Synthesis and Anticancer Activity of NDGA and Analogues

A Thesis submitted in part fulfilment of the requirements of the degree of Doctor of Philosophy

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Abbreviations

b.p.	Boiling point
br.	Broad (NMR spectroscopy)
CI	Cemical Ionisation
d	Day (s)
d	Doublet (NMR spectroscopy)
DCC	*N, N*-Dicyclohexylcarbodiimide
DCM	Dichloromethane
dd	Doublet of doublets (NMR spectroscopy)
dec.	Decomposed (m.p.)
DEPT	Distortionless Enhancement by Polarisation Transfer
DMAP	4-Dimethylamino pyridine
DMF	*N, N*-Dimethylformamide
DMSO	Dimethyl sulphoxide
EDCI	1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride
EI	Electron Impact
Et_2O	Diethylether
EtOAc	Ethyl acetate
EtOH	Ethanol
FAB	Fast Atom Bombardment
h	Hour (s)
IC_{50}	Concentration required to give 50% inhibition of function
IR	Infrared
lit.	Literature value
LRMS	Low Resolution Mass Spectrometry
m	Multiplet (NMR spectroscopy)
MeOH	Methanol
min	Minute (s)
ml	Millilitre (s)
mmol	Millimole (s)
m.p.	Melting point
q	Quartet (NMR spectroscopy)
Rf	Retention factor
rt	Room temperature
s	Singlet (NMR spectroscopy)
t	Triplet (NMR spectroscopy)
THF	Tetrahydrofuran

TLC	Thin layer chromatography

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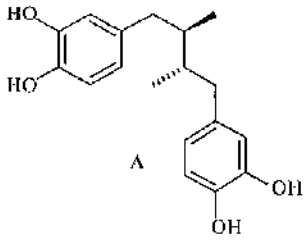
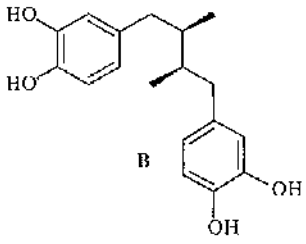
Summary

There is an urgent need to develop novel therapeutic strategies for common solid tumours including small cell lung cancer where the five year survival rate is less than 5%. The natural product nordihydroguaiaretic acid (NDGA) (**A**) has been shown to block the growth of small cell lung cancer *in vitro* and *in vivo*.

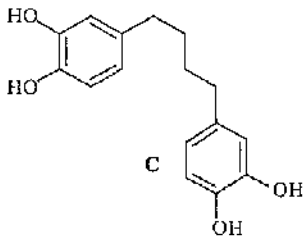


A

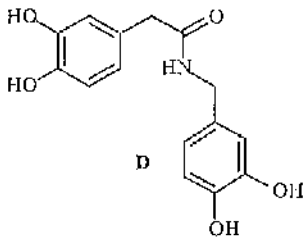


B

In order to realise the potential of NDGA as an effective anti-cancer agent we set up a collaboration with Dr. M. Seckl (Hammersmith Hospital) with the goal of producing a more potent analogue. Initially we concentrated on the synthesis of the racemate of NDGA (**B**) which would ascertain whether the stereochemistry of the methyl groups was important for activity. Our four step synthesis employed a pinacol coupling as the key step affording (**B**) in low overall yield. The preliminary test results showed (**B**) to be equipotent to NDGA suggesting that the stereochemistry of the methyl groups is not important for activity.



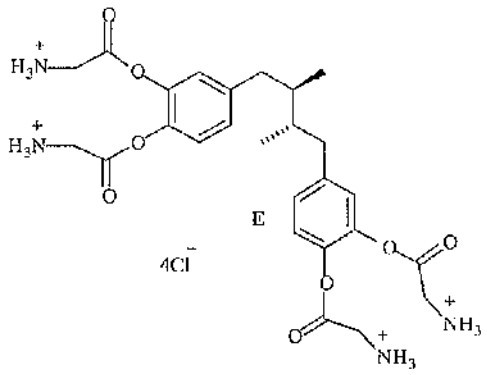
C



D

To help in the determination of structural activity relationships we synthesised a series of analogues of NDGA having different bridging distances between the aromatic nuclei. The synthesis of a series of mono phenolic compounds was also undertaken following the same procedures. The diarylbutane derivative (**C**) was found to be 10 fold more potent than NDGA *in vitro* suggesting that the methyl groups of (**A**) hindered its activity or that improved activity was due to decreased lipophilicity. A number of amide derivatives were also synthesised allowing access to more

conformationally restricted analogues. The test results showed that the secondary amide (**D**) was four times more potent than NDGA. However the corresponding *N*-Me derivative was less active.



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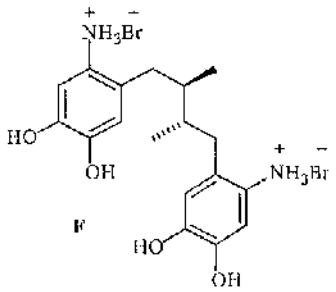


F

The poor aqueous solubility of NDGA has hampered its development as an effective anti-cancer agent. With this in mind, we have been working on the synthesis of a water soluble conjugate of NDGA which would release the active component over a period of time. The tetra glycyl salt (**E**) was synthesised. This is water soluble as expected but has slighty less activity than the parent compound. On the other hand, the ammonium salt (**F**) was found to be water soluble and twice as potent as NDGA and is currently undergoing *in vivo* testing.

1

Introduction

1.1 Cancer - What is it ?

The term cancer is derived from the Latin *cancer* and the Greek *karkinos* meaning crab and is so called as like a crab tumours have a central core and limbs through which the disease can spread throughout the body. Cancer is fundamentally a disease at the cellular level resulting in the uncontrolled cell proliferation of an abnormal cell which has broken free from the normal control mechanisms. A clear example of this is that a normal cultured cell will multiply only until a single layer has been formed whereas a cancer cell will continue to grow into a cell mass until the nutrients of the growth medium have been exhausted. Cancer cells are said to ignore density-dependent inhibition.

If a tumour remains at the original site, the lump is called a benign tumour. If untreated early the cancer cells can invade surrounding tissues, enter the circulation and set up secondary growths or metastases. The tumour is now termed malignant and an individual with a malignant tumour is said to have cancer. In time the involvement of vital organs and general debility will lead to patient death.

1.2 The Cancer Problem

In developed countries cancer is probably the most feared disease of our time. It has afflicted our ancestors throughout human evolution with Egyptian medical tracts reporting diseases recognisable as cancer as long as 3500 years ago. As a cause of mortality it is second only to cardiovascular disease in the Western world. It is a chilling fact that one third of us will develop cancer at some stage in our lives and of these one half will die as a result. In the United States alone one person dies every sixty two seconds from the disease.[1] Cancer can occur at all ages but becomes more prevalent as one grows older undoubtedly due to the increased exposure to cancer causing agents (carcinogens).

On a brighter note, the amount of patients surviving for more than five years after diagnosis has been on the increase since the turn of the century. By the 1930s only one fifth of patients survived over five years and by 1990 this figure had risen to 50%. Although the standard of cancer treatment is far from optimal there have been significant advances. These include the treatment of testicular cancer, Hodgkin's

disease and Wilm's tumour although unfortunately these cancer types account for a relatively low proportion compared to the major common types including breast, lung and prostate cancers.

1.3 Cell Division and The Cell Cycle

It was initially thought that DNA replication was a continual process between the period of cell division (mitosis) but early in the 1950s it became possible to carry out some labelling experiments using the labelled nitrogenous base thymidine. Even in rapidly proliferating cells this revealed a distinct gap during and after DNA formation and led to the discovery of the cell cycle. The process of mitosis is now a well defined sequence of events that can be conveniently represented as shown in **Figure 1**.[2] The cycle has four distinct phases and the time taken for one complete cycle, T_c, varies from one cell type to another (**Table 1**).[3] The T_c of a rapidly dividing duodenum cell is *ca.* 18 h whereas the cell cycle of a liver cell is greater than 10,000 h.

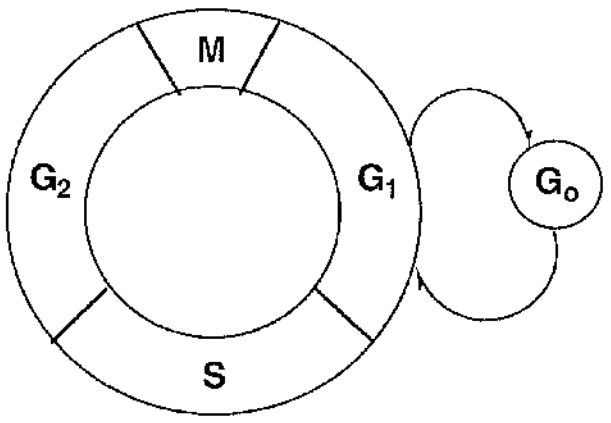
Table 1 - The duration of the cell cycle for a variety of cell types (Hours)

Cell type	T_c	G_1	S	G_2	M
Marrow	~ 13	2	8	2	0.7
Ileum	~ 17	6	8	2	0.7
Duodenum	~ 18	7	8	2	0.7
Colon	~ 33	22	8	2	0.7
Tongue	~ 40	28	8	2	0.7
Esophagus	~ 181	170	8	2	0.7
Skin	~ 1,000	989	8	2	0.7
Liver	> 10,000	> 9,989	8	2	0.7

The G_1 and G_2 phases of the cell cycle are concerned with the synthesis of RNA, proteins and cytoplasmic organelles required for DNA replication and cell division. In the S phase the cell duplicates its DNA and the cycle is completed when mitosis forms two identical daughter cells in the M phase. The two daughter cells can now either be commited to further mitosis or enter a resting phase G_0. The process of events is highly regulated and controlled; however, once the cell enters the S phase it normally proceeds through the rest of the cycle. For the majority of cells the duration of the S, G_2 and M phases tends to be fairly constant whatever the length of the cycle (**Table 1**) and the duration of the cycle seems to be controlled by the length of time spent in the resting G_0 phase. A rapidly proliferating cell will have a short G_1 period whereas a slowly reproducing liver cell has a G_1 period of more than 400 d.

It was initially thought that a tumour's growth arose from a complement of abnormal cells that proliferated at a higher rate than the surronding normal tissue. However, the average T_C of a human tumuor cell is 48 h and this, if anything, is fractionally longer than the T_C of a normal non-malignant cell type. If this was the only factor determining growth then the tumour would grow at the same rate or even slower than normal tissue and would pose little problem.

Figure 1 - The Cell Cycle



There are approximately 25 million cell divisions in the adult human every second and mistakes or malfunctions are very rare. Cells are constantly dividing to replace ones lost from injury or cell death to maintain a constant population but whereas normal cells remain in the G_1 phase until programmed to divide, a cancer cell has apparently lost this capacity and the control mechanisms that govern a normal cell are absent. This loss of control allows a tumour to continue growing and the normal mechanisms that control proliferation including the presence of growth factors, contact inhibition and programmed cell death (apoptosis) have little effect.

1.4 Cancer - The Causes

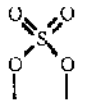
Tobacco smoking is the single largest cause of cancer and accounts for 30 % of all cancers and, including lung cancer, is responsible for cancers of the mouth, larynx, pancreas and kidney to name a few. The next most common cause of cancer concerns the way we live with risks associated with diet, alcohol use, sexual behaviour and exposure to sunlight. It is not surprising that high exposures to carcinogens whether it be through our occupational or social lives have been linked to human

cancers. Only 1-2 % of total cancers arise from inheritance although a high percentage of certain tumour types are genetically determined. Examples in this area include 40 % of retinoblastomas and 20-40 % of Wilm's tumours which are linked to a genetic predisposition. The following three sub-sections discuss the factors that lead to cancer in more detail.

1.4.1 Chemical Carcinogenesis

In 1762 John Hill noticed a high incidence of nasal cancer among tobacco snuff users. The English physician Percival Pott discovered in 1775 a link between scrotal cancer and the exposure of chimney sweeps to soot and tar over many years. It had also been recorded by 1900 that workers in the coal tar and pitch industries stood a higher chance of developing skin cancer. Subsequent animal experiments carried out by two Japanese researchers confirmed the link between coal tar and cancer.[4] Organic solvents such as benzene and toluene are present in coal tar along with phenols, cresols, naphthalenes and aniline dyes, many of which are now proven carcinogens.[5]

The feature common to the diverse range of chemical carcinogens is their ability to generate reactive electrophilic forms that can be attacked by the numerous nucleophilic sites on DNA. These carcinogens either need to be metabolised by a variety of enzymes prior to reaction or may react directly like dimethyl sulfate **1** and uracil mustard **2** which are intrinsically electrophilic.



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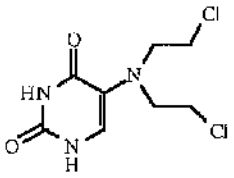


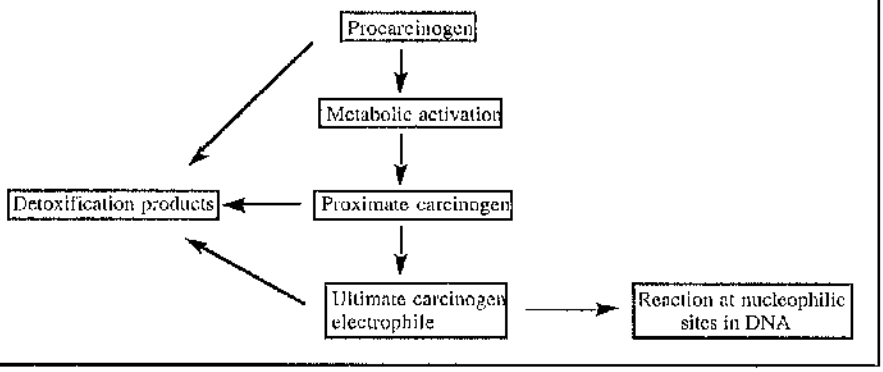
2

The activation of the parent or procarcinogen to the active (ultimate) form may proceed directly or go through a number of less reactive intermediates called proximate forms (**Figure 2**).[6] Detoxification products can also arise from this metabolism and are excreted from the body. The chief role of enzymes in these processes is to convert the foreign lipophilic agent into a more hydrophilic form that can be readily excreted and a consequence of this enzymatic manipulation can be the inadvertent production of a reactive product.

An example of such a process is shown in **Figure 3**[7] involving the polycyclic aromatic hydrocarbon (PAH) benzo[*a*]pyrene which is one of the carcinogens present in tobacco smoke. At first sight this compound looks unreactive but a series of enzymatic oxidation steps form the 7,8-dihydrodiol-9,10-epoxide which is the ultimate

electrophilic form. This in turn can react with the 2-amino group of guanine residues in DNA.

Figure 2 - The metabolic activation and detoxification of chemical carcinogens.



Initiation is the process whereby a cell is exposed to a limited dose of a carcinogenic substance but does not progress into a cancer cell without further alteration. Initiation is irreversible and an initiated cell can only be removed by DNA repair or cell death. An initiated cell may be converted into a cancer cell by a process called promotion which can arise from further exposure to the initiating agent or from an agent incapable of inducing a neoplastic transformation itself. A carcinogen that has the ability to both initiate and promote cancer is called a complete carcinogen.

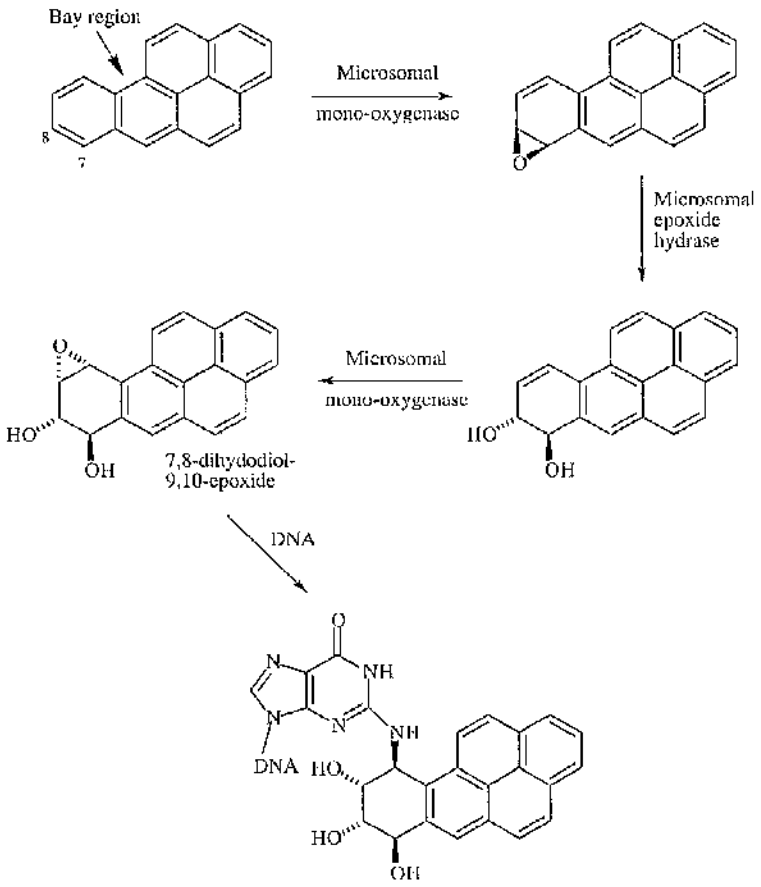
Tobacco smoke is a complex mixture of more than 6000 substances and approximately 50 of these are carcinogenic including a variety of PAHs, aromatic amines and nickel containing compounds. Although the Control of Substances Hazardous to Health act (COSHH) was introduced in 1989 seeking to minimise exposure to potentially dangerous chemicals there are carcinogens present in the air we breathe and the water we drink and although their concentrations are low they must be taken into account. Food and drink have long being attributed to causing cancer and an link between alcohol and cancers of the mouth, pharynx, larynx and oesophagus was discovered more than 50 years ago.[8] In summary, chemical carcinogens are widespread with the majority having been introduced into our environment by Man himself. Taking this into account the possibilities of drastically reducing the cancer problem by prevention of exposure are high.

1.4.2 Radiation Carcinogenesis

Humans are constantly being exposed to radiation from a variety of sources and it is an integral part of our environment. This radiation can be natural like cosmic

rays from outer space, ultraviolet rays from the sun and emissions from radioactive nuclei present in rocks and soil or it can arise from anthropogenic sources including medical X rays and industrial or military radioactivity. In addition to these an increase in our exposure to ultrahigh frequency soundwaves (ultrasound) may be linked to cancer.

Figure 3 - Metabolic activation of benzo[*a*]pyrene



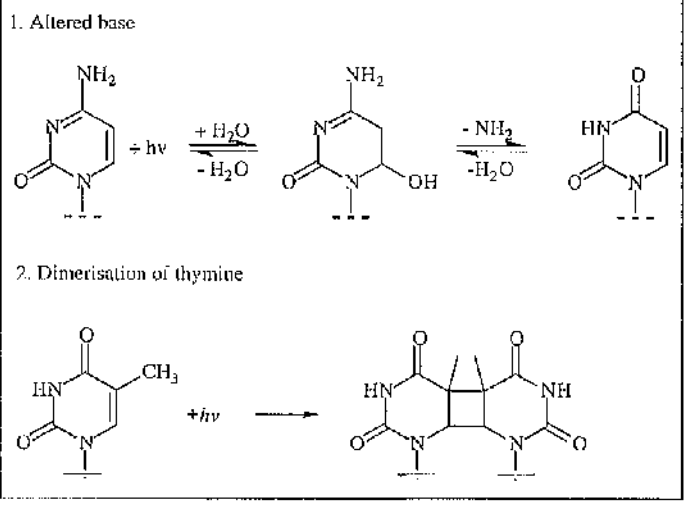
Solar Radiation and Cancer

Ultraviolet (UV) light is the primary source of skin cancer which is most prevalant for people living at tropical latitudes where the sun is at its most intense. Skin cancer is extremely common but rarely lethal due to non-melanoma type skin cancers being highly curable owing to their easy detection and slow metastasis. On the other hand melanoma is a much more serious form of skin cancer. Originating in pigment cells they are highly malignant and commonly metastasise long before recognition. Unfortunately the incidence of melanoma is on the increase throughout the world

probably due to increased sun bathing and tanning lamps and is responsible for perhaps 1-2% of cancer mortality in the United States.

UV light is absorbed by DNA and readily induces mutations by transforming molecules into a short-lived excited state that renders them chemically reactive. For example, excitation of pyrimidine bases (thymine or cytosine) allows them to either react with water thus forming pyrimidine hydrates or dimerise to give a chemically stable cyclobutane type linkage (**Figure 4**).[9] The hydrated base can then eliminate water to give either the original pyrimidine or in the case of cytosine a deaminated derivative, in this case uracil. Interaction with the excited pyrimidine with other molecules including amino acids and proteins can give rise to DNA-protein cross links which could also explain the potent effects of UV radiation.

Figure 4 - Interaction of UV light with bases.



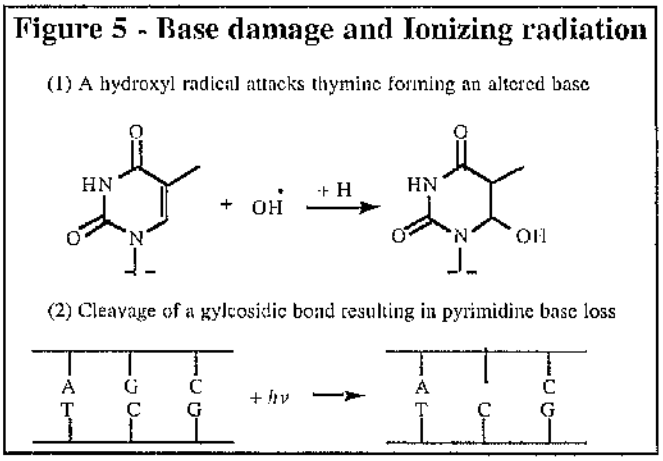
Ionising Radiation and Cancer

Ionising radiation is of a higher energy than UV and includes X rays and radiation arising from the radioactive decay of radioactive nuclei. This increased energy has the ability to break chemical bonds and cause genetic mutations within the DNA sequence. The first cancers resulting from exposure to X rays were observed only seven years after their discovery by Roentgen in 1895. Radiologists who used X rays extensively in the early 1900s had a three to four fold increased chance of developing leukaemia. Subsequent animal experiments revealed the induction of sarcomas in laboratory animals after radiation exposure.[10]

As a cell is composed of 80% water, ionisation results in water fragmentation giving rise to three reactive species namely the hydroxyl radical (OH°), the solvated electron and the hydrogen radical (H°). The radicals are short lived and readily dimerise to give hydrogen peroxide and hydrogen respectively; however they can

damage a cell's DNA. (**Figure 5**).[10] This damage can lead to base alteration or loss and attack on the sugar phosphate backbone which can lead to single or double DNA strand breaks.

Figure 5 - Base damage and Ionizing radiation



Radioactive elements

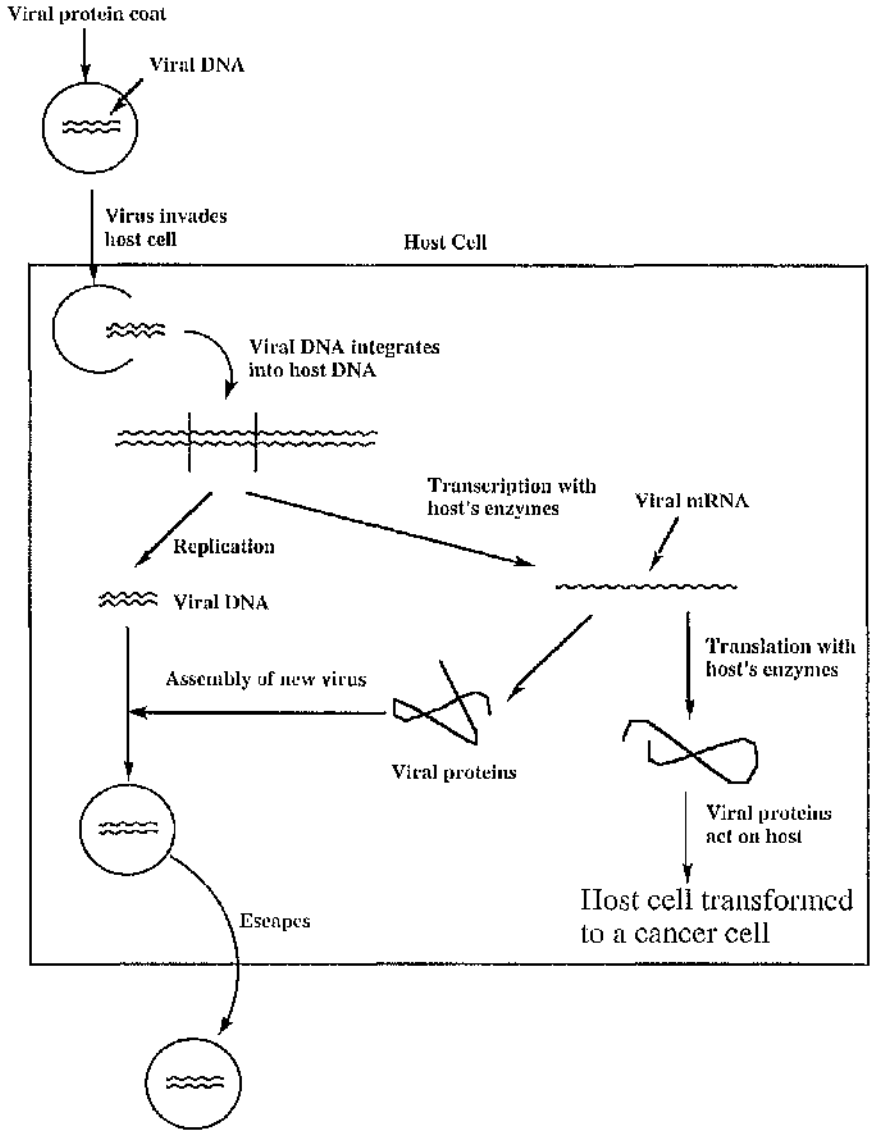
Radioactive elements are known to emit similar forms of radiation as X rays and their carcinogenic nature was known long before X rays were fully understood. Marie Curie who codiscovered the radioactive elements polonium and radium died from an anaemia undoubtedly resulting from her close association with these metals. Another example of radium carcinogenesis was observed in the 1930s when a group of young women developed bone cancer after ingesting radium from paint by licking brushes used to paint watch and clock dials. An increased risk for persons surviving the atomic bombs dropped during World War II over Hiroshima and Nagasaki is well documented.

1.4.3 Viruses and Cancer

Viruses are responsible for a number of disease types including cold sores, influenza, hepatitis and mumps. They are intracellular parasites which invade suitable host cells and use their cellular machinery to reproduce. Unlike the other disease causing viruses, cancer causing (oncogenic) viruses do not kill their host cell but alter their genetic program controlling differentiation and reproduction resulting in the onset of cancer. Structurally a virus is composed of one or a few tightly coiled nucleic acid molecules surrounded by a protein capsule. The nucleic acids within these proteins can be DNA or RNA although their mode of action is similar. On entry into the host cell the protein coat disappears, the nucleic acid is released into the cytoplasm and can become incorporated into the host's DNA now being part of its genetic makeup. After incorporation, some of the viral genes continue to be active and are copied into mRNA

molecules which in turn are translated into viral proteins. Some of these are able to change the activities of the infected cell so it becomes transformed or cancerous. Furthermore, these viral proteins can become incorporated into new viral particles able to leave and infect surrounding cells (**Figure 6**).[11] Oncogenic RNA viruses behave in a similiar fashion although on entry to the host cell the viral RNA must make a DNA copy of itself utilising the enzyme reverse transcriptase.

Figure 6 - Events in the life of a oncogenic DNA virus



There are four types of virus directly associated with human cancer (**Table 2**).[12] Unlike EBV and HTLV which are relatively uncommon, HBV induced hepatocellular carcinoma and HPV induced cervical carcinoma may account for 10-20% of overall cancer incidence. HIV also indirectly causes a high frequency of

Kaposi's sarcoma mainly attributed to the immunodeficiency suffered by the AIDS patient. It is suggested that worldwide viruses may account for 25% of the 80% of cancers derived from environmental factors.

Table 2 - Viruses Associated with Human Cancers	
Virus	**Type of Cancer**
Hepatitis B virus (HBV)	Hepatocellular carcinoma
Human papilloma viruses (HPV)	Cervical and other anogenital carcinomas, squamous cell skin carcinomas
Epstein-Barr virus (EBV)	Burkitt's and other B-cell lymphomas, nasopharyngeal carcinaoma
Human T-cell lymphotropic virus (HTLV-1)	Adult T-cell leukaemia
Human immunodeficiency virus (HIV)	Lymphomas, Kaposi's sarcoma, anogenital carcinomas

1.5 Cancer Treatment

Once a patient has been diagnosed with cancer the choice of treatment is dependent on the type of cancer and how far it has progressed. In most types of cancer the likelihood of a cure is dependent on early detection of the disease and before it has had time to spread. The unfortunate outcome common to the majority of cancers is that by the time of diagnosis the disease has already metastasised. The following sections survey the main methods available for cancer treatment today.

1.5.1 Surgery

Cancer surgery, which is known to date back to the ancient Greeks who amputated cancerous breasts, has evolved along with general surgery becoming safe and effective during this century with the aid of anaesthetics, antibiotics and blood transfusions. Although surgery can be an effective treatment with localised cancer cells, about 70% of cancers by the time of detection have metastasised and cannot be cured by surgery alone. Nonmelanoma skin cancers, which do not readily metastasise, along with easily accessible cancers of the uterine cervix can be surgically removed and offer a high cure rate. Some benign tumours are only life threatening due to occupying inoperable locations, such as some brain tumours. Once the cancer has metastasised it becomes difficult to be sure that all the cancer cells have been eliminated by surgery.

With this in mind, removal of an area of tissue, perhaps including regional lymph nodes which may be infected, is often undertaken in an attempt to eliminate all of the cancer cells.

Although surgery is a local treatment and is not totally effective in the majority of cases it does have its benefits. The removal of tumour specimens along with regional lymph nodes can play an important role in determining how far the cancer has progressed thus giving a valuable insight into the optimal therapy that should be administered. Even in advanced cases with a terminally ill patient removal of a tumour mass may significantly reduce pain and allow a greater quality of life. The combination of surgery along with other modalities (adjuvant therapy) such as those described below is the most common form of treatment today.

1.5.2 Radiation

Radiation therapy is similar to surgery being a local treatment although able to penetrate to areas of infected tissue inoperable by surgical procedures. It is therefore common for radiation therapy to be used in combination with surgery to eradicate cancer cells that have infected surrounding tissue outwith the main tumour mass. An example of this is in early breast cancer where routinely, surgical removal of the primary tumour and nearby lymph nodes is followed by radiation to kill remaining tumour cells.

Both X rays and radioactive nuclei, such as cobalt-60, are used in radiation therapy with their role being to damage DNA directly or by the production of free radicals within cells. This damage is most pronounced in rapidly proliferating cells but unfortunately, this includes cancer cells and some normal tissue cells. The sensitivity of some cells, such as blood-forming cells, the epethial cells that line the intestine, the cells that form hair and the cells of the reproductive organs, are responsible for some of the side effects of radiation therapy including anaemia, diarrhoea, hair loss and sterility. Radiation however is sometimes preferred over surgery for treatment of local tumours. An example is laryngeal cancer which can effectively be treated by radiation whereas surgery would remove the vocal chords resulting in speech loss. Similarly areas that are difficult to operate on, such as the eyelid and tip of the nose, may be effectively treated by radiation.

In summary, radiation can extend the benefits of treatment offered by surgery in that it can penetrate further and kill cells in surrounding tissue that can not be reached by surgery. Radiation therapy selectively targets rapidly proliferating cells but includes some normal cells resulting in unpleasant side effects. The major drawback of the two therapies described above is that if a tumour has metastasised it can no longer be treated by local means and the use of chemotherapy to combat this is required.

1.5.3 Chemotherapy

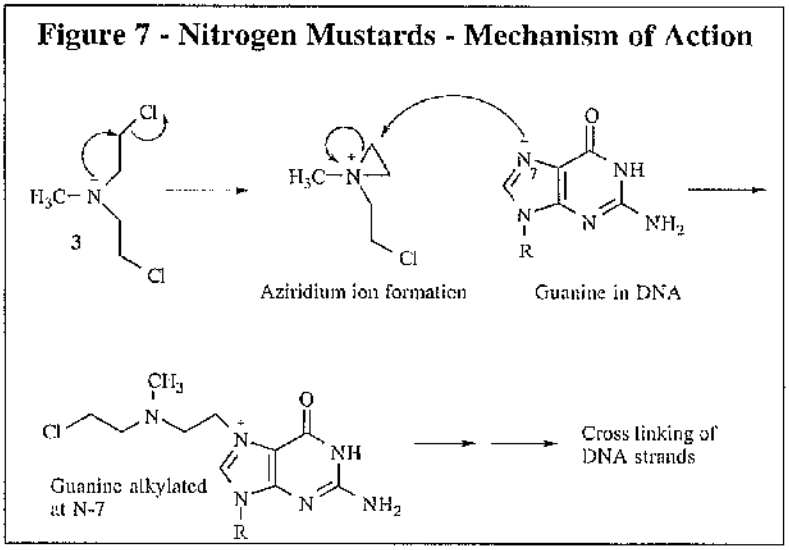
The third major strategy in the fight against cancer is the use of chemotherapy. The majority of chemotherapeutic agents exert their activity by damaging DNA or by interfering with cell division. The major advantage of chemotherapy is that, unlike surgery and radiation which are localised treatments, it can target metastatic growths throughout the body. Unfortunately, like radiation therapy, the drugs used are not specific in targeting only cancer cells and the attack on normal rapidly proliferating cells results in the same undesirable side effects. It is also possible that some cells within the tumour may become resistant to the particular drug as a result of a mutation. Although this is very rare, averaging only once in a million cells, a typical tumour is composed of billions of cells and it is conceivable that a mutation may occur allowing a single cell and its descendants to continue growing. Another problem facing chemotherapy is that some agents are carcinogenic themselves and the result of their use could be the development of another cancer at a later date. In spite of these problems chemotherapeutic agents are used widely in medicine today and the major classes including their mechanism of action are described in the following sections.

1.5.3.1 Nitrogen Mustards

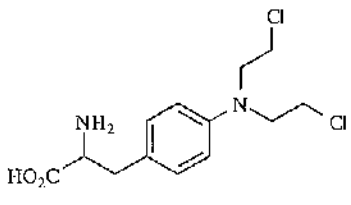
The First World War saw the use of mustard gas (sulfur mustard) as a weapon used in trench warfare. It was later noticed that casualties suffered a distinct drop in their white blood cell count along with damage to both their bone marrow and lymphatic system. This observation posed the question that if this was the outcome in healthy subjects could it be used to treat those suffering from cancer and so led to the first study of cytotoxic agents in the early to mid 1940s. The agents tested were the nitrogen mustards which, although structurally resembling their sulfur counterparts, were considerably less irritant to normal tissue. Over the following twenty years more than three thousand agents were evaluated for testing and of these only about a dozen are in clinical use today.

Mechloroethamine **3** is a typical example of such a nitrogen mustard and its mechanism of action is shown in **Figure 7**.[13] The formation of the highly reactive and electrophilic aziridinium ion is followed by reaction with a nucleophilic site on DNA. Formation of these covalent bonds is most common at the N-7 position of the purine base guanine. The distance between the two alkyl groups is such that the second chloroethyl group can react in a similiar fashion with a second guanine base on a complimentary DNA strand. The process is known as cross linking and prevents the DNA strands from separating at the time of DNA replication.

Figure 7 - Nitrogen Mustards - Mechanism of Action



Due to its severe toxicity and rapid action mechloroethamine **3** is not very clinically useful and is now confined for treatment of Hodgkin's disease and other lymphomas. Its rapid mode of action is exploited in the use of mechloroethamine in clinical emergencies such as superior vena cava obstruction by carcinoma of the bronchus.



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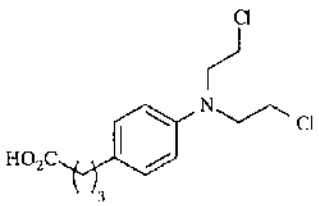

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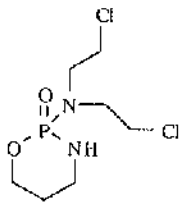

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In an attempt to solve these problems the mustards melphalan **4** and chlorambucil **5** were synthesised in the UK in 1953. The rate of alkylation is considerably slower in these mustards as the nitrogen lone pair is delocalised into the ring system. This decreased activity allows time for absorption and distribution before extensive alkylation occurs and these drugs can be given orally unlike mechlorethamine which is administered intravenously. It was hoped that melphalan which closely resembles the amino acid phenylalanine would become concentrated in dividing cells where it could exert its activity. There is, however, no evidence suggesting this to be the case. It is however clinically useful for multiple myeloma and ovarian cancer whereas chlorambucil is used in the treatment of chronic lymphocytic leukaemia.

Cyclophosphamide **6** evolved as it was known that high concentrations of phosphoamidases were located in tumour cells. It was hypothesised that the drug

would remain inert until reaching the tumour site where it could be activated by a variety of enzymes. Experiments proved this not to be the case and initial metabolism in the liver was required prior to activity. A toxicity unique to cyclophosphamide is haemorrhagic cystitis due to excretion of the metabolites acrolein and 4-hydroxyphosphamide which have an irritant effect on the bladder mucosa. It has however proved to be one of the most successful nitrogen mustards being used in a large variety of cancers including carcinoma of the breast and carcinoma of the bronchus.

1.5.3.2 Nitrosoureas

This family of chemotherapeutic agents arose from the American National Cancer Institute's drug development programme. The three most important drugs are bischloroethylnitrosourea (BCNU) **7**, cyclohexylchloroethylnitrosourea (CCNU) **8** and methyl-cyclohexylchloroethylnitrosourea (methyl-CCNU) **9**. The mechanism of action of these drugs is not as clearly understood as the nitrogen mustards. Although the alkylating action of these drugs is thought to be the major cytotoxic action, inhibition of DNA polymerase prevents the repair of DNA strand breaks and RNA synthesis. **Figure 8** outlines the mechanisms associated with the activity of nitrosoureas.[14] An important aspect common to the nitrosoureas, even those with only one chloroethyl moiety, is their ability to form interstrand cross-links in DNA. Chloroethylation is followed by the slow loss of chloride ion resulting in a second alkylation of a base in a complimentary strand.

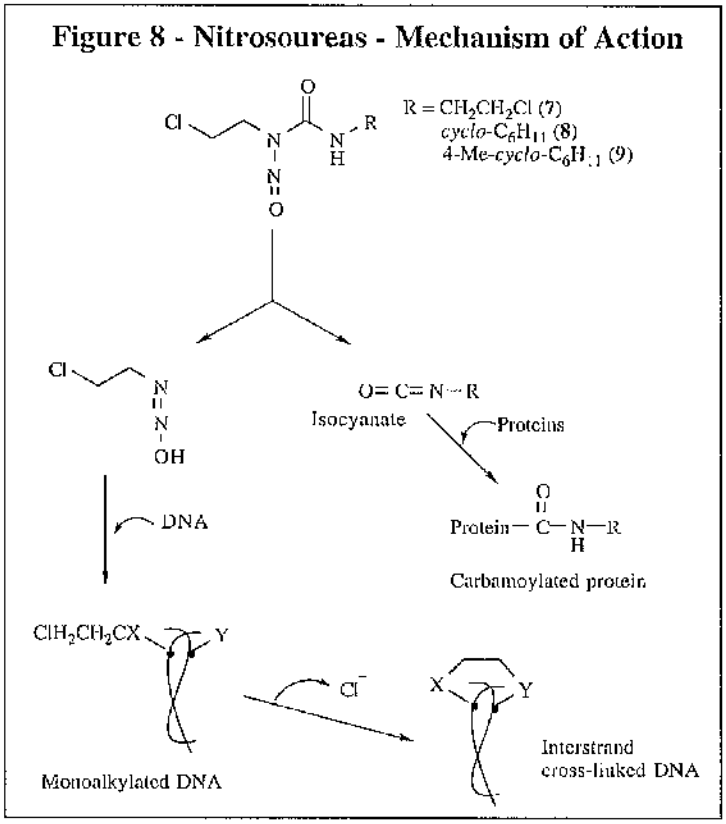
Due to the lipophilicity of these agents, their ability to cross the blood-brain barrier has resulted in their use to treat cerebral tumours. They have also been used in the treatment of gastrointestinal adenocarcinoma, lung cancer and lymphoma but only in the last case have they been used regularly. A major side effect of the nitrosoureas is dose-related delayed bone marrow toxicity with the onset not appearing until four to six weeks after dosing. As a consequence of this the drug is given in a single dose and a second course is not administered for six weeks. Other common side effects include gastrointestinal disturbance leading to nausea and vomiting along with renal and hepatic damage.

1.5.3.3 Other Alkylating Agents

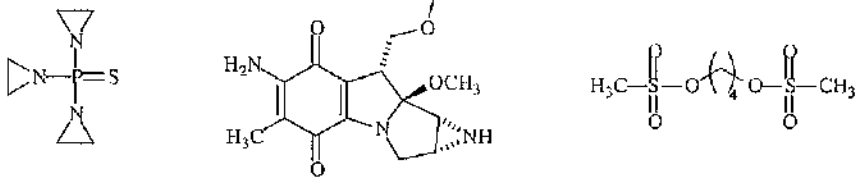
The aziridines are a group of agents that closely resemble the aziridium ion formed from the nitrogen mustards (Figure 7). Examples include thiotepa **10** and mitomycin (mitomycin C) **11** with the latter isolated from *Streptomyces* species. Their

mechanism of action is similar to the mustards although, as the aziridine moieties are not charged, they are more reactive at an acid pH.

Figure 8 - Nitrosoureas - Mechanism of Action



Thiotepa is rarely administered systematically due to bone marrow depression although it is administered topically to treat papillary carcinoma of the bladder. Mitomycin, which is activated by quinone reduction, is a DNA cross-linker. The aziridine and carbamate groups are the sites of alkylation and are activated after quinone reduction by elimination of methanol.



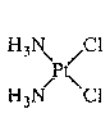
10 11 12

Mitomycin has shown activity against a variety of tumour types including cancers of the stomach, lung and breast. The major side effect is delayed, cumulative myelosuppression.

The alkane sulfonates, such as busulfan **12**, are bifunctional alkylating agents through cleavage of the alkyl-oxy bonds giving rise to an interstrand cross-link. Its major activity is in the management of chronic myeloid (granulocyte) leukaemia with the principal side effects derived for bone marrow suppression.

1.5.3.4 Non Classical Alkylating Agents

The potential of using platinum compounds came from the work of Rosenberg and co-workers who demonstrated that certain transition metal complexes could inhibit bacterial division under the effects of an electric field.[15] They discovered that it was actually electrolysis products from the platinum electrode that were causing this inhibition and in 1970 they demonstrated the efficacy of several platinum complexes against certain tumour types in mice.



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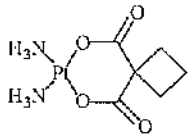

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Although a number of platinum complexes were shown to be active experimentally, cisplatin **13** and carboplatin **14** are the only two approved for clinical use. The complexes that show anti-tumour activity all contain chloride, bromide or malonate leaving groups and not groups, such as nitrate, which are too labile and would be useless *in vivo*. Another observation is that since the *trans*-isomers tested were all ineffective, the *cis*-configuration is needed for activity but the reasons for this are not known. Unlike other alkylating agents, the complexes interact with DNA causing intrastrand links predominately between the *N*-7 atoms of neighbouring guanines. This results in a distortion of the DNA chain and is sufficient to inhibit DNA synthesis.

Cisplatin is one of the most frequently used anti-cancer drugs, frequently in combination therapy with other drugs, and treats a variety of tumour types, most notably testes, lung and bladder. Major toxic effects include nephrotoxicity, peripheral neuropathy and ototoxicity with nephrotoxicity being dose-limiting. Cisplatin is regularly administered in combination with sulfur containing compounds, such as thiosulfate, which do not readily penetrate cells but are excreted by the kidney where they can react with any residual drug. Carboplatin was introduced in an attempt to lower the side effects arising from the use of cisplatin. Although it exhibited the same spectrum of activity and significantly reduced the side effects, its dose-limiting toxicity was myelosuppression. Its use is thus confined as an alternative to cisplatin in patients

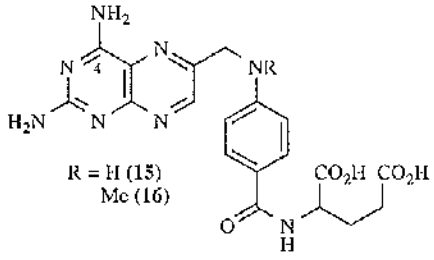
who have pre-existing renal dysfunction or patients with a clear disposition for neurotoxicity or ototoxicity.

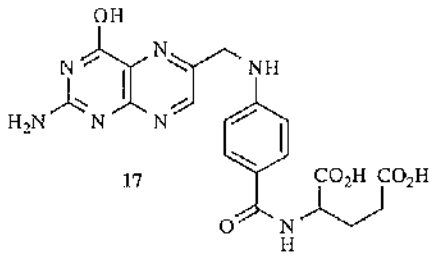
1.5.3.5 Antimetabolites

The first clinical tests of antimetabolites were carried out by Farber and co-workers in 1948 and were the second generation of anti-cancer drugs to be discovered. In preparation for cell division, a cell must build up a complement of nucleic acids and proteins and the antimetabolites interfere with this by either of the following pathways. Some of the drugs prevent the syntheses of DNA by poisoning the enzymes required to synthesise the nucleotide building blocks of DNA. This occurs during the S period of the cell cycle (Figure 1) and cells that cannot complete the cycle will ultimately die. Alternatively, some antimetabolites are so similar in structure to normal purines and pyrimidines they are able to compete for places in the nucleotide pathway. Although many antimetabolites have been evaluated for anti-cancer activity, only a handful are in clinical use today. The principal toxicities attributed to all these agents is myelosuppression and gastrointestinal disturbances.

Methotrexate

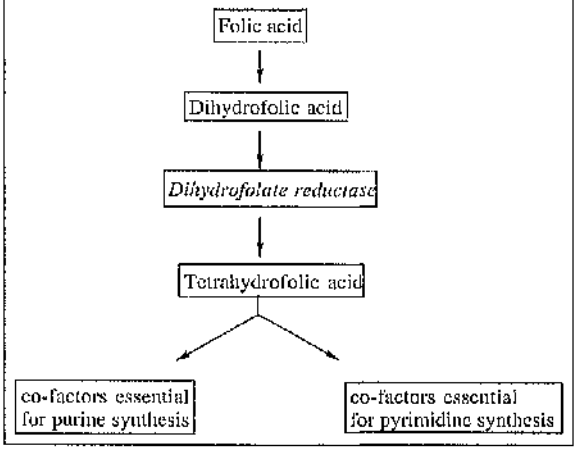
In an attempt to lower the side effects of aminopterin **15**, methotrexate **16** was introduced after the pioneering work of Faber *et al.*[16] proving to be equipotent but less toxic. The vitamin folic acid **17** plays a pivotal role in the synthesis of purine and pyrimidine nucleotides needed for the biosynthesis of DNA. To perform its function as a coenzyme, folic acid must be reduced in two successive steps utilising the enzyme dihydrofolate reductase (DHFR). It is this final reduced form that can transfer single carbon units in a variety of metabolic processes (**Figure 9**).[17]





As methotrexate is similar in structure to folic acid its efficacy as an anti-cancer agent is attributed to folate antagonism. In addition, substitution of the 4-hydroxyl group of folic acid with the amino moiety results in a 100,000 times greater affinity for DHFR. The methotrexate-DHFR complex is almost inseparable once formed leading to enzyme inactivation resulting in the arrest of purine and pyrimidine biosynthesis.

Figure 9 - Dihydrofolate reductase in folic acid metabolism

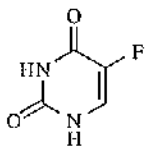


Methotrexate has been used to treat a variety of diseases, achieving its greatest success in the treatment of choriocarcinoma, a highly malignant cancer that arises from the placenta during pregnancy, with a high percentage of women cured. It was first used in the treatment of acute leukaemia and is also used in combination with other drugs for the adjuvant therapy of breast cancer. It has also found value in the treatment of some solid tumours and is particularly active against squamous cell carcinomas.

5-Fluorouracil

The development of 5-flurouracil as an anti-cancer agent arose from the observation in 1954 that the uptake of uracil in rats with chemically induced hepatomas was greater than that of normal cells. This suggested a distinct difference in the biochemistry of these two cell types which could be exploited to target tumour cells selectively. 5-Fluorouracil **18**, which is structurally very similar to uracil **19**, can inhibit cell division in the following two ways. Firstly, the enzyme thymidilate synthetase, which converts deoxyuridilic acid to thymidilic acid, plays an important role in pyrimidine synthesis. 5-Fluorouracil is known to block this enzyme preventing their formation therefore arresting the production of DNA. Secondly as a consequence of the structural similarity of 5-fluorouracil with uracil, it can become incorporated into RNA in place of uracil affecting RNA maturation and processing adversely.

5-Fluorouracil has found extensive use in the treatment of a variety of solid tumours most notably the adenocarcinomas of the gastrointestinal tract and breast cancer. It is commonly administered in combination with other agents some of which are not toxic but are known to modulate the effects of 5-flurouracil.



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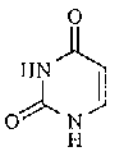

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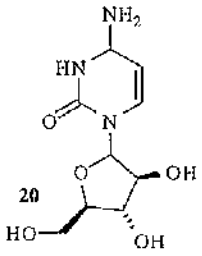

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Cytosine Arabinoside

Cytosine arabinoside (ara-C) **20** is metabolised to its triphosphate prior to exerting its activity. It is a competitive inhibitor of the enzyme DNA polymerase, required for the binding of thymine to DNA during reproduction, resulting in the inhibition of DNA formation and repair. Ara-C can also become incorporated into the DNA chain making it more likely to degrade and prevent replication.

Ara-C is particularly useful for the treatment of myelogenous leukaemia but has found no clinical use against solid tumours. The dose-limiting toxicity is neurological disorders which are most common in older patients.

Purine antagonists

This class of chemotherapeutic agents, such as 6-mercaptopurine and 6-thioguanine, exert their activity by firstly undergoing an enzymatic conversion into their active forms then inhibiting a number of enzymes utilised in the early stages of purine biosynthesis. The net result is that the synthesis of DNA is inhibited due to a lack of the purine bases adenine and guanine. The major clinical use of these agents is in the treatment of leukaemia and in particular acute lymphatic leukaemia.

1.5.3.6 Noncovalent DNA-Binding Drugs

Anthracyclines

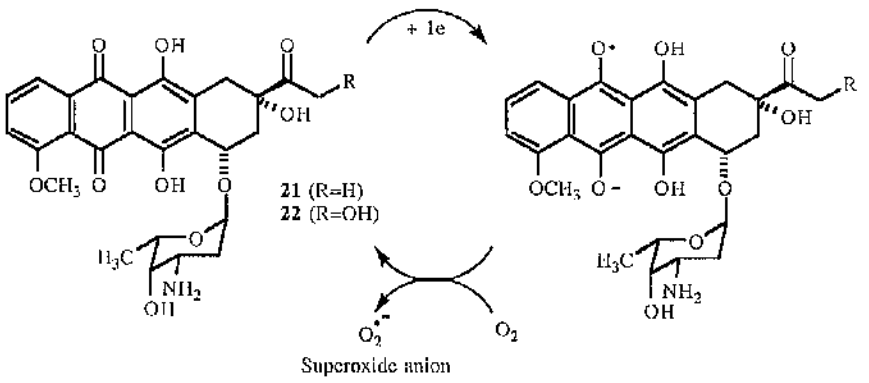
The anthracycline antibiotics were initially studied in the late 1950s being isolated from a variety of strains of *Streptomyces*. Daunorubicin **21** was discovered in 1963 and its potent antileukaemic activity sparked a rush to discover other anthracyclines with doxorubicin **22** isolated in 1969. Structurally these compounds have a four ring structure linked, *via* a glycosidic bond, to the amino sugar daunosamine.

The exact mechanism of the activity of these compounds is not clear but is due partly to intercalation. The molecular structure of the anthracyclines allows the planar ring system to insert between the hydrophobic faces of the base pairs in DNA causing a local unwinding of the helix. This intercalation interferes with the activity of the

enzyme Topoisomerase II which can result in protein-linked double strand breaks. As a result of DNA being twisted extensively, enzymes called Topoisomerases are required to untwist certain regions for processes such as transcription, replication and other essential functions. They are able to break the DNA strands, allow the necessary processes to take place and then reseal the breaks. The enzymes are divided into two classes type-I and type-II enzymes which break one strand and two strands of the DNA double helix respectively.

In addition to intercalation, the cytotoxicity of the anthracyclines is due to the formation of free radicals which predominantly cause single strand breaks. The quinone moiety common to the anthracyclines can undergo a one or two electron reduction, utilising a variety of quinone reductases, resulting in the formation of superoxide (**Figure 10**).[18] This superoxide can dismutate forming hydrogen peroxide which in combination with an iron chelated drug complex can form hydroxyl radicals. The cardiotoxicity shown by these drugs is directly attributed to this free radical formation.

Figure 10 - Superoxide anion formation



Doxorubicin has a wide range of activity against a variety of solid tumours including carcinoma of the breast and lung. Daunorubicin is of limited clinical usefulness and mainly used for the treatment of acute myelogenous leukaemia. In addition to cardiotoxicity, both cause severe bone marrow suppression, nausea, vomiting and alopaecia.

Non-anthracycline Antibiotics

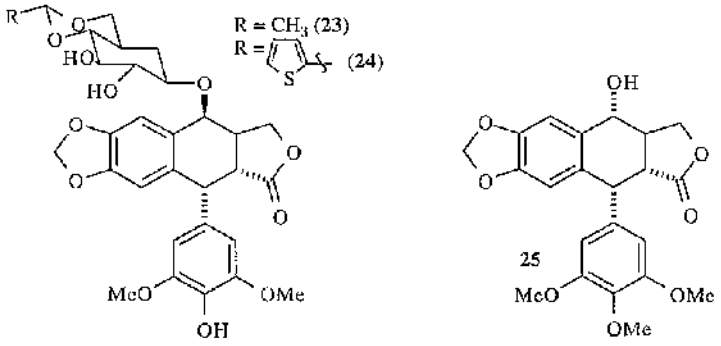
Mitoxantrone belongs to the anthracenedione class of chemotherapeutic agents and, although maintaining the planar polyclic aromatic ring system needed for intercalation, does not contain the sugar moiety. Interestingly, due to an apparent inability to generate free radicals, it does not possess the cardiotoxicity of the

anthracyclines. It is however of less clinical use than doxorubicin although used in the treatment of leukaemias and lymphomas along with advanced breast cancer.

Other examples include actinomycin-D, the bleomycins and mithramycin isolated from a variety of fungi. These agents, which have complex structures, appear to inhibit tumour growth by a variety of pathways including intercalation and free radical formation causing single and double strand breaks. They are used for a number of cancers including paediatric tumours, choriocarcinomas, soft tissue sarcomas, testicular teratomas and lymphomas. Myelosuppression and gastrointestinal disturbances are the major side effects excluding the bleomycins which shows little or no myelosuppression with the major side effect being pulmonary toxicity.

1.5.3.7 Topoisomerase II Inhibitors

As mentioned earlier, Topoisomerase II is an enzyme is used to break DNA strands temporarily allowing vital processes such as replication to occur before resealing the double helix. Etoposide **23** and teniposide **24** are semisynthetic derivatives of the naturally occurring lignan podophyllotoxin **25**, itself a microtubule inhibitor. It was expected that etoposide would inhibit microtubule function also but, as with teniposide, its major activity arises from Topoisomerase II inhibition.[19]



When the Topoisomerase II first associates with DNA a non covalent complex is formed termed noncleavable, as removal of the enzyme at this point would result in no strand breaks. Only when the enzyme has cleaved the DNA strands is the complex cleavable as removal of the enzyme would result in a permanent double strand break. This complex is however short lived, in the absence of inhibitors, and after a topological change has been effected the breaks are resealed with subsequent release of the free enzyme. Etoposide is known to stabilise this cleavable complex thus preventing processes such as replication and ultimately regeneration of the DNA and free enzyme. As a result of the longer lifetime of the cleavable complex, the drug-complex may then undergo spontaneous denaturation resulting in permanent double-strand breaks at vital

sites leading to cell death. In addition inactivation of the protein kinase p34, which plays an important role in the G_2 phase of the cell cycle prior to mitosis, may account for the efficacy of these agents.[20] It is thought that the observed arrest of cells in the G_2 phase, after treatment with etoposide, may be attributed to inhibition of the p34 kinase.

Etoposide has found clinical use towards a variety of tumour types most notably testicular cancer and has a role to play in the management of small cell lung cancer. The major clinical uses of teniposide are in the treatment of lymphocytic leukaemia, neuroblastomas in children and brain tumours in adults with the major toxicity of both these agents being due to myelosuppression.

1.5.3.8 Microtubule Inhibitors

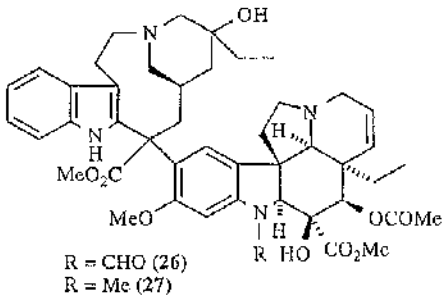
The Vinca Alkaloids

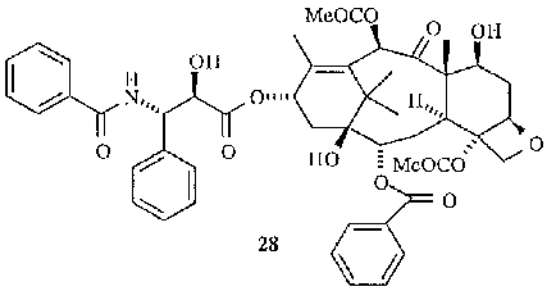
Microtubules are involved in a variety of cellular functions including mitosis, transport of solutes, cell movement and maintaining the structure of the cell. They are composed of the protein tubulin and exist in an equilibrium between free tubulin dimers and assembled polymers. An integral part of mitosis is the polymerisation of tubulin dimers to form microtubules. These then align themselves at opposite poles of the cell and pull apart the two sister chromatids of the chromosome prior to cytoplasmic division (cytokinesis).

The Vinca alkaloids vincristine **26** and vinblastine **27** were isolated from the Madagascan periwinkle plant *Catharanthus roseus*. Their antitumour activity, discovered about thirty years ago, arises from their ability to bind to free tubulin dimers. A consequence of this binding is the disruption in the equilibrium between microtubule polymerisation and depolymerisation. The concentration of free dimers available for polymerisation is significantly reduced resulting in a shift of equilibrium towards disassembly and arrest of cells during mitosis.

Vincristrine has proved useful in the management of leukaemias and lymphomas and for the adjuvant therapy of some solid tumours, particularly breast cancer. It shows little myelosuppression with its major toxicity being neurotoxicity. Vinblastine has found clinical use in the treatment of Hodgkin's disease although it is significantly more myelosuppressive than vincristine which is its dose limiting factor. Taxol **28**, unlike the other microtubule antagonists, is known to disrupt the equilibrium in favour of the assembled microtubules. As a result of Taxol treatment, the microtubules are stabilised and conditions that normally cause their disassembly, such as a high concentration of calcium, are less successful leading to an abnormal bundle

of microtubules. In addition, stabilisation results in a lower concentration of free tubulin dimers required for polymerisation.





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The development of Taxol as a clinical agent has been hampered by a lack of suitable material. Until recently the major source of Taxol was from the bark of the slow growing yew *Taxus brevifolia*[21], but it can now be accessed semi-synthetically from the analogue 10-deacetyl baccatin III itself isolated from the needles of a related tree. As a result of its potential clinical value, its total synthesis has been reported by the groups of Holton[22], Nicolaou[23], Danishefsky[24] and Mukaiyama[25].

Although still in early clinical development, Taxol has been used to treat refractory ovarian cancer and was approved for the treatment of breast cancer in 1994. The dose-limiting toxicity for Taxol is neutropenia although other major side effects due to hypersensitivity, such as breathing difficulties and hypotension, are common. As a result of this the search for analogues showing reduced toxicity and increased water solubility has been reported.[26]

1.5.3.9 Hormone Therapy

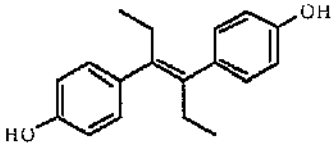
The use of chemotherapeutic agents in this area arose from the observation that certain tumour types, originating from hormone responsive tissues, maintain their sensitivity to hormones and can be selectively targeted. The most common cancers that are activated by hormones are those arising from sexually differentiated tissues, such as breast, endometrium and the prostate. Their growth and function is maintained by the continual supply of sex hormones, steroidal substances produced predominantly in the ovaries of females and the testes of males.

