APPLICATIONS OF BAYLIS-HILLMAN METHODOLOGY IN THE SYNTHESIS OF CHROMENE DERIVATIVES

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ABSTRACT

The reaction of salicylaldehyde with various activated alkenes, *viz.*, methyl vinyl ketone, ethyl vinyl ketone, phenyl vinyl sulfone, phenyl vinylsulfonate, acrolein and acrylonitrile, under Baylis-Hillman conditions, has been found to proceed with the chemoselective formation of chromene derivatives. The reaction conditions have been optimised and chromene derivatives have been obtained in isolated yields up to 87 %. The generality of the reaction, using 1,4-diazabicyclo[2.2.2]octane (DABCO), as the catalyst, and a heterogeneous (chloroform-water) solvent system, has been established using a range of salicylaldehyde derivatives, including 2-hydroxynaphthaldehyde.

The formation of chromene derivatives, under these conditions, has been assumed to proceed *via* an initial, Baylis-Hillman reaction, followed by cyclisation involving intramolecular conjugate addition, and subsequent dehydration. Evidence supporting this sequence has been obtained from the isolation of Baylis-Hillman products from reactions involving the use of *tert*-butyldimethylsilyl-protected salicylaldehyde, 4-hydroxybenzaldehyde and *tert*-butyl acrylate as substrates. The potential of the "Baylis-Hillman zwitterion" to participate as a donor species in Michael-type addition reactions has been explored and a series of dimeric products has been isolated.

The Baylis-Hillman methodology has also been successfully extended to the synthesis of sulfur-containing heterocyclic systems, and a range of 3-substituted thiochromenes has been obtained in moderate yields, using 2,2'-dithiobenzaldehyde and various activated alkenes in the presence of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as catalyst. The electron-impact mass spectra of selected chromene and thiochromene derivatives have been investigated permitting comparison of the fragmentation of the oxygen- and sulfur-containing analogues.

In a study directed at the synthesis of potential HIV-1 protease inhibitors, chromene- and thiochromene-containing analogues of the clinically useful drug, ritonavir, have been prepared. Thiochromene and chromene derivatives were converted to the corresponding 3-carboxylic acids and coupled with a specially prepared, hydroxyethylene dipeptide isostere to afford ritonavir analogues containing chromene and thiochromene termini in *ca.* 60 % yield.

CONTENTS

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Finally, I would like to thank the NRF and Rhodes University for financial support.

1. INTRODUCTION

The chromenes considered in this study contain an oxygen atom adjacent to the carbocyclic ring and a double bond between carbons three and four (Figure 1). While these compounds are sometimes referred to as chrom-3-enes, 2*H*-chromenes or isoflav-3-enes, the systematic name of the parent system is 2*H*-1-benzopyran; in this study we refer to them, simply, as chromenes. Chromenes have been known for more than 50 years and are generally isolated from natural products - mainly from the leaves and stems of plants, but occasionally from the roots. They are important precursors of biologically active benzopyrans, some of which exhibit antihypertensive properties. A comprehensive study of chromene synthesis has been reported by Hepworth[1] while naturally occurring chromenes have been reviewed by Rodriguez and Proksch.[2]

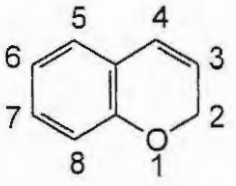


Figure 1. Atom numbering in 2*H*-1-benzopyran

The Sections which follow provide a brief overview of naturally occurring chromenes (Section 1.1), biologically active chromenes (Section 1.2), chromenes as colouring agents (Section 1.3), chromene synthesis (Section 1.4) and thiochromene synthesis (Section 1.5).

1.1 NATURALLY OCCURRING CHROMENES

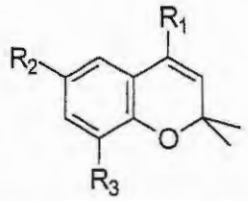
The 2,2-dimethylchromene moiety is very common in nature. Numerous polysubstituted and vinyl -substituted derivatives have been characterised, and some of these are detailed below.

1.1.1 Alkene-substituted 2,2-Dimethylchromenes

Propolis, a resinous product collected by honey-bees from plants, buds and exudates, has been known from as early as 300 BC for its anti-cancer, anti-oxidant, anti-inflammatory, antibiotic and antifungal properties.[3] As a result of the variety of biological activities exhibited by propolis,

there has been considerable interest in its constituents. Two chromene derivatives have been isolated from the Brazilian propolis, *viz.*, 2,2-dimethyl-8-prenylchromene-6-propenoic acid **1** and 2,2-dimethylchromene-6-propenoic acid **2** (Table 1).[3,4] 2,2-Dimethylchromene-6-propenoic acid **2** has also been isolated from the Chilean plant, *Baccharis species*.[5] Other 2,2-dimethylchromenes containing unsaturated substituents have been isolated, including the diastereomeric werneria chromenes **3** and **4** isolated together with the 6,8-disubstituted derivatives **5** and **6** from the aerial parts of *Werneria stuebelii* collected in Peru.[6] 6-Vinylchromene **7** has been isolated from the roots of *Trichogonia villosa*, a Brazilian genus of *Trichogonia species*.[7]

Table 1: Some naturally-occurring, alkene-substituted 2,2-dimethylchromenes.



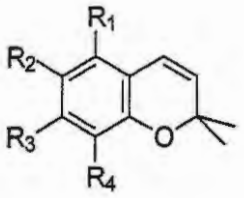
	R_2	R_3	R_1	Ref.
1	CH=CHCOOH	$CH_2CH=CMe_2$	H	3,4
2	CH=CHCOOH	H	H	3,5
3	MeCOOCCH=CH(*E*)	H	H	6
4	MeCOOCCH=CH(*Z*)	H	H	6
5	$CH=CHCO_2Me$	$H_2CCH=CMe_2$	H	6
6	$CH=CHCO_2Me$	$CH=CHC(OH)Me_2$	H	6
7	$H_2C=CH$	H	OMe	7

1.1.2 Polysubstituted 2,2-dimethylchromenes

6-Acetyl-5,7,8-trimethoxy-2,2-dimethylchromene **8** (Table 2) was obtained from *Evodia elleryana* in 1948 by Wright,[8] while the isomeric system, 8-acetyl-5,6,7-trimethoxy-2,2-dimethylchromene **9**, was isolated from the same tree by Kirby *et al.*[9] The latter compound **9** was also found to be present in the Chinese herb, *Evodia lepta,* as alloevodione;[10] two other chromenes, the leptonol **10** and methylleptol A **11** were also isolated from *Evodia lepta*.[10] In

1950, Briggs *et al.*[11] extracted 6-acetyl-7-hydroxy-5-methoxy-2,2-dimethylchromene **12** and 8-acetyl-5,7-dimethoxy-2,2-dimethylchromene **13** from the bark of the *Melicope simplex,* a tree growing in New Zealand.

Table 2: Some naturally occurring, polysubstituted 2,2-dimethylchromenes.



	R_1	R_2	R_3	R_4	Ref.
8	OCH_3	$COCH_3$	OCH_3	OCH_3	8
9	OCH_3	OCH_3	OCH_3	$COCH_3$	9,10
10	OH	$COCH_3$	OCH_3	OCH_3	10
11	OCH_3	$CH(OCH_3)CH_3$	OCH_3	OCH_3	10
12	OCH_3	$COCH_3$	OH	H	11
13	OCH_3	H	OCH_3	$COCH_3$	11
14	H	H	OCH_3	H	12,13
15	H	OCH_3	OCH_3	H	13
16	H	H	OCH_3	OCH_3	13
17	OCH_3	$CH(OH)CH_3$	H	OCH_3	13
18	OH	$COCH_3$	H	OCH_3	13
19	OCH_3	$COCH_3$	H	OCH_3	13
20	H	$CH(OCH_3)CH_3$	OCH_3	H	16
21	H	$CH(OCH_2CH_3)CH_3$	OCH_3	H	16
22	H	CH_2CH_3	OCH_3	H	16
23	H	$COCH_3$	OCH_3	H	16,17
24	H	$COOCH_3$	H	H	20
25	H	OCH_3	OH	H	21
26	H	$COCH_3$	H	H	7

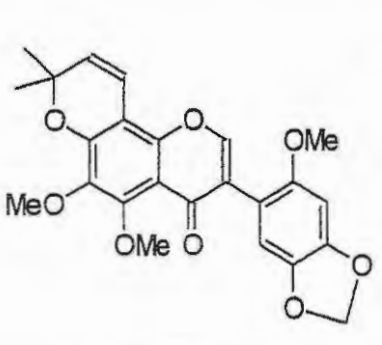
The biologically active chromenes, precocene I **14** and precocene II **15** were obtained from the plant, *Ageratum houstonianum,*[12,56] while precocene I **14** was also isolated from *Eupatorium aschembornianum.*[13] These two chromenes are known for their anti-juvenile hormone activities.[12,14] One of the most serious diseases in Brazil is Chicaga, caused by the insect *Panstrongylus megistus*, and it was found that when the insects were treated with precocene I and

II, anti-juvenile activity was observed.[15] An isomer of precocene II has been isolated from the leaves and flowers of *Eupatorium aschembornianum* as eupatoriochromene B **16**, together with other chromenes, *viz.*, eupatoriochromene C **17**, 6-acetyl-5-hydroxy-8-methoxy-2,2-dimethylchromene **18** and 6-acetyl-5,8-dimethoxy-2,2-dimethylchromene **19**.[13]

Encelia farinosa Gray, a shrub growing in Southern Arizona, is normally characterized by its sticky, fragrant exudate, which has been widely used as an analgesic chewing gum and for incense. Four chromenes have been isolated from the stem and exudate of the *Encelia farinosa Gray*, *viz.*, encecalol methyl ether **20**, encecalol ethyl ether **21**, 6-ethyl-7-methoxy-2,2-dimethylchromene **22** and 6-acetyl-7-methoxy-2,2-dimethylchromene **23**.[16] Compound **23** has also been isolated from the Australian weeds, *Eupatorium species*,[17] *Calea species*,[18] and from *Hemizonia species*.[19] Methyl 2,2-dimethyl-2*H*-benzopyran-6-carboxylate **24** was isolated from the *Piper hostmannianum*, a shrub growing in the Amazon region,[20] while 6-acetyl-7-hydroxy-2,2-dimethychromene **25** was isolated from the aerial parts of *Fleischmannia pycnocephaloides* as eupatoriochromene.[21] 6-Acetyl-2,2-dimethylchromene **26** was obtained from the aerial parts of *Trichogonia scottmorii*.[7]

1.1.3 Naturally occurring fused-ring chromenes

The fused-ring chromene, conrauinone A **27**, has been isolated from the bark of the tree *Millettia conraui*, which grows in Cameroon and which has been widely used for the treatment of intestinal parasites.[22] Another medicinal plant from Cameroon, called *Erythrina senegalensis*, has found use in the treatment of female infertility, stomach pain and gonorrhea;[23] an extract from the bark of this tree afforded the fused-ring chromene, erysenegalensein C **28**.



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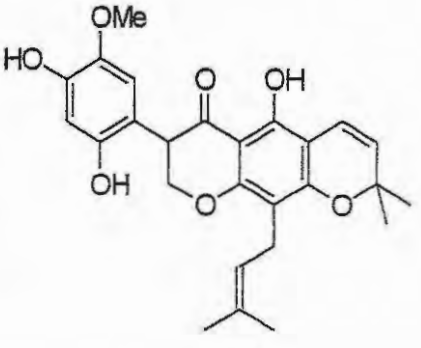

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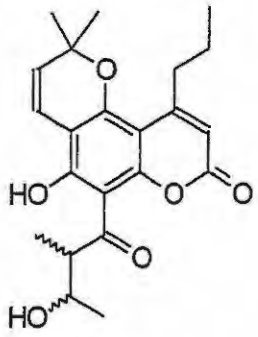
Tricyclic pyranocoumarins, which contain a 2,2-dimethylchromene sub-structure within the fused-ring system, have been isolated from *Calophyllum lanigerum*; calanolide E2 **29** and cordatolide E **30** from the bark and pseudocordatolide C **31** from the leaves.[24] Calanolide F **32** was isolated from the leaves and twigs of *Calophyllum tesymannii*.[24] These four pyranocoumarins (compounds **29**, **30**, **31** and **32**) were tested for anti-HIV activity, and while the tricyclic compouds **29**, **30** and **31** were found to be inactive, calanolide F **32**, which contains a 12-β hydroxy group, was found to be active.[24]



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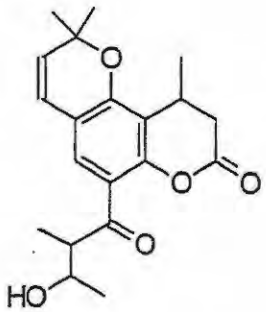

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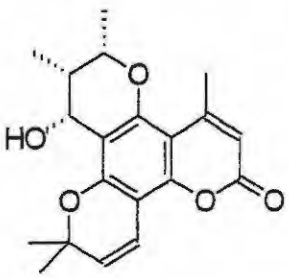

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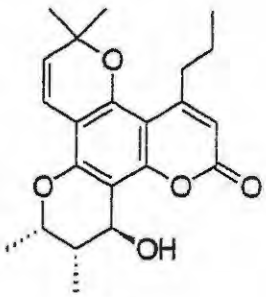

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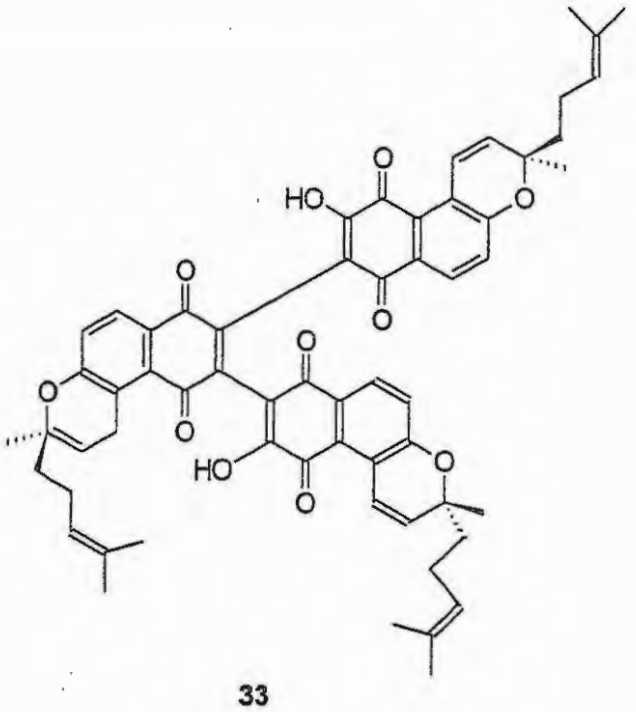
Conocurvone **33**, a trimeric system containing fused-ring chromenes, was first isolated from the Australian shrub, *Conospermum incurvum*. Conocurvone was found to have very strong anti-HIV activity.[25,26] It completely inhibited the killing of human CEM-SS cells, which are targeted by HIV-1, and halted HIV-1 replication in these cells.[25] In contrast, the naturally occurring

monomeric species teretifolione B **34**, and the derivative **35** were found to be completely inactive.[25] The pentacyclic system, rheediaxanthone-A **36**, was obtained from the shrub, *Garcinia staudtii*,[27] while candidin **37** was isolated from the seeds of *Tephrosia candida*.[28]



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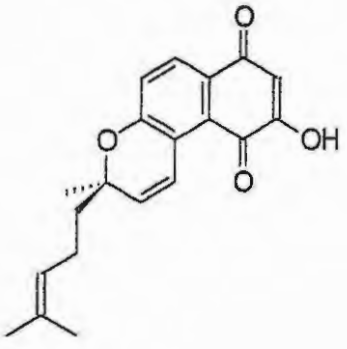

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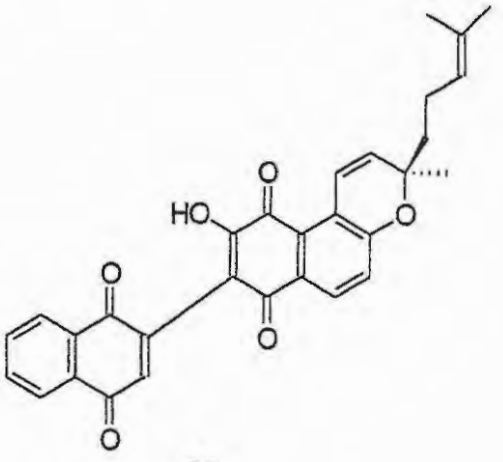

