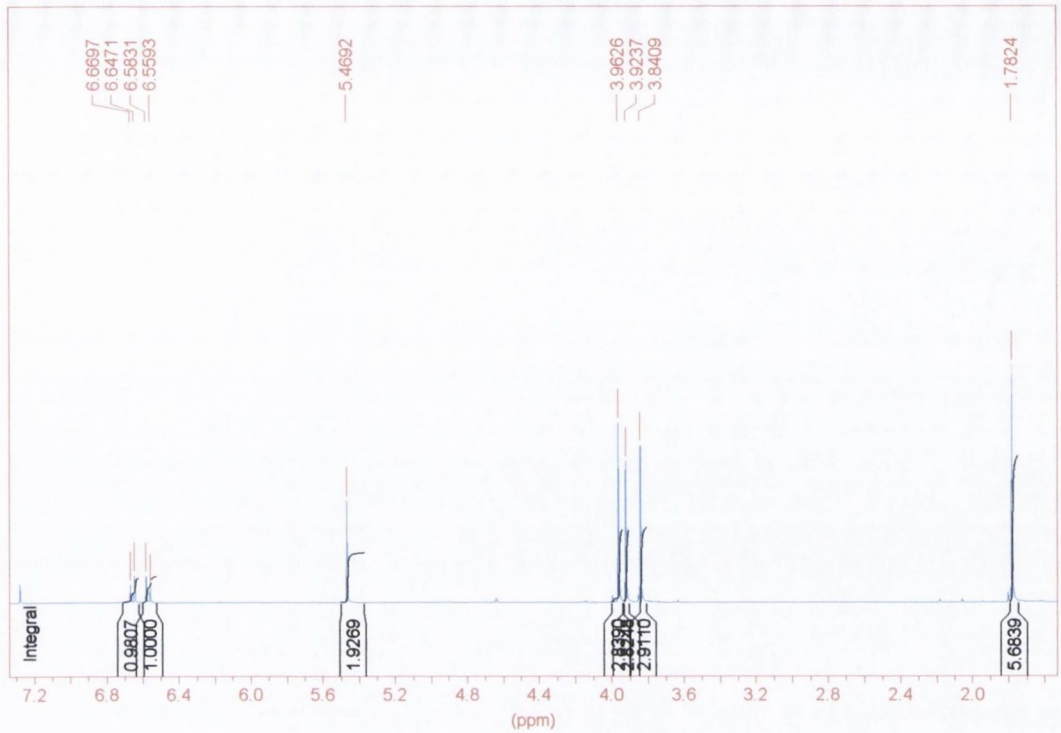


Figure 5.3. ^{1}H NMR spectrum of **(5.10)**.

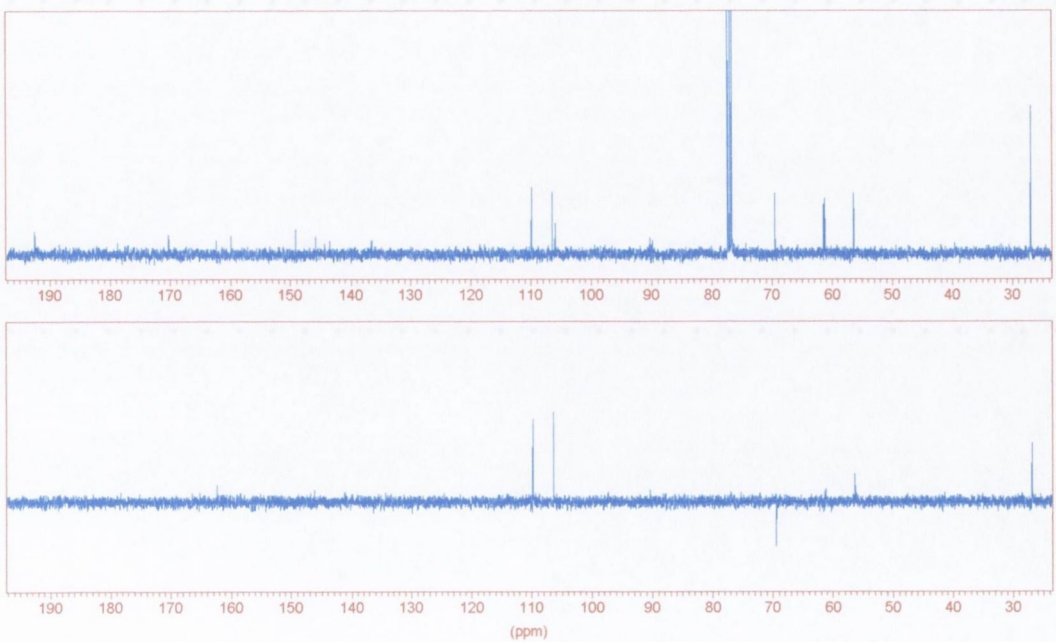
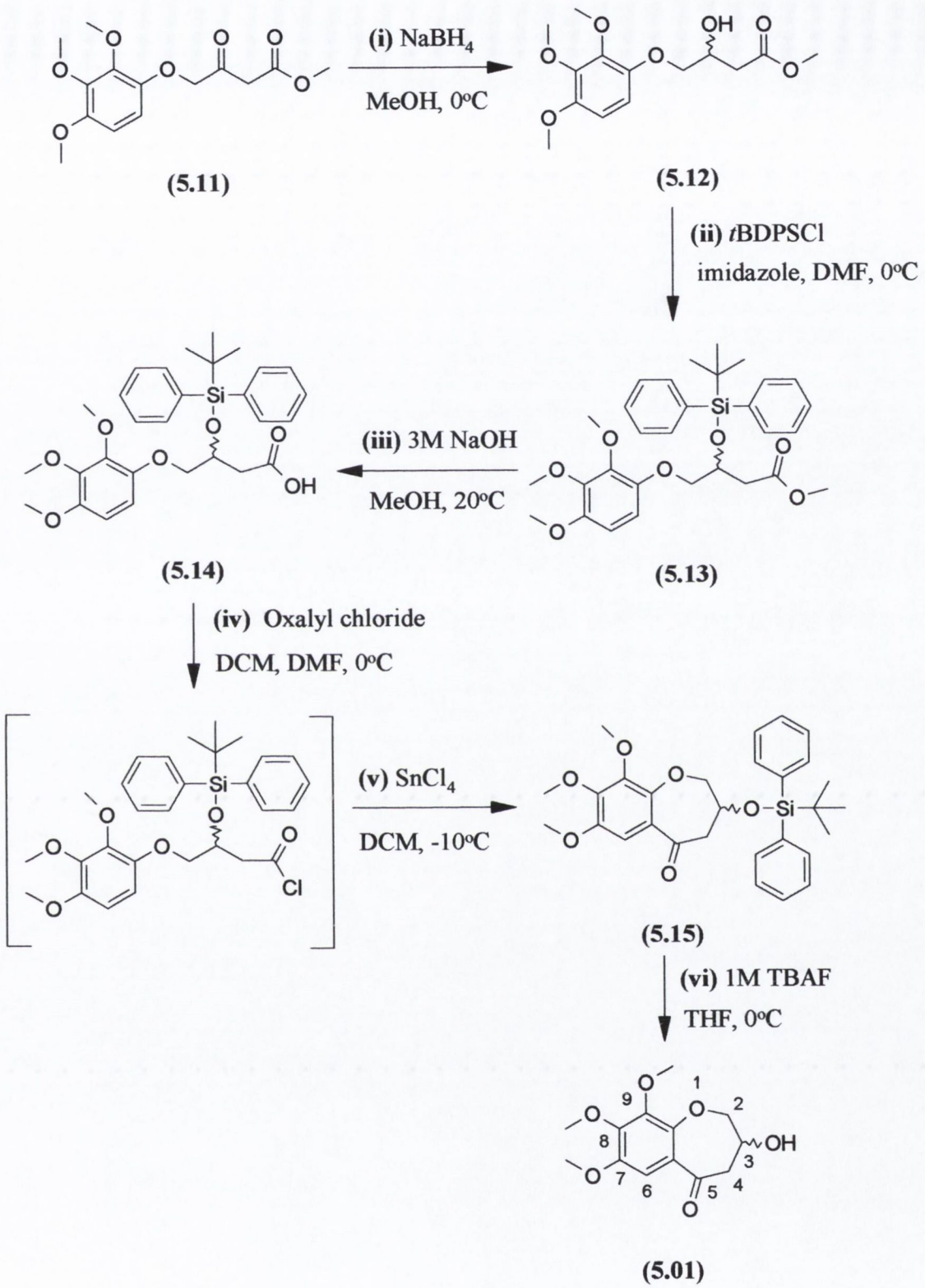


Figure 5.4. ^{13}C NMR and DEPT 135 spectra of **(5.10)**.

Decarboxylation of **(5.10)** was achieved by refluxing it in a solution of methanol/toluene for 12 hours[188]. Decarboxylation was believed to occur *via* a β-elimination pathway induced by methanolysis. After isolation and purification by flash column chromatography, the β-keto-ester **(5.11)** was isolated as an oil in 82% yield.

5.2.3 Synthesis of (5.01) from (5.11)

Reduction of the ketonic functional group in **(5.11)** was accomplished using $NaBH_4$ in methanol at 0°C as previously described in section 3.9.1. This afforded methyl 3-hydroxy-4-(2,3,4-trimethoxyphenoxy)butanoate **(5.12)** as a colourless oil in 72% yield. The successful reduction to the alcohol **(5.12)** was positively identified from its IR spectrum by the presence of a broad peak at 3475 cm^{-1} and the disappearance of the $C{=}O_{str}$ peak, which had previously occurred at 1753 cm^{-1}. As with the synthesis of the cyclic intermediates, **(3.39)** and **(4.24)**, suitable derivatisation was required to protect the alcohol from both the basic and acidic conditions employed in the hydrolysis and cyclisation steps respectively. Therefore, protection of the hydroxyl group was carried out at ambient temperature using *t*BDPSCl with imidazole as the base in DMF to afford the silyl ether **(5.13)** as an oil in 77% yield. Subsequent hydrolysis of the methyl ester **(5.13)** was achieved by using methanolic 3M NaOH to afford the acid **(5.14)** as a white-waxy solid in 66% yield. Following this, cyclisation was effected by converting **(5.14)** to its corresponding acid halide before dissolving it in DCM and treating the solution with $SnCl_4$ at -10°C. This reaction afforded, after isolation and purification by flash column chromatography, **(5.15)** as a clear oil in 78% yield. The silyl-protecting group was then removed after dissolving **(5.15)** in THF at 0°C and treating the solution with TBAF for 3 hours. After isolation and purification, the keto-alcohol **(5.01)** was afforded in 53% yield as a purple solid (Scheme 5.4).


(i) NaBH4
MeOH, 0°C
(5.11)
(5.12)
(ii) tBDPSCl
imidazole, DMF, 0°C
(iii) 3M NaOH
MeOH, 20°C
(5.14)
(5.13)
(iv) Oxalyl chloride
DCM, DMF, 0°C
(v) SnCl4
DCM, -10°C
(5.15)
(vi) 1M TBAF
THF, 0°C
(5.01)

Scheme 5.4.

The ^{1}H NMR spectrum of **(5.01)** (Figure 5.5) revealed the presence of a double- doublet (J=5.5Hz, 12.0Hz) resonating between 3.04-3.18 ppm. These resonances were attributable to the methylene H-4 protons. The double-doublet arises because each methylene H-4 proton couples to each other as well as to the neighbouring proton on C-3. A similar coupling pattern arises for the methylene protons on C-2, which resonates at 4.22 ppm. The three-methoxy group protons resonate as singlets at 3.80 ppm, 3.86 ppm and 3.92 ppm. The broad multiplet observed at 4.48 ppm was assigned as H-3, with the remaining proton, resonating as a singlet at 7.04 ppm, being assigned as H-6.

In the DEPT 135 spectrum of **(5.01)** (Figure 5.6), C-4 resonated at 49.72 ppm, while the additional methylene signal, which resonated at 79.92 ppm and was assigned as C-2. The signals at 56.04 ppm, 61.12 ppm and 61.64 ppm were attributable to the three-methoxy group carbons. The methine carbons resonating at 69.24 ppm and 104.95 ppm were assigned as C-3 and C-6 respectively. The signals that resonated at 143.97 ppm, 146.99 ppm, 148.16 ppm and 152.09 ppm were assigned as the quaternary aromatic carbons. Finally, the peak observed at 195.29 ppm confirmed the presence of the C-5 carbonyl group.

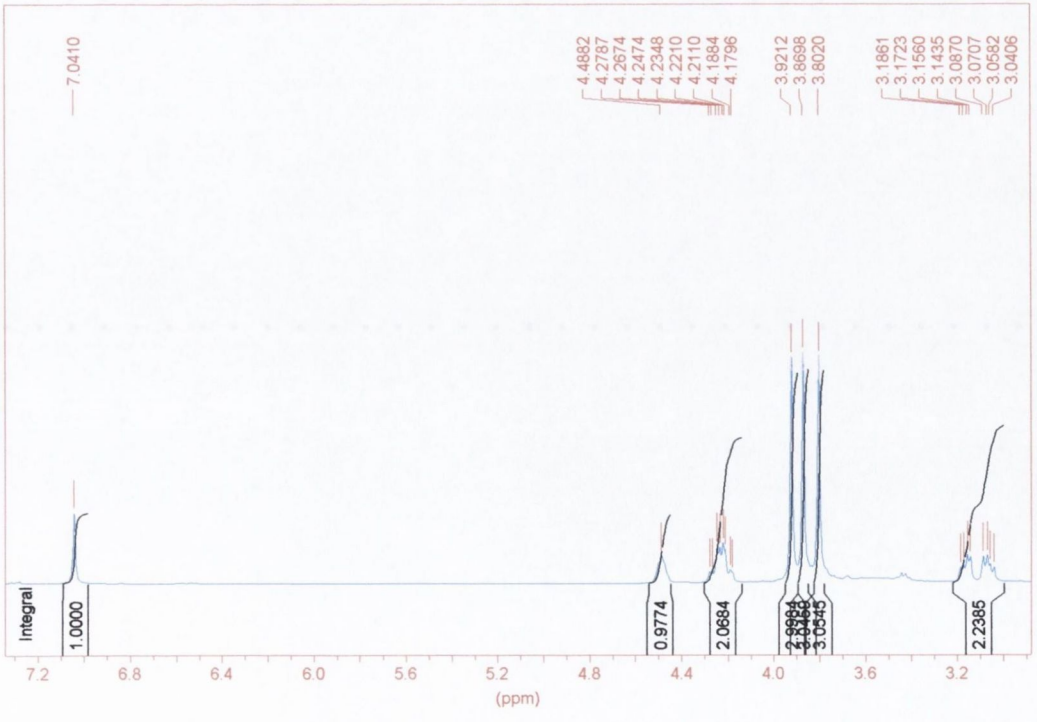


Figure 5.5. ^{1}H NMR spectrum of **(5.01)**.

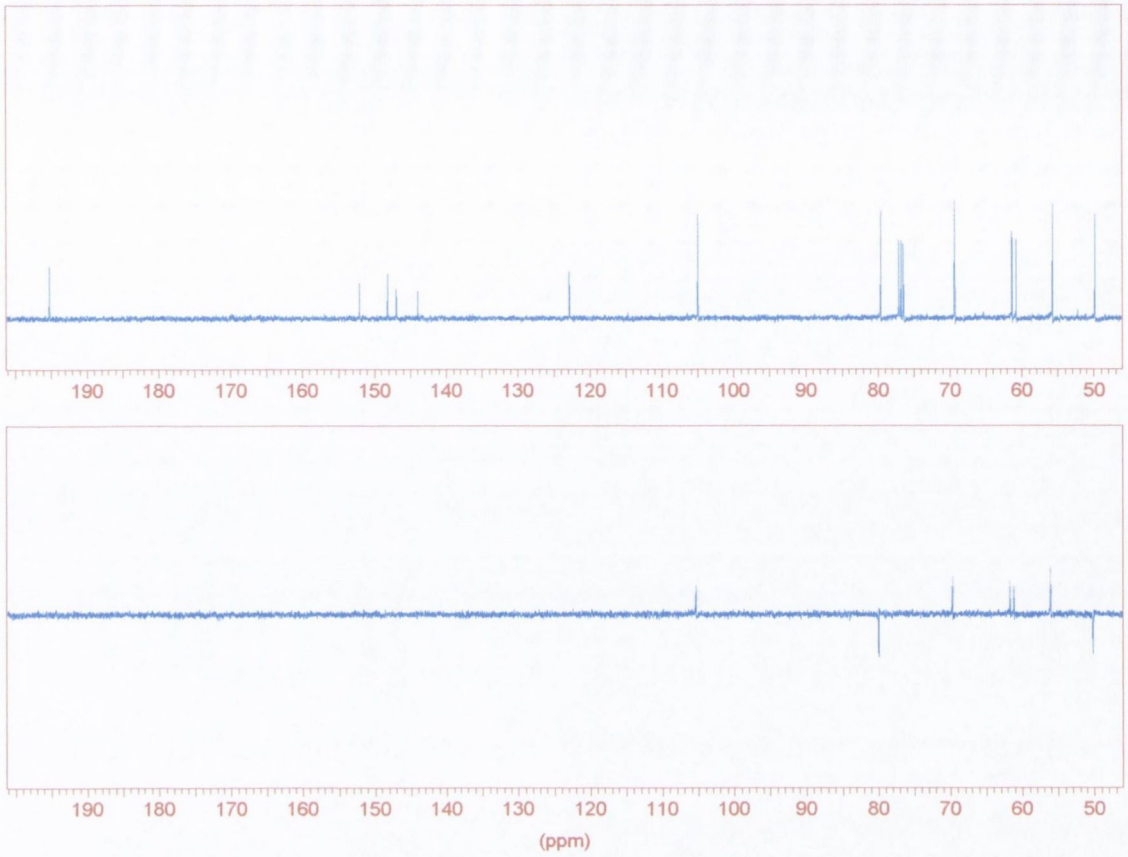


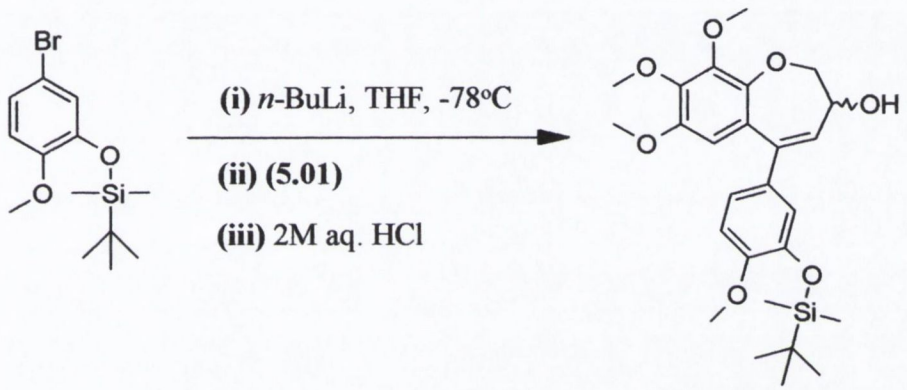
Figure 5.6. ^{13}C NMR and DEPT 135 spectra of **(5.01)**.

5.3 Arylation of (5.01)

The coupling of the aryl units to the ketonic centres of **(5.01)** followed the same approach as that employed in the synthesis of **(3.32)** and **(3.46)**. From the biological results obtained thus far, it was clear that the most potent anti-tubulin derivatives were those that contained, hydroxyanisole and di-hydroxyanisole as their C-ring components. Therefore, it was anticipated that the attachment of these moieties would provide compounds with similar or greater inhibitory activity against microtubule polymerisation.

5.3.1 Synthesis of 5-(3-hydroxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-ol (5.02)

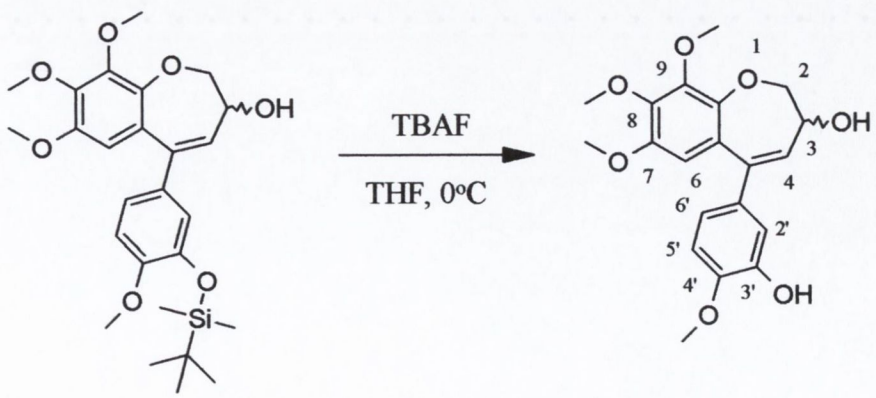
The synthesis of **(5.02)** was accomplished in four steps from the keto-alcohol **(5.01)**. The first step in this synthesis involved the addition of **(5.01)** to the organolithium derivative of **(2.50)** in THF at - 78°C. After 8 hours, the temperature of the reaction was allowed to rise to 20°C. The coupled product, a carbinol, was dehydrated *in situ* by the addition of 2M aq. HCl. After isolation and purification by flash column chromatography, the intermediate **(5.16)** was isolated as a clear oil in 51% yield (Scheme 5.5).



(2.50) **(5.16)**

Scheme 5.5.

Deprotection of **(5.16)** using TBAF in THF afforded the product **(5.02)** as a white solid in 92% yield (Scheme 5.6).



(5.16) **(5.02)**

Scheme 5.6.

In the IR spectrum of **(5.02)**, the most distinguishing feature was the presence of a broad peak at 3458.4 cm^{-1} representative of the hydroxyl group at position-3 and on the aromatic C-ring.

The ^1H NMR spectrum of **(5.02)** (Figure (5.7) identified the presence of the methoxy-group protons resonating as three singlets at 3.60 ppm, 3.94 ppm and 3.98 ppm. The methine proton on C-3 resonated as a condensed quartet at 4.47 ppm. The two protons attached to C-2 each existed in its own chemical and magnetic enviroment and therefore resonated at two different frequencies with one proton recorded as a double-doublet (J = 2.5Hz, 9.0Hz) at 4.11 ppm, while the other was found resonating at 4.51 ppm. The phenolic proton was observed as a broad singlet at 5.63 ppm. The alkenyl proton on C-4 was recorded as a doublet (J = 4.5Hz) resonating at 6.14 ppm. The singlet, which resonated at 6.29 ppm, was assigned as H-6. The aromatic region of the ^1H NMR spectrum clearly identified the existence of the C-ring protons existing in an ABX pattern. Therefore, the double-doublet (J = 1.5Hz, 8.0Hz) resonating at 6.78 ppm was assigned as the proton on C-6'. The H-5' proton resonated as a doublet (J = 8.0Hz) at 6.84 ppm while the proton at C-2' was recorded as a doublet (J = 1.5Hz) resonating at 6.88 ppm.

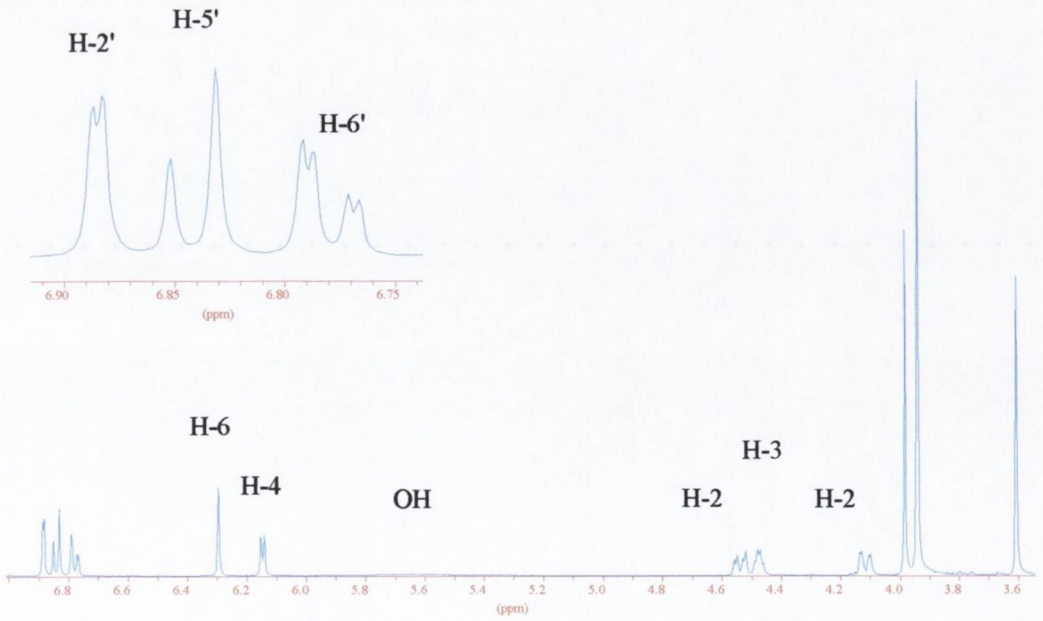


Figure 5.7. ^1H NMR spectrum of **(5.02)**.

An inspection of the ^{13}C NMR spectrum of **(5.02)** identified four-methoxy carbon signals resonating at 55.52 ppm, 55.76 ppm, 60.73 ppm and 61.73 ppm while the methine signal resonating at 66.78 ppm was attributed to C-3 (Figure 5.8). Analysis of the DEPT 135 spectrum (Figure 5.7) revealed the presence of methylene carbon resonating at 78.70 ppm and was therefore assigned as C-2. Four aromatic CH signals were identified resonating at 109.48 ppm, 109.75 ppm, 115.00 ppm and 120.36 ppm while the alkenyl carbon, C-4, was identified resonating at 130.42 ppm. The quaternary signals resonated in the region between 125.21 ppm and 147.86 ppm.

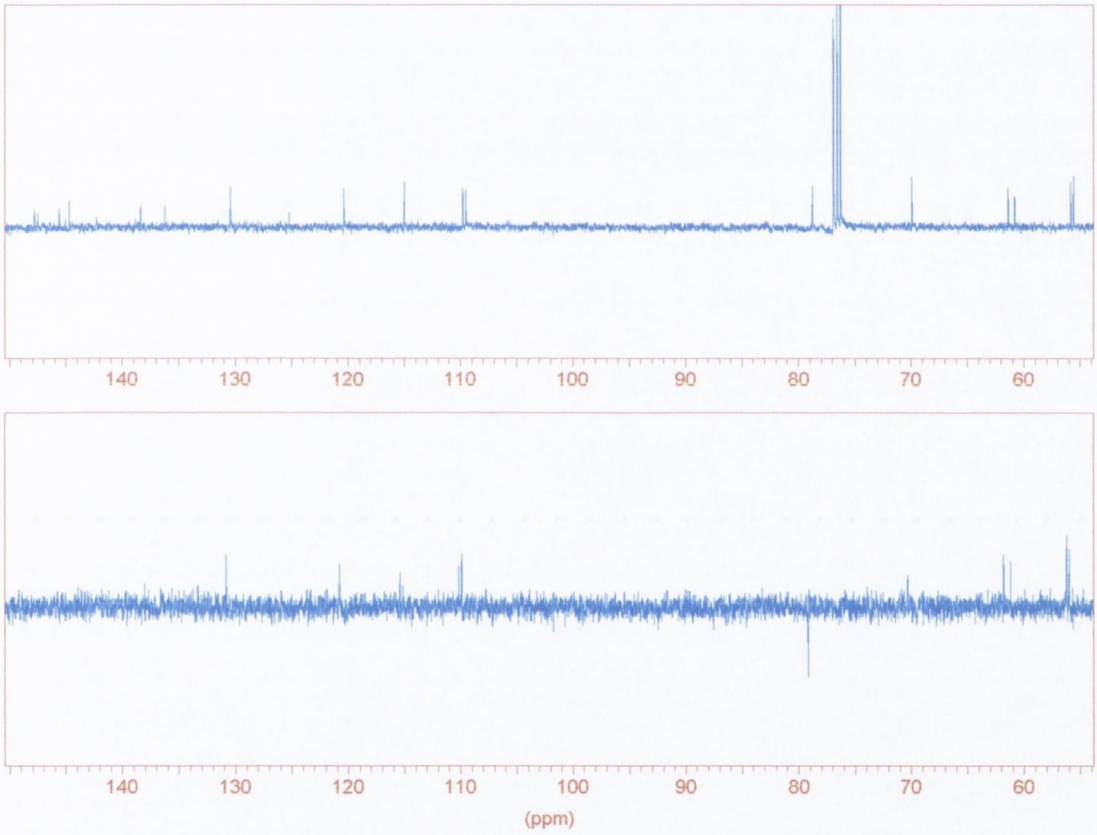
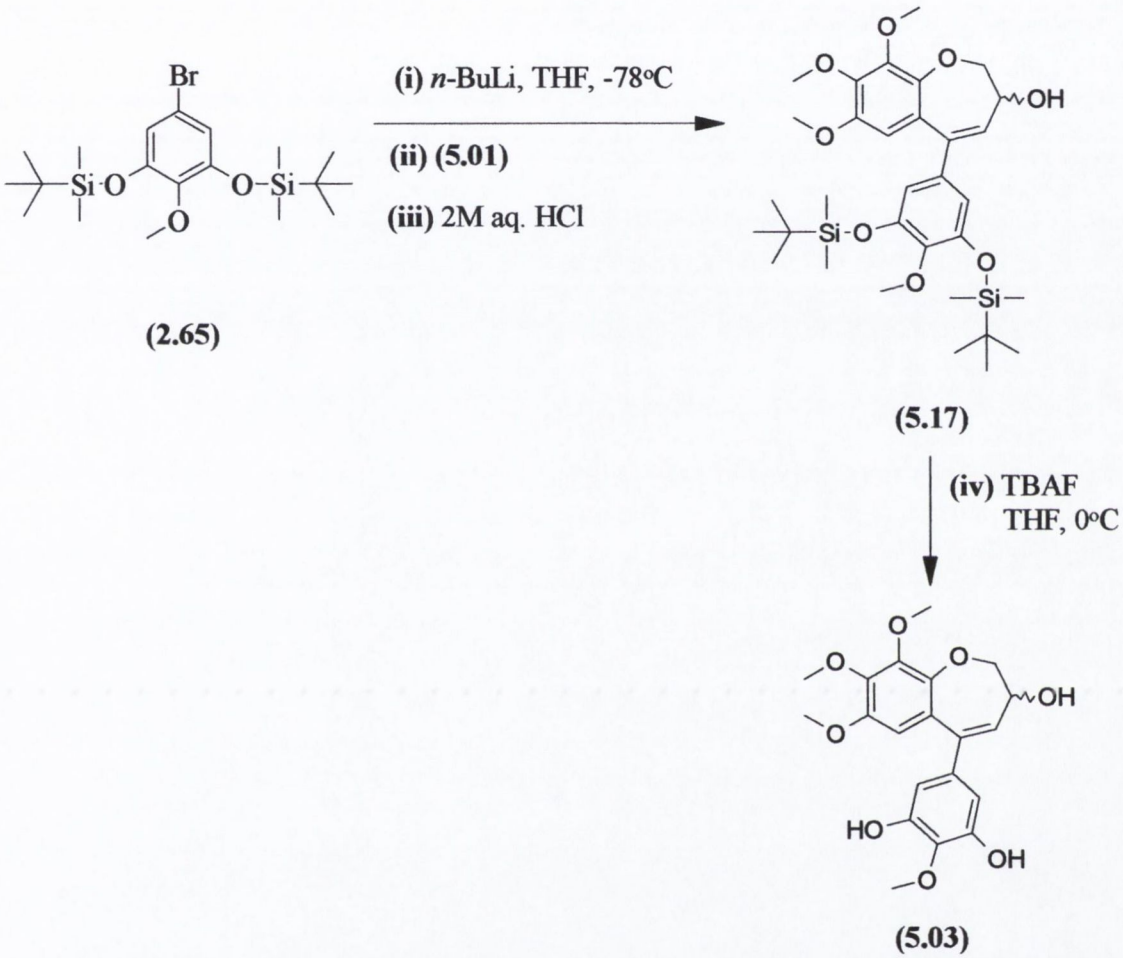


Figure 5.8. ^{13}C NMR and DEPT 135 spectra of **(5.02)**.

5.3.2 Synthesis of 5-(3-hydroxy-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-5-yl)-2-methoxy-1,3-benzenediol (5.03)

The synthesis of **(5.03)** was identical to that used for the preparation of **(5.02)** except, in an attempt to increase the yield of the product, the reaction was maintained at -78°C for 12 hours before being allowed to rise to room temperature. In this coupling step, it was assumed that the rate of nucleophillic attack would have been sluggish due to the steric

bulk of the incoming nucleophile. Upon completion, the reaction was worked up and purified by flash column chromatography to afford **(5.17)** as a mobile oil in 48% yield. The silyl protecting groups were removed after treating **(5.17)** with a solution of TBAF in THF. The product **(5.03)** was obtained as a white solid in 62% yield after purification by flash column chromatography (Scheme 5.7).

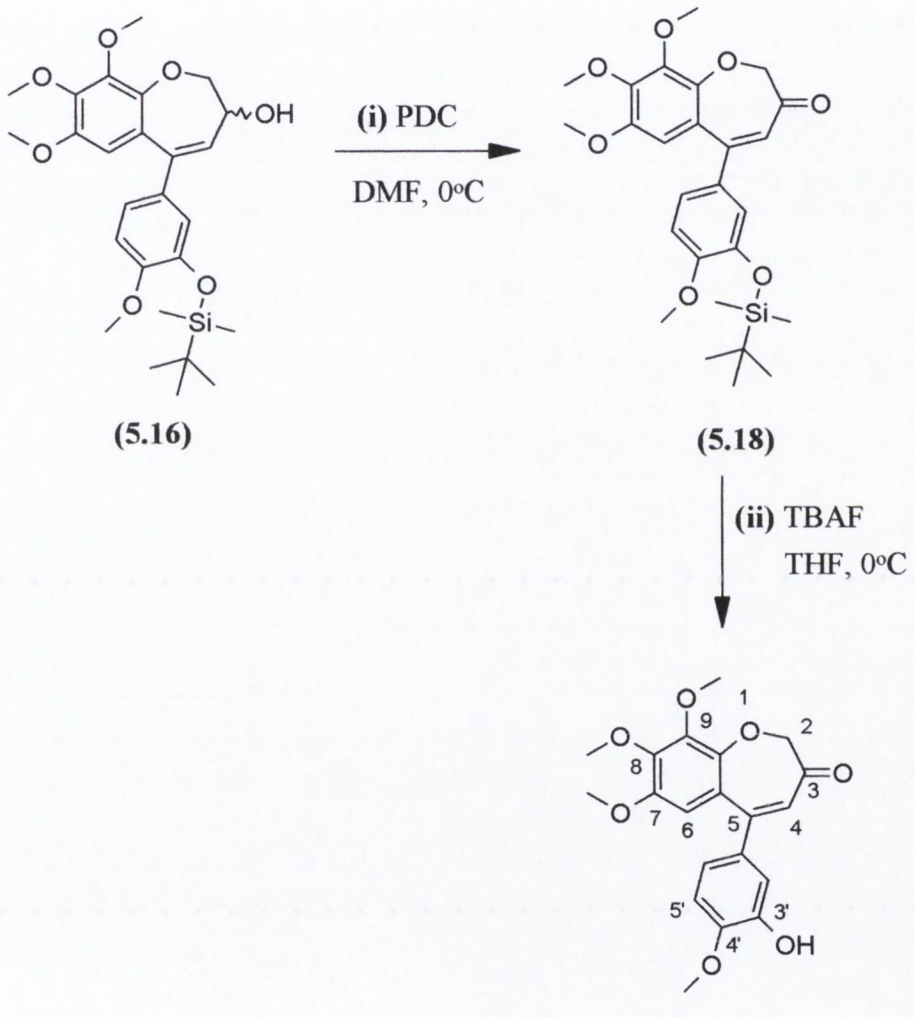


Scheme 5.7.

The ^{1}H NMR spectrum of **(5.03)** was similar to the spectrum of **(5.02)**. The notable difference between the two compounds was the additional phenolic substituent on the C-ring of **(5.03)**. This resulted in a symmetrical C-ring and as such the protons, H-2' and H-6', existed in identical environments resonating as a singlet at 6.40 ppm. This was also shown in the ^{13}C NMR spectrum as an enhanced signal resonating at 108.49 ppm.

5.3.3 Synthesis of 5-(3-hydroxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-one (5.04)

The final compound in this series, **(5.04)**, was synthesised by the oxidation of **(5.16)** to the intermediate-silyl-protected enone **(5.18)** using PDC in DMF at 0°C for 12 hours. Deprotection of the silyl-protecting group using TBAF in THF afforded **(5.04)** as a yellow crystalline solid in 96% yield (Scheme 5.8).



(5.16) **(5.18)** **(5.04)**

Scheme 5.8.

In the infrared spectrum of **(5.04)**, the phenolic hydroxyl functionality was noted as a broad peak at 3298.1 cm^{-1}, while the carbonyl peak of the enone functionality was observed at 1643.8 cm^{-1}.

In the ^{1}H NMR spectrum of **(5.04)**, the four-methoxy protons in this molecule resonated as four singlets at 3.64 ppm, 3.97 ppm, 3.99 ppm and 4.00 ppm. Due to the deshielding effect of the adjacent oxygen atom and carbonyl group, the protons attached to C-2 resonated downfield at 4.63 ppm. The phenolic proton characteristically occurred as a broad peak at 5.67 ppm while the singlet at 6.35 ppm was assigned as the alkenyl H-4 proton. The A-ring H-6 proton resonated at 6.45 ppm as a singlet peak whereas the other aromatic protons, H-2', H-5' and H-6', resonated as coalesced multiplets between 6.89 ppm and 6.95 ppm.

On inspection of the ^{13}C NMR spectrum of **(5.04)** the methoxy carbons resonated at 55.55 ppm, 55.85 ppm, 60.80 ppm and 61.39 ppm, with the C-2 signal being observed at 80.68 ppm. The four aromatic CH signals were recorded at 109.80 ppm, 110.18 ppm, 115.10 ppm and 120.91 ppm and these were assigned as C-6, C-5', C-2' and C-6' respectively while the signal resonating at 127.74 ppm was assigned as C-4. The quaternary aromatic and alkenyl carbons were found resonating at 125.66 ppm, 134.42 ppm, 134.62 ppm, 144.93 ppm, 147.10 ppm, 148.73 ppm and 151.32 ppm with the carbonyl signal at 200.03 ppm.

5.4 Tubulin binding data

The oxygen isosteres **(5.02)**, **(5.03)**, and **(5.04)** were examined as potential disrupters of tubulin polymerisation[149]. A summary of these results is shown in Table 5.1.

Compound	ITP IC_{50} (μM)	R^2 Value
(5.02)	3.18	0.960
(5.03)	Inactive	-
(5.04)	3.12	0.979
Combretastatin A-4	1.45	0.999

Table 5.1. Tubulin polymerisation inhibition data.

In this series, it was clear that substitution of the benzylic carbon atom with an oxygen atom did not result in any substantial decrease in tubulin binding activity. As might have been predicted from the poor tubulin binding data obtained for **(3.48)**, **(5.03)** was inactive.

5.5 Conclusion

This thesis reports on the convergent synthesis employed in designing a series of biaryl compounds as potential tubulin inhibitors. This required the development of innovative synthetic pathways in the synthesis of the cyclic keto-intermediates. Once this was achieved, a second aromatic unit was attached to the ketonic centres of these cyclic compounds *via* organometallic addition.

Ten compounds were found to possess significant activity against tubulin polymerisation. A discernible trend was observed within each series when evaluated[149] and these correlated with the suggested structure-activity relationships.

Trimethoxybenzene A-ring

Clearly, rotation of the trimethoxy-substituent from the less hindered 2,3,4-position to the more hindered 1,2,3-position resulted in the negation of anti-tubulin activity. Presumably, the C-1 methoxy group has a profound effect on the spatial orientation of the C-ring, increasing the dihedral angle between the two aromatic units, and thereby preventing suitable interactions at the C.B.S.

C-ring substituents

Although the work described in the thesis primarily concentrated on hydroxy-, methoxy- and amino-based substituents on this aromatic ring, the positioning of these components was vital for activity. Invariably, the most active compounds contained a hydroxyanisole unit with the methoxy and hydroxy groups occupying the *para*- and *meta*-positions respectively. In almost all cases, a single methoxy substituent on the C-ring resulted in inactive compounds. Two notable exceptions include **(3.46)** (IC_{50} = 2.1 μM) and **(3.53)** (IC_{50} = 2.7 μM). In these cases, the presence of a hydroxyl and ketone functionality at position-7 of the B-ring respectively resulted in active inhibitors of tubulin polymerisation.

It would appear that the C-ring of the compounds described in this thesis, plays a significant role in binding to tubulin. In particular, the requirement of electron-rich substituents possessing a free lone-pair of electrons appear to be necessary for activity. From these results, it would be reasonable to assume that lone-pair and π-bond

interactions take place at the C.B.S. However, the presence of an extra substituent (e.g. hydroxy or methoxy group) results in a loss of anti-tubulin activity.

Aliphatic B-ring; C-7 functionalisation

It is evident that the presence of a C-7 functional group is essential for activity, with eight out of the ten most active compounds possessing a dithianyl, hydroxy- or keto-functional group at this position. In the case of **(3.31)**, the presence of a dithiane group in place of a methylene group (i.e. compound **(2.52)**) increased its inhibitory effect from IC_{50} = 6.7 μM to IC_{50} = 4.35 μM. This bulky group probably modifies the molecules conformation into one more suited to the profile of the C.B.S.

The high inhibitory effect exhibited by functionalising the C-7 position may be two-fold. It may, like the dithianyl group, influence the structure of the molecule permitting an optimal conformation suited to the binding site. Alternatively, the functional group may take part in a nucleophilic interaction at the binding site (Figure 5.9) in much the same way as the lactone group does in podophyllotoxin (see chapter 1).