The production of sex hormones is a highly regulated pathway originating in the brain where the production of Gonadotrophin Releasing Hormone (GnRH) effects the release of a second hormone, Leuteinising Hormone (LH) from the anterior pituitary gland. This in turn stimulates estrogen production and the synthesis of androgens, such as testosterone in the testes of males. These hormones are able to regulate their own concentration by inhibiting the production of GnRH and LH by a

process known as negative feedback. There is a variety of ways in which hormone therapy can treat cancers by interfering with this pathway and they are discussed below for two specific examples, prostate and breast cancer.

Prostate Cancer

The incidence of prostate cancer in men is second only to lung cancer. The use of hormone therapy developed after the pioneering work of Huggins and Clark in 1940. They reported that after castration or estrogen treatment, the hyperplastic prostate of a dog had reduced in size.[27] Prostate cancers are hormone responsive and are known to be stimulated by androgens like testosterone. The production of these androgens can be indirectly inhibited by the administration of oestrogens, such as diethylstilbestrol **29**, which primarily inhibits the production of LH from the pituitary gland. Due to the cardiovascular side effects associated with high dose estrogen use, today the approach is to use GnRH analogues. These initially increase the concentration of LH but with continued therapy, they inhibit LH release by reducing the number of receptors in the pituitary thereby reducing androgen production. In addition the use of antiandrogens, such as flutamide **30** often in combination with therapies discussed above, can prevent the binding of androgens to their tumour receptor site thus causing a remission in the tumour. It should be noted however, that none of these treatments are curative although they can significantly reduce tumour growth, pain and increase the patient's quality of life.



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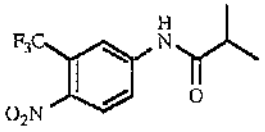

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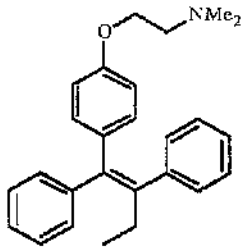

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Breast Cancer

In 1896 Beatson noticed a regression in advanced breast cancer in young women after they had their ovaries removed.[28] It was later shown in the 1960s that a number of breast cancers possessed receptors for the hormone estrogen, which when activated stimulated the proliferation of the epithelial cells of the breast. The antiestrogen tamoxifen **31** was discovered by research into new oral contraceptives but was found to have activity towards breast cancer. It is known to exert its activity by binding to the receptors of the tumour cells but does not activate them properly preventing the release of essential growth factors. In addition, tamoxifen shows a weak

oestrogen like effect which results in an increase in the enzyme called sex hormone binding globulin. This results in a reduction of the concentration of free oestrogen available to bind with the receptors in the tumour cells. The net effect is that tamoxifen antagonises oestrogen-induced effects thereby inhibiting the growth of oestrogen dependent tumours. Breast cancer may also be treated by interfering with the patient's endogenous oestrogen production. The agent aminoglutethimide was originally introduced as an anti-epileptic drug although was withdrawn due to the inhibition of steroid biosynthesis in the adrenal glands. Its activity against breast cancer is due to inhibition of the enzyme aromatase, a vital enzyme in the biosynthesis of androgens and estrogens from cholesterol.

1.6 Cancer And The Future

Chapter 1 has given a brief overview into the mechanisms, causes and treatments of cancer. With few exceptions, our treatment to date can best be described as palliative with our practical gains towards a cure minimal. The majority of chemotherapeutic agents indiscriminately attack cancerous cells along with healthy tissues resulting in high toxicity and stress to the patient. During the last few decades we have gained substantial knowledge towards understanding cancer including, how carcinogens affect DNA, mutate critical control genes and ultimately convert normal cells into cancerous cells. Using this knowledge one could envisage the use of rational drug design to annul these side effects and permit substantial progress towards a cure.

It should come as no surprise that mortality arising from cancer could be drastically reduced by the way we live our lives. It is estimated that *ca.* 33% of all cancers in the United States are due to tobacco use. It is also known that high fat diets, excessive alcohol consumption along with the voluntary exposure to uv radiation contribute highly to the incidence of cancer. An important tool in our fight against cancer must therefore be to educate people early about the importance of maintaining a healthy lifestyle along with being vigilant for the early warning signs of cancer. It is clear that each one of us can drastically reduce our risk of developing cancer by using our own initiative.

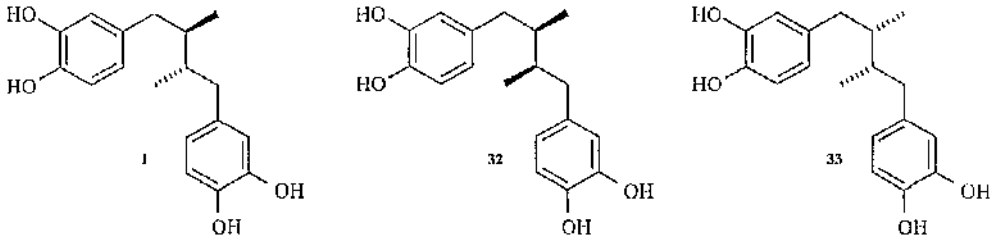
2

The Isolation, Stereochemistry and Proposed Mechanism of Action of NDGA

2.1 Introduction

The compound nordihydroguaiaretic acid (**1**), commonly abbreviated to NDGA, is a phenolic lignan found in the resinous extracts of many plants most notably *Larrea divaricata*. Of the three possible stereoisomers, depicted in **Figure 11**, NDGA is isolated with the optically inactive *meso* configuration (**1**). This Chapter opens with a discussion into the isolation of NDGA from natural sources and highlights how the configuration was established. The rest of the Chapter concentrates on the proposed mechanism of action of NDGA and how one may utilise these actions to produce an effective anti-tumour agent.

Figure 11 - The Three Stereoisomers of NDGA



2.2 Isolation of NDGA

NDGA has been isolated from the resinous extracts of many plants most commonly *Larrea divaricata*, also known as the creosote bush. This name is derived because of an abundance of resinous coated leaves and twigs which have a strong creosote odour when wet or burned. The creosote bush, which is indigenous to the south western United States, is one of the most drought tolerant plants of the region. Its morphology makes is ideally suited to survive periods of drought of up to two years and individual plants are known to live for long periods; often 100-200 years. It has been used medicinally for thousands of years by native Americans for a variety of

ailments. A tea made from the boiled leaves is reported to be effective towards cramping pains, allergic problems and to eliminate parasites. The dried powdered leaves are used to treat inflammation and minor wounds.

The first isolation of NDGA (**1**) from the creosote bush was reported by Waller and Gisvold in 1945.[28] The phenol (**1**) was isolated from an alcoholic extract of powdered plant material and its structure was confirmed from a series of chemical tests and synthesised derivatives.

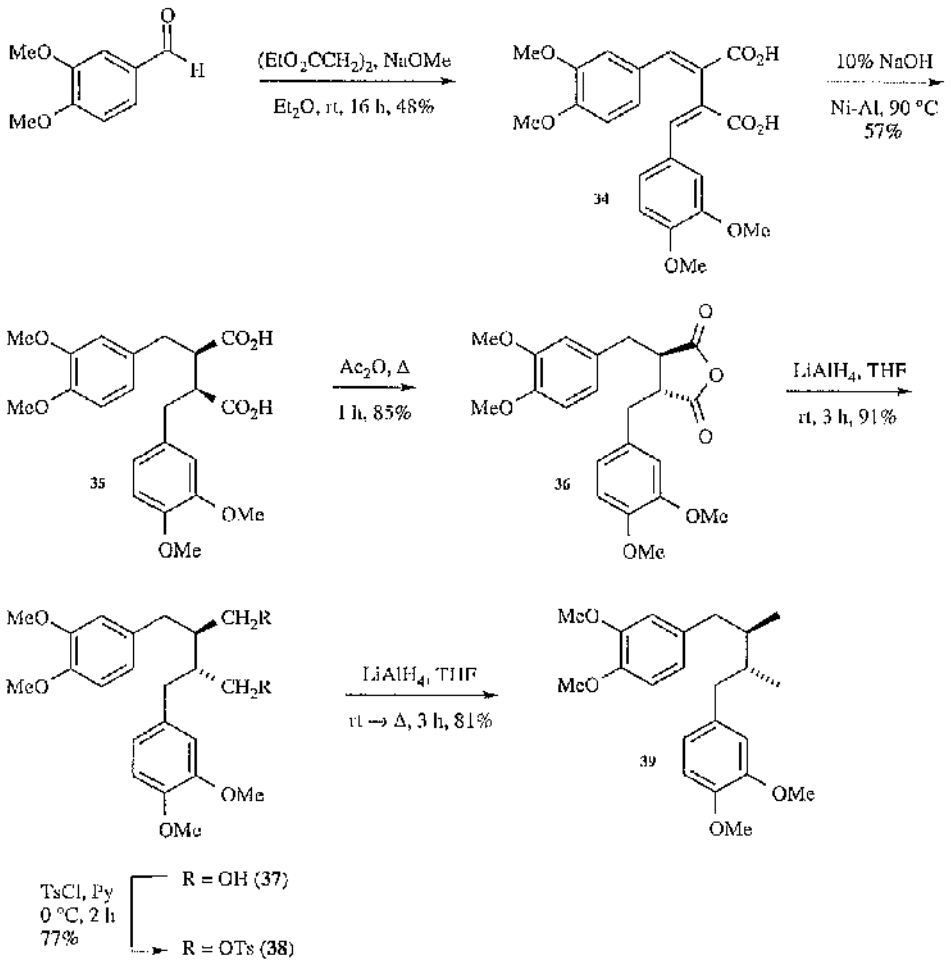
As a result of the anti-oxidant activity of NDGA towards foodstuffs and pharmaceutical preparations[29]; a reliable method for the extraction of NDGA from the creosote bush was patented by Gisvold in 1945.[30] This procedure involved the percolation of plant material with an aqueous hydroxide solution at ambient temperature which was then acidified to release the crude component. The solid mass obtained was taken up in diethyl ether and a second base extraction followed by acidification afforded NDGA in batches of varying purity. It is worthy of note that starting from 6 kg of plant material the method provided 150 g of NDGA representing 2.5% of the total weight of starting material used.

2.3 Determination of Stereochemistry

The tetramethyl ether of NDGA was first synthesised by Schroeter and Lichtenstadt in 1918 *via* the reduction of the dimethyl ether of guaiaretic acid.[37] The authors assigned the compound (m.p. 100-101 °C) the *meso* configuration as a consequence of the inability of a diamino derivative to be resolved. Later Haworth *et al.*[38] prepared the same compound (m.p. 101-102 °C) by a similiar reduction procedure and assigned the compound as the racemate. As a result of these findings; Schrecker set about the synthesis of both the *meso* and racemic stereoisomers of the tetramethyl ether of NDGA and confirmed that Schroter's inactive tetramethyl ether did in fact possess the *meso* configuration.[31]

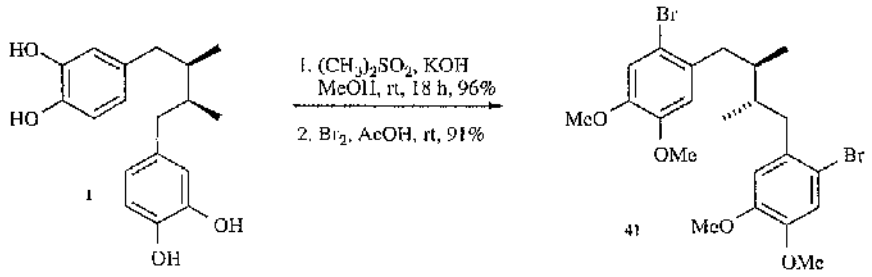
The lengthy reaction sequence, depicted in **Scheme 1**, started with a condensation of veratraldehyde with diethyl succinate employing sodium methoxide as base. The unsaturated acid (**34**) was reduced with Raney nickel at elevated temperature affording the saturated *meso* acid (**35**) in moderate yield. Acid (**35**) was then cyclised following the procedure of Haworth and Woodcock[32] affording the racemic anhydride (**36**) in high yield. The assignment of the stereochemistry arose from the fact that hydrolysis of (**36**) afforded a different acid than (**35**) which could be resolved into its component isomers with strychnine. $LiAlH_4$ reduction of anhydride (**36**) afforded the diol (**37**) which was converted into the bis tosylate (**38**) in excellent yield.[33] Finally $LiAlH_4$ reduction of the tosyl groups of (**38**) afforded the racemic tetramethyl ether of NDGA (**39**) which gave a melting point of 70.4 -71.2 °C.

Scheme 1



The *meso* configuration of acid (**35**) was confirmed by reduction to the diarylbutane in a manner analogous to that used for the anhydride (**36**). This material gave a melting point of 101.5-102 °C which was in agreement with the materials synthesised by Schroeter[37] and Haworth.[38]

Scheme 2



In 1972 Perry *et al.* reported experiments designed to offer unequivocal evidence for the *meso* configuration of NDGA.[42] Methylation of commercially available NDGA afforded the tetramethyl ether of (**1**) in excellent yield (**Scheme 2**) which gave a melting point in agreement with data reported earlier.[31,37,38] Bromination in acetic acid afforded the aryl bromide (**41**) in high yield. A single crystal X-ray analysis of this heavy atom derivative confirmed that NDGA (**1**) had the *meso* configuration.[34]

2.4 Proposed Mechanism of Action

The rational design of novel anti-cancer agents is likely to arise from a better undestanding of the biology of these diseases. Among the many defects which have been identified in cancer cells, we are becoming increasingly aware of the importance of growth factors which may drive the proliferation of tumour cells in autocrine/paracrine loops. The mechanism for driving tumour growth has been extensively studied in small cell lung cancer (SCLC) which secrete and respond to multiple neuropeptide and certain polypeptide growth factors. However, many other tumuor types respond to such agents. As an example, the polypeptide growth factor stem cell factor and its receptor c-kit are co-expressed in nearly all SCLC cell lines but are also widely distributed in gynaecological malignancies. Consequently the development of small molecule inhibitors which block the growth signals of agents such as c-kit, may provide a novel therapeutic approach.

2.4.1 Small Cell Lung Cancer

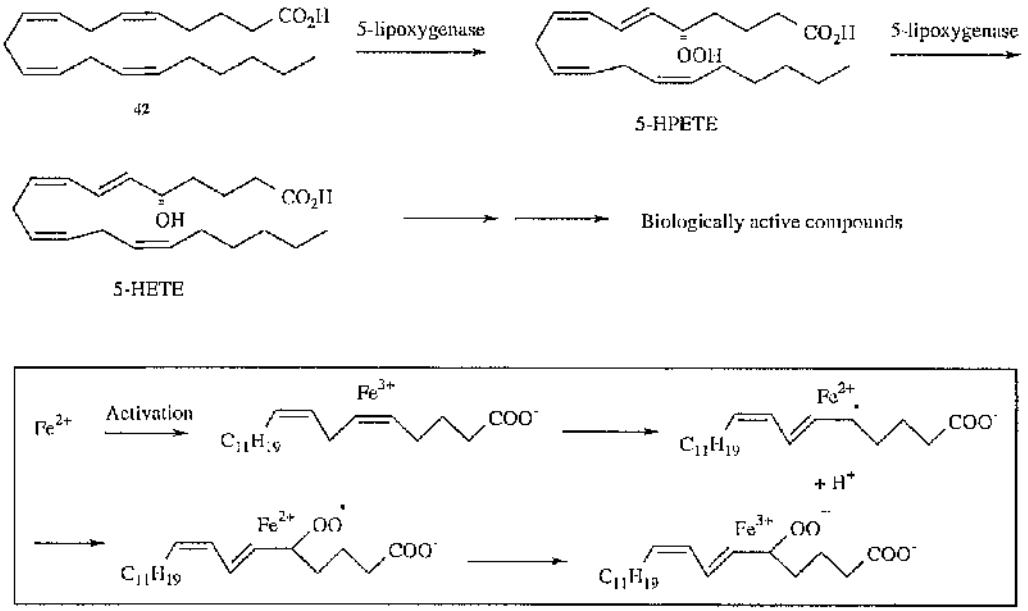
There is an urgent need to develop novel therapeutic strategies for most common solid tumours including small cell lung cancer for which the five year survival rate is less than 5%. SCLC represents about 20% of all lung cancers and is named for the size of the cancerous cells. Although small, these cells can multiply rapidly forming large tumours which can spread to lymph nodes and other organs such as the brain, bones and liver. SCLC is almost always caused by smoking and it is very rare for a non-smoker to suffer from this cancer type.

2.4.2 5-Lipoxygenase

5-Lipoxygenase is one of a family of enzymes that metabolise arachidonic acid to hydroperoxyeicosatetraenoic acids (HPETEs) (**Figure 12**). Each enzyme catalyses the insertion of an oxygen moiety at a specific position in the arachidonic acid (AA) (**42**) backbone. In addition to 5-lipoxygenase two other enzyme types in this family are

known, namely 12- and 15-lipoxygenase with the prefix referring to the position on the AA backbone they oxygenate. 5-Lipoxygenase forms 5-HETE, the precursor of the leukotrienes which are potent bioactive compounds involved in inflammation, allergy and several deteriorative disorders.

Figure 12 - 5-lipoxygenase metabolic pathway



5-Lipoxygenase is an iron containing enzyme that must be activated to the Fe^{3+} state before oxygenation of AA (**Figure 12**). Upon activation, Fe^{3+} specifically oxidises the 5,8 diene system of AA to generate a pentadienyl radical with the iron being reduced to the Fe^{2+} state. This radical then stereospecifically reacts with molecular oxygen at C-5 to generate the 5-*S*-hydroperoxy radical which undergoes electron transfer and protonoylsis regenerating the active Fe^{3+} and 5-HPETE. This in turn is converted into 5-HETE from which leukotrienes are formed.

2.4.3 Inhibitors of 5-lipoxygenase

Inhibitors of the 5-lipoxygenase pathway can be classified under three headings depending on their alleged mechanism of enzyme inhibition.

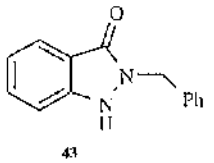
2.4.3.1 Redox Inhibitors

These compounds typified by ICI207968 (**43**) can potentially interact with a number of points on the enzyme mechanism (**Figure 12**). For example, they may act

by reducing the active Fe^{3+} to the inactive Fe^{2+} or reduce one of the radical intermediates, thus leaving iron in the inactive Fe^{2+} state. Redox inhibitors however show poor selectivity for 5-lipoxygenase, often being weak or inactive enzyme inhibitors *in vivo* when dosed orally. Indeed, ICI207968 caused methaemoglobin formation in blood which precluded its development for clinical use.

2.4.3.2 Iron Ligand Inhibitors

One of the most powerful metal binding groups is the hydroxamic acid moiety which has received a lot of research for inclusion in potential 5-lipoxygenase inhibitors. This lead to the discovery of Zileuton (**44**) by the Abbott group. It is a selective 5-lipoxygenase inhibitor showing no activity towards the 12- and 15-lipoxygenase enzymes. In addition to their metal binding properties hydroxamates and *N*-hydroxyureas also possess weak redox potentials and there is increasing evidence that their activity is derived wholely or in part to these effects.



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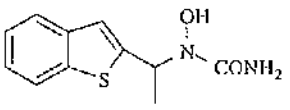

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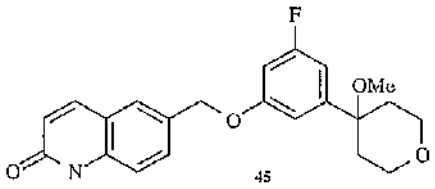

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2.4.3.3 Non-redox Inhibitors

As discussed above, many 5-lipoxygenase enzymes have the potential to participate in redox reactions or to interact with iron. However, the diffuse structure activity relationships of such compounds coupled with the absence of enantiospecificity suggested they did not interact strongly with the enzyme. This lead to a drug hunting programme by ICI with the goal of developing an active site 5-lipoxygenase inhibitor although devoid of redox and iron ligand properties. This led to the discovery of ICID2138 (**45**) as a selective 5-lipoxygenase inhibitor. In leukotriene dependent models of inflammation and bronchoconstriction, ICID2138 was approximately 10 fold more potent than Zileuton (**44**) and as a consequence of this encouraging profile ICID2138 has entered clinical trials.

2.4.3.4 Inhibition of 5-lipoxygenase by NDGA

NDGA (**1**) has been reported to be a selective lipoxygenase inhibitor and blocks SCLC growth *in vitro* and *in vivo*.[35] The preliminary data observed by Seckl *et*

al.[36] agree with these findings but they noticed that NDGA is a better inhibitor of SCLC growth than other more potent lipoxygenase inhibitors. Their results also suggest that NDGA has an alternative mechanism of action in SCLC cells. NDGA appears to inhibit c-kit directly, the receptor for stem cell factor, which is a prominent autocrine growth factor for nearly all SCLC cell lines.

2.4.4 Conclusions

In additon to NDGA's novel mechanism of action there are also several other compelling reasons to initiate an urgent and rapid investigation of NDGA as a new lead compound in cancer therapeutics. Firstly, NDGA has been shown to be active *in vivo*, blocking the growth of SCLC xenografts and human pancreatic xenografts.[35,36] Nevertheless, NDGA has poor water solubility and chemical modifications are required to generate a compound that would be clinically effective. Secondly, the structure of NDGA is distinct from other lipoxygenase inhibitors and has not yet been exploited. Moreover, a patent search has revealed no granted patents on the anti-cancer effects of NDGA and so it is likely that any clinically relevant compounds generated in this research would be patentable.

3

The Synthesis of (±)-NDGA

3.0 Introduction

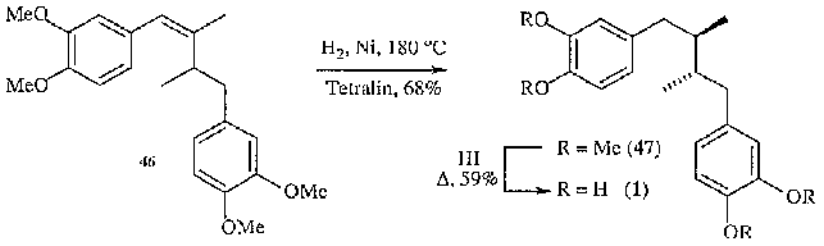
There have been several syntheses of the natural product nordihydroguaiaretic acid (NDGA) (**1**) reported in the literature. However in most cases they involve long reaction sequences or low yielding reactions. The synthesis of (±)-NDGA (**32**) has not received nearly the same amount of attention with only one total synthesis reported in the literature. This chapter opens with a review of the methods reported for the synthesis of the diasterisomers of NDGA including a brief discussion of the pros and cons of each synthetic sequence. The rest of the chapter outlines our attempts to synthesise (±)-NDGA (**32**) culminating in our successful total synthesis of a compound that was a lot more synthetically challenging than one would first envisage.

3.1 Previous Syntheses of NDGA.

3.1.1 Schroeter's partial synthesis of *meso*-NDGA.

The first reported partial synthesis of meso-NDGA (**1**) was reported by Schroeter *et al.*[37] in 1918 employing the dimethyl ether of (-)-Guaiaretic acid (**46**) isolated from *Guaiacum officinale* L. The catalytic reduction of (**46**) was carried out over Nickel affording the diarylbutane (**47**) in 67% yield (**Scheme 2**). Demethylation was effected in refluxing hydroiodic acid affording *meso*-NDGA (**1**) in 59% yield.

Scheme 2



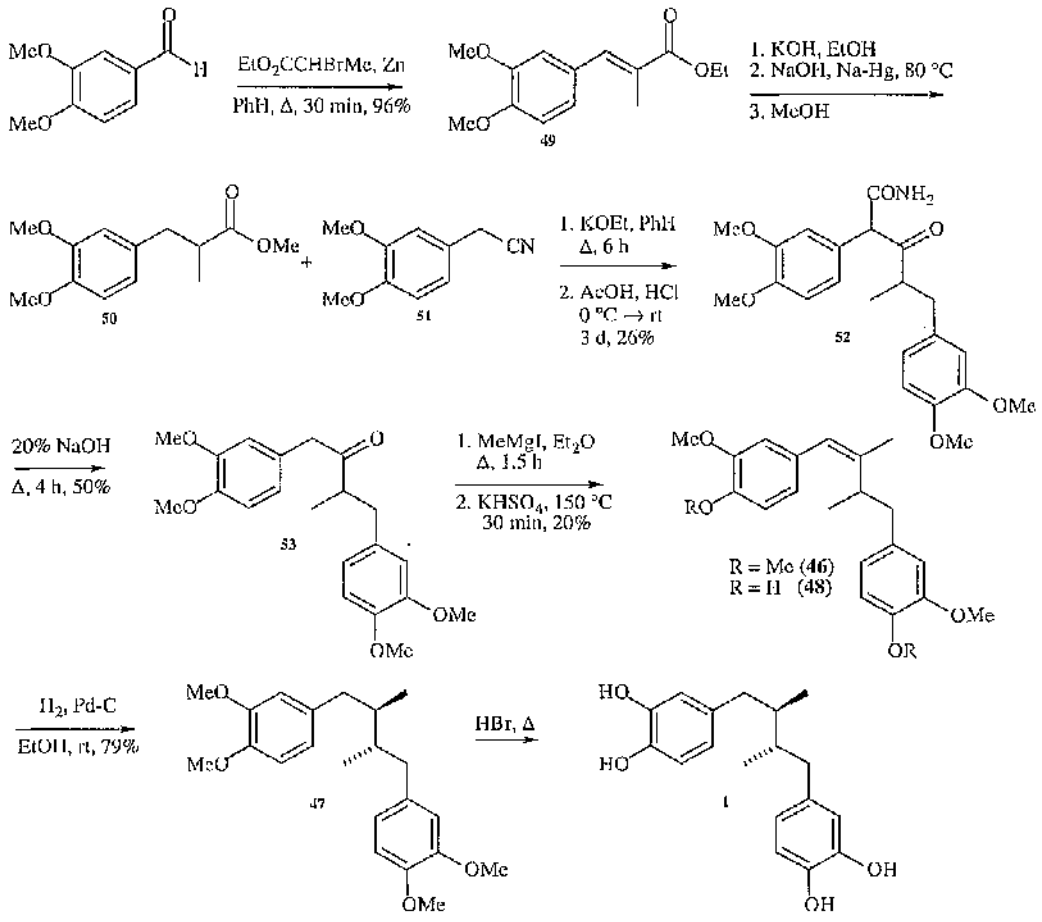
The partial synthesis of NDGA reported by Schroter *et al.* is overall low yielding employing a starting material that is not readily available. Indeed, the 68% yield reported for the reduction relates to a lower melting material and a further

recrystallisation is required, however no yield is reported for this step. The group should however be credited with the first synthesis of *meso*-NDGA (**1**).

3.1.2 Haworth's total synthesis of *meso*-NDGA.

In 1934 Haworth and co-workers[38] reported a series of experiments aimed at synthesising compounds of the guaiaretic acid type (**48**) culminating in the synthesis of NDGA. The lengthy reaction sequence, depicted in **Scheme 3**, starts with a Reformatsky reaction of veratraldehyde with ethyl-2-bromopropionate in refluxing benzene which afforded the unsaturated ester (**49**) in excellent yield.

Scheme 3



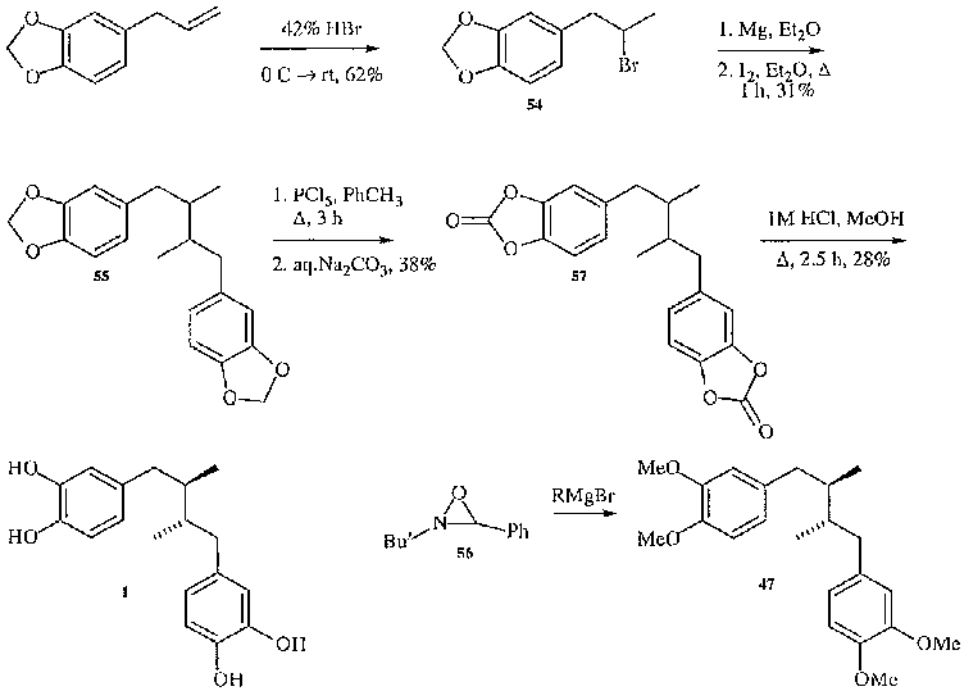
The ester was transformed into the saturated ester (**50**) *via* a series of hydrolysis, reduction and esterification steps although no yield was given for this series of synthetic transformations. The condensation of (**50**) with 3,4-dimethoxyphenylacetonitrile (**51**), itself aquired in 40% yield, was carried out in the presence of potassium ethoxide in refluxing benzene. The intermediate nitrile was

gently hydrolysed to the primary amide (**52**) employing a mixture of AcOH and HCl at low temperatures. Basic hydrolysis and concomitant decarboxylation afforded ketone (**53**) in moderate yield. Haworth reported that attempts to boil amide (**52**) in concentrated HCl gave impure ketone (**53**) which could not be purified. Methylation was effected using methylmagnesium iodide to give a secondary alcohol which underwent an elimination reaction on mild base treatment at elevated temperatures affording guaiaretic acid dimethyl ether (**46**) in poor yield. Catalytic hydrogenation over palladium afforded the tetramethyl ether of NDGA (**47**) in good yield. The ether was demethylated to give *meso*-NDGA (**1**) which did not depress the melting point of a sample obtained from the natural source.

The reaction sequence employed by Haworth *et al.* is quite long at seven steps not taking into account numerous intermediates that were not isolated. With a couple of exceptions the reactions are low yielding and require harsh reaction conditions. Although the final product is obtained in overall low yield, the authors should be credited with the first total synthesis of a compound that until then had only been available from the natural source.

3.1.3 Lieberman's total synthesis of *meso*-NDGA.

Scheme 4



The key step in the synthesis of *meso*-NDGA by Lieberman and co-workers[39] was the homo-coupling of the Grignard reagent derived from 2-bromosafrole (**54**)

using 0.5 equivalents of iodine in diethyl ether. The low yielding reaction afforded the bis dimethylene ether of NDGA (**55**) as a heavy oil presumably composed of a mixture of diastereoisomers. A similar coupling was reported much later by Gunasekaran and Balasubramanian[40] using the reagent 2-*t*-butyl-3-phenyloxaziridine (**56**) affording the *meso*-tetramethyl ether of NDGA (**47**) in 51% yield. The low yield again could be attributed to the formation of two diastereoisomers although the authors gave no indication of this in the paper.

Returning to Lieberman's synthesis, subsequent cleavage of the methylenedioxy groups of (**55**) *via* the carbonate (**57**) afforded NDGA in a 2% overall yield as needles that did not depress the melting point of a sample obtained from the natural source.

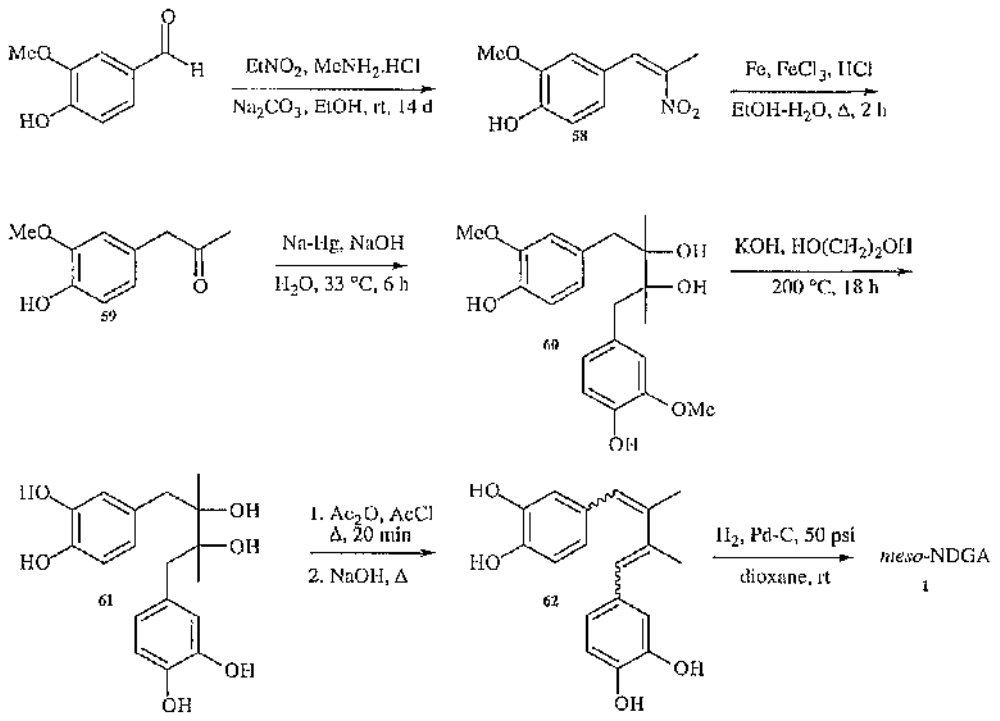
Although Lieberman's synthesis is short with only four synthetic steps, overall it is very low yielding and without the aid of modern spectroscopic techniques it is difficult to ascertain when the diastereoisomeric purity was introduced.

3.1.4 Pearls total synthesis of *meso*-NDGA.

Because there was no commercially viable process to synthesise NDGA its extraction was expensive and far from satisfactory, Pearl patented a synthesis of NDGA in the early 1950s.[41] Although the process was reported as being successful starting from a variety of oxybenzaldehydes, the synthetic route from vanillin is representative as depicted in **Scheme 5**.

Reaction of the anion of nitroethane with vanillin followed by elimination of water gave the nitrostyrene (**58**) which after reduction and hydrolysis with Fe-$FeCl_3$/c.HCl afforded the phenylacetone (**59**) as a viscous oil. The pinacol coupling of the phenylacetone (**59**), discussed more thoroughly in **Section 3.3.2**, was effected using a sodium amalgam under aqueous conditions affording the pinacol (**60**) as a viscous oil, presumably as a mixture of diasterioisomers. Pearl reported that attempted demethylation of the pinacol using acidic reagents resulted in rearrangements giving rise to unwanted ketone by-products. As a consequence, the methyl ethers of (**60**) were cleaved under basic conditions at high temperature to give the highly hydroxylated compound (**61**). Elimination of water from the tertiary alcohols was achieved by heating (**61**) in the presence of acetic anhydride and acetyl chloride to give the phenolic butadiene (**62**) presumably as a mixture of geometrical isomers, after saponification of the phenolic esters arising during the elimination conditions. The final step involved a catalytic hydrogenation of the butadiene over palladium on charcoal affording NDGA (**1**) as colourless crystals melting at 185-186.5 °C in agreement with data for the natural product.

Scheme 5

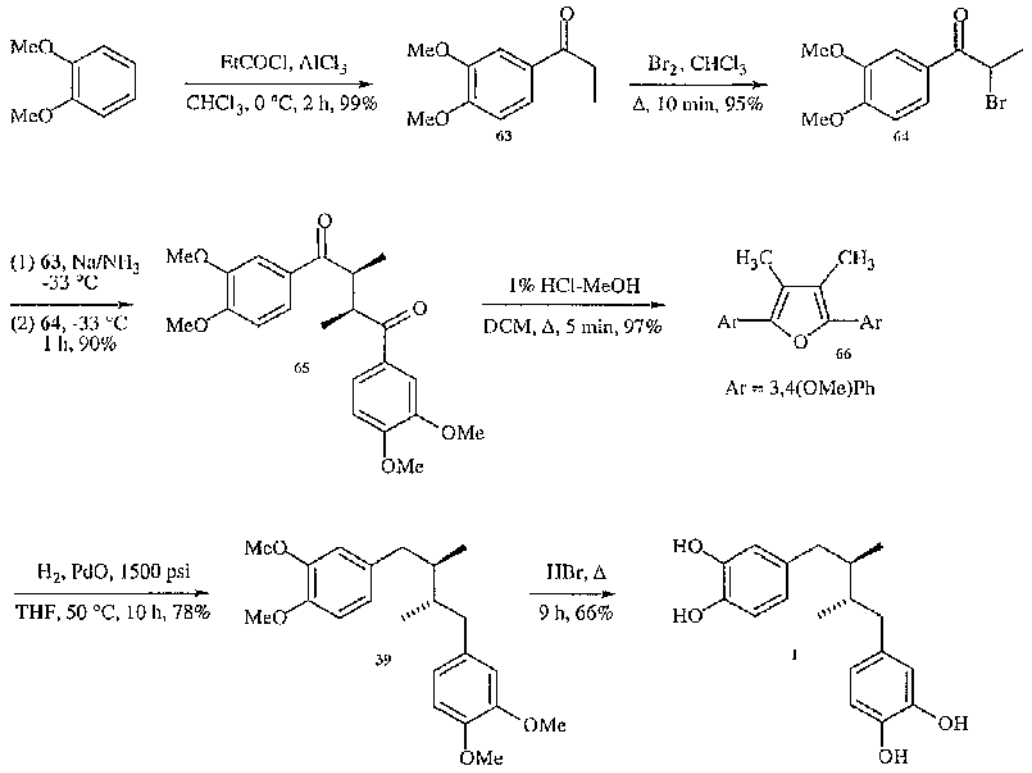


Although the experimental section appearing in the Patent is clear and should be easy to follow, the only methods of characterisation of the intermediates are boiling points or in the case of solids, a melting point. The scheme is quite long at seven steps and the lack of reported yields makes it difficult to determine the effectiveness of this synthetic sequence. Although not reported, it would be sensible to presume that a mixture of isomers was formed in the pinacol, elimination and hydrogenation reactions. In the final reaction the catalyst was simply filtered off and the organic solution was concentrated to a small volume whereupon crystals of NDGA were deposited. No reference was made to the mother liquors and the fact that no yield was given may indicate that all three diasterioisomers were present in the mixture and it is fortuitous that the *meso*-diasterioisomer was deposited.

3.1.5 Perry's total synthesis of *meso*-NDGA.

An efficient synthesis of NDGA by Perry *et al.*,[42,43] appeared in the literature in the early 1970s in an attempt to provide a commercially viable source of NDGA. Research up to that date had been non-productive and the creosote bush had remained the only commercial source of NDGA. The synthetic sequence employed by Perry and co-workers is depicted in **Scheme 6**.

Scheme 6



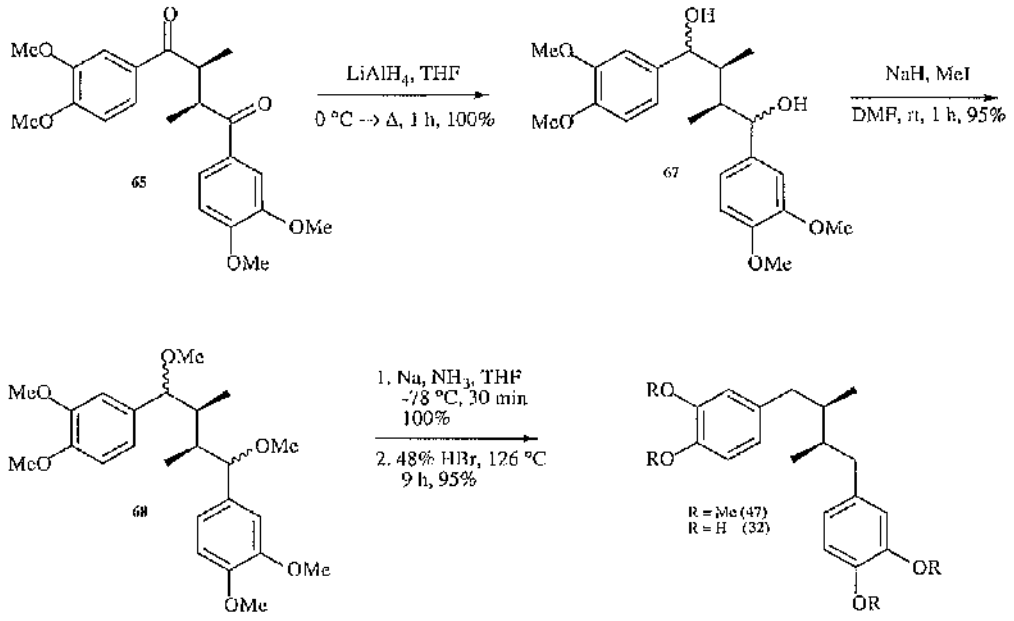
The acylation of 1,2-dimethoxybenzene with propionyl chloride was effected in quantitative yield affording the ketone (**63**) which was brominated in refluxing $CHCl_3$ again in excellent yield. A highly diastereoselective coupling reaction of the sodium enolate of (**63**) with bromoketone (**64**) in refluxing liquid ammonia afforded the racemic diketone (**65**) in high yield and a mechanism to rationalise this result is discussed in **Section 3.2**. The cyclodehydration of diketone (**65**) could be conviently carried out by refluxing a DCM solution of (**65**) in the presence of methanolic HCl affording the furan (**66**) in excellent yield. The furan was hydrogenated and cleaved over powdered palladium oxide utilising high pressure and elevated temperatures. Using this procedure the tetramethyl ether of NDGA (**47**) could be isolated in a crude yield of 78%. This material was demethylated with HBr affording NDGA (**1**) as cream crystals in 66% yield after three recrystallisations from 20% aqueous AcOH. The final product was reported to be identical in all respects with the purified natural product.

This six step synthetic sequence to NDGA would at first sight seem excellent giving high yields of product incorporating short reaction times but the following points should be noted. The yields given in **Scheme 6** are not analytical ones and often the yields are composed of several crops of material with differing melting points. It is common that the authors report an analytical melting point but do not give a yield of final pure product. The hydrogenation of the furan (**66**) to give the tetramethyl ether

(**47**) requires quite harsh conditions and the product was only isolated in 78% crude yield with a melting point of 91.5-95 °C. The same compound was made by the authors by methylating commercial NDGA with a view to working out the configuration of a dibromo derivative.[42] The tetramethyl ether from this reaction, after several recrystallisations from MeOH, had a melting point of 101-102 °C so it is clear that the crude material from the hydrogenation was not analytically pure. Nonetheless the route developed by Perry and co-workers is by far the best synthesis of *meso*-NDGA appearing in the literature to date giving the natural product in good overall yield.

3.1.6 Parkhurst's total synthesis of (±)-NDGA.

Scheme 7



The same racemic diketone (**65**) synthesised by Perry *et al.*[42] was employed as a starting material in the synthesis of (±)-NDGA (**32**) by Parkhurst and Pardini.[44] This diketone was reduced to the diol (**67**) presumably as a mixture of diastereoisomers in quantative yield. Methylation was effected using sodium hydride and an excess of methyl iodide in DMF at ambient temperature affording the hexamethyl ether (**68**) in excellent yield. The benzylic ethers were cleaved by dissolving metal reduction at -78 °C giving the racemic tetramethyl ether (**39**) in quantative yield. The authors reported that use of low temperature and short reaction times was critical to avoid partial reduction of the aromatic nuclei giving rise to

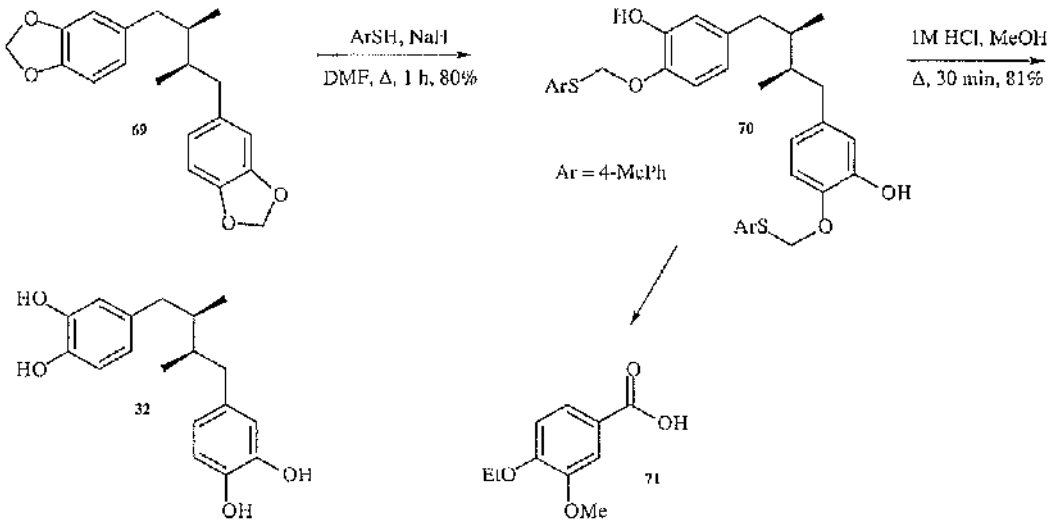
complex mixtures. Demethylation was affected in high yield using hydrobromic acid at high temperatures in a sealed tube affording (±)-NDGA (**32**) as a solid.

The synthetic sequence employed by Parkhurst and Pardini affords racemic NDGA in seven steps in excellent yield. There was however no mention in the paper of purification of the intermediates or the final product and no characterisation was reported with the exception of a melting point of the final product.

3.1.7 Rao's partial synthesis of (-)-NDGA.

The partial synthesis of a single enantiomer of NDGA has been reported by Rao and Chattopadhyay[45] while investigating the regioselective cleavage of the methylenedioxy group of the natural product (-)-austrobailignan-5 (**69**) (**Scheme 8**).

Scheme 8



Reaction of (**69**) with *p*-thiocresol and sodium hydride in refluxing DMF afforded the phenol (**70**) in high yield. The direction of the cleavage was determined by synthetic manipulation of (**70**) to ethylvanillic acid (**71**) giving physical properties identical to an authentic sample. Hydrolysis of (**70**) with dilute HCl afforded enantiopure NDGA (**32**) as a colourless glass in high yield. Unfortunately, the authors did not report any characterisation of the phenol (**32**) although they described the synthesis of both its tetraacetate and tetramethylether which were partially characterised.

3.2 Towards the synthesis of (±)-NDGA

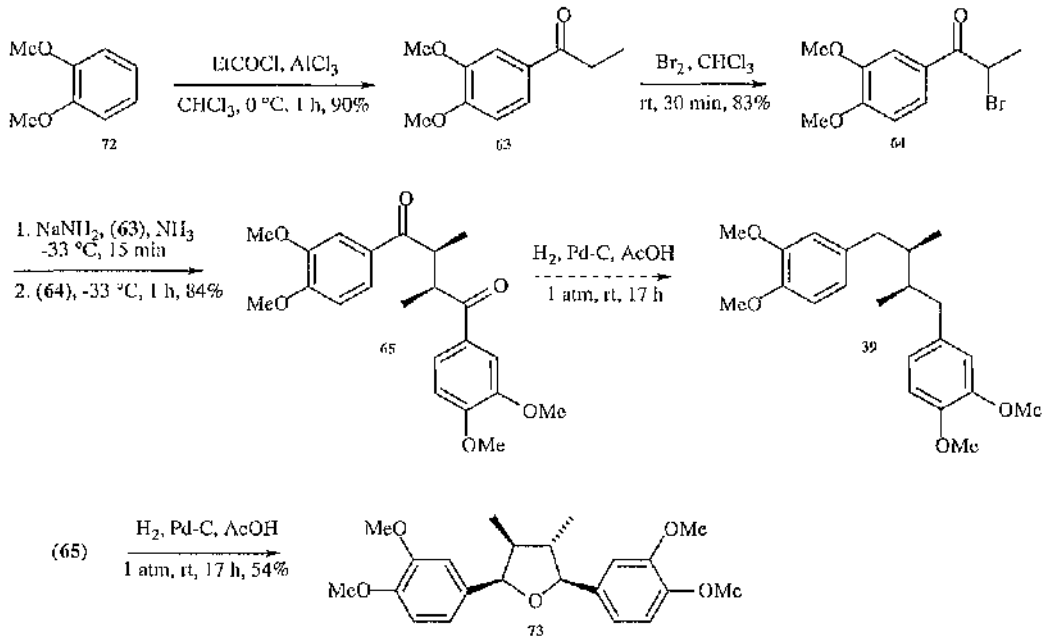
A search of the literature had presented us with a variety of pathways from which to choose a suitable synthesis allowing access to our target compound (**32**). We decided the method of Perry[42,43] (**Scheme 6**) was an excellent pathway to follow for a variety of reasons. The experimental section was clear and well documented, the yields reported were excellent and the starting materials readily available. We felt that once the racemic diketone (**65**) was isolated, it could be directly reduced to the racemic diarylbutane which could be deprotected using standard procedures. This section describes our initial attempts to achieve our goal.

3.2.1 Synthesis of (±)-NDGA - First approach

The acylation of veratrole (**72**) was carried out following the method of Perry *et al.*[42] with best results achieved using freshly distilled propionyl chloride and aluminium chloride ground to a fine powder under a nitrogen atmosphere. The ethyl ketone (**63**) was obtained as large shiny crystals in high yield with analytical data in agreement with those reported (**Scheme 9**). An IR stretch at 1662 cm^{-1} confirmed the presence of the carbonyl group with the regiochemistry of the addition apparent from the ^1H NMR spectrum. Two doublets with coupling constants of 8.3 and 1.9 Hz along with a doublet of doublets giving identical *J* values in the aromatic region clearly indicated the 1,3,4 subsitution pattern of the ring. We felt that the bromination conditions reported by Perry for (**63**) were severe and as a consequence an alternative method was developed. First attempts concentrated on the dropwise addition of 1.4 equivalents of bromine to a stirred solution of (**63**) in $CHCl_3$ at rt under nitrogen. After the mixture was stirred overnight, TLC showed two spots with one running very close to the starting material and one with lower polarity. Separation by silica gel flash chromatography afforded the desired bromoketone (**64**) in *ca.* 60% yield as an off-white solid. The less polar material was shown by ^1H NMR spectroscopy and MS to be the dibromo derivative with both α-hydrogens exchanged. In later experiments, we found that addition of a stoichiometric amount of bromine in portions, with the reaction monitored regularly by TLC, ensured formation of only the monobromo ketone after *ca.* 30 min. Although the starting material and product had almost identical Rf values, the former gave an intense red colour when stained with vanillin whereas the product gave no reaction and thus one could easily determine at what point all the starting material had been consumed. Using this methodology we were able to isolate the α-bromoketone (**64**) as feathers in high yield avoiding the need for column chromatography. A highly deshielded methine quartet at δ 5.31 in the ^1H NMR

spectrum together with an identical melting point to that reported confirmed the proposed structure.

Scheme 9

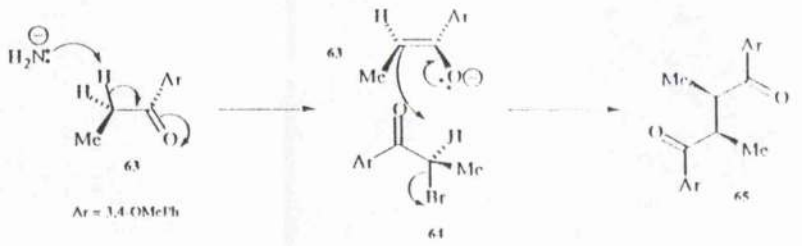


The key step in the synthesis was the highly diastereoselective coupling of the sodium enolate of (**63**) with the α-bromoketone (**64**) in liquid ammonia carried out by employing the method of Perry *et al.*[42] Initial attempts involved the transfer of reagents as THF solutions for ease and control of addition, however only moderate yields were obtained using this method. When the reagents were added as solids, *via* a solid addition funnel, the pure racemic diketone (**65**) could be isolated as crystals in high yield after recrystallisation from MeOH. The crude product contained up to 10% of the *meso*-diastereoisomer as indicated by a doublet in the ^{1}H NMR spectrum at δ 1.13. This minor diastereoisomer could however be removed by a single or more commonly two recrystallisations from MeOH affording (**65**) in high yield giving a melting point and ^{1}H NMR spectrum in agreement with those reported. A mechanism attempting to rationalise this result is depicted in **Figure 13**.

Formation of the enolate of (**63**) should give predominantly the (*Z*)-enolate with reaction of either enantiomer of (**64**) from above or below possible. It would however be sterically more favourable when the aroyl group of (**63**) is furthest away from the aroyl group of (**64**), and the methyl group of (**63**) is towards the oxygen of (**64**) rather than the aryl group. Thus in the example given, displacement of the bromine with concominant inversion would lead to one enantiomer of the diketone (**65**).

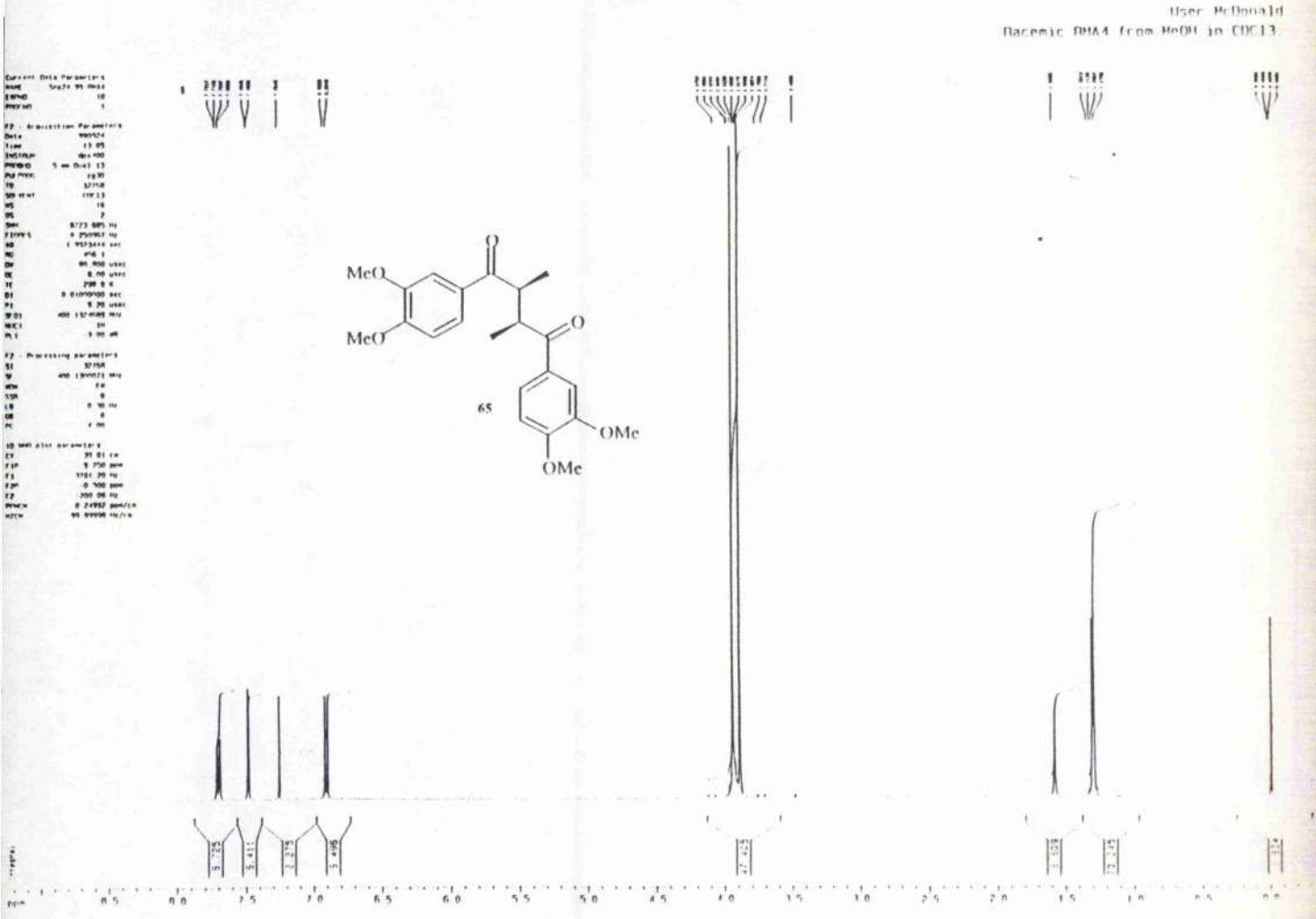
Likewise and with equal probability attack may occur from the opposite face leading to the other enantiomer with the net result being the formation of the racemic diketone.

Figure 13



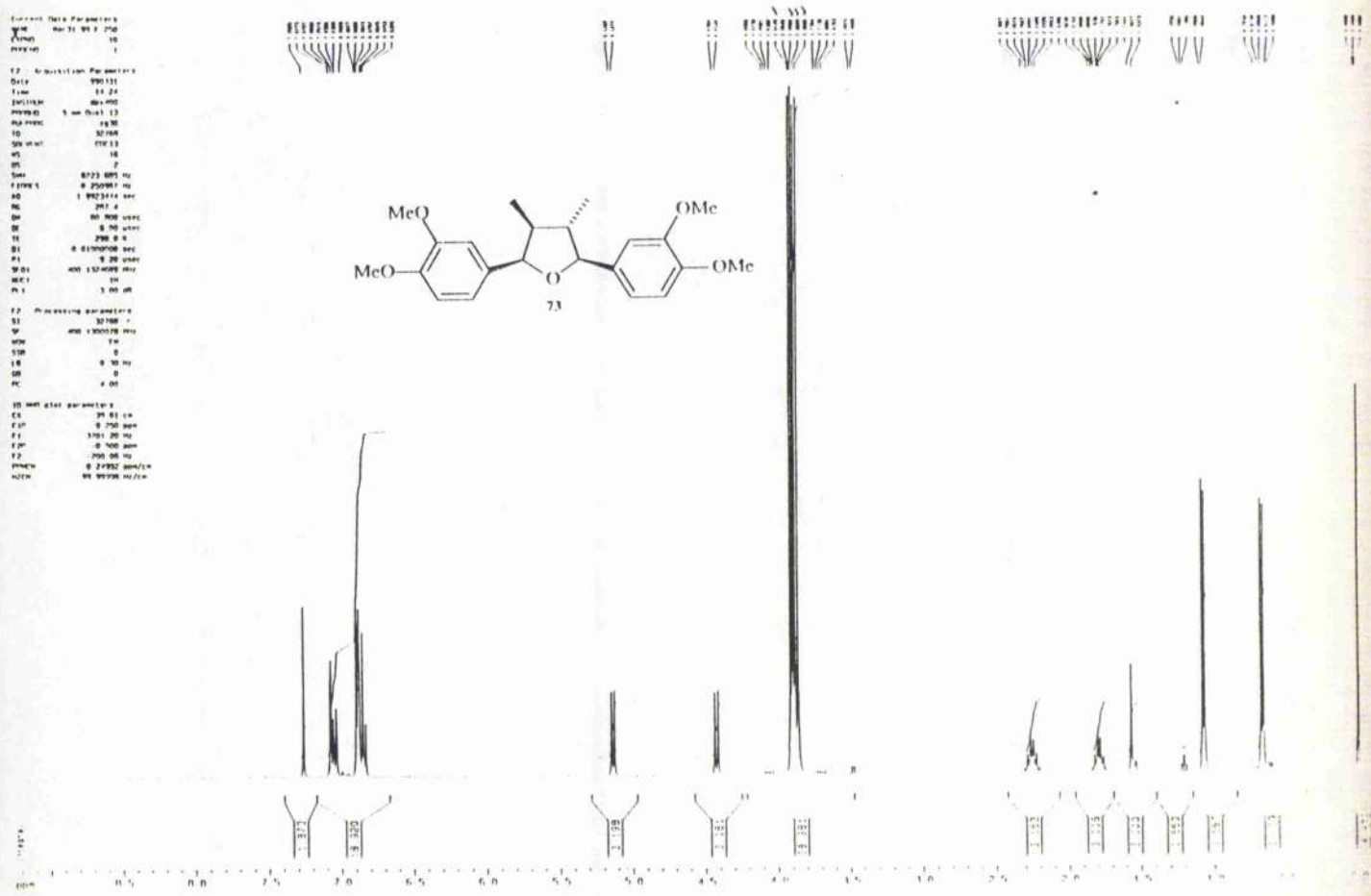
The symmetry of (**65**) was indicated by the NMR spectra with the ^{13}C spectrum showing eleven peaks including the ketone at δ 203 and the secondary methyl groups appearing as a doublet at δ 1.31 in the ^{1}H NMR spectrum (**Figure 14**).

