CHEMICAL STUDIES OF CHROMONE DERIVATIVES

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ABSTRACT

This study has focussed on several aspects of chromone chemistry, *viz.*, (i) the influence of remote substituents on the basicity of 2-(*N*,*N*-dimethylamino)chromones, (ii) Morita-Baylis-Hillman reactions of substituted chromone-3-carbaldehydes and (iii) an investigation into the application of chromone chemistry in the total synthesis of the marine natural product, Rietone A.

Selected 2-(*N*,*N*-dimethylamino)chromones were prepared using two different methods; firstly, *via* cyclisation of salicylate-derived *N*,*N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamide precursors and, secondly, *via* 2-hydroxyacetophenone boron difluoride complexes. ^{13}C NMR analysis of the 6- and 7-methoxy-2-(*N*,*N*-dimethylamino)chromones confirmed that protonation occurs at the chromone carbonyl oxygen rather than the amino nitrogen – a conclusion supported by molecular orbital calculations. Potentiometric analysis of 2-(*N*,*N*-dimethylamino)chromones in ethanol-water afforded pK_a values in the range 2.22 – 2.52. The observed trend has been rationalised in terms of substituent effects with the aid of molecular orbital calculations at the semi-empirical and *ab initio* levels, while hydrogen-bonding effects have been used to account for the apparently anomalous result obtained for the 6-nitro derivative.

A series of seven substituted chromone-3-carbaldehydes, prepared by the application of Vilsmeier-Haack methodology to the corresponding 2-hydroxyacetophenones, have been examined as substrates for Morita-Baylis-Hillman reactions, using DABCO as the catalyst and three different activated alkenes, *viz.*, methyl acrylate, methyl vinyl ketone and acrylonitrile. In all cases, with the exception of 6-nitrochromone-3-carbaldehyde, the reactions have been shown to afford the expected Morita-Baylis-Hillman products. Use of methyl acrylate and methyl vinyl ketone as the activated alkene has been observed to afford additional, unprecedented dimeric products, which have been unambiguously characterised using a combination of single crystal X-ray analysis and spectroscopic (high resolution MS and NMR) techniques. Different dimer-like adducts have been isolated from reactions in which acrylonitrile was used as the activated alkene, and the structures of these novel products have been determined spectroscopically. Tentative mechanistic rationalisations for the formation of the "dimeric" products have been presented.

Optimisation studies, aimed at improving the yields of the Morita-Baylis-Hillman products, have resulted in significant increases in conversion efficiency (up to 95%). It has also been shown that the Morita-Baylis-Hillman products may be readily converted to the corresponding "dimers".

An exploratory study into the synthesis of Rietone A has been initiated. Ring-opening of a chromone derivative was expected to provide access to the aromatic moiety, while retrosynthetic analysis of the aliphatic side chain suggested possible strategies for its construction. These approaches have proved largely unsuccessful, but preliminary studies involving Fries rearrangement of 4-(carbomethoxymethyl)phenyl 3,7-dimethyl-2,6-octadienoate appear to hold some promise for future development.

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1. INTRODUCTION

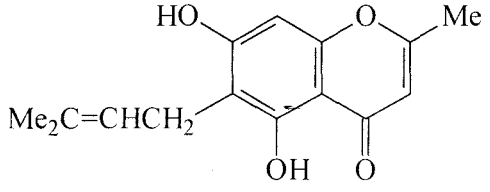
This investigation into the chemistry of chromone derivatives focuses largely on their use in the Morita-Baylis-Hillman reaction. What follows is a brief survey of the known chemistry of chromones, and chromone-3-carbaldehyde in particular, and a detailed account of earlier research on the Morita-Baylis-Hillman reaction.

1.1 CHROMONES

Chromone chemistry has been widely explored and extensively reviewed over the past few years. The following survey is intended to give a broad overview of the chemistry of chromones and is by no means exhaustive. Particular attention has been given to the chemistry of chromone-3-carbaldehydes, since their use in Morita-Baylis-Hillman reactions forms a significant part of this investigation. Chromone synthetic methodology has also been explored for the synthesis of the marine natural product, Rietone A.

1.1.1 Naturally occurring chromones

Only about 55 chromones occur naturally, with the majority containing an alkoxy or hydroxyl group. Several chromone derivatives carry hydroxyl groups at C-5 and C-7 and a methyl group at C-2. The first of these to be identified was peucenin **1**, which was isolated from the rhizome of the masterwort, *Peucedanum ostruthium*.[1] Eugenin **2**, the first alkoxychromone to be identified, was isolated from the wild clove, *Eugenia caryophyllata* (L.) Thunbg..[1]



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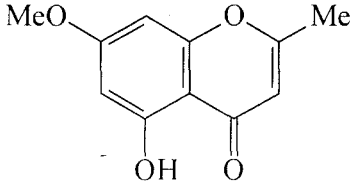
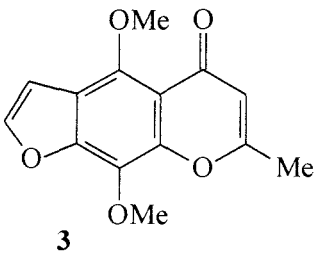


2

Tricyclic chromones also occur abundantly, and many of them are highly coloured; the naphthopyranones have been comprehensively reviewed by Ellis.[1]

1.1.2 Biological activity of chromone derivatives

The resurgent interest in the chemistry of chromones is largely due to their pharmaceutical potential. Perhaps the most useful naturally occurring chromone derivative is khellin **3**, a furochromone found in the fruits and seeds of *Ammi visnaga*,[2] and extracts of this plant have been used in medicinal practices in Eastern Mediterranean countries. The khellin induces muscular relaxation and has been used to alleviate the symptoms of bronchial asthma. This therapeutic property is also found in a number of simpler 2-methylchromones. Another commonly used asthma drug is disodium cromoglycate **4**. The success of this drug and the recognition of the O-C=C-C=O group as the structural requirement for activity in this compound have led to a spate of investigations into chromones bearing a reactive functionality on the pyran ring.[3]



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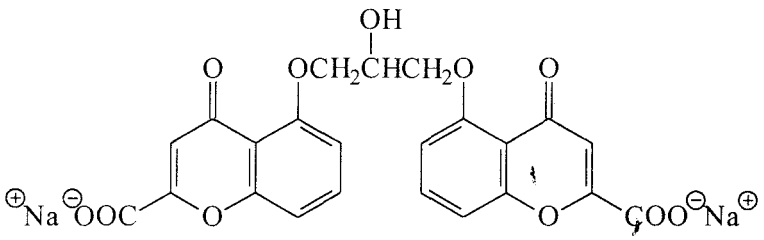
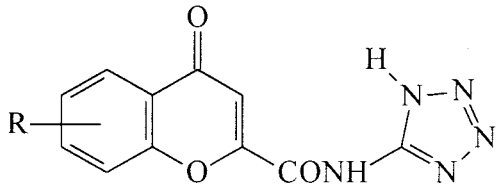


4

The presence of an acidic group at C-2 or C-3 is known to inhibit passive cutaneous anaphylaxis, an allergic reaction which causes asthma, rhinitis and urticaria.[4] Replacement of the carboxyl group by a 5-tetrazolyl amido moiety, as in compound **5**, has been shown, in some cases, to result in increased pharmacological activity.[4] Another class of chromones exhibiting bioactivity are the 2-aminochromones, a series of which has recently been described as a new class of antiplatelet agents with potential in the treatment of unstable angina and other thrombolytic disorders.[5] These compounds, typified by the aminochromone **6**, contain a diethylamino group at C-2 as well as an electron-donating

group such as hydroxy or ethoxy at C-7 – structural features which appear to be necessary for pharmacological activity.[5]



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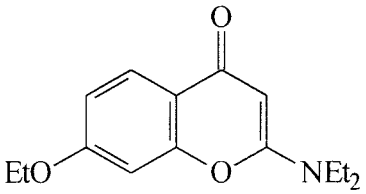
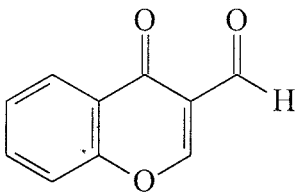


6

Of particular interest is the recent discovery of simple, non-hydroxylated chromones as selective inhibitors of $p56^{lck}$ tyrosine kinase. Specific tyrosine kinases have been implicated in proliferative diseases such as cancer and atherosclerosis,[6] and selective tyrosine kinase inhibitors may therefore be useful in the treatment of these diseases. Moreover, selective inhibitors of $p56^{lck}$ may have efficacy in the treatment of T-cell leukaemias and lymphomas, as well as in the treatment of autoimmune diseases, such as rheumatoid arthritis, in which activated T-cells play a role in the pathogenesis of the disease. It is interesting to note that all chromones which act as $p56^{lck}$ inhibitors have an aldehyde group at either the C-2 or the C-3 position, as in chromone-3-carbaldehyde **7**.[6]



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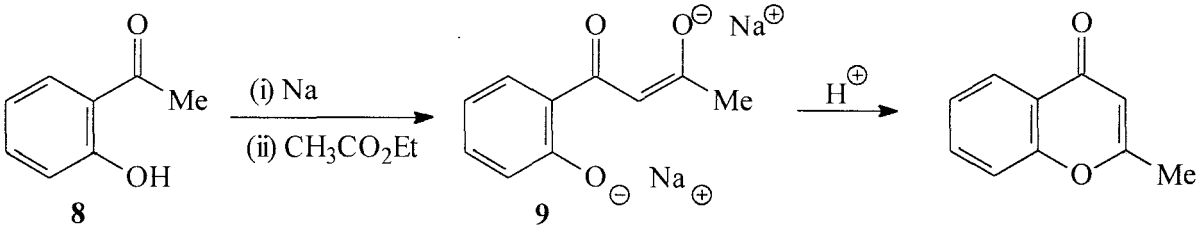
1.1.3 Synthesis of chromones

The synthesis of chromones has been extensively reviewed,[7,8] and a complete survey is beyond the scope of this introduction. The preferred method of synthesis involves the Kostanecki-Robinson strategy[7] shown in Scheme 1. An *o*-hydroxyacetophenone **8** is condensed with an acylating agent to form a β-diketone derivative **9**, which spontaneously

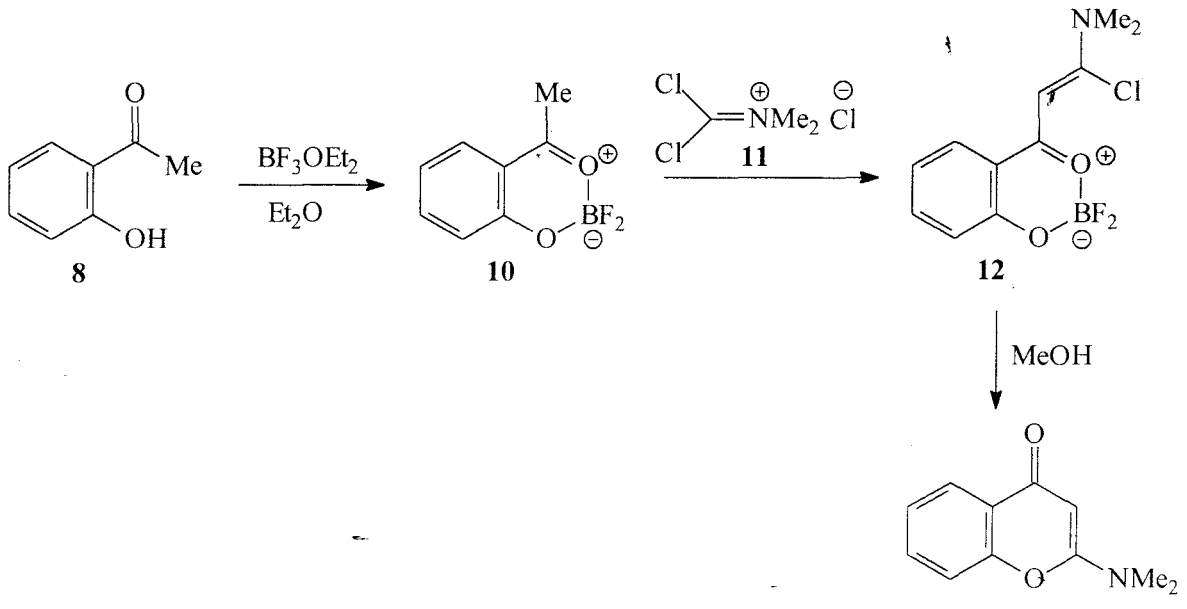
cyclises to the chromone on acidification in what is, effectively, a reverse of chromone hydrolysis.



8 **9**

Scheme 1

Recently, Morris and co-workers[9] published a convenient procedure for the synthesis of 2-aminochromones starting from the *o*-hydroxyacetophenone. Thus, *o*-hydroxy-acetophenone **8** is treated with boron trifluoride etherate to form the *o*-hydroxyacetophenone-BF_2 complex **10**. Reaction of this complex with the phosgen-iminium salt **11** gives a β-chloro-vinylogous amide complex **12**, which undergoes methanolysis to afford the aminochromone (Scheme 2). The initial protection of the phenolic hydroxyl group with boron trifluoride etherate is necessary in order to direct reaction of the phosgeniminium salt to the methyl ketone carbonyl carbon.[9]

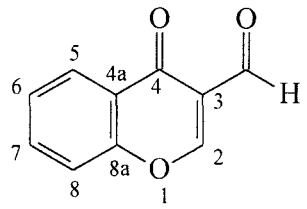


8 **10** **12**

Scheme 2

1.1.4 Chromone-3-carbaldehyde

Of the different functionalised chromones, chromone-3-carbaldehyde **7** occupies a unique position because of the range of heterocycles for which it serves as a precursor. Not surprisingly, this system has been extensively studied.[3] Since 1973, when a convenient synthesis using the Vilsmeier method was first reported,[10] the potential of this compound in the construction of fused heterocyclic systems has attracted the attention of chemists world-wide. Much of the synthetic utility of chromone-3-carbaldehyde **7** is derived from the reactivity of its three electron-deficient centres at C-2, C-4 and the formyl carbon. Chromone-3-carbaldehyde can serve as a Michael acceptor with concomitant opening of the pyrone ring and, in cycloaddition reactions, as either a heterodiene or a dienophile. Bifunctional nucleophiles can react at any two of the three reactive sites to provide a fused heterocyclic compound directly, or two different nucleophiles can attack to produce a new heterocycle.[11]



7

1.1.4.1 Properties of chromone-3-carbaldehyde

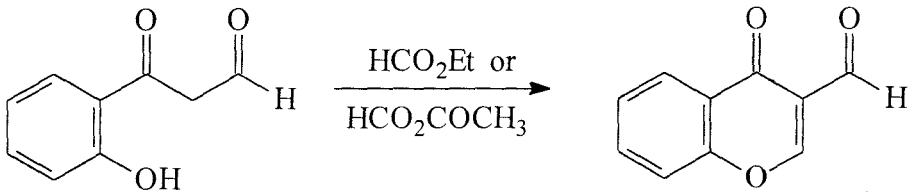
The properties of the γ-pyrone ring are essentially aliphatic, even though it exhibits the reactions characteristic of an aromatic pyrillium betaine rather than an α-pyrone.[3] In addition, the properties of the heterocyclic ring are not significantly modified as a consequence of benzannulation. Being non-aromatic, chromone itself may be regarded as a β-keto-enol ether, this grouping being responsible for its reaction with a number of nucleophiles. Hence, chromone-3-carbaldehyde **7** is likely to behave as an α-benzoyl-β-aryloxy-α,β-unsaturated aldehyde.[3] The formyl group alone does not confer colour on a chromone, but chromone carbaldehydes containing auxochromes, such as hydroxyl,

methoxy, nitro, or amino groups, tend to be pale yellow compounds with fairly high melting points.[7]

Chromone carbaldehydes have been used as intermediates in the synthesis of other chromones or furochromones. Thus, the formyl group may be reduced to either a primary alcohol or a methyl group, depending on the conditions used; it may also be oxidised to a carboxylic acid or converted into an oxime, which may then undergo dehydration to a nitrile.[7]

1.1.4.2 Synthesis of chromone-3-carbaldehyde

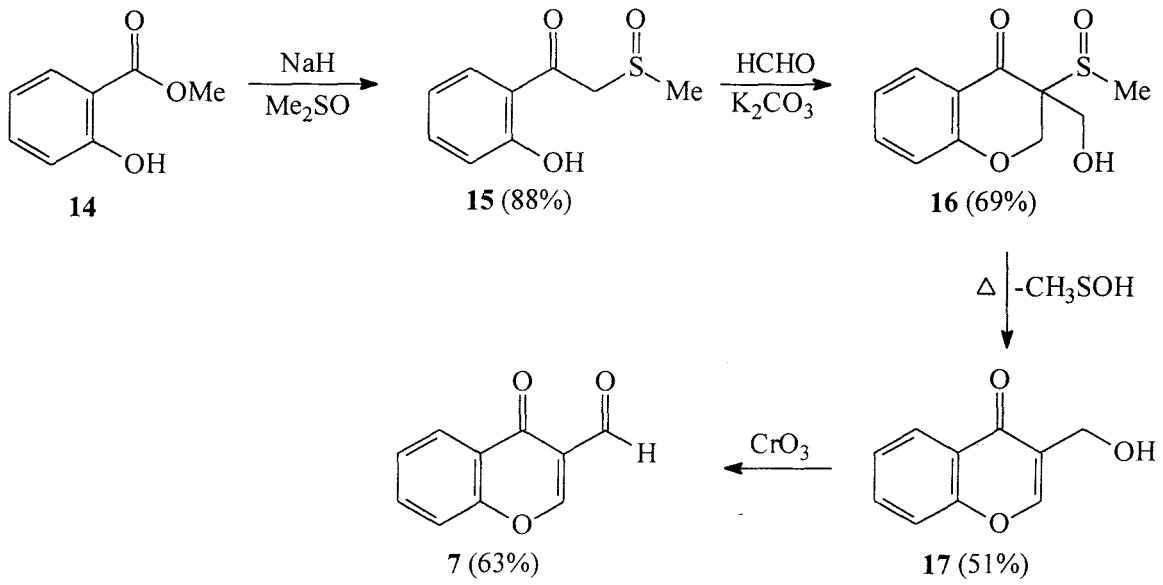
Chromone-3-carbaldehyde can be synthesised, in relatively low yield (≤ 30%), by the reaction of *o*-hydroxy-ω-formylacetophenone **13** with ethyl formate[12,13] or acetic-formic anhydride (Scheme 3).[14]



13 **7**

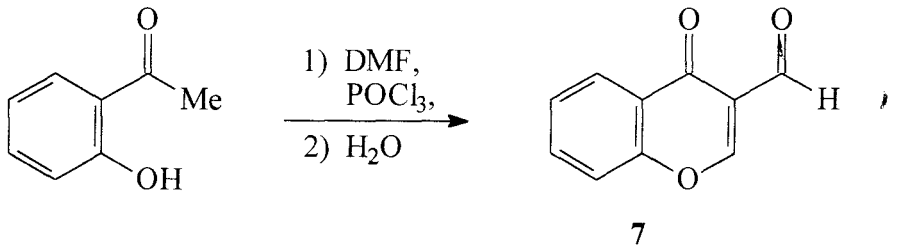
Scheme 3

It can also be obtained in four steps starting with the reaction of methyl salicylate **14** with sodium methylsulfinyl-methide (generated *in situ* by treating dimethylsulfoxide with sodium hydride) (Scheme 4).[15] The *o*-hydroxy-ω-(methyl-sulfinyl)acetophenone **15** thus produced is treated with formaldehyde in the presence of base to give 3-(hydroxymethyl)-3-(methylsulfinyl)-4-chromanone **16**. Thermal elimination of CH_3SOH then affords 3-hydroxymethylchromone **17**, which may be readily oxidised to chromone-3-carbaldehyde **7**.



Scheme 4

By far the most convenient method of synthesising chromone-3-carbaldehyde **7**, however, is by means of the Vilsmeier-Haack reaction as indicated in Scheme 5.[10,16] This one-pot synthesis has been reported to afford chromone-3-carbaldehyde in acceptable yield (61%).

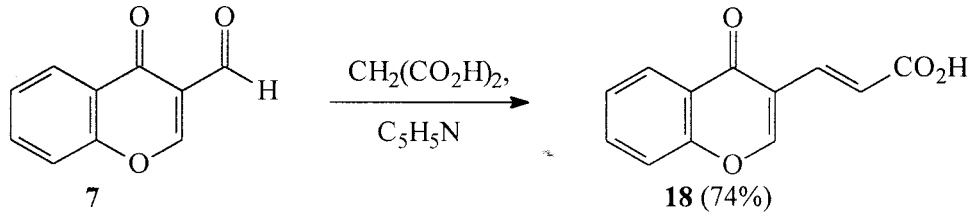


Scheme 5

1.1.4.3 Reactions of chromone-3-carbaldehyde

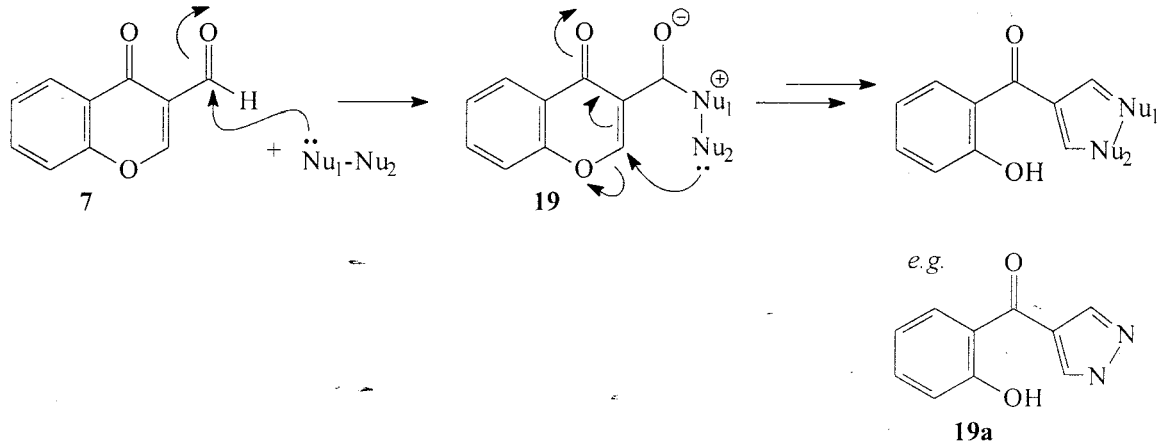
(i) Nucleophilic addition

The majority of reactions reported for chromone-3-carbaldehyde involve nucleophilic addition which generally leads to condensation products. Chromone-3-carbaldehyde **7** may react with monofunctional nucleophiles, as illustrated by its reaction with malonic acid in the presence of pyridine; subsequent dehydration and decarboxylation affords the acrylic acid derivative **18** (Scheme 6).[17] Chromone-3-carbaldehyde also reacts readily with primary aromatic amines[18,19] and secondary amines such as piperidine.[20]



Scheme 6

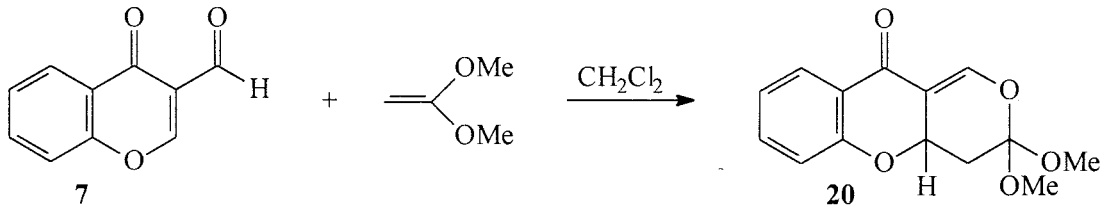
Reaction of chromone-3-carbaldehyde **7** with a bifunctional nucleophile (*i.e.* Nu_1-Nu_2) results in the formation of a new heterocyclic ring. Thus, nucleophilic attack at the formyl carbon gives, initially, intermediate **19** which, following intramolecular attack by Nu_2 at the reactive C-2 position, results in the ring-forming/ring-opening sequence shown in Scheme 7.[11] This approach has been used to prepare products such as 4-(2-hydroxybenzoyl)pyrazole **19a**.[21]



Scheme 7

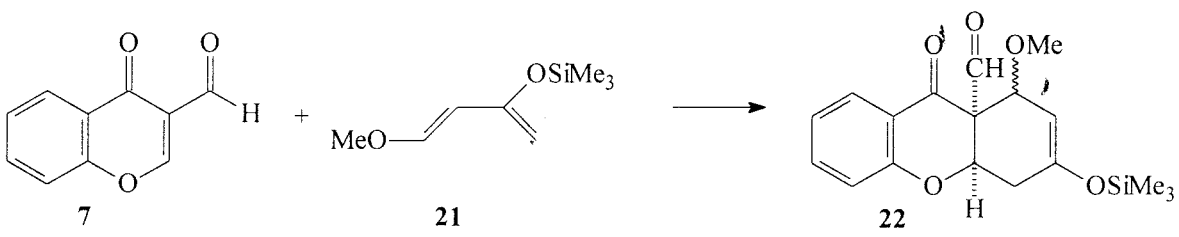
(ii) Cycloaddition reactions

Chromone-3-carbaldehyde **7** may also act as a *heterodiene* in [4 + 2] cycloaddition reactions. Such reactions are facilitated by the electron-withdrawing carbonyl group at the α-position of the heterodiene system. For example, reaction of chromone-3-carbaldehyde **7** with 1,1-dimethoxyethylene gives the cycloadduct **20** (Scheme 8).[22]



Scheme 8

On the other hand, chromone-3-carbaldehyde **7** can also function as a *dienophile* in [4 + 2] cycloadditions. Thus, its reaction with 1-methoxy-3-(trimethylsilyloxy)-1,3-butadiene **21**, in the absence of a Lewis acid catalyst, affords the isomeric cycloadducts **22** in quantitative yield (Scheme 9).[23]

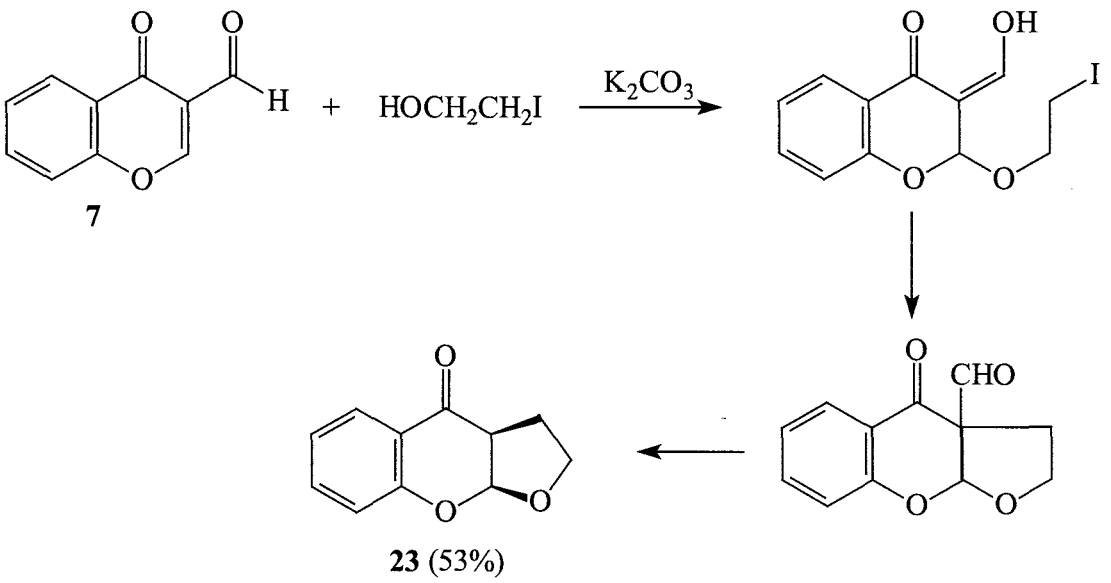


Scheme 9

(iii) Cyclocondensation reactions

In a one-step annulation procedure, chromone-3-carbaldehyde **7** has been shown to react with 2-iodoethanol, in the presence of K_2CO_3, to produce tetrahydrofuro[2,3-*b*][1]benzopyran-4-one **23** (Scheme 10),[24,25] while fused pyridine derivatives are obtained

when chromone-3-carbaldehyde **7** is reacted with various acyclic, alicyclic and heterocyclic enamines in acetic acid, pyridine or DMF.[26]



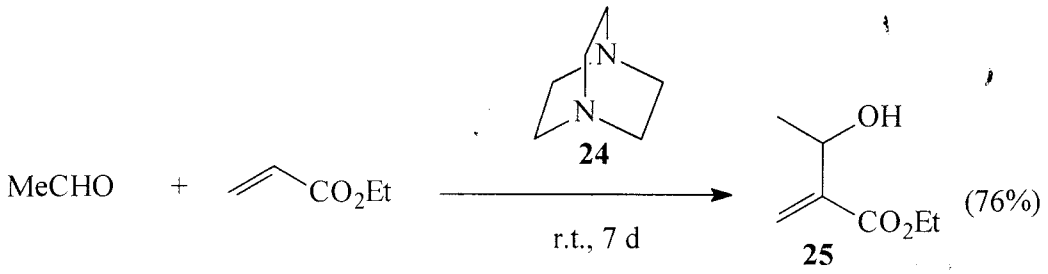
Scheme 10

Further reports in the literature, which illustrate unusual dimerisation and ring-opening reactions of chromone-3-carbaldehyde, will be discussed briefly in section 2.3.

1.2 THE MORITA-BAYLIS-HILLMAN REACTION

Carbon-carbon bond formation is the fundamental process in organic synthesis, and the development of efficient and selective methods for the construction of carbon-carbon bonds continues to be a challenging endeavour.

In a patent application published in 1972, Baylis and Hillman[27] reported the reaction of acetaldehyde with ethyl acrylate in the presence of catalytic amounts of 1,4-diazabicyclo[2.2.2]octane (DABCO) **24** to give the α-hydroxyethylated product **25** in good yield (Scheme 11). However, this initial disclosure was not followed by a journal publication, and this remarkably simple, atom-efficient and useful reaction was ignored for a number of years. Only recently has its potential begun to be explored. The transformation is now commonly referred to as the Baylis-Hillman reaction, although some credit for its invention clearly belongs to Morita[28] who reported a similar reaction five years earlier - the only difference being that tertiary phosphines were used as the catalysts. In the most recent review,[29] the name, Morita-Baylis-Hillman Reaction, has been used. Tertiary amines, in general, are cheaper, less toxic and more readily removed than tertiary phosphines; however, the latter sometimes give higher yields in shorter reaction times, and there are a number of cases in which they are the only useful catalysts.[29]



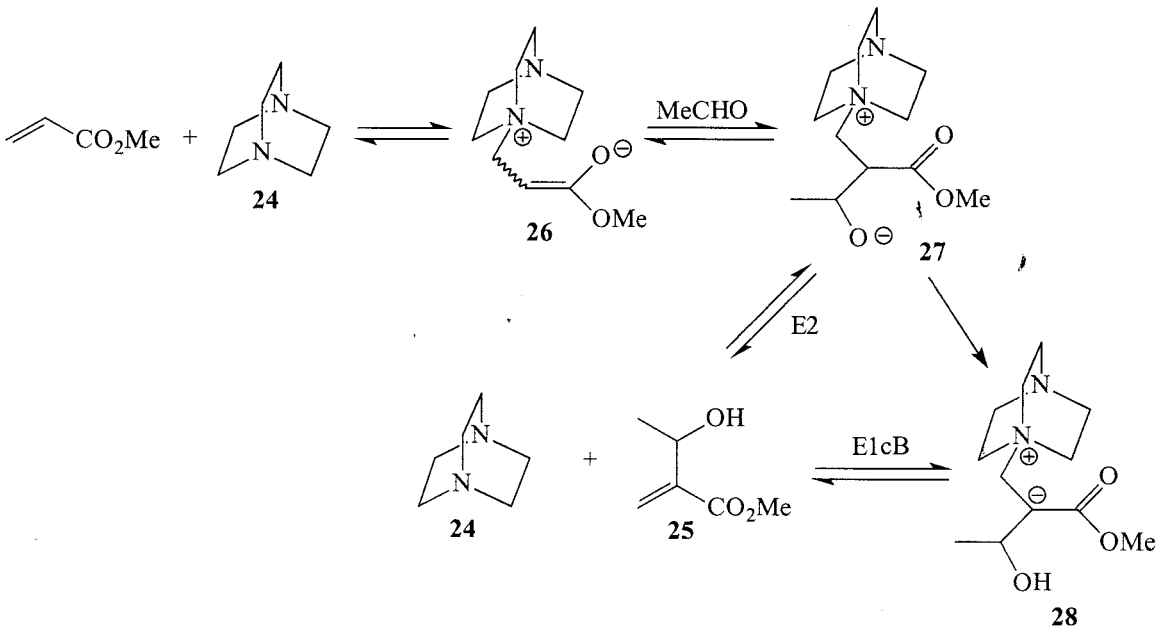
Scheme 11

The Morita-Baylis-Hillman reaction involves the coupling of activated alkenes with carbon electrophiles (typically, aldehydes) under the influence of a tertiary amine catalyst. The reaction is chemo- and regioselective, economical in atom count, requires mild conditions and provides synthetically useful multifunctional molecules.[30] However, the DABCO-catalysed reaction is often slow, and reaction times of days or even weeks are common.

Attempts to remedy this situation by using other amine catalysts, changing the reaction temperature, applying pressure or microwave irradiation have been partially successful.[30] Activated alkenes, which have been shown to undergo the reaction include:- acrylic esters, acrylonitrile, α,β-unsaturated aldehydes and ketones, vinyl sulfoxides, vinyl sulfones, vinyl sulfonates and vinyl phosphonates. β-Substituted activated alkenes do not normally react. Options for replacing the aldehyde appear to be more limited. Unactivated ketones undergo the Morita-Baylis-Hillman reaction only under high pressure,[29] but activated derivatives such as α-halo ketones, α-keto esters, α-keto lactones and non-enolisable α-diketones are often very reactive substrates. Imines can also be used, provided they carry a sufficiently electronegative group on the nitrogen.[31]

1.2.1 Mechanism of the Morita-Baylis-Hillman reaction

The generally accepted mechanism for the DABCO-catalysed reaction of acetaldehyde with methyl acrylate[32,33,34] is illustrated in Scheme 12.



Scheme 12

Nucleophilic addition of the catalyst to the activated alkene affords the zwitterion **26**, which then reacts with the electrophile to give zwitterion **27**. Base-assisted *anti* E2

elimination of the catalyst followed by protonation completes the reaction. Alternatively, internal proton transfer to give the resonance-stabilised zwitterion **28** may precede E1cB elimination. Indications that both pathways may operate stem from a study of the pressure and solvent dependence of the reaction of benzaldehyde with crotononitrile.[35] However, preliminary semi-empirical molecular orbital calculations suggest that, in some cases at least, the proton transfer (**27** → **28**) is strongly exothermic – a result which clearly favours an E1cB process. The Morita-Baylis-Hillman reaction has been shown to be reversible in a number of cases,[36,37] all of which involve acrylic esters, which are among the least reactive substrates in the forward reaction. Whether or not addition to the more reactive activated alkenes, such as acrylonitrile or α,β-unsaturated ketones, is also reversible remains to be established.

The reaction is first order in each reactant.[38,39] No difference has been detected in the rates of the reaction of acetaldehyde with α-protio and α-deuterioacrylonitrile,[38] suggesting that neither the proton transfer (**27** → **28**), nor elimination steps (**27** → **25** or **28** → **25**) are rate-limiting. The second step, involving attack of zwitterion **26** on the electrophile, is thus considered to be rate-determining. None of the intermediates in Scheme 12 have been detected spectroscopically, but indirect evidence for zwitterion **28** has been reported.[40] No radical species indicative of an electron transfer mechanism were detected by ESR spectroscopy in the reaction of 4-pyridinecarbaldehyde with methyl acrylate catalysed by 3-hydroxyquinuclidine.[39]

1.2.2 Reaction parameters

1.2.2.1 Solvents

As a third-order process, the Morita-Baylis-Hillman reaction is slowed significantly by dilution with solvents. Reactions are often carried out neat, preferably with either the activated alkene or the electrophile in excess. However, there are instances where use of a solvent is beneficial, for example, the addition of protic solvents, such as alcohols or acetic acid in small amounts, may accelerate the reaction.[29] Moreover, solvents have been used to overcome the poor solubility of certain substrates. For amine-catalysed reactions,

acetonitrile, chloroform, methylene chloride, ethers and alcohols have been used successfully, while tetrahydrofuran is routinely employed to attenuate the high reactivity of α,β-unsaturated ketones.[29] Phosphine-catalysed reactions have been carried out in benzene or dioxane, while in DABCO-catalysed reactions, the beneficial effect of polar solvents has been attributed to an increase in the equilibrium constant for the formation of zwitterion **26** (Scheme 12). The effect of water is particularly noteworthy since the substrates are, typically, only poorly water-soluble and the reaction is zero order in this solvent. A hydrophobic effect has been invoked as a possible explanation,[41] but the evidence derived from salt effects is ambiguous; addition of lithium iodide or sodium iodide accelerates the reaction in water, potassium iodide has no effect, and cesium iodide and lithium chloride inhibit it.

1.2.2.2 Temperature and microwave irradiation

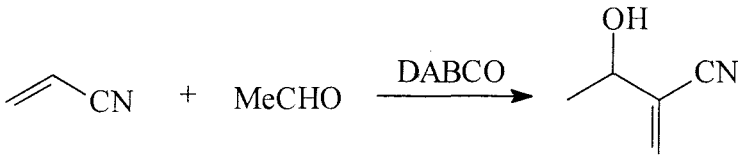
Most amine-catalysed Morita-Baylis-Hillman reactions have been carried out at room temperature, even though reaction rates are often low. These conditions serve to obviate side reactions which, reportedly, compete at elevated temperatures.[29] However, there are a number of examples where satisfactory yields have been obtained after shorter reaction times at higher temperatures. Polymerisation of the activated alkene, one of the more serious side reactions, can be minimised by the addition of a radical inhibitor, and the rapid attainment of elevated reaction temperatures is possible with microwave irradiation. This method has been applied successfully in a number of cases,[42,43] including reactions with acrylamides, which are inert substrates under normal circumstances. However, the use of commercial microwave ovens requires sealed-tube techniques which limit the scale and introduce an explosion hazard. These problems may be overcome with a continuous microwave reactor.[42]

Remarkably, lowering the reaction temperature also appears to increase the rate of amine- and phosphine-catalysed reactions involving acrylates.[44] The effect is particularly dramatic in view of the fact that these reactions have been carried out at rather low concentrations in dioxane or methylene chloride. Differences in equilibrium and rate constants for the formation and reaction of the *E* and *Z* forms of zwitterion **26** (Scheme 12) at different temperatures have been offered as a possible explanation for the rate

acceleration at low temperatures. It remains to be determined whether this phenomenon is general for all Morita-Baylis-Hillman reactions.

1.2.2.3 Pressure and sonication

Because of bond formation and charge development prior to, and in the rate-determining step, the Morita-Baylis-Hillman reaction is expected to have a large negative volume of activation and thus be subject to rate acceleration by increased pressure. Hill and Isaacs[34,45] have shown that these coupling processes are, in fact, highly sensitive to pressure, and pressures of 2 –5 kbar are highly effective in accelerating the reaction. Thus, the DABCO-catalysed α-hydroxyethylation of acrylonitrile, which requires 4 – 5 days at atmospheric pressure to provide the desired product in good yield, goes to completion in 5 minutes when the reaction is conducted at 2 – 5 kbar (Scheme 13). An even more important outcome of these studies has been that previously unreactive ketones and crotonic derivatives may be reacted at 10 kbar pressure. In some cases, it was found that these pressure-accelerated processes were better controlled by using the less reactive triethylamine rather than DABCO.[34] It has also been found that in pressure-induced Morita-Baylis-Hillman reactions, polymerisation of the activated alkene can be minimised by using an excess of the electrophile,[45] increasing the amount of catalyst, or diluting with a solvent.



a) 1 atm; 4-5 d
b) 2-5 kbar; 5 min

Scheme 13

Exposure of reaction mixtures to ultrasound has been reported to produce the same effect as high pressure.[29] However, in the DABCO-catalysed coupling of a series of aliphatic, alicyclic and aromatic aldehydes to methyl acrylate, only small rate increases were observed on sonication.[46] Roos and Rampersadh,[46] who also studied the α-

hydroxyalkylation of methyl acrylate, have claimed that, although the rate acceleration due to sonication is not very remarkable, it is helpful where solid reagents are involved. However, Bhat and co-workers[43] have reported that microwave irradiation provides considerable rate enhancement in the reaction between aldehydes and activated alkenes. Under normal circumstances, acrylamides are inert substrates for this reaction but, under microwave irradiation, acrylamide has been shown to react with 3,4,5-trimethoxybenzaldehyde to provide the corresponding adduct in 40% yield.[30]

1.2.3 Stereochemistry

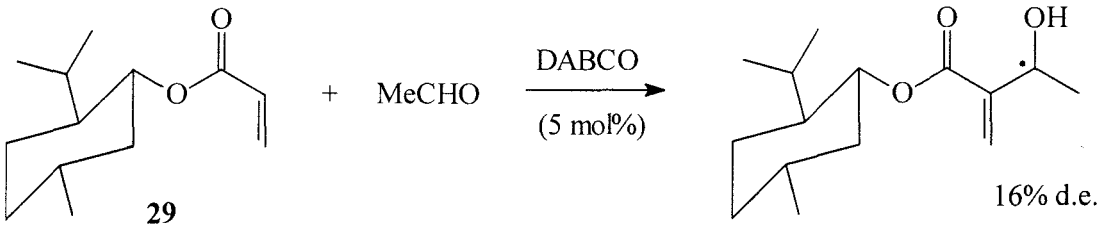
The Morita-Baylis-Hillman reaction generally results in the creation of a new chiral centre and, therefore, there exists the possibility for asymmetric induction. Consequently, efforts have been expended to develop an asymmetric version of this reaction. As in the case of any reaction that affords chiral products, the chiral information for an "asymmetric Morita-Baylis-Hillman reaction" can lie with any one of the four components essential for the reaction. This has provided new avenues for research and efforts have been made to study the levels of asymmetric induction achieved by employing any one of the four components (*i.e.* activated alkene, electrophile, tertiary amine or solvent/additive) in optically active form.

1.2.3.1 Diastereoselectivity

(i) Chiral activated alkenes

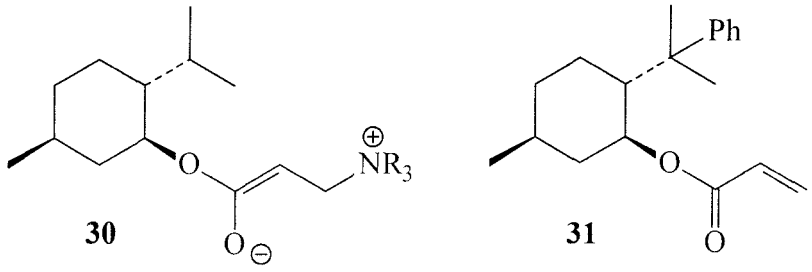
Most of the chiral alkenes studied thus far have been esters of acrylic acid. The ready accessibility of chiral acrylates and the easy removal of the chiral auxiliary from the products have made this approach particularly attractive. The use of other activated alkenes, such as vinyl ketones, sulphones and phosphonates in optically active form has been hampered by their relative inaccessibility. A number of chiral acrylates have been used to good effect in asymmetric Morita-Baylis-Hillman reactions. The first such attempt was by Brown *et al.*[47] who observed a diastereomeric excess of only 16% in the reaction of

(-)-menthyl acrylate **29** with acetaldehyde in the presence of DABCO as catalyst (Scheme 14).



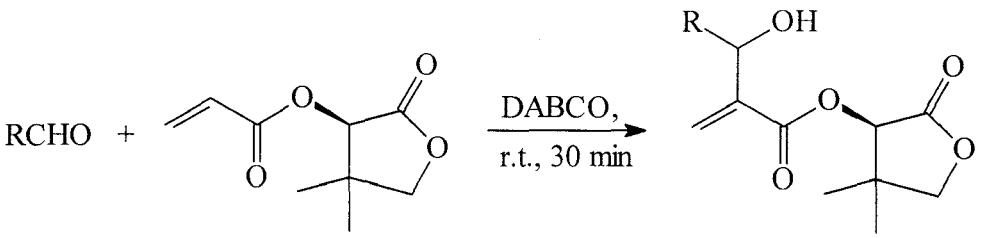
Scheme 14

The generally low stereoselectivity observed when using chiral activated alkenes is usually attributed to the large distance between the chiral directing and reaction centres.[29] In most cases, diastereoselectivity is poor, except for the reaction of (+)-menthyl esters with aromatic aldehydes under high pressure where diastereoselectivities of up to 100% d.e. have been reported.[45] Less bulky aldehydes add to menthyl esters with much lower diastereoselectivity, even under pressure. These results have been interpreted in terms of attack by the aldehyde on the *si*-face of zwitterion **30** to produce the *S*-configuration at the newly created chiral centre, but the absolute configuration has not been determined.[45] Reactions of the 8-phenylmenthyl esters **31** are, in general, more diastereoselective than those of the menthyl esters, an observation that has been attributed to a π-stacking effect.[48]



It has also been argued that, in reactions involving the esters **31**, it is the reactivity of the aldehyde rather than its bulk that determines the degree of diastereoselectivity. Reactive aldehydes should thus give higher % d.e. values since the opportunity for equilibration by the reverse reaction is diminished. However, the very rapid reactions depicted in Scheme

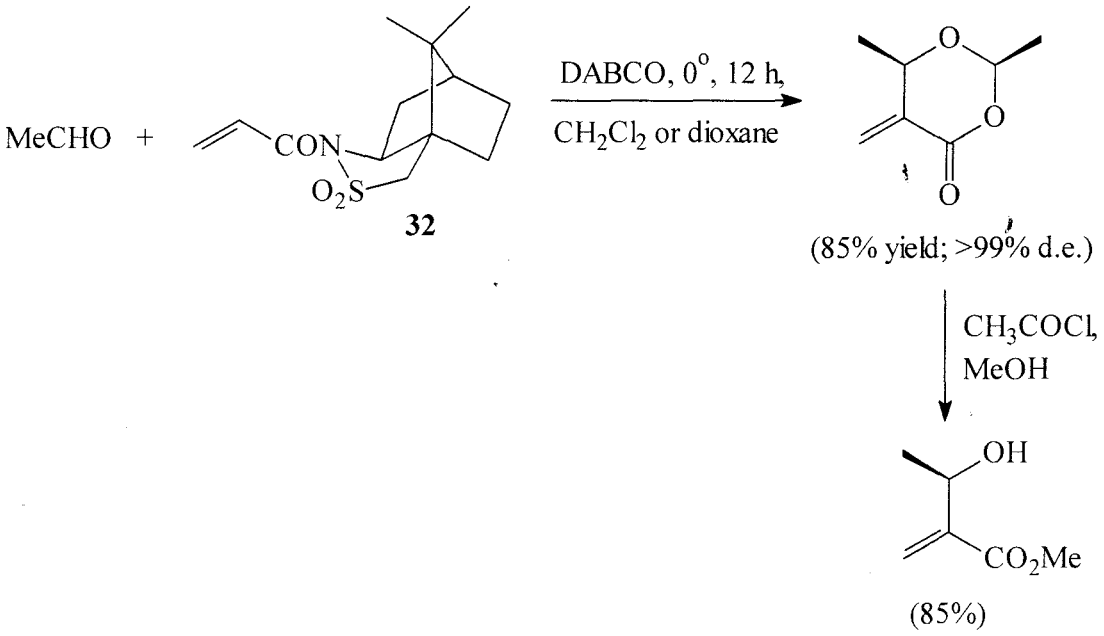
15 show moderate or no diastereoselectivity, depending on the substituent, R.[49] A study of diastereoselectivity as a function of reaction time has not yet been reported.



R = CCl_3 : 83% yield; 48% d.e.
R = Ph : 81% yield; 2% d.e.

Scheme 15

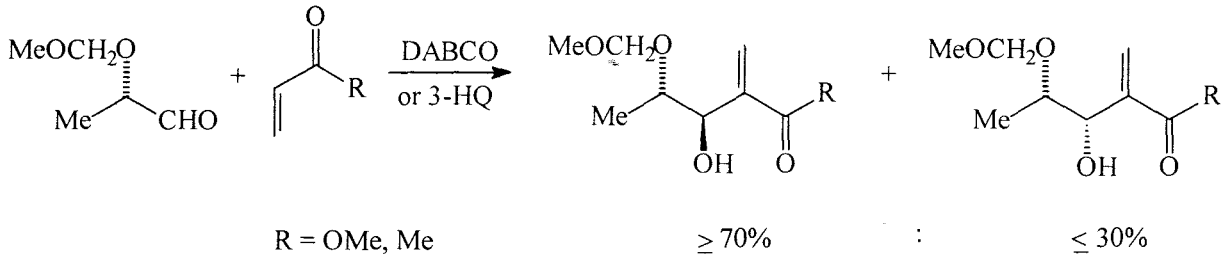
The most impressive results reported to date involve reactions of aliphatic aldehydes with the camphor sultam acrylate **32** to give 2,4-dialkyl-5-methylene-1,3-dioxan-4-ones with high diastereoselectivity[50] (Scheme 16). The products are readily converted into α-hydroxyalkyl acrylates, and the chiral auxiliary is easily recovered.



Scheme 16

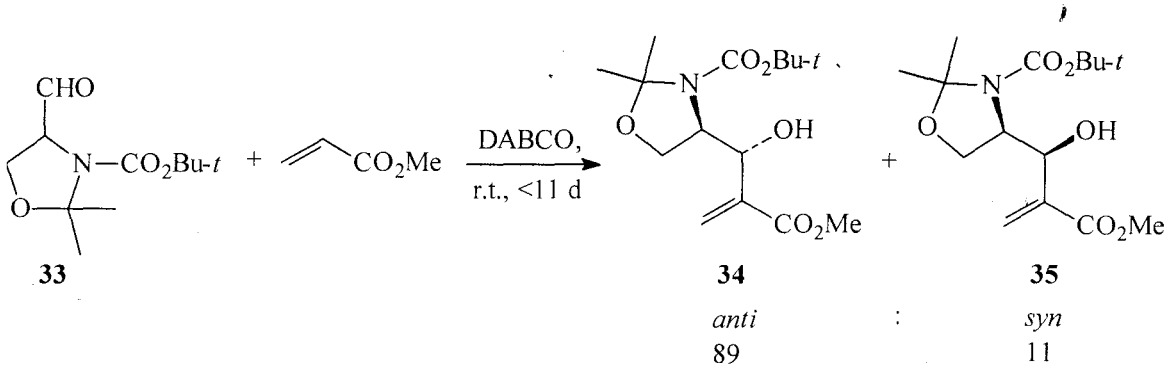
(ii) Chiral electrophiles

Of the various possible electrophiles, only aldehydes have been employed in optically active form thus far. Diastereoselectivity in the Morita-Baylis-Hillman reaction of several racemic and non-racemic aldehydes with methyl acrylate and methyl vinyl ketone has been studied. For example, (*S*)-(-)-2-(methoxymethyloxy)propanal has been shown to react with both methyl acrylate and methyl vinyl ketone, under the influence of either DABCO or 3-hydroxyquinuclidine, (3-HQ), to afford mixtures of diastereomers with the *anti*-isomer predominating (Scheme 17).[51] The nature and amount of the catalyst appears to affect the rate but not the *syn-anti* ratio. Although bulky substituents do not necessarily lead to high selectivity, use of the heterocyclic aldehyde **33** (Scheme 18) affords the *anti*-product **34** in 78% d.e..[37]



R = OMe, Me ≥ 70% : ≤ 30%

Scheme 17



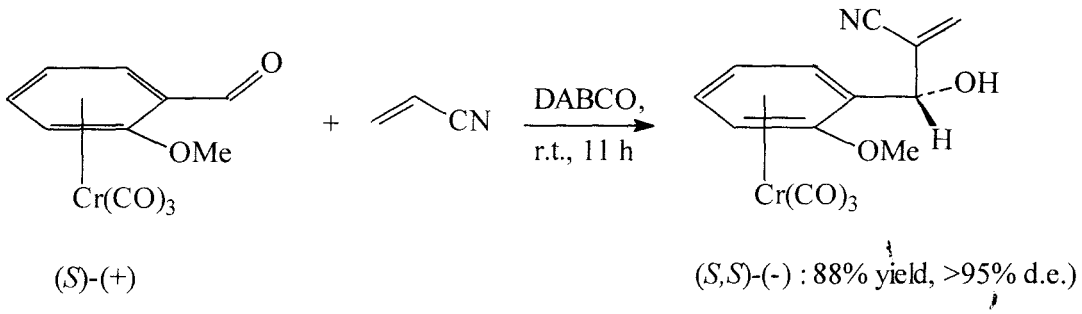
33 **34** *anti* 89 : **35** *syn* 11

Scheme 18

In the examples investigated so far, the application of high pressure does not appear to enhance diastereoselectivity appreciably. (*R*)-Myrtenal and isopropylidene (*R*)-glycer-aldehyde were employed in Morita-Baylis-Hillman reactions with acrylonitrile at 5.5 and 4

kbar pressures respectively, but the diastereoselectivity in both cases was very low (23% d.e.); at ambient pressure both reactions gave equimolar mixtures of the two diastereomers.[45]

Excellent diastereoselectivities, often approaching 100% d.e., have been achieved in reactions involving tricarbonylchromium complexes of *ortho*-substituted aromatic benzaldehydes,[52] as illustrated for *o*-methoxybenzaldehyde in Scheme 19. Similar results were obtained with the reaction of methyl acrylate and the *o*-chlorobenzaldehyde complex. Reactions of methyl acrylate with the tricarbonlychromium complexes of *o*-fluorobenzaldehyde and *o*-tolualdehyde, however, gave somewhat lower diasteroselectivities (84% and 68% d.e. respectively). The dependence of the diastereoselectivity on the nature of the *ortho* substituent is also apparent in reactions of the tricarbonylchromium complexes of *ortho*-substituted benzaldehyde tosylimines with methyl acrylate and acrylonitrile.[53] The products in all cases are readily decomplexed by exposure to air and sunlight.



(*S*)-(+)

(*S,S*)-(-) : 88% yield, >95% d.e.)

Scheme 19

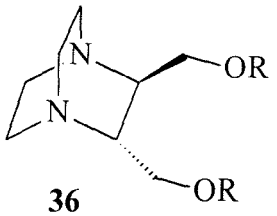
1.2.3.2 Enantioselectivity

(i) Chiral catalysts

The most commonly used catalysts in the Morita-Baylis-Hillman reaction are tertiary amines. The mechanism proposed for this reaction implies the participation of the catalyst throughout the course of the reaction, including the step in which the chiral centre is created. Consequently, the structure of the tertiary amine might be expected to have some

bearing on the stereochemistry of the transition state(s). In other words, if the amine is chiral, it should be able to effect chiral discrimination. However, attempts to achieve high enantioselectivity with chiral catalysts have met with only limited success thus far. Low enantiomeric excesses are often obtained even when the chiral centre is close to the nitrogen atom. The problem is further complicated by the fact that many chiral catalysts suffer from low conversion efficacy, and the application of high pressure is usually required.

A variety of optically active tertiary amines such as quinine, quinidine, cinchonidine and retronecine have been used as catalysts[33] but, in all cases, the asymmetric induction was limited. The most promising results have been obtained with chiral, 2,3-disubstituted DABCO derivatives **36**. The reaction of 4-nitrobenzaldehyde with methyl vinyl ketone, when catalysed by catalyst **36** (R = CH_2Ph) has been shown to proceed with 47% e.e. at 5 kbar and 12% e.e. at ambient pressure.[29] Analogous catalysts containing other R groups (*t*-$BuPh_2Si$, *i*-Pr_3Si, Ph, mesityl, 1-naphthyl, 1-naphthoyl, 1-anthryl, and Cbz-gly) were even less effective. An enantiomeric excess of only 11% was observed in the reaction of benzaldehyde with acrylonitrile at 12 kbar in the presence of the chiral catalyst, *trans*-2,3-diphenyl-1,4-diazabicyclo[2.2.2]octane **37**. Similar results were obtained using (-)-3-hydroxyquinuclidine, brucine, strychnine, cinchonidine, cinchonine, quinine and quinidine as chiral catalysts. The optically active 2,5-diphenyl (**38a**) and 2,5-dibenzyl (**38b**) derivatives of DABCO have been synthesised; the former proved ineffective in Morita-Baylis-Hillman reactions, while results for the latter have not yet been reported.[29]



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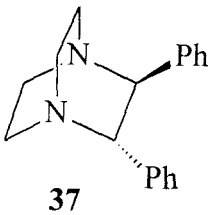

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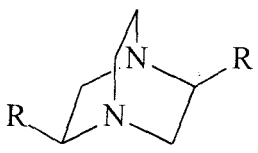
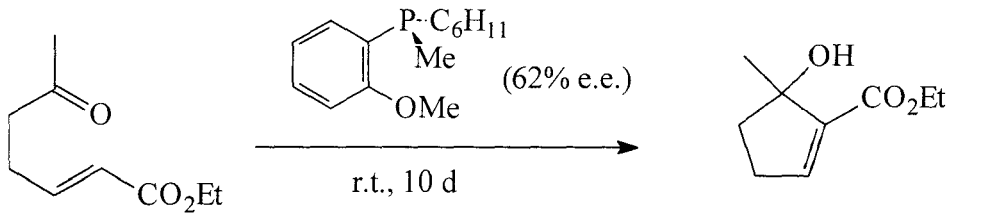


38a : R = Ph
38b : R = Bn

Only two attempts appear to have been made to catalyse a Morita-Baylis-Hillman reaction with a chiral phosphine. The intramolecular reaction illustrated in Scheme 20 proceeded with low asymmetric induction,[36] while in the reaction of benzaldehyde tosylimine with

methyl acrylate catalysed by chiral 2,3-bis(diphenylphosphino)butane, the enantiomeric products were formed in equal quantities.[31]



(40% yield, 14% e.e.)

Scheme 20

(ii) Chiral solvents

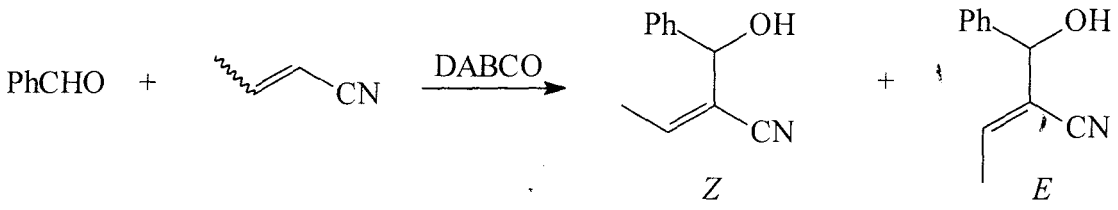
In many cases, a solvent is neither necessary nor desirable for Morita-Baylis-Hillman reactions, since dilution of the reagents would slow the reaction down further. Where the use of a solvent is practicable, however, it might be anticipated that a chiral solvent would induce some enantioselectivity, but the reaction of acetaldehyde with acrylonitrile in ethyl (+)-lactate, at 5 kbar pressure and in the presence of *racemic*-3-hydroxyquinuclidine exhibited essentially no enantioselectivity (3% e.e.).[45]

(iii) Resolution of Morita-Baylis-Hillman adducts

Enantiomeric α-hydroxyalkyl acrylates have been resolved by fractional crystallisation of diastereomeric salt mixtures of the corresponding acids and by kinetic resolution involving hydrogenation with chiral rhodium biphosphine and other optically active catalysts.[54] Other methods which have been used include acetylation of the hydroxyl group with vinyl acetate catalysed by *Pseudomonas AK*,[55] and enantioselective hydrolysis of the acetates by pig liver esterase.[56] Kinetic resolution of *racemic*-3-methylene-4-(4-nitrophenyl)-4-hydroxy-2-butanone has been achieved by Katsuki-Sharpless epoxidation, and that of ethyl 2-(1-acetoxyethyl) acrylate by the action of esterases. α-Aminoalkyl acrylates have been subjected to kinetic resolution by hydrogenation with chiral rhodium and ruthenium biphosphine catalysts.

1.2.3.3 E-Z *selectivity*

Since β-substituted activated alkenes do not generally undergo the Morita-Baylis-Hillman reaction at ambient pressure, relatively little is known about the *E-Z* selectivity of the process. Polar solvents appear to favour formation of the *E*-isomer in the pressure-induced reaction of benzaldehyde with crotononitrile[35] (Scheme 21). *E/Z* ratios at 8 kbar range from *ca.* 1 without solvent, or in tetrahydrofuran, to *ca.* 4 in methanol. Increased pressure appears to result in higher *E/Z* ratios, but this effect is solvent dependent. In chloroform, for example, the *E/Z* ratio ranges from *ca.* 1 at 6 kbar to *ca.* 23 at 15 kbar, whereas when methanol was used as the solvent, the *E/Z* ratio was not observed to vary with changing pressure. The *E/Z* ratios for different catalysts at a constant 8 kbar pressure range from 1 (for DABCO) to 2 (for 3-hydroxyquinuclidine) and 4 (for triethylamine). These results, as well as those of a similar study with methyl crotonate, have been interpreted in terms of the predominance of either an E2 or E1cB mechanism (Scheme 12) under different reaction conditions. In the pressure-induced reaction of the less bulky acetaldehyde with crotononitrile, the *Z*-isomer predominated by a ratio of 4.5:1,[57] while the reaction of formaldehyde with (*E*)-crotonaldehyde in a microwave flow-reactor gave the *E* isomer exclusively, albeit in low yield.



Scheme 21

1.2.4 Scope and limitations

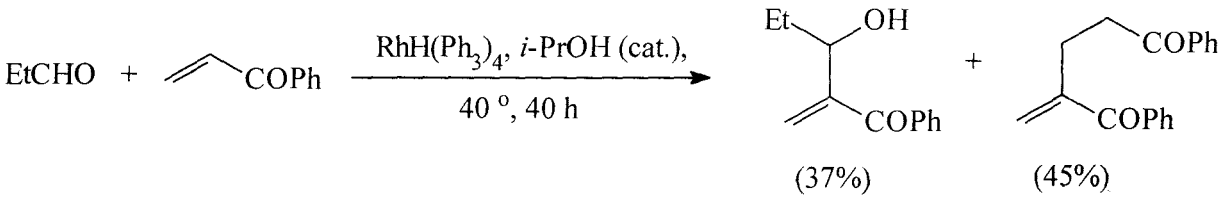
1.2.4.1 The activated alkene

The reactivity of activated alkenes appears to decrease in the order:- acrolein ≅ phenyl vinylsulfonate > α,β-unsaturated ketones > acrylonitrile > acrylic esters ≅ ethyl vinylphosphonate > phenyl vinyl sulfone > phenyl vinyl sulfoxide ≅ acrylamides.[29] With the exception of the unusually high reactivity of phenyl vinylsulfonate, for which only one example exists, the reactivity increases with the electronegativity of the activating group, as would be expected based on the mechanism of the Morita-Baylis-Hillman reaction. The nature of the amine catalyst does not appear to have any influence on the reactivity order.[29]

Since the first report[27] of the reaction of ethyl acrylate and acetaldehyde in 1972 (Scheme 11), acrylic esters have been reacted with a wide range of aldehydes, leaving no doubt about the generality of the reaction. Acrylic esters constitute, by far, the largest group of activated alkenes employed in the Morita-Baylis-Hillman reaction, probably because of the versatility of the ester group for further elaboration. As a rule, aromatic esters of acrylic acid react more rapidly than aliphatic analogues, while β-substituted acrylates are normally unreactive. The only successful reactions of β-substituted alkenes reported to date involve methyl crotonate, crotononitrile and crotonaldehyde, and these reactions were conducted under elevated pressure.[57]

Whereas acrolein reacts rapidly with aldehydes in DABCO-catalysed Morita-Baylis-Hillman reactions, no additions of aldehydes to acrylamides under ambient conditions have been reported. There have, however, been some reports of the reaction at elevated pressure.[34] The low reactivity of acrylamides is not surprising since they are less electrophilic than most other activated alkenes. However, sultam **32** (Scheme 16), which carries a second electron-withdrawing group on the nitrogen, reacts readily with aldehydes.[50] Additions of aldehydes to alkyl vinyl ketones proceed well with a variety of catalysts, with amine-catalysed additions often being cleaner when carried out in a solvent.[29] While α-branched alkyl vinyl ketones do react, aryl vinyl ketones generally do not, possibly because such ketones dimerise rapidly, especially in the presence of DABCO;

there is, however, one report of such a reaction (Scheme 22).[58] β-Substituted alkenes do not readily undergo the Morita-Baylis-Hillman reaction.