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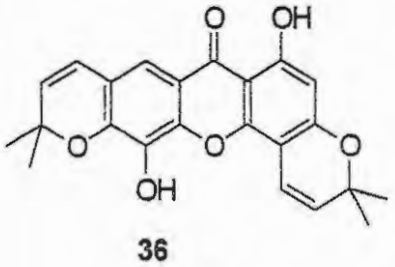

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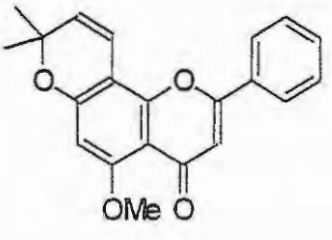

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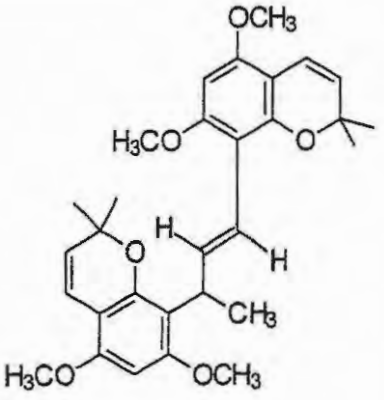
1.1.4 Other, naturally occurring 2,2-dimethylchromenes

Melicope ptelefolia is a shrub which grows in Vietnam. Its leaves and twigs have been used for the treatment of itches and wounds, while its roots and bark serve as appetizers and digestives.[29] Two chromenes have been isolated from the leaves of *Melicope ptelefolia, viz.*, 5,5'-dimethoxy-alloagerasanin **38** and melifolin **39**,[29] while the unusual benzofuranyl derivative **40** was isolated from the exudate of *Encelia farinosa*.[16]



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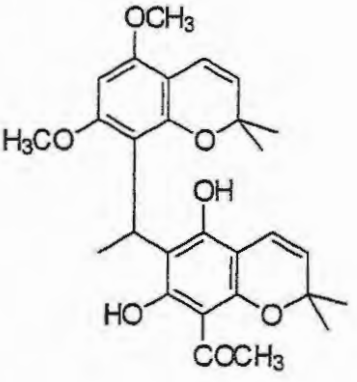

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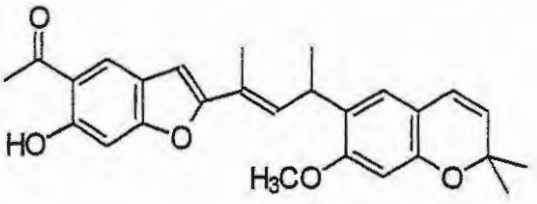

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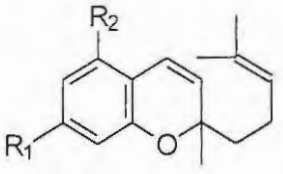
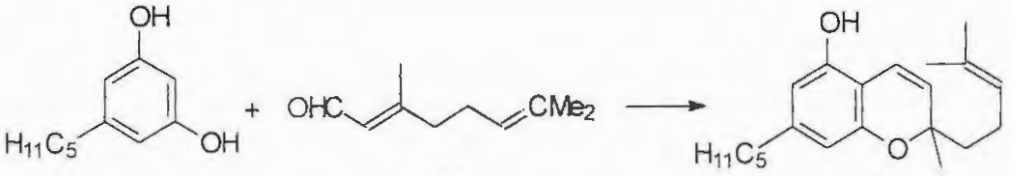
1.2 BIOLOGICALLY ACTIVE SYNTHETIC CHROMENES

Several synthetic chromenes are known for their biological activity. Cannabichromene derivatives **41** are useful for inducing hypothermia, and as anti-inflammatory and antimicrobial agents.[30] Treatment of olivetol **42** with citral **43** gave a mixture of products of which cannabichromene is the main product (Scheme 1).[31] The styrylchromene derivatives **44** were prepared as neoplasm inhibitors and for the treatment of skin diseases, while the *E* and *Z*-isomers prepared from salicylaldehyde (R = H) were both found to inhibit the *in vitro* growth of L1210 leukemia cells.[32]

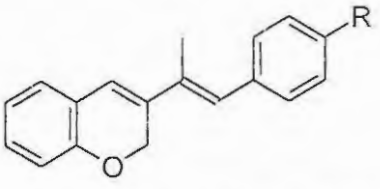


41 (R_1, R_2 = H, OH, alkyl, alkenyl)



42 **43** **41**

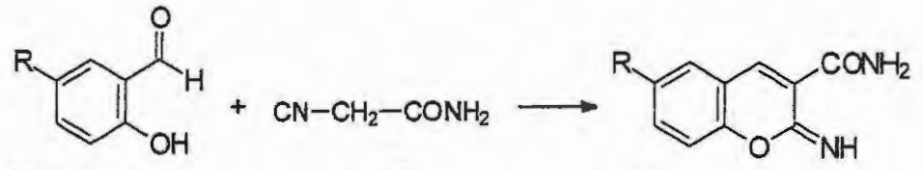
Scheme 1



44 (R = H, OH, halo, alkyl)

The 2-iminochromene derivatives **47a** and **47b**, which were synthesised by Knoevenagel condensation of cyanoacetamide **46** with 2-hydroxy-5-methoxybenzaldehyde **45a** and 2-hydroxy-

5-nitrobenzaldehyde **45b**, respectively (Scheme 2), have shown antitumour activity against the P 388 lymphocytic leukemia.[33]



45a: R = OMe
45b: R = NO_2

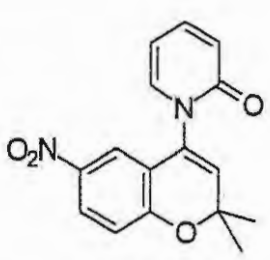
46

47a: R = OMe
47b: R = NO_2

Scheme 2

1.2.1 Antihypertensive chromenes

Various chromenes are known to possess antihypertensive activity, the net effect of which is to relax the blood vessels and, hence, reduce blood pressure.[34,35] One of the most powerful antihypertensive chromenes known is the 2,2-dimethylchromene derivative **48**.[36] The presence of a strong electron-withdrawing group at C-6 is considered to be crucial for antihypertensive activity. Thus, the 6-nitro derivative **48** and the 6-cyano analogue exhibited optimum activity, while other, less efficient electron-withdrawing groups, such as methyl ketone, methyl ester, formyl, 4-pyridyl, vinylogous nitrile and chloro substituents result in considerably weaker antihypertensive activity; with ethyl ester, thioamide and bromo substituents at C-6, the chromenes proved to be completely inactive.[36,37] The 2-pyridone substituent at C-4 was also found to be essential for the antihypertensive activity of the chromene **48**, but the introduction of substituents (*e.g.* 4'-methoxy or 4'-ethoxy) on the 2-pyridone moiety produces a decrease in the antihypertensive activity. Other chromene systems found to possess antihypertensive activity include the 4-pyrazinone **49**[36] and the 4-[-2-(cyanoimino)thiazolidine] **50**.[38]



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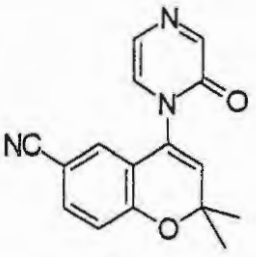

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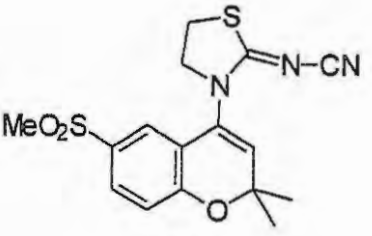

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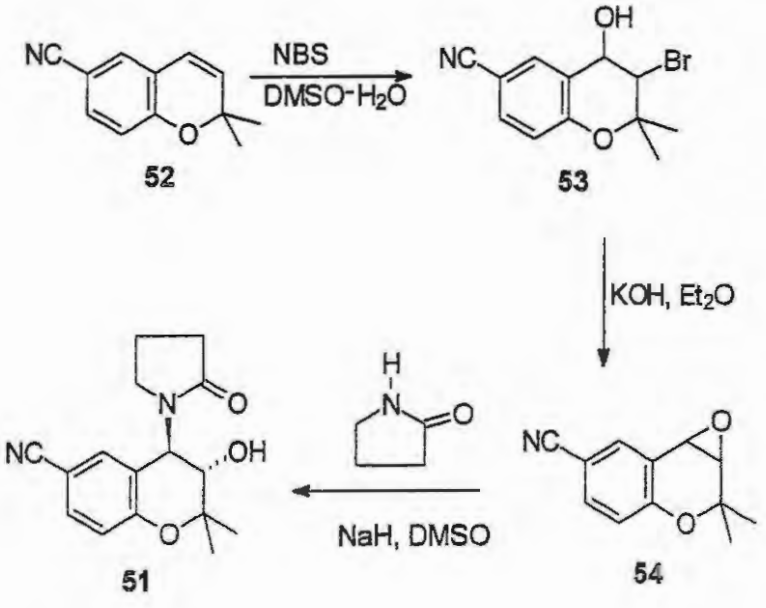
1.2.2 Antihypertensive benzopyrans

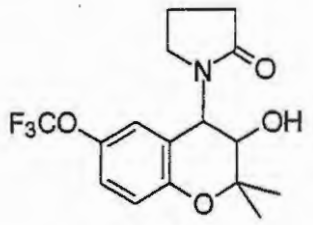
Chromenes are very important precursors of benzopyrans, some of which exhibit antihypertensive activity. Cromakalim **51** was the first compound known to act as a potassium channel opener and, hence, induce relaxation of vascular muscle.[39] Cromakalim has been synthesised by treating 2,2-dimethylchromene **52** with *N*-bromosuccinimide in the presence of aqueous dimethyl sulfoxide to afford the bromohydrin **53** which, on reaction with potassium hydroxide, gave the intermediate epoxide **54**; opening of the epoxide ring with deprotonated pyrrolidin-2-one then yielded the required cromakalim **51** (Scheme 3).[39]



52 53 54 51

Scheme 3

Other benzopyrans similar to cromakalim **51**, which are known to possess antihypertensive activity, include 3-hydroxy-2,2-dimethylbenzopyran **55**,[40] the 6-cyanobenzopyran **56**,[41] the 3,4-*trans*-pyrrolylbenzopyran **57**[42] and the guanidine derivative **58**.[43]



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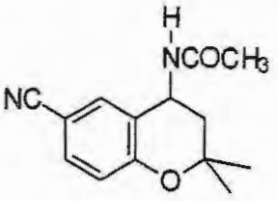

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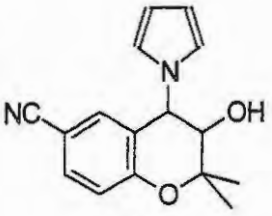

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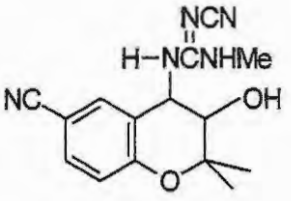
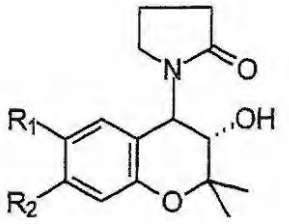


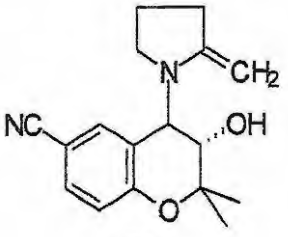
58

As was the case with the chromenes discussed earlier, a strongly electron-withdrawing group (*e.g.* nitro, cyano or trifluoromethyl) at C-6 is crucial for optimum antihypertensive activity in the benzopyran analogues.[36,37,44,47] An electron-donating group (*e.g.* methyl) at C-6 results in a significant decrease in antihypertensive activity.[44,45] Surprisingly, extension of the 6-methyl group to ethyl enhances activity, while further extension to propyl decreases activity.[44] Branched alkyl (*e.g.* isopropyl or *tert*-butyl) groups at C-6, give similar activities to the ethyl group, while a 6-phenyl group reduces the activity. Insertion of an acetylamino or amino group at C-7 (as in compounds **60** and **61**) enhances activity relative to the 6-nitro compound **59**,[37] while changing the substitution pattern (*i.e.* to 6-NH_2, 7-NO_2, as in compound **62**) decreases antihypertensive activity.

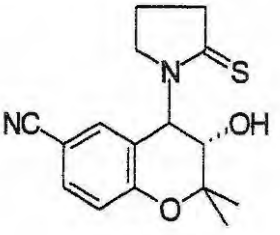


	R_1	R_2
59	NO_2	H
60	NO_2	MeCONH
61	NO_2	NH_2
62	NH_2	NO_2

The substituent at C-4 also plays a very significant role in the antihypertensive activity of the benzopyrans, and the most favoured substituents are five- and six-membered nitrogen-containing heterocycles, *e.g.* 2-pyrrolidinone and 2-piperidinone. The 2-pyrrolidinone derivative, cromakalim **51** (Scheme 3), was found to exhibit greater antihypertensive activity than its methylidine analogue **63**, while replacement of the lactam oxygen with sulfur, as in compound **64**, does not alter the activity, but reduces the duration of action.[37,46]



63

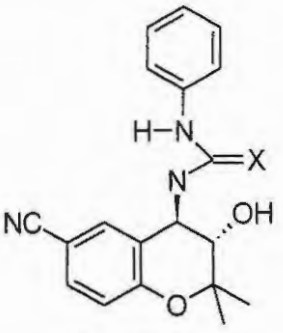


64

Benzopyrans with seven-membered lactam substituents at C-4 appear to be more active than the eight-membered analogues; the presence of the C-4 substituents, 4-amino-1,2-dihydro-2-oxo-1-pyridyl, 4-oxo-1-piperidinyl and 1,4-dihydro-4-oxo-1-pyrimidyl, however, results in reduction or complete loss of activity.[36,46] The stereochemistry at C-4 also appears to be important for antihypertensive activity. In the case of cromakalim **51**, the (-)-enantiomer was found to be considerably more active than the (+)-enantiomer, which is known as lemakalim.[39,37,46]

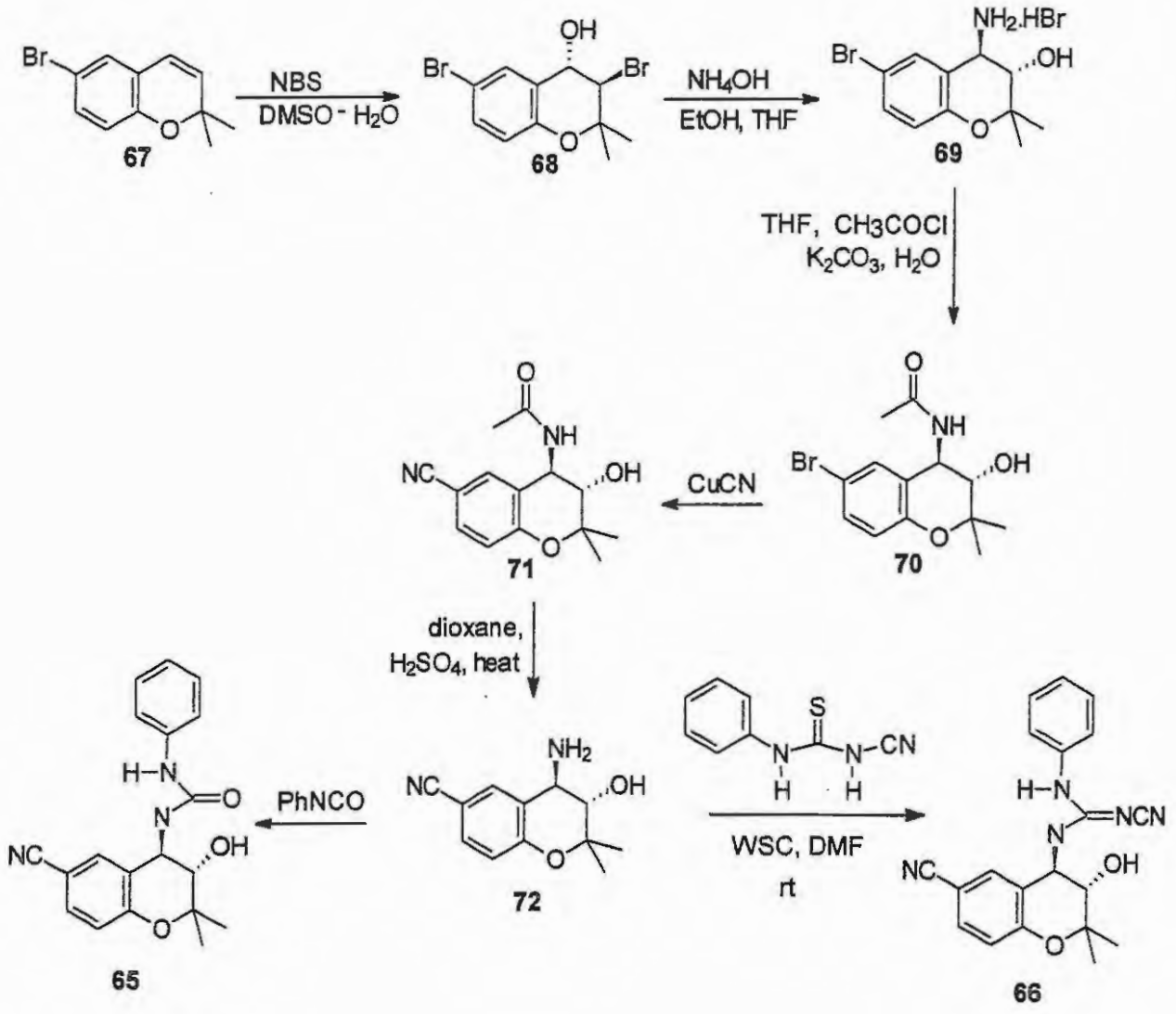
1.2.3 Benzopyrans with anti-ischaemic activities