Figure 14 - ^{1}H NMR spectrum of the racemic diketone



The single α-proton was not readily visible in the spectrum although close inspection of the two singlets arising from the methyl ethers revealed an integration of seven protons. It was clear that the methine proton resonance was being masked by the ethers and this was proved by ^1H-^1H NMR spin decoupling experiments. Irradation over the methyl ethers region resulted in the secondary methyl doublet collapsing to a singlet clearly indicating the presence of the methine resonance in this region. An IR stretch at 1660 cm^{-1} and a parent ion peak of *m/z* 386 in the mass spectrum were also consistent with the desired structure.

Figure 15 - ^1H NMR spectrum of (±)-veraguensin



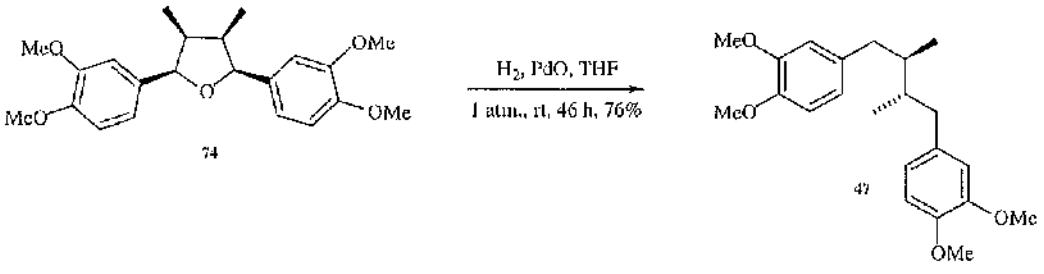
With the racemic diketone in hand we felt that reduction of the carbonyl groups of (**65**) to the corresponding methylenes followed by demethylation would furnish our target compound. It was expected that the reduction could be accomplished in a single step using catalytic hydrogenation over palladium in AcOH. The reaction went smoothly at atmospheric pressure and ambient temperature to give a single less polar spot on TLC. The crystalline product obtained was not the desired tetramethyl ether (**39**) but in fact the natural product (±)-veraguensin (**73**) initially isolated in the (+)-form from the plant *Ocotea veraguensis*[46] and later synthesised by Ahmed *et al.*[47] The

isolated product gave a melting point and ^{1}H NMR spectrum in agreement with those reported.[47] It was clear from the spectrum, shown in **Figure 15**, that we had isolated the unsymmetric diastereoisomer with two doublets arising both from the methyl groups and the methine protons next to the oxygen of the furan ring along with four separate methyl ether singlets. Furthermore the ^{1}H NMR spectrum of the crude product showed some extra minor doublets presumably arising from the other two symmetric diastereoisomers; however no attempt was made to isolate these compounds. It had been reported by Biftu *et al.*[48] that direct reduction of the diketone (**65**) could be achieved by using a high catalyst to substrate ratio in EtOH. Biftu *et al.* reported that using a low catalyst concentration resulted in the formation of the tetrahydrofuran (**73**) and encouraged by this we decided to adopt his reaction conditions. However on several occasions we were unable to repeat his work and even on increasing the catalyst concentration further we isolated solely the tetrahydrofuran with no signs of the desired diarylbutane (**39**) detected by TLC or ^{1}H NMR spectroscopy.

The direct hydrogenation was also attempted at 7 barr in a Baskerville hydrogenator; however only the tetrahydrofuran was isolated. Attempts using alternative catalysts including Raney nickel, palladium oxide, rhodium on carbon and platinum (IV) oxide were not successful. Ammonium formate transfer hydrogenation[49] was also unsuccesful with the tetrahydrofuran being the major product isolated.

Perry and co-workers reported the hydrogenation of the all *cis*-tetrahydrofuran (**74**) to *meso*-NDGA tetramethylether (**47**) using PdO in THF (**Scheme 10**).[42] Encouraged by this result we decided to adopt these conditions and apply them to our diastereoisomeric tetrahydrofuran (**73**); however several runs failed to give any product with only starting material recovered.

Scheme 10

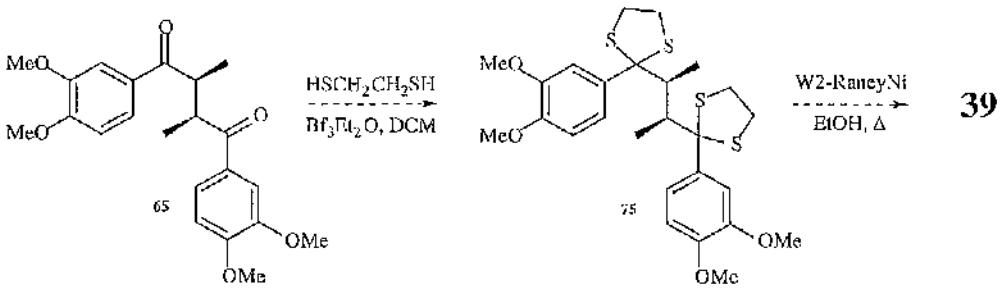


Disappointed by these results and being temporarily unable to attempt the hydrogenations at increased pressures we turned our attention to alternative methodologies. Attempts to form the bis-dithiane (**75**) which could be cleaved with Raney nickel (**Scheme 11**) allowing access to the tetramethylether (**39**) could not be

effected due to the difficulty in the formation of (**75**). The crude product which could be crystallised from MeOH gave a very complex ^{1}H NMR spectrum and could not be identified.

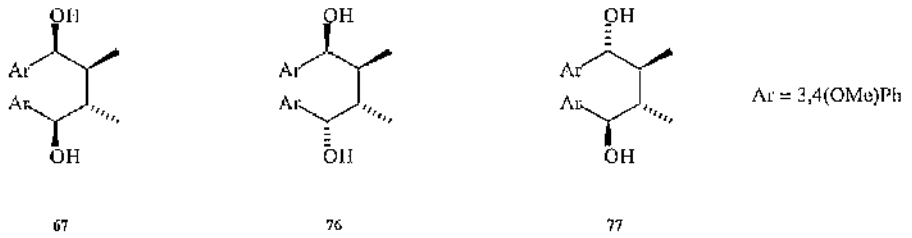
An attempted Wolff-Kischner reduction gave a complex mixture of products identified by TLC and ^{1}H NMR spectroscopy as did the general method of Lau *et al.*,[50] employing a AlCl3-^{t}BuNH2.BH3 system. No reaction was evident from TLC using the general procedures of Lau and Satoh using the ZnI2-NaCNBH3[51] and NaBH4-PdCl2[52] systems, respectively.

Scheme 11



At this point we decided that reduction of the diol (**67**), easily accessible following the procedures of Biftu[48] or Parkhurst[44], would allow access to the tetramethyl ether (**39**) after diol reduction. The reduction with LiAlH4 went in quantative yield (**Scheme 12**) affording the diol (**67**) as a mixture of three diastereoisomers identified by ^{1}H NMR spectroscopy. Biftu *et al.* reported the isolation of the racemic unsymmetrical diastereoisomer (**67**) after crystallisation of the crude product from CHCl3-hexane but did not give a weight or yield isolated.

Figure 16 - The three diastereoisomers of alcohol (67)

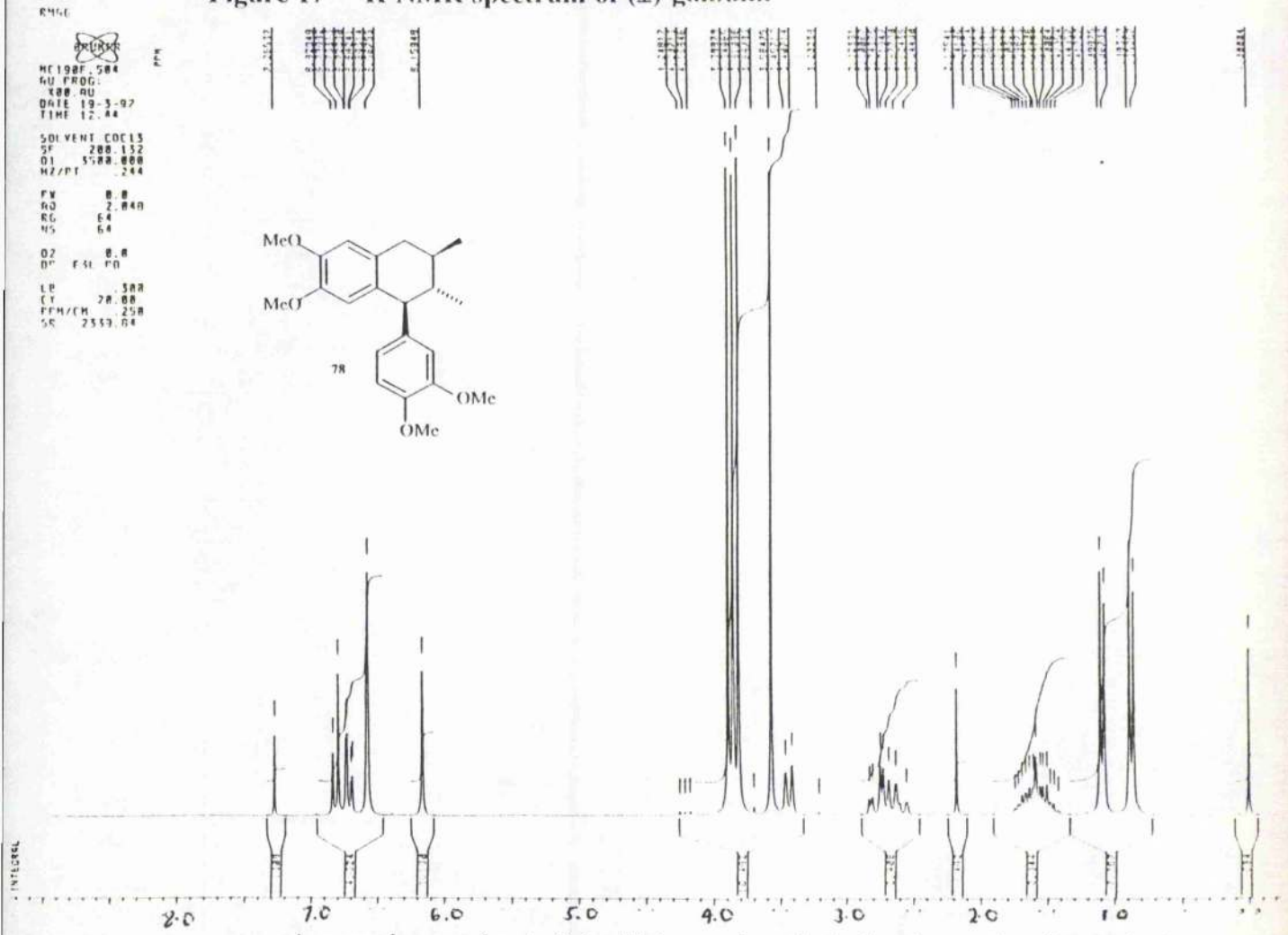


A ^{1}H NMR spectrum of our crude material showed (**67**) to be the major diastereoisomer formed with two doublets for the secondary methyl groups along with two deshielded benzylic methine doublets at δ 4.38 and 4.59. In addition to this compound, the ^{1}H NMR spectrum showed two extra doublets in both of these regions

indicating the presence of the two other possible diastereoisomers (**76**) and (**77**) both of which are symmetrical (**Figure 16**). A broad IR stretch at 3430 cm^{-1} along with a parent ion peak of *m/z* 390 in the mass spectrum were also consistent with the proposed structure.

The proportion of the major diastereoisomer could not be significantly increased by recrystallisation from a variety of solvents without a major loss of material and so, we decided to carry the diol (**67**) forward as a diastereoisomeric mixture. Catalytic hydrogenation of the diol (**67**) was carried out in AcOH at atmospheric pressure affording a product that gave a homogeneous less polar spot by TLC. However, crystallisation of the residue from MeOH did not afford the expected diarylbutane (**39**) but the natural product (±)-galbulin (**78**) in low yield. A m.p. and ^1H NMR spectrum (**Figure 17**) were in agreement with the data reported for the natural product isolated from *Himantandra baccata* Bail.[53] and later *Myristica otoba*.[54]

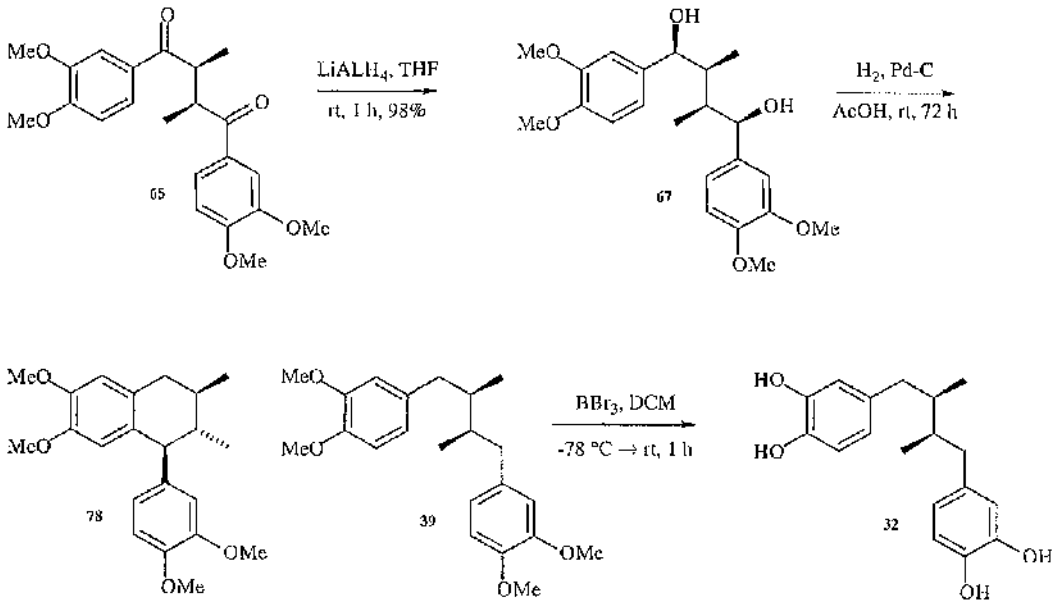
Figure 17 - ^1H NMR spectrum of (±)-galbulin



A second crop of material, which was deposited after the mother liquors had been placed in a freezer overnight, was shown to be the desired diarylbutane (**39**) by ^1H NMR spectroscopy although contaminated with (±)-galbulin. Several attempts to

remove this contaminant by chromatography or recrystallisation proved unsuccesful, so we decided to carry out the deprotection allowing access to our target compound after suitable purification. The methyl ethers were cleaved with boron tribromide[55] in quantitative yield affording a crude oil that showed no signs of the arylmethyl ethers in the ^{1}H NMR spectrum. The product however proved very difficult to crystallise often oiling out of solution and we could not obtain an analytically pure sample by column chromatography.

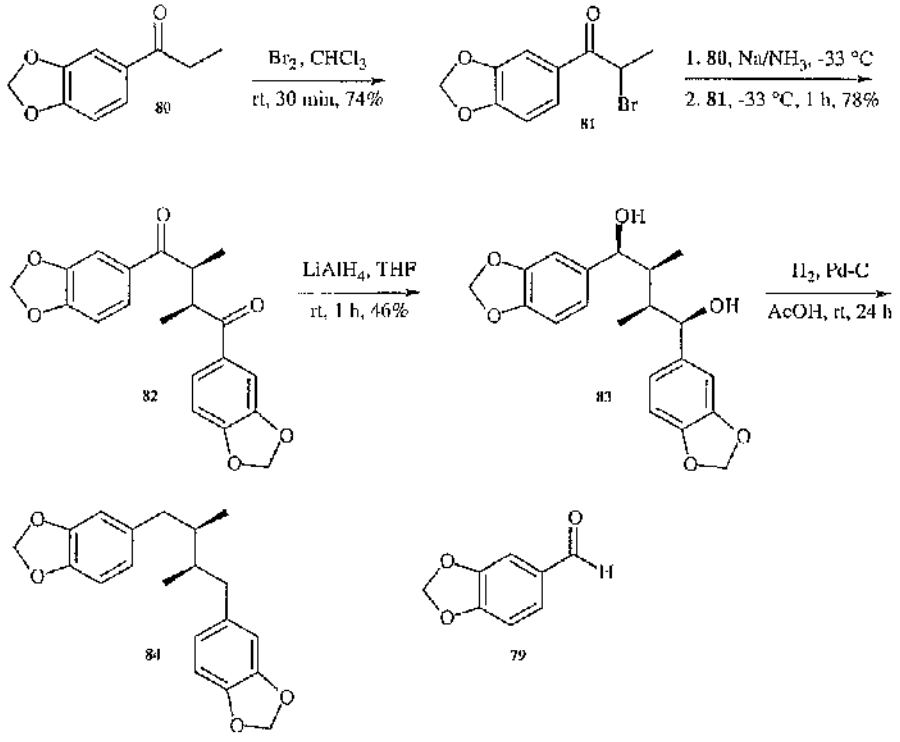
Scheme 12



We decided at this point to return to the reduction of the diol (**67**) and alter our reaction conditions with the aim of producing an analytically pure sample of the diarylbutane (**39**) which could be further manipulated. We found that the catalytic hydrogenation in AcOH was independent of the catalyst concentration with the cyclisation by-product (**78**) consistently formed. The reaction was also carried out in a variety of solvents, however this lead to poor conversion and often a range of compounds detected by TLC. Alternative catalysts were tried including PtO_2, PdO, Rh-C and Raney nickel; however these reactions suffered from the production of a variety of compounds detected by TLC and were not further pursued.

We decided to repeat the work reported by Biftu *et al.*[48] as depicted in **Scheme 13** and although the authors started with piperonal (**79**), we started with commercially available 3,4-methylenedioxypropiophenone (**80**) thus eliminating two steps from the synthetic sequence.

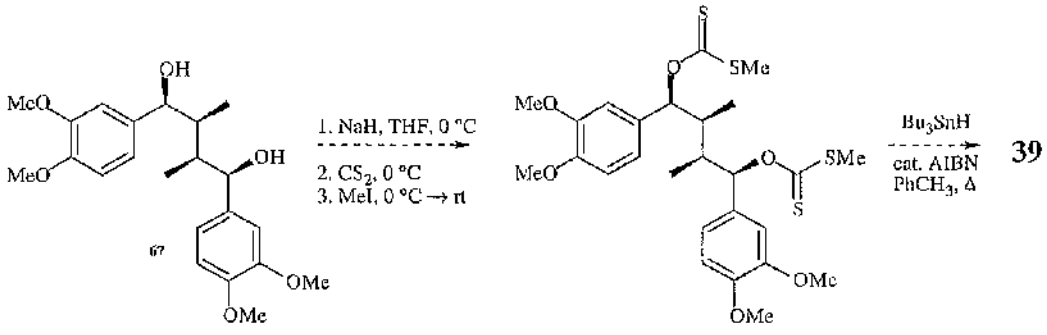
Scheme 13



The bromination was carried out using our modified conditions to synthesise (**64**) and afforded the bromoketone (**81**) in good yield with a melting point and ^{1}H NMR spectrum in agreement with those reported.[48] The coupling reaction in liquid ammonia afforded the pure racemic diketone (**82**) giving analytical data also in agreement with those reported. The methine proton of (**82**), which was masked by the methyl ethers in (**65**), could be observed in the ^{1}H NMR spectrum as a multiplet at δ 3.80-3.89 and an IR stretch at 1670 cm^{-1} was observed for the aryl ketone functionality. Attempted direct hydrogenation of (**82**) was unsuccesful giving similar results as those discussed for (**65**) with tetrahydrofuran formation predominating. Lithium aluminium hydride reduction afforded a solid in quantitative yield composed of a mixture of three diastereoisomers as shown by ^{1}H NMR spectroscopy. Recrystallisation from CHCl3-hexane afforded the pure unsymmetric diasterisomer (**83**) in moderate yield giving analytical data in agreement with those reported.[48] The authors reported the reduction of the diol (**83**) to the diarylbutane (**84**) using catalytic hyrogenation in AcOH but we were unable to obtain a pure sample using this method. A crude ^{1}H NMR of the partly solid residue showed the desired product but like the tetramethyl ether analogue (**39**) it was slightly contaminated with a cyclisation by-product suspected to be the tetrahydronaphthalene. We were unable to obtain an analytical pure sample by chromatography and felt deprotection would present us with the same purification problems as discussed previously.

Before deciding to abandon this route, and having some diol (**67**) in hand, we attempted some alternative methods. The conversion of an alcohol into a tosylate or mesylate followed by reaction with a hydride source is a common way to reduce alcohols. We were however unable to form the tosylate and although mesylation conditions consumed all the starting material by TLC, the ^{1}H NMR spectrum of the crude product was very complex and we felt that cyclisation and elimination reactions hampered the isolation of the bis-mesylate. An attractive method for the indirect reduction of alcohols is the radical reduction of a xanthate and we attempted this approach on our diol (**67**) as depicted in **Scheme 14**.

Scheme 14

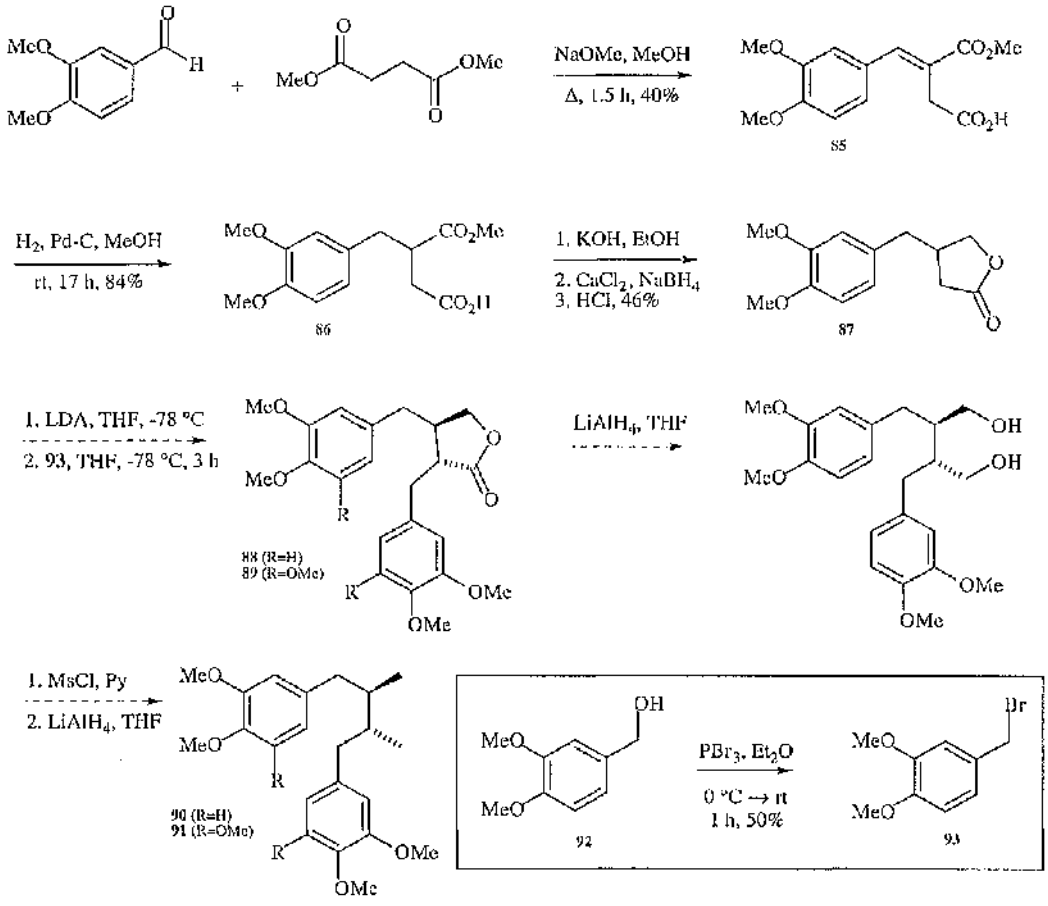


The classical method for the synthesis of a xanthate involves the deprotonation of the alcohol, reaction with dry carbon disulfide and trapping the resultant anion with methyl iodide. Unfortunately although all the starting material was consumed a ^{1}H NMR spectrum of the crude sample showed a complex mixture that was not further investigated. Another approach using phase transfer conditions by the method of Lee *et al.*[56] gave a similar result. Our final attempt concentrated on repeating the work of Parkhurst who was able to cleave the dimethyl ether of (**68**) using dissolving metal reduction (**Scheme 7**).[44] This approach however was not pursued as we isolated only starting diol (**67**) after following the reported methylation conditions.

3.2.2 (±)-NDGA - The Stobbe Condensation route

The alkylation of the butyrolactone (**87**) with 3,4-dimethoxybenzyl bromide (**93**) has been reported by Landais *et al.*[57] to afford exclusively the *trans*-lactone (**87**) in high yield (**Scheme 15**). We decided to adopt this aproach especially as the authors had described the reduction of the corresponding 3,4,5-trimethoxylactone (**89**) to the diarylbutane (**91**) as depicted in **Scheme 15**.[58]

Scheme 15



The Stobbe condensation of veratraldehyde with dimethyl succinate was effected using sodium methoxide in MeOH at reflux temperatures. The unsaturated ester (**85**) was obtained as bright yellow crystals giving analytical data in agreement with those reported.[59] The ^{1}H NMR spectrum showed a highly deshielded benzylic singlet at δ 7.87 along with four separate singlets for the remaining aliphatic protons. The catalytic hydrogenation went smoothly at atmospheric pressure affording the saturated ester (**86**) as a white powder giving a melting point and a ^{1}H NMR spectrum in agreement with those reported.[59] The benzylic singlet was no longer observed and a single methine proton appeared as a complex multiplet along with two methylene resonances which were now diastereotopic. The chemoselective reduction of the saturated half-ester (**86**) was carried out on the potassium salt of the acid with calcium borohydride affording the lactone (**87**) in moderate yield as an oil after column chromatography. A ^{1}H NMR spectrum was in agreement with that reported[59] and an IR stretch at 1778 cm^{-1} confirmed the proposed structure.

With the lactone in hand we turned our attention to the synthesis of the benzylic bromide (**93**). Torrado and Imperiali synthesised bromide (**93**) using a PPh_3-

NBS system in DCM in high yield as an an intermediate in their synthesis of nonstandard amino acids[60] and we decided to repeat their work. The reaction went well by TLC with all the starting material consumed but we were not able to obtain an analytically pure sample. The product when passed through a flash column as described suffered from decomposition and only a very low yield of material was recovered. Enders *et al.*[61] required the similiar benzylic bromide (**94**) as an electrophile in their total synthesis of (+)-(*S*)-[6]-gingerol (**95**) (**Scheme 16**) and we decided to use the conditions on commercially available veratryl alcohol (**92**). The reaction with phosphorous tribromide in dry ether went smoothly affording the desired bromide (**93**) as a fluffy solid in moderate yield after recrystallisation from Et_2O-hexane. A melting point and ^1H NMR spectrum were in agreement with those reported.[60] The bromide was not very stable at rt and gradually turned black over a couple of days and as a consequence was stored under an inert atmosphere in a freezer prior to use.

Scheme 16

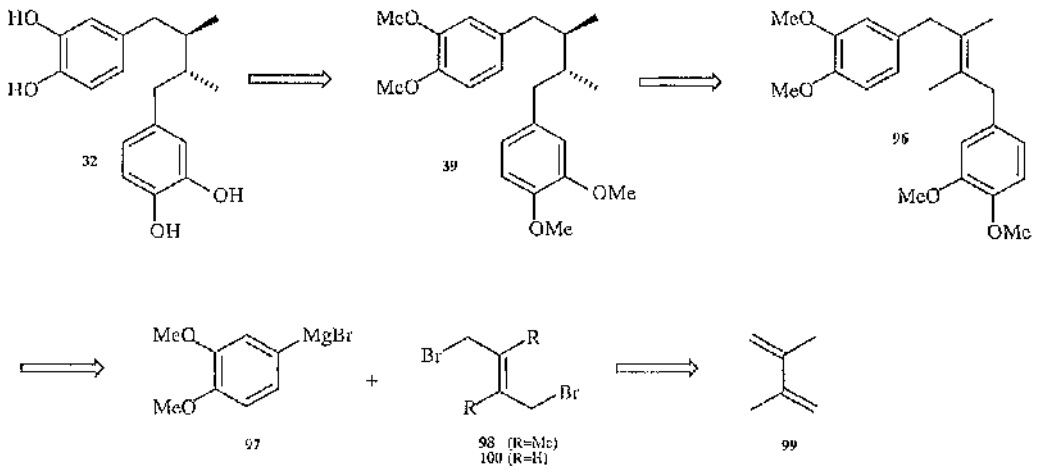
With both coupling partners now in hand we turned our attention to the alkylation following the procedure reported by Landais *et al.*[57] However although all the starting material had been consumed by TLC, a ^1H NMR spectrum of the crude material showed a complex mixture which was not further investigated. The authors reported that the use of lithium hexamethyldisilylamide resulted in increased yields; however this approach was not attempted. This disappointing result coupled with the long-winded reaction sequence persuaded us to abandon this approach. We realised at this point that we had spent a considerable length of time on the synthesis of racemic NDGA trying to follow reported procedures. We felt that a retrosynthetic analysis of (**32**) could help us towards our goal and present us with a novel approach to this synthetically challenging compound.

3.2.3 A Retrosynthetic analysis of (±)-NDGA

A retrosynthetic analysis of (±)-NDGA is depicted in **Figure 17**. It was clear that the final step in any synthesis would involve the cleavage of phenolic protecting groups and we felt that the racemic diarylbutane (**39**) was a suitable precussor to our target. This compound could arise from the catalytic hydrogenation of the (*E*)-alkene

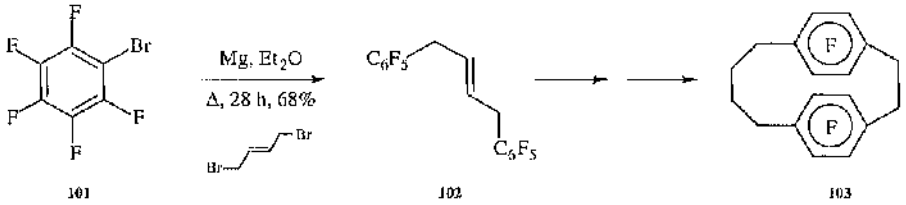
(**96**) which we envisaged arising from the coupling of the aryl Grignard reagent (**97**) with the allylic bromide (**98**), itself a product of bromine addition to the commercially available buta-1,3-diene (**99**).

Figure 17



A similiar synthetic pathway had been reported by Filler and Choe[62] as the first step in the synthesis of octafluoro[4,2]paracyclophane (**103**) (**Scheme 17**). The pentafluoro Grignard reagent (**101**) was successfully coupled with the allylic bromide (**100**) in moderate yield and this further encouraged us to adopt this approach.

Scheme 17

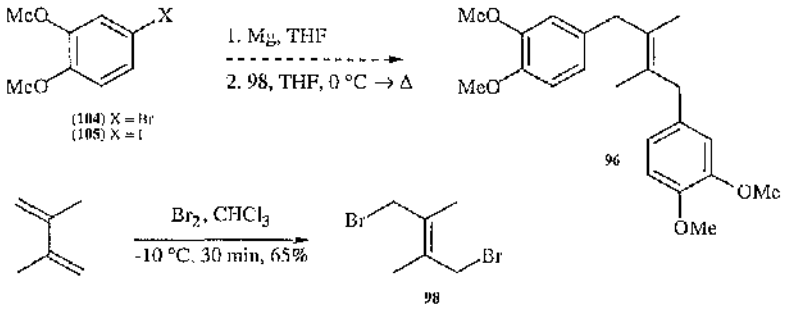


3.2.4 (±)-NDGA - The Grignard route

The bromination of the butadiene (**Scheme 18**) was carried out by the method of Sweeting and Johnson[63] affording the bromide (**98**) in moderate yield as shiny crystals. The melting point was in agreement with that reported and the ^{1}H NMR spectrum revealed two singlets at δ 1.90 and 4.07 integrating for three and two protons respectively. The ^{13}C NMR spectrum showed three resonances including a quaternary peak at δ 132 and a parent ion at *m/z* 242 in the mass spectrum also agreed with the

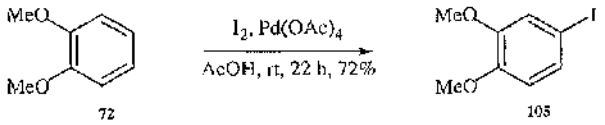
proposed structure. We also found the material to be a strong lachrymator as reported by the authors.

Scheme 18



With the bromide (**98**) in hand, we turned our attention to the synthesis of the Grignard reagent derived from commercially available 4-bromoveratrole (**104**). The reaction was attempted using scrupulously dry glassware and magnesium ribbon that had been washed thoroughly with ether and dried under vacumn. We however witnessed no sign of reaction on addition of an ethereal solution of (**104**) to the magnesium ribbon under nitrogen. Sonication or gentle reflux failed to initiate the reaction as did the addition of a few drops of 1,2-dibromoethane. The reaction was also attempted in dry THF and even use of activated magnesium, obtained by stirring the ribbon under nitrogen overnight, was unsuccessful. We suspected that the aryl iodide (**105**) would form the Grignard reagent more readily as a consequence of easier insertion of the metal into the halide bond. With this in mind, iodide (**105**) was synthesised following the general procedure of Skulski and co-workers.[64] from commercially available veratrole (**72**) using an iodine-lead tetraacetate system (**Scheme 19**). The reaction is believed to follow the pathway outlined with oxidation of the iodine to give the electrophile which reacts with the activated aromatic nucleus in the usual fashion.

Scheme 19



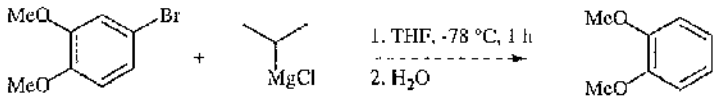
$$Pb(OAc)_4 + I_2 \rightarrow Pd(OAc)_2 + 2AcO^- I^+$$
$$2ArH + 2AcO^- I^+ \rightarrow 2ArI + 2AcOH$$

The consumption of iodine during the reaction was clearly evident with the reaction mixture turning from a deep red-black colour to a light yellow solution after

several hours. The iodide (**105**) was obtained in good yield and of the two possible regioisomers substitution at the 4-position was apparent from the ^{1}H NMR spectrum. In addition to two methyl ether singlets, the spectrum revealed two doublets and one doublet of doublets in the aromatic region giving clear evidence for the regiochemistry proposed. A parent ion at *m/z* 264 in the mass spectrum and a melting point in agreement with that reported[64] were also consistent with the proposed structure. Unfortunately following the same conditions used for the arylbromide we were not able to effect any Grignard formation.

Ricke and Bales[65] have reported the formation of a highly reactive magnesium source showing enhanced reactivity towards Grignard formation by using alkali metal reduction of magnesium salts in THF. We however were unwilling to attempt this procedure for safety reasons but in a final attempt to achieve our goal we attempted a transmetalation of magnesium from commercially available isopropylmagnesium chloride (**106**) in THF as outlined in **Scheme 20**. It was envisaged that due to the enhanced stability of the aryl Grignard over the aliphatic reagent that one could transmetalate under mild conditions and react this with our bromide (**98**). As a trial we decided to attempt such a transmetalation and react the derived Grignard reagent with water resulting in overall reduction of (**104**) to veratrole (**72**) (**Scheme 20**). The crude product was however shown to be starting material by ^{1}H NMR spectroscopy and further runs at 0 °C even using the iodide (**105**) failed to effect reduction of the aryl halide bond.

Scheme 20



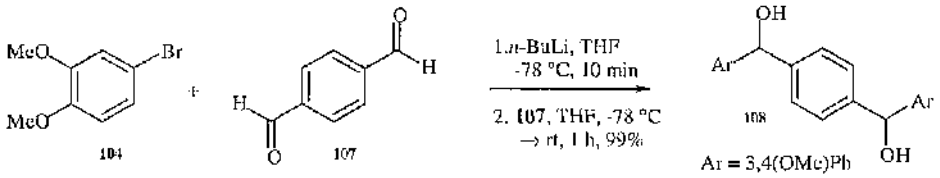
104 106 72

3.2.5 Attempts employing other metals

Disappointed at the stubbornness of bromide (**104**) to form the Grignard reagent we turned our attention to the synthesis of the organolithium species generated by the insertion of lithium into the metal halogen bond of (**104**) using *n*-butyllithium. Our first attempt was a trial reaction using the dialdehyde (**107**) as an electrophile which we had at our disposal (**Scheme 21**). Addition of one equivalent of *n*-BuLi to a solution of 4-bromoveratrole (**104**) in THF at -78 °C followed by 0.5 equivalents of aldehyde (**107**) resulted in smooth conversion to the diol (**108**) in quantitative yield. TLC showed all the starting material had been consumed and revealed a single more polar spot near the baseline which was stained red with vanillin spray. The ^{1}H NMR

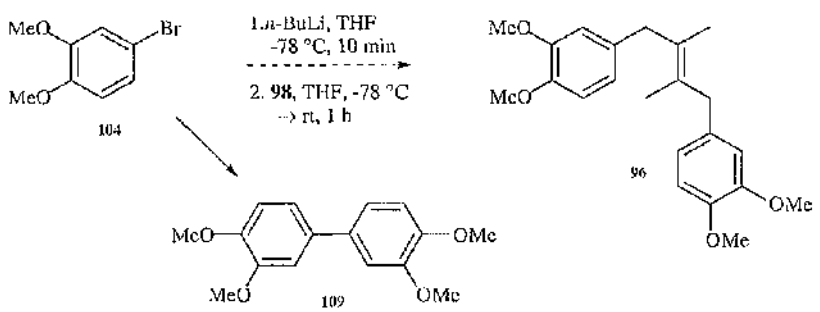
spectrum showed the desired structure exsisting as a mixture of diastereoisomers that was not further purified.

Scheme 21



Encouraged by this result and confident that metal halogen exchange had been effected we decided to carry out the work as depicted in **Scheme 22.** Addition of 1.1 equivalents of *n*-BuLi to a solution of (**104**) in THF at -78 °C followed by reaction with the allylic bromide (**98**) proceeded smoothly giving a single more polar spot by TLC. The crude reaction product was passed through a short silica column to afford a crystalline product which gave a very simple ^{1}H NMR spectrum. The spectrum revealed two doublets and a doublet of doublets in the aromatic region along with two methyl ether singlets but did not show expected resonances for the aliphatic protons of (**96**). The ^{13}C NMR spectrum also showed no signs of aliphatic functionality and gave eight resonances including the two methyl ethers at δ 56. A parent ion at *m/z* 274 in the mass spectrum along with the NMR data confirmed the presence of the tetramethoxybiaryl compound (**109**), a product of homocoupling of the organolithium species. Interestingly, the coupling of aryl Grignard reagents has been reported by Taylor *et al.*[66] using unsaturated 1,4-dihalocompounds. The authors report the use of 1,4-dichlorbut-2-ene and 1,4-dichlorobut-2-yne as being successful giving high yields of coupled product however no reaction is observed with *trans*-1,4-dibromobut-2-ene. Although it was not further investigated, we feel that under our conditions bromide (**98**) was acting in a similiar fashion to that reported, by excepting an electron thus forming the stable aryl radical which then underwent homocoupling.

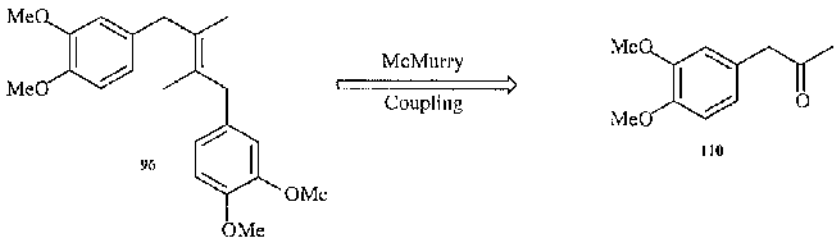
Scheme 22



Attempts to transmetallate from lithium to copper using the reagent lithium thienyl-2-cyanocuprate[67] was unsuccesful along with attempts to form the organozinc using anhydrous zinc chloride. The crude reaction product from each reaction was shown to be a complex mixture of products by ^{1}H NMR spectroscopy and were not further investigated.

Returning to the retrosynthetic analysis of (±)-NDGA (**Figure 17**) it was expected that symmetrical alkene (**96**) could arise from a McMurry type coupling of commercially available 3,4-dimethoxyphenylacetone (**110**) (**Figure 18**). The remainder of this chapter opens with a brief review of some low valent titanium reagents useful in organic synthesis concluding with our succesful total synthesis of (±)-NDGA utilising such a reagent in a key step.

Figure 18



3.3 Successful synthesis of (±)-NDGA

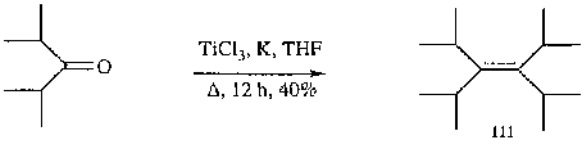
3.3.1 Low Valent Titanium Reagents

The use of low valent titanium reagents for the reductive coupling of aldehydes and ketones to alkenes arose independently from the labs of Tyrlik and Wolochowicz[68], Mukaiyama *et al.*[69] and McMurry and Fleming[70] in the early 1970s. Mukaiyama *et al.* used a reagent prepared from the reduction of titanium (IV) chloride with zinc giving good yields of coupled products. Their reactions afforded the corresponding pinacols at low temperatures whereas alkenes were isolated when the reaction mixtures were heated at reflux. In the case of aliphatic aldehydes and ketones the major products isolated were the pinacols with small ammounts of alkenes formed even under refluxing conditions. McMurry and Fleming developed a reagent derived from the reduction of titanium (III) chloride with $LiAlH_4$ and succesfully coupled a series of aromatic and aliphatic carbonyl compounds. In contrast to the other methods discussed the authors reported the successful coupling of aliphatic ketones to alkenes using this reagent system. McMurry and co-workers have demonstrated considerable effort in an attempt to produce a reagent that shows consistency in the coupling

procedure for a wide variety of substrates. This has resulted in the coupling of carbonyl compounds to alkenes being widely referred to as "The McMurry Reaction".

Shortly after their original paper McMurry and Fleming reported an improved procedure which used three equivalents of potassium metal to reduce the titanium (III) chloride.[71] This was later followed by a more thorough report concentrating on the reduction of $TiCl_3$ with both potassium and lithium including a thorough investigation into the reaction mechanism.[72] These procedures superceded their original work as the ability to repeat their results was dependent on the batch of $TiCl_3$ used. The use of an alkali metal as a reductant however was shown to be consistent for three separate batches used and even the highly hindered olefin tetraisopropylethene (**111**) could be isolated in moderate yield by this route (**Scheme 23**). Several years later McMurry *et al.*[73] reported an optimised procedure for titanium- induced carbonyl-coupling reactions. The reagent system used was $TiCl_3(DME)_{1.5}$ / Zn-Cu and was reported as being particularly effective as even old batches of $TiCl_3$ could be converted into the blue crystalline $TiCl_3$/DME solvate which showed enhanced reactivity. As an example of the reagent's effectiveness the authors reported the isolation of hindered olefin (**111**) in 87% yield which was a significant increase to that previously reported.[71]

Scheme 23

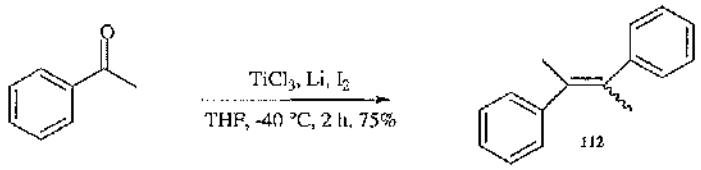


111

Many other research groups have reported the succesful use of low valent titanium reagents. Corey *et al.*[74] introduced the reagent $TiCl_4$ -Mg(Hg) which could effectively couple carbonyl compounds to produce pinacols at low temperature in high yield. The authors claimed that this reagent was more consistent than the original system developed by Mukaiyama *et al.*[69] showing enhanced reactivity towards aliphatic ketones. They also reported that a reagent derived from cyclopentadienyltitanium trichloride-$LiAlH_4$ was equally effective for a variety of processes. In refluxing THF $TiCl_4$-Mg(Hg) allowed access to alkenes derived from both aromatic or aliphatic precursors.[75] The addition of pyridine to $TiCl_4$-Zn was reported as being effective for the reductive coupling of a wide variety of aliphatic ketones affording alkenes in moderate yields.[76] Talukdar *et al.*[77] have recently reported an especially reactive system derived from $TiCl_3$-Li in combination with iodine. The reagent effects the coupling of both aliphatic and aromatic carbonyl

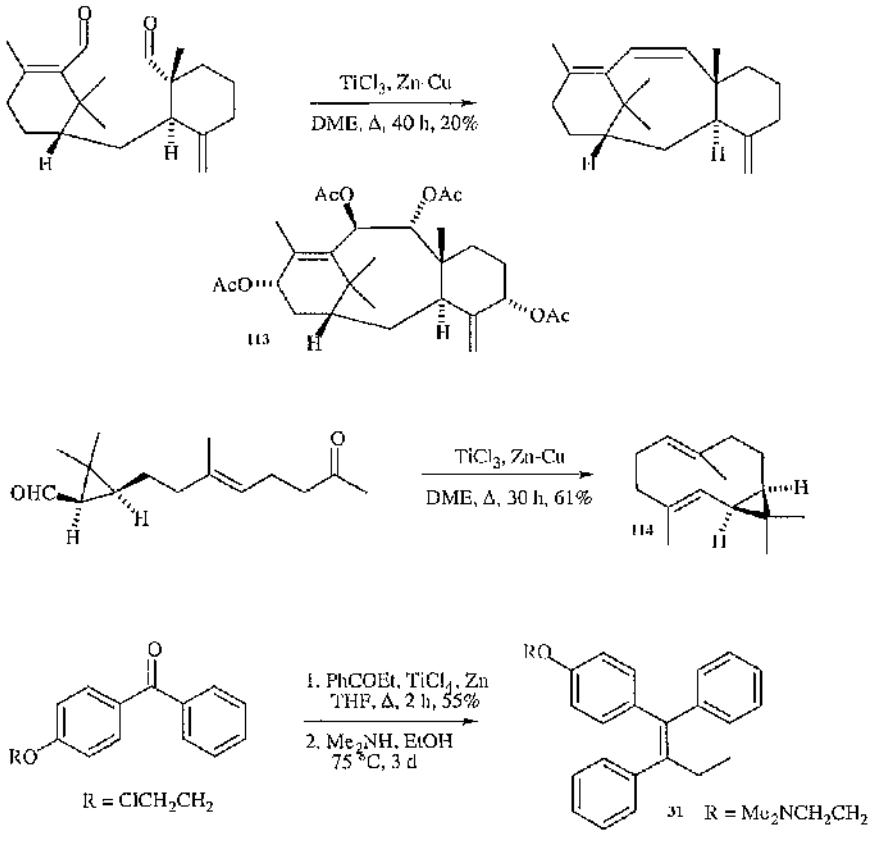
compounds to alkenes at low temperatures in contrast to conventional methodology. In one example acetophenone could be successfully transformed to the corresponding stilbene (**112**) at -40 °C in good yield. (**Scheme 24**).

Scheme 24



The use of low valent titanium reagents is not confined solely to intermolecular couplings with many examples of intramolecular reactions appearing in the literature. The skeleton of the taxane diterpene taxusin (**113**) has been successfully constructed employing an intramolecular coupling reaction by Kende *et al.*[78] (**Scheme 25**).

Scheme 25



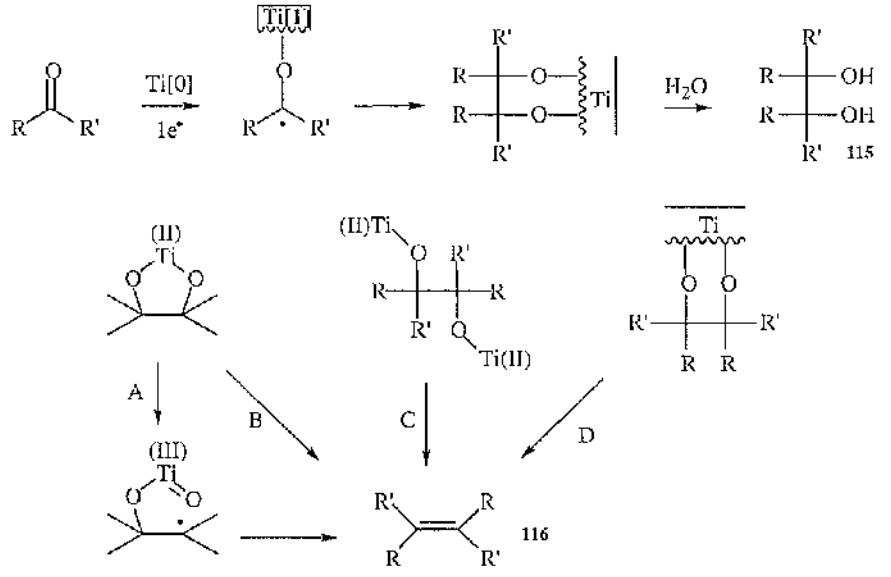
The use of low valent titanium reagents has also found widespread application in the field of natural product synthesis typified by the synthesis of bicyclogermacrene (**114**) by McMurry and Bosch[79] (**Scheme 25**). Mixed coupling of carbonyl

compounds is also possible when one carbonyl component is in excess and its olefin dimer is readily separable from the product mixture. Alternatively if the reduction potential of the carbonyl components are quite different mixed coupling can be synthetically useful. This is particulary true for diaryl ketones where the second reduction potential is less negative than the first reduction potential of the ketones. The initial step is thus a two electon transfer to the diaryl ketone yielding a dianion which adds in the conventional fashion producing a pinacol which is further deoxygenated. This procedure was used by Coe and Scriven in a new stereoselective synthesis of the antitumuor agent Tamoxifen (**31**).[80] The reaction sequence (**Scheme 25**) was a suitable route towards a series of Tamoxifen analogues by simply altering the alkoxy group on the benzophenone nucleus.

3.3.2 Mechanism of the Reductive Coupling

The accepted mechanism of the reductive coupling of carbonyl compounds to alkenes is depicted in **Figure 19**. The initial step is a one electron transfer from the titanium species to the carbonyl group affording a radical anion which dimerises to give the primary pinacol product (**115**). The use of low temperatures ensures that the pinacol (**115**) is the final reaction product with no deoxygenation to the corresponding alkene.

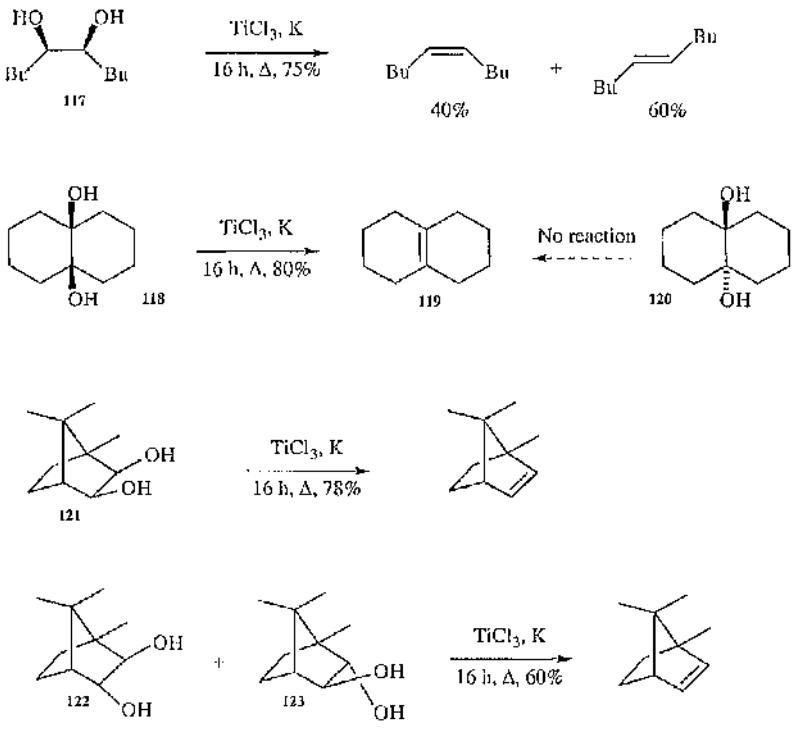
Figure 19 - Mechanism of Reductive Coupling



McMurry *et al.*[72] envisaged four possible mechanisms for the deoxygenation of the intermediate pinacol (**Figure 19**) and devised a series of experiments aimed at distinguising between them. Paths A and B were similiar in that both involved a five

membered-ring intermediate with both oxygens bound to a common titanium atom. It was feasible that this intermediate could break down by a concerted (Path B) or non-concerted pathway (Path A) in which the two C-O bonds were broken at different times. However when a diol of known stereochemistry like *meso*-5,6-dihydroxydecane (**117**) was subjected to the coupling conditions a mixture of geometrical isomers was isolated in good yield suggesting that the deoxygenation was in fact non-concerted (**Scheme 26**). Path C assumed that the two oxygens were not bound within a five-membered intermediate but bound to two separate titanium atoms.

Scheme 26



These pathways were distinguised by realising that reduction of *cis*-9,10-decalindol (**118**) proceeded smoothly affording the octahydronaphthalene (**119**) in high yield however the *trans*-diastereoisomer (**120**) gave no reaction (**Scheme 26**). It was clear that due to the close proximity of the oxygen atoms in the *cis*-isomer, a five-membered ring intermediate could be formed which would further break down. If path C was a viable mechanism one would expect the *trans*-isomer to be reduced as unlike path A the oxygens do not need to be close in space. However as no reduction was observed it was clear that path C did not represent a viable reaction mechanism. Path D differs from path A in that one assumes that the reaction is occurring in a heterogeneous phase on the surface of an active titanium particle. The pathways were distinguised by considering the reaction rate for the deoxygenation of the *cis*-

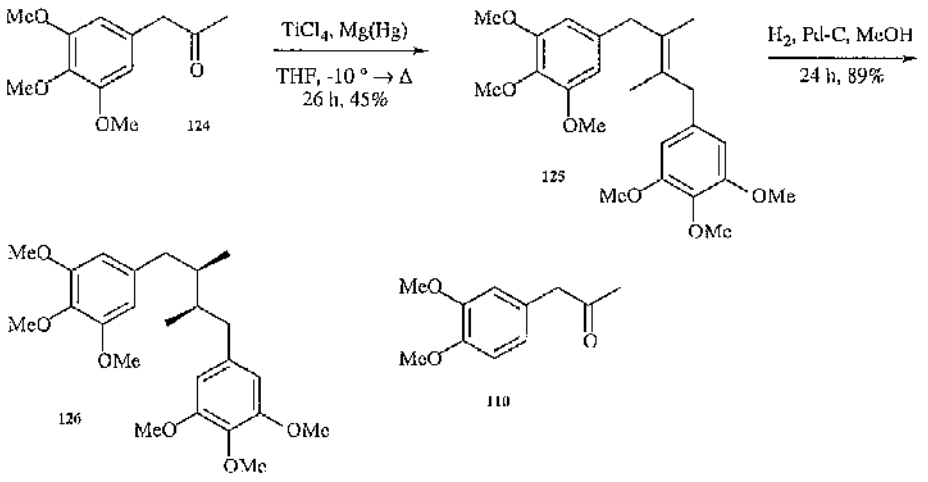
camphanediol (**121**) versus that for a mixture of the *trans*-isomers (**122** + **123**). If a five-membered ring intermediate was involved one would expect the *cis*-isomer to deoxygenate rapidly with respect to the *trans*-isomers where the oxygen atoms are further apart in space. McMurry *et al.* found however that the isomers were reduced at an equal rate strongly suggesting that a five-membered ring intermediate was not involved (**Scheme 26**).

As a consequence of their experiments the authors concluded that the intermediate pinacol was deoxygenated in a heterogeneous fashion on the surface of a broad titanium particle affording the alkene (**116**).

3.3.3 First Attempts at Reductive Coupling

During their investigation on the intramolecular oxidative coupling of aromatic compounds, Carroll *et al.*[81] required the diarylbutane (**126**) arising from the reductive coupling of 3,4,5-trimethoxyphenylacetone (**124**) (**Scheme 27**). The mixture of geometrical isomers formed could be easily separated by recrystallisation from EtOH affording pure (*E*)-alkene (**125**) in good yield. Catalytic hydrogenation of (**125**) in MeOH over palladium on charcoal afforded (±)-(**126**) in high yield. Encouraged by this result on a very similiar substrate coupled with the fact that 3,4-dimethoxyphenylacetone (**110**) is commercially available we decided to adopt this methodology.

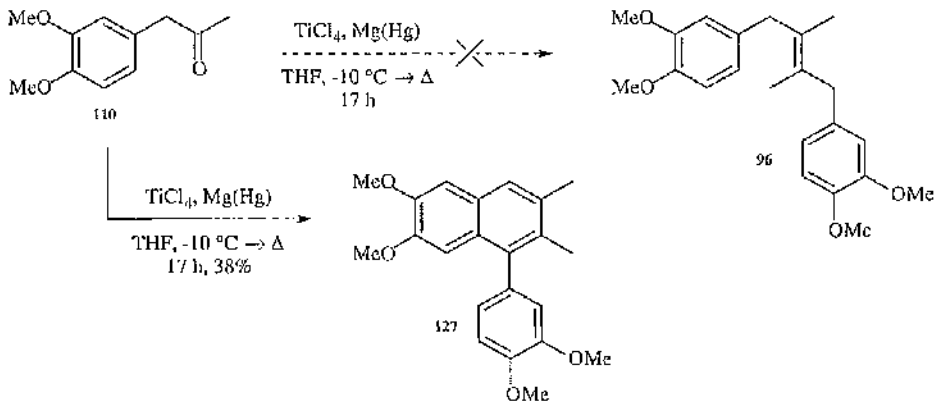
Scheme 27



Addition of a THF solution of (**110**) to the Mg(Hg)-TiCl4 system at 0 °C followed by 17 hours at reflux was carried out as reported[81] on a 2.57 mmol scale (**Scheme 28**). The crude product was obtained as a heavy amber coloured oil which

was crystallised from EtOH affording orange crystals in 38% yield. It was clear however by TLC and ^{1}H NMR spectroscopy that this product was not the expected alkene (**96**). TLC revealed a single less polar spot that was not stained by acidified $KMnO_4$ and the ^{1}H NMR spectrum was more complicated than one would expect. Two singlets at δ 2.07 and 2.28 were observed each integrating for three protons along with four separate methyl ether resonances. A multiplet integrating for two protons along with a doublet and three separate singlets, each integrating for one proton, were recorded in the aromatic region of the spectrum. A parent ion at *m/z* 352 was observed in the mass spectrum and the ^{13}C NMR spectrum showed eighteen peaks excluding the methyl ethers which appeared as a single resonance. The spectrum indicated the presence of six CH groups and six quaternary carbons in the aromatic region along with two separate methyl resonances at δ 17.2 and δ 22.1. It was clear from the analytical data that the product we had isolated was in fact 1-(3,4-dimethoxyphenyl)-2,3-dimethyl-6,7-dimethoxynaphthalene (**127**). The naphthalene (**127**), which had previously been synthesised using an alternative route by Muller and Vajda, gave a melting point in agreement with that reported.[82] We decided to repeat the reaction monitoring regularly by TLC although not heating at reflux which we felt was giving us this curious result. After stirring overnight at ambient temperature TLC showed no starting material and two distinct spots neither of which was stained by $KMnO_4$. The crude product was purified by silica gel flash chromatography and naphthalene (**127**) was isolated in 41% yield along with an unknown compound in low yield which was clearly not alkene (**96**) by ^{1}H NMR spectroscopy. As a consequence of not being able to repeat the work of Carroll *et al.*[81] on our substrate, we turned our attention to alternative methods.