Scheme 22

An obvious extension of the Morita-Baylis-Hillman reaction is to replace carbonyl electron-withdrawing groups (as in esters or ketones) with sulphur- or phosphorus-containing analogues. While the use of only one phosphorus-containing activated alkene [CH_2=CHP(O)$(OEt)_2$] has been reported,[59] numerous sulphur-containing systems have proved effective; in all cases, however, the activating sulphur moiety carried a phenyl group. In the single example involving a vinyl sulfoxide (CH_2=CHSOPh), drastic reaction conditions (19 kbar) were required to drive the reaction.[60] Phenyl vinyl sulfone (CH_2=$CHSO_2$Ph) reacts at ambient pressure and temperature, but reaction times of weeks are common, especially with less reactive aldehydes,[61] and although phenyl vinylsulfonate (CH_2=$CHSO_3$Ph) appears to be surprisingly reactive, only one example of a reaction of this class of compounds has been reported.[62]

1.2.4.2 The electrophile

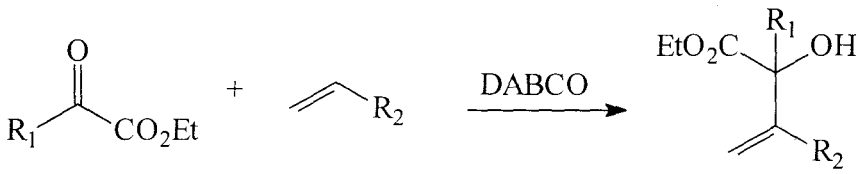
Aldehydes are the most commonly used electrophiles. They are much more reactive than simple ketones - an observation which is predictable on both electronic and steric grounds. The simplest aldehyde, formaldehyde, can be employed as an aqueous solution (formalin), as a polymer (paraformaldehyde), as a solution of the monomer in organic solvent, or as the hemiacetal; data for its reactions with methyl acrylate are summarised in Table 1. Similar results have been obtained for reactions of formaldehyde with acrylonitrile, methyl vinyl ketone and phenyl vinyl sulfone.[29]

Table 1. Data for reactions of methyl acrylate with formaldehyde.[63]

Formaldehyde source	Reaction conditions	Yield (%)
Formalin	DABCO, H_2O, MeOH, r.t., 48 h	75
Paraformaldehyde	Me_3N, H_2O, 60 °C, 3 h	80
Monomer	DABCO, EtOH, r.t., 72 h	59
Cyclohexanol hemiacetal	DABCO, cyclohexanol, r.t., 70 h	45

Aromatic aldehydes, especially those containing electron-withdrawing groups, react with activated alkenes in high yield. Heteroaromatic aldehydes, such as 2-pyridinecarbaldehyde, are excellent electrophiles because of their increased electrophilicity;[32] the heteroatom is also believed to facilitate the proton transfers that are involved in the reaction.

Although ketones do not undergo the Morita-Baylis-Hillman reaction under ambient conditions, acetone, methyl ethyl ketone and cyclohexanone have been reported to react with acrylonitrile at high pressure.[57,34] Ketones, such as diisopropyl ketone and aryl alkyl ketones, are unreactive, even at elevated pressure. However, the reluctance of such ketones to undergo α-hydroxyalkylation appears to be electronic rather than steric in nature, since sterically hindered α-halogenated ketones do, in fact, add readily to acrolein, acrylonitrile and ethyl acrylate.[29] α-Keto esters, on the other hand, are very reactive electrophiles in the Morita-Baylis-Hillman reaction (Scheme 23),[64] as are imines, which carry a sufficiently electronegative substituent (*e.g.* MeOCO) on the nitrogen.[65]

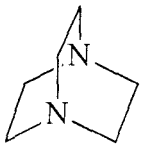


R_1	R_2		
Ph	CO_2Me	r.t., 7 d	49%
EtO_2C	COMe	r.t., 30 min	74%

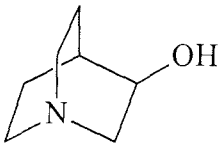
Scheme 23

1.2.4.3 Catalysts

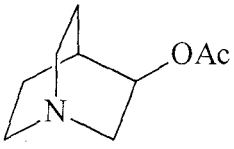
In an effort to find more efficient catalysts, a number of tertiary amines have been investigated. In the series of bicyclic amines **24** and **39-42**, only 3-hydroxyquinuclidine **39** is more effective than DABCO **24**. Four- to tenfold reductions in half-lives have been achieved, and 3-hydroxyquinuclidine is now routinely used in Morita-Baylis-Hillman reactions.[66,67] The bicyclic bases, 3-acetoxyquinuclidine **40**, 3-quinuclidone **41**, and quinuclidine **42** are all poorer catalysts than DABCO.



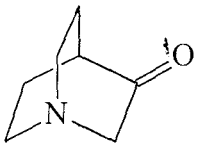
24



39



40



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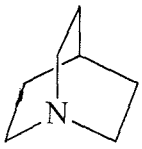
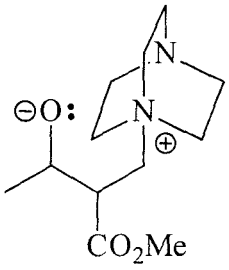


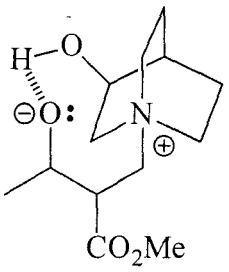
42

The activity of 3-hydroxyquinuclidine was initially attributed to stabilisation of the species corresponding to zwitterion **26** (Scheme 12, p.12) by intramolecular hydrogen-bonding between the 3-hydroxy group and the negatively charged oxygen.[67] However, modelling studies indicate that such an intermediate suffers from unfavourable non-bonded interactions, and the rate-enhancing effect of 3-hydroxyquinuclidine has subsequently been attributed to its ability to protonate the initial zwitterion intermolecularly.[68,69] However, the latter explanation is unlikely for several reasons, *viz.*, i) proton transfer is unlikely to be rate-determining; ii) the kinetics have been shown to be first-order in the catalyst,[70] and

this explanation would require second-order involvement of the catalyst; iii) semi-empirical molecular orbital calculations[71] indicate that the intramolecular proton exchange (**27** → **28**; Scheme 12) is highly exothermic, affording as it does the resonance-stabilised species **28**. The most likely explanation for the rate-enhancement effect exhibited by 3-hydroxyquinuclidine appears to arise from hydrogen-bonding stabilisation of the zwitterionic adduct **43** – an arrangement shown, by both molecular mechanics and semi-empirical molecular orbital calculations, to be feasible.[72] When DABCO is used as the catalyst, such stabilisation is not possible (see structure **27**). Of course, protonation may also be achieved by the addition of catalytic amounts of a protic solvent.[29]



27



43

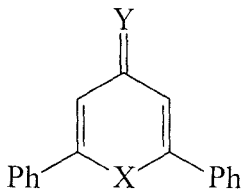
Although the nitrogen atom in simple tertiary amines is more sterically hindered than in the bicyclic amines mentioned above, a number of acyclic tertiary amines have been successfully employed as catalysts for the Morita-Baylis-Hillman reaction. In the reaction of formaldehyde with ethyl acrylate, catalyst efficacy has been reported to decrease in the expected order, *i.e.* trimethylamine > dimethylamine > methyldiethylamine > triethylamine.[73] Branching α to the nitrogen greatly reduces or even eliminates catalytic activity altogether – an observation attributed to steric effects and a reduction in the nucleophilicity of the nitrogen arising from the increased sp^2-like configuration.

It is also possible for the α-hydroxyalkylation reactions to be catalysed by tertiary phosphines, such as triphenylphosphine. Although the mechanism is considered to be identical to that of the amine-catalysed reaction,[74] the initially formed zwitterion can isomerise to a phosphorus ylide, which may then undergo a Wittig reaction when tertiary alkyl or mixed arylalkylphosphines are used as catalysts. When triphenylphosphine is used

as a catalyst, the reactions proceed considerably faster and, apparently, without the concomitant formation of Wittig products.[44] Numerous trialkyl phosphine catalysts of this type have been employed, the most efficient being tributylphosphine.

Transition metal complexes have also been reported to catalyse Morita-Baylis-Hillman reactions. α,β-Unsaturated ketones have been shown to add to aldehydes under the influence of rhodium and ruthenium hydride complexes. Catalysts reported to be effective in these transformations are:- $RhH(PPh_3)_4$; $RuH_2(PPh_3)_4$; $[Rh(cyclooctadiene)\text{-}(Ph_2PCH_2CH_2PPh_2)]^+ PF_6^-$ in the presence of hydrogen; and $[RhH_m(P\text{-}P)S_n]^+ BF_4^-$ where P-P represents various chiral diphosphines and S are solvent molecules.[58] The addition of small amounts of an alcohol appears to enhance rhodium hydride catalysed reactions, but other solvents reduce the yields drastically. This has been taken as evidence against the possibility that the phosphines in the metal complexes are the true catalysts since phosphine-catalysed Morita-Baylis-Hillman reactions proceed well in solution. The rhodium hydride catalysed α-hydroxyalkylation reaction has also been successfully applied to acrylonitrile, but acrylic esters have proved inactive.

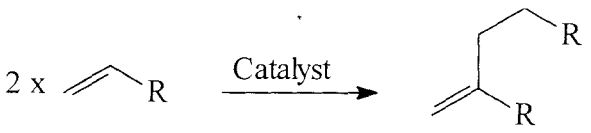
Kataoka and co-workers were the first to report the use of Morita-Baylis-Hillman catalysts containing the group 16 elements, sulphur and selenium. Preliminary yields of the Morita-Baylis-Hillman product arising from the reaction between *p*-nitrobenzaldehyde and cyclohex-2-en-1-one, catalysed by Me_2S and the Lewis acid, $TiCl_4$, were moderate (17%).[75,76] Recently, however, the same group has synthesised a new series of catalysts **44** - **47** which proved to be more efficient than Me_2S.[77] 4*H*-Chalcogenopyran-4-one- and 4*H*-chalcogenopyran-4-thione-catalysed reactions of *p*-nitrobenzaldehyde with methyl vinyl ketone proceed in the presence of $TiCl_4$ at 0 °C to afford Morita-Baylis-Hillman adducts in yields ranging from 86 – 100%. The reaction has also been extended to include a range of other aliphatic and aromatic aldehydes.



	X	Y
44	S	O
45	S	S
46	Se	O
47	Se	S

1.2.4.4 Side reactions

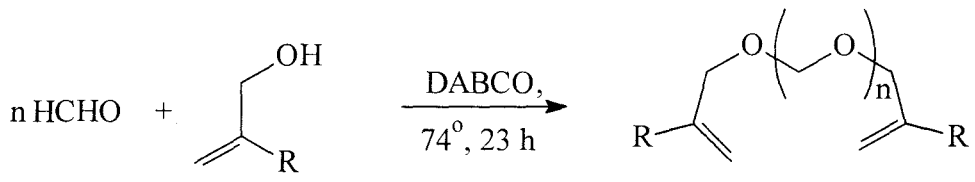
A variety of side reactions has been reported. Head–to-tail dimers are formed when the activated alkene also acts as the electrophile (Scheme 24), the dimerisation appearing to be somewhat more prominent when phosphine catalysts are employed.[57] α,β-Unsaturated ketones, acrylates and acrylonitrile have all been reported to undergo dimerisation. Substrates containing electronegative groups, such as aryl vinyl ketones and acetylmethyl vinyl ketone, are particularly prone to dimerisation with both DABCO and tertiary phosphine catalysis. Polymerisation, however, appears to be a significant problem only with acrolein and with some other activated alkenes at elevated temperatures.



Scheme 24

It is also possible for the initial products of the Morita-Baylis-Hillman reaction to react further. Thus, once formed, methyl α-hydroxymethylacrylate **48** may be converted into the ethers **49** (n = 0, 1, 2) under the influence of DABCO (Scheme 25), the monoether **49** (n = 0) having been obtained in 54% yield.[78] These ethers (**49**; R = CO_2R; n = 0,1,2) are formed as side products in reactions of formaldehyde with acrylic esters, acrylonitrile and,

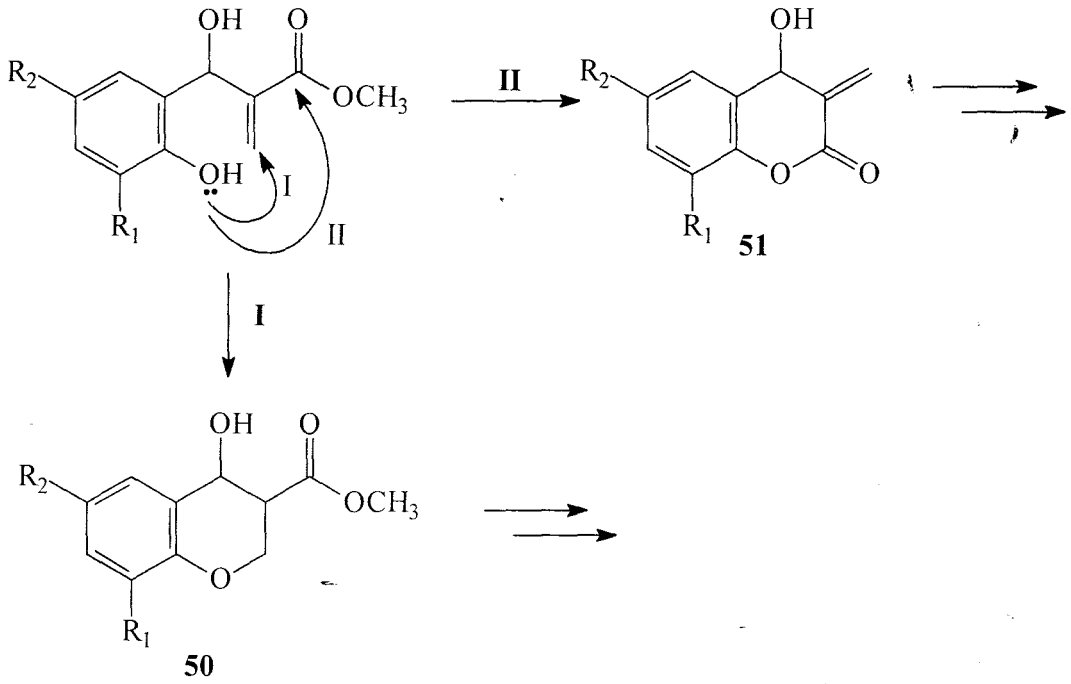
presumably, with other activated alkenes. However, ether formation does not appear to be a problem with α-hydroxyalkylation products derived from other aldehydes.



48 **49** R = CO_2Me; n = 0, 1, 2

Scheme 25

In reactions of salicylaldehydes with methyl acrylate, Kaye and co-workers uncovered a cascade of transformations involving the formation of chromene and coumarin derivatives.[79,80,81] Intramolecular conjugate addition (Scheme 26, path I) accounts for the formation of the 4-hydroxychromans **50**, dehydration of which affords the corresponding conjugated 2*H*-chromenes, which may act, in turn, as Michael acceptors in subsequent reactions. Alternatively, acyl substitution (path II) affords the corresponding coumarin derivatives **51**, which may also act as precursors in further transformations.



Scheme 26

1.2.5 Experimental conditions

Generally, the main experimental hurdle to overcome in amine-catalysed Morita-Baylis-Hillman transformations is the low reaction rate. The simplest solution appears to be the use of stoichiometric amounts of DABCO or the more reactive 3-hydroxyquinuclidine, although phosphine catalysts, such as tributylphosphine, sometimes provide higher reaction rates than tertiary amines. Employing an excess of either the activated alkene or the electrophile is also beneficial, depending on the cost and ease of removing the reagent used in excess. A more than sixfold excess should be avoided, however, since the dilution effect leads to a reduction in rate.[29]

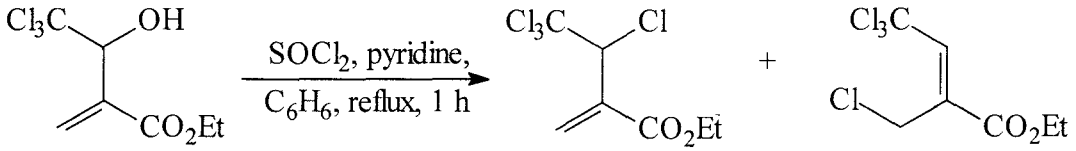
The addition of small amounts of a proton source, such as methanol or acetic acid, has been reported to increase the reaction rate, as do certain salts.[29] The use of solvents usually reduces the rate due to dilution effects, but may be necessary with poorly soluble substrates. Reaction rates have also been increased by raising the temperature but, under these conditions, polymerisation of the activated alkene may occur – a possibility which may be eliminated by the addition of small amounts of a polymerisation inhibitor, such as hydroquinone. High pressure and microwave irradiation have also been used successfully to increase reaction rates; in these cases, obvious precautions must be taken due to the possibility of explosion.

1.2.6 Synthetic utility

Products from the Morita-Baylis-Hillman reaction typically contain three functionalities: the hydroxyl (or amino) group, the double bond and the alkene-activating group. In addition, they generally contain a chiral centre. They may therefore be expected to undergo a variety of transformations, in some of which, issues of regio- and stereochemical control are important.

1.2.6.1 Reactions of the hydroxyl group

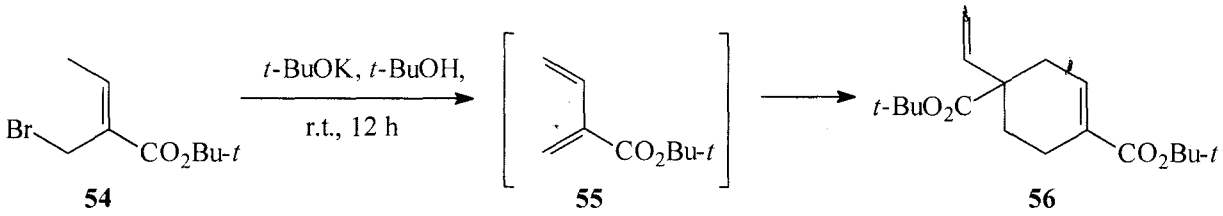
Morita-Baylis-Hillman adducts have been shown to be versatile precursors of trisubstituted stereodefined alkenes. There have been numerous reports of regioselective halogenation, and 2-haloalkyl derivatives can be formed with or without allylic rearrangement, depending on the reagents chosen. In the example illustrated in Scheme 27, however, both normal **52** and rearranged **53** products are formed.[82]



52 (46%) **53** (11%)

Scheme 27

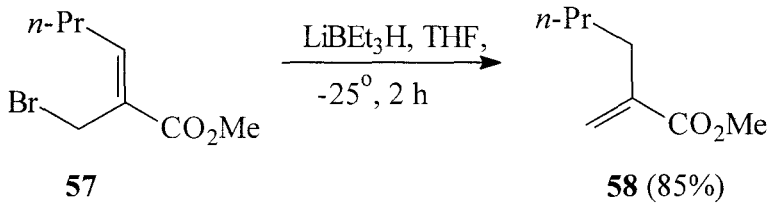
Halogenated derivatives have been shown to be versatile substrates in a number of transformations. Thus, base-induced elimination of the rearranged allyl bromide **54** gives the cyclohexene diester **56** *via* Diels-Alder dimerisation of the very reactive intermediate diene **55** (Scheme 28).[83]



54 **55** **56**

Scheme 28

Allyl acetates, halides and sulphides derived from Morita-Baylis-Hillman adducts have been observed to undergo substitution reactions with hydride ion and a variety of carbon and heteroatom-based nucleophiles. In the case of the bromo derivative **57**, $LiBEt_3H$ reduction involves hydride attack at the vinylic centre (C-3) with consequent elimination of bromide ion and formation of the 2-alkylacrylate **58** (Scheme 29).[84]



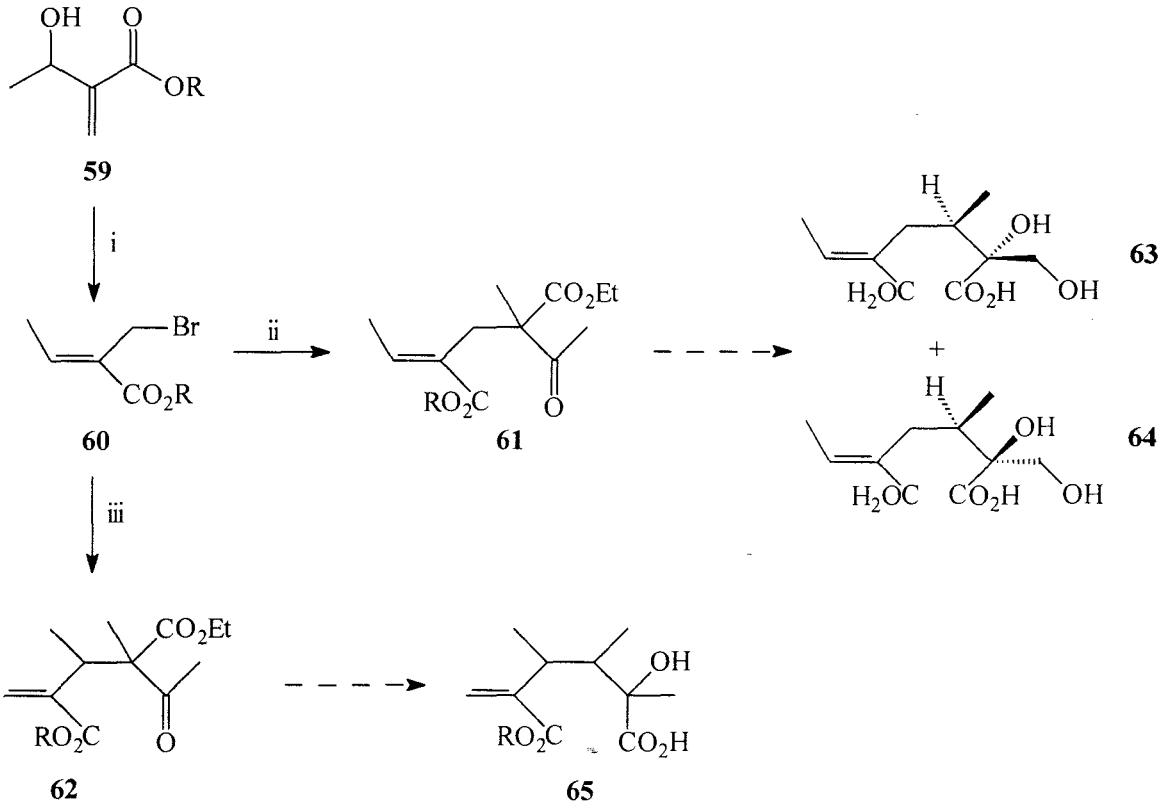
57 **58** (85%)

Scheme 29

Elimination of the hydroxyl group from Morita-Baylis-Hillman products is easily accomplished by refluxing in acetic acid and pyridine,[74] and the resulting dienes readily undergo Diels-Alder cycloaddition reactions.[30] The hydroxyl group may also be oxidised to give highly reactive, doubly activated alkenes.

1.2.6.2 Reactions of the double bond

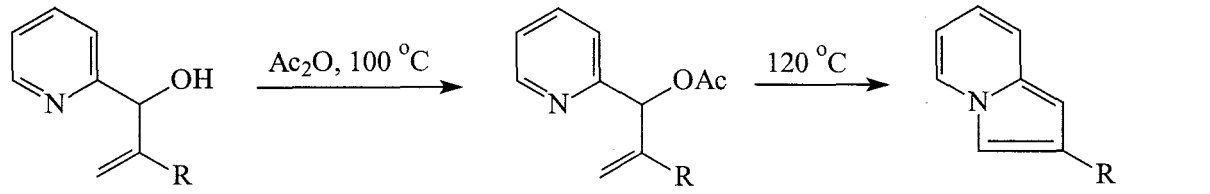
The double bond is susceptible to hydrogenation, halogenation, amination and epoxidation, and some cases of radical addition have been reported.[29] The Morita-Baylis-Hillman products are, therefore, versatile synthons for a range of target molecules. Applications of this strategy to the synthesis of necic acids are outlined in Scheme 30. Thus, regioselective bromination of the Morita-Baylis-Hillman product **59** gave ethyl (*Z*)-2-bromomethyl-2-butenoate **60** which, depending on the conditions, reacted with ethyl 2-methyl-3-oxobutanoate enolate to afford, preferentially, either the diester **61** or the isomeric product **62**. The diester **61** provides access to the stereoisomeric products (±)-retronecic acid **63** and (±)-isoretronecic acid **64**, while the diester **62** led to the senecivernic acid system **65** (Scheme 30).[85,86]



Reagents: (i) conc. HBr, conc. H_2SO_4; (ii) $CH_3COCH(CH_3)CO_2Et$, NaOEt, EtOH; (iii) $CH_3COCH(CH_3)CO_2Et$, NaH, THF

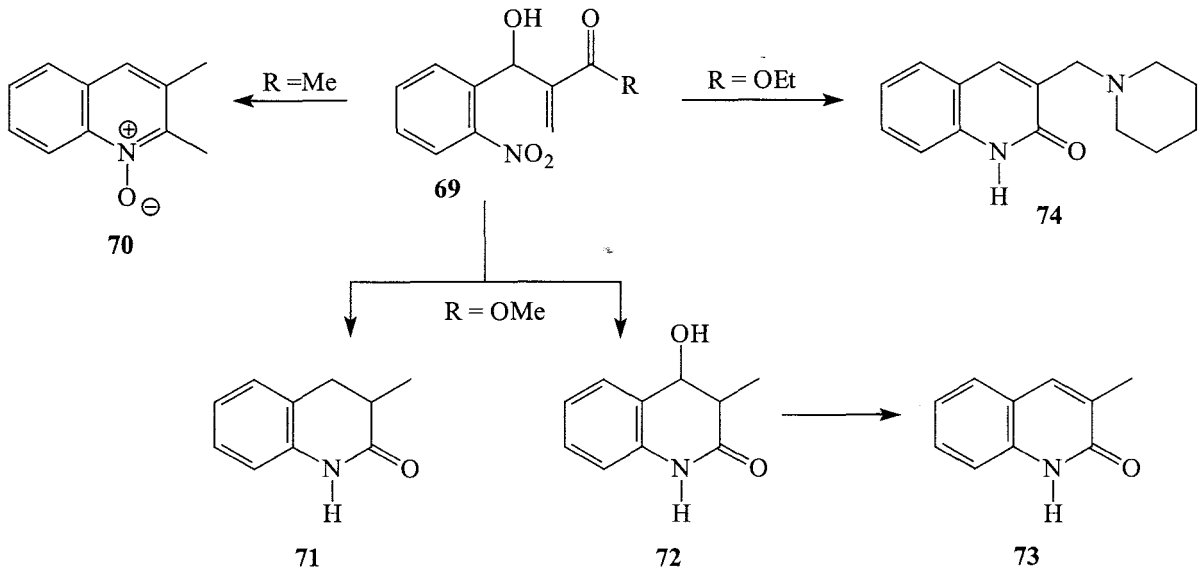
Scheme 30

Morita-Baylis-Hillman products have also provided convenient access to 2-substituted indolizines. Bode and Kaye[87] reported the thermal cyclisation of 3-acetoxy-3-(2-pyridyl)-2-methylenepropanoic esters and related compounds **67** to afford 2-alkoxy-carbonyl- (**68**; R = CO_2R) and 2-cyano- (**68**; R = CN) indolizines (Scheme 31), the hydroxy precursors **66** having been obtained *via* Morita-Baylis-Hillman reactions of 2-pyridinecarbaldehyde. An extension of this methodology to the synthesis of quinoline derivatives was reported by the same group.[88] The Morita-Baylis-Hillman adduct **69**, obtained using 2-nitrobenzaldehyde, provided access to various quinoline derivatives (**70** - **74**) following reductive cyclisation (Scheme 32).



66 **67** **68** (R = CO_2R, CN)

Scheme 31



70 **69** **74** **71** **72** **73**

Scheme 32

From the selected examples it is apparent that the Morita-Baylis-Hillman reaction is an extremely useful transformation, not only as an end in itself, but also for providing synthons for seemingly limitless and novel synthetic applications.

1.3 PREVIOUS WORK IN THE GROUP AND AIMS OF THE PRESENT INVESTIGATION

As discussed above, chromones are versatile molecules and the investigation of their chemistry, which forms the basis of this project, is part of an ongoing programme within our research group.

Infrared studies of substituted chromone-2-carboxylate esters revealed carbonyl band-doubling, which was shown to be solvent-, substituent- and temperature-dependent and which was rationalised in terms of rotameric equilibria between *syn-s-trans* and *anti-s-trans* forms.[89] An efficient synthesis of substituted chromone-2-carboxamides has been developed,[90] and dynamic NMR studies of these compounds revealed a temperature-dependent splitting of the *N*-alkyl ^{1}H and ^{13}C NMR signals, which was attributed to internal rotation of the amide group.[91]

The susceptibility of chromone derivatives to ring-opening *via* nucleophilic attack at C-2 has been illustrated by the amine-mediated ring-opening of substituted chromone-2-carboxamides,[92] and a kinetic-mechanistic study demonstrated the influence of substituents on the ring-opening process.[93] Mass spectrometric analysis of the ring-opened, polyfunctional acrylamide derivatives permitted elucidation of their major fragmentation patterns,[94] while dynamic NMR analysis of rotational isomerism in these systems permitted the calculation of internal rotational barriers.[95]

Another class of chromone derivatives which has been the subject of investigation in the group are the 2-(*N*,*N*-dialkylamino)chromones. Dynamic ^{1}H NMR spectroscopy was used to explore the influence of substituents on the internal rotation of the amino group in these compounds;[96] nitrogen lone-pair delocalisation was presumed to inhibit rotation about the N-C(O) bond – a property which has some influence on the basicity of these compounds, as will be discussed later. Research has also focussed on the influence of various substituents on the electron density at C-2 and, hence, on the acidity of a series of 2-carboxychromones.[97] An investigation of substituent effects on the basicity of 2-(*N*,*N*-dimethylamino)chromones was seen as a logical extension of these studies.

As indicated in sections 1.2.4.4 and 1.2.6.2, applications of the Morita-Baylis-Hillman reaction have also enjoyed considerable attention in our laboratories and chromone-3-carbaldehydes were identified as interesting substrates for the continuation of these studies.

Consequently, the aims of this research have included the following.

(1) Synthesis and characterisation of a series of substituted 2-(*N*,*N*-dimethylamino)-chromones.

(2) Potentiometric analysis of the substituted 2-(*N*,*N*-dimethylamino)chromones to explore substituent effects on basicity.

(3) Synthesis and characterisation of substituted chromone-3-carbaldehydes.

(4) An investigation of Morita-Baylis-Hillman reactions of the substituted chromone-3-carbaldehydes.

(5) Mass spectrometric analysis of Morita-Baylis-Hillman products and dimeric adducts.

(6) An investigation of synthetic approaches to the marine natural product, Rietone A, with a view to utilising chromone synthetic methodology.

2. DISCUSSION

In the discussion which follows, attention will be given to:- the preparation of 2-(*N*,*N*-dimethylamino)chromones (section 2.1), the determination of their pK_a values (section 2.2), the application of chromone-3-carbaldehydes in the Morita-Baylis-Hillman reaction (section 2.3) and, finally, synthetic approaches to Rietone A (section 2.4).

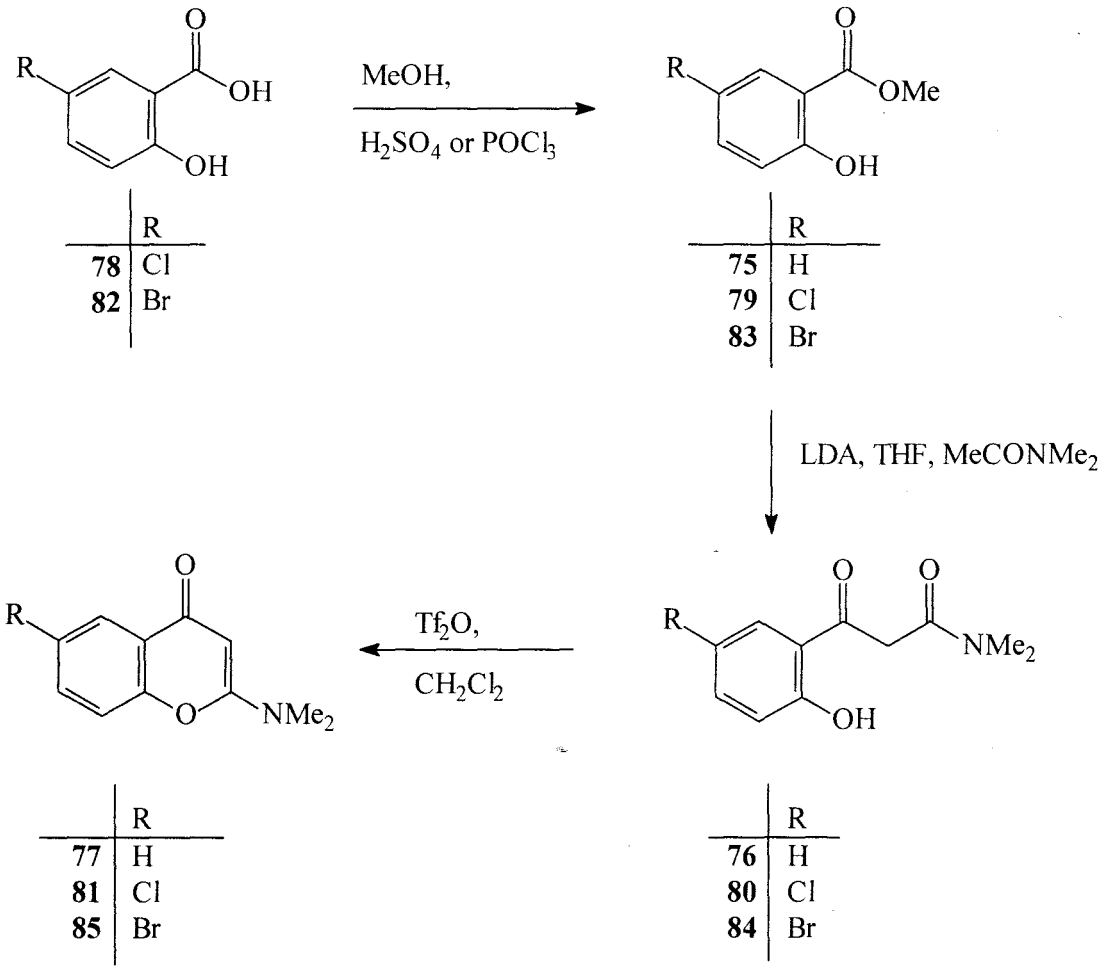
2.1 PREPARATION OF 2-(*N*,*N*-DIMETHYLAMINO)CHROMONES*

As discussed previously (section 1.3), this work aims to continue the investigation of substituent effects on the properties of chromone derivatives, and selected 2-(*N*,*N*-dimethylamino)chromones were prepared in order to examine the effects of the substituents on their basicity. Two established pathways were used, *viz.*, cyclisation of *N*,*N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamides derived from methyl salicylate precursors (section 2.1.1) and cyclisation of phosgeniminium salt intermediates (section 2.1.2).

2.1.1 Preparation of 2-(*N*,*N*-dimethylamino)chromones from methyl salicylates

The first method used for the synthesis of substituted 2-(*N*,*N*-dimethylamino)chromones required the preparation of methyl salicylate precursors. These were obtained by direct methylation of the substituted salicylic acids (**78** and **82**) with methanol in the presence of concentrated sulphuric acid or phosphorus oxychloride (Scheme 33).[98] The resulting methyl esters (**79** and **83**) and commercial methyl salicylate **75** were reacted with lithium diisopropylamide and *N*,*N*-dimethylacetamide in dry tetrahydrofuran to give the substituted *N*,*N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamides (**76**, **80** and **84**). Cyclisation and dehydration were effected using trifluoromethanesulphonic anhydride to afford the known 2-(*N*,*N*-dimethylamino)-chromones[99] (**77**, **81** and **85**) in yields ranging from 39 to 58% .

* The systematic name for such compounds is 2-(*N*,*N*-dimethylamino)-4*H*-1-benzopyran-4-one as stated in the experimental section. However, for convenience, in this discussion they will be referred to as 2-(*N*,*N*-dimethylamino)chromones.



	R
78	Cl
82	Br

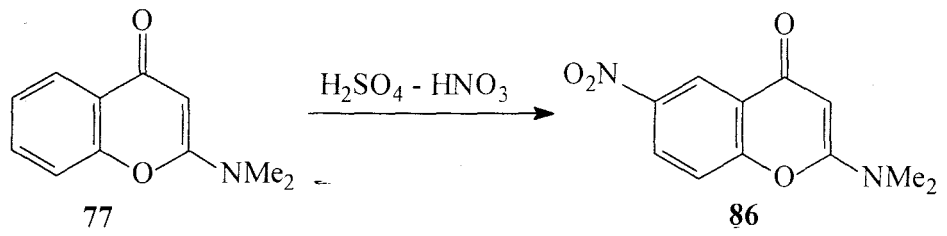
	R
75	H
79	Cl
83	Br

	R
77	H
81	Cl
85	Br

	R
76	H
80	Cl
84	Br

Scheme 33

2-(*N*,*N*-Dimethylamino)-6-nitrochromone **86** was prepared in 68% yield by addition of a mixture of sulphuric acid and fuming nitric acid to a solution of 2-(*N*,*N*-dimethylamino)chromone **77** in sulphuric acid (Scheme 34),[100] substitution occurring regioselectively at the activated position, C-6.

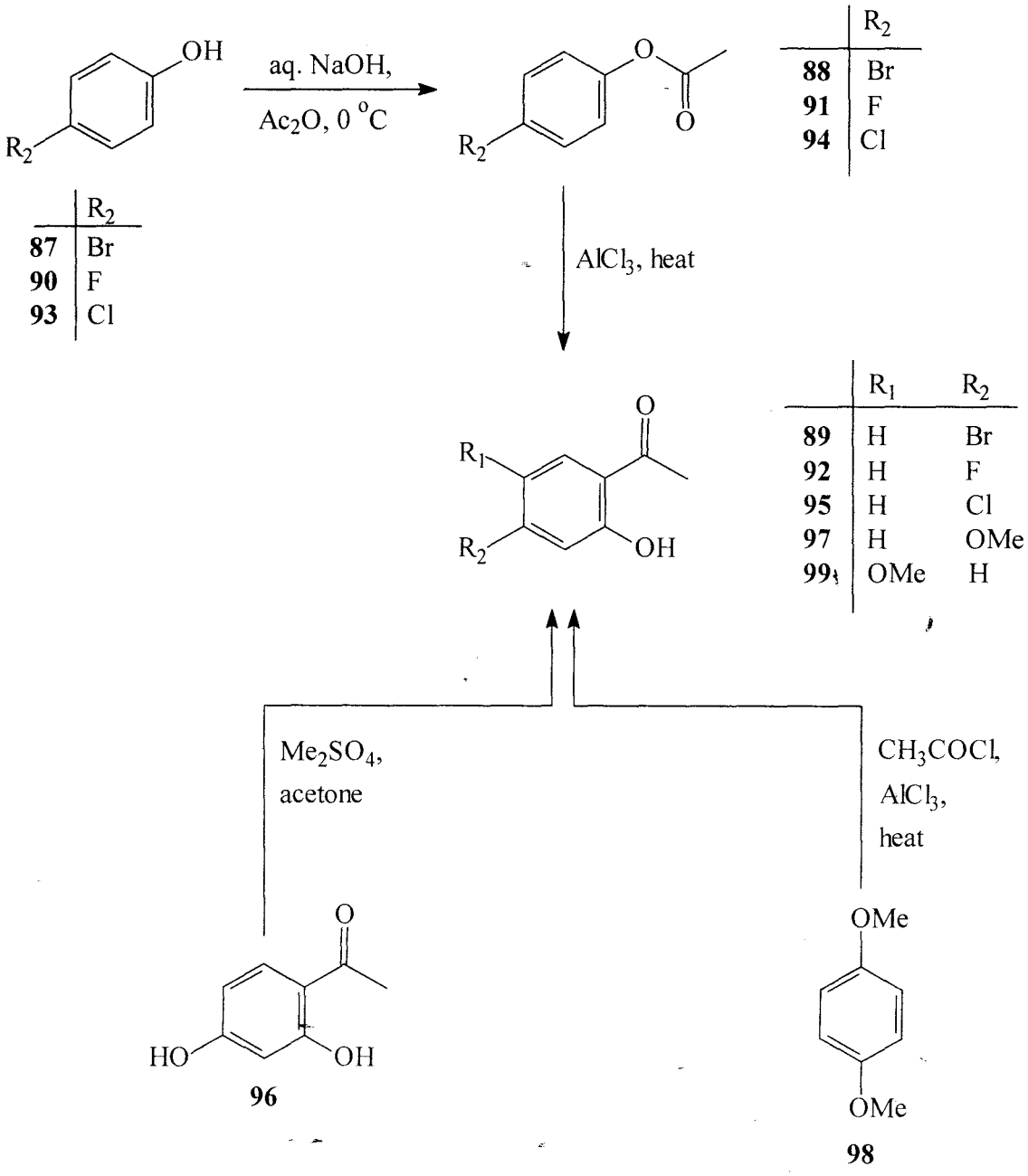


77 **86**

Scheme 34

2.1.2 Preparation of 2-(*N*,*N*-dimethylamino)chromones *via* phosgeniminium salt intermediates

The 2-(*N*,*N*-dimethylamino)chromones (**77**, **105**, **108**, **111**, **114** and **117**; Scheme 36) were obtained following the method reported by Morris *et al.*[9] The substituted *o*-hydroxyacetophenones (**89**, **92** and **95**) required for this procedure were prepared *via* Fries rearrangement of the corresponding phenyl acetates[101] (**88**, **91** and **94**) which, in turn, were obtained by acetylation of the appropriate phenols[102] (**87**, **90** and **93**) (Scheme 35).

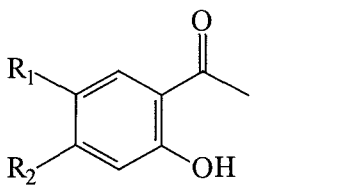


Scheme 35

The acetates (**88**, **91** and **94**) were heated at high temperature (160 °C), which favours rearrangement to the *ortho*-hydroxyacetophenones over the *para* analogues. 2-Hydroxy-4-methoxyacetophenone **97** was obtained *via* methylation of resacetophenone **96**,[103] while 2-hydroxy-5-methoxyacetophenone **99** was prepared by acylating hydroquinone dimethyl ether **98** with acetyl chloride in the presence of anhydrous aluminium trichloride,[104] as shown in Scheme 35. The yields for these reactions ranged from 42 to 83%.

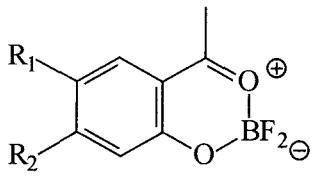
The *o*-hydroxyacetophenones (**100**, **89**, **92**, **95**, **97** and **99**) were then treated with boron trifluoride etherate in diethyl ether to give the corresponding boron difluoride complexes (**101**, **103**, **106**, **109**, **112** and **115**; Scheme 36). Addition of *N*,*N*-dimethyldichloromethyleniminium chloride to these complexes afforded the 3-chloro-(*N*,*N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complexes (**102**, **104**, **107**, **110**, **113** and **116**), which underwent methanolysis and cyclisation at 50 °C to give the required 2-(*N*,*N*-dimethylamino)chromones (**77**, **105**, **108**, **111**, **114** and **117**).[9]

The synthetic approaches described above gave the 2-(*N*,*N*-dimethylamino)chromones of the analytical quality necessary for the subsequent pK_a analysis. Each of the 2-(*N*,*N*-dimethylamino)chromones were fully characterised by spectroscopic analysis and their purity is illustrated by the ^1H and ^{13}C NMR spectra of the 6-methoxy derivative **117** (Figures 1 and 2). The ^1H NMR spectrum clearly shows the *N*,*N*-dimethyl signal at 3.09 ppm, the methoxy signal at 3.88 ppm and the distinctive 3-methine proton signal at 5.38 ppm. The ^{13}C NMR spectrum shows 11 carbon signals with the *N*,*N*-dimethyl nuclei resonating at 37.4 ppm, the methoxy carbon at 55.9 ppm and the 3-methine carbon at 85.9 ppm. Signal assignments were facilitated by the use of Distortionless Enhancement by Polarisation Transfer (DEPT), ^1H-^1H Correlation Spectroscopy (COSY), ^1H-^{13}C Heteronuclear Multiple Quantum Coherence (HMQC) and ^1H-^{13}C Heteronuclear Multiple Bond Correlation (HMBC) spectra.



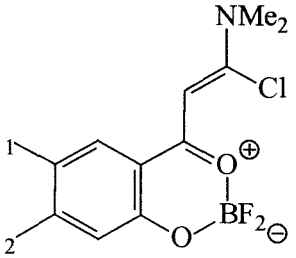
$BF_3.OEt_2$,
Et_2O

	R_1	R_2
100	H	H
89	H	Br
92	H	Cl
95	H	F
97	H	OCH_3
99	OCH_3	H



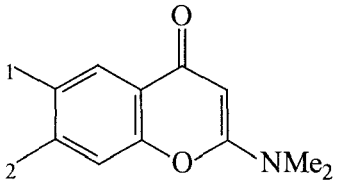
$Cl_2C{=}N^{\oplus}Me_2.Cl^{\ominus}$,
$Cl(CH_2)_2Cl$

	R_1	R_2
101	H	H
103	H	Br
106	H	Cl
109	H	F
112	H	OCH_3
115	OCH_3	H



MeOH,
50 °C

	R_1	R_2
102	H	H
104	H	Br
107	H	Cl
110	H	F
113	H	OCH_3
116	OCH_3	H



	R_1	R_2
77	H	H
105	H	Br
108	H	Cl
111	H	F
114	H	OCH_3
117	OCH_3	H

Scheme 36

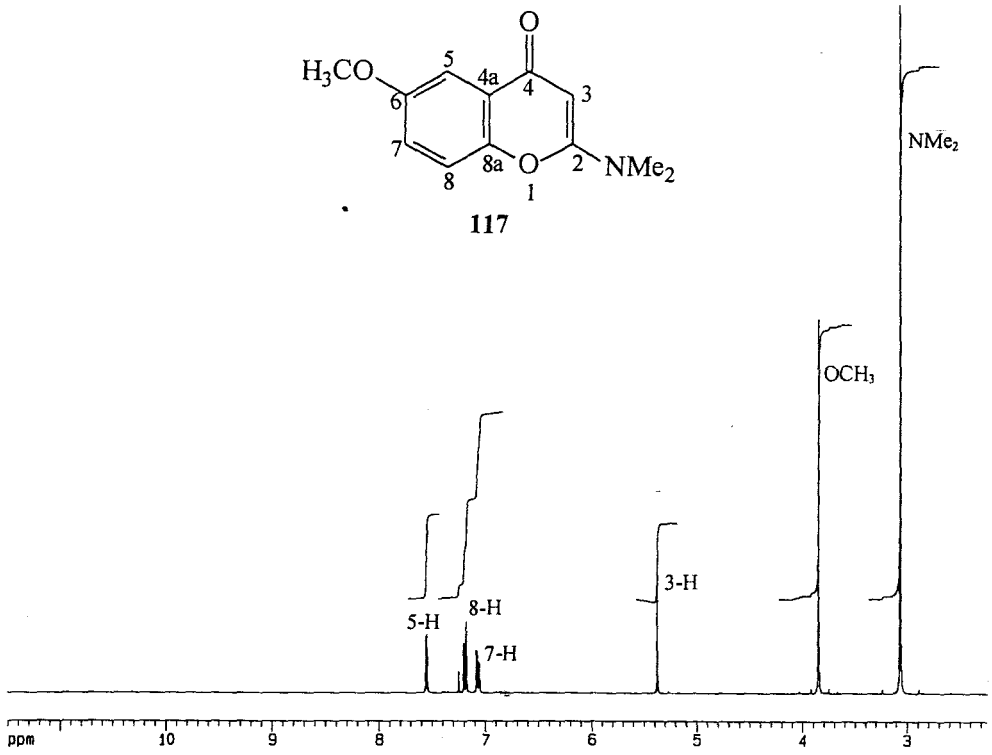


Figure 1: 400 MHz ^{1}H NMR spectrum of 2-(*N,N*-dimethylamino)-6-methoxychromone **117** in $CDCl_3$.

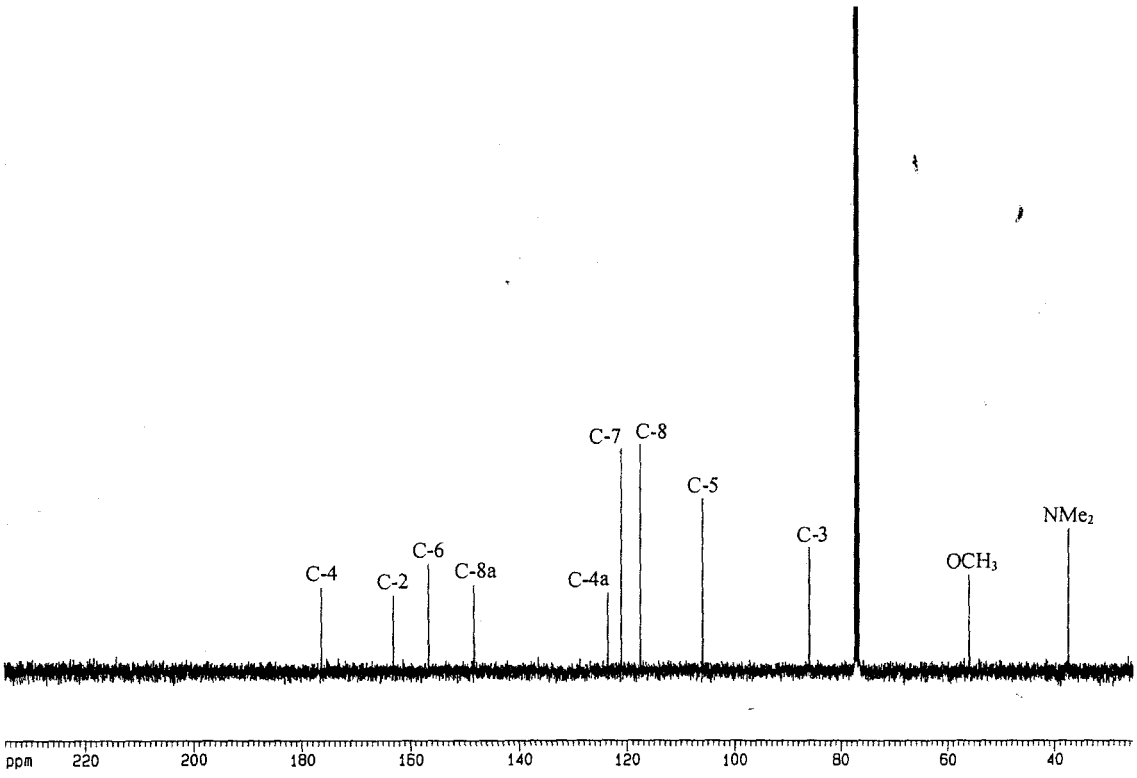


Figure 2: 100 MHz ^{13}C NMR spectrum of 2-(*N,N*-dimethylamino)-6-methoxychromone **117** in $CDCl_3$.

2.2 pK_a ANALYSIS OF 2-(*N*,*N*-DIMETHYLAMINO)CHROMONES

The pK_a study was undertaken to demonstrate the effects of substituents on the basicity of the series of 2-(*N*,*N*-dimethylamino)chromones (**77**, **86**, **105**, **108**, **111**, **114** and **117**). For this purpose, potentiometric titrations were carried out following the procedure described by Albert and Serjeant[105] and the resulting pK_a values are listed in Table 4. Titrations were effected at 0.01-**M** concentrations since activity effects at this concentration are usually small. Due to the poor water-solubility of the compounds being analysed, the titrations were carried out in 1:1 aqueous ethanolic solutions. The 2-(*N*,*N*-dimethylamino)chromones were titrated against hydrochloric acid (0.1063-**M**) in 0.20ml increments, the pH being measured after each addition and the temperature being held constant at 25 °C. Dilution of the solution by the titrant causes little error provided that the titrant is at least ten times as concentrated as the substance being titrated, and that the concentration on which calculations are based is reached at the mid-point of the titration.[105]

The pK_a values were calculated using the ionisation constant K_a:

$$K_a = \frac{[H^+]\,[B]}{[BH^+]}$$

thus $$pK_a = pH + \log [BH^+] - \log [B]$$

where $[BH^+]$ represents the protonated species (*i.e.* the conjugate acid) and [B] the free base.

By way of illustration, Tables 2 and 3 summarise the treatment of the analytical data for the parent system, 2-(*N*,*N*-dimethylamino)chromone **77**. In these tables, BH^+ is the number of moles of hydrogen ions in the volume of acid added, and B is the difference between the number of moles of the aminochromone and BH^+.

Table 2: Concentration of the protonated and non-protonated 2-(*N*,*N*-dimethylamino)-chromone **77** as a function of pH.

Vol. titrant/ml	pH	BH^{+} [a]	B [b]
0.00	4.00		
0.20	3.45	0.00002138	0.00016745
0.40	3.15	0.00004276	0.00014607
0.60	2.97	0.00006414	0.00012469
0.80	2.83	0.00008552	0.00010331
1.00	2.71	0.0001069	0.00008193
1.20	2.63	0.00012828	0.00006055
1.40	2.55	0.00014966	0.00003917
1.60	2.47	0.00017104	0.00001779
1.80	2.44	0.00019242	-0.00000359[c]
2.00	2.40	0.00021380	-0.00002497[c]

[a] Moles of conjugate acid.
[b] Moles of residual free aminochromone.
[c] The negative concentration reflects the excess concentration of titrant.

Since the observed pH values lie outside the range pH 4-10, it is necessary to make corrections for the hydrogen ion activity.[105] These corrections, effected following Albert and Serjeant's method,[105] are summarised in Table 3 and discussed below.

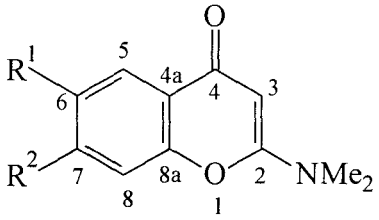
Table 3: Calculation of pK_a values for 2-(*N*,*N*-dimethylamino)chromone **77**, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.00035481	6.81242E-06	0.08359567	-1.0778162	2.372184	0.004244
19.40	0.00070795	1.37341E-05	0.18163391	-0.7408031	2.409197	0.003898
19.60	0.00107152	2.10018E-05	0.29609235	-0.5285728	2.441427	0.003619
19.80	0.00147911	2.92863E-05	0.42409656	-0.3725353	2.457465	0.003488
20.00	0.00194984	3.89969E-05	0.56152198	-0.2506332	2.459367	0.003472
20.20	0.00234423	4.73534E-05	0.74999084	-0.124944	2.505056	0.003126
20.40	0.00281838	5.7495E-05	0.95344723	-0.0207033	2.529297	0.002956
20.60	0.00338844	6.98019E-05	1.15579304	0.06288007	2.53288	0.002932
20.80	0.00363078	7.55202E-05	1.62518257	0.21090216	2.650902	0.002234

pK_a 2.47 ± 0.06

In column 2, $[H^+]$ is the hydrogen ion concentration which is given by the negative antilogarithm of the measured pH. This value is then multiplied by the total volume (in litres) to give the number of moles of H^+. The pK_a (column 6) is given by the sum of the measured pH and column 5. The pK_a values in column 6 cannot be averaged directly and a mean result is obtained as follows. The antilogarithms of the values in column 6 are reflected, in turn, in column 7; the average of these values is calculated, with the exclusion of the first and the last entries, as recommended by Albert and Serjeant,[105] and converted back to pK_a. The variance of the mean value finally obtained for the pK_a (2.47) falls within the limits of ± 0.06, considered acceptable by Albert and Serjeant.[105] All titrations were carried out in duplicate and the results are tabulated in the experimental section. The pK_a values calculated for the series of 2-(*N*,*N*-dimethylamino)chromones (**77**, **86**, **105**, **108**, **111**, **114** and **117**) are detailed in Table 4.

Table 4: pK_a values for the substituted 2-(*N*,*N*-dimethylamino)chromones (**77**, **86**, **105**, **108**, **111**, **114** and **117**) in H_2O-EtOH (1:1) at 25 °C, and corrected for hydrogen ion activity.



Compound	R^1	R^2	pK_a
77	H	H	2.47 ± 0.06
86	NO_2	H	2.27 ± 0.06
105	H	Br	2.26 ± 0.05
108	H	Cl	2.22 ± 0.06
111	H	F	2.25 ± 0.05
114	H	MeO	2.52 ± 0.06
117	MeO	H	2.39 ± 0.06

In chromone itself (pK_a 2.0),[106] protonation is favoured at the carbonyl oxygen, with delocalisation of the ether oxygen lone pair serving to stabilise the conjugate acid (Figure 3a). The increased basicity of the 2-(*N*,*N*-dimethylamino)chromones may be attributed to the additional delocalisation of the nitrogen lone pair (Figure 3b), provided protonation occurs at the chromone carbonyl oxygen.

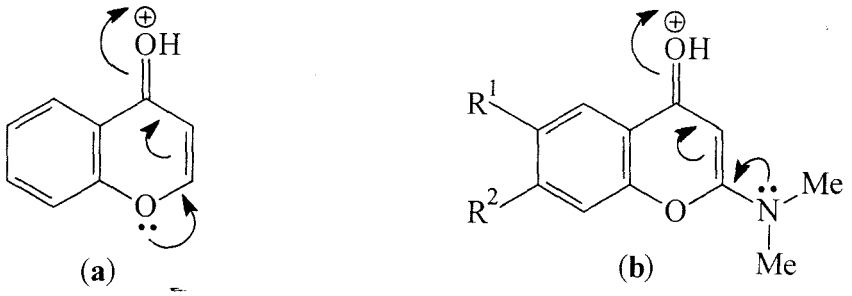


Figure 3: Lone pair delocalisation stabilising the conjugate acids of:-
(a) chromone and
(b) the 2-(*N*,*N*-dimethylamino)chromones (**77**, **86**, **105**, **108**, **111**, **114** and **117**).

Protonation of the 2-(*N*,*N*-dimethylamino)chromones was, in fact, shown by ^{13}C NMR experiments to take place at the carbonyl oxygen. Aliquots of conc. HCl corresponding to 0.25, 0.50, 0.75 and 1.00 equivalents were added to solutions of the methoxy derivatives **114** and **117** in CD_3OD-D_2O (1:1) and, in both cases, the most significant chemical shift changes ($\Delta\delta$ up to 7-8 ppm upfield) were exhibited by the carbonyl carbon C-4 (Figure 4). Moreover, AM1 semi-empirical molecular orbital calculations showed that protonation of the oxygen atom is favoured over that of the nitrogen by *ca.* 27 kcal.mol^{-1}.[71]

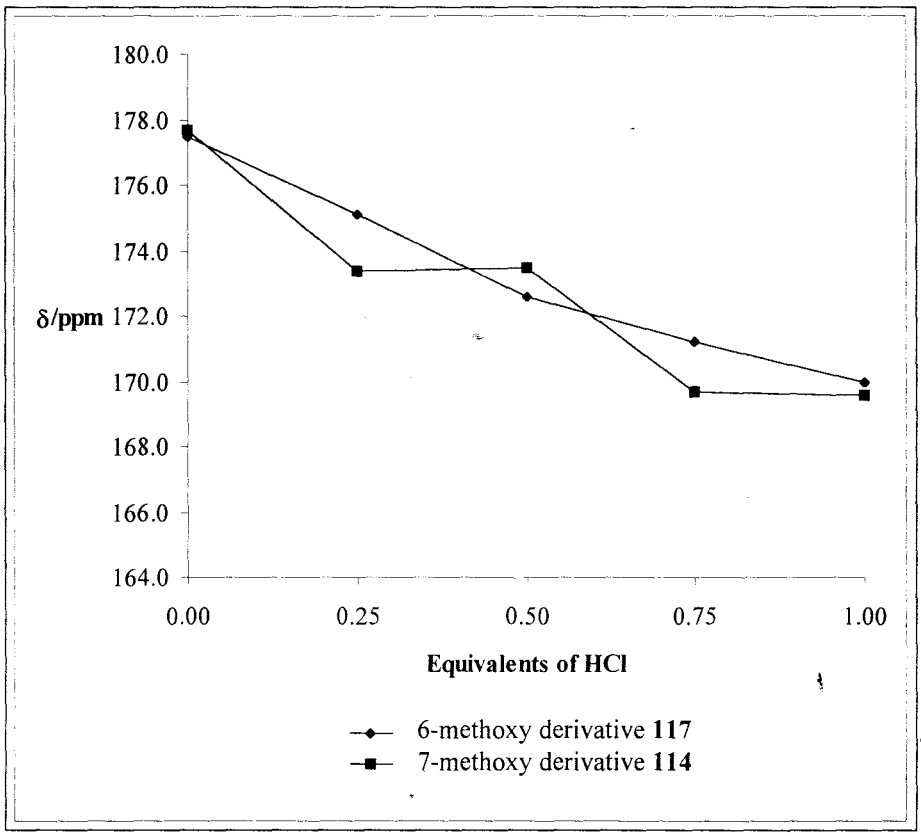


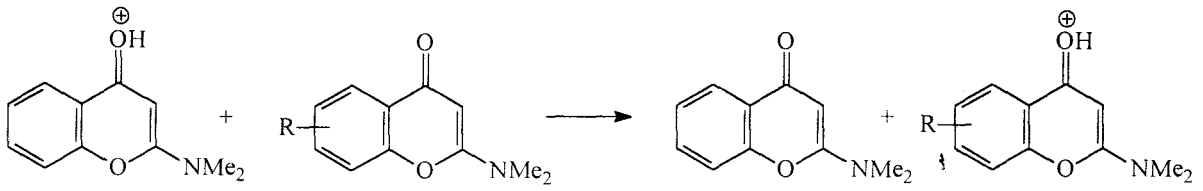
Figure 4: Change in chemical shift of C-4 on addition of HCl to solutions of the methoxy derivatives **114** and **117** in CD_3OD-D_2O.

It is apparent from the data in Table 4 that the measured pK_a values lie within a fairly narrow range (2.22 – 2.52), indicating that the remote 6- and 7- substituents have relatively little effect on the basicity of the 2-(*N*,*N*-dimethylamino)chromones examined. Nevertheless, a general trend is discernable. For the 7-substituted derivatives, pK_a values are seen to decrease in the order pK_a: (R^2 = OMe) > (R^2 = H) > (R^2 = F) ≅ (R^2 = Cl) ≅ (R^2 = Br). This reflects the general expectation that basicity should be increased by electron-

releasing substituents and decreased by electron-withdrawing substituents. However, the data for the 6-substituted derivatives appears to be contradictory; the 6-methoxy compound is less basic than the parent system and, despite the presence of the strongly electron-withdrawing nitro group, the 6-nitro derivative is marginally more basic than the 7-halogeno analogues.

Explanations for the anomalous data were sought in semi-empirical and *ab initio* calculations. Optimised AM1 semi-empirical geometries of the protonated 2-(*N*,*N*-dimethylamino)chromones were used to calculate their heats of formation and the charges on the carbonyl oxygen, consideration being given to the possibility of syn or anti orientations of the proton. The oxygen charges were also calculated at the *ab initio* level (3-21G basis set on the AM1 geometries). Stabilisation energies, which reflect the influence of the substituents (R^1 and R^2) on the relative stability of the protonated species, were calculated from an isodesmic equation for which the AM1 heats of formation were used (equation 1) and in which:-

stabilisation energy = $[\Delta H_f(\mathbf{77}) + \Delta H_f(\mathbf{XH^+})] - [\Delta H_f(\mathbf{77H^+}) + \Delta H_f(\mathbf{X})]$).[71]



Equation 1

Plots of these stabilisation energies against the AM1 and 3-21G charges give reasonably linear correlations (r^2 = 0.94 and 0.92 respectively), as do plots of the charges against pK_a, provided the data points for $R^1 = NO_2$ are omitted. It thus appears that, with the exception of the 6-nitro derivative, the observed pK_a data are essentially consistent with theoretical expectations. The apparently anomalous behaviour of the 6-nitro derivative may reflect substrate-specific intramolecular field effects (Figure 5a) or solvent-mediated hydrogen-bonding (Figure 5b) which serve to stabilise the conjugate acid. AM1 calculations[71] have, in fact, shown that the hydrogen-bonded chelate favours a planar arrangement, as

illustrated in Figure 5b, in which the O···H distances should permit effective hydrogen-bonding [*i.e.* 2.72 Å (NO···H) and 2.09Å (ArOH···O)].

