TOWARDS THE BIOSYNTHESIS OF THE LIGUSTRONES

by

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"If we knew what we were doing it wouldn't be research"

J.M.G. Cowie

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Additional thanks is also due to Professor D.C. Sherrington and his research group who kept me off the streets during the write-up of this thesis.

A special gratitude is also owed to my parents, and I can never thank them enough for all they have done for me. This thesis is dedicated to them.

Contents

Summary

The synthesis of possible precursors of the ligustrone metabolites of *Cercospora ligustrina* was undertaken. These were postulated as hydroxy-substituted anthracenes with a fused pyrone ring. The best approach to the anthracene nucleus was *via* the fusion of two substituted benzenes in such a way as to produce the central ring of the anthracene. Lithiation of *N*, *N*-diethyl-2,4-dimethoxybenzamide and reaction of the anion with 3,5-dimethoxybenzaldehyde gave a substituted phthalide. Hydrogenation cleaved the lactone ring to yield a benzylbenzoic acid which was cyclised to give 1,3,6,8-tetramethoxy-9-anthranol.

1,3,6,8,9-pentamethoxyanthracene was produced by a two stage methylation process from 9-acetoxy-1,3,6,8-tetramethoxyanthracene.

Reaction of the lithiated amide with methyl 2,6-dimethoxy-4-formylbenzoate and reduction of the intermediate phthalide gave a carboxymethyl-substituted benzylbenzoic acid. Attempted ring closure gave 2-carboxymethyl-1,3,6,8-tetramethoxy-9,10-anthraquinone rather than the desired anthracene.

Various approaches to the pyrone ring of the required precursor were also investigated. In model reactions, the best approach involved the treatment of an *o*-acetoxyacetophenone with base.

The fungal metabolites ligustrone A and B were isolated from cultures of *Cercospora ligustrina*. The metabolite ligustrone C was never detected. [1-^{14}C]Acetate feedings of *C. ligustrina* were investigated however incorporations were very low.

Chapter 1

Introduction

1.1 The possible biosynthesis of the ligustrones

Since the dawn of time mankind has used the extracts of plants and animals for its own ends. More recently, a desire for a greater understanding of the chemistry of these "natural products" has arisen. From an original interest in their biological activity has stemmed attempts to elucidate their molecular structure, their biosynthesis and ultimately their total synthesis.

Organic chemists now have many physical and chemical means to aid their discovery and understanding of these natural systems.

It has become evident that all living organisms have many similarities in the way they manufacture and manipulate compounds essential for their existence. For example, amino acids, fatty acids, nucleotides and sugars are all constructed and degraded by a series of reaction sequences catalysed and regulated by enzymes. Collectively these life supporting chemical pathways are termed metabolism.

In addition there are many natural substances produced by organisms that are not altogether necessary for the day to day function of that organism. Alkaloids, terpenes, polyenes, pigments, phenols, mycotoxins and many others are of this class, and these are termed "secondary metabolites".

This is as opposed to the previous type, common to all organisms called "primary metabolites".

Secondary metabolites are produced from primary metabolites by chemical pathways differing from those of primary metabolism. These pathways are often species, if not strain, specific and produce highly functionalized molecules sometimes so transformed that it is difficult to determine their origin.

If not essential for life, what purpose does secondary metabolism serve? Various suggestions have been offered[1].

Secondary metabolites may be a food reserve, accumulated during times of abundance and stored for times of hardship, however this does not explain their diversity. Why should an organism go to all the trouble and expense of synthesizing elaborate secondary metabolites as an energy stock when many organisms have the ability to lay down lipids for this purpose ?

Some secondary metabolites may benefit their producer by conferring on it an advantage in its chosen niche *e.g.* antibiotics. This may hold true for some cases but many secondary metabolites apparently exhibit no biological activity and seem only to have aesthetic value.

Bu'Lock[2] suggested that it is not the secondary metabolites that are important, but the processes of secondary metabolism. During times of stress, secondary metabolism acts as a sink for primary metabolites which would otherwise accumulate, thus allowing the continuation of primary metabolism (*c.f.* E.E.C. butter mountain).

Whatever the reason for the production of secondary metabolites, they have provided the organic chemist with a rich and varied source of molecules for study and contemplation.

Many novel metabolites have been isolated from fungal sources and this thesis will be concerned with the ligustrones, a series of metabolites produced by *Cercospora ligustrina.*

The fungi, along with algae and bacteria, are members of the Thallophyta, a division of the plant kingdom comprised of organisms with no true roots, stems or leaves. Fungi have a vegetative phase, the mycelium, which is an interwoven system of branching tubes called hyphae. Nutrients are absorbed over the whole surface of the mycelium to allow for their maximum uptake from the environment. Fungi lack the ability to photosynthesize organic compounds from carbon dioxide and water, so require oxidizable carbon compounds for energy as well as a source of nitrogen and various minerals. Some parts of the mycelium specialize in the formation of spores which serve to preserve the species during harsh conditions and for dispersal by wind and water. When the spores reach a suitable environment they grow to produce the vegetative phase, continuing the life cycle.

In fungi, an important secondary metabolic pathway responsible for the production of highly oxygenated compounds is the acylpolymalonate or polyketide pathway.

In the polyketide pathway, acetic acid units are joined together to form a chain in which the two carbon unit of acetate is joined in a head to tail manner, the C-C bond formed by a Claisen type condensation. The biosynthesis of the polyketide chain occurs on a large multienzyme complex, polyketide synthetase, from which no free intermediates have been isolated [3].

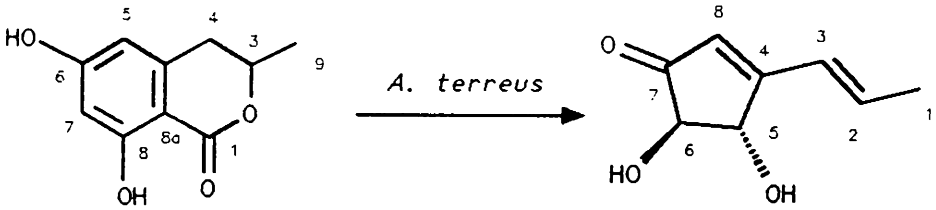
The C-C bond forming reaction is achieved by having an acetate unit bound to the enzyme as its thiol ester (1) which helps activate it towards nucleophilic attack. Another acetate unit bound to the cofactor coenzyme A (Co A), is carboxylated by biotin and bicarbonate to malonyl Co A (2). The malonyl Co A enters the active site and is acylated by the activated acetate starter unit (see Figure 1). Concomitant decarboxylation of the malonyl portion drives the condensation forward to produce acetoacetyl Co A (3) and carbon dioxide[4]. The Co A bound acetoacetate unit is transferred to the thiol of the enzyme and becomes the new starter unit(4). The next acetyl Co A unit gets activated as malonyl Co A and condenses with the activated acetoacetate moiety to give a triketide Co A (5) and carbon dioxide. Repetition of the transfer and activation of the growing acyl starter unit on the enzyme complex and its condensation with malonyl Co A affords an enzyme bound polyketide chain (6).

The polyketide chain can undergo many transformations to produce a variety of cyclic compounds. The active methylene groups can be alkylated, halogenated or oxidized and the carbonyl can be reduced to an alcohol, which can be dehydrated to a double bond, or further reduced to a methylene.

If we consider a tetraketide, it may be chemically elaborated and fold and cyclise in different ways to produce a range of metabolites as illustrated in Figure 2.

Some polyketide derived natural products have been modified beyond recognition from the simple molecules obtained by these aldol-type cyclisations.

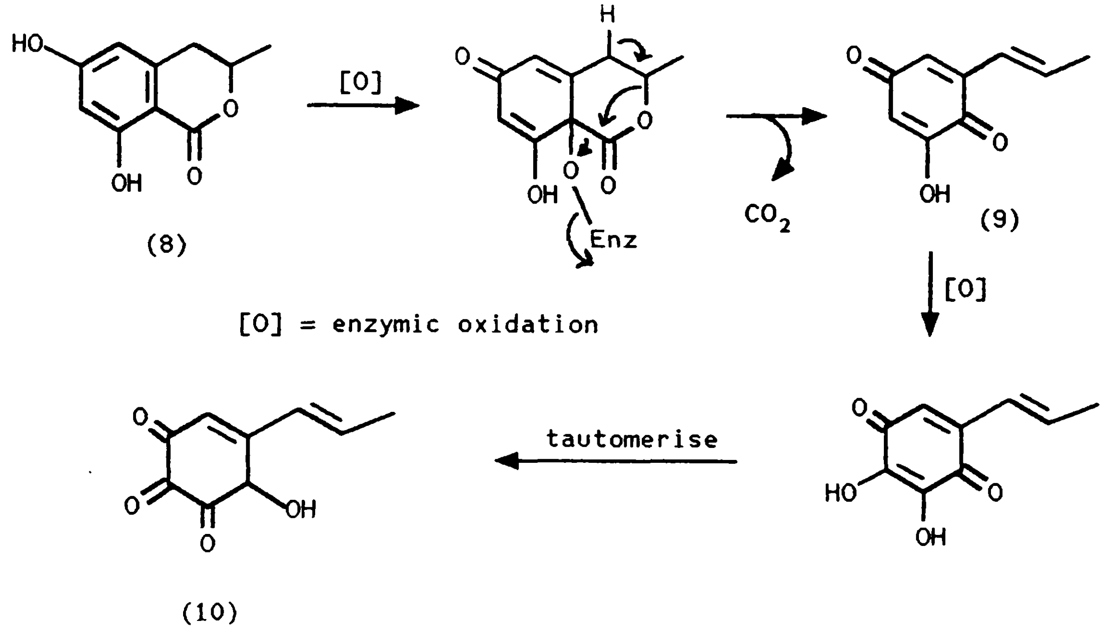
One interesting example is terrein (7), a dihydroxypentenone metabolite isolated from *Aspergillus terreus*[10]. Work by Staunton *et al.*[11] proved that terrein was acetate derived and also that 3,4-dihydro-6,8-dihydroxy-3-methylisocoumarin (8) was transformed by *A. terreus* into terrein. C-6 and C-8 of the dihydroisocoumarin become C-6 and C-5 of terrein with the loss of C-1 and C-7.



(8) (7)

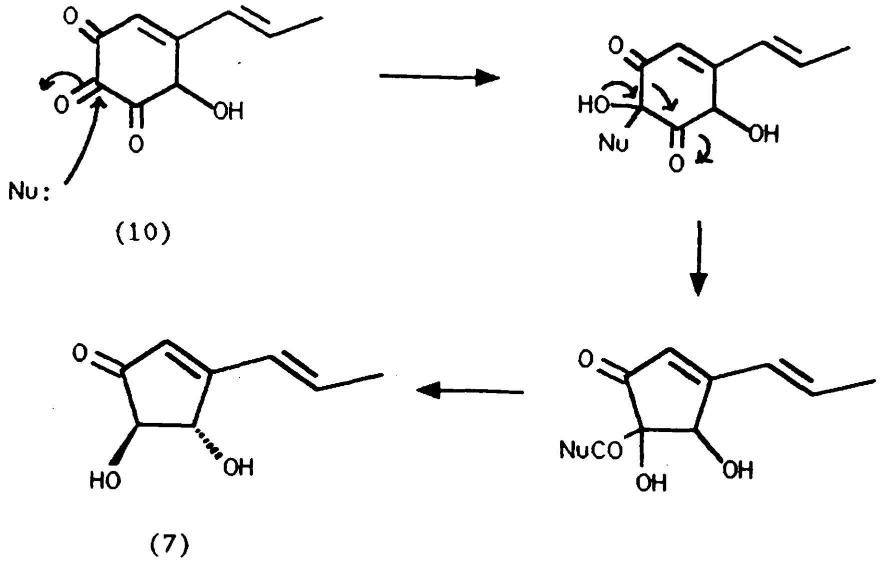
Birch *et al.*[12] proposed that terrein was probably formed by contraction of a six membered precursor. One mechanism to rationalize this aromatic ring contraction was proposed by Holker and Young[13] (Scheme 1).

It involves the enzymatic oxidation of the dihydroisocoumarin (8). Oxidative decarboxylation could produce *p*-quinone (9) with loss of C-1 as carbon dioxide. Further oxidation at C-7 and tautomerisation would yield the triketone (10). Nucleophilic attack on the C-7 ketone of (10) and ring contraction gives a cyclopentenoid skeleton.

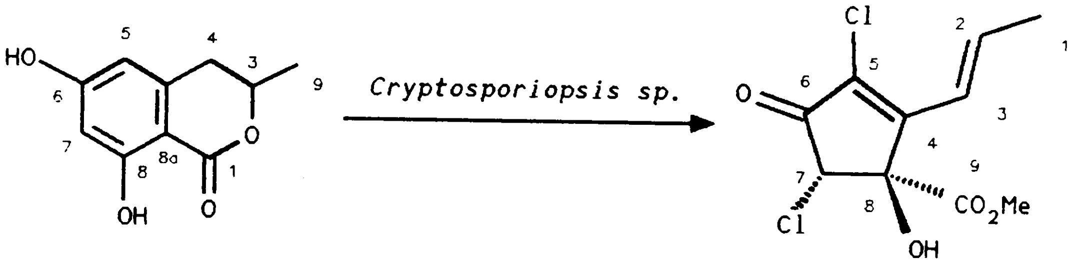


Scheme 1

Hydrolysis and decarboxylation removes C-7 as carbon dioxide and produces the dihydroxyketone functionality of terrein (7).



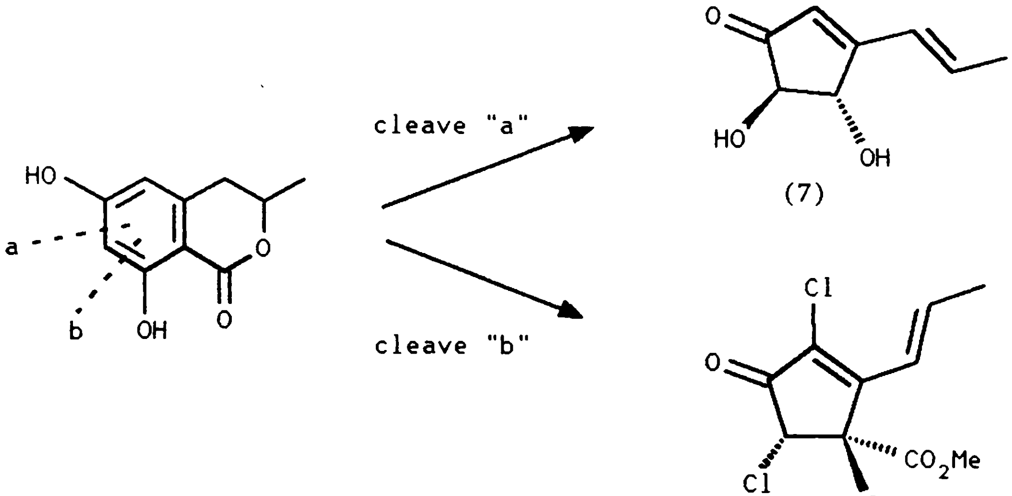
Cryptosporiopsin (11) is a chlorine containing metabolite with a cyclopentenoid skeleton produced by *Cryptosporiopsis* sp[14].



(8)

(11)

3,4-Dihydro-6,8-dihydroxy-3-methylisocoumarin (8) has also been proved to be a biosynthetic precursor of cryptosporiopsin[15]. The ring contraction differs from that of terrein (7) in that C-7 and C-8a of the dihydroisocoumarin become C-7 and C-8 of cryptosporiopsin with the loss of C-1 as carbon dioxide and the excision of C-8 to become the ester carbon. It may undergo a similar type of



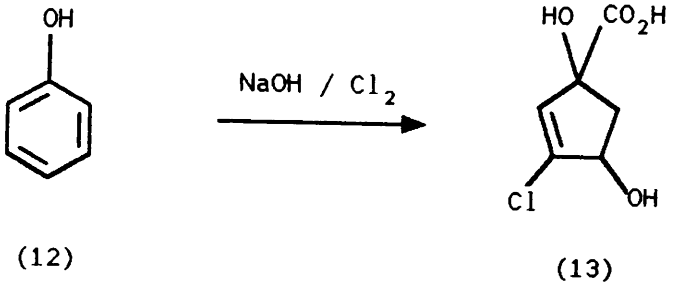
(7)

Figure 3

(11)

ring contraction as proposed for terrein, except enzymes in the *Cryptosporiopsis* sp. cleave the dihydroisocoumarin at site "b" whereas in *A. terreus*, the ring is cleaved at site "a" (Figure 3).

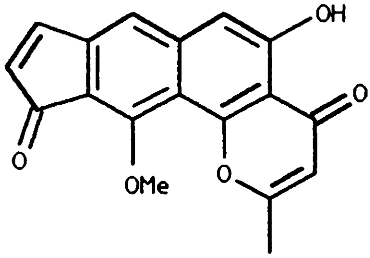
There is a chemical analogy for this type of ring transformation in the reaction of phenol (12) with sodium hydroxide and chlorine[16] to yield the



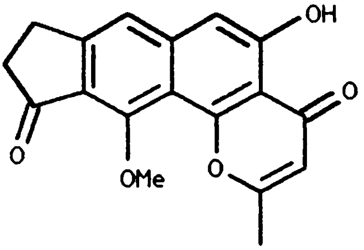
chloropentenone (13). This methodology has actually been used in a racemic synthesis of cryptosporiopsin starting from *m*-propylphenol[17].

Other acetate derived cyclopentenoid natural products have been isolated from fungi[15,18], most having similar structure and functionality to cryptosporiopsin (11) differing only in the level of oxidation, the number of chlorines and their stereochemistry. These probably arise by a similar pathway to that proposed for cryptosporiopsin (11).

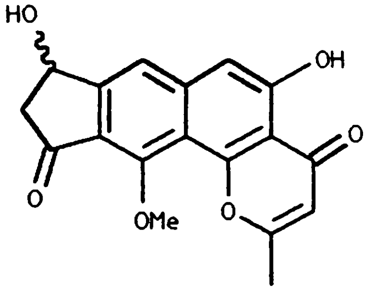
The ligustrone series of fungal metabolites isolated from *Cercospora ligustrina*[19] have a tetracyclic skeleton composed of a naphthalene nucleus with a pyrone and a fused pentanone ring. They differ only in the functionality of



Ligustrone A (14)



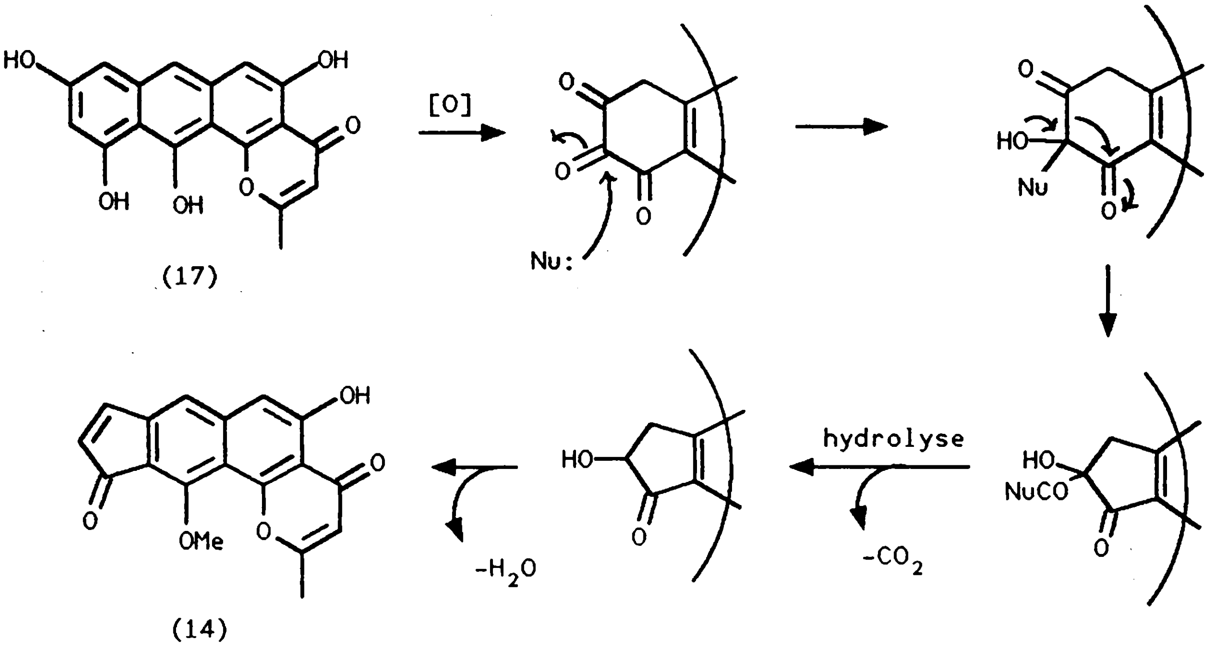
Ligustrone B (15)



Ligustrone C (16)

the 5 membered ring. Ligustrone B (15) is the main metabolite produced by *C. ligustrina* along with the minor metabolites, ligustrone A (14), the 8,9- dehydro derivative and ligustrone C (16), the 8-hydroxy compound.

It is possible that the pentanone ring occurs by ring contraction of a preformed aromatic ring. This would make anthracene (17) a likely precursor if we invoke a similar oxidative ring contraction as that proposed for terrein along the lines of Scheme 2. The oxygen substitution pattern of a molecule like (17)



Scheme 2

strongly suggests a polyketide origin. Anthracene (17) could be biosynthesized by the folding of a nona-acetate chain in one of two ways (Figure 4).

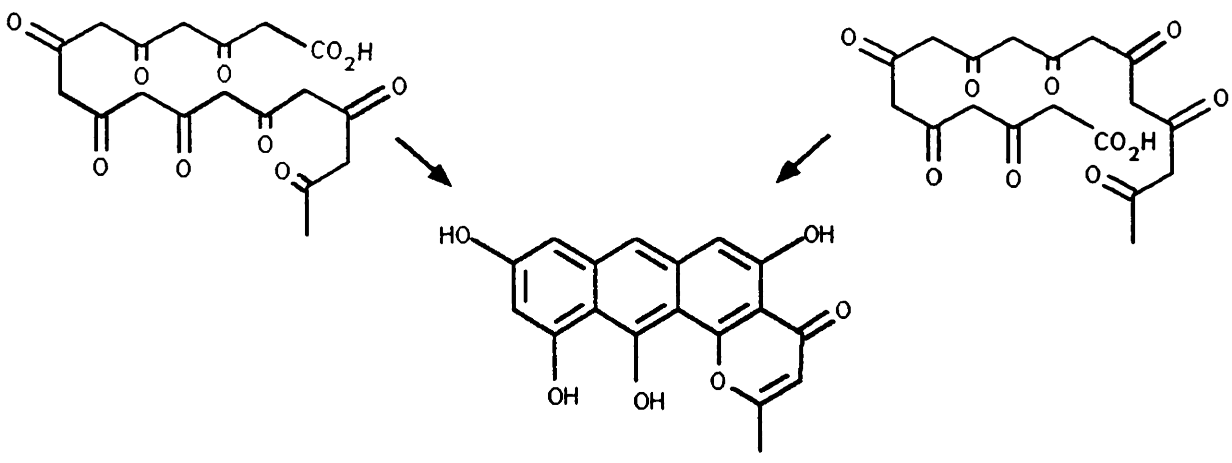
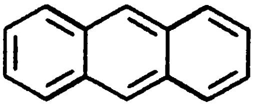


Figure 4

The object of this project was to investigate the possible acetate origin of the ligustrones and to synthesize labelled precursors with a view to proving if the 5-membered ring occurred *via* contraction of a preformed aromatic ring.

1.2 Synthetic approaches to anthracenes, anthrones and anthraquinones

Anthrones and anthraquinones are derivatives of the tricyclic benzenoid hydrocarbon, anthracene (18). Anthracene is composed of three linearly fused benzene rings and contains 14 π electrons.



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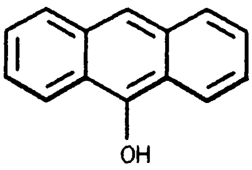

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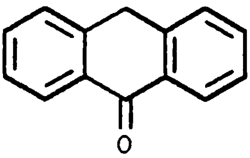

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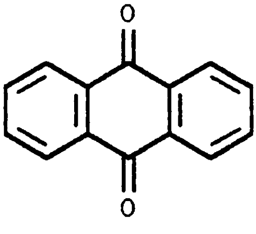
9-Hydroxyanthracene (19) exhibits keto-enol tautomerism, favouring the keto form, anthrone (20)[20] which posseses two complete aromatic rings and a conjugated carbonyl group (*c.f.* phenol reacts entirely in the enol form and no derivatives of the keto form can be prepared).



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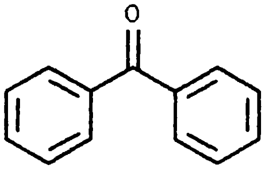
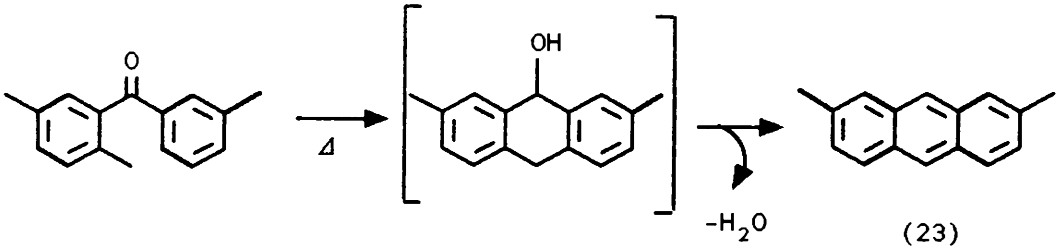


(22)

9,10-Anthraquinone (21) is very stable and shows no true quinonoid character, rather it behaves like an unreactive ketone such as benzophenone (22).

Anthracene was first isolated from coal tar distillate in 1832 by Dumas and Laurent[21].

Synthetic approaches to substituted anthracenes involve the fusing of two correctly functionalized aromatics to give an anthracene directly or constructing the related anthraquinone and reducing this to the required anthracene. The Elbs reaction[22] is important for making various methylanthracenes and involves the thermal cyclisation of aryl-2-toluyl ketones. Scheme 3 illustrates the synthesis of 2,7-dimethylanthracene (23)[23].

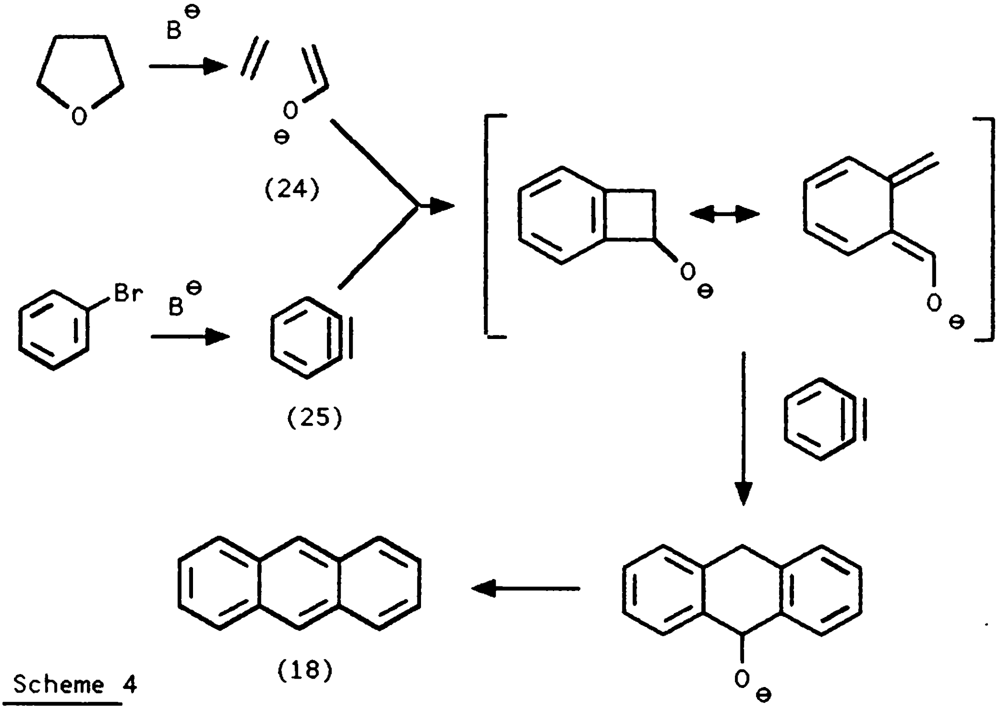


(23)

Scheme 3

An elegantly simple synthesis of anthracenes[24] takes advantage of the strong base initiated retro-cyclisation of tetrahydrofuran to afford ethylene and the enolate anion of acetaldehyde(24).

Reaction of benzyne (25) with (24) in a one pot procedure, yields anthracene (18) as outlined in Scheme 4.

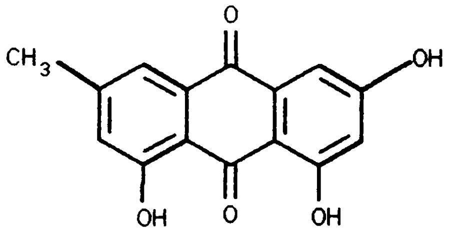


Scheme 4

This strategy can be used to synthesize substituted anthracenes, but the limiting factor is the availability of the substituted benzynes.

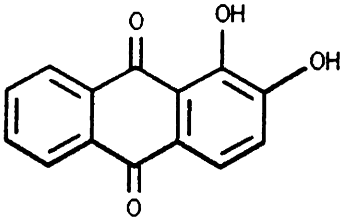
Anthraquinones form an abundant class of natural pigments and dyes which can be isolated from micro-organisms, the bark and roots of trees, the seeds of flowering plants and to a lesser extent in lichens and fungi. Emodin

(26) and its derivatives form a large family of naturally occurring anthraquinones.



(26)

Anthraquinones have shown some biological[25] activity and have a wide use as dyes. Alizarin (27) is the principal colouring matter in the roots of the madder plant, *Rubbia tinctorum*, and carminic acid (28) is responsible for the colour of cochineal. Both anthraquinones were important natural pigments from ancient times.



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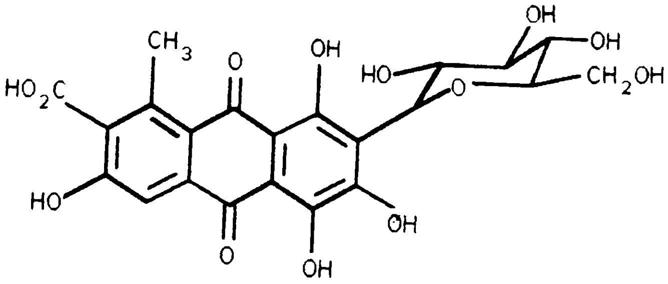
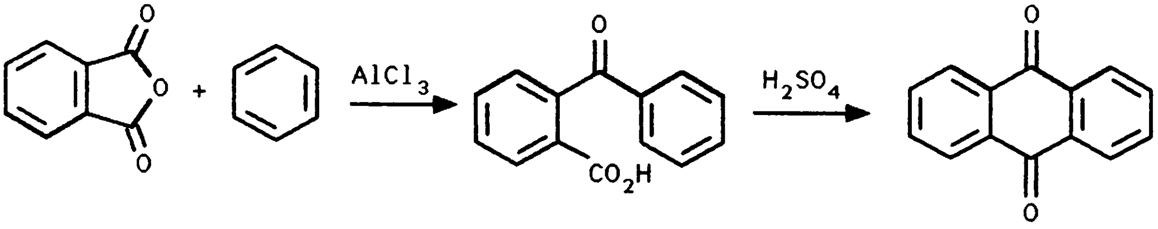


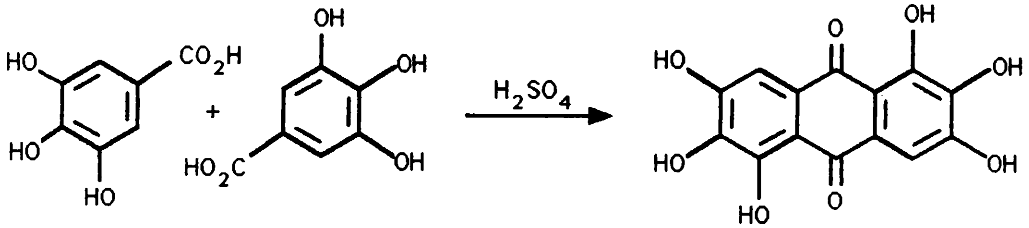
(28)

Synthetic approaches to anthraquinones have utilized a tandem Friedel-Crafts acylation to produce the two carbonyls of the anthraquinone. W.H. Perkins Jr.[26] acylated benzene with phthalic anhydride (29) and cyclized the benzoylbenzoic acid (30) with concentrated sulphuric acid to anthraquinone (21).



(29) (30) (21)

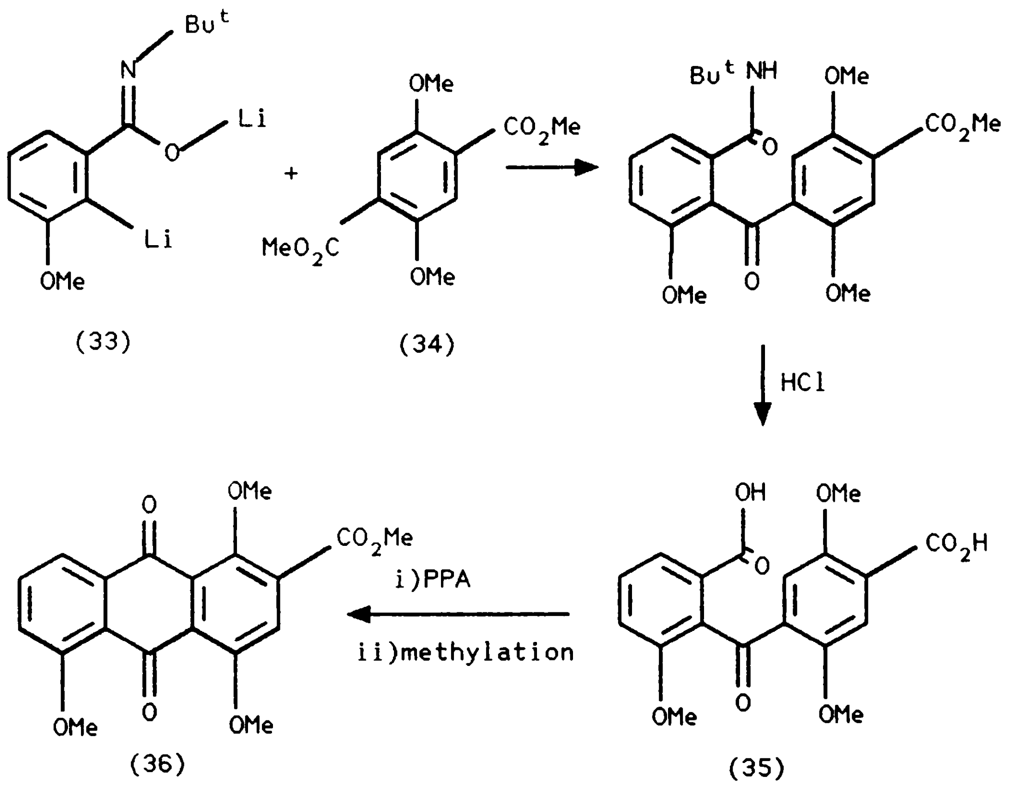
More reactive hydroxybenzoic acids may be condensed directly when heated in concentrated sulphuric acid as illustrated by the self condensation of gallic acid (31) to produce rufigallol (32).



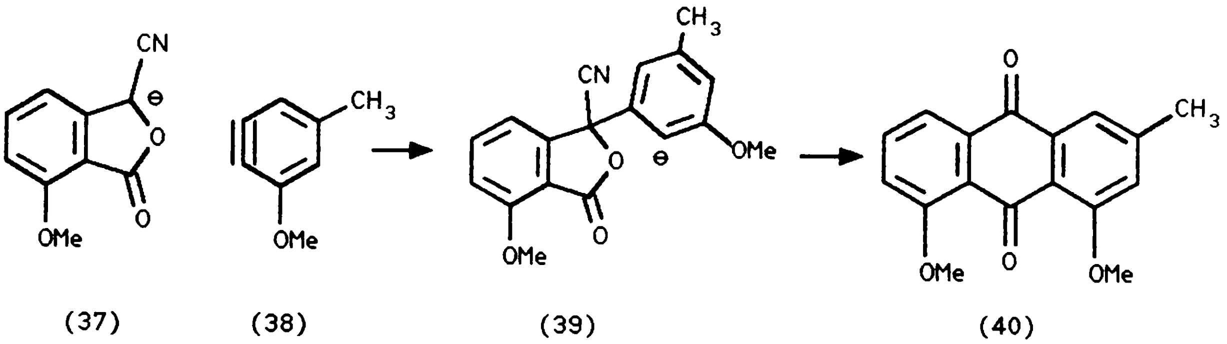
(31) (31) (32)

With less reactive benzoylbenzoic acids it may be advantageous to reduce the carbonyl to the corresponding benzylbenzoic acid, which is easier to cyclise to the anthrone. Oxidation yields the required anthraquinone[27].

Aromatic anions have also been used to produce benzoylbenzoic acids not available by other routes. Acylation of the lithiated amide (33)[28] with the symmetrical diester (34) gave the benzoylbenzoic acid (35) after hydrolysis. Polyphosphoric acid (PPA) catalysed cyclisation followed by esterification gave the anthraquinone ester (36).

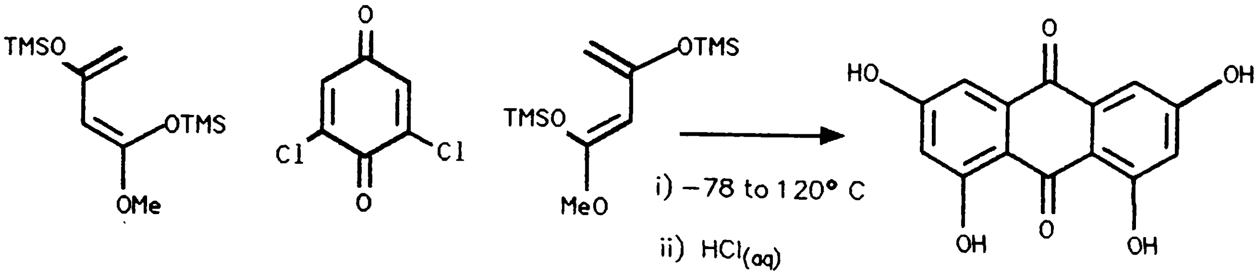


Reddy *et al.*[29] produced the substituted anthraquinone (40) by addition



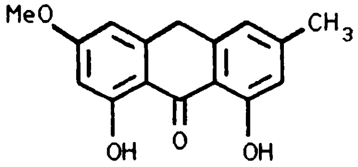
of the phthalide anion (37) onto the benzyne (38). Cyclisation of the aromatic anion (39) by attack back onto the ester of the phthalide furnished the methylanthraquinone (40).