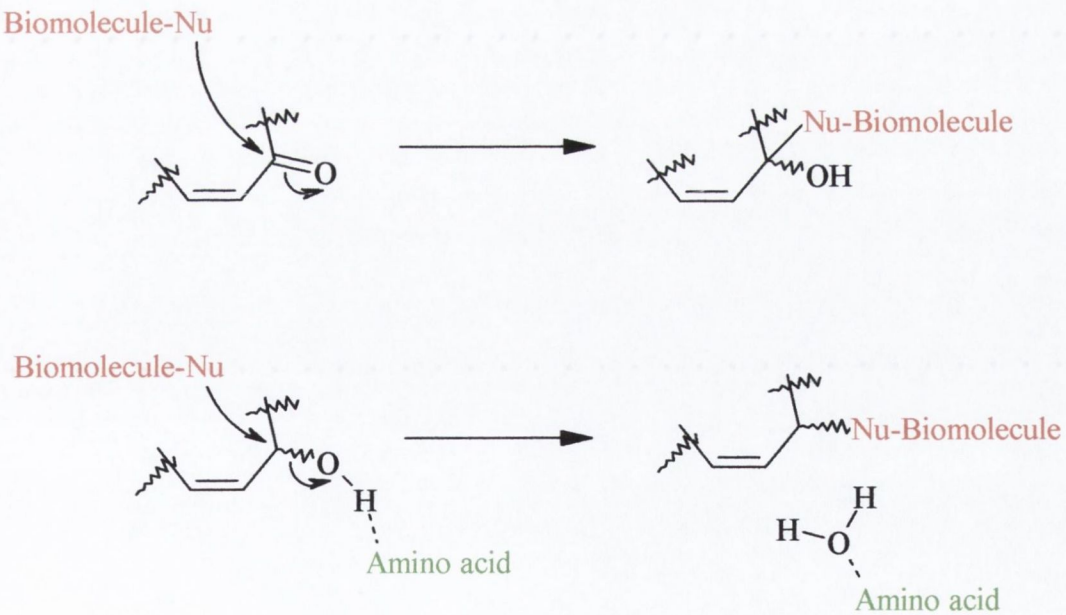


Figure 5.9. Possible interactions occurring at the colchicine-binding site.

Aliphatic B-ring; Oxygen insertion

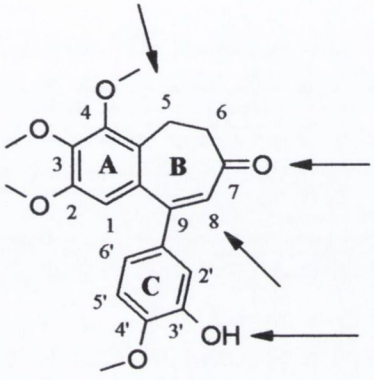
Replacement of the benzylic methylene group with an oxygen atom afforded compounds that were slightly less active than their isosteric counterparts despite an increase in electron density within the A-ring associated with the presence of the alkoxy-group. This decrease in activity may be due to the slight increase in conformational rigidity associated with an ether linkage and thereby prevent the molecule from attaining its optimal conformation.

Aliphatic B-ring; Double bond

The presence of a double bond at C-9 and C-10 is essential for maximum inhibitory activity against tubulin polymerisation as reduction of this bond totally negates all activity associated with its double bond derivative.

5.6 Future work

Having identified **(3.32)** as a potent inhibitor of microtubule polymerisation, future developments should include altering specific positions of this molecule as denoted by the arrows (Figure 5.10).



(3.32)

Figure 5.10. Future modifications to model compound **(3.32)**.

(i) The introduction of an alcohol functionality at position-5 may permit the attachment of water-soluble linker groups at this position.

(ii) The possible attachment of a third aromatic unit at position-8.

(iii) Manipulation of the functional group at position-7 to an oxime or thiol functionality should maintain its activity against tubulin polymerisation whilst allowing the attachment of additional bioactive molecules *via* ester or ether linkages.

(iv) Replace the 3' hydroxy group with small electron donating substituents.

CHAPTER 6

EXPERIMENTAL

EXPERIMENTAL

Melting points (M.pt) were determined on a hot stage apparatus and an electrothermal apparatus, and were uncorrected.

Spectra were obtained on the following instruments:
Infra red (IR): Perkin Elmer FT-IR spectrometer Paragon 1000. Solid samples were analysed by potassium bromide discs (KBr), oils were analysed as films on NaCl plates (CCl_4).

Nuclear magnetic resonance (NMR): All ^{1}H and ^{13}C NMR were determined using Bruker MSL 400. NMR spectra were analysed with Bruker WIN-NMR software. All NMR spectra were taken in $CDCl_3$ (except were indicated). ^{1}H NMR spectra were obtained by irradiating samples at 400 MHz while ^{13}C NMR spectra were obtained by irradiating samples at 100.71 MHz. Peak positions were assigned relative to the $CHCl_3$ resonances at 7.26 ppm for ^{1}H NMR and 78.16 ppm, 76.90 ppm and 75.62 ppm for ^{13}C NMR. In ^{19}F NMR, the peak positions were assigned relative to the signal for trifluorotoluene.

(Abbreviations used s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad, qC = quaternary carbon).

Low resolution mass spectroscopy (MS): All mass spectra, electron impact (EI, 70eV) were obtained from Varian Chrompak® Saturn GC/MS 2000.

High resolution mass spectroscopy (HRMS): All mass spectra, chemical ionisation were obtained from the Department of Chemistry, Trinity College Dublin.

Column chromatography was carried out with silica gel 60 (230-400 mesh). Thin layer chromatography with silica gel 60 G_F-245 pre-coated aluminium sheets (E. Merck Laboratories). Compounds were detected by visualization by Ultra violet (UV) light at 254 nm.

Anhydrous THF was prepared by standing over potassium hydroxide pellets overnight and then over sodium wire. The solvent was further dried by refluxing over sodium (3 g/l) and benzophenone (1 g/l). When a purple colour was observed, the THF was distilled and used immediately.

Anhydrous DCM was prepared by distilling over powdered calcium hydride, rejecting the wet forerun (~ 5%).

Solvents used for column chromatography were HPLC grade hexane and HPLC grade ethyl acetate.

The NMR data pertaining to the synthesis of previously known compounds were referenced.

Assembly-disassembly assay for rapid, reversible tubulin-binding compounds.

Following synthesis and subsequent analysis, the compounds described in this thesis were assayed to determine their ability to inhibit tubulin polymerisation. These experiments were conducted by Mr. Emmet M^{c}Cormack.

Tubulin assembly was monitored and recorded continuously by turbidimetric readings at 350 nm in a UV Spectrometer, equipped with a thermostatted cell at 37°C. Tubulin (2-3mg/ml in MES buffer and 1mM GTP) was prepared while the temperature was maintained < 4°C.

Typically, 1ml of tubulin solution was diluted with EB (5 ml) and supplementary GTPS (25µl, 5 µl/ml of EB) added. An aliquot (150 µl) of this assay solution was pipetted into a disposable micro-centrifuge tube (total volume of tube = 2 ml), which was subsequently placed on ice, and to this was added DMSO (1 µl), and the resultant control/blank solution pipetted immediately to an electronically controlled, thermostatted cell at 37°C. The UV absorption was then spectroscopically monitored over 1 minute. Differences in optical density (OD), from $t = 0$ to $t = 60$ seconds, of 0.1 and 0.15 indicated tubulin protein concentrations of 2 mg/ml and 3 mg/ml, respectively.

Protein concentrations higher or lower than these limits affected sensitivity of the assay and therefore only assay solutions diluted to 2-3 mg/ml were used.

Subsequently, the remaining assay solution was apportioned in aliquots (150 µl) to disposable micro-centrifuge tubes, which were immediately placed on ice. 10 milligram per millilitre (mg/ml) solutions of each potential tubulin polymerisation inhibitor was prepared in DMSO and consequent serial dilution of the stock, afforded incrementally adjusted (10mg/ml-0.05 mg/ml) solutions for assay. These compounds were assayed, as described for DMSO control solution, sequentially and values of concentrations that decreased the maximum rate of tubulin assembly, without drug, by 50% (IC_{50}) determined. The IC_{50} for all compounds were compared to that of combretastatin A-4 and podophyllotoxin, measured on the same day under the same conditions.

Results were analysed using non-linear regression of one-phase exponential decay plots of % tubulin polymerisation versus drug concentration (mg/ml).
% tubulin polymerisation data points were determined from the formula:

$$\left(\frac{mX}{mB}\right)^{-1} \times 100 = \text{\% tubulin polymerisation.}$$

Where mX = Maximum slope of compound with concentration X.

mB = Maximum slope of DMSO blank.

From this plot, IC_{50} values (expressed in µM) were calculated according to the following formula:

$$\frac{X}{(150)(\text{Mol. Wt})} = IC_{50}$$

Where X = The half-life generated by the computer program *Prism*®.

150 = Dilution factor.

Mol. Wt. = Molecular weight of the compound assayed.

Deviations from normal behaviour are quoted as goodness of fit values (R^2), where 1.0 is a perfect fit to the model.

Formation of 6,7,8,9-tetrahydro-1,2,3-trimethoxybenzocyclohepten-5-one (2.01)

1st Step

Synthesis of intermediate, 5-(2,3,4-trimethoxyphenyl)-2,4-pentadienoic acid (2.04)

To a stirred solution of 2,3,4-trimethoxybenzaldehyde (20g, 0.102 mol) in *tert*-butanol (36ml) was added methyl crotonate (20.4g, 0.204 mol) and a solution of potassium *tert*-butoxide (24.12g) in *tert*-butanol (320ml). The reaction was carried out under a nitrogen atmosphere, with the reaction vessel covered with aluminium foil. After the addition was complete, the resulting mixture was allowed to stir for 12 hours at room temperature. The mixture was then acidified with 2M aq. HCl (1000ml) and extracted with DCM (3 x 150ml). The combined organic extracts were dried over sodium sulphate, filtered and concentrated under reduced pressure to afford a yellow oil. This oil **(2.03)** was re-dissolved in absolute ethanol (70ml), treated with 10% aq. NaOH (200ml) and refluxed for 5 hours. The reaction was then allowed to cool to room temperature, quenched using 2M aq. HCl (500ml) and extracted with DCM (3 x 150ml). The combined organic extracts were dried over sodium sulphate, filtered and concentrated under reduced pressure to afford **(2.04)** as an oil (18.61g, 81%). ν_{max} (CCl_4)/ cm^{-1} 3010.1, 2939.4, 1708.8, 1495.1, 1100.2. ^{1}H NMR δ_H ppm 3.80 (9H, s, 3 x OMe), 6.40 (2H, s, ArH), 6.61 (4H, m, CHCHCHCH), 11.06 (1H, br, COOH). ^{13}C NMR δ_c ppm 55.32 (2 x OMe), 60.29 (OMe), 104.80 (2 x ArCH), 115.26 (CH), 123.65 (CH), 131.27 (CH), 124.73 (qC), 141.11 (qC), 141.99 (CH), 152.80 (2 x qC), 171.10 (COOH).

2nd Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl-5-(2,3,4-trimethoxyphenyl) pentanoate (2.06)

The acid **(2.04)** (20.0g, 75.8 mmol) was dissolved in ethanol/ethyl acetate solution (1:1; 200ml) and treated with 10% Pd/C (10g). The resulting mixture was stirred under an atmosphere of hydrogen at 25°C for 1 week. On completion, the catalyst was removed by filtration through Celite™. The solids thus retained were washed with absolute ethanol (~100ml). Concentration of the filtrates under reduced pressure afforded a viscous brown oil which crystallised on

standing to afford **(2.05)** (19.69g, 97%). To a stirred solution of **(2.05)** (20.0g, 74.6 mmol) in DCM (100ml) was added PFP (13.73g, 74.6 mmol) followed by DCC (15.37g, 74.6 mmol) at 0°C. After 5 hours, the reaction mixture was filtered through Celite™ and the filtrate concentrated under reduced pressure. The resulting pale yellow oil was purified by flash column chromatography (stationary phase, silica gel 230-400 mesh; mobile phase, hexane/ethyl acetate 4:1). The homogenous fractions were collected and reduced in volume to afford **(2.06)** as a yellow solid (25.6g, 80% yield). ^{1}H NMR δ_H ppm 1.78 (4H, m, COC$\underline{H_2}$C$\underline{H_2}$), 2.55 (2H, m, C$\underline{H_2}$), 2.75 (2H, m, C$\underline{H_2}$), 3.86 (3H, s, O$\underline{Me}$), 3.88 (6H, s, 2 x O$\underline{Me}$), 6.45 (2H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 23.84 ($\underline{C}H_2$), 29.91 ($\underline{C}H_2$), 32.92 ($\underline{C}H_2$), 35.22 ($\underline{C}H_2$), 55.35 (O$\underline{Me}$), 60.05 (2 x O$\underline{Me}$), 104.82 (2 x Ar$\underline{C}$H), 135.75 (q$\underline{C}$), 137.44 (q$\underline{C}$), 152.61 (2 x q$\underline{C}$), 168.70 ($\underline{C}$=O).

3rd Step-cyclisation of (2.06) to afford (2.01)

Synthesis of 6,7,8,9-tetrahydro-1,2,3-trimethoxybenzocyclohepten-5-one (2.01)

The pentafluorophenyl ester **(2.06)** (20.0g, 46.0 mmol) was dissolved in polyphosphoric acid (140g) and heated to 75°C with occasional stirring for 1 hour. When the reaction was complete, it was quenched by the addition of ice (100g) and the product extracted with diethyl ether (5 x 75ml). The combined organic layers were dried with sodium sulphate, filtered and evaporation of the filtrate afforded the crude product, which was purified by flash column chromatography (stationary phase, silica gel 230-400 mesh; mobile phase, 4:1; hexane/ethyl acetate). The homogenous fractions were collected and the solvent was removed under reduced pressure leaving a pale yellow oil **(2.01)** (10.2g, 89%). ν_{max} (CCl_4)/ cm^{-1} 2938.2, 1673.1, 1589.8, 1134.3. GCMS m/z (%) 250 (M^+, 100), 207 (25), 181 (27). ^{1}H NMR δ_H ppm 1.69-1.82 (4H, m, COC$\underline{H_2}$C$\underline{H_2}$), 2.62 (2H, m, C$\underline{H_2}$), 2.88 (2H, m, C$\underline{H_2}$), 3.77 (3H, s, OMe), 3.86 (6H, s, 2 x OMe) 6.45 (1H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 22.32 ($\underline{C}H_2$), 25.56 ($\underline{C}H_2$), 32.70 ($\underline{C}H_2$), 42.16 ($\underline{C}H_2$), 55.93 (2 x O$\underline{Me}$), 60.86 (O$\underline{Me}$), 107.91 (Ar$\underline{C}$H), 127.37 (q$\underline{C}$), 134.27 (q$\underline{C}$), 140.50 (q$\underline{C}$), 151.12 (q$\underline{C}$), 154.94 (q$\underline{C}$), 205.61 ($\underline{C}$=O).

Formation of 5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-naphthalenone (2.10)

1st Step

Synthesis of intermediate, 4-oxo-4-(2,3,4-trimethoxyphenyl)butanoic acid (2.07)

To a stirred solution of 1,2,3-trimethoxybenzene (5.0g, 29.7 mmol) in anhydrous DCM (50ml) was added succinic anhydride (1.96g, 19.6 mmol). To this mixture was added $AlCl_3$ (5.07g, 38 mmol) portion-wise at -10°C. After 3 hours, the reaction was quenched by the addition of 2M aq. HCl (50ml) and the product was extracted using diethyl ether (3 x 50ml). The combined ether extracts were dried over sodium sulphate, filtered, and the filtrate concentrated to an orange oil. The oil was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ ethyl acetate 1:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford the acid **(2.07)** as a white solid (4.09g, 51%). M.pt. 87-88°C. ν_{max} (CCl_4)/ cm^{-1} 3384.1, 2942.2, 1723.1, 1711.0, 1291.5, 1101.8. ^1H NMR δ_H ppm 2.77 (2H, t, J 6.6Hz, C$\underline{H_2}$), 2.32 (2H, t, J 6.6Hz, C$\underline{H_2}$), 3.88 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 4.00 (3H, s, O$\underline{Me}$), 6.73 (1H, d, J 4.5Hz, Ar$\underline{H}$), 7.57 (1H, d, J 4.5Hz, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 28.02 ($\underline{C}H_2$), 37.09 ($\underline{C}H_2$), 55.64 (O$\underline{Me}$), 60.35 (O$\underline{Me}$), 60.90 (O$\underline{Me}$), 106.72 (Ar$\underline{C}$H), 115.46 (q$\underline{C}$), 125.25 (Ar$\underline{C}$H), 125.43 (q$\underline{C}$), 141.60 (q$\underline{C}$), 157.16 (q$\underline{C}$), 178.22 ($\underline{C}$OOH), 197.58 ($\underline{C}$=O).

2nd Step

Synthesis of intermediate, 4-(2,3,4-trimethoxyphenyl)butanoic acid (2.08)[113]

To a solution of **(2.07)** (0.45g, 1.67 mmol) in acetic acid (3ml) and ethanol (1ml) was added 10% Pd/C (0.2g) with stirring under an atmosphere of H_2. After 12 hours, the reaction mixture was filtered and concentrated to an oil. The product was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: ethyl acetate/hexane 2:1). All homogeneous fractions were collected and the solvent was concentrated *in vacuo* to afford the acid **(2.08)** as a white solid (0.40g, 94%). ν_{max} (CCl_4)/ cm^{-1} 3370.1, 2942.0, 1708.3, 1098.5. ^1H NMR δ_H ppm 1.90 (2H, m, $CH_2C\underline{H_2}$), 2.37 (2H, m, C$\underline{H_2}$COOH), 2.61 (2H, m, ArC$\underline{H_2}$), 3.83 (3H, s, O$\underline{Me}$), 3.86 (3H, s, O$\underline{Me}$), 3.87 (3H, s, O$\underline{Me}$), 6.60 (1H, d, J 4.5Hz, Ar$\underline{H}$), 6.81 (1H, d, J 4.5Hz, Ar$\underline{H}$), 8.46 (1H, br, COO$\underline{H}$). ^{13}C NMR δ_c ppm 25.19 ($\underline{C}H_2$), 28.47 ($\underline{C}H_2$), 33.05 ($\underline{C}H_2$),

55.54 (OMe), 60.21 (OMe), 60.38 (OMe), 106.84 (ArCH), 120.38 (qC), 123.47 (ArCH), 126.77 (qC), 141.82 (qC), 151.41 (qC), 151.70 (qC), 178.99 (COOH).

3rd Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 4-(2,3,4-trimethoxyphenyl)butanoate (2.09)

To a stirred solution of **(2.08)** (0.30g, 1.18 mmol) in DCM (1ml) was added PFP (0.32g, 1.74 mmol) and DCC (0.48g, 2.33 mmol) at 0°C. After 2.5 hours, the reaction was filtered, concentrated to an oil, and the resulting residue was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). All homogeneous fractions were collected and the solvent was concentrated *in vacuo* to afford the ester **(2.09)** as a white solid (0.29g, 57%). ν_{max} (CCl_4)/ cm^{-1} 2934.0, 2853.5, 1788.6, 1100.8. ^1H NMR δ_H ppm 1.92 (2H, m, CH_2CH_2), 2.05 (2H, m, CH_2CO), 2.72 (2H, m, $ArCH_2$), 3.87 (3H, s, OMe), 3.90 (3H, s, OMe), 3.91 (3H, s, OMe), 6.64 (1H, d, J 4.2Hz, ArH), 6.85 (1H, d, J 4.2Hz, ArH). ^{19}F NMR δ_F ppm -153.32 (d, 2 x ArF), -158.81 (t, ArF), -163.02 (t, 2 x ArF). ^{13}C NMR δ_c ppm 25.68 (CH_2), 28.80 (CH_2), 32.62 (CH_2), 55.96 (OMe), 60.63 (OMe), 60.80 (OMe), 107.23 (ArCH), 121.11 (qC), 123.89 (ArCH), 126.22 (qC), 141.93 (qC), 151.52 (qC), 151.95 (qC), 168.95 (C=O).

4th Step-cyclisation of (2.09) to afford (2.10)

Synthesis of 5,6,7-trimethoxy-1,2,3,4-tetrahydro-1-naphthalenone (2.10)[113]

The pentafluorophenyl ester **(2.09)** (0.30g, 0.713 mmol) was dissolved in polyphosphoric acid (2.85g) and the mixture was stirred at 75°C for 1 hour. On completion, the reaction was quenched by the addition of ice (50g) and the product was extracted with diethyl ether (3 x 25ml), dried using sodium sulphate, filtered, and concentrated to an oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.10)** as a white solid (0.15g, 92%). M.pt. 75°C. ^1H NMR δ_H ppm 2.09 (2H, m, CH_2), 2.61 (2H, m, CH_2), 2.89 (2H, m, $ArCH_2$), 3.87 (3H, s, OMe), 3.90 (3H, s, OMe), 3.95 (3H, s, OMe),

7.40 (1H, s, ArH). ^{13}C NMR δ_c ppm 22.44 ($\underline{C}H_2$), 22.55 ($\underline{C}H_2$), 38.26 ($\underline{C}H_2$), 55.56 (O$\underline{Me}$), 60.21 (O$\underline{Me}$), 60.41 (O$\underline{Me}$), 104.78 (Ar$\underline{C}$H), 127.61 (q$\underline{C}$), 131.73 (q$\underline{C}$), 146.71 (q$\underline{C}$), 149.92 (q$\underline{C}$), 151.54 (q$\underline{C}$), 197.28 ($\underline{C}$=O).

Formation of 6,7,8-trimethoxy-1,2,3,4-tetrahydro-1-naphthalenone (2.16)

1st Step

Synthesis of intermediate, 3-(3,4,5-trimethoxyphenyl)propanol (2.11)[189]

To a stirred suspension of $LiAlH_4$ (0.71g, 18.7 mmol) in anhydrous THF (10ml) at 0°C was added 3-(3,4,5-trimethoxyphenyl)propanoic acid (1.5g, 6.25 mmol) portion-wise. The reaction temperature was raised to room temperature and allowed to proceed for 3 hours. On completion, the reaction was quenched by the drop-wise addition of cold 2M aq. HCl (20ml) and the product was extracted with diethyl ether (3 x 20ml). The organic extracts were collected, dried using sodium sulphate, filtered, and the solvent removed *in vacuo* to afford crude **(2.11)** as an off-white solid. This was re-dissolved in DCM (~5ml) and purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.11)** as a white powder (1.25g, 89%). ν_{max} (CCl_4)/ cm^{-1} 3350.1, 2943.0, 2843.2, 1497.5. ^1H NMR δ_H ppm 1.86 (2H, m, C$\underline{H}_2$), 2.64 (2H, t, J 6.5Hz, C$\underline{H}_2$), 3.67 (2H, t, J 6.5Hz, C$\underline{H}_2$), 3.83 (3H, s, O$\underline{Me}$), 3.86 (6H, s, 2 x O$\underline{Me}$), 6.43 (2H, s, 2 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 31.31 ($\underline{C}H_2$), 33.95 ($\underline{C}H_2$), 61.61 ($\underline{C}H_2OH$), 55.64 (O$\underline{Me}$), 55.65 (O$\underline{Me}$) 60.33 (O$\underline{Me}$), 105.12 (2 x Ar$\underline{C}$H), 135.76 (q$\underline{C}$), 136.02 (q$\underline{C}$), 152.71 (q$\underline{C}$), 152.75 (q$\underline{C}$).

2nd Step

Synthesis of intermediate, 3,4,5-trimethoxybenzopropanylbromide (2.12)

To a stirred solution of alcohol **(2.11)** (5.0g, 22.12 mmol) in ether (25ml) was added PBr_3 (3.14ml, 33.4 mmol) at 0°C for 1.5 hours. On completion, the reaction was quenched by the slow addition of ice water (25ml) and the product was extracted using diethyl ether (3 x 35ml). The organic extracts were then washed with 5% aq. $NaHCO_3$ (25ml), dried using sodium

sulphate, filtered, and then concentrated to an oil under reduced pressure. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 5:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford the bromide **(2.12)** as an oil (5.66g, 89%). ν_{max} (CCl_4)/ cm^{-1} 2939.2, 2838.2, 1590.0, 1129.6. ^1H NMR δ_H ppm 2.15 (2H, m, C$\underline{H_2}$), 3.00 (2H, t, J 7.0Hz, C$\underline{H_2}$), 3.40 (2H, t, J 6.7Hz, C$\underline{H_2}$), 3.82 (3H, s, O$\underline{Me}$), 3.85 (6H, s, 2 x O$\underline{Me}$), 6.42 (2H, s, 2 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 32.61 ($\underline{C}H_2$), 33.69 ($\underline{C}H_2$), 36.84 ($\underline{C}H_2$), 55.64 (2 x O$\underline{Me}$), 60.33 (O$\underline{Me}$), 105.10 (2 x Ar$\underline{C}$H), 135.76 (q$\underline{C}$), 136.02 (q$\underline{C}$), 152.72 (q$\underline{C}$), 152.77 (q$\underline{C}$).

3rd Step

Synthesis of intermediate, 3,4,5-trimethoxybenzopropanylnitrile (2.13)

To a stirred solution of bromide **(2.12)** (1.47g, 5.08 mmol) in DMSO (15ml) was added KCN (1.69g, 26.0 mmol) at 25°C for 3 hours. On completion, the reaction was quenched by the addition of water (15ml) and the product was extracted using diethyl ether (3 x 35ml), dried using sodium sulphate, filtered, and then concentrated to an oil under reduced pressure. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford the nitrile **(2.13)** as an oil (1.14g, 96%). ν_{max} (CCl_4)/ cm^{-1} 2940.1, 2840.1, 2250.0, 1589.3. ^1H NMR δ_H ppm 1.97 (2H, m, C$\underline{H_2}$), 2.34 (2H, t, J 7.0Hz, C$\underline{H_2}$), 2.73 (2H, t, J 6.5Hz, C$\underline{H_2}$), 3.83 (3H, s, O$\underline{Me}$), 3.85 (6H, s, 2 x O$\underline{Me}$), 6.40 (2H, s, 2 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 15.91 ($\underline{C}H_2$), 26.47 ($\underline{C}H_2$), 34.25 ($\underline{C}H_2$), 55.63 (O$\underline{Me}$), 55.67 (O$\underline{Me}$), 60.34 (O$\underline{Me}$), 105.02 (2 x Ar$\underline{C}$H), 118.98 ($\underline{C}$N), 134.95 (q$\underline{C}$), 136.48 (q$\underline{C}$), 152.90 (2 x q$\underline{C}$).

4th Step

Synthesis of intermediate, 3,4,5-trimethoxybenzobutanoic acid (2.14)

To a stirred solution of nitrile **(2.13)** (1.17g, 4.97 mmol) in ethanol (20ml) was added NaOH (1.99g, 49.7 mmol) and water (10ml) and the reaction was refluxed for 8 hours. On completion, the solvent was removed *in vacuo*, and to the resulting residue was added a solution of 2M aq. HCl (30ml). The crude product was extracted using diethyl ether (3 x 40ml) and the layers were

combined, dried over sodium sulphate, filtered, and concentrated to a clear oil. The product was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.14)** as a white solid (1.23g, 98%). M.pt. 79-81°C. ν_{max} (CCl_4)/ cm^{-1} 3310.2, 2940.0, 2839.6, 1708.7, 1589.4, 1126.9. ^{1}H NMR δ_H ppm 1.97 (2H, m, C$\underline{H_2}$), 2.40 (2H, m, C$\underline{H_2}$), 2.63 (2H, m, C$\underline{H_2}$), 3.86 (3H, s, O$\underline{Me}$), 3.89 (6H, s, 2 x O$\underline{Me}$), 6.41 (2H, s, 2 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 25.81 (C$\underline{H_2}$), 32.77 (C$\underline{H_2}$), 34.94 (C$\underline{H_2}$), 55.64 (2 x O$\underline{Me}$), 60.36 (O$\underline{Me}$), 104.99 (q$\underline{C}$), 105.05 (2 x Ar$\underline{C}$H), 136.50 (q$\underline{C}$), 152.71 (2 x q$\underline{C}$), 178.41 ($\underline{C}$OOH).

5th Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 4-(3,4,5-trimethoxyphenyl)butanoate (2.15)

To a stirred solution of **(2.14)** (1.0g, 3.93 mmol) in DCM (10ml) was added PFP (0.736g, 4.0 mmol) and DCC (1.03g, 5.0 mmol) at 0°C. After 1.5 hours, the reaction mixture was filtered and concentrated to a clear oil. This oil was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.15)** as a white solid (1.45g, 88%). ν_{max} (CCl_4)/ cm^{-1} 2941.8, 2360.1, 1788.2, 1590.6, 1520.9. ^{1}H NMR δ_H ppm 2.12 (2H, m, C$\underline{H_2}$), 2.71 (4H, m, 2 x C$\underline{H_2}$), 3.85 (3H, s, O$\underline{Me}$), 3.87 (6H, s, 2 x O$\underline{Me}$), 6.44 (2H, s, 2 x Ar$\underline{H}$). ^{19}F NMR δ_F ppm -153.47 (d, 2 x Ar$\underline{F}$), -158.57 (t, Ar$\underline{F}$), -162.86 (t, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 25.87 (C$\underline{H_2}$), 31.04 (C$\underline{H_2}$), 34.61 (C$\underline{H_2}$), 55.63 (2 x O$\underline{Me}$), 60.38 (O$\underline{Me}$), 105.07 (2 x Ar$\underline{C}$H), 135.98 (2 x q$\underline{C}$), 136.05 (q$\underline{C}$), 152.81 (2 x q$\underline{C}$), 168.85 ($\underline{C}$=O).

6th Step-cyclisation of (2.15) to afford (2.16)

6,7,8-trimethoxy-1,2,3,4-tetrahydro-1-naphthalenone (2.16)[190]

The pentafluorophenyl ester **(2.15)** (1.0g, 2.38 mmol) was dissolved in polyphosphoric acid (8.0g) and the mixture was stirred at 75°C for 45 minutes. On completion, the reaction was quenched by the addition of ice (50g) and the product extracted with diethyl ether (3 x 25ml), dried using sodium sulphate, filtered, and concentrated to an oil under reduced pressure. This oil

was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.16)** as a white solid (0.48g, 85%). M.pt. 124°C. ν_{max} (CCl_4)/ cm^{-1} 2932.2, 1687.4, 1587.5. ^1H NMR δ_H ppm 2.05 (2H, t, J 6Hz, C$\underline{H_2}$), 2.58 (2H, t, J 6Hz, C$\underline{H_2}$), 2.88 (2H, m, C$\underline{H_2}$), 3.85 (3H, s, O$\underline{Me}$), 3.90 (3H, s, O$\underline{Me}$), 3.91 (3H, s, O$\underline{Me}$), 6.52 (1H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 22.56 ($\underline{C}H_2$), 30.52 ($\underline{C}H_2$), 39.95 ($\underline{C}H_2$), 55.49 (O$\underline{Me}$), 60.62 (O$\underline{Me}$), 60.97 (O$\underline{Me}$), 106.37 (Ar$\underline{C}$H), 120.22 (q$\underline{C}$), 141.08 (q$\underline{C}$), 141.97 (q$\underline{C}$), 154.68 (q$\underline{C}$), 156.52 (q$\underline{C}$), 195.57 ($\underline{C}$=O).

Formation of 5,6,7,8-tetrahydronaphtho[2,3-*d*][1,3]dioxol-5-one (2.22)

1st Step

Synthesis of intermediate, 3-(1,3-benzodioxol-5-yl)-1-propanol (2.17)[191]

Synthesised from 3-(1,3-benodioxol-5-yl)propanoic acid (1.65g, 8.51 mmol) using the method described for the preparation of **(2.11)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). Clear oil **(2.17)** (1.36g, 89%). ν_{max} (CCl_4)/ cm^{-1} 3350.1, 2943.0, 2843.2, 1497.5. ^1H NMR δ_H ppm 1.86 (2H, m, C$\underline{H_2}$), 2.64 (2H, m, C$\underline{H_2}$), 3.67 (2H, m, C$\underline{H_2}$), 5.92 (2H, s, OC$\underline{H_2}$O), 6.71 (3H, m, 3 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 31.33 ($\underline{C}H_2$), 33.94 ($\underline{C}H_2$), 61.61 ($\underline{C}H_2$OH), 100.28 (O$\underline{C}H_2$O), 107.69 (Ar$\underline{C}$H), 108.41 (Ar$\underline{C}$H), 120.64 (Ar$\underline{C}$H), 135.19 (q$\underline{C}$), 145.17 (q$\underline{C}$), 147.13 (q$\underline{C}$).

2nd Step

Synthesis of 5-(3-bromopropyl)-1,3-benzodioxole (2.18)[192]

Synthesised from **(2.17)** (1.55g, 8.61 mmol) using the method described for the preparation of **(2.12)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 5:1). Clear oil **(2.18)** (1.9g, 91%). ν_{max} (CCl_4)/ cm^{-1} 2931.0, 2880.2, 1496.3, 1110.0. ^1H NMR δ_H ppm 2.14 (2H, qn, J 14.0Hz, 7.0Hz, $CH_2C\underline{H_2}$), 2.72 (2H, t, J 7.2Hz, C$\underline{H_2}$), 3.40 (2H, t, J 6.5Hz, C$\underline{H_2}$), 5.94 (2H, s, OC$\underline{H_2}$O), 6.71 (3H, m, 3 x Ar$\underline{H}$). ^{13}C

NMR δ_c ppm 32.44 ($\underline{C}H_2$), 33.20 ($\underline{C}H_2$), 33.89 ($\underline{C}H_2$), 100.36 ($O\underline{C}H_2O$), 107.78 (Ar$\underline{C}$H), 108.48 (Ar$\underline{C}$H), 120.90 (Ar$\underline{C}$H), 133.82 (q$\underline{C}$), 145.44 (q$\underline{C}$), 147.25 (q$\underline{C}$).

3rd Step

Synthesis of intermediate, 3-(1,3-benzodioxol-5-yl)propyl cyanide (2.19)[193]

Synthesised from **(2.18)** (0.88g, 3.62 mmol) using the method described for the preparation of **(2.13)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). Afforded **(2.19)** as an oil (0.63g, 92%). ν_{max} (CCl_4)/ cm^{-1} 2931.0, 2880.2, 1496.3, 1110.0. ^{1}H NMR δ_H ppm 1.95 (2H, qn, J, 7.2Hz, 14.5Hz, C$\underline{H}_2$), 2.32 (2H, t, J 7.2Hz, C$\underline{H}_2$), 2.71 (2H, t, J 7.5Hz, C$\underline{H}_2$), 5.95 (2H, s, OC$\underline{H}_2$O), 6.70 (3H, m, 3 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 15.79 ($\underline{C}H_2$), 26.66 ($\underline{C}H_2$), 33.61 ($\underline{C}H_2$), 100.50 ($O\underline{C}H_2O$), 107.92 (Ar$\underline{C}$H), 108.30 (Ar$\underline{C}$H), 119.07 ($\underline{C}$N), 120.90 (Ar$\underline{C}$H), 133.97 (q$\underline{C}$), 145.70 (q$\underline{C}$), 147.39 (q$\underline{C}$).

4th Step

Synthesis of intermediate, 4-(1,3-benzodioxol-5-yl)butanoic acid (2.20)[194]

Synthesised from **(2.19)** (0.36g, 1.91 mmol) using the method described for the preparation of **(2.14)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 1:1). White solid **(2.20)** (0.39g, 98%). ν_{max} (KBr)/ cm^{-1} 3104.2, 2926.2, 1700.9. ^{1}H NMR δ_H ppm 1.67 (2H, m, $CH_2C\underline{H}_2$), 2.37 (2H, m, C$\underline{H}_2$), 2.57 (2H, m, C$\underline{H}_2$), 5.93 (2H, s, OC$\underline{H}_2$O), 6.70 (3H, m, 3 x Ar$\underline{H}$), 10.27 (1H, br, COO$\underline{H}$). ^{13}C NMR δ_c ppm 23.68 ($\underline{C}H_2$), 30.57 ($\underline{C}H_2$), 33.48 ($\underline{C}H_2$), 100.29 ($O\underline{C}H_2O$), 107.85 (Ar$\underline{C}$H), 108.36 (Ar$\underline{C}$H), 120.63 (Ar$\underline{C}$H), 135.41 (q$\underline{C}$), 145.12 (q$\underline{C}$), 147.08 (q$\underline{C}$), 179.65 ($\underline{C}$OOH).

5th Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl-4-(1,3-benzodioxol-5-yl) butanoate (2.21)

Synthesised from **(2.20)** (0.34g, 1.63 mmol) using PFP (0.37g, 2.00 mmol) and DCC (0.52g, 2.5 mmol) by the method described for the preparation of **(2.15)**. Purified by flash column

chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). White solid **(2.21)** (0.58g, 95%). ν_{max} (KBr)/ cm^{-1} 2930.2, 1791.2, 1627.8, 1244.8, 1091.6. ^1H NMR δ_H ppm 2.07 (2H, m, $C\underline{H}_2$), 2.57 (4H, m, $C\underline{H}_2C\underline{H}_2$), 5.95 (2H, s, $OC\underline{H}_2O$), 6.71 (3H, m, 3 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 26.07 ($\underline{C}H_2$), 31.89 ($\underline{C}H_2$), 33.95 ($\underline{C}H_2$), 100.42 ($O\underline{C}H_2O$), 107.82 (Ar$\underline{C}$H), 108.37 (Ar$\underline{C}$H), 120.87 (Ar$\underline{C}$H), 133.97 (q$\underline{C}$), 145.50 (q$\underline{C}$), 147.29 (q$\underline{C}$), 168.86 ($\underline{C}$=O).

6th Step-cyclisation of (2.21) to afford (2.22)

Synthesis of 5,6,7,8-tetrahydronaphtho[2,3-d][1,3]dioxol-5-one (2.22)[194]

Synthesised from **(2.21)** (0.35g, 0.94 mmol) using the method described for the preparation of **(2.16)**. Reaction time was 2 hours. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). White solid **(2.22)** (0.14g, 79%). M.pt. 75-76°C. ^1H NMR δ_H ppm 2.10 (2H, m, $C\underline{H}_2$), 2.61 (2H, m, $C\underline{H}_2$), 2.88 (2H, m, $C\underline{H}_2$), 6.01 (2H, s, $OC\underline{H}_2O$), 6.67 (1H, s, Ar$\underline{H}$), 7.46 (1H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 22.98 ($\underline{C}H_2$), 29.54 ($\underline{C}H_2$), 38.07 ($\underline{C}H_2$), 101.17 ($O\underline{C}H_2O$), 105.76 (Ar$\underline{C}$H), 107.52 (Ar$\underline{C}$H), 126.76 (Ar$\underline{C}$H), 141.31 (q$\underline{C}$), 146.47 (q$\underline{C}$), 151.76 (q$\underline{C}$), 196.96 ($\underline{C}$=O).

Formation of 6,7-dihydro-5*H*-indeno[5,6-*d*][1,3]dioxol-5-one (2.24)

1st Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 3-(1,3-benzodioxol-5-yl)propanoate (2.23)

To a stirred solution of 3-(1,3-benzodioxol-5-yl)propanoic acid (1.0g, 5.15 mmol) in DCM (10ml) was added PFP (1.13g, 6.14 mmol) and DCC (1.59g, 7.72 mmol) at 0°C. After 2 hours, the suspension was filtered. The filtrate was concentrated in volume and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.23)** as a white powder (1.60g, 86%). M.pt. 38°C. ν_{max} (CCl_4)/ cm^{-1} 2934.6, 2110.9, 1790.3, 1520.9. ^1H NMR δ_H ppm 2.94 (2H, m, $C\underline{H}_2$), 3.04 (2H, m, $C\underline{H}_2$), 5.96 (2H, s, $OC\underline{H}_2O$),

6.73 (3H, m, ArH). ^{19}F NMR δ_F ppm -153.11 (d, 2 x ArF), -158.57 (t, ArF), -162.88 (t, 2 x ArF). ^{13}C NMR δ_c ppm 30.40 (CH_2), 35.21 (CH_2), 100.90 (OCH_2O), 108.34 (ArCH), 108.62 (ArCH), 121.11 (ArCH), 132.57 (qC), 145.87 (qC), 147.40 (qC), 168.17 (C=O).

2nd Step-cyclisation of (2.23) to afford (2.24)

Synthesis of 6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-one (2.24)[195]

The pentafluorophenyl ester **(2.23)** (1.5g, 4.16 mmol) was dissolved in PPA (12g) and heated to 70°C with occasional stirring for 1 hour. On completion, the reaction was quenched by the addition of ice (100g) and extracted with diethyl ether (5 x 75ml). The organic extracts were combined, dried over sodium sulphate, filtered and evaporated to leave the crude product, which was purified by flash column chromatography (stationary phase, silica gel 230-400 mesh; mobile phase, 2:1; hexane/ethyl acetate). The homogenous fractions were collected and the solvent removed under reduced pressure leaving **(2.24)** as a pale yellow solid (0.65g, 89%). ν_{max} (CCl_4)/ cm^{-1} 2930.1, 1689.7, 1606.8. ^{1}H NMR δ_H ppm 2.67 (2H, m, CH_2), 3.02 (2H, m, CH_2), 6.06 (2H, s, OCH_2O), 6.83 (1H, s, ArH), 7.09 (1H, s, ArH). ^{13}C NMR δ_c ppm 25.31 (CH_2), 36.25 (CH_2), 101.71 (OCH_2O) 101.80 (ArCH), 105.23 (ArCH), 131.27 (qC), 147.78 (qC), 152.14 (qC), 153.74 (qC), 204.31 (C=O).

Formation of 4,5,6-trimethoxy-1-indanone (2.28)

1st Step

Synthesis of intermediate, 3-(2,3,4-trimethoxyphenyl)-2-propenoic acid (2.25)

To a stirred solution of 2,3,4-trimethoxybenzaldehyde (5.0g, 25.5 mmol) in pyridine (15ml) and piperidine (0.3ml) was added malonic acid (5.31g, 51.0 mmol). The reaction mixture was subsequently refluxed for 2 hours. On completion, the reaction was cooled to room temperature and quenched by the addition of 2M aq. HCl (100ml). The crude product was extracted with ethyl acetate (3 x 50ml), and dried over sodium sulphate. After filtration, the solvent was removed *in vacuo* to afford the acid **(2.25)** as an oil (5.23g, 86%). The ^{1}H NMR and ^{13}C NMR data has been previously reported[196].

2nd Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 3-(2,3,4,-trimethoxyphenyl)propanoate (2.27)

To a stirred solution of **(2.25)** (4.0g, 16.8 mmol) in ethanol (15ml) was added 10% Pd/C (3.0g). The reaction mixture was stirred under an atmosphere of hydrogen for 24 hours. The mixture was then filtered and the solvent was removed under reduced pressure to afford **(2.26)** as a white solid (3.96g, 98%). Compound **(2.26)** (1.0g, 4.16 mmol) was subsequently re-dissolved in DCM (10ml) at 0°C. To this solution was added PFP (0.92g, 5.0 mmol) and DCC (1.29g, 6.26 mmol). The reaction was allowed to proceed for two hours. The suspension was filtered and the filtrate was reduced in volume before being purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.27)** as a white waxy solid (1.56g, 93%). M.pt. 81-82°C. ν_{max} (CCl_4)/ cm^{-1} 2931.0, 2118.3, 1782.8, 1522.6. ^{1}H NMR δ_H ppm 2.93-3.07 (4H, m, 2 x C$\underline{H}_2$), 3.86 (3H, s, O$\underline{Me}$), 3.89 (3H, s, O$\underline{Me}$), 3.95 (3H, s, O$\underline{Me}$), 6.63 (1H, d, J 8.5Hz, Ar$\underline{H}$), 6.89 (1H, d, J 8.5Hz, Ar$\underline{H}$). ^{19}F NMR δ_F ppm -153.15 (d, 2 x Ar$\underline{F}$), -158.86 (t, Ar$\underline{F}$), -163.10 (dd, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 25.38 ($\underline{C}H_2$), 34.02 ($\underline{C}H_2$), 55.53 (O$\underline{Me}$), 60.23 (O$\underline{Me}$), 60.38 (O$\underline{Me}$), 106.76 (Ar$\underline{C}$H), 123.37 (Ar$\underline{C}$H), 124.68 (2 x q$\underline{C}$), 141.84 (q$\underline{C}$), 151.42 (q$\underline{C}$), 152.38 (q$\underline{C}$), 168.54 ($\underline{C}$=O).