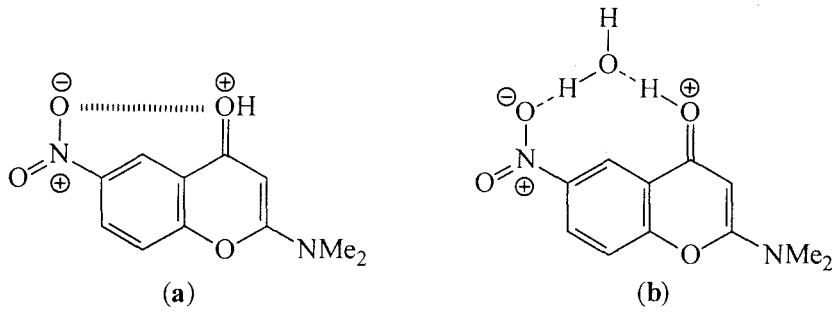
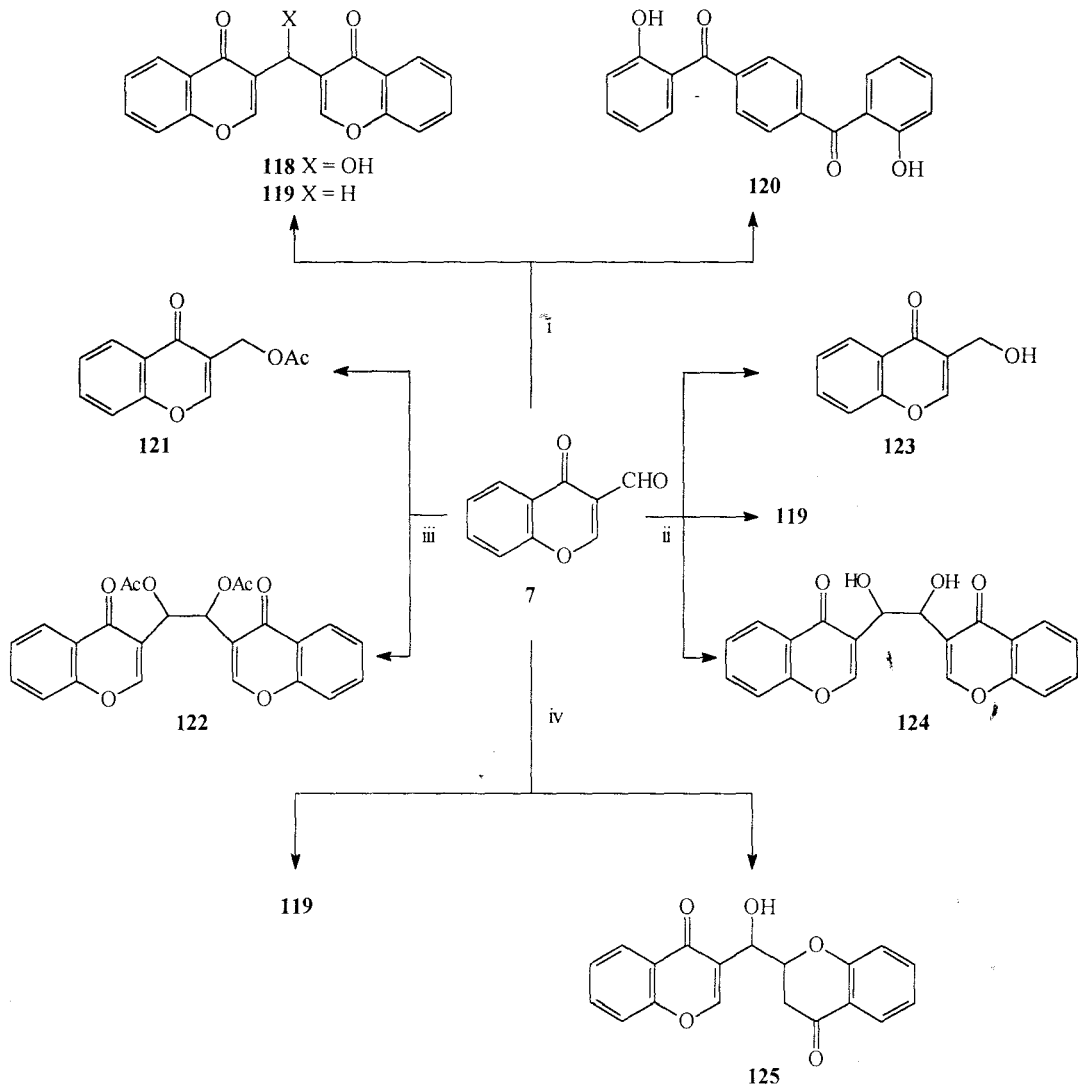


Figure 5: Possible stabilisation of the protonated 6-nitro derivative **86** by:-
(a) an intramolecular field effect; and
(b) solvent-mediated hydrogen bonding.

2.3 THE APPLICATION OF CHROMONE-3-CARBALDEHYDES IN THE MORITA-BAYLIS-HILLMAN REACTION

Chromone-3-carbaldehyde has been extensively studied in the last three decades; its application in organic transformations is well documented,[11] and aspects of its chemistry have been reviewed briefly in section 1.1.4. However, it remains the focus of ongoing research, and novel uses for this versatile compound continue to be discovered.

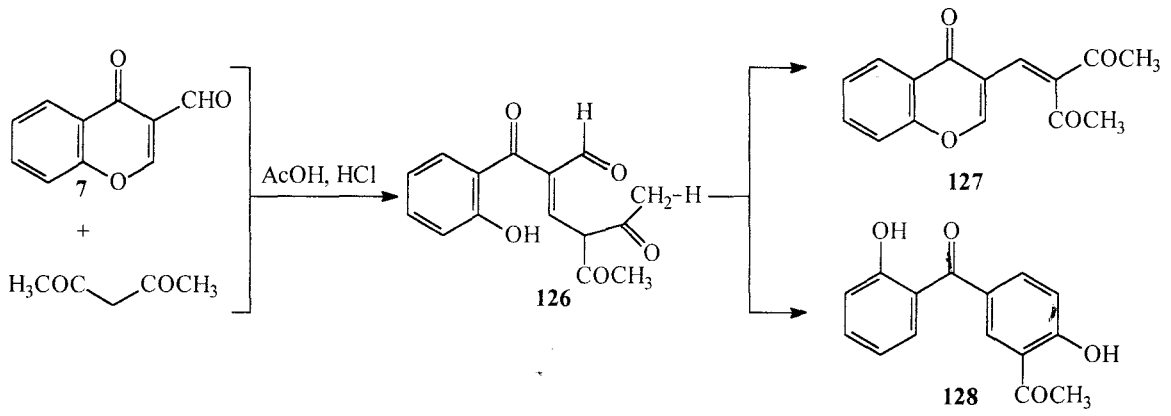


Reagents: (i) Na naphthalenide; (ii) Zn, AcOH; (iii) Zn, Ac_2O; (iv) Zn, MeOH

Scheme 37

Despite the host of publications to date, little attention has been given to its reactions with electron transfer reagents. Recently, Bandyopadhyay and co-workers[107] discovered that treatment of chromone-3-carbaldehyde **7** with electron transfer reagents, under different conditions, led to reductive self-coupling of the aldehyde affording a variety of products (Scheme 37). Thus, on treatment with sodium naphthalenide, chromone-3-carbaldehyde gave a mixutre of the bischromones **118**, **119** and disalicyloylbenzene **120**. Treatment with a mixture of zinc, sodium acetate and acetic anhydride gave the acetates **121** and **122**, while treatment with zinc and acetic acid gave a mixture of **119**, carbinol **123** and diol **124**. A mixture of **119** and chromanone **125** was obtained upon treatment with zinc in methanol.

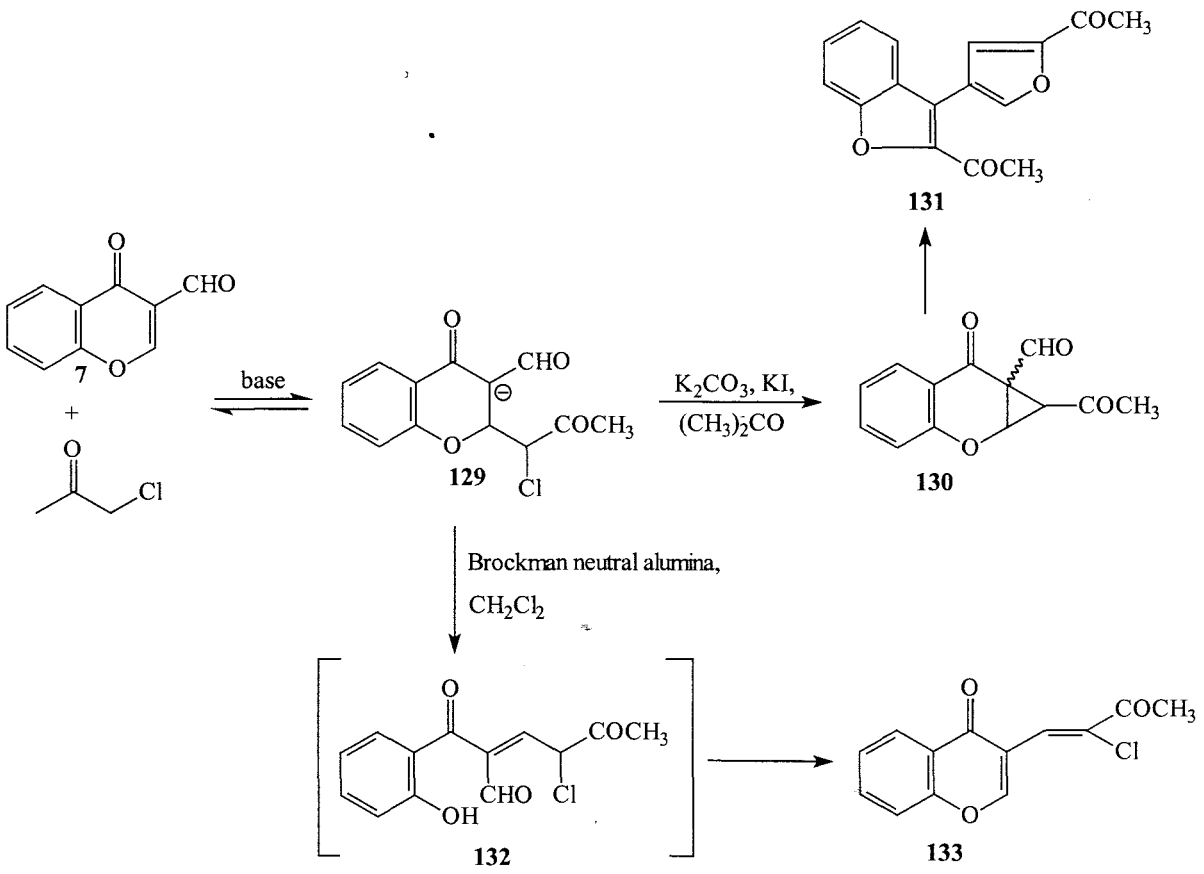
The reaction of chromone-3-carbaldehyde **7** with pentane-2,4-dione was discovered by the same group, and provides a new route to dihydroxybenzophenone derivatives[108] (Scheme 38). Attack of the nucleophile at C-2 of the pyran ring, followed by ring opening affords the intermediate phenoxide **126** which cyclises under acidic conditions by two different pathways, to give the Knoevenagel-type product **127** and the benzophenone **128**.



Scheme 38

Ghosh and co-workers[109] have reported reactions of chromone-3-carbaldehyde with chloroacetone under different conditions (Scheme 39). When the reaction was carried out in acetone containing anhydrous potassium carbonate and a catalytic amount of potassium iodide, base-catalysed Michael addition of chloroacetone to chromone-3-carbaldehyde gave the carbanion **129**; ring closure to the cyclopropane **130**, followed by a sigmatropic rearrangement, opening of the pyran ring and finally reaction with another molecule of chloroacetone, leads to the benzo[*b*]furan **131**. When the reaction is carried out in

dichloromethane containing Brockman neutral alumina, the carbanion **129** rearranges to the diacylalkene **132**, cyclisation of which gives the chromone derivative **133**.

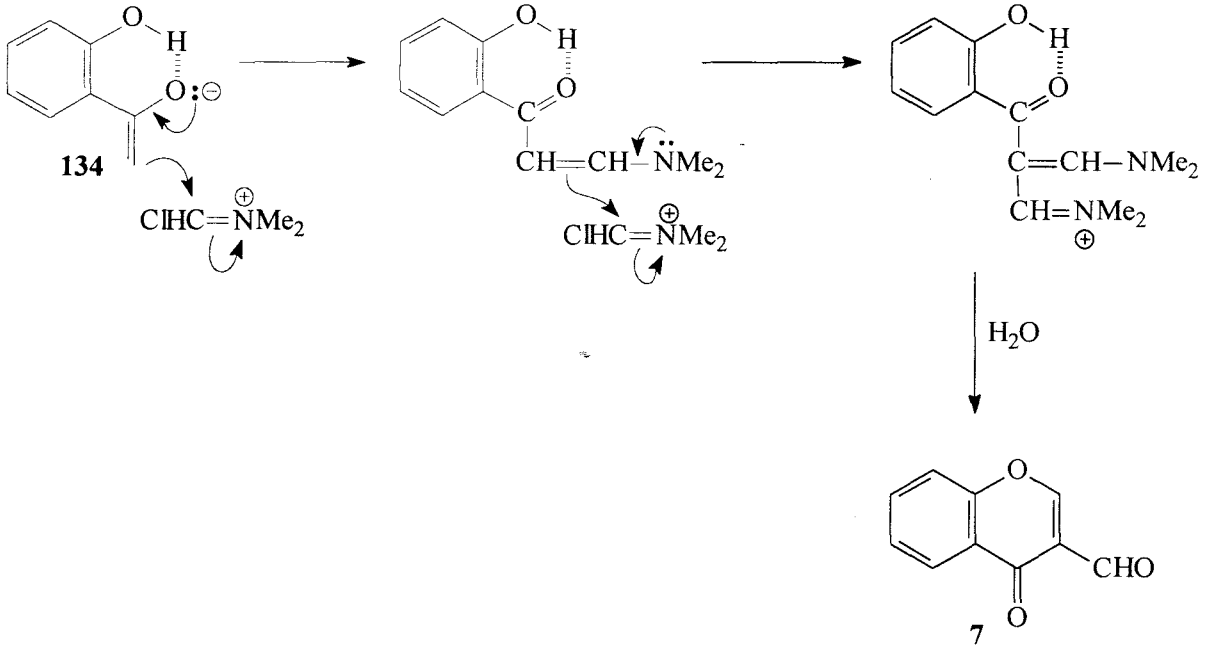


Scheme 39

It is evident from the examples cited above and in the introduction (section 1.1.4.3) that chromone-3-carbaldehyde is a versatile synthon for the construction of unusual heterocyclic systems. In our own study, it was anticipated that application of the Morita-Baylis-Hillman reaction to chromone-3-carbaldehydes could lead to novel and interesting transformations.

2.3.1 Preparation of chromone-3-carbaldehydes[†]

A range of substituted chromone-3-carbaldehydes, chosen to illustrate substituent effects on the subsequent Morita-Baylis-Hillman reactions, were prepared by the Vilsmeier-Haack reaction of the corresponding *o*-hydroxyacetophenones and DMF.[16] This application of the Vilsmeier-Haack reaction involves a double formylation of the acetophenone enolate **134**, followed by hydrolysis, to give the desired chromone-3-carbaldehyde **7** (Scheme 40).

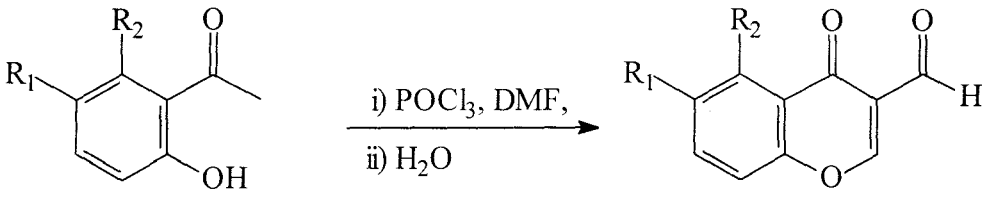


Scheme 40

The *o*-hydroxyacetophenones (**100**, **135**, **137**, **139**, **141** and **144**), which were available commercially, were treated with phosphorus oxychloride in dry DMF at –20 °C to give the substituted chromone-3-carbaldehydes (**7**, **136**, **138**, **140**, **142** and **144**) in yields ranging from 40 to 69% (Scheme 41). 6-Nitrochromone-3-carbaldehyde **145** was prepared in 54% yield by direct nitration of the parent system **7** using a mixture of fuming nitric acid and sulphuric acid (Scheme 42),[16] regioselective substitution at C-6 following the pattern observed for the nitration of 2-(*N*,*N*-dimethylamino)chromone **77** (Scheme 34, p. 40). All

[†] The systematic name for these compounds is 4*H*-1-benzopyran-4-one-3-carbaldehyde as stated in the experimental section. However, for convenience, in this discussion they will be referred to as chromone-3-carbaldehydes.

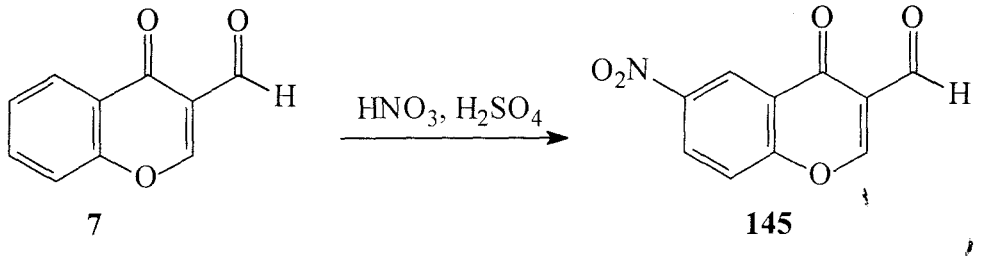
of the chromone-3-carbaldehydes were purified by recrystallisation from acetone and were fully characterised by spectroscopic (IR, MS and ^{1}H and ^{13}C NMR) analysis.



	R_1	R_2
100	H	H
135	Cl	H
137	Br	H
139	F	H
141	OCH_3	H
144	H	OCH_3

	R_1	R_2
7	H	H
136	Cl	H
138	Br	H
140	F	H
142	OCH_3	H
144	H	OCH_3

Scheme 41



7 **145**

Scheme 42

Shown in Figures 6 and 7 are the ^{1}H and ^{13}C NMR spectra of 5-methoxychromone-3-carbaldehyde **144**. The ^{1}H NMR spectrum reveals a singlet at 4.00 ppm corresponding to the methoxy group, while the aromatic protons resonate between 6.82 and 7.61 ppm, the 2-methine proton at 8.39 ppm and the formyl proton at 10.34 ppm, the last-mentioned signals distinguishable as singlets. The expected 11 carbon signals are clearly evident in the ^{13}C NMR spectrum, with the methoxy carbon signal appearing at 56.6 ppm, the 2-methine carbon signal at 158.7 ppm and the two carbonyl carbon signals at 175.8 ppm and 189.1 ppm.

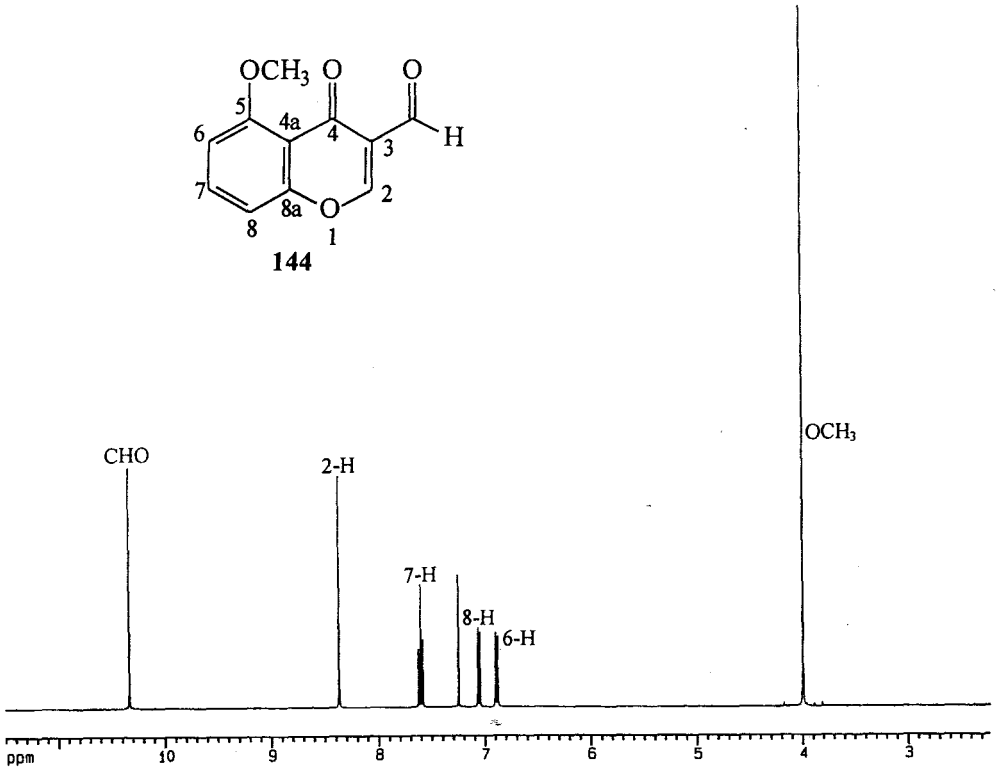


Figure 6: 400 MHz ^{1}H NMR spectrum of 5-methoxychromone-3-carbaldehyde **144** in $CDCl_3$.

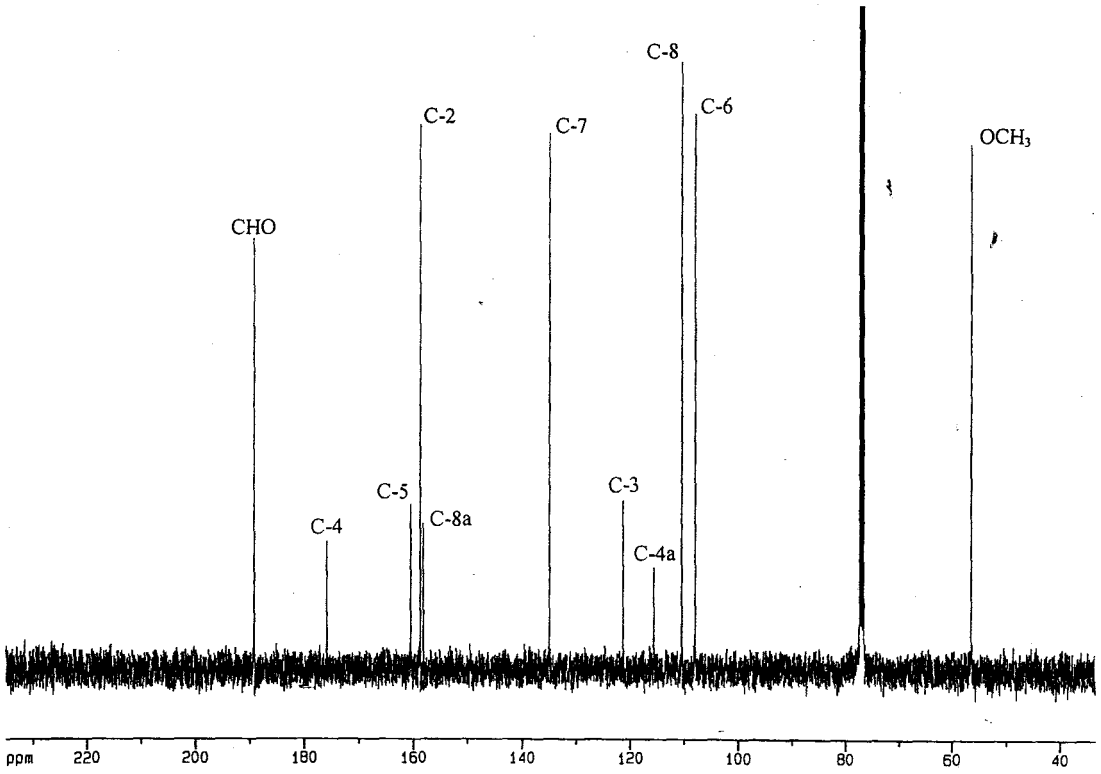


Figure 7: 100 MHz ^{13}C NMR spectrum of 5-methoxychromone-3-carbaldehyde **144** in $CDCl_3$.

2.3.2 Reactions of chromone-3-carbaldehydes with methyl acrylate

The chromone-3-carbaldehydes (**7**, **136**, **138**, **140**, **142**, **144** and **145**) were then subjected to the Morita-Baylis-Hillman reaction in chloroform, using methyl acrylate as the activated alkene and DABCO as the catalyst (Scheme 43). Reaction times were long, typically several weeks – a problem which is not unusual for Morita-Baylis-Hillman reactions and which was undoubtedly exacerbated in our case by the dilution effect of the solvent. Extensive purification procedures were required to obtain the products. In all cases, flash chromatography on silica gel, followed by multiple elutions using HPLC produced the expected Morita-Baylis-Hillman products (**146**, **148**, **150**, **152**, **154** and **156**) in low yields (Table 5), together with the products subsequently identified as "chromone dimers" (**147**, **149**, **151**, **153** and **155**) also in very low yields (Table 5). Extension of the reaction time to eight weeks for the bromo- and fluoro-derivatives failed to effect any improvement in the yields. The Morita-Baylis-Hillman reaction of 6-nitrochromone-3-carbaldehyde **145** afforded neither the expected Morita-Baylis-Hillman product, nor the chromone dimer. The low yields obtained initially may be due to the formation of competition products arising from attack of the Morita-Baylis-Hillman zwitterion at the three electrophilic centres in the chromone-3-carbaldehyde substrates (Figure 8).

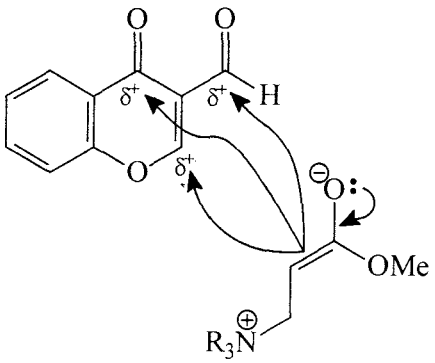
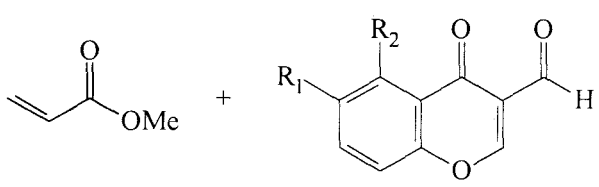
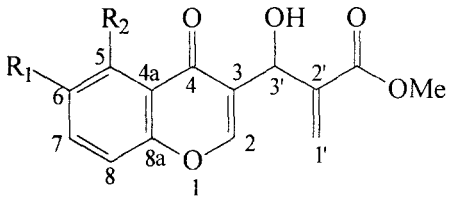


Figure 8

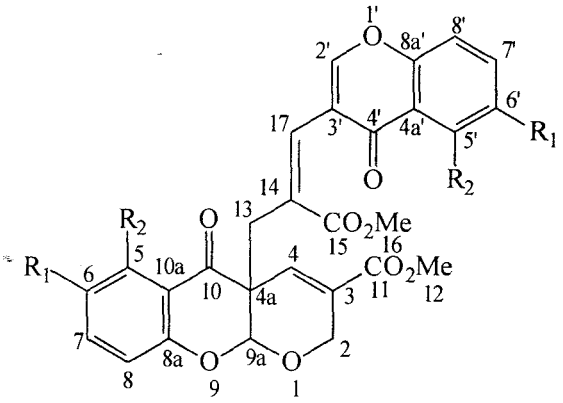


	R_1	R_2
7	H	H
136	Cl	H
138	Br	H
140	F	H
142	OCH_3	H
144	H	OCH_3
145	NO_2	H

DABCO, $CHCl_3$



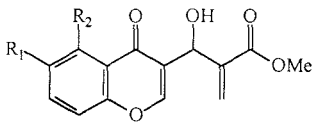
	R_1	R_2
146	H	H
148	Cl	H
150	Br	H
152	F	H
154	OCH_3	H
156	H	OCH_3

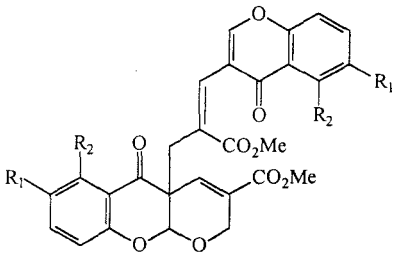


	R_1	R_2
147	H	H
149	Cl	H
151	Br	H
153	F	H
155	OCH_3	H

Scheme 43

Table 5: Yields of Morita-Baylis-Hillman products and the corresponding dimers.

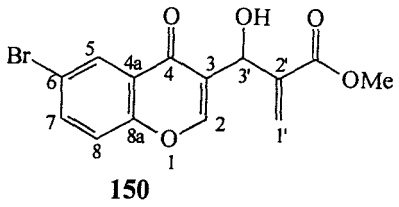




R^1	R^2	Morita-Baylis-Hillman product		Chromone dimer	
		Compound	Yield[a]/%	Compound	Yield[a]/%
H	H	**146**	14	**147**	14
Cl	H	**148**	14	**149**	2
Br	H	**150**	8	**151**	14
F	H	**152**	11	**153**	15
OMe	H	**154**	14	**155**	13
H	OMe	**156**	17	-	-

[a] Determined from ^{1}H NMR spectroscopy of the crude reaction mixtures.

One- and two-dimensional NMR spectroscopy was used to facilitate the characterisation of the products. The ^{1}H NMR spectrum of the brominated Morita-Baylis-Hillman product **150** (Figure 9) reveals a singlet at 3.75 ppm corresponding to the methoxy group, a doublet at 4.38 ppm corresponding to the hydroxyl group, a doublet at 5.60 ppm corresponding to 3'-H and two singlets at 6.11 and 6.42 ppm corresponding to the 1'-methylene group. Amongst the aromatic proton signals, the 2-H singlet is clearly evident at 8.03 ppm. The ^{13}C NMR spectrum (Figure 10) shows 14 carbon signals with the methoxy group resonating at 52.0 ppm and C-3' at 67.5 ppm. The aromatic signals were differentiated using the COSY spectrum and all carbon peaks were assigned using HMQC and HMBC correlations.



150

Figure 9: 400 MHz ^{1}H NMR spectrum of the Morita-Baylis-Hillman product **150** in $CDCl_3$.

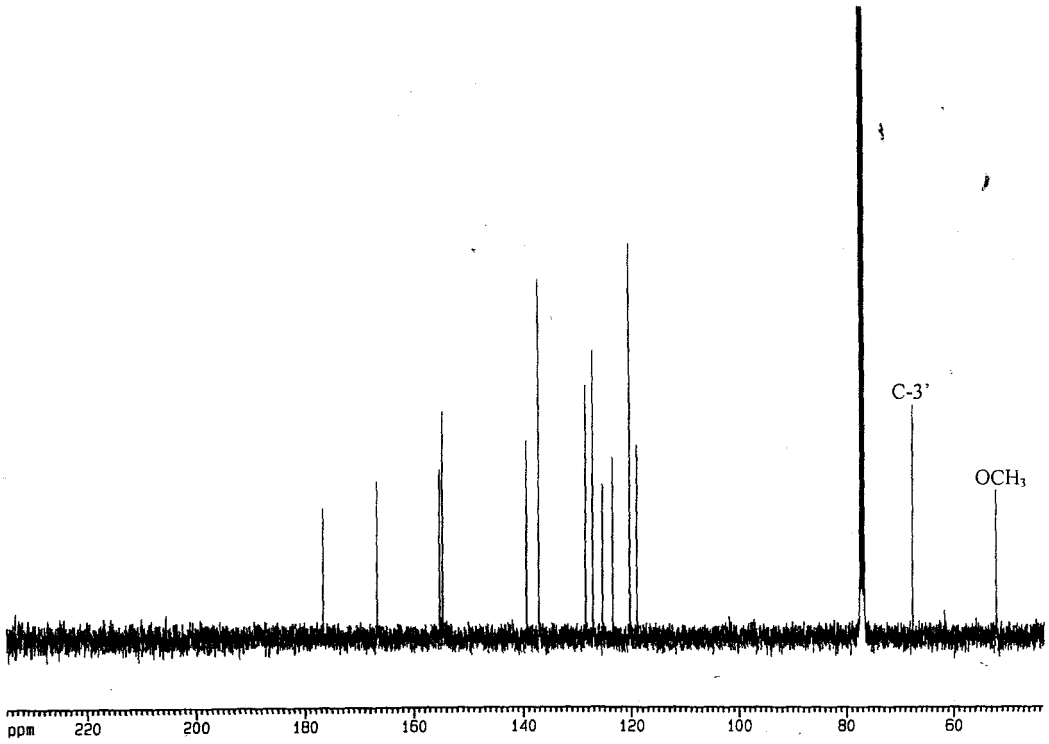


Figure 10: 100 MHz ^{13}C NMR spectrum of the Morita-Baylis-Hillman product **150** in $CDCl_3$.

The initial structural proposal for the chromone dimers is shown in Figure 11. The ^{1}H NMR spectrum of the "parent" system **147** revealed a pair of doublets at 3.12 and 3.38 ppm and a pair of double doublets at 4.47 and 4.54 ppm corresponding to two methylene groups, a singlet at 5.05 ppm corresponding to the proton adjacent to the chromone ether oxygen, and two singlets at 3.61 and 3.65 ppm corresponding to the two methoxy groups. The ^{13}C spectrum indicated the presence of 28 carbon atoms, of which two were methylene carbons and 12 were quarternary. All HMBC correlations supported the structural proposal, as did the high resolution mass spectrometry data (Found: $\mathbf{M}^{+}$ 502.1250. $C_{28}H_{22}O_9$ requires *M*, 502.1257).

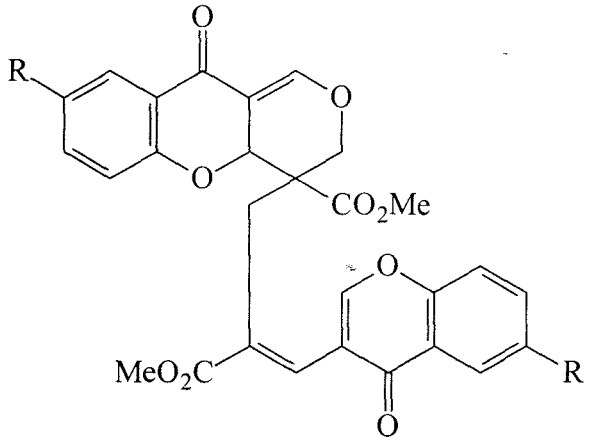


Figure 11: Initial structural proposal for the chromone dimers.

However, single crystal X-ray crystal analysis of the compound **147** (Figure 12) revealed that the correct structure was, in fact, the one shown in Scheme 43, which is also consistent with all spectroscopic data! Thus, in the ^{1}H spectrum (Figure 13), the pair of doublets at 3.12 and 3.38 ppm correspond to the diastereotopic 13-methylene protons, the pair of double doublets at 4.47 and 4.54 ppm belong to the 2-methylene protons, the singlet at 5.05 ppm to the 9a proton and the two singlets at 3.61 and 3.65 ppm to the two methoxy groups. The double doublets at 4.47 and 4.54 ppm reflect coupling between the diastereotopic 2-methylene protons and, presumably, allylic coupling to the 4-H nucleus. The ^{13}C spectrum (Figure 14) shows 28 carbon signals, the two methylene and 12 quarternary signals being confirmed by the DEPT spectrum (Figure 15).

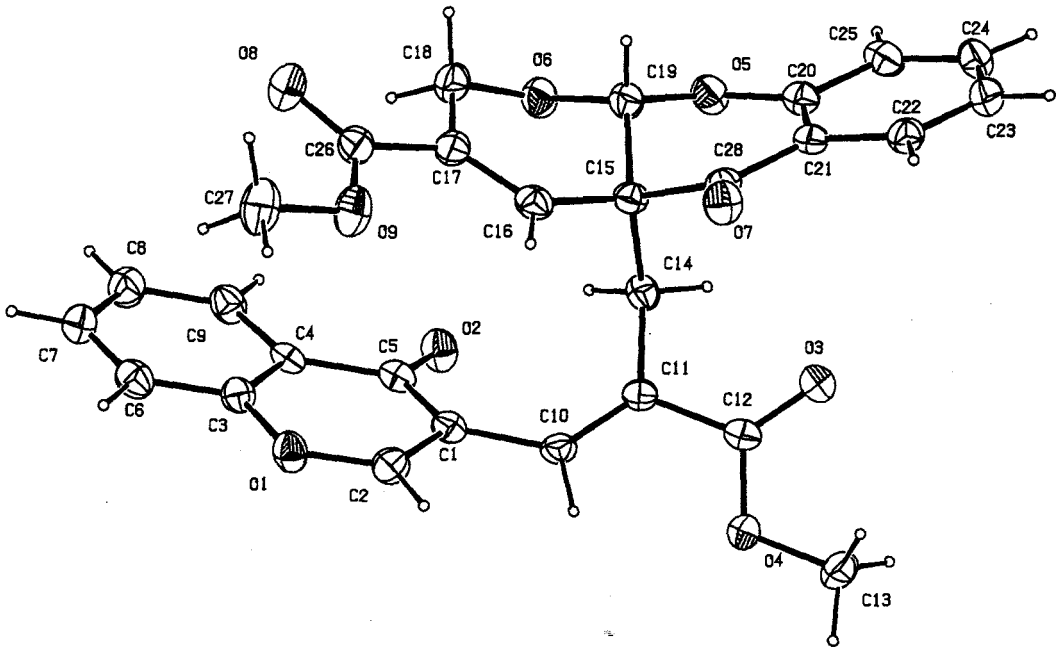


Figure 12: X-Ray crystal structure of the chromone dimer **147**.

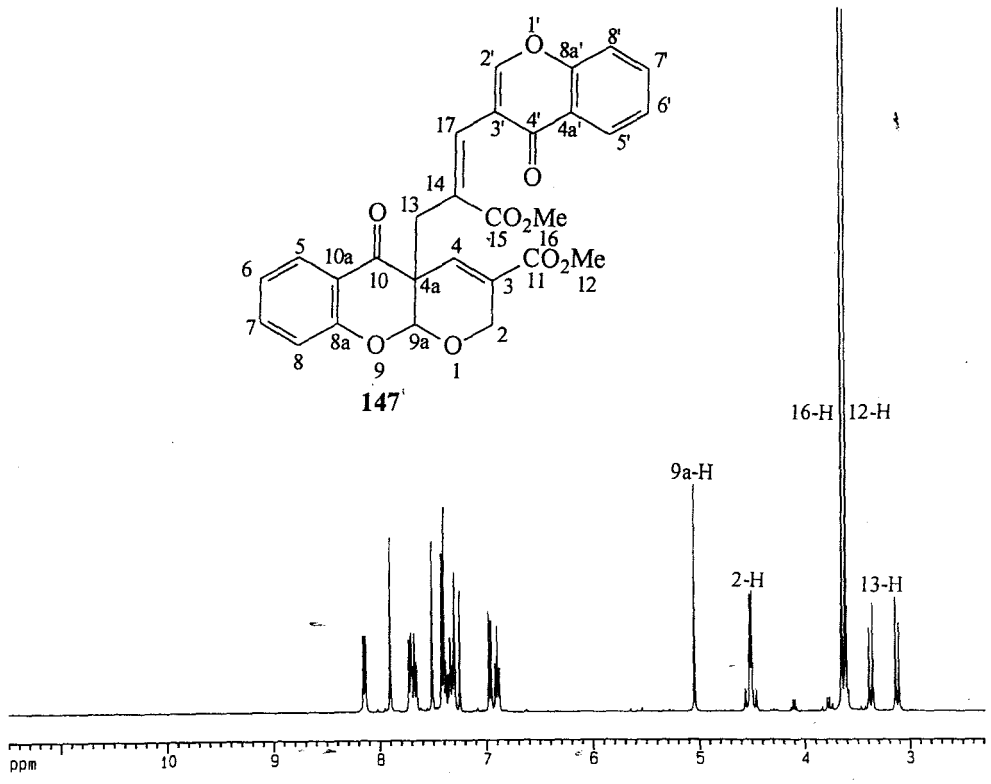


Figure 13: 400 MHz ^{1}H NMR spectrum of the chromone dimer **147** in $CDCl_3$.

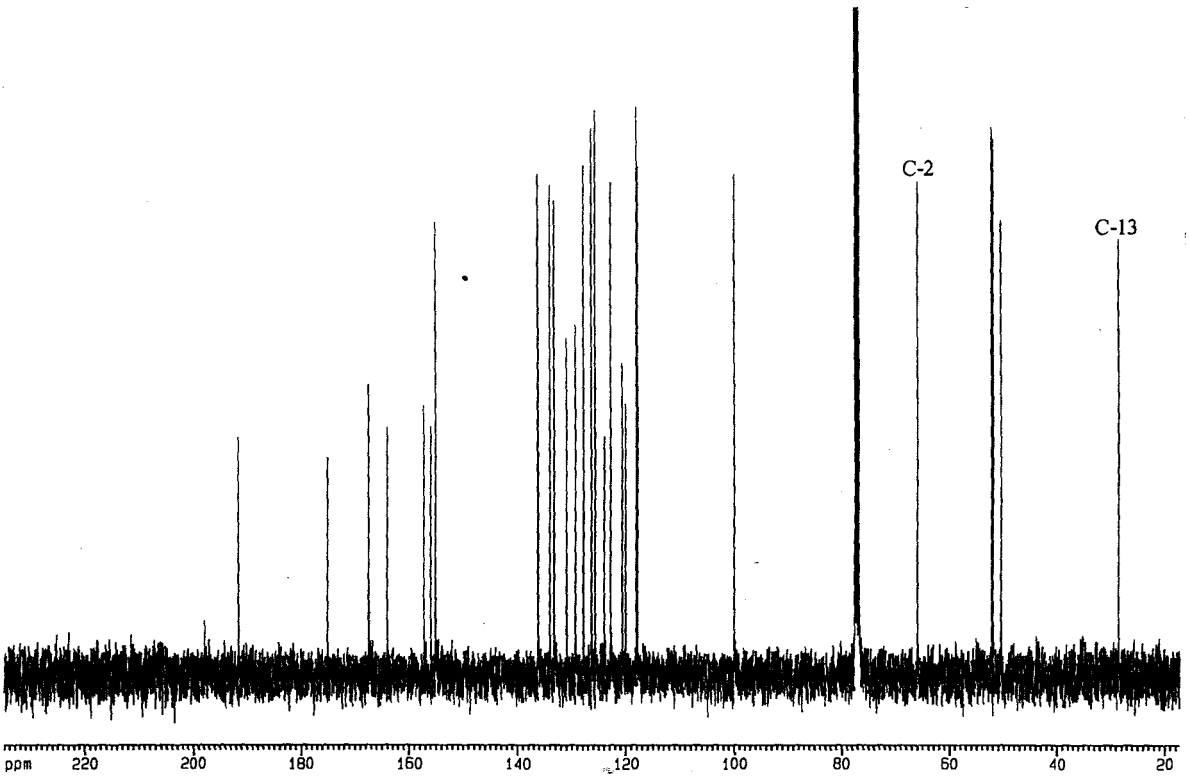
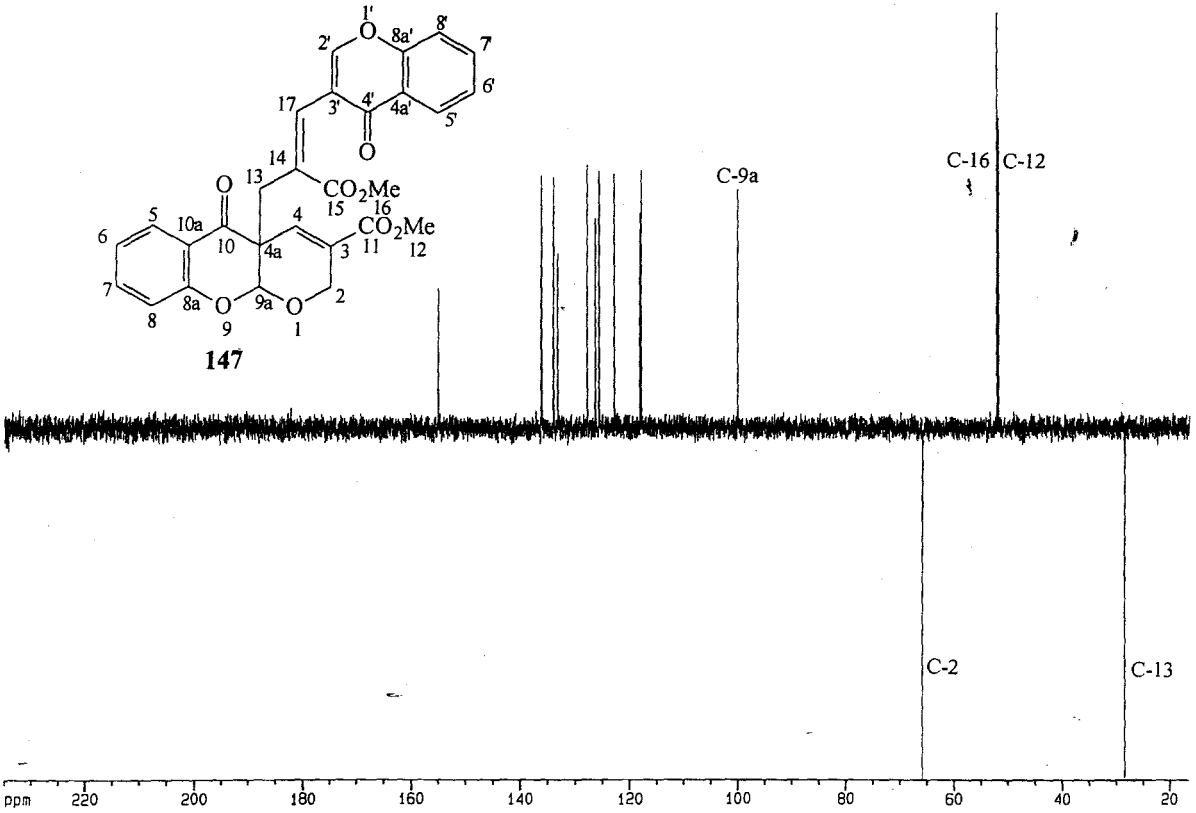


Figure 14: 100 MHz ^{13}C NMR spectrum of the chromone dimer **147** in $CDCl_3$.



147

Figure 15: 400 MHz DEPT NMR spectrum of the chromone dimer **147** in $CDCl_3$.

The aromatic signals corresponding to the two ring systems were differentiated using a COSY spectrum (Figure 16), which clearly shows coupling between protons 5-H, 6-H, 7-H and 8-H belonging to one ring, and between protons 5'-H, 6'-H, 7'-H and 8'-H belonging to the other ring. Coupling constants were used to facilitate the assignment of individual protons. Each proton was then assigned to its respective carbon with the use of the HMQC spectrum (Figure 17). Quarternary carbons, (in particular:- C-4' which correlates with 2'-H and 17-H; C-15 which correlates with 17-H, 16-H and 13-H; C-11 which correlates with 4-H and 12-H; C-8a which correlates with 7-H and 8-H; C-10a which correlates with 5-H and 6-H; C-4a' which correlates with 2'-H; and C-8a' which correlates with 5'-H and 7'-H), were assigned using HMBC correlations (Figure 18). Similar correlations also confirmed all of the other assignments in the molecule. From a comparison of the original structural proposal (Figure 11) with the final structure of compound **147** (as determined by X-ray crystallography), it is apparent that the differences are confined to the arrangement of the additional, fused pyran ring.

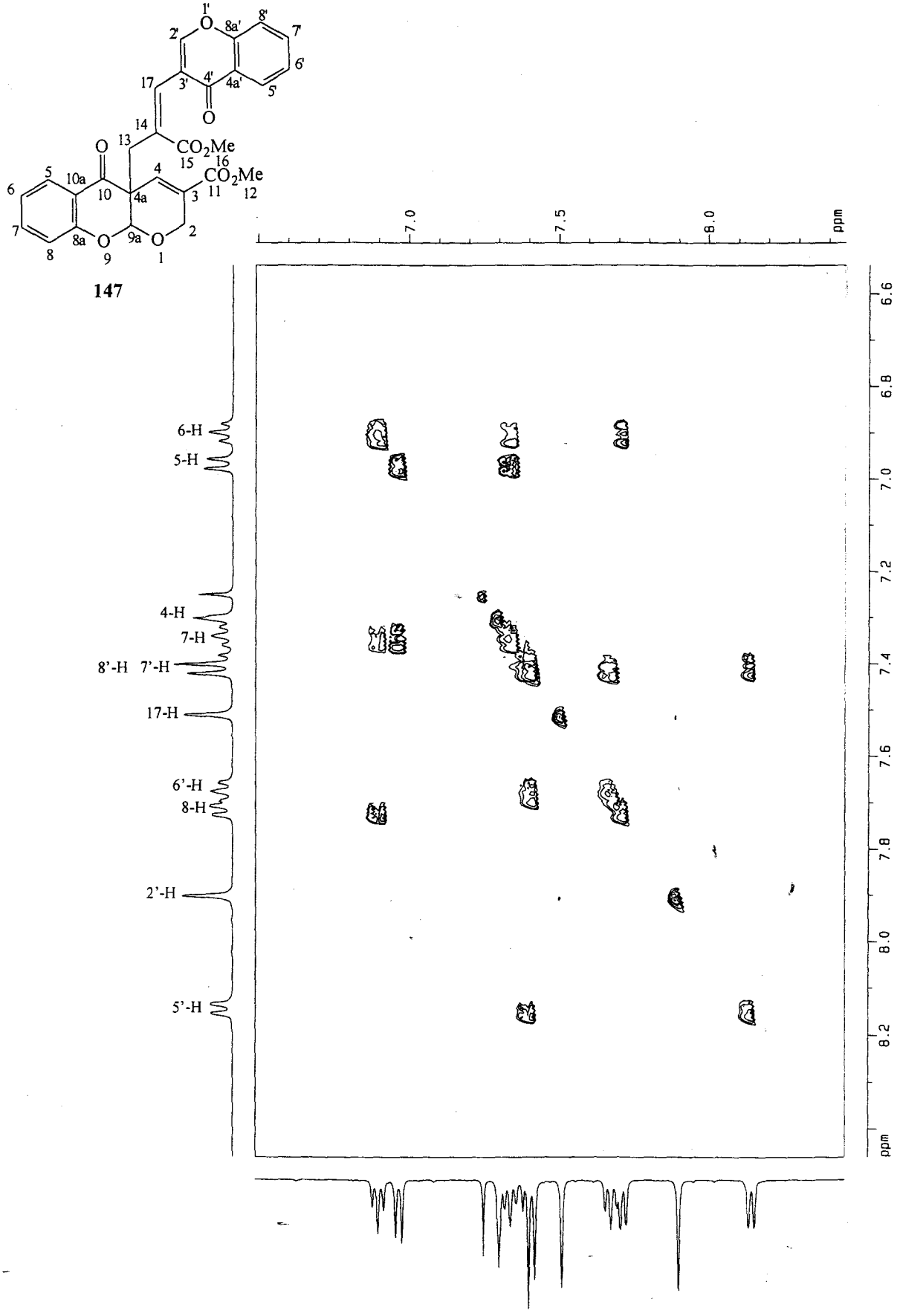


Figure 16: 400 MHz COSY NMR spectrum of the chromone dimer **147** in $CDCl_3$.

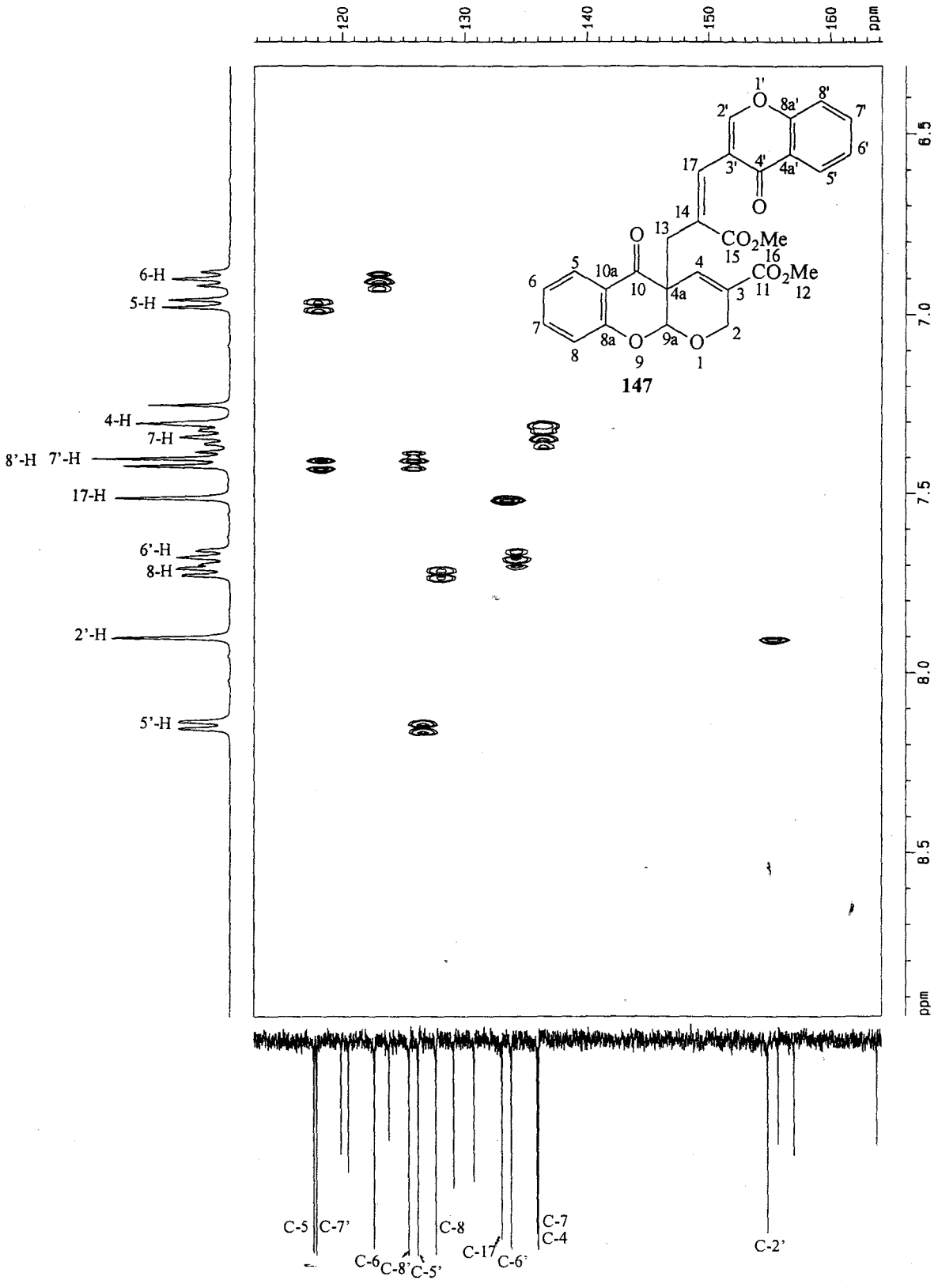


Figure 17: 400 MHz HMQC NMR spectrum of the chromone dimer **147** in $CDCl_3$.

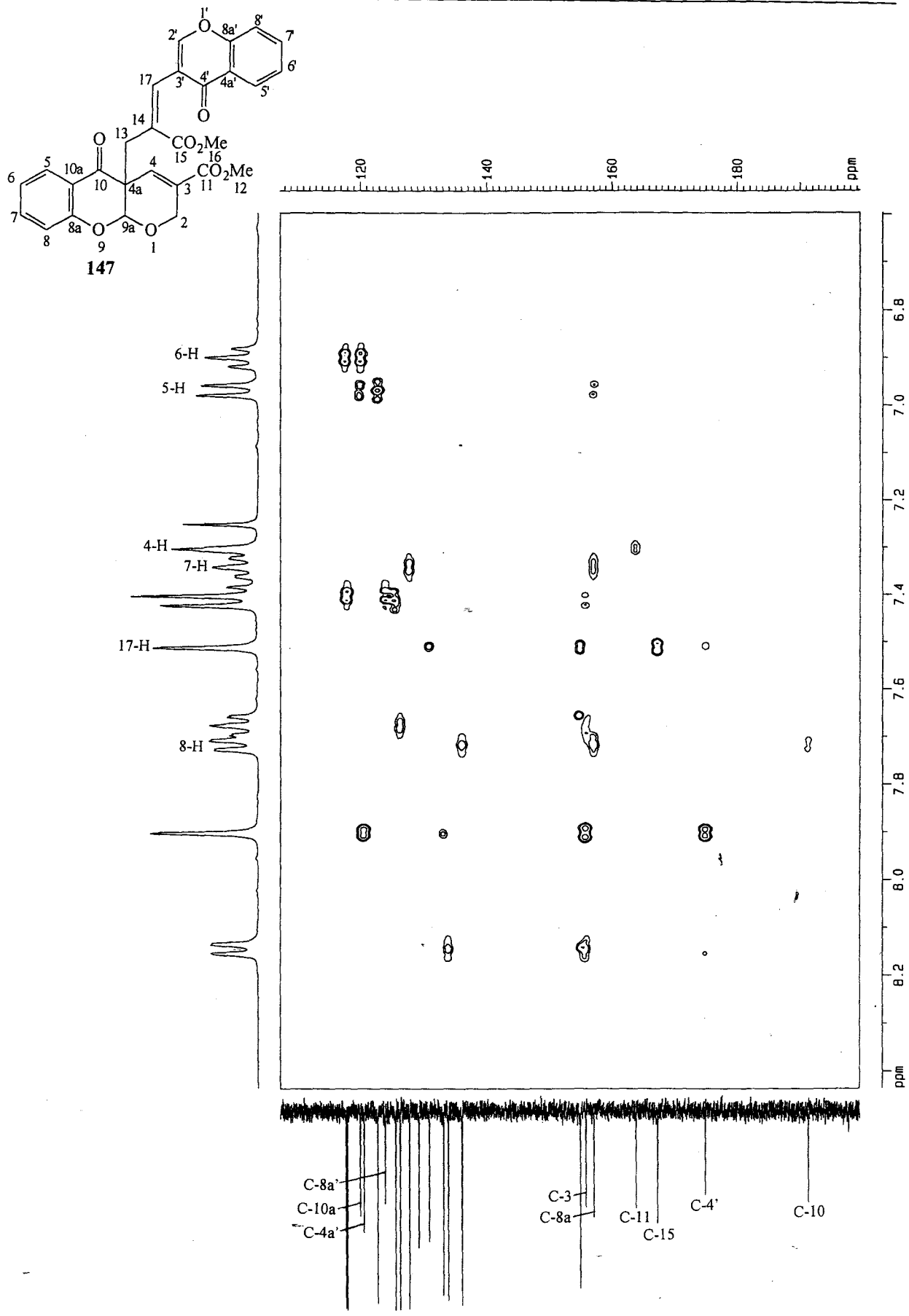
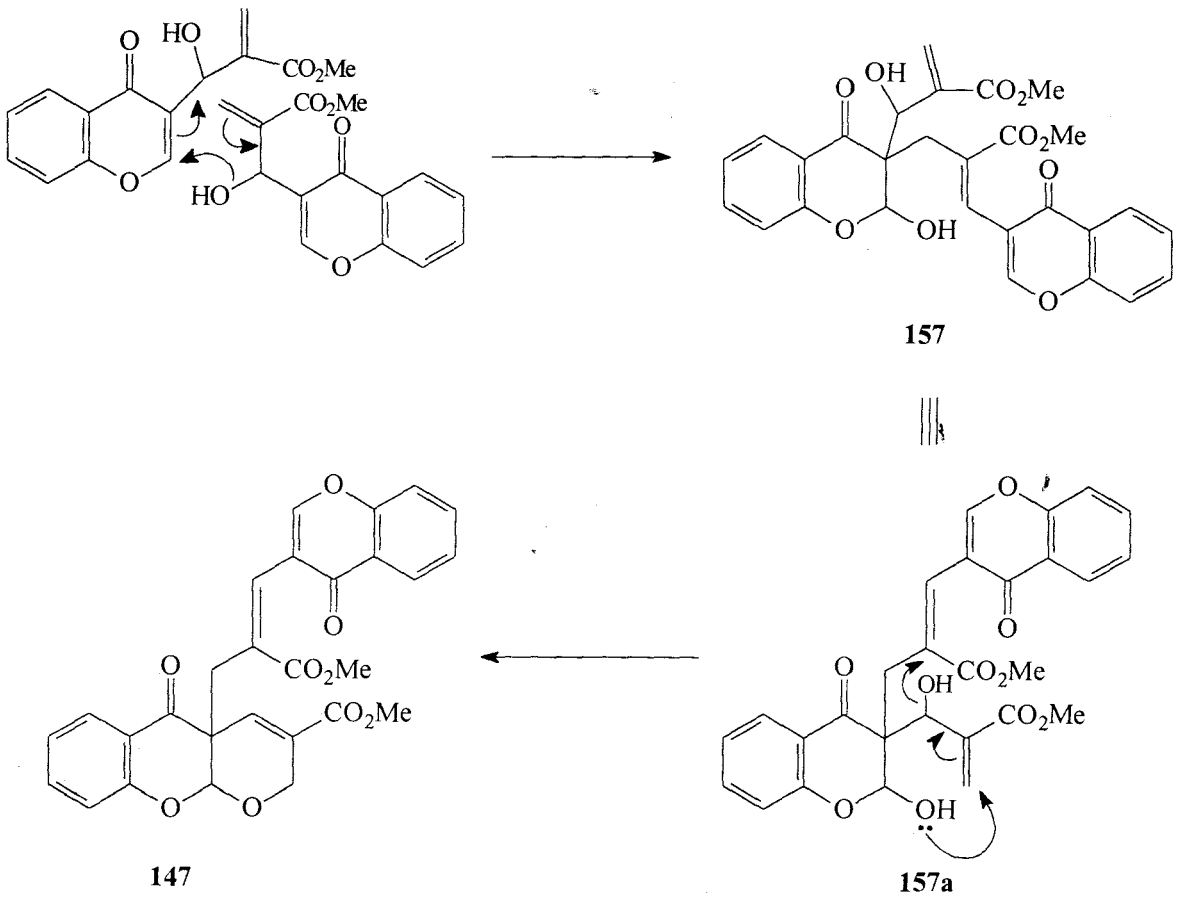


Figure 18: 400 MHz HMBC NMR spectrum of the chromone dimer **147** in $CDCl_3$.

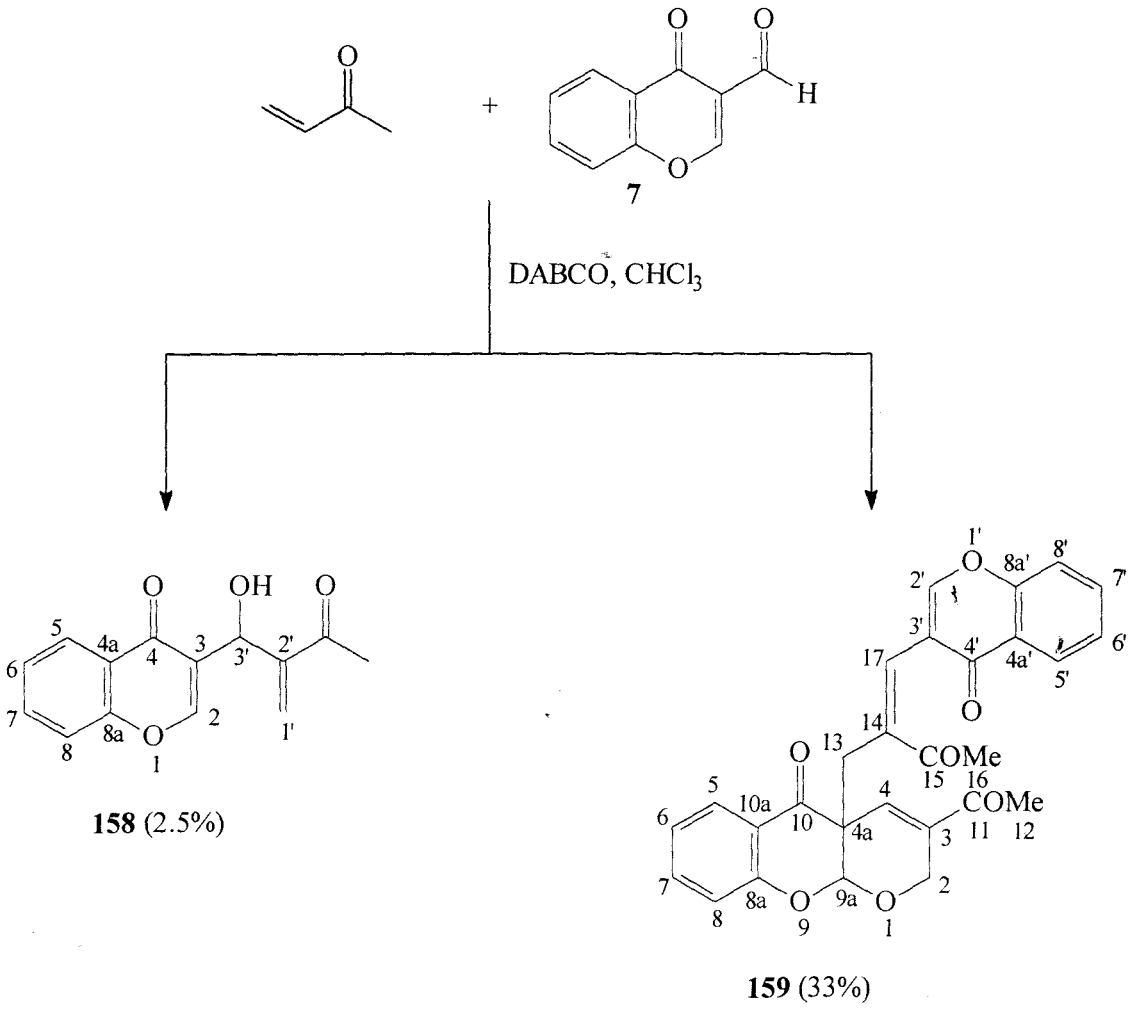
The formation of compound **147** (and its substituted analogues) may be rationalised as outlined in Scheme 44. Thus, concerted nucleophilic attack of the hydroxyl group of one monomer at the electrophilic centre, C-2, of the other and mobilisation of the π-electrons in a six-centred transition state complex results in the migration of the hydroxyl group and the formation of a C-C σ-bond between the two monomers, affording the intermediate **157**. Intramolecular cyclisation then follows from attack of the hemi-acetal hydroxyl oxygen on the α,β-unsaturated carbonyl moiety with consequent displacement of the allylic hydroxyl group, *via* an S_N2' (as in structure **157a**) or conjugate addition-elimination process, to afford the dimeric product **147**. Some evidence for this pathway is provided by the reaction of the Morita-Baylis-Hillman product **146** with DABCO, which produces the dimer **147** in essentially 100% yield after heating at 80 °C for 3 hours.