2,6-Dichlorobenzoquinone (42) has also been elaborated to the tetrahydroxyanthraquinone (43) by a tandem Diels-Alder reaction with (41).



(41) (42) (41) (43)

Naturally occurring anthrones, though not as abundant as anthraquinones, have been found in some plants and animals. Barbaloin (44) is the main constituent of Aloes[31]. Physcion anthrones A and B, (45a) and (45b) have been isolated from *Aspergillus glaucus*[32].



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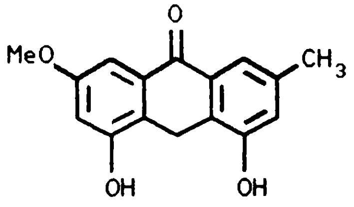

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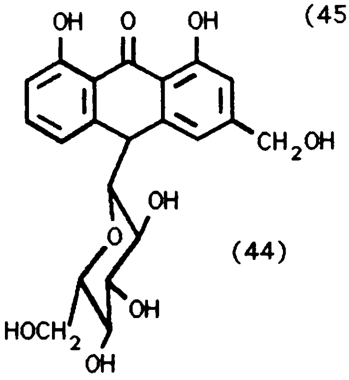

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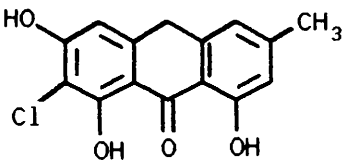
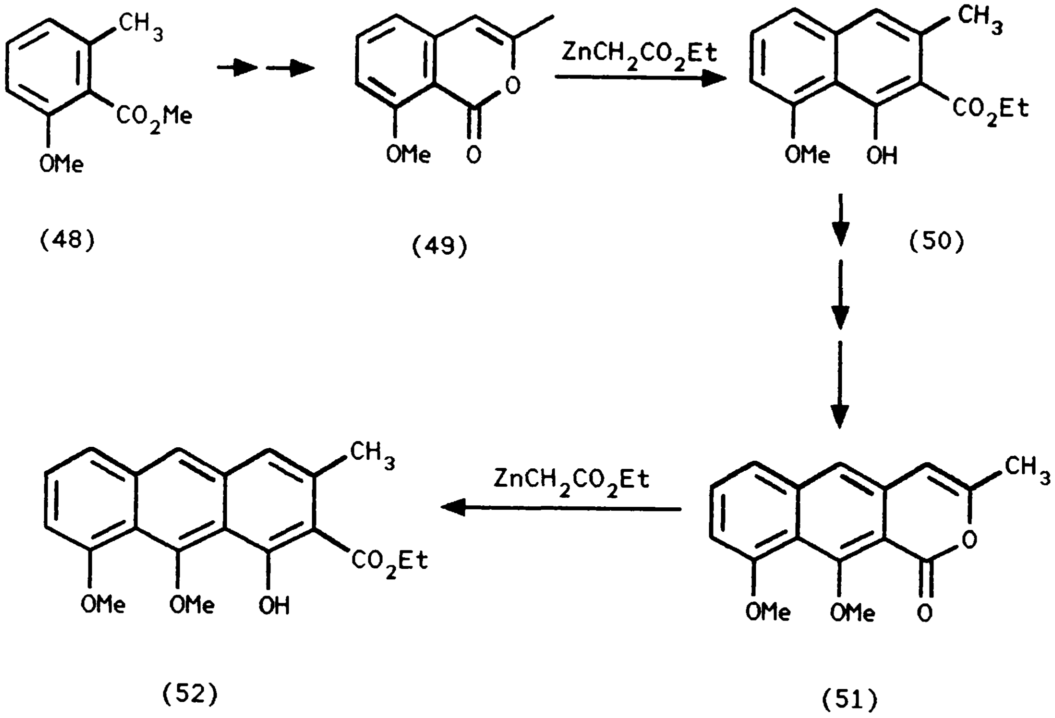


(46)

A halogenated derivative, 2-chloro-6-methyl-1,3,8-trihydroxy-9-anthrone (46) was extracted from *Aspergillus fumigatus*[33]. These anthrones are normally found in conjunction with their associated anthraquinones and bianthrones.

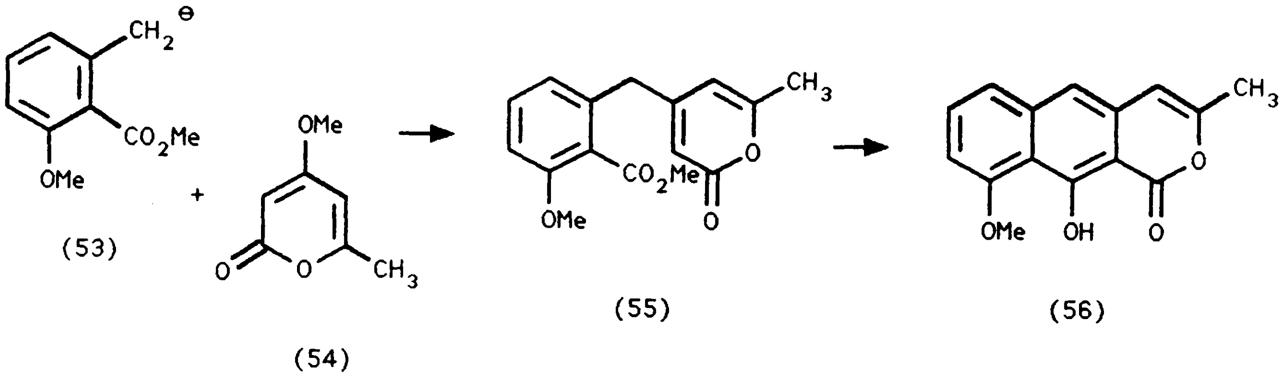
Synthetic approaches to anthrones have involved Friedel-Crafts acylation of aromatics with phthalic anhydride derivatives and the intermediate benzoylbenzoic acids reduced to the benzylbenzoic acid before cyclisation to the anthrone[27].

Hauser and Rhee[34] used a ring addition sequence to build up an anthrone nucleus (Scheme 5).



Scheme 5

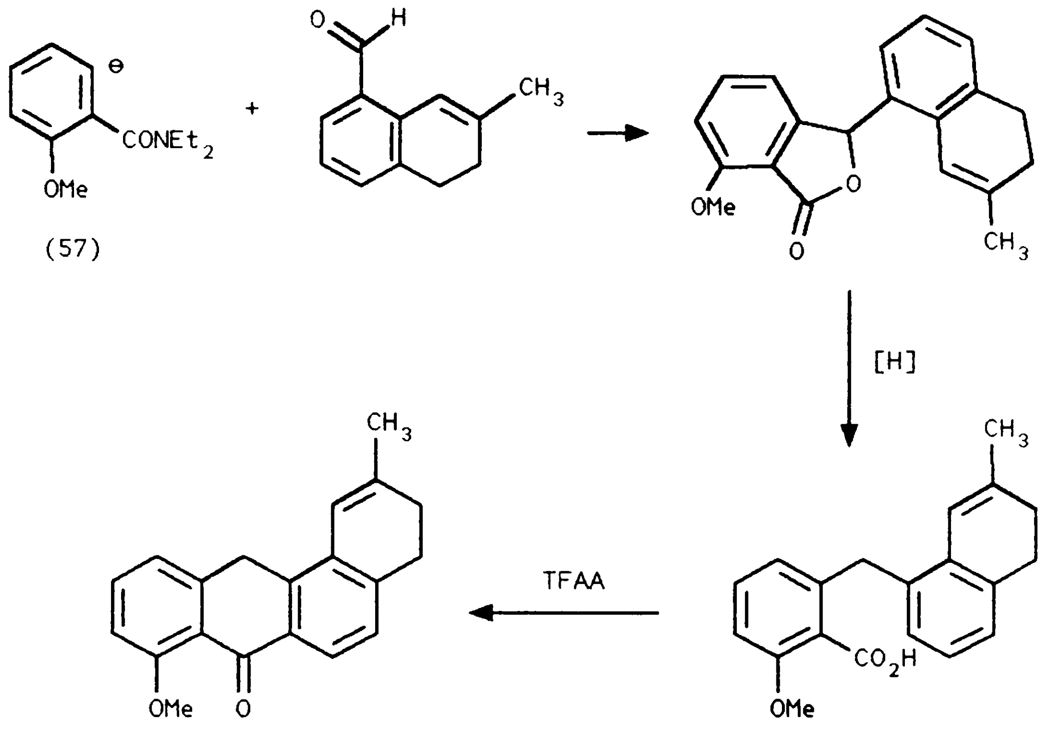
Reaction of the isocoumarin (49), produced from the toluate ester (48), with the Reformatsky reagent formed form zinc and ethyl bromoacetate provided the naphthoate (50). Modification to the naphthpyrone (51) and repetition of the Reformatsky conditions gave an anthrone as its methyl enol ether (52). An improved approach by Staunton *et al.*[35] for the formation of the pyrone (51) involves the reaction of the benzyl anion (53) with the unsaturated lactone (54)


(53) (54) (55) (56)

and base mediated cyclisation to the naphthpyrone (56). Methylation furnished intermediate (51) in fewer steps than in Scheme 5.

Aromatic anions[36,37] have proved useful in the synthesis of anthrones because they can introduce reactivity at sites not normally activated in electrophilic aromatic substitution.

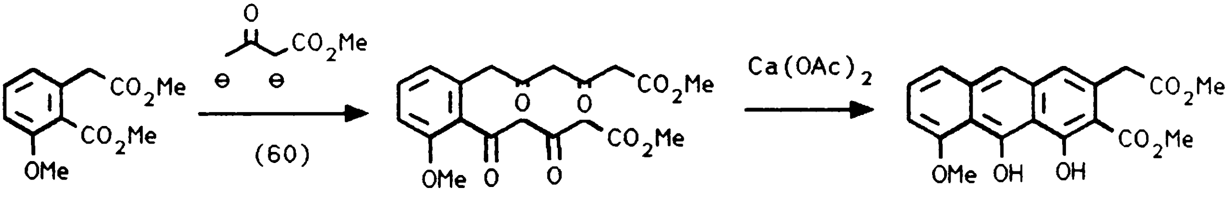
The synthesis of anthrone (58) from amide anion (57) exemplifies this approach.



(57)

(58)

Several groups[38,39] have adopted a more biomimetic approach utilizing the condensation of homophthalic ester (59) with the dilithiated derivative of methyl acetoacetate (60). The polyketide (61) was cyclised by reaction with calcium acetate to the enolized anthrone (62).



(59)

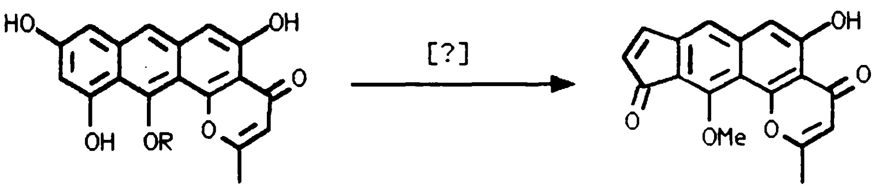
(61)

(62)

Chapter 2

Discussion and Results

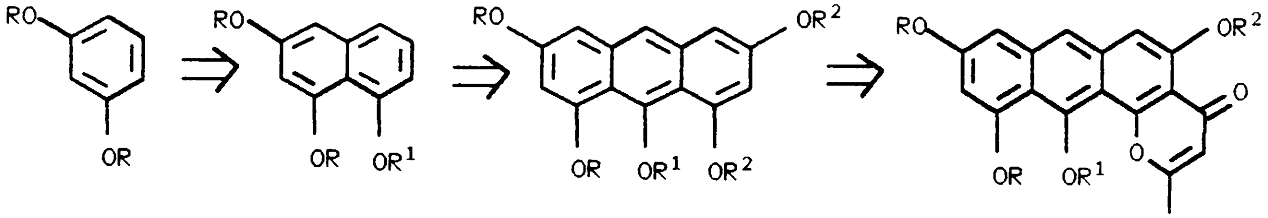
As outlined in the Introduction (Section 1.1), substituted anthracenes were required for the investigation into the biosynthesis of the ligustrones.



(17a) R = H
(17b) R = Me

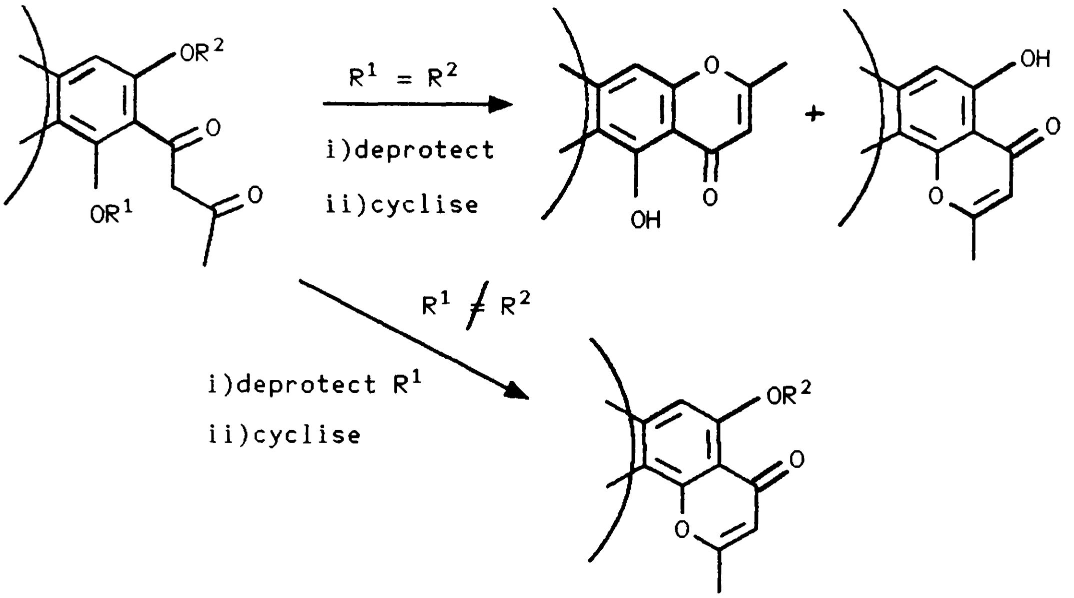
(14)

Suitably labelled tetracyclic precursors such as (17) could be fed to *C. ligustrina* and hopefully incorporated to yield labelled ligustrones. It is uncertain at this point whether the oxygen at C-12 of the proposed anthracene precursors should be as the methyl ether (17b) or as the free phenol (17a). In the proposed ring contraction the oxygen at C-12 of (17) becomes the C-11 oxygen in the skeleton of ligustrone A (14). The C-11 oxygen exists as the methyl ether in all three ligustrones. It was therefore decided to synthesize the proposed anthracene precursor both as the C-12 phenol (17a) and the C-12 methyl ether (17b) which would then permit an investigation into the timing of the methylation and ring contraction. It was proposed to synthesize these tetracycles by making a correctly substituted anthracene nucleus and then constructing the pyrone ring. This order of events was chosen because of the sensitivity of pyrones to acid and base[40]. The incorporation of the pyrone ring should be the final event to exclude it from further reaction or degradation.



Scheme 6

Substituted anthracenes are available by the stepwise addition of rings onto an aromatic starting unit (Scheme 6). This ring addition approach allows the construction of highly functionalized polyaromatics and differentiation of the oxygen substituents on the anthracene nucleus. This differentiation is advantageous in that it allows specific reaction at a chosen oxygen. *i.e.* for the site of methylation or in determining the position of cyclisation of a β-diketone to give a pyrone ring (Scheme 7).



Scheme 7

With this rather simplified reaction scheme in mind work commenced on the anthracene nucleus.

For the purpose of this discussion the four rings of the required tetracycle will be referred to as that shown in Figure 5.

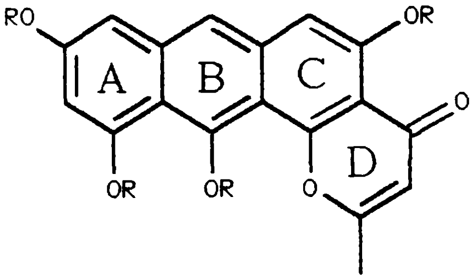
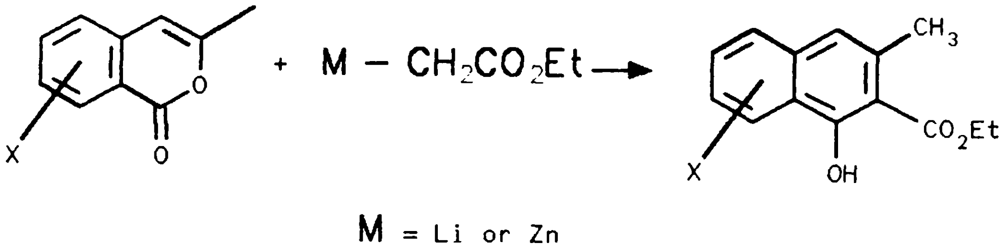


Figure 5

2.1 Approaches to the synthesis of the A-B naphthalene unit

There are many reported syntheses of substituted naphthalenes, anthracenes and tetracenes from an aromatic starting block with the correct reactivity for ring addition reactions (see Introduction, Section 1.2).

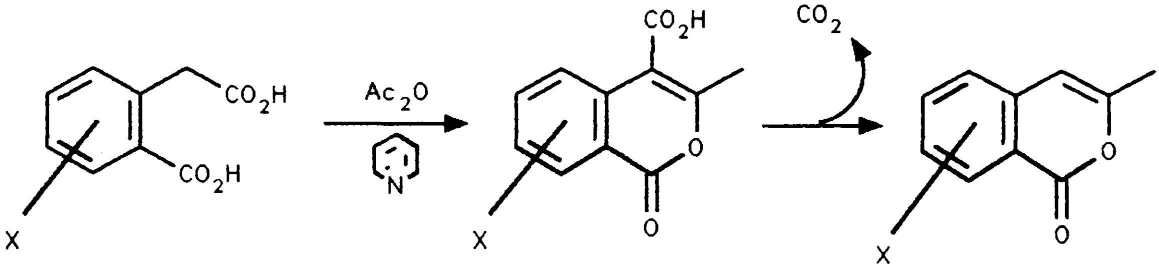
Hauser *et al.* reported that the correctly substituted aromatics could be made by building on successive rings by reaction of ethyl lithioacetate[41] or the Reformatsky reagent[42] derived from zinc and ethyl bromoacetate with a substituted 3-methylisocoumarin (Scheme 8).



Scheme 8

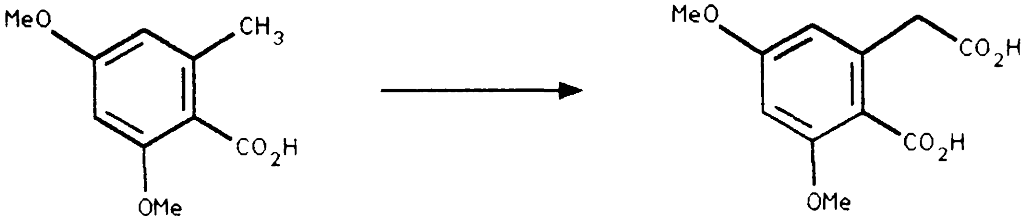
This reaction was chosen because of the familiarity with the synthesis of oxygenated isocoumarins by co-workers in our laboratory. Ethyl lithioacetate was used because of its better reported yields over the Reformatsky reagent.

Using this methodology not only could the correct oxygen substitution be obtained but the new ring also contains a 1,2-arrangement of a methyl and a carboxyethyl substituent which can be used as a handle to build on further rings. 3-Methylisocoumarins of the type required in the Hauser ring-formation reaction can be constructed by treatment of homophthalic acid derivatives with acetic anhydride in the presence of pyridine (Scheme 9). The intermediate 4-carboxy-3-methylisocoumarins can be decarboxylated to the isocoumarin under acidic conditions.



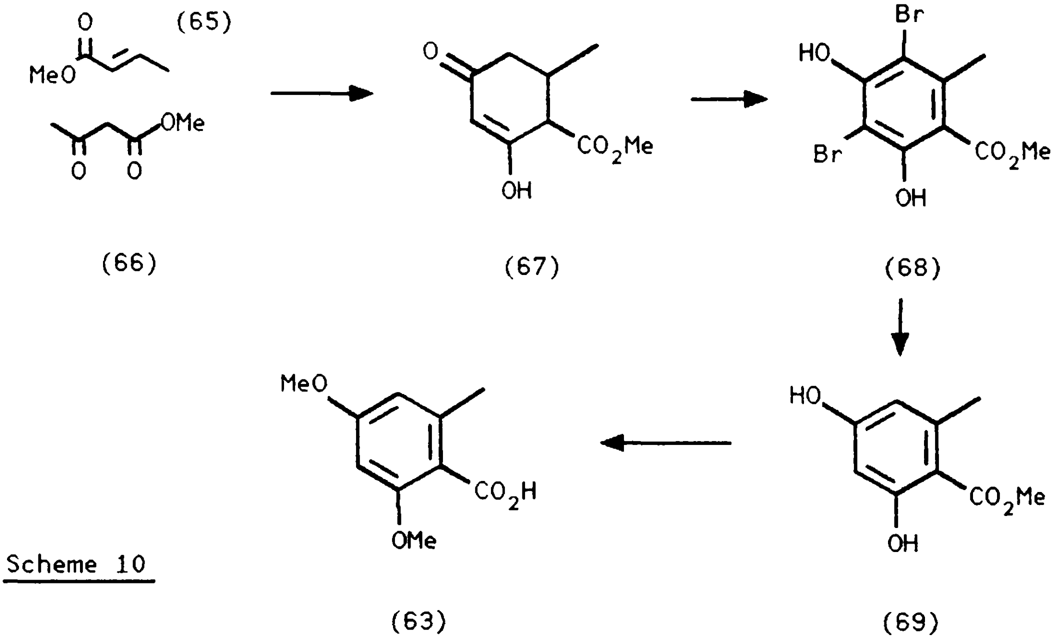
Scheme 9

Carboxylation of the aromatic methyl of 2,4-dimethoxy-6-methylbenzoic acid (63)[43] yields the correctly substituted homophthalic acid (64).



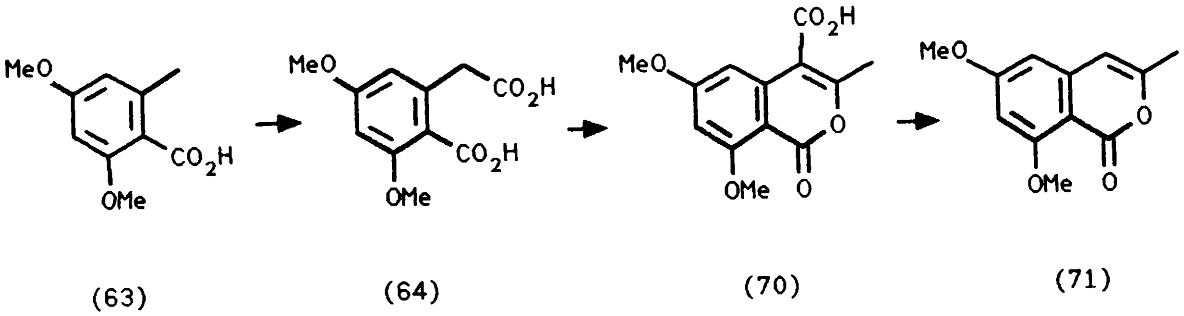
(63) (64)

The substituted benzoic acid (63) is available by the route of Sargent and Vogel[44] shown in Scheme 10. Condensation of methyl acetoacetate (66) with methyl crotonate (65) in the presence of sodium methoxide gave ester (67) which was aromatized by a bromination/reduction sequence to give methyl 2,4-dihydroxy-6-methylbenzoate (69). Protection of the free phenols as their methyl ethers and hydrolysis of the methyl ester furnished the required benzoic acid (63). Carboxylation of the aromatic methyl of (63) by reaction with excess lithium diisopropylamide and dimethyl carbonate gave 3,5-dimethoxyhomophthalic acid(64).

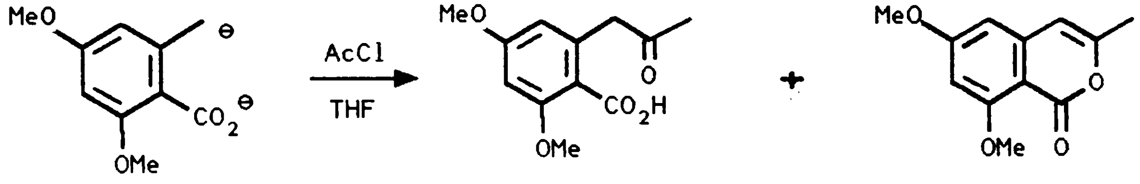


Scheme 10

Conversion of the homophthalic acid (64) to the isocoumarin (71) gave some problems, but improved yields were obtained by a two stage process, isolating the 4-carboxyisocoumarin (70), followed by subsequent decarboxylation with 80% sulphuric acid to give the isocoumarin (71).



In an attempt to shorten this synthesis, Staunton *et al.*[45] investigated the condensation of the dianion (72), of 2,4-dimethoxy-6-methylbenzoic acid with various acetylating agents. The inverse addition of (72) to a dilute solution of acetyl chloride in tetrahydrofuran reportedly produced the best results.



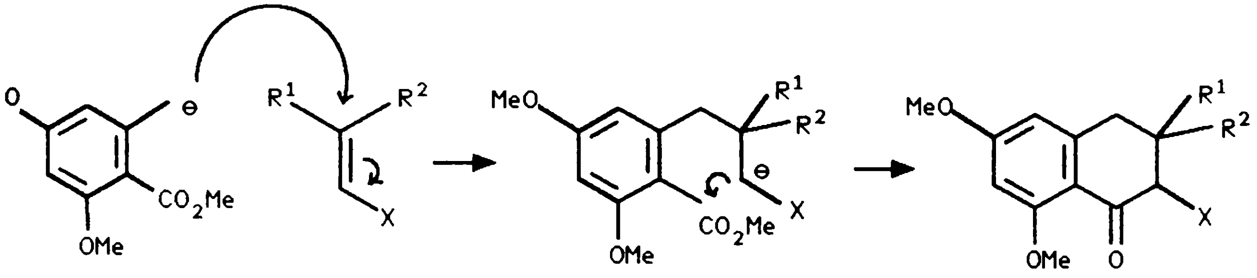
(72) (73) (71)

On repetition of this work only a low yield of the isocoumarin (71) and the uncyclised keto-acid (73) could be obtained.

Reaction of 6,8-dimethoxy-3-methylisocoumarin (71) with ethyl lithioacetate as reported by Hauser and Pogany (Scheme 8) proved troublesome. Only unreacted isocoumarin could be isolated under a variety of conditions. Increasing the ratio of ethyl lithioacetate or altering the temperature of the addition failed to furnish any product. Repetition with the Reformatsky reagent formed from zinc and ethyl bromoacetate also proved fruitless. This scheme was then shelved due to the problems with the key ring forming reaction and the laborious synthesis of the starting isocoumarin.

In a more direct approach it was decided to use anion (74). Reaction of

(74) with Michael type electrophiles is well documented[46–48] and it is possible for the anion (75) produced by the 1,4-addition, to cyclise back onto the ester of the original benzoate anion (Scheme 11).



(74) (75) (76)

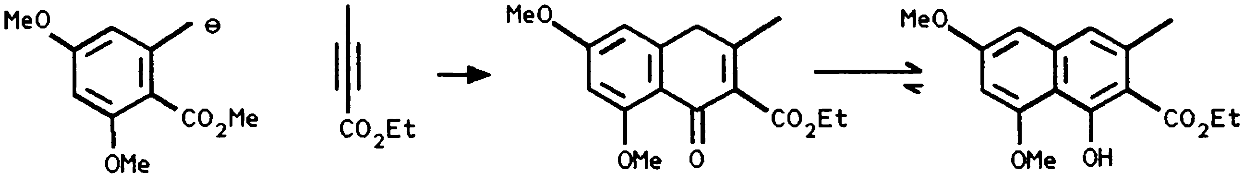
X = electron withdrawing group

Scheme 11

It will be noted that addition onto the electron deficient double bond and cyclisation only yields a dihydronaphthalene (76). To achieve the naphthalene nucleus some form of aromatisation reaction would have to follow the cyclisation, or the Michael acceptor would have to be in the oxidation state of an acetylene or its equivalent.

Ethyl but-2-ynonate (77) could fulfil the role of the Michael acceptor, as the expected product (47) would have the correct substitution and contain a 1,2-arrangement of a methyl and carboxyethyl for further anion mediated reactions.

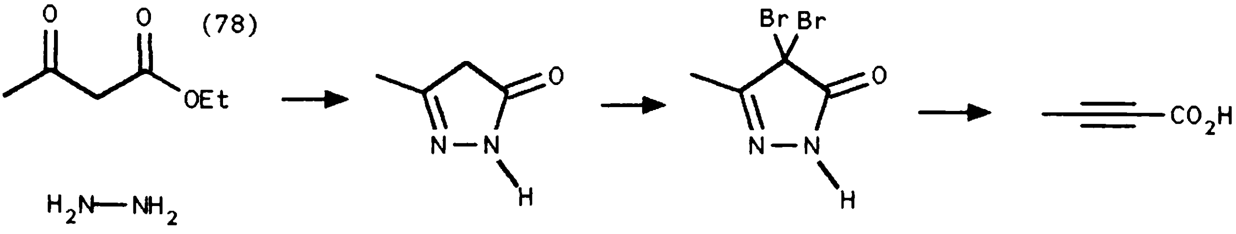
Synthesis of ethyl but-2-ynonate (77) was then undertaken to investigate the possibility of this type of Michael-Claisen reaction (Scheme 12).



(74) (77) (47)

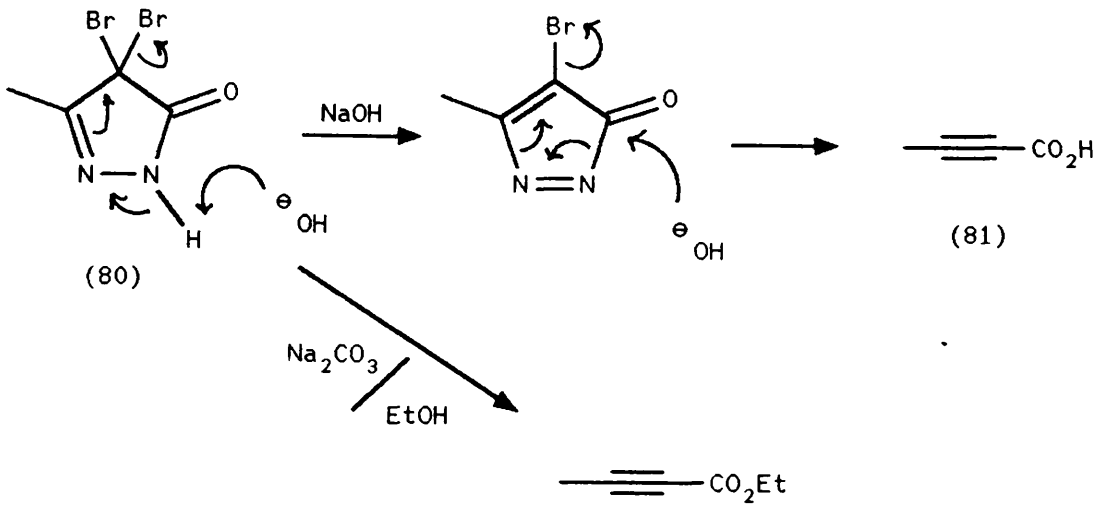
Scheme 12

But-2-ynoic acid (81) was produced by the route of Caprino[49]. Reaction of ethyl acetoacetate (78) with hydrazine hydrate gave 3-methyl-2-pyrazolin-5-one (79).



(78) (79) (80) (81)

Bromination in glacial acetic acid yielded the dibromide (80) which upon treatment with sodium hydroxide gave but-2-ynoic acid (81). The reaction probably proceeds by base catalysed elimination of bromide and nitrogen (Scheme 13).



(77)

Scheme 13

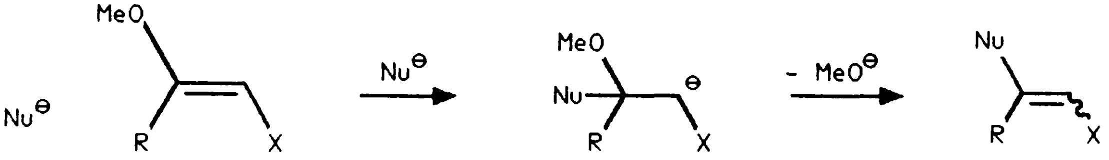
Attempted esterification of (81) with ethanol and concentrated sulphuric acid, dicyclohexylcarbodiimide in ethanol or potassium carbonate and dimethyl sulphate in acetone all gave little or no acetylenic ester. By treating the dibromide (80) with ethanol and sodium carbonate a moderate yield of ethyl but-2-ynoate (77) was produced, presumably by a similar mechanism proposed for the elimination and hydrolysis with sodium hydroxide.

This overcame the difficulties in extracting the very water soluble acid (81) and its esterification.

Addition of acetylenic ester (77) to the benzyl anion (74) in tetrahydrofuran at -78°C yielded only unreacted methyl 2,4-dimethoxy-6-methylbenzoate.

No trace of the acetylenic ester or its degradation products could be detected.

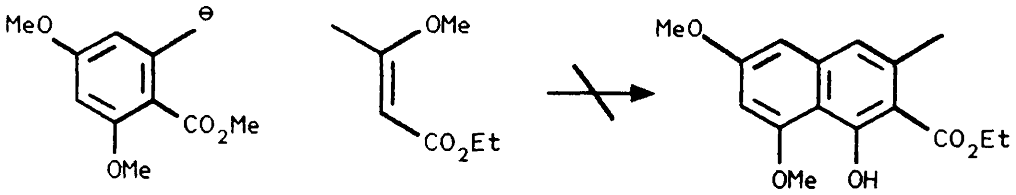
No precedent for the Michael addition of benzyl anions of the type (74) onto electron deficient acetylenes could be found in the literature but there are several examples of 1,4-addition onto α, β-unsaturated-β-alkoxyketones[47] or lactones[35]. These type of compounds are capable of acting as acetylenic precursors by their latent ability to eliminate alkoxide and generate another double bond after the initial Michael addition (Scheme 14).



X = electron withdrawing group

Scheme 14

The condensation reaction was repeated substituting ethyl 3-methoxybut-

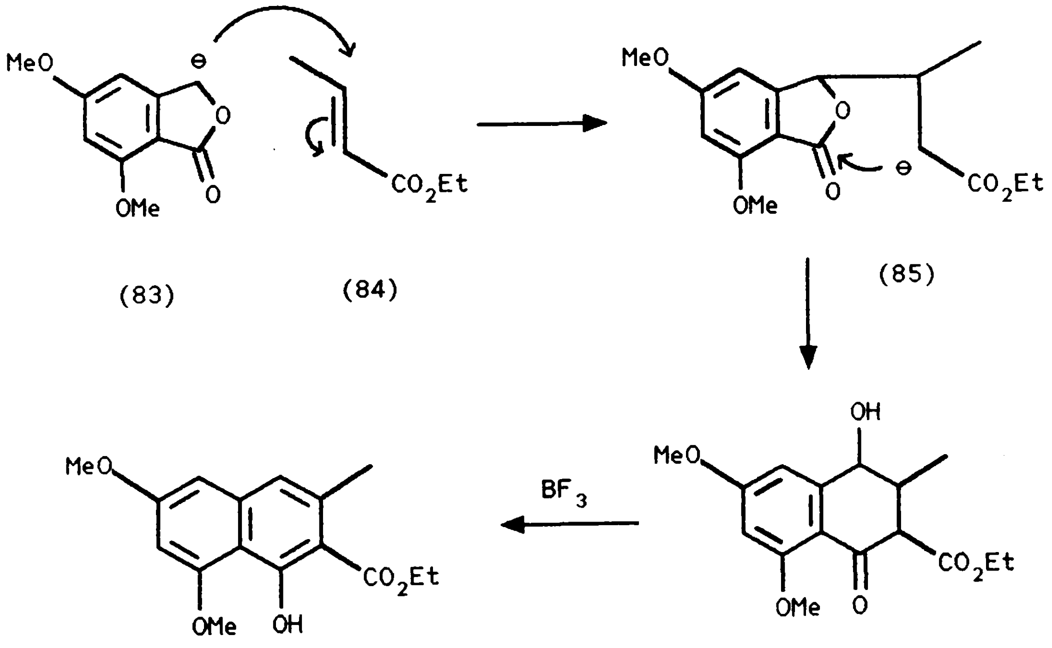


(74) (82)

2-enoate (82) for the acetylenic ester (77). Again only unreacted methyl 2,4-dimethoxy-6-methylbenzoate was recovered.

Weinreb *et al.*[47] found that the benzyl anion (74) reacted cleanly with both cyclic and acyclic α,β-unsaturated-β-methoxyketones to give naphthalene derivatives but they too observed no reaction with ethyl 3-methoxybut-2-enoate (82).

An alternative approach was to increase the oxidation state of the anion moiety and use a simple α,β-unsaturated ester as the Michael acceptor[50]. This was achieved by Franck *et al.*[51] using the anion of 5,7-dimethoxy-phthalide (83) and condensing it with ethyl but-2-enoate (84) as outlined in Scheme 15.



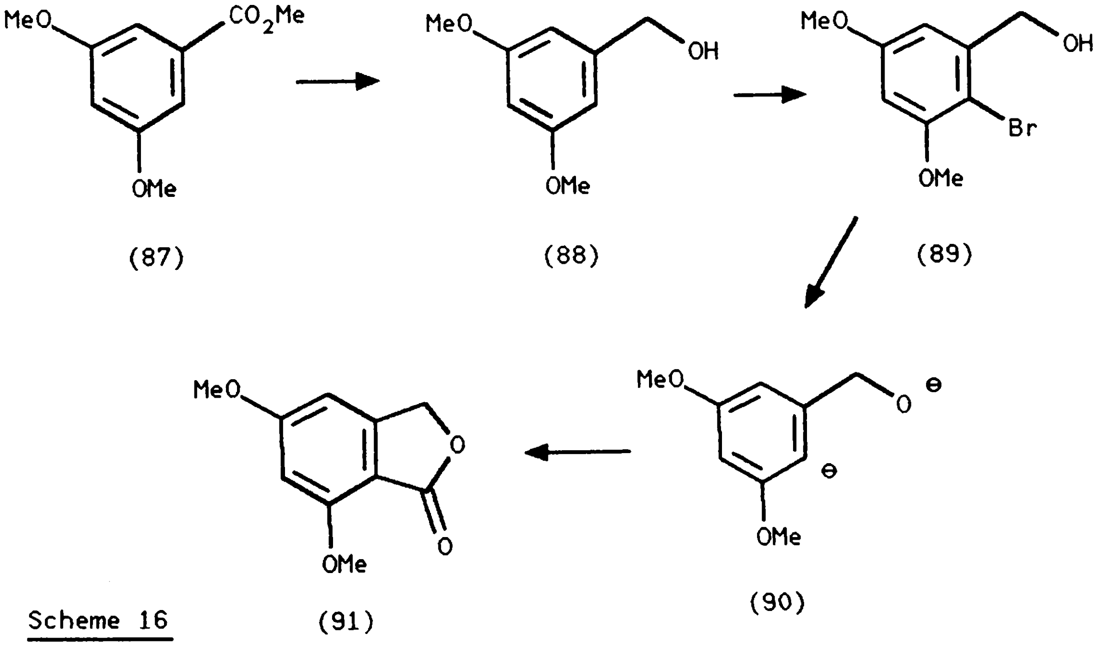
(83) (84) (85)

(47) (86)

Scheme 15

The ester enolate produced by the Michael addition cyclises back onto the phthalide, opening the lactone ring to give the hydroxytetralone (86). Boron trifluoride catalysed dehydration and enolisation leads to the naphthalene (47).