3rd Step-cyclisation of (2.27) to afford (2.28)

Synthesis of 4,5,6-trimethoxy-1-indanone (2.28)[111]

Synthesised from **(2.27)** (1.50g, 3.70 mmol) using the method described for the preparation of **(2.24)**. Reaction time was 3.5 hours. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). Afforded **(2.28)** as a pale yellow solid (0.79g, 96%). M.pt. 76-78°C. ν_{max} (CCl_4)/ cm^{-1} 2945.3, 1687.8, 1601.2. ^{1}H NMR δ_H ppm 2.66 (2H, t, J 5.5Hz, C$\underline{H}_2$), 3.04 (2H, t, J 5.5Hz, ArC$\underline{H}_2$), 3.88 (3H, s, O$\underline{Me}$), 3.95 (3H, s, O$\underline{Me}$), 3.96 (3H, s, O$\underline{Me}$), 7.02 (1H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 22.31 ($\underline{C}H_2$), 36.04 ($\underline{C}H_2$), 56.13 (O$\underline{Me}$), 60.48 (O$\underline{Me}$), 60.96 (O$\underline{Me}$), 100.59 (Ar$\underline{C}$H), 132.02 (q$\underline{C}$), 141.09 (q$\underline{C}$), 147.21 (q$\underline{C}$), 149.56 (q$\underline{C}$), 153.79 (q$\underline{C}$), 205.49 (C=O).

Formation of 5,6,7-trimethoxy-1-indanone (2.32)

1st Step

Synthesis of intermediate, 3-(3,4,5-trimethoxyphenyl)-2-propenoic acid (2.29)

Synthesised from 3,4,5-trimethoxybenzaldehyde (5.01g, 25.59 mmol) and malonic acid (5.32g, 51.19 mmol) in pyridine (15ml) and piperidine (0.3ml) using the method described for the preparation of **(2.25)**. Afforded **(2.29)** as a white solid (4.63g, 76%). The ^{1}H NMR and ^{13}C NMR data has previously published[197].

2nd Step

Synthesis of intermediate, 3-(3,4,5-trimethoxyphenyl)-2-propanoic acid (2.30)

Synthesised from **(2.29)** (3.98g, 16.75 mmol) using the method described for the preparation of **(2.26)**. Afforded **(2.30)** as a clear oil (3.90g, 97%). The ^{1}H NMR and ^{13}C NMR data has been previously published[198].

3rd Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 3-(3,4,5-trimethoxyphenyl)propanoate (2.31)

Synthesised from **(2.30)** (0.97g, 4.04 mmol), PFP (0.9g, 4.89 mmol) and DCC (1.11g, 5.38 mmol) using the method described for the preparation of **(2.27)**. Reaction time was 1.5 hours. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). Afforded **(2.31)** as a white waxy solid (1.42g, 86%). M.pt. 23°C. ν_{max} (CCl_4)/ cm^{-1} 2932.9, 2118.9, 1789.8, 1520.4. ^{1}H NMR δ_H ppm 2.55 (2H, m, C$\underline{H_2}$), 2.96 (2H, m, ArC$\underline{H_2}$), 3.86 (3H, s, O$\underline{Me}$), 3.89 (3H, s, O$\underline{Me}$), 3.95 (3H, s, O$\underline{Me}$), 6.63 (1H, d, Ar$\underline{H}$), 6.89 (1H, d, Ar$\underline{H}$). ^{19}F NMR δ_F ppm -153.15 (d, 2 x Ar$\underline{F}$), -158.62 (t, Ar$\underline{F}$), -163.10 (dd, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 25.38 ($\underline{C}H_2$), 34.02 ($\underline{C}H_2$), 55.92 (O$\underline{Me}$), 60.63 (O$\underline{Me}$), 60.79 (O$\underline{Me}$), 107.13 (Ar$\underline{C}$H), 123.79 (Ar$\underline{C}$H), 124.68 (q$\underline{C}$), 141.84 (q$\underline{C}$), 151.42 (q$\underline{C}$), 152.96 (2 x q$\underline{C}$), 168.95 ($\underline{C}$=O).

4th Step-cyclisation of (2.31) to afford (2.32)

Synthesis of 5,6,7-trimethoxy-1-indanone (2.32)[110]

Synthesised from **(2.31)** (1.4g, 3.45 mmol) using the method described for the preparation of **(2.28)**. Reaction time was 3 hours. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 5:1). Afforded **(2.32)** as a pale yellow solid (0.75g, 98%). M.pt. 106°C. ν_{max} (CCl_4)/ cm^{-1} 2948.3, 1693.5, 1595.2. ^1H NMR δ_H ppm 2.63 (2H, t, J 6.0Hz, C$\underline{H_2}$), 3.00 (2H, t, J 6.0Hz, ArC$\underline{H_2}$), 3.84 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 4.03 (3H, s, O$\underline{Me}$), 6.66 (1H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 25.21 ($\underline{C}H_2$), 36.72 ($\underline{C}H_2$), 55.78 (O$\underline{Me}$), 60.88 (O$\underline{Me}$), 61.43 (O$\underline{Me}$), 103.31 (Ar$\underline{C}$H), 122.42 (q$\underline{C}$), 140.23 (q$\underline{C}$), 151.10 (q$\underline{C}$), 152.69 (q$\underline{C}$), 159.20 (q$\underline{C}$), 202.55 ($\underline{C}$=O).

Formation of 1-indanone (2.39)

1st Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 3-phenylpropanoate (2.33)

Synthesised from 3-phenylpropanoic acid (1.0g, 6.66 mmol), PFP (1.29g, 7.00 mmol) and DCC (1.55g, 7.50 mmol) using the method described for the preparation of **(2.27)**. Reaction time was 65 minutes. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). White solid (1.74g, 83%). M.pt. 30°C. ν_{max} (CCl_4)/ cm^{-1} 2930.3, 1780.9, 1515.4, 1096.7. ^1H NMR δ_H ppm 3.00 (2H, t, J 7.5 Hz, C$\underline{H_2}$), 3.10 (2H, t, J 7.5Hz, C$\underline{H_2}$), 7.28 (5H, m, 5 x Ar$\underline{H}$). ^{19}F NMR δ_F ppm -153.15 (d, 2 x Ar$\underline{F}$), -158.65 (t, Ar$\underline{F}$), -162.96 (t, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 30.20 ($\underline{C}H_2$), 34.46 ($\underline{C}H_2$), 126.23 (Ar$\underline{C}$H), 127.75 (2 x Ar$\underline{C}$H), 128.23 (2 x Ar$\underline{C}$H), 138.82 (q$\underline{C}$), 146.25 (q$\underline{C}$), 168.24 ($\underline{C}$=O).

2nd Step-cyclisation of (2.33) to afford (2.39)

Synthesis of 1-indanone (2.39)

Synthesised from **(2.33)** (0.52g, 1.63 mmol) by the method described for the preparation of **(2.28)**. Reaction time was 5 hours. Purified by flash column chromatography (stationary phase;

silica gel 230-400 mesh, mobile phase; 6:1 hexane/ethyl acetate). Clear oil (0.15g, 72%). The ^{1}H NMR and ^{13}C NMR data has been previously published[199].

Synthesis of 1,2,3,4-tetrahydro-1-naphthalenone (2.40)

1st Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 4-phenylbutanoate (2.34)

Synthesised from 4-phenylbutanoic acid (1.0g, 6.09 mmol), PFP (1.2g, 6.5 mmol) and DCC (1.44g, 7.0 mmol) using the method described for the preparation of **(2.27)**. Reaction time was 65 minutes. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 7:1 hexane/ethyl acetate). White solid (1.94g, 97%). M.pt. 31-32°C. ν_{max} (CCl_4)/ cm^{-1} 2926.4, 1778.3, 1103.8. ^{1}H NMR δ_H ppm 2.14 (2H, qn, J 7.3Hz, C$\underline{H_2}$), 2.70 (2H, t, J 7.3Hz, C$\underline{H_2}$), 2.78 (2H, t, J 7.5Hz, C$\underline{H_2}$), 7.2 (5H, m, 5 x Ar$\underline{H}$). ^{19}F NMR δ_F ppm -153.40 (d, 2 x Ar$\underline{F}$), -158.76 (t, Ar$\underline{F}$), -163.01 (t, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 25.85 ($\underline{C}H_2$), 32.05 ($\underline{C}H_2$), 34.27 ($\underline{C}H_2$), 125.80 (Ar$\underline{C}$H), 128.01 (2 x Ar$\underline{C}$H), 128.09 (2 x Ar$\underline{C}$H), 140.21 (q$\underline{C}$), 168.79 ($\underline{C}$=O).

2nd Step-cyclisation of (2.34) to afford (2.40)

Synthesis of 1,2,3,4-tetrahydro-1-naphthalenone (2.40)

Synthesised from **(2.34)** (1.02g, 3.06 mmol) by the method described for the preparation of **(2.28)**. Reaction time was 4 hours. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 9:1 hexane/ethyl acetate). Clear oil (0.36g, 80%). The ^{1}H NMR and ^{13}C NMR data has been previously published[200].

Formation of 6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (2.41)

1st Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 5-phenylpentanoate (2.35)

Synthesised from 5-phenylpentanoic acid (1.0g, 5.61 mmol), PFP (1.10g, 6.0 mmol) and DCC (1.34g, 6.5 mmol) using the method described for the preparation of **(2.27)**. Reaction time was 40 minutes. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 7:1 hexane/ethyl acetate). White solid (1.68g, 87%). ^{1}H NMR δ_H ppm 1.3-1.4 (2H, m, C$\underline{H}_2$), 1.7-1.95 (4H, m, C$\underline{H}_2$C$\underline{H}_2$), 2.7 (2H, t, J 7.0Hz, C$\underline{H}_2$), 7.22-7.34 (5H, m, Ar$\underline{H}$). ^{19}F NMR δ_F ppm -153.45 (d, 2 x Ar$\underline{F}$), -158.89 (t, Ar$\underline{F}$), -163.11 (t, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 23.88 ($\underline{C}H_2$), 30.06 ($\underline{C}H_2$), 32.69 ($\underline{C}H_2$), 34.97 ($\underline{C}H_2$), 125.46 (Ar$\underline{C}$H), 127.87 (2 x Ar$\underline{C}$H), 127.92 (2 x Ar$\underline{C}$H), 141.24 (q$\underline{C}$), 168.84 ($\underline{C}$=O).

2nd Step-cyclisation of (2.35) to afford (2.41)

Synthesis of 6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (2.41)

Synthesised from **(2.35)** (1.0g, 2.85 mmol) by the method described for the preparation of **(2.28)**. Reaction time was 6 hours. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 9:1 hexane/ethyl acetate). Clear oil (0.32g, 70%). The ^{1}H NMR and ^{13}C NMR data has been previously published[201].

Formation of 4-chromanone (2.42)

1st Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 3-phenoxypropanoate (2.36)

Synthesised from 3-phenoxypropanoic acid (1.0g, 6.02 mmol), PFP (1.29g, 7.0 mmol) and DCC (1.55g, 7.5 mmol) using the method described for the preparation of **(2.27)**. Reaction time was 120 minutes. Purified by flash column chromatography (stationary phase; silica gel 230-400

mesh, mobile phase; 4:1 hexane/ethyl acetate). White solid (1.65g, 83%). M.pt. 38°C. ν_{max} (KBr)/ cm^{-1} 2926.4, 1788.5, 1510.7, 1109.8. ^{1}H NMR δ_H ppm 3.15 (2H, t, J 6.0 Hz, $C\underline{H}_2$), 4.4 (2H, t, J 6.0Hz, $C\underline{H}_2$), 6.9-7.4 (5H, m, 5 x Ar$\underline{H}$). ^{19}F NMR δ_F ppm -152.96 (d, 2 x Ar$\underline{F}$), -158.31 (t, Ar$\underline{F}$), -162.76 (t, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 33.51 ($\underline{C}H_2$), 62.38 (O$\underline{C}H_2$), 114.26 (2 x Ar$\underline{C}$H), 120.98 (Ar$\underline{C}$H), 127.88 (q$\underline{C}$), 129.08 (2 x Ar$\underline{C}$H).

2nd Step-cyclisation of (2.36) to afford (2.42)

Synthesis of 4-chromanone (2.42)

Synthesised using **(2.36)** (1.0g, 3.01 mmol) by the method described for the preparation of **(2.28)**. Reaction time was 6 hours. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 6:1 hexane/ethyl acetate). Clear oil (0.21g, 48%). The ^{1}H NMR and ^{13}C NMR data has been previously published[202].

Formation of 2,3,4,5-tetrahydro-1-benzoxepin-5-one (2.43)

1st Step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 4-phenyoxybutanoate (2.37)

Synthesised from 4-phenoxybutanoic acid (1.0g, 5.56 mmol), PFP (1.2g, 6.5 mmol) and DCC (1.44g, 7.0 mmol) using the method described for the preparation of **(2.27)**. Reaction time was 50 minutes. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ ethyl acetate). White solid (1.79g, 93%). ^{1}H NMR δ_H ppm 2.27 (2H, qn, J 6.0Hz, $CH_2C\underline{H}_2C\underline{H}_2$), 2.93 (2H, t, J 6.0Hz, $C\underline{H}_2C{=}O$), 4.10 (2H, t, J 6.0Hz, $OC\underline{H}_2$), 6.93 (2H, d, 8.0Hz, 2 x Ar$\underline{H}^{meta}$), 6.98 (1H, t, 8.0Hz, Ar$\underline{H}^{para}$), 7.32 (2H, t, 7.0Hz, 2 x Ar$\underline{H}^{ortho}$). ^{19}F NMR δ_F ppm -153.23 (d, 2 x Ar$\underline{F}$), -158.59 (t, Ar$\underline{F}$), -162.88 (t, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 24.10 ($\underline{C}H_2$), 29.57 ($\underline{C}H_2$), 34.46 ($\underline{C}H_2$), 114.05 (2 x Ar$\underline{C}$H), 120.54 (Ar$\underline{C}$H), 129.03 (2 x Ar$\underline{C}$H), 158.20 (q$\underline{C}$), 168.19 ($\underline{C}{=}O$).

2nd Step-cyclisation of (2.37) to afford (2.43)

Synthesis of 2,3,4,5-tetrahydro-1-benzoxepin-5-one (2.43)

Synthesised from **(2.37)** (1.0g, 2.89 mmol) by the method described for the preparation of **(2.28)**. Reaction time was 7 hours. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 9:1 hexane/ethyl acetate). Clear oil (0.33g, 71%). The ^{1}H NMR and ^{13}C NMR data has been previously published[203].

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 4-phenylhexanoate (2.38)

Synthesised from phenylhexanoic acid (1.0g, 5.20 mmol), PFP (1.10g, 5097 mmol) and DCC (1.34g, 6.50 mmol) using the method described for the preparation of **(2.27)**. Reaction time was 120 minutes. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 10:1 hexane/ethyl acetate). White solid (1.45g, 78%). ^{1}H NMR δ_H ppm 1.20-2.70 (10H, complex m, 5 x C$\underline{H}_2$), 7.20-7.31 (5H, m, 5 x Ar$\underline{H}$). ^{19}F NMR δ_F ppm -153.42 (d, 2 x Ar$\underline{F}$), -158.87 (t, Ar$\underline{F}$), -163.09 (t, 2 x Ar$\underline{F}$). ^{13}C NMR δ_c ppm 25.41 ($\underline{C}H_2$), 28.37 ($\underline{C}H_2$), 30.83 ($\underline{C}H_2$), 33.15 ($\underline{C}H_2$), 35.58 ($\underline{C}H_2$), 125.28 (Ar$\underline{C}$H), 127.83 (2 x Ar$\underline{C}$H), 127.88 (2 x Ar$\underline{C}$H), 141.77 (q$\underline{C}$), 168.95 ($\underline{C}$=O).

Synthesis of 2,3,4-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5H-benzo[a]cycloheptene (2.44)

To a stirred 1M solution of 4-methoxyphenylmagnesium bromide (4.0ml, 4.0 mmol) in dry THF was added **(2.01)** (1.0g, 4.0 mmol) dissolved in dry THF (4ml) drop-wise under an N_2 atmosphere at 0°C for 20 minutes. The reaction was then refluxed for 2 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (50ml) and the product was extracted with diethyl ether (3 x 20ml). The extract was dried over sodium sulphate, filtered and the filtrate was concentrated *in vacuo* before being purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.44)** as an oil (0.75g, 55%). ν_{max} (CCl_4)/ cm^{-1} 2932.8, 1508.9, 1115.3. HRMS: found 341.1200 (MH^+), requires

($C_{21}H_{24}O_4$) 340.1675. GCMS m/z (%) 340 (100), 297 (13). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.97 (2H, q, J 7.0Hz, 14.5Hz, CHC$\underline{H_2}$), 2.13 (2H, m, $CH_2C\underline{H_2}CH_2$), 2.67 (2H, t, J 7.0Hz, ArC$\underline{H_2}$), 3.70 (3H, s, O$\underline{Me}$), 3.83 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 3.95 (3H, s, O$\underline{Me}$), 6.35 (1H, t, J 8.0Hz, C=C$\underline{H}$), 6.39 (1H, s, {A-ring}Ar$\underline{H}$), 6.86 (2H, d, J 8.5Hz, {C-ring}Ar$\underline{H}$), 7.24 (2H, d, J 8.5Hz {C-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm 23.15 ($\underline{C}H_2$), 25.06 ($\underline{C}H_2$), 34.5 ($\underline{C}H_2$), 54.8 (O$\underline{Me}$), 55.5 (O$\underline{Me}$), 60.3 (O$\underline{Me}$), 61.04 (O$\underline{Me}$), 113.1 (2 x Ar$\underline{C}$H), 126.39 (q$\underline{C}$), 126.48 (C=$\underline{C}$H), 127.2 (Ar$\underline{C}$H), 127.86 (q$\underline{C}$), 128.52 (2 x Ar$\underline{C}$H), 134.3 (q$\underline{C}$), 135.8 (q$\underline{C}$), 140.7 (q$\underline{C}$), 141.8 (q$\underline{C}$), 150.47 (q$\underline{C}$), 158.44 (q$\underline{C}$).

Synthesis of 2,3,4-trimethoxy-9-(3-methoxyphenyl)-6,7-dihydro-5H-benzo[a]cycloheptene (2.45)

To a stirred 1M solution of 3-methoxyphenylmagnesium bromide (4.0ml, 4.0 mmol) in dry THF was added drop-wise **(2.01)** (1.0g, 4.0 mmol) dissolved in dry THF (4ml) under anhydrous conditions at 0°C for 20 minutes. The reaction was then refluxed for 2 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (50ml) and the product was extracted with diethyl ether (3 x 20ml). The combined extracts were dried over sodium sulphate, filtered and the filtrate concentrated *in vacuo* before being purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.45)** as an oil (0.89g, 66%). ν_{max} (CCl_4)/ cm^{-1} 2935.0, 2842.7, 1596.6, 1115.9. HRMS: found 341.1192 (MH^+), requires ($C_{21}H_{24}O_4$) 340.1675. GCMS m/z (%) 340 (100), 298 (8). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.97 (2H, m, C$\underline{H_2}$), 2.14 (2H, m, C$\underline{H_2}$), 2.68 (2H, t, J 6.7Hz, C$\underline{H_2}$), 3.70 (3H, s, O$\underline{Me}$), 3.81 (3H, s, O$\underline{Me}$), 3.93 (3H, s, O$\underline{Me}$), 3.95 (3H, s, O$\underline{Me}$), 6.39 (1H, s, {A-ring}Ar$\underline{H}$), 6.44 (1H, t, J 7Hz, C=C$\underline{H}$), 6.85 (3H, m, {C-ring}Ar$\underline{H}$), 7.24 (1H, t, J 7.5Hz, {C-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm 23.14 ($\underline{C}H_2$), 25.12 ($\underline{C}H_2$), 34.37 ($\underline{C}H_2$), 54.79 (O$\underline{Me}$), 55.59 (O$\underline{Me}$), 60.39 (O$\underline{Me}$), 61.09 (O$\underline{Me}$), 108.51 (Ar$\underline{C}$H), 111.99 (Ar$\underline{C}$H), 113.21 (Ar$\underline{C}$H), 120.14 (Ar$\underline{C}$H), 127.82 (q$\underline{C}$), 128.23 (Ar$\underline{C}$H), 128.58 (C=$\underline{C}$H), 135.49 (q$\underline{C}$), 140.76 (q$\underline{C}$), 142.28 (q$\underline{C}$), 143.14 (q$\underline{C}$), 150.40 (q$\underline{C}$), 150.54 (q$\underline{C}$), 159.05 (q$\underline{C}$).

Synthesis of 1,2,3-trimethoxy-5-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-benzo[a]cycloheptene (2.46)

To a solution of **(2.44)** (0.10g, 0.29 mmol) in ethanol/ethyl acetate (1:1, 6ml) was added 10% Pd/C (0.10g). The reaction mixture was stirred under an atmosphere of hydrogen for 48 hours. On completion, the reaction was filtered and the solvent was removed *in vacuo* to afford the product as a white solid **(2.46)**. This was re-dissolved in DCM (~2ml) and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 5:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.46)** as a white powder (0.95g, 95%). M.pt 60-61°C. ν_{max} (CCl_4)/ cm^{-1} 2926.7, 2852.3, 1511.7, 1119.1. HRMS: found 343.1877 (MH^+), requires ($C_{21}H_{26}O_4$) 342.1831. GCMS m/z (%) 342 (100) 312 (23), 269 (3) 234 (10). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.47 (1H, m, C<u>H</u>), 1.83 (2H, m, C<u>H</u>$_2$), 2.08 (3H, m, C<u>H</u>C<u>H</u>$_2$), 2.3 (1H, m, C<u>H</u>CH$_2$), 3.03 (1H, m, C<u>H</u>CH$_2$), 3.62 (3H, s, O<u>Me</u>), 3.84 (6H, s, 2 x O<u>Me</u>), 3.89 (3H, s, O<u>Me</u>), 4.20 (1H, d, J 8.5Hz, ArC<u>H</u>Ar), 6.09 (1H, s, {A-ring}Ar<u>H</u>), 6.91 (2H, d, J 8.5Hz, {C-ring}Ar<u>H</u>), 7.13 (2H, d, J 9.0Hz, {C-ring}Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.99 (<u>C</u>H$_2$), 27.24 (<u>C</u>H$_2$), 29.61 (<u>C</u>H$_2$), 33.72 (<u>C</u>H$_2$), 48.67 (<u>C</u>H), 54.78 (O<u>Me</u>), 55.32 (O<u>Me</u>), 60.33 (O<u>Me</u>), 60.85 (O<u>Me</u>), 108.30 (Ar<u>C</u>H), 113.29 (2 x Ar<u>C</u>H), 128.38 (q<u>C</u>), 128.78 (2 x Ar<u>C</u>H), 136.39 (q<u>C</u>), 139.88 (q<u>C</u>), 141.35 (q<u>C</u>), 149.94 (q<u>C</u>), 150.62 (q<u>C</u>), 157.40 (q<u>C</u>).

Synthesis of 1,2,3-trimethoxy-5-(3-methoxyphenyl)-6,7,8,9-tetrahydro-5H-benzo[a]cycloheptene (2.47)

To a solution of **(2.45)** (0.10g, 0.29 mmol) in ethanol/ethyl acetate (1:1, 6ml) was added 10% Pd/C (0.10g). The reaction mixture was stirred under an atmosphere of hydrogen for 48 hours. On completion, the mixture was filtered and the solvent was removed *in vacuo* to afford a pale yellow solid **(2.47)** This was re-dissolved in DCM (~2ml) and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 5:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.47)** as a white powder (0.093g, 94%). M.pt 101-102°C. ν_{max} (CCl_4)/ cm^{-1} 2927.6, 1598.2, 1588.3, 1489.2, 1118.9. HRMS: found 343.1943 (MH^+), requires ($C_{21}H_{26}O_4$) 342.1831. GCMS m/z

(%) 342 (100), 312 (25). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.4 (1H, m, C<u>H</u>), 1.82 (2H, m, C<u>H</u>$_2$), 1.98 (1H, m, C<u>H</u>), 2.15 (2H, m, C<u>H</u>$_2$), 2.74 (1H, m, C<u>H</u>), 3.02 (1H, m, C<u>H</u>), 3.62 (3H, s, O<u>Me</u>), 3.81 (3H, s, O<u>Me</u>), 3.83 (3H, s, O<u>Me</u>), 3.88 (3H, s, O<u>Me</u>), 4.22 (1H, d, J 8.5Hz, ArC<u>H</u>Ar), 6.12 (1H, s, {A-ring}Ar<u>H</u>), 6.79 (3H, m, {C-ring}Ar<u>H</u>), 7.26 (1H, t, J 7.5Hz, {C-ring}Ar<u>H</u>). ^{13}C NMR δ_c ppm 25.01 (<u>C</u>H$_2$), 27.22 (<u>C</u>H$_2$), 29.51 (<u>C</u>H$_2$), 33.42 (<u>C</u>H$_2$), 49.57 (<u>C</u>H), 54.71 (O<u>Me</u>), 55.33 (O<u>Me</u>), 60.34 (O<u>Me</u>), 60.86 (O<u>Me</u>), 108.42 (Ar<u>C</u>H), 110.83 (Ar<u>C</u>H), 113.96 (Ar<u>C</u>H), 120.44 (Ar<u>C</u>H), 128.47 (q<u>C</u>), 128.78 (Ar<u>C</u>H), 139.95 (q<u>C</u>), 140.78 (q<u>C</u>), 145.91 (q<u>C</u>), 149.96 (q<u>C</u>), 150.62 (q<u>C</u>), 159.28 (q<u>C</u>).

<u>Formation of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenol (2.52)</u>

1st Step

Synthesis of intermediate, 5-bromo-2-methoxyphenol (2.48)

To a stirred solution of 5-bromo-2-anisaldehyde (2.0g, 9.3 mmol) in DCM (20ml) was added *m*CPBA (2.4g, 13.9 mmol) at 25°C. After 3 hours, the solvent was removed under reduced pressure and re-dissolved in methanol (100ml) to which potassium hydroxide (10.4g, 18.6 mmol) in water (25ml) was added drop-wise at room temperature. After another 2 hours, the reaction was quenched by the addition of 2M aq. HCl (50ml) and the product extracted with diethyl ether (3 x 30ml). The extracts were combined, dried over sodium sulphate, filtered and the solvent was removed under reduced pressure. The final product was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.48)** as a white waxy solid (1.7g, 90%). M.pt. 62-65°C. GCMS m/z (%) 202 (100), 154 (6). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 3.87 (3H, s, O<u>Me</u>), 5.67 (1H, br, O<u>H</u>), 6.73 (1H, d, J 9.0Hz, <u>H</u>-3'), 6.9 (1H, dd, J 2.5Hz, 9.0Hz, <u>H</u>-4'), 7.09 (1H, d, J 2.5Hz, <u>H</u>-6'). ^{13}C NMR δ_c ppm 55.80 (O<u>Me</u>), 112.78 (q<u>C</u>), 111.53 (Ar<u>C</u>H), 117.55 (Ar<u>C</u>H), 122.12 (Ar<u>C</u>H), 145.45 (q<u>C</u>), 146.05 (q<u>C</u>). The ^{1}H NMR and ^{13}C NMR data has been previously reported[204].

2nd Step

Synthesis of intermediate, (5-bromo-2-methoxyphenoxy)(tert-butyl)dimethylsilane (2.50)

To a stirred solution of phenol **(2.48)** (1.0g, 4.92 mmol) in DMF (5ml) was added imidazole (0.84g, 12.3 mmol) and *tert*-butyldimethylsilyl chloride (1.49g, 9.90 mmol) at room temperature. After 4 hours, the reaction was quenched by the addition of water (10ml) and the crude product was extracted with diethyl ether (3 x 10ml). The combined organic extracts were collected, dried over sodium sulphate, filtered and the solvent was removed under reduced pressure. The final product was isolated by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 9:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.50)** as an oil (1.50g, 96%). ν_{max} (CCl_4)/ cm^{-1} 2944.2, 2859.6, 1586.0, 1498.7. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.18 (6H, s, C<u>H</u>$_3$ SiC<u>H</u>$_3$), 1.02 (2H, m, C(C<u>H</u>$_3$)$_3$), 3.80 (3H, s, O<u>Me</u>), 6.73 (1H, d, J 9.0Hz, <u>H</u>-3'), 7.00 (1H, d, J 2.5Hz, <u>H</u>-6'), 7.04 (1H, dd, J 2.5Hz, 9.0Hz, <u>H</u>-4'). ^{13}C NMR δ_c ppm -4.69 (<u>C</u>H$_3$ Si<u>C</u>H$_3$), 18.41 (<u>C</u>(CH$_3$)$_3$), 55.61 (O<u>Me</u>), 112.36 (q<u>C</u>), 113.30 (Ar<u>C</u>H), 124.08 (Ar<u>C</u>H), 124.39 (Ar<u>C</u>H) 146.02 (q<u>C</u>), 150.45 (q<u>C</u>). The ^{1}H NMR and ^{13}C NMR data has been previously reported[205].

3rd Step

Synthesis of intermediate, tert-butyl[2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenoxy]dimethylsilane (2.51)

To a dry 3-necked 50ml round bottom flask was added magnesium turnings (0.046g, 1.91 mmol), anhydrous THF (2ml) and a crystal of iodine. To this mixture was added drop-wise a solution of **(2.50)** (0.56g, 1.76 mmol) dissolved in anhydrous THF (2ml) with vigorous stirring to maintain a gentle reflux. When the addition was complete, the mixture was refluxed for a further 15 minutes. The mixture was then allowed to cool to room temperature before **(2.01)** (0.3g, 1.2 mmol) dissolved in anhydrous THF (2ml) was added drop-wise. The reaction was then refluxed for a further 2 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (5ml) and the product was extracted with diethyl ether (3 x 10ml), dried over sodium sulphate and filtered before the filtrate was reduced in volume *in vacuo*. The resulting oil was purified by flash column chromatography (stationary phase: silica gel 230-400 mesh,

mobile phase: hexane/ethyl acetate 5:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(2.51)** as a clear oil (0.13g, 23%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.16 (6H, s, $C\underline{H}_3SiC\underline{H}_3$), 1.00 (9H, s, $SiC(C\underline{H}_3)_3$), 1.95 (2H, q, J 7.1Hz, 14.0Hz, $CH_2C\underline{H}_2CH_2$), 2.15 (2H, qn, J 7.04Hz, 14.0Hz, $CHC\underline{H}_2$), 2.66 (2H, t, J 7.04Hz, $ArC\underline{H}_2$), 3.70 (3H, s, O<u>Me</u>), 3.83 (3H, s, O<u>Me</u>), 3.92 (3H, s, O<u>Me</u>), 3.94 (3H, s, O<u>Me</u>), 6.31 (1H, t, J 7.2Hz, C=C<u>H</u>), 6.38 (1H, s, Ar<u>H</u>), 6.82 (3H, m, Ar<u>H</u>). ^{13}C NMR δ_c ppm -5.02 ($\underline{C}H_3Si\underline{C}H_3$), 17.97 ($\underline{C}(CH_3)_3$), 23.12 ($\underline{C}H_2$), 25.04 ($\underline{C}H_2$), 25.27 ($C(\underline{C}H_3)_3$), 34.54 ($\underline{C}H_2$), 55.11 (O<u>Me</u>), 55.46 (O<u>Me</u>), 60.37 (O<u>Me</u>), 61.07 (O<u>Me</u>), 108.43 (Ar<u>C</u>H), 118.30 (Ar<u>C</u>H), 120.19 (Ar<u>C</u>H), 120.85 (Ar<u>C</u>H), 126.34 (C=<u>C</u>H), 134.81 (q<u>C</u>), 135.82 (2 x q<u>C</u>), 140.65 (q<u>C</u>), 141.89 (q<u>C</u>) 144.17 (q<u>C</u>), 149.83 (q<u>C</u>), 150.15 (q<u>C</u>).

Alternative synthesis of intermediate, tert-butyl[2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenoxy]dimethylsilane (2.51)

To a stirred solution of bromide **(2.50)** (0.10g, 0.31 mmol) in anhydrous THF (1ml) was added 2.5M *n*-BuLi (0.12ml, 0.31 mmol) drop-wise at -78°C under anhydrous conditions. After 1 hour, whilst maintaining the reaction temperature at -78°C, a solution of **(2.01)** (0.026g, 0.10 mmol) dissolved in anhydrous THF (1ml) was added. After 12 hours, the reaction was quenched by the addition of 2M aq. HCl (5ml) and the crude product **(2.51)** extracted with diethyl ether, dried over sodium sulphate and filtered before the filtrate was reduced in volume *in vacuo*. The resulting oil was purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 5:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(2.51)** as a clear oil (0.027g, 58%).

4th Step-deprotection of (2.51) to afford (2.52)

Synthesis of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenol (2.52)

To a stirred solution of **(2.51)** (0.13g, 0.27 mmol) in THF (1ml) was added 1M TBAF (0.54ml, 0.54 mmol) at room temperature. After 30 minutes, the reaction was quenched by the addition of water (2ml) was added and the product was extracted with ether (3 x 5ml). The ether extracts

were collected, dried over sodium sulphate, filtered and reduced in volume before being purified by flash column chromatography (solid phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 4:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(2.52)** as a white solid (0.096g, 100%). M.pt. 37-38°C. ν_{max} (CCl_4)/ cm^{-1} 3392.4, 2931.6, 2837.4, 1507.6, 1109.7. GCMS m/z (%) 356 (100), 341 (4), 325 (5), 313 (6), 218 (2). HRMS: found 357.1713 (MH^+), requires ($C_{21}H_{24}O_5$) 356.1624. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.95 (2H, q, J 7.0Hz, 14.5Hz, 2 x H-7), 2.12 (2H, qn, J 7.0Hz, 14.0Hz, 2 x H-6), 2.66 (2H, t, J 6.7Hz, 2 x H-5), 3.71 (3H, s, OMe), 3.91 (6H, s, 2 x OMe), 3.94 (3H, s, OMe), 5.57 (1H, s, br, OH), 6.34 (1H, t, J 7.0Hz, H-8), 6.40 (1H, s, H-1), 6.77-6.82 (2H, m, H-4', H-3'), 6.91 (1H, d, J 1.5Hz, H-6'). ^{13}C NMR δ_c ppm 23.08 (C-5), 25.02 (C-7), 34.46 (C-6), 55.55 (OMe), 55.57 (OMe), 60.38 (OMe), 61.06 (OMe), 108.50 (C-1), 109.86 (C-3'), 113.74 (C-6'), 119.21 (C-4'), 123.29 (qC), 126.76 (C-8), 127.77 (qC) 135.38 (qC), 135.64 (qC), 140.72 (qC), 141.82 (qC) 144.82 (qC), 145.43 (qC), 150.50 (qC).

Synthesis of 2-methoxy-5-(1,2,3-trimethoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-9-yl)phenol (2.53)

To a solution of **(2.52)** (0.11g, 0.308 mmol) in ethanol/ethyl acetate (1:1, 4ml) was added slowly 10% Pd/C (0.10g). The reaction mixture was stirred under an atmosphere of hydrogen for 48 hours. On completion, the mixture was filtered and the solvent was removed under reduced pressure to afford **(2.53)** as a clear oil. This was re-dissolved in DCM (~2ml) and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.53)** as an oil (0.10g, 99%). ν_{max} (CCl_4)/ cm^{-1} 3455.2, 2921.1, 2847.8, 1507.6, 1115.0. HRMS: found 359.1828 (MH^+), requires ($C_{21}H_{26}O_5$) 358.1780. GCMS m/z (%) 358 (100), 327 (11), 233 (4), 191 (10). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.49 (1H, m, HCHCH$_2$), 1.80 (2H, m, CH$_2$), 1.96 (1H, m, HCHCH$_2$), 2.09 (2H, m, CH$_2$CH$_2$), 2.74 (1H, m, HCHCH$_2$), 2.96 (1H, m, HCHCH$_2$), 3.65 (3H, s, OMe), 3.83 (3H, s, OMe), 3.88 (3H, s, OMe), 3.91 (3H, s, OMe), 4.15 (1H, d, J 8.5Hz, ArCHAr), 5.59 (1H, s, OH), 6.15 (1H, s, ArH), 6.66 (1H, dd, J 2Hz, 8.5Hz, ArH), 6.83 (2H, m, ArH). ^{13}C NMR δ_c ppm 24.95 (CH$_2$), 27.22 (CH$_2$), 27.28 (CH$_2$), 33.48 (CH$_2$), 48.94 (CH), 55.41 (OMe), 55.54 (OMe), 60.34 (OMe), 60.85 (OMe), 108.51 (ArCH),

110.07 (ArCH), 114.22 (ArCH), 119.35 (ArCH), 128.41 (qC), 137.56 (qC), 140.97 (qC), 144.31 (qC) 145.06 (qC), 149.95 (qC), 150.61 (qC).

Formation of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-1,3-benzenediol (2.57)

1st Step

Synthesis of intermediate, 5-bromo-2-methoxy-1,3-benzenediol (2.54)

To a stirred suspension of 1,3,5-tribromo-2-methoxybenzene (5.0g, 14.5 mmol) in anhydrous pentane (100ml) was added 2.5M *n*-BuLi (28.96ml, 72.4 mmol) at -20°C under anhydrous conditions, over a 10-minute period. The solution was allowed to warm to -15°C over 15 minutes. Under subsequent cooling to -30°C, trimethylborate (8.55ml, 72.4 mmol) was added all at once. The reaction was subsequently warmed to 0°C over 30 minutes and then cooled to -10°C. To this was added 40% solution of peracetic acid/acetic acid (15ml) over a period of 30-minutes. Upon completion of the addition, the solution was warmed to 0°C over 30 minutes and re-cooled to -10°C whereupon saturated aqueous $NaHSO_3$ (15ml) was added over 30 minutes. On completion, water (100ml) was added and the product was extracted with diethyl ether (3 x 100ml). The ether fractions were collected, dried over sodium sulphate, filtered and concentrated to an oily residue under reduced pressure. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 3:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.54)** as a red solid (2.00g, 63%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 3.84 (3H, s, OMe), 5.84 (2H, br, s, 2 x OH), 6.56 (1H, d, J 2Hz, ArH), 6.77 (1H, d, J 2Hz, ArH). ^{13}C NMR δ_c ppm 24.47 (CH_2), 59.49 (OMe), 114.62 (qC), 117.58 (2 x ArCH), 142.04 (qC), 150.14 (2 x qC). The ^{1}H NMR and ^{13}C NMR data has been previously reported[206].

2nd Step

Synthesis of intermediate, (5-bromo-3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methoxyphenoxy)(tert-butyl)dimethylsilane (2.55)

To a stirred solution of **(2.54)** (3.68g, 16.8 mmol) in DMF (10ml) was added imidazole (6.28g, 92.2 mmol) and *t*BDMSCl (5.57g, 36.9 mmol) at 25°C. After 1 hour, the reaction temperature was raised to 55°C and was allowed to proceed at this temperature for 10 hours. On completion, the reaction was quenched by the addition of sat. aq. NaCl (25ml) and the product extracted with diethyl ether (3 x 25ml). The organic extracts were collected, dried over sodium sulphate, filtered, and then concentrated to an oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 9:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.55)** as a white waxy solid (5.65g, 75%). M.pt. 52-54°C. ν_{max} (KBr)/ cm^{-1} 2930.5, 1574.3, 1482.6, 1085.2, 1011.0. GCMS m/z (%) 447 (100), 375 (94), 73 (99). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.12 (6H, s, $C\underline{H}_3SiC\underline{H}_3$), 0.23 (6H, s, $C\underline{H}_3SiC\underline{H}_3$), 0.93 (9H, s, $C(C\underline{H}_3)_3$), 1.02 (9H, s, $C(C\underline{H}_3)_3$), 3.84 (3H, s, O<u>Me</u>), 6.56 (1H, d, J 2Hz, Ar<u>H</u>), 6.77 (1H, d, J 2Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm -5.12 (2 x $\underline{C}H_3SiCH_3$), 17.86 (2 x $\underline{C}(CH_3)_3$), 25.20 (2 x $C(\underline{C}H_3)_3$), 59.49 (O<u>Me</u>), 114.62 (q<u>C</u>), 117.58 (2 x Ar<u>C</u>H), 142.04 (q<u>C</u>), 150.14 (2 x q<u>C</u>).

3rd Step

Synthesis of intermediate, tert-butyl[3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenoxy]dimethylsilane (2.56)

To a stirred solution of bromide **(2.55)** (0.3g, 0.66 mmol) dissolved in anhydrous THF (2ml), was added 2.5M *n*-BuLi solution in THF (0.26ml, 0.66 mmol) drop-wise at -78°C under anhydrous conditions. After 15 minutes, whilst maintaining the temperature at -78°C, a solution of **(2.01)** (0.055g, 0.22 mmol) in anhydrous THF (2ml) was added. After 2 hours, the temperature was allowed to increase slowly to 0°C and maintained at this temperature for 12 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (5ml) and the product was extracted using diethyl ether (3 x 10ml). It was dried over sodium sulphate, filtered, and the filtrate was concentrated to a clear oil. It was purified by flash column

chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 3:1). All fractions were collected and the solvent was removed in vacuo to afford impure **(2.56)** as an oil (0.046g). This intermediate was too difficult to purify and so was used directly in the next step.

4th Step-deprotection of (2.56) to afford (2.57)

Synthesis of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)-1,3-benzenediol (2.57)

To a stirred solution of **(2.56)** (0.19g, 0.32 mmol) in THF (1ml) was added 1M aq. solution of TBAF (0.80ml, 0.80 mmol) at room temperature. After 1 hour, the reaction was quenched by the addition of water (2ml) and the product was extracted with diethyl ether (3 x 5ml). The ether extracts were collected, dried over sodium sulphate, filtered and reduced in volume before being purified by flash column chromatography (solid phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 1:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(2.57)** as an oil (0.029g, 25%). ν_{max} (CCl_4)/ cm^{-1} 3371.4, 2931.6, 2847.8, 1591.4, 1020.7. HRMS: found 373.1641 (MH^+), requires ($C_{21}H_{24}O_6$) 372.1573. GCMS m/z (%) 372 (100), 358 (14), 329 (10). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.93 (2H, q, J 3.5Hz, 7.2Hz, $CH_2C\underline{H_2}CH_2$), 2.11 (2H, qn, J 3.5Hz, 7.0Hz, $CHC\underline{H_2}CH_2$), 2.63 (2H, t, J 7.0Hz, $ArC\underline{H_2}$), 3.73 (3H, s, O<u>Me</u>), 3.90 (3H, s, O<u>Me</u>), 3.92 (3H, s, O<u>Me</u>), 3.94 (3H, s, O<u>Me</u>), 5.33 (2H, s, 2 x O<u>H</u>), 6.36 (1H, t, J 7.2Hz, C=C<u>H</u>), 6.40 (1H, s, Ar<u>H</u>), 6.46 (2H, d, J 2Hz, 2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 23.05 ($\underline{C}H_2$), 25.01 ($\underline{C}H_2$), 34.29 ($\underline{C}H_2$), 55.65 (O<u>Me</u>), 60.39 (O<u>Me</u>), 60.71 (O<u>Me</u>), 61.07 (O<u>Me</u>), 107.29 (2 x Ar<u>C</u>H), 108.55 (Ar<u>C</u>H), 127.82 (C=<u>C</u>H), 133.38 (q<u>C</u>), 135.16 (q<u>C</u>), 138.55 (q<u>C</u>), 140.82 (q<u>C</u>) 141.59 (q<u>C</u>), 147.99 (2 x q<u>C</u>), 150.40 (2 x q<u>C</u>), 150.53 (q<u>C</u>).