Cromakalim **51** has long been known to possess anti-ischaemic activity. The benzopyrans **65** and **66** are equipotent with cromakalim, but are significantly less active as vasorelaxants.[48,49]



65 : X = O
66 : X = NCN

Benzopyrans **65** and **66** have been prepared from 6-bromochromene **67** as outlined in Scheme 4. Thus, the 6-bromochromene **67** was treated with *N*-bromosuccinimide in dimethyl sulfoxide-water (4:1) to give the bromohydrin **68**, which, on reaction with ammonium hydroxide, gave the *trans* amino alcohol **69** *via* an epoxide intermediate. Acetylation of **69** followed by replacement of the 6-bromo substituent by a cyano group, using copper cyanide, afforded the 6-cyanobenzopyran derivative **71**. The acetyl group was then removed, and treatment of the resulting amine **72** with phenyl isocyanate gave the required benzopyran **65**, while treatment with *N*-cyano-*N*-phenylthiourea in the presence of the coupling agent, 1-[3-(dimethylamino)propyl]-3 ethylcarbodiimide hydrochloride (water soluble carbodiimide, WSC) gave the benzopyran **66**.[48] As in the case of the antihypertensive benzopyrans, studies have shown that a strong electron-withdrawing group, such as cyano, nitro or trifluoromethyl at C-6, is essential for anti-ischaemic activity. 6,7-Disubstitution offers no improvement in activity, and inversion of the configuration at C-3 results in diminished activity. Activity is also decreased by dehydration and it has been suggested that the sp^3 carbon C-3 is essential for activity; the presence of the geminal methyl groups at C-2 is also considered essential for anti-ischaemic activity.[48]

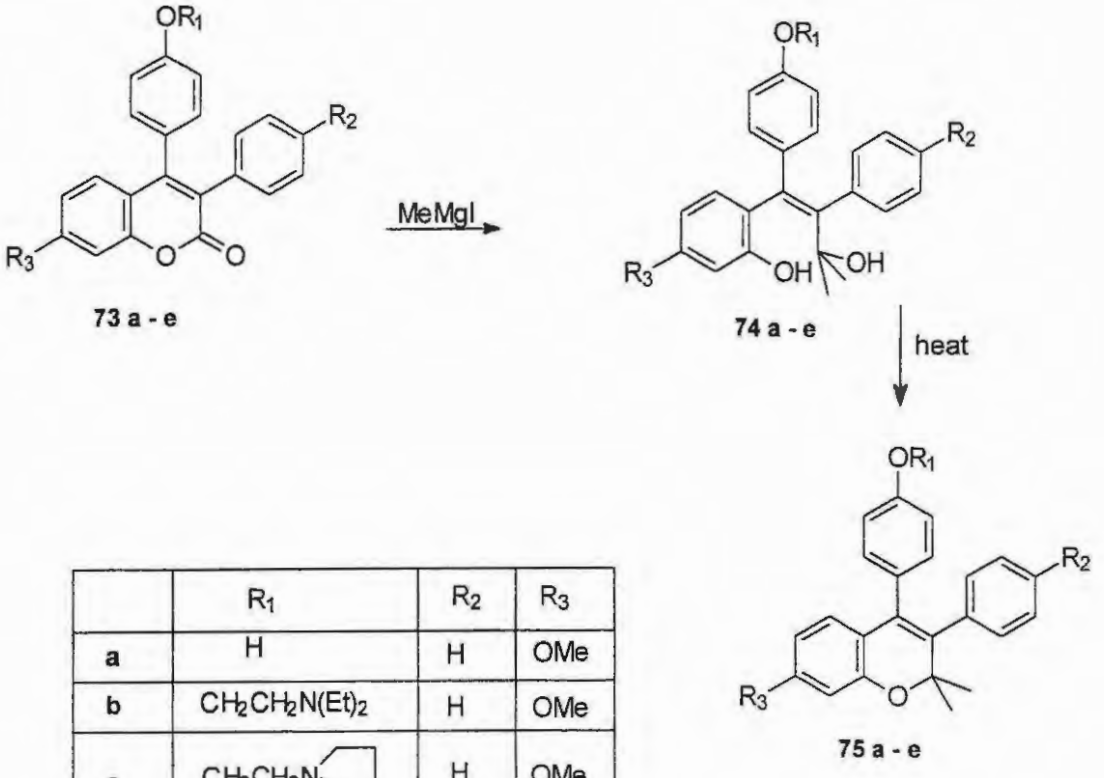


Scheme 4

1.2.4 Chromenes as antifertility agents

The 2,2-dimethyl-3,4-diarylchromene derivatives **75a-e** were studied for their antifertility activity.[50,51] The synthesis of these 3,4-diarylchromene derivatives has been achieved by treating the 3,4-diarylcoumarins **73a-e** with excess Grignard reagent (MeMgI) to obtain the corresponding diols **74a-e**, thermal cyclisation of which affords the expected chromenes (Scheme 5).[50] An ether moiety (R_1) at the *para* position of the 4-phenyl substituent, as in compound **75b** was found to be crucial for antiimplantation activity as the *para*-hydroxy analogue **75a** is inactive.[51] Introduction of a *para*-chloro substituent (R_2) on the 3-phenyl ring, as in compound **75d**,

appeared to have no effect, as compounds **75c** and **75d** showed no difference in antifertility activity. It was noted, however, that removal of the 7-methoxy group, as in compound **75e**, decreased activity, while replacement of the geminal methyl substituents at C-2 resulted in increased activity.[51]

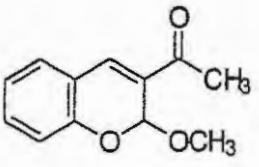


	R_1	R_2	R_3
a	H	H	OMe
b	$CH_2CH_2N(Et)_2$	H	OMe
c	CH_2CH_2N	H	OMe
d	CH_2CH_2N	Cl	OMe
e	CH_2CH_2N	H	H

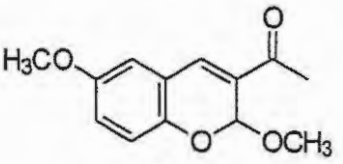
Scheme 5

1.3 CHROMENES AS COLOURING AGENTS

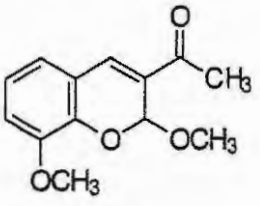
Chromene derivatives which have been used as electroplating brighteners include 3-acetyl-2-methoxychromene **76**, 3-acetyl-2,6-dimethoxychromene **77**, 3-acetyl-2,8-dimethoxychromene **78** and 3-acetyl-6-bromo-2-methoxychromene **79**.[52]



76



77



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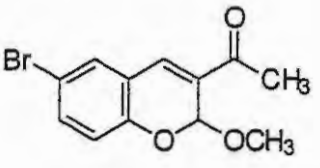
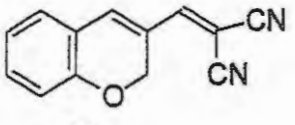
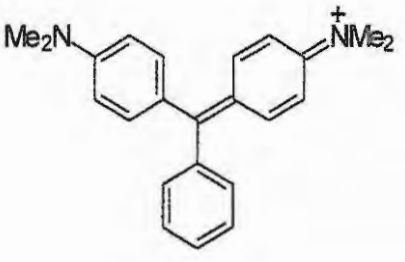


79

Yellow chromene dyes, which exhibit strong fluorescence, have been found to be useful in transfer printing and as colouring agents in thermal imaging materials.[54] Such dyes, for example compound **80**, have a general chromene structure with extended conjugation.[53]



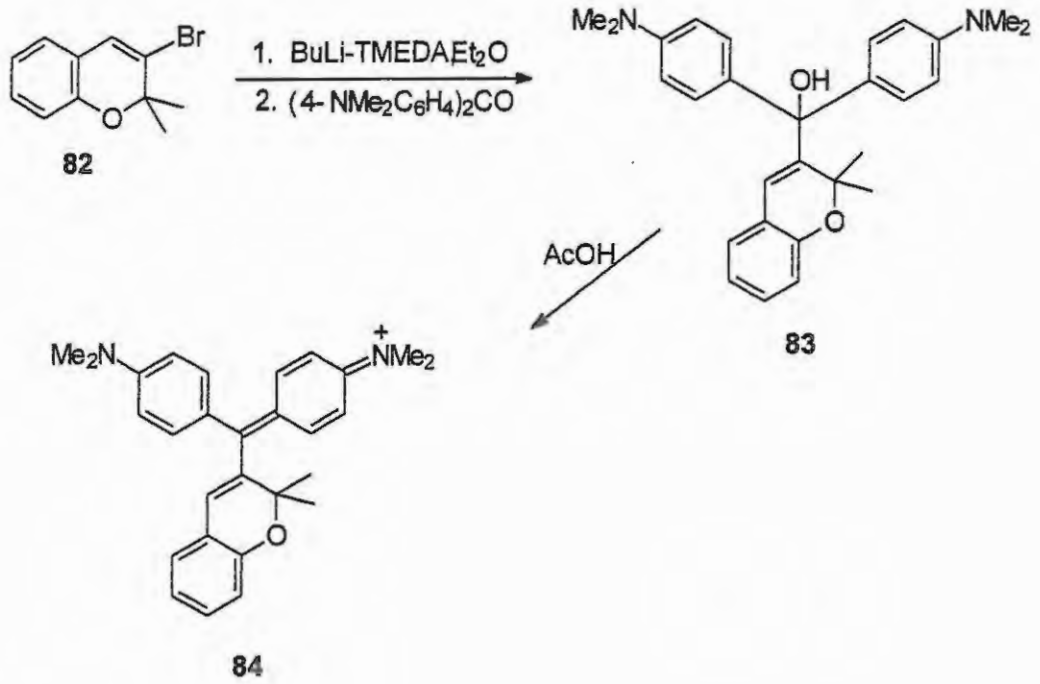
80



81

Malachite green **81** is stabilised by conjugation involving the unsubstituted phenyl ring and the dimethylaminophenyl rings,[55] and, to increase conjugation even further, 2,2-dimethylchromenes have been incorporated in the malachite green system. In a typical example of the synthesis of such dyes, lithiation of the bromochromene **82**, followed by treatment with 4,4'-

bis(dimethylamino)benzophenone (Michler's ketone) affords the carbinol **83**, acid-catalysed dehydration of which leads to the conjugated dye **84** (Scheme 6).[55]



82 83 84

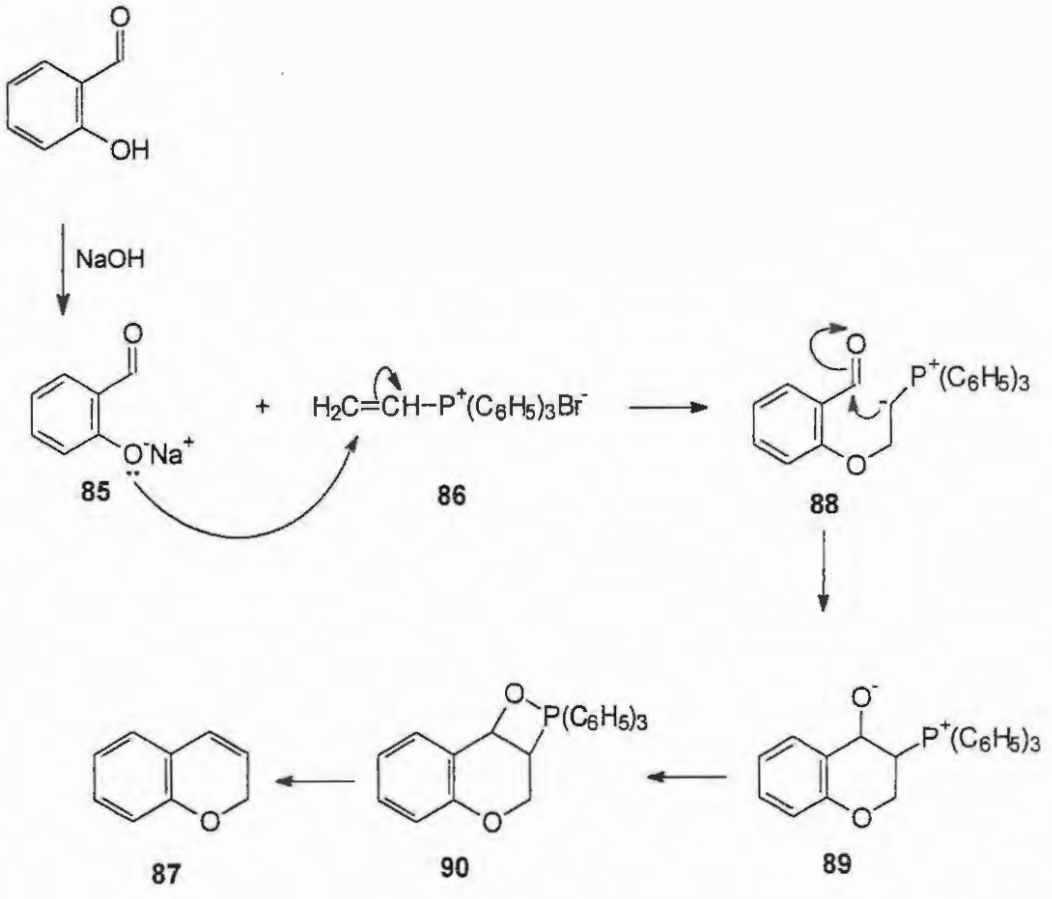
Scheme 6

1.4 SYNTHESIS OF CHROMENES

Several methods for the synthesis of chromenes have been reported. These include the use of Wittig reactions,[57,59,63,66,89] acid catalysed cyclisation,[64,67] Claisen rearrangement,[69,70] microwave irradiation,[74] 3,4-fused ring chromenes,[75] ruthenium catalysed rearrangement,[76] ring-closing olefin metathesis,[77] arynes with α,β-unsaturated aldehydes[79] and benzopyrylium salts.[81]