Methyl 3,5-dimethoxybenzoate (87) was the starting point for the synthesis of the phthalide[52] (Scheme 16). Reduction of the ester to the alcohol (88) and aromatic bromination gave the bromobenzyl alcohol (89).

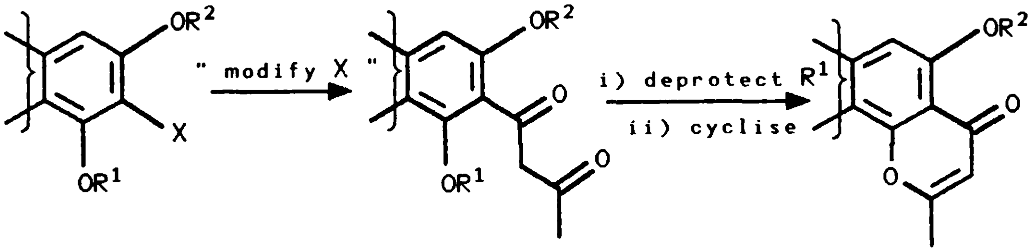


Scheme 16

Carboxylation of the dianion (90), produced by metal/halogen exchange by the action of butyl lithium on the bromo alcohol (89), gave the phthalide (91). Reaction of the phthalide anion (83); formed by deprotonation with lithium diisopropylamide, with ethyl but-2-enoate (84) (Scheme 14) gave complex inseparable mixtures. Variation in the reaction conditions still failed to yield any hydroxytetralone.

2.2 Approaches to the synthesis of ring C

Ring C, the final aromatic ring of the anthracene nucleus requires a 1,3-relationship of oxygen substituents and a carbon substituent between them that can be modified to a β-diketone system and hence cyclised to a pyrone ring. The oxygen substituents would ideally have different protecting groups to allow selectivity in the cyclisation of a β-diketone to give an angled pyrone as shown in Scheme 17.

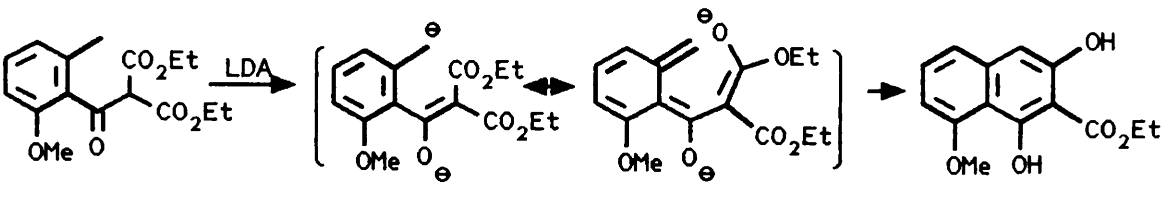


Scheme 17

If this proved difficult then a mixture of linear and angled pyrones could be tolerated provided separation was possible.

From the previous section it will have been noted that attempts to form ring B concentrated on achieving a 1,2-arrangement of methyl and carboxyethyl substituents. This is because it is possible to stabilize an anion on the aromatic methyl due to the influence of the *ortho*-ester grouping. This anion can be used as a handle to build on further rings.

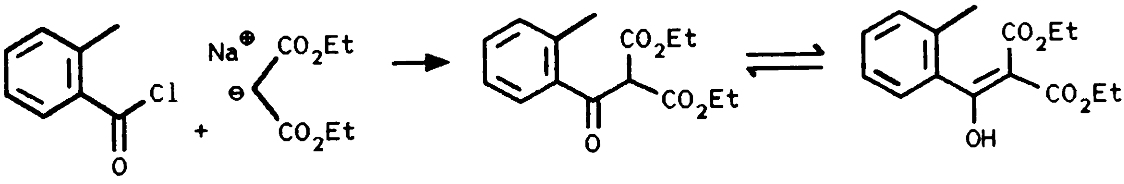
Staunton and Murphy[53] have taken this approach a step further and constructed a molecule in which the group *ortho* to the aromatic methyl not only helps stabilize the anion but also carries the electrophile for an internal cyclisation (see Scheme 18).



Scheme 18

As the keto-diester is both the anion stabilizing group and the electrophile, Staunton suggests the mechanism involves a low temperature (-78°) pericyclic ring closure of a polyene.

Model studies for this cyclisation began with the synthesis of the keto-diester (94) by addition of the sodium salt of diethyl malonate (92) to the acid chloride of *o*-toluic acid (93). The keto-diester existed approximately in the ratio



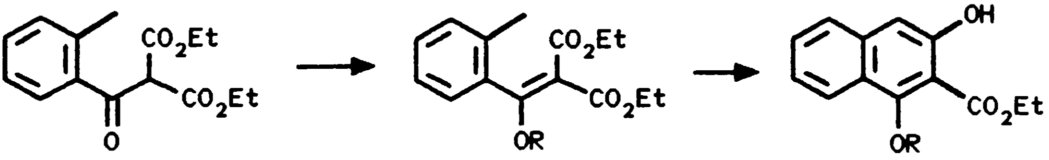
(93) (92) (94) (95)

2:1 enol (95) to ketone (94) form. The enol form (95) contained non-equivalent ethyl ester signals in its ^1H n.m.r. spectrum.

The methylene and methyl signals of one ester appeared at δ 3.91 and 0.85 ppm respectively and the other at δ 4.24 and 1.11 ppm, overlapping with the signals from the equivalent ethyl esters of the keto form (94). This upfield shift occurs because in the enol form the ethyl group of one of the esters lies in the shielding zone of the aromatic ring[53].

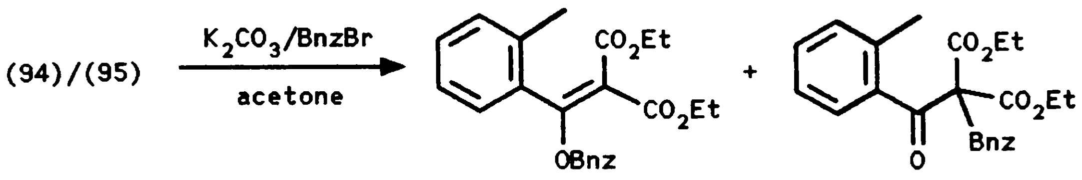
On repetition of Staunton's conditions, reaction of the keto-diester (94/95) with four equivalents of lithium di-isopropylamide at low temperature yielded only a small amount of unreacted starting material. Using a larger excess of base or addition at higher temperatures resulted in the failure to even recover starting material.

As decomposition seemed to occur rather than cyclisation it was decided to form the enol ether of the ketone. This would allow protection of the ketone, use less base as the acidic proton had been removed and differentiation of the oxygen substituents before ring C was even formed (see Scheme 19).



Scheme 19

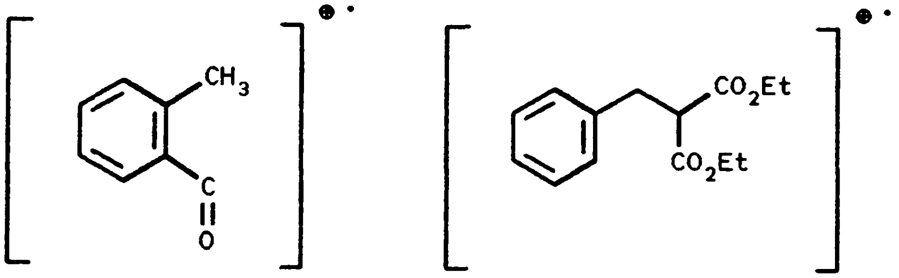
A benzyl group was chosen to protect the oxygen for ease of removal later. Treatment of the keto-diester (94/95) with benzyl bromide (BnzBr) and potassium carbonate in acetone gave two compounds in roughly equal amounts.



(96) (97)

These were separated by column chromatography and appeared to be the products of *O*- and *C*- alkylation, (96) and (97), of the enol. The compound presumed to be the benzyl enol ether diester (96) was a thick oil. Its ^{1}H n.m.r. contained a two proton singlet at δ 4.69 ppm, characteristic of the benzylic hydrogens of an *O*-bonded benzyl group. It also showed signals for the same type of non-equivalent ethyl esters observed in the enol tautomer of the starting keto-diester. The methylenes of the different ethyl esters resonated at δ 4.34 and 3.94 ppm and the methyls at δ 1.31 and 0.95 ppm. The highest absorption in the ultraviolet spectrum in ethanol was 250 nm ($\pi \rightarrow \pi^*$). Its mass spectrum showed C_7H_7 (91, 100%) as the base peak and a peak for fragment A (119, 59%) (Figure 6).

The *C*-alkylated diester was a white crystalline solid. Its ^{1}H n.m.r. showed equivalent ethyl esters and a two proton singlet at δ 3.66 ppm for the *C*-bonded benzylic protons. Its ultraviolet spectrum in ethanol had the highest absorption at 282 nm ($n \rightarrow \pi^*$ of a ketone). The mass spectrum showed the fragment A (119,100%) from α cleavage of the carbonyl as the base peak and also the fragment B (249, 50%) as the other part from the α cleavage. Both molecules show a molecular ion m/e 368.

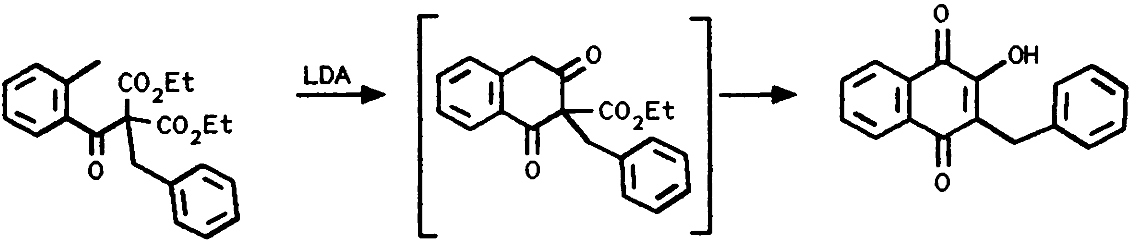


Fragment A m/e 119

Fragment B m/e 249

Figure 6

The compounds were then treated with three equivalents of lithium diisopropylamide at -78° in dry tetrahydrofuran. The benzyl enol ether (96) afforded no characterizable products from its reaction with base under a variety of conditions and little or no recovered starting material whereas the C-benzylated isomer (97) gave a low yield of the known 3-benzyl-2-hydroxynaphth-1,4-quinone (98)[54]. This probably resulted from hydrolysis, decarboxylation and oxidation of the cyclised product during work-up of the reaction mixture and purification on



(97)

(98)

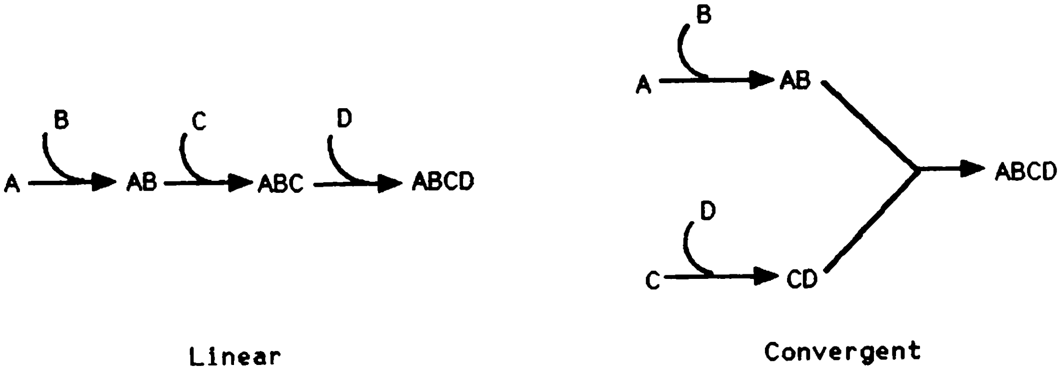
silica.

As the idea of building up an anthracene skeleton by sequential addition of other rings onto an aromatic starting unit was proceeding very slowly, a new approach was sought.

A new convergent synthesis was envisaged where two already functionalized aromatic rings were brought together in such a way as to form the middle ring.

2.3 A convergent approach to the ABC ring system

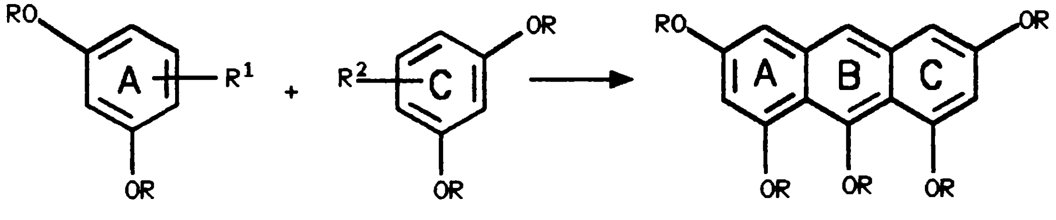
In a linear multistage synthesis a target molecule is constructed by adding functional groups sequentially. Consequently, each stage leads to a decrease in the overall yield and loss of increasingly important intermediates. This loss is reduced in a convergent synthesis in which two parts of the target molecule are formed initially and then combined at a latter stage of the synthesis. Scheme 20 illustrates a linear and a convergent approach to an imaginary target molecule, ABCD.



Scheme 20

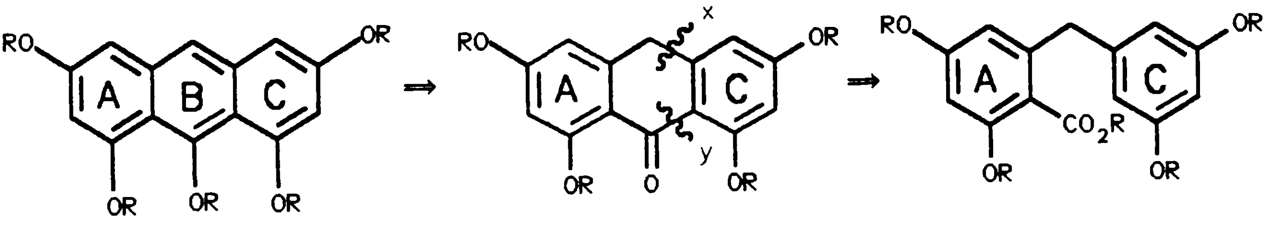
In the convergent approach, the target molecule is formed by combining two relatively easily prepared units, AB and CD, in the convergent step. In the linear approach, the target molecule is formed by reaction of an already complex and valuable intermediate, ABC.

Following these lines, a new convergent synthesis was envisaged for the required functionalized anthracene. Two correctly substituted aromatic rings, A and C, could be fused together in such a way as to form the middle ring B as depicted in scheme 21.



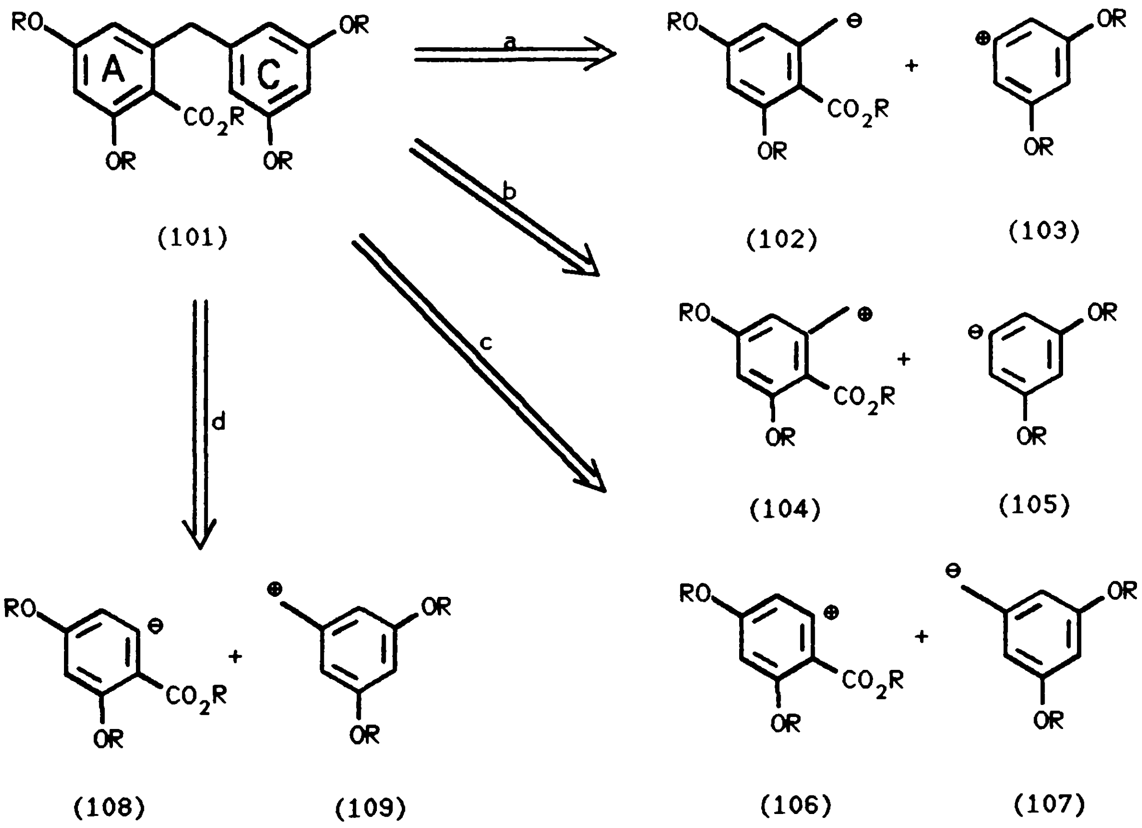
Scheme 21

Retrosynthetic analysis of the penta-alkoxyanthracene (99) would favour its production by *O*-alkylation of a tetra-alkoxyanthrone. The symmetrical anthrone (100) is probably best formed by a Friedel-Crafts type of ring closure



(99) (100) (101)

to form bond ‘y’. The symmetry of the right hand ring (c) and the combined activation of both oxygen substituents looks promising for the cyclisation reaction onto an activated carboxylic acid derivative. This then leaves the more difficult synthesis of the benzylbenzoate type molecule (101) by the formation of bond ‘x’. Some of the retrosynthetic pathways to (101) require unusual synthons (Scheme 22).



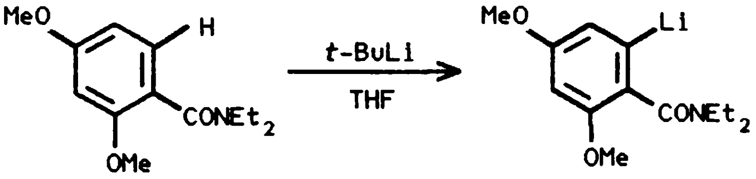
Scheme 22

Path ‘a’ uses the known benzylic anion (102) but would require some sort of diazonium or benzyne as the electrophile (103).

Path ‘b’ could use a benzyl halide for the ester electrophile (104) but the unlikely aromatic anion (105) would be a stumbling block.

Path 'c' has an unusual electrophile (106) and the benzyl anion (107) would require some sort of stabilisation.

Path 'd' has a promising electrophile (109), possibly in the form of a benzyl halide, but the aromatic anion (108) looks difficult to prepare. Aromatic anions of type (108) are available by deprotonation of *N,N*-dimethoxybenzamide (110) with *t*-butyl lithium at -78° in tetrahydrofuran[55] to give the lithiated amide (111).



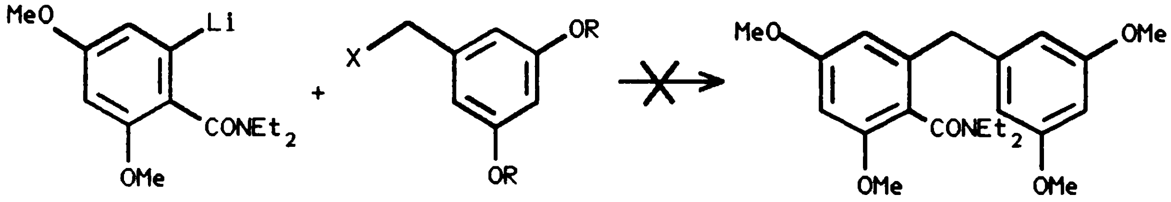
(110) (111)

The *N,N*-diethylamide is used to protect the carboxylic acid and to direct the site of deprotonation. The proton *ortho* to the tertiary amide is the most acidic because:-

- the inductive effect of the amide group.
- The Lewis basicity of the amide group makes it a good ligand for the cation and helps direct its basic counter anion towards the closest (*ortho*) proton.

These combined effects overpower the metallation directing effects of the methoxyl substituents in the molecule.

Reaction of the *N,N*-diethylamide (110) with 1:1 equivalents of *t*-butyl lithium in dry tetrahydrofuran at -78° and quenching the reaction mixture with deuterium oxide achieved a 70% incorporation of deuterium at C-6, *ortho* to the amide. Treatment of a tetrahydrofuran solution of the lithiated amide (111) at -78° with the benzyl electrophiles (112a-d) failed to produce any benzylbenzamide (113).

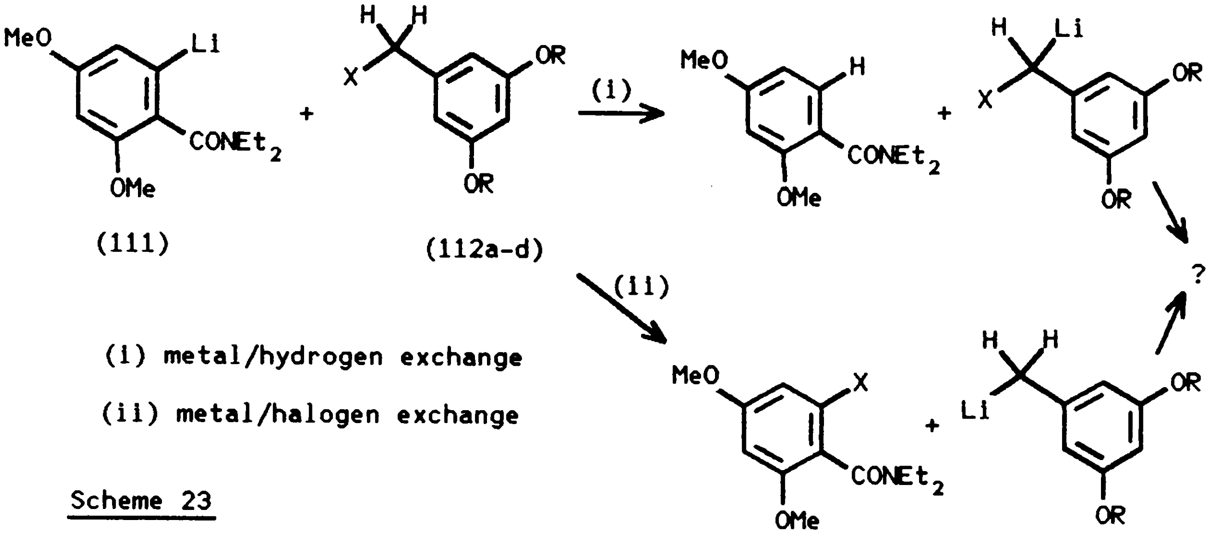


(111) (112a-d) (113)

a) X = Cl
b) X = Br
c) X = I
d) X = OMs

Only a low yield of starting amide (110) could be recovered by chromatography, and no clue to the fate of the benzylic reactant (112a-d) could be found in the reaction mixture.

It was believed that metal/halogen or metal/hydrogen exchange had occurred between the very reactive anion (111) and the halide or benzylic hydrogens of the electrophile (112a-d), as depicted in Scheme 23.



(111)

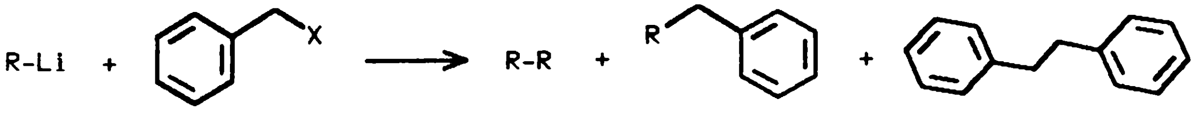
(112a-d)

(i) metal/hydrogen exchange

(ii) metal/halogen exchange

Scheme 23

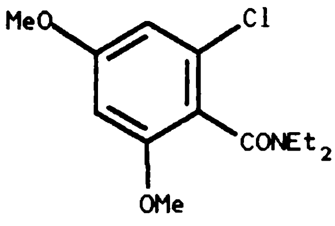
Coupling reactions were observed by Gilman[57] and Wittig[58] when simple alkyl lithiums were treated with benzyl chloride or bromide (Scheme 24).



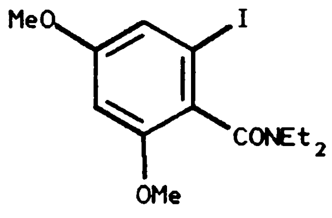
X = Cl or Br

Scheme 24

To investigate the possibility that metal/halogen exchange had occurred, the 6-chloro and 6-iododiethylbenzamides, (114) and (115), were synthesized.



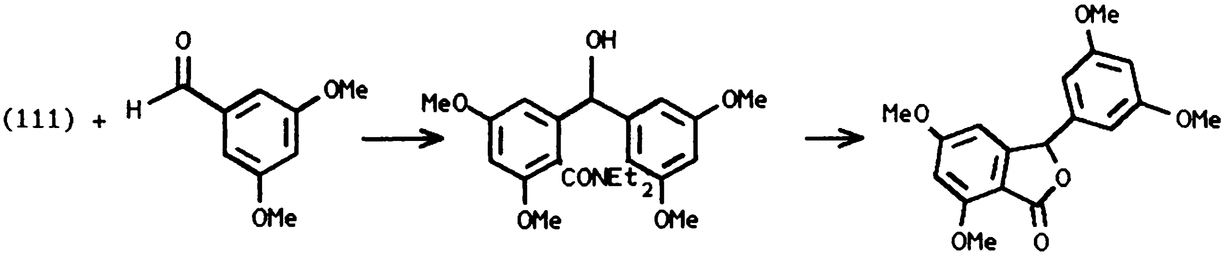
(114)



(115)

These were used for comparison of their thin layer chromatographs and ^{1}H n.m.r. spectra of the reaction mixtures from the attempted reaction of the lithiated amide (111) with the 3,5-dimethoxybenzyl chloride (112a) or iodide (112c). This search proved fruitless as no evidence for metal/halogen exchange could be found. Deuteriation studies to investigate the possibility that metal/hydrogen exchange had occurred were not attempted. Instead, work concentrated on finding an alternative electrophile that would react cleanly with the lithiated amide (111).

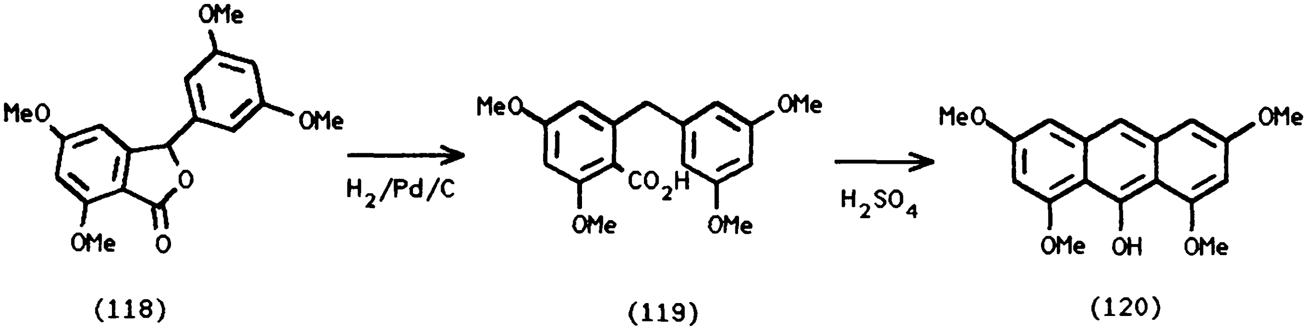
It was postulated that increasing the oxidation state of the electrophile to an aldehyde would eliminate the possibility of halogen or hydrogen



(116) (117) (118)

exchange. Reaction of 3,5-dimethoxybenzaldehyde (116) was assumed to proceed through the hydroxyamide (117), but this was not isolated as reaction was carried through to the phthalide (118). Using the aldehyde (116) as an electrophile had the added advantage that the hydroxyl of intermediate (117) helped displace the tertiary amide and the phthalide produced was easily isolated due to its insolubility in diethyl ether.

The benzylic *C-O* bond of the phthalide (118) now had to be reduced to give the tetramethoxybenzoic acid (119). Zinc in acetic acid [59] or zinc in sodium hydroxide[60] left the phthalide unaffected, but hydrogenation over palladium on charcoal gave the benzylbenzoic acid (119).

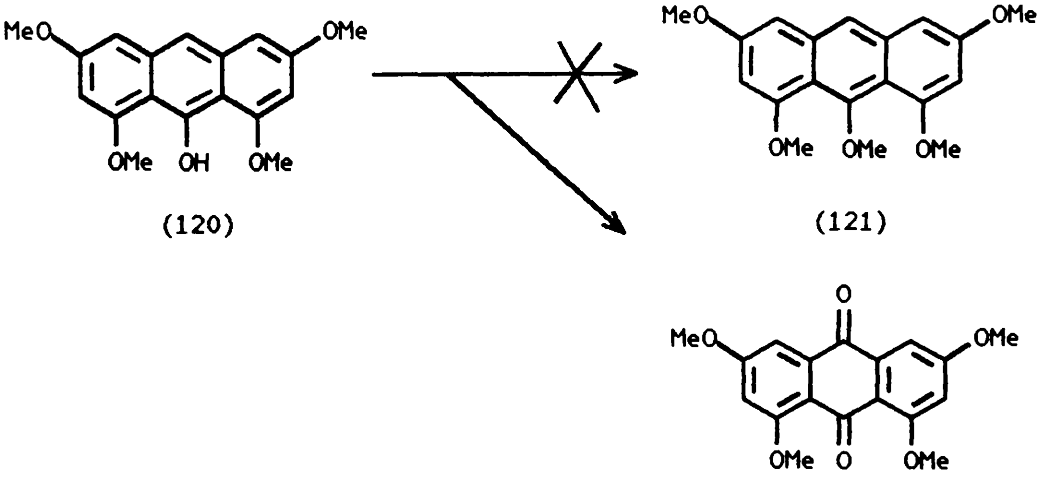


Ring closure of the benzylbenzoic acid (119) in 90% sulphuric acid furnished 1,3,6,8-tetramethoxy-9-anthranol (120) in moderate yield. The central ring is enolized due to hydrogen bonding to the 1- and 8-methoxyl groups and no trace of the anthrone isomer could be detected by ^{1}H n.m.r. spectroscopy in deuterochloroform. The yield in the ring closure step was greatly improved by using trifluoroacetic anhydride in dichloromethane.

As discussed previously, ring B of the anthracene precursor (17) would become ring B of the ligustrone skeleton if the ring contraction occurred.

The oxygen substituent of this ring in all the ligustrones occurs as the methyl ether, therefore it was proposed to methylate the corresponding hydroxyl of the model anthranol (120). This would produce an anthracene nucleus with five correctly positioned oxygen substituents with the required methyl ether at C-9 as in the target tetracyclic precursor (17b).

Attempted methylation using dimethyl sulphate and potassium carbonate in refluxing acetone failed to give the expected 1,3,6,8,9-pentamethoxyanthracene (121). Instead, 1,3,6,8-tetramethoxy-9,10-anthraquinone (122) was isolated.

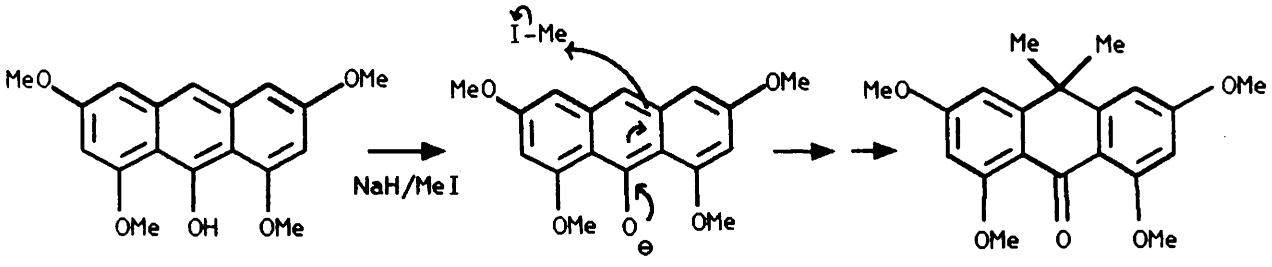


(120)

(121)

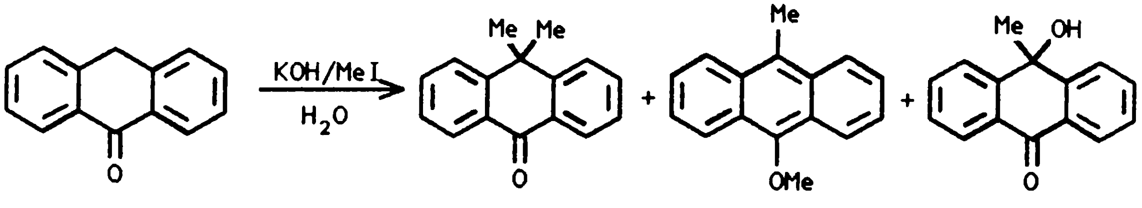
(122)

Repetition of the methylation procedure under a nitrogen blanket yielded only unreacted anthranol (120) and a little anthraquinone presumably due to oxidation during work up. The anthranol (120) was very susceptible to oxidation in a basic medium and this has been exploited preparatively in the synthesis of anthraquinones from the corresponding anthranol[39,60]. Employing harsher conditions by attempting to methylate the anthranol (120) with an excess of iodomethane and sodium hydride in tetrahydrofuran yielded 10,10-dimethyl-1,3,6,8-tetramethoxy-9-anthrone (123) which was produced by *C*-methylation of the centre ring of the anthracene oxide (124) rather than reaction at oxygen. Heymann and Trowbridge[61] found that reaction of the unsubstituted anthrone (20) with potassium hydroxide and iodomethane in water gave a mixture of compounds.



(120)

(123)



(20)

(125)

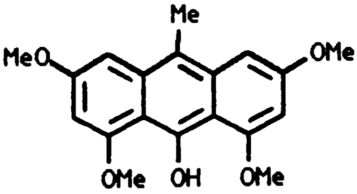
(126)

(127)

They isolated the 9,9 -dimethyl-10-anthrone (125) from double *C*-methylation, the mono *C*-methyl and *O*-methyl ether (126) from *C*- and *O*-methylation and 9-hydroxy-9-methyl-10-anthrone (127) from *C*-methylation and oxidation at C-9.

Kornblum *et al.*[62,63] suggested the ratio of *O*- to *C*-methylation in phenoxides and naphthoxides is decided by the solvent polarity. Aprotic polar solvents encourage reaction at oxygen because they help solvate the cation, leaving a naked oxygen anion to attack the alkyl halide. In solvents of lower polarity, the cation and anion are in a "tight ion pair" allowing *C*-alkylation to predominate.

Substituting the more polar diglyme for tetrahydrofuran in the reaction of the anthranol (120) with sodium hydride and iodomethane still resulted in *C*-methylation. By using a molar equivalent of base and alkyl halide in diglyme it was possible to produce the mono *C*-methylated anthranol (128).

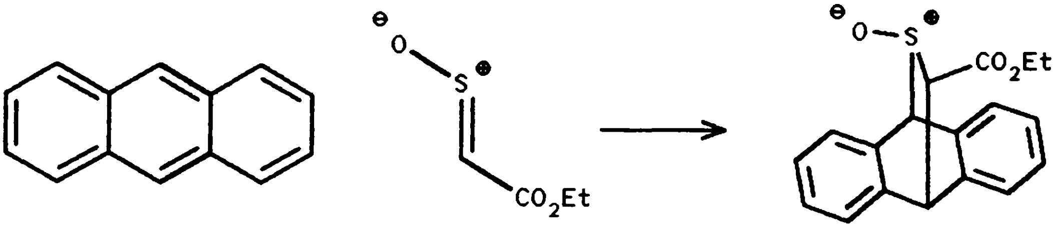


(128)

As *O*-alkylation did not seem able to compete with *C*-alkylation, it was decided to approach this problem from a different angle.

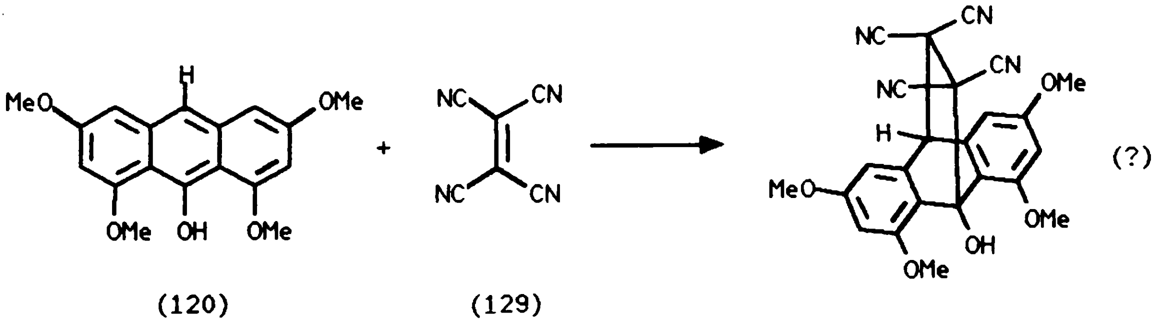
If it were somehow possible to reversibly disrupt the aromaticity in the central ring and separate the conjugation of the negative charge between the oxygen and the *C*-10 carbon. This would then allow the oxygen to be methylated without competition from *C*-10. Aromaticity could then be regenerated giving the overall result of *O*-methylation.