Formation of 2,3,4-trimethoxy-9-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cycloheptene (2.59)

1st Step

Synthesis of intermediate, 5-bromo-1,2,3-trimethoxybenzene (2.58)

To a stirred solution of dihydroxyanisole **(2.56)** (0.10g, 0.46 mmol) in acetone (1ml) was added iodomethane (1ml) followed by K_2CO_3 (0.63g, 4.56 mmol). This mixture was refluxed for 2 hours and on completion, the solvent was removed under reduced pressure to afford an orange oil, which was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 9:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.58)** as a white solid (0.11g, 96%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 3.77 (3H, s, OMe), 3.79 (3H, s, 2 x OMe), 6.67 (2H, m, 2 x ArH). ^{13}C NMR δ_c ppm 55.78 (2 x OMe), 60.25 (OMe), 108.54 (2 x ArCH), 115.59 (qC), 136.96 (qC), 153.42 (qC). The ^{1}H NMR and ^{13}C NMR data has been previously reported[207].

2nd Step

Synthesis of 2,3,4-trimethoxy-9-(3,4,5-trimethoxyphenyl)-6,7-dihydro-5H-benzo[a]cycloheptene (2.59)

To a stirred solution of bromide **(2.58)** (0.198g, 0.80 mmol) dissolved in anhydrous THF (2ml) was added 2.5M *n*-BuLi (0.32ml, 0.80 mmol) drop-wise at -78°C under anhydrous conditions. After 10 minutes, whilst maintaining the temperature at -78°C, a solution of **(2.01)** (0.1g, 0.40 mmol) in anhydrous THF (2ml) was added. After 2 hours, the temperature was raised slowly to 0°C and maintained at this temperature for 12 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (5ml) and the product was extracted using diethyl ether (3 x 10ml). It was dried over sodium sulphate, filtered and concentrated to a clear oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.59)** as an oil (0.14g, 44%). M.pt. 79°C. ν_{max} (CCl_4)/ cm^{-1} 2931.6, 2847.8, 1575.7, 1114.9,. HRMS: found 401.1992 (MH^+), requires ($C_{23}H_{28}O_6$) 400.1886.

GCMS m/z (%) 400 (100), 218 (2). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.97 (2H, q, J 7Hz, 14Hz, $CH_2\underline{CH_2}CH_2$), 2.15 (2H, qn, J 7Hz, 14Hz, $CH\underline{CH_2}CH_2$), 2.67 (2H, t, J 6.8Hz, $ArC\underline{H_2}$), 3.72 (3H, s, O<u>Me</u>), 3.83 (6H, s, 2 x O<u>Me</u>), 3.88 (3H, s, O<u>Me</u>), 3.93 (3H, s, O<u>Me</u>), 3.95 (3H, s, O<u>Me</u>), 6.40 (2H, s, Ar<u>H</u>, C=C<u>H</u>), 6.52 (2H, s, 2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 23.25 ($\underline{C}H_2$), 25.15 ($\underline{C}H_2$), 35.51 ($\underline{C}H_2$), 55.69 (O<u>Me</u>), 55.76 (2 x O<u>Me</u>), 60.37 (O<u>Me</u>), 60.44 (O<u>Me</u>), 61.06 (O<u>Me</u>), 104.93 (2 x Ar<u>C</u>H), 108.90 (Ar<u>C</u>H), 127.66 (C=<u>C</u>H), 127.93 (2 x q<u>C</u>), 135.28 (q<u>C</u>), 137.40 (q<u>C</u>), 140.85 (q<u>C</u>), 142.37 (q<u>C</u>), 150.45 (q<u>C</u>), 150.54 (q<u>C</u>), 152.49 (2 x q<u>C</u>).

Synthesis of 1,2,3-trimethoxy-5-(3,4,5-trimethoxyphenyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cycloheptene (2.60)

To a solution of **(2.59)** (0.07g, 0.17 mmol) in ethanol/ethyl acetate (1:1, 2ml) was added slowly 10% Pd/C (0.07g). The reaction mixture was stirred under an atmosphere of hydrogen for 48 hours. On completion, the mixture was then filtered and the solvent was removed under reduced pressure to afford **(2.60)** as an oil. This was re-dissolved in DCM (~2ml) and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.60)** as an oil (0.07g, 100%). ν_{max} (CCl_4)/ cm^{-1} 2931.6, 2847.8, 1575.7, 1114.9. HRMS: found 403.2155 (MH^+), requires ($C_{23}H_{30}O_6$) 402.2042. GCMS m/z (%) 402 (100), 371 (10.4), 323 (2.6), 297 (3), 234 (16.2), 196 (7.5). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.83 (3H, m, HC<u>H</u>C<u>H</u>$_2$), 2.02 (2H, m, $C\underline{H_2}CH_2$), 2.17 (1H, m, HC<u>H</u>), 2.67 (1H, m, HC<u>H</u>), 3.14 (1H, m, HC<u>H</u>), 3.61 (3H, s, O<u>Me</u>), 3.83 (3H, s, O<u>Me</u>), 3.84 (6H, s, 2 x O<u>Me</u>), 3.87 (3H, s, O<u>Me</u>), 3.88 (3H, s, O<u>Me</u>), 4.17 (1H, d, J 9.0Hz, ArC<u>H</u>Ar), 6.09 (1H, s, {A-ring}Ar<u>H</u>), 6.46 (2H, s, {C-ring}2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 23.46 ($\underline{C}H_2$), 27.58 ($\underline{C}H_2$), 30.54 ($\underline{C}H_2$), 34.34 ($\underline{C}H_2$), 50.01 (<u>C</u>H), 55.70 (O<u>Me</u>), 56.06 (2 x O<u>Me</u>), 60.81 (O<u>Me</u>), 60.90 (O<u>Me</u>), 61.33 (O<u>Me</u>), 105.48 (2 x Ar<u>C</u>H), 108.22 (Ar<u>C</u>H), 128.35 (2 x q<u>C</u>), 135.75 (q<u>C</u>), 139.86 (q<u>C</u>), 141.06 (q<u>C</u>), 149.93 (q<u>C</u>), 150.58 (q<u>C</u>), 152.65 (2 x q<u>C</u>).

Formation of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[a]cyclohepten-9-yl)aniline (2.65)

1st Step

Synthesis of intermediate, 4-bromo-1-methoxy-2-nitrobenzene (2.61)

To a stirred solution of 4-bromo-2-nitrophenol (2.00g, 9.17 mmol) in acetone (20ml) was added iodomethane (0.57ml, 91.7 mmol) followed by K_2CO_3 (3.78g, 27.4 mmol). The reaction mixture was then gently refluxed for 6 hours. On completion, the solvent was removed under reduced pressure to afford **(2.61)** as an oil. The crude product was isolated by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 9:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.61)** as a yellow solid (1.94g, 98%). ν_{max} (CCl_4)/ cm^{-1} 1604.2, 1516.7, 1343.7, 1267.8. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 4.52 (3H, s, OMe), 7.56 (1H, d, J 5.2Hz, ArH), 8.20 (1H, dd, J 1Hz, 8.5Hz, ArH), 8.53 (1H, d, J 2.5Hz, ArH). ^{13}C NMR δ_c ppm 56.77 (OMe), 111.86 (qC), 115.20 (ArCH), 128.31 (ArCH), 136.81 (ArCH), 137.62 (qC), 152.52 (qC). The ^1H NMR and ^{13}C NMR data has been previously published[208].

2nd Step

Synthesis of intermediate, 5-bromo-2-methoxyaniline (2.62)

To a stirred solution of **(2.61)** (1.39g, 6.47 mmol) dissolved in ethanol (20ml) was added conc. HCl (10ml) and powdered tin (1.4g) at room temperature. After 5 hours, the solvent was removed *in vacuo* and 2.5M aq. NaOH (30ml) was added slowly at 0C. The product was extracted with diethyl ether (3 x 20ml) and the combined extracts were dried over sodium sulphate, filtered, and the filtrate concentrated under reduced pressure. The resulting oil was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 9:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.62)** as a white solid (1.21g, 93%). ν_{max} (CCl_4)/ cm^{-1} 3460.7, 3371.5, 1500.1. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 3.84 (3H, s, OMe), 3.86 (2H, br, NH_2), 6.64 (1H, d, J

8.0Hz, ArH), 6.81 (1H, d, J 2.5Hz, ArH), 6.84 (1H, s, ArH). ^{13}C NMR δ_c ppm 55.18 (OMe), 111.22 (ArCH), 112.79 (qC), 116.86 (ArCH), 120.18 (ArCH), 137.26 (qC), 145.91 (qC).

3rd step

Synthesis of intermediate, 1-(5-bromo-2-methoxyphenyl)-2,5-dimethyl-1H-pyrrole (2.63)

To a stirred solution of aniline **(2.62)** (1.17g, 5.79 mmol) in toluene (23ml) was added hexane-2,5-dione (0.82ml, 6.98 mmol) and acetic acid (1ml). The reaction was gently refluxed for 4 hours. On completion, 5% $Na(HCO_3)$ solution (10ml) was added and the product was extracted with diethyl ether (3 x 20ml). The organic extracts were collected, dried over sodium sulphate, and filtered. The solvent was removed *in vacuo* and the final product was isolated by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 9:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(2.63)** as an off-white solid (1.21g, 75%). M.pt. 90-91°C. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.00 (6H, s, {pyrrole ring} 2 x CH_3), 3.79 (3H, s, OMe), 5.93 (2H, s, {pyrrole ring} 2 x CH), 6.94 (1H, d, J 8.5Hz, ArH), 7.33 (1H, d, J 2.5Hz, ArH), 6.84 (1H, dd, J 2.5Hz, 9.04Hz, ArH). ^{13}C NMR δ_c ppm 12.03 (2 x CH_3), 55.50 (OMe), 105.22 ({pyrrole ring} 2 x CH), 111.69 (qC), 113.14 (ArCH), 128.53 (2 x qC), 128.60 (qC), 131.68 (ArCH), 132.56 (ArCH), 154.88 (qC).

4th Step

Synthesis of intermediate, 1-[2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenyl]-2,5-dimethyl-1H-pyrrole (2.64)

To a stirred solution of bromide **(2.63)** (0.23g, 0.82 mmol) dissolved in anhydrous THF (2ml) was added 2.5M *n*-BuLi (0.33ml, 0.82 mmol) drop-wise at -78°C under anhydrous conditions. After 10 minutes, whilst maintaining the temperature at -78°C, a solution of **(2.01)** (0.1g, 0.40 mmol) in anhydrous THF (2ml) was added. After 2 hours, the temperature was raised slowly to 0°C and maintained at this temperature for 12 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (5ml) and the product was extracted with diethyl ether (3 x 10ml). The combined extracts were dried over sodium sulphate, filtered, and concentrated to a clear oil.

The product was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 4:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.64)** as a clear oil (0.08g, 46%). ν_{max} (CCl_4)/ cm^{-1} 2933.6, 1590.7, 1505.6. GCMS m/z (%) 434 (19), 433 (100), 420 (23), 390 (15). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.65 (2H, m, C$\underline{H_2}$), 2.00 (6H, s, {pyrrole ring} 2 x C$\underline{H_3}$), 2.74 (2H, m, C$\underline{H_2}$), 2.97 (2H, m, C$\underline{H_2}$), 3.70 (3H, s, O$\underline{Me}$), 3.86 (3H, s, O$\underline{Me}$), 3.90 (3H, s, O$\underline{Me}$), 3.96 (3H, s, O$\underline{Me}$), 5.90 (2H, s, {pyrrole ring} 2 x C$\underline{H}$), 6.38 (1H, s, {A-ring}Ar$\underline{H}$), 6.41 (1H, t, J 3.7Hz, C=C$\underline{H}$), 6.68 (1H, s, {C-ring}Ar$\underline{H}$), 6.69 (1H, d, J 2.0Hz, {C-ring}Ar$\underline{H}$), 6.75 (1H, d, J 8Hz, {C-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm 12.12 (2 x $\underline{C}H_3$), 22.54 ($\underline{C}H_2$), 24.57 ($\underline{C}H_2$), 40.35 ($\underline{C}H_2$), 55.53 (O$\underline{Me}$), 60.38 (O$\underline{Me}$), 60.91 (O$\underline{Me}$), 61.04 (O$\underline{Me}$), 104.79 ({pyrrole ring} 2 x $\underline{C}$H), 106.55 (Ar$\underline{C}$H), 107.11 (Ar$\underline{C}$H), 111.39 (Ar$\underline{C}$H), 111.59 (q$\underline{C}$), 126.89 (q$\underline{C}$), 126.92 (q$\underline{C}$), 127.55 (Ar$\underline{C}$H), 128.69 (C=$\underline{C}$H), 128.46 (q$\underline{C}$), 135.42 (q$\underline{C}$), 141.14 (q$\underline{C}$), 150.30 (q$\underline{C}$), 150.79 (q$\underline{C}$), 154.52 (q$\underline{C}$).

5th step-deprotection of (2.64) to afford (2.65)

Synthesis of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)aniline (2.65)

To a stirred solution of **(2.64)** (0.08g, 0.18 mmol) in ethanol (2ml) was added a solution of KOH (0.027g, 0.49 mmol) in ethanol/water (0.45ml:0.2ml) followed by hydroxylamine hydrochloride (0.068g, 0.84 mol). The reaction mixture was refluxed for 12 hours and on completion, the reaction was quenched by the addition of water (5ml). The product was extracted using diethyl ether (3 x 10ml) and the combined extracts were subsequently dried over sodium sulphate, filtered and concentrated to a clear oil. The product was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 3:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.65)** as a white solid (0.031g, 49%). M.pt. 36-37°C. ν_{max} (CCl_4)/ cm^{-1} 3473.0, 3373.6, 2933.3, 2853.9, 1513.4. HRMS: found 355.1801, requires ($C_{21}H_{25}NO_4$) 355.1784. GCMS m/z (%) 355 (100), 312 (12), 250 (3). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.93 (2H, q, J 3.2Hz, 7.2Hz, C$\underline{H_2}$), 2.12 (2H, qn, J 3.2Hz, 6.8Hz, C=CHC$\underline{H_2}$), 2.65 (2H, t, J 2.7Hz, ArC$\underline{H_2}$), 3.71 (3H, s, O$\underline{Me}$), 3.88 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 3.94 (3H, s, O$\underline{Me}$), 6.31 (1H, t, J 3.7Hz, C=C$\underline{H}$), 6.42 (1H, s,

{A-ring}ArH), 6.68 (1H, s, {C-ring}ArH), 6.69 (1H, d, J 2.0Hz, {C-ring}ArH), 6.75 (1H, d, J 8Hz, {C-ring}ArH). ^{13}C NMR δ_c ppm 24.30 ($\underline{C}H_2$), 26.77 ($\underline{C}H_2$), 40.79 ($\underline{C}H_2$), 55.29 (O$\underline{Me}$), 55.44 (O$\underline{Me}$), 60.32 (O$\underline{Me}$), 60.81 (O$\underline{Me}$), 104.89 (Ar$\underline{C}$H), 106.55 (Ar$\underline{C}$H), 111.34 (Ar$\underline{C}$H), 126.72 (q$\underline{C}$), 126.92 (q$\underline{C}$), 127.55 (Ar$\underline{C}$H), 128.69 (C=$\underline{C}$H), 136.92 (q$\underline{C}$), 140.70 (q$\underline{C}$), 142.14 (q$\underline{C}$), 150.36 (q$\underline{C}$), 150.45 (q$\underline{C}$), 150.79 (q$\underline{C}$), 154.63 (q$\underline{C}$).

Formation of [2-methoxy-5-(6,7,8-trimethoxy-3,4-dihydro-1-naphthalenyl)phenol (2.67)

1st Step

Synthesis of intermediate, tert-butyl[2-methoxy-5-(5,6,7-trimethoxy-3,4-dihydro-1-naphthalenyl)phenoxy]dimethylsilane (2.66)

To a stirred solution of bromide **(2.50)** (0.64g, 2.02 mmol) in anhydrous THF (4ml) was added 2.5M *n*-BuLi (0.86ml, 2.02 mmol) drop-wise at -78°C under anhydrous conditions. After 10 minutes, whilst maintaining the temperature at -78°C, a solution of tetralone **(2.10)** (0.24g, 1.02 mmol) in anhydrous THF (4ml) was added. After 3 hours, the reaction was quenched by the addition of 2M aq. HCl (5ml) and the product extracted using diethyl ether (3 x 10ml). The combined extracts were dried over sodium sulphate, filtered, and the filtrate concentrated to an orange oil. The product was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ ethyl acetate 3:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.66)** as an oil (0.27g, 58%). ν_{max} (CCl_4)/ cm^{-1} 2953.9, 2847.8, 1507.6, 1115.0. ^{1}H NMR δ_H ppm 0.20 (6H, s, $C\underline{H}_3SiC\underline{H}_3$), 1.02 (9H, s, $C(C\underline{H}_3)_3$), 2.35 (2H, m, $C\underline{H}_2$), 2.82 (2H, t, J 7.5Hz, $ArC\underline{H}_2$), 3.68 (3H, s, O$\underline{Me}$), 3.86 (3H, s, O$\underline{Me}$), 3.90 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 6.00 (1H, t, J 5.0Hz, C=C$\underline{H}$), 6.46 (1H, s, {A-ring}Ar$\underline{H}$), 6.88 (3H, m, {C-ring}3 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm -5.13 ($CH_3Si\underline{C}H_3$), -5.01 ($\underline{C}H_3SiCH_3$), 17.97 ($\underline{C}(CH_3)_3$), 19.89 ($\underline{C}H_2$), 22.67 ($\underline{C}H_2$), 25.27 ($C(\underline{C}H_3)_3$), 55.04 (O$\underline{Me}$), 55.63 (O$\underline{Me}$), 60.39 (O$\underline{Me}$), 60.45 (O$\underline{Me}$), 105.97 (Ar$\underline{C}$H), 111.37 (Ar$\underline{C}$H), 121.08 (Ar$\underline{C}$H), 121.62 (Ar$\underline{C}$H), 122.17 (q$\underline{C}$), 126.10 (C=$\underline{C}$H), 130.67 (q$\underline{C}$), 133.28 (q$\underline{C}$), 138.51 (q$\underline{C}$), 141.04 (q$\underline{C}$), 144.17 (q$\underline{C}$), 149.75 (q$\underline{C}$), 149.90 (q$\underline{C}$), 150.61 (q$\underline{C}$).

2nd Step-deprotection of (2.66) to afford (2.67)

Synthesis of [2-methoxy-5-(6,7,8-trimethoxy-3,4-dihydro-1-naphthalenyl)phenol (2.67)

To a stirred solution of **(2.66)** (0.16g, 0.35 mmol) dissolved in THF (1ml) was added 1M TBAF (0.35ml, 0.35 mmol) at 25°C. After 1 hour, the reaction was quenched by the addition of sat. aq. NaCl solution (2ml) and the product extracted using diethyl ether (3 x 5ml). The combined extracts were dried over sodium sulphate, filtered, and concentrated to a clear oil. The product was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(2.67)** as a white solid (0.11g, 92%). M.pt. 100-101°C. ν_{max} (CCl_4)/ cm^{-1} 3413.7, 2933.5, 2825.9 1506.4, 1113.2. HRMS: found 343.1666 (MH^+), requires ($C_{21}H_{22}O_5$) 342.1467. GCMS m/z (%) 342 (100), 328 (8). ^{1}H NMR δ_H ppm 2.35 (2H, m, C$\underline{H}_2$), 2.80 (2H, t, J 7.5Hz, ArC$\underline{H}_2$), 3.69 (3H, s, O$\underline{Me}$), 3.89 (3H, s, O$\underline{Me}$), 3.91 (3H, s, O$\underline{Me}$), 3.94 (3H, s, O$\underline{Me}$), 5.65 (1H, br, O$\underline{H}$), 6.03 (1H, m, C=C$\underline{H}$), 6.49 (1H, s, {A-ring}Ar$\underline{H}$), 6.87 (2H, m, {C-ring}2 x Ar$\underline{H}$), 6.96 (1H, m, {C-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm 20.34 (Ar$\underline{C}H_2$), 22.67 (C=CH$\underline{C}H_2$), 55.95 (O$\underline{Me}$), 56.18 (O$\underline{Me}$), 60.85 (O$\underline{Me}$), 60.90 ({C-2'}O$\underline{Me}$), 106.12 ({A-ring}Ar$\underline{C}$H), 109.93 ({C-ring}Ar$\underline{C}$H), 114.69 ({C-ring}Ar$\underline{C}$H), 119.93 (C-ring}Ar$\underline{C}$H), 122.30 (q$\underline{C}$), 126.27 (C=$\underline{C}$H), 130.51 (q$\underline{C}$), 133.85 (q$\underline{C}$), 138.51 (q$\underline{C}$), 141.08 (q$\underline{C}$), 144.88 (q$\underline{C}$), 145.37 (q$\underline{C}$), 149.89 (q$\underline{C}$), 150.59 (q$\underline{C}$).

Formation of 5-(7,8-dihydronaphtho[2,3-*d*][1,3]dioxol-5-yl)-2-methoxyphenol (2.69)

1st Step

Synthesis of intermediate, tert-butyl[5-(7,8-dihydronaphtho[2,3-d][1,3]dioxol-5-yl)-2-methoxyphenoxy]dimethylsilane (2.68)

Synthesised using **(2.22)** (0.38g, 2.02 mmol) and **(2.50)** (1.28g, 4.03 mmol) by the method described for the preparation of **(2.66)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 3:1). Afforded **(2.68)** as an oil (0.77g, 93%). ^{1}H NMR δ_H ppm 0.19 (3H, s, $CH_3SiC\underline{H}_3$), 0.21 (3H, s, $C\underline{H}_3SiCH_3$), 1.09 (9H, s, $C(C\underline{H}_3)_3$), 2.34 (2H, m, CHC$\underline{H}_2$), 2.82 (2H, t, J 4.7Hz, ArC$\underline{H}_2$), 3.86 (2H, s, O$\underline{Me}$), 5.90 (2H, s,

OCH_2O), 5.96 (1H, t, J 4.7Hz, C=CH), 6.61 (1H, s, ArH), 6.73 (1H, m, ArH), 6.88 (3H, m, 3 x ArH). ^{13}C NMR δ_c ppm -5.01 (CH_3SiCH_3), 18.00 ($C(CH_3)_3$), 23.11 (CH_2), 25.31 ($C(CH_3)_3$), 28.15 (CH_2), 55.12 (OMe), 100.22 (OCH_2O), 106.27 (ArCH), 107.85 (ArCH), 121.49 (ArCH), 124.28 (C=CH), 128.84 (qC), 130.34 (qC), 133.38 (qC), 138.71 (qC), 144.27 (qC), 145.29 (qC), 145.45 (qC), 149.79 (qC).

2nd Step-deprotection of (2.68) to afford (2.69)

Synthesis of 5-(7,8-dihydronaphtho[2,3-d][1,3]dioxol-5-yl)-2-methoxyphenol (2.69)

Synthesised from **(2.68)** (0.17g, 0.41 mmol) using the method described for the preparation of **(2.67)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). Afforded **(2.69)** as a white solid (0.12g, 98%). M.pt. 161-163°C. ν_{max} (KBr)/ cm^{-1} 3441.2, 1579.7, 1124.2. GCMS m/z (%) 296 (100), 281 (10), 252 (2.6). HRMS: found 297.1140 (MH^+), requires ($C_{18}H_{16}O_4$) 296.1049. ^1H NMR δ_H ppm 2.34 (2H, dt, CH_2), 2.80 (2H, t, J 8.0Hz, $ArCH_2$), 3.94 (3H, s, OMe) 5.61 (1H, br, OH), 5.90 (1H, m, OCH_2O), 5.96 (1H, t, J 4.7Hz, C=CH), 6.61 (1H, s, {A-ring}ArH), 6.72 (1H, s, {A-ring}ArH), 6.84 (2H, m, {C-ring}2 x ArH). 6.84 (1H, m, {C-ring}ArH). ^{13}C NMR δ_c ppm 23.08 (CH_2), 28.14 (CH_2), 55.57 (OMe), 100.21 (OCH_2O), 106.28 (ArCH), 107.85 (ArCH), 110.10 (ArCH), 114.60 (ArCH), 119.87 (ArCH), 124.53 (C=CH), 128.71 (qC), 130.36 (2 x qC), 134.01 (qC), 138.72 (qC), 144.88 (qC), 145.25 (qC), 145.36 (qC).

Formation of 5-(5*H*-indeno[5,6-*d*][1,3]dioxol-7-yl)-2-methoxyphenol (2.71)

1st Step

Synthesis of intermediate, tert-butyl[5-(5H-indeno[5,6-d][1,3]dioxol-7-yl)-2-methoxyphenoxy]dimethylsilane (2.70)

Synthesised using **(2.24)** (0.12g, 0.68 mmol) and **(2.50)** (0.43g, 1.36 mmol) by the method described for the preparation of **(2.66)** except after 2 hours at -78°C, the temperature was raised slowly to 0°C and maintained at this temperature for 12 hours. The product was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl

acetate 4:1). Afforded **(2.70)** as an oil (0.14g, 52%). ^{1}H NMR δ_H ppm 0.27 (6H, s, CH_3SiCH_3), 1.09 (9H, s, $C(CH_3)_3$), 3.42 (2H, m, CH_2), 3.89 (2H, s, OMe), 6.00 (2H, s, OCH_2O), 6.40 (1H, m, C=CH), 7.12 (5H, m, 5 x ArH). ^{13}C NMR δ_c ppm -5.01 (CH_3SiCH_3), 18.05 ($C(CH_3)_3$), 25.31 ($C(CH_3)_3$), 37.45 (CH_2), 55.12 (OMe), 100.50 (OCH_2O), 104.92 (ArCH), 111.87 (ArCH), 119.93 (ArCH), 121.29 (ArCH), 128.15 (C=CH), 137.69 (qC), 138.17 (qC), 143.98 (qC), 144.66 (qC), 145.41 (qC), 146.17 (qC), 150.21 (qC), 150.65 (qC).

2nd Step-deprotection of (2.70) to afford (2.71)

Synthesis of 5-(5H-indeno[5,6-d][1,3]dioxol-7-yl)-2-methoxyphenol (2.71)

Synthesised from **(2.70)** (0.1g, 0.25 mmol) using the method described for the preparation of **(2.67)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ ethyl acetate 2:1). Afforded **(2.71)** as a white solid (0.070g, 98%). M.pt. 140-142°C. HRMS: found 283.0990 (MH^+), requires ($C_{17}H_{14}O_4$) 282.0892. GCMS m/z (%) 282 (100), 268 (50), 239 (10). ν_{max} (KBr)/ cm^{-1} 3459.6, 1575.6, 1505.4, 1118.2. ^{1}H NMR δ_H ppm 3.40 (2H, m, CH_2), 3.96 (3H, s, OMe) 5.69 (1H, br, OH), 5.98 (1H, m, OCH_2O), 6.42 (1H, m, C=CH), 6.94 (1H, d, J 6.5Hz, ArH), 7.02 (1H, s, ArH), 7.05 (1H, dd, J 2Hz, 8.5Hz, ArH), 7.10 (1H, s, ArH), 7.16 (1H, d, J 2Hz, ArH). ^{13}C NMR δ_c ppm 37.46 (CH_2), 55.59 (OMe), 100.49 (OCH_2O), 101.06 (ArCH), 104.88 (ArCH), 110.30 (ArCH), 113.49 (ArC), 118.83 (ArCH), 128.42 (C=CH), 129.27 (qC), 137.52 (qC), 138.12 (qC), 143.91 (qC), 145.24 (qC), 145.38 (qC), 146.11 (qC).

General procedure for the oxidation at the allylic position involving SeO_2

To a stirred solution of the reactant in dioxane (or the other solvents used) was added SeO_2 (5 molar equivalents) at room temperature. The reaction was then refluxed for 10 hours, cooled and filtered. The filtrate was concentrated and the residue purified by flash column chromatography.

General procedure for the oxidation at the allylic position involving Jones' reagent

To a stirred solution of the reactant in acetone at 0°C was added Jones' reagent drop-wise until the colour of the reaction mixture remained green. The reaction was allowed to continue at this temperature for 8 hours. Any unreacted Jones' reagent was quenched by the addition of 2-propanol. Analysis of the reaction by TLC indicated the formation of numerous by-products, it was decided to discontinue trying to pursue the synthesis of the targeted compound employed in this route.

Attempted allylic oxidation of (2.45) using $K_2Cr_2O_7$

To a stirred solution of **(2.45)** (0.3g, 0.88 mmol) in acetic acid/acetic anhydride (2:1; 1.5ml) was added $K_2Cr_2O_7$ (0.26g, 0.13 mmol) portion-wise whilst heating the mixture at 40°C. After 48 hours, the reaction was quenched by the addition of water (5ml) and the product extracted using diethyl ether (3 x 5ml). The organic extracts were collected, dried over sodium sulphate and filtered before being concentrated to an oil under reduced pressure and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected, reduced in volume and the product **(3.01)** was afforded as an oil (0.25g, 76%) and not the anticipated enone. ^{1}H NMR ($CDCl_3$, 400Mhz) δ_H ppm 1.85 (2H, m, C<u>H</u>$_2$), 2.38 (2H, m, C<u>H</u>$_2$), 2.60 (2H, m, C<u>H</u>$_2$), 3.8 (3H, s, O<u>Me</u>), 3.87 (3H, s, O<u>Me</u>), 3.94 (3H, s, O<u>Me</u>), 3.95 (3H, s, O<u>Me</u>), 6.62 (1H, s, Ar<u>H</u>), 7.28 (1H, d, Ar<u>H</u>), 7.4 (3H, m, Ar<u>H</u>), 9.69 (1H, s, C<u>H</u>O).

Formation of 4-[6-(3-hydroxy-4-methoxybenzoyl)-2,3,4-trimethoxyphenyl]butanal (3.02)

1st Step

Synthesis of intermediate, 9-[3-(benzyloxy)-4ethylphenyl]-2,3,4-trimethoxy-6,7-dihydro-5h-benzo[a]cycloheptene (3.03)

To a stirred solution of phenol **(2.52)** (0.14g, 0.39 mmol) in DMF (2ml) was added cesium carbonate (0.19g, 0.59 mmol) and benzyl bromide (0.042ml, 0.32 mmol) at 25°C for 1.5 hours. On completion, the reaction was quenched by the addition of sat. aq NaCl solution (10ml) and the product extracted using diethyl ether (3 x 10ml). The organic extracts were collected, dried over sodium sulphate, filtered, and concentrated to a clear oil under reduced pressure. The oil was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 9:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(3.03)** as a clear oil (0.17g, 95%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.95 (2H, q, J 7.0Hz, 14.5Hz, C$\underline{H_2}$), 2.15 (2H, qn, J 7.0Hz, 14.0Hz, C$\underline{H_2}$), 2.66 (2H, t, J 6.7Hz, ArC$\underline{H_2}$), 3.71 (3H, s, O$\underline{Me}$), 3.91 (6H, s, 2 x O$\underline{Me}$), 3.94 (3H, s, O$\underline{Me}$), 4.82 (2H, s, OC$\underline{H_2}$Ph), 6.34 (1H, t, J 7.0Hz, C=C$\underline{H}$), 6.40 (1H, s, Ar$\underline{H}$), 6.79 (2H, m, Ar$\underline{H}$), 6.91 (1H, d, J 1.5Hz, Ar$\underline{H}$), 7.36 (5H, m, 5 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 23.08 ($\underline{C}H_2$), 25.02 ($\underline{C}H_2$), 34.46 ($\underline{C}H_2$), 55.55 (O$\underline{Me}$), 55.57 (O$\underline{Me}$), 60.38 (O$\underline{Me}$), 61.06 (O$\underline{Me}$), 69.58 (O$\underline{C}H_2$Ph), 108.50 (Ar$\underline{C}$H), 109.13 (Ar$\underline{C}$H), 113.74 (Ar$\underline{C}$H), 119.21 (Ar$\underline{C}$H), 123.29 (q$\underline{C}$), 126.76 (C=$\underline{C}$H), 126.98 (2 x Ar$\underline{C}$H), 127.57 (Ar$\underline{C}$H), 127.77 (q$\underline{C}$), 128.13 (Ar$\underline{C}$H), 135.38 (q$\underline{C}$), 135.64 (q$\underline{C}$), 140.72 (q$\underline{C}$), 141.82 (q$\underline{C}$) 144.82 (q$\underline{C}$), 145.43 (q$\underline{C}$), 150.50 (q$\underline{C}$).

2nd step

Synthesis of intermediate, 4-{6-[3-(benzyloxy)-4-methoxybenzoyl]-2,3,4-trimethoxyphenyl}butanal (3.04)

To a solution of **(3.03)** (0.1g, 0.22 mmol) in acetic anhydride/acetic acid (2:1; 1.5ml) was added $K_2Cr_2O_7$ (0.098g, 0.33 mmol) with stirring at 45°C. After 3 hours, the reaction was quenched by the addition of 5% aq. $NaHCO_3$ (10ml) and the product extracted with diethyl ether (3 x 10ml). The organic extracts were combined, dried over sodium sulphate, filtered and

concentrated, to an orange oil under reduced pressure. The oil was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(3.04)** as a clear oil (0.049g, 47%). ν_{max} (CCl_4)/ cm^{-1} 2934.3, 1721.1, 1655.1, 1592.8. GCMS m/z (%) 461 (M^++1) (96), 460 (100), 400 (3), 370 (12), 341 (14). ^{1}H NMR δ_H ppm 1.81 (2H, m, C$\underline{H}_2$), 2.34 (2H, dt, J 6.5Hz, 1.5Hz, C$\underline{H}_2$), 2.54 (2H, t, J 4.2Hz, ArC$\underline{H}_2$), 3.78 (3H, s, O$\underline{Me}$), 3.95 (6H, s, 2 x O$\underline{Me}$), 3.97 (3H, s, O$\underline{Me}$), 5.19 (2H, s, OC$\underline{H}_2$Ph), 6.54 (1H, s, Ar$\underline{H}$), 6.90 (1H, d, J 8.5Hz, Ar$\underline{H}$), 7.36 (4H, m, 4 x Ar$\underline{H}$), 7.44 (2H, d, 2 x Ar$\underline{H}$), 7.53 (1H, d, J 1.5Hz, Ar$\underline{H}$), 9.67 (1H, s, $\underline{H}$C=O). ^{13}C NMR δ_c ppm 23.12 ($\underline{C}H_2$), 25.93 ($\underline{C}H_2$), 42.93 ($\underline{C}H_2$), 56.04 (O$\underline{Me}$), 56.07 (O$\underline{Me}$), 60.70 (O$\underline{Me}$), 60.95 (O$\underline{Me}$), 70.54 (O$\underline{C}H_2$Ph), 107.21 (Ar$\underline{C}$H), 110.30 (Ar$\underline{C}$H), 114.47 (Ar$\underline{C}$H), 125.48 (Ar$\underline{C}$H), 126.08 (q$\underline{C}$), 126.98 (2 x Ar$\underline{C}$H), 127.57 (Ar$\underline{C}$H), 128.13 (2 x Ar$\underline{C}$H), 129.96 (q$\underline{C}$), 134.16 (q$\underline{C}$), 136.05 (q$\underline{C}$), 143.01 (q$\underline{C}$), 147.67 (q$\underline{C}$), 150.77 (q$\underline{C}$), 151.92 (q$\underline{C}$), 153.87 (q$\underline{C}$), 195.90 (H$\underline{C}$=O), 202.07 ($\underline{C}$=O).

3rd Step-deprotection of (3.04) to afford (3.02)

Synthesis of 4-[6-(3-hydroxy-4-methoxybenzoyl)-2,3,4-trimethoxyphenyl]butanal (3.02)

To a solution of aldehyde **(3.04)** (0.032g, 0.067 mmol) in ethanol (1ml) was added 10% Pd/C (0.02g). The reaction mixture was stirred under an atmosphere of hydrogen for 16 minutes. On completion, the mixture was filtered and concentrated to an oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(3.02)** as as an oil (0.022g, 88%). ν_{max} (CCl_4)/ cm^{-1} 3403.8, 2938.8, 1721.6, 1654.2. GCMS m/z (%) 388 (M^+, 13), 370 (100), 353 (20), 342 (21). ^{1}H NMR δ_H ppm 1.83 (2H, m, C$\underline{H}_2$), 2.36 (2H, dt, J 6.5Hz, 1.5Hz, C$\underline{H}_2$), 2.58 (2H, t, J 4.2Hz, ArC$\underline{H}_2$), 3.81 (3H, s, O$\underline{Me}$), 3.94 (6H, s, 2 x O$\underline{Me}$), 3.99 (3H, s, O$\underline{Me}$), 5.69 (1H, s, OH), 6.60 (1H, s, Ar$\underline{H}$), 6.91 (1H, d, J 8.5Hz, Ar$\underline{H}$), 7.41 (2H, m, Ar$\underline{H}$), 9.69 (1H, s, $\underline{H}$C=O). ^{13}C NMR δ_c ppm 23.14 ($\underline{C}H_2$), 25.93 ($\underline{C}H_2$), 42.94 ($\underline{C}H_2$), 55.67 (2 x O$\underline{Me}$), 60.30 (O$\underline{Me}$), 60.56 (O$\underline{Me}$), 106.96 (Ar$\underline{C}$H), 109.38 (Ar$\underline{C}$H), 115.57 (Ar$\underline{C}$H), 123.59 (Ar$\underline{C}$H), 126.13 (q$\underline{C}$), 130.83 (2 x q$\underline{C}$), 134.17 (q$\underline{C}$), 144.98 (q$\underline{C}$), 150.49 (q$\underline{C}$), 150.80 (q$\underline{C}$), 151.94 (q$\underline{C}$), 201.07 (2 x $\underline{C}$=O).

General procedure for the attempted bromination at the allylic position of biaryl alkenes using *N*-bromosuccinimide

To a stirred solution of biaryl alkene (0.10 mmol) in CCl_4 or ααα-trifluorotoluene (3ml) was added NBS (0.15 mmol) and a catalytic amount of dibenzoyl peroxide or azobiscyclohexanecarbonitrile. The reaction was initiated either by reflux or using a light source for 1 hour. After being allowed to react for this period of time, the reaction mixture was filtered, reduced in volume and the residue was analysed by TLC.

Synthesis of intermediate, 3-(3,4,5-trimethoxyphenyl)-1-propanol (3.05)

Synthesised using the method described for the preparation of **(2.11)**. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.91 (2H, m, C$\underline{H_2}$), 2.65 (2H, m, C$\underline{H_2}$), 3.71 (2H, m, CH_2), 3.84 (3H, s, O$\underline{Me}$), 3.85 (6H, s, 2 x O$\underline{Me}$), 6.45 (2H, s, 2 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 32.11 ($\underline{C}H_2$), 34.96 ($\underline{C}H_2$), 55.70 (2 x O$\underline{Me}$), 60.40 (O$\underline{Me}$), 61.76 ($\underline{C}H_2$), 104.95 (2 x Ar$\underline{C}$H), 137.44 (q$\underline{C}$), 135.98 (q$\underline{C}$), 151.95 (2 x q$\underline{C}$).

Synthesis of intermediate, 3-(3,4,5-trimethoxyphenyl)-1-propanal (3.06)

To a stirred solution of **(3.05)** (0.30g, 1.33 mmol) in DCM was added 20% w/w PCC on basic alumina (1.61g, 1.5 mmol) at 0°C. After 20 minutes, the reaction temperature was raised to 25°C. After 1 hour, the solvent was removed and the residue was then purified by flash column chromatography (solid phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected, reduced in volume to afford **(3.06)** as a yellow oil (0.19g, 66%). ν_{max} (CCl_4)/ cm^{-1} 2940.8, 2839.2, 1723.7, 1589.9. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.70 (2H, t, J 7.2Hz, C$\underline{H_2}$), 2.82 (2H, t, J 7.2Hz, C$\underline{H_2}$), 3.74 (3H, s, O$\underline{Me}$), 3.76 (6H, s, 2 x O$\underline{Me}$), 6.35 (2H, s, 2 x Ar$\underline{H}$), 9.73 (1H, s, C$\underline{H}$O). ^{13}C NMR δ_c ppm 27.91 ($\underline{C}H_2$), 44.76 ($\underline{C}H_2$), 55.52 (2 x O$\underline{Me}$), 60.20 (O$\underline{Me}$), 104.85 (2 x ArC$\underline{H}$), 135.70 (q$\underline{C}$), 135.98 (q$\underline{C}$), 152.74 (2 x q$\underline{C}$), 200.95 ($\underline{C}$=O).

Synthesis of intermediate, 1-(1,3-dioxalan-2-yl)-4-(3,4,5-trimethoxyphenyl)-2-butanol (3.07)

To a dry 100ml 3-necked round bottom flask was added magnesium turnings (0.071g, 2.92 mmol) in dry THF (10ml) and a crystal of I_2. To this stirred suspension was added drop-wise 2-(2-bromoethyl)-1,3-dioxalane (0.24g, 1.33 mmol) ensuring that the reaction was gently refluxing. The aldehyde **(3.06)** (0.3g, 1.33 mmol) was subsequently added at room temperature over 30 minutes. After refluxing the solution for 1 hour, the reaction was quenched by the addition of 2M aq. HCl (10ml). The product was extracted using diethyl ether, dried over sodium sulphate, filtered and the filtrate reduced in volume before being purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.07)** as an orange oil (0.10g, 24%). ν_{max} (CCl_4)/ cm^{-1} 3479.7, 2938.4, 1589.7, 1127.2. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.57 (1H, m, CH_2CH), 1.79 (4H, m, OCH_2CH_2O), 2.55 (2H, m, CH_2), 2.61 (1H, m, CH), 3.63 (1H, m, CHOH), 3.79 (3H, s, OMe), 3.81 (6H, s, 2 x OMe), 3.94 (2H, m, $CHCH_2CH$), 4.87 (1H, m, OCHO), 6.40 (2H, s, 2 x ArH). ^{13}C NMR δ_c ppm 30.05 (CH_2), 31.23 (CH_2), 32.65 (CH_2), 38.00 (CH_2), 55.55 (2 x OMe), 60.02 (OMe), 65.10 ($CH(OH)CH_2CH$), 70.55 (CHOH), 104.32 (OCHO), 105.99 (2 x ArCH), 135.58 (qC), 137.52 (qC), 152.54 (2 x qC).