Scheme 44: Proposed mechanism for the formation of the chromone dimers.

2.3.3 Reaction of chromone-3-carbaldehyde (7) with methyl vinyl ketone

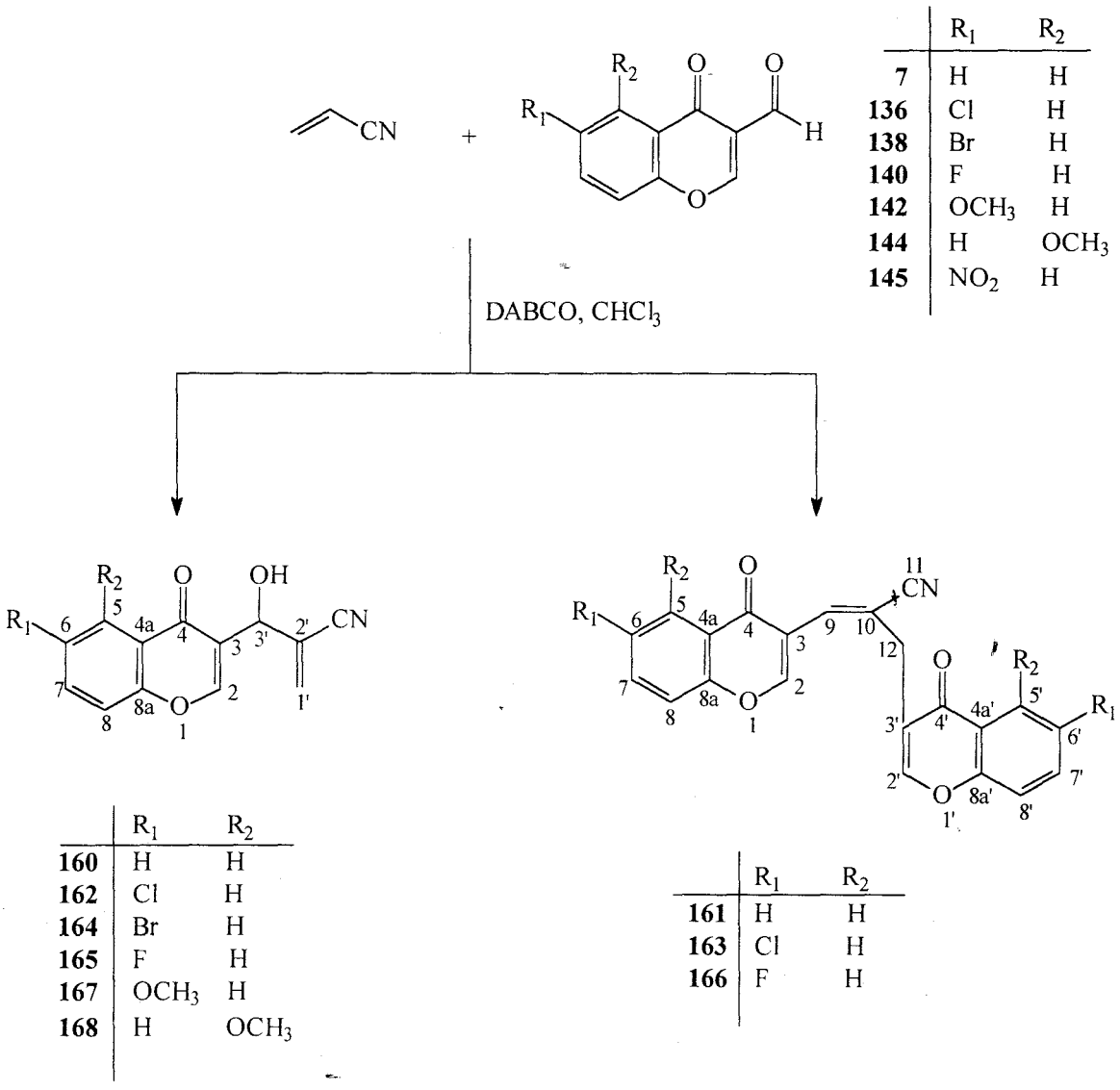
In an attempt to increase the yield, the parent chromone-3-carbaldehyde **7** was subjected to the Morita-Baylis-Hillman reaction in chloroform with the more reactive methyl vinyl ketone as the activated alkene and DABCO as the catalyst (Scheme 45). However, after flash chromatography on silica gel and multiple elutions using HPLC, the expected Morita-Baylis-Hillman product **158** was obtained in only 2.5% yield; the chromone dimer **159**, however, was isolated in 33% yield.



Scheme 45

2.3.4 Reactions of chromone-3-carbaldehydes with acrylonitrile

The chromone-3-carbaldehydes (**7**, **136**, **138**, **140**, **142**, **144** and **145**) were reacted with acrylonitrile and DABCO in chloroform (Scheme 46) over reaction periods of several weeks. In three cases, the expected Morita-Baylis-Hillman product (**160**, **162** and **165**) precipitated out of the reaction mixture and was purified by elution through a silica gel plug using ethyl acetate as solvent; the other three Morita-Baylis-Hillman products (**164**, **167** and **168**) were purified by flash chromatography on silica gel, followed by HPLC.



	R_1	R_2
7	H	H
136	Cl	H
138	Br	H
140	F	H
142	OCH_3	H
144	H	OCH_3
145	NO_2	H

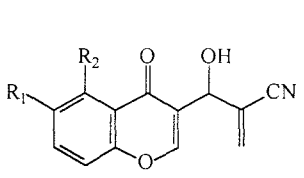
	R_1	R_2
160	H	H
162	Cl	H
164	Br	H
165	F	H
167	OCH_3	H
168	H	OCH_3

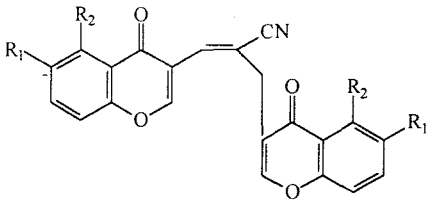
	R_1	R_2
161	H	H
163	Cl	H
166	F	H

Scheme 46

The yields of the isolated products were typically low (Table 6). In some cases, flash chromatography of the crude product mixture also afforded, albeit in low yields, compounds subsequently identified as the bischromone-acrylonitrile adducts (**161**, **163** and **166**) (Table 6). Extending the reaction time to eight weeks resulted in a slight improvement in the yields of the fluorinated Morita-Baylis-Hillman product **165** and the corresponding bischromone-acrylonitrile adduct, but had no effect on the yield of the bromo analogue.

Table 6: Yields of Morita-Baylis-Hillman products and corresponding bischromone-acrylonitrile adducts.

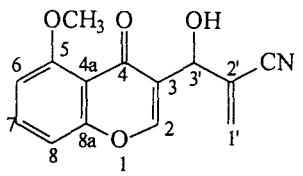




R^1	R^2	Morita-Baylis-Hillman product		Bischromone-acrylonitrile adduct	
		Compound	Yield[a]/%	Compound	Yield[a]/%
H	H	**160**	12	**161**	5
Cl	H	**162**	20	**163**	9
Br	H	**164**	15	-	-
F	H	**165**	31	**166**	24
OMe	H	**167**	20	-	-
H	OMe	**168**	20	-	-

[a] Determined from ^{1}H NMR spectroscopy of the crude reaction mixtures.

All products were identified by one- and two-dimensional NMR spectroscopy. The ^{1}H NMR spectrum (Figure 19) of the Morita-Baylis-Hillman product **168** shows a singlet at 3.99 ppm corresponding to the methoxy group, a doublet at 4.59 ppm corresponding to the hydroxyl group, a doublet at 5.18 ppm corresponding to 3'-H and two singlets at 6.11 and 6.31 ppm corresponding to the 1'-methylene group. The ^{13}C NMR spectrum (Figure 20) shows 14 carbon signals, including 7 quarternary carbons and the C-1' methylene group at 131.2 ppm.



168

Figure 19: 400 MHz ^{1}H NMR spectrum of the Morita-Baylis-Hillman product **168** in $CDCl_3$.

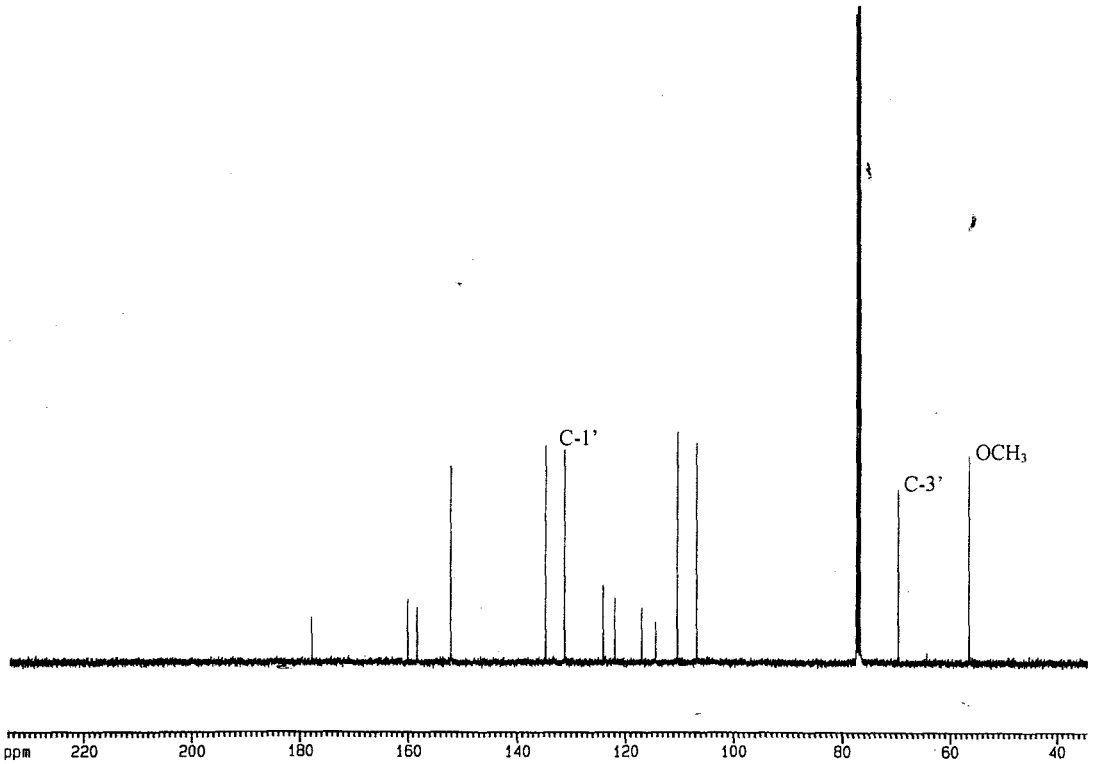
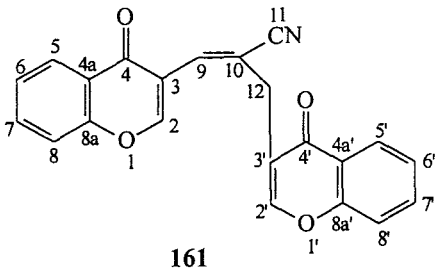


Figure 20: 100 MHz ^{13}C NMR spectrum of the Morita-Baylis-Hillman product **168** in $CDCl_3$.



161

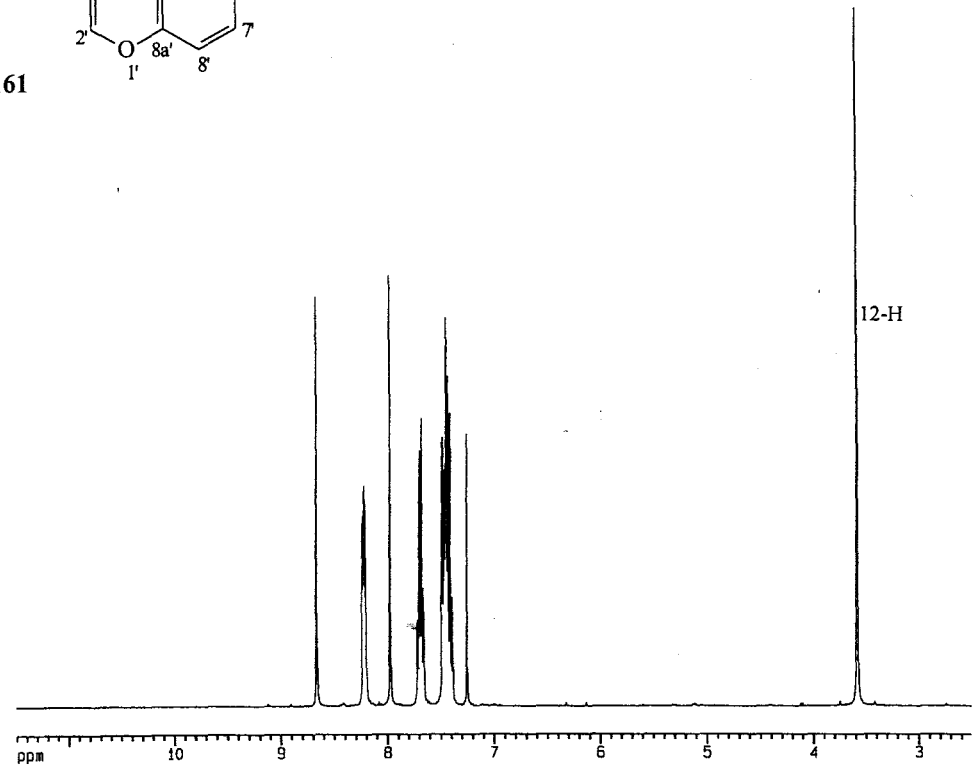


Figure 21: 400 MHz ^{1}H NMR spectrum of the bischromone-acrylonitrile adduct **161** in $CDCl_3$.

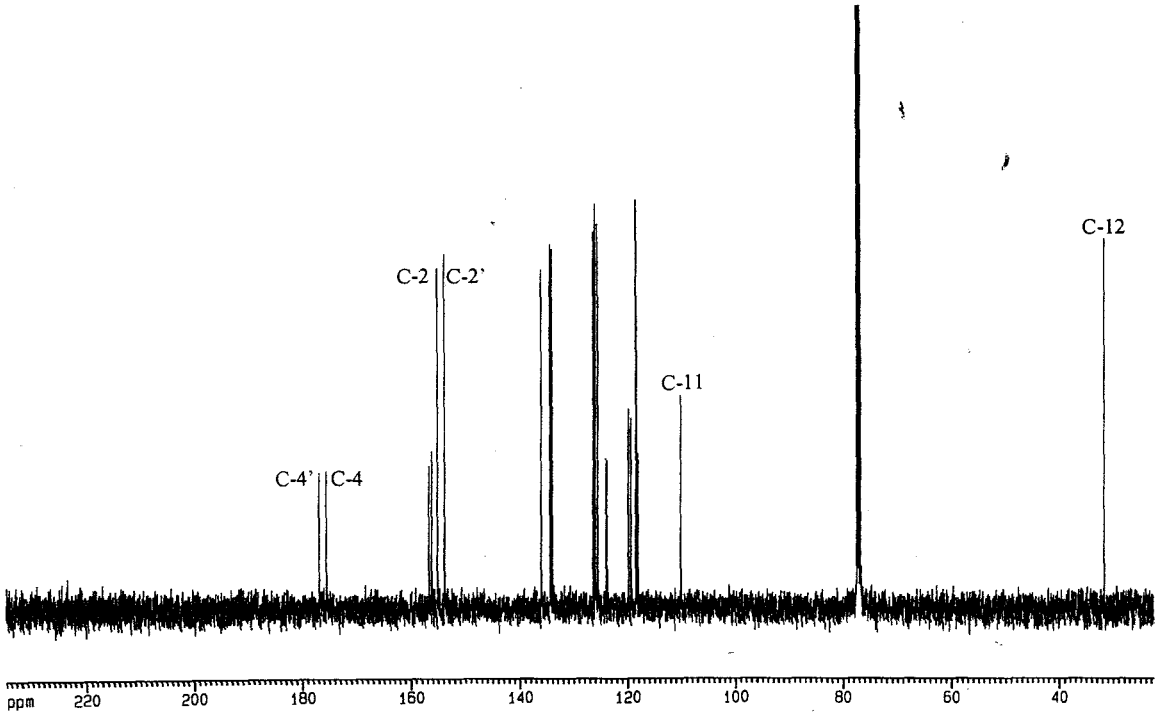
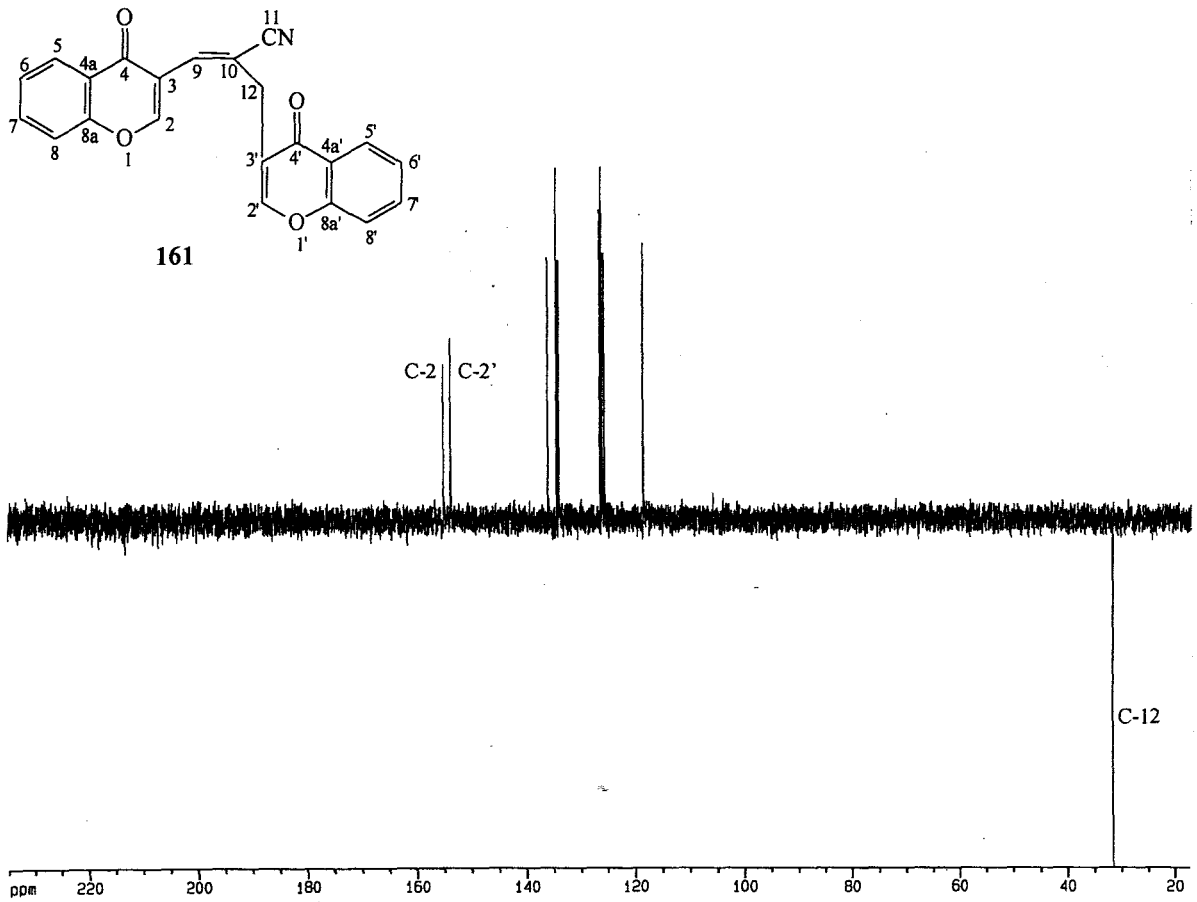


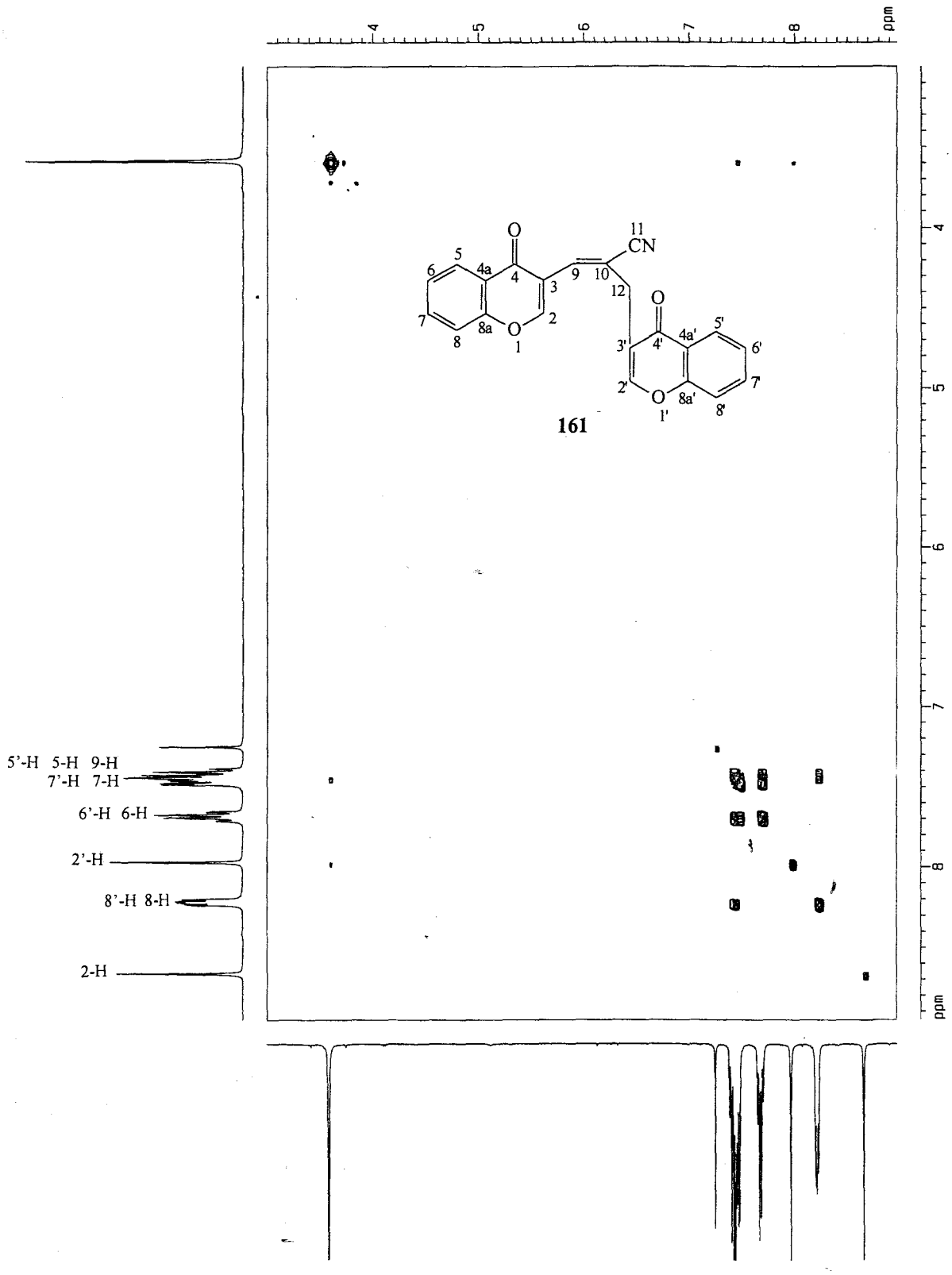
Figure 22: 100 MHz ^{13}C NMR spectrum of the bischromone-acrylonitrile adduct **161** in $CDCl_3$.



161

Figure 23: 400 MHz DEPT NMR spectrum of the bischromone-acrylonitrile adduct **161** in $CDCl_3$.

The bischromone-acrylonitrile adducts were also characterised by one- and two-dimensional NMR spectroscopy. The ^1H NMR spectrum of compound **161** (Figure 21) shows a singlet at 3.59 ppm corresponding to the 12-methylene group and signals corresponding to 11 protons in the aromatic region between 7.68 and 8.66 ppm. The ^{13}C NMR spectrum (Figure 22) shows 22 carbon signals of which one is due to a methylene group and ten to quarternary carbons, as established by comparison with the DEPT spectrum (Figure 23). The COSY spectrum (Figure 24) reveals couplings between ring protons 5-H, 6-H, 7-H and 8-H (and between 5'-H, 6'-H, 7'-H and 8'-H), however, due to the similarity of the two ring systems, corresponding protons from the two rings could not be differentiated. Protons were assigned to their respective carbons with the use of an HMQC spectrum (Figure 25). Quarternary carbons (in particular:- C-4' which correlates with 12-H and 2'-H; C-4 which correlates with 9-H and 2-H; C-8a' which correlates with 2'-H; and C-8a which correlates with 2-H) were assigned with the aid of the HMBC spectrum (Figure 26), which also confirmed all other assignments.



161

Figure 24: 400 MHz COSY NMR spectrum of the bischromone-acrylonitrile adduct **161** in $CDCl_3$.

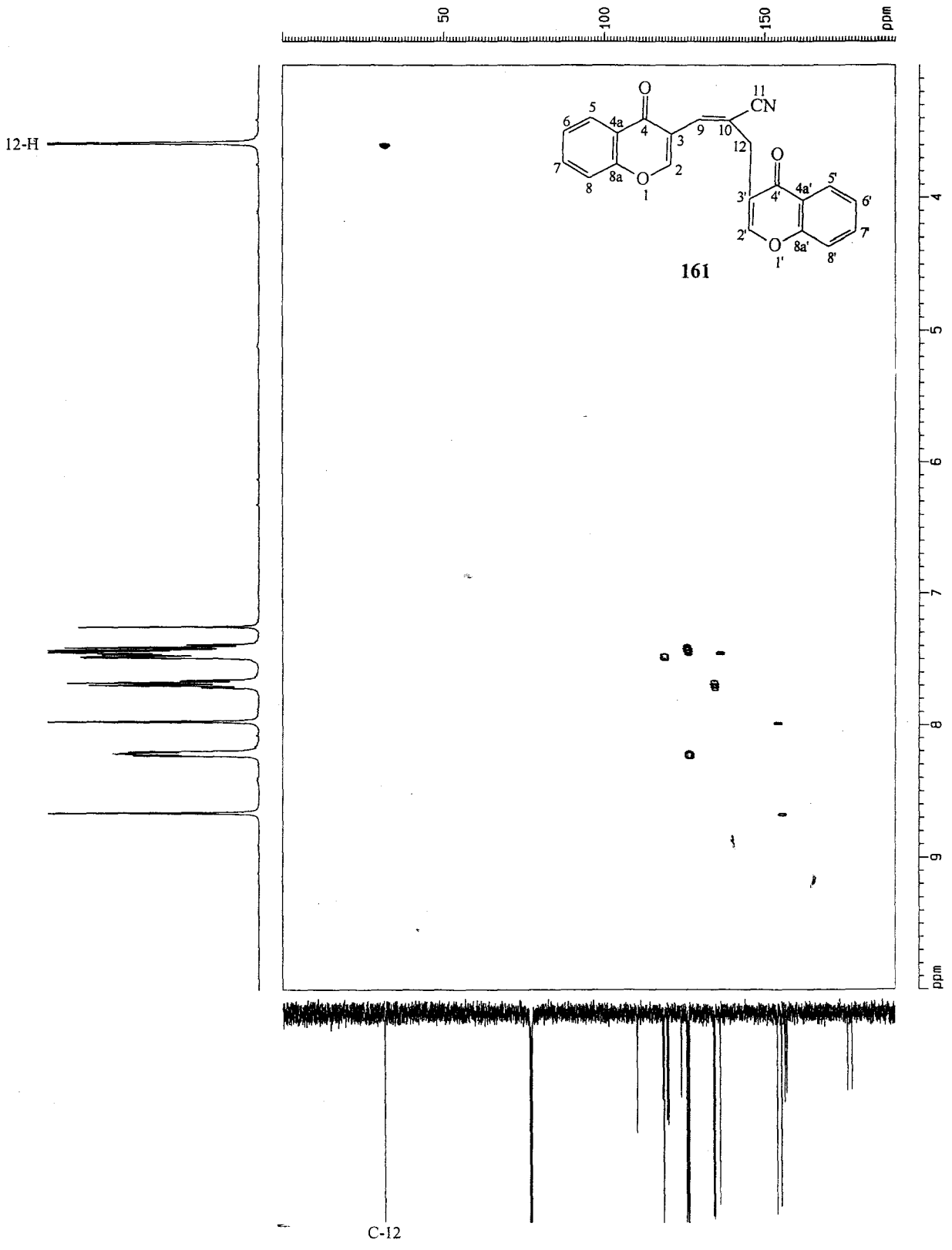


Figure 25: 400 MHz HMQC NMR spectrum of the bischromone-acrylonitrile adduct **161** in $CDCl_3$.

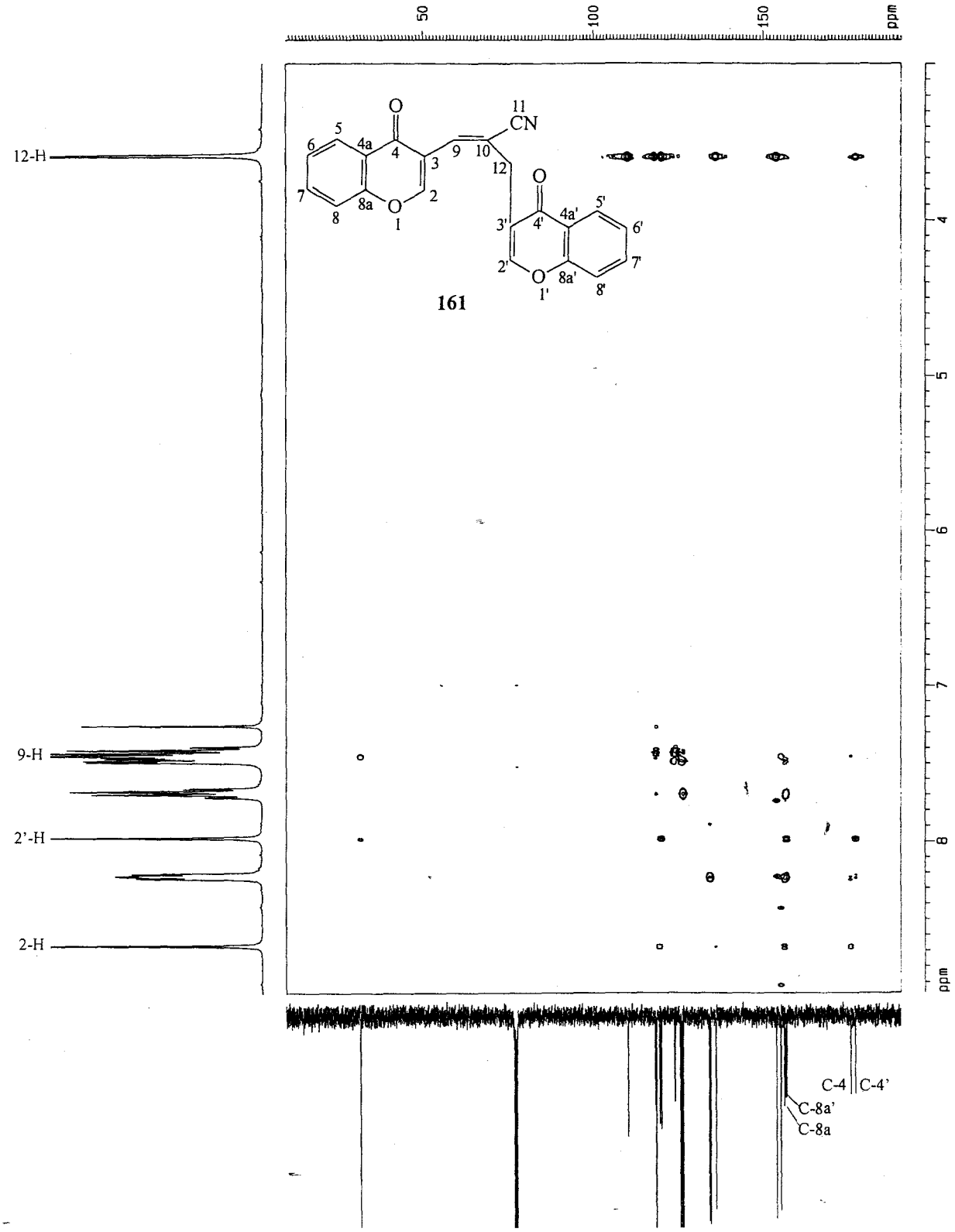
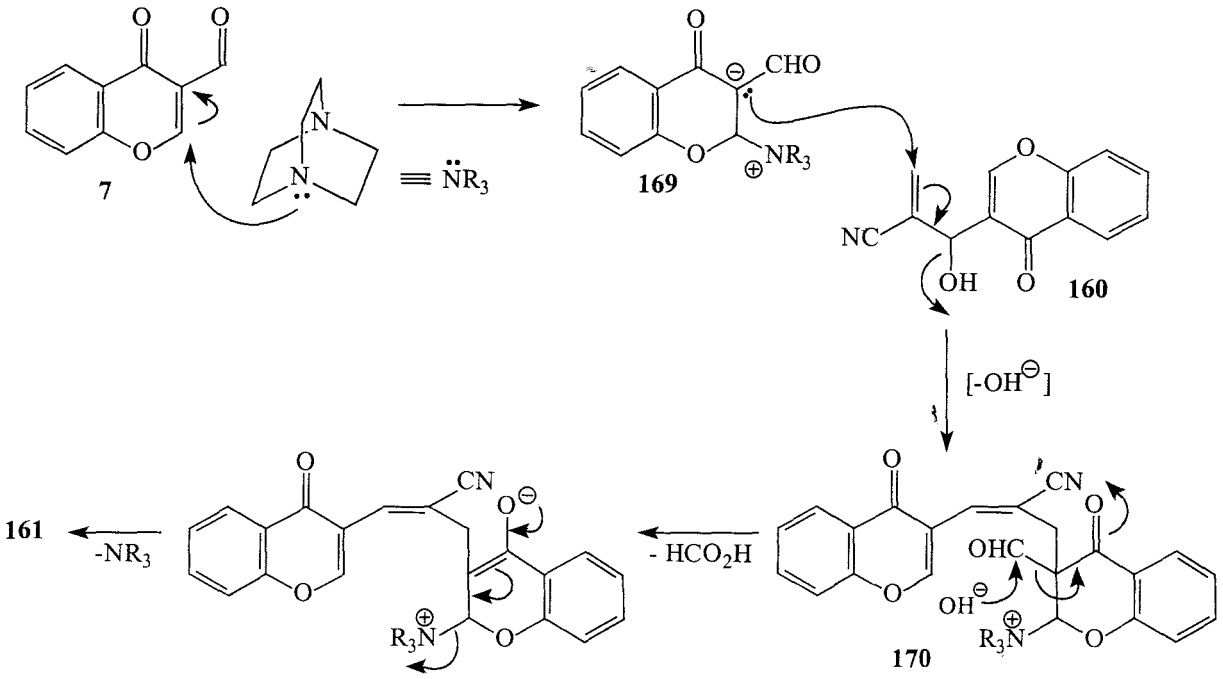


Figure 26: 400 MHz HMBC NMR spectrum of the bischromone-acrylonitrile adduct **161** in $CDCl_3$.

Formation of the bischromone-acrylonitrile adducts is proposed to involve initial attack of DABCO at the electrophilic centre, C-2, of one chromone ring to form a zwitterionic intermediate **169** (Scheme 47). DABCO normally attacks unhindered vinyl systems but examples of attack at more hindered centres have been reported recently;[75] the presence of the two carbonyl groups in chromone-3-carbaldehydes may well serve to activate the double bond towards nucleophilic attack by DABCO. Once formed, the zwitterionic intermediate **169** then attacks the Morita-Baylis-Hillman product, present in the reaction mixture, to form intermediate **170** *via* an S_N2' or addition-elimination sequence. Elimination of formylated DABCO then gives the bischromone-acrylonitrile adduct. Evidence for this pathway is provided by the formation of the adduct **161** on reaction of the Morita-Baylis-Hillman product **160** with the chromone-3-carbaldehyde **7** and DABCO in chloroform, *i.e. in the absence of acrylonitrile!*



Scheme 47: Proposed mechanism for the formation of the bischromone-acrylonitrile adducts.

Treatment of 6-nitrochromone-3-carbaldehyde **145** with acrylonitrile and DABCO afforded neither the expected Morita-Baylis-Hillman product, nor the bischromone-acrylonitrile adduct – a result which is consistent with the lack of reactivity observed when methyl acrylate (section 2.3.2) was used as the activated alkene.

In the Morita-Baylis-Hillman reaction of 6-methoxychromone-3-carbaldehyde **142**, an additional bischromone-acrylonitrile adduct **171** was obtained in trace amounts and was characterised by one- and two-dimensional NMR spectroscopy. The structure bears some similarity to the structure originally proposed for the chromone dimer **147** (section 2.3.2). The ^{1}H NMR spectrum of compound **171** (Figure 27) shows two multiplets at 2.68 and 3.26 ppm corresponding to the 3-methylene group, a singlet at 3.29 ppm corresponding to 11-H, two singlets at 3.80 and 3.90 ppm corresponding to the two methoxy groups, a singlet at 5.43 ppm corresponding to 4a-H, a singlet at 8.71 ppm corresponding to 2'-H and seven signals between 6.99 and 7.58 ppm corresponding to the aromatic protons and the 1-vinylic proton. The ^{13}C NMR spectrum (Figure 28) indicates the presence of 25 carbons, of which one is a methylene carbon and twelve are quarternary. The formation of this adduct, which is supported by high resolution mass spectroscopy (Found: $\mathbf{M}^{+}$ 461.1110. $C_{25}H_{19}NO_8$ requires *M*, 461.1111), is tentatively rationalised in Scheme 48. Thus, attack of the zwitterionic nucleophile on C-2 of the chromone ring affords, *via* proton transfer and elimination of DABCO, intermediate **172**. This intermediate then attacks the formyl group of another chromone-3-carbaldehyde molecule to form intermediate **173**, protonation of which affords the bischromone-acrylonitrile adduct **171**.

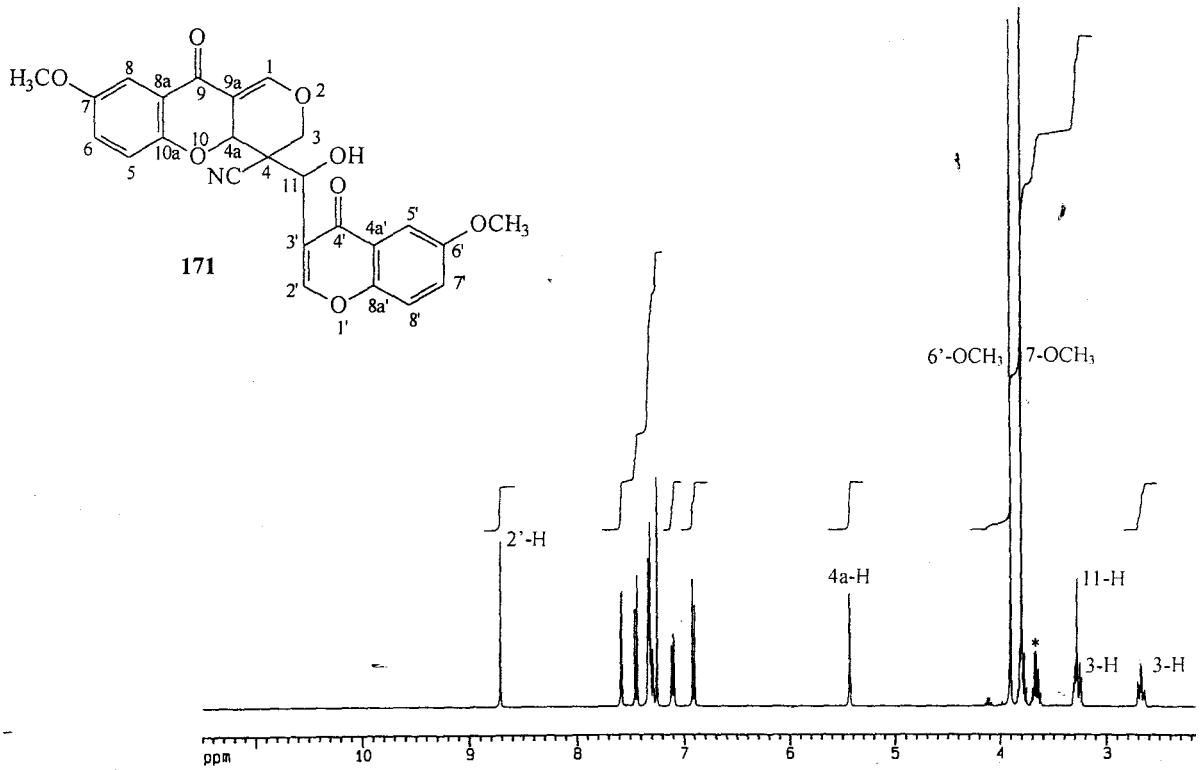


Figure 27: 400 MHz ^{1}H NMR spectrum of the bischromone-acrylonitrile adduct **171** in $CDCl_3$. The peak denoted with an asterisk represents an impurity.

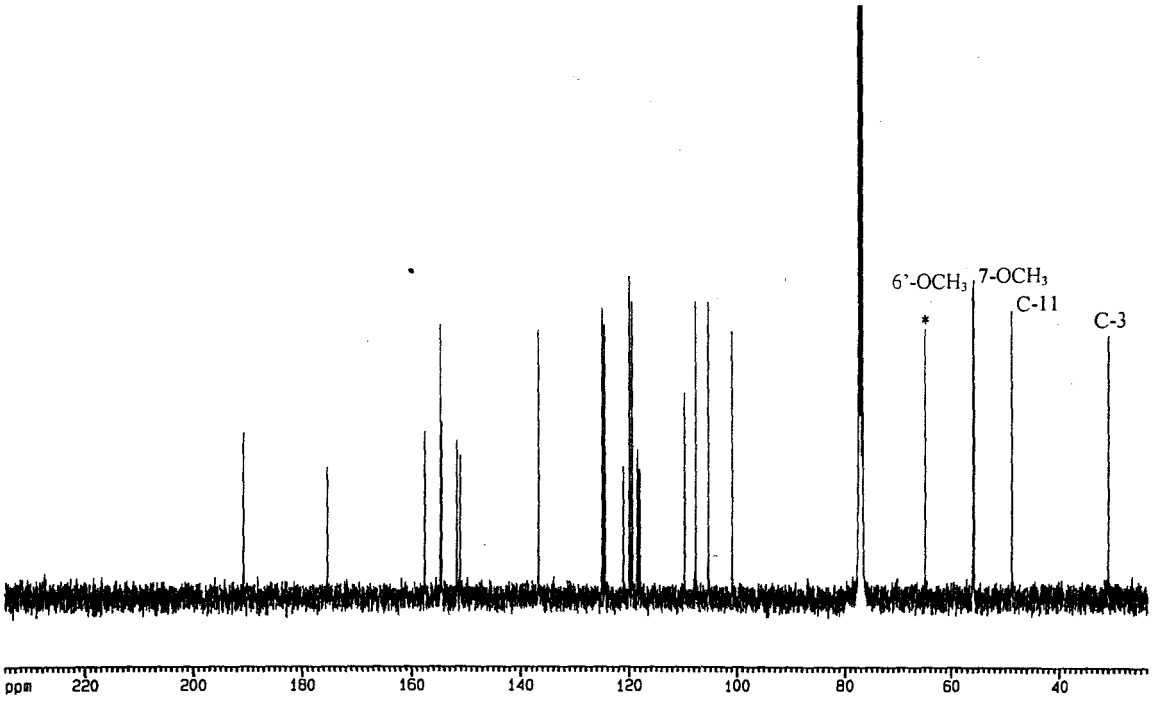
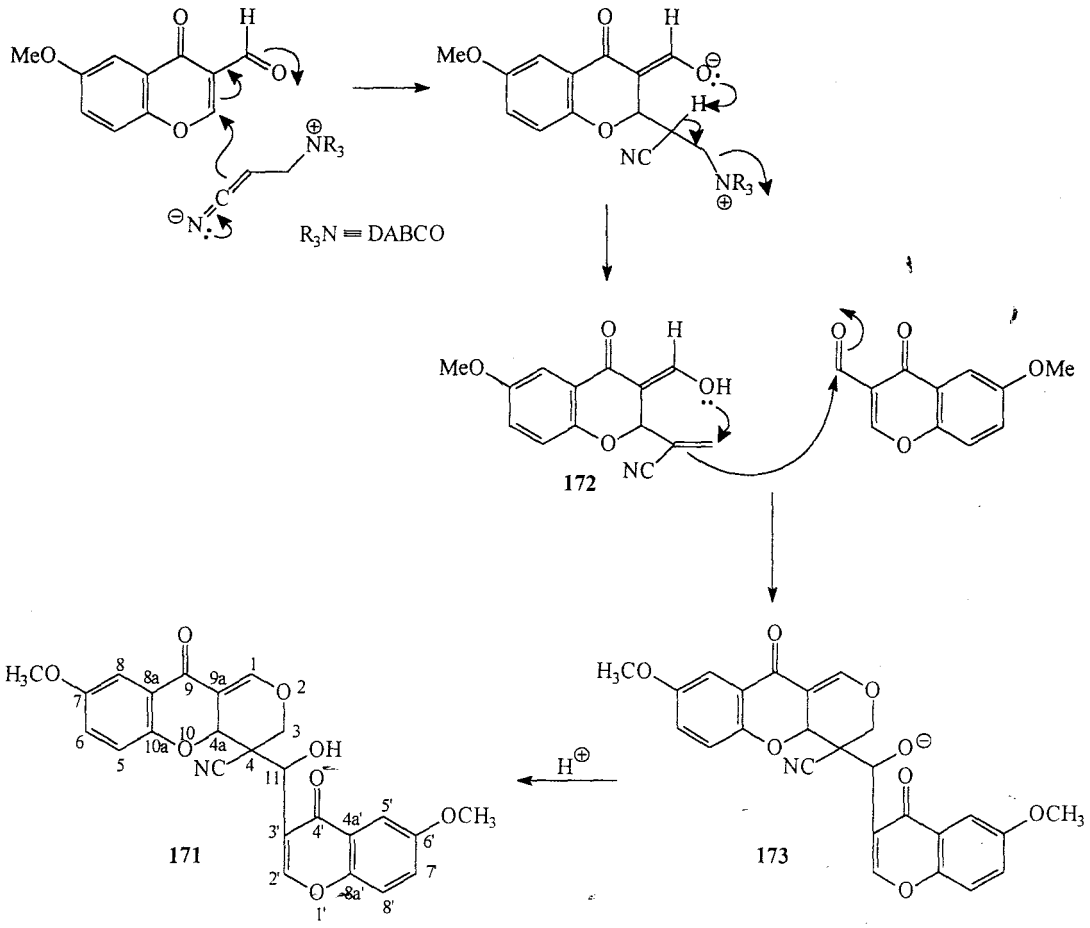


Figure 28: 100 MHz ^{13}C NMR spectrum of the bischromone-acrylonitrile adduct **171** in $CDCl_3$. The peak denoted with an asterisk represents an impurity.



Scheme 48: Proposed mechanism for the formation of adduct **171**.

2.3.5 Yield optimisation studies

While the capacity of chromone-3-carbaldehydes to undergo Morita-Baylis-Hillman reactions was apparent and the formation of the novel "dimeric" derivatives well established, the yields of these compounds were far from satisfactory. In order to demonstrate the synthetic viability of these transformations, yield optimisation studies were undertaken. The various attempts to increase the yields of the Morita-Baylis-Hillman adducts are summarised below (the experimental procedures are detailed in section 3.4.4).

1. When the reaction of chromone-3-carbaldehyde **7** with methyl acrylate was conducted in dry chloroform under an inert atmosphere (N_2), no increase in yield of the Morita-Baylis-Hillman product **146** or the dimer **147** (compared to the original reaction) was achieved.
2. Replacement of chloroform as solvent by tetrahydrofuran produced no change in yield compared to the original reaction of chromone-3-carbaldehyde **7** and methyl acrylate.
3. Use of the above reagents and a vigorously stirred two-phase system of chloroform-water (1:1) as the solvent system afforded no readily identifiable products.
4. Plots of the progress of the reaction (as determined by ^{1}H NMR spectroscopy) of chromone-3-carbaldehyde **7** (1 eq.) and acrylonitrile (1.5 eq.) using DABCO (2 eq.) as the catalyst showed that a maximum conversion of *ca.* 64% to the Morita-Baylis-Hillman product **160** was reached after 35 days (Figure 29). This compares favourably with the original yield of 14%.
5. The reaction of chromone-3-carbaldehyde **7** (1 eq.) and acrylonitrile (1.5 eq.), using 3-hydroxyquinuclidine (3-HQ; 2 eq.) as the catalyst, showed a maximum conversion of *ca.* 79% after 24 hours. When 5 eq. of 3-hydroxyquinuclidine were used, a maximum conversion of *ca.* 92% was achieved after 22 hours (Figure 30)!

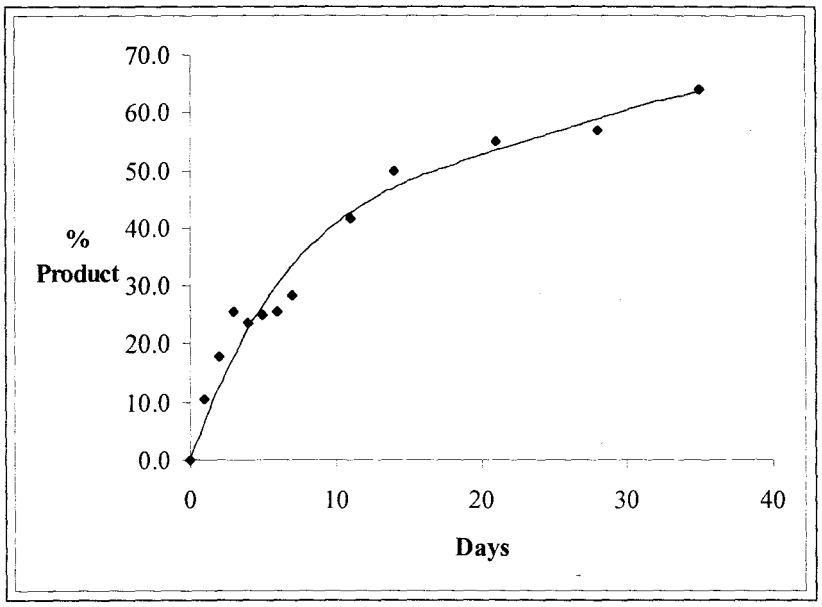


Figure 29: Percentage of the Morita-Baylis-Hillman **160** product formed *vs.* time, using acrylonitrile (1.5 eq.) and DABCO (2 eq.).

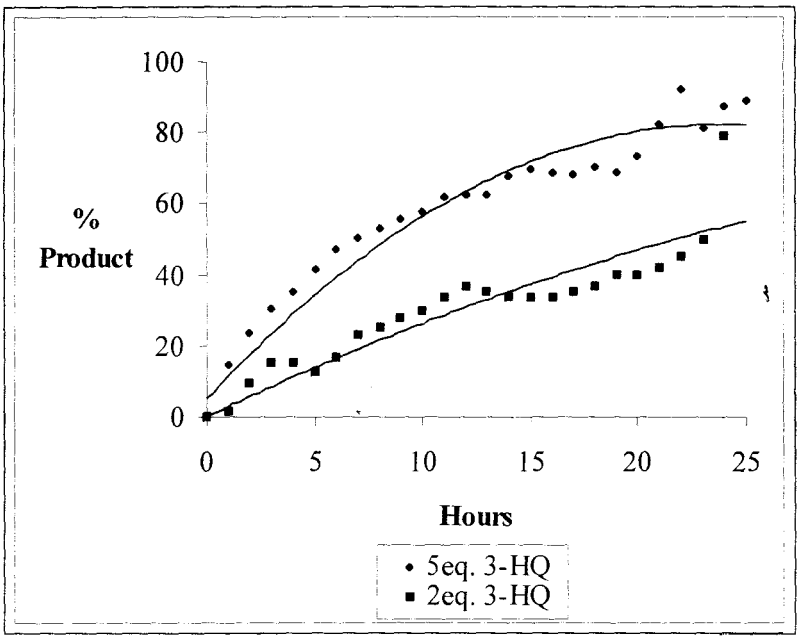


Figure 30: Percentage of Morita-Baylis-Hillman product **160** formed *vs.* time, using acrylonitrile (1.5 eq.) and 3-hydroxyquinuclidine (2 eq. and then 5 eq.).

6. Reactions were also conducted using chromone-3-carbaldehyde **7**, 6-chlorochromone-3-carbaldehyde **136** and 6-methoxychromone-3-carbaldehyde **142** (1 eq. each) with methyl acrylate (1.5 eq.) and DABCO (2 eq.). As shown in Figure 31, the

unsubstituted Morita-Baylis-Hillman product **146** reached a maximum conversion of *ca.* 94% after 7 days, the 6-chloro analogue **148** reached *ca.* 85% after 9 days and the 6-methoxy analogue **154** reached *ca.* 95% after 16 days.

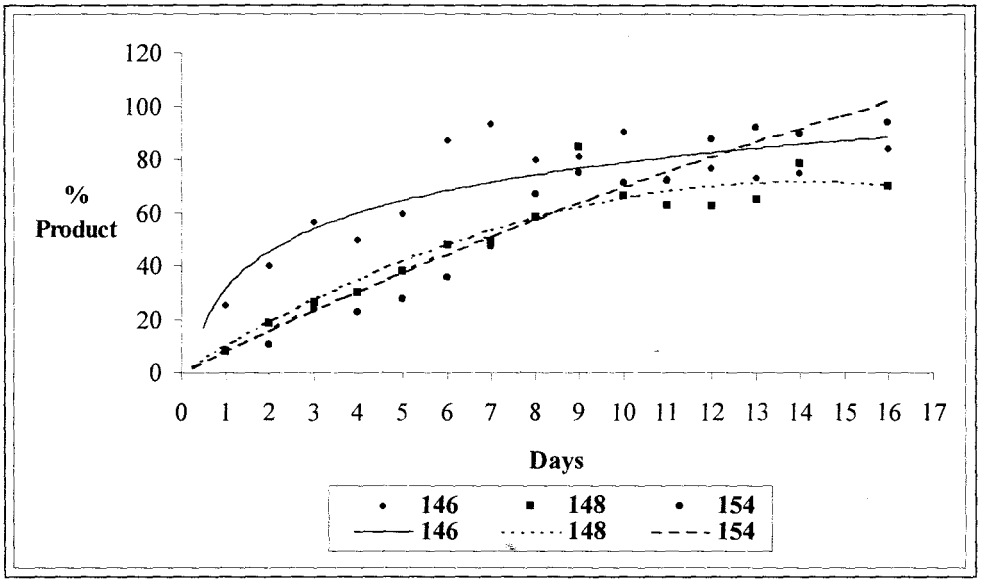


Figure 31: Percentage of the Morita-Baylis-Hillman products **146**, **148** and **154** formed *vs.* time, using methyl acrylate (1.5 eq.), DABCO (2 eq.) and the corresponding chromone-3-carbaldehydes **7**, **136** and **142**.

7. The reaction of chromone-3-carbaldehyde **7** (1 eq.) with acrylonitrile (2 eq.) using DABCO (2 eq.) as the catalyst was carried out as a melt, *i.e.* without the use of a solvent, at 60 °C. Although the overall percentage conversion to the Morita-Baylis-Hillman product **160** did not increase, a conversion of *ca.* 43% was reached after only 1 hour. When 3-hydroxyquinuclidine (2 eq.) was used as the catalyst, a conversion of *ca.* 23% was achieved after 1 hour.
8. As discussed in section 2.3.2, the chromone dimer **147** was readily obtained by heating the Morita-Baylis-Hillman product **146** with DABCO at 80 °C, the conversion being essentially complete after 3 hours.
9. The bischromone-acrylonitrile adduct **161** was observed to precipitate out of a solution of chromone-3-carbaldehyde **7**, the Morita-Baylis-Hillman product **160** and DABCO in deuterated chloroform as described in section 2.3.4.

The low yields observed initially may well reflect the tandem formation of the "dimeric" adducts for which the Morita-Baylis-Hillman products are themselves precursors. However, as demonstrated above, satisfactory conversions to the desired Morita-Baylis-Hillman products are possible by correct application of the appropriate catalyst and reaction period. In general, it appears that optimum conditions for the formation of the Morita-Baylis-Hillman product from the reaction of chromone-3-carbaldehydes with acrylonitrile may be achieved with the use of 2-5 equivalents of 3-hydroxyquinuclidine and a reaction period of *ca.* 24 hours. When methyl acrylate is used, conversions of *ca.* 90% may be achieved with 2 equivalents of DABCO over a reaction period of between one and two weeks. If desired, the "dimeric" products may be readily and efficiently obtained from the Morita-Baylis-Hillman product precursors.

2.3.6 Mass spectrometric fragmentation patterns exhibited by the Morita-Baylis-Hillman products and the corresponding dimers.

A study of the electron impact (EI) mass fragmentation patterns of the Morita-Baylis-Hillman products **146**, **152**, **154**, **160**, **162**, **165** and **167** was undertaken, and the fragmentation pathways were elucidated using a combination of low-resolution, high-resolution and metastable peak data. The chromone dimers **147**, **153** and **155** and the bischromone-acrylonitrile adduct **161** were also subjected to low-resolution electrospray MS^n analysis in an attempt to explore correlations between EI and electrospray (CI) fragmentation pathways.

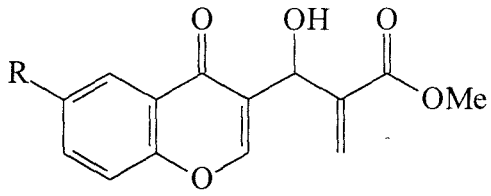
2.3.6.1 EI fragmentation patterns of the Morita-Baylis-Hillman products

Data for the fragmentation of the Morita-Baylis-Hillman products **146**, **152** and **154** (obtained from reaction of the substituted chromone-3-carbaldehydes with methyl acrylate) are summarised in Table 7. The ions, designated **a** – **m**, were consistently observed in the mass spectra of all three compounds analysed.

The proposed fragmentation patterns are outlined in Scheme 49 and it is apparent that fragmentation of the molecular ion may follow three general pathways (I, II and III). In path I, fragmentation associated with loss of a hydroxyl radical leads to the resonance-stabilised ions of type **b**, the formation of which is supported by low-resolution electrospray data where loss of water also gives rise to ion **b**. In path II, loss of methanol from the parent system is proposed to result in the β-lactam radical-cation **c**, while in path III, loss of a methoxy radical results in the formation of acylium ions of type **d**. The formation of ions **b** and **c** is supported by metastable peak data for the parent system (R=H) as shown in Scheme 49. In path II, sequential loss of carbon monoxide (from ion **c**), a hydrogen radical and another molecule of carbon monoxide gives rise to ions **e**, **f** and **g** respectively, where the fragmentations (**c** → **e**) and (**e** → **g**) are supported by metastable peak data. Loss of carbon monoxide from the chromone ring, as required for the formation of ions of type **g**, is a known chromone fragmentation (see Figure 32).[110] Path III involves loss of carbon monoxide and acetylene from ion **d** to form ion **h**, which accounts for the base peak when R=H, F. Two different fragmentations of ion **h** are proposed to give rise

to:- (i) ions **l** and **m** by loss of carbon monoxide followed by a hydrogen radical; and (ii) ions **i**, **j** and **k**. The fragmentation sequence (**h** → **i** → **j**) is supported by metastable peak data, while ion **j** results from a retro-Diels-Alder (RDA) fission[110] (see Figure 32).

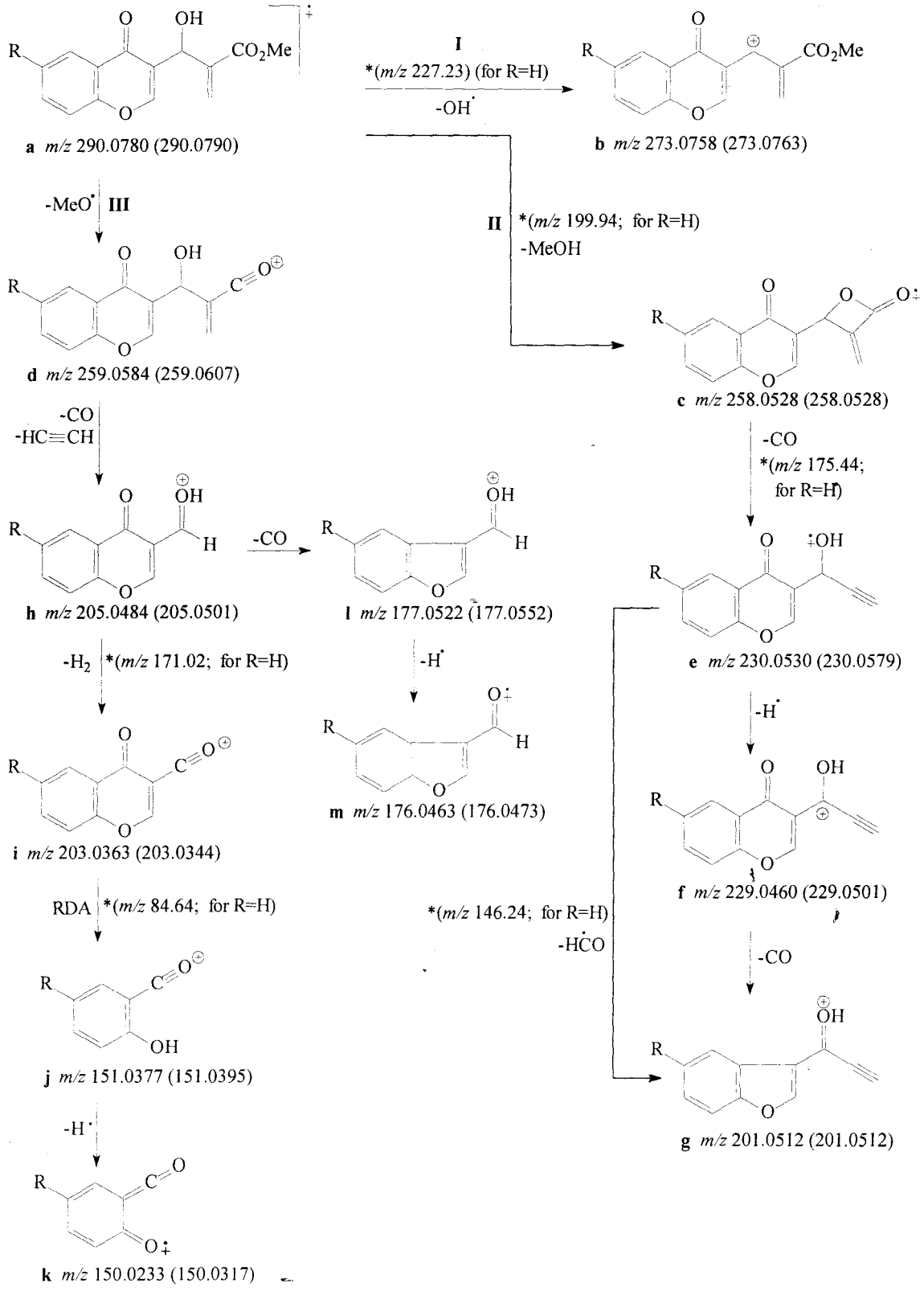
Table 7: Selected peaks (*m/z*; followed, in parentheses, by % relative abundance) from EI mass spectra of the Morita-Baylis-Hillman products **146** (R=H), **152** (R=OMe) and **154** (R=F), classified according to ion types **a**-**m** (Scheme 49).