The Diels-Alder reaction seemed an ideal approach. Other people working in our laboratory have trapped sulphines as their anthracene adducts (Scheme 24)[64].



Scheme 24

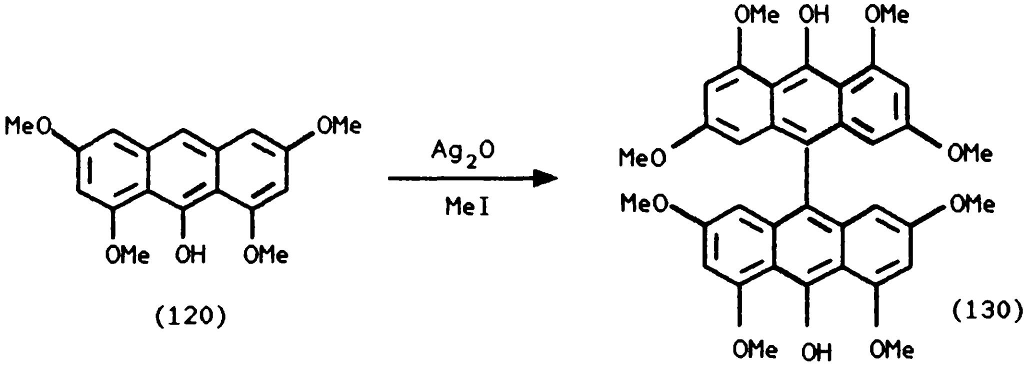
The crystalline adducts were then used as a source of sulphines. Heating the adducts dissociated them back to the sulphine and regenerated the anthracene. A solution of 1,3,6,8-tetramethoxy-9-anthranol (120) and tetracyanoethylene (129) stirred in benzene at room temperature slowly lost the orange colour to produce a white precipitate. The solid decomposed between 140 and 150° and



also on attempted recrystallization. It showed only mass ions for the anthranol (120) and tetracyanoethylene (129). No sensible result could be obtained from the elemental analysis except that it contained nitrogen. The ^1H n.m.r. (90 MHz) spectra of the compound showed a doublet at δ 6.71 ppm, J 2Hz, for two protons, a doublet at δ 6.63 ppm, J 2 Hz, integrating for two protons, a one proton singlet at δ 4.57 ppm and a twelve proton singlet at δ 3.94 ppm. Its infrared spectra showed a weak signal at 2120 cm^{-1} for a non-conjugated cyano and a broad absorption at 3440 cm^{-1} for a hydroxyl. As only ^{1}H n.m.r. and infrared spectroscopy gave any indication of adduct formation, it was decided to abandon this approach. The methylation of the hydroxyl of the adduct may also have been difficult due to the possibility of retro-Claisen reaction (Scheme 25) occurring on formation of the alkoxide.

Work was again directed towards *O*-alkylation of the anthranol (120).

Reaction of (120) with silver(I) oxide in an excess of iodomethane succeeded in coupling the anthranol rather than methylating to yield the bianthranol (130).



(120)

(130)

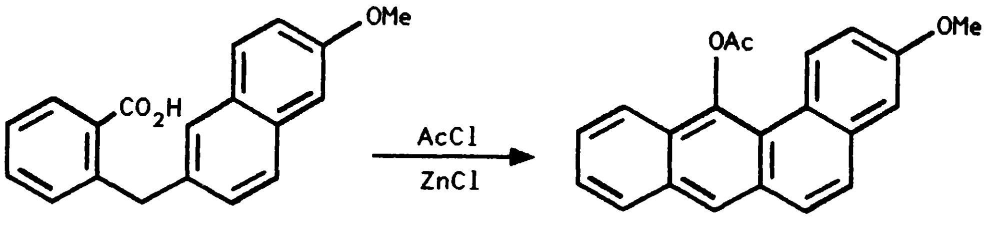
Using only silver(I) oxide in acetone at room temperature gave the same bianthranol (130). Anthranols have been coupled using a variety of oxidizing agents including Fe(III)[65], TeO_2[66] and benzoyl peroxide[67]. Cameron and Schutz[68] also obtained the coupled product when trying to *O* -methylate 2,6-dimethoxyanthrone.

Diazomethane is reported to react with hindered alcohols in the presence of a catalytic amount of tetrafluoroboric acid.[69]

Reaction of a dichloromethane solution of anthranol (120) containing a catalytic amount of tetrafluoroboric acid/diethyl ether complex with an excess of diazomethane gave only unreacted starting material.

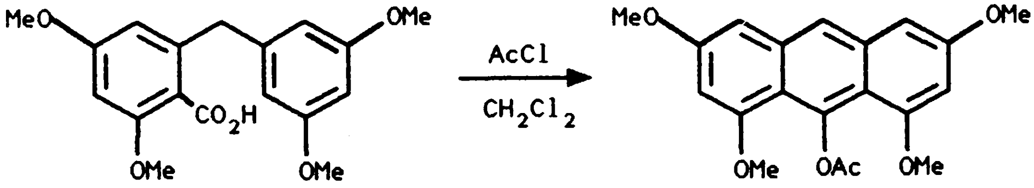
A surprise result at this point led to a more rewarding approach to the methylation.

Harvey[70] had reported closing the benzoic acid derivative (131) with acetyl chloride and zinc chloride to produce acetoxybenzanthracene (132).



(131) (132)

It was thus decided to substitute the trifluoroacetic anhydride used in the ring closure of the benzylbenzoic acid (119) for acetyl chloride. Not only

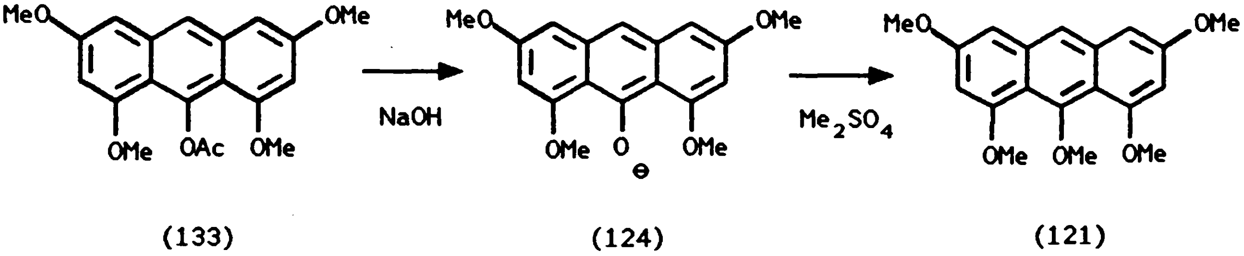


(119) (133)

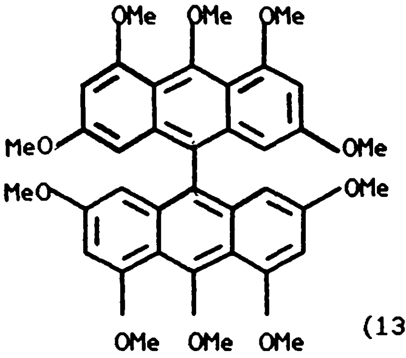
did acetyl chloride succeed in causing the ring closure but also in *O*-acylating the intermediate anthranol (120) to give 9-acetoxy-1,3,6,8-tetramethoxyanthracene (133) as yellow/green needles, m.p. 257-258°C in high yield. Up to this point it had been assumed that the reason for preferential *C*-methylation of anthranol (120) was steric. Attack by the oxygen anion on iodomethane being inhibited by steric hindrance from the 1- and 8-methoxyl groups, forcing methylation to occur (twice!) at the less hindered C-10.

It was now realised that perhaps *C*-methylation predominated because the C-10 carbon reacted faster with iodomethane than the oxygen of the anthracene oxide (124).

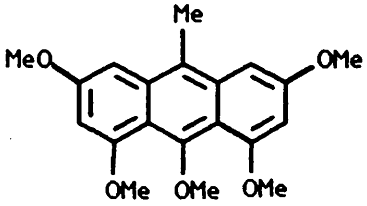
As the acetoxyanthracene (133) was relatively stable, it was decided to generate the alkoxide directly from it. Hydrolysis of the acetoxyanthracene (133) with an excess of sodium hydroxide should produce sodium acetate and the sodium salt of the anthranol (120) which could be methylated *in situ*. A two stage procedure was developed where the acetoxyanthracene (133) was treated with five equivalents of sodium hydroxide in dimethoxyethane under argon at 70° overnight. The hydrolysis mixture was then quenched with an excess of dimethyl



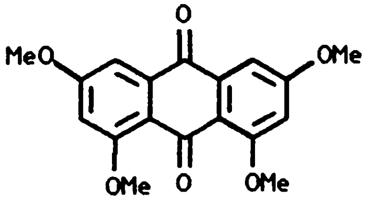
sulphate as Meyer and Schlosser[71] had reported preferential *O*-methylation of anthrone (20) in potassium hydroxide solution with dimethyl sulphate. The organic solvent was then removed at reduced pressure and the aqueous solution extracted with dichloromethane. Drying and evaporation of the solvent gave 1,3,6,8,9-pentamethoxyanthracene, recrystallized as dark orange cubes form di-isopropyl ether. Large scale methylation reactions allowed the isolation of minor products by preparative layer chromatography. 1,1',3,3',6,6',8,8',9,9'-Decamethoxy-10,10'-bianthracene (134), 10-methyl-1,3,6,8,9-pentamethoxyanthracene (135) and 1,3,6,8-tetramethoxy-9,10-anthraquinone (122) were side products isolated from the methylation.



(134)

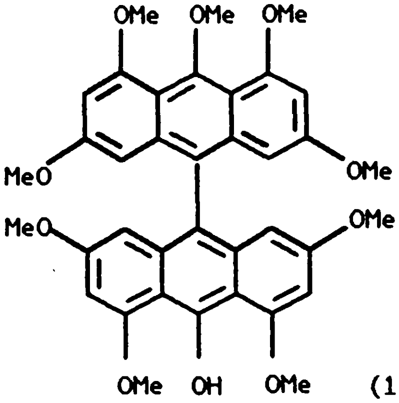


(135)



(122)

It is unclear how compound (134) is formed. The octamethoxybianthranol (130) or monohydroxy compound (136) were never isolated.

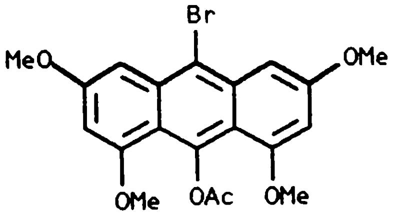


(136)

A control experiment was run in which only dimethoxyethane was added to the hydrolysis mixture instead of dimethyl sulphate. The usual work up produced mainly 1,3,6,8-tetramethoxy-9-anthranol (120) by hydrolysis of the acetate and a little 1,3,6,8-tetramethoxy-9,10-anthraquinone (122). No bianthranol (130) could be detected. Allowing air into the hydrolysis mixture produced a near quantitative yield of the tetramethoxyanthraquinone (122).

The pentamethoxyanthracene (121) was relatively air stable but was easily hydrolised back to the anthranol (120) by stirring in a 2:1 mixture of tetrahydrofuran and 1*N* hydrochloric acid for 30 minutes.

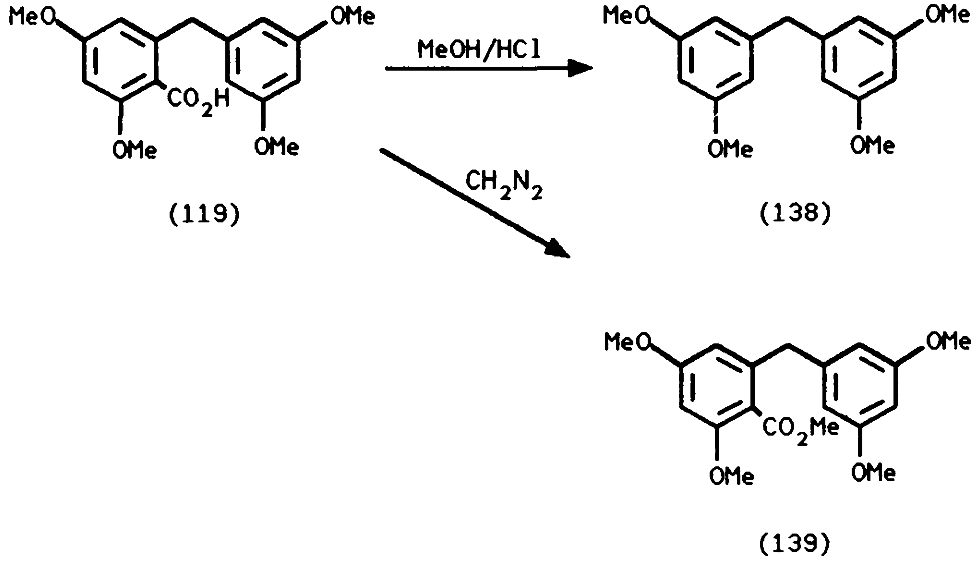
Some chemistry of the 9-acetoxy-1,3,6,8-tetramethoxyanthracene (133) was investigated. (133) Reacted with *N*-bromosuccinimide to produce 9-acetoxy-10-bromo-1,3,6,8-tetramethoxyanthracene (137).



(137)

Attempted Fries rearrangement of (133) with aluminium chloride in dry nitrobenzene produced dark intractable residues.

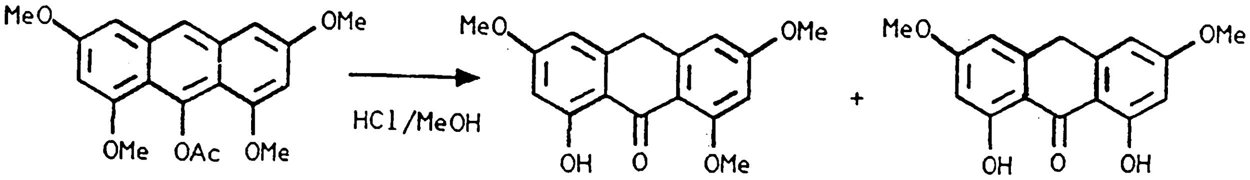
As reactivity seemed dominant in the central ring, rather than in the outer rings (which might have allowed some modifications), attention turned back to the benzylbenzoic acid (119). The possibility of incorporating a bromine into one of the other rings before cyclising to produce the central ring was then examined. It was decided to esterify the benzylbenzoic acid (119) as its solubility was poor. Refluxing the benzylbenzoic acid (119) in dry methanol saturated with hydrogen chloride gave the bis-(3,5-dimethoxyphenyl)methane (138) by decarboxylation.



Base catalysed esterifications using iodomethane or dimethyl sulphate with potassium carbonate in refluxing acetone gave poor yields of the required ester. The esterification was improved using diazomethane in dichloromethane to give the methyl ester (139) in reasonable yield.

Treatment of a solution of the ester (139) in chloroform with *N*-bromosuccinimide led to a complex mixture from which only a small amount of starting material could be identified.

Attention turned back to the acetoxytetramethoxyanthracene (133). Deacetylation of the acetoxyanthracene (133) was very slow with potassium carbonate in refluxing methanol under nitrogen. Attempted acid catalysed deacetylation in refluxing methanol saturated with hydrogen chloride furnished two new hydroxyanthrones (140) and (141).



(133) (140) (141)

The hydrogen chloride had not only catalysed the deacetylation but had also demethylated the 1-and 8-methoxyls. Conditions could be altered to produce mainly one or other of the products by varying the hydrogen chloride concentration and the time of reaction. Both compounds exist as the C-9 anthrone because of hydrogen bonding to the 1-and/or 8-hydroxyls. No demethylation of the 3-or 6-methoxyls occurred on prolonged reflux.

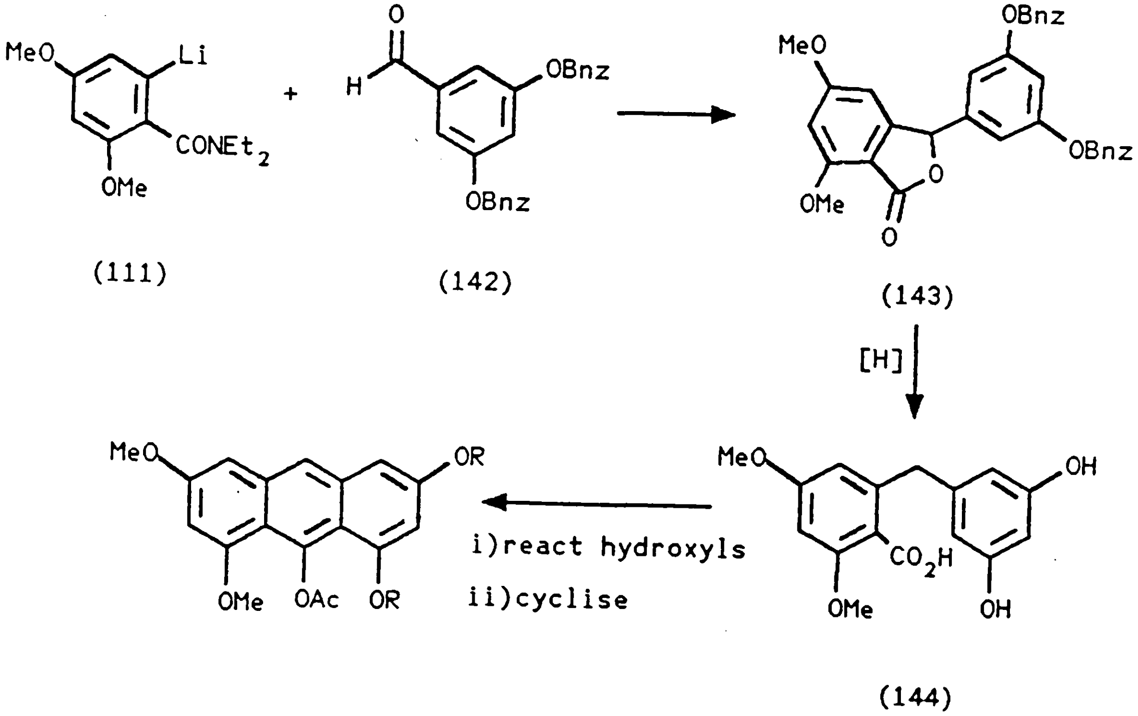
Changing the acid to a catalytic amount of perchloric acid produced solely the desired deacetylation.

Attempted acetylation of the anthrones (140) and (141) with acetyl chloride and zinc chloride in dichloromethane produced complex mixtures with both anthrones. No reaction was detected in the absence of zinc chloride.

Methylation of (140) and (141) with the conditions effective for producing the pentamethoxyanthracene (121) (sodium hydroxide, dimethyl sulphate and dimethoxyethane under argon) gave only inseparable purple mixtures from which no compounds could be identified.

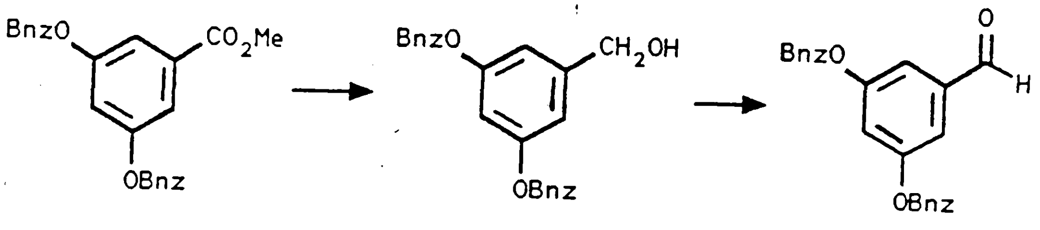
It was of interest to get some sort of useful acylation or alkylation of the 1-or 8-hydroxyl. The right type of group on the oxygen could be transferred to the ring in a Fries or Claisen type of rearrangement to further functionalize the anthracene nucleus on route to the required tetracycle (17).

To try to get round the difficulty in getting the 1-and/or 8-hydroxyl to react, the aldehyde derived part of the anthracene skeleton was synthesized with *O*-benzyl protecting groups (142). These oxygens could be deprotected during the hydrogenation of the phthalide (143) (Scheme 26).



Scheme 26

Hopefully the hydroxyls of the benzylbenzoic acid (144) would be more responsive to acylation or alkylation than the hydroxyls of anthrones (140) and (141). 3,5-Dibenzyloxybenzaldehyde (142) was produced by reduction of methyl 3,5-dibenzyloxybenzoate (145) and the oxidation of the benzyl alcohol (146).



(145) (146) (142)

3,5-Dibenzyloxybenzaldehyde (142) reacted cleanly with the lithiated amide (111) to produce the dibenzyloxyphthalide (143). Hydrogenation over palladium on charcoal gave a white solid which could not be redissolved in any common solvent for ^{1}H n.m.r. analysis. Treatment with acetyl chloride in dichloromethane gave an orange crystalline mass which had many signals in its ^{1}H n.m.r. spectrum and contained many compounds by thin layer chromatography. This approach was abandoned without further investigation as it was deemed more feasible to synthesize a correctly substituted aldehyde than to try to further functionalize a benzylbenzoic acid or an anthracene skeleton.

The amide derived part of the phthalide was retained unaltered since any change to this section of the molecule would have to be compatible with *t*-butyl lithium. The type of molecule required for reaction with the lithiated amide would have to contain the correct oxygen substitution pattern and a group that could be adapted to form the pyrone ring as required in the target tetracyclic precursor (17). Figure 7 shows a molecule that has the correct oxygenation pattern and an aldehyde for reaction with the lithiated amide (111). The molecule is symmetrical and so it does not matter which way round the derived benzylbenzoic acid cyclises. The substituent "X" should be a group that can be modified into a pyrone ring. As will be discussed in the next section, probably the best grouping for "X" is an ester or a methyl ketone. These groups have been transformed to benzopyrones when attached to an aromatic ring possessing an *ortho* hydroxyl substituent[40]. Also the fact that group "X" must not react with the lithiated amide (111) must be taken into account. If "X" was an ester function then it was reasoned that the more electrophilic aldehyde would react faster with the lithiated amide (111) than the ester. If the group was a methyl ketone then some form of protection would be required to prevent nucleophilic attack on the ketone or proton abstraction by the lithiated amide.

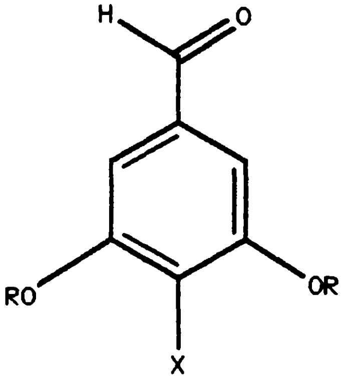
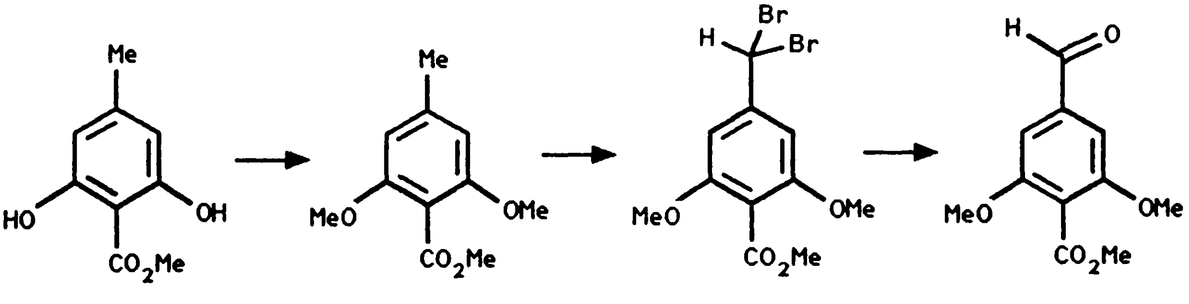


Figure 7

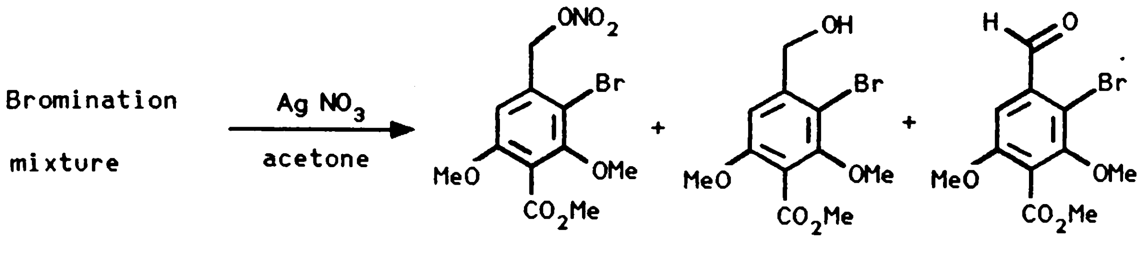
The synthesis of the formylester (147) was first attempted. Methyl 2,6-

dihydroxy-4-methylbenzoate (148) was commercially available but required protection of the hydroxyls and oxidation of the aromatic methyl to an aldehyde. The hydroxyls were thus protected as their methyl ethers by reaction of the dihydroxyester (148) with potassium carbonate and dimethyl sulphate in refluxing acetone. It was decided to form the aldehyde function by dihalogenation of the aromatic methyl[72]. Hydrolysis of the dibromomethyl substituent should yield the aldehyde. Methyl 2,6-dimethoxy-4-methylbenzoate (149) in refluxing carbon tetrachloride was treated with two equivalents of *N*-bromosuccinimide (NBS) spiked with a little benzoyl peroxide and the reaction flask illuminated with a bench lamp. Work up yielded methyl 4-dibromomethyl-2,6-dimethoxybenzoate (150). This compound was unstable and was hydrolysed with aqueous silver nitrate in acetone to give the desired methyl 2,6-dimethoxy-4-formylbenzoate (147). On small scales (< 1g of ester), radical bromination of the aromatic methyl predominated. On larger scales, aromatic substitution began to compete

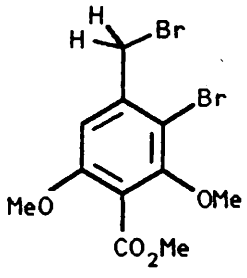


(148) (149) (150) (147)

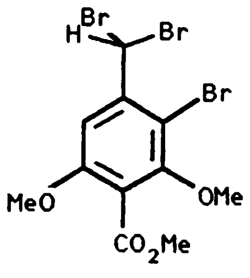
with benzylic bromination. Variation in the rate of addition of *N*-bromosuccinimide and the amount of initiator did little to increase benzyl dihalogenation over aromatic substitution. As the bromomethyl compounds were unstable, the bromination mixtures were hydrolysed with aqueous silver nitrate in acetone to aid analysis. A major component of the hydrolysis mixture was the nitrate ester (151), presumably from the reaction of the mono benzyl bromide, mono ring bromide compound (154) with nitrate ion. The bromoalcohol (152) probably arose by solvolysis of the dibromide (154) or hydrolysis of the bromonitrate ester (151). The bromoaldehyde (153) could occur by solvolysis of the tribromide (155).



(151) (152) (153)

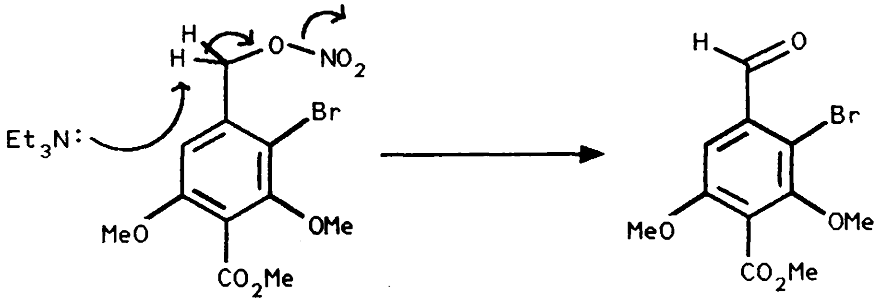


(154)



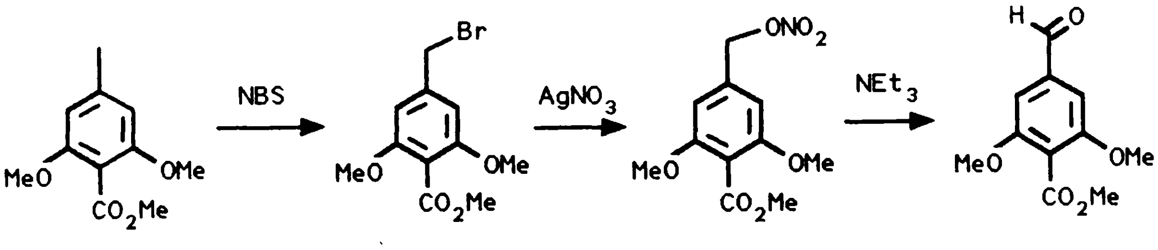
(155)

Treatment of the bromonitrate ester (151) with triethylamine (NEt_3) produced the bromoaldehyde (153) by elimination of nitrite ion to generate the carbonyl double bond.



(151) (153)

Methyl 2,6-dimethoxy-4-methylbenzoate (149) could be mainly monobrominated at the benzylic position without aromatic substitution interfering.

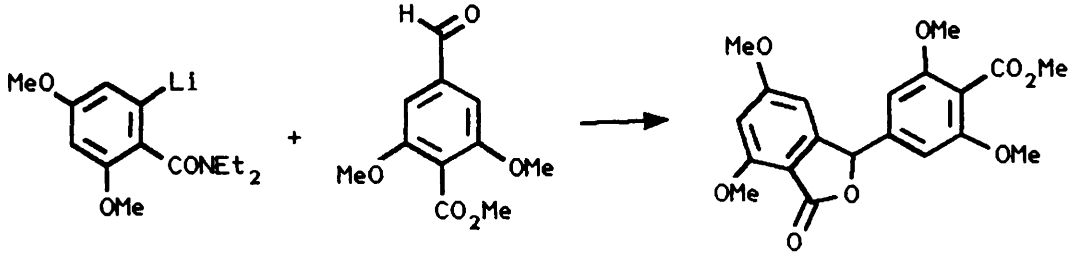


(149) (156) (157) (147)

Reaction of the monobenzyl bromide (156) with silver nitrate in acetone furnished the nitrate ester (157). Triethylamine assisted elimination of nitrite ion in refluxing dichloromethane solution gave the formylester (147). This synthesis of the aldehyde could be run on a five gram scale because of the selectivity of the monobromination step.

The nitrate ester oxidation of alkyl halides has found little use in synthesis, probably due to the expense of the silver nitrate. Some work has been done on the preparation of nitrate esters from alkyl halides and tosylates *via* ion exchange columns[73] and by reaction with the cheaper mercuric nitrate[74].

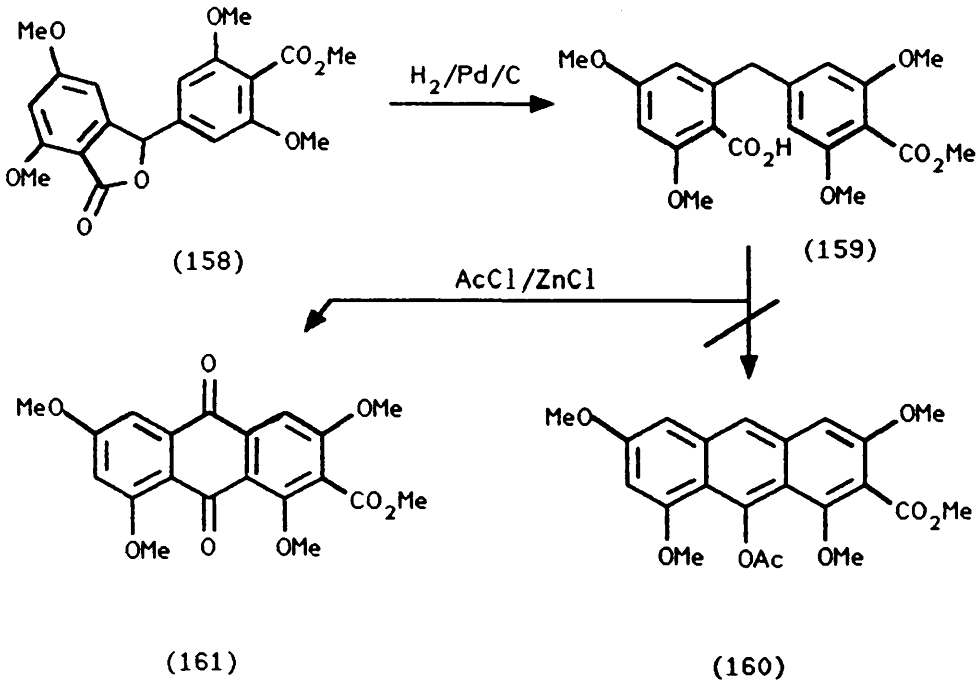
The substituted aldehyde (147) reacted cleanly with the lithiated amide (111) to give the phthalide (158) on work up.



(111) (147) (158)

Reaction was confined to the aldehyde with no attack on the less electrophilic and more sterically hindered ester being detected.

Phthalide (158) proved more resistant to hydrogenation than the simpler tetramethoxyphthalide (118) synthesized earlier. Hydrogenation required 48 hours over palladium on charcoal in acetic acid and methanol (1:1). Ring closure of the benzylbenzoic acid (159) with acetyl chloride in dichloromethane required catalysis by zinc chloride. Instead of the expected acetoxyanthracene ester (160), the known anthraquinone (161)^{75} was the only product isolated.

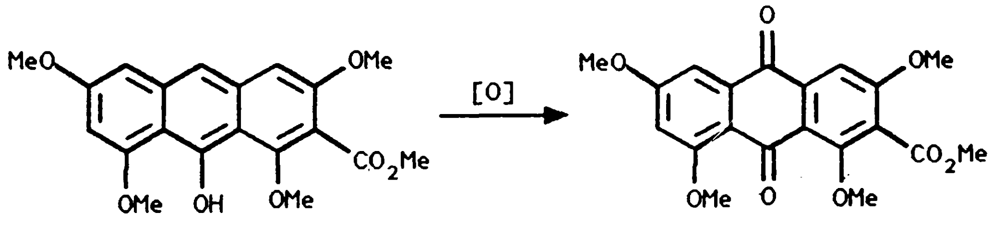


(158) (159) (161) (160)

Repetition under an inert atmosphere still produced the same anthraquinone, presumably by air oxidation during work up.

In the simple tetramethoxy case, the 9-acetoxy-1,3,6,8-tetramethoxyanthracene (133) was more stable to air oxidation than the unprotected 1,3,6,8-tetramethoxy-9-anthranol (120).

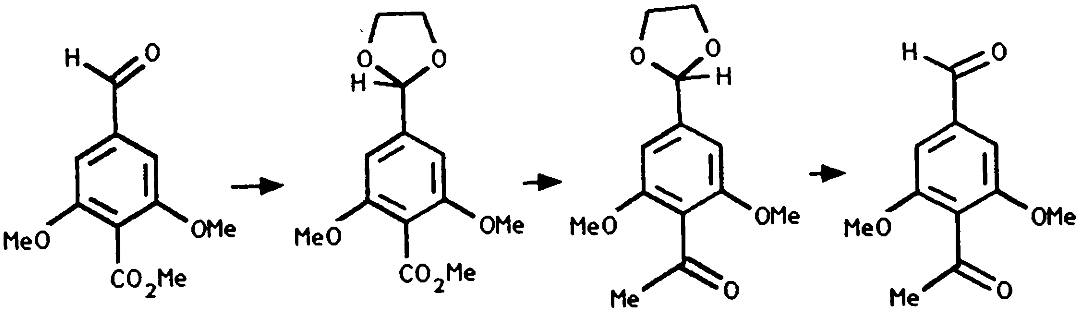
In the ester substituted case it was assumed the acetoxyanthracene was not formed and the reaction stopped at the less stable anthranol (162) which underwent oxidation to the anthraquinone (161). Repetition of the ring closure reaction with a 5 molar excess of acetyl chloride and zinc chloride under argon for 3 days still only produced anthraquinone (161).



(162) (161)

The ester substituted anthranol (162) may be too sterically crowded to allow acylation of the 9-hydroxyl function.

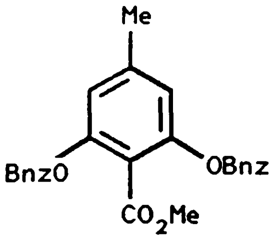
Work was then started on the synthesis of the methyl ketone substituted aldehyde (163). Again utilisation of methyl 2,6-dihydroxy-4-methylbenzoate (148) by way of the formylester (147) seemed a viable route along the lines of Scheme 27.



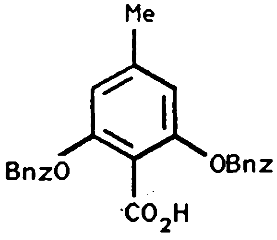
(147) (163)

Scheme 27

The key conversion was that of the ester to the methyl ketone. The reaction of a carboxylic acid with two equivalents of methyl lithium[76] to furnish the methylketone seemed ideal for this step. To test this step in the synthesis, methyl 2,6-dihydroxy-4-methylbenzoate (148) was chosen as the model compound without elaboration to the aldehyde. The hydroxyls were protected as their benzyl ethers for ease of removal later in the synthesis. Methyl 2,6-dibenzyloxy-4-methylbenzoate (164), obtained by benzylation of the hydroxyls of (148), proved very resistant to hydrolysis. The methyl ester was slow to react in sodium hydroxide solution and methanol, and prolonged reaction times were required for reasonable yields of the acid (165).



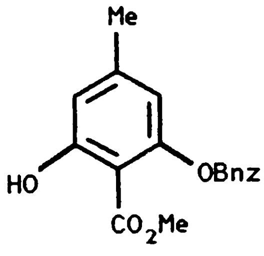
(164)



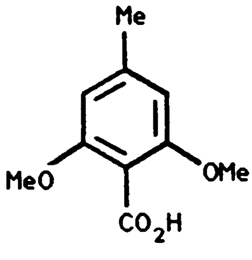
(165)

Treatment of the dibenzyloxybenzoic acid (165) with an excess of methyl lithium in tetrahydofuran at room temperature produced only unreacted acid on work up. This was probably due to the insolubility of the lithium carboxylate produced by the initial reaction of the carboxylic acid with methyl lithium. Repetition of the reaction in refluxing tetrahydrofuran still did not produce any methyl ketone.

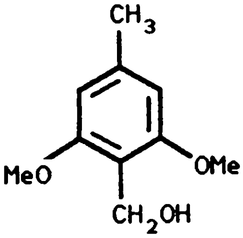
As the methyl ester (164) was so difficult to hydrolyse due to steric hindrance, it was treated with methyl lithium. It was hoped that this hindrance could be used advantageously to limit the reaction of the methyl ester with the organometallic reagent to yield a methyl ketone. The ester did not react with methyl lithium in tetrahydrofuran at room temperature, but at reflux a small amount of methyl 2-benzyloxy-6-hydroxy-4-methylbenzoate (166) was isolated from the unreacted starting material.