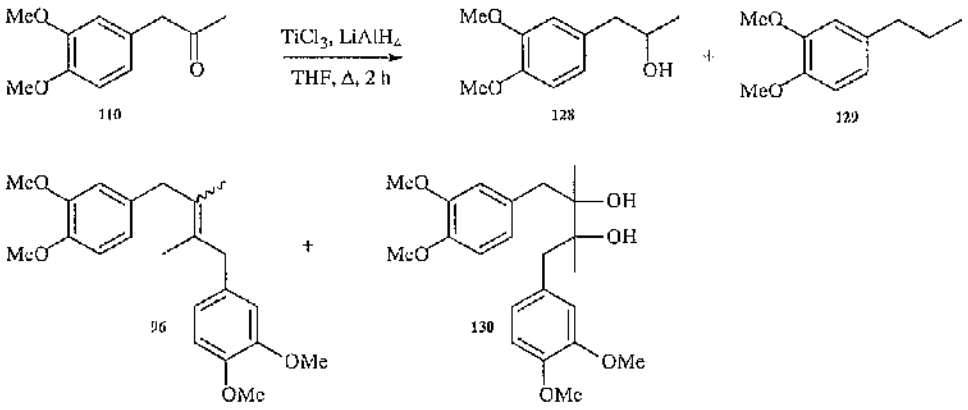
Scheme 28



Addition of three equivalents of lithium to a stirring suspension of $TiCl_3$ in dry DME followed by heating at reflux resulted in a colour change of purple to a deep

black heterogeneous mixture. Ketone (**110**) was added to the cooled solution and reflux maintained for 16 hours following the general procedure of McMurry *et al.*[72] The crude product was shown however to be a complex mixture by ^{1}H NMR spectroscopy and was not further investigated. The same result was observed when potassium metal was used in place of lithium. The $TiCl_3$-$LiAlH_4$ reagent, introduced by McMurry and Fleming[70], was also investigated and the crude product showed several spots by TLC with no starting material evident (**Scheme 29**). A ^{1}H NMR of the crude mixture showed it to be predominately alcohol (**128**) clearly arising as a result of a conventional $LiAlH_4$ type reduction. Silica gel flash chromatography (2:1 hexane-EtOAc) allowed us to isolate a further three compounds in very low yield. The first was identified by ^{1}H and ^{13}C NMR spectroscopy as 3,4-dimethoxyphenylpropane (**129**) isolated as an oil, a product of deoxygenation of the intermediate radical anion. A second fraction gave a solid in low yield which was identified by ^{1}H NMR spectroscopy as the desired alkene although present as a mixture of geometrical isomers in *ca.* 1:1 ratio. Two singlets around δ 1.7 combined with a further two around δ 3.5 arising from the methyl and methylene groups respectively were consistent with the proposed structure. The spectrum was similiar to that of the trimethoxy analogue (**125**) reported by Carroll *et al.*[81] and a TLC sample was intensely stained by $KMnO_4$. The final fraction ran close to the baseline on TLC and was stained red when developed with vanillin. A ^{1}H NMR spectrum revealed the product to be a diastereoisomeric mixture of pinacols (**130**) which was later confirmed during its synthesis by an alternative route (**Section 3.3.4**). The reaction could not be optimised and use of an alternative batch of $TiCl_3$ failed to overcome the problem.

Scheme 29



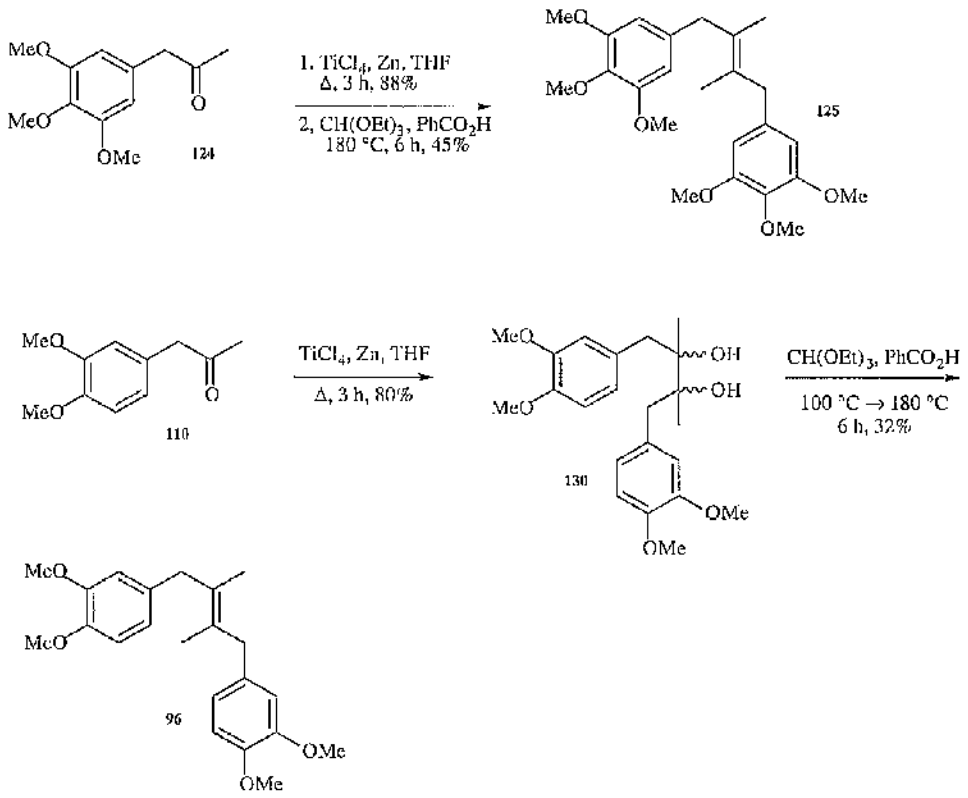
Encouraged by the fact that we had managed to synthesise (**96**) *albeit* in very low yield we attempted to use the optimised procedure for carbonyl coupling reported by McMurry *et al.*[73] The Zn-Cu couple was synthesised as reported; however attempts

to form the crystalline $TiCl_3$ $(DME)_{1.5}$ were disappointing. $TiCl_3$ was suspended in dry DME and heated at reflux under an argon atmosphere for two days as reported. We however isolated an off-white solid after filtration in contrast to a blue crystalline substance reported by the authors. It was clear from this result along with the preceeding experiment (**Scheme 29**) that our $TiCl_3$ was clearly ineffective for this type of chemistry and we sought an alternative approach.

3.3.4 A Successful Coupling Procedure

Takeya *et al.*[83] required alkene (**125**) for the synthesis of some racemic dibenzocyclooctadiene lignans. It was prepared by a two step process *via* an intermediate pinacol which was deoxygenated affording a mixture of alkenes which could be readily separated (**Scheme 30**).

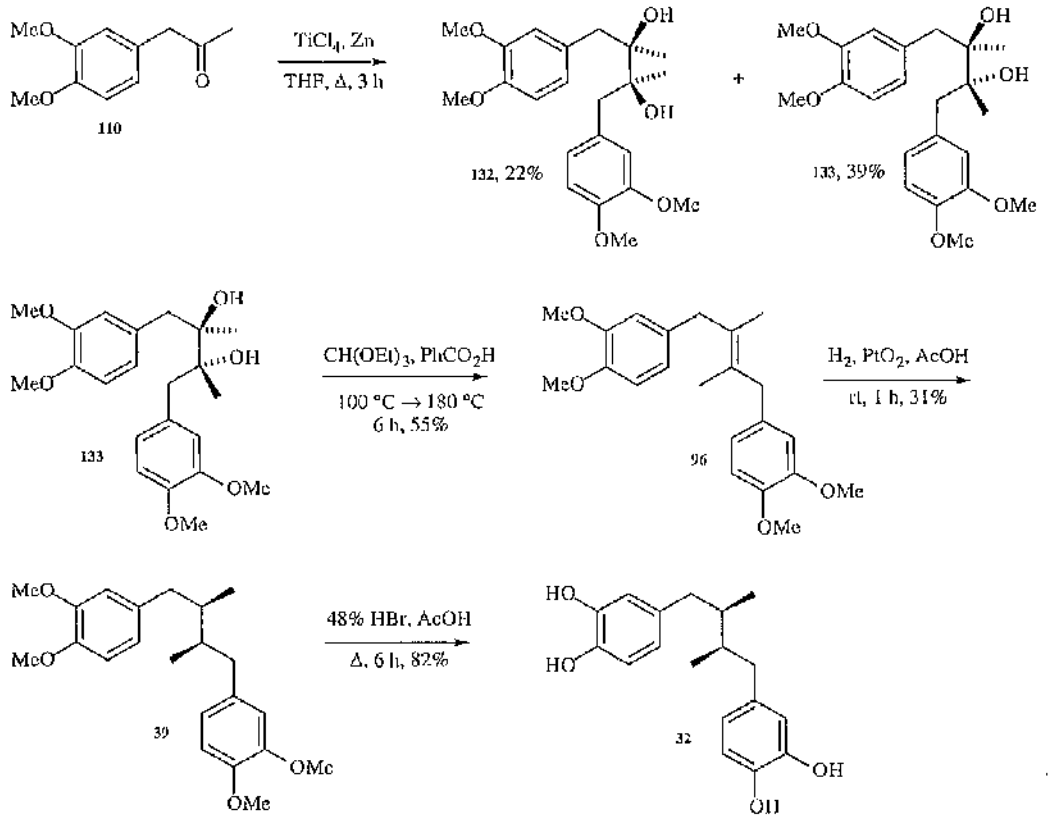
Scheme 30



$TiCl_4$ was added dropwise to a stirring solution of ketone (**110**) in THF resulting in a yellow-green suspension to which was added activated zinc dust portionwise. On heating, the mixture became a deep red homogeneous solution which was heated at reflux for 3 hours as reported. The crude product, isolated as an oil, was

crystallised from Et_2O affording pinacol (**130**) in high yield (**Scheme 30**). Integration of the methyl group singlets in the ^1H NMR spectrum revealed a mixture of diastereoisomers in *ca.* 1:1 ratio.

Scheme 31



Deoxygenation of the pinacol mixture (**130**) was carried out as reported following the general procedure of Josan and Eastwood.[84] A solution of (**130**) in triethyl orthoformate was heated at 180 ^oC in the presence of benzoic acid while allowing EtOH to distil from the reaction mixture. TLC revealed a single less polar spot which was stained by acidified $KMnO_4$. The crude product was recrystallised from EtOH affording the novel (*E*)-alkene (**96**) in relatively good yield. At this point we tentatively assigned (**96**) the *trans*-configuration in accordance with the result reported for the trimethoxy analogue[83] and this was later confirmed by hydrogenation. It was interesting that crystallisation of the mother liquor afforded the *cis*-alkene (**131**) as a solid in low yield whereas the trimethoxy analogue is reported as an oil. Several recrystallisations were however needed to obtain an analytically pure sample, showing no (*E*)-alkene in the ^1H NMR spectrum, resulting in this low yield.

We felt that it would be synthetically more attractive if the separation of isomers could be effected at an earlier stage. We serendipitously discovered that

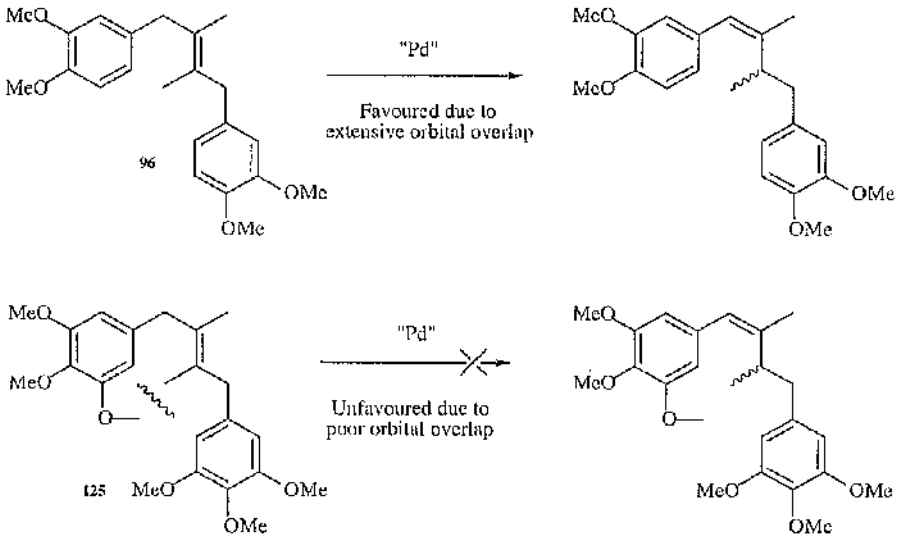
recrystallisation of the pinacol mixture (**130**) from EtOH afforded the pure *meso* pinacol (**132**) in 22% yield which was fully characterised (**Scheme 31**). A futher crop of material was isolated in 39% yield and was shown by ^{1}H NMR spectroscopy to be a mixture of the racemic and *meso* pinacols (**133**) in a 2:1 ratio. Deoxygenation of (**133**) afforded the pure (*E*)-alkene (**96**) in good relative yield which was fully characterised. With (**96**) in hand we turned our attention to reduction of the double bond following the successfully reported methods for the trimethoxy analogue.

Carroll *et al.*[81] has reported the reduction of alkene (**125**) using palladium on charcoal in MeOH affording the racemic diarylbutane (**126**) in excellent yield (**Scheme 27**). A mixture of our alkene (**96**) was thus stirred under a hydrogen balloon over Pd-C overnight. TLC of the mixture showed a very close running spot to starting material that was not stained by $KMnO_4$ and the filtered residue was concentrated to give a semi-solid. ^{1}H NMR spectroscopy showed a more complex spectrum than one would expect with an apparent triplet at δ 0.84 along with four separate resonances for the diastereotopic benzylic protons of (**39**). It was clear that we had formed a mixture of the (±)-and *meso*-diarylbutanes which could not be separated by chromatography or recrystallisation. By comparison of our ^{1}H NMR spectrum with the one reported for the *meso*-compound[6] the ratio was found to be 3:2 in favour of the racemate (**39**).

The same result was obtained when the reaction was carried out in AcOH or EtOAc even at reduced temperatures. We suspect that this curious result is a consequence of our alkene (**96**) being able to adopt a planar conformation. Isomerisation of the double bond into the benzylic position would be thermodynamically favourable due to overlap of the π electrons of the double bond with the aromatic π system. In contrast, the trimethoxy analogue (**125**) should experience steric hindrance between the methyl group of the aliphatic chain and the methoxyl group on the ring (**Figure 20**). As a result of this, we expect that the aromatic ring could pucker out of planarity thus reducing the probability and rate of isomerisation with respect to double bond reduction.

The hydrogenation of (**96**) in EtOAc over 5% rhodium on charcoal gave only starting material. However when the reaction was performed in AcOH, there was a slight conversion into product. It was encouraging that by ^{1}H NMR spectroscopy we could see little of the *meso*-alkene and this prompted us to attempt the reaction at a higher pressure. Reduction of (**96**) in AcOH at an initial pressure of 6 barr gave a mixture chiefly composed of the racemic diarylbutane (**39**).

Figure 20



Close inspection of the ^{1}II NMR spectrum revealed some starting material along with the *meso*-diarylbutane (**47**) although the ratio had dropped significantly from 1:9 in favour of the racemate. There was also signs of extra resonances in the aliphatic region of the spectrum which we assumed to be a result of aromatic ring reduction. The reaction was also performed at 7 barr in an attempt to consume all the starting material. Unfortunately a ^{1}H NMR spectrum of the crude residue showed no signs of aromaticity and a large multiplet in the aliphatic region, clearly a result of aromatic ring reduction. The use of Raney nickel as a catalyst failed to give any useful result with little consumption of the starting material. It was clear from ^{1}H NMR spectroscopy of the crude product that isomerisation had been effected persuading us that high pressure hydrogenation would not give a useful result.

Takeya *et al.* have reported that hydrogenation of (*E*)-1,4-bis-(3,4,5-trimethoxyphenyl)-2,3-dimethylbut-2-ene (**125**) using platinum (IV) oxide afforded the racemic diarylbutane (**126**) in high yield.[83] Encouraged by this result we decided to adopt their reaction conditions and repeated their work on our very similiar substrate. Our initial attempt concentrated on stirring a solution of the (*E*)-alkene (**96**) in AcOH over PtO_2 under hydrogen at atmospheric pressure overnight. To our surprise the ^{1}H NMR spectrum showed no resonances for aromatic protons and a large multiplet in the aliphatic region. This was consistent with aromatic ring reduction as we had experienced using rhodium on carbon at an increased pressure. We decided to repeat the reaction and monitor the consumption of starting material regularly by TLC. After one hour no starting material was evident and a homogeneous compound was observed which did not give an intense yellow spot when developed by acidified $KMnO_4$ stain. The crude residue was shown to be a 10:1 ratio of diastereoisomers of (**39**) in favour

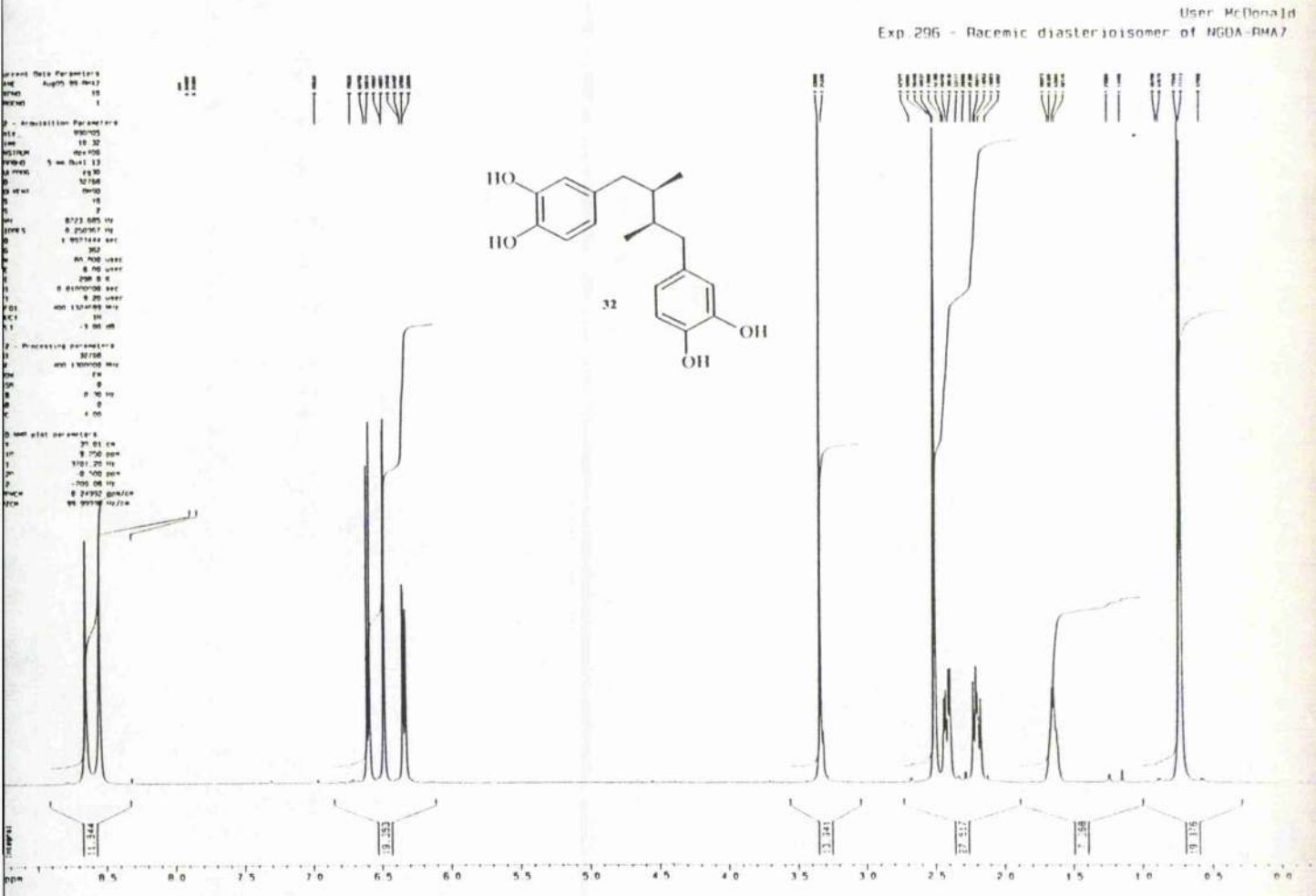
of the racemate. There was also evidence of aromatic ring reduction. However this contaminant could be removed by silica gel chromatography affording pure (**39**) albeit as a ratio of diastereoisomers. We found that attempts to crystallise pure racemic (**39**) out of the mixture could only be effected by slow evaporation of a saturated MeOH solution. Attempts to induce crystallisation by scratching or cooling enriched the concentration of the racemate, however it was not diastereoisomerically pure. We isolated the pure racemic diarylbutane (**39**) as needles in low yield that gave a melting point and ^{1}H NMR spectrum (**Figure 21**) in agreement with those reported.[48] The ^{13}C NMR spectrum showed the expected eleven resonances and a parent ion at *m/z* 358 in the mass spectrum was consistent with the proposed structure.

Figure 21 - ^{1}H NMR spectrum of (±)-diarylbutane (39)

The deprotection of (**39**) to give our target compound thankfully went uneventfully affording (**32**) as a tan coloured solid in high yield. As reported previously (**Section 3.1.6**), this compound has received little interest in the literature and only a melting point is presented. We herein report full characterisation for (**32**) including a melting point which was is agreement with that reported.[44] The ^{1}H NMR spectrum shown in **Figure 22** is clearly in agreement with the proposed structure. A

low field 3H doublet at δ 0.72, a 1H multiplet and two 1H doublet of doublets were observed for the methyl, methine and methylene protons of the aliphatic sidechain respectively. The sustitution patterns of the aromatic nuclei was clear as were the two phenolic protons which appeared as two broad doublets around δ 8.4. The IR spectrum showed two distinct phenol stretches at 3377 cm^{-1} and 3474 cm^{-1} along with two stretches in the 1500-1600 cm^{-1} region for the aromatic nuclei. Nine peaks in the ^{13}C NMR spectrum coupled with a parent ion at *m/z* 302 in the mass spectrum confirmed that we had succesfully isolated our target molecule in high purity.

Figure 22 - ^{1}H NMR spectrum of (±)-NDGA

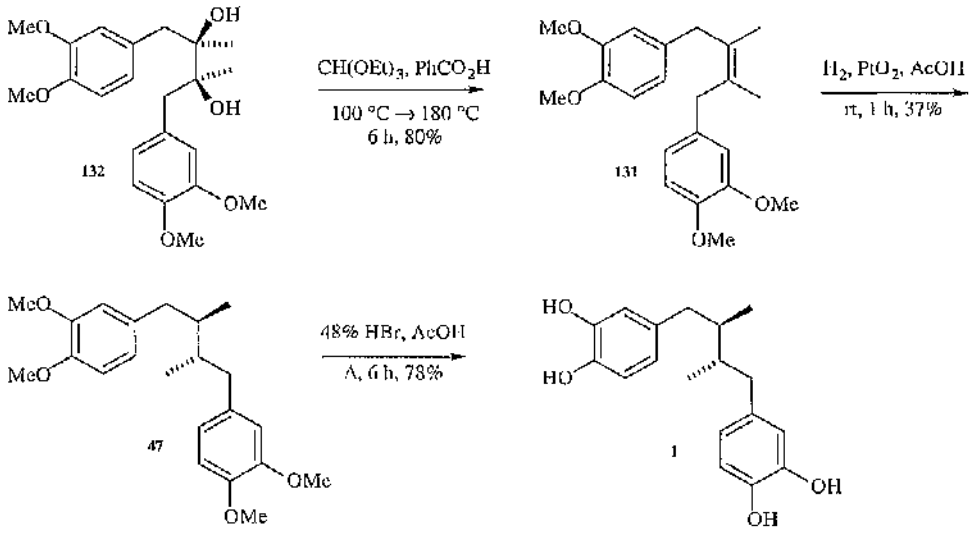


3.3.5 Synthesis of *meso* - NDGA

Having the pure *meso*-pinacol (**132**) in hand we decided to carry out the synthesis of *meso*-NDGA (**1**) as outlined in **Scheme 32**. The *syn*-deoxygenation was carried out as reported previously affording the novel (*Z*)-alkene (**131**) as crystals in good yield. Catalytic hydrogenation over PtO_2 presented us with the same problems we had encountered with the (*E*)-alkene (**96**). Recrystallisation of the crude residue from MeOH gave the *meso*-diarylbutane (**47**) as a 19:1 ratio of diastereoisomers (^{1}H

NMR) in moderate yield. A further recrysallisation was needed to obtain pure (**47**) albeit in a lower yield. The combined mother liquors were shown by ^{1}H NMR spectroscopy to be mainly the *meso*-compound (**47**), however no suitable material could be recovered. Demethylation was carried out in refluxing hydrobromic acid affording NDGA (**1**) as tan coloured crystals in good yield. A ^{1}H NMR spectrum and melting point were in agreement with those reported for the natural product.[42]

Scheme 32



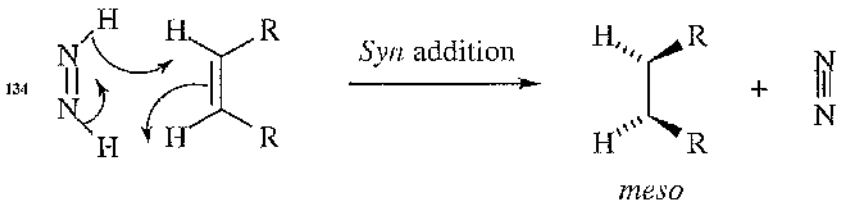
3.3.6 Alternative reduction attempts

Due to the disappointing yields obtained for the reduction of the (*E*)-alkene (**96**) we were keen to attempt an alternative method which would result in no isomerisation or aromatic ring reduction.

3.3.6.1 Diimide chemistry

Diimide (**134**) is an unstable compound that is generated *in situ* and used for the hydrogenation of non-polar multiple bonds. It is generally formed by the oxidation of hydrazine and its derivatives and has been shown to hydrogenate double bonds in a *syn*-fashion. The mechanism of hydrogenation, depicted in **Figure 23**, involves a synchronous delivery of hydrogen through a cyclic transition state. Diimide does not lead to isomerisation of double bonds and its high functional group selectivity gives it some advantages over many catalytic processes.

Figure 23 - Mechanism of Diimide Reduction



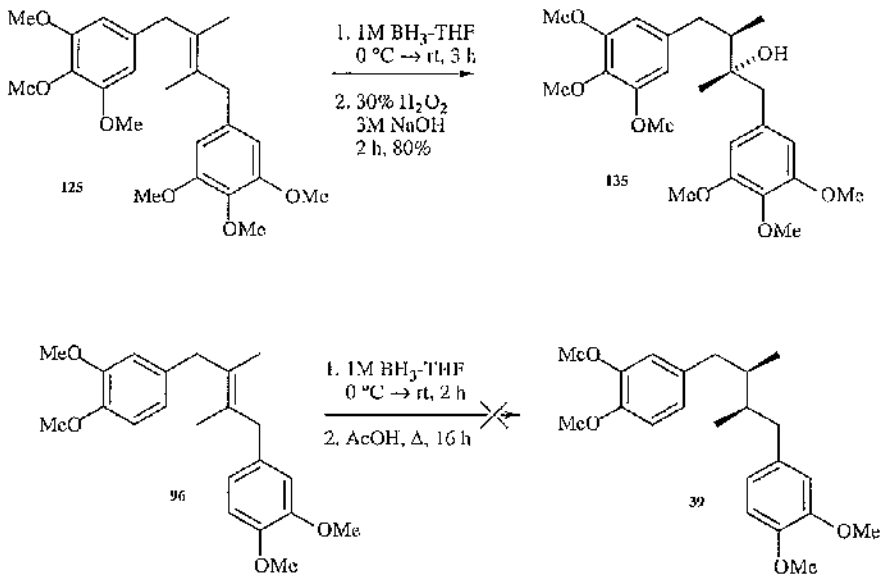
Our first attempt used the general method of Wade and Amin employing a EtOAc-hydroxylamine system.[85] The crude product, isolated as a solid, was shown by ^{1}H NMR spectroscopy to be only starting material with no signs of the reduced product. The same result was obtained using the general procedure of Moriarty *et al.*[86] using hypervalent iodine oxidation of hydrazine to generate diimide. We then turned our attention to more conventional methods; however the thermal decomposition of tosylhydrazine afforded only staring material as did the acid catalysed decomposition of potassium azodicarboxylate. It has been documented in the literature that increased substitution around the double bond is consistent with lower yields of reduced product being isolated.[87] We feel as a consequence of seeing no reduced product in the crude ^{1}H NMR spectra, that the *tetra* substituted double bond of (**96**) is simply too hindered to undergo this type of chemistry.

3.3.6.2 Hydroboration-Protonolysis

Takeya *et al.*[88] required the *threo*-butanol (**135**) for the synthesis of some dibenzocyclooctadiene lignans (**Scheme 33**). It was obtained from the (*E*)-alkene (**125**) by a conventional hydroboration procedure. We realised that the intermediate tri-organoborane could be trapped with AcOH allowing access to the racemic diarylbutane (**39**) using the procedure of Brown and Murray.[89]

Hydroboration of (**96**) was carried out as reported; however the H_2O_2-NaOH mixture was replaced with an excess of AcOH and the mixture was heated at reflux overnight. A ^{1}H NMR spectrum of the crude residue showed no starting material however there was no sign of the racemate (**39**) and the reaction was not further investigated. It is worthwhile to note that Brown and Murray found that when the boron atom was attached to a highly branched alkyl group protonolysis did not proceed even under drastic conditions.[89] These findings pursuaded us not to pursue this type of chemistry.

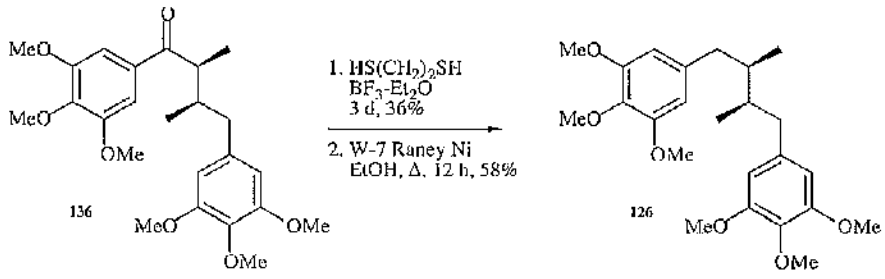
Scheme 33



3.3.7 Conclusion

We have spent a considerable amount of time on the synthesis of the racemic diastereoisomer of NDGA (**32**) resulting in a four step synthesis through which we isolated our target in low overall yield. The initial route we decided to follow (**Section 3.2.1**) was particulary disappointing as the racemic diketone (**65**) could be isolated in high purity with the stereochemistry of the methyl groups successfully in place. It is interesting that the simaliar substrate (**136**) was reduced to the diarylbutane with great difficulty (**Scheme 34**).[90] The Wolff-Kischer and Clemmensen reduction gave no useful product nor did a variety of hydrogenation experiments. The authors isolated (**126**) in low yield *via* reduction of the derived dithioacetal clearly giving further evidence of the difficulty associated with the reduction of these types of systems.

Scheme 34



Our succesful synthesis of racemic NDGA (**32**) is overshadowed by the problems associated with the hydrogenation of the hindered (*E*)-alkene (**96**). It is surprising that the trimethoxy analogue is reported to be succesfully hydrogenated without any signs of isomerisation or over reduction. The first step can be carried out on a large scale using cheap readily available materials giving a mixture of pinacol diastereoisomers that can be partially separated. No attempt was made to carry this reaction out asymmetrically as a result of little work reported in the literature. The pinacol coupling of aromatic and α,β–unsaturated aldehydes using a titanium (III)-magnesium (II) complex has been reported to afford pinacols with a high *threo*-selectivity.[91] There is however no reaction reported with aliphatic substrates warning us not to attempt these conditions. Our route also allows access to *meso*-NDGA (**1**) giving material of higher purity than that obtained commercially. There is however still problems associated with the alkene reduction. However we have to date not discovered a suitable system to overcome this problem.

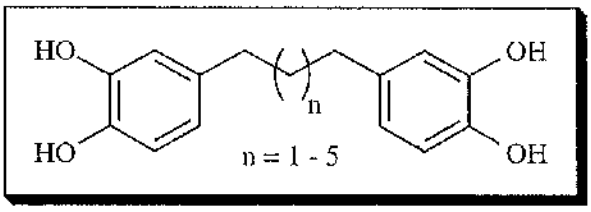
4

Synthesis of NDGA Analogues

4.1 Introduction

We were interested in the synthesis of a series of NDGA analogues which could help in the determination of structure activity relationships. The first set of compounds synthesised is depicted in **Figure 24** which although sharing the bis catechol functionality, differed in the distance between the aromatic nuclei. We also synthesised a range of mono phenolic compounds in an attempt to ascertain whether the catechol functionality was important for activity. The presence of an amide linkage between the aromatic nuclei would give a more conformationally restricted analogue which might show enhanced activity. With this in mind, synthesis of a series of amides was also undertaken containing both catecholic and phenolic aromatic nuclei. This chapter describes our work undertaken in achieving our aims concluding with a series of preliminary test data.

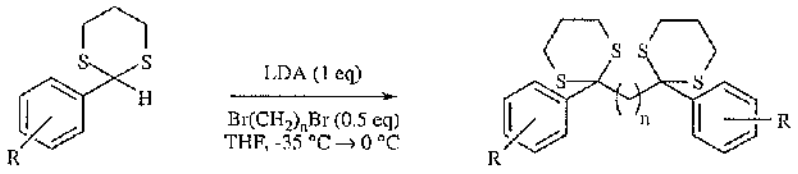
Figure 24



4.1.1 A Common Synthetic Route

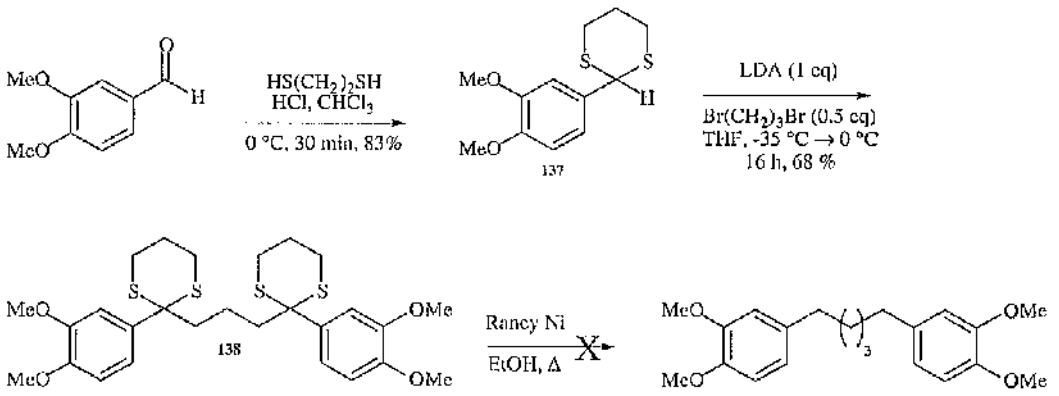
A series of diphenyl alkanediamines have been synthesised by Fliender *et al.*[94] as potential fibrinolytic agents. The key step in their synthesis was the alkylation of an aromatic dithiane with a suitable dihaloalkane (**Scheme 35**). We felt that this method was ideal for our needs as reduction of the dithiane functionality followed by deprotection would furnish our target compounds. Furthermore, simply altering the substituents on the aromatic nucleus along with utilising a variety of commercially available dihaloalkanes would give rise to a range of NDGA analogues.

Scheme 35



The required 2-(3,4-dimethoxyphenyl)dithiane (**137**) was successfully synthesised in high yield following the procedure of Seebach *et al.*[95] for the corresponding 2-phenyl analogue (**Scheme 36**). The product was obtained as shiny crystals giving a melting point in agreement with that reported.[94] The ^{1}H NMR spectrum revealed a 2H and 4H multiplet in the aliphatic region along with a deshielded methine singlet at δ 5.13 giving further evidence for the proposed structure. With dithiane (**137**) in hand, we turned our attention to the coupling procedure following the reported method of Fliedner *et al.*[94] Addition of one equivalent of *n*-BuLi to a cooled solution of dithiane (**137**) in THF gave a yellow solution to which was added 0.5 equivalents of 1,3-dibromopropane dropwise. After the mixture was left at 0 °C overnight, TLC indicated no starting material and a homogeneous slower running spot. We were not able to obtain a suitable sample by recrystallisation, as reported, so the crude residue was purified by silica gel flash chromatography affording the bis(dithiane) (**138**) as a solid in moderate yield. (**138**) gave a melting point in agreement with that reported[94] and a ^{1}H NMR spectrum was consistent with the proposed structure.

Scheme 36



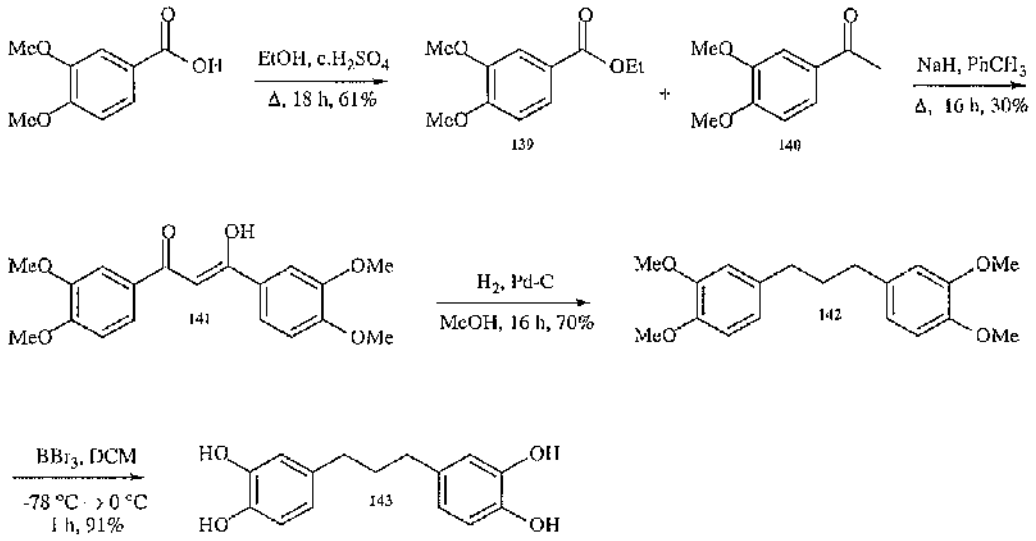
Reduction of the bis(dithiane) (**138**) was attempted in refluxing EtOH over Raney Ni, however TLC of the reaction mixture after heating overnight showed only starting material. The same result was observed using freshly prepared W2-Raney Ni

and even carrying the reaction out under a hydrogen atmosphere showed no product formation by TLC. It was suspected that the catalyst was inactive, however when a small sample was allowed to dry out under controlled conditions, it sparked violently and caught fire so it was clearly active. Attempted reduction of dithioacetal (**137**) was also unsuccessful prompting us to abandon this common synthetic route.

4.1.2 Synthesis of a C3-Bridge analogue

A series of dibenzoylmethane derivatives have been synthesised by Choshi *et al.* as potential inhibitors of the mutagen 2-nitrofluorene.[96] The key step in their synthesis was the coupling of an aromatic ester with a substituted acetophenone using sodium hydride in refluxing benzene. We decided to repeat their method and the synthesis of the C3 bridge analogue (**143**) is depicted in **Scheme 37**.

Scheme 37



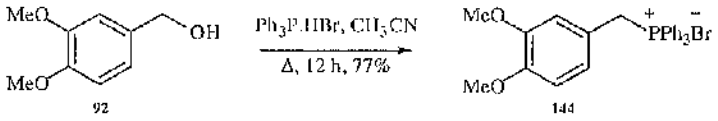
3,4-Dimethoxybenzoic acid was esterified as reported[96] affording the ethyl ester (**139**) as a colourless oil in moderate yield. A 3H triplet and 2H quartet in the ^{1}H NMR spectrum along with a characteristic ester resonance at δ 167 in the ^{13}C NMR spectrum confirmed the proposed structure. The coupling of ester (**139**) with 3,4-dimethoxyacetophenone (**140**) was carried out as reported although benzene was replaced by toluene for toxicity reasons. The crude product was recrystallised from EtOH affording the β-diketone (**141**) as bright orange crystals giving analytical data in agreement with those reported.[96] The low yield was disappointing, however pure (**141**) could be simply obtained by a single recrystallisation of the crude residue avoiding the need for column chromatography. An olefinic and broad hydroxyl proton at δ 6.8 and

δ 14.4, respectively, in the ^{1}H NMR spectrum indicated that (**141**) exists exclusively as the enol form in neutral solution. A characteristic stretch at 1600 cm^{-1} for an enolised 1,3-diketone and a parent ion at *m/z* 344 gave further evidence for the proposed structure. Catalytic hydrogenation of diketone (**141**) was carried out in MeOH over palladium affording the diarylpropane (**142**) in good yield. This compound has been synthesised by Tamura *et al.*[97] by an alternative route and gave a melting point in agreement with that reported. The ^{1}H NMR spectrum revealed a 2H multiplet and a 4H triplet for the methylene and benzylic methylene protons respectively. The IR spectrum showed no stretches in the carbonyl region and a parent ion at *m/z* 316 in the mass spectrum confirmed that reduction had been successful. Boron tribromide demethylation was carried out following the general procedure of McOmie *et al.*[55] The crude product showed a polar homogeneous streaky spot by TLC that was intensely stained by I_2. This product could not be purified by recrystallisation so was subjected to silica gel flash chromatography affording diarylpropane (**143**) as a solid in excellent yield, giving a melting point in accordance with that reported.[97] The ^{1}H NMR spectrum showed no resonances for the methyl ethers while the ^{13}C NMR spectrum showed the expected eight resonances. Broad phenolic stretches at *ca.* 3500 cm^{-1} in the IR spectrum coupled with a parent ion at *m/z* 260 in the mass spectrum were also consistent with the proposed structure.

4.1.3 Synthesis of a C4-Bridge analogue

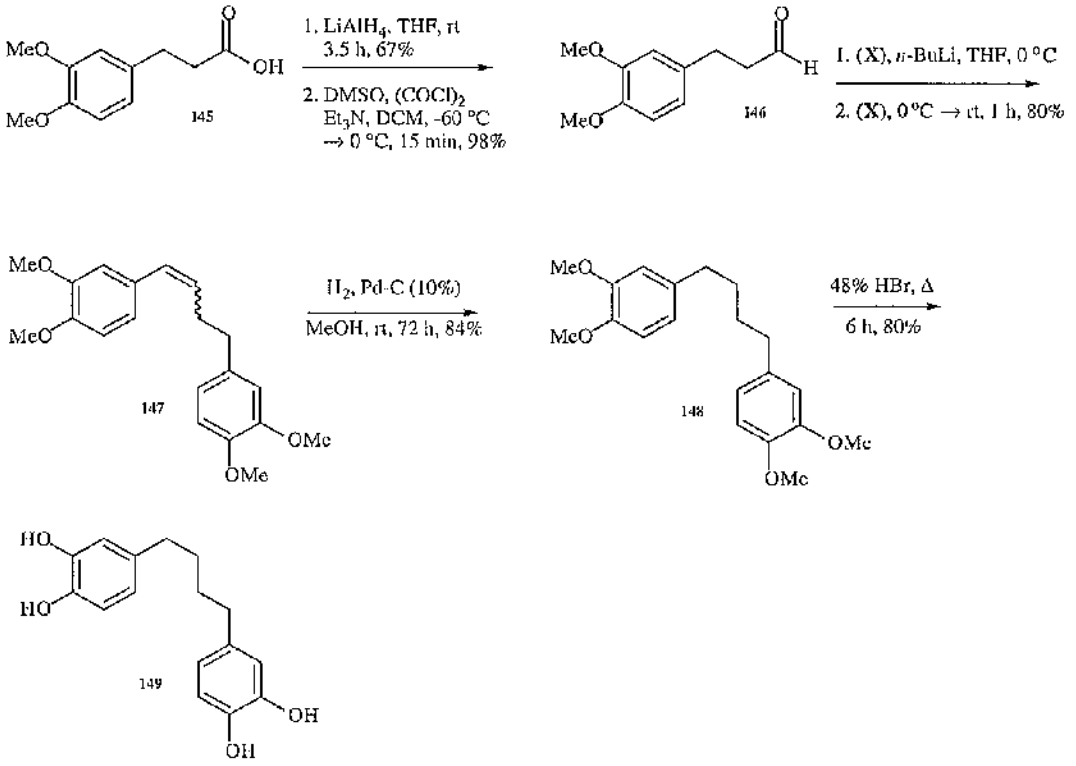
Gisvold *et al.*[98] have reported the synthesis of the diarylbutane (**149**) which showed antiseptic and antioxidant activities comparable with those of NDGA. Their synthesis was however low yielding using harsh conditions and we decided to try an alternative approach. Another procedure reported by Tamura *et al.*[97] involves a total of eight synthetic steps and we felt this was too long and cumbersome to repeat.

Scheme 38



In planning our own synthesis of (**149**) we felt that a 1,4-diketone could be synthesised easily by modifying our first approach to NDGA (**Chapter 3**). Our experience in the difficulty associated with the reduction of such systems however, persuaded us not to attempt such a pathway. Our successful synthesis of diarylbutane (**149**) using a Wittig olefination as the key step is depicted in **Scheme 39**.

Scheme 39



The phosphonium salt (**144**) was readily available from the substitution of 3,4-dimethoxybenzyl alcohol (**92**) with triphenylphosphine hydrobromide in refluxing acetonitrile (**Scheme 38**). The product was isolated as crystals in high yield and was subsequently fully characterised. The ^{1}H NMR spectrum of (**144**) showed a deshielded methylene doublet at δ 5.32 and a 15H multiplet in the aromatic region for the three phenylphosphine groups. A singlet at δ 22.4 in the ^{31}P NMR spectrum and a doublet at δ 30.6 in the ^{13}C NMR spectrum were all in agreement with the proposed structure. Our initial synthetic attempts towards aldehyde (**146**) followed the reported procedure of Padwa *et al.*[99] reducing acid (**145**) with borane followed by oxidation using PCC in DCM. Although the borane reduction went quantitatively giving a single slower running spot by TLC, the oxidation step using freshly prepared PCC was problematic and low yielding. The crude residue was subjected to flash column chromatography affording aldehyde (**146**) as a pale yellow oil in only 48% yield. $LiAlH_4$ reduction of acid (**145**) followed by distillation afforded the corresponding alcohol in moderate yield.[100] Swern oxidation[101] gave aldehyde (**146**) in excellent yield as a colourless oil that was pure enough to use without further purification. Two triplets at δ 2.77 and 2.91 and a broad singlet at δ 9.62 for the aldehyde proton were observed in the ^{1}H NMR spectrum. The expected eleven peaks were recorded in the ^{13}C NMR spectrum including the carbonyl resonance at δ 202 which were in

agreement with data reported.[99] With both coupling partners successfully synthesised, we turned our attention to the Wittig olefination.

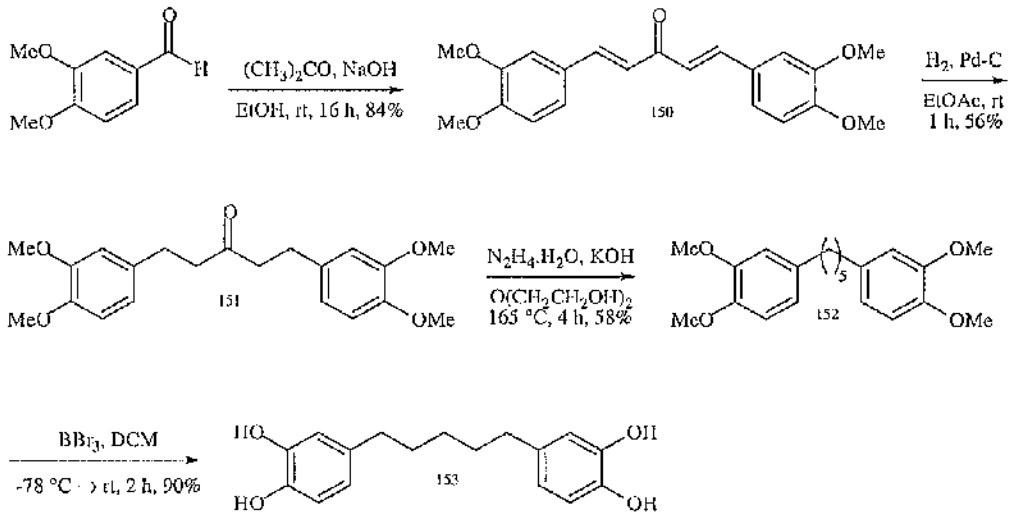
Addition of 1.1 equivalents of *n*-BuLi to a cooled suspension of (**144**) gave a deep red homogeneous solution to which aldehyde (**146**) was added dropwise. After stirring at rt for 1h, TLC showed a single close running spot which was stained red by vanillin unlike the aldehyde which gave a blue colouration. The majority of the triphenylphosphine oxide byproduct could be removed by stirring the crude residue in chilled ether and filtering before final purification was achieved by silica gel flash chromatography. Alkene (**147**) was isolated as a solid in high yield with no attempts made to separate the geometrical isomers. Integration of the pertinent peaks in the ^{1}H NMR spectrum revealed a ratio of 1.9:1 in favour of the *cis* isomer. The two isomers could be easily distinguised by the *J* value for the doublet of triplets arising from the homobenzylic methine proton with the *cis* isomer giving *J* values of 11.6 and 7.1 Hz and the *trans* isomer 15.8 and 6.8 Hz. The ^{13}C NMR spectrum was predictably quite complex, however the aliphatic methylene groups were observed as four distinct resonances between δ 30.9 and 36.0 and a parent ion at *m/z* 328 was also consistent with the proposed structure. In any event, control in the Wittig olefination was irrelevant towards our target as catalytic hydrogenation over palladium afforded the diarylbutane (**148**) as crystals in high yield giving a melting point in agreement with that reported.[98] The symmetry of the system was clearly evident from the NMR spectra with the ^{1}H spectrum revealing two triplets in the aliphatic region and the ^{13}C spectrum showing the expected ten resonances. The IR spectrum showed three stretches in the aromatic region and a parent ion at *m/z* 330 in the mass spectrum showed that hydrogenation had been successful. Although the general demethylation method of McOmie *et al.*[55] was successful, we later found that refluxing hydrobromic acid was just as effective although cheaper and easier to carry out on a large scale. The phenolic diraylbutane (**149**) was obtained in high yield as fawn crystals giving a melting point in agreement with that reported by Gisvold *et al.*[98] No signals for the methyl ethers were observed in the ^{1}H NMR spectrum and two broad singlets at δ 8.6 and 8.7 were indicative of the phenolic groups. These were also observed as broad phenolic stretches at *ca.* 3500 cm^{-1} in the IR spectrum and confirmed by a peak at *m/z* 274 in the mass spectrum.

In summary, the synthesis of the phenolic diarylbutane (**149**) was achieved in five steps using cheap readily available starting materials with a good overall yield of 35%.

4.1.4 Synthesis of a C5-Bridge analogue

The Friedel-Crafts acylation of veratrole with glutaryl dichloride had been reported as problematic by Fliedner *et al.*[94] and an alternative approach was required. Haworth and Lamberton required the diarylpentane (**153**) while investigating its vesicant properties.[102] The route used is depicted in **Scheme 40** which we were happy to follow with a few modifications.

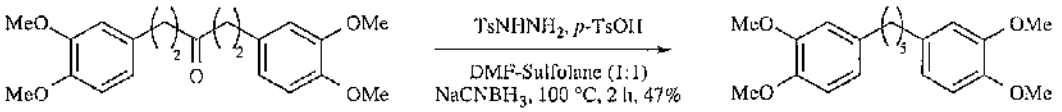
Scheme 40



The aldol condensation of veratraldehyde with acetone was carried out as reported[102] affording the unsaturated ketone (**150**) as bright yellow feathers in high yield. A melting point was in agreement with that reported and the *E* - configuration of the double bond was apparent from the ^{1}H NMR spectrum, showing two 1H doublets with a *J* value of 15.8 Hz. Catalytic hydrogenation over palladium was effected at atmospheric pressure affording the saturated ketone (**151**) in moderate yield. In one run TLC of the reaction mixture after 3 h revealed no starting material and two spots with one slower running and the other faster running than the starting material. The lower spot was stained red by vanillin and was expected to be the alcohol in agreement with data reported by Haworth and Lamberton.[102] Recrystallisation of the crude residue afforded the saturated ketone (**151**) in only 39% yield. However, we found that the mother liquors could be concentrated and oxidised back up to the ketone (**151**) using a standard Jones oxidation protocol. Using this method a further 30% of material could be recovered bringing the total yield up to a more respectable 69%. In latter experiments we discovered that monitoring the reaction regularly by TLC ensured formation of the ketone (**151**) as the major component after only 1 h. Using this

procedure we isolated ketone (**151**) in 56% yield as crystals that gave a melting point in agreement with that reported.[102] No olefinic signals were observed in the ^{1}H NMR spectrum and a 4H multiplet was recorded in the aliphatic region for the methylene funtionalities.

Scheme 41



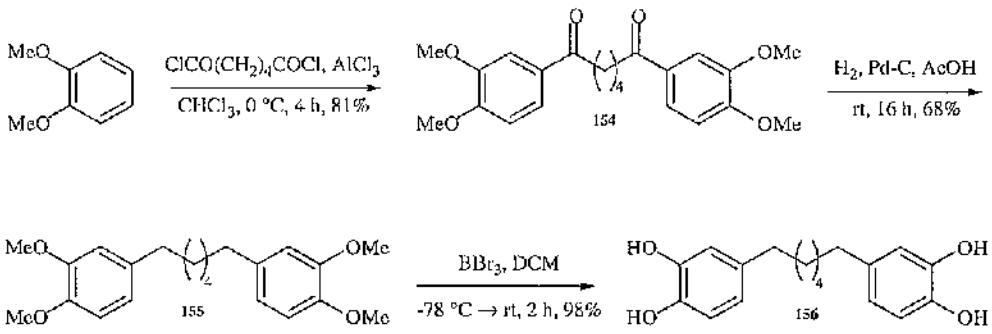
Haworth and Lamberton isolated the diarylpentane (**152**) in 50% yield by the Clemmensen reduction of (**151**) although no experimental detail was given. For toxicity reasons we were not keen to repeat this so initially opted for the general procedure reported by Hutchins *et al.*[103] This route, depicted in **Scheme 41**, involved the reduction of an intermediate tosylhydrazone with sodium cyanoborohydride under acidic conditions. Although the reaction afforded (**152**) after column chromatography in moderate yield, we had problems in obtaining a sample free of the high boiling (245 °C) sulfolane solvent. A Wolff-Kischner reduction was carried out employing the modified general procedure of Haung-Minlon.[104] The reaction involved heating ketone (**151**) at an elevated temperature with hydrazine hydrate in the presence of potassium hydroxide (**Scheme 40**). The diarylpentane (**152**) was isolated as a solid in moderate yield giving a melting point in agreement with that reported.[102] The pertinent features in the ^{1}H NMR spectrum were a 4H triplet at δ 2.56 and two further muliplets in the aliphatic region integrating for a total of six protons. Boron tribromide demethylation following the general procedure of McOmie *et al.*[55] gave the phenolic diarylpentane (**153**) in excellent yield giving a melting point in agreement with that reported.[102] There were no resonances in the methyl ether region of the ^{1}H NMR spectrum and two broad stretches at *ca.* 3500 cm^{-1} in the IR spectrum gave strong evidence for the phenolic moieties. The expected nine resonances were observed in the ^{13}C NMR spectrum and a parent ion at *m/z* 288 in the mass spectrum was consistent with the proposed structure.

4.1.5 Synthesis of a C$_6$-Bridge analogue

The Friedel-Crafts acylation of veratrole with freshly distilled adipoyl dichloride (**Scheme 42**) was carried out as reported by Fliedner *et al.*[94] using anhydrous chloroform in place of tetrachloroethane. The diketone (**154**) was isolated as feathers in high yield giving a melting point in agreement with that reported.[94] The

regiochemistry of the addition was apparent from the ^{1}H NMR spectrum which showed two 1H doublets and a 1H doublet of doublets in the aromatic region. The ^{13}C NMR spectrum revealed the expected eleven resonances including the carbonyl functionality at δ 199. A parent ion at *m/z* 386 in the mass spectrum was consistent with incorporation of the two aromatic nuclei.

Scheme 42



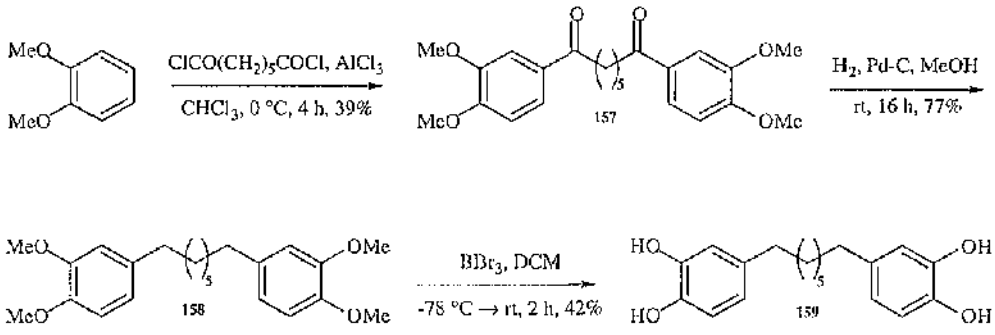
Diketone (**154**) has reportedly been reduced by Clemmensen and Wolff-Kischner reduction by Gisvold *et al.*[98] and Tamura *et al.*[97] respectively. We found that catalytic hydrogenation of (**154**) in AcOH over palladium offered milder reaction conditions affording the diarylhexane (**155**) as plates in moderate yield. A melting point was in agreement with that reported and a new 2H triplet at δ 2.55 in the ^{1}H NMR spectrum was observed for the benzylic methylene group. Boron tribromide demethylation was effected following the general procedure of McOmie *et al.*[55] affording the phenolic diarylhexane (**156**) in excellent yield giving a melting point in agreement with that reported. Broad stretches at *ca.* 3500 cm $^{-1}$ in the IR spectrum were consistent with methyl ether cleavage as were the ^{1}H and ^{13}C NMR spectra which showed no resonances for the methyl ethers. The mass spectrum revealed a parent ion at the expected *m/z* 302 and a combustion analysis offered further evidence for the purity of the compound.

4.1.6 Synthesis of a C7-Bridge analogue

The synthetic route towards the diarylheptane (**159**) was essentially that used for the diarylhexane (**156**) however pimeloyl dichloride was utilised as the linker in the Friedel-Crafts acylation (**Scheme 43**). Diketone (**157**) was isolated as crystals in moderate yield giving a melting point in agreement with that reported.[94] The low yield can be attributed to problems associated with crystallisation of the crude residual oil from a variety of organic solvents. In any case we felt we had isolated sufficient material to continue without having to subject the mother liquors to column

chromatography. As seen previously for (**156**) the ^{1}H NMR spectrum revealed a symmetrical compound showing a 1,3,4-substitution pattern on the aromatic nuclei. A parent ion at *m/z* 400 in the mass spectrum revealed that double addition had been successfully accomplished.

Scheme 43



Diketone (**157**) was sufficiently soluble to allow catalytic hydrogenation over palladium to be carried out in MeOH affording the saturated diarylheptane (**158**) as crystals in high yield. Kakemi *et al.*[105] have prepared diarylheptane (**158**) by a catalytic hydrogenation of diketone (**157**) in AcOH and our material gave a melting point in agreement with that reported. A new benzylic methylene triplet in the ^{1}H NMR spectrum coupled with no absorption observed for the carbonyl functionality in the IR spectrum were consistent with successful reduction. Finally, boron tribromide mediated cleavage of the methyl ethers was carried out following the general procedure of McOmie *et al.*[55]. The phenolic diarylheptane (**159**) was isolated as an off-white powder after column chromatography in moderate yield. A melting point was in agreement with that reported[105] and ^{1}H and ^{13}C NMR spectroscopy highlighted the absence of the methyl ether functionalities. A broad stretch at 3400 cm^{-1} in the IR spectrum along with a parent ion at *m/z* 316 in the high resolution mass spectrum were consistent with the proposed structure.