Synthesis of intermediate, 1-(3,4,5-trimethoxyphenyl)-5-hexen-3-ol (3.08)

To a stirred 2M solution of allyl magnesium bromide (1.32ml, 2.66 mmol) in anhydrous THF (6ml) was added **(3.06)** (0.30g, 1.33 mmol) at 0°C under an anhydrous conditions. When the addition was complete, the reaction temperature was raised to room temperature. After 2 hours, the reaction was quenched by the slow, drop-wise addition of 2M aq. HCl (10ml). The product was isolated after extracting the reaction mixture with diethyl ether (3 x 15ml). The combined organic layers were dried with sodium sulphate, filtered and reduced in volume to afford the crude product, which was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.08)** as an orange oil (0.31g, 88%). ν_{max} (CCl_4)/ cm^{-1} 3436.5, 2936.9, 2838.1, 1589.9, 1128.0. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.76 (2H, m,

$C\underline{H_2}$), 2.22 (2H, m, $C\underline{H_2}$), 2.68 (2H, m, $C\underline{H_2}$), 3.67 (1H, m, C<u>H</u>OH), 3.80 (3H, s, O<u>Me</u>), 3.82 (6H, s, 2 x O<u>Me</u>), 5.12 (2H, m, CHCH=$C\underline{H_2}$), 5.80 (1H, m, $\underline{H}C=CH_2$), 6.41(2H, s, Ar<u>H</u>). ^{13}C NMR δ_c ppm 32.32 ($\underline{C}H_2$), 38.11 ($\underline{C}H_2$), 41.66 ($\underline{C}H_2$), 55.54 (2 x O<u>Me</u>), 60.39 (O<u>Me</u>), 69.50 (<u>C</u>HOH), 104.93 (2 x ArC<u>H</u>), 117.62 (CH=$\underline{C}H_2$), 134.17 ($\underline{C}H=CH_2$) 135.39 (q<u>C</u>), 137.45 (q<u>C</u>), 152.60 (2 x q<u>C</u>).

Attempted synthesis of 3-hydroxy-5-(3,4,5-trimethoxyphenyl)pentanal (3.09)

To a stirred solution of **(3.07)** (0.10g, 0.38 mmol) in THF (10ml) was added water (5ml) and 5% aq. HCl (5ml) at 0°C for 15 minutes. The reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The extracts were collected and the solvent was removed *in vacuo*. As TLC analysis of the reaction indicated the formation of a higher R_f spot, it was decided to discontinue trying to pursue the synthesis of the targeted compound by this route.

Synthesis of intermediate, 4-(3,4,5-trimethoxyphenyl)-2-butanone (3.14)

To a solution of **(3.11)** (0.100g, 0.42 mmol) in ethanol (5ml) and ethyl acetate (5ml) was added 10% Pd/C (0.10g). The reaction was stirred under an atmosphere of H_2 for 12 hours. On completion, the reaction was filtered and the solvent removed under reduced pressure to leave an oil, which was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.14)** as an oil (0.096g, 95%). GCMS m/z (%) 238 (100), 174 (13). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.15 (3H, s, $COC\underline{H_3}$), 2.77 (4H, m, 2 x $C\underline{H_2}$), 3.81 (3H, s, OMe), 3.84 (6H, s, 2 x O<u>Me</u>), 6.40 (2H, s, Ar<u>H</u>). The experimental data has been previously reported[189].

Attempted synthesis of 3-oxo-5-(3,4,5-trimethoxyphenyl)pentanal (3.10)

To a stirred solution of **(3.08)** (0.10g, 0.37 mmol) in acetic acid (1ml) was added potassium dichromate (0.22g, 0.75 mmol) at 40°C for 5 hours. The reaction mixture was quenched by

filtration and the filtrate partitioned between ether and water. The organic layer was isolated and the aqueous layer extracted again with ether. The combined organic layers were dried with sodium sulphate, filtered and evaporation of the solvent left a residue, which was purified by flash column chromatography.

Synthesis of intermediate, 4-(3,4,5-trimethoxyphenyl)-3-buten-2-one (3.11)

To a stirred solution of 3,4,5-trimethoxybenzaldehyde (3.00g, 15.3 mmol) in acetone (3.06ml, 42.0 mmol) was added 2.5M aq. NaOH (1ml) at room temperature for 1.5 hours. On completion, the reaction mixture was filtered and the filtrate evaporated under reduced pressure to afford a yellow sludge. This was re-dissolved in DCM (10ml) and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.11)** as an orange oil (2.0g, 56 %). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.26 (3H, s, $COCH_3$), 3.85 (3H, s, OMe), 3.86 (6H, s, 2 x OMe), 6.38 (2H, s, ArH), 6.67 (1H, d, J 8.5Hz, CH=CH), 7.47 (1H, d, J 8.5Hz, CH=CH). The experimental data has been previously reported [209].

Attempted synthesis of 5-hydroxy-1-(3,4,5-trimethoxyphenyl)-1-penten-3-one (3.12)

To a stirred solution of **(3.11)** (0.30g, 1.27 mmol) in ethanol (10ml) was added formaldehyde (1ml) and 2.5M aq. NaOH (1ml) at room temperature. After 1 hour, the reaction was quenched with the addition of water (10ml) and the products were extracted using diethyl ether, washed with sat. aq. NaCl and dried over sodium sulphate. After filtration, the filtrate was evaporated, however, due to the formation of a large number of by-products, the sample was not purified further.

Attempted synthesis of 3-oxo-5-(3,4,5-trimethoxyphenyl)-4-pentenal (3.13)

To a stirred solution of **(3.11)** (0.10g, 0.42 mmol) in anhydrous THF (5ml) was added LDA (4.72ml, 42.3 mmol) under anhydrous conditions at -78°C. After 10 minutes, ethyl formate (0.03ml, 0.42 mmol) was added drop-wise and the reaction was allowed to proceed for 40

minutes at this temperature before being raised to room temperature for 1 hour. On completion, the reaction was quenched by the addition of 2M aq. HCl and the products were extracted using diethyl ether, dried over sodium sulphate, filtered and then reduced in volume before being purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(3.11)** as an oil (0.10g, 100%).

Attempted synthesis of 3-oxo-5-(3,4,5-trimethoxyphenyl)pentenal (3.15)

To a stirred solution of **(3.14)** (0.10g, 0.42 mmol) in anhydrous THF (5ml) was added LDA (4.72ml, 0.42 mmol) under anhydrous conditions at -78°C. After 10 minutes, ethyl formate (0.03ml, 42.3 mmol) was added drop-wise and the reaction was allowed to proceed for 40 minutes at this temperature before being raised up to room temperature for 1 hour. On completion, the reaction was quenched by the addition of 2M aq. HCl and the products were extracted using diethyl ether, dried over sodium sulphate, filtered and then reduced in volume before being purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(3.14)** as an oil (0.10g, 100%).

Formation of 2,3,4-trimethoxy-7,7-dithian-2-yl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (3.20)

1st Step

Synthesis of intermediate, methyl 5-hydroxy-3-oxo-5-(3,4,5-trimethoxyphenyl)pentanoate (3.16)

To anhydrous THF (10ml) was added NaH (0.12g, 5.09 mmol) at 0°C. To this suspension, was added methyl acetoacetate (0.59g, 5.09 mmol) was added drop-wise over 10 minutes. After the addition was complete, 1.6M *n*-BuLi (3.2ml, 5.09 mmol) was added drop-wise by syringe over a 10 minute period at 0°C. The reaction was allowed to stir for 30 minutes, after which time 3,4,5-trimethoxybenzaldehyde (1.00g, 5.10 mmol) dissolved in dry THF (10ml) was added

drop-wise. After 3 hours, the reaction was quenched with sat. NH_4Cl and extracted with diethyl ether (3 x 25ml). The organic extracts were collected, dried over sodium sulphate, filtered and the solvent was removed under reduced pressure. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ethyl acetate). All homogenous fractions were collected, reduced in volume to afford **(3.16)** as a yellow oil (0.95g, 60%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.98 (2H, m, C(OH)C<u>H</u>$_2$CO), 3.7 (3H, s, COOC<u>H</u>$_3$), 3.51 (2H, s, COC<u>H</u>$_2$CO), 3.85 (3H, s, O<u>Me</u>), 3.88 (6H, s, 2 x O<u>Me</u>), 5.15 (1H, dd, J 3.5Hz, 9.0Hz, C<u>H</u>OH), 6.61 (2H, s, Ar<u>H</u>). ^{13}C NMR δ_c ppm 49.44 (CO<u>C</u>H$_2$CO), 51.21 (ArCH<u>C</u>H$_2$), 53.23 (<u>C</u>H$_3$), 55.65 (2 x O<u>Me</u>), 60.30 (O<u>Me</u>), 69.59 (<u>C</u>HOH), 102.19 (Ar<u>C</u>H), 103.52 (q<u>C</u>), 136.05 (q<u>C</u>), 152.55 (2 x q<u>C</u>), 166.92 (<u>C</u>OOMe), 202.10 (CH$_2$<u>C</u>OCH$_2$).

2nd Step

Synthesis of intermediate, methyl 3-oxo-5-(3,4,5-trimethoxyphenyl)pentanoate (3.17)

To a stirred solution of **(3.16)** (0.20g, 0.64 mmol) in ethanol/ethyl acetate (1:1, 4ml) was added 2M aq. HCl (2ml) and 10% Pd/C (0.20g). The reaction mixture was stirred under a H_2 atmosphere for 72 hours. On completion, the reaction was filtered, washed with 5% aq. $NaHCO_3$ and extracted with diethyl ether. The organic extracts were collected, dried over sodium sulphate, filtered and the solvent was removed under reduced pressure. The resulting residue was purified flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected, reduced in volume to afford an oil **(3.17)** (0.062g, 33%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.85 (4H, s, ArC<u>H</u>$_2$C<u>H</u>$_2$), 3.45 (2H, s, COC<u>H</u>$_2$CO), 3.7 (3H, s, COOC<u>H</u>$_3$), 3.80 (3H, s, O<u>Me</u>), 3.85 (6H, s, 2 x O<u>Me</u>), 6.44 (2H, s, 2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 29.32 (<u>C</u>H$_2$), 44.07 (CO<u>C</u>H$_2$CO), 48.64 (Ar<u>C</u>H$_2$), 51.83 (<u>C</u>H$_3$), 55.66 (2 x O<u>Me</u>), 60.37 (O<u>Me</u>), 104.96 (Ar<u>C</u>H), 135.84 (q<u>C</u>), 136.33 (q<u>C</u>), 152.65 (2 x q<u>C</u>), 166.68 (<u>C</u>OOMe), 201.20 (CH$_2$<u>C</u>OCH$_2$).

Alternative formation of (3.17)

1st Step

Synthesis of intermediate, 3,4,5-trimethoxybenzyl alcohol (3.21)

To a stirred solution of 3,4,5-trimethoxybenzylaldehyde (5.00g, 25.5 mmol) in ethanol (50ml) was added sodium borohydride (1.13g, 30.0 mmol) at 0°C. After 1 hour, the solvent was removed under reduced pressure, washed with water (30ml) and the product was extracted with diethyl ether (3 x 30ml). The combined ether extracts were dried over sodium sulphate, filtered and the filtrate was evaporated. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected, reduced in volume to afford **(3.21)** as an oil (4.85g, 96%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 3.85 (3H, s, OMe), 3.86 (3H, s, OMe), 3.94 (3H, s, OMe), 4.60 (2H, s, CH_2), 6.63 (1H, d, J 8.6Hz, ArH), 6.97 (1H, d, J 8.6Hz, ArH). ^{13}C NMR δ_c ppm 55.55 (OMe), 60.27 (OMe), 60.69 (OMe), 60.82 (CH_2), 106.69 (ArH), 122.86 (ArH), 126.50 (qC), 141.62 (qC), 151.37 (qC), 153.16 (qC).

2nd Step

Synthesis of intermediate, 3,4,5-trimethoxybenzyl bromide (3.22)

To a stirred solution of **(3.21)** (4.50g, 22.7 mmol) in diethyl ether (50ml) was added PBr_3 (5.34ml, 34.0 mmol) drop-wise at -20°C. After 2 hours, the reaction was quenched with ice-water (50ml) and the product was extracted with diethyl ether (5 x 25ml), washed with 5% aq. $NaHCO_3$, dried over sodium sulphate and filtered. The filtrate was evaporated and the residue was dried *in vacuo* for several hours to yield a white solid (4.68g, 79%). GCMS m/z (%) 260 (M^+, 8), 181 (100). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 3.69 (3H, s, OMe), 3.76 (6H, s, 2 x OMe), 4.45 (2H, s, CH_2Br), 6.64 (2H, s, ArH). ^{13}C NMR δ_c ppm 34.92 (CH_2Br), 55.85 (2 x OMe), 61.05 (OMe), 106.11 (2 x ArCH), 132.68 (qC), 137.81 (qC), 154.82 (2 x qC).

3rd Step

Alternative synthesis of (3.17)

To a stirred solution of anhydrous THF (10ml) was added NaH (0.506g, 21.08 mmol) at 0°C. To this suspension was added methyl acetoacetate (2.44g, 21.08 mmol) slowly over 10 minutes. When the addition was complete 1.6M *n*-BuLi (13.17ml, 21.08 mmol) was added by syringe over a 10 minute period at 0°C. The reaction was allowed to stir for 30 minutes, after which time, the bromide **(3.22)** (5.0g, 19.15 mmol), dissolved in dry THF (10ml) was added drop-wise. After 2.5 hours, the reaction was quenched by the addition of sat. aq. NH_4Cl (25ml) and the product was extracted with diethyl ether (3 x 25ml). The combined ether extracts were dried over sodium sulphate, filtered and the filtrate was evaporated. The resulting residue was purified flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.17)** as a yellow oil (3.91g, 69%).

3rd Step

Synthesis of intermediate, methyl 2-[2-(3,4,5-trimethoxyphenethyl)-1,3-dithian-2-yl]acetate (3.18)

To a stirred solution of **(3.17)** (2.8g, 9.45 mmol) in anhydrous DCM (10ml) was added propan-1,3-dithiol (1.41g, 1.13 mmol) at -20°C followed by the drop-wise addition of $BF_3.OEt_2$ (1ml, 6.62 mmol). After 1 hour, the reaction was quenched with water and extracted with diethyl ether (3 x 15ml). The combined ether extracts were washed with water (10ml), washed with 2.5M aq. NaOH (10ml) and water (10ml) again. The organic fractions were subsequently dried over sodium sulphate, filtered and the solvent removed under reduced pressure before purifying the resulting residue by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected, reduced in volume to afford **(3.17)** as a yellow oil (2.44g, 67%). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.97 (2H, m, $SCH_2C\underline{H_2}CH_2S$), 2.35 (2H, m, $SC\underline{H_2}CH_2CH_2S$), 2.85 (4H, m, 2 x $C\underline{H_2}$), 3.06 (2H, m, $SCH_2CH_2C\underline{H_2}S$), 3.13 (2H, s, $C\underline{H_2}CO$), 3.68 (3H, s, $COOC\underline{H_3}$), 3.82 (3H, s, O<u>Me</u>), 3.85 (6H, s, 2 x O<u>Me</u>), 6.45 (2H, s, 2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.33 ($SCH_2\underline{C}H_2CH_2S$), 26.89

($S\underline{C}H_2CH_2\underline{C}H_2S$), 30.12 ($\underline{C}H_2CS$), 41.98 ($\underline{C}H_2CH_2CS$), 42.30 ($\underline{C}H_2CO$), 49.94 ($S\underline{C}S$), 51.20 ($COO\underline{C}H_3$), 55.62 (2 x O$\underline{Me}$), 60.22 (O$\underline{Me}$), 105.02 (2 x Ar$\underline{C}$H), 135.91 (q$\underline{C}$), 136.65 (q$\underline{C}$), 152.97 (2 x q$\underline{C}$), 168.99 ($\underline{C}OOCH_3$). The decarboxylated derivative of **(3.18)** was also formed. GCMS m/z (%) 328 (43), 221 (100). ^{1}H NMR ($CDCl_3$, 400Mhz) δ_H ppm 1.70 (3H, s, $C\underline{H}_3$), 2.0 (2H, m, $SCH_2C\underline{H}_2CH_2S$), 2.35 (2H, m, $SC\underline{H}_2CH_2CH_2S$), 2.75 (2H, m, $SCH_2CH_2C\underline{H}_2S$), 2.85 (4H, m, $ArC\underline{H}_2C\underline{H}_2$), 3.81 (6H, s, 2 x O$\underline{Me}$), 3.86 (3H, s, O$\underline{Me}$), 6.42 (2H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 24.35 ($SCH_2\underline{C}H_2CH_2S$), 26.90 ($S\underline{C}H_2CH_2\underline{C}H_2S$), 28.13 ($\underline{C}H_3$), 31.22 ($\underline{C}H_2CS$), 43.68 ($\underline{C}H_2CH_2CS$), 49.95 ($S\underline{C}S$), 56.66 (2 x O$\underline{Me}$), 60.54 (O$\underline{Me}$), 105.10 (2 x Ar$\underline{C}$H), 136.29 (q$\underline{C}$), 137.76 (q$\underline{C}$), 152.99 (2 x q$\underline{C}$).

4th Step

Synthesis of intermediate, 2-[2-(3,4,5-trimethoxyphenethyl)-1,3-dithian-2-yl]acetic acid (3.19)

To a stirred solution of **(3.17)** (0.10g, 0.26 mmol) in methanol (5ml) was added NaOMe (0.55g, 10.18 mmol). To this solution was added water (2ml) and the reaction was allowed to proceed for 3 hours at room temperature. On completion, the solvent was evaporated and water (10ml) was added to the resulting residue. The aqueous layer was extracted with ether (3 x 10ml) and acidified with 2M aq. HCl. The product was isolated after extraction with ether (3 x 10ml). The organic fractions were combined, dried over sodium sulphate, filtered and the solvent was removed under reduced pressure to afford **(3.19)** as a white solid which was dried under vacuo for several hours (0.067g, 70%). This product was not purified and was used directly in the next step.

5th Step-cyclisation

Synthesis of 2,3,4-trimethoxy-7,7-dithian-2-yl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (3.20) *via* the synthesis of 2-[2-(3,4,5-trimethoxyphenethyl)-1,3-dithian-2-yl]ethanoyl chloride

To a stirred solution of **(3.19)** (0.20g, 0.53 mmol) in dry DCM (1ml) was added DMF (1 drop) and a 2M solution of oxalyl chloride in DCM (0.4ml, 0.80 mmol) under anhydrous conditions at -10°C. After stirring the mixture for 1 hour, the solvent was removed *in vacuo* to afford the acid

chloride as a yellow oil. This was re-dissolved in anhydrous DCM (6ml) and powdered $AlCl_3$ (0.023g, 0.17 mmol) was added portion-wise whilst maintaining the reaction temperature at -10°C. After 3 hours, the solvent was removed and the red residue was purified by flash column chromatography (solid phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(3.20)** as a yellow oil (0.063g, 33%). ν_{max} (CCl_4)/ cm^{-1} 2928.3, 1684.3, 1119.0. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.01 (1H, m, HCH), 2.19 (1H, m, HCH), 2.35 (2H, m, CH_2), 2.85 (2H, m, CH_2), 3.09-3.21 (4H, m, 2 x CH_2), 3.60 (2H, s, CH_2CO), 3.90 (3H, s, OMe), 3.91 3H, s, OMe), 3.97 (3H, s, OMe), 6.38 (1H, s, ArH). ^{13}C NMR δ_c ppm 24.61 (CH_2), 27.42 ($SCH_2CH_2CH_2S$), 32.90 (CH_2), 42.16 (CH_2), 47.61 (SCS), 52.14 (CH_2), 55.99 (OMe), 56.01 (OMe), 60.59 (OMe), 105.49 (ArH), 143.12 (qC), 156.98 (2 x qC), 158.79 (qC), 200.49 (C=O).

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl 3,3-dithianyl-5-(3,4,5-trimethoxyphenyl)pentanoate (3.23)

To a stirred solution of **(3.19)** (1.5g, 4.03 mmol) in DCM (10ml) was added DCC (1.24g, 6.02 mmol) and PFP (1.11g, 6.03 mmol) at 0°C. After 3 hours, the reaction was filtered and the filtrate was concentrated to ~2ml before purifying the residue by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(3.23)** as a white waxy solid (1.54g, 71%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.94 (1H, m, HCH), 2.17 (1H, m, HCH), 2.42 (2H, m, CH_2), 2.85 (4H, m, 2 x SCH_2), 3.12 (2H, m, CH_2), 3.51 (2H, s, CH_2CO), 3.83 (3H, s, OMe), 3.85 (6H, s 2 x OMe), 6.45 (2H, s, 2 x ArH). ^{19}F NMR δ_F ppm -151.94 (2 x F), -158.05 (1 x F), -162.69 (2 x F). ^{13}C NMR δ_c ppm 24.26 (CH_2), 26.06 (2 x CH_2), 30.31 (CH_2), 41.06 (CH_2), 41.84 (CH_2), 49.95 (SCS), 55.60 (2 x OMe), 60.36 (OMe), 105.02 (2 x ArH), 136.39 (qC), 152.77 (qC).

Formation of 1,2,3-trimethoxy-7,7-dithan-2-yl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (3.29)

1st Step

Synthesis of intermediate, 2,3,4-trimethoxybenzyl bromide (3.24)

To a stirred solution of 2,3,4-trimethoxybenzyl alcohol (4.50g, 22.7 mmol) in diethyl ether (50ml) was added PBr_3 (5.34ml, 34.0 mmol) drop-wise at -20°C. The reaction was allowed to proceed for 2 hours. On completion, the reaction was quenched with the addition of ice-water (50ml) and the product was extracted with diethyl ether (5 x 25ml), washed with 5% aq. $NaHCO_3$, dried over sodium sulphate and filtered. The filtrate was then removed under reduced pressure and the residue was dried *in vacuo* for several hours (4.32g, 72%). Due to its instability, the bromide **(3.24)** was used within 2 hours of its synthesis.

2nd Step

Synthesis of intermediate, methyl 3-oxo-5-(2,3,4-trimethoxyphenyl)pentanoate (3.25)

To stirred anhydrous THF (10ml) was added NaH (0.506g, 21.08 mmol) at 0°C. To this suspension, methyl acetoacetate (2.44g, 21.03 mmol) was added slowly over 10 minutes. When the addition was complete 1.6M *n*-BuLi (13.17ml, 21.08 mmol) was also added by syringe over a 10 minute period at 0°C. The reaction was allowed to stir for 30 minutes, after which time, the bromide **(3.24)** (5.0g, 19.15 mmol), dissolved in dry THF (10ml) was added drop-wise. After 3 hours, the reaction was quenched by the addition of sat. aq. NH_4Cl (25ml) and the product was extracted with diethyl ether (3 x 25ml). The combined ether extracts was dried over sodium sulphate, filtered and the filtrate was evaporated. The resulting residue was purified flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.25)** as a yellow oil (4.30g, 76%). ν_{max} (CCl_4)/ cm^{-1} 2940.8, 1748.2, 1716.8. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.80 (4H, m, $ArC\underline{H_2}C\underline{H_2}$), 3.43 (2H, s, $COC\underline{H_2}CO$), 3.67 (3H, s, $COOC\underline{H_3}$), 3.83 (3H, s, O<u>Me</u>), 3.89 (H, s, O<u>Me</u>), 3.91 (H, s, O<u>Me</u>), 6.54 (1H, d, J 8.5Hz, Ar<u>H</u>), 6.61 (1H, d, J 8.5Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm 19.52 ($\underline{C}H_2$), 41.68 ($\underline{C}H_2$), 44.44 ($\underline{C}H_2$), 51.89

(CH$_3$), 56.95 (2 x OMe), 60.70 (OMe), 107.12 (ArCH), 124.62 (ArCH) 125.35 (qC), 141.33 (qC), 151.69 (qC), 151.97 (qC), 173.56 (C=O).

3rd Step

Synthesis of intermediate, 2-[2-(2,3,4-trimethoxyphenethyl)-1,3-dithian-2-yl]acetic acid (3.27)

To a stirred solution of **(3.25)** (2.80g, 9.46 mmol) and propan-1,3-dithiol (1.53g, 14.13 mmol) at -20°C in anhydrous DCM (10ml), was added $BF_3.OEt_2$ (1.0ml, 6.62 mmol) drop-wise over 10 minutes. After the addition was complete, the reaction was allowed to proceed for 1 hour. On completion, the reaction was then quenched with water (10ml), extracted with diethyl ether (3 x 15ml), washed with water (10ml), washed 2.5M aq. NaOH (10ml) and water (10ml) again. The combined organic extracts were dried over sodium sulphate and filtered before removing the solvent under reduced pressure. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(3.26)** as a yellow oil (2.41g, 66%). This intermediate **(3.26)** (0.10g, 0.25 mmol) was subsequently dissolved in 20% aq. methanol (6ml) and NaOMe (0.55g, 0.51 mmol) was added at 25°C. After 24 hours, the solvent was evaporated, water was added and the neutral impurities were extracted with diethyl ether (3 x 15ml). The aqueous layer was then acidified with 2M aq. HCl, and the product was extracted using diethyl ether. The solvent was removed under reduced pressure to afford **(3.27)** as a white solid, which was dried *in vacuo* for several hours (0.051g, 53%). ν_{max} (CCl_4)/ cm^{-1} 3300.0, 2937.3, 2833.3, 1708.8. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.93 (1H, m, CH), 2.09 (1H, m, CH), 2.34 (2H, m, CH$_2$), 2.84 (4H, m, CH$_2$CH$_2$), 3.03 (2H, m, CH$_2$), 3.18 (2H, s, COCH$_2$), 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 3.91 (3H, s, OMe), 6.61 (1H, d, J 8.5Hz, ArH), 6.86 (1H, d, J 8.5Hz, ArH). ^{13}C NMR δ_c ppm 24.22 (CH$_2$), 24.40 (CH$_2$), 25.94 (2 x CH$_2$), 39.97 (CH$_2$), 42.45 (CH$_2$), 49.36 (SCS), 55.60 (OMe), 60.24 (OMe), 60.53 (OMe), 106.94 (ArCH), 123.54 (ArCH), 126.91 (qC), 141.91 (qC), 151.47 (qC), 151.76 (qC), 173.71 (COOH).

4th Step -cyclisation

Synthesis of 1,2,3-trimethoxy-7-dithian-2-yl-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (3.29) via synthesis of 2-[2-(3,4,5-trimethoxyphenethyl)-1,3-dithian-2-yl]ethanoyl chloride (3.28)

To a stirred solution of **(3.27)** (0.20g, 0.54 mmol) in dry DCM (1ml) was added DMF (1 drop) and 2M oxalyl chloride in DCM (0.4ml, 0.81 mmol) under anhydrous conditions. After 1 hour, the solvent was removed to afford **(3.28)** as a yellow oil. This was re-dissolved in anhydrous DCM (6ml) and 1M $SnCl_4$ in DCM (0.17ml, 0.17 mmol) was added drop-wise at 0°C over 10 minutes. The reaction was allowed to proceed for 1.5 hours. On completion, the solvent was removed and the red residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(3.29)** as a yellow oil (0.095g, 50%). GCMS m/z (%) 354 (63), 321 (3.5), 279 (12.5), 248 (100). ^{1}H NMR ($CDCl_3$, 400Mhz) δ_H ppm 1.97 (1H, m, HCH), 2.11 (1H, m, HCH), 2.32 (2H, m, CH_2), 2.82 (2H, m, CH_2), 3.05 (2H, m, CH_2), 3.19 (2H, m, CH_2), 3.44 (2H, s, CH_2CO), 3.84 (3H, s, OMe), 3.89 (3H, s, OMe), 3.94 (3H, s, OMe), 7.31 (1H, s, ArH). ^{13}C NMR δ_c ppm 21.56 (CH_2), 24.46 (CH_2), 26.69 (2 x CH_2), 41.48 (CH_2), 48.32 (SCS), 51.64 (CH_2), 55.52 (OMe), 60.41 (OMe), 60.65 (OMe), 105.40 (ArH), 131.29 (qC), 132.61 (qC), 145.55 (qC), 150.66 (qC), 151.14 (qC), 195.08 (C=O).

Formation of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.32)

1st Step

Synthesis of intermediate, 9-(3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cycloheptene-7,7-dithiane (3.30)

To a dry 50ml, 3-necked round bottom flask was added magnesium turnings (0.078g, 3.25 mmol), anhydrous THF (4ml) and a crystal of iodine. To this mixture, the bromide **(2.50)** (0.10g, 3.16 mmol) was added drop-wise in anhydrous THF (4ml) with vigorous stirring. After refluxing for 15 minutes, the reaction mixture was cooled to room temperature before ketone

(3.29) (0.743g, 2.10 mmol) dissolved in anhydrous THF (4ml) was added drop-wise. The reaction was then heated to reflux for 2 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (10ml) and the product was extracted with diethyl ether (3 x 20ml). The organic extracts were combined, dried over sodium sulphate and filtered. The filtrate was removed under reduced pressure and the resulting residue was isolated by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). All homogenous fractions were collected, reduced in volume to afford **(3.30)** as a white solid (0.52g, 43%). GCMS m/z (%) 574 (21), 542 (2), 503 (20), 468 (100). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.17 (6H, s, $C\underline{H}_3SiC\underline{H}_3$), 1.00 (9H, s, $C(C\underline{H}_3)_3$), 2.02 (2H, m, $C\underline{H}_2$), 2.57 (2H, m, $C\underline{H}_2$), 2.85 (2H, m, $C\underline{H}_2$), 2.94 (4H, m, $C\underline{H}_2C\underline{H}_2$), 3.61 (3H, m, O<u>Me</u>), 3.84 (3H, s, O<u>Me</u>), 3.89 (3H, s, O<u>Me</u>), 3.92 (3H, s, O<u>Me</u>), 6.27 (1H, s, C<u>H</u>), 6.33 (1H, s, C<u>H</u>), 6.80 (2H, m, 2 x Ar<u>H</u>), 6.87 (1H, m, Ar<u>H</u>). ^{13}C NMR δ_c ppm -5.13 ($C\underline{H}_3SiCH_3$), -5.02 ($C\underline{H}_3SiCH_3$), 17.99 ($\underline{C}(CH_3)_3$), 22.26 ($\underline{C}H_2$), 24.62 ($\underline{C}H_2$), 25.26 ($C(\underline{C}H_3)_3$), 27.54 (2 x $\underline{C}H_2$), 45.83 ($\underline{C}H_2$), 52.13 (S<u>C</u>S), 55.08 (O<u>Me</u>), 55.38 (O<u>Me</u>), 60.46 (O<u>Me</u>), 61.05 (O<u>Me</u>), 110.23 (Ar<u>C</u>H), 111.12 (Ar<u>C</u>H), 121.33 (Ar<u>C</u>H), 121.99 (Ar<u>C</u>H), 128.95 (q<u>C</u>), 131.04 (C=<u>C</u>H), 133.08 (q<u>C</u>), 136.59 (q<u>C</u>), 140.61 (q<u>C</u>), 141.50 (q<u>C</u>), 144.04 (q<u>C</u>), 149.57 (q<u>C</u>), 150.25 (q<u>C</u>), 151.00 (q<u>C</u>).

2nd Step

Synthesis of 2-methoxy-5-(2,3,4-trimethoxy-7,7-dithianyl-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenol (3.31)

To a stirred solution of **(3.30)** (0.05g, 0.087 mmol) in THF (1ml) was added 1M TBAF (0.10ml, 0.102 mmol) drop-wise at room temperature. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(3.31)** as a white solid (0.036g, 90%). M.pt. 60-62°C. ν_{max} (CCl_4)/ cm^{-1} 3402.8, 2921.1, 2837.4, 1575.7. HRMS: found 461.1433 (MH^+), requires ($C_{24}H_{28}O_5S_2$) 460.1378. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.01 (2H, m, $C\underline{H}_2$), 2.56 (2H, m, $C\underline{H}_2$), 2.80 (2H, m, $C\underline{H}_2$), 2.95 (4H, m, 2 x $C\underline{H}_2$), 3.63

(3H, m, OMe), 3.88 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 5.61 (1H, s, br, OH), 6.29 (1H, s, CH), 6.38 (1H, s, CH), 6.81 (2H, m, 2 x ArH), 6.94 (1H, m, ArH). ^{13}C NMR δ_c ppm 22.30 (CH_2), 24.64 (CH_2), 27.63 (2 x CH_2), 46.25 (CH_2), 52.03 (SCS), 55.52 (OMe), 55.55 (OMe), 60.47 (OMe), 61.05 (OMe), 109.70 (ArCH), 110.22 (ArCH), 114.77 (ArCH), 120.42 (ArCH), 128.92 (qC), 131.49 (C=CH), 133.07 (qC), 137.03 (qC), 140.74 (qC), 141.56 (qC), 144.70 (qC), 145.76 (qC), 149.63 (qC), 150.50 (qC).

3rd Step

Attempted synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-one (3.32) using $Tl(NO_3)_3.3H_2O$

To a stirred solution of **(3.31)** (0.05g, 0.108 mmol) in methanol (1ml) was added $Tl(NO_3)_3$ $.3H_2O$ (0.11g, 0.24 mmol) at 25°C. The reaction was monitored by TLC analysis every 5 minutes for 30 minutes. As TLC analysis of the reaction indicated the formation of a several compounds, it was decided to discontinue the synthesis of the targeted compound employed in this route.

Attempted synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-one (3.32) using silica gel

To a stirred solution of **(3.31)** (0.05g, 0.108 mmol) in ethyl acetate was added silica gel (0.1g) and 2M aq. HCl (0.1ml) at 25°C. The reaction was monitored by TLC analysis every 15 minutes for 1 hour. No reaction appeared to be taking place so the temperature was increased to 60°C. As TLC analysis of the reaction indicated that no reaction had taken place, it was decided to discontinue the synthesis of the targeted compound employed in this route.

Attempted synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-one (3.32) using N-bromosuccinimide

To a stirred solution of **(3.31)** (0.05g, 0.108 mmol) in acetonitrile (AcCN) or acetone (0.1-0.5ml) was added drop-wise to a solution of NBS (0.15g, 0.84 mmol) in 80% aq. AcCN or 90% aq. acetone (15ml) at -5°C up to 30°C. The reaction was monitored by TLC analysis every 5 minutes for 15 minutes. As TLC analysis of the reaction indicated that no reaction had taken place, it was decided to discontinue trying to pursue the synthesis of the targeted compound employed in this route.

Attempted synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-one (3.32) using iodomethane

To a stirred solution of **(3.31)** (0.05g, 0.108 mmol) in 90% aq. AcCN (1ml) was added iodomethane (0.1ml) at 25°C. The reaction was monitored by TLC analysis every 5 minutes for 45 minutes. As TLC analysis of the reaction indicated the formation of a several compounds, it was decided to discontinue trying to pursue the synthesis of the targeted compound employed in this route.

Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.32) using $Hg(ClO_4)_2$

To a stirred solution of **(3.31)** (0.03g, 0.065 mmol) in 80% aq. THF (0.3ml) was added $CaCO_3$ (0.03g, 0.29 mmol) followed by 2.5M aq. $Hg(ClO_4)_2$ (0.2ml) at 25°C. After 10 minutes, the reaction was quenched by the addition of ether (10ml) to precipitate the product, which was subsequently filtered and dried *in vacuo*. The enone **(3.31)** was then re-dissolved in DCM (~2ml) and purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(3.32)** as a pale yellow solid (0.006g, 25%). M.pt. 142-144°C. ν_{max} (CCl_4)/ cm^{-1} 3400.2, 2926.1, 1652.4, 1592.2, 1497.0, 1116.3. GCMS m/z (%) 370 (100), 327 (20), 267 (3), 137 (8). HRMS: found 371.1460 (MH^+), requires ($C_{21}H_{22}O_6$)

370.1416. ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 2.72 (2H, m, H-5), 3.15 (2H, m, H-6), 3.64 (3H, s, OMe from C-2), 3.91 (3H, s, 2 x OMe), 3.95 (6H, s, OMe from C-4'), 5.67 (1H, s, br, -OH), 6.38 (2H, s, H-1, H-8), 6.86 (1H, m, H-5'), 6.92 (1H, s, H-2'), 6.90 (1H, d, J =1.5Hz, H-6'). ^{13}C NMR δ_c ppm 19.80 (C-6), 45.22 (C-5), 55.54 (OMe from C-4'), 55.62 (OMe from C-2), 60.43 (OMe), 60.92 (OMe), 109.77 (C-5'), 111.58 (C-1), 114.99 (C-2'), 120.68 (C-6'), 127.71 (C-8), 128.66 (C-9a) 132.02 (qC), 135.59 (qC), 142.86 (qC), 144.84 (C-3'), 146.85 (C-4'), 149.51 (MeO-qC) 150.65 (C-2), 151.17 (qC), 203.54 (C=O).

Formation of 7-hydroxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.39)

1st Step

Synthesis of intermediate, methyl 3-hydroxy-5-(2,3,4-trimethoxyphenyl)pentanoate (3.33)

To a stirred solution of the **(3.25)** (0.5g, 1.68 mmol) in methanol (6.5ml) was added $NaBH_4$ (0.02g, 0.52 mmol) at 0°C. After 2 hours, the reaction was quenched with sat. aq. NaCl solution (10ml) and the product was extracted using diethyl ether (3 x 10ml). The organic extracts were collected, dried over sodium sulphate and filtered before the product was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.26)** as a clear oil (0.46g, 92%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.77 (2H, m, CH_2), 2.50 (2H, m, CH_2), 2.70 (2H, m, CH_2), 3.08 (1H, s, br, OH), 3.71 (3H, s, $COOCH_3$), 3.85 (3H, s, OMe), 3.88 (3H, s, OMe), 3.90 (3H, s, OMe), 4.00 (1H, m, CHOH), 6.62 (1H, d, J 8.5Hz, 2 x ArH), 6.85 (1H, d, J 8.5Hz, 2 x ArH). ^{13}C NMR δ_c ppm 25.15 (CH_2), 37.20 (C(OH)CH_2CO), 40.75 (ArCH_2), 51.18 ($COOCH_3$), 55.58 (OMe), 60.25 (OMe), 60.49 (OMe), 66.81 (CHOH), 107.07 (ArCH), 123.45 (ArCH), 126.98 (qC), 141.86 (qC), 151.69 (qC), 151.12 (qC), 172.71 (C=O).

2nd Step

Synthesis of intermediate, 3-hydroxy-5-(2,3,4-trimethoxyphenyl)pentanoic acid (3.34)

To a stirred solution of **(3.33)** (0.78g, 2.62 mmol) in methanol (2.61ml) was added KOH (0.14g, 2.50 mmol) dissolved in H_2O (2.5ml) at 0°C. After 12 hours, the reaction was cautiously acidified to pH 3 and the product was extracted with diethyl ether (3 x 5ml). The organic extracts were collected, dried over sodium sulphate and filtered before the product was concentrated *in vacuo* to afford **(3.34)** as a white solid (0.23g, 31%). ν_{max} (CCl_4)/ cm^{-1} 3459.5, 2938.4, 1714.5, 1602.4. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 169-1.83 (2H, m, C<u>H</u>$_2$), 2.48-2.58 (2H, m, C<u>H</u>$_2$), 2.73 (2H, m, C<u>H</u>$_2$), 3.70 3.86 (3H, s, O<u>Me</u>), 3.89 (3H, s, O<u>Me</u>), 3.92 (3H, s, O<u>Me</u>), 3.95 (1H, m, C<u>H</u>OH), 6.65 (1H, d, J 8.5Hz, Ar<u>H</u>), 6.85 (1H, d, J 8.5Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.86 (<u>C</u>H$_2$), 37.26 (<u>C</u>H$_2$), 40.48 (<u>C</u>H$_2$), 55.60 (O<u>Me</u>), 60.32 (O<u>Me</u>), 60.68 (O<u>Me</u>), 66.46 (<u>C</u>HOH), 107.41 (Ar<u>C</u>H), 123.56 (Ar<u>C</u>H), 126.69 (q<u>C</u>), 141.86 (q<u>C</u>), 151.13 (q<u>C</u>), 151.82 (q<u>C</u>), 174.94 (<u>C</u>OOH).

3rd Step

Synthesis of intermediate, 3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-5-(2,3,4-trimethoxyphenyl)pentanoic acid (3.36) via hydrolysis of 1-(tert-butyl)-1,1-dimethylsilyl 3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-5-(2,3,4-trimethoxyphenyl)pentanoate (3.35)

To a stirred solution of **(3.34)** (0.58g, 2.04 mmol) in DMF (5.0ml) was added *t*BDMSCl (0.64g, 4.28 mmol) at 0°C for 15 minutes. To this solution was then added triethylamine (0.59ml, 4.28 mmol) and DMAP (0.26g, 2.13 mmol) at ambient temperature and the reaction was allowed to proceed for 36 hours. On completion, the reaction was quenched by the addition of sat. aq. NaCl solution and the product extracted using diethyl ether (3 x 10ml). The organic extracts were collected and dried over sodium sulphate, filtered and the filtrate evaporated under reduced pressure to afford **(3.35)** as a clear oil (1.05g, 91%). To a stirred solution of the ester **(3.35)** (0.5g, 0.97 mmol) in methanol (13ml), H_2O (2ml) and THF (2ml) was added K_2CO_3 (0.40g, 2.90 mmol) at room temperature. After 2 hours, the reaction was acidified to pH 2 and the product was extracted using diethyl ether (3 x 25ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The

resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.36)** as a clear oil (0.33g, 85%). ν_{max} (CCl_4)/ cm^{-1} 2945.3, 1711.9, 1495.5, 1101.8. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.09 (3H, s, CH_3SiCH_3), 0.11 (3H, s, CH_3SiCH_3), 0.90 (9H, s, $C(CH_3)_3$), 1.83 (2H, m, CH_2), 2.60 (4H, m, 2 x CH_2), 3.85 (3H, s, OMe), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.20 (1H, m, CHOSi), 6.61 (1H, d, J 8.5Hz, ArH), 6.82 (1H, d, J 8.5Hz, ArH). ^{13}C NMR δ_c ppm -5.32 (CH_3SiCH_3), -5.04 (CH_3SiCH_3), 17.51 ($C(CH_3)_3$), 25.04 (CH_2), 25.16 ($C(CH_3)_3$), 37.97 (CH_2), 41.40 (CH_2), 55.58 (OMe), 60.22 (OMe), 60.35 (OMe), 68.74 (CHOSi), 106.87 (ArCH), 123.07 (ArCH), 127.25 (qC), 141.89 (qC), 151.36 (qC), 151.66 (qC), 175.76 (COOH).