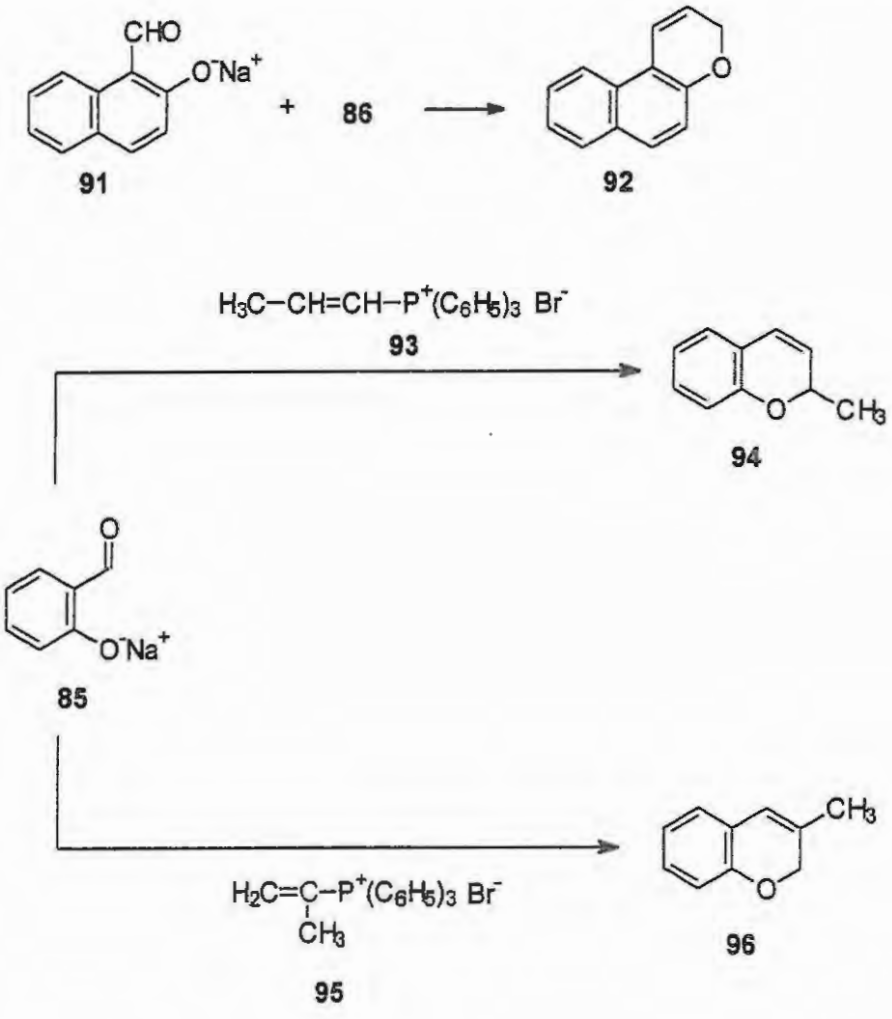
1.4.1 Use of Wittig reactions in the synthesis of chromenes

Early work by Schweizer [57] has shown that chromene **87** itself can be obtained by treating the sodium salt **85** of salicylaldehyde (generated from salicylaldehyde and sodium hydroxide) with vinyltriphenylphosphonium bromide **86** (Scheme 7). This reaction is known to involve initial conjugate addition of the phenoxide ion to the vinyltriphenylphosphonium salt to afford the ylide



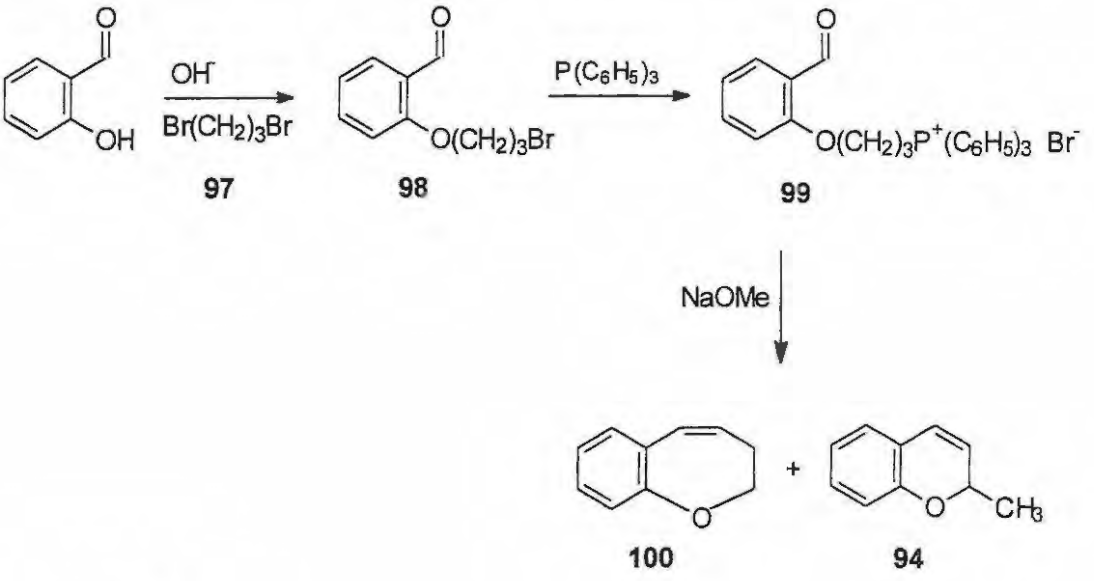
Scheme 7

88 which undergoes Wittig-type cyclisation *via* the intermediates **89** and **90**. Subsequent loss of triphenyphosphine oxide affords the parent chromene **87** in 71 % yield.[57] The generality of this reaction has been demonstrated by the successful synthesis of 3H-naphtho[2,1-*b*]pyran **92** from the sodium salt **91** of naphthaldehyde and vinyltriphenylphosphonium bromide **86**,[58] and by the preparation of 2-methylchromene **94**[59] and 3-methylchromene **96**[60] from the reaction of sodium salt **85** of salicylaldehyde with propenyltriphenylphosphonium bromide **93** and isopropenyltriphenylphosphonium bromide **95**, respectively (Scheme 8).



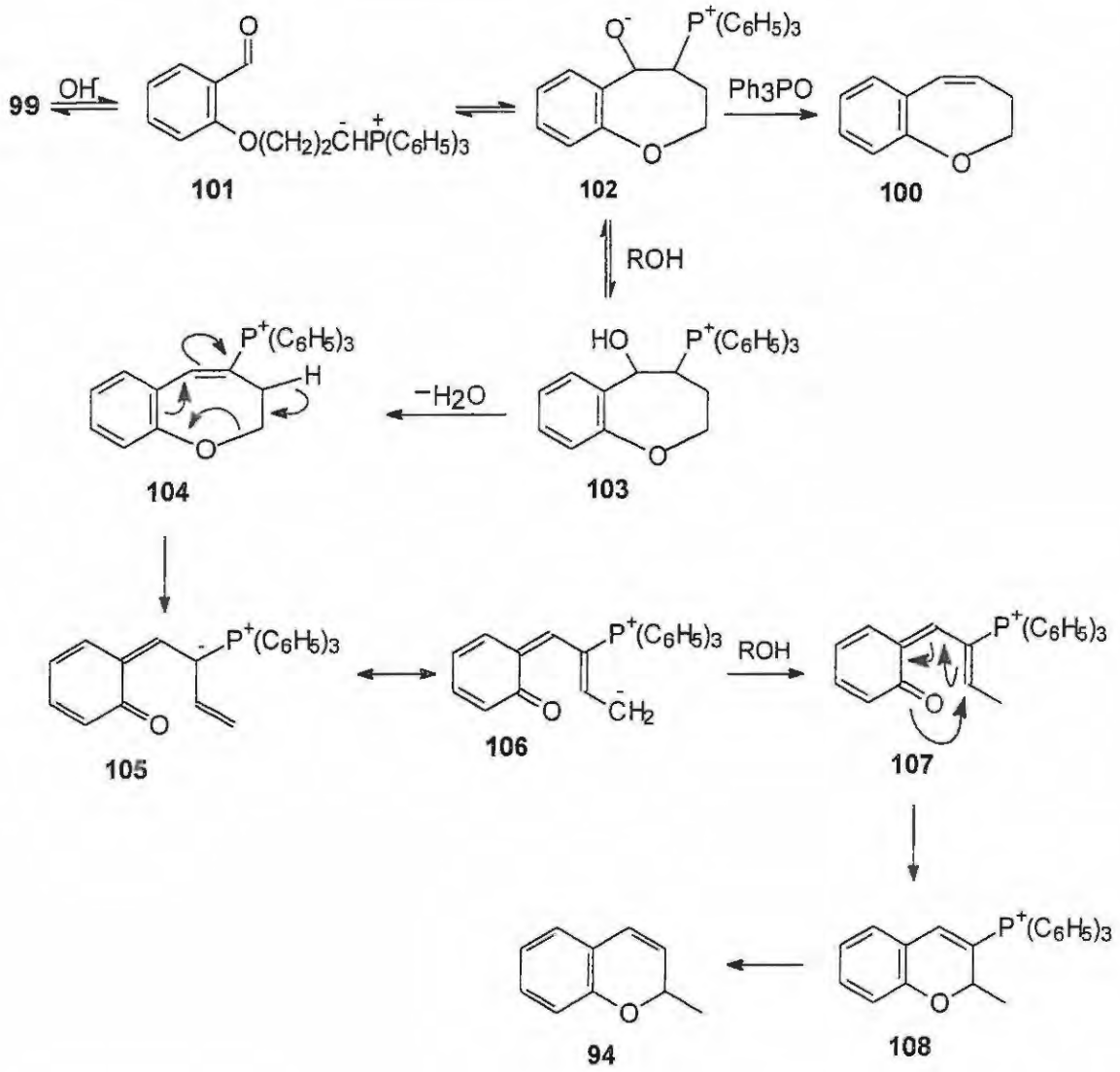
Scheme 8

The 3-(2-formylphenoxy)propylphosphonium salt **99** has been obtained by treating salicylaldehyde with 1,4 dibromobutane **97** in the presence of sodium hydroxide, followed by triphenylphosphine (Scheme 9).[61,62] In the presence of the base, sodium methoxide, the phosphonium salt **99** then undergoes intramolecular cyclisation to give a 52:48 mixture of chromene **94** and 2,3-dihydrobenzoxepine **100**.[63]



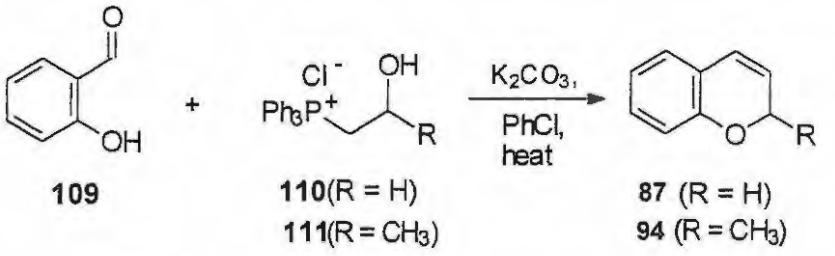
Scheme 9

Cyclisation to the benzoxepine **100** may be optimised by using sodium hydride in dimethylformamide, while the formation of chromene **94** is favoured by conducting the reaction in highly protic solvents which inhibit decomposition of the intermediate betaine **102** produced by intramolecular cyclisation of the ylide **101** (Scheme 10). In protic media, the betaine is considered to undergo protonation to the alcohol **103**, dehydration of which results in the formation of the alkene **104**. Ring-opening, protonation, re-cyclisation and, finally, loss of triphenylphosphine affords the chromene **94**.[63]



Scheme 10

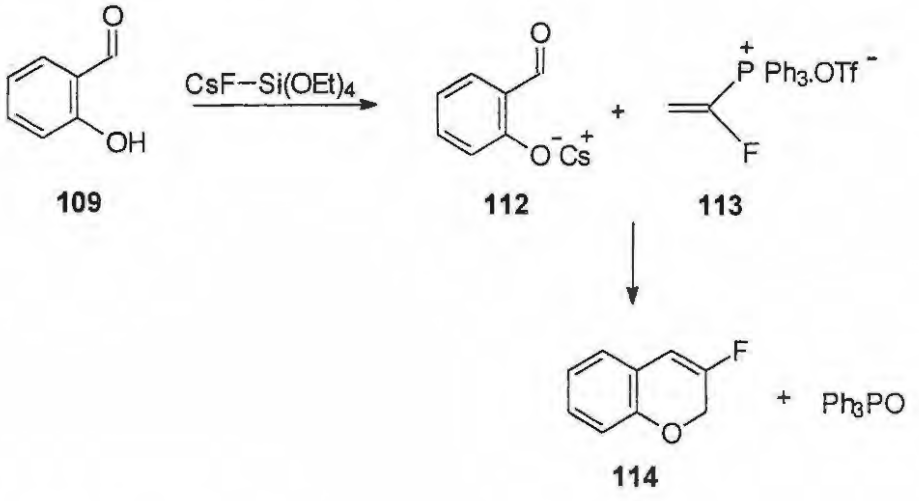
Sliwa *et al.*[64] observed that chromenes can also be prepared by a single-step process involving reaction of salicylaldehyde **109** with (2-hydroxyethyl)triphenylphosphonium chloride **110** in the presence of the base, potassium carbonate, in chlorobenzene (Scheme 11). The mechanism is considered to be similar to that outlined in Scheme 7, following generation of a vinyltriphenylphosphonium spieces. 2-Methylchromene **94** was also synthesised, from 2-hydroxy-2-methylethyl)triphenylphosphonium chloride **111**, using this approach.



109 **110**(R = H) **87** (R = H)
111(R = CH_3) **94** (R = CH_3)

Scheme 11

Recent work by Hanamoto *et al.*[65] has shown that 3-fluorochromene **114** can be obtained by reacting the caesium salt **112** of salicylaldehyde with α-fluorovinyltriphenylphosphine triflate **113** (Scheme 12). The mechanism is, again, presumed to involve conjugate addition followed by a Wittig-type cyclisation to give the 3-fluorinated chromene **114**. 2-Fluoro-3*H*-naphth[2,1-*b*]pyran was similarly obtained from 2-hydroxynaphthaldehyde and α-fluorovinyltriphenylphosphine triflate **113** in the presence of CsF-Si$(OEt)_4$.



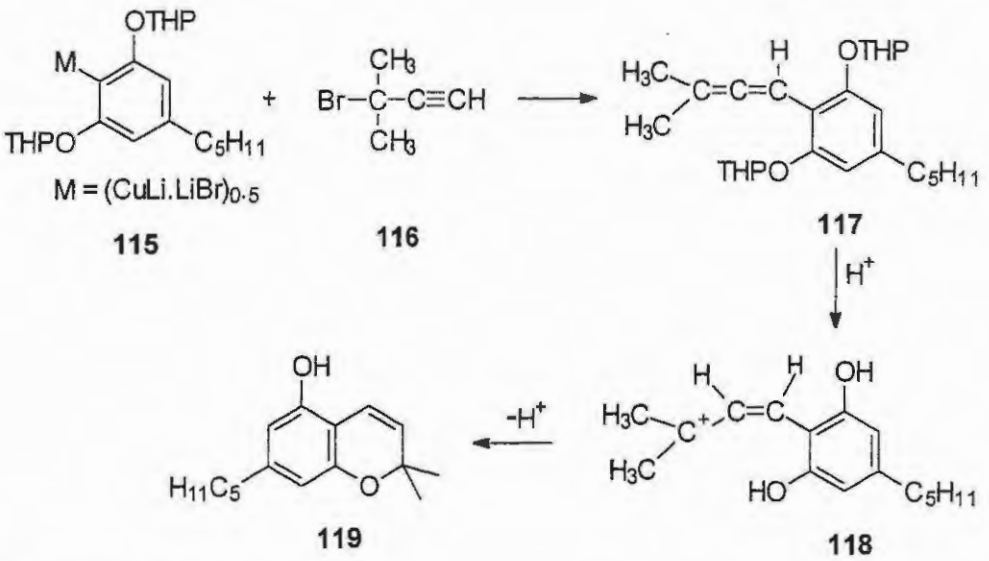
109 **112** **113**

114

Scheme 12

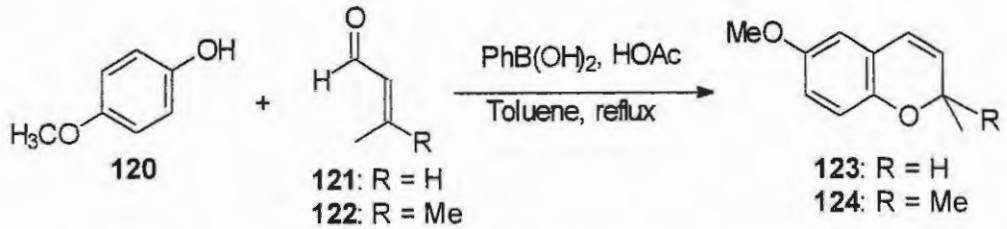
1.4.2 Acid-catalysed cyclisation

Spronck *et al.*[66] have shown that organocopper compounds participate in S_N2' reactions with propargylic substrates to afford allenes, which are important intermediates in the synthesis of oxygen-containing heterocyclic systems. Treatment of the organocopper compound **115** with the propargyl bromide **116** affords an allene **117** which, following protonation, cyclises *via* cation **118**, to give 5-hydroxy-2,2-dimethyl-7-pentylchromene **119** (Scheme 13).