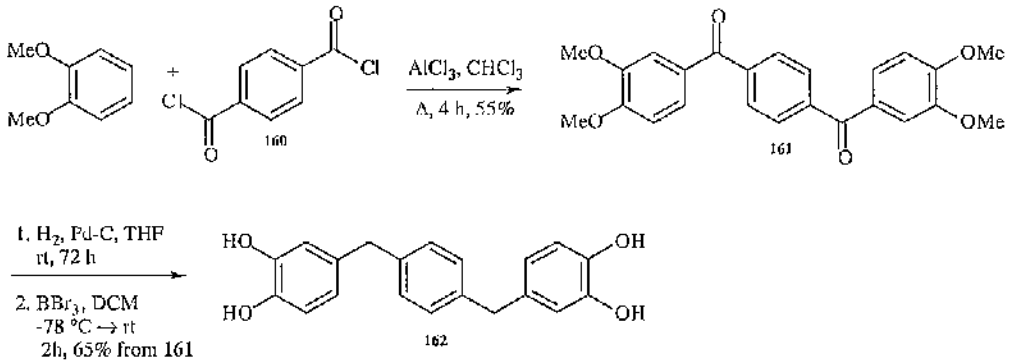
4.1.7 Synthesis of a conformationally restricted analogue

It has been reported by Matsuda and Yamada that the conformationally restricted analogue (**162**) showed enhanced anti-oxidant properties over NDGA in foodstuffs.[106] We were interested to see if this finding could be extended to our field and set about the synthesis of (**162**) as outlined in **Scheme 44**.

Our initial attempts at the Fredel-Crafts acylation of veratrole with commercially available teraphthaloyl chloride (**160**) followed the general procedure used for the synthesis of diketones (**156**) and (**159**). TLC of the crude residual showed

only starting material. However, when the reaction was carried out at elevated temperatures acylation was successful. The diketone (**161**) was isolated in moderate yield as lemon coloured crystals giving a melting point in agreement with that reported.[106] The structure was further confirmed by ^{1}H NMR spectroscopy showing two doublets and a doublet of doublets for the electron rich aromatic nuclei along with a 4H singlet at δ 7.85 for the protons of the central aromatic ring.

Scheme 44



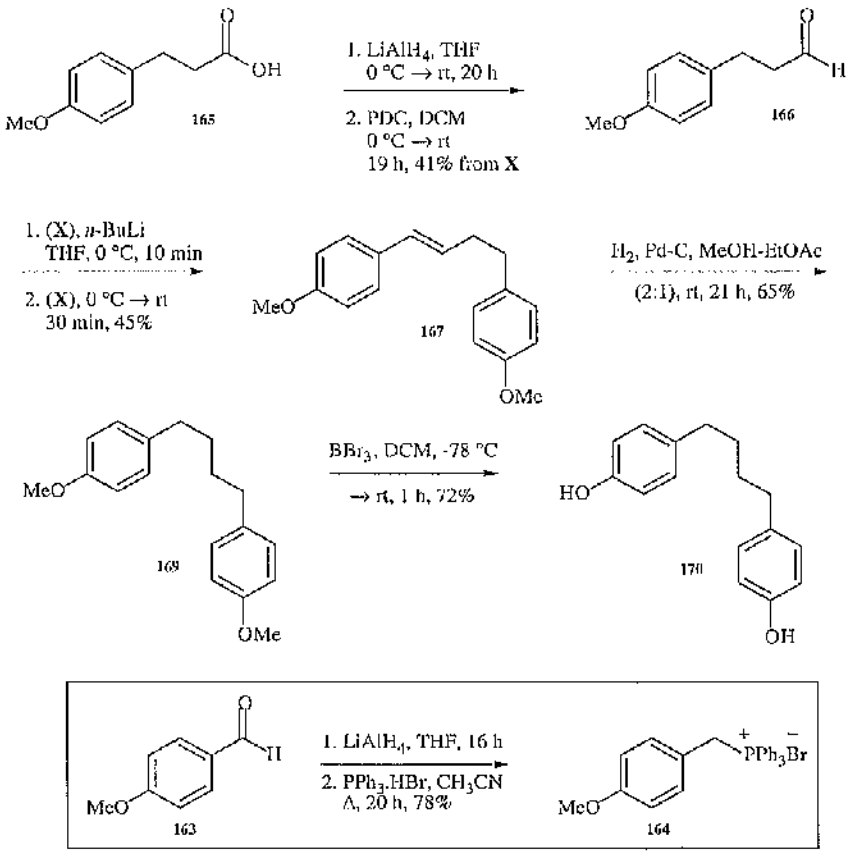
Diketone (**161**) was rather insoluble in common catalytic hydrogenation solvents such as MeOH, EtOH and AcOH, however the reduction could be succesfully carried out in THF. The crude residue so obtained could not be crystallised from a variety of solvents so it was decided to carry the mixture through for demethylation without purification. Boron tribromide demethylation[55] afforded the bis-catechol (**162**) as a cream coloured powder that gave a melting point in agreement with that reported.[106] There were no signs of the methyl ether functionality in the ^{1}H NMR spectrum, however a 4H singlet was now observed at δ 4.83 for the methylene protons arising during the reduction step. The structure was further confirmed by ^{13}C NMR spectroscopy showing a methylene resonance at δ 41.8 and broad phenolic stretches were observed in the IR spectrum around 3500 cm^{-1}. Finally a parent ion at *m/z* 322 in the high resolution mass spectrum gave further evidence for the proposed structure.

4.2 Synthesis of Phenols

4.2.1 Sythesis of a C4-Bridged Phenolic compound

The synthesis of the C4-bridged phenol (**170**) was essentially that used for the C4-bridged catecholic compound (**149**) with a few exceptions (**Scheme 45**).

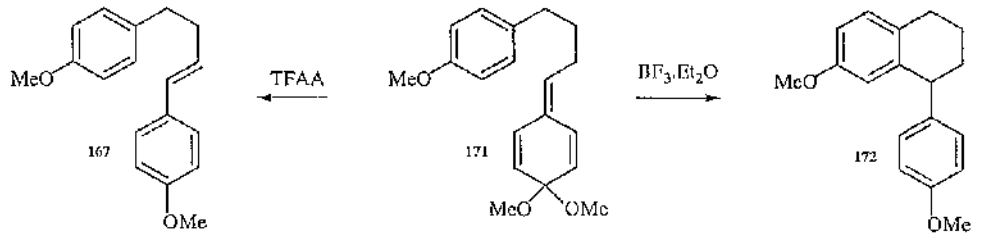
Scheme 45



Reduction of *p*-anisaldehyde (**163**) with LiAlH4 afforded an oil that was homogeneous and slower running by TLC and was stained red with vanillin spray. The crude product was treated directly with triphenylphosphine hydrobromide in refluxing CH3CN affording the phosphonium salt (**164**) as a solid in 78% yield over the two steps. The structure of the salt was verified by a variety of spectroscopic techniques most notably NMR spectroscopy. A 2H doublet at δ 5.26 with a coupling constant of 13.7 Hz was observed in the ^{1}H NMR spectum for the benzylic methylene group. A fine coupling of the doublet, arising from the aromatic proton *meta* to the methoxyl group, with a coupling constant of 2.1 Hz gave further evidence of triphenylphosphine incorporation. The benzylic methylene group of (**164**) also appeared as a doublet at δ 30.5 in the ^{13}C NMR spectrum, however this carbon-phosphorus coupling was not unique with the majority of the resonances appearing as doublets. A significant example was the deshielded carbon bonded directly to the methoxyl group which appeared as a doublet at δ 160 with a J_{CP} of 3.7 Hz. Johnson and Kyllingstad synthesised phosphonium salt (**164**) using an alternative approach, during their investigations into the stereochemistry of the Wittig reaction[107], and our material gave a melting point in accordance with that reported.

Aldehyde (**166**) was synthesised in a two step process starting from commercially available 3-(4-methoxyphenyl)propionic acid (**165**). Reduction of (**165**) with $LiAlH_4$ gave an intermediate alcohol which was homogeneous by TLC and pure enough by ^1H NMR spectroscopy to be used without further purification. Oxidation to the aldehyde (**166**) was carried out employing PDC, freshly prepared on a 0.25 mol scale by the method of Corey and Schmidt.[108] Aldehyde (**166**) was isolated as an oil in moderate yield over the two steps after purification by column chromatography. The pertinent spectroscopic data were an IR stretch at 1732 cm^{-1}, a 1H triplet at δ 9.80 and a carbonyl resonance at δ 202 in the ^{13}C NMR spectrum. Semmelhack *et al.*[109] required aldehyde (**166**) during their synthesis of alnusone and our material gave spectroscopic data in agreement with those reported. The proposed structure was further confirmed by a parent ion at *m/z* 164 in the high resolution mass spectrum. With both coupling partners in hand, we turned our attention to their coupling employing a Wittig olefination.

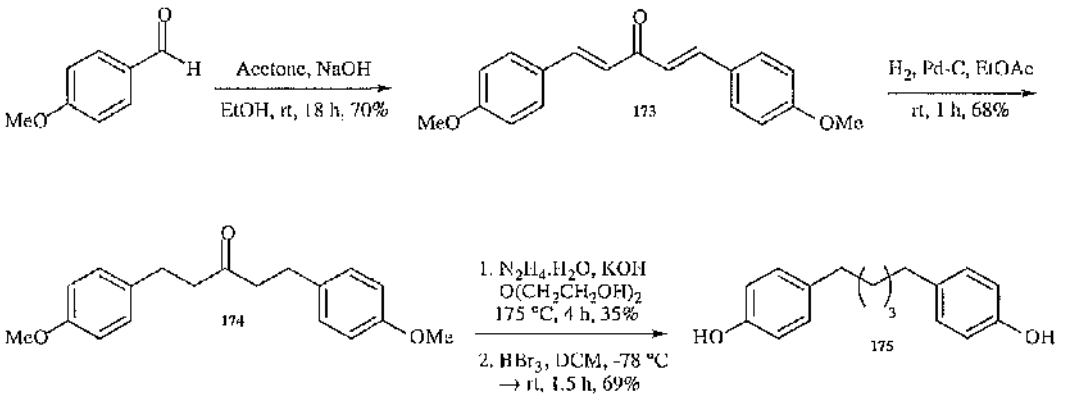
Scheme 46



Addition of 1.1 equivalents of *n*-BuLi to a suspension of phosphonium salt (**164**) in THF resulted in a blood red solution to which was added aldehyde (**166**) at 0 °C. The reaction was shown to be complete by TLC after 30 min showing a slightly slower running compound which was stained red by vanillin unlike aldehyde (**166**) which gave a blue colouration. The crude residue was recrystallised from MeOH affording the pure (*E*)-alkene (**167**) as plates in 45% yield. The compound was fully characterised. The stereochemistry was clearly evident from the ^1H NMR spectrum showing a doublet (J = 15.8 Hz) and a doublet of triplets (J = 15.8 and 6.8 Hz) in the olefinic region for the benzylic and homo-benzylic methine protons respectively. The concentrated mother liquors were purified by flash chromatography affording an oil in 30% yield chiefly composed of the (*Z*)-alkene (**168**). The exact ratio of isomers was calculated by integration over the doublet of triplets arising from the homo-benzylic olefin proton in the ^1H NMR spectrum and was shown to be 12:1 in favour of the (*Z*)-isomer. While investigating a novel approach to aryltetralin lignans Pelter *et al.*[110] claim to have isolated alkene (**167**) as an undesirable reaction product (**Scheme 46**).

TFAA catalysed cyclisation of the quinone-methide ketal (**171**) gave alkene (**167**) in 55% yield however the use of $BF_3.Et_2O$ resulted in smooth conversion to the desired aryltetralin (**172**). On the basis of their reported ^1H NMR spectrum run in $CDCl_3$ we suspect that the authors have isolated an alternative compound and not alkene (**167**). In their spectrum they report the methylene protons as a muliplet at δ 1.2-1.8 and the olefin and aryl protons as a multiplet at δ 6.6-7.8. Our spectrum reveals a different compound with the methylene protons appearing as two distinct multiplets between δ 2.4 and δ 2.7 and the olefin and aryl protons giving distinct resonances between δ 6.1 and δ 7.3.

Scheme 47



Catalytic hydrogenation of the (*E*)-alkene (**167**) over palladium afforded the diarylbutane (**169**) as plates in moderate yield. Richardson and Reid have synthesised (**169**) by a more laborious route allowing access to phenol (**170**) required for bactericidal testing.[111] Diarylbutane (**169**) gave a melting point in agreement with that reported and the resultant symmetry of the system was apparent from the NMR spectra with the ^{13}C spectrum revealing the expected seven resonances. Kadkhodayan *et al.* have reported the synthesis of (**169**), along with a series of bis-*para*-anisylalkanes, utilising a copper catalysed coupling of suitable dihaloalkanes with aryl Grignard reagents.[112] The ^1H NMR spectrum, which was in agreement with that reported[112], showed two distinct resonances for the methylene groups along with two doublets in the aromatic region for the AA'BB' system. Catalytic hydrogenation of the (*Z*)-isomer (**168**) also gave diarylbutane (**169**) in moderate yield. Spectroscopic data were identical to those of the material isolated from the (*E*)-isomer. Boron tribromide demethylation afforded the phenolic diarylbutane (**170**) as fawn crystals in high yield giving a melting point in agreement with that reported.[111] The ^1H NMR spectrum showed no signs of the methyl ethers being replaced with a broad phenol singlet at δ 9.1. This finding was reinforced by IR spectroscopy which showed a broad stretch at 3410 cm^{-1}.

4.2.2 Sythesis of a C5-Bridged Phenolic compound

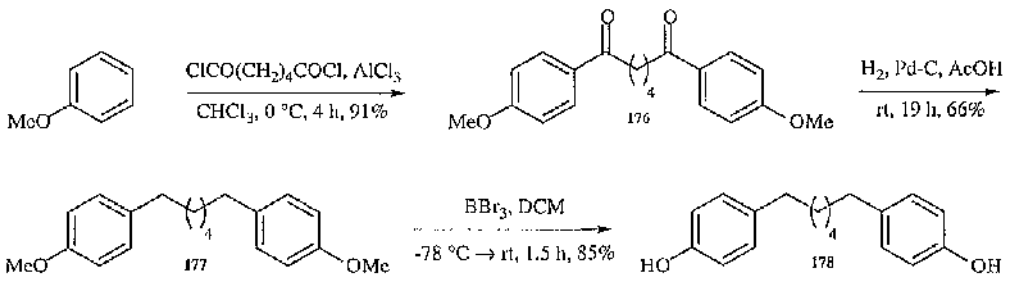
The aldol condensation of anisaldehyde with acetone in the presence of NaOH afforded the unsaturated ketone (**173**) in high yield as bright yellow feathers. Two olefinic doublets in the ^{1}H NMR spectrum with a coupling constant of 15.8 Hz confirmed the (*E*)-stereochemistry of the double bond. A resonance at δ 189 for the carbonyl moiety was observed in the ^{13}C NMR spectrum and a melting point was in agreement with that reported.[113] Catalytic hydrogenation of an intensely yellow solution of (**173**) in EtOAc gave a colourless solution from which was isolated the saturated ketone (**174**) in good yield after workup. The two olefinic doublets were now absent in the ^{1}H NMR spectrum being replaced with two methylene triplets in the aliphatic region of the spectrum confirming successful reduction. The identity of (**174**) was further confirmed by ^{13}C NMR spectroscopy showing two methylene singlets at δ 45.2 and δ 29.3 for the benzylic and homo-benzylic methylene groups, respectively. Wolff-Kishner reduction of ketone (**174**) was carried out as reported for the catecholic analogue (**151**). The protected diarylpentane was isolated as a colourless oil in low yield after purification by silica gel flash chromatography offering a ^{1}H NMR spectrum in agreement with that reported.[112] The structure was further confirmed by ^{13}C NMR spectroscopy which revealed the expected eight peaks including three methylene resonances in the aliphatic region. The ^{1}H NMR of the crude reaction product showed the diarylpentane along with another product suspected of being the intermediate hydrazone. Integration over the pertinent peaks revealed a ratio of *ca.* 1:1 and we feel that a longer reaction time would allow cleavage of this intermediate resulting in a higher yield. In any case, we felt enough material had been isolated to continue with the synthesis and the reaction was not repeated at this stage. Finally the aryl methyl ethers were cleaved with boron tribromide affording the phenolic diarylpentane (**175**) as an off-white solid in good yield. In addition to (**175**) giving a melting point in agreement with that of Richardson and Reid[111] the ^{1}H NMR spectrum confirmed the identity of (**175**) showing no resonance for the aryl methyl ethers and a broad phenolic singlet at δ 9.1. The identity of (**175**) was further confirmed by ^{13}C NMR, IR spectroscopy and accurate mass spectrometry.

4.2.3 Sythesis of a C6-Bridged Phenolic analogue

The synthetic route for the synthesis of the bis-anisylhexane derivative (**178**) was identical to that used for the catecholic analogue (**156**) and is depicted in **Scheme 48**. Friedel-Crafts acylation of anisole with freshly distilled adipoyl dichloride was carried out following the method of Fliedner *et al.*[94] affording the 1,6-diketone (**176**)

as crystals in excellent yield. The stereochemistry of the addition was readily apparent from the ^{1}H NMR spectrum showing two doublets (J = 8.9 Hz) in the aromatic region for the AA'BB' system. The ^{13}C NMR spectrum showed the expected eight peaks including the carbonyl resonance at δ 199.

Scheme 48



Catalytic hydrogenation was effected in AcOH over palladium at ambient temperature affording the saturated diarylhexane derivative (**177**) as plates in moderate yield. A melting point and ^{1}H NMR spectrum were in agreement with that reported by Kadkhodayan *et al.*[112] Boron tribromide demethylation afforded the phenolic dianisylhexane (**178**) in excellent yield and gave a melting point consistent with that reported.[111] The proposed structure was further confirmed by ^{13}C NMR, IR and accurate mass spectrometry.

4.3 Synthesis of amides

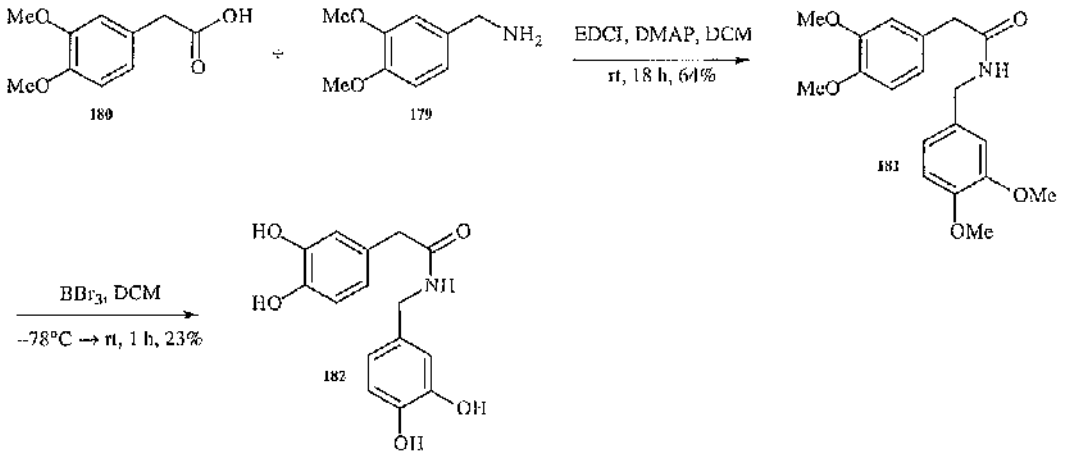
Our experience in designing new analogues of biologically active compounds suggests that more rigid compounds with fewer degrees of freedom and restrictions in the number of possible conformations adopted are often superior in biological activity. With this in mind synthesis of a series of amide analogues was undertaken utilising readily available starting materials. Our preliminary test data identified the diarylbutane derivative (**149**) as being ten fold more active than NDGA and as a consequence of this, we decided to maintain the four atom unit between the aromatic nuclei.

4.3.1 Synthesis of Secondary Amides

The coupling of 3,4-dimethoxybenzylamine (**179**) with 3,4-dimethoxy phenylacetic acid (**180**) was successful affording amide (**181**) as fine needles in 64% yield (**Scheme 49**). We investigated two coupling agents for this transformation, namely DCC and its water soluble derivative EDCI with the latter giving superior yields. Unlike the insoluble DCU by-product resulting from DCC coupling, the urea by-product from EDCI could easily be removed by an aqueous wash thus simplifying

purification. Amide (**181**) has previously been synthesised by Battersby *et al.*[114] *via* the acid chloride while investigating the biosynthesis of alkaloids. Our material gave a melting point in agreement with that reported and the identity of (**181**) was further confirmed by a variety of spectroscopic techniques. An IR stretch at 1639 cm^{-1} and a quaternary resonance at δ 172 in the ^{13}C NMR spectrum confirmed the presence of the amide moiety. The ^{1}H NMR spectrum showed a broad singlet at δ 5.79 for the amide proton along with a 2H doublet at δ 4.34 which collapsed to a singlet after shaking the sample with D_2O.

Scheme 49

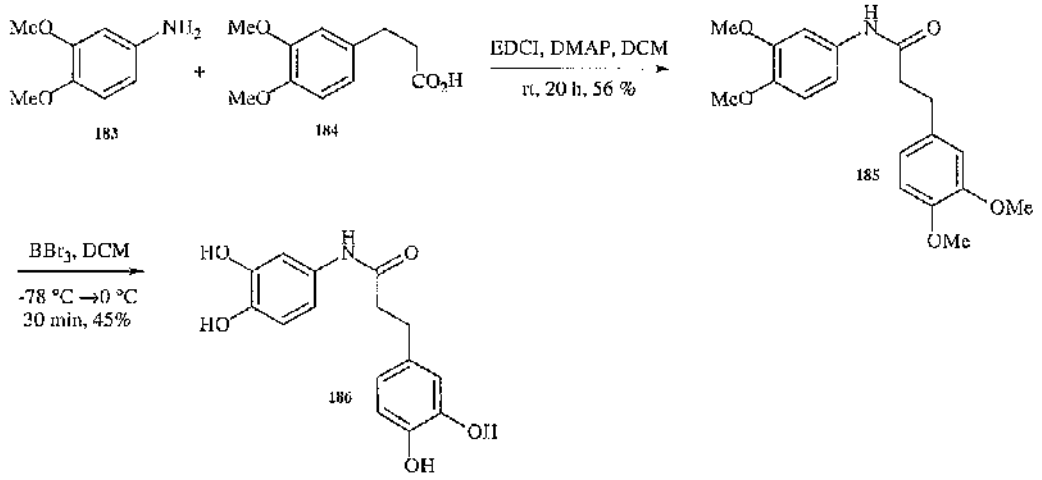


Deprotection of (**181**) was carried out using boron tribromide affording the novel phenolic amide (**182**) as a beige solid in low yield. TLC (2:1 EtOAc-acetone) of the reaction mixture after 1 h at rt showed no staring material and a streaky spot at R_f 0.4 which was intensely stained with iodine. The reaction was worked up in the usual fashion however we obtained a relatively poor crude yield (52%) from which pure novel (**182**) was isolated in only 23% yield. The amide bond was shown to be intact with an IR stretch at 1600 cm^{-1} along with a resonance at δ 171 in the ^{13}C NMR spectrum. In the ^{1}H NMR spectrum four distinct peaks were observed for the phenols at δ 8.7 to δ 8.9 and the amide proton now came into resonance at δ 8.2, presumably a consequence of hydrogen bonding.

The amide coupling of 3,4-dimethoxyaniline (**183**) with 3-(3,4-dimethoxyphenyl)propionic acid (**184**) was again achieved in best yield using the EDCI-DMAP system as depicted in **Scheme 50**. The novel amide (**185**) was obtained in moderate yield as pale pink needles and was fully characterised. The pertinent spectroscopic data included two methylene triplets in the aliphatic region of the ^{1}H NMR spectrum along with an amide resonance at δ 171 in the ^{13}C NMR spectrum.

An IR stretch at 1655 cm^{-1} was representative of the amide moiety and a parent ion at *m/z* 345 in the high resolution mass spectrum confirmed the identity of amide (**185**).

Scheme 50

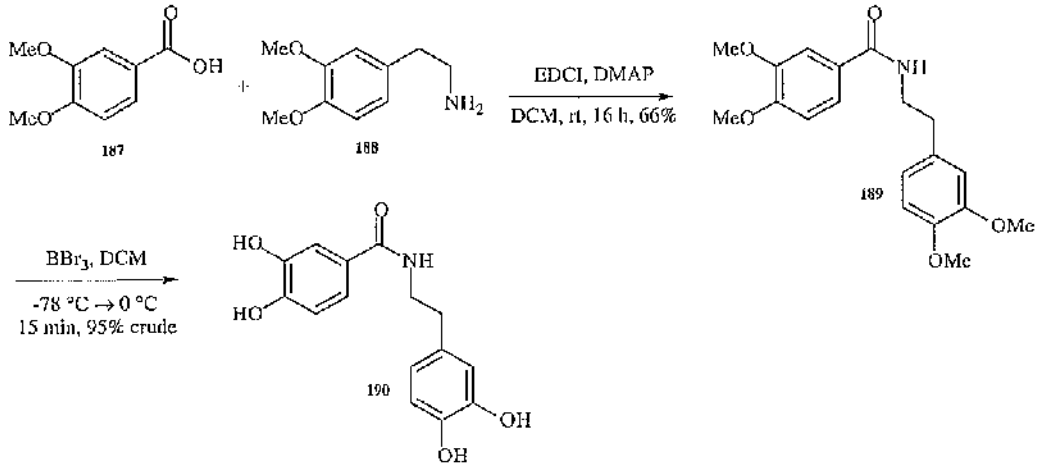


We suspected that the low yield experienced for the demethylation of (**181**) could be attributed to partial amide bond cleavage and decided to attempt the deprotection of (**185**) at a reduced temperature. Addition of boron tribromide to a solution of (**185**) in DCM at -78 °C was carried out as normal except that the reaction mixture was allowed to warm slowly to 0 °C and not room temperature. TLC (EtOAc-acetone {2:1} + 2% AcOH) after 30 min showed no starting material and the reaction was worked up in the usual way. Using this procedure we obtained a better yield (64%) of the crude product from which was isolated the novel phenolic amide (**186**) as an off-white solid in moderate yield. Four phenolic singlets around δ 8.7 were again observed in the ^{1}H NMR spectrum along with a deshielded singlet at δ 9.5 for the amide proton. The amide bond of (**186**) was shown to be intact with a resonance and stretch at δ 170 and 1636 cm^{-1} in the ^{13}C NMR and IR spectrum respectively.

Synthesis of amide (**189**) was readily achieved in good yield employing the commercially available acid (**187**) and amine (**188**) as depicted in **Scheme 51**. This compound has previously been synthesised in 60% yield by Landais and Robin using an alternative approach.[115] Our material gave a melting point, IR and ^{1}H NMR spectrum in agreement with that reported and was further characterised by ^{13}C NMR and high resolution mass spectrometry. The deprotection of (**189**) was carried out as normal however we were unable to obtain a sample of suitable purity for testing. Crude (**190**) was obtained as a foam in excellent yield that could not be recrystallised from a variety of solvents or suitably purified by column chromatography. The reaction was

attempted on numerous occasions, however a ^{1}H NMR spectrum of the residue revealed extra resonances in the aromatic region.

Scheme 51

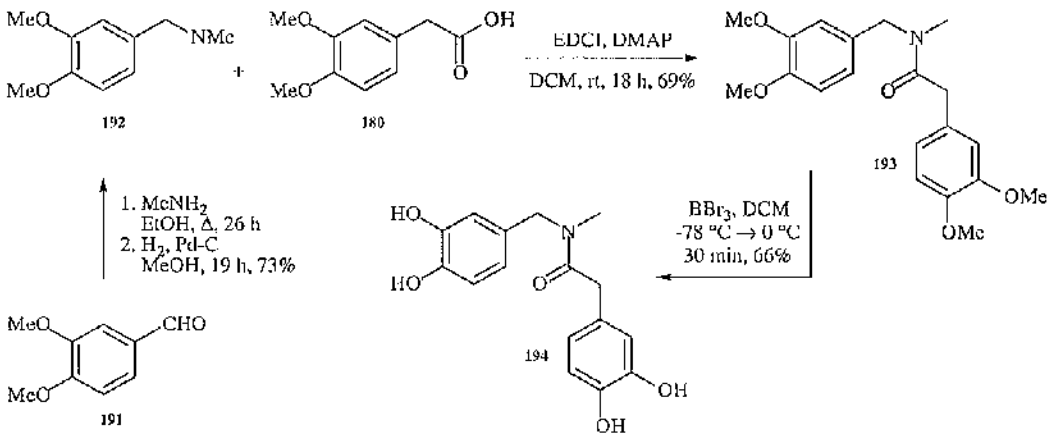


We suspected these extra peaks were a result of amide bond cleavage however we were unable to obtain a sample free of these impurities. We expected a change of protecting groups would alleviate this problem especially choice of one that could be removed under mild conditions. As a consequence of no suitably protected starting materials being commercially available, we decided to await the test results of the isomeric amides (**182**) and (**186**) before employing a new approach.

4.3.2 Synthesis of Tertiary Amides

The tertiary amide (**194**) is a structural analogue of NDGA and we were therefore keen to investigate its synthesis. The secondary amine (**192**) was not commercially available and was thus synthesised from 3,4-dimethoxybenzaldehyde (**191**) using a reductive amination procedure. Addition of 1.1 equivalents of an 8M ethanolic solution of methylamine followed by heating at reflux resulted in smooth conversion to the intermediate imine. A ^{1}H NMR spectrum of the yellow syrup thus obtained showed no starting material and a deshielded singlet at δ 8.2 for the benzylic proton. Catalytic hydrogenation was carried out over palladium at 4 atm. affording the methylamine (**192**) as a colourless oil after distillation. The structure of (**192**) was confirmed by a variety of spectroscopic techniques most notably NMR spectroscopy. Singlets integrating for 3H and 2H at δ 2.46 and δ 3.69, respectively, were observed in the ^{1}H NMR spectrum and are consistent with the proposed structure. Amine (**192**) has previously been synthesised by Neidigh *et al.*[116] and our material gave a ^{1}H NMR spectrum in agreement with that reported.

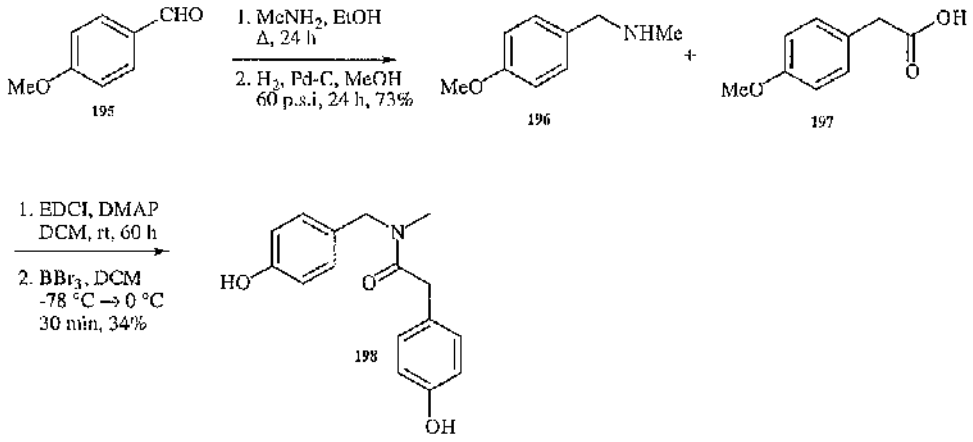
Scheme 52



Coupling of amine (**192**) with the commercially available acid (**180**) was conveniently achieved employing EDCI in the presence of 10 mol % DMAP affording the novel amide (**193**) as shiny crystals (**Scheme 52**). The rotameric nature of the tertiary amide (**193**) was evident from NMR spectroscopy. The ^{1}H NMR spectrum showed two distinct singlets at δ 4.49 and δ 4.52 for the methylene protons adjacent to the nitrogen in a ratio of *ca.* 3:2. The exsistence of rotamers also gave rise to a complicated ^{13}C NMR spectrum showing doubling of peaks including eight resonances for the carbons in the central bridge. The identity of (**193**) was further confirmed by an amide stretch at 1631 cm^{-1} in the IR spectrum coupled with a parent ion at *m/z* 359 in the high resolution mass spectrum. Boron tribromide demethylation afforded the novel phenolic amide (**194**) as shiny crystals in good yield. The rotameric nature of (**194**) was even more pronounced in the ^{1}H NMR spectrum which showed twin singlets for both the methylene groups and methyl protons. A broad muliplet at δ 8.7-8.9 was observed for the phenols, which were confirmed with a broad stretch at 3406 cm^{-1} in the IR spectrum. The structure of (**194**) was further confirmed by ^{13}C NMR and high resolution mass spectrometry.

In an attempt to ascertain the importance of the catecholic functionality, we undertook the synthesis of the mono-phenolic amide (**198**) employing the route used for the synthesis of the catechol derivative (**194**). Reductive amination of *p*-anisaldehyde (**195**) with methylamine afforded the secondary amine (**196**) in high yield after distillation (**Scheme 53**). The amine (**196**) offered a ^{1}H NMR spectrum in agreement with that reported by Neidigh *et al.*[116] who had employed an alternative synthesis. EDCI coupling of amine (**196**) with 4-methoxyphenylacetic acid (**197**) gave the protected rotameric amide that was used without further purification.

Scheme 53



Boron tribromide demethylation gave the amide (**198**) as a foam that refused to crystallise from a variety of solvents. Column chromatography (EtOAc-acetone {2:1}) gave a hydroscopic solid that was further purified by recrystallisation affording the novel phenolic amide (**198**) as a flaky solid in low yield. A broad resonance at δ 9.2 in the ^{1}H NMR spectrum was indicative of the phenols and a quaternary peak at δ 171 in the ^{13}C NMR spectrum was observed for the amide moiety. Further characterisation included stretches at 3365 and 1624 cm^{-1} in the IR spectrum coupled with a parent ion at *m/z* 271 in the high resolution mass spectrum.

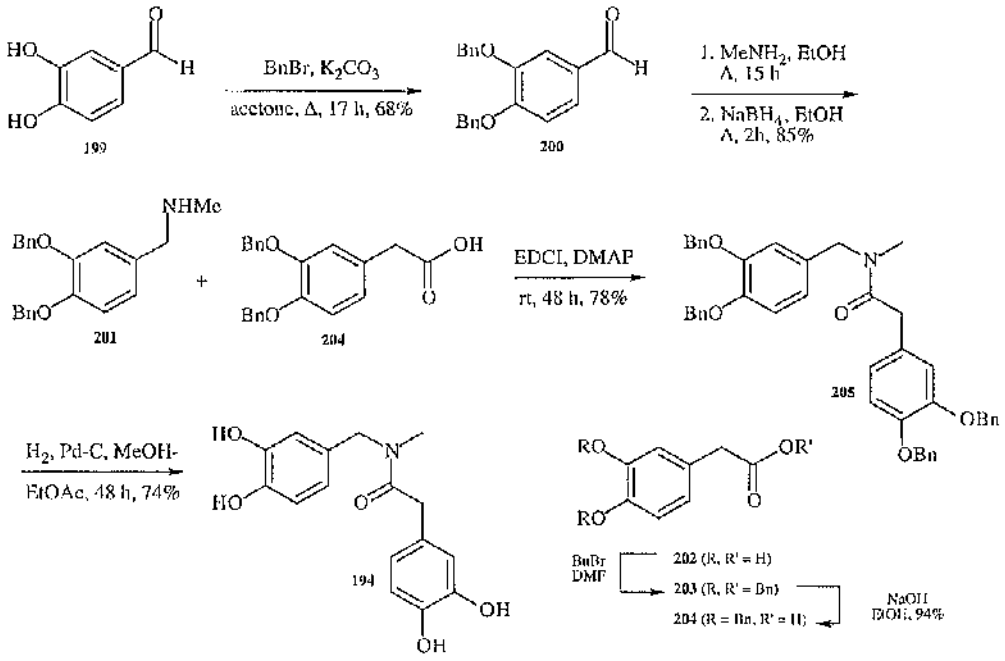
4.3.3 Synthesis of amide (194) - An alternative approach

At this juncture we decided to investigate the synthesis of (**194**) employing an alternative protecting group that could be cleaved under mild conditions. We decided that the benzyl protected group would be suitable for our needs as it is readily cleaved by catalytic hydrogenation at atmospheric pressure. This would also allow a further series of compounds containing acid sensitive functionalities between the rings, including amide (**190**), to be synthesised in the future.

Our alternative synthesis of the tertiary phenolic amide (**194**) is depicted in **Scheme 54** starting with the synthesis of the secondary amine (**201**). Benzyl protection of commercially available 3,4-dihydroxybenzaldehyde (**199**) was carried out following the method of Barrero *et al.*[117] Protected aldehyde (**200**) was isolated as lemon coloured crystals in moderate yield giving a melting point in agreement with that reported. Two singlets at δ 5.21 and δ 5.26 were observed for the benzylic protons in the ^{1}H NMR spectrum confirming the proposed structure. Reductive amination of (**200**) with methylamine was carried out as normal, however the intermediate imine was reduced with an excess of $NaBH_4$ in refluxing EtOH. The secondary amine (**201**) was

isolated in high yield as a light yellow oil that was pure enough to use without further purification. A ^{1}H NMR spectrum of (**201**) was again identical to that reported by Neidigh *et al.*[116] for material made by an alternative procedure and our sample was characterised by IR, MS and ^{13}C NMR spectroscopy.

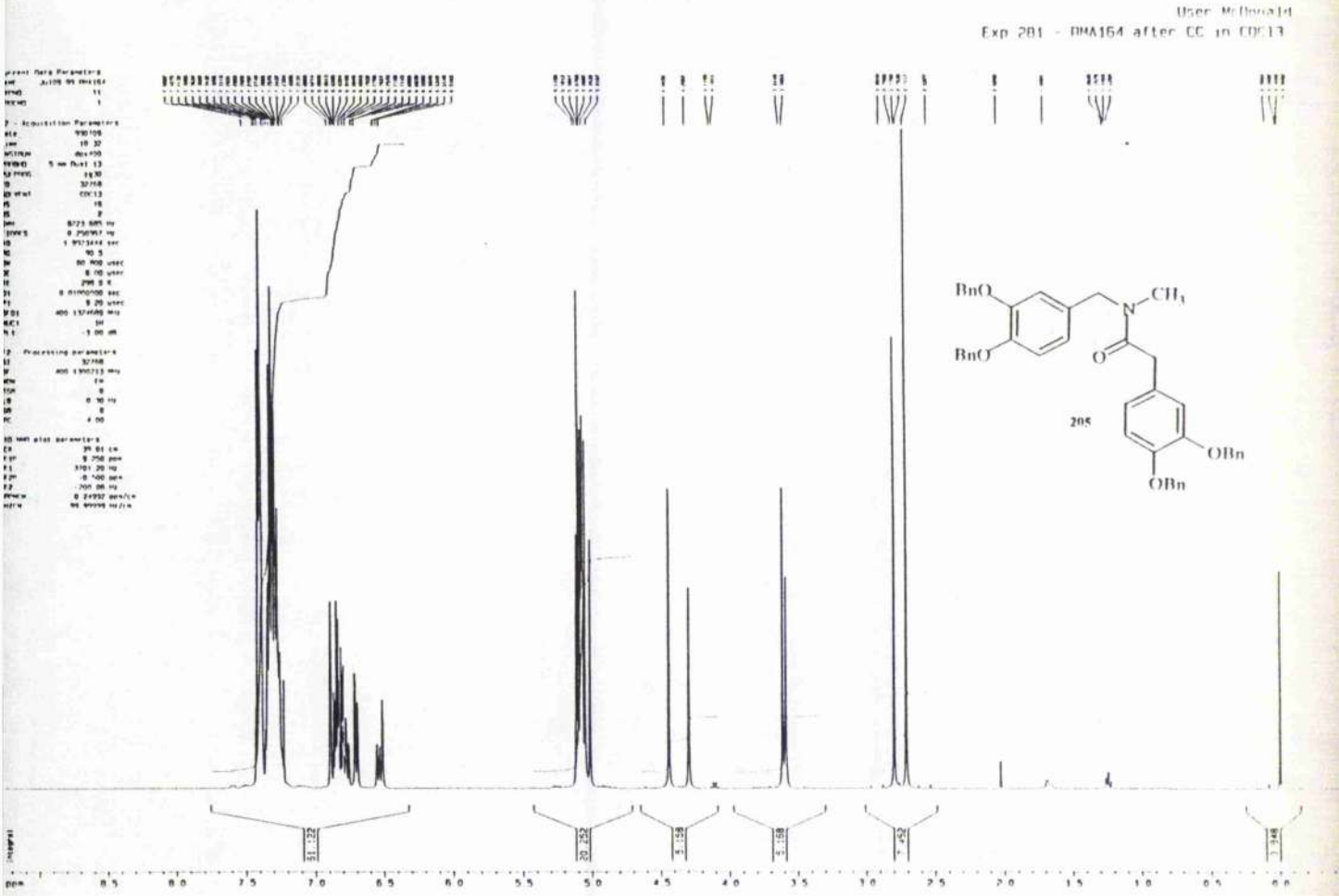
Scheme 54



Synthesis of the acid portion (**204**) was carried out following the reported procedure of He *et al.*[119] utilising commercially available 3,4-dihydroxyphenylacetic acid (**202**). The intermediate benzyl ester (**203**) was smoothly hydrolysed with ethanolic NaOH affording the protected acid (**204**) in high yield which gave a melting point in agreement with that reported.[118] Two benzylic singlets were observed in the ^{1}H NMR spectrum and integration over the pertinent peaks was consistent with successful ester cleavage. The amine (**201**) and acid (**204**) were successfully coupled employing EDCI in the presence of 10 mol% DMAP affording the novel amide (**205**) in good yield after column chromatography. It was surprising that this compound was isolated as an oil refusing to crystallise when its tetramethyl ether analogue (**193**) was isolated as a solid. In any case the structure was confirmed by a variety of spectroscopic techniques including a ^{1}H NMR spectrum as shown in **Figure 25**. Twin peaks for the methyl and two methylene groups of the central bridge of (**205**) are clearly a result of amide rotamers in a ratio of *ca.* 4:3. Numerous peaks are observed for the benzylic singlets around δ 5.1 and two resonances at δ 171.5 and δ 171.8 were observed in the ^{13}C NMR spectrum for the amide moiety. Catalytic hydrogenation of

(**205**) over palladium at atmospheric pressure afforded the phenolic amide (**194**) in high yield. This compound gave a homogeneous spot by TLC which co-spotted with a reference sample. The melting point was identical to the material obtained from the tetramethyl ether.

Figure 25 - ^{1}H NMR spectrum of protected amide (205)



In the synthesis of the tertiary amide (**194**), using the benzyl protecting group offers no distinct advantage over the methyl ether approach. In fact the yields obtained from the methyl ether route (**Scheme 52**) are good and because the starting materials are commercially available, this route would be favoured in this case. However the chemical stability of the methyl ether protecting group requires the use of quite harsh reaction conditions for its removal, thus limiting the functionality available between the aromatic nuclei. Indeed, we have found attempts to cleave methyl ethers with BBr_3 on substrates that contained ester, alkene and alcoholic linkages resulted in decomposition giving complex ^{1}H NMR spectra. In these cases the use of a benzyl protecting group could offer a distinct advantage although the starting materials would not be commercially available. Although not investigated, the synthesis of the secondary

amides (**Section 4.3.1**) would benefit from this approach undoubtedly resulting in easier purifications and improved yields. We suspect that the use of the benzyl ether protecting group is pivotal in the development of a larger range of analogues including compounds containing acid labile groups in the future.

4.4 Biological Test Results

The compounds synthesised throughout this project have been screened for their ability to inhibit SCLC cells *in vitro* by Dr. Michael Seckl at the Medical Oncology Department of Charing Cross Hospital (subsequently Hammersmith Hospital), London. The preliminary test data are presented in **Table 3**.

4.4.1 Method of Testing[120]

Cell Culture : SCLC cell lines H-69 were maintained in RPMI 1640 supplemented with 10% (v/v) fetal bovine serum (heat inactivated at 57 °C for 1 h) in a humidified atmosphere of 10% CO_2 / 90% air at 37 °C. They were passaged every 7 days. For experimental purposes, the cells were grown in HITESA which consisted of RPMI 1640 supplemented with 10nM hydrocortisone, 5μg/ml insulin, 10 μg/ml transferrin, 10nM oestradiol, 30nM selenium and 0.25% bovine serum albumin.

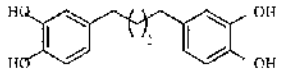
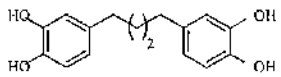
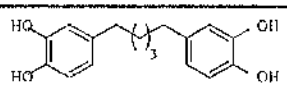
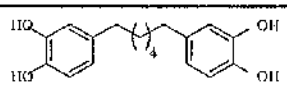
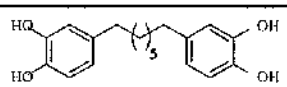
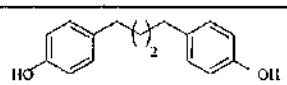
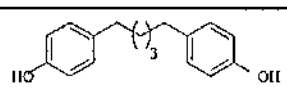
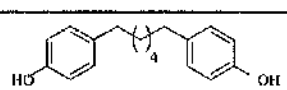
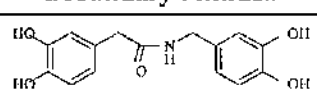
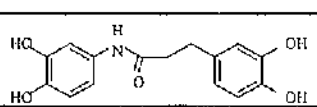
Liquid Culture Assay : SCLC cells, 3-5 days post passage, were washed and resuspended in HITESA. Cells were then aliquoted in 24 well Falcon plates at a density of 50,000 cells in 1 ml HITESA in the presence or absence of increasing concentrations of NDGA analogues. One and two weeks later, cell number was determined from a minimum of 3 wells per condition using a Coulter counter, after cell clumps were disaggregated by passing the cell suspension 5 times through a 19 and subsequently 21 gauge needle. These times were chosen to coincide with log phase and plateau phase growth of the cells.

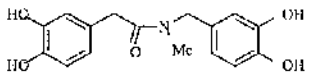
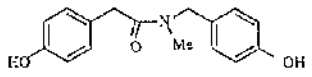
4.4.2 Preliminary Results

The racemate of NDGA (**32**) was found to be only slightly more active than *meso*-NDGA (**1**) suggesting that then orientation of the secondary methyl groups is not important for activity. This theory was further justified when the C_4-bridged analogue (**149**) was discovered to be greater than ten times more active than NDGA. The other analogues of this series were found to be relatively inactive with the exception of the C_6-bridged analogue (**156**) which was found to be equipotent with NDGA. The C_5 and C_6-bridged phenolic compounds were approximately equipotent to NDGA however the C_4-bridged phenol (**170**) lacked activity. It is interesting to

point out that although the mono phenolic compounds gave a similiar effect over one week they were more active over two weeks suggesting a greater stability. The results obtained from the amide analogues have been particularly encouraging with the majority showing enhanced IC_{50} values over NDGA. The phenolic tertiary amide (**198**) was found to be inactive interestingly in accordance with the result observed for the phenolic diarylbutane (**170**).

Table 3

NDGA Analogue	Number	IC_{50} (μmol)
	NDGA (**1**)	3.5
	(±) - **32**	3
Catechol Derivatives		
	**143**	> 100
	**149**	0.3
	**153**	> 3
	**156**	3.5
	**159**	35
Phenolic Derivatives		
	**170**	8
	**175**	3.5
	**178**	3
Secondary Amides		
	**182**	0.8
	**186**	1.5
Tertiary Amides		

	**194**	3
	**198**	> 100

4.4.3 Future Work

There is a large diverse range of NDGA analogues that can be envisaged with the ultimate goal of producing a more potent anti-cancer agent. Within our group we are actively investigating the synthesis of polyhydroxylated compounds which could provide a more potent analogue. The methylene groups between the aromatic nuclei could be replaced with heteroatoms such as NH, O or S offering hydrogen bonding sites which could be important for activity. In the case of amines their derived salts could allow access to a more water soluble analogue and such a compound type is synthesised in **Chapter 5**. The encouraging test results observed with the amide analogues suggests that the synthesis of conformationally restricted compounds should be further investigated. Included in this group could be esters, ketones, thioamides and alkenes present in various positions between the aromatic nuclei. The intermediate alkenes in our synthesis of (±)-NDGA (**Chapter 3**) fall into this category and could be valuable analogues. As noted previously these types of derivatives would require alternative protecting groups that could be cleaved easily in the presence of sensitive functionalities.

5

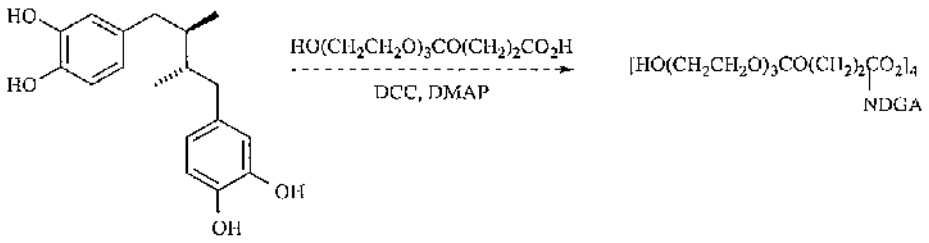
Solubilisation of NDGA and Derivatives

5.1 Introduction

As mentioned previously NDGA (1) suffers from a lack of solubility in water thus greater solubility is essential for *in vivo* studies. It was our intention to prepare covalent conjugates of NDGA which would be more solouble in serum releasing the active component over a period of time. In addition to NDGA, it was our objective that any promising NDGA analogues should be solubilised using the same procedures.

Initial work in this area was carried out by McAllister[121] who attempted to esterify triethylene glycol-succinate esters to NDGA using DCC coupling techniques with little success (**Scheme 55**). Attempts to synthesise M-PEG-5000 acetals of NDGA also proved unsuccesful hindered by poor solubility of NDGA and PEG-aldehyde in common solvents used for Dean-Stark azeotropic distillation.

Scheme 55



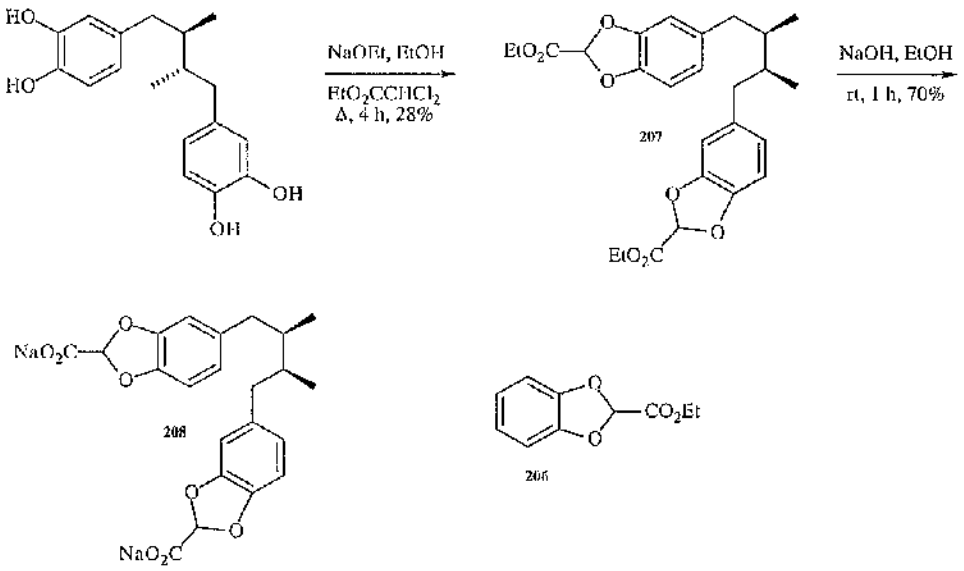
5.2 Towards the Synthesis of Acetals

Although the synthesis of PEG-acetals could be an effective NDGA solubilisation tool, we felt that due to their large molecular weights large quantities of drugs would have to be administered to be effective. We were interested to re-investigate the synthesis of acetal conjugates of NDGA albeit of low molecular weight containing a polar tail that would induce water solubility.

Hartzfeld *et al.*[122] have reported the reaction of catechol with ethyl dichloroacetate to afford the ethyl-*o*-phenylenedioxyacetate (**206**) in 28% yield. This encouraged us to adopt this approach on the bis-catechol NDGA which could be

hydrolysed to afford the water soluble acid salt (**Scheme 56**). Addition of NDGA to sodium ethoxide gave a deep green solution to which was added 2 equivalents of ethyl dichloroacetate. The reaction mixture became black on reflux and was shown by TLC to be a complex mixture of products. The crude product was purified by flash chromatography affording the acetal (**207**) as a yellow oil in low yield. The symmetrical nature of (**207**) was evident from the ^{1}H NMR spectrum showing a single doublet at δ 0.82 for the secondary methyl groups. The acetal methine proton came into resonance as a singlet at δ 6.28 and the expected thirteen peaks were observed in the ^{13}C NMR spectrum including the ester carbonyl moiety at δ 165.

Scheme 56

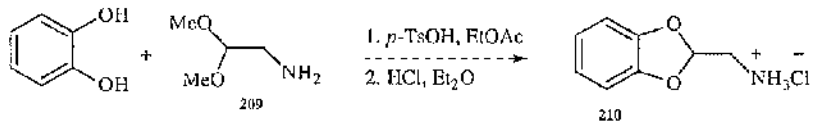


The ester (**207**) was hydrolysed with ethanolic NaOH at ambient temperature affording the acid salt (**208**) as a brown solid which was readily soluble in water. A ^{1}H NMR spectrum run in D_2O showed the desired structure; however it was not pure enough for testing and attempts to recrystallise this material proved unsuccesful. We felt that the initial step of the reaction scheme warranted further investigation to give the acetal (**207**) in high purity to be used in the hydrolysis. The reaction was repeated on a number of occasions with varying reactant concentrations and temperatures with little success. Indeed on some occasions following the original method failed to give any material highlighting the sluggish nature of the reaction. Attempts to carry out the acetal formation with milder bases such as triethylamine and potassium carbonate proved unsuccesful giving only starting material. Using the sodium salt of dichloroacetic acid as the electrophile was also unsuccesful. It was clear that we could carry out the reaction on a large scale to afford a pure enough sample for testing;

however the expense of the starting material coupled with the inconsistent reaction conditions encouraged us to seek an alternative approach.

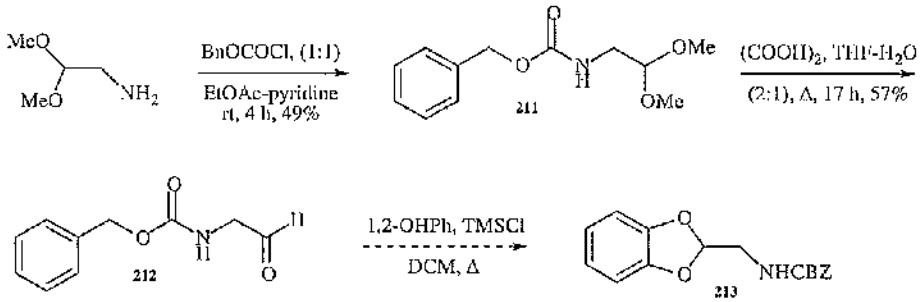
An attempted transacetalation of catechol with aminoacetaldehyde dimethylacetal (**209**) was attempted as depicted in **Scheme 57** with the prospect of forming the amine salt (**210**) to enhance water solubilty. The reaction was however unsuccesful with only starting material recovered even when an acid catalyst was used and the reaction was heated to drive off MeOH thus displacing the equilibrium.

Scheme 57



We decided to synthesise aldehyde (**212**) which could be used directly to acetalate our model catechol system prior to forming the amine salt. Aminoacetaldehyde dimethylacetal was thus protected as the CBZ derivative following the reported procedure of Bischofberger *et al.*[123] (**Scheme 58**). Protected aldehyde (**211**) was isolated in moderate yield as a colourless oil after distillation and gave spectroscopic data in agreement with those reported. A 2H benzylic singlet at δ 5.12 and a 5H multiplet in the aromatic region of the ^{1}H NMR spectrum were consistent with succesful carbamate formation.

Scheme 58



Oxalic acid induced cleavage of the dimethylacetal functionality of (**211**) was carried out as reported affording aldehyde (**212**) as a colourless liquid in moderate yield. Our first run followed the conditions reported[123] heating the reaction at reflux for 4 d; however the crude product was shown by ^{1}H NMR spectroscopy to be a complex mixture with little signs of the aldehyde (**212**). In another run the reaction mixture was heated for 17 h and TLC showed no signs of starting material and a new

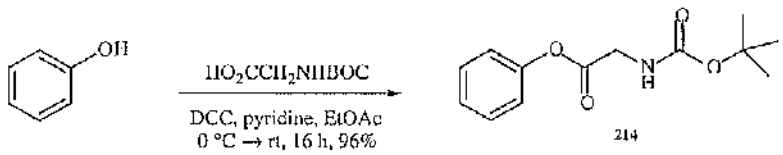
slower running spot that was stained red with DNP reagent. Using this procedure we isolated aldehyde (**212**) in 57% giving data in agreement with those reported. The singlet from the methyl ethers was now absent in the ^{1}H NMR spectrum being replaced with a deshielded singlet at δ 9.64 for the aldehyde proton. The structure was further confirmed by ^{13}C NMR spectroscopy revealing the expected eight resonances including the aldehyde moiety at δ 197. We suspect that heating the reaction for too long resulted in cleavage of the CBZ group and subsequent polymerisation. We also investigated other acetal cleavage conditions including CF_3CO_2H, CH_3CO_2H, moist silica and *p*-TsOH; however most just gave starting material highlighting the stability of acetal (**211**).

With aldehyde (**212**) in hand we attempted to acetalate catechol using the general procedure of Chan *et al.*[124] employing TMSCl as a dehydrating agent. The crude reaction product gave several spots by TLC and a ^{1}H NMR spectrum of the crude residue obtained showed a complex mixture that was not further investigated. We also carried out a reaction with *p*-TsOH in THF over molecular sieves but this method gave only starting material. At this juncture we decided to abandon the acetal approach and concentrate on an alternative strategy.

5.3 Synthesis of a Glycine Ester

Singh *et al.*[125] have reported the DCC promoted esterification of phenol with *N*-(*tert*-butoxycarbonyl)glycine affording the glycine ester (**214**) in 96% yield (**Scheme 59**). We decided to apply their reaction conditions to NDGA which could then be deprotected under acidic conditions affording the water soluble glycine salt (**216**) as depicted in **Scheme 60**.

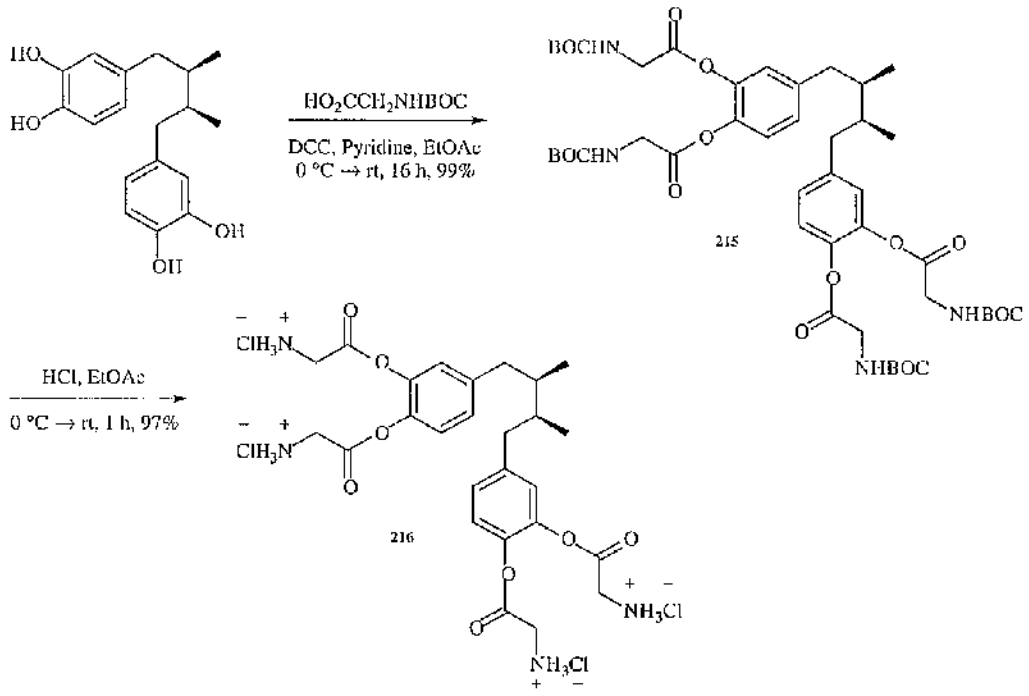
Scheme 59



Addition of 4.4 equivalents of *N*-(*tert*-butoxylcarbonyl)glycine was carried out as reported under DCC conditions and the reaction mixture was stirred overnight at ambient temperature (**Scheme 60**). After filtration of the insoluble DCU by-product, TLC showed that all the starting material had been consumed and a homogeneous faster running spot was observed. The crude product was obtained as a foam that was shown by ^{1}H NMR spectroscopy to be the desired product contaminated with residual

DCU. Unfortunately several attempts to crystallise this foam proved unsuccessful with the product oiling out on several occasions. Attempts to purify the crude product by silica gel chromatography or alumina chromatography resulted in decomposition with several spots observed by TLC. The use of alternative coupling agents including EDCI and CDI proved worthless giving a variety of spots by TLC that could not be purified owing to chromatographic instability of the product. A sample of sufficent purity was obtained by taking up the crude residue in the mininum volume of DCM and allowing the solution to stand in a freezer overnight. Crystals of DCU were carefully filtered off and the mixture was concentrated to give the glycine ester (**215**) as a foam that was used without further purification.