Synthesis of intermediate, methyl 3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-5-(2,3,4-trimethoxyphenyl)pentanoate (3.37)

To a stirred solution of **(3.33)** (0.50g, 1.68 mmol) in DMF (5ml) was added imidazole (0.29g, 4.26 mmol) and *t*BDMSCl (0.38g, 2.52 mmol) at 0°C. After 3 hours, the reaction was quenched by the addition of sat. NaCl solution (10ml) and the products were extracted using diethyl ether (3 x 10ml). The organic extracts were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.37)** as a clear oil (0.54g, 78%). ν_{max} (CCl_4)/ cm^{-1} 2932.6, 1740.6, 1495.2, 1102.6. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.07 (3H, s, CH_3SiCH_3), 0.10 (3H, s, CH_3SiCH_3), 0.90 (9H, s, $C(CH_3)_3$), 1.77 (2H, m, CH_2), 2.53-2.65 (4H, m, 2 x CH_2), 3.68 (3H, s, COOMe), 3.84 (3H, s, OMe), 3.87 (3H, s, OMe), 3.88 (3H, s, OMe), 4.22 (1H, m, CHOSi), 6.61 (1H, d, J 8.5Hz, ArH), 6.81 (1H, d, J 8.5Hz, ArH). ^{13}C NMR δ_c ppm -5.30 (CH_3SiCH_3), -5.01 (CH_3SiCH_3), 17.51 ($C(CH_3)_3$), 25.04 (CH_2), 25.30 ($C(CH_3)_3$), 38.29 (CH_2), 41.94 (CH_2), 50.91 (COOMe), 55.57 (OMe), 60.19 (OMe), 60.32 (OMe), 68.74 (CHOSi), 106.86 (ArCH), 123.05 (ArCH), 127.62 (qC), 141.92 (qC), 151.39 (qC), 151.57 (qC), 171.68 (COOMe).

Synthesis of intermediate, 3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-5-(2,3,4-trimethoxyphenyl)pentanoic acid (3.36)

To a stirred solution of ester **(3.40)** (0.50g, 1.21 mmol) in methanol (50ml) was added 2M aq. NaOH (10ml) at room temperature. After 12 hours, the reaction was acidified to pH 2 and the product was extracted with diethyl ether (3 x 10ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.41)** as a clear oil (0.41g, 85%). Data previously described.

4th Step-cyclisation

Synthesis of 7-hydroxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.39) *via* the synthesis of 3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-5-(2,3,4-trimethoxyphenyl)pentanoyl chloride (3.38)

To a stirred solution of **(3.36)** (0.50g, 1.25 mmol) in dry DCM (1ml) was added DMF (1 drop) and 2M oxalyl chloride in DCM (1.25ml, 2.50 mmol) under anhydrous conditions at 0°C. After 1 hour, the solvent was removed to afford **(3.38)** as a yellow oil. This was re-dissolved in anhydrous DCM (2ml) and 1.0M $SnCl_4$ in DCM (0.41ml, 0.41 mmol) was added at -10°C. After 3 hours, the reaction was quenched by the addition of sat. aq. NaCl (5ml) and the product extracted with diethyl ether (3 x 10ml). The organic extracts were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.39)** as a yellow oil (0.027g, 8%). ν_{max} (CCl_4)/ cm^{-1} 3431.5, 2934.6, 1673.3, 1589.1, 1324.3. GCMS m/z (%) 266 (100), 248 (22), 208 (95), 181 (25). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.89 (1H, m, H-6), 2.19 (1H, m, H-6), 3.01 (2H, s, H-9), 3.09 (2H, m, H-8), 3.86 (3H, s, OMe), 3.89 (3H, s, OMe), 3.95 (3H, s, OMe), 4.35 (1H, m, H-7), 7.18 (1H, s, H-4). ^{13}C NMR δ_c ppm 20.48 (CH_2), 35.51 (CH_2), 49.91 (CH_2), 55.53 (OMe), 60.39 (OMe), 60.65 (OMe), 66.78 (C-7), 107.08 (C-4), 130.21 (qC), 198.94 (C=O).

Formation of 7-hydroxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.39) *via* deprotection of (3.43)

1st Step

Synthesis of intermediate, methyl 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-5-(2,3,4-trimethoxyphenyl)pentanoate (3.40)

To a stirred solution of **(3.33)** (1.00g, 3.35 mmol) in DMF (5ml) was added imidazole (0.35g, 5.14 mmol) and *tert*-butyldiphenylsilyl chloride (1.89g, 6.88 mmol) at room temperature. After 2 hours, the reaction was quenched with sat. NaCl (10ml) and the product extracted with diethyl ether (3 x 10ml). The organic extracts were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 6:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.40)** as a pale oil (1.71g, 95%). ν_{max} (CCl_4)/ cm^{-1} 2932.4, 2857.3, 1739.6, 1106.3. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.11 (9H, s, $C(C\underline{H}_3)_3$)) 1.76 (2H, m, $C\underline{H}_2$), 2.59 (4H, m, 2 x $C\underline{H}_2$), 3.57 (3H, s, $COOC\underline{H}_3$), 3.79 (3H, s, O<u>Me</u>), 3.84 (3H, s, O<u>Me</u>), 3.86 (3H, s, O<u>Me</u>), 4.15 (1H, dd, J 7Hz, 14.0Hz, C<u>H</u>OSi), 6.56 (1H, d, J 8.5Hz, Ar<u>H</u>), 6.61 (1H, d, J 8.5Hz, Ar<u>H</u>), 7.41 (6H, m, 6 x Ar<u>H</u>), 7.74 (4H, m, 4 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 18.54 ($\underline{C}(CH_3)_3$), 24.60 ($\underline{C}H_2$), 26.12 ($C(\underline{C}H_3)_3$), 38.18 ($\underline{C}H_2$), 41.75 (Ar$\underline{C}H_2$), 51.28 ($\underline{C}H_3$), 55.58 (O<u>Me</u>), 60.20 (O<u>Me</u>), 60.28 (O<u>Me</u>), 69.91 (<u>C</u>HOSi), 107.23 (Ar<u>C</u>H), 123.42 (Ar<u>C</u>H), 127.44 (Ar<u>C</u>H), 127.46 (q<u>C</u>), 127.47 (Ar<u>C</u>H), 127.64 (2 x Ar<u>C</u>H), 129.54 (Ar<u>C</u>H), 129.55 (Ar<u>C</u>H), 133.61 (q<u>C</u>), 134.75 (2 x Ar<u>C</u>H), 135.84 (Ar<u>C</u>H), 135.89 (Ar<u>C</u>H), 141.82 (q<u>C</u>), 151.32 (q<u>C</u>), 151.48 (q<u>C</u>), 171.40 (<u>C</u>OOMe).

2nd Step

Synthesis of intermediate, 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-5-(2,3,4-trimethoxyphenyl)pentanoic acid (3.41)

To a stirred solution of ester **(3.40)** (2.81g, 5.24 mmol) in methanol (50ml) was added 1M aq. NaOH (20ml) at room temperature. After 12 hours, the reaction was acidified to pH 2 and the product was extracted with diethyl ether (3 x 25ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.41)** as a clear oil (1.39g, 51%). ν_{max} (CCl_4)/ cm^{-1} 3048.4, 2933.5, 2857.9, 1710.1. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.08 (9H, s, C(C$\underline{H}_3$)$_3$) 1.80 (2H, m, C$\underline{H}_2$), 2.50 (4H, m, 2 x C$\underline{H}_2$), 3.7 (3H, s, O$\underline{Me}$), 3.84 (3H, s, O$\underline{Me}$), 3.84 (3H, s, O$\underline{Me}$), 4.25 (1H, m, C$\underline{H}$OSi), 6.52 (1H, d, J 8.5Hz, Ar$\underline{H}$), 6.60 (1H, d, J 8.5Hz, Ar$\underline{H}$), 7.39 (6H, m, 6 x Ar$\underline{H}$), 7.69 (4H, m, 4 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 18.84 (C(C$\underline{H}_3$)$_3$), 24.69 (C$\underline{H}_2$), 26.49 (C(C$\underline{H}_3$)$_3$), 37.50 (C$\underline{H}_2$), 40.85 (ArC$\underline{H}_2$), 55.57 (O$\underline{Me}$), 60.19 (O$\underline{Me}$), 60.26 (O$\underline{Me}$), 69.73 (C$\underline{H}$OH), 106.82 (ArC$\underline{H}$), 123.00 (ArC$\underline{H}$), 127.13 (3 x ArC$\underline{H}$), 129.25 (ArC$\underline{H}$), 133.14 (q$\underline{C}$), 133.28 (q$\underline{C}$), 134.75 (ArC$\underline{H}$), 135.41 (2 x ArC$\underline{H}$), 135.46 (2 x ArC$\underline{H}$), 141.80 (q$\underline{C}$), 151.28 (q$\underline{C}$), 151.53 (q$\underline{C}$), 175.83 ($\underline{C}$OOH).

3rd Step

Synthesis of intermediate, 7-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (3.43)

To a stirred solution of acid (1.12g, 2.14 mmol) in anhydrous DCM (5ml) was added 2M oxalyl chloride in DCM (2.14ml, 4.28 mmol) and DMF (1 drop) at -10°C. After two hours, the excess oxalyl chloride was removed under reduced pressure to afford **(3.42)** as an oil. This was re-dissolved in anhydrous DCM (12ml) and 1.0M $SnCl_4$ in DCM (0.64ml, 0.64 mmol) was added at -10°C. After 30 minutes, the reaction was quenched with sat. aq. NaCl (15ml) and the product extracted using diethyl ether (3 x 15ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting

residue was then purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford a pale yellow oil (0.85g, 79%). ν_{max} (CCl_4)/ cm^{-1} 2933.7, 2857.3, 1674.2, 1104.7. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.05 (9H, s, C(CH_3)$_3$), 1.88 (1H, m, C$\underline{H}$), 1.97 (1H, m, C$\underline{H}$), 2.92 (2H, m, C$\underline{H_2}$), 3.02 (2H, m, C$\underline{H_2}$), 3.84 (3H, s, O$\underline{Me}$), 3.88 (3H, s, O$\underline{Me}$), 3.94 (3H, s, O$\underline{Me}$), 4.32 (1H, m, C$\underline{H}$OSi), 7.17 (1H, s, Ar$\underline{H}$), 7.40 (6H, m, 6 x Ar$\underline{H}$), 7.65 (4H, m, 4 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 18.68 ($\underline{C}$(CH_3)$_3$), 20.49 ($\underline{C}H_2$), 26.11 (C($\underline{C}H_3$)$_3$), 35.87 ($\underline{C}H_2$), 49.85 ($\underline{C}H_2$), 55.52 (O$\underline{Me}$), 60.37 (O$\underline{Me}$), 60.65 (O$\underline{Me}$), 67.82 ($\underline{C}$HOSi), 107.14 (Ar$\underline{C}$H), 127.16 (Ar$\underline{C}$H), 127.20 (Ar$\underline{C}$H), 127.24 (Ar$\underline{C}$H), 129.16 (Ar$\underline{C}$H), 129.24 (Ar$\underline{C}$H), 129.30 (Ar$\underline{C}$H), 130.34 (q$\underline{C}$), 133.32 (q$\underline{C}$), 133.51 (q$\underline{C}$), 134.19 (q$\underline{C}$), 134.34 (Ar$\underline{C}$H), 135.21 (Ar$\underline{C}$H), 135.29 (Ar$\underline{C}$H), 145.13 (q$\underline{C}$), 150.61 (q$\underline{C}$), 150.96 (q$\underline{C}$), 199.15 ($\underline{C}$=O).

4th Step-deprotection

Synthesis of 7-hydroxy-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (3.39) *via* (3.43)

To a stirred solution of ketone **(3.43)** (0.10g, 0.19 mmol) in THF (1.0ml) was added 1M TBAF (0.19ml, 0.19 mmol) drop-wise at -10°C. The reaction was allowed to proceed for 5 hours before being quenched by the addition of water (5ml) and the product was extracted using diethyl ether (3 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.43)** as a pale yellow oil (0.020g, 38%). ν_{max} (CCl_4)/ cm^{-1} 3431, 2934.6, 1673.3, 1589.1, 1324.3. GCMS m/z (%) 266 (100), 248 (22), 208 (95), 181 (25). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.89 (1H, m, C$\underline{H}$), 2.19 (1H, m, C$\underline{H}$), 3.01 (2H, s, C$\underline{H_2}$), 3.08 (2H, m, C$\underline{H_2}$), 3.86 (3H, s, O$\underline{Me}$), 3.89 (3H, s, O$\underline{Me}$), 3.95 (3H, s, O$\underline{Me}$), 4.35 (1H, qn, J = 6Hz, C$\underline{H}$OH), 7.18 (1H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 20.58 ($\underline{C}H_2$), 35.51 ($\underline{C}H_2$), 49.91 ($\underline{C}H_2$), 55.53 (O$\underline{Me}$), 60.39 (O$\underline{Me}$), 60.65 (O$\underline{Me}$), 66.78 ($\underline{C}$HOH), 107.08 (Ar$\underline{H}$), 130.21 (q$\underline{C}$), 198.94 ($\underline{C}$=O).

Synthesis of 2,3,4-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.44)

To a stirred solution of *para*-bromoanisole (0.21g, 1.12 mmol) in anhydrous THF (2ml) was added 2.5M *n*-BuLi (0.45ml, 1.12 mmol) at -78°C under anhydrous conditions. After 20 minutes, whilst maintaining the temperature at -78°C, keto-alcohol **(3.39)** (0.10g, 0.37 mmol) dissolved in anhydrous THF (2ml), was added. The reaction was allowed to continue for 30 minutes before being quenched by the addition of 2M aq. HCl (6ml) and the product was extracted with diethyl ether (3 x 6ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.44)** as a white solid (0.084g, 63%). M.pt. 44-45°C. ν_{max} (CCl_4)/ cm^{-1} 3398.2, 2933.4, 1606.4, 1510.0, 1113.9. GCMS m/z (%) 356 (2), 338 (100). HRMS: found 379.1488 (M^++Na), requires ($C_{21}H_{24}O_5$) 356.1624. ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 2.06 (1H, m, C<u>H</u>), 2.30 (1H, m, C<u>H</u>), 2.44 (1H, m, C<u>H</u>), 3.05 (1H, m, C<u>H</u>), 3.65 (3H, s, O<u>Me</u>), 3.82 (3H, s, O<u>Me</u>), 3.88 (3H, s, O<u>Me</u>), 3.90 (3H, s, O<u>Me</u>), 4.02 (1H, s, C<u>H</u>OH), 6.23 (1H, m, C=C<u>H</u>), 6.37 (1H, s, Ar<u>H</u>), 6.89 (2H, dd, J 2Hz, 6.5Hz, 2 x Ar<u>H</u>), 7.22 (2H, dd, J 2Hz, 6.5 Hz, 2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 21.00 (<u>C</u>H$_2$), 42.33 (<u>C</u>H$_2$), 53.87 (O<u>Me</u>), 54.59 (O<u>Me</u>), 59.39 (O<u>Me</u>), 60.19 (O<u>Me</u>), 68.43 (<u>C</u>HOH), 108.25 (Ar<u>C</u>H), 112.90 (2 x Ar<u>C</u>H), 127.51 (q<u>C</u>), 128.27 (2 x Ar<u>C</u>H), 130.84 (C=<u>C</u>H), 133.20 (q<u>C</u>), 135.23 (q<u>C</u>), 138.04 (q<u>C</u>), 140.94 (q<u>C</u>), 150.21 (q<u>C</u>), 150.81 (q<u>C</u>), 158.94 (q<u>C</u>).

Formation of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.46)

1st Step

Synthesis of intermediate, 9-(3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-ol (3.45)

To a stirred solution of **(2.50)** (0.36g, 1.13 mmol) in anhydrous THF (2ml) was added 2.5M *n*-BuLi (0.45ml, 1.12 mmol) at -78°C under anhydrous conditions. After 20 minutes, **(3.39)** (0.1g, 0.38 mmol), dissolved in anhydrous THF (2ml), was added and the reaction was allowed to proceed for 1 hour. On completion, the reaction was quenched by the addition of 2M aq. HCl (6ml) and the product was extracted using diethyl ether (3 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(3.45)** as a white solid (0.15g, 81%). M.pt. 61-62°C. ν_{max} (CCl_4)/ cm^{-1} 3396.2, 2930.1, 1507.8, 1113.2. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.16 (3H, s, SiC<u>H</u>$_3$), 0.17 (3H, s, SiC<u>H</u>$_3$), 1.00 (9H, s, C(C<u>H</u>$_3$)$_3$), 2.11 (1H, m, C<u>H</u>), 2.37 (1H, m, C<u>H</u>), 2.52 (1H, m, C<u>H</u>), 3.04 (1H, m, C<u>H</u>), 3.69 (3H, s, O<u>Me</u>), 3.83 (3H, s, O<u>Me</u>), 3.92 (3H, s, O<u>Me</u>), 3.93 (3H, s, O<u>Me</u>), 4.18 (1H, m, C<u>H</u>OH), 6.26 (1H, d, J 4.5Hz, C=C<u>H</u>), 6.36 (1H, s, Ar<u>H</u>), 6.83 (3H, m, 3 x Ar<u>H</u>). ^{13}C NMR δ_c ppm -5.02 (<u>C</u>H$_3$Si), -4.99 (<u>C</u>H$_3$Si), 17.97 (<u>C</u>(CH$_3$)$_3$), 21.33 (<u>C</u>H$_2$), 25.26 (C(<u>C</u>H$_3$)$_3$), 43.04 (<u>C</u>H$_2$), 55.07 (O<u>Me</u>), 55.49 (O<u>Me</u>), 60.38 (O<u>Me</u>), 61.07 (O<u>Me</u>), 69.38 (<u>C</u>HOH), 108.39 (Ar<u>C</u>H), 111.27 (Ar<u>C</u>H), 120.21 (Ar<u>C</u>H), 120.04 (Ar<u>C</u>H), 127.53 (q<u>C</u>) 130.74 (C=<u>C</u>H), 133.69 (q<u>C</u>), 134.88 (q<u>C</u>), 138.32 (q<u>C</u>), 141.03 (q<u>C</u>), 144.26 (q<u>C</u>), 150.17 (q<u>C</u>), 150.29 (q<u>C</u>), 150.67 (q<u>C</u>).

2nd Step-deprotection

Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.46)

To a stirred solution of **(3.45)** (0.05g, 0.10 mmol) in THF (1ml) was added 1M TBAF (0.10ml, 0.10 mmol) at 0°C. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted using diethyl ether (3 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(3.46)** a white solid (0.036g, 95%). M.pt. 48-50°C. ν_{max} (CCl_4)/ cm^{-1} 3403.2, 2932.8, 1509.5. HRMS: found 395.0399 (M^++Na), requires ($C_{21}H_{24}O_6$) 372.1573. GCMS m/z (%) 354 (M^+-18, 100), 340 (6), 327 (8), 307 (11). ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 2.09 (1H, m, H-6), 2.35 (1H, m, H-5), 2.51 (1H, m, H-6), 3.03 (1H, m, H-5), 3.66 (3H, s, OMe), 3.87 (3H, s, OMe), 3.89 (3H, s, OMe), 3.89 (3H, s, OMe), 4.00 (1H, m, H-7), 5.66 (1H, s, br, OH), 6.22 (1H, d, J 5.0Hz, H-8), 6.40 (1H, m, H-1), 6.74 (1H, dd, J 2.0Hz, 8.5 Hz, H-2'), 6.76 (1H, d, J 2.0Hz, H-6'), 6.88 (1H, d, J 8.0Hz, H-5'). ^{13}C NMR δ_c ppm 21.39 (C-6), 42.28 (C-8), 54.59 (OMe), 54.61 (OMe), 59.40 (OMe), 60.21 (OMe), 68.41 (C-7), 108.78 (C-1), 111.09 (C-2'), 114.59 (C-5), 119.14 (C-6'), 127.41 (qC), 131.19 (C-8), 133.92 (qC), 135.19 (qC), 138.12 (qC), 140.89 (qC), 145.48 (qC), 146.93 (qC) 150.14 (qC), 150.72 (qC).

Synthesis of 5-(7-hydroxy-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-2-methoxy-1,3-benzenediol (3.48) *via* 9-(3,5-di[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.47)

To a stirred solution of bromide **(2.55)** (0.60g, 1.34 mmol) in anhydrous THF (1ml) was added 2.5M *n*-BuLi (0.54ml, 1.34 mmol) drop-wise at -78°C under anhydrous conditions during over 10 minutes. This was followed by the addition of **(3.39)** (0.12g, 0.45 mmol) dissolved in anhydrous THF (1ml) was added. After 4 hours, the temperature was raised to 0°C and maintained at this temperature for 12 hours. On completion, the reaction was quenched by the

addition of 2M aq. HCl (5ml) and the product was extracted using diethyl ether (3 x 10ml). The combined ether extracts were dried over sodium sulphate, filtered and the filtrate concentrated to afford **(3.47)** as a clear oil. **(3.47)** (0.04g, 0.065 mmol) was re-dissolved in THF (0.5ml) was added 1M TBAF (0.065ml, 0.065 mmol) at room temperature. After 1 hour, the reaction was quenched by the addition of water (2ml) and the product was extracted with diethyl ether (3 x 5ml). The ether extracts were collected, dried over sodium sulphate and reduced in volume before being purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 1:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(3.48)** as a white solid (0.012g, 48%). M.pt. 60-62°C. ν_{max} (CCl_4)/ cm^{-1} 3400.2, 2926.2, 1638.4, 1591.0. HRMS: found 411.1433 (M^++Na), requires ($C_{21}H_{24}O_7$) 388.1522. GCMS m/z (%) 370 (M^+-18, 100), 323 (20). ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 2.11 (1H, m, HCH), 2.33 (1H, m, HCH), 2.50 (1H, m, HCH), 3.02 (1H, m, HCH), 3.71 (3H, s, OMe), 3.91 (3H, s, OMe), 3.93 (3H, s, OMe), 3.93 (3H, s, OMe), 4.16 (1H, m, CHOH), 6.29 (1H, d, J 5.0Hz, C=CH), 6.38 (1H, s, {A-ring}ArH), 6.47 (2H, s, 2 x {C-ring}ArH). ^{13}C NMR δ_c ppm 21.26 (CH_2), 42.79 (CH_2), 55.67 (OMe), 60.40 (OMe), 60.63 (OMe), 61.08 (OMe), 69.37 (CHOH), 107.36 (2 x {C-ring}ArCH), 108.55 ({A-ring}ArCH), 127.47 (qC), 132.01 (C=CH), 133.80 (qC), 134.25 (qC), 137.30 (qC), 138.12 (qC), 148.26 (2 x qC), 150.28 (qC), 150.77 (qC).

Attempted formation of 9-[3-(amino-4-methoxyphenyl]-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-ol (3.50)

1st Step

Synthesis of intermediate, 9-[3-(2,5-dimethyl-1H-1-pyrrolyl)-4-methoxyphenyl]-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-ol (3.49)

To a stirred solution of pyrrole **(2.63)** (0.63g, 2.25 mmol) in anhydrous THF (4ml) was added drop-wise 2.5M *n*-BuLi (0.90ml, 2.25 mmol) at -78°C under anhydrous conditions during a 10 minute period. To this solution, whilst maintaining the temperature at -78°C, the keto-alcohol **(3.39)** (0.20g, 0.75 mmol) in anhydrous THF (4ml) was added. After 2 hours, the reaction temperature was raised to 0°C and was kept at this temperature for 12 hours. On completion,

the reaction was quenched by the addition of 2M aq. HCl (10ml) and the product was extracted using diethyl ether (3 x 10ml). It was dried over sodium sulphate, filtered and concentrated *in vacuo* to a clear oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(3.49)** as a white solid (0.20g, 60%). M.pt. 78-81°C. ν_{max} (CCl_4)/ cm^{-1} 3429.1, 2935.4, 1509.9, 1115.4. GCMS m/z (%) 433 (40), 432 (100), 412 (15), 401 (11). ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 1.99 (6H, s, 2 x C$\underline{H}_3$), 2.14 (1H, m, C$\underline{H}$), 2.37 (1H, m, C$\underline{H}$), 2.54 (1H, m, C$\underline{H}$), 3.03 (1H, dd, J 5Hz, 13.0Hz, C$\underline{H}$), 3.68 (3H, s, O$\underline{Me}$), 3.82 (3H, s, O$\underline{Me}$), 3.91 (3H, s, O$\underline{Me}$), 3.93 (3H, s, O$\underline{Me}$), 4.20 (1H, m, C$\underline{H}$OH), 5.80 (2H, s, $\underline{H}$C=C$\underline{H}$), 6.35 (1H, d, J 4.5Hz, Ar$\underline{H}$), 6.36 (1H, s, Ar$\underline{H}$), 7.03 (2H, m, 2 x Ar$\underline{H}$), 7.50 (1H, dd, J 2Hz, 8.5Hz, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 12.02 ($\underline{C}H_3$), 12.25 ($\underline{C}H_3$), 21.28 ($\underline{C}H_2$), 43.04 ($\underline{C}H_2$), 55.35 (O$\underline{Me}$), 55.39 (O$\underline{Me}$), 60.38 (O$\underline{Me}$), 61.02 (O$\underline{Me}$), 69.35 ($\underline{C}$HOH), 104.77 ($\underline{C}$H), 104.97 ($\underline{C}$H), 108.93 (Ar$\underline{C}$H), 111.47 (Ar$\underline{C}$H), 126.72 (q$\underline{C}$) 127.85 (Ar$\underline{C}$H), 128.09 (q$\underline{C}$), 128.76 (q$\underline{C}$), 129.77 (Ar$\underline{C}$H), 131.58 (C=$\underline{C}$H), 133.48 (q$\underline{C}$), 134.41 (q$\underline{C}$), 137.51 (q$\underline{C}$), 150.49 (q$\underline{C}$) 150.83 (q$\underline{C}$), 154.87 (q$\underline{C}$).

2nd Step

Attempted synthesis to afford 9-[3-(amino-4-methoxyphenyl]-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-ol (3.50)

To a stirred solution of **(3.49)** (0.05g, 0.11 mmol) in ethanol (1ml) was added a solution of potassium hydroxide (0.017g, 0.30 mmol) in 50% aq. ethanol (2ml) followed by hydroxylamine hydrochloride (0.039g, 0.55 mmol) at 25°C. The reaction was allowed to proceed for 12 hours and. As TLC analysis of the reaction mixture showed only the presence of starting material, the mixture was refluxed for several hours. However, TLC analysis of the reaction indicated that several decomposition products had formed.

Synthesis of 1,2,3-trimethoxy-5-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-ol (3.51)

To a solution of **(3.44)** (0.044g, 0.12 mmol) in ethanol/ethyl acetate (1:1, 2ml) was added 10% Pd/C (0.050g). The reaction mixture was allowed to stir under a hydrogen atmosphere for 48 hours. On completion, the reaction was filtered and the filtrate was concentrated to an oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 1:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(3.51)** as a white solid (0.04g, 98%). M.pt. 37-39°C. ν_{max} (KBr)/ cm^{-1} 3423.8, 2931.6, 2847.1, 1607.1, 1116.3. HRMS: found 381.1704 (M^++Na), requires ($C_{21}H_{26}O_5$) 358.1780. GCMS m/z (%) 358 (100), 297 (7.5), 225 (12), 181 (14), 121 (10). ^{1}H NMR ($CDCl_3$, 400Mhz) δ_H ppm 1.30 (2H, m, C$\underline{H}_2$), 2.32-2.50 (4H, m, $CH_2C\underline{H}_2$), 3.39 (1H, dd, J 7.0Hz, 15Hz, ArC$\underline{H}$Ar), 3.52 (3H, s, O$\underline{Me}$), 3.84 (3H, s, O$\underline{Me}$), 3.85 (3H, s, O$\underline{Me}$), 3.86 (3H, s, O$\underline{Me}$), 4.03 (1H, m, C$\underline{H}$OH), 5.88 (1H, s, {A-ring}Ar$\underline{H}$), 6.94 (2H, d, J 8.5Hz, 2 x Ar$\underline{H}$), 7.18 (2H, d, J 8.5Hz, 2 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 19.87 ($\underline{C}H_2$), 36.00 ($\underline{C}H_2$), 42.91 (Ar$\underline{C}$HAr), 43.29 ($\underline{C}H_2$), 54.83 (O$\underline{Me}$), 55.27 (O$\underline{Me}$), 60.30 (O$\underline{Me}$), 60.85 (O$\underline{Me}$), 74.06 ($\underline{C}$HOH), 107.37 (Ar$\underline{H}$), 113.46 (2 x Ar$\underline{H}$), 126.67 (q$\underline{C}$), 129.18 (2 x Ar$\underline{H}$), 136.29 (q$\underline{C}$), 139.99 (q$\underline{C}$), 140.99 (q$\underline{C}$), 150.25 (q$\underline{C}$), 150.39 (q$\underline{C}$), 157.72 (q$\underline{C}$).

Synthesis of 5-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*benzo[a]cyclohepten-7-ol (3.52)

To a solution of **(3.46)** (0.10g, 0.27 mmol) in ethanol/ethyl acetate (1:1, 4ml) was added 10% Pd/C (0.1g). The reaction mixture was stirred under a hydrogen atmosphere for 48 hours. On completion, the reaction was filtered and the filtrate was concentrated to an oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 1:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(3.52)** as a clear oil (0.098g, 97%). ν_{max} (CCl_4)/ cm^{-1} 3423.8, 2931.6, 2847.1, 1591.4. HRMS: found 397.1727 (M^++Na), requires ($C_{21}H_{26}O_6$) 374.1729. GCMS m/z (%) 374 (100), 342 (12.5), 314 (10), 223 (55). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.84 (2H, m, C$\underline{H}_2$), 2.31-2.48 (4H, m, $CH_2C\underline{H}_2$), 3.37 (1H, dd, J 7.0Hz, 15Hz, ArC$\underline{H}$Ar), 3.55 (3H, s, O$\underline{Me}$), 3.83 (3H, s,

OMe), 3.85 (3H, s, OMe), 3.93 (3H, s, OMe), 4.13 (1H, m, CHOH), 5.71 (1H, br, OH), 5.95 (1H, s, {A-ring}ArH), 6.74 (1H, dd, J 2Hz, 8.5Hz, H-6'), 6.85 (2H, m, 2 x ArH). ^{13}C NMR δ_c ppm 19.86 (CH_2), 39.84 (CH_2), 43.15 (ArCHAr), 43.21 (CH_2), 55.39 (OMe), 55.55 (OMe), 60.32 (OMe), 60.87 (OMe), 73.98 (CHOH), 107.44 (ArCH), 110.19 (ArCH), 114.61 (ArCH), 119.64 (ArCH), 126.67 (qC), 137.49 (qC), 140.01 (qC), 140.78 (qC), 144.69 (qC), 145.19 (qC), 150.26 (qC), 150.33 (qC).

Synthesis of 2,3,4-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.53)

To a stirred solution of **(3.44)** (0.05g, 0.14 mmol) in DMF (1ml) was added PDC (0.10g, 0.27 mmol) portion-wise at 0°C. After 12 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted using diethyl ether (5 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before being concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated to afford **(3.53)** as a white solid (0.03g, 60%). M.pt 26-27°C. ν_{max} (CCl_4)/ cm^{-1} 2935.4, 1657.7, 1603.8, 1509.8, 1116.4. HRMS: found 355.1571 (MH^+), requires ($C_{21}H_{22}O_5$) 354.1467. GCMS m/z (%) 354 (100), 312 (15), 121 (22). ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 2.67 (2H, m, CH_2), 3.15 (2H, m, CH_2), 3.59 (3H, s, OMe), 3.85 (3H, s, OMe), 3.89 (6H, s, 2 x OMe), 6.33 (1H, d, J 2.5Hz, C=CH), 6.40 (1H, d, J 2.5Hz, ArH), 6.97 (2H, dd, J 9.0Hz, 2.5Hz, 2 x ArH), 7.26 (2H, dd, J 9.0Hz, 2.5Hz, 2 x ArH). ^{13}C NMR δ_c ppm 19.37 (CH_2), 44.65 (CH_2), 53.99 (OMe), 54.59 (OMe), 59.44 (OMe), 60.08 (OMe), 111.53 (ArCH), 113.04 (2 x ArCH), 126.93 (C=CH), 128.68 (qC), 129.63 (2 x ArCH), 131.97 (qC), 134.25 (qC), 143.01 (qC), 149.48 (qC), 150.77 (qC), 152.27 (qC), 160.29 (qC), 204.42 (C=O).

Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-one (3.32)

To a stirred solution of **(3.45)** (0.04g, 0.082 mmol) in DMF (1ml) was added PDC (0.10g, 0.28 mmol) at 0°C. After 24 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (5 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered, before being concentrated *in vacuo*. The resulting ketone **(3.54)** (0.02g, 0.041 mmol) was subsequently re-dissolved in THF (1ml) and 1M TBAF (0.08ml, 0.082 mmol) was added drop wise with vigorous stirring at 0°C. After 2hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The organic fractions were collected, dried over sodium sulphate, filtered and the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated to afford **(3.32)** as a white solid (0.015g, 99%). Data already described.

Formation of 9-(3,5-dihydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.56)

1st Step

Synthesis of intermediate, 9-(3,5-di[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-one (3.55)

To a stirred solution of **(3.47)** (0.10g, 0.16 mmol) in DMF (1ml) was added PDC (0.061g, 0.16 mmol) at 0°C. After 24 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (5 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before being concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated to afford **(3.55)** as a clear oil (0.05g, 50%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.17

(12H, s, 2 x $C\underline{H}_3SiC\underline{H}_3$), 1.00 (18H, s, $C(C\underline{H}_3)_3$), 2.72 (2H, m, $C\underline{H}_2$), 3.14 (2H, m, $C\underline{H}_2$), 3.64 (3H, s, O<u>Me</u>), 3.79 (3H, s, O<u>Me</u>), 3.92 (3H, s, O<u>Me</u>), 3.94 (3H, s, O<u>Me</u>), 6.31 (1H, s, C=C<u>H</u>), 6.35 (1H, s, Ar<u>H</u>), 6.46 (2H, m, 2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm -5.05 (2 x $\underline{C}H_3Si\underline{C}H_3$), 17.85 ($\underline{C}(CH_3)_3$), 19.80 ($\underline{C}H_2$), 25.22 ($C(\underline{C}H_3)_3$), 45.17 ($\underline{C}H_2$), 55.42 (O<u>Me</u>), 55.57 (O<u>Me</u>), 60.43 (O<u>Me</u>), 60.94 (O<u>Me</u>), 111.34 (Ar<u>C</u>H), 115.06 (2 x Ar<u>C</u>H), 125.67 (C=<u>C</u>H), 128.50 (q<u>C</u>), 132.04 (q<u>C</u>), 137.48 (Ar<u>C</u>H), 143.18 (q<u>C</u>), 149.08 (2 x q<u>C</u>), 149.30 (q<u>C</u>), 150.63 (q<u>C</u>), 203.68 (<u>C</u>=O).

2nd Step-deprotection

Synthesis of 9-(3,5-dihydroxy-4-methoxyphenyl)-2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (3.56)

To a stirred solution of **(3.55)** (0.05g, 0.08 mmol) in THF (0.5ml) was added 1M TBAF (0.1ml, 0.10 mmol) drop-wise at 25°C. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated to afford **(3.56)** as an oil (0.03g, 95%). HRMS: found 387.1481 (MH^+), requires ($C_{21}H_{22}O_7$) 386.1366. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.73 (2H, m, $C\underline{H}_2$), 3.13 (2H, m, $C\underline{H}_2$), 3.66 (3H, s, O<u>Me</u>), 3.90 (3H, s, O<u>Me</u>), 3.95 (3H, s, O<u>Me</u>), 3.98 (3H, s, O<u>Me</u>), 5.83 (2H, br, 2 x O<u>H</u>), 6.37 (1H, s, C=C<u>H</u>), 6.40 (1H, s, Ar<u>H</u>), 6.53 (2H, s, 2 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 19.74 ($\underline{C}H_2$), 43.16 ($\underline{C}H_2$), 55.71 (O<u>Me</u>), 60.45 (O<u>Me</u>), 60.69 (O<u>Me</u>), 60.94 (O<u>Me</u>), 108.67 (2 x Ar<u>C</u>H), 111.60 (Ar<u>C</u>H), 127.94 (C=<u>C</u>H), 128.54 (q<u>C</u>), 131.62 (q<u>C</u>) 134.77 (q<u>C</u>), 138.67 (q<u>C</u>), 142.99 (q<u>C</u>), 148.23 (2 x q<u>C</u>), 149.51 (q<u>C</u>), 150.74 (q<u>C</u>), 151.29 (q<u>C</u>), 203.98 (C=O).

Synthesis of 5-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-7-one (3.59)

To a solution of **(3.47)** (0.10g 0.20 mmol) in ethanol/ethyl acetate (1:1, 4ml) was added 10% Pd/C (0.1g). The reaction mixture was stirred under a hydrogen atmosphere for 48 hours. On

completion, the reaction was filtered and the filtrate was concentrated to afford **(3.57)** as an oil. This was re-dissolved in DMF (1ml) and PDC (0.077g, 0.20 mmol) was added at 0°C. After 24 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (5 x 5ml). The organic fractions were collected, dried under sodium sulphate and filtered before the filtrate was concentrated *in vacuo* to afford **(3.58)** as an oil. This was re-dissolved in THF (0.5ml) and 1M TBAF (0.1ml, 0.10 mmol) was added drop-wise at 0°C. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The organic fractions were collected, dried under sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(3.59)** as a white solid (0.036g, 49%). M.pt. 124-126°C. ν_{max} (KBr)/ cm^{-1} 3402.1, 2936.7, 1701.6, 1593.2, 1511.8, 1123.3. GCMS m/z (%) 371 (M^++1, 85), 370 (100), 328 (16). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.57 (2H, m, C$\underline{H}_2$), 2.95 (4H, m, 2 x C$\underline{H}_2$), 3.74 (3H, s, O$\underline{Me}$), 3.86 (3H, s, O$\underline{Me}$), 3.90 (6H, s, 2 x O$\underline{Me}$), 4.33 (1H, dd, J 3.4, 8.0Hz, C$\underline{H}$OH), 5.62 (1H, br, O$\underline{H}$), 6.36 (1H, s, Ar$\underline{H}$), 6.69 (2H, m, 2 x Ar$\underline{H}$), 6.81 (1H, d, J 8.0Hz, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 19.32 (C$\underline{H}_2$), 43.75 (C$\underline{H}_2$), 45.46 (ArC$\underline{H}$Ar), 48.67 (C$\underline{H}_2$), 55.49 (2 x O$\underline{Me}$), 60.34 (O$\underline{Me}$), 60.89 (O$\underline{Me}$), 109.12 (ArC$\underline{H}$), 110.13 (ArC$\underline{H}$), 113.63 (ArC$\underline{H}$), 118.60 (ArC$\underline{H}$), 125.64 (q$\underline{C}$) 135.53 (q$\underline{C}$), 137.77 (q$\underline{C}$), 144.82 (q$\underline{C}$), 145.21 (q$\underline{C}$), 150.98 (q$\underline{C}$), 151.57 (q$\underline{C}$), 210.28 (C$\underline{=}$O).

Formation of 6,7,8,9-tetrahydro-2,3,4-trimethoxybenzocyclohepten-5-one (2.02)

1st Step

Synthesis of intermediate, methyl-5-(3,4,5-trimethoxyphenyl)-2,4-pentadienoic acid (4.02)

To a stirred solution of 3,4,5-trimethoxybenzaldehyde (20g, 0.102 mol) in *tert*-butanol (36ml) was added methyl crotonate (20.4g, 0.204 mol) and a solution of potassium *tert*-butoxide (24.12g, 0.21 mol) in *tert*-butanol (320ml). The reaction was carried out under a nitrogen atmosphere, with the reaction vessel covered with aluminium foil. After the addition was complete, the resulting mixture was allowed to stir for 12 hours at room temperature. The

mixture was then acidified with 2M aq. HCl (1000ml) and extracted with DCM (3 x 150ml). The combined organic extracts were dried under sodium sulphate, filtered and concentrated under reduced pressure to afford **(4.01)** as a yellow oil. This oil **(4.01)** (20g, 71.4 mmol) was then dissolved in absolute ethanol (70ml), treated with 10% aq. NaOH (200ml) and refluxed for 5 hours. The reaction was then allowed to cool to room temperature and was acidified using 2M aq. HCl (500ml) and extracted with DCM (3 x 150ml). The combined organic extracts were dried over sodium sulphate, filtered and concentrated under reduced pressure to afford the acid **(4.02)** as an orange oil (21.81g, 81%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 3.80 (9H, s, 3 x OMe), 5.72 (1H, s, ArH), 6.66 (4H, m, 4 x CH), 6.95 (2H, s, ArH), 11.06 (1H, br, COOH). ^{13}C NMR δ_c ppm 23.81 (CH_2), 29.98 (CH_2), 32.45 (CH_2), 35.22 (CH_2), 55.35 (2 x OMe), 60.05 (OMe), 104.84 (2 x ArCH), 135.78 (qC), 137.00 (qC), 152.84 (2 x qC), 171.10 (C=O).

2nd Step

Synthesis of intermediate, 5-(3,4,5-trimethoxyphenyl)pentanoic acid (4.03)

This acid **(4.02)** (20g, 75.67 mmol) was re-dissolved in an ethanol/ethyl acetate solution (1:1; 200ml) and treated with 10% Pd/C (10g). The resulting mixture was stirred under an atmosphere of hydrogen at 25°C for 1 week. On completion, the catalyst was removed by filtration through Celite™. The solids retained were washed with absolute ethanol (~100ml). Concentration of the filtrates under reduced pressure gave a viscous brown oil which crystallised out to afford **(4.03)** (20.1g, 99%). ^{1}H NMR ($CDCl_3$, 400Mhz) δ_H ppm 1.68 (4H, m, 2 x CH_2), 2.31 (2H, m, CH_2), 2.57 (2H, m, CH_2), 3.87 (9H, s, 3 x OMe), 6.36 (2H, s, 2 x ArH), 10.05 (1H, br, COOH). ^{13}C NMR δ_c ppm 23.81 (CH_2), 29.98 (CH_2), 32.45 (CH_2), 35.22 (CH_2), 55.35 (2 x OMe), 60.05 (OMe), 106.89 (2 x ArCH), 131.27 (qC), 138.92 (qC), 152.84 (2 x qC), 168.75 (C=O).