Scheme 13

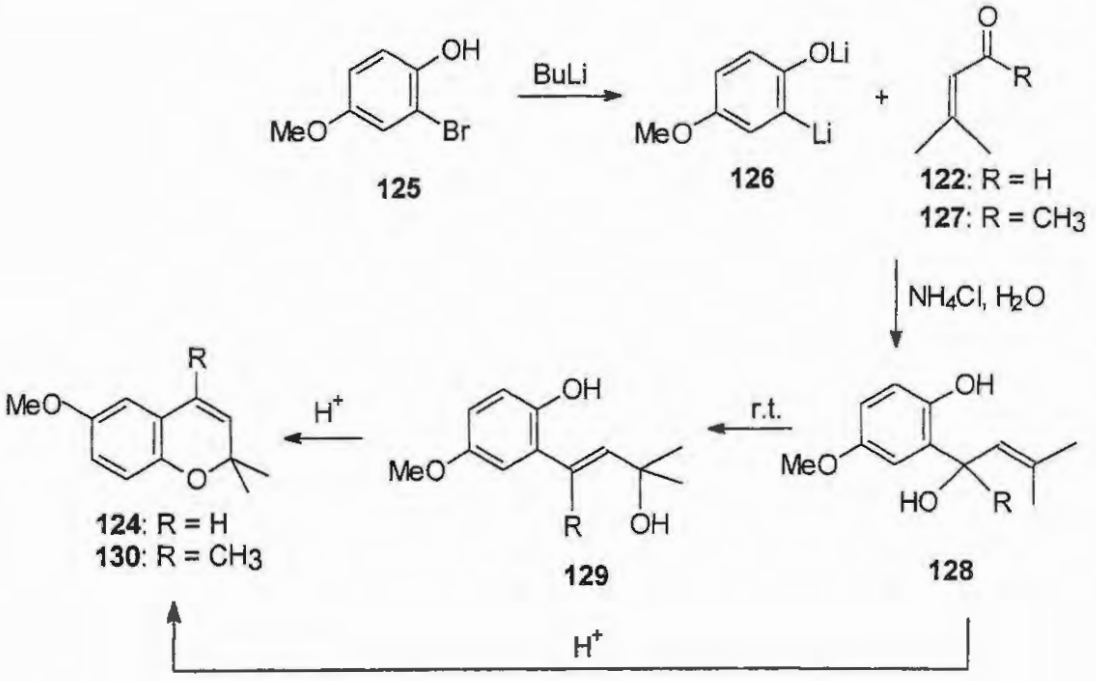
The use of phenylboronic acid in the synthesis of 6-methoxy-2-methylchromene **123** and 6-methoxy-2,2-dimethylchromene **124** has been reported by Lopes *et al.*[67] In these syntheses *p*-methoxyphenol **120** was condensed with but-2-enal **121** or 3-methylbut-2-enal **122** in the presence of phenylboronic acid in acetic acid-toluene.(Scheme 14).



Scheme 14

A different approach to synthesis of 6-methoxy-2,2-dimethylchromene **124** has been reported by Talley.[68] In this approach (Scheme 15), 2-bromo-4-methoxyphenol **125** is lithiated by treatment with excess butyllithium to give the lithium *o*-lithiophenoxide **126** which, upon treatment with 3-methylbut-2-enal, **122** affords the allylic alcohol **128**. On standing at room temperature for a long period, the allylic alcohol **128** isomerises to the more stable, conjugated system **129**. Treatment of both alcohols (**128** and **129**) with a catalytic quantity of acid gives the expected chromene **124**. This method was also applied to the synthesis of 2,2,4-trimethylchromene **130**.

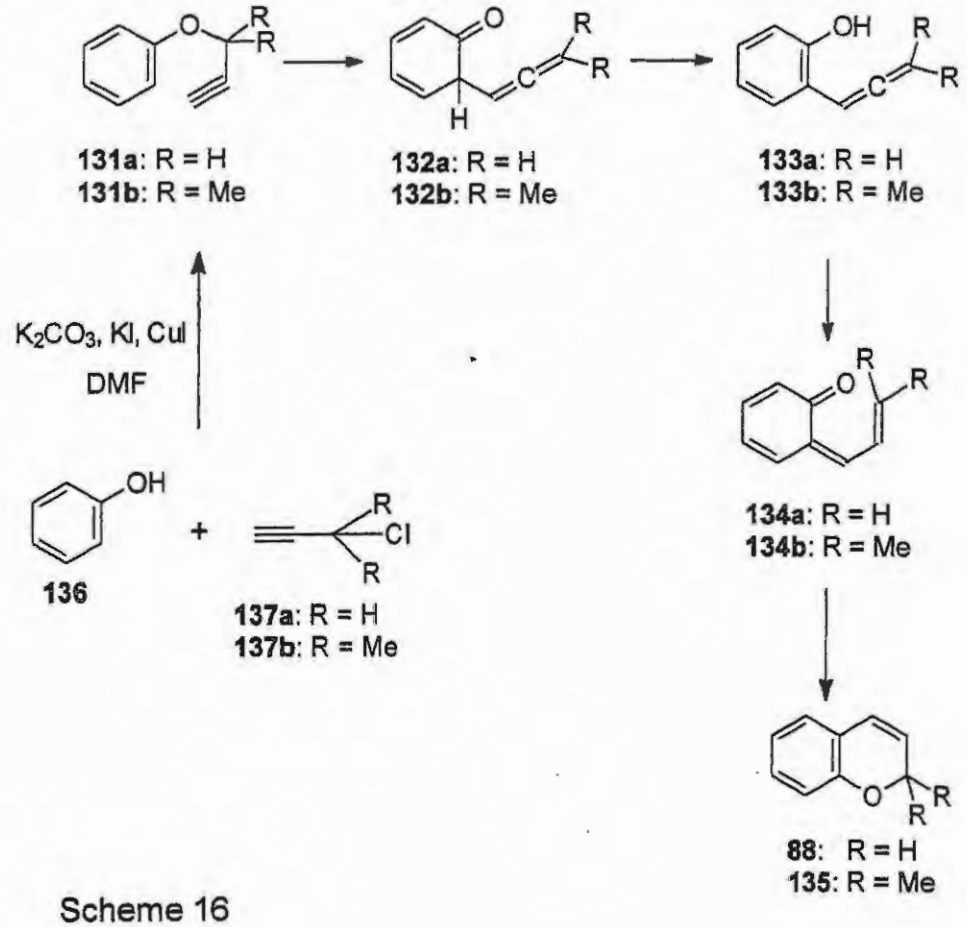
using the ketone **127** instead of the aldehyde **122**.



Scheme 15

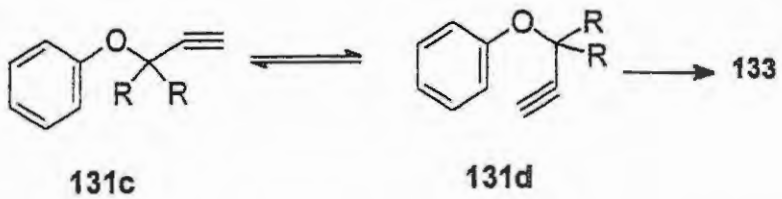
1.4.3 Claisen rearrangement

Chromenes, including 2,2-dimethylchromenes, have been conveniently synthesised by thermal cyclisation (Claisen rearrangement) of propargyl ethers.[69,70] The mechanistic sequence involves a 3,3-sigmatropic rearrangement of an aryl propargyl ether **131** to an allene **132**, followed by tautomerism to the 2-substituted phenol **133**. A 1,5 hydrogen shift results in the formation of the non-aromatic system **134**, cyclisation of which affords the chromene **88** or **135** (Scheme 16).[69,70] The aryl propargyl ether precursors **131** are conveniently obtained by treatment of phenol **136** with the appropriate dialkyl propargyl chloride in the presence of potassium carbonate and the catalyst, copper iodide.[71]



Scheme 16

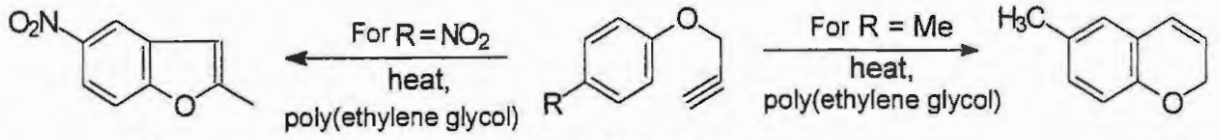
The effect of the *gem*-dimethyl substituents on the Claisen rearrangement has been explained in terms of conformational preferences. Thus, when R = H, conformation **131c** is favoured, inhibiting the Claisen rearrangement, but when R = Me, conformation **131d** is favoured and the alkyne moiety is suitably orientated for the initial cyclisation to the allene **133**.



131c **131d**

This '*gem*-dimethyl effect', which increased the rate of cyclisation,[73] was confirmed by Brown and Lewis[72] using molecular mechanics calculations. Claisen rearrangements are also affected

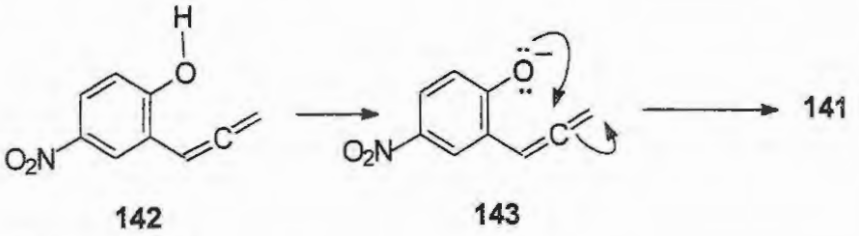
by the nature of the ring substituents; electron-donating groups increase the rate of reaction, while electron-withdrawing groups decrease the rate (*e.g.* a *p*-amino system reacts 10 to 20 times faster than a *p*-nitro analogue[74]). Later work by Rao and Balasubramanian[69] showed that for reactions in poly(ethylene glycol) the electronic properties of the ring substituents may also influence the nature of product. Thus, the aryl propargyl ether **138**, containing a 4-methyl substituent, gives the expected 6-methylchromene **140** in good yield, whereas the 4-nitro analogue **139** gives the benzofuran **141** in moderate yield (Scheme 17).[69]



141 **138**: R = Me; **139**: R = NO_2 **140**

Scheme 17

Formation of the benzofuran is presumed to involve nucleophilic attack by an intermediate phenoxide species on the central allenic carbon. The electron-withdrawing group increases the acidity of the phenolic hydrogen, facilitating formation of the phenoxide ion as illustrated in Scheme 18.[69] Interestingly, a chlorinated aryl propargyl ether gave a mixture of the corresponding chromene and benzofuran derivatives.[69]

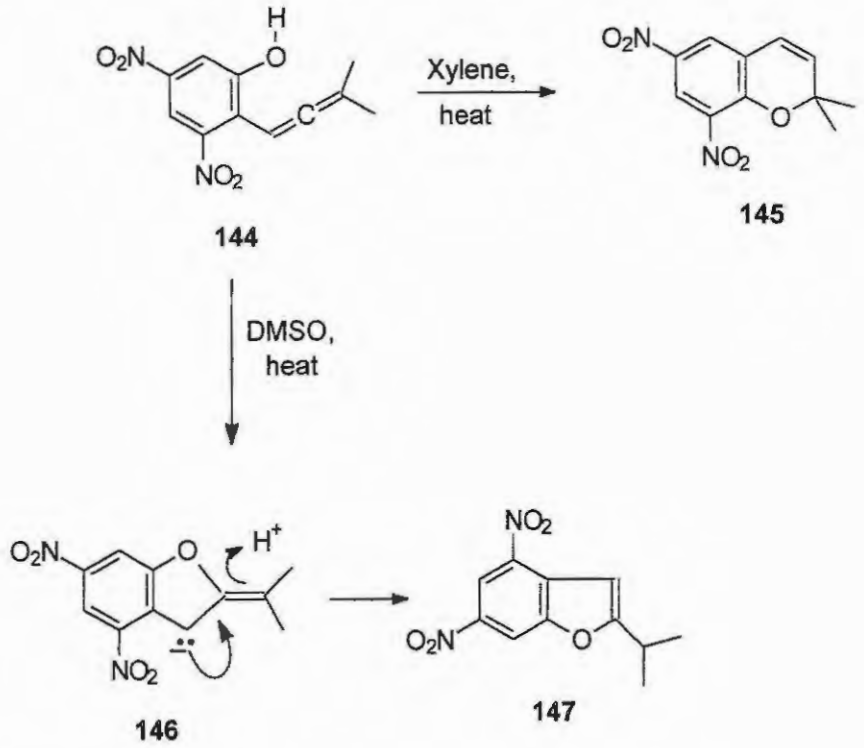


142 **143**

Scheme 18

Recently, Brown and Lewis have shown that cyclisation of the dinitro analogue **144** is solvent dependent,[72] giving the expected 2,2-dimethyl-6,8-dinitrochromene **145** in xylene, but the benzofuran **147** in dimethyl sulfoxide. Apparently, in dimethyl sulfoxide, the allenic phenol

cyclises to the carbanion **146**, which is stabilised by the strong electron-withdrawing groups in the aromatic ring (Scheme 19).[72] In the less polar solvent, xylene, however, this pathway is not favoured.

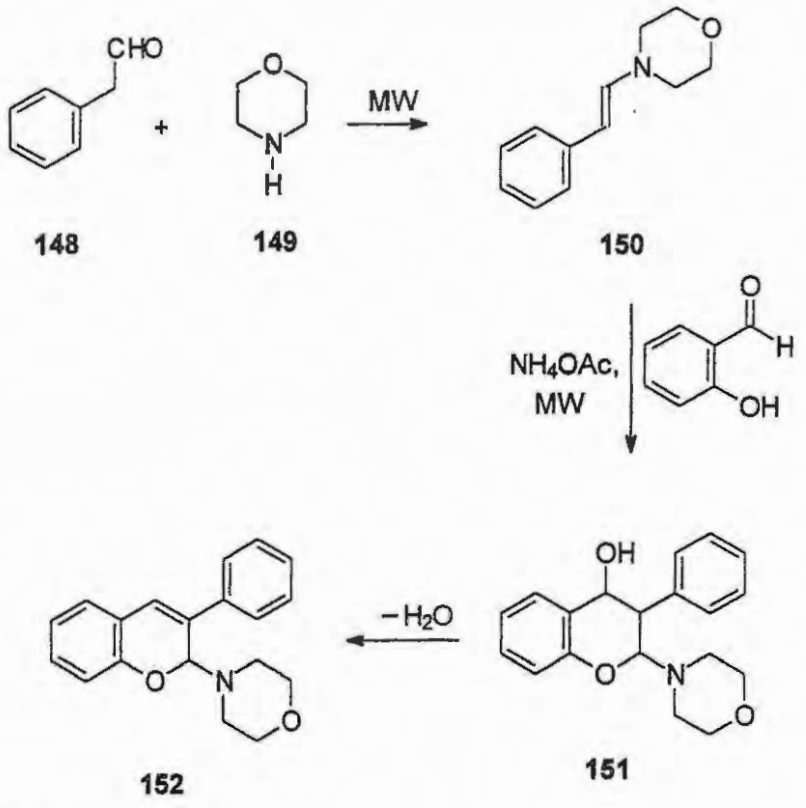


144 **145** **146** **147**

Scheme 19

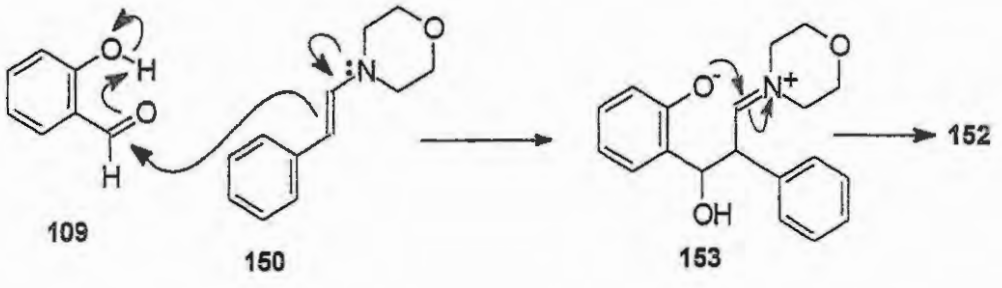
1.4.4 Microwave assisted synthesis

A domestic microwave oven has been used to achieve a convenient one-pot synthesis of 2-morpholino-3-phenylchromene **152**. Irradiation of a mixture of phenylacetaldehyde **148** and morpholine **149** to generate the enamine **150**, followed by *in situ* treatment with salicylaldehyde in the presence of a catalytic quantity of ammonium acetate afforded the the chroman-4-o1 **151**, dehydration of which gave the expected chromene **152** (Scheme 20).[75]