Scheme 60



The identity of the ester (**215**) was verified by a number of spectroscopic techniques including NMR, IR and accurate mass spectrometry. A 3H doublet at δ 0.84 was observed for the secondary methyl groups of symmetrical (**215**) along with a 18H singlet for the BOC group. The glycidic methylene protons came into resonance as a doublet at δ 4.13 and two non-equivalent amide multiplets were observed at δ 5.6-5.7. Peaks at δ 156.6 and δ 168.7 were observed in the ^{13}C NMR spectrum for the carbamate and ester functionalites respectively which were further confirmed with stretches at 1704 and 1786 cm^{-1}, respectively, in the IR spectrum. The incorporation of all four ester functionalites was confirmed by accurate mass spectroscopy with an observed peak at *m/z* 953 for $(M+Na)^{+\bullet}$ run in the FAB+ mode.

Deprotection of the BOC groups with subsequent formation of the HCl salt was conveniently achieved by bubbling dry HCl into a chilled solution of protected ester (**215**) in anhydrous EtOAc. After a few minutes colourless crystals of the amine salt (**216**) precipitated from the solution and the mixture was stirred until TLC showed the consumption of all the starting material. The crude product was further purified by washing with EtOAc affording the water soluble amine salt (**216**) as a powder in excellent yield. The removal of the BOC protecting groups was clearly apparent in the ^{1}H NMR spectrum which showed the absence of the large BOC singlet in the aliphatic region and the glycidic methylene protons now came into resonance as a singlet at δ 4.09. The IR spectrum showed only an ester stretch at 1778 cm^{-1} in that region and the structure was further confirmed with a $(M+H)^{+\bullet}$ peak at *m/z* 531 in the high resolution mass spectrum.

5.3.1 Synthesis of a C$_6$-Bridged Glycine Ester

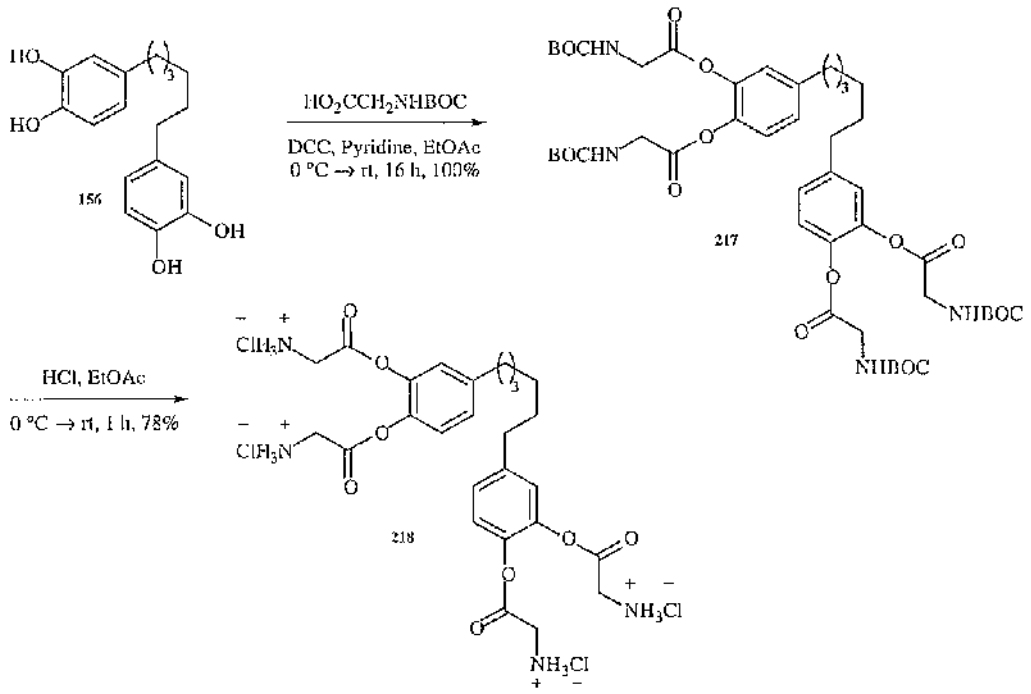
As reported previously the C$_6$-bridged phenolic analogue (**156**) had been shown to be equipotent to NDGA (**4.4.2**) and we were thus keen to extend our solubilisation methodology to this derivative.

The synthesis of the water soluble glycine adduct (**218**) is depicted in **Scheme 61** starting from the diarylhexane (**156**), itself obtained in three steps as discussed previously (**4.1.5**). DCC promoted coupling of the diarylhexane (**156**) with 4.4 equivalents of *N*-(*tert*-butoxycarbonyl)glycine gave the protected glycine ester (**217**) in quantative yield. Ester (**217**) could not be recrystallised from a variety of solvents but was shown to be homogeneous by TLC. Furthermore, any residual DCU could be removed by taking up the crude product in a mininum volume of DCM and allowing the solution to stand in a freezer overnight. Filtration and concentration of the resultant solution furnished (**217**) as shiny crystals with no signs of the DCU by-product observed in the ^{1}H NMR spectrum. The pertinent feautures of the ^{1}H NMR spectrum included a 18H singlet for the BOC methyl protons and a 2H doublet at δ 4.12 for the glycine methylene protons. The ^{13}C NMR spectrum highlighted the presence of the ester linkages with two resonances observed at δ 168.5 and δ 168.6 and there was a stretch at 1788 cm^{-1} in the IR spectrum. A peak at *m/z* 953 in the mass spectrum was recorded for the $(M+Na)^{+\bullet}$ radical giving evidence for the presence of all four ester linkages and the identity of (**217**) was further confirmed by combustion analysis.

Treatment of the protected ester (**217**) with dry HCl under anhydrous conditions resulted in the chemoselective removal of the BOC protecting groups affording the water soluble glycine salt (**218**) as a powder in good yield. A stretch at 1771 cm^{-1} was observed in the IR spectrum for the ester moiety; however no stretch was now observed for the carbamate carbonyl. The ^{1}H NMR spectrum offered

conclusive evidence that the BOC groups had been successively cleaved. There was no resonance detected for the BOC methyl protons and the glycidic methylene protons now appeared as two singlets at δ 4.23. The structure was further confirmed by ^{13}C NMR and accurate mass spectrometry.

Scheme 61



We expected that the glycine ester (**218**) would hydrolyse slowly in water under the acidic conditions and decided to check this by monitoring a sample of (**218**) in D_2O by NMR spectroscopy after regular intervals. After 1 h there was little signs of decomposition but it was clear after 24 h that significant cleavage of the ester linkages had been effected. The benzylic methylene triplet at δ 2.58 collapsed to an unresolved multiplet with a new multiplet observed in close proximity. The aromatic protons of (**218**) were originally observed as a close multiplet between δ 7.18 and δ 7.27; however after 24 h in D_2O the aromatic region was quite complex showing resonances between δ 6.7 and δ 7.2. After 44 h almost all of the original material had been hydrolysed and a solid presumably that of the diarylhexane (**156**) had precipitated in the NMR tube.

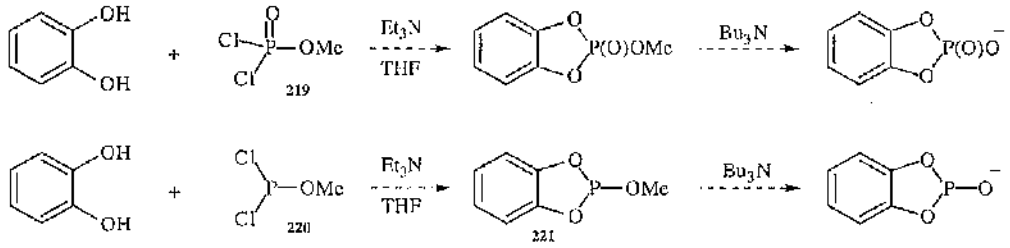
5.4 Attempts Towards Phosphate Esters

We were keen to investigate the synthesis of phosphate and phosphite esters of NDGA which could be hydrolysed following the method of Gray and Smith[126]

affording water soluble salts. As a consequence of having catechol in abundance it was decided that initial work in this area should be carried out on that substrate. If successful we intended to extend the methodology to the bis-catechol NDGA affording a water soluble adduct.

Addition of one equivalent of commercially available methyl dichlorophosphate (**219**) to a solution of catechol and two equivalents of triethylamine resulted in the rapid precipitation of a white solid (**Scheme 62**). TLC after 1 h showed consumption of all the starting material and a new spot present on the baseline. A ^{1}H NMR spectrum of the concentrated solution gave however a very complex spectrum. Further runs of the reaction in THF and Et_2O at reduced temperatures failed to alleviate the problem and the reaction was not further investigated.

Scheme 62



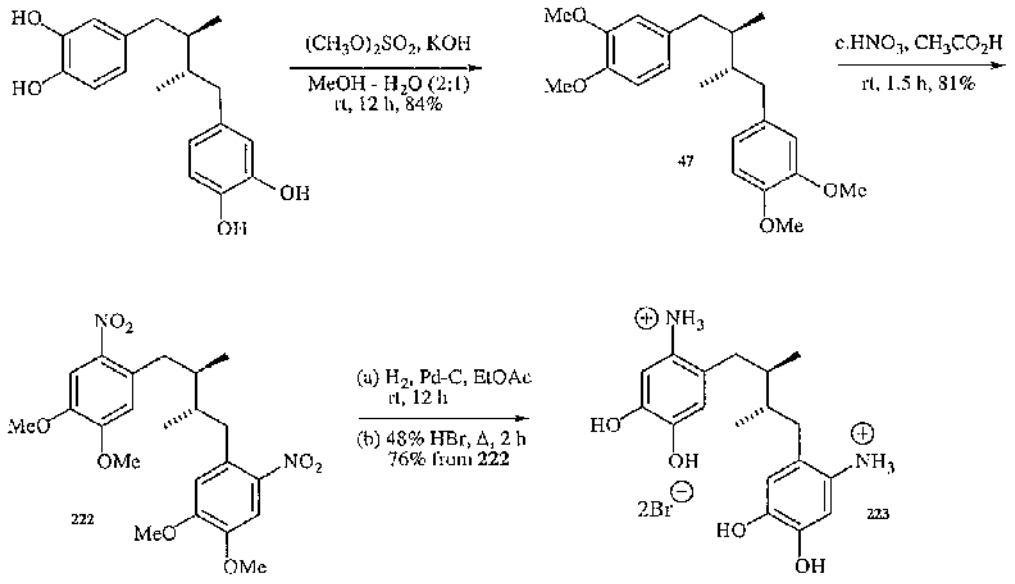
We turned our attention to the synthesis of the phosphite ester (**221**) employing the less reactive dichloromethyl phosphite (**220**). Unfortunately although reaction was again clearly evident with precipitation of NEt3.HCl a ^{1}H NMR spectrum revealed a complex mixture which was not further investigated. TLC revealed a single spot on the baseline and this coupled with the complex NMR spectrum suggested that polymerisation was being effected.

5.5 Synthesis of Amine salts

In 1918 Schroeter *et al.*[37] reported the nitration of the tetramethyl ether of NDGA (**1**) for characterisation purposes. We decided to repeat this work as reduction of the nitro group followed by demethylation would furnish a water soluble derivative.

Commercially available NDGA was methylated following the method of Perry *et al.*[42] furnishing the tetramethyl ether (**47**) as fawn crystals in high yield (**Scheme 63**). A melting point analysis and ^{1}H NMR spectrum were in agreement with those reported.

Scheme 63

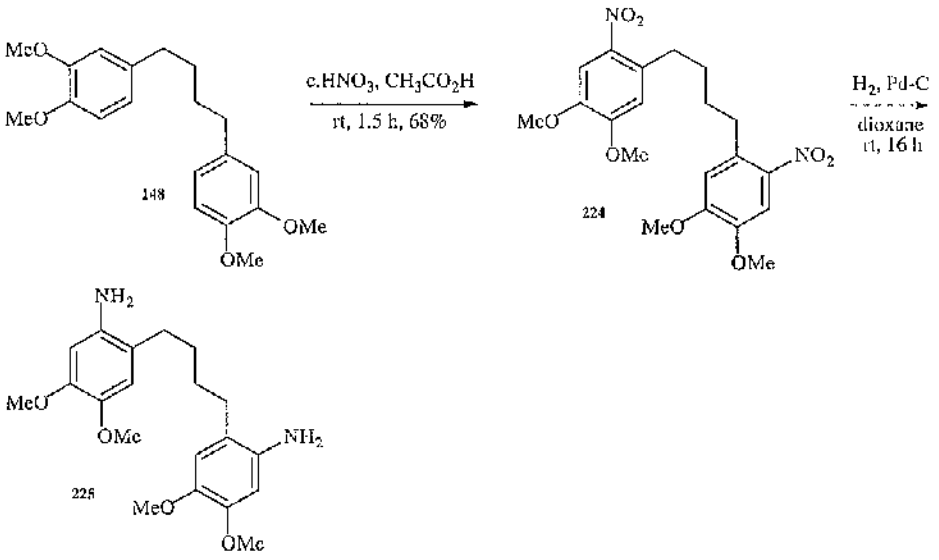


Addition of an excess of conc.HNO_3 to a solution of (**47**) in glacial AcOH gave a yellow solution which deposited crystals after 1.5 h. A modified workup to that reported[37] afforded the nitrated diarylbutane (**222**) as bright orange crystals in high yield giving a melting point in agreement with that reported. The regiochemistry of the addition was apparent from the ^1H NMR spectrum which showed two singlets in the aromatic region confirming that nitration had been effected in the 2-position. ^{13}C NMR spectroscopy now showed only two aromatic methine protons. The structure of (**222**) was confirmed by accurate mass spectrometry and combustion analysis. Catalytic hydrogenation over palladium went smoothly affording the amino intermediate as a sticky oil after silica gel chromatography. The aromatic singlet at δ 7.54 for the H-3 proton of (**222**) came into resonance at δ 6.21 as a result of being *ortho* to two activating groups. Attempted demethylation of the amino derivative of (**222**) using boron tribromide afforded a crude product that gave a complex ^1H NMR spectrum. The demethylation could however be succesfully achieved in refluxing 48% HBr affording the amino salt (**223**) as brown crystals in 76% yield from (**222**). The ^1H NMR spectrum of (**223**) gave two aromatic singlets and the expected nine resonances were observed in the ^{13}C NMR spectrum. Accurate mass spectrometry and combustion analysis also confirmed the identity of the water soluble amine salt.

At this stage we had received the results of the enhanced activity of the C_4-bridged analogue (**Chapter 4**) and thus set about the synthesis of its amine salt. Haworth *et al.*[38] reported the nitration of the diarylbutane (**148**) in 1934 for

characterisation purposes; however no suitable experimental details were given. The diarylbutane (**148**) was thus nitrated following the procedure to synthesise (**222**) affording the nitrated compound (**224**) in good yield as golden crystals that gave a melting point in agreement with that reported (**Scheme 64**). The pertinent spectroscopic data included two aromatic singlets in the ^{1}H NMR spectrum, two aromatic methine resonances in the ^{13}C NMR spectrum and a parent ion at *m/z* 420 in the mass spectrum.

Scheme 64

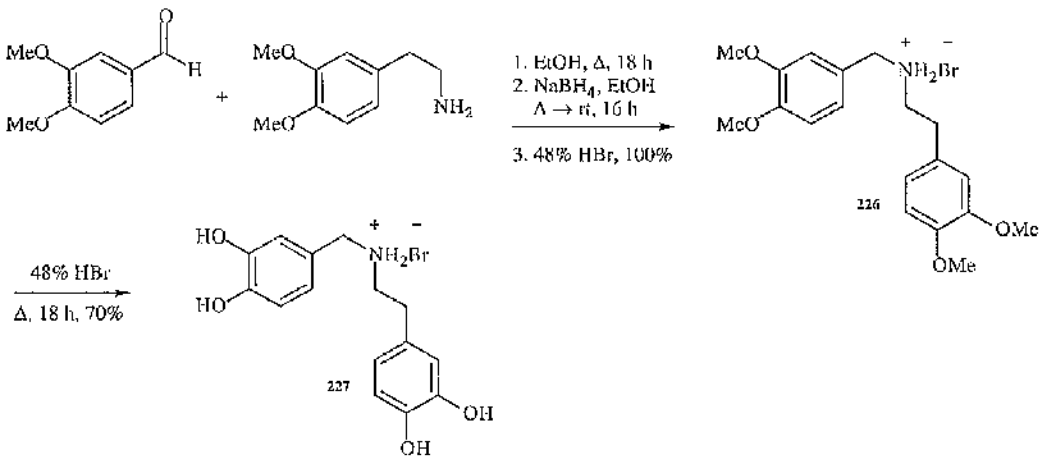


Unlike (**222**) which had two secondary methyl groups in the aliphatic chain, the diarylbutane (**224**) was insoluble in all the common hydrogenation solvents. A partial solubility was observed in dioxane; however an attempted catalytic hydrogenation over palladium gave poor conversion. The crude filtered product contained mostly starting material by TLC along with the expected product (**225**) which resided close to the baseline and was stained red with Dragendorff reagent. As a consequence of time constraints we were unable to investigate the hydrogenation at elevated temperatures or a alternative procedure such as dissolving metal reduction.

Concentrating on the C4-bridged analogue we were interested to see if using a NH group as an isosteric replacement for one of the bridging methylene moieties could afford a water soluble derivative as its HBr salt. Condensation of 3,4-dimethoxybenzaldehyde with 2-(3,4-dimethoxyphenyl)ethylamine was carried out in refluxing EtOH affording the intermediate imine as an amber oil that was directly reduced with an excess of $NaBH_4$ (**Scheme 65**). The crude reaction product was recrystallised from 48% HBr affording the secondary amine (**226**) as its HBr salt in quantitative yield. Buck has synthesised amine (**226**) by a more elaborate procedure

while investigating the synthesis of a series of substituted β-phenylethylamines[127]. Our material gave a melting point in agreement with that reported and was further characterised. The non-symmetrical nature of (**226**) was clearly evident from the ^{1}H NMR spectrum which revealed six clearly defined resonances in the aromatic region. The structure was further confirmed by ^{13}C NMR and high resolution mass spectrometry.

Scheme 65



Demethylation was effected in refluxing 48% HBr depositing the crude product as tan coloured crystals which were further purified by trituration in EtOAc affording the phenolic amine (**227**) as its HBr salt in good yield. The ^{1}H NMR spectrum showed no signs of the methyl ether functionality and the aliphatic chain was shown to be intact giving the expected two triplets and singlet in the aliphatic region.

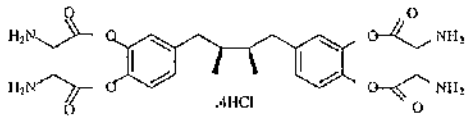
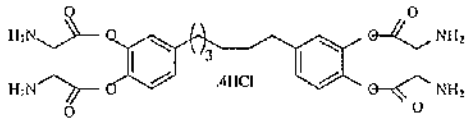
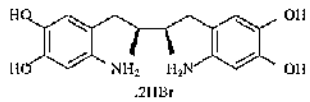
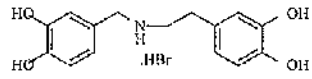
5.6 Results and Future Work

The preliminary test data for the water soluble analogues are shown in **Table 4**. The glycine esters appear to be less potent than NDGA; however they have provided the first generation of compounds for *in vivo* studies. The amine salt of NDGA (**223**) was found to be more potent and we still await the results of the C4-bridged analogue (**227**) containing an amine salt in the central bridge.

The encouraging results observed for diamino NDGA (**223**) suggest that we should investigate the synthesis of the racemate along with the C4-bridged analogue (**225**) by overcoming the reduction problems discussed previously. The position of the amino group in the C4-bridged analogue (**227**) should also be investigated starting with commercially available 3,4-dimethoxyaniline. If the test results of these two

compounds prove encouraging the synthesis of tertiary amine and quaternary ammonium salts in both positions should also be undertaken.

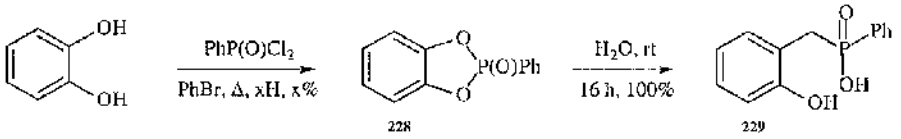
Table 4

NDGA Analogue	Number	IC_{50} (μmol)
	NDGA (**1**)	3.5
	**216**	10
	**218**	11
	**223**	2.0
	**227**	Unknown

Berlin and Nagabhushanam[128] have reported the succesful condensation of catechol with phenyldichlorophosphonate affording the bicyclic phosphonate in low yield (**Scheme 66**). The reaction was carried out in refluxing bromobenzene in the absence of a suitable base to mop up the generated HCl. Furthermore reaction of the ester (**228**) with one molar equivalent of water resulted in the smooth conversion into the acid (**229**) in quantitative yield. The authors also discuss the synthesis of a further two catechol derivatives which are substituted in the 4-position. However in these cases the bicyclic esters were not isolated as they underwent cleavage on cooling affording the acids as the reaction product.

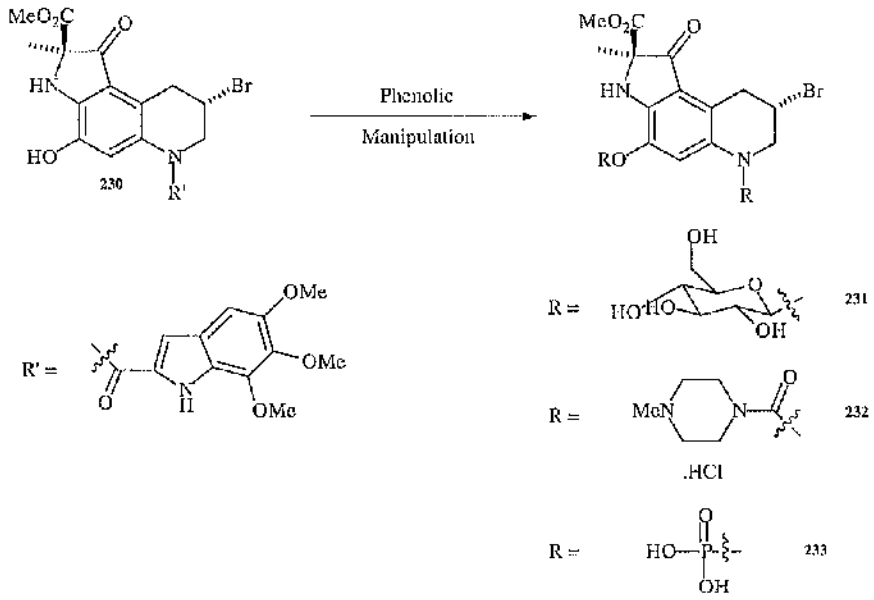
We feel that attempted synthesis of phosphonate esters, as discussed in **Section 5.4**, warrants further investigation utilising these alternative reaction conditions. The presence of the lipophilic phenyl moiety in (**228**) would clearly be disadvantageous with respect to water solubility; however the switch to methyldichlorophosphonate could eliminate this problem. One further problem that could be envisaged would be a lack of solubility of NDGA in refluxing benzene; however if the reaction was successful we expect that the reaction medium would become homogeneous.

Scheme 66



A good example of drug solubilisation has been recently reported by Asai *et al.* while investigating the synthesis of water soluble Duocarmycin B1 (DUMB1) prodrugs.[129] The limited anti-tumour *in vivo* activity of DUMB1 (**230**) had been attributed to its poor aqueous solubility so three lipophilic groups were attached to the free phenolic moeity of (**230**) as depicted in **Scheme 67**.

Scheme 67



Of the three derivatives investigated the carbamate (**232**) and phosphate (**233**) showed excellent water solubility of >20mg / ml. The glycoside (**231**) was 100 fold less soluble in water and unlike the other derivatives was totally resistant to cleavage in mouse serum.

In extending this work to NDGA containing four phenolic moieties we feel that the synthesis of a tetraglycoside could pose many problems. The reaction would undoubtedly generate a mixture of anomers that could be difficult to seperate and characterise sufficiently. Furthermore, as discussed previously, if all four groups could

be successfully introduced one would have a prodrug of considerable mass of which a large amount would have to be administered to release a sufficient quantity of the active component.

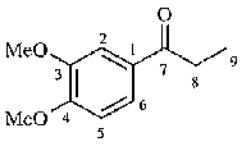
Use of a carbamate derivative on the other hand, such as (**232**), should be investigated especially as it was reported to show the highest potency.[129] Indeed one would expect, due to the less sterically demanding nature of the carbamate, that all four phenols of NDGA could be succesfully protected. With no stereogenic centres present in the protecting groups the product would be easier to characterise and as the tetra HCl salt should offer good water solubility.

6

Experimental

Reagents were purchased from Aldrich Chemical Company (Gillingham, UK) or Lancaster Synthesis (UK) and were used without further purification. Organic solvents were obtained from Rhône-Poulenc Rorer and were dried, where necessary, using the procedures described by Leonard, Lygo and Procter.[93] Melting points were recorded in open capillaries using a Gallenkamp apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded for solutions in $CDCl_3$ with tetramethylsilane as an internal standard on a Bruker AM-200 spectrometer operating at 200 and 50 MHz, respectively, or on a Bruker DPX/400 spectrometer operating at 400 and 100 MHz, respectively, unless otherwise stated. ^{13}C NMR spectra were assigned with the aid of Distortionless Enhancement by Polarisation Transfer (DEPT)-edited spectra. The numbering schemes shown are used for ease of assigning the NMR spectra and do not refer to the system of nomenclature. All coupling constants are measured in Hz. Thin layer chromatography was performed using Merck aluminium-backed silica plates of 0.25 mm thickness eluting with EtOAc-hexane (1:1), unless otherwise stated. Chromatograms were visualised using UV conditions at 254 nm, staining with iodine or using a variety of common stains prepared by the methods described in Leonard, Lygo and Procter.[93] Column chromatography was carried out on silica gel (particle size 70-230 mesh) using the same solvent system as above, unless otherwise stated. Mass spectra (MS) were recorded on AEI MS12 or MS902 spectrometers using the electron-impact ionisation (EI) mode or, if stated, chemical ionisation (CI) or fast atom bombardment (FAB) modes. Infra-red (IR) spectra were recorded on a Perkin Elmer PU 9800 FT-IR spectrometer. Combustion analysis was carried out on a Carlo-Erba 1106 elemental analyser.

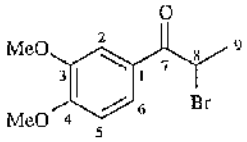
1-(3,4-Dimethoxyphenyl)propan-1-one (63)



Acylation of veratrole with freshly distilled propionyl chloride on a 45.09 mmol scale as previously described[42] afforded ethyl ketone (**63**) as shiny crystals (7.86 g, 90%), m.p. 59-61 °C (lit.[42] 58.5-59.5 °C); δ_H 1.22 (3H, t, *J* 7.2 Hz, H-9), 2.97 (2H, q,

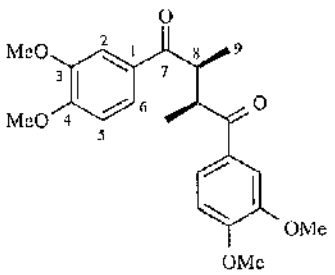
J 7.3 Hz, H-8), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.89 (1H, d, *J* 8.3 Hz, H-5), 7.54 (1H, d, *J* 1.9 Hz, H-2), 7.59 (1H, dd, *J* 8.3 Hz and 2.0 Hz, H-6).

2-Bromo-(3,4-dimethoxyphenyl)propan-1-one (64)



The procedure of Perry *et al.*[42] was modified as follows. Bromine (2.48 g, 0.80 ml, 15.53 mmol) in $CHCl_3$ (15 ml) was added portionwise under N_2 at rt to a solution of ketone (**63**) (3.00 g, 15.5 mmol) in $CHCl_3$ (50 ml) over 30 min with constant stirring until TLC showed no signs of starting material. The resultant mixture was washed with 10% sodium thiosulpfate (2 x 25 ml) and brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a light yellow solid which was recrystallised from MeOH affording bromoketone (**64**) as pale white feathers (3.49 g, 83%), m.p. 83-85 °C (lit.[42] 82-82.6 °C); δ_H 1.89 (3H, d, *J* 6.6 Hz, H-9), 3.95 (3H, s, OCH_3), 3.96 (3H, s, OCH_3), 5.31 (1H, q, *J* 6.6 Hz, H-8), 6.91 (1H, d, *J* 8.4 Hz, H-5), 7.58 (1H, d, *J* 2.0 Hz, H-2), 7.67 (1H, dd, *J* 6.4 Hz and 2.0 Hz, H-6).

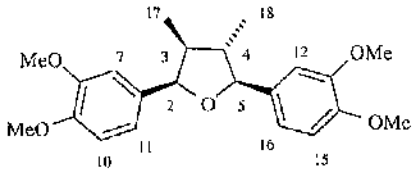
(±)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethylbutane-1,4-dione (65)



The procedure developed by Perry *et al.*[42] was used on a 10.99 mmol scale affording racemic diketone (**65**) as crystals (3.56 g, 84%), m.p. 146-148 °C (lit.[42] 145-146 °C); δ_H 1.31 (3H, d, *J* 6.6 Hz, H-9), 3.90 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.92 (1H, d, *J* 8.4 Hz, H-5), 7.50 (1H, d, *J* 1.9 Hz, H-2), 7.72 (1H, dd, *J* 8.4 Hz and 1.9 Hz, H-6).

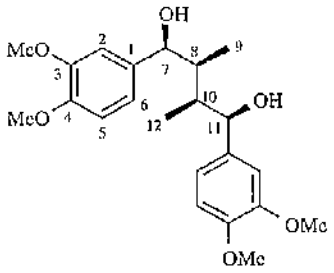
New data : δ_C 16.1 (C-9), 43.3 (C-8), 55.9 and 56.1 (OCH_3), 110.1 and 110.6 (C-2 and C-5), 123.1 (C-6), 129.2 (C-1), 149.0 and 153.2 (C-3 and C-4), 203.0 (C-7).

(±)-3,4-Dimethyl-2,5-bis-(3,4-dimethoxyphenyl)tetrahydrofuran (73)



Palladium on charcoal (10%, 100 mg) was added to a stirring solution of diketone (**65**) (250 mg, 0.65 mmol) in EtOH-EtOAc [(5:1), 30 ml] and the mixture was stirred under a hydrogen balloon for 17 h at rt. The mixture was filtered through Celite® and the residue washed with EtOAc (2 x 10 ml). Concentration *in vacuo* gave a solid which was recrystallised from ether-hexane affording the title compound (**73**) as crystals (130 mg, 54%), m.p. 119-121 °C (lit.[47] 121-122 °C); δ_H 0.67 (3H, d, *J* 7.0 Hz, H-17 or H-18), 1.07 (3H, d, *J* 6.6 Hz, H-17 or H-18), 1.74-1.84 (1H, m, H-3 or H-4), 2.21-2.30 (1H, m, H-3 or H-4), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 4.42 (1H, d, *J* 9.3 Hz, H-2 or H-5), 5.14 (1H, d, *J* 8.6 Hz, H-2 or H-5), 6.83-6.90 (4H, m, Ar-H), 7.03-7.08 (2H, m, Ar-H).

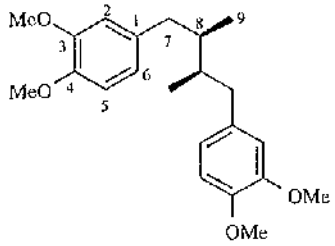
(±)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethylbutane-1,4-diol (67)



Reduction of the diketone (**65**) with $LiAlH_4$ as previously described[48] was modified as follows. A solution of diketone (**65**) (400 mg, 1.04 mmol) in dry THF (25 ml) was added dropwise to a stirring suspension of $LiAlH_4$ (400 mg, 10.54 mmol) in dry THF (10 ml) at rt. After the addition was complete, the grey slurry was stirred at rt for 1 h before being quenched cautiously at 0 °C with moist ether. The solids were dissolved by the addition of 1M HCl with vigorous stirring and the resultant mixture transferred to a separating funnel. The layers were separated, the aqueous layer was further extracted with EtOAc (2 x 10 ml) and the combined organic extracts were washed with brine (15 ml) and dried over $MgSO_4$. Concentration *in vacuo* afforded the title compound (**67**) as a mixture of diastereoisomers giving an indefinite melting point (403 mg, 98.3%); ν_{max} (KBr)/cm^{-1} 3430 (OH); δ_H (360 MHz) (major diastereoisomer) 0.59 (3H, d, *J* 7.0 Hz, H-9 or H-12), 1.07 (3H, d, *J* 6.9 Hz, H-9 or H-12), 1.66-1.70 (1H, m, H-8 or H-10), 2.31-2.36 (1H, m, H-8 or H-10), 3.82-3.90 (12H,

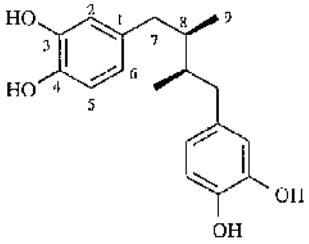
4s, 4 x OCH_3), 4.38 (1H, d, *J* 8.7 Hz, H-7 or H-11), 4.59 (1H, d, *J* 6.8 Hz, H-7 or H-11), 6.72-6.95 (6H, m, Ar-H).

(±)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethylbutane (39)



Palladium on charcoal (10%, 850 mg) was added to a stirring solution of the diol (**67**) (1.00g, 2.56 mmol) in AcOH (50 ml) and the mixture stirred under a hydrogen balloon at rt for 72 h. The mixture was filtered through Celite® and the residue washed with AcOH (2 x 10 ml). Concentration *in vacuo* followed by silica gel flash chromatography afforded a white solid (620 mg). Recrystallisation from MeOH afforded (±)-galbulin (**78**) as a fluffy solid (93 mg), m.p. 132-134 °C (lit.[53] 135 °C). The ^1H NMR spectrum was in excellent agreement with that reported.[53] A second crop of material, obtained after chilling the mother liquors in a freezer overnight, afforded the title compound (**39**) as white crystals contaminated with (±)-galbulin (350 mg, 38.3%), m.p. 77-80 °C (lit.[48] 71 °C); δ_H 0.83 (3H, d, *J* 6.7 Hz, H-9), 1.76 (1H, m, H-8), 2.34-2.62 (2H, m, H-7), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.57-6.83 (3H, m, Ar-H). This material could not be further purified by recrystallisation or column chromatography.

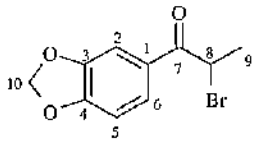
(±)-1,4-Bis-(3,4-dihydroxyphenyl)-2,3-dimethylbutane (32)



The general procedure of McOmie *et al.*[55] was used as follows. Boron tribromide (1.89 ml, 1M in DCM, 1.89 mmol) was added dropwise to a stirring solution of crude diarylbutane (**39**) (150 mg, 0.42 mmol) in dry DCM (10 ml) at -78 °C. After the addition was complete, the orange solution was allowed to warm to rt and stirred for a further 1 h before being poured cautiously into iced-H_2O (75 ml). After stirring for 15 min, the layers were separated and the aqueous layer was further

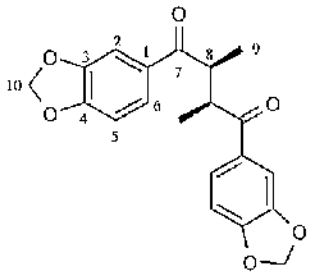
extracted with DCM (2 x 50 ml). The combined organic extracts were washed with brine (25 ml), dried over $MgSO_4$ and concentrated affording crude (**32**) as a light yellow oil (170 mg) that could not be purified; δ_H (d_6-Acet) 0.79 (3H, d, *J* 6.6 Hz, H-9), 1.70-1.80 (1H, m, H-8), 2.23-2.56 (2H, m, H-7), 6.45 (1H, dd, *J* 8.0 Hz and 1.9 Hz, H-6), 6.62 (1H, d, *J* 1.9 Hz, H-2), 6.71 (1H, d, *J* 8.0 Hz, H-5).

2-Bromo-1-(3,4-methylenedioxyphenyl)propan-1-one (81)



The procedure of Biftu *et al.*,[48] was modified as follows. Bromine (370 mg, 0.12 ml, 2.30 mmol) in $CHCl_3$ (5 ml) was added rapidly in portions over 15 min at rt to a vigorously stirring solution of 1-(3,4-methylenedioxyphenyl)propan-1-one (410 mg, 2.30 mmol) in $CHCl_3$ (20 ml). After TLC had shown no starting material present, the mixture was washed with 10% sodium thiosulfate (2 x 10 ml) and brine (15 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a yellow solid which was recrystallised from MeOH affording the title compound as off-white prisms (369 mg, 62.4%), m.p. 50-52 °C (lit.[48] 54-55 °C); δ_H 1.88 (3H, d, *J* 6.6 Hz, H-9), 5.21 (1H, q, *J* 6.6 Hz, H-8), 6.06 (2H, s, H-10), 6.87 (1H, d, *J* 8.2 Hz, H-5), 7.49 (1H, d, *J* 1.7 Hz, H-2), 7.64 (1H, dd, *J* 8.2 Hz and 1.7 Hz, H-6).

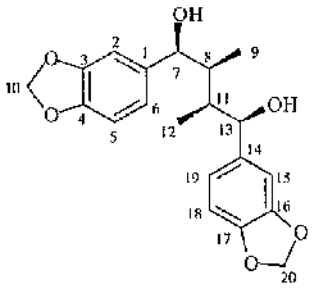
(±)-1,4-Bis-(3,4-methylenedioxyphenyl)-2,3-dimethylbutane-1,4-dione (82)



The procedure of Biftu *et al.*,[48] was used on a 1.32 mmol scale affording the title compound as an off-white solid from EtOH-acetone (364 mg, 77.8%), m.p. 195-196 °C (lit.[48] 206-207 °C (DCM-MeOH)); δ_H 1.27 (3H, d *J* 6.6 Hz, H-9), 3.80-3.89 (1H, m, H-8), 6.03 (2H, s, H-10), 6.86 (1H, d, *J* 8.2 Hz, H-5), 7.42 (1H, d, *J* 1.5 Hz, H-2), 7.63 (1H, dd, *J* 8.2 Hz and 1.6 Hz, H-6).

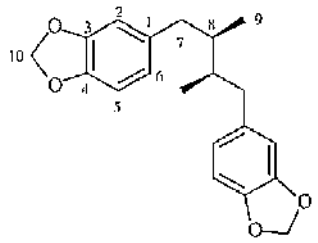
New data : ν_{max} (KBr)/cm^{-1} 1670 (C=O), 1611 and 1505 (C=C); δ_C 16.2 (C-9), 43.9 (C-8), 102.1 (C-10), 108.3 and 108.8 (C-2 and C-5), 125.1 (C-6), 131.3 (C-1), 148.5 and 152.0 (C-3 and C-4), 202.8 (C-7).

(±)-1,4-Bis-(3,4-methylenedioxyphenyl)-2,3-dimethylbutane-1,4-diol (83)



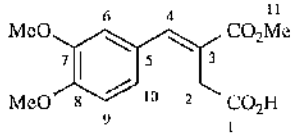
The method of Biftu *et al.*,[48] was modified as follows. A solution of the diketone (**82**) (300 mg, 0.85 mmol) in dry THF (10 ml) was added dropwise to a stiring suspension of $LiAlH_4$ (300 mg, 7.91 mmol) and THF (20 ml) at rt. After stirring for a further 1 h, the reaction was cooled to 0 °C and quenched by the cautious addition of moist ether followed by 1M HCl to dissolve all solids. The layers were separated and the aqueous layer further extracted with Et_2O (15 ml). The combined organic extracts were washed with brine (15 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a solid which was recrystallised from $CHCl_3$-hexane affording the title compound as a flaky solid (140 mg, 46.2%), m.p. 136-137 °C (lit.[48] 141-142 °C) δ_H 0.56 (3H, d, *J* 7.0 Hz, H-9 or H-12), 1.05 (3H, d, *J* 6.9 Hz, H-9 or H-12), 1.61-1.69 (1H, m, H-8 or H-11), 1.94 (1H, bs, OH), 2.17 (1H, bs, OH), 2.28-2.35 (1H, m, H-8 or H-11), 4.33 (1H, d, *J* 9.2 Hz, H-7 or H-12), 4.54 (1H, d, *J* 7.4 Hz, H-7 or H-12), 5.93 (2H, s, H-10 or H-20), 6.66 (1H, dd, *J* 7.6 Hz and 1.6 Hz, H-6 or H-19), 6.71 (2H, bs, Ar-H), 6.77 (2H, bs, Ar-H), 6.85 (1H, bs, Ar-H).

(±)-1,4-Bis-(3,4-methylenedioxyphenyl)-2,3-dimethylbutane (84)



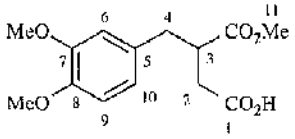
The method of Biftu *et al.*,[48] was used on a 0.14 mmol scale affording the crude title compound as a pale yellow oil that could not be purified; δ_H 0.80 (3H, d, *J* 6.6 Hz, H-9), 1.67-1.76 (1H, m, H-8), 2.34 (1H, dd, *J* 13.6 Hz and 8.3 Hz, H-7), 2.54 (1H, dd, *J* 13.5 Hz and 6.1 Hz, H-7), 5.91 (2H, s, H-10), 6.54 (1H, dd, *J* 7.8 Hz and 1.4 Hz, H-6), 6.58 (1H, d, *J* 1.4 Hz, H-2), 6.70 (1H, d, *J* 7.9 Hz, H-5).

4-(3,4-Dimethoxyphenyl)-3-methoxycarbonylbut-3-enoic acid (85)



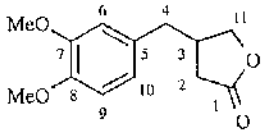
The method of Ganeshpure *et al.*[59] was used on a 30.12 mmol scale affording the unsaturated half ester (**85**) as bright yellow crystals from toluene (3.38 g, 40.1%), m.p. 145-148 °C (lit.[59] 149-150 °C {MeOH}); δ_H 3.64 (2H, s, H-2), 3.86 (3H, s, H-11), 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.89-7.03 (3H, m, Ar-H), 7.87 (1H, s, H-4).

4-(3,4-Dimethoxyphenyl)-3-methoxycarbonylbutanoic acid (86)



The method of Ganeshpure *et al.*[59] was used on a 8.93 mmol scale affording the saturated half ester (**86**) as white crystals from toluene (2.12 g, 84.1%), m.p. 107-109 °C (lit.[59] 108-109 °C {benzene-hexane}); δ_H 2.39-2.50 (1H, m, H-3), 2.65-2.76 (2H, m, H-2 or H-4), 2.96-3.06 (2H, m, H-2 or H-4), 3.68 (3H, s, H-11), 3.86 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.66-6.81 (3H, m, Ar-H). The potassium salt of (**86**) was prepared by the addition of 40% ethanolic KOH to a solution of (**86**) (500 mg, 1.77 mmol) in EtOH (4 ml) until basic to phenolphthalein followed by concentration and high vacuum drying.

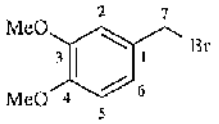
3-(3,4-Dimethoxybenzyl)butyrolactone (87)



The method of Ganeshpure *et al.*[59] was modified as follows. $NaBH_4$ (201 mg, 5.31 mmol) was added portionwise *via* a solid addition funnel to a stirring suspension of anhydrous $CaCl_2$ (196 mg, 1.77 mmol) and dry EtOH (20 ml) at 0 °C. After stirring for an additional 30 min, a solution of the potassium salt of (**86**) (1.77 mmol) in dry EtOH (5 ml) was added dropwise over 5 min. The mixture was stirred at 0 °C for 1 h, allowed to warm to rt and stirred overnight. The resultant white mixture was concentrated *in vacuo* and partioned between $CHCl_3$ (20 ml) and water (20 ml) before acidifying the aqueous layer to pH 1-2 with concentrated HCl. The clear solution was

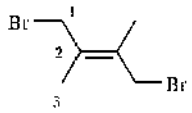
heated at reflux for 30 min, cooled to rt and the layers were separated. The aqueous layer was further extracted with $CHCl_3$ (2 x 10 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (10 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a crude oil (341 mg) which was purified by silica gel flash chromatography affording the lactone (**87**) as a colourless oil (191 mg, 45.7%). This material gave a ^1H NMR identical to that reported.[59]

3,4-Dimethoxybenzyl bromide (93)



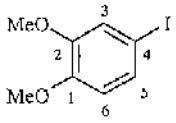
The procedure of Torrado and Imperiali[60] was modified as follows. Phosphorous tribromide (0.55 g, 0.19 ml, 2.00 mmol) was added dropwise at 0 °C to a stirring solution of 3,4-dimethoxybenzyl alcohol (1.02 g, 6.06 mmol) in dry Et_2O (20 ml). After the addition was complete, the mixture was allowed to reach rt and stirred for a further 1 h. The mixture was re-cooled to 0 °C and saturated $NaHCO_3$ (10 ml) added dropwise. The layers were separated and the aqueous layer was further extracted with Et_2O (5 ml). The combined organic extracts were washed with brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a white solid (1.23 g) which was recrystallised from Et_2O-hexane affording the title compound (**93**) as a fluffy solid (704 mg, 50.3%), m.p. 49-50 °C (lit.[60] 50-51 °C); δ_H 3.90 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 4.52 (2H, s, H-7), 6.83 (1H, d, *J* 8.2 Hz, H-5), 6.93 (1H, d, *J* 2.0 Hz, H-2), 6.97 (1H, dd, *J* 8.2 Hz and 2.1 Hz, H-6).

(*E*)-1,4-Dibromo-2,3-dimethylbut-2-ene (98) :



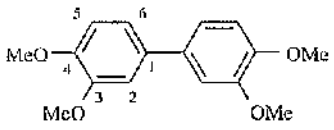
The method of Sweeting *et al.*[63] was used as follows. A solution of Br_2 (1.95 g, 0.63 ml, 12.20 mmol) in $CHCl_3$ (4 ml) was added dropwise over 30 min to a stirring solution of 2,3-dimethylbuta-1,3-diene (1.00 g, 1.38 ml, 12.17 mmol) in $CHCl_3$ (5 ml) at -10 °C. After the addition was complete, the light yellow solution was concentrated *in vacuo* to give a pale brown liquid which solidified on standing. Recrystallisation from light petroleum-ether afforded the title compound as cream crystals (1.90 g, 64.4%), m.p. 45-47.5 °C (lit.[63] 47.0-47.5 °C); δ_H 1.90 (3H, s, H-3), 4.02 (2H, s, H-1); δ_C 17.6 (C-1), 35.5 (C-3), 132.3 (C-2).

1,2-Dimethoxy-4-Iodo-benzene (105) :



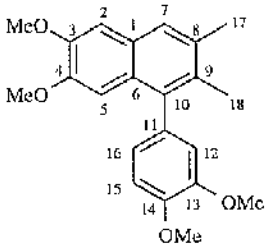
The general method of Skulski *et al.*[64] was modified as follows. Lead tetraacetate (4.88 g, 11.00 mmol) was added to a stirring solution of I_2 (2.55 g, 10.04 mmol) and 1,2-dimethoxybenzene (2.78 g, 2.56 ml, 20.12 mmol) in glacial AcOH (50 ml). After stirring at rt for 22 h, the light yellow reaction mixture was concentrated to *ca.* 15 ml and H_2O (20 ml) was added. The mixture was extracted with Et_2O (2 x 25 ml) and the combined organic extracts were washed with 10% $NaHSO_4$ (3 x 10 ml) and brine (20 ml) before drying over $MgSO_4$. The mixture was concentrated *in vacuo* to give a yellow oil (5.41 g) which was crystallised from chilled EtOH affording the title compound (3.80 g, 71.6%), m.p. 34.5-35.5 °C (lit.[64] 34-35 °C); δ_H 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.62 (1H, d, *J* 8.4 Hz, H-6), 7.12 (1H, d, *J* 1.7 Hz, H-3), 7.22 (1H, dd, *J* 8.4 Hz and 1.8 Hz, H-5).

3,3',4,4'-Tetramethoxybiphenyl (109)



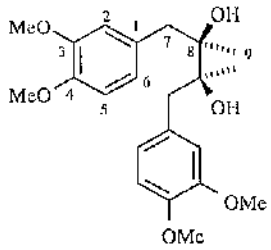
n-BuLi (0.90 ml, 1.4 M in hexanes, 1.26 mmol) was added dropwise to a stirring solution of 4-bromo-1,2-dimethoxybenzene (250 mg, 0.15 ml, 1.15 mmol) in dry THF (10 ml) at -78 °C. After stirring for 10 min, a solution of bromide (**98**) (167 mg, 0.69 mmol) in dry THF (2 ml) was added dropwise and the mixture was stirred at -78 °C for 30 min. The light yellow solution was allowed to warm to rt and stirred for 15 h before diluting with Et_2O (25 ml). The organic solution was washed with H_2O (2 x 20 ml) and brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a pale yellow solid which was purified by silica gel flash chromatography affording the title compound as crystals, m.p 123-125 °C (lit.[92] 124-126 °C); δ_H 3.94 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.96 (1H, d, *J* 8.3 Hz, H-5), 7.08 (1H, d, *J* 2.0 Hz, H-2), 7.12 (1H, dd, *J* 8.2 Hz and 2.1 Hz); δ_C 56.4 (OCH_3), 56.4 (OCH_3), 110.7 and 111.8 (C-2 and C-5), 119.5 (C-6), 134.6 (C-1), 148.7 and 149.5 (C-3 and C-5); LRMS : *m/z* = 274.1 ($M^{+\bullet}$, 100%).

1-(3,4-dimethoxyphenyl)-2,3-dimethyl-6-7-dimethoxynapthalene (127) :



The method of Carroll *et al.*[81] was used on a 2.57 mmol scale affording the crude product as an amber coloured oil (2.38 g). Crystallisation of this oil from EtOH afforded the title compound (**127**) as orange crystals (171 mg, 37.8%), m.p. 175-178 °C (lit.[82] 177-178 °C); δ_H 2.07 (3H, s, H-17 or H-18), 2.28 (3H, s, H-17 or H-18), 3.78 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.64-6.67 (2H, m, H-12 and H-16), 6.87 (1H, d, J 8.0 Hz, H-15), 7.01 (1H, s, ArH), 7.15 (1H, s, ArH), 7.38 (1H, s, ArH); δ_C 15.2 and 20.1 (C-17 and C-18), 54.2 (OCH_3), 101.9 (CH), 104.7 (CH), 109.4 (CH), 111.2 (CH), 120.0 (CH), 122.8 (CH), 123.0 (C), 127.0 (C), 128.8 (C), 131.4 (C), 132.9 (C), 136.8 (C), 146.0, 147.1, 147.3 and 147.5 (C-3, C-4, C-13 and C-14); LRMS : $m/z = 352$ ($M^{+\bullet}$, 100%).

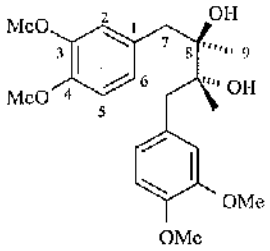
***meso*-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethyl-2,3-butanediol (132) :**



The procedure of Takeya *et al.*[83] was modified as follows. Activated zinc dust (2.00 g, 30.60 mmol) was added in portions to a stirring mixture of 3,4-dimethoxyphenylacetone (2.00 g, 1.8 ml, 10.30 mmol) and $TiCl_4$ (2.92 g, 1.69 ml, 15.38 mmol) in dry THF (60 ml) at 0 °C. The resultant dull green mixture was allowed to warm to rt and then heated at reflux for 3 h whereupon the mixture became a deep red homogeneous solution. After cooling to rt the mixture was quenched with saturated K_2CO_3 solution (15 ml) and stirring was continued for a further 1 h. After the resultant thick slurry was filtered through Celite® and the residue washed with $CHCl_3$ (4 x 30 ml), the light yellow organic solution was washed with water (80 ml) and brine (30 ml) before drying over $MgSO_4$. Concentration *in vacuo* afforded a yellow oil which was crystallised from ether affording a 4:3 ratio (^1H NMR) of diastereoisomeric pinacols as a colourless solid (1.47 g, 73.5%). Recrystallisation of this product three times from EtOH afforded the *meso*-pinacol (**132**) as shiny crystals (439 mg, 22.0%),

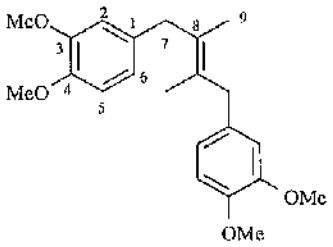
m.p. 156-159 °C; ν_{max} (KBr)/cm^{-1} 3547 (OH), 1588 and 1514 (C=C); δ_H 1.14 (3H, s, H-9), 2.00 (1H, s, OH), 2.68 (1H, d, *J* 13.4 Hz, H-7), 3.12 (1H, d, *J* 13.4 Hz, H-7), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 6.79-6.86 (3H, m, Ar-H); δ_C 20.9 (C-9), 40.4 (C-7), 55.0 (OCH_3), 75.8 (C-8), 110.1 and 113.3 (C-2 and C-5), 122.0 (C-6), 129.2 (C-1), 146.9 and 147.7 (C-3 and C-4); (Found: C 67.82%; H 7.84%; $M^{+\bullet}$, 390.2042. $C_{22}H_{30}O_6$ requires C 67.7%; H 7.69%; M, 390.2043).

(±)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethyl-2,3-butanediol (133) :



The mother liquors from above were concentrated *in vacuo* and recrystallised from ether affording the title compound (**133**) as a mixture of diastereoisomers [(±):*meso* = 2:1] (787 mg, 39.4%), m.p. 136-139 °C; ν_{max} (KBr)/cm^{-1} 3513 (OH), 1590 and 1514 (C=C); δ_H (major diastereoisomer) 1.18 (3H, s, H-9), 2.01 (1H, s, OH), 2.67 (1H, d, *J* 13.5 Hz, H-7), 3.09 (1H, d, *J* 13.4 Hz, H-7), 3.88 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.77-6.86 (3H, m, Ar-H); δ_C 21.8 (C-9), 42.1 (C-7), 77.1 (C-8), 111.4 and 114.7 (C-2 and C-5), 123.4 (C-6), 130.5 (C-1), 148.2 and 149.0 (C-3 and C-4); (Found: C 67.75%; H 7.82%; $M^{+\bullet}$, 390.2041. $C_{22}H_{30}O_6$ requires C 67.7%; H 7.69%; M, 390.2042).

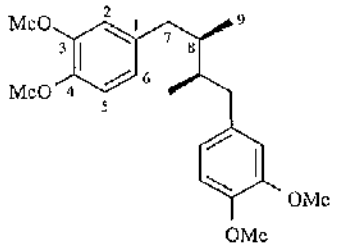
(*E*)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethyl-2-butene (96) :



The procedure of Takeya *et al.*[83] was modified as follows. A mixture of the pinacol (**133**) (400 mg, 1.03 mmol), triethyl orthoformate (430 mg, 0.48 ml, 2.90 mmol) and benzoic acid (85 mg, 0.70 mmol) was heated in a distillation apparatus under nitrogen at 110 °C for 2 h. After cooling, additional benzoic acid (43 mg, 0.35 mmol) was added and heating was continued at 180 °C for 2 h at atmospheric pressure followed by 15 min under vacuum (rotary pump) while EtOH was distilled over. The

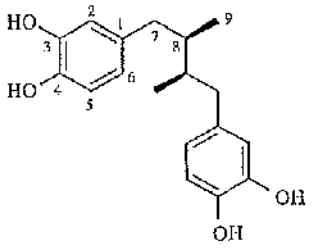
resultant yellow solution was allowed to cool to rt, taken up in DCM (30 ml) and washed successively with sat. $NaHCO_3$ (15 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave an oil which solidified on standing. Excess triethyl orthoformate was removed by column chromatography eluting with ether-hexane (2:1) and the resultant yellow solid was recrystallised from EtOH affording the title compound (**96**) as colourless needles (255 mg, 69.9%), m.p. 121-123 °C; ν_{max} (KBr)/cm^{-1} 1589 and 1515 (C=C); δ_H 1.76 (3H, s, H-9), 3.41 (2H, s, H-7), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.70-6.80 (3H, m, Ar-H); δ_C 19.0 (C-9), 40.2 (C-7), 56.1 and 56.3 (OCH_3), 111.5 and 112.1 (C-2 and C-5), 120.6 (C-6), 129.3 and 133.8 (C-1 and C-8), 147.6 and 149.2 (C-3 and C-4); (Found: C 74.01%; H 7.91%; $M^{+\bullet}$, 356.1985. $C_{22}H_{28}O_4$ requires C 74.16%; H 7.87%; M, 356.1987).

(±)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethylbutane (39) :



Platinum (IV) oxide (25 mg, 0.11 mmol) was added to a stirring solution of the (*E*)-alkene (**96**) (150 mg, 0.42 mmol) in glacial AcOH (20 ml) and the mixture was stirred under a hydrogen balloon, after degassing the solvent three times, for 1 h. The mixture was filtered through Celite®, the residue washed with $CHCl_3$ (2 x 10 ml) and the colourless solution concentrated *in vacuo*. Saturated by-products were removed by column chromatography eluting with ether-hexane (3:1) affording a colourless oil (104 mg) which crystallised on standing. Recrystallisation from MeOH afforded pure racemic (**39**) as needles (46 mg, 30.5%), m.p. 70-72 °C (lit.,[48] 71 °C); δ_H 0.83 (3H, d, *J* 6.6 Hz, H-9), 2.40 (1H, dd, *J* 13.6 Hz and 7.8 Hz), 2.56 (1H, dd, *J* 13.6 Hz and 6.8 Hz), 1.74-1.78 (1H, m, H-8), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.59 (1H, d, *J* 1.8 Hz, H-2), 6.63 (1H, dd, *J* 8.1 Hz and 1.8 Hz, H-6), 6.76 (1H, d, *J* 8.1 Hz, H-5).

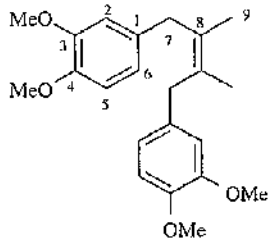
(±)-1,4-Bis-(3,4-dihydroxyphenyl)-2,3-dimethylbutane (32) :



A mixture of (**39**) (58 mg, 0.16 mmol) and 48% HBr-AcOH (2:1) (3 ml) was heated at reflux under nitrogen for 6 h. After cooling to rt, the light pink mixture was poured into water (10 ml) and extracted into EtOAc (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a light yellow oil that crystallised on standing. Purification by column chromatography afforded the title compound as a light brown solid (40 mg, 81.6%), m.p. 155-157 °C (lit.,[44] 157-160 °C).

New data. ν_{max} (KBr)/cm^{-1} 3474 and 3377 (OH), 1610 and 1527 (C=C); δ_H (d_6-DMSO) 0.73 (3H, d, *J* 6.5 Hz, H-9), 1.62-1.67 (1H, m, H-8), 2.20 (1H, dd, *J* 13.2 Hz and 8.4 Hz, H-7), 2.41 (1H, dd, *J* 13.2 Hz, and 5.6 Hz, H-7), 6.34 (1H, dd, *J* 7.9 Hz and 1.8 Hz, H-6), 6.48 (1H, d, *J* 1.8 Hz, H-2), 6.60 (1H, d, *J* 7.9 Hz, H-5), 8.55 (1H, bs, OH), 8.65 (1H, bs, OH); δ_C (d_6-DMSO) 14.1 (C-9), 38.2 (C-8), 40.6 (C-7), 115.7 and 116.5 (C-2 and C-5), 119.8 (C-6), 132.4 (C-1), 143.3 and 145.2 (C-3 and C-4); (Found: C 71.35%; H 7.34%; $M^{+\bullet}$, 302.1516. $C_{18}H_{22}O_4$ requires C 71.52%; H 7.28%; M, 302.1518).