3rd step

Synthesis of intermediate, 2,3,4,5,6-pentafluorophenyl-5-(3,4,5-trimethoxyphenyl) pentanoate (4.04)

To a stirred solution of **(4.03)** (20g, 74.5 mmol) in DCM (100ml) was added PFP (13.73g, 74.6 mmol) followed by DCC (15.37g, 74.6 mmol) at 0°C. After 3 hours, the reaction mixture was filtered through Celite™ and the filtrate was collected and concentrated to an oil under reduced pressure. The pale yellow oil was then purified by flash column chromatography (stationary phase, silica gel 230-400 mesh; mobile phase, hexane/ethyl acetate 4:1 ratio). The homogenous fractions were collected and reduced in volume to afford a pale yellow solid **(4.04)** (25.54g, 79% yield). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.68 (4H, m, 2 x C$\underline{H}_2$), 2.59 (2H, m, C$\underline{H}_2$), 2.67 (2H, m, C$\underline{H}_2$), 3.78 (3H, s, O$\underline{Me}$), 3.84 (6H, s, 2 x O$\underline{Me}$), 6.38 (2H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 23.81 ($\underline{C}H_2$), 29.98 ($\underline{C}H_2$), 32.45 ($\underline{C}H_2$), 35.22 ($\underline{C}H_2$), 55.35 (2 x O$\underline{Me}$), 60.05 (O$\underline{Me}$), 104.84 (2 x Ar$\underline{C}$H), 135.78 (q$\underline{C}$), 137.00 (q$\underline{C}$), 152.64 (2 x q$\underline{C}$), 168.75 ($\underline{C}$=O).

4th step-cyclisation of (4.04) to afford (2.02)

Synthesis of 6,7,8,9-tetrahydro-2,3,4-trimethoxybenzocyclohepten-5-one (2.02)

Synthesised from **(4.04)** (19.94g, 45.9 mmol) using the method described for the preparation of **(2.01)**. Purified by flash column chromatography (stationary phase, silica gel 230-400 mesh; mobile phase, hexane/ethyl acetate 4:1 ratio). Recrystallised from hot methanol to produce white crystals of **(2.02)** (10.8g, 94%). M.pt. 99°C. ν_{max} (KBr)/ cm^{-1} 2938.1, 1672.2, 1592.1. GCMS m/z (%) 250 (100), 221 (80), 181 (68). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H 1.83 (4H, m, 2 x CH_2), 2.64 (2H, m, CH_2), 2.74 (2H, m, CH_2), 3.85 (3H, s, OMe), 3.89 (6H, s, 2 x OMe), 6.45 (1H, s, ArH). ^{13}C NMR δ_c ppm 22.39 (CH_2), 25.51 (CH_2), 32.75 (CH_2), 42.10 (CH_2), 55.53 (OMe), 60.40 (OMe), 61.83 (OMe), 107.51 (2 x ArCH), 127.36 (q$\underline{C}$), 134.27 (q$\underline{C}$), 140.53 (q$\underline{C}$), 151.11 (q$\underline{C}$), 154.91 (q$\underline{C}$), 205.60 (C=O).

Synthesis of 1,2,3-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5H-benzo[a]cycloheptene (4.06)

Synthesised from *para*-bromanisole (1.5g, 8.02 mmol) and **(2.02)** (1.0g, 4.01 mmol) using the method described for the preparation of **(2.44)**. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). Afforded **(4.06)** as an orange oil (0.60g, 44%). ν_{max} (CCl_4)/ cm^{-1} 2934.9, 2853.2, 1509.5, 1117.9. HRMS: found 341.1792 (MH^+), requires ($C_{21}H_{24}O_4$) 340.1675. GCMS m/z (%) 340 (100), 313 (12). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.0 (2H, m, $CH_2C\underline{H_2}CH_2$), 2.08 (2H, m, $CHC\underline{H_2}$), 2.58 (2H, m, $ArC\underline{H_2}$), 3.42 (3H, s, O<u>Me</u>), 3.81 (3H, s, O<u>Me</u>), 3.84 (3H, s, O<u>Me</u>), 3.93 (3H, s, O<u>Me</u>), 6.35 (1H, t, J 7.2Hz, C=C<u>H</u>), 6.65 (1H, s, Ar<u>H</u>), 6.85 (2H, d, J 8.0Hz, Ar<u>H</u>), 7.19 (2H, d, J 8.0Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.55 (<u>C</u>H_2), 31.89 (<u>C</u>H_2), 34.07 (<u>C</u>H_2), 54.75 (O<u>Me</u>), 55.48 (O<u>Me</u>), 59.62 (O<u>Me</u>), 60.32 (O<u>Me</u>), 106.88 (Ar<u>C</u>H), 112.97 (2 x Ar<u>C</u>H), 113.28 (q<u>C</u>), 125.25 (q<u>C</u>), 126.51 (2 x Ar<u>C</u>H), 127.16 (C=<u>C</u>H), 135.24 (q<u>C</u>), 137.27 (q<u>C</u>), 139.48 (q<u>C</u>), 140.31 (q<u>C</u>), 150.99 (q<u>C</u>), 152.13 (q<u>C</u>).

Synthesis of 1,2,3-trimethoxy-9-(3-methoxyphenyl)-6,7-dihydro-5H-benzo[a]cycloheptene (4.07)

Synthesised from *meta*-bromoanisole (1.5g, 8.02 mmol) and **(2.02)** (0.99g, 3.95 mmol) using the method described for the preparation of **(2.44)**. Purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 4:1 hexane/ethyl acetate). Afforded **(4.07)** as an off-white solid (0.39g, 29%). M.pt. 83-84°C. ν_{max} (CCl_4)/ cm^{-1} 2936.9, 1596.2, 1582.8, 1487.8, 1117.7. HRMS: found 341.1812 (MH^+), requires ($C_{21}H_{24}O_4$) 340.1675. GCMS m/z (%), 340 (100), 313 (11). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 2.00 (2H, m, $CH_2C\underline{H_2}CH_2$), 2.10 (2H, m, $CHC\underline{H_2}$), 2.58 (2H, m, $ArC\underline{H_2}$), 3.41 (3H, s, O<u>Me</u>), 3.79 (3H, s, O<u>Me</u>), 3.83 (3H, s, O<u>Me</u>), 3.93 (3H, s, O<u>Me</u>), 6.43 (1H, t, J 7.3Hz, C=C<u>H</u>), 6.64 (1H, s, {A-ring} Ar<u>H</u>), 6.82 (3H, t, {C-ring} Ar<u>H</u>), 7.20 (1H, t, J 7.7Hz, {C-ring} Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.59 (<u>C</u>H_2), 31.84 (<u>C</u>H_2), 33.93 (<u>C</u>H_2), 54.72 (O<u>Me</u>), 55.48 (O<u>Me</u>), 59.65 (O<u>Me</u>), 60.29 (O<u>Me</u>), 106.90 (Ar<u>C</u>H), 111.34 (Ar<u>C</u>H), 111.62 (Ar<u>C</u>H), 118.46 (Ar<u>C</u>H), 125.12 (q<u>C</u>), 128.40 (Ar<u>C</u>H), 128.89 (C=<u>C</u>H), 137.27 (q<u>C</u>), 139.96 (q<u>C</u>), 144.18 (q<u>C</u>), 150.86 (q<u>C</u>), 152.21 (q<u>C</u>), 159.02 (2 x q<u>C</u>).

Formation of 2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenol (4.09)

1st Step

Synthesis of intermediate, tert-butyl[2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenoxy]dimethylsilane (4.08)

Synthesised using **(2.50)** (0.77g, 2.42 mmol) and **(2.02)** (0.3g, 1.20 mmol) employing the method described for the preparation of **(2.51)**. Purified by flash column chromatography (solid phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 5:1). Afforded **(4.08)** as a clear oil (0.17g, 30%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.16 (6H, s, $C\underline{H}_3SiC\underline{H}_3$), 1.00 (9H, s, $C(C\underline{H}_3)_3$), 2.00 (2H, m, $C\underline{H}_2$), 2.08 (2H, m, $C\underline{H}_2$), 2.55 (2H, m, $ArC\underline{H}_2$), 3.39 (3H, s, O<u>Me</u>), 3.80 (3H, s, O<u>Me</u>), 3.81 (3H, s, O<u>Me</u>), 3.93 (3H, s, O<u>Me</u>), 6.29 (1H, t, J 7.5Hz, C=C<u>H</u>), 6.61 (1H, s, {A-ring}Ar<u>H</u>), 6.68 (1H, dd, J 2.5Hz, 8.5Hz, {C-ring}Ar<u>H</u>), 6.75 (1H, d, J 8.5Hz, {C-ring}Ar<u>H</u>), 6.86 (1H, d, J 2Hz, {C-ring}Ar<u>H</u>). ^{13}C NMR δ_c ppm -5.04 ($\underline{C}H_3Si\underline{C}H_3$), 24.50 ($\underline{C}H_2$), 25.31 ($C(\underline{C}H_3)_3$), 31.84 ($\underline{C}H_2$), 34.04 ($\underline{C}H_2$), 55.12 (O<u>Me</u>), 55.46 (O<u>Me</u>), 59.97 (O<u>Me</u>), 60.25 (O<u>Me</u>), 106.73 (Ar<u>C</u>H), 111.12 (Ar<u>C</u>H), 118.48 (Ar<u>C</u>H), 119.45 (Ar<u>C</u>H), 125.25 (q<u>C</u>), 127.22 (C=<u>C</u>H), 136.71 (q<u>C</u>), 137.59 (q<u>C</u>), 140.62 (q<u>C</u>), 145.15 (q<u>C</u>), 145.44 (q<u>C</u>), 150.53 (q<u>C</u>), 152.02 (q<u>C</u>).

Alternative synthesis of tert-butyl[2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenoxy]dimethylsilane (4.08)

To a stirred solution of bromide **(2.50)** (0.10g, 0.31 mmol) in anhydrous THF (1ml) was added 2.5M *n*-BuLi (0.12ml, 0.31 mmol) drop-wise at -78°C under anhydrous conditions. After 1 hour, whilst maintaining the reaction temperature at -78°C, a solution of **(2.02)** (0.026g, 0.10 mmol) dissolved in anhydrous THF (1ml) was added. After 12 hours, the reaction the reaction was quenched by the addition of 2M aq. HCl (5ml) and the crude product **(4.08)** was extracted into diethyl ether, dried over sodium sulphate and filtered before the filtrate was reduced in volume *in vacuo*. The resulting oil was purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 5:1). All homogenous

fractions were collected and the solvent was removed *in vacuo* to afford **(4.08)** as a clear oil (0.02g, 42%).

2nd Step-deprotection

Synthesis of 2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenol (4.09)

Synthesised from **(4.08)** (0.1g, 0.21 mmol) using the method described for the preparation of **(2.52)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 3:1). Afforded **(4.09)** as a pale yellow oil (0.074g, 99%). ν_{max} (CCl_4)/ cm^{-1} 3413.3, 2921.1, 2847.8, 1591.4, 1507.6, 1115.0. HRMS: found 357.1759 (MH^+), requires ($C_{21}H_{24}O_5$) 356.1624. GCMS m/z (%) 356 (100), 215 (1). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.58 (2H, m, $CH_2C\underline{H_2}CH_2$), 2.08 (2H, m, $CHC\underline{H_2}CH_2$), 2.55 (2H, m, $ArC\underline{H_2}$), 3.44 (3H, s, O<u>Me</u>), 3.82 (3H, s, O<u>Me</u>), 3.89 (3H, s, O<u>Me</u>), 3.92 (3H, s, O<u>Me</u>), 5.52 (1H, s, O<u>H</u>), 6.33 (1H, t, J 7.3Hz, C=C<u>H</u>), 6.61 (1H, s, Ar<u>H</u>), 6.70 (1H, dd, J 2.0Hz, 8.0Hz, Ar<u>H</u>), 6.72 (1H, d, J 8.0Hz, Ar<u>H</u>), 6.87 (1H, d, J 2.0Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.50 ($\underline{C}H_2$), 31.81 ($\underline{C}H_2$), 33.95 ($\underline{C}H_2$), 55.81 (2 x O<u>Me</u>), 59.67 (O<u>Me</u>), 60.35 (O<u>Me</u>), 106.81 (Ar<u>C</u>H), 109.78 (ArC<u>H</u>), 112.03 (Ar<u>C</u>H), 117.34 (Ar<u>C</u>H), 125.17 (q<u>C</u>), 127.55 (C=<u>C</u>H), 136.31 (q<u>C</u>), 137.19 (q<u>C</u>), 139.41 (q<u>C</u>), 140.02 (q<u>C</u>), 144.75 (q<u>C</u>), 145.04 (q<u>C</u>), 150.01 (q<u>C</u>), 152.11 (q<u>C</u>).

<u>Formation of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[a]cyclohepten-9-yl)aniline (4.11)</u>

1st Step

Synthesis of intermediate, 1-[2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenyl]-2,5-dimethyl-1H-pyrrole (4.10)

Synthesised using **(2.61)** (2.25g, 0.80 mmol) and **(2.02)** (0.099g, 0.39 mmol) employing the method described for the preparation of **(2.64)**. Purification was attempted by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All fractions were collected and the solvent was removed *in vacuo* to afford crude **(4.10)** as an off-white solid (0.086g). This intermediate was used directly in the next step.

2nd Step

Synthesis of 2-methoxy-5-(2,3,4-trimethoxy-6,7-dihydro-5*H*-benzo[a]cyclohepten-9-yl)aniline (4.11)

Synthesised from **(4.10)** (0.049g, 0.11 mmol) using the method described for the preparation of **(2.65)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 3:1). Afforded **(4.11)** as a white solid (0.017g, 37%). M.pt. 38-40°C. ν_{max} (CCl_4)/ cm^{-1} 3460.0, 3370.1, 2934.0, 2853.1, 1510.2. HRMS: found 355.1789 (M^+), requires ($C_{21}H_{25}O_4N$) 355.1784. GCMS m/z (%) 356 (100), 325 (42), 293 (20). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.90 (2H, m, C$\underline{H}_2$), 2.05 (2H, m, C$\underline{H}_2$), 2.56 (2H, m, C$\underline{H}_2$), 3.43 (3H, s, O$\underline{Me}$), 3.82 (3H, s, O$\underline{Me}$), 3.85 (3H, s, O$\underline{Me}$), 3.93 (3H, s, O$\underline{Me}$), 6.30 (1H, t, J 3.7Hz, C=C$\underline{H}$), 6.61 (1H, s, {A-ring}Ar$\underline{H}$), 6.62 (2H, m, 2 x {C-ring}Ar$\underline{H}$), 6.72 (1H, d, J 8.0Hz, {C-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm 24.47 ($\underline{C}H_2$), 31.83 ($\underline{C}H_2$), 34.01 ($\underline{C}H_2$), 55.09 (O$\underline{Me}$), 55.46 (O$\underline{Me}$), 59.67 (O$\underline{Me}$), 60.28 (O$\underline{Me}$), 106.67 (Ar$\underline{C}$H), 109.62 (Ar$\underline{C}$H), 112.73 (Ar$\underline{C}$H), 115.97 (Ar$\underline{C}$H), 125.48 (q$\underline{C}$), 127.55 (Ar$\underline{C}$H), 127.43 (C=$\underline{C}$H), 135.11 (a$\underline{C}$), 135.82 (q$\underline{C}$), 137.18 (2 x q$\underline{C}$), 139.71 (q$\underline{C}$), 140.25 (Q$\underline{C}$), 146.13 (q$\underline{C}$), 152.00 (q$\underline{C}$).

Formation of 2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-1,3-benzenediol (4.13)

1st Step

Synthesis of intermediate, tert-butyl[3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-9-yl)phenoxy]dimethylsilane (4.12)

Synthesised using **(2.55)** (0.35g, 0.80 mmol) and **(2.02)** (0.1g, 0.40 mmol) employing the method described for the preparation of **(2.56)**. Purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 3:1). Afforded **(4.12)** as an oil (0.1g, 42%). ν_{max} (CCl_4)/ cm^{-1} 2932.0, 2850.1, 1596.4, 1083.5, 832.2. GCMS m/z (%) 601 (20), 544 (100) 471 (20). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.14 (6H, s C$\underline{H}_3$SiC$\underline{H}_3$), 0.15 (6H, s C$\underline{H}_3$SiC$\underline{H}_3$), 0.98 (18H, s, 2 x C(C$\underline{H}_3$)$_3$), 1.94 (2H, m, C$\underline{H}_2$), 2.06 (2H, m, C$\underline{H}_2$) 2.53 (2H,

m, ArC$\underline{H}_2$), 3.47 (3H, s, O$\underline{Me}$), 3.82 (3H, s, O$\underline{Me}$), 3.88 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 6.34 (1H, t, J 7.2Hz, C=C$\underline{H}$), 6.40 (2H, s, 2 x {C-ring}Ar$\underline{H}$), 6.60 (1H, s, {A-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm -5.11 ($\underline{C}H_3Si\underline{C}H_3$), -5.06 ($\underline{C}H_3Si\underline{C}H_3$), 17.83 (2 x $\underline{C}(CH_3)_3$), 26.2 (2 x C($\underline{C}H_3)_3$), 24.9 ($\underline{C}H_2$), 32.17 ($\underline{C}H_2$), 34.21 ($\underline{C}H_2$), 55.88 (O$\underline{Me}$), 60.10 (O$\underline{Me}$), 60.68 (O$\underline{Me}$), 61.11 (O$\underline{Me}$), 105.57 (2 x Ar$\underline{C}$H), 106.86 (Ar$\underline{C}$H), 128.69 (C=$\underline{C}$H), 133.10 (q$\underline{C}$), 136.33 (q$\underline{C}$), 139.66 (q$\underline{C}$), 139.65 (q$\underline{C}$) 140.10 (q$\underline{C}$), 147.94 (q$\underline{C}$), 147.97 (2 x q$\underline{C}$), 150.2 (q$\underline{C}$), 152.18 (q$\underline{C}$).

2nd Step-deprotection

Synthesis of 2-methoxy-5-(1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-1,3-benzenediol (4.13)

Synthesised from **(4.12)** (0.21g, 0.35 mmol) using the method described for the preparation of **(2.57)**. Purified by flash column chromatography (solid phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 1:1). Afforded **(4.13)** as a white solid (0.11g, 85%). M.pt 74-75°C. ν_{max} (CCl_4)/ cm^{-1} 3413.3, 2931.6, 1591.4, 1115.0. GCMS m/z (%) 372 (19), 341 (100), 309 (43). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.94 (2H, m, C$\underline{H}_2$), 2.06 (2H, m, C$\underline{H}_2$) 2.53 (2H, m, ArC$\underline{H}_2$), 3.47 (3H, s, O$\underline{Me}$), 3.82 (3H, s, O$\underline{Me}$), 3.88 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 5.35 (2H, s, 2 x O$\underline{H}$), 6.34 (1H, t, J 7.2Hz, C=C$\underline{H}$), 6.40 (2H, s, 2 x {C-ring}Ar$\underline{H}$), 6.60 (1H, s, {A-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm 24.9 ($\underline{C}H_2$), 32.13 ($\underline{C}H_2$), 34.23 ($\underline{C}H_2$), 55.90 (O$\underline{Me}$), 60.11 (O$\underline{Me}$), 60.74 (O$\underline{Me}$), 61.11 (O$\underline{Me}$), 105.55 (2 x Ar$\underline{C}$H), 106.85 (Ar$\underline{C}$H), 128.47 (C=$\underline{C}$H), 133.04 (q$\underline{C}$), 137.17 (q$\underline{C}$), 139.26 (q$\underline{C}$), 139.48 (q$\underline{C}$), 140.21 (q$\underline{C}$), 147.94 (q$\underline{C}$), 147.97 (2 x q$\underline{C}$), 150.88 (q$\underline{C}$), 152.20 (q$\underline{C}$).

Synthesis of 1,2,3-trimethoxy-9-(4-methoxyphenyl)-6,7,8,9-tetrahydro-5H-benzo[a]cycloheptene (4.14)

Synthesised from **(4.06)** (0.1g, 0.29 mmol) using the method described for the preparation of **(2.46)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 4:1). Afforded **(4.14)** as a viscous oil (0.097g, 96%). ν_{max} (CCl_4)/ cm^{-1} 2928.8, 2853.5, 1509.4, 1244.8, 1122.6. HRMS: found 365.1708 (M^++Na), requires ($C_{21}H_{26}O_4$) 342.1831. GCMS m/z (%) 342 (100), 311 (10), 269 (2.5), 235 (31). ^{1}H

NMR ($CDCl_3$, 400MHz) δ_H ppm 1.39 (1H, m, C<u>H</u>), 1.75 (3H, m, C<u>H</u>C<u>H</u>$_2$), 1.89 (3H, m C<u>H</u>C<u>H</u>$_2$), 2.53 (3H, m, C<u>H</u>C<u>H</u>$_2$), 3.61 (3H, s, O<u>Me</u>), 3.84 (6H, s, 2 x O<u>Me</u>), 3.89 (3H, s, O<u>Me</u>), 4.94 (1H, m, ArC<u>H</u>Ar), 6.53 (1H, s, Ar<u>H</u>), 6.82 (2H, d, J 8.5Hz, Ar<u>H</u>), 7.00 (2H, d, J 8.5Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.82 (<u>C</u>H$_2$), 27.52 (<u>C</u>H$_2$), 31.68 (<u>C</u>H$_2$), 36.04 (<u>C</u>H$_2$), 38.38 (<u>C</u>H), 54.70 (O<u>Me</u>), 55.41 (O<u>Me</u>), 60.33 (O<u>Me</u>), 60.80 (O<u>Me</u>), 109.50 (Ar<u>C</u>H), 113.15 (2 x Ar<u>C</u>H), 128.00 (2 x Ar<u>C</u>H), 128.98 (q<u>C</u>), 134.64 (q<u>C</u>), 138.76 (q<u>C</u>), 139.92 (q<u>C</u>), 150.61 (q<u>C</u>), 151.68 (q<u>C</u>), 156.84 (q<u>C</u>).

Synthesis of 1,2,3-trimethoxy-9-(3-methoxyphenyl)-6,7,8,9-tetrahydro-5H-benzo[a]cycloheptene (4.15)

Synthesised from **(4.07)** (0.1g, 0.29 mmol) using the method described for the preparation of **(2.47)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 4:1). Afforded **(4.15)** a white solid (0.92g, 93%). M.pt. 85-86°C. ν_{max} (CCl_4)/ cm^{-1} 2928.2, 1597.2, 1491.0, 1122.5. HRMS: found 365.1901 (M^++Na), requires ($C_{21}H_{26}O_4$) 342.1831. GCMS m/z (%) 342 (100), 312 (10), 235 (11), 121 (11). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.4 (1H, m, CH$_2$C<u>H</u>), 1.75 (3H, m, C<u>H</u>$_2$C<u>H</u>), 1.89 (1H, m, C<u>H</u>), 2.52 (2H, m, C<u>H</u>$_2$), 2.68 (1H, m, CH$_2$C<u>H</u>), 3.68 (3H, s, O<u>Me</u>), 3.76 (3H, s, O<u>Me</u>), 3.89 (3H, s, O<u>Me</u>), 3.90 (3H, s, O<u>Me</u>), 4.96 (1H, m, ArC<u>H</u>Ar), 6.52 (1H, s, {A-ring}Ar<u>H</u>), 6.70 (3H, m, {C-ring}Ar<u>H</u>), 7.18 (1H, t, J 7.5Hz, {C-ring}Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.90 (<u>C</u>H$_2$), 27.42 (<u>C</u>H$_2$), 31.52 (<u>C</u>H$_2$), 36.07 (<u>C</u>H$_2$), 39.16 (<u>C</u>H), 54.62 (O<u>Me</u>), 55.43 (O<u>Me</u>), 60.33 (O<u>Me</u>), 60.80 (O<u>Me</u>), 109.43 (Ar<u>C</u>H), 109.56 (Ar<u>C</u>H), 113.64 (Ar<u>C</u>H), 119.68 (ArCH), 128.56 (q<u>C</u>), 128.60 (Ar<u>C</u>H), 138.82 (q<u>C</u>), 139.30 (q<u>C</u>), 144.57 (q<u>C</u>), 150.67, (q<u>C</u>), 151.64 (q<u>C</u>), 159.25 (q<u>C</u>).

Synthesis of 2-methoxy-5-(2,3,4-trimethoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-yl)phenol (4.16)

Synthesised from **(4.09)** (0.11g, 0.31 mmol) using the method described for the preparation of **(2.47)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 2:1). Afforded **(4.16)** as a clear oil (0.11g, 99%). ν_{max} (CCl_4)/ cm^{-1} 3402.0, 2930.1, 2854.8, 1598.8. GCMS m/z (%) 358 (100), 327 (11), 233 (4.2),

191 (10). HRMS: found 359.1988 (MH^+), requires ($C_{21}H_{26}O_5$) 358.1780. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.42 (1H, m, HC<u>H</u>CH_2), 1.7-1.8 (4H, m, 2 x C<u>H</u>$_2$), 1.93 (1H, m, HC<u>H</u>CH_2), 2.48 (2H, m, C<u>H</u>$_2$), 3.65 (3H, s, O<u>Me</u>), 3.86 (3H, s, O<u>Me</u>), 3.89 (3H, s, O<u>Me</u>), 3.91 (3H, s, O<u>Me</u>), 4.87 (1H, dd, J 3.5Hz, 6.0Hz, ArC<u>H</u>Ar), 5.93 (1H, s, br, O<u>H</u>), 6.30 (1H, s, Ar<u>H</u>), 6.57 (1H, dd, J 1.2Hz, 8.5Hz, Ar<u>H</u>), 6.73 (1H, d, J 1.5Hz, Ar<u>H</u>), 6.76 (1H, d, J 8.0Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.82 (<u>C</u>H_2), 27.42 (<u>C</u>H_2), 31.54 (<u>C</u>H_2), 36.09 (<u>C</u>H_2), 38.60 (<u>C</u>H), 55.25 (O<u>Me</u>), 55.49 (O<u>Me</u>), 60.47 (O<u>Me</u>), 60.48 (O<u>Me</u>), 105.32 (Ar<u>C</u>H), 110.10 (Ar<u>C</u>H), 113.55 (Ar<u>C</u>H), 118.44 (Ar<u>C</u>H), 121.34 (q<u>C</u>), 132.93 (q<u>C</u>), 135.93 (q<u>C</u>), 139.10 (q<u>C</u>) 143.87 (q<u>C</u>), 144.96 (q<u>C</u>), 146.98 (q<u>C</u>), 149.21 (q<u>C</u>).

Synthesis of 2-methoxy-5-(2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-yl)-1,3-benzenediol (4.17)

To a stirred solution of **(4.13)** (0.07g, 1.88 mmol) in ethanol/ethyl acetate (1:1, 2ml) was added slowly 10% Pd/C (0.07g). The reaction proceeded under an atmosphere of hydrogen for 48 hours at room temperature. The mixture was then filtered and the solvent removed under reduced pressure to afford a white solid. This was re-dissolved in DCM (~2ml) and was then purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was removed in vacuo to afford **(4.17)** as a white solid (0.068g, 99%). M.pt. 55-57°C. ν_{max} (KBr)/ cm^{-1} 3371.4, 2931.6, 2847.8, 1591.4. HRMS: found 375.1895 (MH^+), requires ($C_{21}H_{26}O_6$) 372.1573. GCMS m/z (%) 372 (100), 358 (25), 329 (12.5). ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.69-2.4 (6H, m, 3 x C<u>H</u>$_2$), 2.49 (2H, dd, J 2.5Hz, 14.0Hz, C<u>H</u>$_2$CH_2), 3.70 (3H, s, O<u>Me</u>), 3.87 (3H, s, O<u>Me</u>), 3.88 (3H, s, O<u>Me</u>), 3.88 (3H, s, O<u>Me</u>), 4.84 (1H, m, C<u>H</u>CH_2), 5.33 (2H, s, 2 x O<u>H</u>), 6.25 (2H, s, 2 x {C-ring}Ar<u>H</u>), 6.50 (1H, s, {A-ring}Ar<u>H</u>). ^{13}C NMR δ_c ppm 24.9 (<u>C</u>H_2), 27.38 (<u>C</u>H_2), 31.40 (<u>C</u>H_2), 36.51 (<u>C</u>H_2), 38.73 (<u>C</u>H), 55.42 (O<u>Me</u>), 60.34 (O<u>Me</u>), 60.64 (O<u>Me</u>), 60.82 (O<u>Me</u>), 106.88 (2 x Ar<u>C</u>H), 109.60 (Ar<u>C</u>H), 128.39 (q<u>C</u>), 131.71 (q<u>C</u>), 138.82 (q<u>C</u>), 139.86 (q<u>C</u>), 139.92 (q<u>C</u>), 148.11 (2 x q<u>C</u>), 150.69 (q<u>C</u>), 151.59 (q<u>C</u>).

Formation of 7-hydroxy-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (4.18)

1st Step

Synthesis of intermediate, methyl 3-hydroxy-5-(3,4,5-trimethoxyphenyl)pentanoate (4.19)

Synthesised from **(3.16)** (0.49g, 1.66 mmol) using the method described for the preparation of **(3.33)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 2:1). Afforded **(4.19)** as a clear oil (0.45g, 92%). ν_{max} (CCl_4)/ cm^{-1} 3501.7, 2943.3, 2840.0, 1734.6, 1126.8. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.76 (2H, m, C$\underline{H}_2$), 2.50 (2H, m, C$\underline{H}_2$), 2.65 (1H, m, C$\underline{H}$CH$_2$), 2.74 (1H, m, C$\underline{H}$CH$_2$), 3.70 (3H, s, COOC$\underline{H}_3$), 3.81 (3H, s, O$\underline{Me}$), 3.83 (6H, s, 2 x O$\underline{Me}$), 4.03 (1H, m, C$\underline{H}$OH), 6.42 (2H, s, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 25.54 (C$\underline{H}_2$), 37.76 (C$\underline{H}_2$), 40.71 (C$\underline{H}_2$), 51.26 (COOC$\underline{H}_3$), 55.60 (2 x O$\underline{Me}$), 60.32 (O$\underline{Me}$), 66.78 (C$\underline{H}$OH), 104.96 (2 x ArC$\underline{H}$), 135.77 (q$\underline{C}$), 137.02 (q$\underline{C}$), 152.69 (q$\underline{C}$), 172.81 ($\underline{C}$=O).

2nd Step

Synthesis of methyl 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-5-(3,4,5-trimethoxyphenyl)pentanoate (4.20)

Synthesised from **(4.19)** (0.99g, 3.32 mmol) using the method described for the preparation of **(3.40)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 6:1). Afforded **(4.20)** as a clear oil (1.74g, 98%). ν_{max} (CCl_4)/ cm^{-1} 3481.3, 2932.4, 2857.3, 1739.6. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.11 (9H, s, C(C$\underline{H}_3$)$_3$) 1.82 (2H, m, C$\underline{H}_2$), 2.52 (2H, m, C$\underline{H}_2$), 2.82 (2H, m, C$\underline{H}_2$), 3.72 (3H, s, COOC$\underline{H}_3$), 3.81 (3H, s, O$\underline{Me}$), 3.84 (3H, s, O$\underline{Me}$), 3.86 (3H, s, O$\underline{Me}$), 4.19 (1H, m, C$\underline{H}$OH), 6.42 (2H, s, {A-ring}2 x Ar$\underline{H}$), 7.41 (6H, m, 6 x Ar$\underline{H}$), 7.78 (4H, m, 4 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 18.54 (C(CH$_3$)$_3$), 24.60 (C$\underline{H}_2$), 26.12 (C(C$\underline{H}_3$)$_3$), 24.68 (C$\underline{H}_2$), 39.53 (C$\underline{H}_2$), 51.30 (COO$\underline{Me}$) 55.80 (O$\underline{Me}$), 60.60 (O$\underline{Me}$), 60.68 (O$\underline{Me}$), 65.32 (C$\underline{H}$OH), 105.10 (2 x ArC$\underline{H}$), 123.46 (ArC$\underline{H}$), 127.44 (ArC$\underline{H}$), 127.47 (ArC$\underline{H}$), 127.64 (ArC$\underline{H}$), 129.56 (ArC$\underline{H}$), 134.75 (ArC$\underline{H}$), 135.92 (ArC$\underline{H}$), 135.56 (ArC$\underline{H}$), 141.82 (q$\underline{C}$), 151.32 (q$\underline{C}$), 151.48 (q$\underline{C}$), 172.00 ($\underline{C}$=O).

3rd step

Synthesis of intermediate, 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-5-(3,4,5-trimethoxyphenyl)pentanoic acid (4.21)

To a stirred solution of **(4.20)** (2.81g, 5.24 mmol) in methanol (50ml) was added 1M aq. NaOH (20ml) at room temperature. After 12 hours, the reaction was acidified to pH 2 and the product was extracted with diethyl ether (3 x 25ml). The organic fractions were collected and dried over sodium sulphate before being concentrated *in vacuo* to afford crude **(4.21)** as a white solid (2.13g). The product was used directly in the next step without further purification.

4th Step

Synthesis of intermediate, 7-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-5-one (4.22)

Synthesised from **(4.21)** (1.12g, 2.15 mmol) using the method described for the preparation of **(3.43)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 6:1). Afforded **(4.22)** as a pale yellow oil (0.76g, 70%). ν_{max} (CCl_4)/ cm^{-1} 2934.9, 1696.3, 1591.5, 1458.9. ^1H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.08 (9H, s, $C(C\underline{H}_3)_3$), 1.96 (2H, m, $C\underline{H}_2$), 2.55 (2H, m, $C\underline{H}_2$), 2.88 (2H, m, $C\underline{H}_2$), 3.83 (3H, s, O<u>Me</u>), 3.85 (3H, s, O<u>Me</u>), 3.88 (3H, s, O<u>Me</u>), 4.19 (1H, m, C<u>H</u>OH), 6.44 (1H, s, ArH), 7.41 (6H, m, 6 x Ar<u>H</u>), 7.68 (4H, m, 4 x Ar<u>H</u>). ^{13}C NMR δ_c ppm 18.74 ($\underline{C}(CH_3)_3$), 26.45 ($C(\underline{C}H_3)_3$), 29.16 ($\underline{C}H_2$), 35.16 ($\underline{C}H_2$), 51.90 ($\underline{C}H_2$), 55.53 (O<u>Me</u>), 60.38 (O<u>Me</u>), 61.8 (O<u>Me</u>), 68.74 (<u>C</u>HOH), 107.82 (Ar<u>C</u>H), 127.48 (Ar<u>C</u>H), 127.53 (2 x Ar<u>C</u>H), 127.62 (2 x Ar<u>C</u>H), 135.69 (2 x Ar<u>C</u>H), 135.81 (3 x Ar<u>C</u>H), 104.76 (q<u>C</u>), 128.38 (q<u>C</u>), 133.18 (q<u>C</u>), 133.56 (q<u>C</u>), 150.94 (q<u>C</u>), 153.79 (2 x q<u>C</u>), 200.49 (<u>C</u>=O).

5th Step-deprotection

Synthesis of 7-hydroxy-2,3,4-trimethoxy-6,7,8,9-tetrahydro-5*H*-benzo[*a*]cyclohepten-5-one (4.18)

To a stirred solution of **(4.22)** (0.1g, 0.19 mmol) in THF (1.0ml) was added 1M TBAF (0.19ml, 0.19 mmol) drop-wise at -10°C. After 5 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The ether extracts were combined, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The residue was then purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(4.18)** as a pale yellow solid (0.021g, 42%). M.pt 111-112°C. ν_{max} (KBr)/ cm^{-1} 3444.0, 2934.5, 1673.6, 1589.3, 1133.0. GCMS m/z (%) 267 (M^++1, 100), 266 (82), 248 (35), 239 (31), 181 (75). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.92 (1H, m, H-9), 2.18 (1H, m, H-9), 2.65 (1H, m, H-8), 2.89 (1H, m, H-6), 2.97 (1H, m, H-8), 3.02 (1H, m, H-6), 3.86 (3H, s, OMe), 3.89 (6H, s, 2 x OMe), 4.20 (1H, m, H-7), 6.47 (1H, s, H-1). ^{13}C NMR δ_c ppm 29.79 (C-9), 35.17 (C-8), 52.30 (C-6), 55.95 (OMe), 60.81 (OMe), 62.31 (OMe), 68.07 (C-7), 108.44 (C-1), 127.98 (qC), 134.80 (qC), 140.56 (qC), 150.85 (qC), 154.04 (qC), 200.64 (C=O).

Synthesis of 1,2,3-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (4.23)

Synthesised using *para*-bromoanisole (0.07g, 0.37 mmol) and **(4.18)** (0.03g, 0.11 mmol) employing the method described for the preparation of **(3.44)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 1:1). Afforded **(4.23)** as a white solid (0.033g, 83%). M.pt. 41-43°C. ν_{max} (KBr)/ cm^{-1} 3422.4, 2936.2, 1594.4, 1246.0, 1117.1. HRMS: found 357.1687 (MH^+), requires ($C_{21}H_{24}O_5$) 356.1624. GCMS m/z (%) 338 (M^+-18, 100), 308 (6), 264 (2). ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 2.01 (1H, m, CH), 2.45 (1H, m, CH), 2.55 (1H, m, CH), 2.65 (1H, m, CH), 3.55 (3H, s, OMe), 3.76 (3H, s, OMe), 3.79 (3H, s, OMe), 3.90 (3H, s, OMe), 4.06 (1H, s, CHOH), 6.20 (1H, m, C=CH), 6.77 (1H, s, ArH), 6.85 (2H, m, 2 x ArH), 7.12 (2H, m, 2 x ArH). ^{13}C NMR δ_c ppm 29.84

($\underline{C}H_2$), 41.95 ($\underline{C}H_2$), 53.85 (O$\underline{Me}$), 54.70 (O$\underline{Me}$), 58.85 (O$\underline{Me}$), 59.39 (O$\underline{Me}$), 68.05 ($\underline{C}$HOH), 107.05 (Ar$\underline{C}$H), 112.64 (2 x Ar$\underline{C}$H), 124.34 (q$\underline{C}$), 126.46 (2 x Ar$\underline{C}$H), 131.47 (C=$\underline{C}$H), 134.10 (q$\underline{C}$), 135.68 (q$\underline{C}$), 137.21 (q$\underline{C}$), 140.32 (q$\underline{C}$), 150.52 (q$\underline{C}$), 152.46 (q$\underline{C}$), 158.47 (q$\underline{C}$).

Formation of 9-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (4.25)

1st step

Synthesis of intermediate, 9-(3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-ol (4.24)

Synthesised using **(2.50)** (0.35g, 1.11mmol) and **(4.18)** (0.10g, 0.37 mmol) employing the method described for the preparation of **(3.45)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 1:1). Afforded **(4.24)** as a white solid (0.15g, 82%). ν_{max} (CCl_4)/ cm^{-1} 3402.2, 2932.6, 1507.9, 1117.5. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.16 (3H, s, SiC$\underline{H}_3$), 0.17 (3H, s, SiC$\underline{H}_3$), 1.00 (9H, s, C(C$\underline{H}_3$)$_3$), 2.50 (2H, m, C$\underline{H}_2$), 2.71 (2H, m, ArC$\underline{H}_2$), 3.40 (3H, s, O$\underline{Me}$), 3.80 (6H, s, 2 x O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 4.23 (1H, m, C$\underline{H}$OH), 6.22 (1H, d, J 5.0Hz, C=C$\underline{H}$), 6.62 (1H, s, {A-ring}Ar$\underline{H}$), 6.75 (2H, m, {C-ring}2 x Ar$\underline{H}$), 6.89 (1H, m, {C-ring}Ar$\underline{H}$). ^{13}C NMR δ_c ppm -5.04 ($\underline{C}H_3Si\underline{C}H_3$), 17.99 ($\underline{C}(CH_3)_3$), 25.30 (C($\underline{C}H_3$)$_3$), 30.34 ($\underline{C}H_2$), 42.51 ($\underline{C}H_2$), 55.08 (O$\underline{Me}$), 55.48 (O$\underline{Me}$), 59.72 (O$\underline{Me}$), 60.25 (O$\underline{Me}$), 68.92 ($\underline{C}$HOH), 106.75 (Ar$\underline{C}$H), 111.09 (Ar$\underline{C}$H), 118.49 (Ar$\underline{C}$H), 119.25 (Ar$\underline{C}$H), 124.33 (q$\underline{C}$) 131.67 (C=$\underline{C}$H), 134.75 (q$\underline{C}$), 136.92 (2 x q$\underline{C}$), 140.41 (q$\underline{C}$), 144.30 (q$\underline{C}$), 149.77 (q$\underline{C}$), 150.86 (q$\underline{C}$), 152.40 (q$\underline{C}$).

2nd Step-deprotection

Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-ol (4.25)

Synthesised from **(4.24)** (0.49g, 0.10 mmol) using the method described for the preparation of **(3.46)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 1:1). Afforded **(4.25)** as a white powder (0.034g, 90%).

M.pt. 59-60°C. ν_{max} (KBr)/ cm^{-1} 3423.8, 2931.6, 1591.4, 1507.6, 1115.0. HRMS: found 395.1469 (M^++Na), requires ($C_{21}H_{24}O_6$) 372.1573. GCMS m/z (%) 354 (M^+-18, 100), 323 (10), 292 (9), 231 (2.5). ^{1}H NMR (CD_3OD, 400MHz) δ_H ppm 2.36-2.66 (4H, m, 2 x C$\underline{H}_2$), 3.36 (3H, s, O$\underline{Me}$), 3.74 (3H, s, O$\underline{Me}$), 3.83 (3H, s, O$\underline{Me}$), 3.88 (3H, s, O$\underline{Me}$), 4.02 (1H, m, C$\underline{H}$OH), 6.16 (1H, m, C=C$\underline{H}$), 6.64 (1H, m, Ar$\underline{H}$), 6.67 (1H, s, Ar$\underline{H}$), 6.74 (1H, s, Ar$\underline{H}$), 6.81 (1H, d, J 8.0Hz, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 29.79 ($\underline{C}H_2$), 41.90 ($\underline{C}H_2$), 54.64 (O$\underline{Me}$), 54.69 (O$\underline{Me}$), 58.90 (O$\underline{Me}$), 59.39 (O$\underline{Me}$), 68.03 ($\underline{C}$HOH), 106.98 (Ar$\underline{H}$), 110.62 (Ar$\underline{H}$), 112.67 (Ar$\underline{H}$), 116.91 (Ar$\underline{H}$), 124.41 (q$\underline{C}$), 131.44 (C=$\underline{C}$H), 134.94 (q$\underline{C}$), 135.77 (q$\underline{C}$), 137.14 (q$\underline{C}$), 140.30 (q$\underline{C}$), 145.30 (q$\underline{C}$), 146.42 (q$\underline{C}$), 150.53 (q$\underline{C}$), 152.43 (q$\underline{C}$).