R	a	b	c	d	e
H	260 (27)	243 (73)	228 (49)	229 (25)	173 (73)
OMe	290 (26)	273 (53)	258 (54)	259 (20)	230 (45)
F	278 (34)	261 (71)	246 (77)	247 (36)	191 (76)

R	f	g	h	i	j
H	199 (17)	171 (46)	175 (100)	200 (92)	121 (71)
OMe	229 (13)	201 (25)	205 (60)	203 (44)	151 (100)
F	217 (19)	189 (48)	193 (100)	218 (84)	139 (77)

R	k	l	m
H	120 (11)	147 (12)	146 (20)
OMe	150 (18)	177 (5)	176 (11)
F	138 (13)	165 (13)	164 (21)



Scheme 49: EI mass fragmentation pathways for compounds **146** (R=H), **152** (R=OMe) and **154** (R=F): accurate masses (*m/z*) for the methoxy derivative **154** are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by the metastable peak given in parentheses.

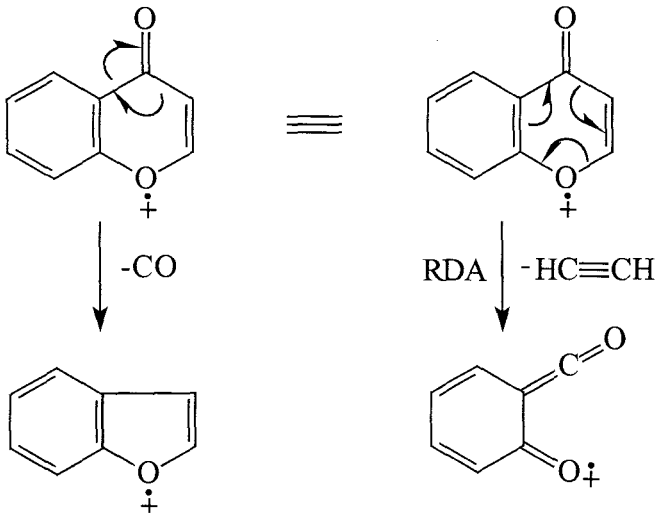
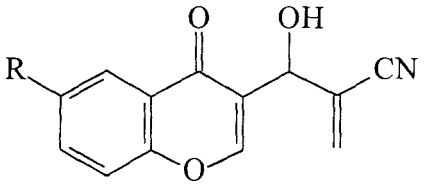


Figure 32: Known fragmentation patterns of chromone.[110]

Data for the fragmentation of the Morita-Baylis-Hillman products **160, 162, 165** and **167** (obtained from reaction of the substituted chromone-3-carbaldehydes with acrylonitrile) are summarised in Table 8. All ions (with the exception of ions **f** and **h**, as indicated) were consistently observed in the mass spectra of all compounds analysed. From the patterns outlined in Scheme 50, fragmentation of the molecular ion appears to follow four general pathways (I, II, III and IV). In path I, fragmentation associated with loss of a hydroxyl radical leads to the resonance-stabilised ions of type **b**, which parallel those observed for the ester analogues (Scheme 49); the formation of these ions is also supported by low-resolution electrospray data (loss of water giving rise to ion **b**). In path II, loss of HCN from the parent system results in the hydroxy alkyne radical cation **c**, while in paths III and IV, loss of the radical species C_3H_2N• and C_3H_4N• results in the formation of ions **d** and **e** respectively. The formation of ions **b**, **c**, **d** and **e** are all supported by metastable peak data for the parent system (R=H) as shown in Scheme 50.

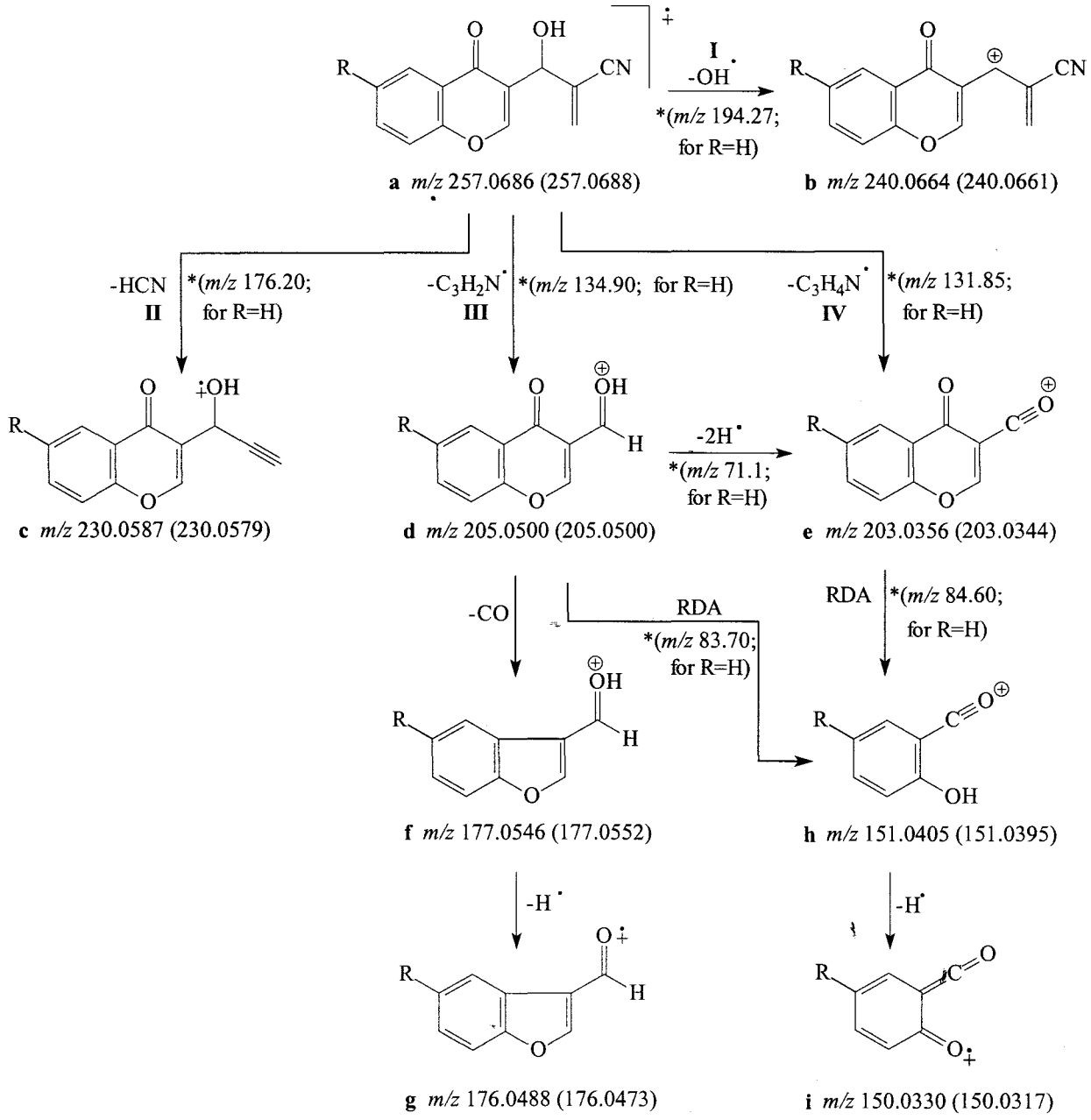
Paths III and IV converge with the formation of the acylium ions of type **h** - again the result of retro-Diels-Alder fission (see Figure 32). Elimination of carbon monoxide from ion **d**, followed by loss of a hydrogen atom, gives rise to ions **f** and **g** respectively, while loss of a hydrogen atom affords the odd-electron ketene species **i**.

Table 8: Selected peaks (*m/z*; followed, in parentheses, by % relative abundance) from EI mass spectra of the Morita-Baylis-Hillman products **160** (R=H), **162** (R=Cl), **165** (R=F) and **167** (R=OMe), classified according to ion types **a-i** (Scheme 50).



R	a	b	c	d	e
H	227 (68)	210 (53)	200 (18)	175 (100)	173 (49)
OMe	257 (75)	240 (48)	230 (10)	205 (100)	203 (45)
F	245 (57)	228 (51)	218 (15)	193 (100)	191 (63)
Cl	261 (52)	244 (46)	234 (14)	209 100)	207 (48)

R	f	g	h	i
H	147 (7)	146 (17)	121 (50)	120 (13)
OMe	177 (6)	176 (17)	151 (85)	150 (53)
F	-	164 (19)	139 (72)	138 (21)
Cl	-	180 (17)	-	154 (26)



Scheme 50: EI mass fragmentation pathways for **160** (R=H), **162** (R=Cl), **165** (R=F) and **167** (R=OMe): accurate masses (*m/z*) for the methoxy derivative **167** are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by the metastable peak given in parentheses.

2.3.6.2 Fragmentation patterns of the chromone dimers and bischromone-acrylonitrile adducts.

EI data for the fragmentation of the chromone dimers **147**, **153** and **155** are summarised in Table 9, and the proposed fragmentation pathways outlined in Schemes 51 and 52. In addition, low-resolution, electrospray MS^n data, acquired for comparative purposes, for the chromone dimer **147** are summarised in Figure 33.

In the case of the dimeric systems in general, the assignment of structures to the various *m/z* fragments is necessarily tentative, since common fragments, such as MeO•, CO and H•, could be lost from either monomeric unit. Interestingly, the electrospray MS^n spectra, which establish parent → daughter fragmentations (Figure 33) parallel closely the fragments observed in the high-resolution EI spectra (*e.g.* Figure 34). In correlating the data from both techniques, it has been assumed that there is a structural correspondence between the (high-resolution) EI fragments and the electrospray fragments having the same (nominal) *m/z* value.

From the low-resolution MS^n data for compound **147** (Figure 33), it is apparent that fragmentation of the molecular ion follows two pathways, I and II, which should be examined in conjunction with the high-resolution EI data in Schemes 51 and 52 respectively. Thus, in path I (Scheme 51), loss of a methoxy radical from the molecular ion (*m/z* 502) results in the formation of ions of type **b**. Sequential loss of carbon monoxide, methanol and another carbon monoxide molecule results in the formation of ions **d**, **e**, and **f** respectively. It is suggested that loss of methanol from ion **d** is accompanied by a skeletal rearrangement and formation of the allylic carbocation **e**. Elimination of a ketene moiety from the acylium ion **b** (as proposed in Scheme 51), followed by loss of a hydrogen atom, affords the resonance-stabilised radical cation **c** (*m/z* 350; R=H). In the electrospray spectrum, however, a peak is observed at *m/z* 351 (for R=H); presumably, under these conditions, the formation of radical species is not favoured, inhibiting loss of the hydrogen atom.

In path II (Scheme 52), fragmentation of the molecular ion (*m/z* 502) results in ion **g**, which loses a hydrogen atom to afford the acylium ion **h**, which accounts for the base

peak in both the parent compound and the fluoro analogue. Loss of a methyl radical from ion **g** affords the even-electron species **i**.

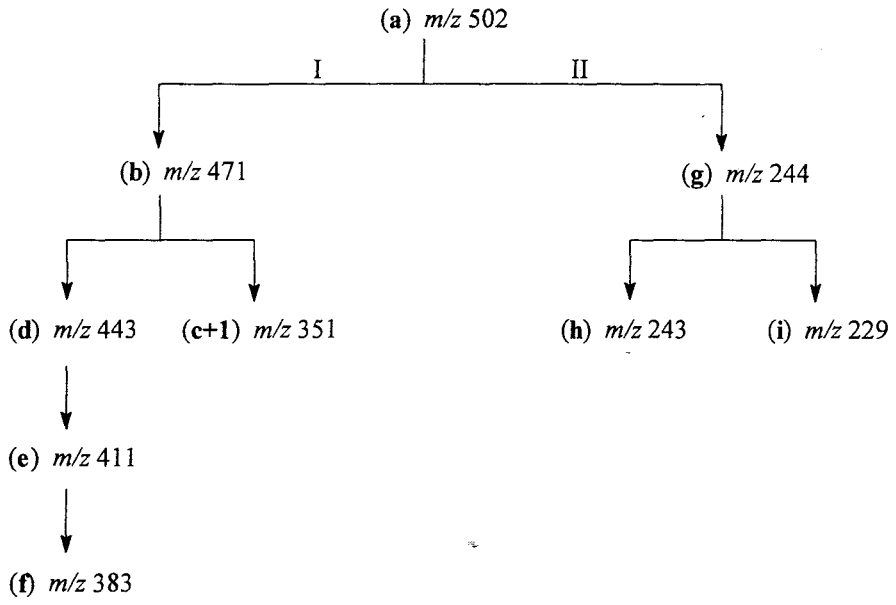


Figure 33: Electrospray MS^n fragmentation data for the chromone dimer **147**.

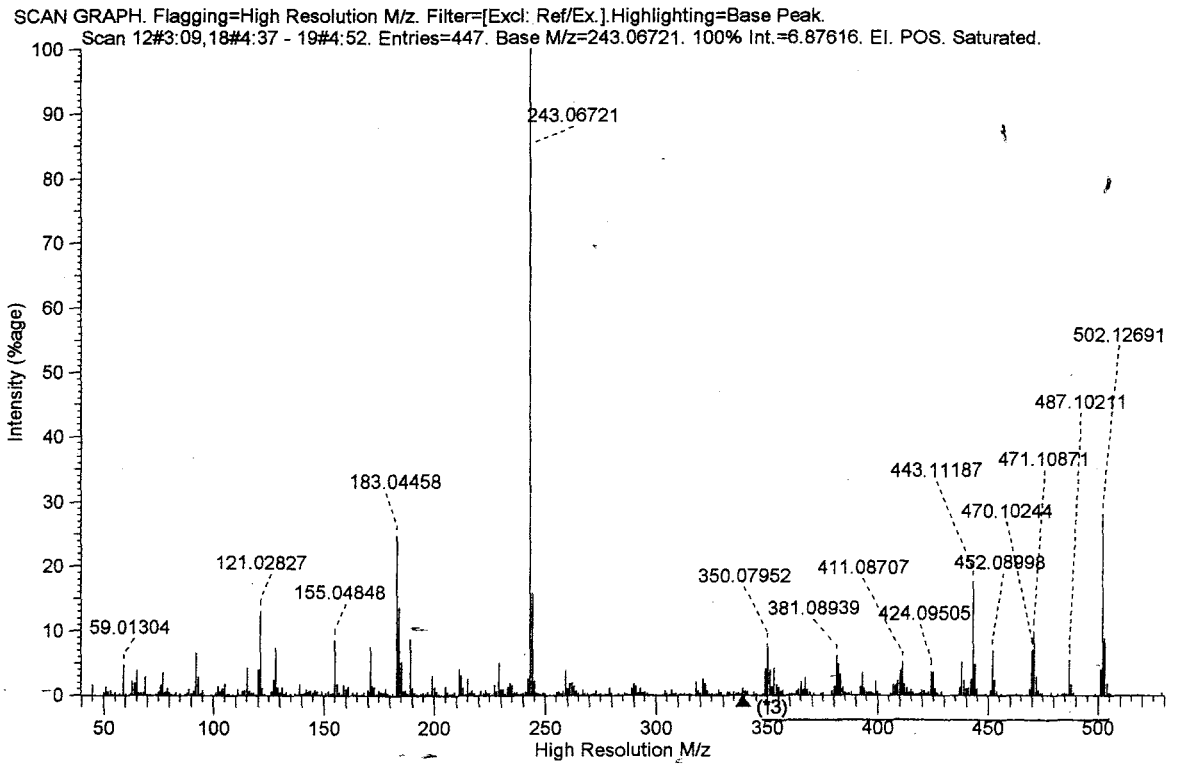
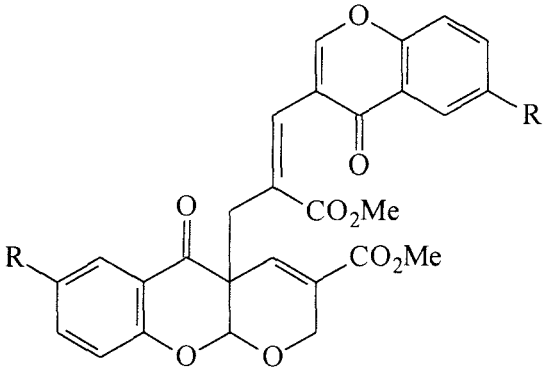


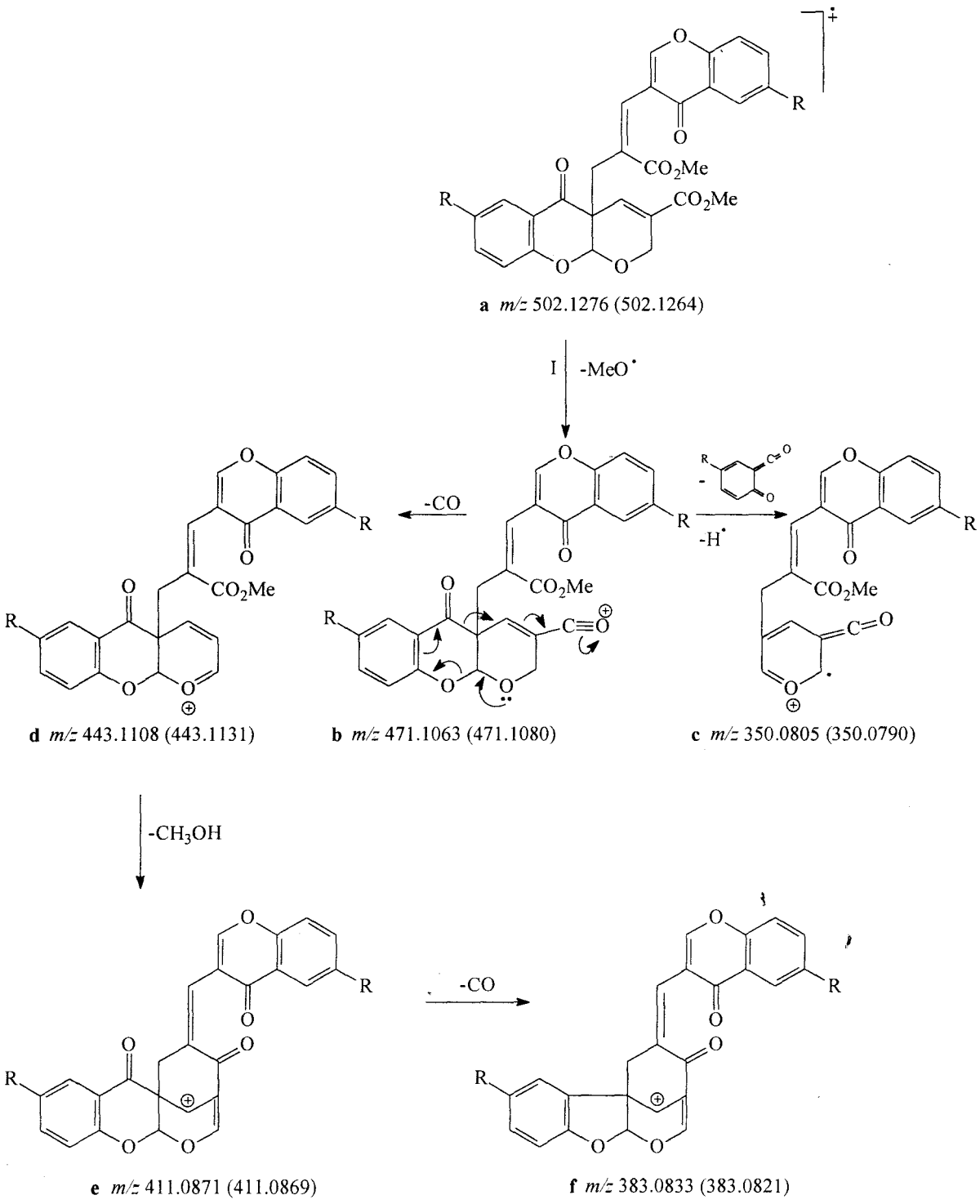
Figure 34: High-resolution EI spectrum of the chromone dimer **147**.

Table 9: Selected peaks (*m/z*; followed, in parentheses, by % relative abundance) from EI mass spectra of the chromone dimers **147** (R=H), **153** (R=F) and **155** (R=OMe), classified according to ion types **a-i** (Schemes 51 and 52).

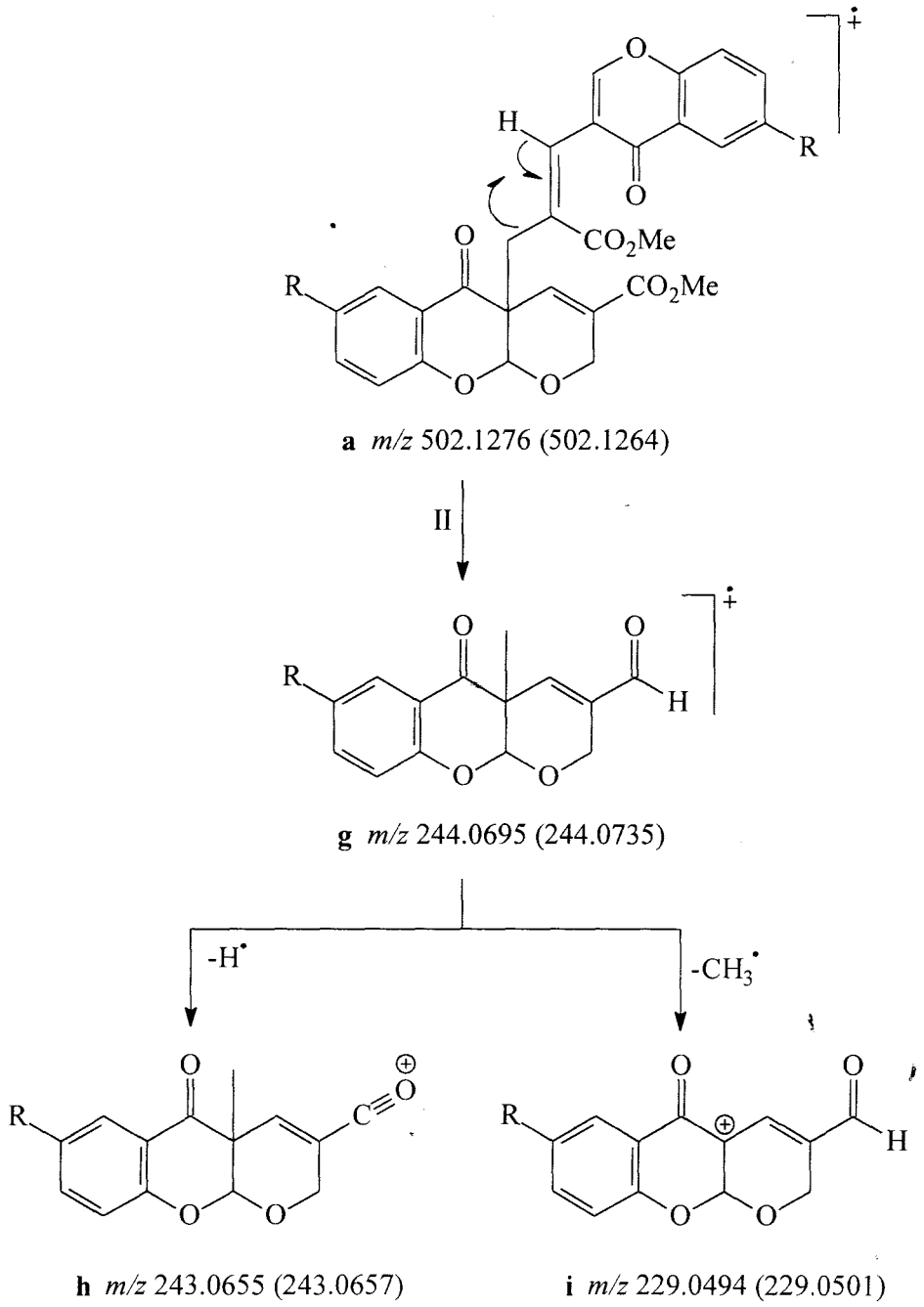


R	a	b	c	d	e
H	502 (24)	471 (4)	350 (3)	443 (7)	411 (2)
OMe	562 (37)	-	-	503 (19)	-
F	538 (21)	507 (5)	-	479 (7)	-

R	f	g	h	i
H	383 (1)	244 (17)	243 (100)	229 (6)
OMe	-	274 (43)	273 (59)	259 (27)
F	-	262 (19)	261 (100)	247 (10)



Scheme 51: EI mass fragmentation pathway I for the chromone dimers **147** (R=H), **153** (R=F) and **155** (R=OMe): accurate masses (*m/z*) for the parent dimer **147** are followed, in parentheses, by calculated formula masses. The mechanism proposed for the formation of ion **c** from ion **b** is also shown.



a *m/z* 502.1276 (502.1264)

g *m/z* 244.0695 (244.0735)

h *m/z* 243.0655 (243.0657)

i *m/z* 229.0494 (229.0501)

Scheme 52: EI mass fragmentation pathway II for the chromone dimers **147** (R=H), **153** (R=F) and **155** (R=OMe): accurate masses (*m/z*) for the parent dimer **147** are followed, in parentheses, by calculated formula masses.

Low-resolution electrospray MS^n analysis was also done on the bischromone-acrylonitrile adduct **161**, and Figure 35 illustrates the parent-daughter relationships observed. The following analysis has been limited to peaks for which reasonable structures and fragmentation pathways can be proposed. In some cases, EI peaks corresponding to electrospray fragments were not observed thus precluding high-resolution elemental analysis. High resolution EI analysis confirmed the atomic composition of ions **a**, **b**, **c** and **e**.

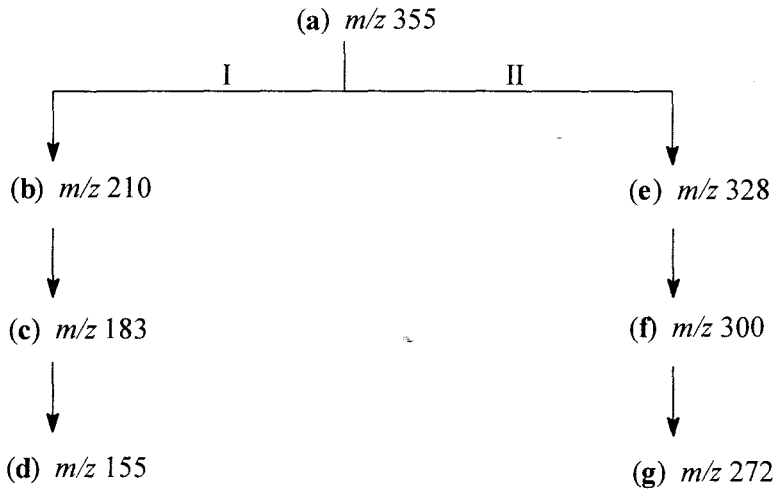
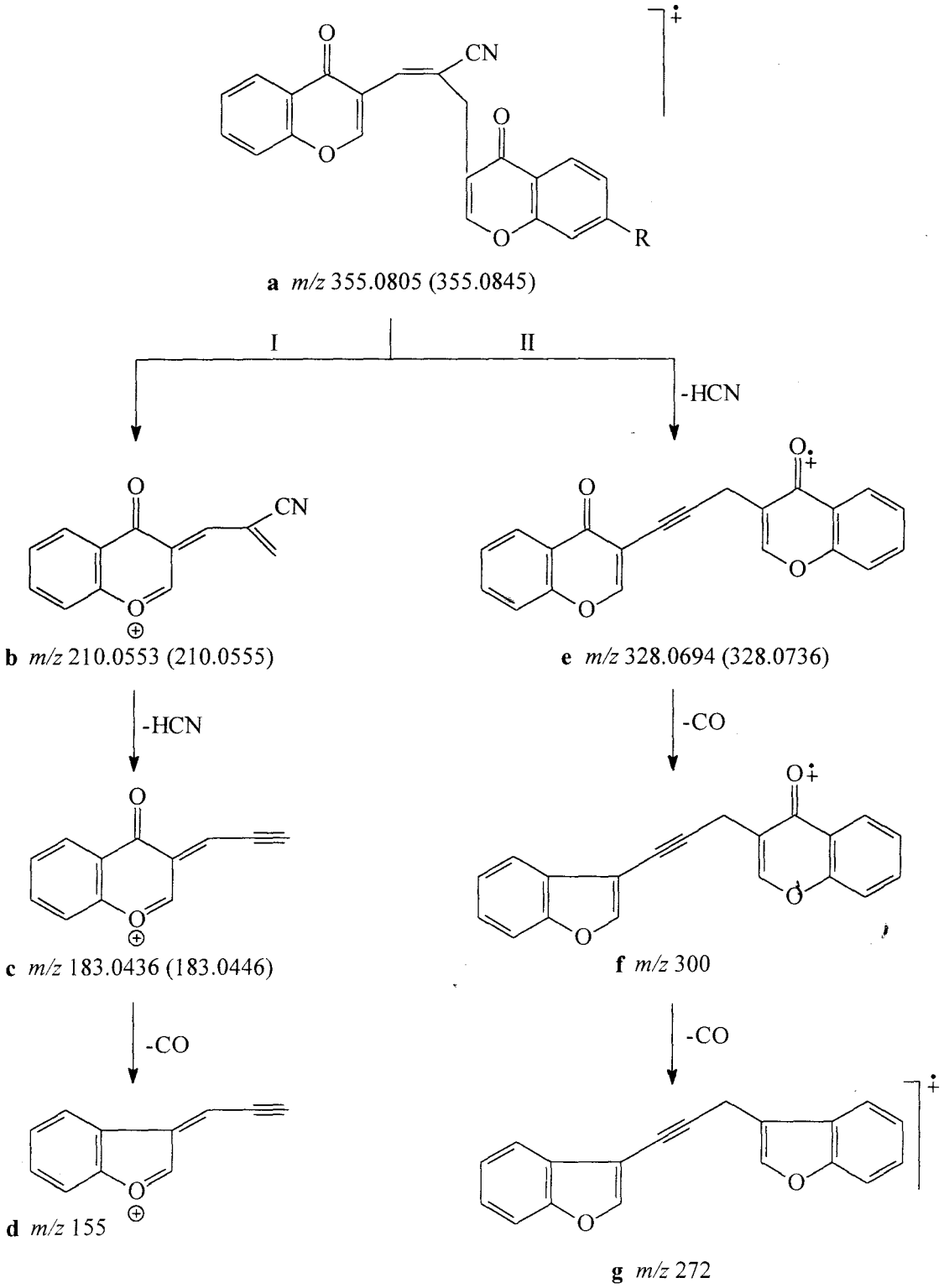


Figure 35: Electrospray MS^n fragmentation data for the bischromone-acrylonitrile adduct **161**.

Two fragmentation pathways in the electrospray spectrum of the bischromone-acrylonitrile adduct **161** are apparent, and these are outlined in Scheme 53. In path I, loss of a chromone moiety affords ions of type **b**. Successive loss of HCN and carbon monoxide then gives rise to ions of type **c** and **d**, while loss of HCN in path II affords ions of type **e**. Finally, tandem loss of carbon monoxide from each chromone nucleus would account for the benzofuran radical-cations **f** and **g**.

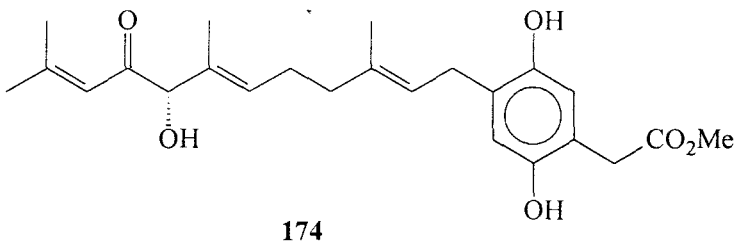


Scheme 53: Electrospray mass fragmentation pathways for the bischromone-acrylonitrile adducts **161** (R=H): accurate masses (*m/z*) from high-resolution EI analysis are followed, in parentheses, by calculated formula masses.

2.4 SYNTHETIC APPROACHES TO RIETONE A

Nature has long been the source of drugs used to alleviate human suffering. Penicillin, aspirin and morphine are just a few examples of the multitude of natural products which exhibit useful medicinal properties. In past years, the search for bioactive compounds has focussed mainly on terrestrial organisms. It is now believed that marine plants and animals constitute a vast, untapped reservoir for discovering new drugs to improve the treatment of human illnesses, particularly cancer. This is a logical deduction since sponges, sharks and most marine organisms don't seem to suffer from cancer and, in fact, have very few, if any, medical problems.[111] The search for potential pharmaceuticals has been the major occupation of marine natural products chemists for the past decade. Marine organisms produce some of the most cytotoxic compounds ever discovered, but the yields of these compounds are invariably so small that natural sources are unlikely to provide enough material for commercial development.[112] It is therefore the task of the synthetic chemist to develop efficient syntheses for these compounds.

Rietone A **174**, a sesquiterpene hydroquinone, has been isolated from the marine soft coral *Alcyonium fauri* off the warm, temperate, south-east coast of South Africa, and its structure has been determined by one- and two-dimensional NMR spectroscopy.[113] The strong anti-HIV reverse-transcriptase and cytotoxic activities of this compound have made it a worthy synthetic target.



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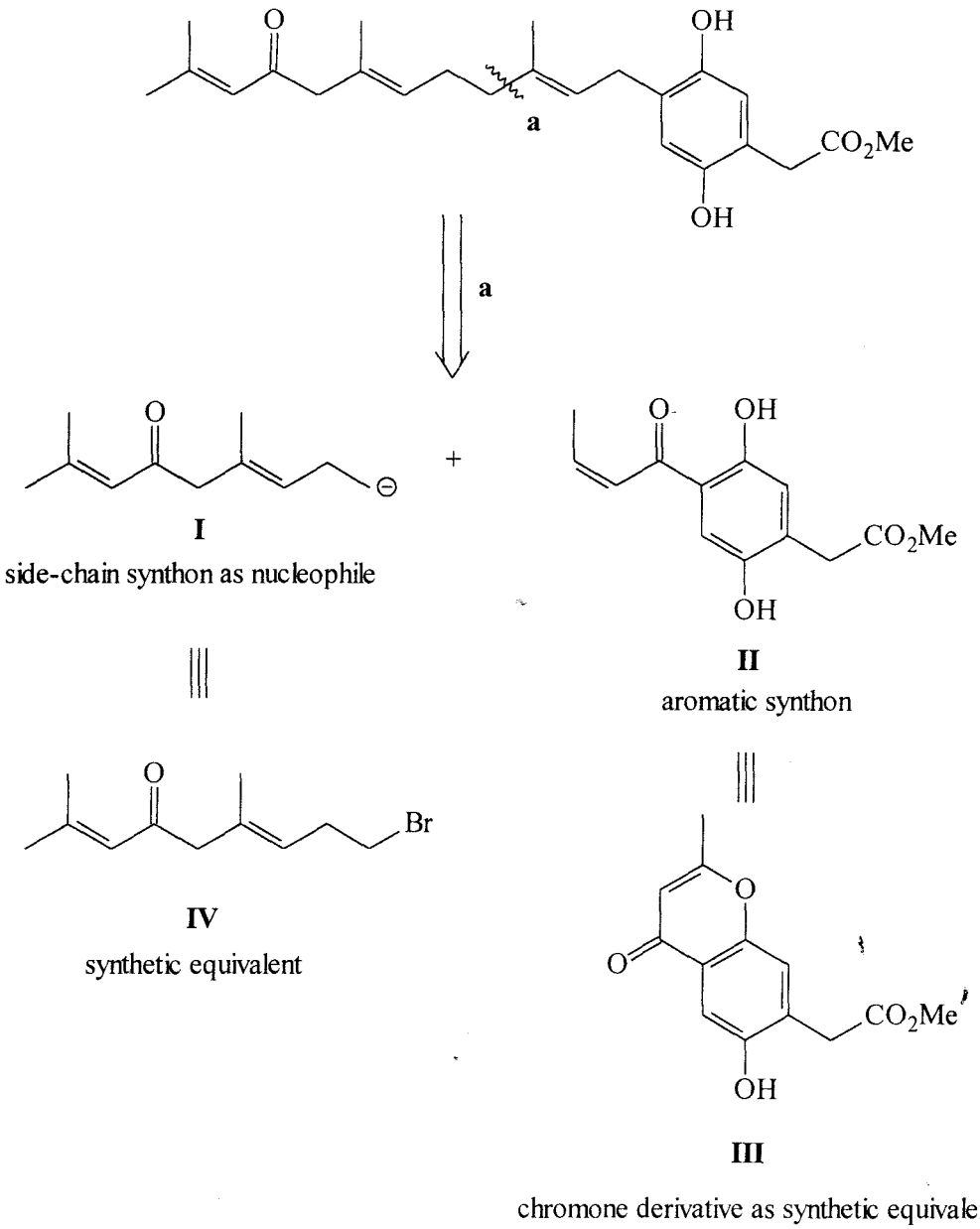
Chromones have been shown to readily undergo ring-opening following nucleophilic attack at C-2,[92,114] and it was envisaged that this property could be used as a key reaction in the construction of the Rietone A skeleton. Thus, disconnection **a** (Scheme 54) affords the side-chain nucleophile **I** and the aromatic moiety **II**, for which the chromone system **III**

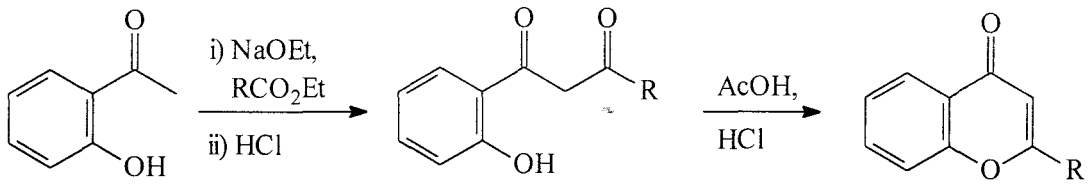
was identified as a possible synthetic equivalent. It was thus hoped that chromone chemistry could be used in a convergent synthesis of Rietone A.



Scheme 54

2.4.1 Preparation of chromone derivatives as synthetic equivalents for the aromatic synthon II

The susceptibility of chromones to attack by nitrogen and oxygen nucleophiles is well known,[114] and it was hoped that this methodology could be extended to include the use of carbon nucleophiles. To this end, 2-methylchromone **176** and ethyl chromone-2-carboxylate **178** were synthesised by the Kostanecki-Robinson method[115] (Scheme 55). The dicarbonyl compounds **175** and **177** were obtained by reaction of *o*-hydroxyacetophenone with the appropriate reagents; these intermediates were then treated with boiling glacial acetic acid to effect ring-closure to the substituted chromones **176** and **178**.

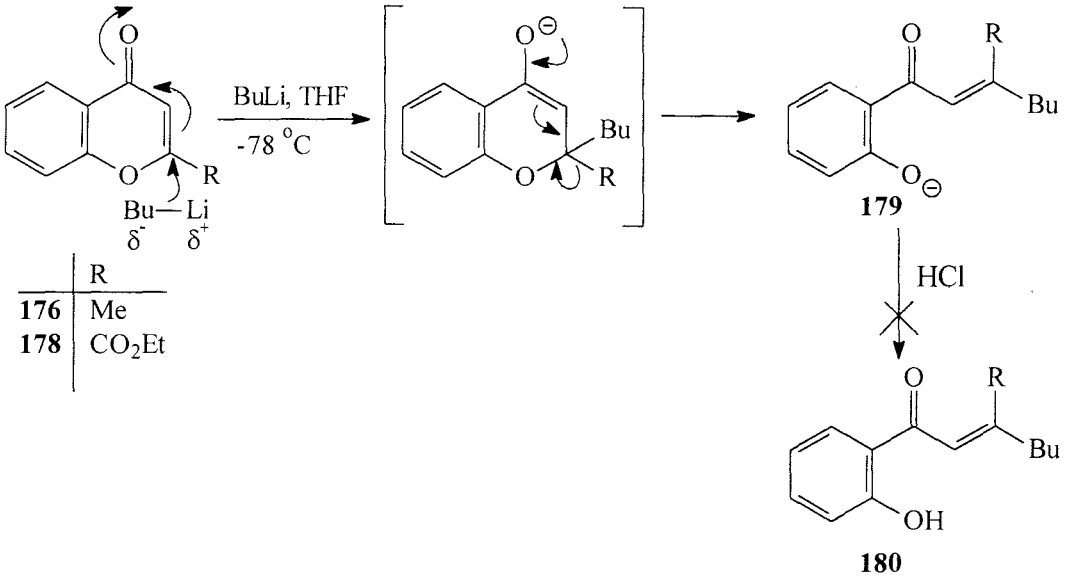


	R
175	Me
177	CO_2Et

	R
176	Me
178	CO_2Et

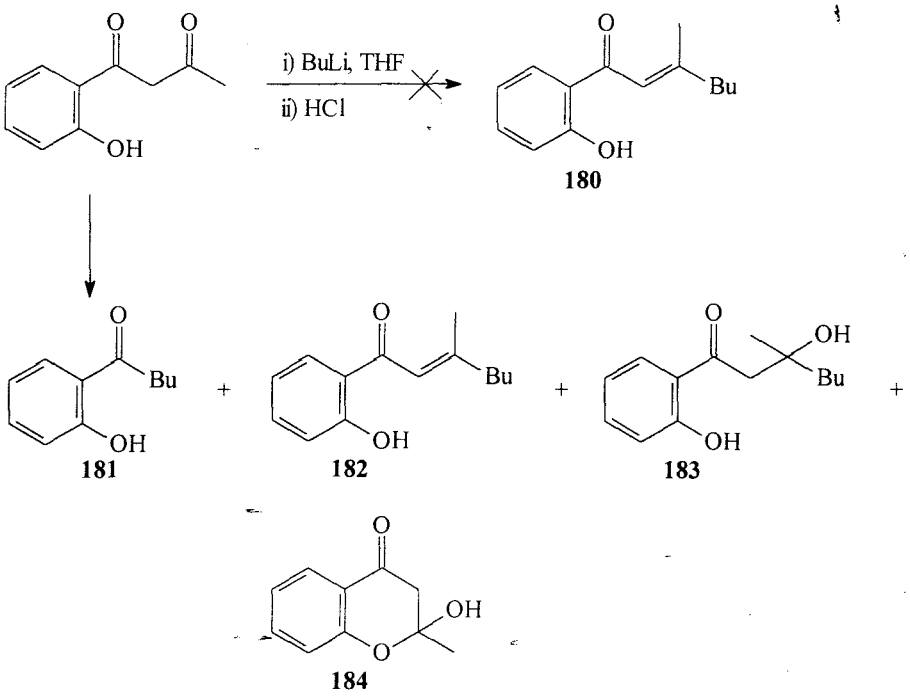
Scheme 55

Ring-opening of chromones **176** and **178** was explored using butyllithium in dry tetrahydrofuran at –78 °C (Scheme 56) but, in both instances, complex mixtures were produced which could not be separated chromatographically. An attempt to prevent side reactions by acetylation of the phenoxide anion **179** using acetyl chloride, prior to work-up, was unsuccessful.



Scheme 56

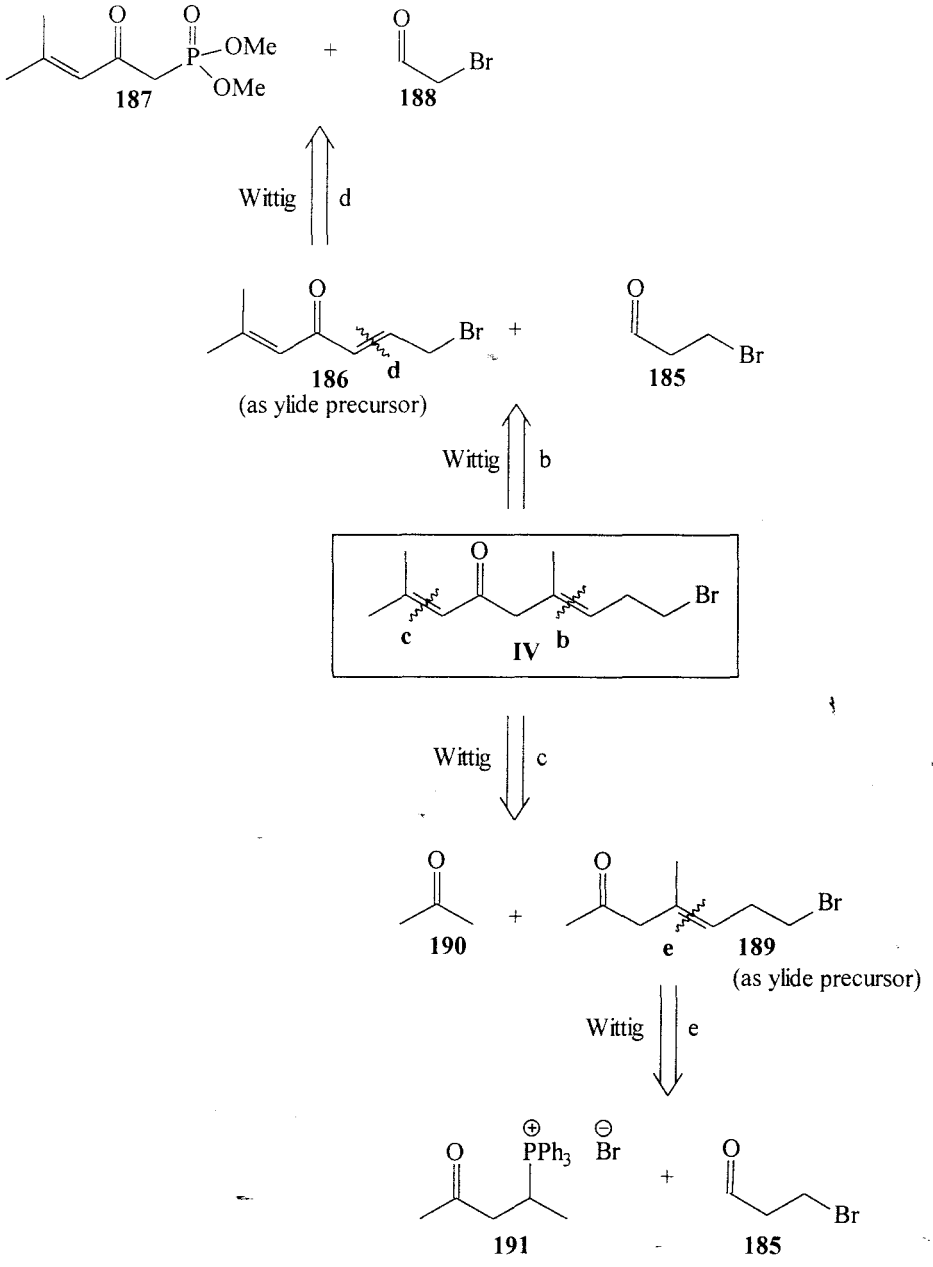
An alternative approach to compound **180** was then explored, in which the intermediate diketone **175** was treated directly with butyllithium in dry tetrahydrofuran at –78 °C (Scheme 57). However, this reaction yielded an oil indicated by ^{1}H NMR spectroscopy to contain a mixture of products **181**, **182**, **183** and **184**. In view of these difficulties, it was decided to continue with the synthesis of the side-chain equivalent **IV** and explore alternative approaches to the aromatic synthon **II**.



Scheme 57

2.4.2 Synthesis of the side-chain equivalent IV

It was expected that the bromoketone **IV**, suitably protected, could be used to generate a Grignard reagent and thus act as a synthetic equivalent for the side-chain nucleophile **I**. Consequently, a retrosynthetic analysis of the side-chain synthetic equivalent **IV** (Scheme 58) was undertaken which provided two possible initial disconnections, **b** and **c**.

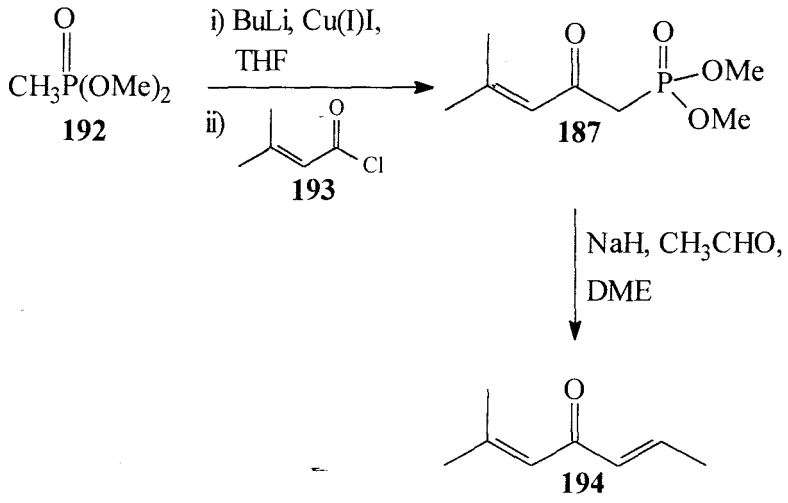


Scheme 58

In the first, disconnection **b** gives rise to synthetic equivalents **185** and **186**, and the latter may be further disconnected (**d**) to provide equivalents **187** and **188**. In the alternative strategy, disconnection **c** affords the synthetic equivalents **189** and **190**, of which **189** may be further disconnected (**e**) to give equivalents **185** and **191**. Both analyses outlined in Scheme 58 clearly involve extensive use of Wittig disconnections and were investigated concurrently.

2.4.2.1 Approaches to the unsaturated bromoketone **186** *(path b)*

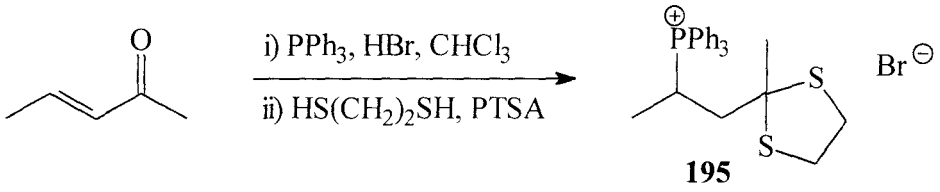
Dimethyl methanephosphonate **192** was treated with copper(I) iodide and butyllithium to generate the corresponding copper reagent *in situ*. This was then reacted with senecyl chloride **193** to produce the phosphonate synthon **187**, which, following treatment with sodium hydride, underwent a Wittig-type reaction with acetaldehyde to afford the unsaturated ketone **194** in 53% yield (Scheme 59).[116] The formation of this intermediate was confirmed by NMR spectroscopy. Preparation of the unsaturated bromoketone **186** then required either regioselective allylic bromination of intermediate **194**, or the use of bromoacetaldehyde **188** in place of acetaldehyde in the Wittig sequence outlined in Scheme 59. However in view of the difficulties encountered in the construction of the bromoaldehyde synthon **185** (discussed later), these options were not explored further.



Scheme 59

2.4.2.2 Approach to the unsaturated bromoketone 189 *(path c)*

Equivalent **191** was produced by Wittig reaction of 3-penten-2-one and triphenyl-phosphine.[117] However, due to its high reactivity (on reaction with base, it either dissociates into the starting materials or undergoes intermolecular cyclisation), it was necessary to mask the carbonyl group. Equivalent **191** was therefore isolated as the thioacetal **195** in 87% yield (Scheme 60).

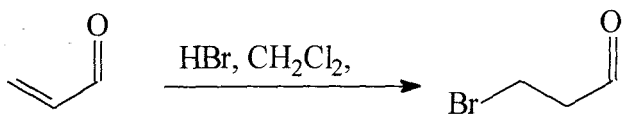


195

Scheme 60

2.4.2.3 Approaches to the bromoaldehyde 185 *(paths b and c)*

Several attempts were made to obtain the bromoaldehyde **185**. In the first, HBr gas was bubbled through a solution of acrolein[118] in dichloromethane (Scheme 61). Isolation of the product, however, proved to be problematic, since concentration of the solution containing the product is known to induce polymerisation. Moreover, while it was necessary to ensure that the reaction went to completion (since the presence of acrolein would interfere in the following step), extended reaction times are known to decrease the yield.[119] Despite variation of the concentration and reaction time and the use of dicinnamalacetone as an indicator,[119] attempts to isolate the bromoaldehyde **185** proved to be unsuccessful.

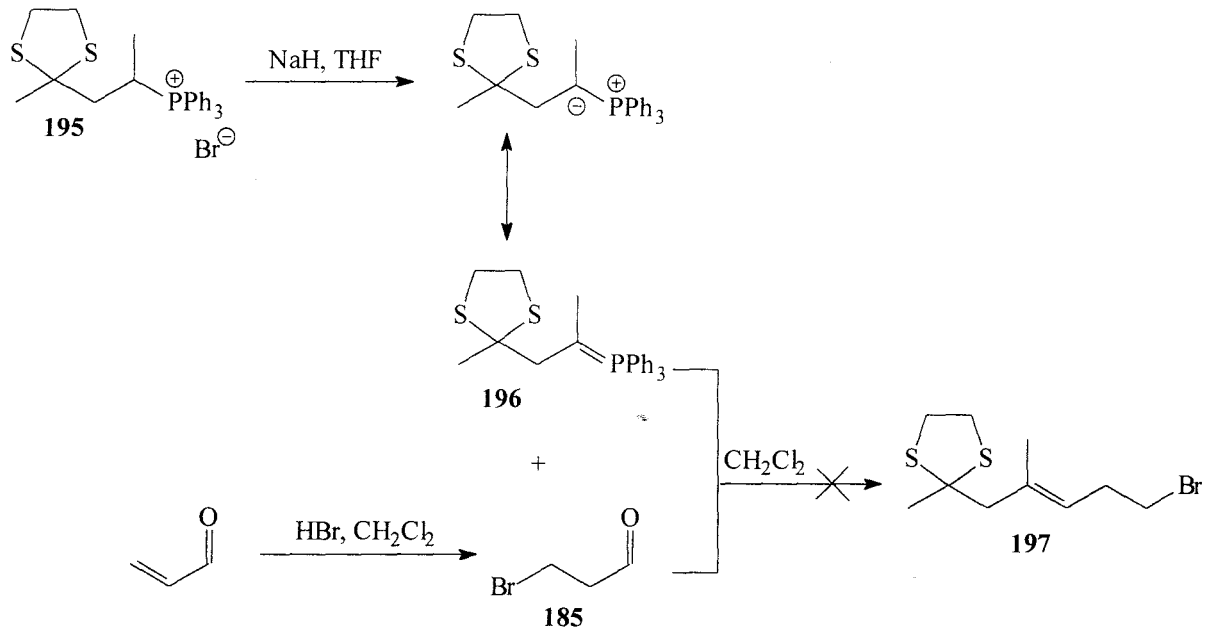


185

Scheme 61

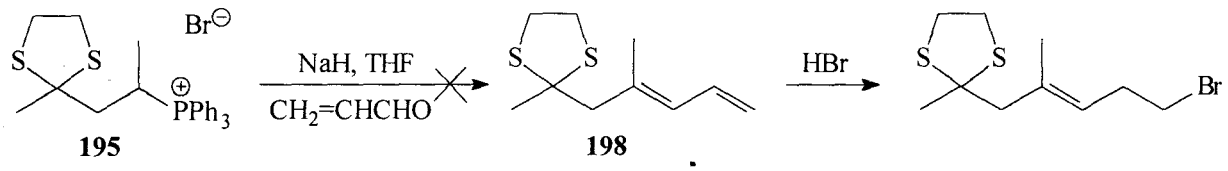
In order to circumvent the purification step, it was decided to carry out the Wittig reaction *in situ* in the dichloromethane solution.[120] To this end, the protected ylide **196** was

synthesised in 77% yield by adding sodium hydride to the phosphonium salt **195** (Scheme 62),[116] and then added to the crude 3-bromopropanal reaction mixture after bromination was complete (indicated by the colour change of dicinammalacetone). However, a multitude of products were formed which could not be readily separated by chromatography.



Scheme 62

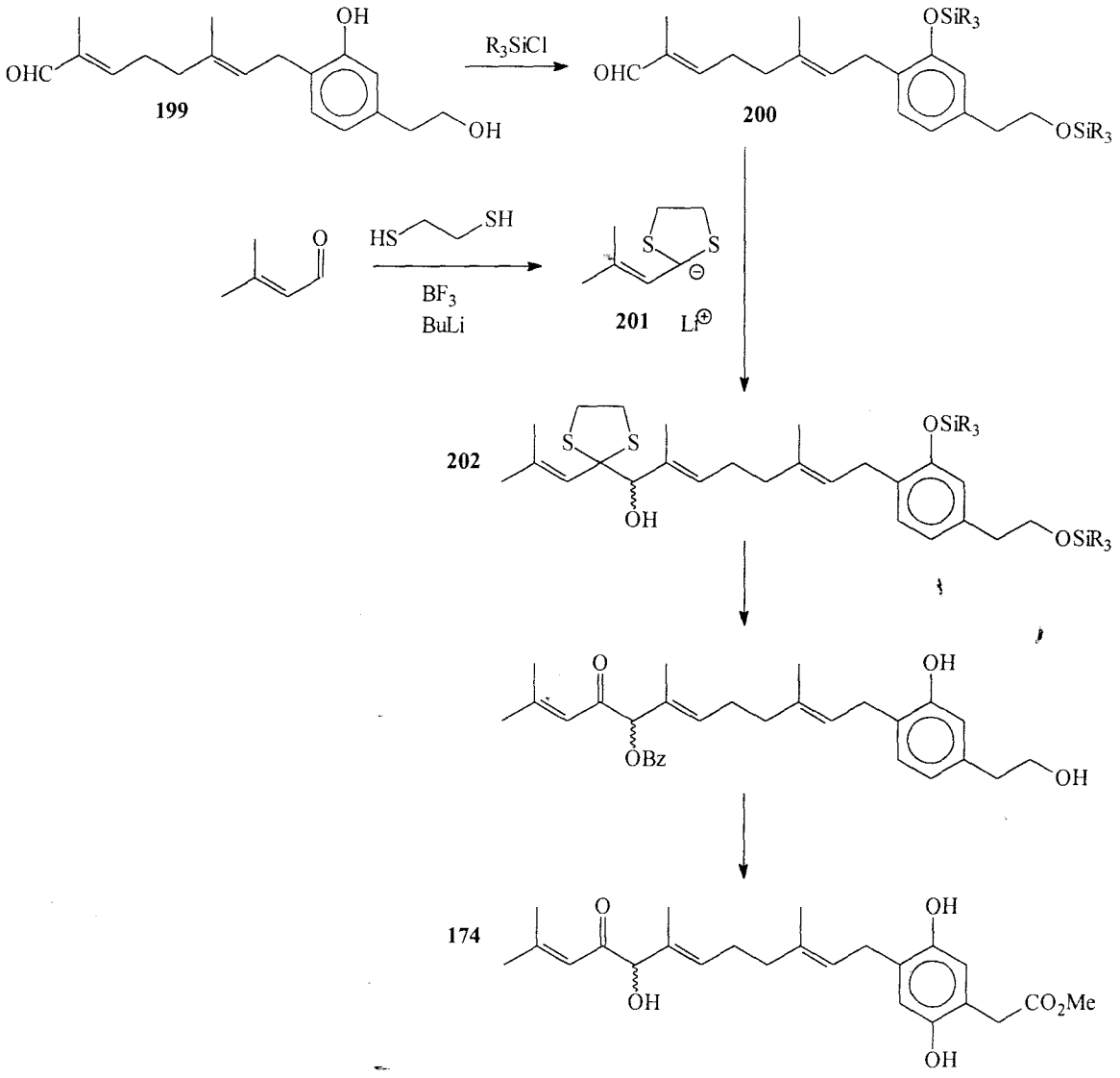
An attempt to overcome this problem by carrying out the Wittig reaction with acrolein (Scheme 63), and hydrobrominating the product was also unsuccessful. The product **198** was not formed, possibly due to conjugate addition of the ylide **196** to acrolein.



Scheme 63

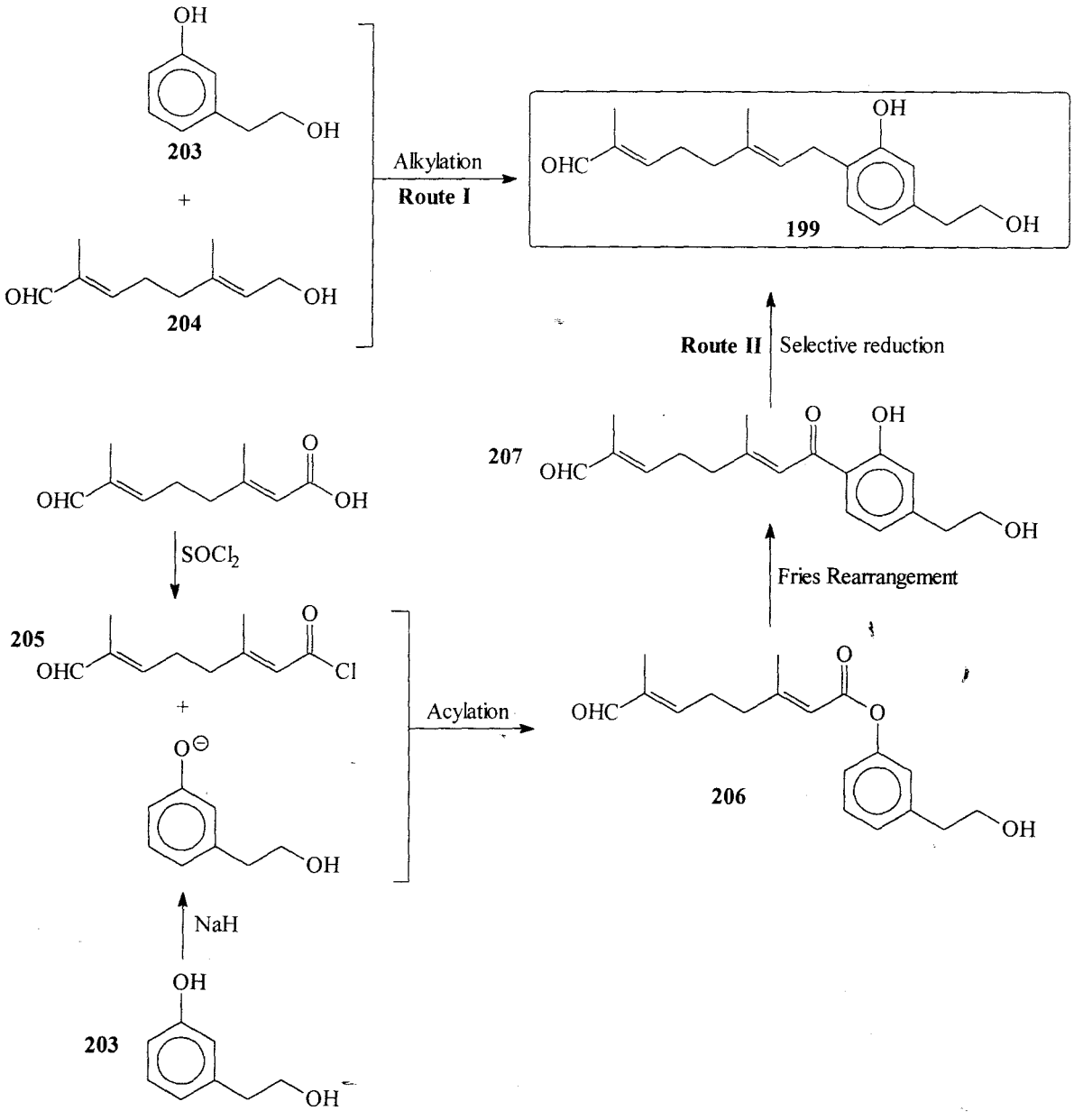
2.4.3 Alternative approach using geraniol and geranic acid

Due to the problems encountered with the synthetic route outlined in Scheme 54, an alternative pathway, which required the preparation of the key intermediate **199**, was explored (Scheme 64). This was expected to involve protection of the two hydroxyl groups, nucleophilic addition of the thioacetal **201** to the resulting disilyl ether **200** to afford compound **202**, which contains the required carbon skeleton. Further functional elaboration was expected to lead to the target molecule Rietone A **174**.



Scheme 64

Central to the success of this pathway, of course, is the synthesis of the aldehyde **199**, and two approaches were envisaged *viz.*, i) regioselective alkylation of 3-hydroxyphenethyl alcohol **203** with the alcohol **204** (Route I; Scheme 65), or ii) selective reduction of compound **207** which could be generated by Fries rearrangement of the phenolic ester **206**, accessible, in turn, *via* acylation of 3-hydroxyphenethyl alcohol **203** with the acid chloride **205** (Route II).

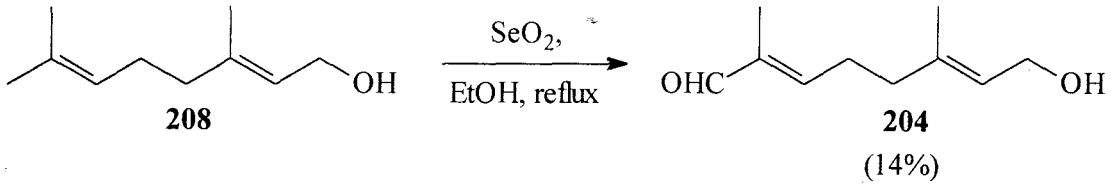


Scheme 65

It was decided to explore the more direct approach, *i.e.* Route I, first. This, of course, requires regioselective alkylation of the aryl system **203**.