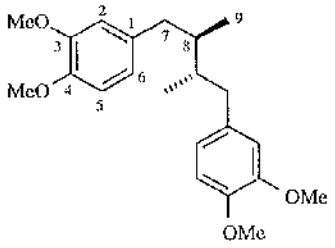
(Z)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethyl-2-butene (131) :



This compound was prepared by the method used to prepare (**96**) using the *meso*-pinacol (**132**) (400 mg, 1.03 mmol) affording the title compound as feathers (290 mg, 79.5%), m.p. 78-80 °C; ν_{max} (KBr)/cm^{-1} 1588 and 1514 (C=C); δ_H 1.69 (3H, s, H-9), 3.48 (2H, s, H-7), 3.82 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.67 (1H, d, *J* 2.0 Hz, H-2), 6.71 (1H, dd, *J* 8.0 and 2.0 Hz, H-6), 6.79 (1H, d, *J* 8.0 Hz, H-5); δ_C 18.6 (C-9), 39.7 (C-7), 55.8 (OCH_3), 55.9 (OCH_3), 111.1 and 112.0 (C-2 and C-5), 120.4 (C-6), 128.7 and 133.3 (C-1 and C-8), 147.2 and 148.9 (C-3 and C-4); (Found:

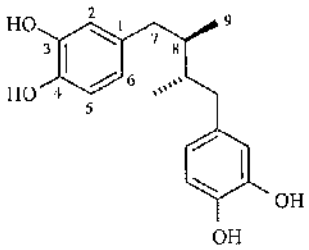
C 74.15%; H 7.91%; $M^{+\bullet}$, 356.1990. $C_{22}H_{28}O_4$ requires C 74.16%; H 7.87%; M, 356.1987).

***meso*-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethylbutane (47) :**



Platinum (IV) oxide (20 mg, 0.09 mmol) was added to a stirring solution of the (*Z*)-alkene (**131**) (200 mg, 0.56 mmol) and the mixture was stirred under a hydrogen balloon at rt, after degassing the solvent three times. After 1 h, when TLC showed no signs of starting material, the mixture was filtered through Celite® and the residue was washed with $CHCl_3$ (2 x 10 ml). Concentration *in vacuo* afforded a pale yellow oil which solidified on standing and was recrystallised two times from MeOH affording the title compound as shiny crystals (75 mg, 37.3%), m.p. 99-100 °C (lit.,[42] 100-102 °C); δ_H 0.85 (3H, d, *J* 6.6 Hz, H-9), 1.75-1.80 (1H, m, H-8), 2.30 (1H, dd, *J* 13.5 Hz and 9.3 Hz, H-7), 2.75 (1H, dd, *J* 13.5 Hz and 5.0 Hz, H-7), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.65 (1H, d, *J* 1.7 Hz, H-2), 6.70 (1H, dd, *J* 8.1 Hz and 1.7 Hz, H-6), 6.79 (1H, d, *J* 8.1 Hz, H-5).

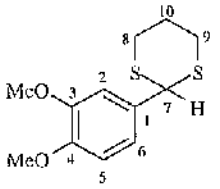
***meso*-1,4-Bis-(3,4-hydroxyphenyl)-2,3-dimethylbutane (NDGA) (1) :**



A mixture of (**47**) (60 mg, 0.17 mmol) and 48% HBr-AcOH (2:1) (3 ml) was heated at reflux under nitrogen for 6 h. After cooling to rt, the light pink mixture was poured into water (10 ml) and extracted into EtOAc (2 x 10 ml). The combined organic extracts were washed with brine (10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a light yellow oil that crystallised on standing. Recrystallisation from Et_2O-hexane afforded NDGA (**1**) as shiny brown crystals (40 mg, 78.4%), m.p. 184-186 °C (lit.,[42] 184.5-186); δ_H 0.75 (3H, d, *J* 6.6 Hz, H-9), 1.60-1.62 (1H, m, H-8), 2.10 (1H, dd, *J* 13.2 and 9.2 Hz, H-7), 2.57 (1H, dd, *J* 13.3 and 4.8 Hz, H-7), 6.39 (1H, dd, *J* 8.0

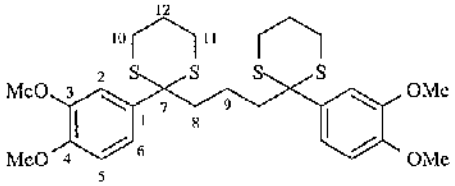
and 1.9 Hz, H-6), 6.53 (1H, d, *J* 1.9 Hz, H-2), 6.62 (1H, d, *J* 7.9 Hz, H-5), 8.57 (1H, bs, OH), 8.64 (1H, bs, OH).

2-(3,4-Dimethoxyphenyl)-1,3-dithiane (137)



The method of Seebach *et al.*[95] was modified as follows : Dry HCl was bubbled into a solution of 3,4-dimethoxybenzaldehyde (2.00 g, 12.00 mmol) and 1,3-propanedithiol (1.21 ml, 12.10 mmol) in dry $CHCl_3$ (5 min) at 0 °C for 5 min. The mixture was stirred for 30 min then washed successively with H_2O (2 x 5 ml), 10% KOH (2 x 5 ml) and H_2O (2 x 5 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a pale yellow solid (2.91 g) which was recrystallised from EtOH affording dithiane (**137**) as crystals (2.56 g, 83.1 %), m.p. 92-92.5 °C (lit.[94] 92-93 °C); δ_H 1.82-2.21 (2H, m, H-10), 2.85-3.14 (4H, m, H-8 and H-9), 3.87 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.13 (1H, s, H-7), 6.82 (1H, d, *J* 8.8 Hz, H-5), 7.01-7.05 (2H, m, H-2 and H-6).

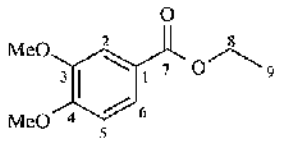
1,5-Bis-(3,4-dimethoxyphenyl)pentane-1,5-bis dithiane (138)



The method of Fliedner *et al.*[94] was used as follows : *n*-BuLi (1.60 ml, 1.35 M in hexanes, 2.16 mmol) was added dropwise at -35 °C to a stirring solution of dithiane (**137**) (500 mg, 1.95 mmol) in dry THF (25 ml). The resultant yellow solution was stirred for 1.5 h, allowed to warm to -15 °C and a solution of 1,3-propanedithiol (0.10 ml, 0.99 mmol) in dry THF (1 ml) was introduced dropwise. After standing in a fridge overnight the solution was re-cooled to -35 °C and quenched by the cautious addition of H_2O (0.5 ml) and the mixture concentrated *in vacuo*. The residue was suspended in H_2O (5 ml), the mixture acidified to pH 2-3 by the addition of c.HCl and extracted with $CHCl_3$ (30 ml). The organic layer was washed succesively with 5 % $NaHSO_3$ (3 x 10 ml), 5 % KOH (3 x 10 ml) and H_2O (3 x 10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a pale yellow oil which was purified by silica gel flash chromatography affording the title compound (**138**) as a pale yellow solid (369 mg,

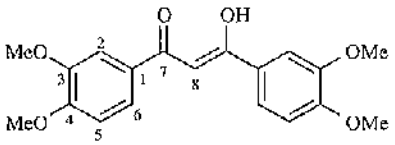
68.6 %), m.p. 111-114 °C (lit.[94] 115-117 °C); δ_H 1.24-1.34 (2H, m, H-9), 1.83-1.91 (4H, m, H-8 and H-12), 2.62-2.69 (4H, m, H-10 and H-11), 3.86 (3H, s, OCH_3), 3.89 (3H, s, OCH_3), 6.79 (1H, d, J 8.3 Hz, H-5), 7.31-7.38 (2H, m, H-2 and H-6).

Ethyl-(3,4-dimethoxyphenyl)benzoate (139)



The method of Choshi *et al.*[96] was modified as follows : Concentrated H_2SO_4 (2 drops) was added to a stirring suspension of 3,4-dimethoxybenzoic acid (1.00 g, 5.49 mmol) and EtOH (5 ml) and the whole mixture heated at reflux for 18 h. After cooling to rt, the solution was poured into water (30 ml) and extracted into EtOAc (2 x 20 ml). The combined organics were washed with 1M NaOH (10 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a yellow oil which was distilled under reduced pressure affording the title compound as a viscous oil (705 mg, 61.3%), b.p. 134-136 °C (>1 mmHg) (lit.,[96] 152-153 °C/6 mmHg); δ_H 1.38 (3H, t, *J* 7.1 Hz, H-9), 3.91 (3H, s, OCH_3), 3.93 (3H, s, OCH_3), 4.35 (2H, q, *J* 7.1 Hz, H-8), 6.87 (1H, d, *J* 8.4 Hz, H-5), 7.55 (1H, d, *J* 1.9 Hz, H-2), 7.67 (1H, dd, *J* 8.4 Hz and 2.0 Hz, H-6); δ_C 14.7 (C-9), 56.2 (OCH_3), 61.0 (C-8), 110.5 and 112.2 (C-2 and C-5), 123.3 (C-1), 123.8 (C-6), 148.9 and 153.2 (C-3 and C-4), 166.6 (C-7).

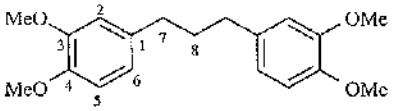
1,3-Bis-(3,4-dimethoxyphenyl)propan-1,3-dione (141)



The method of Choshi *et al.*[94] was modified as follows : A solution of 3,4-dimethoxyacetophenone (180 mg, 1.00 mmol) in $PhCH_3$ (3 ml) was added dropwise to a stirring suspension of NaH (50 mg, 60% in oil, 1.25 mmol) (pre-washed in hexane (2 x 2 ml)) and ester (**139**) (231 mg, 1.10 mmol) in dry $PhCH_3$ (8 ml) at rt. After the addition complete the mixture was heated at reflux for 16 h, cooled to rt and quenched by the cautious addition of 10% HCl (5 ml). The mixture was extracted with EtOAc (2 x 10ml) and the combined organics washed with brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave an orange solid which was recrystallised from EtOH affording the diketone (**141**) as orange crystals (104 mg, 30.2 %), m.p. 127-129 °C (lit.,[94] 100.5-101 °C (ether)); $\nu_{max.}$ (KBr)/cm^{-1}, 1600 (C=O); δ_H 3.97 (6H, s,

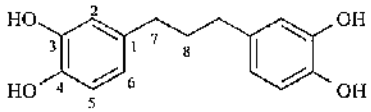
OCH_3), 3.99 (6H, s, OCH_3), 6.75 (1H, s, H-8), 6.94 (2H, d, *J* 8.4 Hz, H-5), 7.56 (2H, d, *J* 1.9 Hz, H-2), 7.61 (2H, dd, *J* 8.4 Hz and 2.0 Hz, H-6), 14.4 (1H, bs, OH).
New data : δ_C 56.4 (OCH_3), 92.1 (C-8), 110.1 and 110.9 (C-2 and C-5), 121.4 (C-6), 128.8 (C-1), 149.5 and 153.1 (C-3 and C-4), 184.9 (C-7); (Found: $M^{+\bullet}$, 344.1259. $C_{19}H_{20}O_6$ requires M, 344.1260).

1,3-Bis-(3,4-dimethoxyphenyl)propane (142)



Palladium on charcoal (10 %, 150 mg) was added to a solution of the diketone (**141**) (250 mg, 0.73 mmol) in MeOH (50 ml) and the mixture stirred under a hydrogen balloon at rt for 72 h. The mixture was filtered through Celite®, the catalyst washed with MeOH (2 x 20 ml) and the solvent removed on a rotary evaporator. Flash chromatography of the residue afforded the title compound (**142**) as a powder (160 mg, 70 %), m.p. 61-63 °C (lit.,[97] 62-63 °C).
New data : $\nu_{max.}$ ($CDCl_3$)/cm^{-1}, 1509 and 1588 (C=C); δ_H 1.88-1.96 (2H, m, H-8), 2.60 (4H, t, *J* 7.6 Hz, H-7), 3.86 (6H, s, OCH_3), 3.87 (6H, s, OCH_3), 6.71 (2H, d, *J* 1.8 Hz, H-2), 6.73 (2H, dd, *J* 8.2 Hz and 1.9 Hz, H-6), 6.80 (2H, d, *J* 8.0 Hz, H-5); δ_C 33.7 (C-8), 35.4 (C-7), 56.2 (OCH_3), 56.3 (OCH_3), 111.6 and 112.2 (C-2 and C-5), 120.6 (C-6), 135.3 (C-1), 147.5 and 149.2 (C-3 and C-4); (Found: $M^{+\bullet}$, 316.1675. $C_{19}H_{24}O_4$ requires M, 316.1675).

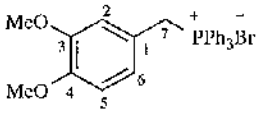
1,3-Bis-(3,4-dihydroxyphenyl)propane (143)



The general procedure of McOmie *et al.*[55] was used as follows : Boron tribromide (1.71 ml, 1M in DCM, 1.71 mmol) was added dropwise to a stirring solution of diarylpropane (**142**) (120 mg, 0.38 mmol) in dry DCM (8 ml) at -78 °C. After the addition complete, the orange solution was allowed to come to rt and stirred for 1h before pouring into iced-H_2O (50 ml). The resultant mixture was extracted with EtOAc (2 x 25 ml) and the combined organics washed with brine (10 ml) and dried over $MgSO_4$. Concentration *in vacuo* afforded a light orange oil which was purified by silica gel dry flash column chromatography giving the title compound (**143**) as a colourless oil that solidified on standing (90 mg, 91.2 %), m.p. 115-117 °C (lit.,[97] 117-119 °C); (Found : C 68.91%; H 6.07%. $C_{15}H_{16}O_4$ requires C 69.23%; H 6.15%).

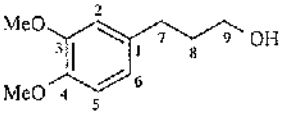
New data: $\nu_{max.}$ (KBr)/cm^{-1}, 3425 and 3367 (OH), 1608, 1560 and 1526 (C=C); δ_H (CD_3OD) 1.95-2.06 (2H, m, H-8), 2.64 (4H, t, *J* 7.4 Hz, H-7), 5.06 (4H, bs, OH), 6.67 (2H, dd, *J* 8.0 Hz and 2.0 Hz, H-6), 6.79 (2H, d, *J* 1.9 Hz, H-2), 6.85 (2H, d, *J* 8.0 Hz, H-5); δ_C (CD_3OD) 35.3 (C-8), 36.0 (C-7), 116.5 and 116.8 (C-2 and C-5), 121.0 (C-6), 135.7 (C-1); 144.4 and 146.3 (C-3 and C-4); (Found: $M^{+\bullet}$, 260.1043. $C_{15}H_{16}O_4$ requires M, 260.1049).

3,4-Dimethoxybenzyl triphenylphosphonium bromide (144)



A mixture of triphenylphosphine hydrobromide (2.04g, 5.95 mmol) and 3,4-dimethoxybenzyl alcohol (1.00 g, 5.95 mmol) in dry CH_3CN (100 ml) was heated at reflux for 12 h. After cooling to rt the mixture was concentrated *in vacuo* to give a pale yellow solid which was recrystallised from EtOH affording (**144**) as white crystals (2.26 g, 77.0%), m.p. 235-237 °C; ν_{max} (KBr)/cm^{-1} 1588 and 1515 (C=C); δ_H 3.54 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 5.36 (2H, d, J_{H-P} 13.8 Hz, CH_2), 6.60 (1H, d, *J* 8.3 Hz, H-6), 6.64-6.67 (1H, m, H-5), 6.85-6.86 (1H, m, H-3), 7.60-7.78 (15H, m, PPh_3); δ_C 30.6 (d, J_{C-P} 46.1 Hz, CH_2), 56.2 and 56.4 (OCH_3), 111.3, 115.3 and 115.4 (CH), 117.8, 118.7 and 119.4 (C), 124.1, 130.4, 130.5, 134.9, 135.0 and 135.2 (CH), 149.1 and 149.2 (C-1 and C-2); δ_P (81 Hz, CDCl3) 22.4; (Found: C 65.54%; H 5.29%; $M^{+\circ}$(-HBr), 412.1591. $C_{27}H_{26}BrO_2P$ requires C 65.72%; H 5.27%; M(-HBr), 412.1592).

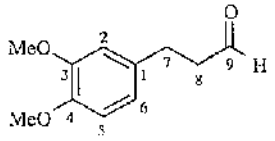
3-(3,4-Dimethoxyphenyl)propan-1-ol



The method of Frydman *et al.*[100] was modified as follows : A solution of 3-(3,4-dimethoxyphenyl)propionic acid (1.50 g, 7.14 mmol) in dry THF (5 ml) was added dropwise to a stirring slurry of $LiAlH_4$ (0.41 g, 10.70 mmol) and THF (20 ml) at 0 °C. After stirring at rt for 3.5 h the reaction was quenched by the cautious addition of moist ether followed by 1M HCl to dissolve the inorganic solids. The layers were separated, the aqueous layer extracted with EtOAc (25 ml) and the combined organics washed with brine (15 ml) before drying over $MgSO_4$. Concentration *in vacuo* followed by distillation afforded the title compound as a viscous oil (0.93 g, 66.5%) giving b.p. 150-152 °C / > 1 mmHg, (lit., [100] 134-142 °C / 0.5 mmHg), δ_H 1.82-1.89

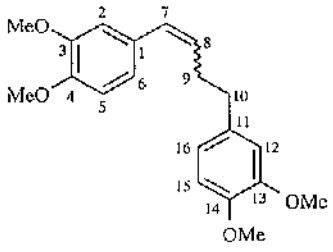
(2H, m, H-8), 2.22 (1H, bs, OH), 2.64 (2H, t, *J* 7.5 Hz, H-7), 3.65 (2H, t, *J* 6.5 Hz, H-9), 3.84 (3H, s, OCH_3), 3.85 (3H, s, OCH_3), 6.71-6.83 (3H, m, Ar-H).

3-(3,4-Dimethoxyphenyl)propionaldehyde (146)



The method of Padwa *et al.*,[99] was modified employing the general procedure of Swern *et al.*[101] as follows : A solution of DMSO (438 mg, 0.40 ml, 5.62 mmol) in dry DCM (2 ml) was added dropwise to a stirring solution of oxalyl chloride (356 mg, 0.24 ml, 2.80 mmol) in dry DCM (20 ml) at -60 °C. After 2 min a solution of the alcohol (500 mg, 2.56 mmol) in dry DCM (4 ml) was introduced dropwise at the same temperature and stirring continued for 15 min. Et_3N (1.29 g, 1.78 ml, 12.76 mmol) was added dropwise to the cloudy solution and the mixture allowed to warm to rt over 45 min when TLC showed no signs of starting material. Water (20 ml) was added and the resultant two layers separated with the aqueous layer further extracted with DCM (15 ml). The combined organics were washed with 10% HCl (10 ml) and brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* afforded the title compound (**146**) as a light yellow oil (486 mg, 98.2%) pure enough to be used without further purification. δ_H 2.77 (2H, t, *J* 7.2 Hz, H-7 or H-8), 2.91 (2H, *t*, *J* 7.4 Hz, H-7 or H-8), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.72-6.74 (2H, m, H-2 and H-6), 6.80 (1H, d, *J* 8.6 Hz, H-5), 9.82 (1H, bs, CHO); δ_C 27.6 (C-7), 45.4 (C-8), 55.7 (OCH_3), 55.8 (OCH_3), 111.2 and 111.5 (C-2 and C-5), 120.0 (C-6), 132.9 (C-1), 147.3 and 148.8 (C-3 and C-4), 201.7 (C-9).

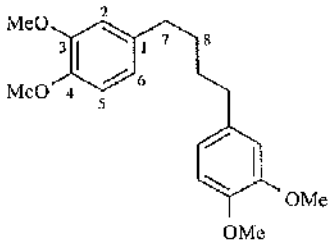
1,4-Bis-(3,4-dimethoxyphenyl)but-1-ene (147)



To a stirring suspension of (**144**) (1.25 g, 2.54 mmol) in dry THF (25 ml) was added *n*-BuLi (1.74 ml, 1.6 M in hexanes, 2.79 mmol) dropwise at 0 °C. After stirring the dark red solution for a further 15 min aldehyde (**146**) (469 mg, 2.42 mmol) in THF (5 ml) was introduced dropwise at the same temperature. The resultant fawn coloured suspension was stirred at 0 °C for 30 min allowed to warm to rt and stirred for a

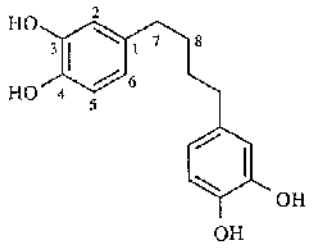
further 1 h before pouring into iced water (50 ml). The mixture was extracted into EtOAc (3 x 25 ml) and the combined organics washed with brine (25 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a yellow solid which was purified by column chromatography affording alkene (**147**) as a mixture of geometrical isomers (630 mg, 79.5%, *Z*:*E* = 1.9-1), m.p. 150-156 °C; ν_{max} (KBr)/cm^{-1} 1590 and 1600 (C=C); δ_H (*E*-isomer) 2.47-2.52 (2H, m, CH_2), 2.71-2.75 (2H, m, CH_2), 3.84-3.94 (12H, m, OCH_3), 6.13 (1H, dt, *J* 15.8 Hz and 6.8 Hz, H-8), 6.35 (1H, d, *J* 15.6 Hz, H-7), 6.71-6.89 (6H, m, Ar-H), (Z-isomer) 2.63-2.68 (2H, m, CH_2), 2.71-2.75 (2H, m, CH_2), 3.84-3.94 (12H, m, OCH_3), 5.62 (1H, dt, *J* 11.6 Hz and 7.1 Hz, CH), 6.38 (1H, d, *J* 11.6 Hz, Ar-CH), 6.71-6.89 (6H, m, Ar-H); δ_C 30.9, 35.5, and 36.0 (CH_2), 56.2 and 56.3 (OCH_3), 109.0, 111.3, 111.6, 112.2, 112.3, 112.5, 119.3, 120.6, 121.6, 128.5, 129.5 and 130.4 (CH), 130.9 (C), 131.0 (CH), 131.3 , 134.7, 134.9, 147.6, 148.2, 148.7, 148.9, 149.2 and 149.4 (C); (Found: $M^{+\bullet}$, 328.1674. $C_{20}H_{24}O_4$ requires M, 328.1675).

1,4-Bis-(3,4-dimethoxyphenyl)butane (148)



Palladium on charcoal (10%, 50 mg) was added to a stirring solution of (**147**) (578 mg, 1.76 mmol) in MeOH-EtOAc (5:1) (50 ml) and the mixture stirred under a hydrogen balloon at room temperature for 72 h. The mixture was filtered through Celite® and the residue washed with ethyl acetate (2 x 10 ml). Concentration *in vacuo* gave a white solid which was recrystallised from aqueous MeOH affording the diarylbutane (**148**) as crystals (489 mg, 84.2%), m.p. 89-90 °C (lit.,[98] 90 °C).
New data : ν_{max} (KBr)/cm^{-1} 1606, 1589 and 1517 (C=C); δ_H 1.62-1.66 (2H, m, H-8), 2.58 (2H, t, *J* 6.6 Hz, H-7), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.69-6.71 (2H, m, H-2 and H-6), 6.78 (1H, d, *J* 7.8 Hz, H-5); δ_C 31.6 and 35.8 (C-7 and C-8), 56.2 (OCH_3), 56.3 (OCH_3), 111.6 and 112.1 (C-2 and C-5), 120.6 (C-6), 135.6 (C-1), 147.5 and 149.2 (C-3 and C-4); (Found: $M^{+\bullet}$, 330.1833. $C_{20}H_{26}O_4$ requires M, 330.1822).

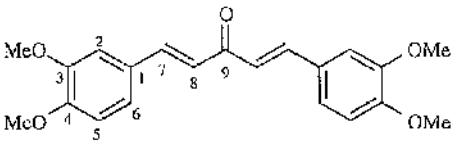
1,4-Bis-(3,4-dihydroxyphenyl)butane (149)



A mixture of the diarylbutane (**148**) (300 mg, 0.91 mmol), 48% HBr (5 ml) and glacial AcOH (2 ml) was heated at reflux under N_2 for 6 h. After cooling to rt, the mixture was poured into water (50 ml) and extracted with EtOAc (2 x 20 ml). The combined organics were washed with brine (2 x 10 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give an off-white solid. Recrystallisation from ether-hexane afforded the title compound (**149**) as tan coloured crystals (199 mg, 79.9%), m.p. 136-138 °C (lit.,[98] 141-142 °C {aq. MeOH}).

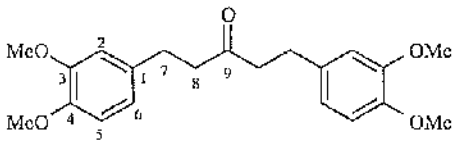
New data : ν_{max} (KBr)/cm^{-1} 3385 and 3268 (OH), 1619, 1610 and 1530 (C=C); δ_H (d_6-DMSO) 1.47 (2H, bs, H-8), 2.39 (2H, bs, H-7), 6.39 (1H, dd, *J* 8.0 Hz and 1.8 Hz, H-6), 6.53 (1H, d, *J* 1.8 Hz, H-2), 6.60 (1H, d, *J* 7.9 Hz, H-5), 8.55 (1H, bs, OH), 8.66 (1H, bs, OH); δ_C (d_6-DMSO) 31.2 and 34.7 (C-7 and C-8), 115.7 and 116.0 (C-2 and C-5), 119.1 (C-6), 133.4 (C-1), 143.4 and 145.3 (C-3 and C-4); (Found: $M^{+\circ}$, 274.1207. $C_{16}H_{18}O_4$ requires M, 274.1205).

1,5-Bis-(3,4-dimethoxyphenyl)-penta-1,4-dien-3-one (150)



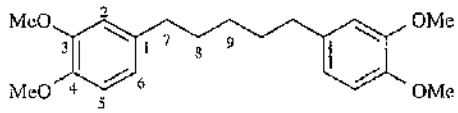
The method of Haworth *et al.*[102] was used on a 12.04 mmol scale affording the unsaturated ketone (**150**) as bright yellow feathers (1.63 g, 83.6 %), m.p. 84-85 °C (lit.,[102] 84 °C); δ_H 3.92 (3H, s, OCH_3), 3.94 (3H, s, OCH_3), 6.89 (1H, d, *J* 8.3 Hz, H-5), 6.96 (1H, d, *J* 15.9 Hz, H-8), 7.14-7.21 (2H, m, H-2 and H-6), 7.70 (1H, d, *J* 15.8 Hz, H-7).

1,5-Bis-(3,4-dimethoxyphenyl)pentan-3-one (151)



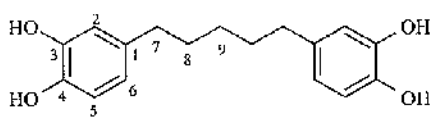
The procedure of Haworth *et al.*,[102] was modified as follows : Palladium on charcoal (10 %, 50 mg) was added to a solution of the unsaturated ketone (**150**) (810 mg, 2.29 mmol) in EtOAc (20 ml) and the mixture stirred under a hydrogen balloon for 1 hr. The resultant colourless mixture was filtered through Celite®, the catalyst washed with EtOAc (2 x 10 ml) and the solvent was removed on a rotary evaporator. Recrystallisation of the residue from EtOH gave (**151**) as crystals (457 mg, 55.8 %), m.p. 80-82 °C (lit.,[102] 85 °C); δ_H 2.64-2.88 (4H, m, H-7 and H-8), 3.85 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.66-6.80 (3H, m, Ar-H).

1,5-Bis-(3,4-dimethoxyphenyl)pentane (152)



The method of Haung-Minlon[104] was modified as follows : Hydrazine hydrate (146 mg, 0.14 ml, 2.92 mmol) was added dropwise to a stirring mixture of the ketone (**151**) (500 mg, 1.40 mmol) and powdered KOH (206 mg, 3.68 mmol) in diethylene glycol (6 ml). After the addition complete, the mixture was heated at 165 °C for 4 h under a N_2 atmosphere before allowing to cool to rt and pouring into water (40 ml). The resultant mixture was extracted with Et_2O (2 x 20 ml) and the combined organics washed with water (2 x 20 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a yellow oil which was purified by silica gel flash column chromatography affording diarylpentane (**152**) as a powder (280 mg, 58.3 %), m.p. 50-53 °C (lit.,[102] 56-57 °C); δ_H 1.38-1.45 (2H, m, H-9), 1.56-1.71 (4H, m, H-8), 2.56 (4H, t, *J* 7.3 Hz, H-7), 3.86 (6H, s, OCH_3), 3.87 (6H, s, OCH_3), 6.69-6.73 (4H, m, H-2 and H-6), 6.79 (2H, d, *J* 8.6 Hz, Ar-5).

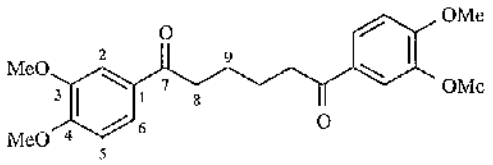
1,5-Bis-(3,4-dihydroxyphenyl)pentane (153)



The method of Haworth *et al.*,[102] was modified employing the general method of McOmie *et al.*,[55] on a 0.61 mmol scale as outlined for compound (**149**). The

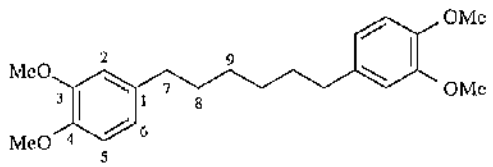
diarylpentane (**153**) was isolated as a tan coloured solid after flash column chromatography (158 mg, 90.0 %), m.p. 130-132 °C (lit.,[102] 129-130 °C).
New data: $\nu_{max.}$ (KBr)/cm^{-1}, 3473 and 3377 (OH), 1608 and 1519 (C=C); δ_H (CD_3OD) 1.28-1.38 (2H, m, H-9), 1.48-1.63 (4H, m, H-8), 2.43 (4H, t, *J* 7.3 Hz, H-7), 4.90 (4H, bs, OH), 6.45 (2H, dd, *J* 8.0 Hz and 2.0 Hz, H-6), 6.58 (2H, d, *J* 1.9 Hz, H-2), 6.64 (2H, d, *J* 8.0 Hz, H-5); δ_C (CD_3OD) 30.15 (C-9), 33.13 (C-8), 36.53 (C-7), 116.4 and 116.8 (C-2 and C-5), 120.9 (C-6), 136.0 (C-1), 144.3 and 146.3 (C-3 and C-4); (Found: $M^{+\bullet}$, 288.1361. $C_{17}H_{20}O_4$ requires M, 288.1362).

1,6-Bis-(3,4-dimethoxyphenyl)hexan-1,6-dione (154)



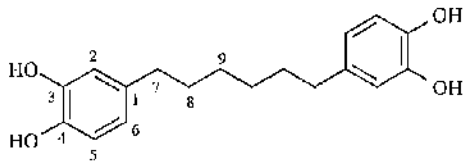
The procedure of Fliedner *et al.*[94] was adopted using dry $CHCl_3$ and freshly distilled adipoyl dichloride on a 7.24 mmol scale affording diketone (**154**) as feathers (1.03 g, 81.1%), m.p. 148-150 °C (lit.,[94] 149-150 °C); δ_H 1.82-1.87 (2H, m, H-9), 3.00 (2H, m, H-8), 3.94 (3H, s, OCH_3), 3.95 (3H, s, OCH_3), 6.89 (1H, d, *J* 8.4 Hz, H-5), 7.53 (1H, d, *J* 1.9 Hz, H-2), 7.59 (2H, dd, *J* 8.3 Hz and 2.0 Hz, H-6).

1.6-Bis-(3,4-dimethoxyphenyl)hexane (155)



Palladium-charcoal (10 %, 200 mg) was added to a solution of the diketone (**154**) (500 mg, 1.3 mmol) in glacial AcOH (100 ml) and the mixture stirred under a hydrogen balloon overnight. The mixture was filtered through Celite®, the catalyst was washed with AcOH (2 x 10 ml) and the solvent was removed on a rotary evaporator. Recrystallisation of the residue from MeOH afforded the diarylhexane (**155**) as plates (317 mg, 68.2 %), m.p. 76-77 °C (lit.,[97] 78-79 °C); δ_H 1.34-1.40 (2H, m, CH_2), 1.56-1.60 (2H, m, CH_2), 2.55 (4H, t, *J* 7.2 Hz, H-7), 3.85 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.69-6.73 (2H, m, H-2 and H-6), 6.79 (2H, d, *J* 8.6 Hz, H-5).

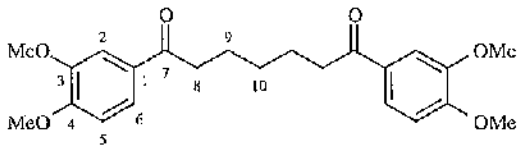
1,6-Bis-(3,4-dihydroxyphenyl)hexane (156)



The general procedure of McOmie *et al.*[55] was used on a 0.70 mmol scale, as outlined for compound (**149**), to give the diarylhexane (**156**) from EtOAc-hexane (200 mg, 94.8 %), m.p. 131-133 °C (lit.,[97] 132-133 °C).

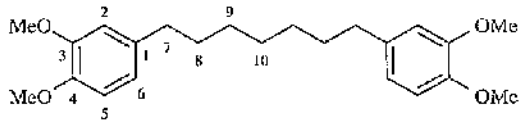
New data: $\nu_{max.}$ (KBr)/cm^{-1}, 3452 and 3398 (OH); δ_H (d_6-Acet) 1.15-1.23 (2H, m, CH_2), 1.34-1.44 (2H, m, CH_2), 2.31 (2H, t, *J* 7.2 Hz, H-7), 6.37 (1H, dd, *J* 8.0 Hz and 2.0 Hz, H-6), 6.54 (2H, d, *J* 2.0 Hz, H-2), 6.57 (2H, d, *J* 8.0 Hz, H-5), 7.46 (4H, bs, OH); δ_C (d_6-Acet) 29.7 (C-9), 32.5 (C-8), 35.8 (C-7), 115.8 and 116.2 (C-2 and C-5), 120.3 (C-6), 135.2 (C-1), 143.7 and 145.8 (C-3 and C-4); (Found: C 71.65; H 7.38 %; $M^{+\bullet}$, 302.1520. $C_{18}H_{22}O_4$ requires C 71.52; H 7.28 %; M, 302.1518).

1,7-Bis-(3,4-dimethoxyphenyl)heptan-1,7-dione (157)



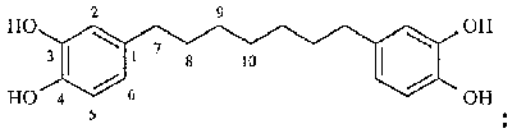
The method of Fliedner *et al.*[94] was adopted using dry $CHCl_3$ on a 3.62 mmol scale affording diketone (**157**) as crystals (282 mg, 39.0 %), m.p. 90-92 °C (lit.,[94] 91-93 °C); δ_H 1.18-1.88 (6H, m, 3 x CH_2), 2.96 (4H, t, *J* 7.1 Hz, H-8), 3.94 (6H, s, OCH_3), 3.95 (6H, s, OCH_3), 6.89 (2H, d, *J* 8.4 Hz, H-5), 7.55 (2H, dd, *J* 7.4 Hz and 2.0 Hz, H-6), 7.61 (2H, d, *J* 2.0 Hz, H-2).

1,7-Bis-(3,4-dimethoxyphenyl)heptane (158)



Palladium on charcoal (10%, 50 mg) was added to a stirring solution of diketone (**158**) in MeOH (75 ml) and the mixture stirred under a hydrogen balloon overnight. The resultant mixture was filtered through Celite® and the residue washed with MeOH (2 x 25 ml). The combined organics were concentrated *in vacuo* to give an oil which was crystallised from aqueous MeOH affording the diarylheptane (**158**) as crystals (179 mg, 76.8%), m.p. 52-53 °C (lit.,[105] 56 °C).

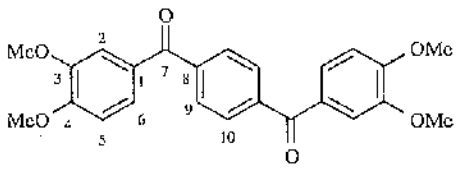
1,7-Bis-(3,4-dihydroxyphenyl)heptane (159)



The general procedure of McOmie *et al.*[55] was used on a 0.44 mmol scale, as outlined for compound (**149**), affording the phenolic diarylheptane (**159**) from $PhCH_3$ as a cream powder (58 mg, 41.7%), m.p. 100-102 °C (lit.,[105] 106 °C).

New data : ν_{max} (KBr)/cm^{-1} 3399 (OH), 1613, 1601 and 1515 (aromatic); δ_H 1.20-1.22 (6H, m, H-9 and H-10), 1.40-1.46 (4H, m, H-8), 2.33 (4H, t, *J* 7.8 Hz, H-7), 4.79 (4H, s, OH), 6.35 (2H, dd, *J* 8.0Hz and 2.1 Hz, H-6), 6.49 (2H, d, *J* 2.0 Hz, H-2), 6.55 (2H, d, *J* 8.0 Hz, H-5); δ_C 30.2, 30.5 and 32.9 (C-8, C-9 and C-10), 36.3 (C-7), 116.2 and 116.5 (C-2 and C-5), 120.6 (C-6), 135.7 (C-1), 144.0 and 146.0 (C-3 and C-4); (Found: C 72.12%; H 7.60%; $M^{+\bullet}$, 316.1661. $C_{19}H_{24}O_4$ requires C 72.15%; H 7.59%; M, 316.1674).

1,4-Bis-(3,4-dimethoxybenzoyl)benzene (161)

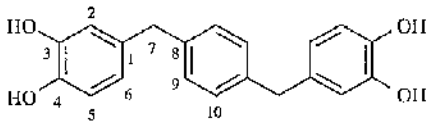


To a stirring suspension of aluminium chloride (0.72g, 5.43 mmol) in dry $CHCl_3$ (25 ml) was added veratrole (0.50g, 0.46 ml, 3.62 mmol) dropwise at 0 °C followed by terephthaloyl chloride (0.37g, 1.81 mmol) *via* solid addition funnel at the same temperature. The mixture was allowed to warm to rt stirred for a further 1 h then heated at reflux for 4 h whereupon a brown solid separated. The mixture was allowed to cool to rt then poured cautiously into acidified iced-water and extra $CHCl_3$ added to ensure two clear layers. The aqueous layer was extracted with $CHCl_3$ (2 x 20 ml) and the combined organics washed successively with water (2 x 20 ml), saturated $NaHCO_3$ (2 x 20 ml) and brine (1 x 10 ml) before drying over $MgSO_4$. Concentration *in vacuo* afforded a yellow solid which was recrystallised from glacial AcOH affording the diketone (**161**) as lemon coloured crystals (0.405g, 55.1%), m.p. 187-188 °C (lit.,[106] 193.5-194.5 °C).

New data : ν_{max} (KBr)/cm^{-1} 1647 (C=O), 1595, 1581 and 1510 (Ar); δ_H 3.97 (6H, s, OCH_3), 3.98 (6H, s, OCH_3), 6.92 (2H, d, *J* 8.4 Hz, H-6), 7.40 (2H, dd, *J* 8.3 Hz and 2.0 Hz, H-5), 7.56 (2H, d, *J* 2.0 Hz, H-3), 7.85 (4H, s, H-9); δ_C 56.7 and 56.8 (OCH_3), 110.5 and 112.6 (C-2 and C-5), 126.4 (C-6), 130.0 (C-9), 130.3 (C-1), 141.7

(C-8), 149.9 and 154.1 (C-3 and C-4), 195.6 (C-7); (Found: $M^{+\bullet}$, 406.1417. $C_{24}H_{22}O_6$ requires M, 406.1416).

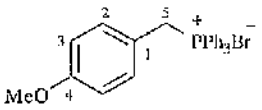
1,4-Bis-(3,4-dihydroxybenzyl)benzene (162)



Palladium on charcoal (10%, 50 mg) was added to a stirring solution of the diketone (**161**) (200 mg, 0.49 mmol) in THF (50 ml) and the mixture stirred under a hydrogen balloon at rt for 72 h. The mixture was filtered through Celite® and the residue washed with EtOAc. Concentration *in vacuo* afforded a yellow oil which was taken up in dry DCM (10 ml) and treated dropwise with boron tribromide (2.12 ml, 1M in DCM, 2.12 mmol) at -78 °C. The orange solution was allowed to warm to rt and stirred for 1 h before being poured cautiously into iced-water. The resultant mixture was extracted into EtOAc (50 ml), the aqueous layer further extracted with EtOAc (2 x10 ml) and the combined organic extracts washed with brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* afforded a beige solid which was recrystallised from $PhCH_3$ to give (**162**) as an cream powder (103 mg, 64.8% from **X**), m.p. 209-211 °C (lit.,[106] 212-214 °C).

New data : ν_{max} (KBr)/cm^{-1} 3462 and 3314 (OH), 1624, 1597 and 1518 (Ar); δ_H 4.83 (4H, s, OH), 6.39 (2H, dd, *J* 8.0 Hz and 1.9 Hz, H-5), 6.46 (2H, d, *J* 1.9 Hz, H-3), 6.55 (2H, d, *J* 8.0 Hz, H-6), 6.95 (4H, s, CH_2); δ_C 41.8 (C-7), 116.2 and 117.0 (C-3 and C-6), 121.1 (C-5), 129.8 (C-9), 134.5 and 140.7 (C-4 and C-8), 144.4 and 146.1 (C-1 and C-2); (Found: $M^{+\bullet}$, 322.1212. $C_{20}H_{18}O_4$ requires M, 322.1205).

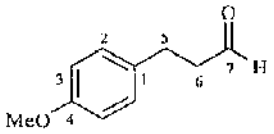
4-Methoxybenzyl triphenylphosphonium bromide (164)



A solution of *p*-anisaldehyde (300 mg, 0.27 mmol, 2.20 mmol) in dry THF (2 ml) was added dropwise to a stirring slurry of $LiAlH_4$ (125 mg, 3.31 mmol) and dry THF (10 ml) at 0 °C. After the addition complete, the mixture was allowed to warm to rt and stirred for a further 16 h before being quenched by the cautious addition of moist ether at 0 °C. The solids were filtered through Celite® and the residue washed with EtOAc (2 x 10 ml). The combined organic extracts were washed with water (20 ml) and brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* afforded a yellow oil which was taken up in dry CH_3CN (10 ml) and heated at reflux in the

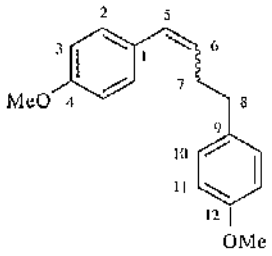
presence of triphenylphosphine hydrobromide (793 mg, 2.31 mmol) for 20 h. After cooling to rt, the mixture was concentrated giving a white foam which was recrystallised from *i*-PrOH affording the title compound (**164**) as a powder (790 mg, 77.6%), m.p. 227-228 °C (lit.,[107] 236-238 °C); ν_{max} (KBr)/cm^{-1} 1606, 1585 and 1511 (Ar); δ_H 3.72 (3H, s, OCH_3), 5.26 (2H, d, $J_{H\text{-}P}$ 13.7 Hz, H-5), 6.64 (2H, d, *J* 8.5 Hz, H-3), 7.01 (2H, dd, *J* 8.5 Hz and 2.1 Hz, H-2), 7.61-7.79 (15H, m, Ph-H); δ_C 30.5 (d, $J_{C\text{-}P}$ 46.4 Hz, C-5), 55.6 (OCH_3), 114.6 (d, *J* 3.0 Hz, CH), 118.2 (d, *J* 84.8 Hz, C), 118.8 (d, *J* 8.6 Hz, C), 130.5 (d, *J* 12.5 Hz, CH), 133.0 (d, *J* 5.5 Hz, CH), 134.7 (d, *J* 9.6 Hz, CH), 135.4 (d, *J* 2.5 Hz, CH), 160.0 (d, *J* 3.7 Hz, C); δ_P (81 Hz) 22.4 (Found: $M^{+\bullet}$ (-HBr), 382.1485. $C_{26}H_{24}BrOP$ requires M (-HBr), 382.1487).

3-(4-methoxyphenyl)propionaldehyde (166)



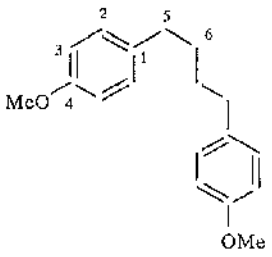
The method of Semmelhack *et al.*,[109] was modified as follows. A solution of 3-(4-methoxyphenyl)propionic acid (1.00g, 5.55 mmol) in dry THF (5 ml) was introduced dropwise to a stirring slurry of $LiAlH_4$ (0.32 g, 8.32 mmol) and dry THF (25 ml) at 0 °C. After the addition complete, the mixture was allowed to warm to rt and stirred for a further 20 h before being quenched by the cautious addition of moist ether at 0 °C. The solids were removed through Celite®, the residue washed with EtOAc (2 x 10 ml) and the combined organics washed with brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* afforded a pale yellow oil (0.85 g, 5.13 mmol) which was taken up in dry DCM (6 ml) and added dropwise at 0 °C to a stirring slurry of freshly prepared PDC[108] (2.51 g, 6.67 mmol) and dry DCM (25 ml). The mixture was allowed to warm to rt and stirred for a further 19 h before filtering through a silica plug eluting with EtOAc. The organics were washed with brine (2 x 15 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a brown oil which was subjected to column chromatography affording aldehyde (**166**) as a light yellow oil (0.37 g, 40.7%), ν_{max} (neat)/cm^{-1} 1732 (CHO), 1612, 1584 and 1517 (Ar); δ_H 2.74 (2H, t, *J* 7.8 Hz, H-5 or H-6), 2.90 (2H, t, *J* 7.5 Hz, H-5 or H-6), 3.78 (3H, s, OCH_3), 6.83 (2H, d, *J* 8.4 Hz, H-3), 7.11 (2H, d, *J* 8.4 Hz, H-2), 9.80 (1H, t, *J* 1.6 Hz, CHO); δ_C 27.7 (C-5), 45.9 (C-6), 55.6 (OCH_3), 114.4 (C-3), 129.6 (C-2), 132.7 (C-1), 158.5 (C-4), 202.2 (C-7); (Found: $M^{+\bullet}$, 164.0839. $C_{10}H_{12}O_2$ requires M, 164.0837).

1,4-Bis-(4-methoxyphenyl)but-1-ene (167)



n-BuLi (1.00 ml, 1.6M in hexanes, 1.60 mmol) was added dropwise at 0 °C to a stirring suspension of the phosphonium salt (**164**) (672 mg, 1.45 mmol) and dry THF (15 ml). After stirring for a further 10 min, aldehyde (**166**) (238 mg, 1.45 mmol) in dry THF (3 ml) was introduced dropwise to the blood red homogeneous solution and the mixture stirred for 30 min at 0 °C then allowed to warm to rt. After stirring for 1 h at rt, the light orange reaction mixture was poured into iced-water (50 ml) and extracted into EtOAc (2 x 25 ml). The combined organic extracts were washed with brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* giving a cream solid which was recrystallised from MeOH affording the pure (*E*)-isomer (**167**) as shiny plates (175 mg, 45.0%), m.p. 110-112 °C; ν_{max} (KBr)/cm^{-1} 1607 and 1511 (C=C), 828 and 849 (*para*-disubstituted benzene); δ_H 2.44-2.50 (2H, m, H-7), 2.72 (2H, t, *J* 7.3 Hz, H-8), 3.79 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 6.10 (1H, dt, *J* 15.8 Hz and 6.8 Hz, H-6), 6.35 (1H, d, *J* 15.8 Hz, H-5), 6.83 and 6.84 (4H, 2 x d, *J* 8.8 Hz, H-3 and H-11), 7.13 (2H, d, *J* 8.4 Hz, H-2 or H-10), 7.26 (2H, d, *J* 8.8 Hz, H-2 or H-10); δ_C 35.5 (C-7), 35.5 (C-8), 55.6 (OCH_3), 55.7 (OCH_3), 114.1 and 114.3 (C-3 and C-11), 127.4, 128.3, 129.7 and 130.0 (C-2, C-5, C-6 and C-10), 131.0 and 134.4 (C-1 and C-9), 158.2 and 159.1 (C-4 and C-12); (Found: $M^{+\bullet}$, 268.1463. $C_{18}H_{20}O_2$ requires M, 268.1463). The mother liquors were concentrated and subjected to silica gel column chromatography eluting with hexane-ether (3:1) affording an oil (116 mg, 29.8%, *Z*:*E* = 12:1). (Z)-isomer : ν_{max} (neat)/cm^{-1} 1608 and 1513 (C=C), 839 (*para*-disubstituted benzene); δ_H 2.58-2.64 (2H, m, H-7), 2.68-2.72 (2H, m, H-8), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 5.59 (1H, dt, *J* 11.6 Hz and 6.8 Hz, H-6), 6.36 (1H, d, *J* 11.6 Hz, H-5), 6.81-6.85 (4H, m, H-3 and H-11), 7.10 (2H, d, *J* 8.4 Hz, H-2 or H-10), 7.18 (2H, d, *J* 8.4 Hz, H-2 or H-10); δ_C 31.1 and 35.6 (C-7 and C-8), 55.6 (OCH_3), 55.6 (OCH_3), 114.0 and 114.2 (C-3 and C-11), 129.1, 129.7, 130.3 and 130.7 (C-2, C-5, C-6 and C-10), 134.3 (C-1 and C-9), 158.2 and 158.6 (C-4 and C-12); (Found: $M^{+\bullet}$, 268.1461. $C_{18}H_{20}O_2$ requires M, 268.1464).

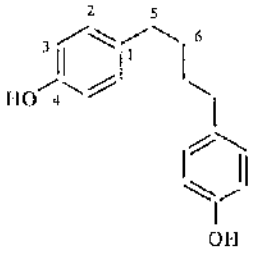
1,4-Bis-(4-methoxyphenyl)butane (169)



Method 1 : Palladium on charcoal (10%, 50 mg) was added to a solution of the (*E*)-alkene (**167**) (125 mg, 0.47 mmol) in MeOH-EtOAc (2:1, 30 ml) and the mixture stirred under a hydrogen balloon for 21 h at rt. The catalyst was filtered through Celite®, washed with EtOAc (2 x 5 ml) and the mixture concentrated *in vacuo* to give a solid which was recrystallised from aq.MeOH affording the title compound as shiny plates (82 mg, 65.1%), m.p. 77-78 °C (lit.,[111] 78-79 °C); ν_{max} (KBr)/cm^{-1} 1611, 1582 and 1513 (Ar); δ_H 1.59-1.63 (2H, m, H-6), 2.55-2.56 (2H, m, H-5), 3.78 (3H, s, OCH_3), 6.81 (2H, d, *J* 8.4 Hz, H-3), 7.07 (2H, d, *J* 8.4 Hz, H-2); δ_C 31.7 and 35.3 (C-5 and C-6), 55.6 (OCH_3), 114.1 (C-3), 129.6 (C-2), 135.1 (C-1), 158.0 (C-4); (Found: $M^{+\bullet}$, 270.1619. $C_{18}H_{22}O_2$ M, 270.1620).

Method 2 : Palladium on charcoal (10%, 25 mg) was added to a solution of the alkene (**168**) (*Z*:*E* = 12:1, 100 mg, 0.37 mmol) in MeOH-EtOAc (2:1, 15 ml) and the mixture stirred under a hydrogen balloon for 16 h at rt. The catalyst was filtered through Celite®, washed with EtOAc (2 x 5 ml) and concentrated *in vacuo* to give a white solid. Recrystallisation from aq.MeOH afforded the title compound as shiny crystals (65 mg, 64.5%) giving a m.p. and ^{1}H NMR spectrum identical with those reported in method **1**.

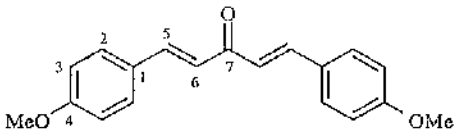
1,4-Bis-(4-hydroxyphenyl)butane (170)



The general procedure of McOmie *et al.*[55] was used on a 0.22 mmol scale, as outlined for compound (**149**), affording the diarylbutane (**170**) as fawn crystals from ether-hexane (39 mg, 72.4%), m.p. 153-155 °C (lit.,[111] 158-159 °C); ν_{max} (KBr)/cm^{-1} 1614 and 1512 (Ar), 816 (*para*-disubstituted benzene); δ_H (d_6-DMSO) 1.49 (2H, bs, H-6), 2.46 (2H, bs, H-5), 6.65 (2H, d, *J* 8.4 Hz, H-3), 6.94 (2H, d, *J* 8.4 Hz, H-2), 9.09 (1H, bs, OH); δ_C (d_6-DMSO) 31.2 and 34.5 (C-5 and C-6), 115.3 (C-3), 129.4

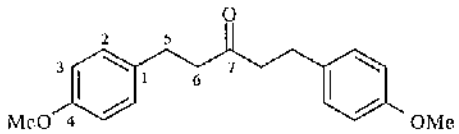
(C-2), 132.6 (C-1), 155.5 (C-4); (Found: $M^{+\bullet}$, 242.1307. $C_{16}H_{18}O_2$ requires M, 242.1307).

1,5-Bis-(4-methoxyphenyl)penta-1,4-dien-3-one (173)



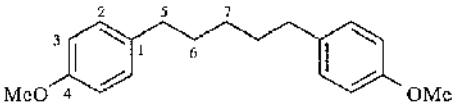
The method for the synthesis of ketone (**150**) was followed employing anisaldehyde (1.63 g, 1.46 ml, 12.00 mmol), acetone (0.32 g, 0.40 ml, 5.52 mmol) and 10% NaOH (1.00 ml). The unsaturated ketone (**173**) was isolated as bright yellow feathers from EtOH (1.14 g, 70.4%), m.p. 128-130 °C (lit.,[113] 136-138 °C); δ_H 3.84 (3H, s, OCH_3), 6.92 (4H, d, *J* 8.6 Hz, H-3), 6.95 (2H, d, *J* 15.7 Hz, H-6), 7.56 (4H, d, *J* 8.7 Hz, H-2), 7.69 (2H, d, *J* 15.8 Hz, H-5).

1,5-Bis-(4-methoxyphenyl)pentan-3-one (174)



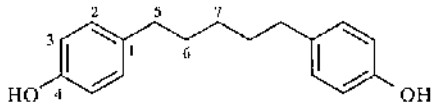
Palladium on charcoal (10%, 50 mg) was added to a stirring solution of the unsaturated ketone (**173**) (1.00 g, 3.40 mmol) in EtOAc (30 ml) and the mixture stirred under a hydrogen balloon at rt for 1 h. The resultant colourless solution was filtered through Celite® and the residue washed with EtOAc (2 x 10 ml). The combined organics were concentrated *in vacuo* to give a colourless oil which crystallised on scratching. Recrystallisation from MeOH afforded the title compound (**174**) as fine needles (0.69 g, 68.2%), m.p. 52-54 °C (lit.,[111] 55.0-55.2 °C); ν_{max} (KBr)/cm^{-1} 1687 (C=O); δ_H 2.66 (2H, t, *J* 7.6 Hz, H-5 or H-6), 2.82 (2H, t, *J* 7.6 Hz, H-5 or H-6), 3.77 (3H, s, OCH_3), 6.80 (2H, d, *J* 8.5 Hz, H-3), 7.06 (2H, d, *J* 8.5 Hz, H-2); δ_C 29.3 and 45.2 (C-5 and C-6), 55.6 (OCH_3), 114.3 (C-3), 129.6 (C-2), 133.5 (C-1), 158.3 (C-4), 209.9 (C-7).

1,5-Bis-(4-methoxyphenyl)pentane



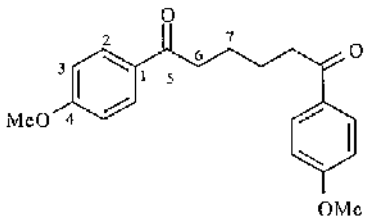
A mixture of the saturated ketone (**174**) (500 mg, 1.68 mmol), powdered KOH (248 mg, 4.42 mmol) and hydrazine hydrate (175 mg, 0.17 ml, 3.50 mmol) was heated in diethylene glycol (6 ml) at 175 °C for 4 h under N_2. After cooling to rt the mixture was poured into water (40 ml), the resultant suspension extracted into Et_2O (2 x 20 ml) and the combined organics washed with brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a cloudy oil that was purified by dry flash column chromatography eluting with ether-hexane (1:1) affording the diarylpentane as a colourless oil (167 mg, 35.0%); δ_H 1.32-1.39 (2H, m, H-7), 1.56-1.64 (4H, m, H-6), 2.53 (4H, t, *J* 7.6 Hz, H-5), 3.77 (6H, s, OCH_3), 6.81 (4H, d, *J* 8.6 Hz, H-3), 7.07 (4H, d, *J* 8.6 Hz, H-2); δ_C 29.3 (C-7), 32.1 (C-6), 35.4 (C-5), 55.6 (OCH_3), 114.1 (C-3), 129.7 (C-2), 135.3 (C-1), 158.0 (C-4).

1,5-Bis-(4-hydroxyphenyl)pentane (175)



The general procedure of McOmie *et al.*[55] was used on a 0.59 mmol scale, as outlined for compound (**149**), affording the title compound (**175**) as an off-white solid from $PhCH_3$ (104 mg, 69%), m.p. 100-103 °C (lit.,[111] 104-105 °C); ν_{max} (KBr)/cm^{-1} 3539 (OH), 1612, 1598 and 1514 (Ar); δ_H (d_6-DMSO) 1.22-1.30 (2H, m, H-7), 1.51 (4H, qt, *J* 7.6 Hz, H-6), 2.43 (4H, t, *J* 8.0 Hz, H-5), 6.65 (4H, d, *J* 8.4 Hz, H-3), 6.94 (4H, d, *J* 8.3 Hz, H-2), 9.08 (2H, bs, OH); δ_C (d_6-DMSO) 28.5 (C-7), 31.5 and 34.6 (C-5 and C-6), 115.3 (C-3), 129.4 (C-2), 132.7 (C-1), 155.5 (C-1); (Found: $(M+H)^{+\bullet}$, 257.1540. $C_{17}H_{20}O_2$ requires (M+H), 257.1541).

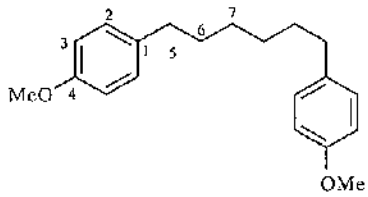
1,6-Bis-(4-methoxyphenyl)hexan-1,6-dione (176)



The method of Fliender *et al.*[94] was adopted using anisole (744 mg, 0.75 ml, 6.88 mmol), $AlCl_3$ (1.01 g, 7.58 mmol) and freshly distilled adipoyl dichloride (567

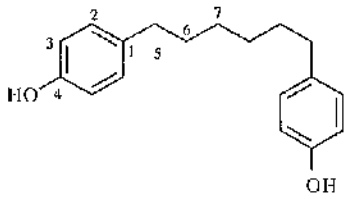
mg, 0.45 ml, 3.10 mmol) in dry $CHCl_3$ (15 ml). The 1,6-diketone (**176**) was isolated as a solid from MeOH (0.92 g, 91.0%), m.p. 143-144 °C (lit.,[94] 144-146 °C {EtOAc}); δ_H 1.74-1.89 (2H, m, H-7), 2.95-3.01 (2H, m, H-6), 3.86 (3H, s, OCH_3), 6.93 (2H, d, *J* 8.9 Hz, H-3), 7.94 (2H, d, *J* 8.9 Hz, H-2); δ_C 24.6 (C-7), 38.5 (C-6), 55.8 (OCH_3), 114.1 (C-3), 130.5 and 130.7 (C-1 and C-2), 163.8 (C-4), 199.1 (C-5).