Formation of 5-(7-hydroxy-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-2-methoxy-1,3-benzenediol (4.27)

1st Step

Synthesis of intermediate, 9-(3,5-di[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-ol (4.26)

To a stirred solution of bromide **(2.55)** (0.19g, 0.425 mmol) in anhydrous THF (1ml) was added 2.5M *n*-BuLi (0.17ml, 0.425 mmol) drop-wise at -78°C under anhydrous conditions for 10 minutes. To this solution at -78°C, was added a solution of **(4.18)** (0.032g, 0.12 mmol) in anhydrous THF (1ml). After 4 hours, the temperature was raised slowly to 0°C and maintained at this temperature for 12 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (5ml) and the product was extracted with diethyl ether (3 x 10ml). The ether extracts were combined, dried over sodium sulphate, filtered and concentrated to a clear oil. This was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 2:1). All homogeneous fractions were collected and the solvent was removed in vacuo to afford **(4.26)** as an oil (0.056g, 76%). ν_{max} (CCl_4)/ cm^{-1} 2932.0, 2850.1, 1596.4, 1083.5, 832.2. ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.14 (6H, s C$\underline{H}_3$SiC$\underline{H}_3$), 0.15 (6H, s C$\underline{H}_3$SiC$\underline{H}_3$), 0.98 (18H, s, 2 x C(C$\underline{H}_3$)$_3$), 2.05 (2H, m, C$\underline{H}_2$), 2.51 (2H, m, C$\underline{H}_2$) 2.67 (2H, m, ArC$\underline{H}_2$), 3.43 (3H, s, O$\underline{Me}$), 3.73 (3H, s, O$\underline{Me}$), 3.79 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 4.21 (1H, m, C$\underline{H}$OH), 6.21 (1H, d, J 5.5Hz, C=C$\underline{H}$), 6.38 (2H, s, 2 x {C-ring}Ar$\underline{H}$), 6.61 (1H, s, {A-

ring} ArH). ^{13}C NMR δ_c ppm -5.11 ($\underline{C}H_3Si\underline{C}H_3$), -5.06 ($\underline{C}H_3Si\underline{C}H_3$), 17.83 (2 x $\underline{C}(CH_3)_3$), 26.2 (2 x $C(\underline{C}H_3)_3$), 30.25 ($\underline{C}H_2$), 42.48 ($\underline{C}H_2$), 55.49 (O$\underline{Me}$), 59.53 (O$\underline{Me}$), 59.67 (O$\underline{Me}$), 60.25 (O$\underline{Me}$), 68.88 ($\underline{C}$HOH), 106.76 (Ar$\underline{C}$H), 112.27 (2 x Ar$\underline{C}$H), 124.24 (q$\underline{C}$), 132.23 (C=$\underline{C}$H), 136.77 (q$\underline{C}$), 137.15 (q$\underline{C}$), 140.38 (q$\underline{C}$), 141.58 (q$\underline{C}$) 148.83 (2 x q$\underline{C}$), 150.78 (q$\underline{C}$), 152.38 (q$\underline{C}$).

2nd step-deprotection

Synthesis of 5-(7-hydroxy-1,2,3-trimethoxy-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-9-yl)-2-methoxy-1,3-benzenediol (4.27)

To a stirred solution of **(4.26)** (0.04g, 0.065 mmol) in THF (0.5ml) was added 1M TBAF (0.065ml, 0.065 mmol) at room temperature. After 1 hour, the reaction was quenched by the addition of water (2ml) and the product was extracted using diethyl ether (3 x 5ml). The ether extracts were collected, dried over sodium sulphate and filtered before being reduced in volume and purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 1:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(4.27)** as a white solid (0.012g, 48%). M.pt 107-109°C. ν_{max} (KBr)/ cm^{-1} 3409.7, 2935.7, 1595.7, 1112.2. GCMS m/z (%) 370 (M$^+$-18, 100), 339 (77.5), 308 (36), 279 (30). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 1.70 (2H, m, C$\underline{H}_2$), 2.49 (2H, m, C$\underline{H}_2$), 3.45 (3H, s, O$\underline{Me}$), 3.81 (3H, s, O$\underline{Me}$), 3.89 (3H, s, O$\underline{Me}$), 3.91 (3H, s, O$\underline{Me}$), 4.21 (1H, m, C$\underline{H}$OH), 6.26 (1H, d, J 5.0Hz, C=C$\underline{H}$), 6.39 (2H, s, 2 x {C-ring} Ar$\underline{H}$), 6.60 (1H, s, {A-ring} Ar$\underline{H}$). ^{13}C NMR δ_c ppm 30.20 ($\underline{C}H_2$), 42.22 ($\underline{C}H_2$), 55.54 (O$\underline{Me}$), 59.91 (O$\underline{Me}$), 60.30 (O$\underline{Me}$), 60.59 (O$\underline{Me}$), 68.90 ($\underline{C}$HOH), 105.57 (2 x Ar$\underline{C}$H), 106.99 (Ar$\underline{C}$H), 123.99 (q$\underline{C}$), 132.77 (q$\underline{C}$), 133.40 (C=$\underline{C}$H), 136.85 (q$\underline{C}$), 138.34 (q$\underline{C}$), 140.42 (q$\underline{C}$), 148.24 (2 x q$\underline{C}$), 150.58 (q$\underline{C}$), 152.58 (q$\underline{C}$).

Synthesis of 1,2,3-trimethoxy-9-(4-methoxyphenyl)-6,7-dihydro-5*H*-benzo[*a*]cyclohepten-7-one (4.28)

Synthesised from **(4.23)** (0.048g, 0.13 mmol) using the method described for the preparation of **(3.53)**. Purified by flash column chromatography (stationary phase: silica gel 230-400 mesh, mobile phase: hexane/ethyl acetate 3:1). Afforded **(4.28)** as a white solid (0.031g, 68%). M.pt

36-38°C. HRMS: found 355.1572 (MH^+), requires ($C_{21}H_{24}O_6$) 354.1467. GCMS m/z (%) 354 (100), 312 (20), 251 (4), 219 (2). ν_{max} (KBr)/ cm^{-1} 2939.8, 1659.8, 1593.6, 1509.8, 1117.5. ^1H NMR (CD_3OD, 400MHz) δ_H ppm 2.67 (2H, m, ArC$\underline{H}_2$), 3.25 (3H, s, O$\underline{Me}$), 3.32 (2H, m, COC$\underline{H}_2$), 3.73 (3H, s, O$\underline{Me}$), 3.81 (3H, s, O$\underline{Me}$), 3.93 (3H, s, O$\underline{Me}$), 6.30 (1H, m, C=C$\underline{H}$), 6.83 (1H, s, Ar$\underline{H}$), 6.91 (2H, d, J 8.5Hz, 2 x Ar$\underline{H}$), 7.18 (2H, d, J 8.5Hz, 2 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 29.40 (Ar$\underline{C}H_2$), 46.65 (CO$\underline{C}H_2$), 53.93 (O$\underline{Me}$), 54.70 (O$\underline{Me}$), 59.06 (O$\underline{Me}$), 59.26 (O$\underline{Me}$), 106.24 (Ar$\underline{H}$), 112.85 (2 x Ar$\underline{C}$H), 126.85 (C=$\underline{C}$H), 126.87 (2 x Ar$\underline{C}$H), 129.09 (q$\underline{C}$), 135.70 (q$\underline{C}$), 137.84 (q$\underline{C}$), 140.79 (q$\underline{C}$), 149.89 (q$\underline{C}$), 152.32 (q$\underline{C}$), 153.90 (q$\underline{C}$), 159.68 (q$\underline{C}$), 205.62 ($\underline{C}$=O).

Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7-dihydro-5H-benzo[a]cyclohepten-7-one (4.30)

To a stirred solution of **(4.24)** (0.040g, 0.08 mmol) in DMF (1ml) was added PDC (0.061g, 0.164 mmol) portion-wise at 0°C. After 12 hours, the reaction was quenched by the addition of water (5ml) and the product was then extracted with diethyl ether (5 x 5ml). The ether extracts were combined, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 3:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(4.29)** as a clear oil (0.02g, 50%). The enone **(4.29)** (0.02g, 0.041 mmol) was subsequently re-dissolved in THF (1ml) and 1M TBAF (0.08ml, 0.082 mmol) was added drop-wise at room temperature. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted using diethyl ether (3 x 5ml). The ether extracts were combined, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(4.30)** as a white solid (0.015g, 99%). M.pt. 44-46°C. ν_{max} (KBr)/ cm^{-1} 3402.7, 2935.2, 1652.2, 1508.7, 1115.8. HRMS: found 371.1465 (MH^+), requires ($C_{21}H_{22}O_6$) 370.1416. GCMS m/z (%) 371 (M^++1, 100), 370 (96), 328 (22.5). ^1H NMR (CD_3OD, 400MHz) δ_H ppm 2.77 (2H, m, ArC$\underline{H}_2$), 3.05 (2H, m, COC$\underline{H}_2$), 3.37 (3H, s, O$\underline{Me}$), 3.82 (3H, s, O$\underline{Me}$), 3.96 (3H, s,

OMe), 4.02 (3H, s, OMe), 6.38 (1H, s, C=CH), 6.80 (1H, s, ArH), 6.91 (1H, d, ArH), 7.00 (2H, m, 2 x ArH). ^{13}C NMR δ_c ppm 24.24 (CH_2), 29.37 (CH_2), 54.60 (OMe), 54.70 (OMe), 59.09 (OMe), 59.25 (OMe), 106.12 (ArCH), 110.56 (ArCH), 112.81 (ArCH), 117.27 (ArCH), 126.70 (C=CH), 136.47 (qC), 137.75 (qC), 140.76 (qC), 145.55 (qC), 147.67 (qC), 150.08 (qC), 152.36 (qC), 153.87 (qC), 205.68 (C=O).

Formation of 9-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*benzo[a]cyclohepten-7-one (4.33)

1st step

Synthesis of intermediate, 9-(3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5H-benzo[a]cyclohepten-7-ol (4.31)

To a solution of **(4.24)** (0.1g, 0.20 mmol) in ethanol/ethyl acetate (1:1, 2ml) was added 10% Pd/C (0.1g). The reaction was stirred under a hydrogen atmosphere for 48 hours. On completion, the reaction was filtered and the filtrate was concentrated to an oil. It was purified by flash column chromatography (stationary phase: silica gel G_{254}; mobile phase: hexane/ethyl acetate 1:1). All homogeneous fractions were collected and the solvent was removed *in vacuo* to afford **(4.31)** as a clear oil (0.099g, 99%). ^{1}H NMR ($CDCl_3$, 400MHz) δ_H ppm 0.10 (6H, s CH_3SiCH_3), 0.96 (9H, s, $C(CH_3)_3$), 1.82 (1H, m, HCH), 1.97 (1H, m, HCH), 2.26 (1H, m, HCH), 2.47-2.59 (2H, m, CH_2), 3.11 (1H, m, HCH), 3.50 (3H, s, OMe), 3.77 (3H, s, OMe), 3.84 (3H, s, OMe), 3.90 (3H, s, OMe), 4.03 (1H, m, CHOH), 4.86 (1H, t, J 6.7Hz, ArCHAr), 6.54 (1H, s, {A-ring}ArH), 6.65 (1H, s, {C-ring}ArH), 6.71 (1H, d, J 8.0Hz, {C-ring}ArH), 6.76 (1H, d, J 8.0Hz, {C-ring}ArH). ^{13}C NMR δ_c ppm -5.08 (CH_3SiCH_3), 17.96 (2 x $C(CH_3)_3$), 25.26 (2 x $C(CH_3)_3$), 29.86 (CH_2), 34.76 (CH_2), 37.57 (ArCHAr), 39.90 (CH_2), 55.15 (OMe), 55.47 (OMe), 60.27 (OMe), 60.54 (OMe), 70.04 (CHOH), 108.68 (ArCH), 111.77 (ArCH), 119.65 (2 x ArCH), 126.71 (qC), 136.69 (qC), 136.81 (qC), 140.29 (qC), 144.51 (qC) 148.71 (qC), 151.07 (qC), 151.70 (qC).

2nd step-deprotection

Synthesis of 9-(3-hydroxy-4-methoxyphenyl)-1,2,3-trimethoxy-6,7,8,9-tetrahydro-5*H*benzo[a]cyclohepten-7-one (4.33)

To a stirred solution of **(4.31)** (0.03g, 0.061 mmol) in DMF (1ml) was added PDC (0.045g, 0.119 mmol) over a period of 2 hours at 0°C. The reaction was allowed to proceed for 12 hours before being quenched by the addition of water (5ml). The product was then extracted with diethyl ether (5 x 5ml) and the organic fractions were collected and dried over sodium sulphate before being concentrated *in vacuo* to afford the enone **(4.32)**. The enone **(4.32)** (0.02g, 0.041 mmol) was subsequently re-dissolved in THF (1ml) and 1M TBAF (0.05ml, 0.050 mmol) was added drop-wise at room temperature. After 1 hour, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The ether extracts were combined, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(4.33)** as a white solid (0.015g, 99%). M.pt. 44-46°C. HRMS: found 395.1461 (M^++Na), requires ($C_{21}H_{24}O_6$) 372.1573. ν_{max} (KBr)/ cm^{-1} 3400.5, 2936.7, 1701.6, 1595.6. ^{1}H NMR (CD_3Cl, 400MHz) δ_H ppm 2.46 (1H, m, H-6), 2.63 (1H, m, H-5), 2.67 (1H, m, H-6), 2.87 (2H, m, H-8), 2.94 (1H, m, H-5), 3.37 (1H, dd, J 6.8Hz, 13.8Hz, H-8), 3.69 (3H, s, OMe), 3.86 (3H, s, OMe), 3.88 (3H, s, OMe), 3.89 (3H, s, OMe), 4.95 (1H, t, J 6.2Hz, H-9), 5.53 (1H, s, br, -OH), 6.53 (1H, s, H-4), 6.62 (1H, d, J 2.0Hz, H-2'), 6.67 (1H, dd, J 2Hz, 8.7Hz, H-6'), 6.76 (1H, d, J 8.5Hz, H-5'). ^{13}C NMR δ_c ppm 29.67 (C-5), 37.04 (C-9), 43.85 (C-6), 47.55 (C-8), 55.46 (OMe), 55.49 (OMe), 60.26 (OMe), 60.60 (OMe), 109.00 (C-4), 110.07 (C-2'), 112.98 (C-6'), 118.02 (C-5'), 126.98 (qC), 131.22 (qC), 135.53 (qC) 136.46 (qC), 144.43 (qC), 145.09 (qC), 151.79 (qC), 210.47 (C=O).

Formation of 3-hydroxy-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1-benzoxepin-5-one (5.01)

1st Step

Synthesis of intermediate, ethyl 2-(2,3,4-trimethoxyphenoxy)acetate (5.08)

To a stirred solution of 2,3,4-trimethoxybenzaldehyde (3.0g, 15.3 mmol) in DCM (60ml) was added a solution of *m*CPBA (3.26g, 18.9 mmol) dissolved in DCM (60ml). After 5 hours, the solvent was concentrated to half its volume and filtered to remove the precipitated *m*-chlorobenzoic acid. The filtrate was then washed with 5% aq. $NaHCO_3$, water and sat. NaCl. The solvent was subsequently removed under reduced pressure to afford an oily residue. This was re-dissolved in methanol (30ml) and 2.5M aq. NaOH (25ml) was added to the solution at 0°C. After 1.5 hours, the reaction was acidified with 2M aq. HCl and the product was isolated by extraction with ether (3 x 20ml). The combined organic layers were dried under sodium sulphate, filtered and concentrated to an oil. This was purified by flash column chromatography (stationary phase: silica gel; mobile phase: hexane/ethyl acetate 2:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(5.07)** as a yellow solid (2.22g, 79%). The phenol **(5.07)** (1.5g, 8.15 mmol) was re-dissolved in acetone (40ml) and K_2CO_3 (5.0g, 36.2 mmol) was subsequently added followed by ethyl bromoacetate (2ml, 17.3 mmol). The reaction was refluxed for 12 hours. On completion, the solvent was concentrated *in vacuo* and a solution of sat. NaCl (40ml) was added. The product was extracted using diethyl ether (3 x 30ml), dried under sodium sulphate, filtered and concentrated to an oil. It was purified by flash column chromatography (stationary phase: silica gel; mobile phase: hexane/ethyl acetate 5:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(5.08)** as a yellow oil (1.67g, 76%). ν_{max} (CCl_4)/ cm^{-1} 2984.0, 2939.2, 1748.5, 1591.4, 1120.2. ^1H NMR δ_H ppm 1.08 (3H, t, J 7.2Hz, $C\underline{H}_3$), 3.60 (3H, s, O<u>Me</u>), 3.68 (3H, s, O<u>Me</u>), 3.70 (3H, s, O<u>Me</u>), 4.04 (2H, q, J 3.8Hz, 7.2Hz, $OC\underline{H}_2CH_3$), 4.42 (2H, s, $C\underline{H}_2CO$), 6.35 (1H, d, J 9.0Hz, Ar<u>H</u>), 6.40 (1H, d, J 9.0Hz, Ar<u>H</u>). ^{13}C NMR δ_c ppm 13.40 ($CH_2\underline{C}H_3$), 55.53 (O<u>Me</u>), 60.31 (2 x O<u>Me</u>), 60.43 ($\underline{C}H_2CH_3$), 66.47 ($O\underline{C}H_2$), 105.90 (Ar<u>C</u>H), 108.94 (Ar<u>C</u>H), 142.83 (q<u>C</u>), 143.63 (q<u>C</u>), 145.39 (q<u>C</u>), 148.23 (q<u>C</u>), 168.37 (<u>C</u>=O).

2nd Step

Synthesis of intermediate, 2,2-dimethyl-5-[-2(2,3,4-trimethoxyphenoxy)acetyl]-1,3-dioxane-4,6-dione (5.10)

To a stirred solution of ester **(5.08)** (1.5g, 5.55 mmol) in ethanol (40ml) was added 2.5M aq. NaOH (30ml) at 25°C. After 3 hours, the solvent was removed *in vacuo* and 2M aq. HCl (40ml) was added. The product was extracted with diethyl ether (3 x 30ml), dried over sodium sulphate, filtered and the solvent was removed under reduced pressure to afford the acid **(5.09)** as a white solid (1.34g, 100%). The acid **(5.09)** (0.88g, 3.63 mmol) was then re-dissolved in anhydrous DCM (4ml) and 2M oxalyl chloride solution in DCM (3.63ml, 7.27 mmol) was added together with DMF (1 drop) under anhydrous conditions at 0°C for 1 hour. On formation of the acid chloride, the solvent was removed *in vacuo* to afford a syrupy residue. To this residue was added a solution of Meldrum's acid (0.52g, 3.61 mmol) dissolved in anhydrous DCM (10ml) followed by DMAP (0.88g, 7.21 mmol) at 0°C for 1 hour. The reaction temperature was then raised to 25°C and the reaction was allowed to continue for an additional hour. On completion, the solvent was removed *in vacuo* and 1M aq. HCl (10ml) was added. The product was extracted with diethyl ether (3 x 20ml) and the organic layers were combined, dried under sodium sulphate, filtered and concentrated to afford a yellow solid. This was re-dissolved in DCM (2ml) and purified by flash column chromatography (stationary phase: silica gel; mobile phase: hexane/ethyl acetate 3:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(5.10)** as a pale-yellow solid (0.83g, 62%). ^{1}H NMR δ_H ppm 1.78 (6H, s, 2 x C$\underline{H}_3$), 3.84 (3H, s, O$\underline{Me}$), 3.92 (3H, s, O$\underline{Me}$), 3.96 (3H, s, O$\underline{Me}$), 5.46 (2H, s, 2 x $\underline{H}$-2), 6.57 (1H, d, J 7.0Hz, Ar$\underline{H}$), 6.65 (1H, d, J 7.0Hz, Ar$\underline{H}$). ^{13}C NMR δ_c ppm 26.90 (2 x $\underline{C}H_3$), 56.33 (O$\underline{Me}$), 60.17 (O$\underline{Me}$), 61.33 (O$\underline{Me}$), 69.48 ($\underline{C}$-2), 105.98 ($\underline{C}$-2'), 106.49 (Ar$\underline{C}$H), 109.92 (Ar$\underline{C}$H), 145.92 (q$\underline{C}$), 149.20 (q$\underline{C}$), 159.91 (q$\underline{C}$), 162.42 (q$\underline{C}$), 169.91 ($\underline{C}$-4', $\underline{C}$-6'), 192.13 ($\underline{C}$-1).

3rd Step

Synthesis of intermediate, methyl 3-oxo-4-(2,3,4-trimethoxyphenoxy)butanoate (5.11)

To a stirred solution of **(5.10)** (0.50g, 1.36 mmol) in toluene (40ml) was added methanol (10ml). The reaction was refluxed for 12 hours. On completion, the solvent was removed *in vacuo* and concentrated to an oil. This oil was purified by flash column chromatography (stationary phase: silica gel; mobile phase: hexane/ethyl acetate 3:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(5.11)** as a clear oil (0.33g, 82%). ν_{max} (CCl_4)/ cm^{-1} 2931.6, 2826.9, 1753.7, 1738.0, 1491.9, 1115.0. ^1H NMR δ_H ppm 3.65 (2H, s, $C\underline{H}_2COOMe$), 3.69 (3H, s, $COO\underline{Me}$), 3.77 (3H, s, $O\underline{Me}$), 3.85 (3H, s, $O\underline{Me}$), 3.86 (3H, s, $O\underline{Me}$), 4.58 (2H, s, $OC\underline{H}_2CO$), 6.51 (2H, s, 2 x $Ar\underline{H}$). ^{13}C NMR δ_c ppm 45.06 ($\underline{C}H_2CO$), 51.81 ($COO\underline{Me}$), 55.79 ($O\underline{Me}$), 60.58 ($O\underline{Me}$), 60.73 ($O\underline{Me}$), 74.20 ($O\underline{C}H_2CO$), 106.14 ($Ar\underline{C}H$), 109.14 ($Ar\underline{C}H$), 143.11 (q$\underline{C}$), 143.71 (q$\underline{C}$), 145.22 (q$\underline{C}$), 148.64 (q$\underline{C}$), 166.80 ($\underline{C}$=OOMe), 200.04 ($\underline{C}$=O).

4th step

Synthesis of intermediate, methyl 3-hydroxy-4-(2,3,4-trimethoxyphenoxy)butanoate (5.12)

To a stirred solution of **(5.11)** (0.25g, 0.84 mmol) in methanol (61.6ml) was added $NaBH_4$ (0.011g, 0.29 mmol) at 0°C. After 3 hours, the reaction was quenched by the addition of sat. NaCl solution (20ml) and the product was extracted using diethyl ether (5 x 25ml). The ether extracts were combined, dried over sodium sulphate, filtered and the filtrate was concentrated *in vacuo* to afford an oil. This oil was purified by flash column chromatography (solid phase: silica gel; mobile phase: hexane/ethyl acetate 2:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(5.08)** an oil (0.18g, 72%). ν_{max} (CCl_4)/ cm^{-1} 3475.1, 2934.2, 2830.2, 1733.8, 1489.4. ^1H NMR δ_H ppm 2.66 (2H, m, $\underline{C}H_2COH$), 3.42 (1H, br, s, $CHO\underline{H}$), 3.71 (3H, s, $COO\underline{Me}$), 3.81 (3H, s, $O\underline{Me}$), 3.85 (3H, s, $O\underline{Me}$), 3.85 (3H, s, $O\underline{Me}$), 3.97 (2H, s, $OC\underline{H}_2CHOH$), 4.39 (1H, br, s, $C\underline{H}OH$), 6.56 (1H, d, J 4.5Hz, $Ar\underline{H}$), 6.63 (1H, d, J 4.5Hz, $Ar\underline{H}$). ^{13}C NMR δ_c ppm 37.86 ($\underline{C}H_2COOMe$), 51.32 ($COO\underline{Me}$), 55.89 ($O\underline{Me}$), 60.67 ($O\underline{Me}$), 60.86 ($O\underline{Me}$), 66.35 ($\underline{C}HOH$), 73.31 ($O\underline{C}H_2CHOH$), 106.37 ($Ar\underline{C}H$), 109.66 ($Ar\underline{C}H$), 142.97 (q$\underline{C}$), 143.95 (q$\underline{C}$), 146.11 (q$\underline{C}$), 148.26 (q$\underline{C}$), 171.77 ($\underline{C}$=O).

5th Step

Synthesis of methyl 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-4-(2,3,4-trimethoxyphenoxy)butanoate (5.13)

To a stirred solution of **(5.12)** (0.23g, 0.77 mmol) in DMF (2ml) was added *t*BDPSCl (0.17g, 1.15 mmol) followed by imidazole (0.084g, 1.23 mmol) at 0°C. After 3 hours, the reaction was quenched by the addition of sat. aq. NaCl solution (10ml) and the product was extracted using diethyl ether (3 x 15ml). The ether extracts were combined, dried over sodium sulphate, filtered and the solvent was removed *in vacuo* to afford an oil. This oil was purified by flash column chromatography (stationary phase: silica gel; mobile phase: hexane/ethyl acetate 6:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(5.13)** as an oil (0.32g, 77%). ν_{max} (CCl_4)/ cm^{-1} 2931.6, 2850.3, 1738.0, 1491.9. ^{1}H NMR δ_H ppm 1.09 (9H, s, C(C$\underline{H}_3$)$_3$), 2.77 (2H, 2 x dd, J 6.25Hz, 15.0Hz, 32.6Hz, C$\underline{H}_2$COOMe), 3.61 (3H, s, COO$\underline{Me}$), 3.81 (3H, s, O$\underline{Me}$), 3.82 (3H, s, O$\underline{Me}$), 3.90 (3H, s, O$\underline{Me}$), 3.90 (2H, s, OC$\underline{H}_2$CHOSi), 4.55 (1H, m, C$\underline{H}$OSi), 6.32 (1H, d, J 9.0Hz, Ar$\underline{H}$), 6.47 (1H, d, J 9.0Hz, Ar$\underline{H}$), 7.41 (4H, m, 4 x Ar$\underline{H}$), 7.75 (6H, m, 6 x Ar$\underline{H}$). ^{13}C NMR δ_c ppm 18.80 (C(C$\underline{H}_3$)$_3$), 26.41 (C($\underline{C}$H$_3$)$_3$), 39.50 ($\underline{C}$H$_2$), 51.37 (COO$\underline{Me}$), 56.35 (O$\underline{Me}$), 61.04 (O$\underline{Me}$), 61.08 (O$\underline{Me}$), 68.86 ($\underline{C}$HOSi), 72.03 (O$\underline{C}$H$_2$CHOSi), 106.16 (Ar$\underline{C}$H), 108.32 (Ar$\underline{C}$H), 127.16 (2 x Ar$\underline{C}$H), 127.21 (2 x Ar$\underline{C}$H), 129.29 (Ar$\underline{C}$H), 129.36 (Ar$\underline{C}$H), 132.93 (q$\underline{C}$), 133.22 (q$\underline{C}$), 135.40 (2 x Ar$\underline{C}$H), 135.44 (2 x Ar$\underline{C}$H), 143.00 (q$\underline{C}$), 143.63 (q$\underline{C}$), 146.28 (q$\underline{C}$), 147.73 (q$\underline{C}$), 171.06 ($\underline{C}$=O).

6th step

Synthesis of intermediate, 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-4-(2,3,4-trimethoxyphenoxy)butanoic acid (5.14)

To a stirred solution of **(5.13)** (0.25g, 0.46 mmol) in methanol (10ml) was added 10% aq. NaOH (20ml) at room temperature. After 24 hours, the reaction was quenched by the addition of 2M aq. HCl (20ml) and the product was extracted with diethyl ether (3 x 30ml). The ether extracts were combined, dried over sodium sulphate, filtered and the filtrate was concentrated *in vacuo* to afford an oil. This was purified by flash column chromatography (solid phase: silica gel; mobile phase: hexane/ethyl acetate 2:1). All homogenous fractions were collected and the

solvent was removed *in vacuo* to afford **(5.14)** as a white solid (0.16g, 66%). ν_{max} (CCl_4)/ cm^{-1} 2925.3, 2848.3, 1710.6. ^1H NMR δ_H ppm 1.0 (9H, s, C(CH_3)$_3$), 2.74 (1H, dd, J 6.3Hz, 15.0Hz, HCHCOOMe), 2.84 (1H, dd, J 6.3Hz, 15.0Hz, HCHCOOMe), 3.810 (3H, s, OMe), 3.818 (3H, s, OMe), 3.98 (3H, s, OMe), 3.90 (2H, s, OCH_2CHOSi), 4.49 (1H, m, CHOSi), 6.30 (1H, d, J 9.0Hz, ArH), 6.46 (1H, d, J 9.0Hz, ArH), 7.41 (6H, m, 6 x ArH), 7.73 (4H, m, 4 x ArH). ^{13}C NMR δ_c ppm 18.78 (C(CH_3)$_3$), 26.38 (C(CH_3)$_3$), 38.86 (CH_2), 55.95 (2 x OMe), 60.67 (OMe), 68.18 (CHOSi), 71.86 (CH_2), 106.13 (ArCH), 108.35 (ArCH), 127.17 (2 x ArCH), 127.24 (2 x ArCH), 129.31 (ArCH), 129.42 (ArCH), 132.64 (qC), 133.10 (qC), 135.36 (2 x ArCH), 135.44 (2 x ArCH), 142.98 (qC), 143.61 (qC), 143.76 (qC), 146.15 (qC), 147.86 (qC), 175.91 (C=O).

7th Step

Synthesis of intermediate, 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1-benzoxepin-5-one (5.15) via 3-[1-(tert-butyl)-1,1-diphenylsilyl]oxy-4-(2,3,4-trimethoxyphenoxy)butanoyl chloride

To a stirred solution of acid **(5.14)** (0.66g, 1.26 mmol) in anhydrous DCM (5ml) was added 2M oxalyl chloride in DCM (1.29ml, 2.58 mmol) and DMF (1 drop) under anhydrous conditions at 0°C. After 1.5 hours, the excess oxalyl chloride was removed under reduced pressure to afford the corresponding acid halide as an oil. This was re-dissolved in anhydrous DCM (12ml) and a 1.0M $SnCl_4$ in DCM (0.42ml, 0.42 mmol) was added at -10°C. After 30 minutes, the reaction was quenched with sat. NaCl (15ml) and the product extracted using diethyl ether (3 x 15ml). The organic fractions were collected, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The resulting residue was then purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 2:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(5.15)** as a clear oil (0.50g, 78%). ν_{max} (CCl_4)/ cm^{-1} 2931.6, 2858.3, 1675.2, 1591.4, 1109.7. ^1H NMR δ_H ppm 1.06 (9H, s, C(CH_3)$_3$), 3.04 (1H, dd, J 4.5Hz, 12.5Hz, HCHCO), 3.11 (1H, dd, J 6.0Hz, 12.5Hz, HCHCO), 3.87 (3H, s, OMe), 3.92 (3H, s, OMe), 3.98 (3H, s, OMe), 4.08 (1H, dd, J 4.7Hz, 12.2Hz, HCHCHOSi), 4.16 (1H, dd, J 5.7Hz, 12.2Hz, HCHCHOSi), 4.48 (1H, m, CHOSi), 7.15 (1H, s, ArH), 7.41 (6H, m, 6 x ArH), 7.67 (4H, m, 4 x ArH). ^{13}C NMR δ_c ppm 18.66 (C(CH_3)$_3$), 26.34 (C(CH_3)$_3$), 49.35 (CH_2CO), 55.69 (OMe), 60.75 (OMe), 61.27 (OMe),

70.50 (CHOSi), 79.31 (OCH_2CHOSi), 105.00 (ArCH), 123.67 (qC), 127.34 (4 x ArCH), 129.49 (ArCH), 129.52 (ArCH), 132.65 (qC), 132.92 (qC), 135.21 (2 x ArCH), 135.35 (2 x ArCH), 144.23 (qC), 146.88 (qC), 148.29 (qC), 151.67 (qC), 194.97 (C=O).

8th Step-deprotection

Synthesis of 3-hydroxy-7,8,9-trimethoxy-2,3,4,5-tetrahydro-1-benzoxepin-5-one (5.01)

To a stirred solution of **(5.15)** (0.36g, 0.71 mmol) in THF (2ml) was added 1M TBAF (0.78ml, 0.78 mmol) at 0°C. After 3 hours, the reaction was quenched by the addition of sat. NaCl solution (10ml) and the product was extracted with diethyl ether (3 x 10ml). The ether extracts were collected, dried over sodium sulphate, filtered and the solvent was concentrated *in vacuo* to afford an oil. This was purified by flash column chromatography (stationary phase: silica gel; mobile phase: hexane/ethyl acetate 1:1). All homogenous fractions were collected and the solvent was removed *in vacuo* to afford **(5.01)** as a purple solid. (0.10g, 53%). ν_{max} (KBr)/ cm^{-1} 3367.8, 2939.4, 1657.7, 1592.9. ^1H NMR δ_H ppm 3.06 (2H, dd, J = 5.5Hz, 12.0Hz, 2 x H-4), 3.80 (3H, s, OMe), 3.86 (3H, s, OMe), 3.92 (3H, s, OMe), 4.22 (2H, m, 2 x H-2), 4.48 (1H, m, H-3), 7.04 (1H, s, H-6). ^{13}C NMR δ_c ppm 50.12 (C-4), 55.69 (OMe), 60.71 (OMe), 61.24 (OMe), 69.24 (C-3), 79.92 (C-2), 104.95 (C-6), 122.84 (qC), 143.97 (qC), 146.99 (qC), 148.16 (qC), 152.09 (qC), 195.29 (C=O).

Formation of 5-(3-hydroxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-ol (5.02)

1st Step

Synthesis of intermediate, 5-(3-[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-ol (5.16)

To a stirred solution of bromide **(2.50)** (0.32g, 1.00 mmol) in anhydrous THF (2ml) was added 2.5M *n*-BuLi (0.40ml, 1.00 mmol) at -78°C under anhydrous conditions. After 1 hour, the keto-alcohol **(5.01)** (0.09g, 0.33 mmol) dissolved in anhydrous THF (2ml) was added. The reaction was allowed to continue at -78°C for 8 hours. On completion, the reaction was quenched by the

addition of 2M aq. HCl (6ml) and the product was extracted with diethyl ether (3 x 5ml). The ether extracts were combined, dried over sodium sulphate before being concentrated *in vacuo*. The residue was then purified by flash column chromatography (solid phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(5.16)** as a white solid (0.083g, 51%). ^{1}H NMR δ_H ppm 0.16 (6H, s, CH_3SiCH_3), 0.99 (9H, s, $C(CH_3)_3$), 3.57 (3H, s, OMe), 3.84 (3H, s, OMe), 3.92 (3H, s, OMe), 3.97 (3H, s, OMe), 4.10 (2H, m, CHOH), 4.51 (1H, m, OCH_2), 6.10 (1H, d, J 4.5Hz, C=CH), 6.25 (1H, s, ArH), 6.78 (1H, s, ArH), 6.81 (2H, s, 2 x ArH). ^{13}C NMR δ_c ppm -5.06 (CH_3SiCH_3), 17.95 ($C(CH_3)_3$), 25.24 ($C(CH_3)_3$), 55.00 (OMe), 55.61 (OMe), 60.71 (OMe), 61.31 (OMe), 69.83 (CHOH), 78.56 (OCH_2), 109.76 (ArCH), 111.10 (ArCH), 121.34 (ArCH), 122.01 (ArCH), 125.30 (qC), 130.25 (C=CH), 135.71 (qC), 138.37 (qC), 142.22 (qC), 144.07 (qC), 144.74 (qC) 147.49 (qC), 147.79 (qC), 150.02 (qC).

2nd Step-deprotection

Synthesis of 5-(3-hydroxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-ol (5.02)

To a stirred solution of **(5.16)** (0.017g, 0.035 mmol) in THF (1.0ml) was added 1M TBAF (0.035ml, 0.035 mmol) drop-wise at 0°C. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted using diethyl ether (3 x 5ml). The ether extracts were combined, dried over sodium sulphate and filtered before being concentrated *in vacuo*. The residue was then purified by flash column chromatography (solid phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(5.02)** as a white solid (0.012g, 92%). M.pt. 165-166°C. ν_{max} (KBr)/ cm^{-1} 3458.4, 2931.6, 1578.8, 1124.9. HRMS: found 375.1463 (MH^+), requires ($C_{20}H_{22}O_7$) 374.1366. GCMS m/z (%) 356 (M^+-18, 100), 342 (38), 309 (32), 281 (9). ^{1}H NMR δ_H ppm 3.60 (3H, s, OMe), 3.94 (6H, s, 2 x OMe), 3.98 (3H, s, OMe), 4.11 (1H, dd, J 2.5Hz, 9.0Hz, H-2), 4.47 (1H, q, CHOH), 4.51 (1H, dd, H-2), 5.63 (1H, br, s, OH), 6.14 (1H, d, J 4.5Hz, C=CH), 6.29 (1H, s, ArH), 6.78 (1H, dd, J 1.5Hz, 8.0Hz, H-6'), 6.84 (1H, d, J 8.0Hz, H-5'), 6.88 (1H, d, J 1.5Hz, H-2'). ^{13}C NMR δ_c ppm 55.52 (OMe), 55.76 (OMe), 60.73 (OMe), 61.33 (OMe), 69.87 (CHOH), 78.70 (OCH_2), 109.48 (ArCH), 109.75 (ArCH),

115.00 (ArCH), 120.36 (ArCH), 125.21 (qC), 130.42 (C=CH), 136.29 (qC), 138.42 (qC), 142.31 (qC), 144.76 (qC), 144.78 (qC), 145.64 (qC), 147.58 (qC), 147.86 (qC).

Formation of 5-(3-hydroxy-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-5-yl)-2-methoxy-1,3-benzenediol (5.03)

1st Step

Synthesis of 5-(3,5-di[1-(tert-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-ol (5.17)

To a stirred solution of bromide **(2.55)** (0.60g, 1.34 mmol) in anhydrous THF (2ml) was added 2.5M *n*-BuLi (0.54ml, 1.34 mmol) at -78°C under anhydrous conditions. After 1 hour, the keto alcohol **(5.01)** (0.12g, 0.45 mmol) dissolved in anhydrous THF (2ml) was added. The reaction was allowed to continue at -78°C for 12 hours. On completion, the reaction was quenched by the addition of 2M aq. HCl (6ml) and the product was extracted with diethyl ether (3 x 5ml). The ether extracts were collected, dried over sodium sulphate and filtered before being concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and reduced in volume to afford **(5.17)** as an oil (0.13g, 48%). ν_{max} (CCl_4)/ cm^{-1} 3434.2, 2941.6, 1578.0. ^{1}H NMR δ_H ppm 0.13 (12H, s, 2 x CH_3SiCH_3), 0.99 (18H, s, 2 x $C(CH_3)_3$), 3.65 (3H, s, OMe), 3.74 (3H, s, OMe), 3.88 (3H, s, OMe), 3.92 (3H, s, OMe), 4.05 (2H, m, OCH_2), 4.22 (1H, dd, J 3.7Hz, 11.7Hz, CHOH), 6.10 (1H, d, J 4.0Hz, C=CH), 6.39 (1H, s, ArH), 6.48 (2H, s, 2 x ArH). ^{13}C NMR δ_c ppm -5.06 (2 x CH_3SiCH_3), 17.95 (2 x $C(CH_3)_3$), 25.25 (2 x $C(CH_3)_3$), 55.48 (OMe), 59.46 (OMe), 60.64 (OMe), 61.24 (OMe), 69.26 (CHOH), 77.74 (OCH_2), 106.94 (ArCH), 112.13 (2 x ArCH), 130.25 (C=CH), 132.67 (qC), 141.30 (qC), 141.42 (qC), 141.80 (qC), 145.22 (qC) 146.05 (qC), 148.20 (qC), 148.87 (qC).

2nd Step-deprotection

Synthesis of 5-(3-hydroxy-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-5-yl)-2-methoxy-1,3-benzenediol (5.03)

To a stirred solution of **(5.17)** (0.053g, 0.086 mmol) in THF (1ml) was added 1M TBAF (0.17ml, 0.17 mmol) drop-wise at 0°C. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The organic fractions were collected, dried over sodium sulphate and filtered before being concentrated *in vacuo*. The resulting residue was then purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated to afford **(5.03)** as a white solid (0.021g, 62%). M.pt. 60-62°C. ν_{max} (KBr)/ cm^{-1} 3392.7, 2937.1, 1587.9, 1491.5, 1123.4. HRMS: found 391.1410 (MH^+), requires ($C_{20}H_{22}O_8$) 390.1315. ^1H NMR δ_H ppm 3.61 (3H, s, OMe), 3.92 (3H, s, OMe), 3.93 (3H, s, OMe), 3.95 (3H, s, OMe), 4.09 (1H, m, CHOH), 4.48 (2H, m, OCH_2), 5.84 (2H, br, s, 2 x OH), 6.09 (1H, d, J 4.5Hz, C=CH), 6.30 (1H, s, ArH), 6.40 (2H, s, 2 x ArH). ^{13}C NMR δ_c ppm 55.86 (OMe), 60.64 (OMe), 60.75 (OMe), 61.36 (OMe), 69.75 (CHOH), 78.62 (OCH_2), 108.49 (2 x ArCH), 109.53 (ArCH), 124.85 (qC), 130.52 (C=CH), 133.68 (qC), 138.24 (qC), 139.25 (qC), 142.32 (qC), 144.67 (qC), 147.37 (qC), 147.90 (qC), 148.93 (2 x qC).

Synthesis of 5-(3-hydroxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-one (5.04) *via* the synthesis of 5-(3-[1-(*tert*-butyl)-1,1-dimethylsilyl]oxy-4-methoxyphenyl)-7,8,9-trimethoxy-2,3-dihydro-1-benzoxepin-3-one (5.18)

To a stirred solution of **(5.16)** (0.043g, 0.088 mmol) in DMF (1ml) was added PDC (0.066g, 0.175 mmol) portion-wise at 0°C. After 12 hours the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (4 x 5ml). The ether extracts were combined, dried over sodium sulphate and filtered before the filtrate was concentrated *in vacuo*. The residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(5.18)** as a white solid (0.017g, 55%). A solution of 1M TBAF (0.10ml, 0.103 mmol) was subsequently added to a stirred solution of **(5.18)** (0.05g,

0.103 mmol) in THF (1ml) at 0°C. After 2 hours, the reaction was quenched by the addition of water (5ml) and the product was extracted with diethyl ether (3 x 5ml). The ether extracts were combined, dried over sodium sulphate and filtered before being concentrated *in vacuo*. The resulting residue was purified by flash column chromatography (stationary phase; silica gel 230-400 mesh, mobile phase; 1:1 hexane/ethyl acetate). All homogenous fractions were collected and the solvent was evaporated off to afford **(5.04)** as a yellow solid (0.036g, 95%). M.pt. 150-152°C. HRMS: found 373.1310 (MH^+), requires ($C_{20}H_{20}O_7$) 372.1209. GCMS m/z (%) 372 (100), 329 (25). ν_{max} (KBr)/ cm^{-1} 3298.1, 2936.7, 1643.8, 1122.6. ^1H NMR δ_H ppm 3.64 (3H, s, OMe), 3.97 (3H, s, OMe), 3.99 (3H, s, OMe), 4.00 (3H, s, OMe), 4.63 (2H, m, 2 x H-2), 5.67 (1H, br, s, OH), 6.35 (1H, s, H-4), 6.45 (1H, s, H-6), 6.89 (2H, br, H-5', H-6'), 6.95 (1H, s, H-2'). ^{13}C NMR δ_c ppm 55.55 (OMe), 55.85 (OMe), 60.80 (OMe), 61.39 (OMe), 80.68 (C-2), 109.80 (C-6), 110.18 (C-5'), 115.10 (C-2'), 120.91 (C-6'), 125.66 (qC), 127.74 (C-4), 134.42 (qC), 134.62 (qC), 144.93 (qC), 147.10 (qC), 148.73 (qC), 151.32 (qC), 200.03 (C=O).

CHAPTER 7

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