(166)



(167)



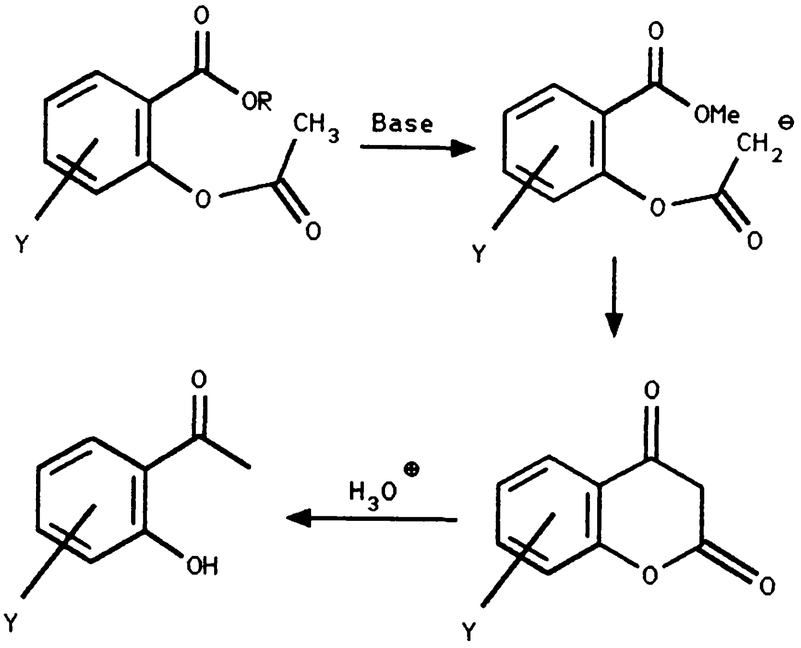
(168)

The *O*-protecting group was now changed to a methyl to see if the smaller methoxyl groups would allow attack of the organometallic reagent. Reaction of 2,6-dimethoxy-4-methylbenzoic acid (167) or its methyl ester (149) with excess methyl lithium in tetrahydrofuran proved fruitless with none of the required methyl ketone being isolated.

To test the feasibility of the reaction of the more electrophilic acid chloride with methyl lithium required the synthesis of 2,6-dimethoxy-4-methylbenzoyl chloride. Treatment of the dimethoxybenzoic acid (167) with phosphorous pentachloride or the action of thionyl chloride failed to produce any acid chloride.

Although it was believed steric hindrance was the cause of the lack of reactivity of these 2,6-dialkoxy substituted acids and esters, it was possible to hydrolyse the esters (149) and (164) and reduce methyl 2,6-dimethoxy-4-methylbenzoate (149) with lithium aluminium hydride to give a moderate yield of the benzyl alcohol (168) but still with recovery of some unreacted ester (149).

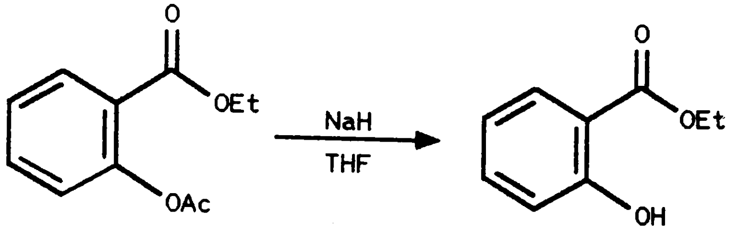
Modification of the ester was abandoned in favour of a Dieckmann



Scheme 28

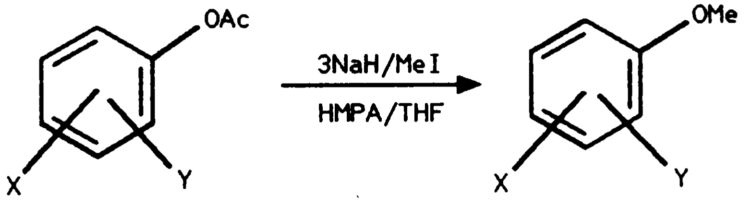
cyclisation approach (Scheme 28). It was envisaged that internal cyclisation of the enolate of an *o*-acetoxy substituted benzoate would produce a β-keto lactone which could be hydrolysed and decarboxylated to the *o*-hydroxyacetophenone.

To test this, ethyl *o*-acetoxybenzoate (169) was treated with sodium hydride in tetrahydrofuran. Instead of cyclisation, ethyl salicylate was the only product isolated. No ethyl ester hydrolysis could be detected.



(169) (170)

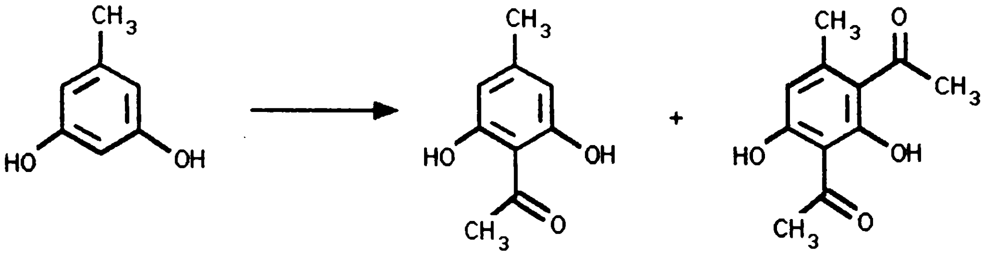
Yamashita[77] reported the methylation of phenyl acetates with sodium hydride and iodomethane in tetrahydrofuran and suggested the acetate was lost as the ketene and the phenoxide trapped as its methyl ether (Scheme 29).



Scheme 29

The classic synthesis of hydroxy substituted aromatic methyl ketones or acetophenones is the Fries rearrangement[78]. This is the reaction of a phenyl acetate with a Lewis acid to yield *ortho-* or *para*-hydroxy substituted acetophenones.

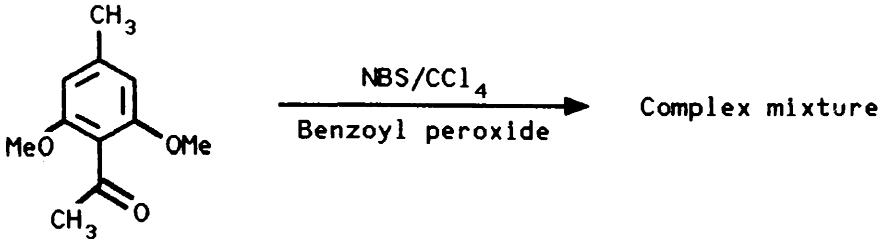
It was reported[79] that the reaction of orcinol (171) with acetyl chloride in nitrobenzene catalyzed by aluminium chloride yielded 2,6-dihydroxy-4-methylacetophenone (172). Repetition of the literature procedure gave a low yield of the required ketone (172) but mainly the diacylated product (173).



(171) (172) (173)

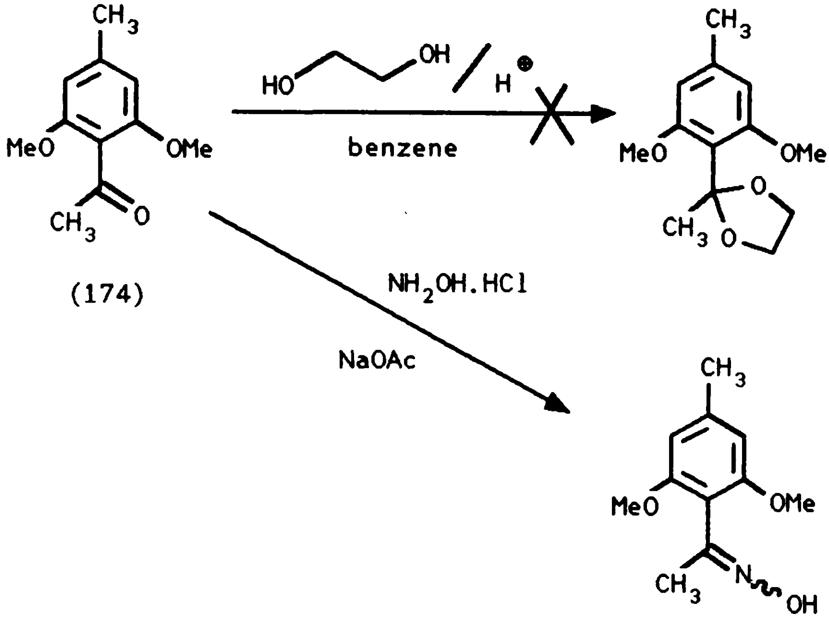
Variation of the reaction conditions, temperature, rates of addition or quantities of reactants failed to produce any significant effect on the product ratio. Unknown at this point was that it had also been reported[80] that the diacylated orcinol derivative (173) can be mono deacylated to the required dihydroxyacetophenone (172) by treatment with cold concentrated sulphuric acid.

The dihydroxyacetophenone (172) was *O*-methylated with dimethyl sulphate to produce 2,6-dimethoxy-4-methylacetophenone (174). This was treated with one equivalent of *N*-bromosuccinimide containing a catalytic amount of benzoyl peroxide in refluxing carbon tetrachloride illuminated with a bench lamp in an analogous manner to the bromination of methyl 2,6-dimethoxy-4-methylbenzoate (149). The hope that benzylic bromination would predominate over aromatic substitution or reaction with the methyl ketone was unfounded as the bromination reaction produced a complex mixture.



(174)

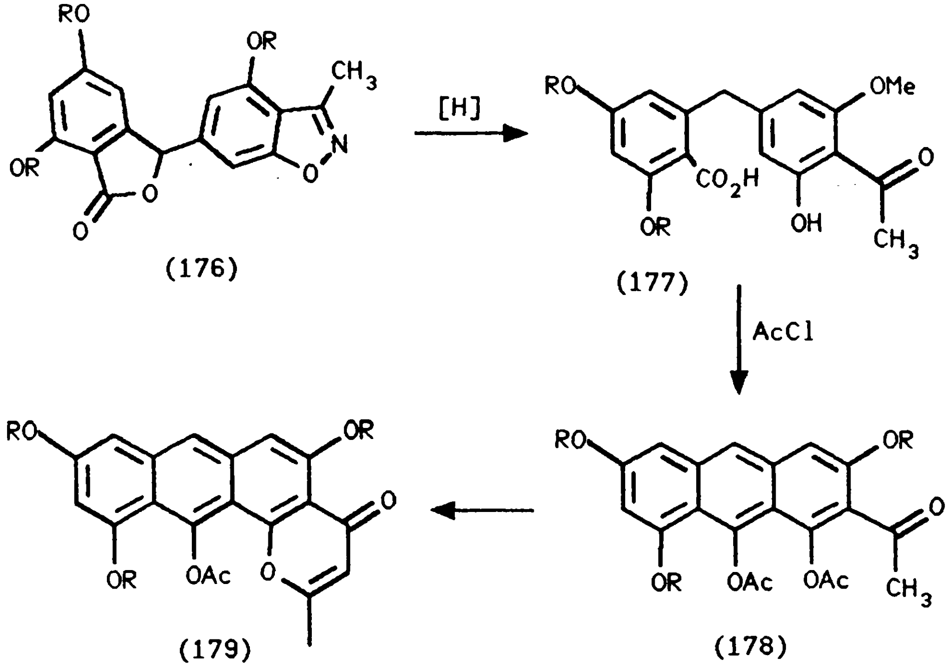
Protection of the methyl ketone was then attempted to at least prevent this group from taking part in the bromination. The 1,3-dioxolane of the acetophenone (174) could not be formed under Dean-Stark conditions using ethylene glycol, benzene and a catalytic amount of *p*-toluenesulphonic acid.



(174)

(175)

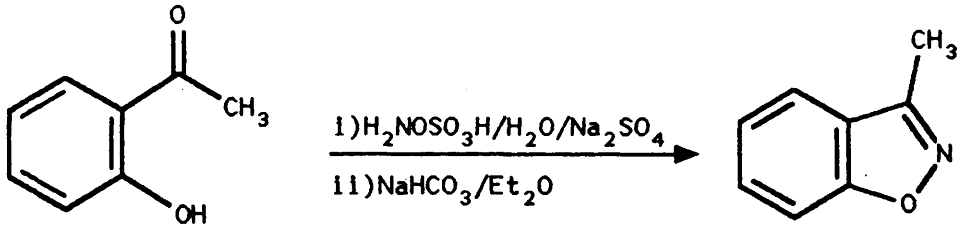
Again, failure of this reaction was probably due to steric congestion about the ketone. Alternatively, it was possible to produce an oxime (175) from the ketone by the reaction of the acetophenone (174) with hydroxylamine hydrochloride and sodium acetate. This introduced the possibility that the ketone and one of the



Scheme 30

ortho hydroxyls could be protected as a cyclic oxime, an isoxazole. This would then allow deprotection of one hydroxyl and the ketone by reduction of the $O-N$ bond during hydrogenation of the phthalide (176) (Scheme 30). If selective cyclisation of the benzylbenzoic acid (177) was possible then the *o*-acetoxyacetophenone (178) could be elaborated to the benzopyrone (179) (see later).

The model benzoisoxazole (181) was prepared by reaction of *o*-hydroxyacetophenone (180) and hydroxylamine-*O*-sulphonic acid.



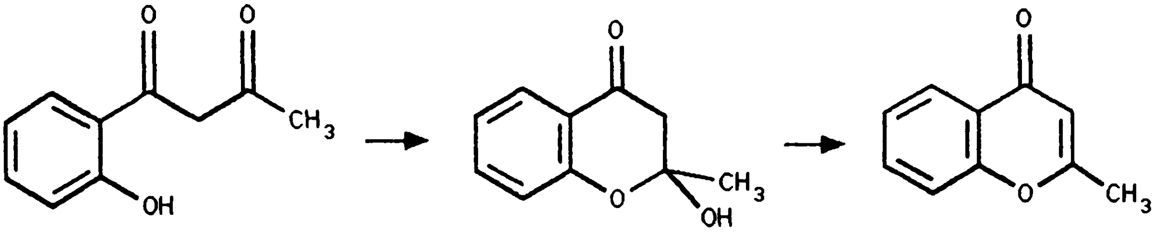
(180) (181)

Analogous reduction conditions as for the phthalides (118) and (158), palladium on carbon in methanol and ethyl acetate under a hydrogen atmosphere at standard pressure failed to reduce the $N-O$ bond. Tougher conditions using Raney nickel as catalyst at 45°C under one atmosphere of hydrogen still did not reduce the $N-O$ bond.

This investigation was abandoned without further work due to the difficulties encountered with the $N-O$ bond reduction and attention focussed on the synthesis of the pyrone ring portion.

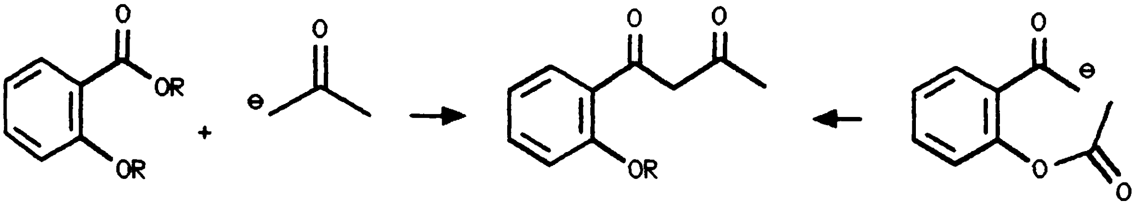
2.4 Construction of the pyrone ring

There are many reported syntheses of compounds containing 2-methylbenzopyranone rings since they occur widely in natural products. This ring system is often constructed biosynthetically by the cyclisation of a polyacetate chain. Synthetic approaches to this ring system mimic the biosynthetic pathway . 2-Methylbenzopyrones are normally constructed by cyclisation of an *o*-hydroxybenzoylacetone (Scheme 31).



Scheme 31

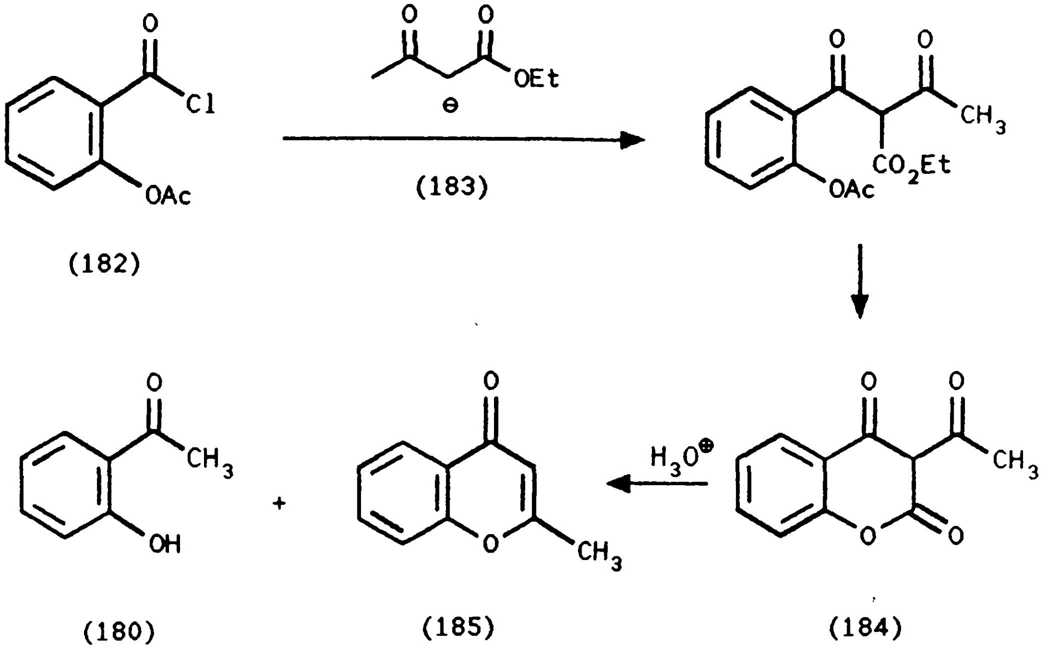
The *β*-diketone is available by the Claisen condensation approach with an *o*-hydroxybenzoate and the anion of acetone or its equivalent. The other classical synthesis of benzopyrones is the Baker-Venkataraman reaction[82] which is an internal Claisen reaction of an *o*-acetoxyacetophenone. These approaches are illustrated in Scheme 32.



Scheme 32

The Claisen condensation approach was investigated first because it was at this point still deemed feasible to synthesize the carboxymethyl substituted anthracene (160).

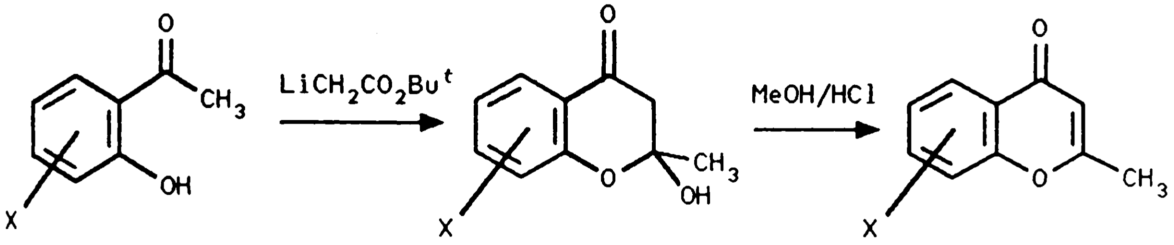
An ideal model seemed to be *o*-acetoxybenzoyl chloride (182) which contained a protected *ortho*-oxygen substituent and an acid chloride. The sodium salt of ethyl acetoacetate (183) was chosen as the acetone anion equivalent. These reacted in diethyl ether to yield on work up the acetyllactone (184). Mild acid hydrolysis and decarboxylation gave a low yield of the benzopyrone (185)



together with a larger amount of *o*-hydroxyacetophenone (180). This idea was abandoned due to low yields of benzopyrone (185) obtained on hydrolysis in the model case and also as highlighted previously, the low reactivity found for

2,6-disubstituted benzoic acid derivatives that would be required for the synthesis of the target tetracycle (17).

Nagasawa *et al.*[83] reported a new synthesis of benzopyrones by treatment of *o*-hydroxyacetophenones with an excess of *t*-butyl lithioacetate (Scheme 33).

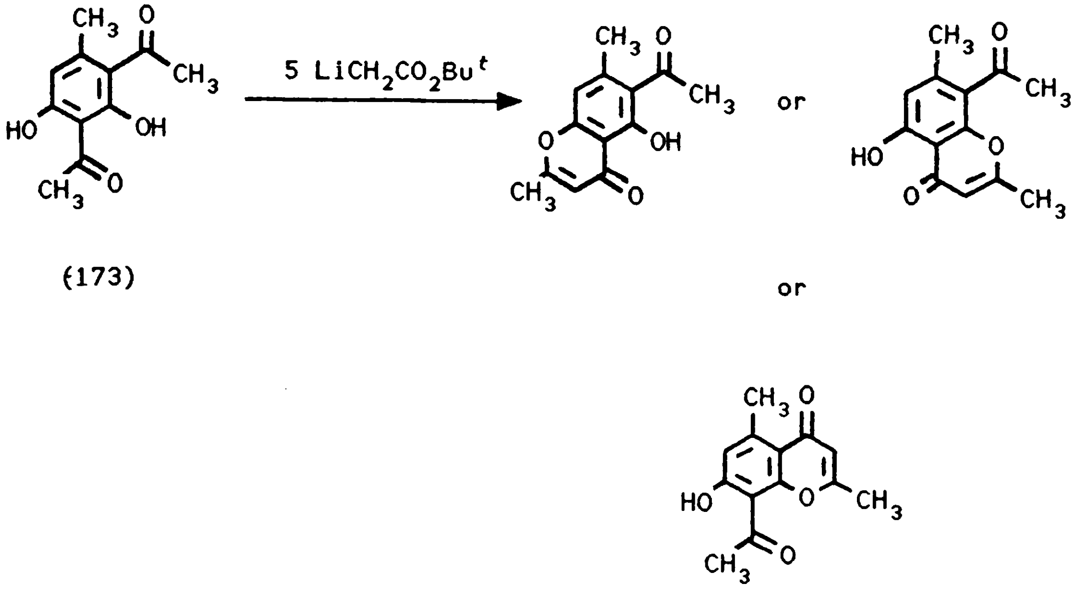


Scheme 33

The reaction seems to be a Claisen-type condensation and it is possible to isolate the intermediate chromanone acetals, which can be dehydrated to the benzopyrones.

However reaction of five equivalents of *t*-butyl lithioacetate with 2,6-dihydroxy-4-methylacetophenone (172) led to a mixture from which no pyrone containing molecules could be isolated.

Interestingly the reaction of 2,4-diacetylorcinol (173), the unwanted product from the acylation of orcinol, yielded a monopyrone.



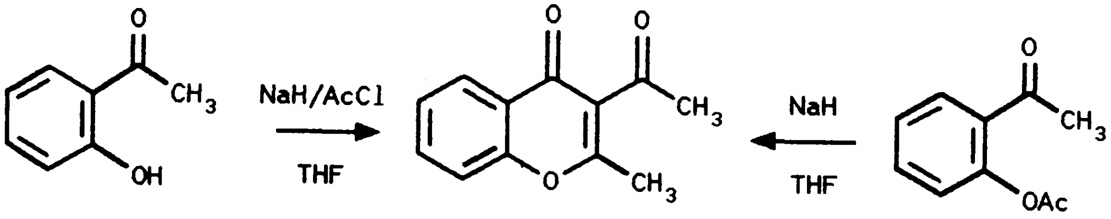
(173)

It could not be determined which methyl ketone reacted and with which hydroxyl it cyclized with to give the benzopyrone. The infrared spectrum (CCl_4) of the product contained a broad hydroxyl stretch (3270 cm^{-1}), and absorptions corresponding to an α,β-unsaturated ketone (1670 cm^{-1}) and a hydrogen bonded ketone (1628 cm^{-1}) (carbonyl absorptions at 1630 and 1610 cm^{-1} in 2,4-diacetylorcinol). High field (200 MHz) ^1H n.m.r. spectroscopy in deuteriochloroform revealed a hydrogen bonded phenol resonating at δ 13.69 ppm, an aromatic proton at δ 6.73 ppm (q, J 0.9 Hz) coupled to an aromatic methyl at δ 2.81 ppm (d, J 0.9 Hz) and a vinylic proton at δ 2.16 ppm (q, J 0.8 Hz) coupled to a vinyl methyl at δ 2.39 ppm (d, J 0.8Hz) and a methyl singlet at δ 2.82 ppm.

Mass spectra showed a molecular ion m/e 232 (M^+, 61%, $C_{13}H_{12}O_4$) and 217(M^+-15, 100%) but not enough information could be gained to positively identify the isomer.

Attention now concentrated on the Baker-Venkataraman reaction, well known for the production of benzopyrones but sometimes suffering from low yields and side products.

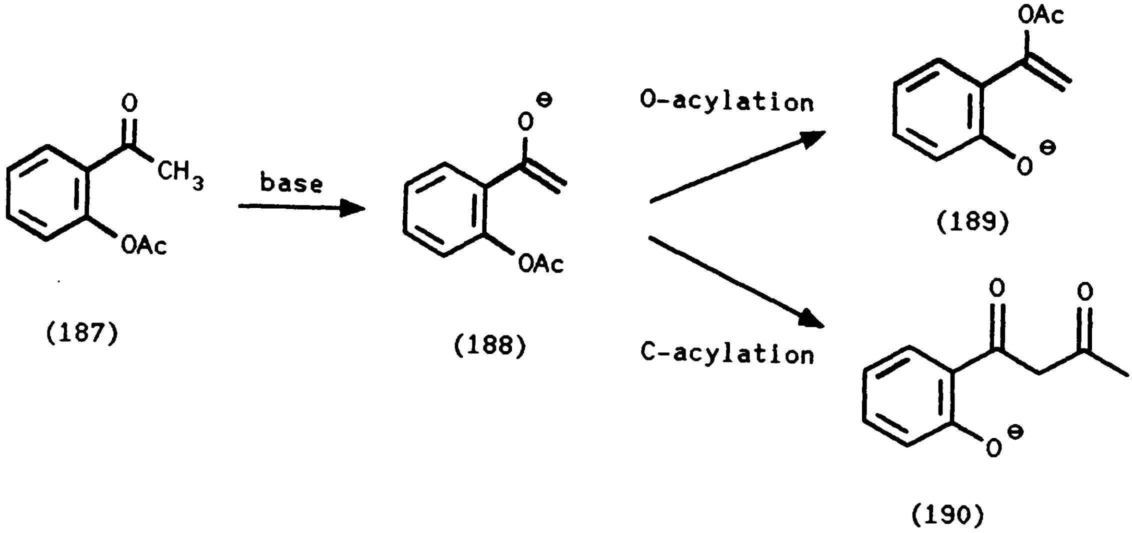
Exploratory reactions concentrated on treating *o*-hydroxyacetophenone (180) with sodium hydride and acetyl chloride in tetrahydrofuran. This produced low yields of 3-acetyl-2-methylbenzopyrone (186).



(180) (186) (187)

A two stage reaction with isolation of the presumed intermediate, *o*-acetoxyacetophenone (187) and then treatment with sodium hydride in tetrahydrofuran still gave a low yield of the benzopyrone (186) with the main product being *o*-hydroxyacetophenone (180).

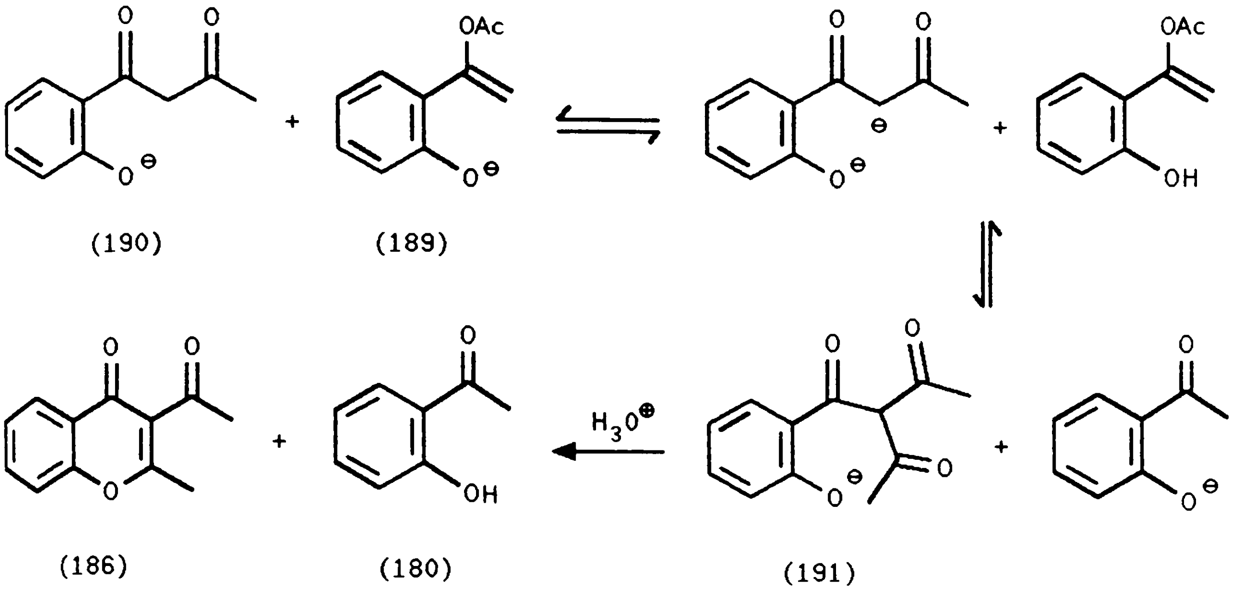
It is believed this occurs because the enolate of *o*-acetoxycetophenone (188) can either *O*- or *C*- acylate to give (189) or (190).



(187) (188) (189) (190)

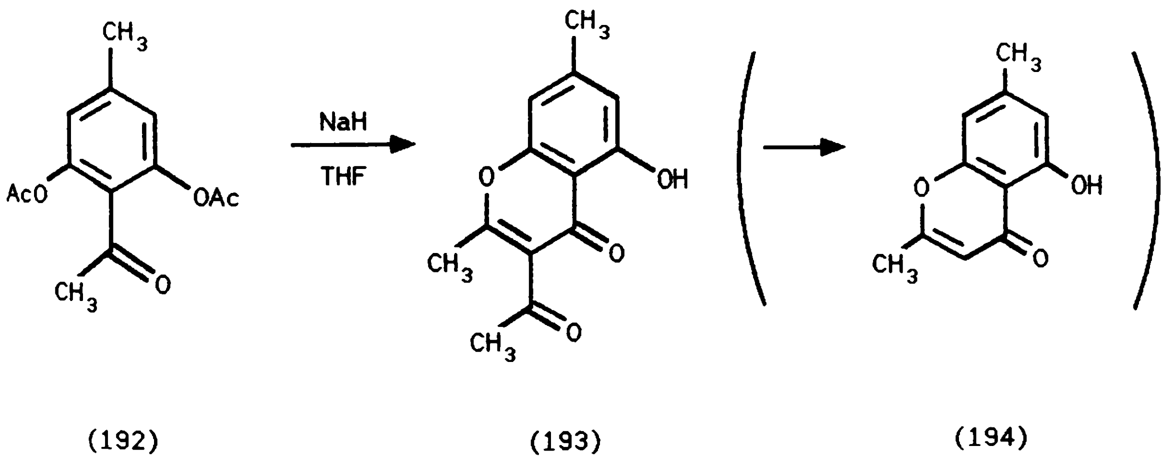
The *C*-acylated product can then react with the product of *O*-acylation (189) to give the triketone (191) which cyclises on acidification yielding the acetylbenzopyrone (186) and the deacylated product *o*-hydroxyacetophenone (180) (Scheme 34).

b



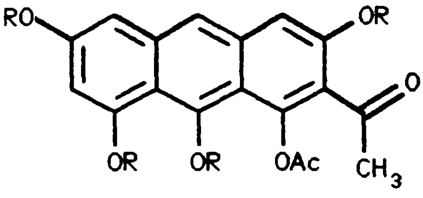
Scheme 34

A similar result was found for 2,6-diacetoxy-4-methylacetophenone (192) which on treatment with sodium hydride in tetrahydrofuran gave 3-acetyl-5-hydroxy-2,7-dimethylbenzopyrone (193).



The deacetylation to give 5-hydroxy-2,7-dimethylbenzopyrone (194) has been reported[84].

Unfortunately this route was not attempted on an acetyl substituted anthracene skeleton such as (195) because of the difficulties encountered in the synthesis of molecules of this type. Time ran out before the synthesis of the formylpyrone (196) could be attempted and its reaction with the lithiated amide investigated with the possibilty of elaboration to a tetracycle such as (17).



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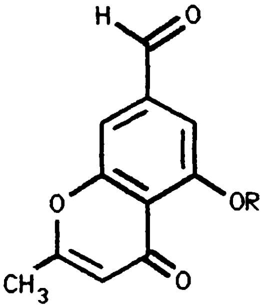

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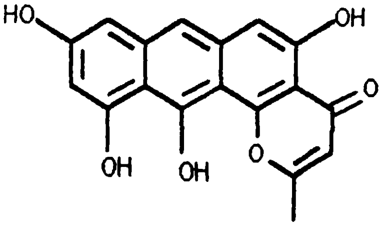


(17)

2.5 Cultivation and labelling experiments on *Cercospora ligustrina*

Cercospora ligustrina was obtained from the Centraalbureau voor Schimmelcultures, Baarn, Holland (culture no. CBS 148.59).

Attempts to grow the fungus on liquid media gave poor results as growth was inhibited when the mycelium sank below the surface. Better results were obtained on a solid medium in Roux flasks. Best results were obtained using potato dextrose agar in 1 litre beakers and was advantageous in allowing easy access for manipulations on the agar and fungus. *C. ligustrina* was grown for three weeks at room temperature in twenty-five 1 litre beakers. The agar was cut into pieces and subjected to continuous extraction with ethyl acetate. The weight of the crude extract varied from 400 to 1000 mg and the amount of ligustrone B from 10 to 120 mg. The amount of extract was not always related to the amount of ligustrone B isolated.

In fifteen different harvests, ligustrone A was isolated only once with ligustrone B always being present. Ligustrone C was never detected. The major components of the extract were fats and lipids and purple inextractable pigments that proved very difficult to elute off a column of silica. No other metabolites could be isolated in large enough amounts or purity for identification.

As outlined in the introduction, molecules derived from the polyketide pathway are biosynthesized by the folding of a polyacetate chain from the condensation of a starter acetate unit with malonyl units. These malonyl units are also derived from acetate.

The incorporation of ^{14}C-labelled acetate into a metabolite has been used to infer its acetate origin[85]. In theory the incorporation of C-1 or C-2 labelled acetate into a molecule should disclose from which carbon of acetate each carbon in the metabolite was derived form. In practice the position of a ^{14}C-label can only be located by degradation of the metabolite.

Due to recent advances in spectroscopy, the use of ^{13}C as a label is more advantageous. The ^{13}C isotope of carbon is not radioactive and can be detected by n.m.r. spectroscopy. The site of labelling can be revealed by the enhancement of the signals due to the labelled carbon atoms over that of the carbon atoms unlabelled in the natural abundance spectrum of the metabolite.

An extra advantage is that incorporation of doubly labelled [1,2-$^{13}C_2$]acetate can yield information on the folding of the polyacetate chain[86] and on skeletal rearrangements[11].

To investigate the biosynthetic hypothesis for ligustrone B, a culture of *C. ligustrina* was grown on potato dextrose agar spiked with [1-^{14}C]acetate. Incorporation was very low (see Table 1 for results). Increasing the amount of labelled acetate fed produced a corresponding increase in the activity of the ligustrone B.

A special medium was prepared to try and eliminate the possibility that some of the labelled acetate was unavailable to the fungus due to very slow diffusion through the agar. A layer of agar was placed in the flasks, allowed to set and then covered with a layer of agar (approximately 1mm thick) containing the labelled acetate. The fungus was then grown as normal on this agar sandwich. This method yielded a large amount of extract and a better incorporation into ligustrone B but still too poor to provide any conclusions.

If acetate had some other fate before the production of the ligustrones occurred, then this would account for the low incorporation levels . To test this, a time study was initiated to pinpoint the best time after inoculation of the fungus on the medium to feed the labelled acetate. The results (see Graph I) show a steady increase in the weight of extract as the fungus establishes itself on the agar. The amount of isolated ligustrone B seems to stay reasonably constant with the exception of the 18 day extract, but falls as a percentage of the total extract over time. There was no investigation before the 10 day mark as the fungus was not well established before this point.

Feeding was then attempted at the 5 day mark in the hope that at this point the secondary metabolic processes responsible for the biosynthesis of ligustrone B would be active.

The growing fungus was to be fed at 5 and 10 days after inoculation on the agar. At the 5 day mark, a labelled acetate solution was injected into wells made on the agar surface and allowed to difuse into the medium. This seemed to inhibit the growth of the fungus and the second feeding was abandoned to allow the fungus to recover. The weight of extract was much reduced compared to other feedings and the activity of the isolated ligustrone B was not improved.

Lack of time cut short any more labelling studies with *C. ligustrina*. Although conditions were kept as constant as possible during the growth and cultivation of the fungus and the isolation of the metabolites, yields of crude extracts and weights of isolated ligustrone B were very variable.

The biosynthesis of ligustrone B is still unclear. No investigations were undertaken to discover the fate of the rest of the labelled acetate. Acetate may not be taken up well by the growing fungus, or may inhibit the production of the ligustrones. A more alarming hypothesis is that acetate is not a precursor of the ligustrone skeleton. One other possibility is that ligustrone B is part of a metabolic pool, undergoing constant synthesis and degradation and might explain the low incorporation levels.