2.4.3.1 Alkylation of 3-hydroxyphenethyl alcohol 203 *(Route I)*

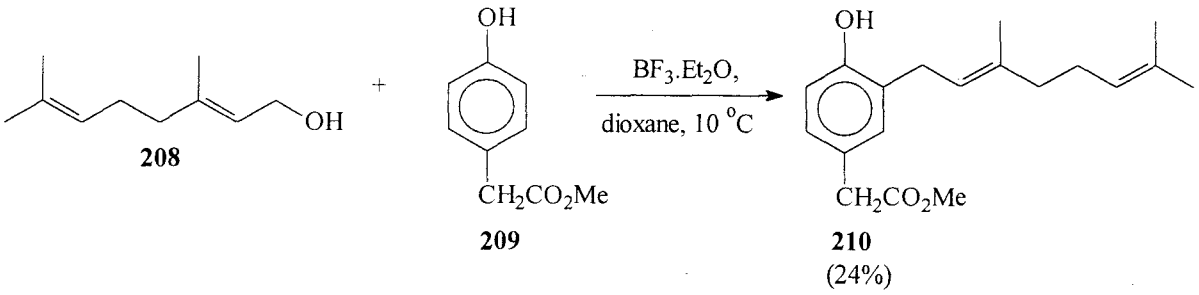
Preparation of the hydroxy aldehyde **204** was attempted by selenium dioxide oxidation of geraniol **208** (Scheme 66).[121,122] It was found that only by stirring the reaction mixture at room temperature, instead of refluxing as stated in the published procedure,[122] could the product be obtained. However, the yield of the required product was extremely low (14%), possibly due to oxidation at other active sites in the substrate molecule. It was therefore decided to explore the feasibility of the alkylation step (**203** + **204** → **199**) before attempting to optimise the oxidation (**208** → **204**).



208 **204** (14%)

Scheme 66

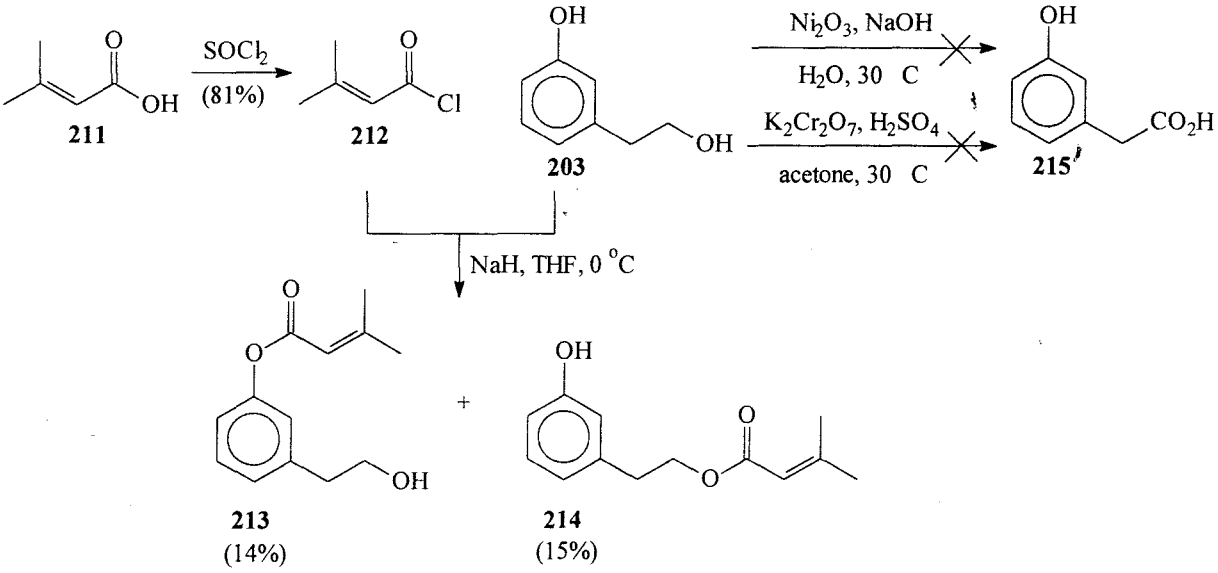
The alkylation step was investigated using commercially available geraniol **208** and the model compound methyl (4-hydroxyphenyl)acetate **209**, which was used instead of compound **203** for the purpose of simplification (Scheme 67). After many unsuccessful attempts to apply a patent procedure,[123] it was found that by carrying out the reaction at 10 °C instead of the reported 50 °C, the expected product **210** was obtained, albeit in 24% yield. When the reaction time was extended in order to increase the yield, an intractable mixture was obtained, which could not be purified by flash chromatography or by HPLC. It was therefore decided to examine formation of the desired compound *via* acylation and Fries rearrangement (Route II).



Scheme 67

2.4.3.2 Acylation of 3-hydroxyphenethyl alcohol 203 *(Route II)*

O-Acylation[101] of 3-hydroxyphenethyl alcohol **203** was effected using, as a model compound, 3,3-dimethylacryloyl chloride **212** (generated in 81% yield by addition of thionyl chloride to 3,3-dimethylacrylic acid **211**),[124] The acylation reaction, however, was not selective and both mono-acylated products **213** and **214** were obtained in 14% and 15% yield respectively (Scheme 68). The isomeric products were distinguished by two-dimensional NMR spectroscopy.

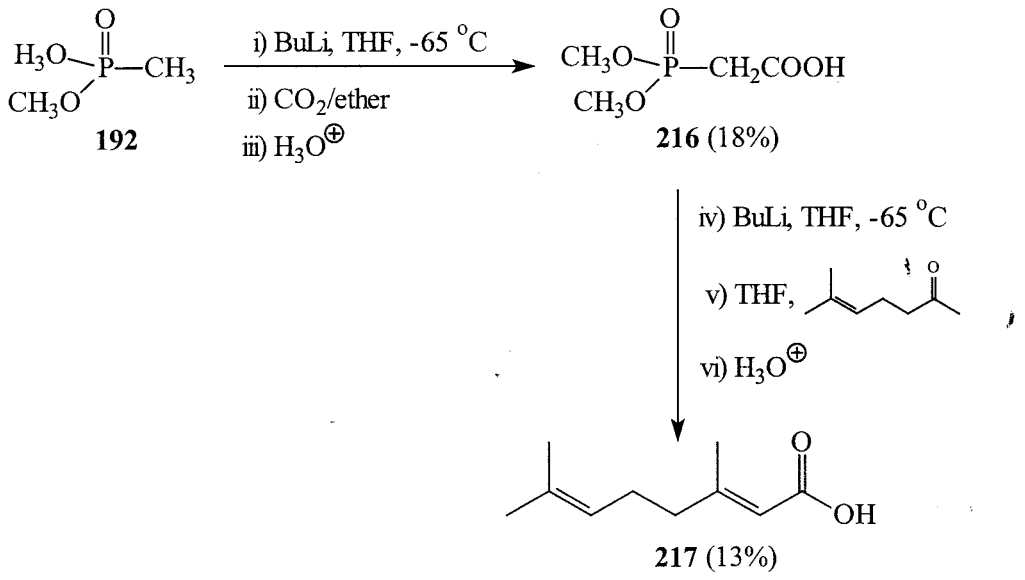


Scheme 68

It was then decided to oxidise the primary alcohol **203** before attempting the acylation of the phenolic hydroxy group thus avoiding the selectivity problem. However, attempts to

oxidise 3-hydroxyphenethyl alcohol **203** with nickel peroxide[125] and potassium dichromate[126] failed to produce the required acid **215**. 3,3-Dimethylacrylic acid was, of course, being used as a model for geranic acid **217**. However, since commercially available geranic acid is only available in 85% purity and as a mixture of isomers, synthesis of pure geranic acid by oxidation of geraniol **208** was investigated. However, use of Jones reagent[126] and silver oxide[127] both proved uncooperative.

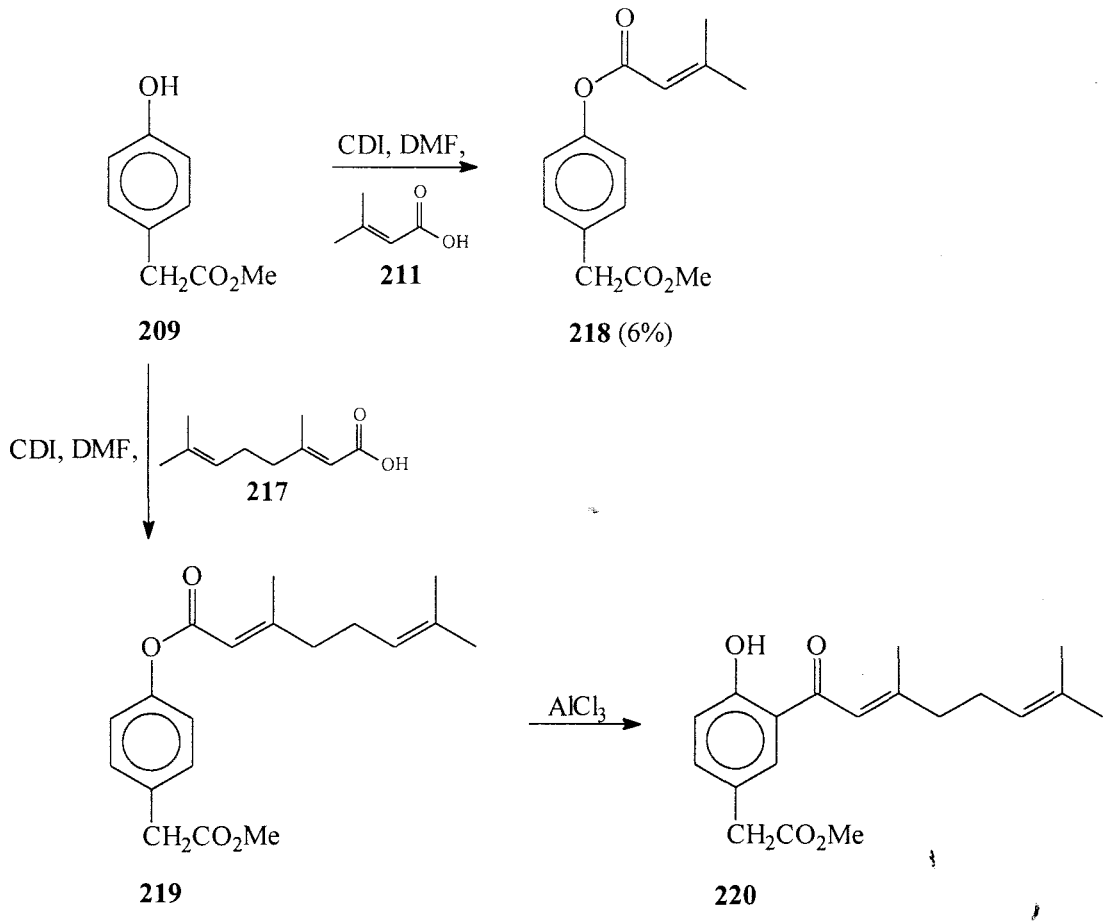
Given the failure of these attempts, an alternative approach to geranic acid **217** was examined. This involved carboxylation of dimethyl methanephosphonate **192** to give dimethyl carboxymethanephosphonate **216** in 18% yield. The disappointing result may be due to our use of butyllithium in hexane instead of diethyl ether as reported by Coutrot *et al.*[128] The acid **216** was then subjected to a Wittig-type reaction with 6-methyl-5-hepten-2-one to afford geranic acid **217** as a mixture of isomers, also in very low yield (13%) (Scheme 69).



Scheme 69

Exploratory studies into the acylation[129] of methyl (4-hydroxyphenyl)acetate **209** (using both the acid **211**, as a model compound, and the synthon **217**) and Fries rearrangement[101] of the resulting ester **219** (Scheme 70) were complicated by low yields and separation difficulties. Some spectroscopic evidence for the formation of compounds **219** and **220** was obtained, but unfortunately, due to time constraints, these reactions could not be

pursued. Future research will focus on the optimisation of the reaction conditions and an assessment of the synthetic viability of the various approaches to Rietone A explored thus far.



Scheme 70

2.5 CONCLUSIONS

Although not widely abundant in nature, chromones find many applications in the pharmaceutical industry, particularly in the treatment of asthma, and a 2-diethylamino-chromone has been shown to be potentially useful in the treatment of thrombolytic disorders.[5] In the present study, a series of substituted 2-(*N*,*N*-dimethylamino)chromones was successfully synthesised as substrates for a pK_a study, using two different approaches. In the first, the use of methyl salicylate precursors afforded the 2-(*N*,*N*-dimethylamino)chromones in yields ranging from 39 to 58%, while in the second, the use of boron difluoride complex intermediates gave the required 2-(*N*,*N*-dimethylamino)-chromones in yields ranging from 42 to 83% and in sufficient purity for the subsequent pK_a analysis. A potentiometric analysis of selected examples (compounds **77**, **86**, **105**, **108**, **111**, **114** and **117**) has provided insight into the effects of various substituents on the pK_a. The 2-(*N*,*N*-dimethylamino)chromones in question proved to be slightly more basic than chromone itself and, since protonation was shown by ^{13}C NMR spectroscopy and molecular orbital calculations to occur at the chromone carbonyl oxygen, this increased basicity has been attributed to additional stabilisation of the conjugate acid by delocalisation of the nitrogen lone pair. Moreover, the general trend in the pK_a values observed for the series of substituted 2-(*N*,*N*-dimethylamino)chromones has confirmed the general expectation that basicity should be increased by electron-releasing substituents and decreased by electron-withdrawing substituents. These results are supported by molecular orbital calculations at the semi empirical and *ab initio* level. The apparently anomalous result obtained for the 6-nitro derivative **86** has been rationalised in terms of field or hydrogen bonding effects, which may serve to stabilise the conjugate acid, thus resulting in a higher basicity than expected.

The relatively recent exploitation of the Morita-Baylis-Hillman reaction has prompted significant research interest. Much work has been done to establish the generality of the reaction for a variety of electrophiles, and the present investigation was aimed at bringing chromone-3-carbaldehydes into the scope of this reaction. To this end, a series of substituted chromone-3-carbaldehydes were prepared, using Vilsmeier-Haack methodology, in yields ranging from 40 to 69%. The application of these compounds in the Morita-Baylis-Hillman reaction was investigated using DABCO as catalyst and three

different activated alkenes, *viz.*, methyl acrylate, methyl vinyl ketone and acrylonitrile. In all cases (with the exception of 6-nitrochromone-3-carbaldehyde), the expected products were obtained, albeit, initially in low yield. In addition, each of the reactions with methyl acrylate and methyl vinyl ketone was observed to afford an unexpected dimer, which was isolated in all but one case. The formation of these dimers has been tentatively rationalised in terms of a six-centred transition state complex arising from nucleophilic attack of the hydroxyl group of one monomer, at C-2 of the other. The structures of these dimers, the formation of which appears to be unprecedented, were established using a combination of single crystal X-ray and spectroscopic analysis.

When the reaction was carried out with acrylonitrile, however, three of the systems investigated afforded different dimer-like adducts which were characterised using high resolution MS and one- and two-dimensional NMR techniques. Formation of these bischromone-acrylonitrile adducts has been proposed to involve initial attack of DABCO at the electrophilic centre, C-2, of one chromone ring to form a zwitterionic intermediate, which then attacks the Morita-Baylis-Hillman product present in the reaction mixture; elimination of formylated DABCO from a resulting intermediate then gives the bischromone-acrylonitrile adduct.

Although initial yields of the Morita-Baylis-Hillman products were low, kinetic studies showed that this need not be the case if reaction times are shortened. Reaction of chromone-3-carbaldehyde **7**, 6-chlorochromone-3-carbaldehyde **136** and 6-methoxy-chromone-3-carbaldehyde **142** with methyl acrylate and 2 equivalents of DABCO each afforded the corresponding Morita-Baylis-Hillman product in excess of 85% yield after a reaction period of 16 days or less (rather than the several weeks used initially). The use of 5 equivalents of 3-hydroxyquinuclidine as catalyst in the reaction of chromone-3-carbaldehyde **7** with acrylonitrile produced the Morita-Baylis-Hillman product in 92% yield after 22 hours, while the reaction of chromone-3-carbaldehyde **7** with acrylonitrile at elevated temperature, in the absence of a solvent reduced the reaction time to 1 hour! Conversion of the Morita-Baylis-Hillman products to the corresponding "dimers" was shown to take place readily and, on application of heat, the conversion was essentially complete after 3 hours. The Morita-Baylis-Hillman reaction has therefore been shown to be a viable synthetic method for the generation of polyfunctional alkylated chromone

derivatives, which also provide convenient access to the corresponding dimers and bischromone-acrylonitrile adducts.

The investigation into the synthesis of the marine natural product, Rietone A, was initially expected to involve application of chromone synthetic methodology. Although this approach proved to be unsuccessful, preliminary results obtained for the synthesis of a key intermediate **199** (Scheme 62), in an alternative strategy, show some potential for the development of a viable synthetic pathway to Rietone A.

Future research is expected to focus on:-

(1) Application of microwave irradiation and ultrasound to improve conversion efficiency in the Morita-Baylis-Hillman reaction.

(2) Application of 2-substituted chromone-3-carbaldehydes in the Morita-Baylis-Hillman reaction to direct nucleophilic attack to the formyl carbon.

(3) A more detailed comparison of the EI and electrospray fragmentation pathways of the dimeric products of the Morita-Baylis-Hillman reaction.

(4) Optimisation of reaction conditions for the synthesis of intermediate **199** with a view to achieving a total synthesis of Rietone A.

3. EXPERIMENTAL

3.1 GENERAL

All melting points were determined using a Kofler hot-stage apparatus. NMR spectra were recorded on a Bruker AMX400 spectrometer at 303 K in $CDCl_3$. Spectra recorded in $CDCl_3$ were calibrated on the chloroform signal at 7.25ppm for ^1H and 77.0ppm for ^{13}C. Infra-red spectra were recorded on a Perkin Elmer FT-IR Spectrum 2000 spectrometer, the samples being analysed as KBr discs, or as a thin film on CsI discs. Low-resolution mass spectroscopy was carried out on a Finnigan GCQ mass spectrometer using the electron ionisation (EI) mode.

HPLC was effected on a Whatman Partisil 10 Magnum 6 normal phase column using a Spectra-Physics P100 Isocratic pump and a Waters RI410 differential refractometer detector. Flash chromatography was carried out using Merck silica gel 60 (particle size 0.040 – 0.063mm) and preparative layer chromatography with Merck silica gel 60 PF_{254}. Chromatotron plates were made with silica gel 60 PF_{254} containing $CaSO_4$.

All dry solvents were prepared by conventional methods described by Perrin and Armarego.[130]

(1) Et_2O and THF were pre-dried over CaH_2 and then distilled from Na wire and benzophenone under N_2.

(2) EtOH was dried by reaction with Mg turnings and iodine and then distilled from the resulting MgOEt under N_2.

(3) $CHCl_3$, CH_2Cl_2 and 1,2-dichloroethane were distilled from $CaCl_2$ under N_2.

(4) Acetone was distilled from 3A molecular sieves under N_2.

(5) 1,2-Dimethoxyethane (DME) and dioxane were distilled from Na wire and benzophenone under N_2.

(6) CS_2 was distilled from $CaCl_2$.

(7) *N*,*N*-dimethylformamide (DMF) was distilled from 3A molecular sieves under reduced pressure.

3.2 PREPARATION AND pK_a ANALYSIS OF 2-(*N,N*-DIMETHYLAMINO)-4*H*-1-BENZOPYRAN-4-ONES

3.2.1 Preparation of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-ones from methyl salicylates

N,N-*Dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamide*[99] **76**

Butyllithium (1.5-**M** solution in hexane; 50ml, 75mmol) was added dropwise to a solution of dry, distilled diisopropylamine (8.5ml, 75mmol) in dry THF (80ml) under dry N_2 at 0 °C, and the resulting solution stirred for 40 min. *N,N*-Dimethylacetamide (3.48ml, 37.5mmol) was then added and the solution stirred for 30 min before adding methyl salicylate (**75**) (4.94ml, 23.4mmol) in THF (5ml) at 0 °C. The resulting solution was stirred overnight at room temperature, cooled, neutralized with 10% HCl and then extracted with CH_2Cl_2 (3 x 150ml). The combined organic extracts were dried over anhydrous $MgSO_4$ and the solvent was evaporated *in vacuo*. The residue was then triturated with Et_2O and filtered to afford *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxo-propanamide **76** (2.7g, 56%), m.p. 66-68 °C (lit.,[99] 71-73 °C); υ_{max} (KBr)/cm^{-1} 3450 (OH), 1640 (CO) and 1630 (CO); δ_H (400 MHz; $CDCl_3$) 2.99 and 3.06 (6H, 2 x s, NMe_2), 4.10 (2H, s, CH_2), 6.90 (1H, t, *J* 7.2 Hz, 5-H), 6.97 (1H, d, *J* 8.5 Hz, 3-H), 7.47 (1H, m, 4-H) 7.81 (1H, dd, *J* 1.4 and 8.1 Hz, 6-H) and 11.90 (1H, br s, OH); *m/z* 207 (M^+, 100%).

*2-(*N,N-*Dimethylamino)-4*H-*1-benzopyran-4-one*[99] **77**

Method 1

Triflic anhydride (7.30ml, 43.4mmol) was added to a solution of *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamide **76** (2.50g, 12.1mmol) in dry CH_2Cl_2 (60ml), and the solution stirred overnight at room temperature. The solvent was then evaporated, the residue dissolved in MeOH and the resulting solution stirred for 4 h. The MeOH was then evaporated and the residue diluted with half-saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 70ml). The combined organic extracts were washed with saturated aq. NaCl (70ml) and dried over anhydrous $MgSO_4$, and the solvent was evaporated *in vacuo* to afford an oil (1.69g) which was chromatographed [flash chromatography on silica gel; elution with MeOH-CH_2Cl_2 (5:95)] to afford 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (0.90g, 39%), m.p. 121-123 °C (lit.[99] 123.5-124.5 °C); υ_{max} (KBr)/cm^{-1} 1620 (CO);

δ_H (400 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 5.40 (1H, s, 3-H), 7.28 (2H, m, 6-H and 8-H), 7.51 (1H, m, 7-H) and 8.14 (1H, dd, *J* 1.5 and 7.9 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.4 (NMe_2), 86.1 (C-3), 116.2 and 124.5 (C-6 and C-8), 122.9 (C-4a), 125.5 (C-5), 131.8 (C-7), 153.7 (C-8a), 163.0 (C-2) and 176.4 (C-4); *m/z* 189 (M^+, 100%).

Methyl 5-chlorosalicylate[98] **79**

A solution of 5-chlorosalicylic acid **78** (10g, 58mmol) and $POCl_3$ (5ml) in MeOH (50ml) was boiled under reflux for 5 h. The solution was allowed to cool, and the solid precipitate was filtered off to afford methyl 5-chlorosalicylate **79** (5.9g, 55%), m.p. 42-44 °C (lit.,[98] 43-50 °C); υ_{max} (KBr)/cm^{-1} 3200 (OH) and 1660 (CO); δ_H (400 MHz; $CDCl_3$) 3.94 (3H, s, OCH_3), 6.91 (1H, d, *J* 8.9 Hz, 3-H), 7.38 (1H, dd, *J* 2.7 and 8.9 Hz, 4-H), 7.79 (1H, d, *J* 2.6 Hz, 6-H) and 10.63 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 52.5 (OCH_3), 113.2 (C-1), 119.1 (C-3), 123.9 (C-5), 129.2 (C-6), 135.6 (C-4), 160.1 (C-2) and 169.6 (CO); *m/z* 186 (M^+, 100%).

N,N-*Dimethyl-3-(5-chloro-2-hydroxyphenyl)-3-oxopropanamide*[99] **80**

The experimental procedure employed for the synthesis of *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamide **76** was followed using butyllithium (42ml, 62mmol), dry, distilled diisopropylamine (8.8ml, 62mmol) in dry THF (50ml), *N,N*-dimethylacetamide (2.9ml, 31mmol) and methyl 5-chlorosalicylate **79** (3.62g, 19.4mmol). Work-up afforded *N,N*-dimethyl-3-(5-chloro-2-hydroxyphenyl)-3-oxopropanamide **80** (0.75g, 16%), m.p. 110-112 °C (from hexane-EtOAc) (lit.,[100] 106 – 108 °C); υ_{max} (KBr)/cm^{-1} 3400 (OH), 1640 (CO) and 1630 (CO); δ_H (400 MHz; $CDCl_3$) 3.01 and 3.09 (6H, 2 x s, NMe_2), 4.05 (2H, s, CH_2), 6.95 (1H, d, *J* 9.0 Hz, 3-H), 7.41 (1H, dd, *J* 2.6 and 8.9 Hz, 4-H) and 7.78 (1H, d, *J* 2.5 Hz, 6-H); *m/z* 241 (M^+, 100%).

*2-(*N,N-*Dimethlyamino)-6-chloro-4*H*-1-benzopyran-4-one*[99] **81**

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** was followed, using *N,N*-dimethyl-3-(5-chloro-2-hydroxyphenyl)-3-oxopropanamide **80** (1.5g, 6.2mmol), triflic anhydride (3.76ml, 22.4mmol) and dry CH_2Cl_2 (30ml). Work-up afforded *2-(N,N*-dimethylamino)-6-chloro-4*H*-1-benzopyran-4-one **81** (0.80g, 58%), m.p. 158-160 °C (from EtOAc) (lit.,[100] 158 – 160 °C); υ_{max} (KBr)/cm^{-1} 1610

(CO); δ_H (400 MHz; $CDCl_3$) 3.10 (6H, s, NMe_2), 5.40 (1H, s, 3-H), 7.25 (1H, d, *J* 8.8 Hz, 8-H), 7.46 (1H, dd, *J* 2.6 and 8.8 Hz, 7-H) and 8.11 (1H, d, *J* 2.6 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 86.1 (C-3), 117.8 (C-8), 124.0 (C-6), 125.2 (C-5), 130.4 (C-4a), 131.9 (C-7), 152.0 (C-2), 163.0 (C-8a) and 175.0 (C-4); *m/z* 223 (M^+, 100%).

Methyl 5-bromosalicylate[98] **83**

A solution of 5-bromosalicylic acid **82** (13g, 58mmol) and $POCl_3$ (5ml) in MeOH (50ml) was boiled under reflux for 5 h. The solution was allowed to cool, and the solid precipitate was filtered off to afford methyl 5-bromosalicylate **83** (12g, 89%), m.p. 54-55 °C (lit.,[131] 61 °C); υ_{max} (KBr)/cm^{-1} 3450 (OH) and 1680 (CO); δ_H (400 MHz; $CDCl_3$) 3.96 (3H, s, OCH_3), 6.87 (1H, d, *J* 8.9 Hz, 3-H), 7.50 (1H, dd, *J* 2.5 and 8.9 Hz, 4-H), 7.92 (1H, d, *J* 2.6 Hz, 6-H) and 10.40 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 52.5 (OCH_3), 110.8 (C-1), 113.8 (C-5), 119.5 (C-3), 132.2 (C-6), 138.4 (C-4), 160.5 (C-2) and 169.4 (CO); *m/z* 230 (M^+, 100%).

N,N-*Dimethyl-3-(5-bromo-2-hydroxyphenyl)-3-oxopropanamide*[99] **84**

The experimental procedure employed for the synthesis of *N,N*-dimethyl-3-(2-hydroxyphenyl)-3-oxopropanamide (**76**) was followed using butyllithium (42ml, 62mmol), dry, distilled diisopropylamine (8.8ml, 62mmol) in dry THF (50ml), *N,N*-dimethylacetamide (2.9ml, 31mmol) and methyl 5-chlorosalicylate **79** (3.62g, 19.4mmol). Work-up afforded *N,N*-dimethyl-3-(5-bromo-2-hydroxyphenyl)-3-oxopropanamide **84** (2.8g, 51%), m.p. 78-80 °C (from hexane-EtOAc); υ_{max} (KBr)/cm^{-1} 3450 (OH), 1640 (CO) and 1630 (CO); δ_H (400 MHz; $CDCl_3$) 3.01 and 3.09 (6H, 2 x s, NMe_2), 4.08 (2H, s, CH_2), 6.89 (1H, d, *J* 8.9 Hz, 3-H), 7.55 (1H, dd, *J* 2.3 and 8.9 Hz, 4-H) and 7.90 (1H, d, *J* 2.4 Hz, 6-H); *m/z* 285 (M^+, 100%).

*2-(*N,N-*Dimethlyamino)-6-bromo -4*H*-1-benzopyran-4-one*[99] **85**

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** was followed, using *N,N*-dimethyl-3-(5-bromo-2-hydroxyphenyl)-3-oxopropanamide **84** (1.5g, 5.3mmol), triflic anhydride (3.18ml, 18.9mmol) and dry CH_2Cl_2 (60ml). Work-up afforded *2-(N,N*-dimethylamino)-6-bromo-4*H*-1-benzopyran-4-one **85** (0.59g, 42%), m.p. 145-147 °C (lit.,[99] 151.5 – 152 °C); υ_{max} (KBr)/cm^{-1} 1630 (CO); δ_H (400 MHz; $CDCl_3$) 3.07 (6H, s, NMe_2), 5.29 (1H, s, 3-H), 7.09 (1H, d, *J* 8.8 Hz, 8-H), 7.50

(1H, dd, *J* 2.4 and 8.8 Hz, 7-H) and 8.18 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.4 (NMe_2), 85.9 (C-3), 117.6 (C-8), 118.1 (C-5), 124.3 (C-6), 128.0 (C-4a), 134.5 (C-7), 152.3 (C-2), 162.8 (C-8a) and 174.7 (C-4); *m/z* 267 (M^+, 100%).

*2-(*N,N-*Dimethylamino)-6-nitro-4*H-*1-benzopyran-4-one*[100] **86**

Conc. HNO_3 (0.23ml, 5.7mmol) and cold conc. H_2SO_4 (1.50ml) were added to a solution of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (1.1g, 6.0mmol) in conc. H_2SO_4 (7.5ml) cooled in an ice bath. The resulting solution was poured onto ice, basified with Na_2CO_3, and the precipitated solid filtered off to give 2-(*N,N*-dimethylamino)-6-nitro-4*H*-1-benzopyran-4-one **86** (0.95g, 68%), m.p. 218-220 °C (from EtOH) (lit.,[100] 216 – 218 °C); υ_{max} (KBr)/cm^{-1} 1630 (CO) and 1560 and 1380 (NO_2); δ_H (400 MHz; $CDCl_3$) 3.15 (6H, s, NMe_2), 5.44 (1H, s, 3-H), 7.40 (1H, d, *J* 9.1 Hz, 8-H), 8.35 (1H, dd, *J* 2.8 and 9.0 Hz, 7-H) and 9.01 (1H, d, *J* 2.8 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.8 (NMe_2), 86.4 (C-3), 117.7 (C-8), 122.2 (C-5), 123.6 (C-4a), 126.6 (C-7), 144.8 (C-6), 156.6 (C-2), 162.9 (C-8a) and 174.2 (C-4); *m/z* 234 (M^+, 100%).

3.2.2 Preparation of substituted 2-hydroxyacetophenones

4-Bromophenyl acetate[102] **88**

Ac_2O (8.70ml, 92.2mmol) was added to a stirred solution of 4-bromophenol **87** (10.0g, 57.8mmol) and NaOH (3.70g, 92.5mmol) in H_2O (70ml), maintained at 0 °C in an ice-salt bath. After stirring for 1 h, the resulting solution was extracted with EtOAc (3 x 50ml); the combined organic extracts washed sequentially with 5% aq. $NaHCO_3$ (2 x 50ml) and saturated aq. NaCl (50ml), and then dried over anyhydrous $MgSO_4$. The solvent was evaporated *in vacuo* to afford a yellow oil which was distilled to give 4-bromophenyl acetate **88** (9.8g, 79%), b.p. 74-75 °C/0.7mmHg (lit.,[132] 81 – 82 °C/13mmHg); ν_{max}(thin film)/cm^{-1} 1760 (CO); δ_H (400 MHz; $CDCl_3$) 2.29 (3H, s, CH_3), 7.04 (1H, ddd, 6-H), 7.23 (1H, t, *J* 8.1 Hz, 5-H), 7.28 (1H, t, *J* 1.9 Hz, 2-H) and 7.36 (1H, ddd, 4-H); δ_C (100 MHz; $CDCl_3$) 21.0 (CH_3), 120.4 (C-6), 122.3 (C-3), 125.1 (C-2), 129.0 (C-4), 130.4 (C-5), 151.2 (C-1) and 168.9 (CO); *m/z* 214 (M^+, 100%).

4-Bromo-2-hydroxyacetophenone[101] **89**

A stirred mixture of 4-bromophenyl acetate **88** (9.80g, 45.6mmol) and anhydrous $AlCl_3$ (20.0g, 150mmol) was heated in an oil bath at 160 °C for 3 h. The cooled reaction mixture was then treated with 2 **M**-HCl (110ml) and steam distilled until no more product was collected. The distillate was extracted with $CHCl_3$ (3 x 55ml). The $CHCl_3$ extracts were combined and then extracted with 0.5 **M**-KOH (3 x 50ml). The aqueous solution was washed with $CHCl_3$ (3 x 50ml), acidified and then re-extracted with $CHCl_3$ (3 x 50ml). The combined organic extracts were dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo* to afford an oil which was distilled to give 4-bromo-2-hydroxy-acetophenone **89** (4.1g, 42%), m.p. 38-42 °C (lit.,[101] 42-43 °C); ν_{max}(thin film)/cm^{-1} 3450 (OH) and 1640 (CO); δ_H (400 MHz; $CDCl_3$) 2.59 (3H, s, CH_3), 7.01 (1H, dd, *J* 1.9 and 8.5 Hz, 5-H), 7.15 (1H, d, *J* 1.9 Hz, 3-H), 7.35 (1H, d, *J* 8.6 Hz, 6-H) and 12.32 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 26.6 (CH_3), 118.6 (C-4), 121.6 (C-3), 122.4 (C-5), 130.7 (C-1), 131.6 (C-6), 162.8 (C-2) and 203.9 (CO); *m/z* 214 (M^+, 100%).

4-Fluorophenyl acetate[102] **91**

The experimental procedure employed for the synthesis of 4-bromophenyl acetate **88** was followed, using Ac_2O (14.8ml, 157mmol), 4-fluorophenol **90** (10.0g, 89.3mmol) and NaOH (5.20g, 155mmol) in H_2O (100ml). Work-up afforded an oil which was distilled to give 3-fluorophenyl acetate **91** (11g, 79%), b.p. 37-39 °C/0.6mmHg (lit.,[133] 81 – 82 °C/13mmHg); ν_{max}(thin film)/cm^{-1} 3450 (OH) and 1640 (CO); δ_H (400 MHz; $CDCl_3$) 2.30 (3H, s, CH_3), 6.89 (3H, m, 2-H, 4-H and 6-H) and 7.32 (1H, dd, *J* 8.2 and 6.6 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 21.0 (CH_3), 109.7 (C-2), 112.8 (C-4), 117.3 (C-6), 130.1 (C-5), 151.5 (C-1), 162.9 (C-3) and 169.0 (CO); *m/z* 154 (M^+, 100%).

4-Fluoro-2-hydroxyacetophenone[101] **92**

The experimental procedure employed for the synthesis of 4-bromo-2-hydroxy-acetophenone **89** was followed, using 4-fluorophenyl acetate **91** (9.0g, 58.4mmol) and $AlCl_3$ (18.6g, 139mmol). Work-up afforded an oil which crystallised to give 4-fluoro-2-hydroxyacetophenone **92** (6.4g, 71%), m.p. 27-29 °C (lit.,[133] 24 °C); ν_{max}(thin film)/cm^{-1} 3400 (OH) and 1640 (CO); δ_H (400 MHz; $CDCl_3$) 2.59 (3H, s, CH_3), 6.58 (2H, m, 3-H and 5-H), 7.70 (1H, dd, *J* 6.5 and 8.8 Hz, 6-H) and 12.55 (1H, s, OH); δ_C (100 MHz;

$CDCl_3$) 26.4 (CH_3), 104.8 (C-3), 107.1 (C-5), 116.8 (C-1), 133.0 (C-6), 164.9 (C-2), 167.4 (C-4) and 203.2 (CO); *m/z* 154 (M^+, 100%).

4-Chlorophenyl acetate[102] **94**

The experimental procedure employed for the synthesis of 4-bromophenyl acetate **88** was followed, using Ac_2O (10.4ml, 100mmol), 4-chlorophenol **93** (10.0g, 77.8mmol) and NaOH (4.40g, 110mmol) in H_2O (75ml). Work-up afforded an oil which was distilled to give 4-chlorophenyl acetate **94** (11g, 85%), b.p. 54-56 °C/0.2mmHg (lit.,[132] 109 °C/ 13mmHg); ν_{max}(thin film)/cm^{-1} 3400 (OH) and 1640 (CO); δ_H (400 MHz; $CDCl_3$) 2.29 (3H, s, CH_3), 6.99 (1H, ddd, 6-H), 7.12 (1H, t, *J* 2.0 Hz, 2-H), 7.20 (1H, ddd, 4-H) and 7.29 (1H, t, *J* 8.1 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 20.9 (CH_3), 119.9 (C-6), 122.2 (C-2), 126.0 (C-4), 130.1 (C-5), 134.6 (C-3), 151.1 (C-1) and 168.9 (CO); *m/z* 170 (M^+, 100%).

4-Chloro-2-hydroxyacetophenone[101] **95**

The experimental procedure employed for the synthesis of 4-bromo-2-hydroxy-acetophenone **89** was followed, using 4-chlorophenyl acetate **94** (10.0g, 58.7mmol) and $AlCl_3$ (18.6g, 139mmol). Work-up afforded an oil which was distilled to give 4-chloro-2-hydroxyacetophenone **95** (5.5g, 55%), b.p. 56 °C/0.4mmHg (lit.,[101] 121-124°C/15mmHg); ν_{max}(thin film)/cm^{-1} 3450 (OH) and 1640 (CO); δ_H (400 MHz; $CDCl_3$) 2.60 (3H, s, CH_3), 6.87 (1H, dd, *J* 2.0 and 8.6 Hz, 5-H), 6.98 (1H, d, *J* 2.0 Hz, 3-H), 7.64 (1H, d, *J* 8.6 Hz, 6-H) and 12.36 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 26.6 (CH_3), 118.3 (C-4), 118.5 (C-3), 119.6 (C-5), 131.6 (C-6), 142.2 (C-1), 163.1 (C-2) and 203.7 (CO); *m/z* 170 (M^+, 100%).

2-Hydroxy-4-methoxyacetophenone[103] **97**

A mixture of resacetophenone **96** (10.0g, 65.8mmol), Me_2SO_4 (4.80ml, 50.7mmol), dry acetone (100ml) and K_2CO_3 (10.2g, 73.8mmol) was boiled under reflux for 6 h. The resulting solution was allowed to cool and the acetone removed under reduced pressure. The excess Me_2SO_4 was destroyed with a 25% ammonia-ice mixture (50ml). The resulting solution was then extracted with EtOAc (3 x 60ml); the combined organic solutions were dried over anhydrous $MgSO_4$, evaporated *in vacuo* and distilled to afford 2-hydroxy-4-methoxyacetophenone **97** (5.9g, 71%), b.p. 58 °C/0.1mmHg, m.p. 46-47 °C (lit.,[103] 48 °C);

ν_{max}(KBr)/cm^{-1} 3450 (OH) and 1620 (CO); δ_H (400 MHz; $CDCl_3$) 2.54 (3H, s, $CO.CH_3$), 3.82 (3H, s, OCH_3), 6.41 (1H, dd, *J* 2.5 and 4.3 Hz, 5-H), 6.44 (1H, d, *J* 2.5 Hz, 3-H), 7.62 (1H, d, *J* 8.7 Hz, 6-H) and 12.72 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 26.2 ($CO.CH_3$), 55.5 (OCH_3), 100.9 (C-3), 107.6 (C-5), 113.9 (C-1), 132.3 (C-6), 165.3 (C-2), 166.1 (C-4) and 202.5 (CO); *m/z* 166 (M^+, 100%).

2-Hydroxy-5-methoxyacetophenone[104] **99**

Acetyl chloride (8.90ml, 125mmol) and anhydrous $AlCl_3$ (18.7g, 140mmol) were added to a cold solution of 1,4-dimethoxybenzene **98** (18.7g, 136mmol) in dry CS_2 (50ml). The resulting mixture was stirred for 24 h; the CS_2 was distilled off and dry Et_2O (150ml) and anhydrous $AlCl_3$ (66.7g, 500mmol) were added to the residue. The mixture was boiled under reflux for 12 h and, after cooling, cautiously poured over ice and stirred. The Et_2O layer was separated off and the aqueous layer shaken with more Et_2O. The combined ethereal solutions were shaken with aqueous NaOH, while the combined aqueous layers were acidified with 10% HCl and then re-extracted with Et_2O (3 x 100ml). All of the Et_2O extracts were then combined, dried over anhydrous $MgSO_4$ and evaporated to afford 2-hydroxy-5-methoxyacetophenone **99** (17.3g, 83%), m.p. 45-46 °C (lit.,[104] 47-48 °C); ν_{max}(KBr)/cm^{-1} 3450 (OH) and 1610 (CO); δ_H (400 MHz; $CDCl_3$) 2.60 (3H, s, $COCH_3$), 3.80 (3H, s, OCH_3), 6.91 (1H, d, *J* 9.0 Hz, 3-H), 7.09 (1H, dd, *J* 3.0 and 9.0 Hz, 4-H), 7.16 (1H, d, *J* 3.1 Hz, 6-H) and 11.85 (1H, s, OH); δ_C (100 MHz; $CDCl_3$) 26.7 ($COCH_3$), 56.0 (OCH_3), 113.5 (C-6), 119.2 (C-3), 124.1 (C-4), 151.7 (C-1), 156.8 (C-1 and C-5) and 204.0 (CO); *m/z* 166 (M^+, 100%).

3.2.3 Preparation of 2-(*N*,*N*-dimethylamino)-4*H*-1-benzopyran-4-ones *via* phosgen-iminium salt intermediates

2-Hydroxyacetophenone boron difluoride complex[9] **101**

$BF_3.OEt_2$ (7.86ml, 62.6mmol) was added to a solution of 2-hydroxyacetophenone **100** (7.22ml, 60.0mmol) in dry Et_2O (60ml) under dry N_2. The resulting mixture was stirred at room temperature for 1 h, before filtering off the solid material, which was washed with Et_2O (45ml) to give the 2-hydroxyacetophenone boron difluoride complex **101** (7.3g, 66%), m.p. 145-146 °C (lit.,[9] 143-144.5 °C); ν_{max}(KBr)/cm^{-1} 1630 (CO); δ_H (400 MHz;

$CDCl_3$) 2.87 (3H, s,$COCH_3$), 7.03 (1H, m ArH), 7.10 (1H, dd, *J* 0.8 and 9.0 Hz, ArH) and 7.76-7.80 (2H, m, ArH).

*3-Chloro-3-(*N,N-*dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex*[9] **102**

A suspension of 2-hydroxyacetophenone boron difluoride complex **101** (5.66g, 30.8mmol) and *N,N*-dimethyldichloromethyleniminium chloride (5.26g, 32.4mmol) in dry 1,2-dichloroethane (100ml) was heated at 80 °C for 2 h under dry N_2. The mixture was then cooled to 0 °C and the resulting solid was filtered off and washed with cold 1,2-dichloro-ethane (45ml) and Et_2O (50ml) to afford crude 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex **102** [(6.1g, 72%), ν_{max}(KBr)/cm^{-1} 1630 (CO); δ_H (400 MHz; $CDCl_3$) 3.11 (6H, s, NMe_2), 5.41 (1H, s, 2-H), 7.31 (2H, m, 3'-H and 5'-H), 7.52 (1H, t, *J* 7.7 Hz, 4'-H) and 8.16 (1H, d, *J* 8.2 Hz, 6'-H)], which was used without further purification.

*2-(*N,N-*Dimethylamino)-4*H-*1-benzopyran-4-one*[9] **77**

Method 2

A solution of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex **102** (6.00g, 22.0mmol) in MeOH (200ml) was stirred at 50 °C for 45 min. The solvent was then evaporated and the residue dissolved in saturated aq. $NaHCO_3$. The resulting mixture was extracted with CH_2Cl_2 (3 x 75ml) and the combined extracts washed with brine (75ml), dried over anhydrous $MgSO_4$ and evaporated to give 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (3.9g, 93%), m.p. 121-123 °C (lit.,[9] 122-123.5 °C); ν_{max}(KBr)/cm^{-1} 1620 (CO); δ_H (400 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 5.40 (1H, s, 3-H), 7.28 (2H, m, 6-H and 8-H), 7.51 (1H, m, 7-H) and 8.14 (1H, dd, *J* 1.5 and 7.9 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.4 (NMe_2), 86.1 (C-3), 116.2 (C-8), 122.9 (C-4a), 124.5 (C-6), 125.5 (C-5), 131.8 (C-7), 153.7 (C-8a), 163.0 (C-2) and 176.4 (C-4); *m/z* 189 (M^+, 100%).

4-Bromo-2-hydroxyacetophenone boron difluoride complex[9] **103**

The experimental procedure employed for the synthesis of 2-hydroxyacetophenone boron difluoride complex **101** was followed, using 4-bromo-2-hydroxyacetophenone **89** (4.00g,

18.6mmol), dry Et_2O (20ml) and $BF_3.OEt_2$ (2.44ml, 19.5mmol). In this case, the solution was stirred for 3 h. Work-up afforded 4-bromo-2-hydroxyacetophenone boron difluoride complex **103** (3.1g, 63%), m.p. 159-161 °C; ν_{max}(KBr)/cm^{-1} 1610 (CO); δ_H (400 MHz; $CDCl_3$) 2.85 (3H, s, $COCH_3$), 7.17 (1H, dd, *J* 1.7 and 8.8 Hz, 5-H), 7.34 (1H, d, *J* 1.7 Hz, 3-H) and 7.62 (1H, d, *J* 8.8 Hz, 6-H).

*1-(4-Bromo-2-hydroxyphenyl)-3-chloro-3-(*N,N-*dimethylamino)propenone boron difluoride complex*[9] **104**

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex **102** was followed, using 4-bromo-2-hydroxyacetophenone boron difluoride complex **103** (2.80g, 10.7mmol), dry 1,2-dichloroethane (50ml) and *N,N*-dimethyldichloromethyleniminium chloride (1.80g, 11.1mmol). Work-up afforded 1-(4-bromo-2-hydroxyphenyl)-3-chloro-3-(*N,N*-dimethylamino)propenone boron difluoride complex **104** (2.3g, 61%) [ν_{max}(KBr)/cm^{-1} 1550 (CO); δ_H (400 MHz; $CDCl_3$) 3.10 (6H, s, NMe_2), 5.39 (1H, s, 2-H), 7.44 (1H, dd, *J* 1.5 and 8.4 Hz, 5'-H), 7.50 (1H, d, *J* 1.5 Hz, 3'-H) and 8.00 (1H, d, *J* 8.4 Hz, 6'-H)], which was used without further purification.

*7-Bromo-2-(*N,N-*dimethylamino)-4*H*-1-benzopyran-4-one*[9] **105**

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (**Method 2**) was followed, using 1-(4-bromo-2-hydroxyphenyl)-3-chloro-3-(*N,N*-dimethylamino)propenone boron difluoride complex **104** (2.00g, 5.68mmol) and MeOH (90ml). Work-up afforded 7-bromo-2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one (**105**) (1.5g, 97%), m.p. 203-204 °C (lit.,[100] 203 °C); ν_{max}(KBr)/cm^{-1} 1610 (CO); δ_H (400 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 5.36 (1H, s, 3-H), 7.42 (1H, dd, *J* 1.6 and 8.4 Hz, 6-H), 7.47 (1H, d, *J* 1.6 Hz, 8-H) and 7.99 (1H, d, *J* 8.3 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 86.2 (C-3), 119.4 (C-8), 121.9 (C-4a), 125.6 (C-6), 127.0 (C-7), 128.1 (C-5), 153.7 (C-8a), 162.9 (C-2) and 175,6 (C-4); *m/z* 267 (M^+, 100%).

4-Chloro-2-hydroxyacetophenone boron difluoride complex[9] **106**

The experimental procedure employed for the synthesis of 2-hydroxyacetophenone boron difluoride complex **101** was followed, using 4-chloro-2-hydroxyacetophenone **95** (5.10g, 29.9mmol), dry Et_2O (30ml) and $BF_3.OEt_2$ (3.90ml, 31.0mmol). In this case, the solution

was stirred overnight. Work-up afforded 4-chloro-2-hydroxyacetophenone boron difluoride complex **106** (3.5g, 53%), m.p. 132-136 °C; ν_{max}(KBr)/cm^{-1} 1610 (CO); δ_H (400 MHz; $CDCl_3$) 2.86 (3H, s, $COCH_3$), 7.01 (1H, dd, *J* 1.9 and 8.8 Hz, 5-H), 7.14 1H, d, *J* 1.9 Hz, 3-H) and 7.71 (1H, d, *J* 8.8 Hz, 6-H).

*3-Chloro-1-(4-chloro-2-hydroxyphenyl)-3-(*N,N*-dimethylamino)propenone boron difluoride complex*[9] **107**

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex **102** was followed, using 4-chloro-2-hydroxyacetophenone boron difluoride complex **106** (2.00g, 9.16mmol), dry 1,2-dichloroethane (30ml) and *N,N*-dimethyldichloromethyleniminium chloride (1.60g, 9.85mmol). Work-up afforded 3-chloro-1-(4-chloro-2-hydroxyphenyl)-3-(*N,N*-dimethylamino)propenone boron difluoride complex **107** (1.7g, 60%) [ν_{max}(KBr)/cm^{-1} 1550 (CO); δ_H (400 MHz; $CDCl_3$) 3.49 (6H, s, NMe_2), 5.88 (1H, s, 2-H), 6.83 (1H, dd, *J* 2.1 and 8.7 Hz, 5'-H), 7.05 (1H, d, *J* 2.0 Hz, 3'-H) and 7.47 (1H, d, *J* 8.8 Hz, 6'-H)], which was used without further purification.

*7-Chloro-2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one*[9] **108**

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (**Method 2**) was followed, using 3-chloro-1-(4-chloro-2-hydroxyphenyl)- 3-(*N,N*-dimethylamino)propenone boron difluoride complex (**107**) (1.60g, 5.20mmol) and MeOH (55ml). Work-up afforded 7-chloro-2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **108** (1.1g, 91%), m.p. 183-185 °C (lit.,[100] 185 °C); ν_{max}(KBr)/cm^{-1} 1610 (CO); δ_H (400 MHz; $CDCl_3$) 3.10 (6H, s, NMe_2), 5.39 (1H, s, 3-H), 7.28 (1H, dd, *J* 1.8 and 8.4 Hz, 6-H), 7.32 (1H, d, *J* 1.8 Hz, 8-H) and 8.08 (1H, d, *J* 8.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.6 (NMe_2), 86.2 (C-3), 116.5 (C-8), 121.9 (C-4a), 125.3 (C-6), 126.9 (C-5), 137.6 (C-7), 153.8 (C-8a), 163.0 (C-2) and 175.6 (C-4); *m/z* 223 (M^+, 100%).

4-Fluoro-2-hydroxyacetophenone boron difluoride complex[9] **109**

The experimental procedure employed for the synthesis of 2-hydroxyacetophenone boron difluoride complex **101** was followed, using 4-fluoro-2-hydroxyacetophenone **92** (4.60g, 29.9mmol), dry Et_2O (30ml) and $BF_3.OEt_2$ (3.90ml, 31.0mmol). In this case, the solution

was stirred for 3.5 h. Work-up afforded 4-fluoro-2-hydroxyacetophenone boron difluoride complex **109** (3.4g, 57%), m.p. 138-140 °C; ν_{max}(KBr)/cm^{-1} 1620 (CO); δ_H (400 MHz; $CDCl_3$) 2.86 (3H, s, $COCH_3$), 6.77 (2H, m, 3-H and 5-H) and 7.85 (1H, dd, *J* 6.2 and 9.1 Hz, 6-H).

*3-Chloro-3-(*N,N-*dimethylamino)-1-(4-fluoro-2-hydroxyphenyl)propenone boron difluoride complex*[9] **110**

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex **102** was followed, using 4-fluoro-2-hydroxyacetophenone boron difluoride complex **109** (2.75g, 13.6mmol), dry 1,2-dichloroethane (45ml) and *N,N*-dimethyldichloromethyleniminium chloride (2.30g, 14.2mmol). Work-up afforded 3-chloro-3-(*N,N*-dimethylamino)-1-(4-fluoro-2-hydroxyphenyl)propenone boron difluoride complex **110** (3.0g, 75%) [ν_{max}(KBr)/cm^{-1} 1550 (CO); δ_H (400 MHz; $CDCl_3$) 3.49 (6H, s, NMe_2), 5.85 (1H, s, 2-H), 6.60 (1H, dt, *J* 2.5 and 8.5 Hz, 3'-H), 6.72 (1H, dd, *J* 2.5 and 10.3 Hz, 5'-H) and 7.56 (1H, dd, *J* 6.4 and 9.1 Hz, 6'-H)], which was used without further purification.

*2-(*N,N-*Dimethylamino)-7-fluoro-4*H*-1-benzopyran-4-one*[9] **111**

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (**Method 2**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-1-(4-fluoro-2-hydroxyphenyl)propenone boron difluoride complex **110** (2.50g, 8.58mmol) and MeOH (90ml). Work-up afforded 2-(*N,N*-dimethylamino)-7-fluoro-4*H*-1-benzopyran-4-one **111** (1.8g, 84%), m.p. 134-136 °C (lit.,[100] 138 -140 °C); ν_{max}(KBr)/cm^{-1} 1630 (CO); δ_H (400 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 5.36 (1H, s, 3-H), 7.01 (2H, m, 6-H and 8-H) and 8.14 (1H, dd, *J* 6.5 and 8.7 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 85.9 (C-3), 103.4 (C-8), 112.8 (C-6), 119.9 (C-4a), 127.7 (C-5), 154.5 (C-8a), 163.2 (C-7), 165.9 (C-2) and 175.7 (C-4); *m/z* 207 (M^+, 100%).

2-Hydroxy-4-methoxyacetophenone boron difluoride complex[9] **112**

The experimental procedure employed for the synthesis of 2-hydroxyacetophenone boron difluoride complex **101** was followed, using 2-hydroxy-4-methoxyacetophenone **97** (5.00g, 30.1mmol), dry Et_2O (30ml) and $BF_3.OEt_2$ (3.76ml, 30.0mmol). In this case, the solution was stirred for 3.5 h. Work-up afforded 2-hydroxy-4-methoxyacetophenone boron

difluoride complex **112** (6.1g, 96%), m.p. 170-172 °C; ν_{max}(KBr)/cm^{-1} 1620 (CO); δ_H (400 MHz; $CDCl_3$) 2.74 (3H, s, $COCH_3$), 3.93 (3H, s, OCH_3), 6.44 (1H, d, *J* 2.3 Hz, 3-H), 6.57 (1H, dd, *J* 2.4 and 9.2 Hz, 5-H) and 7.62 (1H, d, *J* 9.3 Hz, 6-H).

*3-Chloro-3-(*N,N-*dimethylamino)-1-(2-hydroxy-4-methoxyphenyl)propenone boron difluoride complex*[9] **113**

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex **102** was followed, using 2-hydroxy-4-methoxyacetophenone boron difluoride complex **112** (5.00g, 23.4mmol), dry 1,2-dichloroethane (100ml) and *N,N*-dimethyldichloromethyleniminium chloride (3.80g, 23.4mmol). Work-up afforded 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxy-4-methoxyphenyl)propenone boron difluoride complex **113** (6.1g, 86%) [ν_{max}(KBr)/cm^{-1} 1550 (CO); δ_H (400 MHz; $CDCl_3$) 3.44 (3H, s, OCH_3), 3.74 (6H, s, NMe_2), 5.80 (1H, s, 2-H), 6.91 (1H, d, *J* 19.6 Hz, 5'-H), 7.46 (1H, d, *J* 8.8 Hz, 3'-H) and 8.00 (1H, d, *J* 8.8 Hz, 6'-H)], which was used without further purification.

*2-(*N,N-*Dimethylamino)-7-methoxy-4*H-*1-benzopyran-4-one*[9] **114**

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (**Method 2**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxy-4-methoxyphenyl)propenone boron difluoride complex **113** (2.80g, 9.23mmol) and MeOH (100ml). Work-up afforded 2-(*N,N*-dimethylamino)-7-methoxy-4*H*-1-benzopyran-4-one **114** (1.1g, 53%), m.p. 172-174 °C (lit.,[9] 175 -175.5 °C); ν_{max}(KBr)/cm^{-1} 1630 (CO); δ_H (400 MHz; $CDCl_3$) 3.08 (6H, s, NMe_2), 3.89 (3H, s, OCH_3), 5.31 (1H, s, 3-H), 6.72 (1H, d, *J* 2.2 Hz, 8-H), 6.88 (1H, dd, *J* 2.3 and 8.8 Hz, 6-H) and 8.04 (1H, d, *J* 8.8, 5-H); δ_C (100 MHz; $CDCl_3$) 37.5 (NMe_2), 55.7 (OCH_3), 85.6 (C-3), 100.1 (C-8), 112.4 (C-6), 116.5 (C-4a), 126.8 (C-5), 155.1 (C-8a), 162.8 (C-2), 163.1 (C-7) and 176.5 (C-4); *m/z* 219 (M^+, 100%).

2-Hydroxy-5-methoxyacetophenone boron difluoride complex[9] **115**

The experimental procedure employed for the synthesis of 2-hydroxyacetophenone boron difluoride complex **101** was followed, using 2-hydroxy-5-methoxyacetophenone **99** (5.00g, 30.1mmol), dry Et_2O (30ml) and $BF_3.OEt_2$ (3.90ml, 31.0mmol). In this case, the solution was stirred for 2.75 h. Work-up afforded 2-hydroxy-5-methoxyacetophenone boron

difluoride complex **115** (5.2g, 78%), m.p. 144-146 °C (lit.,[100] 144 – 146 °C); ν_{max}(KBr)/cm^{-1} 1630 (CO); δ_H (400 MHz; $CDCl_3$) 2.83 (3H, s, $COCH_3$), 3.84 (3H, s, OCH_3), 6.96 (1H, d, *J* 3.1 Hz, 6-H), 7.03 (1H, d, *J* 9.3 Hz, 3-H) and 7.45 (1H, dd, *J* 3.1 and 9.3 Hz, 4-H).

*3-Chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxy-5-methoxyphenyl)propenone boron difluoride complex*[9] **116**

The experimental procedure employed for the synthesis of 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxyphenyl)propenone boron difluoride complex **102** was followed, using 2-hydroxy-5-methoxyacetophenone boron difluoride complex **115** (3.95g, 18.5mmol), dry 1,2-dichloroethane (60ml) and *N,N*-dimethyldichloromethyleniminium chloride (3.20g, 19.7mmol). Work-up afforded 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxy-5-methoxyphenyl)propenone boron difluoride complex **116** (1.9g, 34%) [ν_{max}(KBr)/cm^{-1} 1550 (CO); δ_H (400 MHz; $CDCl_3$) 3.49 (6H, s, NMe_2), 3.80 (3H, s, OCH_3), 6.50 (1H, s, 2-H), 7.13 (1H, dd, *J* 2.7 and 9.2 Hz, 4'-H), 7.28 (1H, d, *J* 3.1 Hz, 3'-H) and 7.60 (1H, d, *J* 3.0 Hz, 6'-H)], which was used without further purification.

*2-(*N,N*-Dimethylamino)-6-methoxy-4*H*-1-benzopyran-4-one*[9] **117**

The experimental procedure employed for the synthesis of 2-(*N,N*-dimethylamino)-4*H*-1-benzopyran-4-one **77** (**Method 2**) was followed, using 3-chloro-3-(*N,N*-dimethylamino)-1-(2-hydroxy-5-methoxyphenyl)propenone boron difluoride complex **116** (1.60g, 5.28mmol) and MeOH (50ml). Work-up afforded 2-(*N,N*-dimethylamino)-6-methoxy-4*H*-1-benzopyran-4-one **117** (1.1g, 93%), m.p. 152-153 °C (lit.,[100] 150 – 152 °C); ν_{max}(KBr)/cm^{-1} 1610 (CO); δ_H (400 MHz; $CDCl_3$) 3.09 (6H, s, NMe_2), 3.88 (3H, s, OCH_3), 5.38 (1H, s, 3-H), 7.07 (1H, dd, *J* 3.2 and 9.0 Hz, 7-H), 7.19 (1H, d, *J* 9.0 Hz, 8-H) and 7.56 (1H, d, *J* 3.1 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 37.4 (NMe_2), 55.9 (OCH_3), 85.9 (C-3), 105.9 (C-5), 117.4 (C-8), 121.0 (C-7), 123.5 (C-4a), 148.2 (C-8a), 156.5 (C-6), 163.1 (C-2) and 176.4 (C-4); *m/z* 219 (M^+, 100%).

3.2.4 Procedure for the determination of pK_a values for 2-(*N*,*N*-dimethylamino)-chromones (77), (86), (105), (108), (111), (114) and (117)

Aqueous ethanolic solutions of the 2-(*N*,*N*-dimethylamino)chromones **77**, **86**, **105**, **108**, **111**, **114** and **117** were prepared by dissolving the appropriate quantity in distilled absolute ethanol (10ml) and boiled water (9ml) to afford, at half-neutralisation point, aliquots (20ml) having a concentration of 0.01 $mol.dm^{-3}$. The stirred 2-(*N*,*N*-dimethylamino)-chromone solutions were titrated against hydrochloric acid (0.1063 $mol.dm^{-3}$) at 25 ± 0.1 °C, the titrant being added in 0.20ml portions. The hydrochloric acid solution was standardised against freshly recrystallised sodium tetraborate decahydrate. The pH was measured after each addition using a Beckman ϕ50 pH meter fitted with a Beckman Type 39849 epoxy body calomel electrode. The pH meter was calibrated at pH 4.008 (using a potassium hydrogen phthalate buffer) and at pH 1.679 (using a potassium tetroxalate buffer). All titrations were done in a water bath to maintain a constant temperature and were replicated to ensure reproducibility. The resulting data are detailed in Table 4 (section 2.2, p. 48). Tables 10 to 35 below illustrate the method used to calculate the pK_a value for each compound, a detailed example of which is described in section 2.2 of the discussion.