1,6-Bis-(4-methoxyphenyl)hexane (177)



To a stirring solution of the 1,6-diketone (**176**) (350 mg, 1.07 mmol) in glacial AcOH (50 ml) was added palladium on charcoal (10 %, 100 mg) and the mixture stirred under a hydrogen balloon overnight at rt. The catalyst was filtered through Celite®, washed with AcOH (2 x 10 ml) and the mixture concentrated. The resultant yellow solid (424 mg) was recrystallised from EtOH affording the diarylhexane (**177**) as plates (242 mg, 66%), m.p. 66-69 °C (lit.,[112] 64.5-65.5 °C); ν_{max} (KBr)/cm^{-1} 1611 and 1511 (Ar); δ_H 1.32-1.57 (8H, m, 4 x CH_2), 2.53 (4H, t, *J* 7.9 Hz, H-5), 3.78 (6H, s, OCH_3), 6.82 (4H, d, *J* 8.7 Hz, H-3), 7.08 (4H, d, *J* 8.6 Hz, H-2); (Found : $M^{+\bullet}$, 298.1935. $C_{20}H_{26}O_2$ requires M, 298.1932).

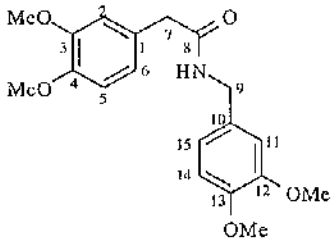
1,6-Bis-(4-hydroxyphenyl)hexane (178)



The general method of McOmie *et al.*[55] was used on a 0.67 mmol scale, as outlined for compound (**149**) using BBr_3 (2.01 ml, 1M in DCM, 2.01 mmol), affording the diarylhexane (**178**) from $PhCH_3$ as an amorphous solid (153 mg, 84.5%), m.p. 143-144 °C (lit.,[111] 144.5-145.5 °C).

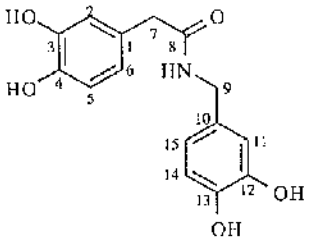
New data : ν_{max} (KBr)/cm^{-1} 3402 (OH), 1512, 1599 and 1613 (aromatic); δ_H (CD_3OD) 1.22-1.25 (4H, m, H-7), 1.44 (4H, m, H-6), 2.38 (4H, t, *J* 7.2 Hz, H-5), 4.83 (2H, s, OH), 6.57 (4H, d, *J* 8.4 Hz, H-3), 6.86 (4H, d, *J* 8.4 Hz, H-2); δ_C (d_6-Acet) 29.7 and 32.6 (C-6 and C-7), 35.5 (C-5), 115.8 (C-3), 130.0 (C-2), 134.1 (C-1), 156.1 (C-4); (Found : $M^{+\bullet}$, 270.1621. $C_{18}H_{22}O_2$ requires M, 270.1620).

***N*-(3,4-dimethoxybenzyl)-3',4'-dimethoxyphenyl acetamide (181)**



EDCI (0.25g, 1.33 mmol) was added in one portion to a stirring solution of 3,4-dimethoxybenzylamine (0.20g, 0.18 ml, 1.20 mmol), 3,4-dimethoxyphenylacetic acid (0.26g, 1.33 mmol) and DMAP (16 mg, 0.13 mmol) in dry DCM (10 ml) at rt. After stirring for 18 h, H_2O (10 ml) was added and the layers separated. The organic extracts were washed successively with 5 % $NaHCO_3$ (5 ml), 5 % citric acid (5 ml) and brine (5 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a light yellow solid (339 mg) which was recrystallised from MeOH affording amide (**181**) as fine white needles (0.24 g, 59 %), m.p. 133-135 °C (lit.,[114] 127-129 °C [EtOAc])
New data : ν_{max} (KBr)/cm^{-1} 3310 (NH), 1639 (amide); δ_H 3.56 (2H, s, H-7), 3.81 (3H, s, OCH_3), 3.85 (6H, s, 2 x OCH_3), 3.86 (3H, s, OCH_3), 4.34 (2H, d, *J* 5.8 Hz, H-9), 5.79 (1H, um, NH), 6.71-6.83 (6H, m, Ar-H); δ_C 43.7 (CH_2), 43.8 (CH_2), 56.2 (CH_3), 56.3 (CH_3), 111.2 (CH), 111.4 (CH), 111.8 (CH), 112.7 (CH), 120.1 (CH), 121.9 (CH), 127.6 (C), 131.1 (C), 148.7 (C), 149.4 (C), 149.6 (C), 171.5 (C); ($M^{+\bullet}$, 345.1579. $C_{19}H_{23}NO_5$ requires M, 345.1577).

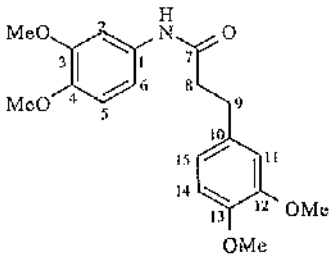
***N*-(3,4-dihydroxybenzyl)-3',4'-dihydroxyphenyl acetamide (182)**



A solution of amide (**181**) (150 mg, 0.43 mmol) in dry DCM (2 ml) was added dropwise to a stirring solution of boron tribromide (2.83 ml, 1M in DCM, 2.83 mmol) in dry DCM (10 ml) at -78°C. The mixture was allowed to warm to rt, stirred for a further 1 h then quenched by pouring into iced-water (20 ml). The resultant mixture was extracted with EtOAc (1 x 35 ml and 1 x 10 ml) and the combined organic extracts washed with brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a light yellow sticky oil (66 mg) which was crystallised from acetone-ether-hexane affording the phenolic amide (**182**) as a light brown solid (29 mg, 23%), m.p. 179-182 °C; ν_{max} (KBr)/cm^{-1} 3450 (OH), 1600 (amide); δ_H (d_6-DMSO) 3.23 (2H, s, H-7),

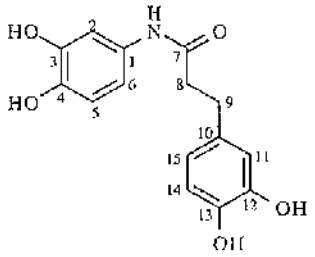
4.05 (2H, d, *J* 5.6 Hz, H-9), 6.46-6.50 (2H, m, Ar-H), 6.61-6.67 (4H, m, Ar-H), 8.24 (1H, m, NH), 8.69 (1H, s, OH), 8.76 (1H, s, OH), 8.80 (1H, s, OH), 8.85 (1H, s, OH); δ_C (d_6-DMSO) 42.1 and 42.3 (C-7 and C-9), 115.3 (CH), 115.6 (CH), 116.8 (CH), 118.6 (CH), 120.1 (CH), 127.5 and 130.6 (C-1 and C-10), 144.1, 144.5, 145.2 and 145.4 (C-3, C-4, C-12 and C-13), 170.7 (C-8); (Found: $M^{+\bullet}$, 289.0952. $C_{15}H_{15}NO_5$ requires M, 289.0950).

_N_-(3,4-dimethoxyphenyl)-3-(3',4'-dimethoxyphenyl)propanamide (185)



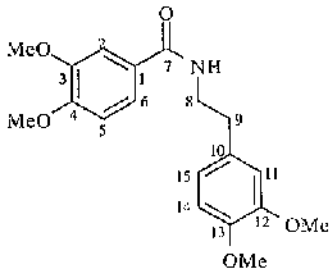
EDCI (274 mg, 1.43 mmol) was added in one portion to a stirring solution of 3,4-dimethoxyaniline (200 mg, 1.31 mmol), DMAP (20 mg, 0.16 mmol) and 3-(3,4-dimethoxyphenyl)propionic acid (300 mg, 1.43 mmol) in dry DCM (15 ml) at rt. After stirring for 16 h, the mixture was washed successively with saturated $NaHCO_3$ (10 ml), 5% citric acid (10 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a mauve coloured solid (372 mg) which was recrystallised from MeOH affording the title compound (**185**) as fine pale pink needles (244 mg, 54.0%), m.p. 116-118 °C; ν_{max} (KBr)/cm^{-1} 3294 (NH), 1655 (amide); δ_H 2.69 (2H, t, *J* 7.6 Hz, H-9), 3.07 (2H, t, *J* 7.6 Hz, H-8), 3.90 (3H, s, OCH_3), 3.92 and 3.93 (9H, 2 x s, 3 x OCH_3), 6.83-6.89 (5H, m, Ar-H), 7.36 (1H, d, *J* 1.6 Hz, H-11); δ_C 31.7 (C-9), 40.2 (C-8), 56.2, 56.3 and 56.4 (OCH_3), 105.2 (CH), 111.5 (CH), 111.7 (CH), 112.1 (CH), 112.2 (CH), 120.6 (CH), 131.8 and 133.7 (C-1 and C-10), 146.1, 147.9 and 149.3 (C-3, C-4, C-12 and C-13), 170.8 (C-7); (Found: $M^{+\bullet}$, 345.1575. $C_{19}H_{23}NO_5$ requires M, 345.1576).

***N*-(3,4-dihydroxyphenyl)-3-(3',4'-dihydroxyphenyl)propanamide (186)**



Boron tribromide (2.83 ml, 1M in DCM, 2.83 mmol) was introduced dropwise to a stirring solution of amide (**185**) (150 mg, 0.43 mmol) in dry DCM (15 ml) at -78 °C. The light orange solution was allowed to warm to 0 °C and stirred for a further 30 min before pouring into iced-H_2O (20 ml). The resultant suspension was extracted with EtOAc (45 ml) and the organic extracts washed with brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a fawn coloured solid (81 mg) which was recrystallised from acetone-$CHCl_3$ affording the phenolic amide (**186**) as an off-white solid (57 mg, 45.2%), m.p. 193-195 °C; ν_{max} (KBr)/cm^{-1} 3429 (OH), 1636 (amide); δ_H 2.44 (3H, t, *J* 7.2 Hz, H-9), 2.69 (2H, t, *J* 7.2 Hz, H-8), 6.46 (1H, d, *J* 7.6 Hz, H-5), 6.60-6.62 (3H, m, Ar-H), 6.75 (1H, dd, *J* 8.4 Hz and 1.6 Hz, H-6), 7.13 (1H, d, *J* 2.0 Hz, H-11), 8.56 (1H, s, OH), 8.64 (1H, s, OH), 8.73 (1H, s, OH), 8.92 (1H, s, OH), 9.51 (1H, s, NH); δ_C 30.8 (C-9), 38.7 (C-8), 108.2 (CH), 110.6 (CH), 115.5 (CH), 115.7 (CH), 116.0 (CH), 119.1 (CH), 131.7 and 132.5 (C-1 and C-10), 141.4, 143.6, 145.2 and 145.3 (C-3, C-4, C-12 and C-13), 170.1 (C-7); (Found: $M^{+\bullet}$, 289.0950. $C_{15}H_{15}NO_5$ requires M, 289.0951).

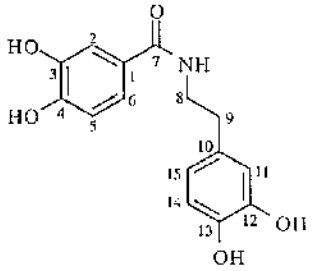
***N*-[2-(3,4-dimethoxyphenyl)ethyl]-3',4'-dimethoxybenzamide (189)**



EDCI (0.23 g, 1.21 mmol) was added in one portion to a stirring solution of 2-(3,4-dimethoxyphenyl)ethyl amine (0.2 g, 0.18 ml, 1.10 mmol), 3,4-dimethoxybenzoic acid (0.22 g, 1.21 mmol) and DMAP (15 mg, 0.12 mmol) in dry DCM (15 ml) at rt. Stirring was continued for a further 16 h then the mixture transferred to a separating funnel and washed successively with saturated $NaHCO_3$ (10 ml), 5 % citric acid (10 ml), and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a cream solid which was recrystallised from *i*-PrOH affording the title compound (**189**)

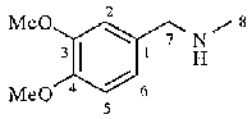
as a flaky solid (0.25 g, 65.8%), m.p. 139-140 °C (lit.,[115] 140-142 °C {DCM-ether}); ν_{max} (KBr)/cm^{-1} 3296 (NH), 1629 (amide); δ_H 2.88 (2H, t, *J* 6.9 Hz, H-9), 3.66-3.71 (2H, m, H-8), 3.84 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 3.92 (3H, s, OCH_3), 6.09 (1H, bs, NH), 6.75-6.84 (4H, m, Ar-H), 7.15 (1H, dd, *J* 8.4 Hz and 2.0 Hz, H-6), 7.39 (1H, d, *J* 2.0 Hz, H-2).
New data : δ_C 35.7 and 41.7 (C-8 and C-9), 56.2, 56.3 and 56.4 (OCH_3), 110.6 (CH), 110.9 (CH), 111.7 (CH), 112.3 (CH), 119.5 (CH), 121.1 (CH), 127.6 and 131.9 (C-1 and C-10), 148.1, 149.3, 149.4 and 152.0 (C-3, C-4, C-12 and C-13), 167.5 (C-7); (Found $M^{+\bullet}$, 345.1575. $C_{19}H_{23}NO_5$ requires M, 345.1576).

_N_-[2-(3,4-dihydroxyphenyl)ethyl]-3',4'-dihydroxybenzamide (190)



Boron tribromide demethylation was used on a 0.36 mmol scale, as outlined for compound (**149**), affording the crude amide (**190**) as a tan coloured foam (100 mg) that could not be recrystallised from a variety of solvents. Column chromatography (silica, 2:1 EtOAc-acetone + 2% AcOH) gave a tan coloured solid (39 mg) which was not pure enough for testing as shown by ^{1}H NMR spectroscopy.

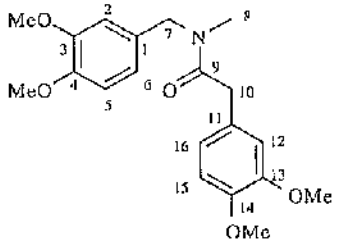
_N_-Methyl-(3,4-dimethoxyphenyl)benzylamine (192)



Methylamine (0.82 ml, 8.03M in EtOH, 6.62 mmol) was added dropwise to a stirring solution of 3,4-dimethoxybenzaldehyde (1.00 g, 6.02 mmol) in dry EtOH (10 ml) at rt. After heating at reflux for 26 h, the resultant yellow solution was concentrated *in vacuo* to give a yellow syrup which solidified on standing, δ_H 3.50 (3H, d, *J* 1.5 Hz, NMe), 3.92 (OCH_3), 3.94 (OCH_3), 6.88 (1H, d, *J* 8.2 Hz, Ar-H), 7.12 (1H, dd, *J* 8.2 Hz and 1.8 Hz, Ar-H), 7.41 (1H, d, *J* 1.8 Hz, Ar-H), 8.20 (1H, s, ArC<u>H</u>). The resultant solid was taken up in MeOH (20 ml) and hydrogenated over palladium on charcoal (10%, 100 mg) at an initial pressure of 60 p.s.i. for 24 h. The mixture was filtered through Celite®, the residue washed with MeOH (2 x 10 ml) and concentrated to give the amine (**192**) as a colourless oil (798 mg, 73.2%) b.p. 92-98 °C / 0.22 mmHg; ν_{max}

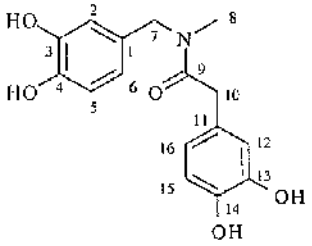
(neat)/cm^{-1} 3325 (NH), 1607, 1592 and 1515 (aromatic); δ_H 1.51 (1H, bs, NH), 2.46 (3H, s, H-9), 3.69 (2H, s, H-7), 3.87 (3H, s, OCH3), 3.89 (3H, s, OCH3), 6.80-6.89 (3H, m, Ar-H); δ_C 36.1 (C-9), 55.8 (OCH_3), 55.9 (OCH_3), 56.0 (C-7), 110.9 and 111.3 (C-2 and C-5), 120.2 (C-6), 132.9 (C-1), 148.0 and 148.9 (C-3 and C-4); (Found $M^{+\bullet}$, 181.1101. $C_{10}H_{15}NO_2$ requires M, 181.1103).

_N_-Methyl-_N_-(3,4-dimethoxybenzyl)-3,4-dimethoxyphenylacetamide (193)



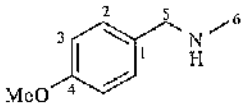
EDCI (247 mg, 1.29 mmol) was added in one portion to a stirring solution of amine (**192**) (213 mg, 1.18 mmol), 3,4-dimethoxyphenylacetic acid (254 mg, 1.29 mmol) and DMAP (16 mg, 0.13 mmol) in dry DCM (15 ml) at rt. After stirring for 18 h, the mixture was washed successively with saturated $NaHCO_3$ (10 ml), 5% citric acid (10 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a light yellow oil which was crystallised from acetone-Et_2O affording amide (**193**) as shiny crystals (293 mg, 69.2%), m.p. 87-90 °C; ν_{max} (KBr)/cm^{-1} 1631 (amide), 1590 and 1515 (aromatic); δ_H 2.91 (3H, s, H-8), 3.72 and 3.73 (H-10), 3.76, 3.79, 3.85, 3.86 and 3.87 (12H, OCH_3), 4.50 and 4.54 (2H, 2 x s, H-7), 6.45-6.87 (6H, m, Ar-H); δ_C 34.0 and 35.5 (C-8), 40.9 and 41.2 (C-10), 51.0 and 53.8 (C-7), 56.2 and 56.3 (OCH_3), 109.8 (CH), 111.2 (CH), 111.6 (CH), 112.1 (CH), 119.2 (CH), 120.8 (CH), 121.2 (CH), 127.8, 128.1, 129.2 and 130.3 (C-1 and C-11), 148.3 (C), 148.9 (C), 149.5 (C), 171.7 and 171.9 (C-9); (Found $M^{+\bullet}$, 359.1736. $C_{20}H_{25}NO_5$ requires M, 359.1733).

N-Methyl-N-(3,4-dihydoxybenzyl)-3,4-dihydoxyphenylacetamide (194)



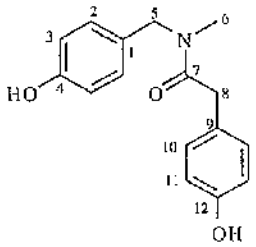
Boron tribromide demethylation was carried out as reported for compound (**149**) on a 0.35 mmol scale affording the phenolic amide (**194**) as shiny fawn crystals from acetone-$CHCl_3$ (70 mg, 66%), m.p. 151-154 °C; ν_{max} (KBr)/cm^{-1} 3406 (OH), 1586 (amide); δ_H 2.74 and 2.82 (3H, 2 x s, H-8), 3.51 and 3.53 (2H, 2 x s, H-10), 4.30 and 4.36 (2H, 2 x s, H-7), 6.39-6.70 (6H, m, Ar-H), 8.72-8.95 (4H, m, OH); δ_C 33.5 and 35.0 (C-8), 39.6 and 39.8 (C-10), 49.8 and 52.6 (C-7), 114.4 (CH), 115.6 (CH), 115.7 (CH), 115.8 (CH), 116.0 (CH), 116.5 (CH), 116.6 (CH), 117.9 (CH), 119.1 (CH), 119.9 (CH),126.6, 126.8, 128.4 and 128.9 (C-1 and C-11), 144.1 (C), 144.2 (C), 144.7 (C), 144.8 (C), 145.4 (C), 145.5 (C), 145.8 (C), 171.0 and 171.1 (C-9); (Found $M^{+\bullet}$, 303.1110. $C_{16}H_{17}NO_5$ requires M, 303.1106).

N-Methyl-(4-methoxyphenyl)benzylamine (196)



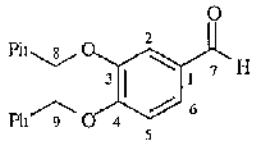
Methylamine (1.00 ml, 8.03M in EtOH, 8.03 mmol) was added dropwise to a stirring solution of *p*-anisaldehyde (1.00 g, 0.89 ml, 7.34 mmol) in dry EtOH (10 ml) at rt. After heating at reflux for 24 h, the resultant yellow solution was concentrated *in vacuo* to give a yellow syrup which was taken up in MeOH (20 ml) and hydrogenated over palladium on charcoal (10%, 100 mg) at an initial pressure of 60 p.s.i. for 24 h. The mixture was filtered through Celite®, the residue washed with MeOH (2 x 10 ml) and concentrated to give the title compound (**196**) as a colourless oil (806 mg, 73.3%) b.p. 76-80 °C/>1 mmHg; ν_{max} (neat)/cm^{-1} 3321 (NH), 1612, 1585 and 1517 (Ar), 815 (*para*-disubstituted benzene); δ_H 1.77 (1H, bs, NH), 2.42 (3H, s, H-6), 3.67 (2H, s, H-5), 3.79 (3H, s, OCH_3), 6.86 (2H, d, *J* 8.8 Hz, H-3), 7.22 (2H, d, *J* 8.4 Hz, H-2); δ_C 36.3 (C-6), 55.6 (OCH_3), 55.8 (C-5), 114.2 (C-3), 129.7 (C-2), 132.7 (C-1), 159.0 (C-4); (Found: $M^{+\bullet}$, 150.0917. $C_9H_{12}NO$ requires M, 150.0919).

_N_-Methyl-_N_-(4-hydroxybenzyl)-4-hydroxyphenylacetamide (198)



EDCI (342 mg, 1.78 mmol) was added in one portion to a stirring solution of amine (**196**) (243 mg, 1.62 mmol), 4-methoxyphenylacetic acid (296 mg, 1.78 mmol) and DMAP (20 mg, 0.162 mmol) in dry DCM (25 ml) at rt. After stirring for 60 h, the mixture was washed successively with saturated $NaHCO_3$ (20 ml), 1M HCl (10 ml) and brine (10 ml) before drying over $MgSO_4$. The resultant solution was concentrated *in vacuo* to give a cloudy oil (396 mg) which was taken up in dry DCM (25 ml) and treated portionwise with boron tribromide (6.62 ml, 1M in DCM, 6.62 mmol) at -78 °C. After the addition complete, the dark brown mixture was allowed to slowly warm to 0 °C and stirred at this temperature for 30 min before being poured cautiously into iced-H_2O (100 ml) and extracted into EtOAc (2 x 25 ml). The combined organic extracts were washed with brine (20 ml), dried over $MgSO_4$ and concentrated *in vacuo* to give a foam (364 mg). The crude product was purified by column chromatography eluting with EtOAc-acetone (2:1) to give a pale yellow solid which was recrystallised from acetone-$CHCl_3$ affording the title compound (**198**) as a flaky solid (122 mg, 34.0% from **196**), m.p. 194-196 °C; ν_{max} (KBr)/cm^{-1} 3365 (OH), 1624 (amide), 1596 and 1515 (Ar); δ_H 2.72 and 2.85 (3H, 2 x s, H-6), 3.60 (2H, s, H-8), 4.37 and 4.45 (2H, 2 x s, H-5), 6.68-6.74 (4H, m, Ar-H), 6.93-7.02 (4H, m, Ar-H), 9.24 (bs, OH), 9.30 (bs, OH), 9.38 (bs, OH); δ_C 33.4 and 35.0 (C-6), 39.1 and 39.5 (C-8), 49.7 and 52.6 (C-5), 115.4 (CH), 115.5 (CH), 115.7 (CH), 126.1, 126.3, 127.7 and 128.3 (C-1 and C-9), 128.5 (CH), 129.3 (CH), 130.2 (CH), 156.1, 156.2, 156.8 and 156.9 (C-4 and C-12), 171.1 (C-7); (Found: $M^{+\bullet}$, 271.1207. $C_{16}H_{17}NO_3$ requires M, 271.1208).

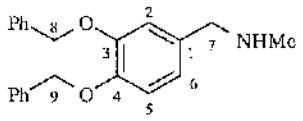
3,4-Dibenzyloxybenzaldehyde (200)



The method of Barrero *et al.*[117] was used as follows. Benzyl bromide (1.44 g, 1.0 ml, 8.42 mmol) was added dropwise to a stirring suspension of 3,4-dihydroxybenzaldehyde (0.50 g, 3.62 mmol) and K_2CO_3 (1.00 g, 7.24 mmol) in

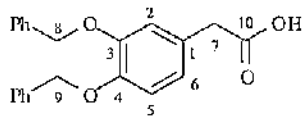
acetone (20 ml) at rt. After the addition complete the mixture was heated at reflux for 17 h, cooled to rt and filtered through Celite®. The resultant solution was concentrated *in vacuo* to give an orange oil which crystallised with scratching. Recrystallisation from Et_2O-acetone afforded the aldehyde (**200**) as a lemon coloured solid (0.78 g, 68%), m.p. 86-88 °C (lit.,[117] 87 °C); δ_H 5.21 (2H, s, H-8 or H-9), 5.26 (2H, s, H-8 or H-9), 7.02 (1H, d, *J* 8.2 Hz, H-5), 7.30-7.51 (12H, m, H-2, H-6 and Ph-H), 9.79 (1H, s, H-7).

N-Me-3,4-dibenzyloxybenzylamine (201)



The method of Neidigh *et al.*[116] was modified as follows. A mixture of aldehyde (**200**) (0.50 g, 1.57 mmol) and methylamine (0.22 ml, 8.03M in EtOH, 1.77 mmol) in dry EtOH (10 ml) was heated at reflux for 15 h. After cooling to rt, the yellow solution was concentrated to give an amber oil which was taken up in fresh EtOH (25 ml) to which was added $NaBH_4$ (0.30 g, 7.85 mmol) portionwise *via* a solid addition funnel. The mixture was heated at reflux for 2 h then cooled and stirred at rt for 24 h before pouring into H_2O (100 ml). The resultant suspension was extracted with Et_2O (2 x 20 ml) and the combined organic extracts washed with 1M HCl (2 x 20 ml). The aqueous layer was basified with 2M NaOH then extracted with $CHCl_3$ (2 x 20 ml), the organic solution dried over $MgSO_4$ and concentrated to give the amine (**201**) as a yellow oil (0.44 g, 84.6%); δ_H 2.39 (3H, s, NMe), 3.63 (2H, s, H-7), 5.12 (2H, s, H-8 or H-9), 5.15 (2H, s, H-8 or H-9), 6.80 (1H, dd, *J* 8.2 Hz and 1.9 Hz, H-6), 6.87 (1H, d, *J* 8.1 Hz, H-5), 6.96 (1H, d, *J* 1.9 Hz, H-2), 7.26-7.45 (10H, m, Ph-H); δ_C 36.2 (NMe), 56.1 (C-7), 71.7 and 71.9 (C-8 and C-9), 115.6 (CH), 121.6 (CH), 127.7 (CH), 127.8 (CH), 128.1 (CH), 128.8 (CH), 133.9 (C-1), 137.8 (C), 137.9 (C), 148.5 and 149.4 (C-3 and C-4).

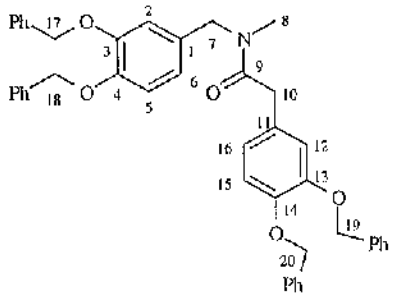
3,4-Dibenzyloxyphenylacetic acid (204)



The procedure of He *et al.*[119] was used on a 2.38 mmol scale affording acid (**204**) as a fawn solid (781 mg, 94.3%), m.p. 106-107 °C (aq. EtOH) (lit.,[119] 106-108 °C); δ_H 3.52 (2H, s, H-7), 5.12 (2H, s, H-8 or H-9), 5.13 (2H, s, H-8 or H-9), 6.78 (1H, dd, *J* 8.2 Hz and 1.8 Hz, H-6), 6.88 (1H, d, *J* 8.4 Hz, H-5), 6.89 (1H, d, *J* 2.0 Hz,

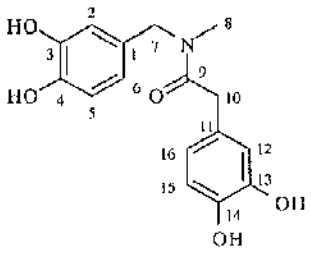
H-2), 7.27-7.44 (10H, m, Ph-H); δ_C 40.9 (C-7), 71.8 (C-8 and C-9), 115.5 and 116.7 (C-2 and C-5), 122.8 (C-6), 126.8 (C), 126.9 (CH), 127.7 (CH), 127.8 (CH), 128.2 (CH), 128.9 (CH), 137.5 (C), 137.7 (C), 148.8 and 149.4 (C-3 and C-4), 178.3 (C-10); (Found: $M^{+\bullet}$, 348.1362. $C_{22}H_{20}O_4$ requires M, 378.1362).

_N_-Methyl-_N_-(3,4-dibenzyloxybenzyl)-3,4-dibenzyloxyphenylacetamide (205)



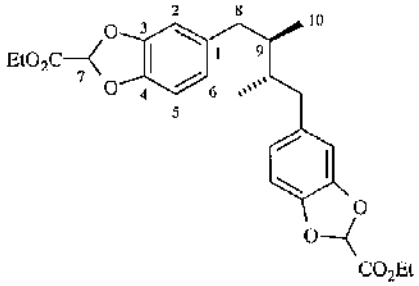
EDCI (68 mg, 0.36 mmol) was added in one portion to a stirring solution of amine (**201**) (108 mg, 0.32 mmol), acid (**204**) (124 mg, 0.36 mmol) and DMAP (4 mg, 0.03 mmol) in dry DCM (20 ml) at rt. After stirring at rt for 48 h, the mixture was washed with H_2O (10 ml), saturated $NaHCO_3$ (10 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a cloudy oil (210 mg) which was purified by silica gel flash chromatography affording the tertiary amide (**205**) as a colourless oil (168 mg, 78.1%); ν_{max} ($CDCl_3$)/cm^{-1} 1637 (amide); δ_H 2.71 and 2.80 (3H, 2 x s, H-8), 3.59 and 3.61 (2H, 2 x s, H-10), 4.30 and 4.44 (2H, 2 x s, H-7), 5.02, 5.05, 5.07, 5.08, 5.10 and 5.12 (8H, 7 x s, H-17, H-18, H-19 and H-20), 6.51-6.90 (6H, m, Ar-H), 7.21-7.51 (20H, m, Ph-H); δ_C 34.1 and 35.4 (C-8), 40.8 and 41.1 (C-10), 50.9 and 53.7 (C-7), 71.6, 71.7 and 71.8 (C-17, C-18, C-19 and C-20), 113.7 (CH), 115.3 (CH), 115.5 (CH), 115.7 (CH), 115.9 (CH), 116.0 (CH), 120.0 (CH), 121.6 (CH), 122.1 (CH), 127.7 (CH), 127.8 (CH), 127.9 (CH), 128.2 (CH), 128.3 (CH), 128.7 (CH), 128.8 (CH), 128.9 (CH), 130.0 (C), 131.1 (C), 137.4 (C), 137.6 (C), 137.7 (C), 137.8 (C), 148.3 (C), 148.7 (C), 149.5 (C), 149.7 (C), 171.5 and 171.8 (C-9); (Found: $M^{+\bullet}$, 663.2983. $C_{44}H_{41}NO_5$ requires M, 663.2985).

_N_-Methyl-_N_-(3,4-dihydroxybenzyl)-3,4-dihydroxyphenylacetamide (194)



Palladium on charcoal (10%, 30 mg) was added to a solution of amide (**205**) (168 mg, 0.25 mmol) in MeOH-EtOAc (3:1, 20 ml) and the mixture stirred under a hydrogen balloon at rt for 48 h. The catalyst was filtered through Celite®, the residue washed with EtOAc (2 x 10 ml) and the combined extracts concentrated to give an oil. Purification by silica gel flash chromatography (2:1 EtOAc-acetone) gave a colourless oil which was crystallised from acetone-$CHCl_3$ affording the title compound as a solid (57 mg, 74.0%). This material gave a TLC and melting point analysis identical to that prepared from the tetramethylether.

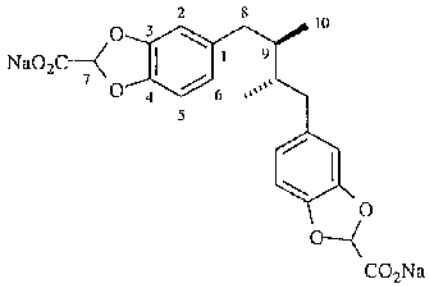
***meso*-1,4-Bis-(ethoxycarbonylmethinyl-3,4-dioxyphenyl)-2,3-dimethylbutane (207)**



The method of Hartzfeld *et al.*[122] was modified as follows. NDGA (150 mg, 0.50 mmol) in anhydrous EtOH (2 ml) was added dropwise to a stirring solution of sodium ethoxide (from sodium {46 mg, 2.00 mmol}) in EtOH (5 ml) at 0 °C. After stirring for 15 min, ethyl dichloroacetate (157 mg, 0.12 ml, 1.00 mmol) was added dropwise to the dark green solution and the mixture allowed to warm to rt. The resultant brown solution was stirred at rt for 1 h, heated at reflux for 6 h then allowed to cool to rt before concentrating *in vacuo*. The brown solid so obtained was taken up in Et_2O (20 ml), washed with 5% $NaHCO_3$ (10 ml) and water (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* afforded the title compound (**207**) as a crude yellow oil (65 mg, 28%). A purified sample was obtained by silica gel flash chromatography collecting the fraction at Rf 0.65; δ_H 0.82 (3H, d, *J* 6.6 Hz, H-10), 1.33 (3H, t, *J* 7.1 Hz, $OCH_2C\underline{H}_3$), 1.72 (1H, m, H-9), 2.20-2.32 (1H, m, H-8), 2.66-2.75 (1H, m, H-8), 4.32 (2H, q, *J* 7.1 Hz, $OC\underline{H}_2CH_3$), 6.28 (1H, s, H-7), 6.61-6.80

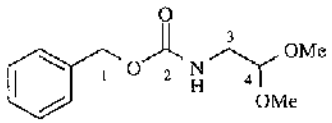
(3H, m, Ar-H); δ_C 14.0 and 16.0 (C-10 and CH_3), 38.9 (C-8), 39.3 (C-9), 62.4 (CH_2), 102.8 (C-7), 108.1 and 109.4 (C-2 and C-5), 122.3 (C-6), 136.2 (C-1), 144.6 and 146.6 (C-3 and C-4); m/z (CI/NH_3) 488 $(M+NH_4)^{+\bullet}$.

meso-1,4-Bis-(ethoxycarbonylmethinyl-3,4-dioxyphenyl)-2,3-dimethylbutane disodium salt (208)



To a stirring solution of NaOH (5 mg, 0.13 mmol) in EtOH (2 ml) was added ester (**207**) (25 mg, 0.05 mmol) in EtOH (2 ml) dropwise at rt. After stirring for 1 h, the resultant precipitate was collected by centrifuge and washed several times with EtOH affording the acid salt (**208**) as a pale brown solid (17 mg, 70%); δ_H (D_2O) 0.61 (3H, d, *J* 6.4 Hz, H-10), 1.52 (2H, m, H-9), 2.13 (1H, m, H-8), 2.52 (1H, m, H-8), 5.98 (1H, s, H-7), 6.56-6.68 (3H, m, Ar-H); $\upsilon_{max.}$ (KBr)/cm^{-1}, 1640 (C=O).

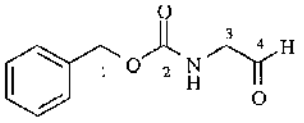
***N*-(Benzyloxycarbonyl)aminoacetaldehyde dimethylacetal (211)**



The method of Bischofberger *et al.*[123] was used as follows. Benzyl chloroformate (4.23 g, 3.54 ml, 24.81 mmol) was added dropwise to a stirring solution of aminoacetaldehyde dimethylacetal (2.00g, 2.07 ml, 19.02 mmol) in dry (1:1) EtOAc-pyridine (12 ml) at 0 °C. After the addition was complete, the mixture was allowed to warm to rt and stirred for 4 h. The resultant mixture was filtered through a sinter funnel and the residue extracted with EtOAc (3 x 10 ml). The combined organic extracts were washed successively with H_2O (20 ml), 1M KOH (2 x 15 ml), 5% citric acid (4 x 20 ml) and brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a light yellow oil (4.27 g) which was purified by distillation under reduced pressure giving carbamate (**211**) as a colourless oil (2.23 g, 49.0%), b.p 132-140 °C / 0.02 mmHg (lit.,[123] 145 °C / 0.03 mmHg); $\upsilon_{max.}$ (neat)/cm^{-1} 3342 (NH), 1716 (C=O); δ_H 3.35 (2H, t, *J* 5.7 Hz, H-3), 3.40 (6H, s, OCH_3), 4.40 (1H, t, *J* 5.3 Hz, H-4), 5.12 (2H, s, H-

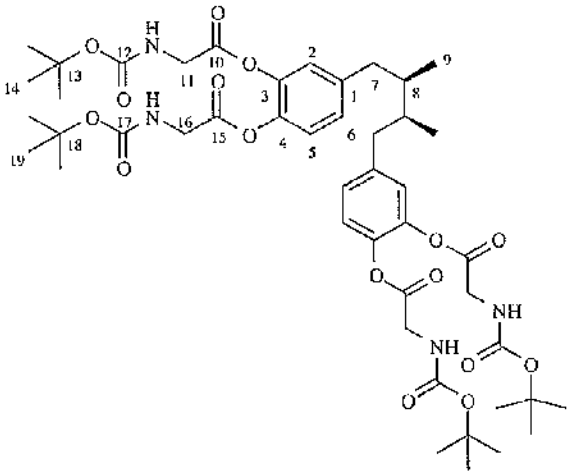
1), 7.31-7.40 (5H, m, Ar-H); δ_C 42.9 (C-3), 54.7 (OCH_3), 67.2 (C-1), 103.2 (C-4), 128.5 and 128.9 (CH), 136.8 (C), 156.8 (C-2).

_N_-(Benzyloxycarbonyl)aminoacetaldehyde (212)



The method of Bischofberger *et al.*[123] was used as follows. A mixture of acetal (**211**) (500 mg, 2.09 mmol) and oxalic acid (42 mg, 0.47 mmol) in (2:1) THF-H_2O (6 ml) was heated at reflux for 17 h. After cooling to rt, the mixture was transferred to a separating funnel containing Et_2O (30 ml) and washed with 5% $NaHCO_3$ (15 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a clear oil (363 mg) which was purified by silica gel flash chromatography affording the aldehyde (**212**) as a colourless liquid (228 mg, 56.6%); δ_H 4.14 (2H, d, *J* 5.1 Hz, H-3), 5.14 (2H, s, H-1), 5.56 (1H, s, NH), 7.32-7.42 (5H, m, Ar-H), 9.64 (1H, s, CHO); δ_C 52.0 (C-3), 67.6 (C-1), 128.5, 128.7 and 129.0 (CH), 136.5 (C), 156.7 (C-2), 197.0 (CHO).

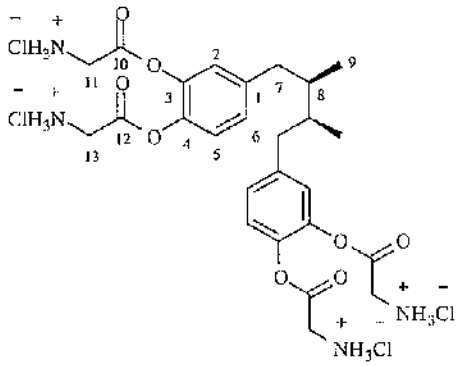
***meso*-1,4-Bis-(3,4-di-{*N*-*tert*butoxycarbonyl}aminoacetoxyphenyl)-2,3-dimethylbutane (215)**



To a stirring solution of *meso*-NDGA (100 mg, 0.33 mmol) and *N*-(*tert*-butoxycarbonyl)glycine (255 mg, 1.46 mmol) in dry EtOAc (5 ml) was added pyridine (0.12 ml, 1.46 mmol) dropwise. The mixture was cooled to 0 °C and DCC (300 mg, 1.46 mmol) was added in one portion and the mixture allowed to warm to rt and stirred for 16 h. The resultant suspension was filtered through Celite® and the residue washed with EtOAc (2 x 20 ml). The filtrate was washed successively with 5 % $NaHCO_3$ (2 x 20 ml), 5 % citric acid (2 x 20 ml) and brine (1 x 10 ml) before drying over $MgSO_4$.

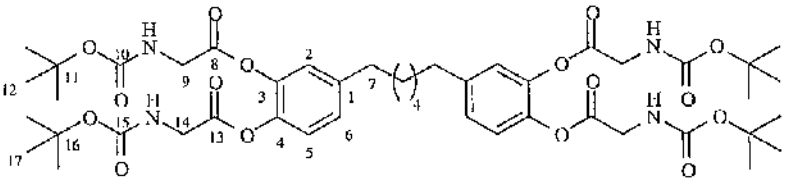
The resultant mixture was allowed to stand at 0 °C overnight to precipitate any remaining DCU which was filtered off and the solvent removed *in vacuo* to yield the glycine ester (**215**) as pale yellow crystals of indefinite melting point (308 mg, 100 %); $\upsilon_{max.}$ (KBr)/cm^{-1}, 1704 (carbamate), 1786 (ester); δ_H 0.84 (3H, d, *J* 6.4 Hz, H-9), 1.46 (18H, s, H-14 and H-19), 1.78 (1H, m, H-8), 2.34-2.39 (1H, m, H-7), 2.69-2.74 (1H, m, H-7), 4.13 (4H, d, *J* 5.9 Hz, H-11 and H-16), 5.59 (1H, s, NH), 5.67 (1H, s, NH), 6.86-7.10 (3H, m, Ar-H); δ_C 16.2 (C-9), 26.6 (C-8), 28.3 (C-14 and C-19), 38.2 (C-7), 42.3 (C-11 and C-16), 80.0 and 80.3 (C-13 and C-18), 122.8, 123.3 (C-2 and C-5), 127.4 (C-6), 139.7, 140.8 and 141.4 (C-1, C-3 and C-4), 156.2 (C-12 and C-17), 168.3 (C-10 and C-15); (Found *m/z* {FAB+}, {M+Na}$^{+\bullet}$ 953.4374. $C_{46}H_{66}N_4O_{16}Na$ requires M, 953.4372).

meso-1,4-Bis-(3,4-diammoniumacetoxyphenyl)-2,3-dimethylbutane tetrachloride (216)



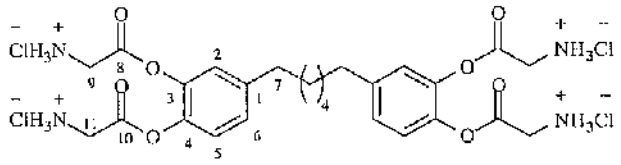
Dry HCl was bubbled into an ice cold solution of the protected ester (**215**) (150 mg, 0.16 mmol) in dry EtOAc (10 ml) for 3 min whereupon a white precipitate soon separated from the reaction mixture. The mixture was allowed to slowly warm to rt and stirred for a further 1 hr before being concentrated *in vacuo*. The resultant solid was washed with EtOAc (2 x 10 ml) to give the glycine ester (**216**) as a white solid (106 mg, 97 %), m.p. 205-210 °C dec.; $\upsilon_{max.}$ (KBr)/cm^{-1}, 1778 (ester); δ_H (D_2O) 0.64 (6H, d, *J* 6.5 Hz, H-9), 1.62 (1H, m, CH), 2.20-2.31 (1H, m, H-7), 2.64-2.71 (1H, m, H-7), 4.09 (4H, s, H-11), 7.06-7.09 (3H, m, Ar-H); (Found *m/z* {FAB+}, {M+H}$^{+\bullet}$ 531.2452. $C_{26}H_{35}N_4O_8$ requires M, 531.2455).

1,6-Bis-(3,4-di-{*N*-*tert*butoxycarbonylamino)acetoxyphenyl)hexane (217)



Pyridine (116 mg, 0.12 ml, 1.46 mmol) was added to a stirring solution of diarylhexane (**156**) (100 mg, 0.33 mmol) and *N*-(*tert*-butoxycarbonyl)glycine (256 mg, 1.46 mmol) in dry EtOAc (8 ml) at 0 °C. After stirring for 5 min, DCC (300 mg, 1.46 mmol) was added in one portion and the mixture allowed to warm to rt and stirred for a further 16 h. The mixture was filtered through Celite® and the residue extracted with EtOAc (2 x 10 ml). The combined organic extracts were washed successively with 5% $NaHCO_3$ (10 ml), 5% citric acid (10 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration of the organic exrtracts gave an oily residue which was taken up in DCM (2 ml) and allowed to stand in a freezer overnight. Filtration and concentration *in vacuo* afforded the title compound as shiny crystals (307 mg, 100%), m.p. 58-65 °C; $\upsilon_{max.}$ (KBr)/cm^{-1}, 1788 (ester), 1702 (carbamate); δ_H 1.33 (2H, m, CH_2), 1.46 (18H, s, H-12 and H-17), 1.59-1.61 (2H, m, CH_2), 2.58 (2H, t, *J* 7.5 Hz, H-7), 4.12 (4H, d, *J* 4.6 Hz, H-9 and H-14), 5.49-5.51 (2H, m, NH), 6.98-7.08 (3H, m, Ar-H); δ_C 28.7 (C-12 and C-17), 29.2 (CH_2), 31.2 (CH_2), 35.5 (C-7), 42.8 (C-9 and C-14), 80.6 (C-11 and C-16), 123.1 and 123.3 (C-2 and C-5), 127.2 (C-6), 139.9 (C-1), 141.8 and 142.4 (C-3 and C-4), 156.6 (C-10 and C-15), 168.5 and 168.6 (C-8 and C-13); (Found: C 59.41; H 7.28; N 6.04; $(M+Na)^{+\bullet}$ (FAB+), 953.4374. $C_{46}H_{66}N_4O_{16}Na$ requires C 59.35; H 7.10; N 6.02; M, 953.4372).

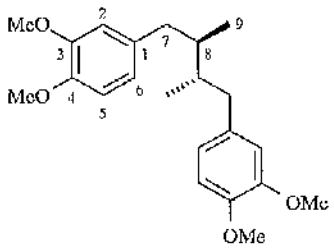
1,6-Bis-(3,4-diammoniumacetoxyphenyl)hexane tetrachloride (218)



Dry HCl was bubbled into a solution of the protected amine (**217**) (220 mg, 0.24 mmol) in dry EtOAc (7 ml) at 0 °C for 2 min. A white solid quickly precipitated and the mixture was allowed to warm to rt and stirred for a further 20 min. The solid was collected by filtration, washed with Et_2O (2 x 10 ml) and dried over P_2O_5 to afford the amine salt (**218**) as a powder (124 mg, 78%), m.p 185-190 °C; $\upsilon_{max.}$ (KBr)/cm^{-1}, 1771 (ester); δ_H 1.25 (2H, bs, CH_2), 1.53 (2H, bs, CH_2), 2.58 (2H, t, *J* 7.4 Hz, H-7), 4.23 (4H, 2 x s, H-9 and H-11), 7.18-7.27 (3H, m, Ar-H); δ_C 28.2 and 30.6 (CH_2), 34.7 (C-7), 40.5 (C-9 and C-11), 123.3 and 123.4 (C-2 and C-5), 128.6

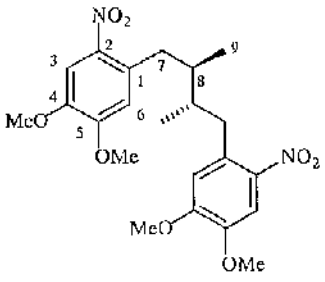
(C-6), 138.4 (C-1), 140.4 and 144.6 (C-3 and C-4), 167.1 and 167.2 (C-8 and C-10); (Found: $(M+H)^{+\bullet}$ (FAB+), 531.2453. $C_{26}H_{35}N_4O_8Na$ requires M, 531.2455.

(*meso*)-1,4-Bis-(3,4-dimethoxyphenyl)-2,3-dimethylbutane (47)



The procedure of Perry *et al.*[42] was modified as follows : A solution of KOH (210 mg, 3.75 mmol) in MeOH (0.65 ml) and water (1 ml) was added dropwise to a stirring solution of NDGA (250 mg, 0.83 mmol) in MeOH (2 ml). To the resultant green solution was added dimethyl sulfate (840 mg, 0.63 ml, 6.66 mmol) dropwise and the mixture stirred for a further 23 h ensuring the mixture was maintained at pH 8-9 by periodical addition of more KOH solution. Ammonia solution (35%, 5 ml) was added to the tan coloured suspension and the mixture stirred for a further 30 min. The resultant mixture was extracted with EtOAc (30 ml) and the organic extracts washed with water (10 ml) and brine (10 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a fawn coloured solid (285 mg) which was recrystallised from aq. MeOH affording the protected diaryl butane (**47**) as shiny tan coloured crystals (249 mg, 83.8%), m.p. 99-101 °C (lit.,[42] 100-102 °C); δ_H 0.78 (6H, d, *J* 6.6 Hz, H-9), 1.68-1.72 (2H, m, H-8), 2.20-2.26 (2H, dd, *J* 13.2 and 9.2 Hz, H-7), 2.66-2.70 (2H, dd, *J* 13.2 and 4.8 Hz, H-7), 6.65 (2H, d, *J* 1.8 Hz, H-2), 6.70 (2H, dd, *J* 8.1 and 1.8 Hz, H-6), 6.79 (2H, d, *J* 8.1 Hz, H-5).

(*meso*)-1,4-Bis-(4,5-dimethoxy-2-nitrophenyl)-2,3-dimethylbutane (222)

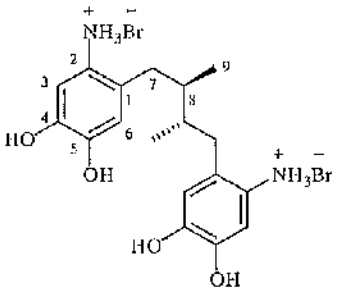


The procedure of Schroeter *et al.*[37] was modified as follows. Concentrated HNO_3 (0.19 ml, *d* 1.42, 4.22 mmol) was added dropwise at rt to a stirring solution of diarylbutane (**47**) (400 mg, 1.12 mmol) in glacial AcOH (2.5 ml). A yellow solid precipitated from the solution and stirring was continued for a further 1.5 h at rt. Water

(15 ml) was added, the mixture extracted with $CHCl_3$ (50 ml) and the organic extracts washed with saturated $NaHCO_3$ (20 ml) and brine (15 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a orange solid (233 mg) which was recrystallised from MeOH affording the nitrated diarylbutane (**222**) as orange crystals (203 mg, 81.2%), m.p. 149-151 °C (lit.,[37] 150-151 °C).

New data : ν_{max} (KBr)/cm^{-1} 1523 and 1335 (NO_2); δ_H 0.80 (3H, d, *J* 6.7 Hz, H-9), 1.79-1.81 (1H, m, H-8), 2.58-2.63 (1H, dd, *J* 13.2 and 9.2 Hz, H-7), 3.27-3.31 (1H, dd, *J* 13.2 and 4.0 Hz, H-7), 3.86 (3H, s, OCH_3), 3.91 (3H, s, OCH_3), 6.68 (1H, s, H-6), 7.54 (1H, s, H-3); δ_C 16.6 (C-9), 37.3 (C-7), 39.3 (C-8), 56.6 (OCH_3), 56.8 (OCH_3), 108.8 and 114.9 (C-3 and C-6), 132.7 (C-1), 141.7 and 147.5 (C-2 and C-4), 153.0 (C-5); (Found: C 58.88%; H 6.36%; N 6.20%; $M^{+\bullet}$, 448.1844. $C_{22}H_{28}N_2O_8$ requires C 58.93%; H 6.25%; N 6.25%; M, 448.1846).

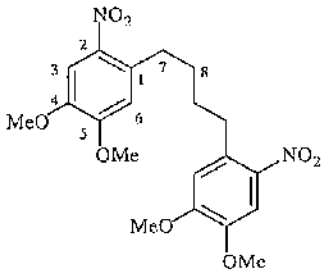
(*meso*)-1,4-Bis-(4,5-dihydroxy-2-aminophenyl)-2,3-dimethylbutane diHBr (223)



Palladium on charcoal (10%, 150 mg) was added to a stirring solution of (**222**) (325 mg, 0.73 mmol) in EtOAc (20 ml) and the mixture stirred at rt under a hydrogen balloon overnight. The catalyst was removed through Celite® and the residue extracted with EtOAc (3 x 10 ml). Concentration *in vacuo* afforded a sticky white solid which was purified by flash column chromatography eluting with EtOAc affording the free amine as a sticky off-white solid (0.26 g, 91%); δ_H 0.85 (3H, d, *J* 6.6 Hz, H-9), 1.79-1.84 (1H, m, H-8), 2.19 (1H, dd, *J* 14.0 Hz and 9.6 Hz, H-7), 2.59 (1H, dd, *J* 14.0 Hz and 4.8 Hz, H-7), 3.72 (3H, s, OCH_3), 3.75 (3H, s, OCH_3), 6.21 (1H, s, H-5), 6.51 (1H, s, H-2). The protected amine was taken up in 48% hydrobromic acid (5 ml) and heated at reflux for 2 h. After cooling to rt the precipitated brown solid was filtered and washed with 48% HBr (10 ml) affording the amine salt (**223**) as a tan solid (279 mg, 76% from **222**), m.p. > 250 °C; ν_{max} (KBr)/cm^{-1} 1619, 1570 and 1532 (aromatic); δ_H (D_2O) 0.73 (3H, d, *J* 6.4 Hz, H-9), 1.73 (1H, m, H-8), 2.30 (1H, dd, *J* 14.4 Hz and 10.4 Hz, H-7), 2.66 (1H, dd, *J* 14.5 Hz and 4.1 Hz, H-7), 6.74 (1H, s, H-3 or H-6), 6.79 (1H, s, H-3 or H-6); δ_C (D_2O) 15.3 (C-9), 32.8 (C-7), 38.0 (C-8), 111.5 and 118.3 (C-3 and C-6), 120.8 and 127.5 (C-1 and C-2), 143.2 and 144.9 (C-4 and C-5);

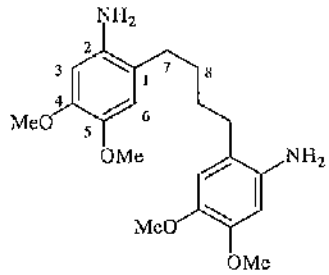
(Found: C 42.57%; H 5.30%; N 5.44%; $M^{+\bullet}$, 332.1735. $C_{18}H_{24}N_2O_4.H_2O$ requires C 42.19%; H 5.47%; N 5.47; M, 332.1736).

1,4-Bis-(4,5-dimethoxy-2-nitrophenyl)butane (224) :



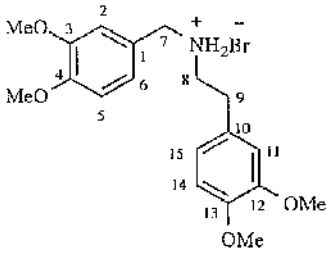
Concentrated HNO_3 (0.15 ml, 3.39 mmol) was added dropwise to a stirring solution of diarylbutane (**148**) (150 mg, 0.45 mmol) in glacial AcOH at rt resulting in precipitation of a yellow solid. The resultant suspension was stirred for a further 1.5 h before water (20 ml) was added and the mixture extracted into $CHCl_3$ (2 x 20 ml). The combined organic extracts were washed with saturated $NaHCO_3$ (20 ml) and brine (15 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave an orange solid (173 mg, 91%) which was recrystallised from *i*-PrOH affording the nitrated diarylbutane (**224**) as golden crystals (130 mg, 68.1%), m.p. 183-184 °C (lit.,[38] 184-185 °C {AcOH}); ν_{max} (KBr)/cm^{-1} 1581 and 1518 (aromatic), 1325 (NO_2); δ_H 1.76 (2H, bs, H-8), 2.98 (2H, bs, H-7), 3.93 (3H, s, OCH_3), 3.98 (3H, s, OCH_3), 6.74 (1H, s, H-6), 7.59 (1H, s, H-3); δ_C 31.0 and 34.0 (C-7 and C-8), 56.7 (OCH_3), 56.8 (OCH_3), 108.6 (C-3), 113.6 (C-6), 133.3 (C-1), 141.4 (C-2), 147.5 (C-4), 153.4 (C-5); (Found: $M^{+\bullet}$ 420.1533. $C_{20}H_{24}N_2O_8$ requires M, 420.1533).

1,4-Bis-(4,5-dimethoxy-2-aminophenyl)butane (225)



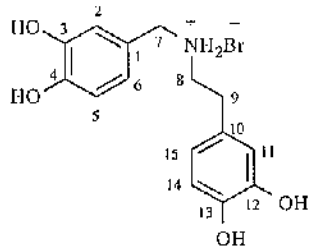
Palladium on carbon (10%, 25 mg) was added to a solution of the diarylbutane (**224**) (95 mg, 0.23 mmol) in dioxane (15 ml) and the mixture stirred under a hydrogen balloon overnight. The mixture was filtered through Celite® and the residue extracted with $CHCl_3$ (2 x 5 ml) to give a lilac coloured solution. TLC of this mixture showed mostly starting material and a minor lower running spot that gave a positive result with Dragendorff stain. The reaction mixture was not further investigated.

_N_-(3,4-Dimethoxybenzyl)-_N_-(2-{3,4-dimethoxyphenyl)ethylammonium bromide (226)



2-(3,4-Dimethoxyphenyl)ethylamine (0.57 g, 0.53 ml, 3.16 mmol) was added to a solution of 3,4-dimethoxybenzaldehyde (0.50 g, 3.01 mmol) in anhydrous EtOH (15 ml) and the mixture heated at reflux under nitrogen for 18 h. After cooling to rt the mixture was concentrated *in vacuo* to gave the intermediate imine as an amber coloured oil; δ_H 8.05 (CH=N). The crude imine was taken up in fresh EtOH (20 ml) and treated portionwise with $NaBH_4$ (569 mg, 15.04 mmol) *via* a solid addition funnel. The mixture which almost became colourless was heated at reflux for 1 h allowed to cool and stirred overnight at rt. The resultant mixture was poured into water (60 ml), extracted with $CHCl_3$ (2 x 20 ml) and the combined organic extracts washed with water (20 ml) and brine (20 ml) before drying over $MgSO_4$. Concentration *in vacuo* gave a white solid which was recrystallised from 48% HBr to give the amine salt (**226**) as a tan coloured solid (1.24 g, 100%), m.p. 184-186 °C (lit.,[127] 187 °C); ν_{max} (KBr)/cm^{-1} 1596 and 1519; δ_H (d_6-DMSO) 2.91 (2H, *t*, J 9.1 Hz, H-9), 3.08-3.12 (2H, m, H-8), 3.72 (3H, OCH_3), 3.75 (3H, OCH_3), 3.76 (3H, s, OCH_3), 3.78 (3H, s, OCH_3), 4.11 (2H, *t*, J 5.6 Hz, H-7), 6.75 (1H, dd, *J* 8.1 Hz and 1.9 Hz, H-6 or H-15), 6.85 (1H, d, *J* 1.9 Hz, H-2 or H-11), 6.90 (1H, d, *J* 8.2 Hz, H-5 or H-14), 6.99 (1H, d, *J* 8.3 Hz, H-5 or H-14), 7.04 (1H, dd, *J* 8.2 Hz and 1.9 Hz, H-6 or H-15), 7.23 (1H, d, *J* 1.8 Hz, H-2 or H-11), 8.34 (2H, bs, NH_2); δ_C (d_6-DMSO) 31.3 (C-8), 47.7 and 50.2 (C-7 and C-9), 55.8, 55.9 and 56.0 (OCH_3), 111.9, 112.4, 112.8 and 114.0 (C-2, C-5, C-11 and C-14), 120.9 and 123.0 (C-6 and C-15), 124.3 and 129.8 (C-1 and C-10), 148.0, 149.0, 149.2 and 149.6 (C-3, C-4, C-12 and C-13); (Found: $M^{+\bullet}$ 331.1781. $C_{19}H_{24}NO_4$ requires M, 331.1784).

***N*-(3,4-Dihydroxybenzyl)-*N*-(2-{3,4-dihydroxyphenyl)ethylammonium bromide (227)**



A mixture of the amine salt (**226**) (250 mg, 0.61 mmol) and 48% HBr (10 ml) was heated at reflux under nitrogen for 18 h. After cooling to rt the light orange solution was concentrated *in vacuo* to give a brown solid which was triturated with EtOAc affording the title compound (**227**) as a light brown powder (151 mg, 70.0%), m.p.> 250 °C; δ_H (D_2O) 2.79 (2H, t, *J* 7.5 Hz, H-9), 3.15 (2H, t, *J* 7.4 Hz, H-8), 4.00 (2H, s, H-7), 6.62 (1H, dd, *J* 8.1 Hz and 2.1 Hz, H-6 or H-15), 6.70 (1H, d, *J* 2.0 Hz, H-2 or H-11), 6.76-6.86 (4H, m, Ar-H).

7

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