Scheme 20

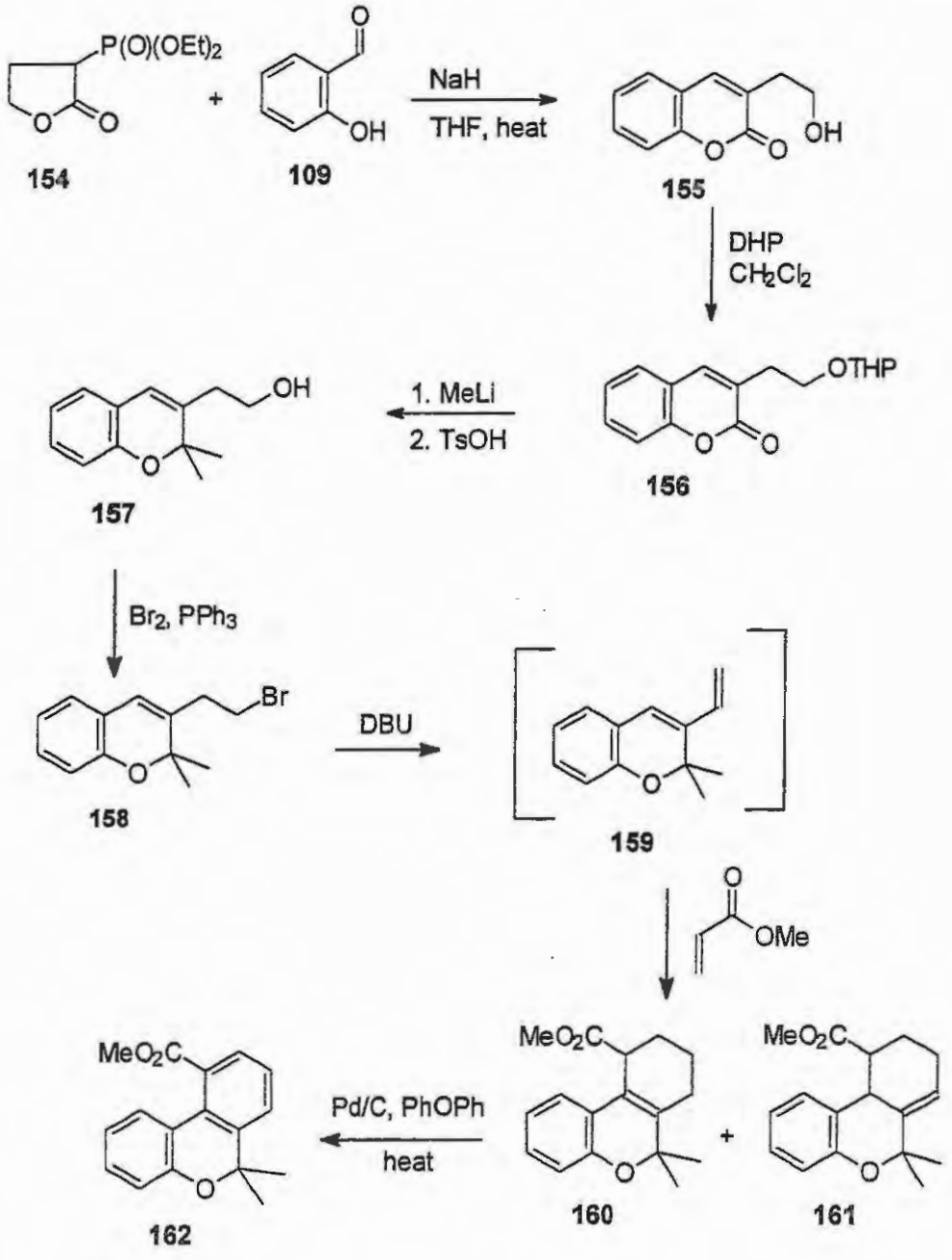
The mechanism of the cyclisation phase is considered to involve nucleophilic addition by the enamine **150** at the carbonyl carbon of salicylaldehyde **109**, a step aided by neighbouring-group participation of the phenolic hydroxyl group (Scheme 21);[75] subsequent cyclisation and dehydration then leads to the chromene **152**.



Scheme 21

1.4.5 Synthesis of 3,4-fused-ring chromenes

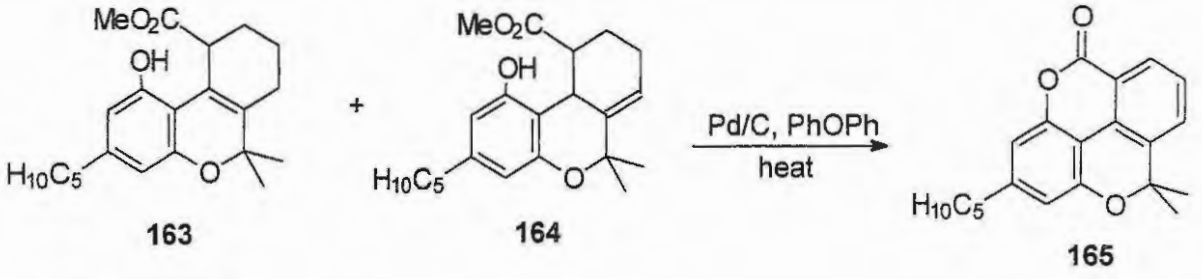
3,4-Fused-ring chromenes have been prepared *via* the Diels-Alder reaction of 2,2-dimethyl-3-vinylchromene **159** with methyl acrylate,[76] as illustrated in Scheme 22.



Scheme 22

Thus, reaction of the α-(diethylphosphono)-γ-butyrolactone **154** with salicylaldehyde **109** in the presence of sodium hydride gave 3-(2-hydroxyethyl)coumarin **155**. The hydroxy group was then

protected as a pyranyl ether, and the resulting coumarin **156** converted to the 2,2-dimethylchromene **157** by treatment with methyllithium, followed by *p*-toluenesulphonic acid. Bromination led to the 3-bromoethylchromene **158**, which underwent dehydrobromination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford the vinylchromene **159**. The vinychromene **159** was not isolated, and *in situ* treatment with methyl acrylate afforded a mixture of the isomeric cycloadducts **160** and **161** which, on reaction with palladium on charcoal at high temperature (250 °C), gave the 3,4-fused-ring chromene **162** as the sole product.[76] These observations suggest that the Diels-Alder reaction of the vinylchromene **159** with methyl acrylate gives the cycloadduct **161**, which then isomerises to the more stable adduct **160**. The Diels-Alder reaction of 5-hydroxy-2,2-dimethyl-7-pentyl-3-vinylchromene gave a corresponding mixture of cycloadducts **163** and **164** which, on treatment with palladium on charcoal at 250 °C, afforded the lactone **165** in 76 % yield (Scheme 23).[76]

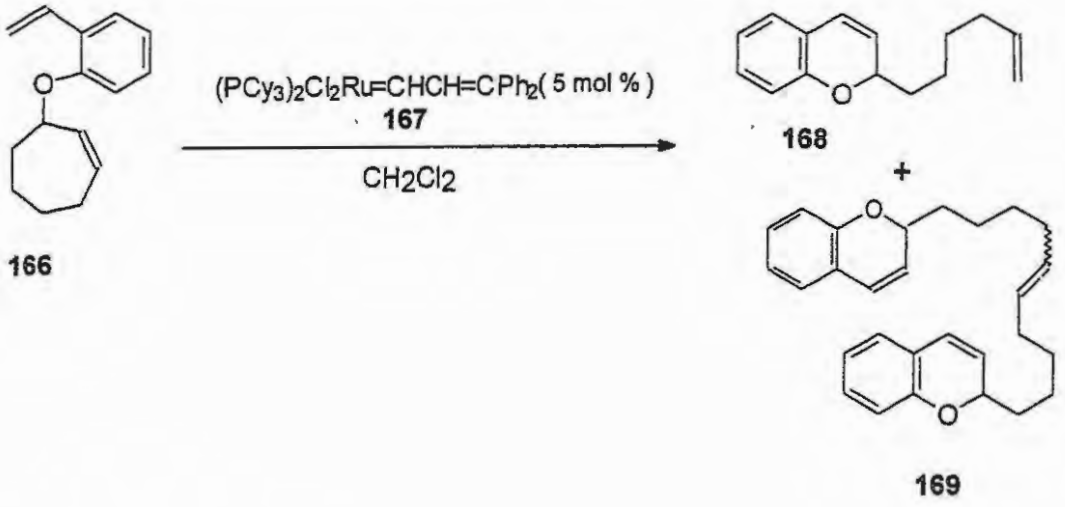


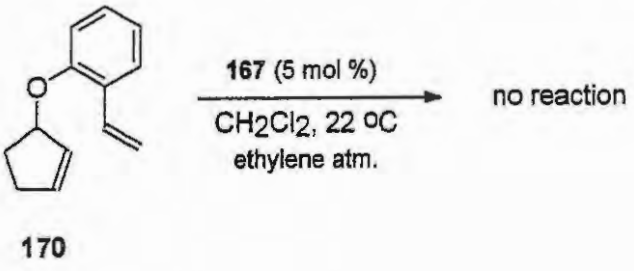
163 **164** **165**

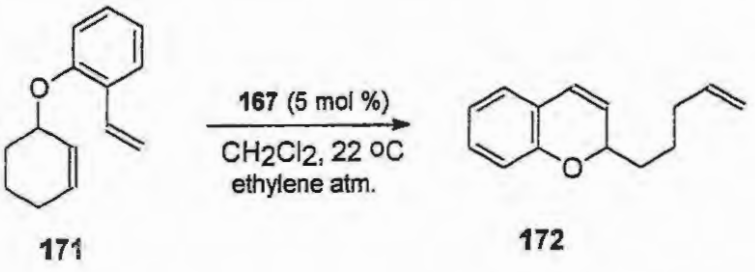
Scheme 23

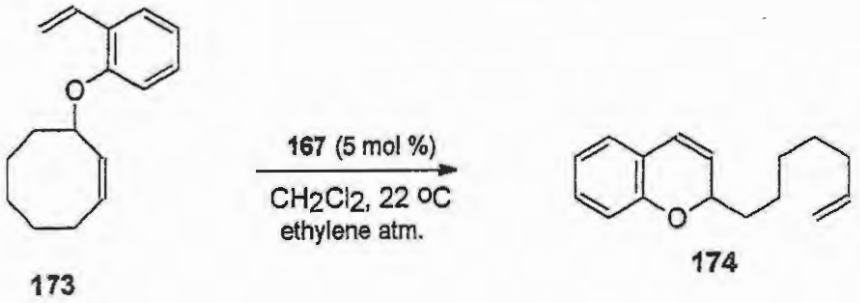
1.4.6 Ru-catalysed rearrangement of styrenyl ethers

The 2-substituted chromene **168** and its "dimer" **169** have been obtained in 44 % and 56 % yields, respectively, by treating cycloheptene styrenyl ether **166** with 5 mole % of the Grubbs metathesis catalyst **167** under an argon atmosphere (Scheme 24).[77] Under more dilute conditions the chromene was obtained as the major product (50 %), its predominance increasing to 92 % when the reaction was carried out under an ethylene atmosphere. Surprisingly, strained seven- and eight-membered rings appear to react more efficiently than the five- and six- membered analogues. Thus, when the cyclopentenyl styrenyl ether **170** was treated with the Grubbs catalyst under an ethylene atmosphere, no reaction was observed, while the cyclohexenyl styrenyl ether