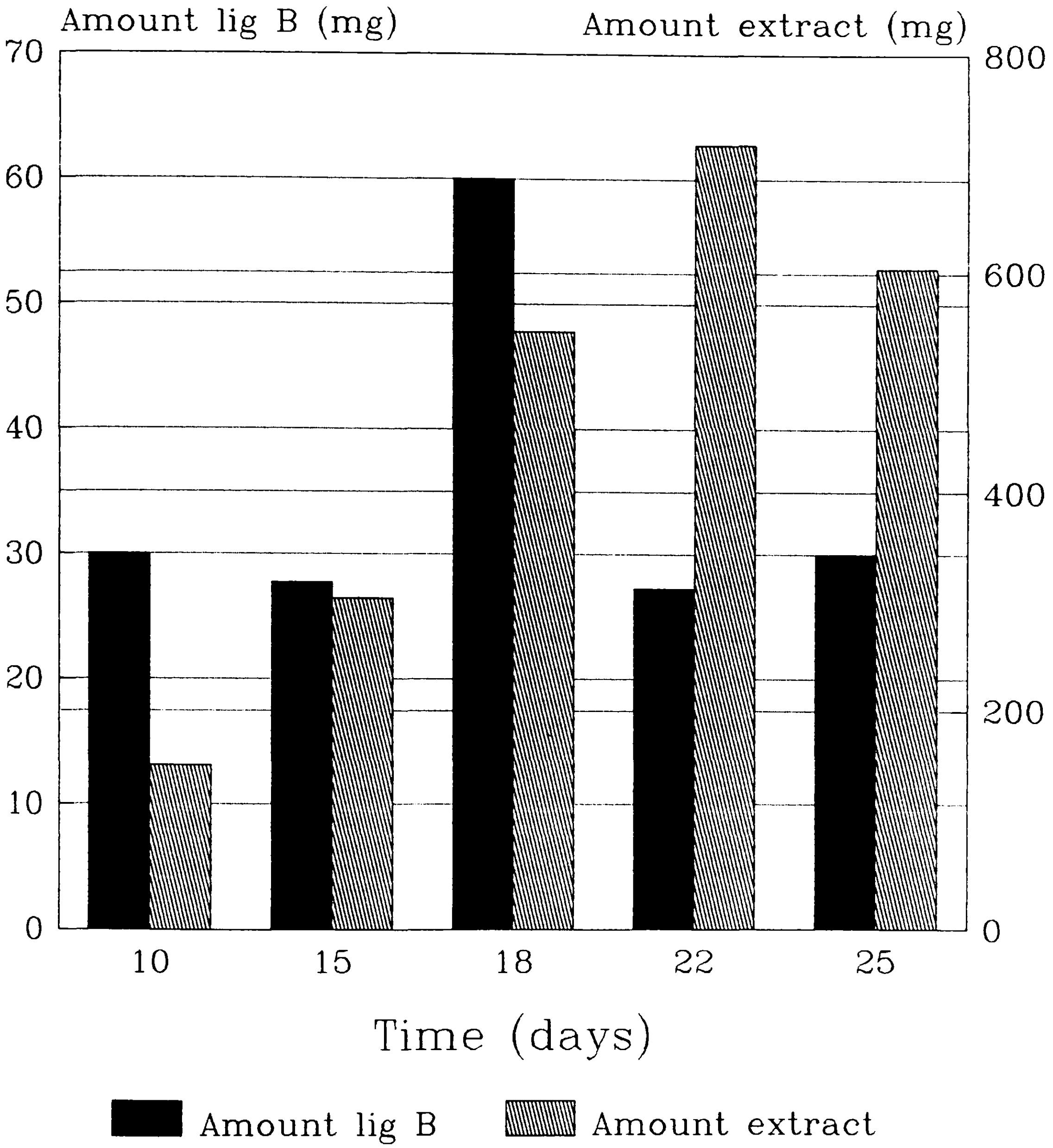
One thing is clear, much more work than is embodied in this thesis needs to be done on the biosynthesis of the ligustrone metabolites of *C. ligustrina*.

Table 1

Results of [1- ^{14}C]acetate feedings to *Cercospora ligustrina*

Conditions of feeding	Amount of ^{14}C acetate	Amount of extract (mg)	Amount of lig B isolated (mg)	Activity of lig B per mg (Bq)	Total recovered activity (Bq)	% incorporation	Comments
labelled acetate in agar	14.8	1093	157	57.7	9059	6.12×10^{-4}	
labelled acetate in agar	54.0	973	20	189	3780	7.0×10^{-6}	
labelled acetate in layer on top of cold agar	89.9	1752	124	577	71548	7.96×10^{-4}	Fed very large dose
labelled acetate fed after 5 days	18.0	612	30	148	4440	2.45×10^{-4}	Only one small feeding-inhibited growth

Graph 1
Time study on C. ligustria



Chapter 3

Experimental

General Procedures

Melting points were determined on a Kofler hot-stage apparatus and are uncorrected. Ultra-violet spectra were measured on a Unicam SP8-100 spectrometer. Infra-red spectra were recorded on a Perkin-Elmer S80 spectrometer. Proton nuclear magnetic resonance spectra were determined on a Perkin-Elmer RB 32 spectrometer using deuteriochloroform as solvent (unless otherwise stated) and using tetramethysilane as internal standard. The following abbreviations are used:

- s- singlet, d- doublet, t- triplet, q- quartet, m- multiplet, and br- broad.

Mass spectra were obtained with an MS 12 or MS 902 spectrometer.

All apparatus and solutions involved in the growth of the micro-organism were sterlized before and after use in an autoclave.

Preparative layer and short column chromatography was carried out using Merck Kieselgel GF_{254}. Analytical thin layer chromatography was carried out on commercially prepared plates with a 0.25mm layer of the same silica gel. Organic solutions were evaporated on a rotary evaporator under reduced pressure. Solutions of organic solvents were dried over anhydrous magnesium sulphate. Solvents were purified according to the methods set out in "Purification of laboratory compounds[122]".

The following abbreviations were also used:

- THF - tetrahydrofuran, light petrol - petroleum ether (40-60°C) and petrol - petroleum ether (60-80°C).

Cultivation of *C. ligustrina* and isolation of the metabolites

Cercospora ligustrina, obtained from the Centraalbureau voor Schimmelcultures, Baarn, Holland (culture no. CBS 148.59) was inoculated onto potato dextrose agar[121] in Roux flasks. The cultures were grown at room temperature for 21 days and then harvested. The agar was diced and subjected to constant extraction with ethyl acetate (1 litre). The organic extracts were dried and evaporated to a dark purple mass. Column chromatography on silica was used to isolate the metabolites. The column was first eluted with methylene chloride to remove non-polar material and then with methylene chloride/diethyl ether (1:1) to elute the ligustrones. Ligustrone A came off as a dark yellow band. The fractions containing this band were evaporated to a yellow crystalline mass which was purified by sublimation (160°/0.1mmHg) to give ligustrone A as needles, m.p. 241°C; (lit.[19], m.p. 226-227°C); $\nu_{max.}$ 3 400- 3 060, 2 930, 1 702, 1 667, and 1 613cm^{-1}; δ_H 7.57(1H, d, J 6Hz, C-9(H)), 7.05(1H, s, C-6 or 7(H)), 6.97(1H, s, C-6 or 7(H)), 6.33(1H, s, C-3(H)), 6.16(1H, d, J 6Hz, C-8(H)), 4.22(3H, s, OMe), and 2.54(3H, s, Me); m/e 308 (M^+).

Continued elution gave a second yellow band which on evaporation of these fractions gave a yellow residue which was recrystallized from ethyl acetate to give ligustrone B as yellow needles, m.p. 218-219°C; (lit.[19], m.p. 221-222°C) (Found: C, 69.72; H, 4.58%; M^+, 310. $C_{18}H_{14}O_5$ requires C, 69.67; H, 4.55%; M, 310); $\nu_{max.}$ 3 435, 2 940, 1 705, 1 670, and 1 600cm^{-1}; δ_H 12.94(1H, s, OH), 7.40(1H, s, C-7(H)), 6.95(1H, s, C-6(H)), 6.38(1H, s, C-3(H)), 4.16(3H, s, OMe), 3.23(2H, s, C-8(H_2)), 2.80(2H, m, C-9(H_2)), and 2.59(3H, s, Me).

The masses of crude extract varied from 400 to 1000mg and ligustrone B was the main metabolite. Ligustrone A was only isolated once. In that case 400mg of extract yielded 10mg of ligustrone A and 28mg of ligustrone B. Ligustrone C was never detected.

Methyl 5,6-dihydro-*o*-orsellinate (67)

Sodium (23g, 1mole) was added with stirring to dry methanol (500ml). After the reaction had subsided, methyl acetoacetate (108ml, 1mole) was added followed by methyl crotonate (106ml, 1mole) and the mixture stirred and refluxed for 2 hours by which time a white precipitate appeared. The slurry was then stirred at room temperature overnight. The thick slurry was then cooled in ice and filtered. The solid was washed with a little cold methanol and diethyl ether (200ml x 2) and dried (under vacuum). The white powder was dissolved in the minimum amount of water and cooled to 0°C. The solution was then carefully acidified with ice cold concentrated hydrochloric acid and the precipitate collected, washed with cold water and dried (115g, 63%). A sample was crystallized from methanol to give methyl 5,6-dihydro-*o*-orsellinate, m.p. 124-125°C (lit.[44], 122-124°C); ν_{max} (KBr) 3 200 and 1 730 cm^{-1}; δ_H 9.5 (1H, s, OH), 5.5 (1H, s, H-3), 3.8 (3H, s, OMe), 3.1 (1H, d, *J* 10Hz, H-1), 2.9-2.0 (3H, m, H-5 and H-6), and 1.05 (3H, d, CHCH_3); m/e 184 (M$^+$).

Methyl 3,5-dibromo-2,4-dihydroxy-6-methyl benzoate (68)

A solution of bromine (22ml, 0.43moles) in glacial acetic acid (25ml) was added to a vigorously stirred solution of methyl 5,6-dihydro-*o*-orsellinate (25g, 0.14moles) in glacial acetic acid (150ml) at such a rate as to keep the temperature of the reaction above 60°C. Stirring was continued for another hour, then the reaction was allowed to stand overnight.

The mixture was then poured into 1 litre of iced water and the products separated by filtration, washed with water and air dried to give methyl 3,5-dibromo-2,4-dihydroxy-6-methylbenzoate as needles (42.8g, 90%) from dichloromethane/light petrol, m.p. 105-106°C (lit.[44], 105-106°C); δ_H (CD_3OD) 3.95 (3H, s, OMe), and 2.65 (3H, s, ArMe); m/e 342/340/338 (M^+).

Methyl 2,4-dihydroxy-6-methylbenzoate (69)

To methyl 3,5 -dibromo-2,4-dihydroxy-6-methylbenzoate (20g) dissolved in 2*N* sodium hydroxide solution (240ml) was added Raney nickel alloy (20g) portionwise with vigorous stirring at 0°C. (A few drops of ethanol was used to moderate excessive frothing). After complete addition of the alloy, the mixture was stirred for a further hour and filtered under suction. The filtrate was cooled to 0°C and ice cold concentrated hydrochloric acid was added dropwise till the solution was acidic. The precipitate was filtered and the solid washed with water, air dried and recrystallized from petrol as needles (7.2g, 67%), m.p. 139-140°C (lit.[87], 142°C); $\nu_{max.}$ (KBr) 3 360, 1 650, and 1 585cm^{-1}; δ_H ($(CD_3)_2CO$) 6.3-6.2 (2H, br s, ArH), 3.85 (3H, s, OMe), and 2.5 (3H, s, ArMe); m/e 182(M^+).

Methyl 2,4-dimethoxy-6-methylbenzoate

To 2,4-dihydroxy-6-methylbenzoate (8g, 44mmoles) in dry acetone (150ml) was added anhydrous potassium carbonate (14g) and dimethyl sulphate (9ml, 95mmoles). The mixture was stirred and heated at reflux for 6 hours, cooled, and the potassium salts removed by filtration. The acetone was evaporated off to leave a yellow oil which was suspended in diethyl ether (100ml) and washed with concentrated ammonia solution (2x30ml) and 1N sodium hydroxide solution (2x30ml). The ether layer was then dried and evaporated to a yellow oil which was crystallized from cold pentane to give methyl 2,4-dimethoxy-6-methylbenzoate as needles (7.7g, 84%), m.p. 42°C (lit.[88], 42-43.5°C); $\nu_{max.}$ (KBr) 2 950, and 1 725cm^{-1}; δ_H 6.34(2H, s, ArH), 3.89(3H, s, OMe), 3.82 (6H, s, OMe), and 2.29 (3H, s, ArMe); m/e 210(M$^+$).

2,4-Dimethoxy-6-methylbenzoic acid (63)

Methyl 2,4-dimethoxy-6-methylbenzoate (5g, 24mmoles) was suspended in water (120ml) and sodium hydroxide (1.2g, 30mmoles) was added and the mixture heated at reflux for 6 hours. On cooling, the basic solution was washed with diethyl ether (2x30ml) then acidified with concentrated hydrochloric acid and the precipitate filtered, washed with water and dried. 2,4-Dimethoxy-6-methylbenzoic acid was recrystallized as needles from dichloromethane/hexane (3.9g, 82%), m.p. 142°C (lit.[89], 143-144°C); $\nu_{max.}$ (KBr) 2 950, 2 600, 1 685, and

1 600 cm^{-1}; δ_H 7.0(1H, br s, OH), 6.4(2H, br s, ArH), 3.93(3H, s, OMe), 3.83(3H, s, OMe), and 2.52(3H, s, ArMe); m/e 196(M$^+$).

3,5-Dimethoxyhomophthalic acid (64)

n-Butyl lithium (28ml, 1.5M) in hexane was added to a stirred solution of di-isopropylamine (5.8ml, 42mmoles) in dry THF (50ml) under nitrogen at 0°C. After 5 minutes, the solution was cooled to -78°C and a solution of 2,4-dimethoxy-6-methylbenzoic acid (4g, 20mmoles) and dimethyl carbonate (1.9g, 23mmoles) in dry THF (25ml) was added dropwise over 15 minutes. The cooling bath was removed and the solution allowed to come to room temperature. After 4 hours, water (30ml) was added and the suspension stirred for 16 hours. The organic solvents were removed by evaporation and the resulting aqueous solution was extracted with diethyl ether (2x30ml). The aqueous solution was then acidified with 1*N* hydrochloric acid and extracted with ethyl acetate (3x30ml). The extracts were then dried and evaporated to give 3,5-dimethoxyhomophthalic acid as a light yellow solid which was recrystallized from dichloromethane/hexane (3.2g, 65%) as prisms, m.p. 170-172°C (lit.[90], 172-173°C); $\nu_{max.}$ 3 000-2 500, 1 700, 1 605, and 1 580cm^{-1}; δ_H ($(CD_3)_2CO$) 6.57(2H, s, ArH), 3.88(3H, s, OMe), 3.84(3H, s, OMe), and 3.76(2H, s, ArCH_2 CO_2H); m/e 240 (M$^+$).

6,8-Dimethoxy-3-methylisocoumarin (71)

To a stirred solution of dry pyridine (1ml) and acetic anhydride (4ml) in a dry 25ml round bottomed flask at room temperature was added 3,5-dimethoxyhomophthalic acid (2g, 8.3mmoles) in small portions over 15 minutes. The solution went yellow and after complete addition more acetic anhydride (1ml) and dry diethyl ether (8ml) were added to aid stirring. The mixture was stirred for a further hour, then the precipitate was filtered and washed several times with diethyl ether. The solid was then added in small portions to 80% sulphuric acid (15ml) and the mixture heated on a steam bath for 45 minutes. The mixture was poured onto crushed ice and extracted with ethyl acetate (3x20ml), and the combined extracts washed with saturated sodium bicarbonate solution (2x20ml), dried and evaporated. The solid was recrystallized from chloroform/petrol (0.96g, 53%) as needles, m.p. 157-158 ° (lit.[91], 157-158°C); $\nu_{max.}$(CHCl$_3$) 1 740, 1 700, 1 640, and 1 610cm^{-1}; δ_H 6.41(1H, d, J 2Hz, ArH), 6.29(1H, d, J 2Hz, ArH), 6.08(1H, s, H-4), 3.94(3H, s, OMe), 3.88(3H, s, OMe), and 2.20(3H, s, Me); m/e 220(M$^+$).

Attempted synthesis of ethyl 6,8-dimethoxy-1-hydroxy-3-methyl-2-naphthoate (47)[41]

n-Butyl lithium (1.6ml, 1.6M, 2.5mmoles) in hexane was added to a stirred solution of di-isopropylamine (0.35ml, 2.5mmoles) in dry THF under nitrogen at 0°C. After 10 minutes the mixture was cooled to -78°C and dry ethyl acetate (024ml, 2.5mmoles) in dry THF (5ml) was added and the solution stirred for 30 minutes at -78°C. The reaction mixture was then rapidly transferred through a teflon tube to a stirred solution of 6,8-dimethoxy-3-methylisocoumarin (0.2g, 1.25mmoles) in a mixture of dry dimethyl sulphoxide (5ml) and dry THF (5ml) at 0°C. After 5 minutes the reaction mixture was quenched with glacial acetic acid (3.5ml) and stirred at room temperature for 48 hours. The THF was evaporated and the residue taken up in diethyl ether (50ml), washed with water (3x25ml) and the the ether layer dried and evaporated to give 0.17g of a solid which was identical in all respects with 6,8-dimethoxy-3-methylisocoumarin.

Inverse addition of dianion (72) to acetyl chloride

n-Butyl lithium (3ml, 1.65M, 4.95mmoles) in hexane was added to a stirred solution of di-isopropylamine (0.7ml, 5mmoles) in dry THF (20ml) at 0°C under nitrogen. After 5 minutes the solution was cooled to -78°C and 2,4-dimethoxy-6-methylbenzoic acid (0.45g, 2.3mmoles) in dry THF (10ml) was added dropwise. The solution instantly turned orangy red. The reaction mixture was stirred for 10 minutes at -78°C then hastily transferred down a teflon tube into a rapidly stirred solution of acetyl chloride (0.78g, 0.7ml, 10mmoles) in dry THF (20ml) at -78°C under nitrogen. The colour quickly discharged and the solution was allowed to come to room temperature and stirred overnight. Water (20ml) was added and the THF removed by evaporation. The aqueous phase was diluted with 1*N* hydrochloric acid (30ml) and extracted with diethyl ether (3x20ml), dried and evaporated to give a yellow oil. The oil was chromatographed using chloroform/diethyl ether (3:1) as eluent to give 6,8-dimethoxy-3-methylisocoumarin (66mg, 13%) as needles from chloroform/light petrol, m.p. 157-158°C (lit.[91], 157-158°C); 2,4-dimethoxy-6-methylbenzoic acid (110mg, 25%) as needles from dichloromethane/light petrol, m.p. 142°C (lit.[89]; 143°C) and 1-(2-carboxy-3,5-dimethoxyphenyl)propan-2-one (153mg, 28%) as needles from ethyl acetate/hexane, m.p. 139-140°C (lit.[90], 139-140°C); $\nu_{max.}$(KBr) 2 960, 1 690, and 1 670cm^{-1}; δ_H ($(CD_3)_2CO$) 6.49(2H, m, ArH), 3.99(6H, s, OMe); 3.87(2H, s, benzylic), and 1.69(3H, s, Me); m/e 238(M^+).

<u>But-2-ynoic acid</u> (81)

Ethyl acetoacetate (10ml, 78.5mmoles) in ethanol (40ml) was stirred at room temperature and hydrazine hydrate (4.3g, 4.2ml) in ethanol (5ml) was added carefully, not allowing the temperature to rise too much. Before the end of the addition the 3-methyl-2-pyrazolin-5-one started to precipitate. The mixture was stirred for a further hour then ice cooled for 1 hour and the precipitate filtered, and washed with a little cold ethanol (5.8g, 86%), m.p. 224-225°C (lit.[49]; 221.5-224.5°C).

This precipitate (5g) was dissolved with stirring in glacial acetic acid (25ml) and the solution cooled in ice. Bromine (17.9g 5.5ml) in glacial acetic acid (10ml) was added dropwise. After about half the addition, a yellow compound started to crystallize out. Glacial acetic acid (25ml) was added to aid stirring and the addition continued. After complete addition of the bromine the mixture was stirred for a further hour and then poured onto iced water, the precipitate collected, washed with water and air dried to give 4,4-dibromo-3-methyl-2-pyrazolin-5-one (9.18g, 70%), m.p. 129-130°C (lit.[49]; 130-132°C); δ_H 9.1(1H, br s, amide H), and 2.31(3H, s, Me); m/e 254/256/258(M^+).

The dibromopyrazolinone (8g) was added carefully to an ice cooled sodium hydroxide solution (10.24g in 240ml of water) with stirring (vigorous frothing occurs). After 2 hours at 0°C the mixture was allowed to come to room temperature and stirred for a further hour, then carefully neutralized with concentrated hydrochloric acid and the solution saturated with ammonium sulphate and extracted with diethyl ether till a few drops of the extract no longer turned a solution of potassium permanganate in acetone brown. The combined extracts were dried and evaporated to a yellow/brown oil which crystallized on standing. The solid was sublimed (water pump and oil bath at 120°C) to give but-2-ynoic acid as prisms (1.2g, 48%), m.p. 75-76°C (lit.[49], 74-76°C); δ_H 10.43ppm (1H, br s, OH) and 1.99(3H, s, Me); m/e 84(M^+).

Ethyl but-2-ynoate (77)

4,4-Dibromo-3-methylpyrazolin-5-one (10g, 39mmoles) was vigorously stirred in ethanol (30ml) at 0°C and sodium carbonate (10g, excess) was added in small portions over 90 minutes. The solution went dark purply/orange and was allowed to come to room temperature and stirred for two days. The reaction mixture was poured into water (500ml) and extracted with dichloromethane (5x50ml) and the extracts dried and evaporated (bath temperature not above 30°C) to give a purple oil. This residue was distilled to give ethyl but-2-ynoate (2.2g, 48%) as a clear oil, b.p. 163-164°C (lit.[93], 165°C); $\nu_{max.}$ (CCl_4) 2 985, 2 245, 1 715, and 1 258cm^{-1}; δ_H 4.24(2H, q, J 7Hz, OCH_2CH_3), 2.0(3H, s, Me), and 1.31(3H, t, J 7Hz, OCH_2CH_3); m/e 112(M^+).

Ethyl 3-methoxycrotonate (82)

Ethyl acetoacetate (10ml, 78.5mmoles) was stirred with trimethyl orthoformate (9.4ml, 86mmoles) and a few crystals of *p*-toluenesulphonic acid overnight at reflux. The mixture was then stirred with the oil bath kept at 65-70°C and a gentle vacuum applied (water pump) to draw off methanol. After 3 hours the reaction was complete and the mixture was distilled and the fraction boiling at 183-188°C was collected and redistilled to yield ethyl 3-methoxycrotonate (8.3g, 73%) as a clear oil, b.p. 185-186°C (lit.[92], 185-188°C); $\nu_{max.}$ (CCl_4) 2 980, 1 718, and 1 629cm^{-1}; δ_H 5.0(1H, s, vinyl H), 4.15(2H, q, J 7Hz, OCH_2CH_3); 3.45(3H, s, OMe), 2.3(3H, s, vinyl Me), and 1.3(3H, t,J 7Hz,OCH_2CH_3); m/e 144(M^+).

Attempted reaction of the anion of methyl 2,4-dimethoxy -6-methylbenzoate(74) with ethyl 3-methoxycrotonate(84)

n-Butyl lithium (0.67ml, 1.65M, 1.1mmole) in hexane was added dropwise to a stirred solution of di-isopropylamine (0.16ml, 1.2mmoles) in dry THF (10ml) under nitrogen at 0°C. After 10 minutes the mixture was cooled to -78°C and methyl 2,4-dimethoxy-6-methylbenzoate (0.21g, 1mmole) in dry THF (10ml) added dropwise. The solution was stirred for a further 10 minutes then ethyl 3-methoxycrotonate (0.15g, 1mmole) in dry THF (10ml) was added dropwise. The solution turned light yellow and was allowed to warm to room temperature over 1 hour. Water (10ml) was added and the organics evaporated. The aqueous phase was diluted with 1*N* hydrochloric acid (30ml) and extracted with dichloromethane (3x20ml) and the combined extracts dried and evaporated to a yellow oil. Preparative layer chromatography on silica gel using dichloromethane as eluent gave the two starting materials as the only identifiable compounds.

Attempted reaction of anion (74) with ethyl but-2-ynoate (77)

A similar procedure to that outlined above was carried out, except ethyl but-2-ynoate (0.11g, 1mmole) in dry THF (10ml) was added instead of ethyl 3-methoxycrotonate. Work up as above gave a yellow oil which when submitted to preparative layer chromatography on silica gel using dichloromethane as eluent gave methyl 2,4-dimethoxy-6-methylbenzoate as the only identifiable compound.

Methyl 3,5-dimethoxybenzoate (87)

3,5-Dihydroxybenzoic acid (30g, 0.19moles), anhydrous potassium carbonate (150g) and dimethyl sulphate (64ml, 0.68moles) were stirred and refluxed overnight in dry acetone(500ml). The reaction mixture was cooled, filtered to remove the potassium salts and evaporated to a yellow oil. This was taken up in diethyl ether (400ml) and washed with concentrated ammonia solution (2x100ml), 1*N* sodium hydroxide solution (2x100ml) and once with water (100ml). The diethyl ether layer was dried and evaporated to a yellow oil which crystallized on standing (31.6g, 80%). A small portion was recrystallized from diethyl ether to give methyl 3,5-dimethoxybenzoate as needles, m.p. 41-42°C (lit.[94]; 40°C); $\nu_{max.}$ ($CHCl_3$) 2 955, 1 725, and 1 595cm^1; δ_H 7.20(2H, d, J 2Hz, ArH), 6.65(1H, t, J 2Hz, ArH), 3.92(3H, s, ester-OMe), and 3.83ppm(6H, s, OMe); m/e 196(M^+).

3,5-Dimethoxybenzyl alcohol (88)

Methyl 3,5-dimethoxybenzoate (30g, 0.15moles) in dry THF (300ml) was added carefully to a stirred slurry of lithium aluminium hydride (7.2g, 0.19moles) in dry THF (100ml) and the mixture heated at reflux for 5 hours. After cooling, water (7.2ml) was added very cautiously with vigorous stirring, and then 15% sodium hydroxide solution (7.2ml) and finally more water (21.6ml). The white aluminium hydroxide was filtered off and washed with diethyl ether (3x50ml) and the combined filtrates evaporated to a clear oil which was crystallized from diisopropyl ether/petrol as large needles (14.7g, 60%), m.p. 46-47°C (lit.[95], 46°C); $\nu_{max.}$(CCl_4) 2 945 and 1 600cm$_{-1}$; δ_H 6.52(2H, d, *J* 2Hz, ArH), 6.38(1H, t, *J* 2Hz, ArH), 4.59(2H, s, ArC*H*$_2$OH) and 3.79(6H, s, OMe); m/e 168(M^+).

2-Bromo-3,5-dimethoxybenzyl alcohol (89)

To a stirred solution of 3,5-dimethoxybenzyl alcohol (2g, 11.9mmoles) in carbon tetrachloride (25ml) at room temperature, was added N-bromosuccinimide (2.12g, 11.9mmoles) in small portions over an hour. The mixture was stirred overnight, then the succinimide was removed by filtration and the solvent evaporated to give an amorphous mass. Crystallization of the residue from cyclohexane gave 2-bromo-3,5-dimethoxybenzyl alcohol as needles (2.7g, 91%), m.p. 92-94°C (lit.[52], 95-96°C);$\nu_{max.}$ (CCl_4) 2 940 and 1 590cm^{-1}; δ_H 6.72(1H, d, *J* 2Hz, ArH), 6.46(1H, d, *J* 2Hz, ArH), 4.75(2H, s, ArC*H*$_2$OH); 3.90(3H, s, OMe), 3.83(3H, s, OMe), and 1.95(1H, br s, OH); m/e 248/246(M^+).

5,7-Dimethoxyphthalide (91)

A stirred solution of 2-bromo-3,5-dimethoxybenzyl alcohol (1g, 4mmoles) in dry THF (25ml) under nitrogen was cooled to -78°C and *n*-butyl lithium (5.6ml, 1.65M, 9.2mmoles) in hexane was added dropwise. The light olive green solution was stirred for 5 minutes, then carbon dioxide (generated from cardice) was bubbled into the rapidly stirred solution *via* a wide bore needle. The solution turns orange, milky lemon and then milky. The carbon dioxide flow was continued for another 10 minutes then the solution was allowed to come to room temperature. Water (25ml) was added and the organics evaporated. The aqueous mixture was diluted with water (75ml), then the solution was extracted with dichloromethane (2x30ml). The aqueous phase was then carefully acidified (care, vigorous effervescence) with concentrated hydrochloric acid and extracted with dichloromethane (3x30ml) and the combined extracts dried and evaporated to a solid. Recrystallization from chloroform/di-isopropyl ether gave 5,7-dimethoxyphthalide (0.72g, 92%) as needles, m.p. 152-153°C (lit.[96], 151-153°C); $\nu_{max.}$ (CCl_4) 2 960, 1 780, and 1 605cm^{-1}; δ_H 6.52(1H, br s, ArH), 6.45(1H, br s, ArH), 5.19(2H, s, CH_2), 3.97(3H, s, OMe), and 3.92(3H, s, OMe); m/e 194(M^+).

Attempted synthesis of methyl -6,8-dimethoxy-1-hydroxy-3-methyl-2-naphthoate

To a stirred solution of di-isopropylamine (0.32ml, 2,3mmoles) in dry THF (10ml) at 0°C was added *n*-butyl lithium (1.3ml, 1.65M, 2.1mmoles) in hexane and the mixture stirred for five minutes then cooled to -78°C. 5,7-Dimethoxyphthalide (200mg, 1mmole) in dry THF (20ml) was added dropwise and the solution turned orange/green and was stirred for a further 10 minutes. The cooling bath temperature was allowed to rise to -40°C and freshly distilled methyl crotonate (0.12ml, 1.1mmoles) in dry THF (10ml) was added dropwise to the stirred solution. The reaction mixture was kept at -40°C for 30 minutes then allowed to come to room temperature. The mixture was then poured into 1*N* hydrochloric acid (100ml) and extracted with diethyl ether (3x30ml), dried and evaporated to a brown oil. N.m.r. showed many products, so without further purification the oil was dissolved in dichloromethane (50ml) and treated with a few drops of boron trifluoride etherate and stirred for an hour. The dark reaction mixture was poured into water (100ml) and extracted with dichloromethane (2x30ml), dried and evaporated to a dark brown oil. Thin layer chromatography showed a multicomponent mixture and no identifiable products could be isolated by preparative layer chromatography on silica gel using diethyl ether as eluent. Repetition using different quantities of base and /or temperature proved ineffective and neither starting material nor condensation products could be isolated by preparative chromatography on the crude reaction mixture from the first stage.

Diethyl *o*-toluylmalonate (94/95)

o-Toluic acid (10g, 0.073moles) was dissolved in thionyl chloride (50ml, excess) and stirred for 24 hours. The excess thionyl chloride was removed by distillation and the crude acid chloride used without further purification. To a mechanically stirred slurry of sodium hydride (3.7g, 0.154mmoles) in dry diethyl ether (200ml) under nitrogen was added diethyl malonate (23.4ml, 0.154mmoles) dropwise and after addition, stirring was continued for 12 hours. To the rapidly stirred white slurry cooled in ice was added the crude acid chloride in dry diethyl ether (50ml) dropwise. The mixture was stirred overnight then filtered and the precipitate washed with a little dry diethyl ether. The precipitate was dissolved in water (100ml) and washed with ethyl acetate (3x30ml), then the aqueous phase was cooled to 0°C and acidified with ice cold concentrated hydrochloric acid. The mixture was then extracted with petrol (3x40ml) and the combined organics dried and evaporated to an oil which was distilled using a Kugelrohr apparatus to give diethyl *o*-toluylmalonate (8.9g, 44%) as a clear oil, b.p. 150°C (furnace temperature) /0.05mmHg. The compound existed in 2:1 ratio of enol to keto forms. (Found: C, 64.89; H, 6.65%; M^+, 278. $C_{15}H_{18}O_5$ requires C, 64.73; H, 6.52%; M, 278); $\nu_{max.}$ (thin film) 3 450, 2 985, 1 756, and 1 743cm^{-1}; δ_H (enol form) 13.40(1H, s, enol OH), 7.26(4H, br m, ArH), 4.24(2H, q, J 8Hz, CH_2CH_3), 3.91(2H, q, J 8Hz, CH_2CH_3), 1.11(3H, t, J 8Hz, OCH_2CH_3), and 0.85(3H, t, J 8Hz, OCH_2CH_3); (Keto form) 7.26(4H, br m, ArH), 5.30(1H, s, $COCH(CO_2CH_2CH_3)_2$), 4.36(4H, q, J 8Hz, OCH_2CH_3), and 1.41(6H, t, J 8Hz, OCH_2CH_3).

Reaction of diethyl *o*-toluylmalonate (95/96) with lithium di-isopropylamide

To a stirred solution of di-isopropylamine (0.42ml, 3mmoles) in dry THF (20ml) at 0°C under nitrogen was added *n*-butyl lithium (1.8ml, 2.9mmoles, 1.6M) in hexane and the mixture stirred for 5 minutes, then cooled to -78°C. A solution of diethyl *o*-toluylmalonate (200mg, 0.72mmoles) in dry THF (10ml) was added dropwise and the orange/red mixture was stirred for an hour then allowed to come to room temperature and stirred overnight. Water (10ml) was added and the organics were removed by evaporation. The aqueous phase was diluted with 1*N* hydrochloric acid (10ml) and extracted with dichloromethane (3x10ml) and the combined extracts were dried and evaporated to a dark oil. Preparative chromatography on silica using dichloromethane/petrol (1:1) as eluent gave the starting diethyl ester (111mg, 55%) as the only identifiable compound.

Reaction of diethyl *o*-toluylmalonate (95/96) with benzyl bromide

To ethyl *o*-toluylmalonate (5g, 18mmoles) and dry potassium carbonate (5.3g) in anhydrous acetone (120ml) was added benzyl bromide (4.5g, 38mmoles) and the whole mixture stirred and refluxed for 6 hours. After cooling the mixture was filtered and the solid washed with acetone (30ml) and the combined acetone solutions evaporated. The residue was taken up in diethyl ether (100ml), washed with concentrated ammonia solution (2x30ml) and 2*N* sodium hydroxide solution (2x30ml) and dried and evaporated to a thick oil. Short column chromatography on silica using dichloromethane/petrol (1:1) as eluent gave diethyl benzyl-*o*-toluylmalonate (2.5g, 38%), recrystallized from petrol as needles, m.p. 65-66°C (found: C, 71.59; H, 6.69%; M^+, 368. $C_{22}H_{24}0_5$ requires C, 71.72; H, 6.57%; *M*, 368); $\lambda_{max.}$(EtOH) 208, 245, and 282 nm; $\nu_{max.}$ 2 990, 1 757, 1 740, and 1 700cm^{-1}; δ_H 7.22(9H, br s, ArH), 4.05(4H, q, *J* 8Hz, OCH_2CH_3); 3.66(2H, s, benzylic), 2.38(3H, s, ArMe), and 1.01(6H, t, *J* 8HZ, OCH_2CH_3) and the benzyl enol ether of *o*-toluylmalonate (2.25g, 34%) as a gum (Found: C, 71.61; H, 6.61%; M^+, 368. $C_{22}H_{24}05$ requires C, 71.72; H, 6.57%; *M* , 368); $\lambda_{max.}$(EtOH) 206 and 250 nm, $\nu_{max.}$ (CCl_4) 2 990, 1 725 and 1 627 cm^{-1}; δ_H 7.28(9H, br s, ArH), 4.69(2H, s, benzylic), 4.34(2H, q, *J* 8 Hz, OCH_2CH_3), 3.94(2H, q, *J* 8Hz, OCH_2CH_3), 2.26(3H, s, ArMe), 1.31(3H, t, *J* 8 Hz, OCH_2CH_3), and 0.95(3H, t, *J* 8 Hz, CH_2CH_3).

Reaction of the benzyl enol ether of diethyl o-toluyl -malonate (96) with lithium di-isopropylamide

To a stirred solution of di-isopropylamine (0.35ml, 2.5mmoles) in dry THF (20ml) at 20°C under nitrogen was added *n*-butyl lithium (1.6ml, 2.5mmoles, 1.6M) in hexane dropwise. The solution was stirred for 5 minutes then cooled to -78°C and a solution of the benzyl enol ether of diethyl *o*-toluylmalonate (400mg, 1.1mmoles) in dry THF (20ml) was added dropwise. The dark orange solution was stirred for an hour at -78°C then allowed to come to room temperature and stirred under nitrogen overnight. Water (20ml) was added and the THF removed by evaporation. The aqueous phase was diluted with 1*N* hydrochloric acid (10ml) and extracted with dichloromethane (3x15ml) and the combined organic extracts dried and evaporated to a dark residue (360mg), from which no identifiable products or starting material could be isolated by preparative chromatography on silica.

Reaction of the diethyl benzyl-*o*-toluylmalonate (97) with lithium di-isopropylamide

The foregoing procedure was repeated using di-isopropylamine (0.35ml, 2.5mmoles), *n*-butyl lithium (1.6ml, 2.5mmoles, 1.6M) in hexane and diethyl benzyl-*o*-toluylmalonate (400mg, 1.1mmoles) to give a dark red residue (310mg). Preparative layer chromatography on silica using dichloromethane as eluent gave only one identifiable compound as a dark red residue. Crystallization from chloroform/petrol gave 2-benzyl-3-hydroxy-1,4-naphthaquinone (56mg) as dark red plates, m.p. 179-181°C (lit.[54], 181-182°*C*); (Found: M^+, 264.0783. $C_{17}H_{12}O_3$ requires M, 264.0786); $\nu_{max.}$(KBr) 3 320, 2 910, 1 660, 1 642, and 1 590 cm^{-1}; δ_H 8.09(2H, m, ArH), 7.70(2H, m, ArH), 7.30(5H, m, ArH), and 3.97(2H, m, benzylic).

2,4-Dimethoxybenzoic acid

To 2,4-dihydroxybenzoic acid (30g, 0.2mmoles) in dry acetone (500ml) was added anhydrous potassium carbonate (150g) and dimethyl sulphate (60ml, 0.63moles) and the mixture mechanically stirred and refluxed overnight. The reaction mixture was cooled and the potassium salts removed by filtration and the acetone evaporated to leave a yellow oil. The oil was then taken up in diethyl ether (300ml) and was washed with concentrated ammonia solution (2x50ml) and with 2*N* sodium hydroxide solution (2x50ml). The ether layer was dried and evaporated to a yellow oil (33.2g). Without further purification, the oil was dissolved in ethanol (50ml) and added to a solution of potassium hydroxide (12g, 0.21moles) in water (200ml) and the mixture stirred and refluxed for 4 hours. The ethanol was removed by evaporation and the aqueous mixture was extracted with diethyl ether (2x50ml). The aqueous layer was then acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3x50ml) and the organics dried and evaporated to a white solid (29.3g, 82%). A small portion was recrystallized from di-isopropyl ether to give 2,4-dimethoxybenzoic acid as needles, m.p. 107-108°C (lit.[97]; 108°C).