Calculation of pK_a value for 2-(N,N-dimethylamino)chromone **77** *(duplicate)*

Table 10: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.49	0.00002138	0.00017564
0.40	3.17	0.00004276	0.00015426
0.60	2.98	0.00006414	0.00013288
0.80	2.85	0.00008552	0.0001115
1.00	2.75	0.0001069	0.00009012
1.20	2.63	0.00012828	0.00006874
1.40	2.56	0.00014966	0.00004736
1.60	2.49	0.00017104	0.00002598
1.80	2.47	0.00019242	0.0000046
2.00	2.43	0.0002138	-0.00001678

Table 11: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000323594	6.213E-06	0.08340254	-1.078820728	2.4111793	0.0038799
19.40	0.000676083	1.3116E-05	0.17711015	-0.751756548	2.4182435	0.0038173
19.60	0.001047129	2.05237E-05	0.28432349	-0.546187263	2.4338127	0.00368288
19.80	0.001412538	2.79682E-05	0.41265133	-0.384416747	2.4655833	0.00342308
20.00	0.001778279	3.55656E-05	0.56756238	-0.245986397	2.5040136	0.00313319
20.20	0.002344229	4.73534E-05	0.69708151	-0.156716437	2.4732836	0.00336292
20.40	0.002754229	5.61863E-05	0.90272434	-0.044444847	2.5155552	0.00305102
20.60	0.003235937	6.66603E-05	1.12672038	0.051816151	2.5418162	0.002872
20.80	0.003388442	7.04796E-05	1.62414878	0.21062581	2.6806258	0.00208629

pK_a 2.46 ± 0.06

Calculation of pK_a value for *6-nitro-2-(*N,N-*dimethylamino)chromone* **86**

Table 12: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.49	0.00002138	0.0001652
0.40	3.04	0.00004276	0.00014382
0.60	2.84	0.00006414	0.00012244
0.80	2.71	0.00008552	0.00010106
1.00	2.60	0.0001069	0.00007968
1.20	2.51	0.00012828	0.0000583
1.40	2.45	0.00014966	0.00003692
1.60	2.38	0.00017104	0.00001554
1.80	2.34	0.00019242	-0.00000584
2.00	2.29	0.0002138	-0.00002722

Table 13: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000323594	6.21E-06	0.08848222	-1.05314401	2.43685599	0.0036572
19.40	0.000912011	1.7693E-05	0.15520106	-0.80910533	2.23089467	0.0058763
19.60	0.00144544	2.83306E-05	0.23750901	-0.62431991	2.21568009	0.0060858
19.80	0.001949845	3.86069E-05	0.33589254	-0.47379965	2.23620035	0.005805
20.00	0.002511886	5.02377E-05	0.43613964	-0.36037444	2.23962556	0.0057594
20.20	0.003090295	6.2424E-05	0.54550918	-0.26319794	2.24680206	0.005665
20.40	0.003548134	7.23819E-05	0.70701467	-0.15057158	2.29942842	0.0050185
20.60	0.004168694	8.58751E-05	0.83976561	-0.07584192	2.30415808	0.0049641
20.80	0.004570882	9.50743E-05	1.09089901	0.037784546	2.37778455	0.00419

pK_a 2.25 ± 0.05

Calculation of pK_a value for *6-nitro-2-(*N,N-*dimethylamino)chromone* **86** *(duplicate)*

Table 14: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.43	0.00002138	0.00014799
0.40	3.02	0.00004276	0.00012661
0.60	2.83	0.00006414	0.00010523
0.80	2.69	0.00008552	0.00008385
1.00	2.60	0.0001069	0.00006247
1.20	2.52	0.00012828	0.00004109
1.40	2.44	0.00014966	0.00001971
1.60	2.37	0.00017104	-0.00000167
1.80	2.35	0.00019242	-0.00002305
2.00	2.31	0.0002138	-0.00004443

Table 15: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000371535	7.13348E-06	0.091839894	-1.03696863	2.39303137	0.00404547
19.40	0.000954993	1.85269E-05	0.16696754	-0.77736795	2.24263205	0.00571963
19.60	0.001479108	2.89905E-05	0.261878545	-0.58190008	2.248100	0.00564807
19.80	0.002041738	4.04264E-05	0.362849138	-0.4402739	2.2497261	0.00562696
20.00	0.002511886	5.02377E-05	0.502736343	-0.29865972	2.301340	0.00499643
20.20	0.003019952	6.1003E-05	0.658977197	-0.18112961	2.338870	0.00458279
20.40	0.003630781	7.40679E-05	0.806075399	-0.09362433	2.34637567	0.00450427
20.60	0.004265795	8.78754E-05	0.964726544	-0.01559577	2.35440423	0.00442177
20.80	0.004466836	9.29102E-05	1.424413774	0.153636165	2.50363616	0.00313591

pK_a 2.29 ± 0.06

Calculation of pK_a value for *7-bromo-2-(*N,N*-dimethylamino)chromone* **105**

Table 16: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.38	0.00002138	0.00018536
0.40	3.05	0.00004276	0.00016398
0.60	2.87	0.00006414	0.0001426
0.80	2.74	0.00008552	0.00012122
1.00	2.64	0.0001069	0.00009984
1.20	2.55	0.00012828	0.00007846
1.40	2.47	0.00014966	0.00005708
1.60	2.42	0.00017104	0.0000357
1.80	2.39	0.00019242	0.00001432
2.00	2.34	0.0002138	-0.00000706

Table 17: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000416869	8.00389E-06	0.06917583	-1.1600456	2.21995438	0.0060262
19.40	0.000891251	1.72903E-05	0.14050695	-0.8523022	2.19769779	0.0063431
19.60	0.001348963	2.64397E-05	0.22302651	-0.6516435	2.21835648	0.0060484
19.80	0.001819701	3.60301E-05	0.31472114	-0.5020741	2.23792591	0.0057819
20.00	0.002290868	4.58174E-05	0.41935849	-0.3774146	2.26258543	0.0054628
20.20	0.002818383	5.69313E-05	0.52698103	-0.278205	2.27179498	0.0053482
20.40	0.003388442	6.91242E-05	0.63813872	-0.1950849	2.2749151	0.0053099
20.60	0.003801894	7.8319E-05	0.81320632	-0.0897993	2.31020075	0.0046752
20.80	0.004073803	8.47351E-05	1.08712126	0.03627799	2.42627799	0.0037473

pK_a 2.25 ± 0.06

Calculation of pK_a value for *7-bromo-2-(*N,N-*dimethylamino)chromone* **105** *(duplicate)*.

Table 18: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.40	0.00002138	0.00018599
0.40	3.07	0.00004276	0.00016461
0.60	2.88	0.00006414	0.00014323
0.80	2.75	0.00008552	0.00012185
1.00	2.64	0.0001069	0.00010047
1.20	2.57	0.00012828	0.00007909
1.40	2.49	0.00014966	0.00005771
1.60	2.43	0.00017104	0.00003633
1.80	2.38	0.00019242	0.00001495
2.00	2.33	0.0002138	-0.00000643

Table 19: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000398107	7.64366E-06	0.07093985	-1.14910974	2.2508903	0.0056119
19.40	0.000851138	1.65121E-05	0.1449184	-0.83887646	2.2311235	0.0058732
19.60	0.001318257	2.58378E-05	0.22654912	-0.64483763	2.2351624	0.0058189
19.80	0.001778279	3.52099E-05	0.32032401	-0.4944105	2.2555895	0.0055515
20.00	0.002290868	4.58174E-05	0.41755248	-0.37928893	2.2607111	0.0054864
20.20	0.002691535	5.4369E-05	0.5538105	-0.25663882	2.3133612	0.00486
20.40	0.003235937	6.60131E-05	0.67608143	-0.170001	2.319999	0.0047863
20.60	0.003715352	7.65363E-05	0.83730732	-0.07711511	2.3528849	0.0044373
20.80	0.004168694	8.67088E-05	1.03986212	0.01697576	2.3969758	0.0040089

pK_a 2.27 ± 0.05

Calculation of pK_a value for *7-chloro-2-(*N,N*-dimethylamino)chromone* **108**

Table 20: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.35	0.00002138	0.000180982
0.40	3.03	0.00004276	0.000159602
0.60	2.84	0.00006414	0.000138222
0.80	2.74	0.00008552	0.000116842
1.00	2.63	0.0001069	0.000095462
1.20	2.55	0.00012828	0.000074082
1.40	2.47	0.00014966	0.000052702
1.60	2.42	0.00017104	0.000031322
1.80	2.36	0.00019242	0.000009942
2.00	2.33	0.0002138	-0.000011438

Table 21: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000446684	8.57632E-06	0.06754478	-1.1704082	2.1795918	0.0066131
19.40	0.000933254	1.81051E-05	0.13873876	-0.8578022	2.1721978	0.0067267
19.60	0.00144544	2.83306E-05	0.21500341	-0.6675547	2.1724453	0.0067229
19.80	0.001819701	3.60301E-05	0.32373422	-0.4898114	2.2501886	0.005621
20.00	0.002344229	4.68846E-05	0.4216148	-0.3750841	2.2549159	0.0055601
20.20	0.002818383	5.69313E-05	0.54459086	-0.2639297	2.2860703	0.0051752
20.40	0.003388442	6.91242E-05	0.66107116	-0.1797518	2.2902482	0.0051257
20.60	0.003801894	7.8319E-05	0.8456779	-0.072795	2.347205	0.0044957
20.80	0.004365158	9.07953E-05	1.00880919	0.00380903	2.363809	0.004327

pK_a 2.23 ± 0.06

Calculation of pK_a value for *7-chloro-2-(*N,N-*dimethylamino)chromone* **108** *(duplicate)*

Table 22: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.34	0.00002138	0.000179462
0.40	3.02	0.00004276	0.000158082
0.60	2.85	0.00006414	0.000136702
0.80	2.73	0.00008552	0.000115322
1.00	2.61	0.0001069	0.000093942
1.20	2.53	0.00012828	0.000072562
1.40	2.46	0.00014966	0.000051182
1.60	2.41	0.00017104	0.000029802
1.80	2.36	0.00019242	0.000008422
2.00	2.32	0.0002138	-0.000012958

Table 23: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000457088	8.77609E-06	0.06695726	-1.1742023	2.1657977	0.0068266
19.40	0.000954993	1.85269E-05	0.13721364	-0.8626027	2.1573973	0.0069599
19.60	0.001412538	2.76857E-05	0.22175781	-0.6541211	2.1958789	0.0063697
19.80	0.001862087	3.68693E-05	0.31966786	-0.495301	2.234699	0.0058251
20.00	0.002454709	4.90942E-05	0.40413427	-0.3934743	2.2165257	0.006074
20.20	0.002951209	5.96144E-05	0.5194994	-0.284415	2.245585	0.0056809
20.40	0.003467369	7.07343E-05	0.64737587	-0.1888435	2.2711565	0.005356
20.60	0.003890451	8.01433E-05	0.82674476	-0.0826286	2.3273714	0.0047057
20.80	0.004365158	9.07953E-05	1.02426405	0.01041193	2.3704119	0.0042618

pK_a 2.21 ± 0.06

Calculation of pK_a value for *7-fluoro-2-(*N,N*-dimethylamino)chromone* **111**

Table 24: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	3.82		
0.20	3.39	0.00002138	0.00018156
0.40	3.05	0.00004276	0.00016018
0.60	2.87	0.00006414	0.0001388
0.80	2.74	0.00008552	0.00011742
1.00	2.64	0.0001069	0.00009604
1.20	2.55	0.00012828	0.00007466
1.40	2.48	0.00014966	0.00005328
1.60	2.42	0.00017104	0.0000319
1.80	2.37	0.00019242	0.00001052
2.00	2.33	0.0002138	-0.00001086

Table 25: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.00040738	7.8217E-06	0.07159244	-1.1451328	2.24486718	0.00569027
19.40	0.000891251	1.72903E-05	0.14351549	-0.8431012	2.20689877	0.00621014
19.60	0.001348963	2.64397E-05	0.22815542	-0.6417692	2.2282308	0.00591247
19.80	0.001819701	3.60301E-05	0.32251481	-0.4914503	2.24854967	0.00564222
20.00	0.002290868	4.58174E-05	0.43059204	-0.365934	2.274066	0.00532027
20.20	0.002818383	5.69313E-05	0.54219881	-0.2658414	2.28415856	0.00519806
20.40	0.003311311	6.75507E-05	0.67953937	-0.1677854	2.31221462	0.00487288
20.60	0.003801894	7.8319E-05	0.84124308	-0.0750785	2.34492151	0.00451938
20.80	0.004265795	8.87285E-05	1.0447656	0.01901886	2.38901886	0.00408302

pK_a 2.26 ± 0.05

Calculation of pK_a value for *7-fluoro-2-(*N,N*-dimethylamino)chromone* **111** *(duplicate)*

Table 26: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	3.52		
0.20	3.37	0.00002138	0.00017765
0.40	3.05	0.00004276	0.00015627
0.60	2.85	0.00006414	0.00013489
0.80	2.73	0.00008552	0.00011351
1.00	2.63	0.0001069	0.00009213
1.20	2.55	0.00012828	0.00007075
1.40	2.47	0.00014966	0.00004937
1.60	2.42	0.00017104	0.00002799
1.80	2.37	0.00019242	0.00000661
2.00	2.32	0.0002138	-0.00001477

Table 27: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.00042658	8.19033E-06	0.07097315	-1.1489059	2.2210941	0.0060104
19.40	0.000891251	1.72903E-05	0.14674863	-0.8334259	2.2165741	0.0060733
19.60	0.001412538	2.76857E-05	0.22422943	-0.6493074	2.2006926	0.0062995
19.80	0.001862087	3.68693E-05	0.3235197	-0.4900993	2.2399007	0.0057557
20.00	0.002344229	4.68846E-05	0.43172037	-0.3647975	2.2652025	0.00543
20.20	0.002818383	5.69313E-05	0.55880262	-0.2527416	2.2972584	0.0050436
20.40	0.003388442	6.91242E-05	0.67966016	-0.1677082	2.3022918	0.0049855
20.60	0.003801894	7.8319E-05	0.87218364	-0.0593921	2.3606079	0.0043591
20.80	0.004265795	8.87285E-05	1.08761326	0.03647449	2.4064745	0.0039222

pK_a 2.25 ± 0.05

Calculation of pK_a value for *7-methoxy-2-(*N,N*-dimethylamino)chromone* **114**

Table 28: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.20		
0.20	3.58	0.00002138	0.00018893
0.40	3.23	0.00004276	0.00016755
0.60	3.03	0.00006414	0.00014617
0.80	2.89	0.00008552	0.00012479
1.00	2.77	0.0001069	0.00010341
1.20	2.68	0.00012828	0.00008203
1.40	2.60	0.00014966	0.00006065
1.60	2.54	0.00017104	0.00003927
1.80	2.47	0.00019242	0.00001789
2.00	2.41	0.0002138	-0.00000349

Table 29: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000263027	5.05011E-06	0.0841833	-1.0747741	2.5052259	0.0031245
19.40	0.000588844	1.14236E-05	0.17508973	-0.7567393	2.4732607	0.0033631
19.60	0.000933254	1.82918E-05	0.27877732	-0.5547426	2.4752574	0.0033477
19.80	0.00128825	2.55073E-05	0.39929288	-0.3987084	2.4912916	0.0032263
20.00	0.001698244	3.39649E-05	0.53092043	-0.2749706	2.4950294	0.0031987
20.20	0.002089296	4.22038E-05	0.69285678	-0.1593565	2.5206435	0.0030155
20.40	0.002511886	5.12425E-05	0.87957219	-0.0557285	2.5442715	0.0028558
20.60	0.002884032	5.9411E-05	1.13120961	0.05354309	2.5935431	0.0025495
20.80	0.003388442	7.04796E-05	1.37989124	0.13984486	2.6098449	0.0024556

pK_a 2.51 ± 0.06

Calculation of pK_a value for *7-methoxy-2-(*N,N*-dimethylamino)chromone* **114** *(duplicate)*

Table 30: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.20		
0.20	3.60	0.00002138	0.00019482
0.40	3.25	0.00004276	0.00017344
0.60	3.05	0.00006414	0.00015206
0.80	2.90	0.00008552	0.00013068
1.00	2.79	0.0001069	0.0001093
1.20	2.70	0.00012828	0.00008792
1.40	2.63	0.00014966	0.00006654
1.60	2.57	0.00017104	0.00004516
1.80	2.51	0.00019242	0.00002378
2.00	2.45	0.0002138	0.0000024

Table 31: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000251189	4.82282E-06	0.082934001	-1.0812674	2.5187326	0.0030288
19.40	0.000562341	1.09094E-05	0.172772868	-0.7625245	2.4874755	0.0032548
19.60	0.000891251	1.74685E-05	0.275301655	-0.5601912	2.4898088	0.0032374
19.80	0.001258925	2.49267E-05	0.389400121	-0.4096039	2.4903961	0.003233
20.00	0.00162181	3.24362E-05	0.525368939	-0.2795356	2.5104644	0.003087
20.20	0.001995262	4.03043E-05	0.686107876	-0.1636076	2.5363924	0.0029081
20.40	0.002344229	4.78223E-05	0.890483672	-0.050374	2.579626	0.0026325
20.60	0.002691535	5.54456E-05	1.14898538	0.0603145	2.6303145	0.0023425
20.80	0.003090295	6.42781E-05	1.455195939	0.16292147	2.6729215	0.0021236

pK_a 2.52 ± 0.06

Calculation of pK_a value for *6-methoxy-2-(*N,N-*dimethylamino)chromone* **117**

Table 32: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.41	0.00002138	0.0001654
0.40	3.09	0.00004276	0.00014402
0.60	2.91	0.00006414	0.00012264
0.80	2.78	0.00008552	0.00010126
1.00	2.68	0.0001069	0.00007988
1.20	2.59	0.00012828	0.0000585
1.40	2.50	0.00014966	0.00003712
1.60	2.44	0.00017104	0.00001574
1.80	2.39	0.00019242	-0.00000564
2.00	2.36	0.0002138	-0.00002702

Table 33: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000389045	7.46967E-06	0.08046717	-1.0943813	2.3156187	0.00483483
19.40	0.000812831	1.57689E-05	0.16891715	-0.7723262	2.3176738	0.00481201
19.60	0.001230269	2.41133E-05	0.27274849	-0.5642376	2.3457624	0.00451063
19.80	0.001659587	3.28598E-05	0.39263532	-0.4060106	2.3739894	0.00422679
20.00	0.002089296	4.17859E-05	0.53518747	-0.2714941	2.4085059	0.00390386
20.20	0.002570396	5.1922E-05	0.69151083	-0.160201	2.429799	0.00371707
20.40	0.003162278	6.45105E-05	0.83783476	-0.0768416	2.4231584	0.00377435
20.60	0.003630781	7.47941E-05	1.06309051	0.02657024	2.4665702	0.00341531
20.80	0.004073803	8.47351E-05	1.36146114	0.13400525	2.5240053	0.00299223

pK_a 2.37 ± 0.05

Calculation of pK_a value for *6-methoxy-2-(*N,N-*dimethylamino)chromone* **117** *(duplicate)*

Table 34: Concentration of the protonated and non-protonated species as a function of pH.

Vol. titrant/ml	pH	BH^+	B
0.00	4.00		
0.20	3.46	0.00002138	0.0001784
0.40	3.13	0.00004276	0.00015702
0.60	2.95	0.00006414	0.00013564
0.80	2.82	0.00008552	0.00011426
1.00	2.71	0.0001069	0.00009288
1.20	2.63	0.00012828	0.0000715
1.40	2.54	0.00014966	0.00005012
1.60	2.48	0.00017104	0.00002874
1.80	2.44	0.00019242	0.00000736
2.00	2.39	0.0002138	-0.00001402

Table 35: Calculation of pK_a values, corrected for hydrogen ion activity.

(1) Total vol./ml	(2) $[H^+]$	(3) H^+	(4) $\frac{BH^+-H^+}{B+H^+}$	(5) log (col.4)	(6) pK_a	(7) (-antilog)
19.20	0.000346737	6.65735E-06	0.07955724	-1.0993203	2.3606797	0.0043583
19.40	0.00074131	1.43814E-05	0.16556795	-0.7810237	2.3489763	0.0044774
19.60	0.001122018	2.19916E-05	0.26738578	-0.5728617	2.3771383	0.0041963
19.80	0.001513561	2.99685E-05	0.385163	-0.4143554	2.4056446	0.0039297
20.00	0.001949845	3.89969E-05	0.5148977	-0.2882791	2.4217209	0.0037869
20.20	0.002344229	4.73534E-05	0.68089397	-0.1669205	2.4630795	0.0034429
20.40	0.002884032	5.88342E-05	0.83361377	-0.0790351	2.4609649	0.0034597
20.60	0.003311311	6.8213E-05	1.06058582	0.02554582	2.5055458	0.0031222
20.80	0.003630781	7.55202E-05	1.41046613	0.14936266	2.5893627	0.0025742

pK_a 2.40 ± 0.06

3.3 PREPARATION OF SUBSTITUTED 4*H*-1-BENZOPYRAN-4-ONE-3-CARBALDEHYDES

*4*H-*1-benzopyran-4-one-3-carbaldehyde*[16] **7**

$POCl_3$ (18.7ml, 200mmol) was added dropwise to a stirred solution of *o*-hydroxyacetophenone **100** (6.01ml, 50.0mmol) in dry DMF (50ml) under dry N_2, maintained at -20° C using a dry ice-acetone bath, over 30 min. The resulting mixture was stirred overnight at room temperature and then poured into ice-water (75 ml). The resulting precipitate was filtered off, washed successively with water and EtOH, and recrystallised from acetone to afford 4*H*-1-benzopyran-4-one-3-carbaldehyde **7** (5.0g, 57%), m.p. 152-153 °C, (lit.,[16] 152-153 °C); ν_{max}(KBr)/cm^{-1} 2924 and 2869 (CHO), and 1690 and 1648 (2 x CO); δ_H (400 MHz; $CDCl_3$) 7.46 (1H, t, *J* 7.6 Hz, 6-H), 7.50 (1H, d, *J* 8.5 Hz, 8-H), 7.72 (1H, t, *J* 7.4 Hz, 7-H), 8.25 (1H, d, *J* 7.8 Hz, 5-H), 8.50 (1H, s, 2-H) and 10.33 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 118.5 (C-8), 120.3 (C-3), 125.2 (C-4a), 126.1 (C-5), 126.5 (C-6), 134.7 (C-7), 156.1 (C-8a), 160.5 (C-2), 175.8 (C-4) and 188.4 (CHO); *m/z* 174 (M^+, 6%) and 146 (100).

*6-Chloro-4*H-*1-benzopyran-4-one-3-carbaldehyde*[16] **136**

The experimental procedure employed for the synthesis of 4*H*-1-benzopyran-4-one-3-carbaldehyde **7** was followed, using $POCl_3$ (18.7ml, 200mmol) and 5-chloro-2-hydroxyacetophenone **135** (8.53g, 50.0mmol). Work-up afforded 6-chloro-4*H*-1-benzopyran-4-one-3-carbaldehyde **136** (5.0g, 48%), m.p. 166-168 °C (lit.,[16] 166-168 °C); ν_{max}(KBr)/cm^{-1} 3050 and 2870 (CHO), and 1691 and 1656 (2 x CO); δ_H (400 MHz; $CDCl_3$) 7.49 (1H, d, *J* 8.9 Hz, 8-H), 7.68 (1H, dd, *J* 2.6 and 8.9 Hz, 7-H), 8.22 (1H, d, *J* 2.5 Hz, 5-H), 8.50 (1H, s, 2-H) and 10.35 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 120.3 (C-8), 125.6 (C-5), 126.3 (C-4a), 132.8 (C-6 and C-3), 135.0 (C-7), 155.5 (C-8a), 160.6 (C-2), 174.8 (C-4) and 188.0 (CHO); *m/z* 208 (M^+, 4%) and 180 (100).

*6-Bromo-4*H-*1-benzopyran-4-one-3-carbaldehyde*[16] **138**

The experimental procedure employed for the synthesis of 4*H*-1-benzopyran-4-one-3-carbaldehyde **7** was followed, using $POCl_3$ (16.7ml, 179mmol) and 5-bromo-2-hydroxyacetophenone **137** (9.60g, 44.6mmol). Work-up afforded 6-bromo-4*H*-1-benzopyran-4-one-3-carbaldehyde **138** (7.8g, 69%), m.p. 192-194 °C (lit.,[15] 186 – 188 °C);

ν_{max}(KBr)/cm^{-1} 3045 and 2865 (CHO), and1700 and 1656 (2 x CO); δ_H (400 MHz; $CDCl_3$) 7.42 (1H, d, *J* 8.9 Hz, 8-H), 7.82 (1H, dd, *J* 2.5 and 8.9 Hz, 7-H), 8.39 (1H, d, *J* 2.4 Hz, 5-H), 8.52 (1H, s, 2-H) and 10.34 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 120.3 and 120.4 (C-3 and C-6), 120.5 (C-8), 126.6 (C-4a), 128.8 (C-5), 137.8 (C-7), 154.9 (C-8a), 160.6 (C-2), 174.6 (C-4) and 188.0 (CHO); *m/z* 252 (M^+, 4%) and 226 (100).

*6-Fluoro-4*H-*1-benzopyran-4-one-3-carbaldehyde*[16] **140**

The experimental procedure employed for the synthesis of 4*H*-1-benzopyran-4-one-3-carbaldehyde **7** was followed, using $POCl_3$ (18.7ml, 200mmol) and 5-fluoro-2-hydroxy-acetophenone **139** (9.60g, 44.6mmol). Work-up afforded 6-fluoro-4*H*-1-benzopyran-4-one-3-carbaldehyde **140** (3.8g, 40%), m.p. 158 °C; ν_{max}(KBr)/cm^{-1} 3020 and 2882 (CHO), and 1698 and 1655 (2 x CO); δ_H (400 MHz; $CDCl_3$) 7.45 (1H, m, 7-H), 7.55 (1H, m, 8-H), 7.90 (1H, dd, *J* 3.1 and 7.9 Hz, 5-H), 8.52 (1H, s, 2-H) and 10.35 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 111.3 (C-5), 119.7 (C-4a), 120.8 (C-8), 122.9 (C-7), 126.7 and 126.8 (C-3 and C-6), 152.4 (C-8a), 160.6 (C-2), 175.2 (C-4) and 188.1 (CHO); *m/z* 192 (M^+, 4%) and 164 (100).

*6-Methoxy-4*H-*1-benzopyran-4-one-3-carbaldehyde*[16] **142**

The experimental procedure employed for the synthesis of 4*H*-1-benzopyran-4-one-3-carbaldehyde **7** was followed, using $POCl_3$ (13.5ml, 144mmol) and 2-hydroxy-5-methoxy-acetophenone **141** (6.00g, 36.1mmol). Work-up afforded 6-methoxy-4*H*-1-benzopyran-4-one-3-carbaldehyde **142** (3.9g, 63%), m.p. 164-165 °C (lit.,[16] 164-166 °C); ν_{max}(KBr)/cm^{-1} 2910 and 2835 (CHO), and 1687 and 1645 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.91 (3H, s, OCH_3), 7.31 (1H, dd, *J* 3.1 and 9.2 Hz, 7-H), 7.46 (1H, d, *J* 9.1 Hz, 8-H), 7.64 (1H, d, *J* 3.0 Hz, 5-H), 8.51 (1H, s, 2-H) and 10.40 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 56.1 (OCH_3), 105.5 (C-5), 119.6 (C-3), 120.0 (C-8), 124.4 (C-7), 126.2 (C-6), 151.0 (C-8a), 158.0 (C-4a), 160.2 (C-2), 175.9 (C-4) and 188.7 (CHO); *m/z* 204 (M^+, 1%) and 176 (100).

*5-Methoxy-4*H-*1-benzopyran-4-one-3-carbaldehyde*[16] **144**

The experimental procedure employed for the synthesis of 4*H*-1-benzopyran-4-one-3-carbaldehyde **7** was followed, using $POCl_3$ (11.2ml, 120mmol) and 2-hydroxy-6-methoxy-acetophenone **143** (5.00g, 30.1mmol). Work-up afforded 5-methoxy-4*H*-1-benzopyran-4-

one-3-carbaldehyde **144** (2.5g, 41%), m.p. 112-114 °C (lit.,[16] 115-116 °C); ν_{max}(KBr)/cm^{-1} 2925 and 2870 (CHO), and 1694 and 1649 (2 x CO); δ_H (400 MHz; $CDCl_3$) 4.00 (3H, s, OCH_3), 6.82 (1H, d, *J* 8.7 Hz, 6-H), 7.06 (1H, dd, *J* 0.8 and 8.4 Hz, 8-H), 7.61 (1H, t, *J* 8.4 Hz, 7-H), 8.39 (1H, s, 2-H) and 10.34 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 56.6 (OCH_3), 108.0 (C-6), 110.4 (C-8), 115.6 (C-4a), 121.3 (C-3), 134.9 (C-7), 158.1 (C-8a), 158.7 (C-2), 160.4 (C-5), 175.8 (C-4) and 189.1 (CHO); *m/z* 204 (M^+, 2%) and 176 (100).

*6-Nitro-4*H*-1-benzopyran-4-one-3-carbaldehyde*[16] **145**

4*H*-1-benzopyran-4-one-3-carbaldehyde **7** (2.00g, 11.5mmol) was dissolved in conc. H_2SO_4 (4.60ml). The resulting orange solution was cooled using an ice-water bath, and fuming HNO_3 (4.60ml) was added dropwise with stirring. After stirring for 3 h, the mixture was poured into ice-water. The precipitated solid was filtered off and recrystallised from acetone to afford 6-nitro-4*H*-1-benzopyran-4-one-3-carbaldehyde **145** (1.4g, 54%), m.p. 162-164 °C (lit.,[16] 163-164 °C); ν_{max}(KBr)/cm^{-1} 2924 and 2870 (CHO), 1700 and 1661 (2 x CO), and 1531 and 1350 (NO_2); δ_H (400 MHz; $CDCl_3$) 7.72 (1H, d, *J* 9.2 Hz, 5-H), 8.57 (1H, s, 2-H), 8.58 (1H, dd, *J* 2.7 and 8.8 Hz, 7-H), 9.12 (1H, d, *J* 2.7 Hz, 8-H) and 10.35 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 120.5 (C-5), 120.6 (C-3), 122.7 (C-8), 125.7 (C-4a), 129.1 (C-7), 158.8 (C-8a), 145.7 (C-6), 160.8 (C-2), 174.4 (C-4) and 187.4 (CHO); *m/z* 219 (M^+, 0.4%) and 191 (100).

3.4 MORITA-BAYLIS-HILLMAN REACTIONS OF SUBSTITUTED 4*H*-1-BENZOPYRAN-4-ONE-3-CARBALDEHYDES[‡]

3.4.1 Reactions of 4*H*-1-benzopyran-4-one-3-carbaldehydes with methyl acrylate[§]

*3-(3-Hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **146** *and the corresponding dimer* **147**

4*H*-1-benzopyran-4-one-3-carbaldehyde **7** (1.00g, 5.75mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl acrylate (0.57ml, 6.3mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 3 weeks. The solvent was then evaporated to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:1)] to give, as a powder, *the chromone dimer* **147** (14%), m.p. 193-194 °C (Found: $\mathbf{M}^+$ 502.1250. $C_{28}H_{22}O_9$ requires *M*, 502.1257); ν_{max}(thin film)/cm^{-1} 1703, 1710, 1650 and 1630 (4 x CO); δ_H (400 MHz; $CDCl_3$) 3.12 and 3.38 (2H, dd, *J* 14.1 and 100.8 Hz, 13-H), 3.61 (3H, s, 12-H), 3.65 (3H, s, 16-H), 4.47 (1H, dd, *J* 1.8, and 16.9 Hz, 2-H_a) and 4.54 (1H, dd *J* 1.4 and 16.9 Hz, 2-H_b), 5.05 (1H, s, 9a-H), 6.90 (1H, t, *J* 7.7 Hz, 6-H), 6.97 (1H, d, *J* 8.3 Hz, 5-H), 7.30 (1H, s, 4-H), 7.34 (1H, t, *J* 8.4 Hz, 7-H), 7.41 (2H, m, 8'-H and 7'-H), 7.51 (1H, s, 17-H), 7.68 (1H, t, *J* 7.1 Hz, 6'-H), 7.72 (1H, dd, *J* 1.3 and 7.8 Hz, 8-H), 7.90 (1H, s, 2'-H) and 8.15 (1H, d, *J* 7.1 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.3 (C-4a), 51.8 (C-12), 52.1 (C-16), 65.8 (C-2), 99.9 (C-9a), 117.7 (C-5), 117.9 (C-7'), 119.9 (C-10a), 120.5 (C-4a'), 122.7 (C-6), 123.9 (C-8a'), 125.5 (C-8'), 126.2 (C-5'), 127.7 (C-8), 129.2 (C-3), 130.8 (C-14), 133.1 (C-17), 133.9 (C-6'), 136.0 (C-7), 136.1 (C-4), 154.9 (C-2'), 155.8 (C-3'), 157.1 (C-8a), 163.8 (C-11), 167.3 (C-15), 174.9 (C-4') and 191.3 (C-10); *m/z* 502 (M^+, 24%) and 243 (100).

Further chromatography of the residual material [HPLC on Partisil 10; elution with hexane-EtOAc (1:1)] gave, as a powder, *3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **146** (14%), m.p. 109-112 °C (Found: $\mathbf{M}^+$ 260.0690. $C_{14}H_{12}O_5$ requires *M*, 260.0685); ν_{max}(thin film)/cm^{-1} 3420 (OH), and 1718 and 1638 (2 x CO);

[‡] All yields, with the exception of adduct **171**, determined by ^{1}H NMR spectroscopy of the product mixture following work-up.

[§] Atom numbering follows the conventions adopted in Scheme 43 (p.59).

δ_H (400 MHz; $CDCl_3$) 3.73 (3H, s, OCH_3), 4.58 (1H, br s, 3'-OH), 5.60 (1H, s, 3'-H), 6.14 (1H, s, 1'-H), 6.41 (1H, s, 1'-H), 7.40 (1H, m, 7-H), 7.46 (1H, d, *J* 8.4 Hz, 5-H), 7.67 (1H, m, 6-H), 8.02 (1H, s, 2-H) and 8.18 (1H, dd, *J* 1.3 and 8.0 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 51.9 ($CO.OCH_3$), 67.6 (C-3'), 118.2 (C-5), 123.0 (C-3), 123.9 (C-4a), 125.4 (C-7), 125.6 (C-8), 126.7 (C-1'), 134.0 (C-6), 139.5 (C-2'), 154.3 (C-2), 156.2 (C-8a), 166.5 (CO.O) and 177.9 (C-4); *m/z* 260 (M^+, 7%) and 200 (100).

*6-Chloro-3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **148** *and the corresponding dimer* **149**

6-Chloro-4*H*-1-benzopyran-4-one-3-carbaldehyde **136** (1.00g, 4.80mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl acrylate (0.48ml, 5.3mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 4 weeks. The solvent was then evaporated to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (3:2)] to give, as a powder, *the chromone dimer* **149** (2%), m.p. 210-212 °C (Found: $\mathbf{MH}^+$ 572.0636. $C_{28}H_{20}{}^{35}Cl_2O_9$ requires *MH*, 572.0641); ν_{max}(thin film)/cm^{-1} 1712, 1710, 1649 and 1647 (4 x CO); δ_H (400 MHz; $CDCl_3$) 3.10 and 3.35 (2H, dd, *J* 14.1 and 89.3 Hz, 13-H), 3.67 (3H, s, 12-H), 3.70 (3H, s, 16-H), 4.50 and 4.59 (2H, 2 x d, *J* 16.9 and 28.9 Hz, 2-H), 5.04 (1H, s, 9a-H), 6.93 (1H, d, *J* 8.9 Hz, 8-H), 7.27 (1H, s, 4-H), 7.29 (1H, m 7-H), 7.42 (1H, d, *J* 8.9 Hz, 8'-H), 7.48 (1H, s, 17-H), 7.61 (1H, m 7'-H), 7.65 (1H, d, *J* 2.4 Hz, 5-H), 7.89 (1H, s, 2'-H) and 8.10 (1H, d, *J* 2.5 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.3 (C-4a), 51.9 (C-12), 52.2 (C-16), 66.0 (C-2), 100.0 (C-9a), 119.5 (C-8), 119.8 (C-8'), 120.5 (C-4a'), 120.8 (C-8a), 125.5 (C-5'), 127.0 (C-5), 128.5 (C-10a), 129.4 (C-3), 131.2 (C-14), 131.7 (C-6'), 132.3 (C-17), 134.3 (C-7'), 135.4 (C-7), 136.0 (C-4), 154.0 (C-8a'), 155.1 (C-2'), 155.6 (C-6), 163.8 (C-11), 167.1 (C-15), 173.6 (C-3'), 175.7 (C-4') and 190.3 (C-10); *m/z* 571 (M^+, 38%) and 277 (100).

Further chromatography of the residual material [HPLC on Partisil 10; elution with hexane-EtOAc (1:1)] gave, as a powder, *6-chloro-3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **148** (14%), m.p. 108-110 °C (Found: $\mathbf{MH}^+$ 295.0373. $C_{14}H_{11}{}^{35}ClO_5$ requires *MH*, 295.0373); ν_{max}(thin film)/cm^{-1} 3423 (OH), and 1718 and 1638 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.75 (3H, s, OCH_3), 4.50 (1H, d, *J* 6.1 Hz, 3'-OH),

5.60 (1H, s, 3'-H), 6.12 (1H, s, 1'-H), 6.44 (1H, s, 1'-H), 7.42 (1H, d, *J* 8.9 Hz, 8-H), 7.61 (1H, dd, *J* 2.4 and 8.9 Hz, 7-H), 8.04 (1H, s, 2-H) and 8.12 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 52.0 ($CO.OCH_3$), 67.5 (C-3'), 120.0 (C-8), 123.2 (C-3), 124.8 (C-6), 125.1 (C-5), 127.0 (C-1'), 131.4 (C-4a), 134.2 (C-7), 139.2 (C-2'), 154.5 (C-2), 154.6 (C-8a), 166.5 (CO.O) and 176.6 (C-4); *m/z* 294 (M^+, 3%) and 234 (100).

*6-Bromo-3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **150** *and the corresponding dimer* **151**

6-Bromo-4*H*-1-benzopyran-4-one-3-carbaldehyde **138** (1.00g, 3.95mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl acrylate (0.39ml, 4.4mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 8 weeks. The solvent was then evaporated to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (7:3)] to give, as a powder, *the chromone dimer* **151** (14%), m.p. 223-225 °C (Found: $\mathbf{M}^+$ 657.9471. $C_{28}H_{20}{}^{79}Br_2O_9$ requires *M*, 657.9474); ν_{max}(thin film)/cm^{-1} 1714, 1704, 1651 and 1646 (4 x CO); δ_H (400 MHz; $CDCl_3$) 3.11 and 3.33 (2H, dd, *J* 14.1 and 83.8 Hz, 13-H), 3.65 (3H, s, 16-H), 3.69 (3H, s, 12-H), 4.50 (1H, dd, *J* 2.1 and 17.0 Hz, 2-H_a) and 4.59 (1H, dd, *J* 1.8 and 17.0 Hz, 2-H_b), 5.02 (1H, s, 9a-H), 6.88 (1H, d, *J* 8.8 Hz, 8-H), 7.27 (1H, m, 4-H), 7.35 (1H, d, *J* 8.9 Hz, 7'-H), 7.41 (1H, dd, *J* 2.5 and 8.9 Hz, 7-H), 7.48 (1H, s, 17-H), 7.78 (1H, dd, *J* 2.5 and 8.9 Hz, 8'-H), 7.81 (1H, d, *J* 2.5 Hz, 5-H), 7.88 (1H, d, *J* 1.1 Hz, 2'-H) and 8.26 (1H, d, *J* 2.5 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.3 (C-4a), 52.0 (C-16), 52.2 (C-12), 66.0 (C-2), 100.0 (C-9a), 115.7 (C-8a), 119.2 (C-4a'), 119.8 (C-8), 120.1 (C-7'), 120.6 (C-3'), 121.3 (C-10a), 125.0 (C-6'), 128.8 (C-5'), 129.3 (C-3), 130.1 (C-5), 131.2 (C-14), 132.8 (C-17), 135.4 (C-4), 137.0 (C-8'), 138.8 (C-7), 154.4 (C-8a'), 155.0 (C-2'), 156.0 (C-6), 163.8 (C-15), 167.1 (C-11), 173.5 (C-4') and 190.2 (C-10); *m/z* 658 (M^+, 10%) and 323 (100).

Further chromatography of the residual material [HPLC on Partisil 10; elution with hexane-EtOAc (2:3)] gave, as a powder, *6-bromo-3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **150** (8%), m.p. 114-116 °C (Found: $\mathbf{M}^+$ 337.9790. $C_{14}H_{11}{}^{79}BrO_5$ requires *M*, 337.9789); ν_{max}(thin film)/cm^{-1} 3441 (OH), and 1716 and 1642 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.75 (3H, s, OCH_3), 4.38 (1H, d, *J* 7.8 Hz, 3'-OH), 5.60 (1H, d, *J* 7.7 Hz, 3'-H), 6.11 (1H, s, 1'-H), 6.42 (1H, s, 1'-H), 7.37 (1H, d, *J* 8.9 Hz, 8-H),

7.75 (1H, dd, *J* 2.5 and 8.9 Hz, 7-H), 8.03 (1H, d, *J* 0.6 Hz, 2-H) and 8.30 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 52.0 ($CO.OCH_3$), 67.5 (C-3'), 118.8 (C-6), 120.2 (C-8), 123.3 (C-3), 125.2 (C-4a), 127.0 (C-1'), 128.3 (C-5), 137.0 (C-7), 139.2 (C-2'), 154.5 (C-2), 155.0 (C-8a), 166.5 (CO.O) and 176.5 (C-4); *m/z* 338 (M^+, 17%) and 280 (100).

*6-Fluoro-3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **152** *and the corresponding dimer* **153**

6-Fluoro-4*H*-1-benzopyran-4-one-3-carbaldehyde **140** (1.00g, 5.21mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl acrylate (0.52ml, 5.7mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 8 weeks. The solvent was then evaporated to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (2:3)] to give, as a powder, *the chromone dimer* **153** (15%), m.p. 198-200 °C (Found: $\mathbf{M}^+$ 538.1074. $C_{28}H_{20}F_2O_9$ requires *M*, 538.1075); ν_{max}(thin film)/cm^{-1} 1723, 1715, 1651 and 1646 (4 x CO); δ_H (400 MHz; $CDCl_3$) 3.10 and 3.35 (2H, dd, *J* 4.1 and 92.7 Hz, 13-H), 3.64 (3H, s, 12-H), 3.69 (3H, s, 16-H), 4.49 (1H, dd, *J* 1.7 and 17.0 Hz, 2-H_a) and 4.56 (1H, dd, *J* 1.3 and 17.0 Hz, 2-H_b), 5.01 (1H, s, 9a-H), 6.97 (1H, dd, *J* 4.1 and 9.1 Hz, 5-H), 7.05 (1H, m, 7-H), 7.25 (1H, s, 4-H), 7.32 (1H, dd, *J* 2.9 and 8.0 Hz, 8-H), 7.39-7.48 (2H, m, 7'-H and 5'-H), 7.49 (1H, s, 17-H), 7.78 (1H, dd, *J* 2.8 and 8.1 Hz, 8'-H) and 7.90 (1H, s, 2'-H); δ_C (100 MHz; $CDCl_3$) 28.4 (C-13), 50.2 (C-4a), 51.9 (C-12), 52.2 (C-16), 65.9 (C-2), 100.1 (C-9a), 111.0 (C-8'), 112.7 (C-8), 119.5 (C-5), 119.8 (C-3'), 120.2 (C-5'), 120.6 (C-6), 122.3 (C-7'), 123.6 (C-7), 124.9 (C-6'), 129.4 (C-3), 131.1 (C-14), 132.8 (C-17), 135.4 (C-4), 151.9 (C-8a'), 153.3 and 157.8 (C-10a and C-8a), 155.1 (C-2'), 159.7 (C-4a'), 163.8 (C-11), 167.1 (C-15), 174.0 (C-4') and 190.6 (C-10); *m/z* 538 (M^+, 21%) and 261 (100).

Further chromatography of the residual material [HPLC on Partisil 10; elution with hexane-EtOAc (2:3)] gave, as a powder, *6-fluoro-3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-4*H*-1-benzopyran-4-one* **152** (11%), m.p. 140-142 °C (Found: $\mathbf{M}^+$ 278.0596. $C_{14}H_{11}FO_5$ requires *M*, 278.0591); ν_{max}(thin film)/cm^{-1} 3417 (OH), and 1714 and 1634 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.75 (3H, s, OCH_3), 4.42 (1H, d, *J* 7.8 Hz, 3'-OH), 5.60 (1H, d, *J* 7.9 Hz, 3'-H), 6.12 (1H, s, 1'-H), 6.46 (1H, s, 1'-H), 7.40 (1H, m, 7-H), 7.49 (1H, dd, *J* 4.2 and 9.2 Hz, 8-H), 7.81 (1H, dd, *J* 3.0 and 8.2 Hz, 5-H) and 8.05 (1H, s, 2-H); δ_C

(100 MHz; $CDCl_3$) 60.0 ($CO.OCH_3$), 67.6 (C-3'), 110.5 (C-5), 120.4 (C-8), 122.3 (C-7), 122.5 (C-3), 125.8 (C-4a), 126.9 (C-1'), 139.2 (C-2'), 152.5 (C-8a), 154.6 (C-2), 159.6 (C-6), 166.5 (CO.O) and 177.1 (C-4); *m/z* 278 (M^+, 34%) and 193 (100).

*3-(3-Hydroxy-2-methoxycarbonylpropen-3-yl)-6-methoxy-4*H*-1-benzopyran-4-one* **154** *and the corresponding dimer* **155**

6-Methoxy-4*H*-1-benzopyran-4-one-3-carbaldehyde **142** (1.00g, 4.90mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl acrylate (0.49ml, 5.4mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 4 weeks. The solvent was then evaporated to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:1): followed by HPLC on Partisil 10; elution with hexane-EtOAc (2:3)] to give two fractions:

i) *the chromone dimer* **155** (13%) (Found: $\mathbf{M}^+$ 562.1467. $C_{30}H_{26}O_{11}$ requires *M*, 562.1475); ν_{max}(thin film)/cm^{-1} 1722, 1715, 1651 and 1646 (4 x CO); δ_H (400 MHz; $CDCl_3$) 3.11 and 3.35 (2H, dd, *J* 14.3 and 87.6 Hz, 13-H), 3.60 (3H, s, 12-H), 3.70 (3H, s, 6-OCH_3), 3.78 (3H, s, 16-H), 3.89 (3H, s, 6'-OCH_3), 4.40 (1H, dd, *J* 2.1 and 16.9 and Hz, 2-H_a) and 4.53 (1H, dd, *J* 1.5 and 16.9 Hz, 2-H_b), 5.45 (1H, s, 9a-H), 6.70 (1H, s, 4-H), 6.73 (1H, d, *J* 9.0 Hz, 8-H), 6.99 (1H, dd, *J* 3.1 and 9.0 Hz, 7-H), 7.10 (1H, d, *J* 3.1 Hz, 5-H), 7.26 (1H, dd, *J* 3.1 and 9.0 Hz, 7'-H), 7.38 (1H, d, *J* 9.1 Hz, 8'-H), 7.50 (1H, d, *J* 3.1 Hz, 5'-H), 7.55 (1H, d, *J* 0.8 Hz, 17-H) and 7.91 (1H, d, *J* 1.1 Hz, 2'-H); δ_C (100 MHz; $CDCl_3$) 31.2 (C-13), 51.0 (C-4a), 51.7 (C-12), 52.2 (C-16), 55.7 (6-OCH_3), 55.9 (6'-OCH_3), 62.9 (C-2), 99.2 (C-9a), 105.3 (C-5'), 107.6 (C-5), 119.0 (C-10a), 119.2 (C-8), 119.4 (C-8'), 119.6 (C-8a'), 123.9 (C-7'), 124.5 (C-4a'), 125.6 (C-7), 129.9 (C-3), 130.6 (C-14), 133.3 (C-17), 134.9 (C-4), 150.7 (C-3'), 151.8 (C-8a), 154.3 (C-2'), 154.7 (C-6), 157.1 (C-6'), 163.9 (C-11), 167.8 (C-15), 175.1 (C-4') and 192.4 (C-10); *m/z* 562 (M^+, 37%) and 289 (100).

ii) *3-(3-hydroxy-2-methoxycarbonylpropen-3-yl)-6-methoxy-4*H*-1-benzopyran-4-one* **154** as an oil (14%) (Found: $\mathbf{M}^+$ 290.0780. $C_{15}H_{14}O_6$ requires *M*, 290.0790); ν_{max}(thin film)/cm^{-1} 3424 (OH), and 1722 and 1641 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.69 (3H, s, $CO.OCH_3$), 3.81 (3H, s, 6-OCH_3), 4.68 (1H, d, *J* 4.5 Hz, 3'-OH), 5.60 (1H, d, *J* 2.2 Hz, 3'-H), 6.09 (1H, s, 1'-H), 6.38 (1H, s, 1'-H), 7.18 (1H, dd, *J* 3.0 and 9.2 Hz, 7-H), 7.30 (1H, d, *J* 9.2 Hz, 8-H), 7.43 (1H, d, *J* 3.0 Hz, 5-H) and 7.97 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 51.7 ($CO.OCH_3$), 55.7 (6-OCH_3), 67.1 (C-3'), 104.3 (C-5), 119.4 (C-8), 122.2 (C-3), 123.9

(C-7), 124.3 (C-4a), 126.3 (C-1'), 139.7 (C-2'), 150.9 (C-8a), 154.0 (C-2), 156.8 (C-6), 166.3 (CO.O) and 177.3 (C-4); *m/z* 290 (M^+, 26%) and 151(100).

*3-(3-Hydroxy-2-methoxycarbonylpropen-3-yl)-5-methoxy-4*H*-1-benzopyran-4-one* **156**

5-Methoxy-4*H*-1-benzopyran-4-one-3-carbaldehyde **144** (1.00g, 4.90mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl acrylate (0.49ml, 5.4mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 6 weeks. The solvent was then evaporated to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:4): followed by HPLC on Partisil 10; elution with hexane-EtOAc (1:9)] to give *3-(3-hydroxy-2-methoxycarbonyl-propen-3-yl)-5-methoxy-4*H*-1-benzopyran-4-one* **156** as an oil (17%) (Found: $\mathbf{MH^+}$ 291.0869. $C_{15}H_{14}O_6$ requires *MH*, 291.0869); ν_{max}(thin film)/cm^{-1} 3417 (OH), and 1716 and 1651 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.70 (3H, s, $CO.OCH_3$), 3.96 (3H, s, 5-OCH_3), 4.75 (1H, br s, 3'-OH), 5.51 (1H, s, 3'-H), 6.28 (1H, s, 1'-H), 6.42 (1H, s, 1'-H), 6.79 (1H, d, *J* 8.3 Hz, 6-H), 7.00 (1H, dd, *J* 0.6 and 8.5 Hz, 8-H), 7.55 (1H, t, *J* 8.4 Hz, 7-H) and 7.87 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 51.8 ($CO.OCH_3$), 56.4 (5-OCH_3), 67.9 (C-3'), 106.4 (C-6), 110.2 (C-8), 114.6 (C-4a), 123.6 (C-3), 126.9 (C-1'), 134.1 (C-7), 139.3 (C-2'), 152.5 (C-2), 158.2 (C-8a), 160.0 (C-5), 166.5 (CO.O) and 178.1 (C-4); *m/z* 290 (M^+, 41%) and 230 (100).

*Attempted Morita-Baylis-Hillman reaction using 6-nitro-4*H*-1-benzopyran-4-one-3-carbaldehyde* **145**

6-Nitro-4H-1-benzopyran-4-one-3-carbaldehyde **145** (1.00g, 4.57mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl acrylate (0.45ml, 5.02mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 5 weeks. The solvent was then evaporated and the residue chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:1)]. However, no readily identifiable products were obtained.

3.4.2 Reaction of 4*H*-1-benzopyran-4-one-3-carbaldehyde (7) with methyl vinyl ketone[¶]

*3-(3-Hydroxy-2-acetylpropen-3-yl)-4*H*-1-benzopyran-4-one* **158** *and the corresponding dimer* **159**

4*H*-1-benzopyran-4-one-3-carbaldehyde **7** (1.00g, 5.75mmol) was dissolved in a minimum volume of $CHCl_3$. Methyl vinyl ketone (0.53ml, 6.3mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 3 weeks. The resulting precipitate was filtered off and then eluted through silica with EtOAc. Evaporation of the solvent gave, as a powder, *the chromone dimer* **159** (33%), m.p. 266-268 °C (Found: $\mathbf{M}^+$ 470.1364. $C_{28}H_{22}O_7$ requires *M*, 470.1366); ν_{max}(thin film)/cm^{-1} 1698, 1669, 1642 and 1606 (4 x CO); δ_H (400 MHz; $CDCl_3$) 2.30 (3H, s, 12-H), 2.42 (3H, s, 16-H), 3.25 (2H, s, 13-H), 4.47 (1H, dd. *J* 1.7 and 17.0 Hz, 2-H_a) and 4.58 (1H, dd, *J* 1.2 and 17.0 Hz, 2-H_b), 5.00 (1H, s, 9a-H), 6.87-6.95 (2H, m, 6-H and 5-H), 7.17 (1H, s, 4-H), 7.26 (1H, m, 8-H), 7.40-7.47 (3H, m, 17-H, 7'-H and 8'-H), 7.69-7.75 (2H, m, 6'-H and 7-H), 7.89 (1H, s, 2'-H) and 8.13 (1H, dd, *J* 1.3 and 7.9 Hz, 5'-H); δ_C (100 MHz; $CDCl_3$) 25.3 (C-12), 25.8 (C-16), 25.9 (C-13), 50.1 (C-4a), 65.9 (C-2), 99.8 (C-9a), 117.5 (C-5), 118.1 (C-7'), 120.0 (C-10a), 120.3 (C-4a'), 122.9 (C-6), 123.5 (C-8a'), 125.8 (C-8'), 126.1 (C-5'), 128.0 (C-7), 133.6 (C-17), 134.2 (C-6'), 136.1 (C-8), 136.6 (C-3), 136.7 (C-4), 139.1 (C-14), 154.1 (C-2'), 155.9 (C-3'), 157.0 (C-8a), 175.6 (C-4'), 191.5 (C-10), 196.9 (C-11) and 199.0 (C-15); *m/z* 470 (M^+, 23%) and 185 (100).

Following filtration, the solvent was evaporated from the filtrate to give an oil, which was then chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (7:3)]. Further chromatography [HPLC on Partisil 10; elution with hexane-EtOAc (2:3), followed by re-elution with the same mobile phase] gave, as a powder, *3-(3-hydroxy-2-acetylpropen-3-yl)-4*H*-1-benzopyran-4-one* **158** (3%), m.p. 86-88 °C (Found: $\mathbf{M}^+$ 244.0741. $C_{14}H_{12}O_4$ requires *M*, 244.0736); ν_{max}(thin film)/cm^{-1} 3420 (OH), and 1674 and 1638 (2 x CO) ; δ_H (400 MHz; $CDCl_3$) 2.34 (3H, s, $COCH_3$), 4.71 (1H, d, *J* 8.3 Hz, 3'-OH), 5.61 (1H, d, *J* 8.3 Hz, 3'-H), 6.29 (1H, s, 1'-H), 6.35 (1H, s, 1'-H), 7.41 (1H, m, 7-H), 7.47 (1H, d, *J* 8.0 Hz, 5-H), 7.68 (1H, m, 6-H), 8.07 (1H, s, 2-H) and 8.17 (1H, dd, *J*

[¶] Atom numbering follows the conventions adopted in Scheme 45 (p.70).

1.6 and 8.0 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 26.3 ($COCH_3$), 67.6 (C-1'), 118.3 (C-5), 122.8 (C-3), 123.9 (C-4a), 125.3 (C-7), 125.5 (C-8), 127.3 (C-1'), 134.0 (C-6), 147.6 (C-2'), 154.7 (C-2), 156.2 (C-8a), 178.1 (C-4) and 199.8 (CO.O); *m/z* 244 (M^+, 19%) and 201 (100).

3.4.3 Reactions of 4*H*-1-benzopyran-4-one-3-carbaldehydes with acrylonitrile**

*3-(3-Hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **160** *and the corresponding bischromone-acrylonitrile adduct* **161**

4*H*-1-benzopyran-4-one-3-carbaldehyde **7** (1.00g, 5.75mmol) was dissolved in a minimum volume of $CHCl_3$. Acrylonitrile (0.42ml, 6.3mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 5 weeks. The resulting precipitate was filtered off and then eluted through silica gel with EtOAc. Evaporation of the solvent from the eluate gave, as a powder, *3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **160** (12%), m.p. 68-70 °C (Found: $\mathbf{M}^+$ 227.0570. $C_{13}H_9NO_3$ requires *M*, 227.0582); ν_{max}(thin film)/cm^{-1} 3429 (OH), 2225 (CN) and 1629 (CO); δ_H (400 MHz; $CDCl_3$) 4.40 (1H, br s, 3'-OH), 5.31 (1H, s, 3'-H), 6.14 (1H, s, 1'-H), 6.32 (1H, s, 1'-H), 7.44 (1H, m, 7-H), 7.50 (1H, d, *J* 8.3 Hz, 5-H), 7.72 (1H, m, 6-H), 8.08 (1H, s, 2-H) and 8.18 (1H, dd, *J* 1.6 and 8.1 Hz, 8-H); δ_C (100 MHz; $CDCl_3$) 69.2 (C-3'), 116.7 and 124.2 (CN or C-2'), 118.4 (C-5), 121.3 (C-3), 123.7 (C-4a), 125.6 (C-8), 125.8 (C-7), 131.2 (C-1'), 134.5 (C-6), 153.9 (C-2), 156.3 (C-8a) and 177.7 (C-4); *m/z* 227 (M^+, 46%) and 210 (100).

Following filtration, the solvent was evaporated from the filtrate and the residue was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:1)] to give, as a powder, *the bischromone-acrylonitrile adduct* **161** (5%), m.p. 179-182 °C (Found: $\mathbf{M}^+$ 355.0849. $C_{22}H_{13}NO_4$ requires *M*, 355.0844); ν_{max}(thin film)/cm^{-1} 2225 (CN), and 1630 and 1600 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.59 (2H, s, 12-H), 7.39-7.49 (5H, m, 9-H, 5-H, 5'-H, 7-H and 7'-H), 7.68 (2H, m, 6-H and 6'-H), 7.97 (1H, s, 2'-H), 8.21 (2H, m, 8-H and 8'-H) and 8.66 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 31.6 (C-12), 110.0 (C-11),

** Atom numbering follows the conventions adopted in Scheme 46 (p.71).

118.0 (C-10), 119.3 (C-3), 119.8 (C-3'), 123.7 (C-4a), 123.8 (C-4a'), 118.2, 118.3, 125.4 and 126.2 (C-5, C-5', C-7, C-7'), 125.8 and 125.9 (C-8 and C-8'), 133.9 and 134.3 (C-6 and C-6'), 135.9 (C-9), 153.7 (C-2'), 155.0 (C-2), 156.1 (C-8a), 156.6 (C-8a'), 175.4 (C-4) and 176.8 (C-4'); *m/z* 355 (M^+, 61%) and 121(100).

*6-Chloro-3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **162** *and the corresponding bischromone-acrylonitrile adduct* **163**

6-Chloro-4*H*-1-benzopyran-4-one-3-carbaldehyde **136** (1.00g, 4.80mmol) was dissolved in a minimum volume of $CHCl_3$. Acrylonitrile (0.35ml, 5.3mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 4 weeks. The resulting precipitate was filtered off and then eluted through silica gel with EtOAc. Evaporation of the solvent from the eluate gave, as a powder, *6-chloro-3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **162** (20%), m.p. 131-133 °C (Found: $\mathbf{M}^+$ 261.0196. $C_{13}H_8{}^{35}ClNO_3$ requires *M*, 261.0193); ν_{max}(thin film)/cm^{-1} 3449 (OH), 2366 (CN) and1655 (CO); δ_H (400 MHz; $CDCl_3$) 4.12 (1H, d, *J* 3.9 Hz, 3'-OH), 5.34 (1H, s, 3'-H), 6.14 (1H, s, 1'-H), 6.31 (1H, s, 1'-H), 7.48 (1H, d, *J* 9.0 Hz, 8-H), 7.66 (1H, dd, *J* 2.5 and 9.0 Hz, 7-H), 8.09 (1H, s, 2-H) and 8.11 (1H, d, *J* 2.4 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 60.8 (C-3'), 116.6 and 124.0 (C-2' or CN), 120.1 (C-8), 121.6 (C-3), 124.6 (C-4a), 125.0 (C-5), 131.5 (C-1'), 131.8 (C-6), 134.7 (C-7), 154.1 (C-2), 154.7 (C-8a) and 176.3 (C-4); *m/z* 261 (M^+, 52%) and 209 (100).

Following filtration, the solvent was evaporated from the filtrate and the residue was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (3:2)] to give, as a powder, *the bischromone-acrylonitrile adduct* **163** (9%), m.p. 218-220 °C (Found: $\mathbf{M}^+$ 424.0143. $C_{22}H_{11}{}^{35}Cl_2NO_4$ requires *M*, 424.0144); ν_{max}(thin film)/cm^{-1} 2361 (CN), and 1700 and 1654 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.59 (2H, s, 12-H), 7.40 (1H, s, 9-H), 7.42-7.50 (2H, m, 8'-H and 7'-H), 7.60-7.69 (2H, m, 5-H and 7-H), 7.98 (1H, s, 2'-H), 8.16-8.21 (2H, m, 5'-H and 8-H) and 8.65 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 31.6 (C-12), 110.3 (C-11), 117.7 (C-10), 119.3 (C-3), 119.8 (C-3'), 120.0 and 120.1 (C-8' and C-7'), 124.6 and 124.7 (C-4a and C-6), 125.4 (C-5'), 125.6 (C-8), 131.5 and 132.0 (C-6' and C-4a'), 134.2 (C-5), 134.6 (C-7), 135.6 (C-9), 153.8 (C-2'), 154.4 (C-8a), 154.9 (C-8a'), 155.0 (C-2), 174.3 (C-4) and 175.7 (C-4'); *m/z* 424 (M^+, 17%) and 155 (100).

*6-Bromo-3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **164**

6-Bromo-4*H*-1-benzopyran-4-one-3-carbaldehyde **138** (1.00g, 3.95mmol) was dissolved in a minimum volume of $CHCl_3$. Acrylonitrile (0.29ml, 4.4mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 8 weeks. The resulting precipitate was filtered off and then eluted through silica gel with EtOAc. Evaporation of the solvent from the eluate gave, as a powder, *6-bromo-3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **164** (15%), m.p. 122-125 °C (Found: $\mathbf{M}^+$ 304.9724. $C_{13}H_8{}^{79}BrNO_3$ requires *M*, 304.9688); ν_{max}(thin film)/cm^{-1} 3419 (OH), 2228 (CN) and 1645 (CO); δ_H (400 MHz; $CDCl_3$) 4.10 (1H, br s, 3'-OH), 5.34 (1H, s, 3'-H), 6.13 (1H, s, 1'-H), 6.31 (1H, s, 1'-H), 7.40 (1H, d, *J* 8.9 Hz, 8-H), 7.79 (1H, dd, *J* 2.4 and 8.9 Hz, 7-H), 8.09 (1H, s, 2-H) and 8.30 (1H, d, *J* 2.3 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 68.8 (C-3'), 116.6 (CN), 119.3 (C-6), 120.3 (C-8), 121.7 (C-2'), 123.9 (C-3), 125.0 (C-4a), 128.2 (C-5), 131.5 (C-1'), 137.5 (C-7), 154.1 (C-2), 155.1 (C-8a) and 176.1 (C-4); *m/z* 305 (M^+, 44%) and 253 (100).

*6-Fluoro-3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **165** *and the corresponding bischromone-acrylonitrile adduct* **166**

6-Fluoro-4*H*-1-benzopyran-4-one-3-carbaldehyde **140** (1.00g, 5.21mmol) was dissolved in a minimum volume of $CHCl_3$. Acrylonitrile (0.38ml, 5.7mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 8 weeks. The resulting precipitate was filtered off and then eluted through silica gel with EtOAc. Evaporation of the solvent from the eluate gave, as a powder, *6-fluoro-3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one* **165** (31%), m.p. 58-60 °C (Found: $\mathbf{M}^+$ 245.0490. $C_{13}H_8FNO_3$ requires *M*, 245.0488); ν_{max}(thin film)/cm^{-1} 3183 (OH), 2230 (CN) and 1634 (CO); δ_H (400 MHz; $CDCl_3$) 4.13 (1H, d, *J* 7.2 Hz, 3'-OH), 5.32 (1H, d, *J* 6.7 Hz, 3'-H), 6.15 (1H, s, 1'-H), 6.33 (1H, s, 1'-H), 7.46 (1H, m, 7-H), 7.53 (1H, dd, *J* 4.2 and 9.2 Hz, 8-H), 7.81 (1H, dd, *J* 3.0 and 8.0 Hz, 5-H) and 8.09 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 68.7 (C-3'), 110.4 (C-5), 116.6 and 124.0 (C-2' or CN), 120.6 (C-8), 121.0 (C-3), 122.8 (C-7), 124.8 (C-4a), 131.5 (C-1'), 152.6 (C-8a), 154.2 (C-2), 159.7 (C-6) and 176.7 (C-4); *m/z* 245 (M^+, 57%) and 193 (100).

Following filtration, the solvent was evaporated from the filtrate and the residue was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:1)] to give, as a powder, *the bischromone-acrylonitrile adduct* **166** (24%), m.p. 242-244 °C (Found: $\mathbf{M}^+$ 391.0651. $C_{22}H_{11}F_2NO_4$ requires *M*, 391.0656); ν_{max}(thin film)/cm^{-1} 2216 (CN), and 1650 and 1646 (2 x CO); δ_H (400 MHz; $CDCl_3$) 3.60 (2H, s, 12-H), 7.39-7.45 (3H, m, 9-H, 7'-H and 7-H), 7.48-7.53 (2H, m, 8'-H and 8-H), 7.85 (2H, m, 5'-H and 5-H), 7.98 (1H, s, 2'-H) and 8.67 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 31.6 (C-13), 110.2 (C-11), 110.8 and 111.2 (C-5 and C-5'), 117.8 (C-10), 118.6 (C-3), 119.1 (C-3'), 120.4 and 120.6 (C-8' and C-8), 122.3 and 122.6 (C-7' and C-7), 124.8 and 124.9 (C-4a' and C-4a), 135.6 (C-9), 152.3 (C-8a), 152.8 (C-8a'), 153.8 (C-2'), 155.1 (C-2), 158.5 (C-6), 161.0 (C-6'), 174.7 (C-4) and 176.1 (C-4'); *m/z* 391 (M^+, 100%).

*3-(3-Hydroxy-2-cyanopropen-3-yl)-6-methoxy-4*H*-1-benzopyran-4-one* **167** *and the bischromone-acrylonitrile adduct* **171**[††]

6-Methoxy-4*H*-1-benzopyran-4-one-3-carbaldehyde **142** (1.00g, 4.90mmol) was dissolved in a minimum volume of $CHCl_3$. Acrylonitrile (0.36ml, 5.4mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 4 weeks. The solvent was then removed and the residue chromatographed [flash chromatography on silica gel; elution with $CHCl_3$-EtOAc (1:1)] to give two fractions:

i) *3-(3-hydroxy-2-cyanopropen-3-yl)-6-methoxy-4*H*-1-benzopyran-4-one* **167** as a powder [(20%), m.p. 114-117 °C (Found: $\mathbf{M}^+$ 257.0686. $C_{14}H_{11}NO_4$ requires *M*, 257.0688); ν_{max}(thin film)/cm^{-1} 3403 (OH), 2227 (CN) and 1638 (CO); δ_H (400 MHz; $CDCl_3$) 3.87 (3H, s, OCH_3), 4.50 (1H, br s, 3'-OH), 5.35 (1H, s, 3'-H), 6.09 (1H, s, 1'-H), 6.29 (1H, s, 1'-H), 7.27 (1H, dd, *J* 3.0 and 9.2 Hz, 7-H), 7.40 (1H, d, *J* 9.2 Hz, 8-H), 7.48 (1H, d, *J* 3.1 Hz, 5-H) and 8.09 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 55.9 (OCH_3), 68.8 (C-3'), 104.4 (C-5), 116.7 (C-3), 119.7 (C-8), 120.7 (C-4a), 124.2 and 124.3 (CN or C-2'), 124.6 (C-7), 131.1 (C-1'), 151.2 (C-8a), 153.7 (C-2), 157.3 (C-6) and 177.2 (C-4); *m/z* 257 (M^+, 75%) and 205 (100).

ii) *the bischromone-acrylonitrile adduct* **171** as a powder (4.0mg, 0.2%), m.p. 179 - 181 °C (Found: $\mathbf{M}^+$ 461.1110. $C_{25}H_{19}NO_8$ requires *M*, 461.1111); ν_{max}(thin film)/cm^{-1} 2930 (OH),

[††] Atom numbering for the adduct **171** follows the convention adopted in Scheme 48 (p.81).