(PCy3)2Cl2Ru=CHCH=CPh2(5 mol %)
167
CH2Cl2
168
+
169
166

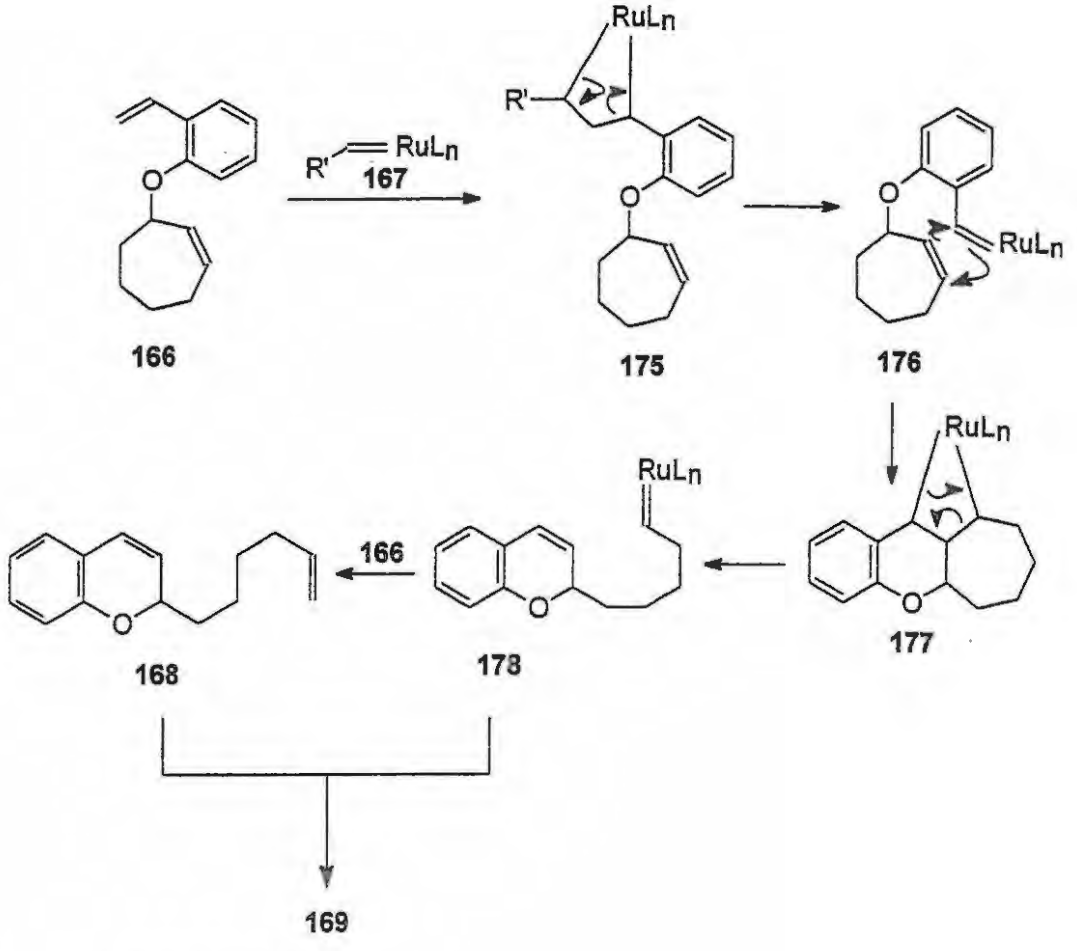

167 (5 mol %)
CH2Cl2, 22 oC
ethylene atm.
no reaction
170


167 (5 mol %)
CH2Cl2, 22 oC
ethylene atm.
171
172


167 (5 mol %)
CH2Cl2, 22 oC
ethylene atm.
173
174

Scheme 24

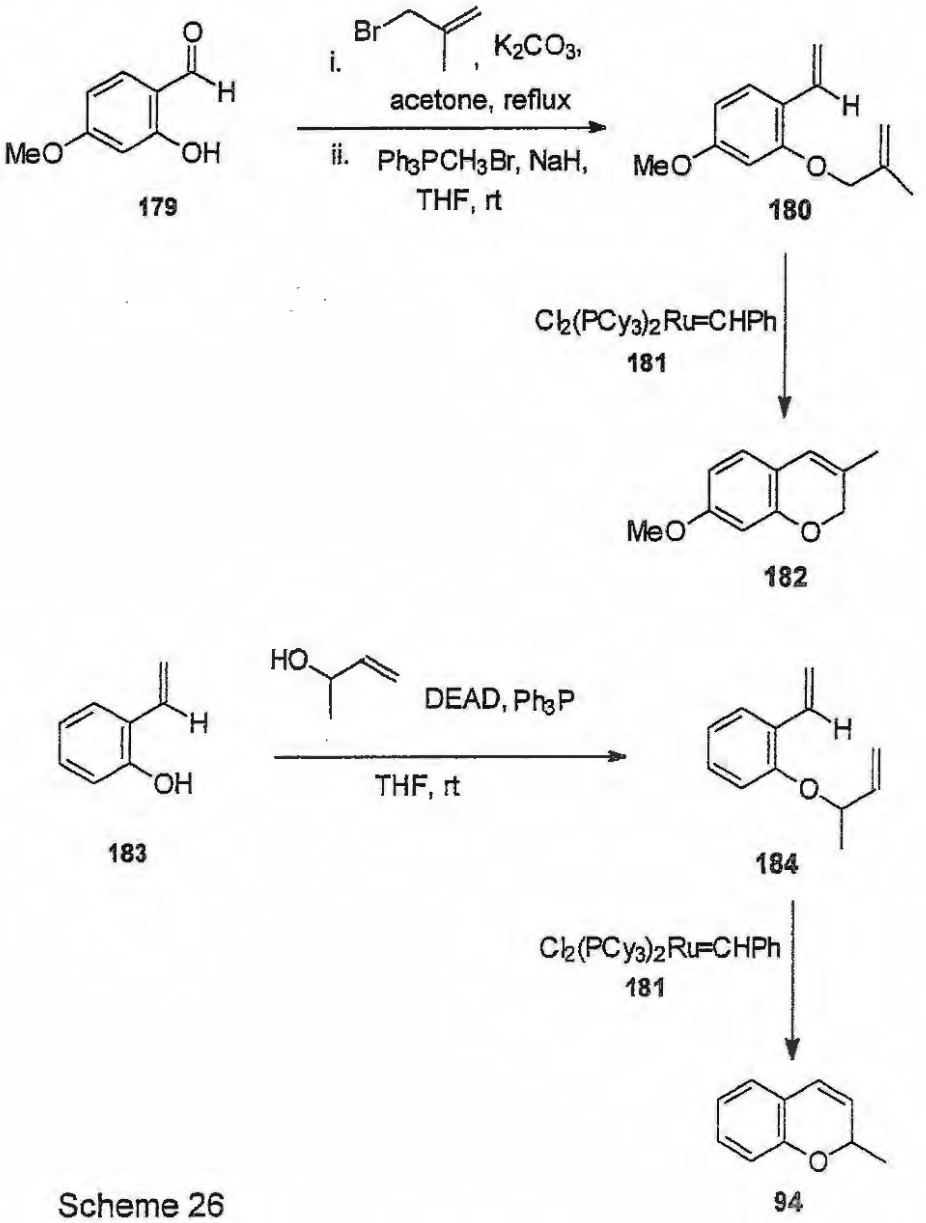
171 gave 35 % of the chromene **172** and less than 2 % of the corresponding dimer. The cyclooctenyl styrenyl ether **173**, on the other hand, gave the monomer **174** in 90 % yield and the dimer in less than 2 % yield under similar conditions (Scheme 24).[77] The mechanism proposed for the formation of the 2-substituted chromene **168** and the corresponding dimer **169** is outlined in Scheme 25.[77] The cycloheptene styrenyl ether **166** is considered to react with the Grubbs catalyst **167** to form complex **175**, which is cleaved to give the styryl ruthenium complex **176**. Intramolecular cycloaddition then affords the complex **177**, which rearranges to the chromene derivative **178**. Reaction of this derivative with a second equivalent of the substrate **166** yields the chromene **168** and regenerates the intermediate complex **176**. As the chromene **168** is produced, it may also react with the metallated intermediate **178** to produce the dimer **169**.[77]



Scheme 25

1.4.7 Ring-closing olefin metathesis

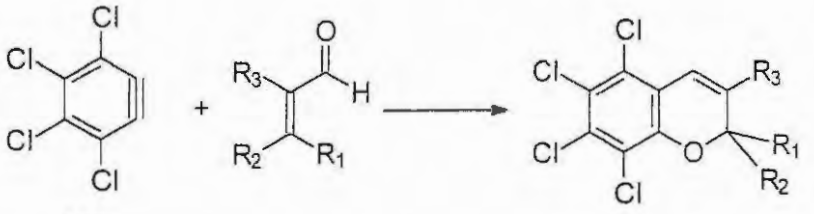
Previous work by Grubbs *et al.*[78] had shown that carbon-carbon double bonds can be constructed by treating dienes with a molybdenum catalyst. This approach was subsequently used to synthesise the chromene derivatives **182** and **94** from the dienes **180** and **184** respectively, using the ruthenium carbene catalyst **181** (Scheme 26).[79] The diene **180** was readily prepared by treating 4-methoxysalicylaldehyde **179** with an allyl bromide in the presence of potassium carbonate, and then subjecting the product to a Wittig reaction. Synthesis of 2-methylchromene **94** was achieved by reacting the diene **184** (obtained from the Mitsunobu reaction of 2-vinylphenol **183** with an allylic alcohol) with the ruthenium catalyst **181**.[79]



Scheme 26

1.4.8 Cycloaddition of arynes and α,β-unsaturated aldehydes

The reaction between arynes and α,β-unsaturated aldehydes provides a convenient route for the formation of chromenes. Heaney *et al.*[80] showed that treatment of tetrachlorobenzyne **185** with an α,β-unsaturated aldehyde results in the formation of the 5,6,7,8-tetrachlorochromenes **186** (Scheme 27). The 5,6,7,8-tetrachlorobenzyne precursor can be generated from various substrates, *viz.*, tetrachloroanthranilic acid, tetrachlorobenzenediazonium-2-carboxylate hydrochloride and 3,4,5,6-tetrachloro-2-(3,3-dimethyltriazeno)benzoic acid.[80] The generality of this reaction was demonstrated by treating tetrachlorobenzyne **185** with crotonaldehyde, 2-butenal, 2-methyl-2-butenal, 3-methyl-2-butenal and 3-phenyl-2-propenal to afford the corresponding products **186a-e**.

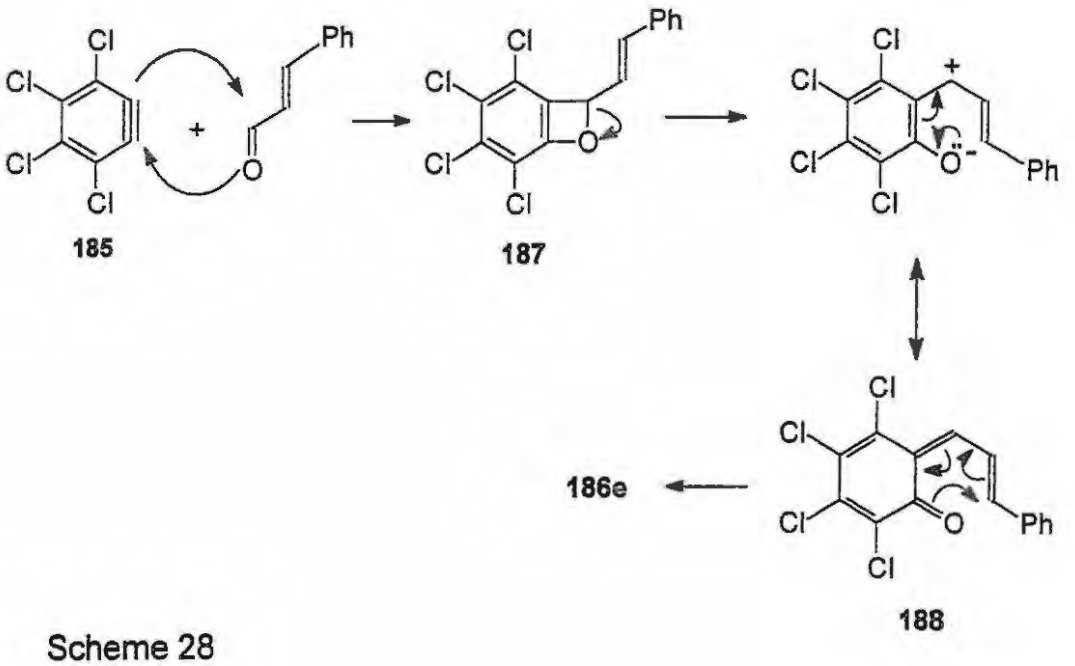


185

186a: $R_1 = R_2 = R_3 = H$
186b: $R_1 = CH_3$, $R_2 = R_3 = H$
186c: $R_1 = H$, $R_2 = R_3 = CH_3$
186d: $R_1 = R_2 = CH_3$, $R_3 = H$
186e: $R_1 = Ph$, $R_2 = R_3 = H$

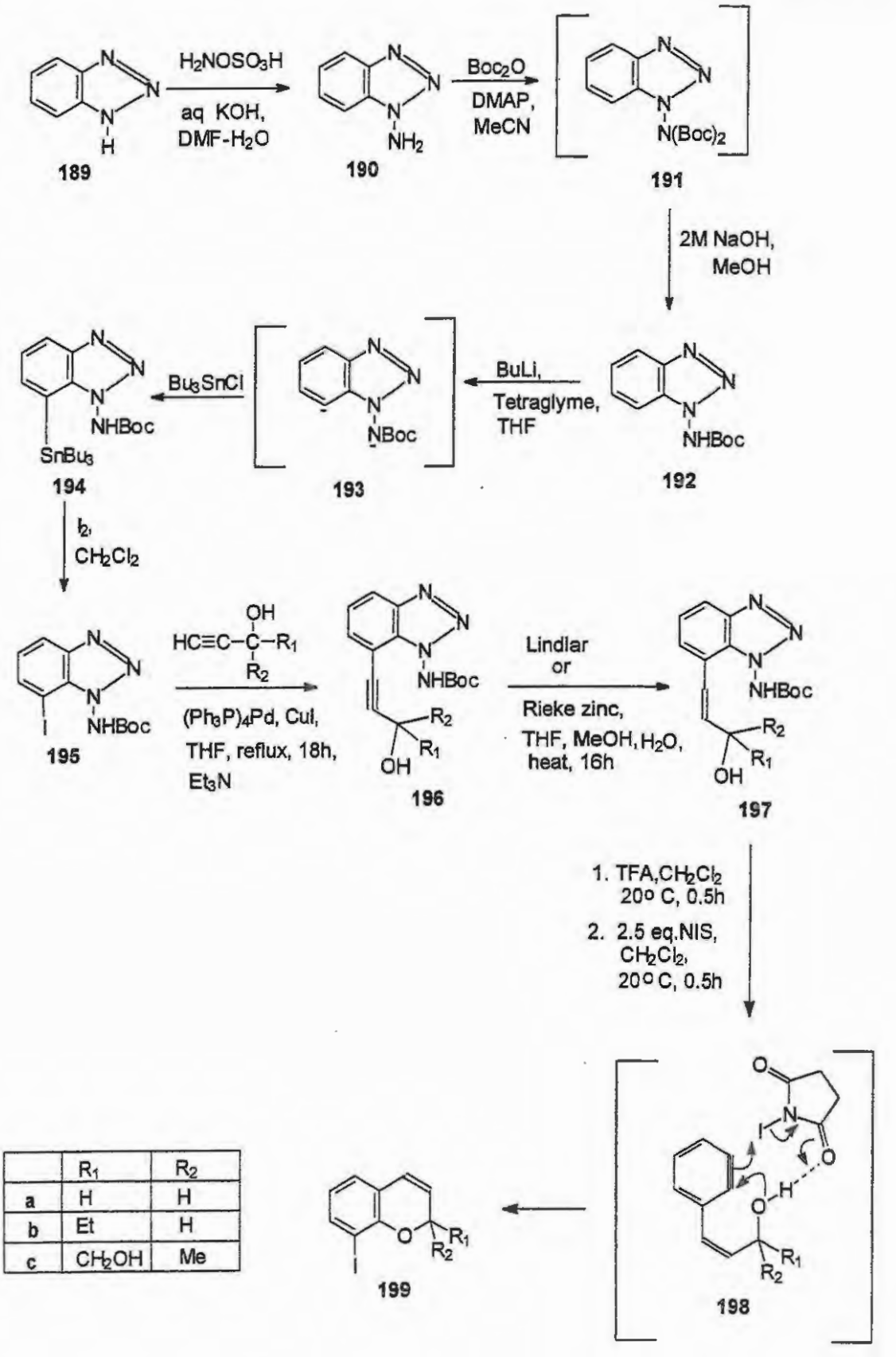
Scheme 27

The mechanism proposed for this reaction, which has been studied using ^{14}C and ^{2}H labelled substrates, is illustrated in Scheme 28. The first crucial step involves 1,2-cycloaddition to form the benzoxete ring system **187** and is followed by ring-opening to form a quinone methide intermediate **188**, which undergoes electrocyclic ring-closure to form the chromene **186e**.[80]



Scheme 28

Knight and Little [81] successfully synthesised the 8-iodochromenes **199a-c** *via* benzyne generation, intramolecular trapping by the hydroxyl group and iodine incorporation. The synthetic sequence (Scheme 29) involved generation of the benzyne precursor **190** by *N*-amination of benzotriazole **189** using hydroxylamine-*O*-sulfonic acid in the presence of potassium hydroxide. The amino group was protected using excess *tert*-butyl dicarbonate to afford the intermediate **191** , which was selectively hydrolysed, using methanolic sodium hydroxide, to afford the *N*-Boc derivative **192**. The dianion **193** [generated by reacting the *N*-Boc derivative **192** with 2.2 equivalents of butyllithium and 5 equivalents of tetra(ethylene glycol) dimethyl ether] was treated with tributyltin chloride to afford the stannane **194**, which was converted, in turn, to the iodide **195** with iodine in dichloromethane. The iodide **195** was then subjected to Sonogashira coupling with an alkynol to afford the corresponding arylalkyne **196**. Partial reduction of the arylalkyne **196a**, using the Lindlar catalyst, gave the required (Z)-allyl alcohol **197a**, but for the alcohols **197b** and **c**, this method was not the preferred approach. Instead, Rieke zinc reduction was used to give the allylic alcohols **197b** and **c** in excellent yields. Finally, deprotection of the amine and exposure to *N*-iodosuccinimide gave the required 8-iodochromenes**199a-c** *via* intramolecular trapping by the hydroxy group and transfer of iodine to the intermediate benzyne **198**.