N,*N*-Diethyl-2,4-dimethoxybenzamide (110)

2,4-Dimethoxybenzoic acid (25g, 0.14mmoles) was added in one portion to thionyl chloride (50ml, excess) and the mixture stirred until the acid went into solution. The excess thionyl chloride was removed by distillation, stirring the mixture in an oil bath heated at 60°C under reduced pressure produced by a water pump. After all the thionyl chloride was removed the crude acid chloride was dissolved in dry diethyl ether (50ml) and added carefully to a mechanically stirred solution of freshly distilled diethylamine (31ml, 0.3moles) in dry diethyl ether (200ml). Ice cooling was required during the addition and the reaction mixture became very thick. After complete addition the reaction mixture was stirred for a further hour, then water (200ml) added and the ether layer separated and washed with $2N$ hydrochloric acid (2x70ml) and $2N$ sodium hydroxide solution (2x70ml). The ether layer was then dried and evaporated to a very thick oil. The oil was distilled (Kugelrohr) to give *N*, *N*-diethyl-2,4-dimethoxybenzamide (25g, 79%) as a yellow oil, b.p. 180°C/0.01mmHg (Found: C, 65.88; H, 8.10; N, 5.94 %; M^+, 237. $C_{13}H_{19}NO_3$ requires C, 65.80; H, 8.07; N, 5.90%; M, 237); $\nu_{max.}(CCl_4)$ 2 940, 1 635, and 1 615 cm^{-1}; δ_H 7.13(1H, d, J 8Hz, H-6), 6.57(1/2H, d, J 2Hz, 1/2 AB quartet of H-5), 6.48(1.5H, d, J 2Hz, H-3 and 1/2 AB quartet of H-5), 3.83(6-H, s, OMe), 3.59(2H, q, J 8Hz, NCH_2CH_3), 3.19(2H, q, J 8Hz, NCH_2CH_3), 1.24(3H, t, J 8Hz, NCH_2CH_3), and 1.03(3H, t, J 8Hz, NCH_2CH_3).

Deuteration of *N,N*-diethyl-2,4-dimethoxybenzamide (110)

To a stirred solution of freshly distilled *N,N*-diethyl-2,4-dimethoxybenzamide (0.126g, 0.53mmoles) in dry THF (20ml) at -78°C under argon, was added t-butyl lithium (0.32ml, 0.57mmoles, 1.8M) in hexane dropwise. The yellow solution was stirred for 10 minutes, then a deuterium oxide solution in dry THF (0.5ml of a solution of 0.1ml of deuterium oxide in 4.9ml of dry THF) was added cautiously by syringe. The cooling bath was removed and the reaction mixture was allowed to come to room temperature. Water (25ml) was added and the organics evaporated. The aqueous mixture was then extracted with diethyl ether (3x10ml), and the organic extracts dried and evaporated to give a clear oil (0.121g, 96%) which showed a 70% reduction in the integration trace of H-6 compared to that of the other signals.

3,5-Dimethoxybenzyl chloride (112a)

Thionyl chloride (4ml, 55mmoles) and pyridine (0.2ml, 2.4mmoles) in dry diethyl ether (20ml) were added dropwise to a stirred solution of 3,5-dimethoxybenzyl alcohol (5g, 30mmoles) in dry diethyl ether (25ml). After complete addition, stirring was continued for 2 hours then water (20ml) was added to destroy the excess thionyl chloride. The diethyl ether layer was separated and washed with water (20ml), 2*N* sodium hydroxide solution (2x20ml) and water (20ml) and the ether layer dried and evaporated to a solid. The solid was recrystallized from petrol to give 3,5-dimethoxybenzyl chloride (5g, 90%) as needles, m.p. 46°C (lit.[98], 46°C); ν_{max} ($CHCl_3$) 1 620 and 1 600cm^{-1}; δ_H 6.51(2H, d, *J* 2Hz, ArH), 6.40(1H, t, *J* 2Hz, ArH), 4.49(2H, s, benzylic H's) and 3.77(6H, s, OMe); m/e 186,188(M^+).

3,5-Dimethoxybenzyl bromide (112b)

3,5-Dimethoxybenzyl alcohol (1g, 6mmoles) was added to 45% hydrobromic acid (30ml) and the mixture stirred overnight. The reaction mixture was then added to iced water (100ml) and the white precipitate produced was filtered, washed with a little cold water and air dried. The solid was recrystallized from petrol to give 3,5-dimethoxybenzyl bromide (1.1g, 79%) as cubes, m.p. 71-72°C (lit.[99], 70°C); $\nu_{max.}$(KBr) 1 614 and 1 596 cm^{-1}; δ_H 6.51(2H, d, *J* 2Hz, ArH), 6.36(1H, t, *J* 2Hz, ArH), 4.36(2H, s, benzylic H's), and 3.72(6H, s, OMe); m/e 380,382(M^+).

3,5-Dimethoxybenzyl iodide (112c)

A mixture of 3,5-dimethoxybenzyl chloride (1g, 5.4mmoles) and sodium iodide (1.6g, 10.8mmoles) was stirred and refluxed in anhydrous acetone (50ml). After 4 hours the reaction mixture was cooled and the acetone removed by evaporation. The residue was partitioned between dichloromethane (30ml) and saturated sodium sulphite solution (30ml). The organic layer was separated, dried and evaporated to a crystalline residue. Recrystallization from diethyl ether/petrol gave 3,5-dimethoxybenzyl iodide (1.3g, 87%) as needles,m.p. 86-87°C (Found: C, 38.97; H, 3.99; I, 45.70%; M^+, 278. $C_9H_{11}O_2I$ requires C, 38.87; H, 3.99; I, 45.63%; M, 278); ν_{max}(KBr) 2 900, 2 825, and 1 585cm^{-1}; δ_H 6.53(2H, d, *J* 2Hz, ArH), 6.35(1H, t, *J* 2Hz, ArH), 4.40(2H, s, benzylic H), and 3.79(6H, s, OMe).

3,5-Dimethoxybenzyl methanesulphonate (112d)

To a stirred solution of 3,5-Dimethoxybenzyl alcohol (1g, 6mmoles) and methanesulphonyl chloride (0.55ml, 7mmoles) in dry dichloromethane (40ml) cooled in ice, was added a solution of triethylamine (1ml, 7mmoles) dropwise. After an hour the reaction mixture was poured into iced water (100ml) and the dichloromethane layer separated and the aqueous layer extracted again with dichloromethane (30ml). The combined extracts were dried and evaporated to a dark green oil. Short column chromatography on silica using dichloromethane/petrol as eluent gave a light green oil (1.4g, 90%).

The crude 3,5-dimethoxybenzyl methanesulphonate was used without further purification as attempted distillation led to decomposition. $\nu_{max.}$(CCl_4) 2 960, 1 717, and 1 600 cm^{-1}; δ_H 6.54(2H, d, J 2Hz, ArH), 6.45(1H, t, J 2Hz, ArH), 5.14(2H, s, benzylic), 3.78(6H, s, OMe), and 2.91(3H, s, SO_2Me); m/e 246 (M^+).

Reaction of lithiated *N,N*-diethyl-2,4-dimethoxybenzamide with 3,5-dimethoxybenzyl electrophiles (112 a-d)

To *N,N*-diethyl-2,4-dimethoxybenzamide (100mg, 0.4mmoles) in dry THF

(10ml) cooled to -78° under argon was added t-butyl lithium (0.25ml, 0.44mmoles, 1.8M) in hexane dropwise and the yellow solution stirred for 5 minutes. The 3,5-dimethoxybenzyl electrophile (0.44mmoles) in dry THF (10ml) was added in one lot and the solution stirred for an hour, then the cooling bath was removed and the reaction mixture was allowed to come to room temperature. Water (20ml) was added and the THF evaporated. The aqueous mixture was then extracted with dichloromethane (3x10ml), dried and evaporated to give a dark oil from which only *N,N*-diethyl-2,4-dimethoxybenzamide could be isolated by preparative layer chromatography using diethyl ether as eluent.

N, N-**Diethyl-6-chloro-2,4-dimethoxybenzamide** (114)

To a stirred solution of *N, N*-dimethoxybenzamide (2g, 8.4mmoles) in dry THF (30ml) at -78°C under argon was added *t*-butyl lithium (5.2ml, 9.3mmoles, 1.8M) in hexane dropwise. After 2 minutes, *p*-toluenesulphonyl chloride (1.6g, 8.4mmoles) in dry THF (10ml) was added rapidly. The solution was stirred at -78°C for 10 minutes then allowed to come to room temperature over 2 hours. Water (20ml) was added and the organics removed at reduced pressure. The aqueous solution was extracted with dichloromethane (3x15ml) and the combined extracts dried and evaporated to a clear oil. Short column chromatography on silica using dichloromethane/diethyl ether as eluent (1:1) gave *N,N*-diethyl-6-chloro-2,4-dimethoxybenzamide (1.2g, 44%), recrystallized from di-isopropyl ether as needles, m.p. 65-66°C (Found: C, 57.44; H, 6.75; N, 5.13%; M^+, 271/273.

$C_{13}H_{18}ClNO_3$ requires C, 57.46; H, 6.68; N, 5.15%; *M*, 271/273); $\nu_{max.}$(CCl$_4$) 2 980, 1 644, and 1 606 cm^{-1}; δ_H 6.51(1H, d, *J* 2Hz, ArH), 6.37(1H, d, *J* 2Hz, ArH), 3.80(6H, br s, OMe), 3.70-3.30(2H, m, NC*H*$_2$CH$_3$), 3.14(2H, q,*J* 8Hz,NC*H*$_2$CH$_3$), 1.22(3H, t, *J* 8Hz, NCH$_2$C*H*$_3$), and 1.13(3H, t, *J* 8Hz, NCH$_2$C*H*$_3$).

N, *N*-Diethyl-2,4-dimethoxy-6-iodobenzamide (115)

To a stirred solution of *N*,*N*-diethyl-2,4-dimethoxybenzamide (2g, 8.4mmoles) in dry THF (30ml) at -78°C under argon was added *t*-butyl lithium (5.2ml, 9.3mmoles, 1.8M) in hexane dropwise. After 2 minutes iodine (2.1g, 8.4mmoles) in dry THF (10ml) was added rapidly and the solution stirred at -78°C for 10 minutes then allowed to come to room temperature over 2 hours. Water (20ml) was added and the the organics removed at reduced pressure. The aqueous layer was extracted with dichloromethane (3x15ml) and the combined extracts dried and evaporated to a purple oil. Short column chromatography on silica using dichloromethane/diethyl ether (2:1) as eluent gave *N*,*N*-2,4-dimethoxy-6-iodobenzamide (1.6g, 52%), recrystallized from di-isopropyl ether as needles, m.p. 64-65°C (Found: C, 42.91; H, 5.02; N, 3.79; I, 34.73%; M^+, 363. $C_{13}H_{18}INO_3$ requires C, 42.99; H, 5.07; N, 3.86; I, 34.90%; *M*, 363); $\nu_{max.}$(CCl$_4$) 2 980, 1 642, and 1 599 cm^{-1}; δ_H 6.86(1H, d, *J* 2Hz, ArH), 6.39(1H, d, *J* 2Hz, ArH), 3.79(6H, br s, OMe), 3.80-2.94(4H, m, NC*H*$_2$CH$_3$), 1.20(3H, t,*J* 8Hz,NCH$_2$*CH*$_3$), 1.00(3H, t, *J* 8Hz, NCH$_2$C*H*$_3$); and recovered *N*,*N*-diethyl-2,4-dimethoxybenzamide (0.7g, 35%).

3,5-Dimethoxybenzaldehyde (116)

Pyridinium chlorochromate (1.9g, 8.8mmoles) was added in one portion to a vigorously stirred solution of 3,5-dimethoxybenzyl alcohol (1g, 6mmoles) in dry dichloromethane (50ml). The orange solution quickly turned dark green and stirring was continued for another 3 hours. Neutral alumina (10g) was added to aid filtration and the mixture stirred at room temperature for 10 minutes then filtered through a short plug of silica. The dichloromethane was evaporated to give a green oil which crystallized on standing. Column chromatography on silica using dichloromethane/petrol (1:1) as eluent gave a clear oil which slowly crystallized. Recrystallization from di-isopropyl ether gave 3,5-dimethoxybenzaldehyde as needles, m.p. 45-46°C (lit.[101], 45-46°C); $\nu_{max.}$(KBr) 2 940, 1 694, and 1 598 cm^{-1}; δ_H 9.87(1H, s, aldehyde H), 7.00(2H, d, J 2Hz, ArH), 6.69(1H, t, J 2Hz, ArH), and 3.83(6H, s, OMe); m/e 166 (M^+).

5,7-Dimethoxy-3-(3',5'-dimethoxyphenyl)phthalide (118)

To a stirred solution of *N,N*-diethyl-2,4-dimethoxybenzamide (2g, 8.43mmoles) in dry THF (25ml) at -78°C under argon was added *t*-butyl lithium (5.2g, 9.36mmoles, 1.8M) in hexane dropwise. The solution went yellow and was stirred for 5 minutes then, 3,5-dimethoxybenzaldehyde (1.65g, 8.43mmoles) in dry THF (20ml) was quickly added. The solution went dirty green on complete addition of the aldehyde and the mixture was stirred for an hour at -78°C, then allowed to come to room temperature. Water (20ml) was added and the THF evaporated. The aqueous mixture was extracted with dichloromethane (3x20ml) and the organic extracts dried and evaporated to a thick yellow oil. The oil was redissolved in benzene (50ml) and a few drops of a solution of perchloric acid in ethyl acetate[102] added and the mixture refluxed overnight. The benzene was evaporated to an oily solid which was taken up, in the minimum amount of hot dichloromethane, then diethyl ether was added dropwise till crystallization occurred. On cooling, the crystals were filtered, washed with ether and air dried to give 5,7-dimethoxy-3-(3',5'-dimethoxyphenyl)phthalide (1.75g, 63%) as needles, m.p. 183-184°C (Found: C, 65.45; H, 5.49%; M^+, 330. $C_{18}H_{18}O_6$ requires C, 65.38; H, 5.48%; *M*, 330.);$\nu_{max.}$(KBr) 3 000, 1 768, and 1 600cm^{-1}; δ_H 6.40(4H, s, ArH), 6.31(1H, br s, ArH), 6.11(1H, s, benzylic H), 3.96(3H, s, OMe), 3.80(3H, s, OMe), and 3.75(6H, s, OMe).

2,4-Dimethoxy-6-(3',5'-dimethoxybenzyl)benzoic acid (119)

A stirred mixture of 5,7-dimethoxy-3-(3',5'-dimethoxyphenyl)phthalide (3g, 9.1mmoles) in methanol (25ml) and ethyl acetate (25ml) containing 10% palladium on charcoal was hydrogenated at atmospheric pressure for 48 hours. The catalyst was removed by filtration through Celite and the filtrate evaporated to give a white solid. Recrystallization from dichloromethane gave 2,4-dimethoxy-6-(3',5'-dimethoxybenzyl)benzoic acid (2.5g, 83%) as cubes, m.p. 141-142°C (Found: C, 64.86; H, 6.05%; M^+, 332. $C_{18}H_{20}O_6$ requires C, 65.05; H, 6.07%; M, 332); $\nu_{max.}$(KBr) 3 450, 2 950, 1 770, and 1 600cm^{-1}; δ_H 6.35(5H, m, ArH), 3.98(2H, s, benzylic H's), 3.81(3H, s, OMe), and 3.73(9H, s, OMe).

1,3,6,8-Tetramethoxy-9-anthranol (120)

2,4-Dimethoxy-6-(3',5'-dimethoxybenzyl)benzoic acid (75mg, 0.23mmoles) was added in one portion to 90% sulphuric acid (2ml) cooled in ice. The reaction mixture went olive green and was stirred overnight by which time it had gone dark purple. The mixture was carefully diluted with iced water and added to an excess of sodium bicarbonate solution. The mixture was extracted with dichloromethane (3x20ml) and the organic extracts dried and evaporated to a purple/orange solid. Recrystallization from dichloromethane/diethyl ether gave 1,3,6,8-tetramethoxy-9-anthranol(48mg, 56%) as orange plates, m.p. 207-208°C (Found: C, 68.69; H, 5.94%; M^+, 314. $C_{18}H_{18}O_5$ requires C, 68.78; H, 5.77%; M, 314);$\nu_{max.}$(KBr) 3 310 and 2 950cm^{-1}; δ_H 10.57(1H, s, OH), 7.35(1H, s, H-10), 6.53(2H, d, J 2Hz, ArH), 6.24(2H, d, J 2Hz, ArH), 3.95(6H, s, OMe), and 3.82(6H, s, OMe).

Reaction of 2,4-dimethoxy-6-(3',5'-dimethoxybenzyl)-benzoic acid (119) with trifluoroacetic anhydride

To a stirred solution of 2,4-dimethoxy-6-(3',5'-dimethoxybenzyl)benzoic acid (0.5g, 1.5mmoles) in dry dichloromethane (25ml) was added trifluoroacetic anhydride (0.45ml, 3.2mmoles). The solution went green then purple and was stirred overnight. The solution was then poured into excess of dilute sodium bicarbonate solution and extracted with dichloromethane (3x20ml). The combined dichloromethane extracts were then washed with dilute sodium bicarbonate solution till they turned orange and then dried and evaporated to an orange crystalline mass. Recrystallization from dichloromethane/diethyl ether gave 1,3,6,8-tetramethoxy-9-anthranol (0.46g, 97%) as orange plates, m.p. 207-208°C, identical in all respects with a sample produce by sulphuric acid catalyzed ring closure.

Attempted methylation of 1,3,6,8-tetramethoxy-9-anthranol (120)

To 1,3,6,8-tetramethoxy-9-anthranol (200mg, 0.63mmoles) in dry acetone (50ml) was added dimethyl sulphate (0.1ml, excess) and anhydrous potassium carbonate (100mg). The mixture was stirred and refluxed overnight and then filtered and the acetone evaporated to leave a purple solid. The solid was dissolved in ethyl acetate (20ml), and washed with concentrated ammonia solution (2×10ml) and 2*N* sodium hydroxide solution (2×10ml) and dried and evaporated to give a purple solid. Recrystallization from acetone/petrol gave 1,3,6,8-tetramethoxy-9,10-anthraquinone (180mg, 87%) as purple orange plates, m.p. 224-225° (lit.[103], 225-226°C); $\nu_{max.}$ (KBr) 2 950, 1 658, and 1 600cm^{-1}; δ_H 7.31(2H, d, *J* 2Hz, ArH), 6.77(2H, d, *J* 2Hz, ArH), and 3.95(12H, s, OMe); m/e 328(M^+). Repetition of the reaction under argon gave starting anthranol with only a little oxidation to the anthraquinone during work up.

Methylation of anthranol (120) with sodium hydride and methyl iodide

To a stirred mixture of sodium hydride (50mg, 2mmoles) in dry THF (10ml) under argon at room temperature was added 1,3,6,8-tetramethoxy-9-anthranol (0.3g, 0.95mmoles) in dry THF(10ml) and methyl iodide (0.15ml, 2.4mmoles). Stirring was continued for 2 hours then water (20ml) was added carefully and the THF removed by evaporation. The aqueous layer was extracted with dichloromethane (3x10ml) and the combined organic extracts dried and evaporated to a dark red oil. Column chromatography using dichloromethane/diethyl ether (1:1) gave a yellow solid, recrystallized from dichloromethane/diethyl ether to give 10,10-dimethyl-1,3,6,8-tetramethoxy-9-anthrone (0.13g, 40%) as yellow prisms, m.p. 158-159°C (Found: C, 70.13; H, 6.63%; M^+, 342. $C_{20}H_{22}O_5$ requires C, 70.16; H, 6.48%; M, 342); $\nu_{max.}$(KBr) 2 920, 1 690, and 1 600 cm^{-1}; δ_H 6.68(2H, d, *J* 2Hz, ArH), 6.40(2H, d, *J* 2Hz, ArH), 3.92(6H, s, OMe), 3.88(6H, s, OMe), and

1.62(6H, s, ArMe).

Reaction of anthranol (120) with silver(I) oxide and methyl iodide

1,3,6,8-Tetramethoxy-9-anthranol (100mg, 0.32mmoles) was treated with silver(I) oxide (100mg, 0.32mmoles) in methyl iodide (1ml, excess) and the mixture stirred for 6 hours. The mixture was diluted with ethyl acetate (25ml) and filtered through Celite (care!). The ethyl acetate solution was cautiously washed with concentrated ammonia solution (2x20ml) and 2*N* sodium hydroxide solution (2x10ml) and then the organic layer dried and evaporated to a dark crystalline mass. Short column chromatography using dichloromethane as eluent gave 1,3,6,8-tetramethoxy-9,10-anthraquinone (10mg, 10%) as purple/orange plates from acetone/petrol, m.p. 224-225°C. The column was then eluted with ethyl acetate/methanol (1:1) to give a purple residue that crystallized from chloroform to give 1,1',3,3',6,6',8,8'-octamethoxy-10,10'-bianthran-9,9'-diol (72mg, 72%) as cubes , m.p. 304-305°C (Found: M^+, 626.2119. $C_{36}H_{34}O_{10}$ requires M, 626.2152); $\nu_{max.}$(KBr) 3 450, 2 940, 1 660, and 1 600 cm^{-1}; δ_H 6.42(4H, d, J 2Hz, ArH), 5.6(4H, d, J 2Hz, ArH), 3.90(12H, s, OMe), and 3.60(12H, s, OMe).

Reaction of 1,3,6,8-tetramethoxy-9-anthranol (120) with silver(I) oxide

1,3,6,8-Tetramethoxy-9-anthranol (100mg, 0.32mmoles) and silver (I) oxide (100mg, 0.32mmoles) were stirred in dry acetone at room temperature for 6 hours. The mixture was then filtered through Celite and evaporated to a purple mass. Short column chromatography as for previous experiment gave 1,3,6,8-tetramethoxy-9,10-anthraquinone (11mg, 11%) and 1,1',3,3',6,6',8,8'-octamethoxy-10,10'-bianthran-9,9'-diol (83mg, 83%).

Reaction of 1,3,6,8-tetramethoxy-9-anthranol (120) with sodium hydride and methyl iodide in diglyme

To a stirred suspension of sodium hydride (17mg, 0.7mmoles) in dry diglyme (20ml) under argon was added 1,3,6,8-tetramethoxy-9-anthranol (100mg, 0.32mmoles) and methyl iodide (50μl, 0.8mmoles). The mixture was stirred for 7 hours then carefully added to concentrated ammonia solution (100ml). The ammonia solution was then extracted with dichloromethane (3x20ml) and the combined organic extracts back washed with water then dried and evaporated to a purple solid. Preparative chromatography using diethyl ether with 5% methanol as eluent gave 10,10-dimethyl-1,3,6,8-tetramethoxy-9-anthrone (30mg, 27%) and a compound recrystallized as yellow needles from chloroform/diethyl ether that appeared to be 10-methyl-1,3,6,8-tetramethoxy-9-anthranol (20mg, 19%) m.p. 218-219°C ;$\nu_{max.}$(KBr) 3 455, 2 985, 1 645, and 1 600cm^{-1}; δ_H 6.94(2H, d, J 2Hz, ArH), 6.37(2H, d, J 2Hz, ArH), 3.82(6H, s, OMe), 3.80(6H, s, OMe), and 2.53(3H, s, ArMe); m/e 328(M^+) and 1,3,6,8-tetramethoxy-9,10-anthraquinone (50mg, 48%) recrystallized from acetone/petrol as purple/orange plates, m.p. 224-225°C.

Reaction of 2,4-dimethoxy-6-(3',5'-dimethoxybenzyl)benzoic acid (119) with acetyl chloride

To a stirred solution of 2,4-dimethoxy-6-(3',5'-dimethoxybenzyl)benzoic acid (2g, 6mmoles) in dry dichloromethane (50ml) at room temperature was added acetyl chloride (13ml, 18.2mmoles) dropwise. The solution turned green and was stirred overnight, by which time the colour had intensified. The dark green solution was washed several times with saturated sodium bicarbonate solution till it turned orange . The dichloromethane layer was dried and evaporated to a green solid which was crystallized from dichloromethane/di-isopropyl ether to give 9-acetoxy-1,3,6,8-tetramethoxyanthracene (2g, 90%) as green/yellow rhombics, m.p. 257-258°C (Found: C, 67.40; H, 5.79%; M^+, 356. $C_{20}H_{20}O_6$ requires C, 67.40; H, 5.66%; M, 356); $\nu_{max.}$(KBr) 2 940, 1 748, and 1 628cm^{-1}; δ_H 7.85(1H, s, ArH), 6.69(2H, d, J 1Hz, ArH), 6.38(2H, d, J 1Hz, ArH), 3.91(12H, s, OMe), and 2.9(3H, s, OAc).

Reaction of 9-acetoxy-1,3,6,8-tetramethoxyanthracene (133) with sodium hydroxide and dimethyl sulphate

To a stirred suspension of powdered sodium hydroxide (33mg, 0.8mmoles) and dimethyl sulphate (30μl, 0.3mmoles) in dry diglyme (10ml) under argon was added 9-acetoxy-1,3,6,8-tetramethoxyanthracene (100mg, 0.28mmoles) in dry diglyme (5ml) and the mixture heated at 70° for 12 hours. The contents of the reaction vessel were poured into concentrated ammonia solution (50ml) and the precipitate collected by filtration through a pad of Celite and washed several times with water to remove traces of diglyme. The Celite pad was then washed with hot dichloromethane (5x10ml) and the combined washings dried and evaporated to an orange crystalline mass. Recrystallization from di-isopropyl ether gave 1,3,6,8,9-pentamethoxyanthracene (55mg, 60%) as dark orange cubes, m.p. 137-138°C; (Found: C,69.58; H, 6.19%; M^+, 328. $C_{19}H_{20}O_5$ requires C, 69.50; H, 6.14%; M, 328); $\nu_{max.}$(KBr) 2 840, 1 622, and 1 576cm^{-1}; δ_H 7.75(1H, s, ArH), 6.68(2H, d, J 2Hz, ArH), 6.40(2H, d, J 2Hz, ArH), 4.00(6H, s, OMe), 3.93(6H, s, OMe), and 3.90(3H, s, OMe).

Methylation of 9-acetoxy-1,3,6,8-tetramethoxyanthracene (133) using dimethoxyethane, dimethyl sulphate and sodium hydroxide

To a stirred suspension of powdered sodium hydroxide (0.28g, 7mmoles) in dry 1,2-dimethoxyethane (20ml) under argon was added 9-acetoxy-1,3,6,8-tetramethoxyanthracene (500mg, 1.4mmoles) and the mixture heated to 70°C overnight. To the dark green mixture was added dimethyl sulphate (0.66ml, 7mmoles) in one portion. The mixture was stirred and heated for another hour, by which time it was a light orange colour, then it was allowed to cool and added to concentrated ammonia solution (50ml) and the the organics evaporated. The aqueous phase was extracted with dichloromethane (3x20ml) and the combined extracts dried and evaporated to an orange powder. Short column chromatography using dichloromethane/diethyl ether (1:1) gave 1,3,6,8,9-pentamethoxyanthracene contaminated with another compound. The impurity could not be separated by chromatography but fractional crystallization from methanol gave 10-methyl-1,3,6,8,9-pentamethoxyanthracene (10mg, 4%) as yellow prisms, m.p. 173-174°C (Found: C, 70.15; H, 6.54%; M^+, 342. $C_{20}H_{22}O_5$ requires C, 70.16; H, 6.48%; M, 342.); $\nu_{max.}$ (CCl_4) 2 936, 1 615, and 1 572cm^{-1}; δ_H 6.90(2H, d, J 2Hz, ArH), 6.40(2H, d, J 2Hz, ArH), 4.00(6H, s, OMe), 3.96(6H, s, OMe), 3.85(3H, s, OMe), and 2.80(3H, s, ArMe).

Crystallization of the mother liquors from di-isopropyl ether gave 1,3,6,8,9-

pentamethoxyanthracene (0.32g, 70%) as dark orange cubes m.p. 137-138°C. Further elution gave 1,1',3,3',6,6',8,8',9,9'-decamethoxy-10,10'-bianthracene (25mg, 5%) as yellow prisms from methanol m.p. 256°C (Found: C, 69.73; H, 5.79%; M^+, 654. $C_{38}H_{38}O_{10}$ requires C, 69.71; H, 5.85%; M, 654); $\nu_{max.}$(KBr) 2 917, 1 610, and 1 570 cm^{-1}; δ_H 6.35(4H, d, J 2Hz, ArH), 5.81(4H, d, J 2Hz, ArH), 4.00(18H, s, OMe) and 3.28(12H, s, OMe) and 1,3,6,8,-tetramethoxy-9,10-anthraquinone (32mg 7%) as purple/orange plates from acetone/petrol, m.p. 224-225°C.

Reaction of 9-acetoxy-1,3,6,8-tetramethoxyanthracene (133) with aluminium chloride

A solution of 9-acetoxy-1,3,6,8-tetramethoxyanthracene (100mg, 0.28mmoles) in dry nitrobenzene (10ml) was stirred and heated to 100°C with anhydrous aluminium chloride (45mg, 0.34mmoles) for 6 hours. The reaction mixture was poured into 1N hydrochloric acid (50ml) and the nitrobenzene removed by steam distillation. The aqueous mixture was allowed to cool and then extracted with dichloromethane (3x10ml) and the combined organic extracts dried and evaporated to an orange mass. Thin layer chromatography and ^1H n.m.r. showed a complex mixture. Varying reaction conditions and chromatography on the extracts failed to yield any identifiable compounds.

9-Acetoxy-10-bromo-1,3,6,8-tetramethoxyanthracene (137)

To a stirred solution of 9-acetoxy-1,3,6,8-tetramethoxyanthracene (50mg, 0.14mmoles) in dry dichloromethane (10ml) was added *N*-bromosuccinimide (50mg, 0.14mmoles) and the mixture was stirred and refluxed for 5 hours. The mixture was cooled and filtered through a plug of Celite and the solvent removed by evaporation. The dark residue was crystallized twice from dichloromethane/diethyl ether to give 9-acetoxy-10-bromo-1,3,6,8-tetramethoxyanthracene (30mg, 49%) as orange cubes, m.p. 240°C (Found: C: 55.18; H, 4.42; Br, 18.35%; M^+, 436/438. $C_{20}H_{19}O_6Br$ requires C, 55.18; H, 4.40; Br, 18.36%; M, 436/438); $\nu_{max.}$ (KBr) 2 820, 1 762, and 1 620 cm^{-1}; δ_H 7.30(2H, d, J 2Hz, ArH), 6.40(2H, d, J 2Hz, ArH), 3.95(6H, s, OMe), 3.90(6H, s, OMe), and 2.35(3H, s, OAc).

Reaction of 2,4-dimethoxy-6-(3',5'-dimethoxybenzyl)-benzoic acid (119) with methanolic hydrogen chloride

A solution of 2,4-dimethoxy-6-(3',5'-dimethoxybenzyl)benzoic acid in dry methanol (25ml) was cooled in ice and saturated with dry hydrogen chloride gas. The solution was refluxed overnight, then added to an excess of saturated sodium bicarbonate solution. The solution was extracted with dichloromethane (3x20ml) and the organic extracts dried and evaporated to give a light yellow oil. Crystallisation from methanol gave bis-(3,5-dimethoxyphenyl)methane (72mg, 83%)

as needles, m.p. 65°C (Found: C, 70.81; H, 6.99%; M^+, 288. $C_{17}H_{20}O_4$ requires C, 70.81; H, 7.00%; M, 288); $\nu_{max.}$(KBr) 2 900 and 1 592cm^{-1}; δ_H(CCl$_4$) 6.2(6H, br s, ArH), 3.73(2H, s, benzylic H), and 3.65(12H, s, OMe).

Methyl 2,4-dimethoxy-6-(3',5'-dimethoxybenyl)-benzoate (139)

To a stirred solution of 2,4-dimethoxy-6-(3',5'-dimethoxybenyl)benzoic acid (200mg, 6mmoles) in dry ethyl acetate (20ml) was added an ethereal solution of diazomethane, generated from Nitrosan[104] (5g) and 30% sodium hydroxide solution (15ml), till the reaction mixture turned yellow. The excess diazomethane was destroyed with acetic acid and the reaction mixture was poured into the sodium bicarbonate solution.

The ethyl acetate layer was separated and washed with dilute sodium bicarbonate solution, then dried and evaporated to a yellow gum. Crystallization from di-isopropyl ether gave methyl 2,4-dimethoxy-6-(3',5'-dimethoxybenyl)-benzoate (200mg, 96%) as needles, m.p. 64-65°C (Found: C, 65.69; H, 6.33%; M^+, 346. $C_{19}H_{22}O_6$ requires C, 65.88; H, 6.40%; M, 346.); $\nu_{max.}$(KBr) 2 960, 1 730, and 1 600cm^{-1}; δ_H 6.3(5H, m, ArH), 3.86(2H, s, benzylic H s'), 3.79(3H, s, OMe), 3.78(3H, s, OMe), and 3.7(9H, s, OMe).

Reaction of 9-acetoxy-1,3,6,8-tetramethoxyanthracene (133) with methanolic hydrogen chloride

A solution of 9-acetoxy-1,3,6,8-tetramethoxyanthracene (100mg, 0.28mmoles) in dry methanol cooled in ice was saturated with dry hydrogen chloride gas. The solution was then refluxed for 6 hours by which time it was dark green. The mixture was cooled and then added to an excess of saturated sodium bicarbonate (50ml) solution and the aqueous phase extracted with dichloromethane (3x20ml). The organic extracts were dried and evaporated to a dark purple residue. Column chromatography on silica using dichloromethane/diethyl ether (1:1) as eluent gave 1-hydroxy-3,6,8-trimethoxy-9-anthrone (25mg, 30%) as yellow rods from dichloromethane/ diethyl ether, m.p. 174-175°C (Found: C, 67.99; H, 5.51%; M^+, 300. $C_{17}H_{16}O_5$ requires C, 67.88; H, 5.37%; M, 300); $\nu_{max.}$(KBr) 3 420, 1 625, and 1 598 cm^{-1}; δ_H 13.70(1H, s, H-bonded phenol), 6.40(2H, br s, ArH), 6.32(2H, br s, ArH), 4.19(2H, br s, benzylic H s'), 3.95(3H, s, OMe), 3.88(3H, s, OMe), and 3.82(3H, s, OMe), and 1,8-dihydroxy-3,6-dimethoxy-9-anthrone (40mg, 50%) as needles from dichloromethane/diethyl ether, m.p. 215-216°C (Found: C, 67.05; H, 5.04%; M^+, 286. $C_{16}H_{14}O_5$ requires C, 67.12; H, 4.93%; M, 286); $\nu_{max.}$(KBr) 3 440, 2 940, 1 627, 1 600, and 1 570 cm^{-1}; δ_H 12.65(2H, br s, H-bonded phenols), 6.40(4H, br s, ArH), 4.22(2H, br s, benzylic H s'), and 3.87(6H, br s, OMe).

It was possible to produce mainly 1-hydroxy-3,6,8-trimethoxy-9-anthrone by lowering the concentration of hydrogen chloride and shortening the reaction time.

Methyl 3,5-dihydroxybenzoate

A solution of 3,5-dihydroxybenzoic acid (20g, 0.13moles) in dry methanol (200ml) cooled in ice, was saturated with dry hydrogen chloride gas. The solution was then refluxed for 4 hours, allowed to cool and poured into water (700ml). The aqueous mixture was then extracted with dichloromethane (3x100ml) and the combined organic extracts back washed with saturated sodium bicarbonate solution (2x50ml), then dried and evaporated to a yellow oil which crystallized on standing. Recrystallization from chloroform gave methyl 3,5-dihydroxybenzoate (20g, 90%) as needles, m.p. 163-164°C (lit.[105], 163-164°C); $\nu_{max.}$(KBr) 3 390, 1 697, and 1 603cm^{-1}; δ_H 7.00(2H, d, *J* 2Hz, ArH), 6.55(1H, t, *J* 2Hz, ArH), 4.55(2H, br s, OH) and 3.85(3H, s, OMe); m/e 168(M$^+$).

Methyl 3,5-dibenzyloxybenzoate (145)

To a mixture of methyl 3,5-dihydroxybenzoate(6g, 35.7mmoles) and anhydrous potassium carbonate (11g) in dry acetone (120ml) was added benzyl bromide (9.4mls, 79mmoles) and the lot stirred and refluxed for 6 hours. The mixture was cooled and filtered and the filtrate evaporated to a yellow oil. The oil was suspended in diethyl ether (150ml) and washed with concentrated ammonia solution (2x50ml) and 2*N* sodium hydroxide solution (2x50ml) and the diethyl ether layer dried and evaporated to a clear oil which gradually solidified. Crystallization from methanol gave methyl 3,5-dibenzyloxybenzoate (10.1g, 81%) as needles m.p. 68-69°C (lit.[106]; 69-69.5°C); $\nu_{max.}$(KBr) 2 948, 1 714, and 1 598cm^{-1};δ_H 7.35(10H, br s, ArH), 7.28(2H, d, *J* 2Hz, ArH), 6.78(1H, t, *J* 2Hz, ArH), 5.03(4H, s, benzylic), and 3.87(3H, s, OMe); m/e 348(M$^+$).

3,5-Dibenzyloxbenzyl alcohol (146)

To a stirred suspension of lithium aluminium hydride (1.21g, 31.8mmoles) in dry THF (20ml) was carefully added a solution of methyl 3,5-dibenzyloxybenzoate (10g, 28.7mmoles) in dry THF (100ml) at such a rate as to cause gentle reflux. After complete addition, stirring and heating were continued for 6 hours. The mixture was allowed to cool, and water (1.2ml) was added very carefully with stirring, then 15% sodium hydroxide solution (1.2ml) and then more water (3.6ml) and the mixture stirred for 20 minutes till the precipitate was white. The precipitate was removed by filtration and the filter cake washed with a little THF. The filtrate was evaporated to a clear oil which solidified. Crystallization from di-isopropyl ether gave 3,5-dibenzyloxybenzyl alcohol (8g, 87%) as needles m.p. 78-79°C (lit.[106]; 79- 79.5°C); $\nu_{max.}$ 3 320, 2 868, and 1 594cm^{-1}; δ_H 7.36(10H, br s, ArH), 6.58(3H, m, ArH), 5.01(4H, s, benzylic), 4.60(2H, s, benzylic), and 1.64(1H, s, OH); m/e 320(M$^+$).

3,5-Dibenzyloxybenzaldehyde (142)

To a rapidly stirred solution of 3,5-dibenzyloxybenzyl alcohol (5g, 15.6mmoles) in dry dichloromethane (100ml) was added pyridinium chlorochromate[100] (5g, 23mmoles) in one portion. The mixture turned dark green and was stirred overnight. Neutral alumina (20g) was added (to aid filtration) and the mixture stirred for a further hour, then filtered through a small pad of silica. The filtrate was evaporated to a green residue which was subjected to column chromatography on silica using dichloromethane as eluent to give a solid which was crystallized from di-isopropyl ether to give 3,5-dibenzyloxybenzaldehyde (4g, 81%) as leafs, m.p.75-76°C (lit.[107], 76.5-77°C); $\nu_{max.}$ 3 030, 1 688, 1 608, and 1 594cm^{-1}; δ_H 9.89(1H, s, C*H*O), 7.41(10H, br s, ArH), 7.13(2H, d, *J* 2Hz, ArH), 6.89(1H, t, *J* 2Hz, ArH), and 5.11(4H, s, benzylic); m/e 318(M$^+$).