2213 (CN), and 1694 and 1646 (2 x CO); δ_H (400 MHz; $CDCl_3$) 2.68 and 3.26 (2H, 2 x m, 3-H), 3.29 (1H, s, 11-H), 3.80 (3H, s, 7-OCH_3), 3.90 (3H, s, 6'-OCH_3), 5.43 (1H, d, *J* 2.8 Hz, 4a-H), 6.99 (1H, d, *J* 8.9 Hz, 8-H), 7.14 (1H, dd, *J* 3.2 and 8.9 Hz, 6-H), 7.29 (1H, d, *J* 3.1 Hz, 7'-H), 7.31 (1H, t, *J* 3.3 Hz, 5-H), 7.33 (1H, s, 1-H), 7.44 (1H, d, *J* 9.2 Hz, 5'-H), 7.58 (1H, d, *J* 3.0 Hz, 8'-H) and 8.71 (1H, s, 2'-H); δ_C (100 MHz; $CDCl_3$) 31.0 (C-3), 48.7 (C-11), 55.8 (7-OCH_3), 56.0 (6'-OCH_3), 100.8 (C-4a), 105.3 (C-8'), 107.6 (C-5), 109.7 (C-4), 118.0 (C-4a'), 118.4 (C-3'), 119.4 (C-8), 119.9 (C-5'), 121.0 (C-8a), 124.3 (C-9a and CN), 124.4 (C-7'), 124.9 (C-6), 136.6 (C-1), 151.0 (C-8a'), 151.6 (C-10a), 154.4 (C-7), 154.6 (C-2'), 157.5 (C-6'), 175.3 (C-4') and 190.8 (C-9); *m/z* 461 (M^+, 8%) and 415 (100).

*3-(3-Hydroxy-2-cyanopropen-3-yl)-6-methoxy-4*H*-1-benzopyran-4-one* **168**

5-Methoxy-4*H*-1-benzopyran-4-one-3-carbaldehyde **144** (1.00g, 4.90mmol) was dissolved in a minimum volume of $CHCl_3$. Acrylonitrile (0.36ml, 5.4mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 6 weeks. The solvent was then removed and the residue chromatographed [flash chromatography on silica gel; elution with 5% EtOH in $CHCl_3$: followed HPLC on Partisil 10; elution with hexane-EtOAc (3:7)] to give, as a powder, *3-(3-hydroxy-2-cyanopropen-3-yl)-6-methoxy-4*H*-1-benzopyran-4-one* **168** (20%), m.p. 97-100 °C (Found: $\mathbf{MH^+}$ 258.0766. $C_{14}H_{11}NO_4$ requires *MH*, 258.0766); ν_{max}(thin film)/cm^{-1} 3370 (OH), 2360 (CN) and 1645 (CO); δ_H (400 MHz; $CDCl_3$) 3.99 (3H, s, OCH_3), 4.59 (1H, d, *J* 7.3 Hz, 3'-OH), 5.18 (1H, d, *J* 5.6 Hz, 3'-H), 6.11 (1H, s, 1'-H), 6.31 (1H, s, 1'-H), 6.83 (1H, d, *J* 8.4 Hz, 6-H), 7.15 (1H, d, *J* 8.5 Hz, 8-H), 7.60 (1H, t, *J* 8.4 Hz, 7-H) and 7.92 (1H, s, 2-H); δ_C (100 MHz; $CDCl_3$) 56.5 (OCH_3), 69.6 (C-3'), 106.8 (C-6), 110.3 (C-8), 114.4 (C-4a), 116.9 (CN), 121.9 (C-3), 124.1 (C-2'), 131.2 (C-1'), 134.7 (C-7), 152.1 (C-2), 158.3 (C-8a), 160.0 (C-5) and 177.8 (C-4); *m/z* 257 (M^+, 19%) and 239 (100).

*Attempted Morita-Baylis-Hillman reaction using 6-nitro-4*H*-1-benzopyran-4-one-3-carbaldehyde* **145**

6-Nitro-4*H*-1-benzopyran-4-one-3-carbaldehyde **145** (1.00g, 4.57mmol) was dissolved in a minimum volume of $CHCl_3$. Acrylonitrile (0.33ml, 5.0mmol) and DABCO (0.20g, 1.8mmol) were added, and the resulting solution was stirred at room temperature for 5 weeks. The solvent was then evaporated and the residue chromatographed [flash

chromatography on silica gel; elution with 2 % EtOH in $CHCl_3$]. However, no readily identifiable products were obtained.

3.4.4 Yield optimisation studies

The use of ^{1}H NMR spectroscopy to calculate conversion efficiency was based on the assumption that the expected Morita-Baylis-Hillman product is the only product formed during the reaction period studied. Since all calculations were based on spectroscopic data obtained prior to dimer formation, this assumption appears to be justified. Due to the insolubility of the dimers and their consequent precipitation, yields of these products could not be quantified from an examination of the reaction solutions.

1. Morita-Baylis-Hillman reaction in dry chloroform under inert conditions

4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (1.00g, 5.75mmol), methyl acrylate (0.57ml, 6.3mmol) and DABCO (0.20g, 1.8mmol) were dissolved in a minimum volume of dry $CHCl_3$. The solution was then stirred under dry N_2 for 3 weeks. ^{1}H NMR spectroscopy of the crude reaction mixture showed no improvement in the yield of the Morita-Baylis-Hillman product **146** or the chromone dimer **147** as compared to the initial reaction (see p. 147).

2. Morita-Baylis-Hillman reaction in tetrahydrofuran

4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (1.00g, 5.75mmol), methyl acrylate (0.57ml, 6.3mmol) and DABCO (0.20g, 1.8mmol) were dissolved in a minimum volume of THF. The solution was then stirred for 3 weeks. ^{1}H NMR spectroscopy of the crude reaction mixture showed no improvement in the yield of the Morita-Baylis-Hillman product **146** or the chromone dimer **147** as compared to the initial reaction (see p. 147).

3. Morita-Baylis-Hillman reaction in chloroform-water

4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (1.00g, 5.75mmol), methyl acrylate (0.57ml, 6.3mmol) and DABCO (0.20g, 1.8mmol) were dispersed in a minimum volume of $CHCl_3$-water (1:1). The mixture was then stirred vigorously for 3 weeks. ^{1}H NMR spectroscopy

of the crude reaction mixture indicated a mixture of products containing none of the Morita-Baylis-Hillman product **146** nor the chromone dimer **147**.

4. Reaction of 4H-1-benzopyran-4-one-3-carbaldehyde **7** *with acrylonitrile and DABCO*

4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (12.9mg, 0.0741mmol) was dissolved in $CDCl_3$ (0.5ml). Acrylonitrile (7.34μl, 0.111mmol) and DABCO (16.6mg, 0.148mmol) were added to the stirred solution and the reaction was monitored daily by ^{1}H NMR spectroscopy for 35 d (Table 36).

Table 36: % Conversion to the Morita-Baylis-Hillman product **160** during 35 days.

Days	% Conversion	Days	% Conversion
1	11	7	28
2	18	11	42
3	25	14	50
4	23	21	55
5	25	28	57
6	26	35	64

5. Reactions of 4H-1-benzopyran-4-one-3-carbaldehyde **7** *with acrylonitrile and 3-hydroxyquinuclidine*

(a) 4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (12.9mg, 0.0741mmol) was dissolved in $CDCl_3$ (0.5ml). Acrylonitrile (7.34μl, 0.111mmol) and 3-hydroxyquinuclidine (18.8mg, 0.148mmol) were added to the stirred solution and the reaction was monitored hourly by ^{1}H NMR for the first 24 h, and thereafter, daily for 35 d (Tables 37 and 38).

Table 37: % Conversion to the Morita-Baylis-Hillman product **160** during the first 24 hours.

Hours	% Conversion	Hours	% Conversion
0	0	7	23
1	2	8	25
2	10	9	28
3	15	10	30
4	15	11	33
5	13	12	37
6	17	13	35

Hours	% Conversion	Hours	% Conversion
14	33	21	42
15	33	22	45
16	33	23	50
17	35	24	79
18	37		
19	40		
20	40		

Table 38: % Conversion to the Morita-Baylis-Hillman product **160** during the next 35 days.

Days	% Conversion	Days	% Conversion
2	57	11	50
3	59	14	50
4	44	21	43
5	60	28	39
6	64	35	47
7	56		

(b) 4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (12.9mg, 0.0741mmol) was dissolved in $CDCl_3$ (0.5ml). Acrylonitrile (7.34µl, 0.111mmol) and 3-hydroxyquinuclidine (47.1mg, 0.370mmol) were added to the stirred solution and the reaction was monitored hourly by ^1H NMR spectroscopy for 25 h (Table 39).

Table 39: % Conversion to the Morita-Baylis-Hillman product **160** during 25 hours.

Hours	% Conversion	Hours	% Conversion
0	0	7	50
1	14	8	53
2	24	9	55
3	30	10	58
4	35	11	62
5	41	12	62
6	47	13	62

Hours	% Conversion	Hours	% Conversion
14	67	21	82
15	69	22	92
16	69	23	81
17	68	24	88
18	70	25	89
19	68		
20	73		

6. *Reactions of* 4H-*1-benzopyran-4-one-3-carbaldehyde* **7**, *6-chloro-4*H-*1-benzopyran-4-one-3-carbaldehyde* **136** *and 6-methoxy-4*H-*1-benzopyran-4-one-3-carbaldehyde* **142** *with methyl acrylate and DABCO*

(a) 4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (12.9mg, 0.0741mmol) was dissolved in $CDCl_3$ (0.5ml). Methyl acrylate (10.0µl, 0.111mmol) and DABCO (16.6mg,

0.148mmol) were added to the stirred solution and the reaction was monitored daily by ^{1}H NMR spectroscopy for 15 d (Table 40).

Table 40: % Conversion to the Morita-Baylis-Hillman product **146** during 15 days.

Days	% Conversion	Days	% Conversion
1	26	9	81
2	40	10	90
3	57	11	73
4	50	12	77
5	60	13	74
6	87	14	75
7	94	15	84
8	80		

(b) 6-Chloro-4*H*-1-benzopyran-4-one-3-carbaldehyde **136** (15.4mg, 0.0741mmol) was dissolved in $CDCl_3$ (0.5ml). Methyl acrylate (10.0µl, 0.111mmol) and DABCO (16.6mg, 0.148mmol) were added to the stirred solution and the reaction was monitored daily by ^{1}H NMR spectroscopy for 15 d (Table 41).

Table 41: % Conversion to the Morita-Baylis-Hillman product **148** during 15 days.

Days	% Conversion	Days	% Conversion
1	8	9	85
2	18	10	67
3	27	11	63
4	30	12	63
5	38	13	65
6	48	14	79
7	49	15	70
8	58		

(c) 6-Methoxy-4*H*-1-benzopyran-4-one-3-carbaldehyde **142** (13.9mg, 0.0741mmol) was dissolved in $CDCl_3$ (0.5ml). Methyl acrylate (10.0μl, 0.111mmol) and DABCO (16.6mg, 0.148mmol) were added to the stirred solution and the reaction was monitored daily by ^{1}H NMR spectroscopy for 15 d (Table 42).

Table 42: % Conversion to the Morita-Baylis-Hillman product **154** during 15 days.

Days	% Conversion	Days	% Conversion
1	9	9	75
2	11	10	72
3	24	11	72
4	23	12	88
5	28	13	92
6	36	14	90
7	48	15	95
8	67		

7. *Morita-Baylis-Hillman reaction conducted as a melt*

(a) 4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (100mg, 0.575mmol), acrylonitrile (75.6μl, 1.15mmol) and DABCO (0.129g, 1.15mmol) were stirred at 60 °C in an oil bath. ^{1}H NMR spectroscopy of the crude reaction mixture showed a yield of *ca.* 43% of the Morita-Baylis-Hillman product **160** after 1 h and *ca.* 15% after 2 h.

(b) 4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (100mg, 0.575mmol), acrylonitrile (75.6μl, 1.15mmol) and 3-hydroxyquinuclidine (0.146g, 1.15mmol) were stirred at 60 °C in an oil bath. ^{1}H NMR spectroscopy of the crude reaction mixture showed a yield of *ca.* 23% of the Morita-Baylis-Hillman product **160** after 1 h and *ca.* 12% after 2 h.

8. Formation of the chromone dimer **147**

3-(3-Hydroxy-2-methoxycarbonylpropen-3-yl)-4H-1-benzopyran-4-one **146** (20mg, 0.077mmol) and DABCO (20.0mg, 178mmol) were heated at 80 °C in an oil bath for 3 h, following which ^{1}H NMR spectroscopy showed essentially 100% conversion to the chromone dimer **147**.

9. Formation of the bischromone-acrylonitrile adduct **161**

4*H*-1-Benzopyran-4-one-3-carbaldehyde **7** (12.9mg, 0.0741mmol), 3-(3-hydroxy-2-cyanopropen-3-yl)-4*H*-1-benzopyran-4-one **160** (16.8mg, 0.0741mmol) and DABCO (16.6mg, 0.148mmol) were dissolved in $CDCl_3$ (0.5ml). A precipitate was formed after 1 week which ^{1}H NMR spectroscopy showed to be the bischromone-acrylonitrile adduct **161**. Due to the insolubility of this compound, the yield could not be quantified, however, ^{1}H NMR spectroscopy showed the disappearance of the starting material.

3.5. MASS SPECTRAL FRAGMENTATION STUDIES

3.5.1 Electron Impact (EI) MS analysis of the Morita-Baylis-Hillman products (146), (152), (154), (160), (162), (165) and (167)

High-resolution EI data and metastable peak data were collected on a VG-70SEQ mass spectrometer equipped with an MSS MASPECII/32 data station (Cape Technikon Mass Spectrometry Unit).

3.5.2 Electrospray MS^n analysis of the chromone dimer (147) and the bischromone-acrylonitrile adduct (161)

Low resolution MS^n analyses were accomplished on a Finnigan Mat LCQ mass spectrometer. Samples, to which aliquots of trifluoroacetic acid were added, were injected into the Atmospheric Pressure Chemical Ionisation (APCI) source using an ethyl acetate mobile phase and vaporised at 450 °C. Fragmentation pathways described in section 2.3.6 (pp. 86 - ff) of the discussion and shown in Figures 33 and 35 were obtained by sequential fragmentation beginning with the molecular ion. By way of illustration, spectra for the fragmentation of the chromone dimer **147** (path I) summarised in Figure 33 are shown in Figure 36.

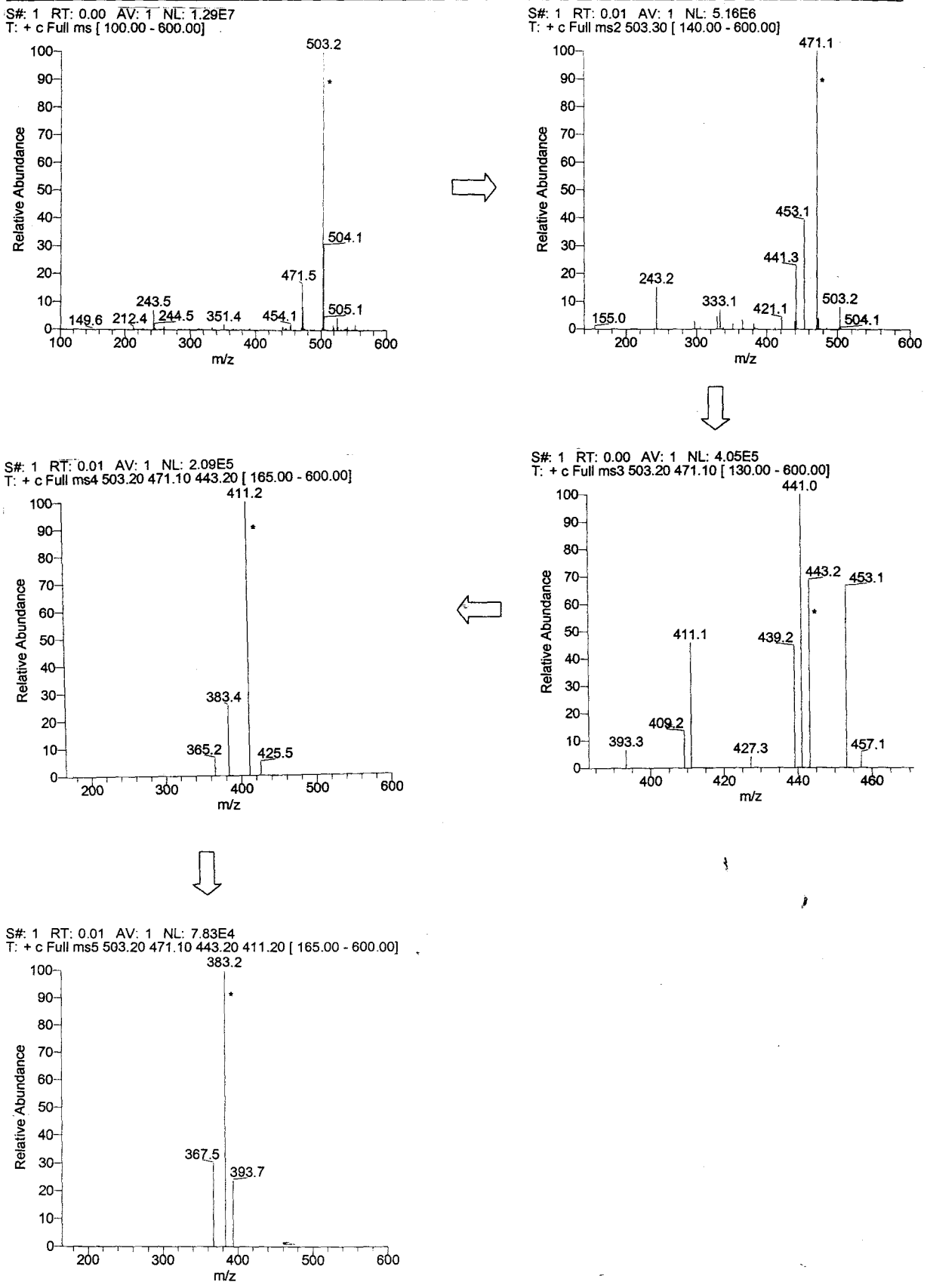


Figure 36: MS^4 fragmentations of the chromone dimer **147** showing the pathway: *m/z* 502 → *m/z* 471 → *m/z* 443 → *m/z* 411 → *m/z* 383. Each ion chosen to be fragmented is denoted with an asterisk.

3.6 SYNTHETIC APPROACHES TO RIETONE A

3.6.1 Preparation of 2-substituted chromones

1-(2-Hydroxyphenyl)-1,3-butanedione[134] **175**

Sodium sand (4.0g, 0.17mol) was added to a solution of *o*-hydroxyacetophenone (4.4ml, 37mmol) in EtOAc (30ml, 0.3mol) under dry N_2. The mixture was then boiled under reflux for 0.5 h and left to stand overnight at room temperature. Ice (25g) was added and the resulting precipitate filtered off and dissolved in Et_2O. The solution was acidified with dilute glacial acetic acid and the resulting precipitate filtered off to give 1-(2-hydroxyphenyl)-1,3-butanedione **175** (3.7g, 56%), m.p. 88-90 °C (lit.,[134] 95 °C); υ_{max} (KBr)/cm^{-1} 1705 (CO) and 3400 (OH); *m/z* 178 (M^+, 38%) and 121 (100).

2-Methylchromone[135] **176**

1-(2-hydroxyphenyl)-1,3-butanedione **175** (3.10g, 17.4mmol) was dissolved in glacial acetic acid (14ml) and conc. HCl (0.5ml) and the solution was boiled under reflux for 40 min. The mixture was then added to ice water (50ml) and the aqueous solution extracted with Et_2O (3 x 30ml). The organic layer was separated, washed successively with 10% aq. NaOH (3 x 20ml) and brine (30ml) and then dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give 2-methylchromone **176** (0.95g, 25%), m.p. 63 - 65 °C (lit.,[136] 71 °C); ν_{max}(KBr)/cm^{-1} 1705 (CO); δ_H (400 MHz; $CDCl_3$) 2.30 (3H, s, CH_3), 6.10 (1H, s, 3-H), 7.30 (2H, m 6-H and 8-H), 7.55 (1H, m, 7-H) and 8.10 (1H, dd, *J* 0.3 and 6.3 Hz, 5-H); δ_C (100 MHz; $CDCl_3$) 20.4 (CH_3), 110.4 (C-8), 117.6 (C-5), 123.4 (C-7), 124.7 (C-6), 125.4 (C-4a), 133.3 (C-3), 156.3 (C-8a), 166.0 (C-2) and 178.0 (C-4); *m/z* 160 (M^+, 100%).

Ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate[115] **177**

A solution of *o*-hydroxyacetophenone (7.20ml, 59.8mmol) and diethyl oxalate (12.0ml, 88.4mmol) was added dropwise to an ethanolic solution of sodium ethoxide [generated *in situ* by adding sodium (4.10g, 178mmol) to dry EtOH (120ml)] under dry N_2, and the resulting mixture was boiled under reflux for 30 min. The resulting yellow slurry was then added to Et_2O (450ml) and the mixture left to stand for 0.5 h, after which 2-**M**-HCl (150ml) was added. The organic layer was separated, dried with anhydrous $MgSO_4$ and

the solvent removed *in vacuo* to give, as an oil, ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate **177** (10g, 74%); δ_H (60 MHz; $CDCl_3$) 1.45 (3H, t, CH_3), 4.40 (2H, q, CH_2CH_3), 7.05 (2H, s, $COCH_2$) and 7.30 – 8.30 (4H, m, ArH).

Ethyl chromone-2-carboxylate[115] **178**

Ethyl 4-(2-hydroxyphenyl)-2,4-dioxobutanoate **177** (10.0g, 42.4mmol) was dissolved in a mixture of glacial acetic acid (60ml) and conc. HCl (1.0ml) and the resulting solution boiled under reflux for 40 min. The solution was then added to ice water (200ml) and the resulting precipitate filtered off and dissolved in EtOAc (100ml). The organic layer was separated, washed with 5% aq. $NaHCO_3$ (3 x 30ml) and dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* to give ethyl chromone-2-carboxylate **178** (5.5g, 60%), m.p. 69 - 70 °C (lit.,[137] 71 – 72 °C); ν_{max}(KBr)/cm^{-1} 1740 (CO.O) and 1650 (CO); δ_H (400 MHz; $CDCl_3$) 1.45 (3H, t, *J* 7.2 Hz, CH_3), 4.50 (2H, q, *J* 7.2 Hz, CH_2), 7.15 (1H, s, 3-H), 7.38 (1H, m, 6-H), 7.54 (1H, dd, *J* 0.6 and 8.6 Hz, 8-H), 7.68 (1H, m, 7-H) and 8.12 (1H, dd, *J* 1.4 and 8.0 Hz ,5-H); δ_C (100 MHz; $CDCl_3$) 14.0 (CH_3), 62.9 (CH_2), 114.6 (C-7), 118.6 (C-6), 124.3 (C-8), 125.6 (C-4a), 125.7 (C-3), 134.6 (C-5), 152.1 (C-8a), 155.8 (C-2), 160.4 (CO.O) and 178.2 (C-4); *m/z* 218 (M^+, 100%).

3.6.2 Ring-opening studies

Ring-opening of 2-methylchromone[92] **176**

A solution of 2-methylchromone **176** (2.07g, 12.9mmol) in dry THF (25ml) was cooled, under dry N_2, to –78 °C in an acetone-liquid nitrogen bath. Butyllithium (1.6-**M** solution in hexane; 8.13ml, 13.0mmol) was added dropwise and the resulting solution stirred for 0.5 h. The reaction was quenched with 7% aq. $NaHCO_3$; after acidification with 10% HCl, the mixture was extracted with EtOAc and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (7:3): followed by preparative TLC on silica gel; elution with hexane-EtOAc (7:3)]. ^{1}H NMR spectroscopy of the chromatographed material indicated the absence of the desired product.

The reaction was repeated with the addition of acetyl chloride (1.01g, 12.9mmol) prior to work-up. The solution was extracted and chromatographed as before. However, ^{1}H NMR spectroscopy of the isolated material showed the reaction had been unsuccessful.

***Ring opening of ethyl chromone-2-carboxylate*[92] 178**

Ethyl chromone-2-carboxylate **178** (1.42g, 6.52mmol) was dissolved in dry THF (25ml) and the solution cooled, under dry N_2, to –78 °C in an acetone-liquid nitrogen bath. Butyllithium (1.6-**M** solution in hexane; 5.00ml, 8.00mmol) was added dropwise and the resulting solution stirred for 0.5 h. The solution was then quenched with 7% aq. $NaHCO_3$, acidified with 10% HCl and extracted with EtOAc. The organic solution was dried over anhydrous $MgSO_4$, and the solvent removed *in vacuo* to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane- EtOAc (7:3): followed by HPLC on Partisil 10; elution with hexane- EtOAc (7:3)]. ^{1}H NMR spectroscopy of the isolated material indicated the absence of the desired product.

3.6.3 Attempted alternative approach to 1-(2-hydroxyphenyl)-3-methylhept-2-en-1-one (180)

1-(2-Hydroxyphenyl)-1,3-butanedione **175** (1.16g, 6.52mmol) was dissolved in dry THF (30ml) and the solution cooled, under dry N_2, to –78 °C in an acetone-liquid nitrogen bath. Butyllithium (1.6-**M** solution in hexane; 10.0ml, 16.0mmol) was added dropwise and the solution stirred for 0.5 h. The solution was then quenched with 7% aq. $NaHCO_3$, acidified with 10% HCl and extracted with EtOAc. The organic solution was dried over anhydrous $MgSO_4$, and the solvent removed *in vacuo* to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (7:3)]. ^{1}H NMR spectroscopy of the isolated material showed that the mixture contained a number of side products consistent with the presence of compounds **181**, **182**, **183** and **184** but none of the desired compound.

3.6.4 Synthesis of the side-chain equivalent IV

Dimethyl (4-methyl-2-oxo-3-pentenyl)phosphonate[116] **187**

Dimethyl methanephosphonate **192** (3.41g, 27.5mmol) was dissolved in dry THF (30ml) under dry N_2 and the temperature lowered to –78 °C in an acetone-liquid nitrogen bath. Butyllithium (15% in hexane; 20.0ml, 33.0mmol) was then added dropwise and the resulting solution stirred for 30 min. The temperature was raised to –40 °C and Cu(I)I (5.24g, 27.5mmol) added. Senecyl chloride **193** (3.26g, 27.5mmol) was then added dropwise at –35 °C, and the yellow solution allowed to warm to room temperature. The resulting precipitate was removed, the solution concentrated and the residue diluted with CH_2Cl_2 (50ml). The organic solution was then washed with brine (3 x 40ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated and the resulting oil distilled *in vacuo* to give dimethyl (4-methyl-2-oxo-3-pentenyl)phosphonate **187** (2.3g, 42%), b.p. 116 °C/1.5mmHg (lit.,[116] 113 - 118 °C/1mmHg); ν_{max}(thin film)/cm^{-1} 1683 (CO) and 1251 (PO); δ_H (400 MHz; $CDCl_3$) 1.79 (3H, s, 5-H), 2.04 (3H, s, 6-H), 2.97 (2H, d, *J* 22.4 Hz, 4-H), 3.65 and 3.68 [6H, 2 x s, $PO(OCH_3)_2$] and 6.10 (1H, s, 3-H); δ_C (100 MHz; $CDCl_3$) 20.5 (C-6), 27.2 (C-5), 42.0 (C-1), 54.2 [$PO(OCH_3)_2$], 123.2 (C-3), 157.9 (C-4) and 190.0 (C-2); *m/z* 206 (M^+, 100%).

(E)-2-Methyl-2,5-heptadien-4-one[116] **194**

A solution of the phosphonate ester **187** (1.00g, 4.85mmol) in dry DME (2ml) was added dropwise to NaH (60% dispersion in oil; 0.19g, 4.9mmol) in dry DME (2ml) under dry N_2. A solution of acetaldehyde (0.21g, 4.8mmol) in dry DME (2ml) was then added, and the resulting mixture heated at 70 °C for 3 h. The solvent was then removed, the residue diluted with Et_2O (20ml), and the resulting precipitate filtered. The filtrate was washed with brine (2 x 20ml) and dried over anhydrous $MgSO_4$. The solvent was then evaporated and the resulting oil distilled *in vacuo* to afford (*E*)-2-methyl-2,5-heptadien-4-one **194** (0.31g, 53%), b.p. 80 °C/15mmHg (lit.,[137] 75 - 85 °C/15mmHg); ν_{max}(thin film)/cm^{-1} 1720 (CO); δ_H (400 MHz; $CDCl_3$) 1.82 (3H, dd, *J* 1.7 and 6.9 Hz, 7-H), 1.87 (3H, d, *J* 1.2 Hz, 1-H), 2.09 (3H, d, *J* 1.1 Hz, 8-H), 6.09 (1H, dq, *J* 1.7 and 15.6 Hz, 5-H), 6.15 (1H, m, 3-H) and 6.78 (1H, m, 6-H); δ_C (100 MHz; $CDCl_3$) 18.0 (C-7), 20.7 (C-8), 27.6 (C-1), 122.7 (C-3), 133.5 (C-5), 141.5 (C-6), 155.2 (C-2) and 190.3 (C-4); *m/z* 124 (M^+, 100%).

4,4-(Ethylenedithio)-2-butylphosphonium bromide[117] **195**

A solution of 3-penten-2-one (0.84g, 10mmol) in $CHCl_3$ (20ml) was added dropwise to a solution of triphenylphosphine (2.88g, 11.0mmol) and 48% aq. HBr (2.40ml) in $CHCl_3$ (20ml). The mixture was stirred overnight, after which 1,2-ethanedithiol (1.13g, 12.0mmol) and PTSA (0.10g) were added and the resulting mixture boiled under reflux for 4 h. Triethylamine (1.60ml) was added to the cooled mixture which was then stirred for 5 min. The organic layer was separated, washed with water (4 x 20ml), dried over anhydrous $MgSO_4$ and then added dropwise to Et_2O (700ml). The resulting precipitate was filtered to afford 4,4-(ethylenedithio)-2-butylphosphonium bromide **195** (4.4g, 87%), m.p. 172 - 174 °C (lit.,[117] 172 °C); δ_H (400 MHz; $CDCl_3$) 1.69 (3H, dd, *J* 6.9 and 20.2 Hz, 1-H), 1.89 (3H, s, 5-H), 1.99 (1H, m, 3-H) and 2.45 (1H, m, 3-H), 3.29 and 3.39 (4H, m, 1'- and 2'-H), 4.45 (1H, m, 2-H) and 7.87 (15H, m, PPh_3); δ_C (100 MHz; $CDCl_3$) 16.9 (C-5), 26.7 (C-1), 34.2 and 44.4 (C-1' and C-2'), 40.5 (C-3), 116.7 (C-4), 117.6 (C-2), 130.6, 130.7, 130.8, 130.9, 134.0, 134.1, 134.2, 135.1 and 135.2 (PPh_3); *m/z* 502 (M^+, 4%) and 189 (100).

3-Bromopropanal[118,119] **185**

HBr gas was bubbled through a solution of acrolein (18.7g, 334mmol) and dicinnamalacetone indicator (0.010g, 0.035mmol) in CH_2Cl_2 (100ml) under dry N_2 until saturation (achieved when the indicator changes from yellow to red), and stirred overnight. The solution was then washed with water (3 x 30ml) and the solvent removed *in vacuo*. ^1H NMR spectroscopy showed the presence of 3-bromopropanal, however, during attempted distillation, the product appeared to polymerise.

In a subsequent preparation, the crude reaction mixture was used without purification in the synthesis of the thioacetal **197** (see page 173).

The Ylide[116] **196**

A suspension of the phosphonium bromide **195** (1.0g, 2.0mmol) in dry THF (5ml) was added dropwise to NaH (60% dispersion in oil; 0.08g, 2mmol) in dry THF (2ml) under dry N_2 and the mixture stirred overnight. The resulting mixture was washed with brine (10ml), dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo* to afford the ylide **196** (0.65g, 77%) [δ_H (400 MHz; $CDCl_3$) 1.38 (3H, dd, *J* 7.0 and 17.3 Hz, 5-H), 1.70 (3H, s, 1-

H), 2.02 (1H, ddd, *J* 2.1, 8.7 and 15.0 Hz, 3-H), 2.39 (1H, t, *J* 15.7 Hz, 3-H), 3.18 and 3.29 (4H, m, 1'- and 2'-H) and 7.50 (15H, m, PPh_3)], which was used without further purification.

Synthesis of the thioacetal **197**

The ylide **196** (0.65g, 1.5mmol) was dissolved in a minimum volume of dry CH_2Cl_2 under dry N_2. Crude 3-bromopropanal **185** (*ca.* 2mmol) solution in CH_2Cl_2 was then added and the reaction mixture was stirred, the progress of the reaction being monitored by TLC. After completion of the reaction, the residue was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (7:3): followed by preparative layer chromatography on silica gel; elution with hexane-EtOAc (9:1)]. However, the expected product could not be detected by ^{1}H NMR spectroscopy.

The Ylide[116] **(198)**

A suspension of 4,4-(ethylenedithio)-2-butylphosphonium bromide **195** (0.5g, 1.0mmol) in dry THF (5ml) was added dropwise to NaH (60% dispersion in oil; 0.04g, 1.0mmol) in dry THF (2ml) under dry N_2. The mixture was then heated at 50 °C for 3 h and stirred overnight at room temperature. The solvent was removed and the residue chromatographed [preparative layer chromatography on silica gel; elution with hexane-EtOAc (7:3)]. However, ^{1}H NMR spectroscopy of the isolated material showed that the reaction had been unsuccessful.

3.6.5 Alkylation of 3-hydroxyphenethyl alcohol (203) (Route I)

2,6-Dimethyl-8-hydroxy-2,6-octadienal[121,122] **204**

Selenium dioxide (147mg, 1.32mmol) in absolute EtOH (1ml) was added to geraniol **208** (204mg, 1.32mmol) in absolute EtOH (2ml) at 50 °C and the solution stirred overnight at room temperature. The resulting black precipitate was filtered off, the solvent removed from the filtrate and the residue dissolved in Et_2O. The organic solution was then washed with 10% aq. $NaHCO_3$ (4 x 20ml) and brine (2 x 20ml), and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give an oil which was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (2:3)] to afford 2,6-dimethyl-8-

hydroxy-2,6-octadienal **204** (31mg, 14%); δ_H (400 MHz; $CDCl_3$) 1.69 and 1.73 (6H, 2 x s, 2- and 6-CH_3), 2.20 (2H, t, *J* 7.5 Hz, 4-H), 2.48 (2H, t, *J* 7.5 Hz, 5-H), 4.15 (2H, d, *J* 6.7 Hz, 8-H), 3.30 (1H, br s, OH), 5.44 (1H, t, *J* 6.7 Hz, 7-H), 6.45 (1H, t, *J* 7.2 Hz, 3-H) and 9.38 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 9.2 (2-CH_3), 16.1 (6-CH_3), 27.0 (C-4), 37.8 (C-5), 59.2 (C-8), 124.6 (C-7), 137.7 (C-6), 139.6 (C-2), 153.6 (C-3) and 195.1 (CHO); *m/z* 168 (M^+, 100%).

Methyl [3-(3,7-dimethyl-2,6-octadienyl)-4-hydroxyphenyl]acetate[123] **210**

Geraniol **208** (1.00g, 6.48mmol) and methyl (4-hydroxyphenyl)acetate **209** (1.80g, 10.8mmol) were dissolved in dry dioxane (15ml) under dry N_2 and the resulting solution was cooled to 10 °C in an ice bath. $BF_3.OEt_2$ (1.43ml, 11.3mmol) was added dropwise and the solution stirred at 10 °C for 1.5 h and then overnight at room temperature. The solution was then poured into water (15ml) and extracted with hexane (3 x 20ml). The organic layers were combined, washed with water (2 x 20ml) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give an oil which was chromatographed [chromatography on silica gel on a chromatotron, 4mm plate; elution with hexane-EtOAc (4:1)] to afford the ester **210** (0.46g, 24%); δ_H (400 MHz; $CDCl_3$) 1.58, 1.66 and 1.68 (9H, 3 x s, 3 x CH_3), 2.01 (2H, m, 4"-H), 2.08 (2H, m, 5"-H), 3.50 (2H, s, 2-H), 3.67 (3H, s, OCH_3), 4.13 (2H, d, *J* 6.9 Hz, 1"-H), 5.09 (1H, m, 6"-H), 5.40 (1H, m, 2"-H), 6.70 (1H, m, 5'-H) and 6.96 (2H, m, 2'- and 6'-H); δ_C (100 MHz; $CDCl_3$) 16.1, 17.6 and 25.6 (3 x CH_3), 26.4 (C-5"), 39.6 (C-2), 40.4 (C-4"), 51.9 (OCH_3), 59.2 (C-1"), 115.6 (C-5'), 123.3 (C-2"), 123.9 (C-6"), 125.4 (C-3'), 127.5 (C-1'), 127.8 (C-2'), 130.5 (C-6'), 131.6 (C-7"), 137.5 (C-3"), 153.7 (C-4') and 172.6 (C-1); *m/z* 302 (M^+, 100%).

3.6.6 Acylation of 3-hydroxyphenethyl alcohol (203) (Route II)

3,3-Dimethylacryloyl chloride[124] **212**

Freshly distilled $SOCl_2$ (2.19ml, 30.0mmol) was added to 3,3-dimethylacrylic acid (**211**) and the resulting solution stirred for 3.5 h. The residual $SOCl_2$ was removed *in vacuo* to give an oil which was distilled *in vacuo* to afford 3,3-dimethylacryloyl chloride (**212**) (2.9g, 81%), b.p. 62 °C/30mmHg (lit.,[124] 59–61 °C/30mmHg). Infra-red spectroscopy

confirmed the disappearance of the OH group, and the product was used without further purification.

The isomeric esters[101] **213** and **214**

3-Hydroxyphenethyl alcohol **203** (0.50g, 3.6mmol) in dry THF (2ml) was added to NaH (60% dispersion in oil; 0.15g, 3.6mmol) in dry THF (2ml) under dry N_2 and the mixture cooled to 0 °C in an ice-salt bath. 3,3-Dimethylacryloyl chloride **212** (0.64g, 5.4mmol) was then added and the mixture stirred at 0 °C for 1 h and then overnight at room temperature. The solvent was removed *in vacuo* and the residue dissolved in EtOAc, washed with 5% aq. $NaHCO_3$ (3 x 50ml) and brine (50ml). The organic layer was then dried over anhydrous $MgSO_4$ and the solvent removed *in vacuo* to give an oil which was distilled to afford a mixture. The mixture was chromatographed [flash chromatography on silica gel; elution with hexane-EtOAc (1:1)] to give the phenyl ester **213** (0.11g, 14%) [δ_H (400 MHz; $CDCl_3$) 1.98 and 2.20 (6H, 2 x s, 2 x CH_3), 2.50 (1H, br s, OH), 2.80 (2H, d, *J* 6.6 Hz, $ArCH_2$), 3.77 (2H, d, *J* 6.6 Hz, OCH_2), 5.90 (1H, s, 2-H), 6.91 (1H, s, 2'-H), 6.94 (1H, m, 6'-H), 7.05 (1H, d, *J* 7.6 Hz, 4'-H) and 7.28 (1H, m, 5'-H); δ_C (100 MHz; $CDCl_3$) 20.3 and 27.5 (2 x CH_3), 38.8 ($ArCH_2$), 63.0 (OCH_2), 115.0 (C-2), 119.6 (C-6'), 122.2 (C-2'), 126.2 (C-4'), 129.1 (C-5'), 140.4 (C-3'), 150.6 (C-1'), 159.9 (C-3) and 165.0 (C-1); *m/z* 220 (M^+, 100%)] and the isomeric ester **214** (0.12g, 15%) [δ_H (400 MHz; $CDCl_3$) 1.89 and 2.16 (6H, 2 x s, 2 x CH_3), 2.55 (1H, br s, OH), 2.89 (2H, t, *J* 7.1 Hz, 2'-H), 4.30 (2H, t, *J* 7.1 Hz, 1'-H), 5.68 (1H, s, 2-H), 6.75 (3H, m, 4"-, 2"- and 6"-H) and 7.13 (1H, t, *J* 7.6 Hz, 5"-H); δ_C (100 MHz; $CDCl_3$) 20.2 and 27.3 (2 x CH_3), 34.9 (C-2'), 64.2 (C-1'), 113.5 (C-4"), 115.8 (C-2 and C-2"), 120.8 (C-6"), 129.5 (C-5"), 139.5 (C-1"), 156.1 (C-3"), 157.4 (C-3) and 167.2 (C-1); *m/z* 220 (M^+, 100%)].

Preparation of nickel peroxide[125]

A solution of 6 % aq. NaOCl (150ml) and NaOH (21g) was added dropwise to $NiSO_4.6H_2O$ (65g) in water (200ml) and the resulting solution stirred for 0.5 h. The precipitated black solid was filtered off, washed with water, crushed to a fine powder and then dried under reduced pressure to afford Ni_2O_3.

Attempted preparation of (3-hydroxyphenyl)acetic acid **215**

Method 1[125]

3-Hydroxyphenethyl alcohol **203** (0.50g, 3.6mmol) and NaOH (0.18g, 4.5mmol) were dissolved in water (10ml). Ni_2O_3 (2.27g, 7.24mmol) was then added and the mixture stirred at 30 °C for 1 h and overnight at room temperature. The mixture was filtered and the filtrate extracted with Et_2O (5 x 75ml). The organic layers were combined and dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo* to give an oil (0.61g), which ^{1}H NMR and infra-red spectroscopy showed to be identical to the starting material.

Method 2[126]

3-Hydroxyphenethyl alcohol **203** (0.50g, 3.6mmol) was dissolved in acetone (10ml). Jones reagent [prepared by dissolution of $K_2Cr_2O_7$ (19.4g, 70.0mmol) in water (60ml) and conc. H_2SO_4 (15ml)][138] was added dropwise, maintaining the temperature at 30°C with the use of an ice bath, until the solution was a permanent orange colour. The solution was then stirred overnight and extracted with Et_2O (5 x 50ml). The organic layers were combined and dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo* to give an oil which ^{1}H NMR spectroscopy showed to be identical to the starting material.

Dimethyl carboxymethanephosphonate[128] **216**

A solution of dimethyl methanephosphonate **192** (13.8g, 0.111mol) in dry THF (20ml) was added dropwise to a solution of butyllithium (15% in hexane; 50.0ml, 0.117mol) in dry THF (70ml) at –65 °C under dry N_2. The mixture was stirred at –65 °C for 10 min, then poured into a saturated dry ice/Et_2O solution, and the resulting mixture stirred for 10 min. The mixture was then allowed to warm to room temperature. Water (100ml) was added, the aqueous layer separated, acidified to pH 1 with 2-**M** H_2SO_4, saturated with NaCl and extracted into CH_2Cl_2 (3 x 50ml). The organic layers were combined and dried over anhydrous $MgSO_4$, and the solvent was removed *in vacuo* to give an oil, which was distilled *in vacuo* to afford *dimethyl carboxymethanephosphonate* **216** (3.3g, 18%), b.p. 44 °C/15mmHg (Found: $\mathbf{M}^+$ 168.0190. $C_4H_9O_5P$ requires *M*, 168.0188); ν_{max}(thin film)/cm^{-1} 3449 (OH), 1726 (CO) and 1245 (PO); δ_H (400 MHz; $CDCl_3$) 2.97 (2H, d, *J* 21.7, CH_2), 3.76 (6H, 2 x s, 2 x CH_3) and10.19 (1H, br s, COOH); δ_C (100 MHz; $CDCl_3$) 33.04 (CH_2), 53.3 (2 x CH_3) and 167.2 (COOH); *m/z* 168 (M^+, 2%) and 127 (100).

3,7-Dimethyl-2,6-octadienoic acid (geranic acid) **217**

Method 1[126]

Geraniol **208** (1.0g, 6.5mmol) was dissolved in acetone (4ml) and Jones reagent (4-**M** CrO_3-H_2SO_4) (10ml, 40mmol) was added dropwise. The solution was boiled under reflux until the disappearance of geraniol (monitored by TLC). The reaction was then quenched with 10% aq. $NaHCO_3$ and extracted into Et_2O (3 x 20ml). The ether layers were combined, washed with brine (40ml) and dried over anhydrous $MgSO_4$. The solvent was then removed *in vacuo* to give an oil which was shown by ^1H NMR spectroscopy not to contain the expected product.

Method 2[127]

Geraniol **208** (1.0g, 6.5mmol) was added dropwise to a suspension of freshly prepared Ag_2O [prepared by adding a solution of $AgNO_3$ (4.41g, 25.9mmol) in water (20ml) to a solution of NaOH (1.04g, 25.9mmol) in water (20ml), and filtering off the product] in water (15ml) and the resulting mixture stirred overnight. The precipitate was filtered off, and the filtrate acidified with HCl and extracted into Et_2O (3 x 50ml). The organic layers were combined, washed with water (3 x 40ml) and dried over anhydrous $MgSO_4$, and the solvent was removed to give an oil which was shown by ^1H NMR spectroscopy to be starting material.

Method 3[128]

A solution of dimethyl carboxymethanephosphonate **216** (2.87g, 17.1mmol) in dry THF (30ml) was added dropwise to a solution of butyllithium (15% in hexane; 15.3ml, 35.9mmol) in dry THF (40ml) at –65 °C under dry N_2, and the resulting solution stirred at –65 °C for 30 min. A solution of 6-methyl-5-hepten-2-one (2.52ml, 17.1mmol) in dry THF (20ml) was then added dropwise and the solution stirred at –65 °C for 1 h and overnight at room temperature. Water (50ml) was added and the organic layer separated and washed with 10% aq. $NaHCO_3$ (2 x 25ml). The aqueous layers were combined, washed with Et_2O (2 x 50ml), acidified to pH 4 with 6-**M** HCl, saturated with NaCl and extracted with Et_2O (3 x 50ml). The organic layers were combined and dried over anhydrous $MgSO_4$, and the solvent was removed to give an oil, which was distilled to afford 3,7-dimethyl-2,6-octadienoic acid (geranic acid) **217** as a mixture of isomers (0.36g, 13 %), b.p. 100 °C/0.15mmHg (lit.,[128] 95 – 105 °C/0.098mmHg); δ_H (400 MHz; $CDCl_3$)

1.59, 1.67 and 2.17 (9H, 3 x s, 3 x CH_3), 1.91 (2H, d, *J* 1.2 Hz, 5-H), 2.15 (2H, d, *J* 1.2 Hz, 4-H), 5.05 (1H, t, *J* 1.4 Hz, 6-H), 5.69 (1H, s, 2-H) and 11.68 (1H, br s, OH); δ_C (100 MHz; $CDCl_3$) 17.5, 19.1 and 25.6 (3 x CH_3), 26.0 (C-5), 41.2 (C-4), 115.5 (C-2), 123.1 (C-6), 132.5 (C-7), 163.1 (C-3) and 172.1 (C-1); *m/z* 168 (M^+, 2%) and 123 (100).

4-(Carbomethoxymethyl)phenyl 3,3-dimethylacrylate[129] **218**

1,1'-Carbonyldiimidazole (CDI) (0.40g, 2.5mmol) was added to 3,3-dimethylacrylic acid **211** (0.24g, 2.4mmol) in dry DMF (3ml) under dry N_2 and the resulting solution was stirred for 0.5 h. Methyl (4-hydroxyphenyl)acetate **209** (0.41g, 2.4mmol) in dry DMF (2ml) was then added dropwise and the resulting solution stirred overnight at room temperature. The solvent was removed *in vacuo* and the residue chromatographed [chromatography on silica gel on a chromatotron, 4mm plate; elution with hexane-EtOAc (3:2)] to afford 4-(carbomethoxymethyl)phenyl 3,3-dimethylacrylate **218** (36mg, 6.0%), ν_{max}(thin film)/cm^{-1} 1738 and 1651 (2 x CO); δ_H (400 MHz; $CDCl_3$) 1.98 and 2.22 (6H, 2 x s, 2 x CH_3), 3.61 (2H, s, CH_2), 3.68 (3H, s, OCH_3), 5.90 (1H, s, CO.CH), 7.05 (2H, d, *J* 8.5 Hz, 2'- and 6'-H and 7.28 (2H, d, *J* 8.5 Hz, 3'- and 5'-H); δ_C (100 MHz; $CDCl_3$) 20.5 and 27.6 (2 x CH_3), 40.6 (CH_2), 52.1 (OCH_3), 115.1 and 115.5 (C-2' and C-6'), 121.9 (CO.*C*H), 130.2 and 130.4 (C-3' and C-5'), 131.1 (C-4'), 155.0 (C-1'), 160.1 [$(CH_3)_2C$], 164.9 (*C*O.CH) and 171.9 (CH_2CO), *m/z* 248 (M^+, 100%).

4-(Carbomethoxymethyl)phenyl 3,7-dimethyl-2,6-octadienoate[129] **219**

1,1'-Carbonyldiimidazole (CDI) (0.40g, 2.5mmol) was added to 3,7-dimethyl-2,6-octadienoic acid (geranic acid) **217** (0.41g, 2.4mmol) in dry DMF (3ml) under dry N_2 and the resulting solution was stirred for 0.5 h. Methyl (4-hydroxyphenyl)acetate **209** (0.41g, 2.4mmol) in dry DMF (2ml) was then added dropwise and the resulting solution stirred overnight at room temperature. The solvent was then removed *in vacuo* and the residue chromatographed [chromatography on silica gel on a chromatotron, 4mm plate; elution with hexane-EtOAc (3:2): followed by HPLC on Partisil 10; elution with hexane-EtOAc (7:3)] to afford 4-(carbomethoxymethyl)phenyl 3,7-dimethyl-2,6-octadienoate **219** (91mg, 12%); ν_{max}(thin film)/cm^{-1} 1738 and 1645 (2 x CO); *m/z* 316 (M^+, 5%) and 81 (100). ^1H NMR spectroscopy indicated the presence of all the required signals, but adequate separation of the isomeric products could not be achieved.

Methyl [4-hydroxy-3-(3,7-dimethyl-2,6-dienoyl)phenyl]acetate[101] **220**

Anhydrous $AlCl_3$ (139mg, 1.0mmol) was added to 4-(carbomethoxymethyl)phenyl 3,7-dimethyl-2,6-octadienoate **219** (100mg, 0.32mmol) under dry N_2 and the resulting mixture was heated at 160 °C in an oil bath for 3 h. 2-**M** HCl (5ml) was added and the mixture extracted with $CHCl_3$ (3 x 10ml), followed by 0.5-**M** KOH (3 x 10ml). The aqueous layer was then separated, acidified and extracted with $CHCl_3$ (3 x 20ml). The $CHCl_3$ layer was separated, washed with brine (40ml), dried over anhydrous $MgSO_4$ and the solvent removed to afford an oil, shown to be a mixture by ^1H NMR spectroscopy. However, the presence of an OH band (ν_{max}(thin film)/cm^{-1} 3146) in the infra-red spectrum suggests the presence of the rearranged product.

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5. APPENDIX

5.1 CRYSTALLOGRAPHIC DATA FOR THE CHROMONE DIMER (147)

Table 43: Crystal data and structure refinement for the chromone dimer **147**

Empirical formula	$C_{28}H_{22}O_9$	
Formula weight	502.46	
Temperature	293(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P 1bar	
Unit cell dimensions	a = 6.670(1) Å	= 102.90(1)°.
	b = 12.601(1) Å	= 94.28(1)°.
	c = 13.723(1) Å	= 93.20(1)°.
Volume	1118.0(2) $Å^3$	
Z	2	
Density (calculated)	1.493 Mg/m^3	
Absorption coefficient	0.112 mm^{-1}	
F(000)	524	
Crystal size	0.16 x 0.13 x 0.11 mm^3	
Theta range for data collection	1.7 to 25.5°.	
Index ranges	0<=h<=8, -15<=k<=15, -16<=l<=16	
Reflections collected	14182	
Independent reflections	4067 [R(int) = 0.067]	
Completeness to theta = 25.52°	97.7 %	
Max. and min. transmission	0.9877 and 0.9822	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	4067 / 0 / 337	
Goodness-of-fit on F^2	0.991	
Final R indices [I>2sigma(I)]	R1 = 0.0703, wR2 = 0.1296	
R indices (all data)	R1 = 0.1416, wR2 = 0.1583	
Extinction coefficient	0.011(3)	
Largest diff. peak and hole	0.272 and -0.286 $e.Å^{-3}$	

Table 44: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$ x 10^3) for the chromone dimer **147**. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
O(5)	3913(3)	3669(2)	7008(2)	34(1)
O(1)	11674(3)	-188(2)	8580(2)	33(1)
O(4)	12365(3)	4780(2)	9295(2)	35(1)
O(3)	9952(3)	5235(2)	8279(2)	36(1)
O(2)	6780(3)	1549(2)	9303(2)	34(1)
O(6)	3946(3)	1907(2)	7082(2)	35(1)
O(7)	9543(3)	3544(2)	6007(2)	37(1)
O(9)	9511(4)	-265(2)	6215(2)	44(1)
C(4)	8146(4)	-159(2)	8841(2)	24(1)
O(8)	6357(4)	-1057(2)	5927(2)	50(1)
C(5)	8244(5)	1036(2)	9024(2)	27(1)
C(22)	7372(5)	5462(2)	6005(2)	32(1)
C(11)	9612(4)	3469(2)	8631(2)	25(1)
C(1)	10179(4)	1543(2)	8867(2)	25(1)
C(12)	10626(4)	4572(3)	8707(2)	27(1)
C(10)	10673(4)	2712(2)	8926(2)	27(1)
C(3)	9839(5)	-729(2)	8621(2)	28(1)
C(25)	3522(5)	5398(3)	6640(3)	35(1)
C(21)	6690(4)	4566(2)	6372(2)	27(1)
C(7)	7998(5)	-2440(3)	8481(3)	36(1)
C(2)	11752(5)	905(3)	8721(2)	31(1)
C(28)	7996(5)	3660(2)	6422(2)	28(1)
C(17)	6792(5)	854(3)	6541(2)	31(1)
C(9)	6365(5)	-776(3)	8899(3)	32(1)
C(15)	7162(4)	2863(2)	7008(2)	26(1)
C(14)	7470(4)	3340(2)	8162(2)	27(1)
C(18)	4557(5)	861(3)	6625(3)	38(1)
C(8)	6291(5)	-1885(3)	8720(3)	38(1)

C(6)	9791(5)	-1859(3)	8441(3)	33(1)
C(16)	7999(5)	1770(2)	6727(2)	29(1)
C(24)	4258(5)	6275(3)	6309(3)	40(1)
C(19)	4907(4)	2706(2)	6677(3)	31(1)
C(23)	6184(5)	6307(3)	5978(3)	40(1)
C(13)	13462(5)	5809(2)	9324(3)	37(1)
C(26)	7510(5)	-251(3)	6200(3)	34(1)
C(20)	4740(5)	4540(3)	6669(3)	31(1)
C(27)	10255(6)	-1333(3)	5855(3)	50(1)

Table 45: Bond lengths [Å] and angles [°] for the chromone dimer **147**

O(5)-C(20)	1.387(4)
O(5)-C(19)	1.416(4)
O(1)-C(2)	1.345(4)
O(1)-C(3)	1.379(3)
O(4)-C(12)	1.341(4)
O(4)-C(13)	1.444(3)
O(3)-C(12)	1.210(4)
O(2)-C(5)	1.238(3)
O(6)-C(19)	1.401(4)
O(6)-C(18)	1.424(4)
O(7)-C(28)	1.215(4)
O(9)-C(26)	1.334(4)
O(9)-C(27)	1.454(4)
C(4)-C(3)	1.388(4)
C(4)-C(9)	1.400(4)
C(4)-C(5)	1.468(4)
O(8)-C(26)	1.209(4)
C(5)-C(1)	1.460(4)
C(22)-C(23)	1.367(5)
C(22)-C(21)	1.403(4)
C(11)-C(10)	1.335(4)
C(11)-C(12)	1.490(4)
C(11)-C(14)	1.507(4)
C(1)-C(2)	1.357(4)
C(1)-C(10)	1.474(4)
C(3)-C(6)	1.388(4)
C(25)-C(24)	1.366(5)
C(25)-C(20)	1.393(4)
C(21)-C(20)	1.393(4)
C(21)-C(28)	1.485(4)
C(7)-C(6)	1.378(4)

C(7)-C(8)	1.391(4)
C(28)-C(15)	1.526(4)
C(17)-C(16)	1.334(4)
C(17)-C(26)	1.485(4)
C(17)-C(18)	1.504(4)
C(9)-C(8)	1.361(4)
C(15)-C(16)	1.496(4)
C(15)-C(19)	1.527(4)
C(15)-C(14)	1.558(4)
C(24)-C(23)	1.396(5)

C(20)-O(5)-C(19)	111.9(2)
C(2)-O(1)-C(3)	117.9(2)
C(12)-O(4)-C(13)	115.8(3)
C(19)-O(6)-C(18)	109.5(2)
C(26)-O(9)-C(27)	115.3(2)
C(3)-C(4)-C(9)	116.9(3)
C(3)-C(4)-C(5)	121.2(3)
C(9)-C(4)-C(5)	121.9(3)
O(2)-C(5)-C(1)	124.3(3)
O(2)-C(5)-C(4)	121.0(3)
C(1)-C(5)-C(4)	114.7(3)
C(23)-C(22)-C(21)	120.8(3)
C(10)-C(11)-C(12)	118.6(3)
C(10)-C(11)-C(14)	127.7(3)
C(12)-C(11)-C(14)	113.5(3)
C(2)-C(1)-C(5)	118.0(3)
C(2)-C(1)-C(10)	115.1(3)
C(5)-C(1)-C(10)	126.7(3)
O(3)-C(12)-O(4)	122.1(3)
O(3)-C(12)-C(11)	123.5(3)
O(4)-C(12)-C(11)	114.5(3)
C(11)-C(10)-C(1)	131.8(3)

O(1)-C(3)-C(6)	116.6(3)
O(1)-C(3)-C(4)	121.0(3)
C(6)-C(3)-C(4)	122.5(3)
C(24)-C(25)-C(20)	119.1(3)
C(20)-C(21)-C(22)	118.1(3)
C(20)-C(21)-C(28)	121.0(3)
C(22)-C(21)-C(28)	120.9(3)
C(6)-C(7)-C(8)	119.6(3)
O(1)-C(2)-C(1)	126.6(3)
O(7)-C(28)-C(21)	123.2(3)
O(7)-C(28)-C(15)	123.3(3)
C(21)-C(28)-C(15)	113.5(3)
C(16)-C(17)-C(26)	123.4(3)
C(16)-C(17)-C(18)	122.3(3)
C(26)-C(17)-C(18)	114.2(3)
C(8)-C(9)-C(4)	121.3(3)
C(16)-C(15)-C(28)	112.2(3)
C(16)-C(15)-C(19)	107.4(2)
C(28)-C(15)-C(19)	104.6(3)
C(16)-C(15)-C(14)	111.3(3)
C(28)-C(15)-C(14)	111.9(2)
C(19)-C(15)-C(14)	109.1(2)
C(11)-C(14)-C(15)	116.3(2)
O(6)-C(18)-C(17)	113.1(2)
C(9)-C(8)-C(7)	120.7(3)
C(7)-C(6)-C(3)	119.0(3)
C(17)-C(16)-C(15)	120.9(3)
C(25)-C(24)-C(23)	120.9(3)
O(6)-C(19)-O(5)	105.7(2)
O(6)-C(19)-C(15)	111.5(3)
O(5)-C(19)-C(15)	112.2(2)
C(22)-C(23)-C(24)	119.8(3)
O(8)-C(26)-O(9)	123.9(3)

O(8)-C(26)-C(17)	122.0(3)
O(9)-C(26)-C(17)	114.1(3)
O(5)-C(20)-C(21)	122.1(3)
O(5)-C(20)-C(25)	116.7(3)
C(21)-C(20)-C(25)	121.2(3)

Table 46: Anisotropic displacement parameters ($Å^2 \times 10^3$) for the chromone dimer **147**. The anisotropic displacement factor exponent takes the form: $-2p^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
O(5)	30(1)	35(1)	39(2)	14(1)	3(1)	4(1)
O(1)	26(1)	29(1)	46(2)	13(1)	6(1)	6(1)
O(4)	36(1)	28(1)	40(2)	12(1)	-7(1)	-5(1)
O(3)	40(1)	32(1)	37(2)	12(1)	-4(1)	4(1)
O(2)	28(1)	32(1)	45(2)	12(1)	10(1)	7(1)
O(6)	33(1)	33(1)	41(2)	15(1)	3(1)	-2(1)
O(7)	35(1)	37(1)	40(2)	12(1)	9(1)	2(1)
O(9)	51(2)	29(1)	52(2)	3(1)	13(1)	6(1)
C(4)	24(2)	29(2)	21(2)	10(1)	1(1)	7(1)
O(8)	60(2)	31(1)	55(2)	9(1)	-1(1)	-5(1)
C(5)	26(2)	32(2)	24(2)	8(2)	1(2)	6(2)
C(22)	36(2)	32(2)	26(2)	7(2)	0(2)	-4(2)
C(11)	25(2)	27(2)	22(2)	5(1)	1(1)	2(1)
C(1)	22(2)	29(2)	26(2)	9(1)	1(1)	4(2)
C(12)	25(2)	34(2)	22(2)	7(2)	1(2)	4(2)
C(10)	21(2)	31(2)	28(2)	8(2)	-2(1)	-3(1)
C(3)	30(2)	29(2)	26(2)	11(2)	4(2)	-1(2)
C(25)	35(2)	39(2)	31(2)	9(2)	-2(2)	9(2)
C(21)	30(2)	29(2)	22(2)	6(1)	-4(2)	0(1)
C(7)	43(2)	27(2)	37(2)	6(2)	-2(2)	2(2)
C(2)	26(2)	33(2)	35(2)	10(2)	2(2)	-1(2)
C(28)	28(2)	28(2)	24(2)	2(2)	-3(2)	-1(2)
C(17)	45(2)	29(2)	19(2)	7(1)	-1(2)	-3(2)
C(9)	27(2)	34(2)	38(2)	13(2)	4(2)	7(2)
C(15)	24(2)	30(2)	23(2)	9(1)	-1(1)	-1(1)
C(14)	31(2)	27(2)	26(2)	10(2)	4(2)	4(1)
C(18)	45(2)	31(2)	37(2)	11(2)	-2(2)	-8(2)
C(8)	33(2)	33(2)	48(3)	13(2)	-1(2)	-2(2)

C(6)	35(2)	35(2)	32(2)	9(2)	5(2)	10(2)
C(16)	34(2)	34(2)	20(2)	6(2)	1(2)	6(2)
C(24)	49(2)	31(2)	40(2)	10(2)	-5(2)	10(2)
C(19)	29(2)	29(2)	35(2)	12(2)	0(2)	-1(2)
C(23)	53(2)	31(2)	37(2)	12(2)	-7(2)	-3(2)
C(13)	39(2)	31(2)	38(2)	7(2)	-3(2)	-10(2)
C(26)	48(2)	31(2)	25(2)	10(2)	0(2)	-2(2)
C(20)	35(2)	33(2)	26(2)	8(2)	-3(2)	-1(2)
C(27)	61(3)	32(2)	56(3)	4(2)	20(2)	7(2)

Table 47: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for the chromone dimer **147**

	x	y	z	U(eq)
H(22)	8649	5482	5777	38
H(10)	11960	2968	9223	33
H(25)	2224	5373	6844	42
H(7)	7930	-3198	8348	43
H(2)	13012	1259	8718	37
H(9)	5209	-421	9063	38
H(14A)	6922	4050	8305	33
H(14B)	6687	2870	8487	33
H(18B)	3859	622	5959	45
H(18A)	4159	343	7015	45
H(8)	5087	-2276	8759	45
H(6)	10950	-2218	8296	40
H(16)	9377	1729	6682	35
H(24)	3465	6858	6304	48
H(19)	4714	2486	5943	37
H(23)	6658	6901	5741	48
H(13C)	13807	5831	8661	55
H(13A)	14670	5885	9767	55
H(13B)	12636	6397	9561	55
H(26B)	9936	-1795	6300	74
H(26C)	11690	-1255	5834	74
H(26A)	9630	-1653	5194	74