3-(3',5'-Dibenzyloxyphenyl)-5,7-dimethoxyphthalide (143)

To a stirred solution of *N*, *N*-diethyl-2,4-dimethoxybenzamide (2g, 8.43mmoles) in dry THF (30ml) cooled to -78°C under argon was added *t*-butyl lithium (3.5ml, 9.1mmoles, 2.6 M) in hexane dropwise . The yellow solution was stirred for two minutes and 3,5-dibenzyloxybenzaldehyde (2.9g, 9.1mmoles) in dry THF (20ml) was added in one portion. The solution turned dark red and then light red and was allowed to come to room temperature over an hour. Water (30ml) was added and the organics evaporated. The aqueous layer was extracted with dichloromethane (3x20ml) and the extracts dried and evaporated to a yellow oil. The oil was dissolved in benzene (50ml) and a few drops of a solution of perchloric acid in ethyl acetate[102] added and the mixture refluxed overnight. The benzene was evaporated and the yellow residue was crystallized by dissolving in the minimum amount of hot dichloromethane and adding diethyl ether till crystallization occurred to give 3-(3',5'-dibenzyloxyphenyl)-5,7-dimethoxyphthalide as rods, m.p. 160-161°C (Found: C, 74.47; H, 5.47%; M^+ 482. $C_{30}H_{26}O_6$ requires C, 74.67; H, 5.43%; *M*, 482); $\nu_{max.}$(KBr) 3 030, 1 760, and 1 600 cm^{-1}; δ_H 7.38(10H, br s, ArH), 6.61(1H, t, *J* 2Hz, ArH), 6.52(2H, d, *J* 2Hz, ArH), 6.43(1H, br s, ArH), 6.27(1H, br s, ArH), 6.12(1H, s, benzylic), 5.00(4H, s, benzylic), 3.98(3H, s, OMe), and 3.80(3H, s, OMe).

Attempted hydrogenation of 3-(3',5'-dibenzyloxyphenyl)-5,7-dimethoxyphthalide (143)

A mixture of 3-(3',5'-dibenzyloxyphenyl)-5,7-dimethoxyphthalide (0.5g, 1mmole) in methanol (25ml) and ethyl acetate (25ml) was stirred over 10% palladium on carbon catalyst (0.5g) under an atmosphere of hydrogen at atmospheric pressure. After 2 days the catalyst was removed by filtration and the solvent evaporated to an amorphous solid which would not run in common solvents for analysis by thin layer chromatography on silica or dissolve for ^1H n.m.r. The solid was then stirred overnight in a solution of acetyl chloride (1ml) and dichloromethane (50ml). The dark green solution was poured into saturated sodium bicarbonate solution (100ml) and the organic layer separated and the aqueous layer extracted with dichloromethane (30ml). The combined dichloromethane extracts were washed with saturated sodium bicarbonate solution (50ml) and dried and evaporated to an orange mass which contained many compounds by thin layer chromatography and ^1H n.m.r. spectroscopy, but from which no one pure compound could be isolated.

Methyl 2,6-dimethoxy-4-methylbenzoate (149)

To methyl 2,6-dihydroxy-4-methylbenzoate (30g, 0.16moles) in dry acetone (500ml) was added anhydrous potassium carbonate (51g) and dimethyl sulphate (34ml, 0.36moles) and the mixture mechanically stirred and refluxed overnight. The reaction mixture was cooled and the potassium salts filtered off and the acetone solution evaporated to give a yellow oil. This residue was taken up in diethyl ether (300ml) and washed with concentrated ammonia solution (2x50ml) and 2*N* sodium hydroxide solution (2x50ml). The diethyl ether layer was dried and evaporated to a clear oil. Crystalisation from diethyl ether gave methyl 2,6-dimethoxy-4-methylbenzoate (23.2g, 67%) as plates, m.p. 84°C (lit.[89], 86°C); $\nu_{max.}$(KBr) 2 945, 1 735, and 1 610cm^{-1}; δ_H 6.36(2H, s, ArH), 3.86(3H, s, OMe), 3.78(6H, s, OMe), and 2.31(3H, s, ArMe); m/e 210(M$^+$).

Methyl 4-dibromomethyl-2,6-dimethoxybenzoate (150)

To a stirred solution of methyl 2,6-dimethoxy-4-methylbenzoate (0.5g, 2.38mmoles) in refluxing carbon tetrachloride (50ml), irradiated with a bench lamp (60W bulb), was added *N*-bromosuccinimide (0.89g, 5mmoles) spiked with benzoyl peroxide (20mg), over 15 minutes. The mixture was refluxed for another hour then allowed to cool and filtered through Celite and the carbon tetrachloride removed by evaporation. The oily residue was crystallized from diethyl ether to give methyl 4-dibromomethyl-2,6-dimethoxybenzoate (0.62g, 72%) as rhombics, m.p. 124-125°C; $\nu_{max.}$(KBr) 3 000, 1 729, 1 605, and 1 588 cm^{-1}; δ_H 6.79(2H, s, ArH), 6.60(1H, s, benzylic), 3.92(3H, s, OMe), and 3.87(6H, s, OMe); m/e 366/368/370(M^+).

Methyl 2,6-dimethoxy-4-formylbenzoate (147)

To methyl 4-dibromomethyl-2,6-dimethoxybenzoate (0.62g, 1.7mmoles) in THF at room temperature was added silver nitrate (0.6g, 3.5mmoles) in water (10ml) with stirring. A yellow precipitate appears instantly and the mixture was stirred overnight and then filtered through Celite and the THF removed by evaporation. The slurry that was left was taken up in diethyl ether (100ml) and washed with water (2x30ml) and the diethyl ether layer separated , dried and evaporated to a crystalline mass. Recrystallization from diethyl ether gave methyl 2,6-dimethoxy-4-formylbenzoate (0.35g, 91%) as needles, m.p. 113-114°C (Found: C, 59.02; H, 5.24%; M^+, 224. $C_{11}H_{12}O_5$ requires C, 58.92; H, 5.48%; M, 224); $\nu_{max.}$(KBr) 2 960, 1 732, and 1 698 cm^{-1}; δ_H 9.82(1H, s, aldehyde), 7.05(2H, s, ArH), 3.91(3H, s, OMe), and 3.86(6H, s, OMe).

Larger scale reaction of *N*-bromosuccinimide with methyl 2,6-dimethoxy-4-methylbenzoate (149)

To a stirred solution of methyl 2,6-dimethoxy-4-methylbenzoate (5g, 23.8mmoles) in refluxing carbon tetrachloride (100ml), irradiated with a bench lamp (60W), was added an intimate mixture of *N*-bromosuccinimide (8.9g, 50mmoles) and benzoyl peroxide (100mg) in small portions over an hour. The reaction mixture was refluxed for a further hour after complete addition then cooled and filtered through a pad of Celite and the carbon tetrachloride removed by evaporation. Thin layer chromatography and ^1H n.m.r. showed several compounds and it was decided to carry on and hydrolyse them before attempted separation to avoid decomposition.

To a stirred solution of acetone (50ml) and the residue from the bromination reaction (50ml) was added silver nitrate (8.5g, 50mmoles) in water (25ml) in one portion. A yellow precipitate was formed and the mixture was stirred overnight. The precipitate was removed by filtration and the filter cake washed with a little acetone. The solvent was removed from the filtrate by evaporation to leave a light yellow slurry. This was taken up in ethyl acetate (100ml) and washed with water (2x30ml) and the ethyl acetate layer dried and evaporated to a thick yellow oil. Column chromatography using dichloromethane as eluent gave 2-bromo-4-carboxymethyl-3,5-dimethoxybenzyl nitrate, m.p. 71-72°C (4.49g, 60%) as cubes from di-isopropyl ether (Found: C, 37.73; H, 3.34; N, 4.00;Br, 22.79%;

M^+, 349/351. $C_{11}H_{12}O_7NBr$ requires C, 37.73; H, 3.46; N, 4.00; Br, 22.79%; M, 349/351); $\nu_{max.}(CCl_4)$ 2 950, 1 738, 1 650, and 1 270 cm^{-1}; δ_H 6.80(1H, s, ArH), 5.58(2H, br s, benzylic), 3.95(3H, s, OMe), 3.90(3H, s, OMe), and 3.85(3H, s, OMe), and methyl 3-bromo-2,6-dimethoxy-4-formylbenzoate (0.65g, 10%) as large needles from di-isopropyl ether, m.p. 117-118°C (Found: C, 43.58; H, 3.56; Br, 26.71%; (M^+)302/304. $C_{11}H_{11}O_5Br$ requires C, 43.59; H, 3.66; Br, 26.39%; M, 302/304); $\nu_{max.}$(KBr) 1 740, 1 697, 1 590, and 1 560 cm^{-1}; δ_H 10.37(1H, s, C*H*O), 7.30(1H, s, ArH), 3.98(3H, s, OMe), 3.95(3H, s, OMe) and 3.92(3H, s, OMe), and methyl 3-bromo-2,6-dimethoxy-4-hydroxymethylbenzoate (1.3g, 20%) as needles from dichloromethane/di-isopropyl ether, m.p. 120-121°C (Found: C, 43.23; H, 4.33; Br, 26.15%; (M^+), 304/306. $C_{11}H_{13}O_5Br$ requires C, 43.30; H, 4.29; Br, 26.19%; M, 304/306); $\nu_{max.}$(KBr) 3 460, 1 170, 1 592, 1 564 cm^{-1}; δ_H 6.9(1H, s, ArH), 4.67(2H, s, benzylic H), 4.1(1H, br s, OH), 3.95(3H, s, OMe), 3.88(3H, s, OMe), and 3.80(3H, s, OMe).

Reaction of 2-bromo-4-carboxymethyl-3,5-dimethoxybenzyl nitrate (151) with triethylamine

To a stirred solution of 2-bromo-4-carboxymethyl-3,5-dimethoxybenzyl nitrate (500g, 1.4mmoles) in dry dichloromethane (20ml) was added freshly distilled triethylamine (0.5ml, 3.6mmoles) at room temperature. The solution was stirred overnight, then washed with 1*N* hydrochloric acid (2x20ml) and the dichloromethane layer dried and evaporated to a yellow solid. The residue was recrystallized from di-isopropyl ether to give 3-bromo-2,6-dimethoxy-4-formylbenzoate (425mg, quantitative) as needles, m.p.117-118°C.

4-Bromomethyl-2,6-dimethoxybenzoate (156)

To a stirred solution of methyl 2,6-dimethoxy-4-methylbenzoate (1g, 4.76mmoles) in refluxing carbon tetrachloride (50ml) was added an intimate mixture of *N*-bromosuccinimide (0.85g, 4.76mmoles) and benzoyl peroxide (20mg). The flask was illuminated with a bench lamp (60W) as the *N*-bromosuccinimide was added in small protions over 15 minutes. The mixture was stirred and illuminated at reflux for a further hour then allowed to cool and filtered through Celite. The solvent was evaporated to a yellow oil which was crystallized from diethyl ether to give methyl 4-bromomethyl-2,6-dimethoxybenzoate (1.1g, 82%) as cubes, m.p. 73-74°C; $\nu_{max.}$(KBr) 2 940, 1 740, 1 605, and 1 587 cm^{-1}; δ_H 6.6(2H, s, ArH), 4.44(2H, s, benzylic), 3.9(3H, s, OMe), and 3.84(6H, s, OMe); m/e 288/290(M^+).

4-Carboxymethyl-3,5-dimethoxybenzyl nitrate (157)

To a stirred solution of methyl 4-bromomethyl-2,6-dimethoxybenzoate (1g, 3.5mmoles) in bulk acetone (30ml) was added finely powdered silver nitrate (0.65g, 3.8mmoles) and the mixture stirred overnight. The mixture was filtered through Celite and evaporated to a clear oil which was recrystallized from di-isopropyl ether to give 4-carboxymethyl-3,5-dimethoxybenzyl nitrate (0.89g, 95%) as rhombics, m.p. 88-89°C (Found: C, 48.75; H, 4.86; N, 5.18%; M^+, 271. $C_{11}H_{13}O_7N$ requires C, 48.70; H, 4.83; N, 5.16%; M, 271); $\nu_{max.}(CCl_4)$ 2 940, 1 735, 1 615, 1 590, and 1 280 cm^{-1}; δ_H 6.60(2H, s, ArH), 5.40(2H, s, benzylic), 3.93(3H, s, OMe), and 3.85(3H, s, OMe).

Methyl 2,6-dimethoxy-4-formylbenzoate

To a stirred solution of 4-carboxymethyl-3,5-dimethoxybenzyl nitrate (220mg, 6.81mmoles) in dry dichloromethane (25ml) was added freshly distilled triethylamine (0.23ml, 1.6mmoles) and the mixture refluxed for 12 hours. The solution was allowed to cool, then washed with 1*N* hydrochloric acid (2x15ml) and the dichloromethane layer dried and evaporated to a tan coloured solid. Recrystallization from diethyl ether gave methyl 2,6-dimethoxy-4-formylbenzoate (150mg, 85%) as needles, m.p. 113-114°C.

3-(4'-Carboxymethyl-3',5'-dimethoxyphenyl)-5,7-dimethoxyphthalide (158)

To a stirred solution of *N*,*N*-diethyl-2,4-dimethoxybenzamide (0.19g, 0.8mmoles) in dry THF (20ml) cooled to -78°C under argon was carefully added *t*-butyl lithium (0.4ml, 1mmole, 2.6M) in hexane. The yellow solution was stirred for 2 minutes then methyl 2,6-dimethoxy-4-formylbenzoate (0.18g, 0.8mmoles) in dry THF (10ml) was added in one portion and the reaction mixture gradually allowed to come to room temperature over an hour. Water was carefully added and the THF evaporated off. The aqueous layer was extracted with dichloromethane (3x15ml) and the combined extracts dried and evaporated to a yellow oil. This residue was taken up in benzene (50ml) and a few drops of a solution of perchloric acid in ethyl acetate[102] added and the whole mixture refluxed overnight. The benzene was evaporated off to give a yellow foam which was crystallized from dichloromethane/diethyl ether to give 3-(4'-carboxymethyl-3',5'-dimethoxyphenyl)-5,7-dimethoxyphthalide (0.18g, 59%) as cubes, m.p. 206-207°C (Found: C, 61.59; H, 5.22%; M^+, 388. $C_{20}H_{20}O_8$ requires C, 61.85; H, 5.19%; M, 388); $\nu_{max.}$(KBr) 2 940, 1 760, 1 735, and 1 610 cm^{-1}; δ_H 6.50(2H, s, ArH), 6.45(1H, d, J 2Hz, ArH), 6.30(1H, d, J 2Hz, ArH), 6.15(1H, s, benzylic), 4.00(3H, s, OMe), 3.91(3H, s, OMe), 3.83(3H, s, OMe), and 3.80(6H, s, OMe).

2-(4'-Carboxymethyl-3',5'-dimethoxybenzyl)-4,6-dimethoxy benzoic acid (159)

A mixture of 3-(4'-carboxymethyl-3',5'-dimethoxyphenyl)-5,7-dimethoxyphthalide (100mg, 0.26mmoles) in methanol (16ml) and glacial acetic acid (8ml) was stirred over 5% palladium on charcoal catalyst (100mg) under an atmosphere of hydrogen gas at atmospheric pressure. After 2 days the catalyst was filtered off through Celite and the filtrate diluted with water (100ml) and extracted with ethyl acetate (2x30ml) and the extract dried and evaporated to a thick gum which was crystallized from acetone to give 2-(4'-carboxymethyl-3',5'-dimethoxybenzyl)-4,6-dimethoxybenzoic acid (75mg, 75%) as cubes, m.p. 205-206 °C (Found: C, 61.52; H, 5.41%; M^+, 390. $C_{20}H_{22}O_8$ requires C, 61.53; H, 5.68%; M, 390); $\nu_{max.}$(KBr) 3 450, 2 940, 1 760, 1 739, and 1 610 cm^{-1}; δ_H 7.50(1H, br s, CO_2H), 6.41(2H, s, ArH), 6.38(1H, d, J 2Hz, ArH), 6.29(1H, d, J 2Hz, ArH), 4.13(2H, br s, benzylic), 3.88(3H, s, OMe), 3.87(3H, s, OMe), and 3.74(9H, s, OMe).

Attempted cyclisation of 2-(4'-carboxymethyl-3',5'-dimethoxybenzyl)-4,6-dimethoxybenzoic acid (159)

To a stirred solution of 2-(4'-carboxymethyl-3',5'-dimethoxybenzyl)-4,6-dimethoxybenzoic acid (100mg, 0.26mmoles) in dry dichloromethane (25ml) was added acetyl chloride (0.3ml, 4.2mmoles) and anhydrous zinc chloride (40mg, 0.3mmoles).The solution turned orange and was stirred overnight. The reaction mixture was diluted with ethyl acetate (50ml) and washed with saturated bicarbonate solution (2x30ml). The organic layer was dried and evaporated to an orange solid which was recrystallized from ethyl acetate to give 2-carboxymethyl-1,3,6,8-tetramethoxy-9,10-anthraquinone (35mg, 35%) as orange cubes, m.p. 206-207°C (lit.[75], 204°C) (Found: C, 61.73; H, 4.63%; M^+, 386. $C_{20}H_{18}O_8$ requires C, 62.17; H, 4.69%; M, 386); $\nu_{max.}$(CCl_4) 2 970, 1 745, 1 672, and 1 590 cm^{-1}; δ_H 7.55(1H, s, ArH), 7.35(1H, d, J 2Hz, ArH), 6.8(1H, d, J 2Hz, ArH), and 4.00(15H, br s, OMe).

2,6-Dibenzyloxy-4-methylbenzoate (164)

A mixture of methyl 2,6-dihydroxy-4-methylbenzoate (10g, 55mmoles), dry potassium carbonate (16.1g) and benzyl bromide (13.7ml, 115mmoles) was stirred and refluxed in dry acetone (250ml) for 6 hours. The potassium salts were removed by filtration and the acetone evaporated to leave a yellow solid. The solid was then taken up in ethyl acetate (150ml) and washed with concentrated ammonia solution (2x50ml) and 2*N* sodium hydroxide (2x50ml) and the organic layer dried and evaporated to a solid which was recrystallized from methanol to give methyl 2,6-dibenzyloxy-4-methylbenzoate (10.2g, 51%) as needles, m.p. 135-136°C (lit.[108], 136-139°C); $\nu_{max.}$(KBr) 3 033, 1 629, 1 607, and 1 581 cm^{-1}; δ_H 7.38(10H, br s, ArH), 6.45(2H, s, ArH), 5.12(4H, s, benzylic), 3.89(3H, s, OMe), and 2.30(3H, s, ArMe); m/e 362 (M^+).

2,6-Dibenzyloxy-4-methylbenzoic acid (165)

A mixture of methyl 2,6-dibenzyloxy-4-methylbenzoate (5g, 12.9mmoles), potassium hydroxide (1g, 18mmoles), THF (20ml) and water (30ml) was stirred and refluxed for 12 hours.The mixture was cooled and diluted with water (200ml) and extracted with dichloromethane (3x50ml) and the combined organic extracts dried and evaporated to give unhydrolyzed ester (3.9g, 78%). The aqueous layer was then acidified with concentrated hydrochloric acid and extracted with ethyl acetate (3x50ml) and the combined organic extracts dried and evaporated to a solid which was recrystallized from methanol to give 2,6-dibenzyloxy-4-methylbenzoic acid (0.9g, 19%) as needles, m.p. 160-163°C (lit.[108], 164°C); $\nu_{max.}$(KBr) 2 950, 1 695, and 1 604 cm^{-1}; δ_H 7.55(10H, s, ArH), 6.22(2H, s, ArH), 5.28(4H, s, benzylic), and 2.56(3H, s, ArMe); m/e 348 (M^+).

Reaction of methyl 2,6-dibenzyloxy-4-methylbenzoate (166) with methylmagnesium iodide

To magnesium turnings (50mg, 2mmoles) in dry diethyl ether (20ml) under nitrogen was added methyl iodide (0.13ml, 2.1mmoles). Rapid stirring initiated the reaction and gradually the magnesium was consumed. Once all the magnesium was used up methyl 2,6-dibenzyloxy-4-methylbenzoate (0.5g, 1.4mmoles) in dry THF (40ml) was added dropwise and the mixture stirred overnight. Water (10ml) was added carefully and the organics removed by evaporation. The mixture was then acidified with 1N hydrochloric acid (100ml) and extracted with dichloromethane (3x20ml). The organic extracts were dried and evaporated to a yellow powder. Short column chromatography using dichloromethane/ether (4:1) as eluent gave the starting ester (0.35g, 70%), recrystallized from methanol as needles, m.p 135-136°C (lit.[108], 136-139°C); and a thick yellow oil (0.12g) which seemed to be methyl 2-benzyloxy-6-hydroxy-4-methylbenzoate; $\nu_{max.}$(KBr) 3 420, 1 645, 1 620, and 1 590 cm^{-1}; δ_H 11.50(1H, s, OH), 7.42(5H, m, ArH), 6.45(1H, br s, ArH), 6.30(1H, br s, ArH), 5.10(2H, s, benzylic), 3.93(3H, s, OMe), and

2.28(3H, s, ArMe); m/e 272 (M^+).

2,6-Dimethoxy-4-methylbenzyl alcohol (168)

To a rapidly stirred slurry of lithium aluminium hydride (42mg, 1.1mmoles) in dry THF (20ml) was added a solution of methyl 2,6-dibenzyloxy-4-methylbenzoate (210mg, 1mmole) in dry THF dropwise and the mixture stirred overnight. Stirring was continued and water (0.04ml) was carefully added, then 15% sodium hydroxide (0.04ml) and finally more water (0.13ml). The mixture was stirred for 20 minutes then the aluminium salts were removed by filtration and washed with a little THF. The filtrate was removed by evaporation to give a clear oil. Short column chromatography using dichloromethane/diethyl ether (1:1) gave methyl 2,6-dimethoxy-4-methylbenzoate (53mg, 25%) as plates from diethyl ether, m.p. 84°C (lit.[89]; 86°C); and 2,6-dimethoxy-4-methylbenzyl alcohol as a clear oil (113mg, 62%) (Found: M^+, 182.0943. $C_{10}H_{14}O_3$ requires M, 182.0942); $\nu_{max.}$(CHCl$_3$) 3 600, 3 000, 1 611, and 1 590 cm^{-1}; δ_H 6.38(2H, s, ArH), 4.74(2H, s, benzylic), 3.82(6H, s, OMe), 2.49(1H, br s, OH), and 2.32(3H, s, ArMe).

Ethyl *o*-acetoxybenzoate (169)

A mixture of ethyl salicylate (10ml, 68mmoles) and acetic anhydride (7ml, 74mmoles) was heated on a steam bath with anhydrous zinc chloride (50mg) for 6 hours. The mixture was taken up in diethyl ether (100ml) and washed with

$1N$ sodium hydroxide (2x30ml). The organic layer was dried and evaporated to an oil. Fractional distillation gave ethyl *o*-acetoxybenzoate (9.5g, 67%) as a clear oil, b.p. 104-106°C/0.2mmHg (lit.[109], 106-107°C at 0.2mmHg); $\nu_{max.}$(CCl_4) 2 940, 1 725, and 1 775 cm^{-1}; m/e 208(M^+).

Reaction of ethyl *o*-acetoxybenzoate (169) with sodium hydride

To sodium hydride (100mg, excess) in dry THF (30ml) was added ethyl *o*-acetoxybenzoate (200mg, 0.96mmoles) and the mixture stirred under nitrogen for 12 hours. Water (20ml) was carefully added, then more water (150ml) and the aqueous solution extracted with dichloromethane (3x40ml) and the combined organic layers dried and evaporated to give only a small amount of residue. The aqueous layer was then acidified with concentrated hydrochloric acid and extracted with dichloromethane (3x40ml) and the combined extracts dried and evaporated to give a clear oil which was identical in all respects with ethyl salicylate (0.14g, 88%).

Friedel-Crafts acetylation of orcinol (171)

To orcinol monohydrate (5.72g, 40mmoles) was added benzene (50ml) and the solvent removed by evaporation. This was repeated till the melting point of the orcinol was 107°C (anhydrous). The dry orcinol (~5g) and anhydrous aluminium chloride (10.85g, 81mmoles) were stirred in dry nitrobenzene (120ml) till dissolved and freshly distilled acetyl chloride (8.35ml, 120mmoles) was added at such a rate as not too much frothing occured (HCl evolved). The mixture was then heated to 100°C for 2 hours, allowed to cool and stirred at room temperature for 2 hours. The reaction mixture was cautiously poured into $1N$ hydrochloric acid (400ml) and the nitrobenzene was removed by steam distillation. After the nitrobenzene came across, the condenser was switched off and a compound was carried across by the steam which was collected and recrystallized from dichloromethane/petrol to give 2,4-diacetylorcinol (2g, 24%) as needles, m.p. 92-93°C (lit.[110], 95°C); $\nu_{max.}$ 3 240, 2 990, and 1 630 to 1 570 cm^{-1} (very broad); δ_H 15.30(1H, s, OH), 14.10(1H, s, OH), 6.30(1H, s, ArH), 2.75(3H, s, Me), 2.65(3H, s, Me), and 2.57(3H, s, ArMe); m/e 208 (M^+). Once all the 2,4-diacetylorcinol had distilled over and the pot appeared clear, the reaction mixture was filtered through Celite and cooled in ice. The precipitate was collected and washed with a little cold water and crystallized from ethyl acetate/petrol to give 4-acetylorcinol (0.5g, 7.5%) as light brown needles, m.p. 146°C (lit.[111], 159-160°C); $\nu_{max.}$(KBr) 3 270, 1 638, and 1 580 cm^{-1}; $\delta_H(CD_3OD)$ 6.21(2H, s, ArH), 2.70(3H, s, ArMe), and 2.20(3H, s, COMe); m/e 166 (M^+).

4-Acetylorcinol dimethyl ether (174)

To 4-acetylorcinol (0.5g, 3mmoles) in dry acetone (50ml) was added dimethyl sulphate (0.62ml, 6.5mmoles) and anhydrous potassium carbonate (0.9g). The mixture was stirred and refluxed for 10 hours. The mixture was cooled and filtered to remove the potassium salts and the acetone evaporated at reduced pressure. The yellow oil was taken up in diethyl ether (50ml) and washed with concentrated ammonia (2x20ml) and 2*N* sodium hydroxide (2x20ml) and the diethyl ether layer dried and evaporated to a yellow oil which was crystallized from di-isopropyl ether to give 4-acetyl orcinol dimethyl ether (0.46g, 79%) as cubes, m.p. 83-84°C (lit.[112], 89°C); $\nu_{max.}(CCl_4)$ 2 940, 1 705, 1 608, and 1 582 cm^{-1}; δ_H 6.40(2H, s, ArH), 3.83(6H, s, OMe), 2.48(3H, s, Me), and 2.36(3H, s, Me); m/e 194 (M^+).

Reaction of 4-acetylorcinol dimethyl ether (174) with *N*-bromosuccinimide

To a stirred solution of 4-acetylorcinol dimethyl ether (200mg, 1mmole) in refluxing carbon tetrachloride (50ml) irradiated with a bench top lamp (60W) was added a mixture of *N*-bromosuccinimide (200mg, 1.1mmoles) spiked with a few crystals of benzoyl peroxide, in small portions over 15 minutes. The reaction was refluxed and irradiated for an hour after addition, then cooled and filtered through Celite and the solvent removed by evaporation to a light yellow oil. ^1H

n.m.r. and thin layer chromatography showed a mixture of several compounds and a small amount of starting material.

4-Acetylorcinol dimethyl ether oxime (175)

To 4-acetylorcinol dimethyl ether (50mg, 0.258mmoles) in methanol (20ml) was added hydroxylamine hydrochloride (100mg, 1.4mmoles) and sodium acetate (100mg, 1.2mmoles). The mixture was stirred for 6 hours then poured into water (100ml) and extracted with dichloromethane (3x20ml), and the combined organic extracts dried and evaporated to give a white solid. Recrystallization from dichloromethane/di-isopropyl ether gave 4-acetylorcinol dimethyl ether oxime (47mg, 87%) as needles, m.p. 197°C (Found: C, 63.17; H, 7.25; N, 6.75%; M^+, 209. $C_{11}H_{15}O_3N$ requires C, 63.14; H, 7.23; N,6.69%; M, 209); $\nu_{max.}$(KBr) 3 220, 2 920, 1 610, and 1 580 cm^{-1}; δ_H 6.40(2H, br s, ArH), 3.80(6H, s, OMe), 3.00(1H, s, OH), 2.36(3H, s, Me), and 2.12(3H, s, Me).

3-Methyl-1,2-benzisoxazole

To a stirred solution of hydroxylamine-*O*-sulphonic acid (1.24g, 11mmoles) and sodium sulphate (1.2g, 8.4mmoles) in water (20ml) was added 2'-hydroxyacetophenone (1.2ml, 10mmoles) in one portion. Stirring was continued for an hour as the acetophenone went into solution and the sodium salt of the oxime precipitated out. Sodium hydrogen carbonate (1g, 12mmoles) was added to the reaction mixture followed by dichloromethane (20ml) while vigorous stirring was maintained. After two hours the dichloromethane layer was separated off and washed with $1N$ sodium hydroxide (20ml) and dried and evaporated to a clear oil. Distillation (Kugelrohr) gave 3-methyl-1,2-benzisoxazole (1.1g, 82%) as a clear oil, b.p. 110°C (water pump) (lit.[113], 92.5°C at 11mmHg); $\nu_{max.}(CCl_4)$ 3 060, 1 620, and 1 579 cm^{-1}; δ_H 7.75-7.21(4H, m, ArH), and 2.62(3H, s, Me); m/e 133 (M^+).

3-Acetyl-4-hydroxycoumarin (184)

2-Acetoxybenzoic acid (5g, 28mmoles) was stirred in thionyl chloride (40ml, excess) for 12 hours at room temperature. The excess thionyl chloride was removed by evaporation at reduced pressure to give a thick brown oil. The acid chloride was used without further purification.

Ethyl acetoacetate (8.2ml, 64mmoles) in dry diethyl ether (30ml) was added with mechanical stirring to sodium hydride (1.5g, 64mmoles) in dry diethyl ether (100ml) under nitrogen and the white slurry produced was stirred for 2 hours. The crude acid chloride was added dropwise over 20 minutes in diethyl ether (30ml) with stirring. The mixture was then stirred and refluxed overnight. The precipitate was then filtered off and washed with diethyl ether and dried. It was then dissolved in iced water (50ml) and carefully acidified with concentrated hydrochloric acid. The solution was then extracted with dichloromethane (3x20ml) and the extracts dried and evaporated to a semi-solid which crystallized from di-isopropyl ether to give 3-acetyl-4-hydroxycoumarin (2.7g, 47%) as needles, m.p.

135°C (lit.[114], 137-138°C); δ_H 8.05(1H, d d, J 9+2Hz, H-5), 7.7(1H, br t, J 8Hz, H-7), 7.35(2H, m, J 8Hz, H-6 and H-8), and 2.78(3H, s, Me); m/e 204 (M^+).

2-Methyl-1-benzopyran-4-one (185)

3-Acetyl-4-hydroxycoumarin (200mg, 1mmole) was added to 1N sulphuric acid (25ml) and the mixture heated on a steam bath for 2 hours. The mixture was then extracted with dichloromethane (3x10ml) and the combined extracts back washed with 1N sodium bicarbonate solution (10ml). The organic extracts were dried and evaporated to a yellow oil. Preparative chromatography on silica using diethyl ether as eluent gave 2-methyl-1-benzopyran-4-one (44mg, 28%) as needles from cyclohexane, m.p. 74°C (lit.[115], 72-73°C); δ_H 8.12(1H, d d, J 8 and 2Hz, H-5), 7.7-7.2(3H, m, H-5, H-6, and H-7), 6.14(1H, s, vinyl H), and 2.3(3H, s, Me); m/e 160 (M^+), and 2'-hydroxyacetophenone as an oil (30mg, 25%), $\nu_{max.}$(thin film) 3 135 and 1 640 cm^{-1}; δ_H [116] 7.7(1H, d d, J 9 and 2Hz, H-6), 7.44(1H, m, H-4), 6.4(2H, m, H-3 and H-5) and 2.58(3H, s, Me); m/e 136 (M^+).

Reaction of 2,4-diacetylorcinol (173) with *t*-butyl lithioacetate

To a stirred solution of di-isopropylamine (1.35ml, 9.6mmoles) in dry THF (20ml) at 0°C under nitrogen was added *n*-butyl lithium (3.7ml, 9.6mmoles, 2.6M) in hexane. The solution was stirred for 5 minutes then cooled to -78°C. A solution of *t*-butyl acetate[117] (1.3ml, 9.6mmoles) in THF (10ml) was added dropwise. The mixture was stirred for 10 minutes, then a solution of 2,4-diacetylorcinol (200mg, 0.96mmoles) in dry THF (10ml) was added dropwise. The solution went lime green and was allowed to warm to room temperature and stirred overnight. The reaction mixture was carefully poured into saturated ammonium chloride (50ml) and the THF removed by evaporation. The aqueous phase was extracted with dichloromethane (3x20ml) and the combined extracts dried and evaporated to a brown oil. The oil was then taken up in a mixture of methanol (40ml) and 1*N* hydrochloric acid (10ml) and refluxed for 2 hours. The volume of methanol was reduced by evaporation and the mixture diluted with water (80ml) and extracted with dichloromethane (3x20ml) and the combined organic extracts dried and evaporated to a brown oil. Preparative thin layer chromatography on silica using dichloromethane as eluent gave a compound (36mg), crystallized from di-isopropyl ether as needles, m.p. 169-170°C (see discussion for possible structures); $\nu_{max.}$(CCl_4) 3 270, 1 670, 1 628, and 1 565 cm^{-1}; δ_H 13.69(1H, s, OH), 6.74(1H, br s, ArH), 6.15(1H, s, olefinic), 2.83(6H, br s, Me) and 2.40(3H, s, Me); δ_H (200MHz) 6.73(1H, q, *J* 0.9Hz, ArH), 6.12(1H, q, *J* 0.8Hz, olefinic), 2.82(3H, s, COMe), 2.81(3H, d, *J* 0.9Hz, ArMe), and 2,39(3H, d, *J* 0.8Hz, olefinic Me); m/e 232 (M^+).

2'-Acetoxyacetophenone (187)

To a stirred solution of 2'-hydroxyacetophenone (10ml, 83mmoles) and dry pyridine (7ml, 87mmoles) cooled in ice, was added acetic anhydride (7.8ml, 83mmoles) dropwise. The mixture was stirred for a further 2 hours then allowed to come to room temperature and stirred overnight. Water (25ml) was added and the reaction mixture stirred for a further 2 hours. The layers were separated and the aqueous layer extracted with diethyl ether (2x10ml). The combined organics were extracted with 1*N* sodium bicarbonate solution (20ml) and then dried and evaporated to give a solid. 2'-Acetoxyacetophenone (9g, 61%) was recrystallized from di-isopropyl ether as needles, m.p 87-88°C (lit.[118], 87-88°C); $\nu_{max.}$(KBr) 1 757, and 1682 cm^{-1};δ_H 7.78(1H, d d, *J* 8 and 2Hz, 6-H), 7.6-7.0(3H, m, H-3, H-4 and H-5), 2.5(3H, s, Me), and 2.3(3H, s, Me); m/e 178 (M^+).

Reaction of 2'-acetoxyacetophenone (187) with sodium hydride

2'-Acetoxyacetophenone (1g, 5.6mmoles) in dry THF (20ml) was added to a rapidly stirred suspension of sodium hydride (0.14g, 5.8mmoles) in dry THF (20ml). Stirring was continued for 4 hours then water (20ml) was carefully added and the THF removed by evaporation. The aqueous layer mixture was extracted with dichloromethane (2x10ml), dried and evaporated to give unreacted 2'-acetoxyacetophenone (130mg, 13%). The aqueous was then acidified with concentrated hydrochloric acid and extracted with dichloromethane (3x10ml). The combined extracts were back washed with 1*N* sodium hydroxide solution (3x25ml) and the organic layer dried and evaporated to give a solid which was recrystallized to give 3-acetyl-2-methyl-1-benzopyran-4-one (360mg, 31%) as long needles from di-isopropyl ether, m.p. 88-89°C (lit.[119], 89°C); $\nu_{max.}(CCl_4)$ 1 690, 1 649, and 1 618 cm^{-1}; δ_H 8.15(1H, d d, *J* 9 and 2Hz, H-4), 7.75-7.25(3H, m, H-5, H-6 and H-7), 2.6(3H, s, Me), and 2.5(3H, s, Me); m/e 202 (M^+).

The combined sodium hydroxide extracts were acidified with concentrated hydrochloric acid and extracted with dichloromethane (3x15ml) and the organic extracts dried and evaporated to give 2'-acetoxyacetophenone (334mg, 44%), identical in all respects with an authentic sample.

Reaction of 2'-hydroxyacetophenone (180) with sodium hydride and acetyl chloride

To a stirred suspension of sodium hydride (0.69g, 29mmoles) in dry THF (20ml) cooled in ice was added 2'-hydroxyacetophenone (1ml, 8.3mmoles) in dry THF (20ml). After 5 minutes, acetyl chloride (0.65ml, 9mmoles) in dry THF (10ml) was added dropwise and the yellow reaction mixture was allowed to come to room temperature and stirred overnight. A similar work up to the previous experiment gave 3-acetyl-2-methyl-1-benzopyran-4-one (300mg, 18%) as long needles from di-isopropyl ether, m.p. 87-88°C (lit.[119], 87-88°C).

3-Acetyl-2,7-dimethyl-5-hydroxy-1-benzopyran-4-one (193)

To 4-acetylorcinol (180mg, 1mmole) in dry toluene (30ml) was added acetic anhydride (0.5ml, 5.3mmoles) and anhydrous sodium acetate (500mg, 6mmoles) and the mixture was refluxed overnight. On cooling, the mixture was washed with water (3x10ml) and the toluene layer was dried and evaporated to give a brown oil; δ_H 6.85(2H, s, ArH), 2.40(3H, s, Me), 2.30(3H, s, Me), and 2.21(6H, s, OAc).

A solution of the oil in dry THF (20ml) was added to a stirred suspension of sodium hydride (200mg, 8.3mmoles) in dry THF (20ml) and the mixture was stirred overnight. Water (10ml) was carefully added then saturated ammonium chloride solution (10ml). The THF was removed by evaporation and the aqueous phase was extracted with dichloromethane (3x10ml) and the combined organics dried and evaporated to a brown crystalline mass. Recrystallization from di-isopropyl ether ether gave 3-acetyl-2,7-dimethyl-5-hydroxy-1-benzopyran-4-one (127mg, 55%) as needles, m.p 137-138°C (lit.[120], 141°C); (Found: C, 66.98; H, 5.25%; M^+, 232. $C_{13}H_{12}O_4$ requires C, 67.23; H, 5.21%; M, 232); $\nu_{max.}(CCl_4)$ 3 000, 1 696, 1 655, and 1 610 cm^{-1}; δ_H 12.30(1H, s, OH), 6.70(2H, br s,ArH), 2.67(3H, s, Me), 2.52(3H, s, Me), and 2.42(3H, s, Me).

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