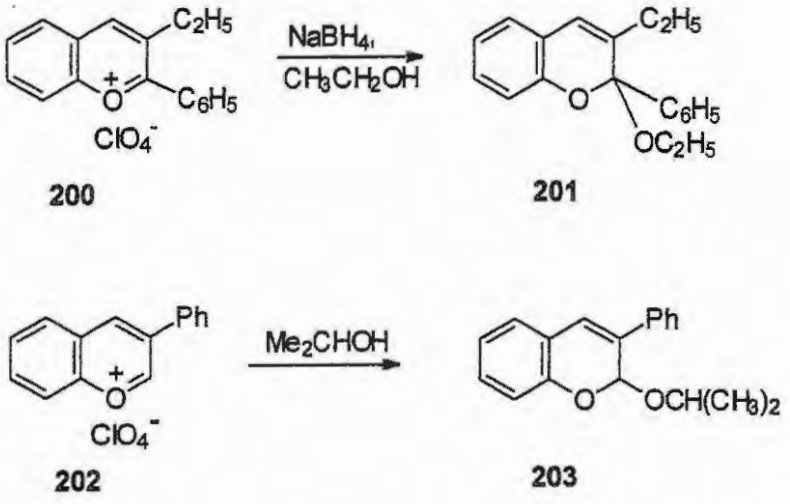


	R_1	R_2
a	H	H
b	Et	H
c	CH_2OH	Me

Scheme 29

1.4.9 Synthesis *via* benzopyrylium salts

Benzopyrylium salts have been found to undergo nucleophilic attack at C-2 resulting in the formation of chromenes.[82] Thus, treatment of 3-ethylflavylium perchlorate **200** with sodium borohydride in ethanol gave the 2,2-disubstituted chromene **201** (Scheme 30).[82] In this process, the borohydride clearly acts as a base, generating the nucleophilic ethoxide ion. However, treatment of the isoflavylium salt **202** with isopropyl alcohol in the *absence* of added base, afforded the 2-substituted chromene **203**.[83] It has also been reported that benzopyrylium salts react with lithium aluminium hydride to give chromenes, the reagent acting as a source of nucleophilic hydride ions.[84]

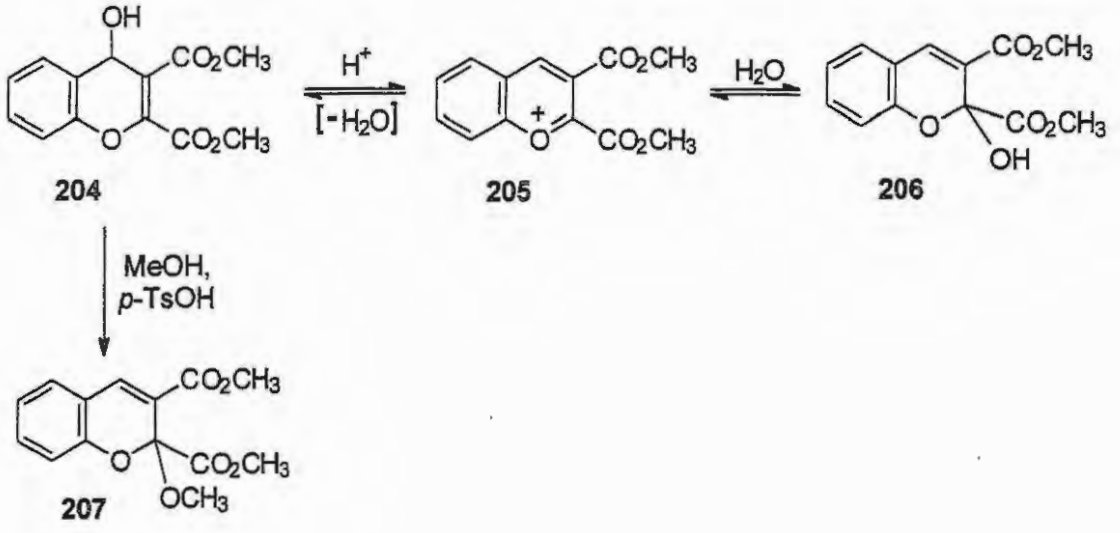


200 **201**

202 **203**

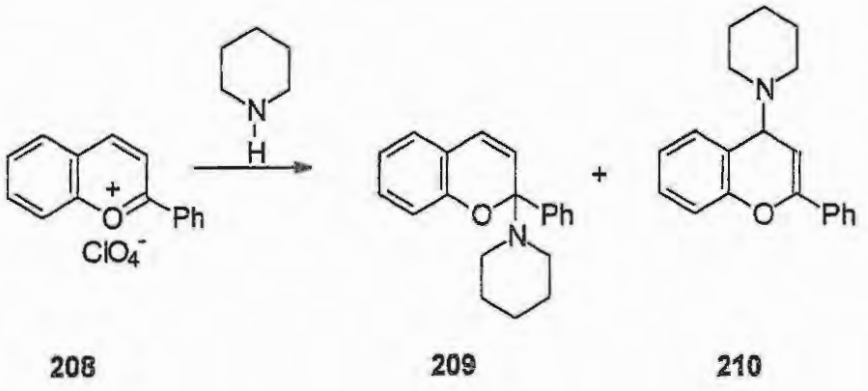
Scheme 30

Gupta and George[85] observed that isomerisation of the chromen-4-ol **204** under acidic conditions resulted in formation of the chromene **206** *via* the benzopyrylium cation **205** (Scheme 31). The methoxy analogue **207** was obtained in 99 % yield, by heating the chroman-4-ol **204** in the presence of absolute methanol and a catalytic amount of *para*-toluenesulphonic acid.[82]



Scheme 31

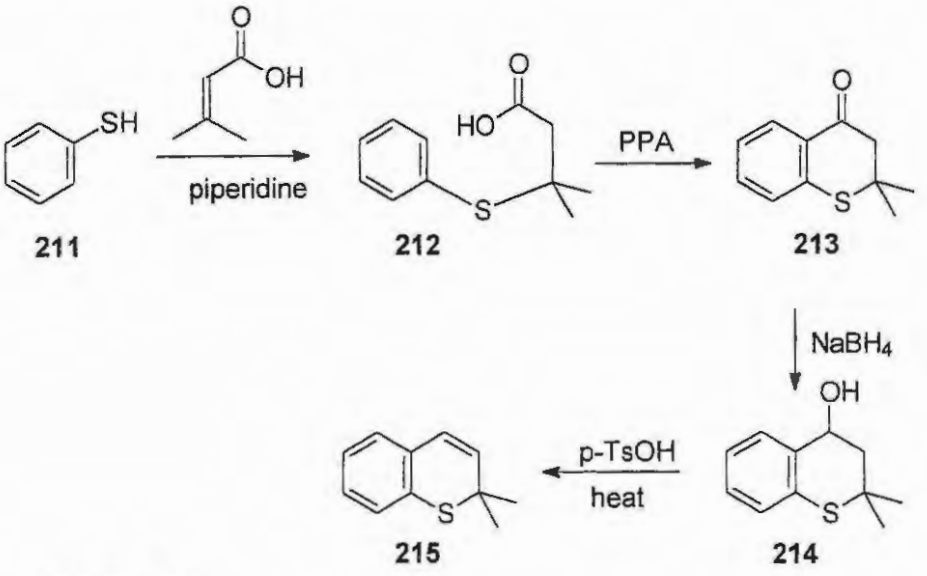
Benzopyrylium salts are, in fact, known to be reactive at two postions, *viz.*, C-2 and C-4, and Sutton [86] showed that flavylium perchlorate **208** reacts with piperidine to afford a mixture of 2- and 4-substituted products, *viz.*, the chrom-3-ene **209** and chrom-2-ene **210** (Scheme 32).



Scheme 32

1.5 SYNTHESIS OF THIOCHROMENES

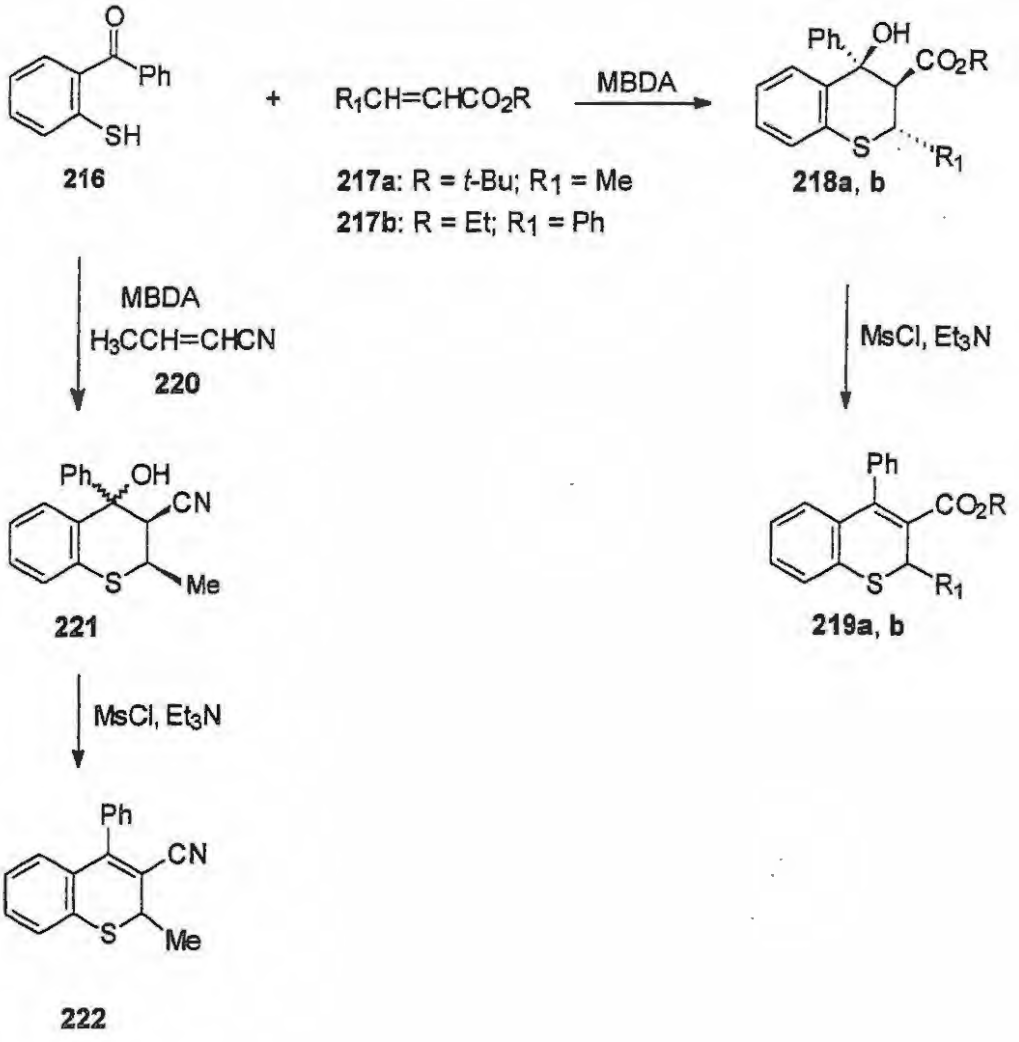
Sulphur analogs of the biologically active chro`menes, precocene I and II, discussed earlier (see Section 1.1.2, p.3) have been prepared by Ferreira *et al.*[87] The first step in their synthesis, which is illustrated in Scheme 33, involves, conjugate addition of benzenethiol **211** to a 2-alkenoic acid in the presence of piperidine to afford the 3-arylthiobutenoic acid **212**. Friedel-Crafts cyclisation, using polyphosphoric acid as catalyst, then gives the chromanone **213**, and sodium borohydride reduction of the carbonyl group, followed by dehydration using *para*-toluenesulphonic acid in benzene, leads to the desired 2,2-dimethylthiochromene **215**.



211 **212** **213** **214** **215**

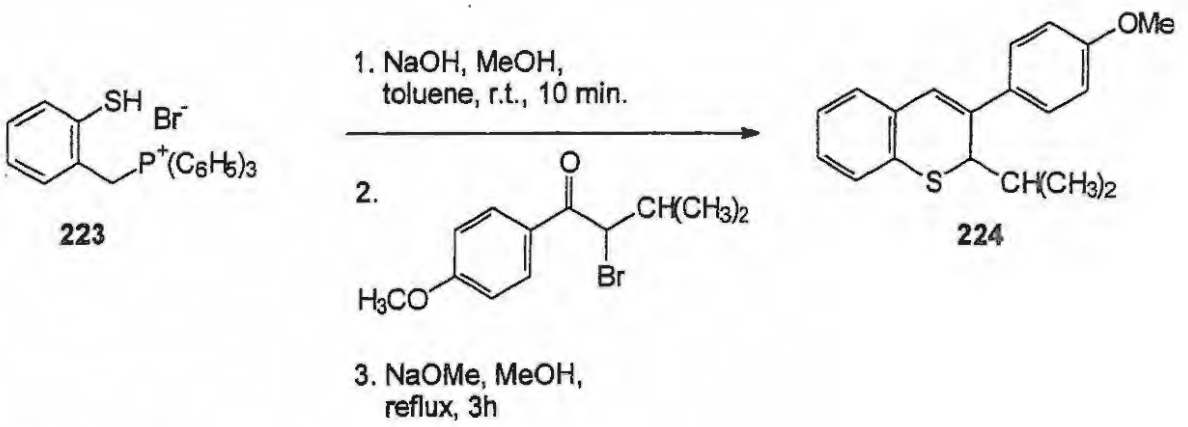
Scheme 33

A different approach to the synthesis of thiochromenes was used by Kobayashi *et al.*[88] In their method, 2-mercaptobenzophenone **216** is subjected to a sequential conjugate-aldol type condensation with α,β-unsaturated carboxylic acid derivatives **217** in the presence of magnesium bis(diisopropyl)amide (MBDA; generated *in situ* from diisopropylamine and ethylmagnesium bromide) to afford the thiochromanols **218** (Scheme 34). Dehydration of the chromanol intermediates **218** using methylsulphonyl chloride in the presence of triethylamine affords the required thiochromenes **219**. Similar treatment of 2-mercaptobenzophenone **216** with crotononitrile **220** leads to the corresponding thiochromene nitrile **222**.



Scheme 34

Arnoldi and Carughi[89] have shown that thiochromenes can also be obtained using Wittig-type reactions. Thus, (2-mercaptophenyl)methyltriphenylphosphonium bromide **223** (obtained from the reaction of 2-mercaptobenzyl alcohol with triphenylphosphine in acetonitrile) was treated with excess sodium methoxide and a haloketone to produce the thiochromene **224** (Scheme 35).



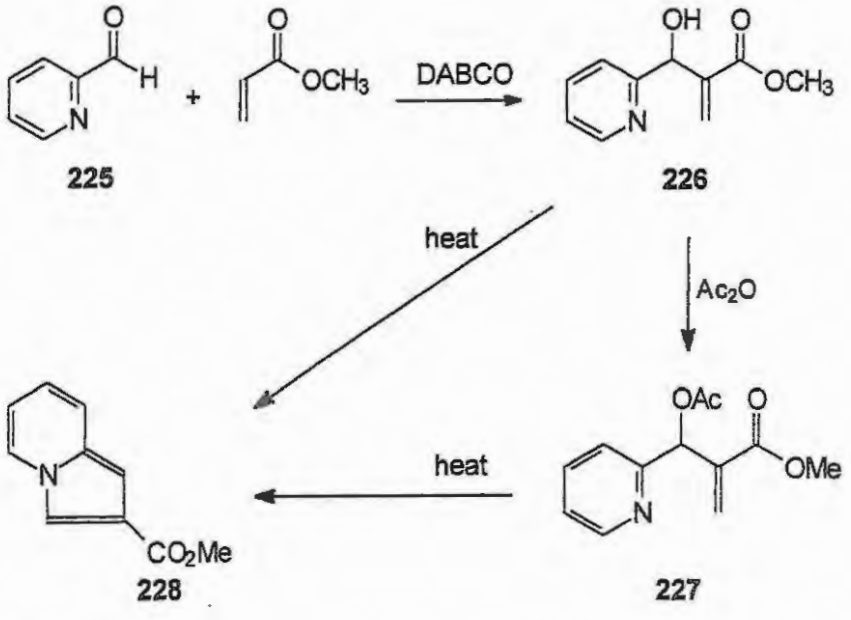
223 **224**

Scheme 35

1.6 EARLIER STUDIES AND AIMS OF THE CURRENT INVESTIGATION

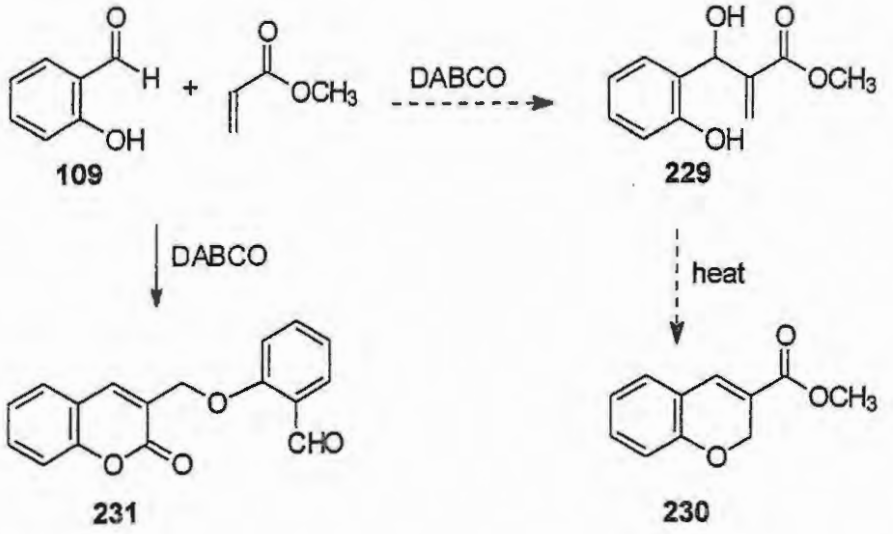
Previous work in our research group has demonstrated the potential of the Baylis-Hillman reaction in the construction of various heterocyclic systems, the key step, in each case, being the intramolecular cyclisation of an appropriate Baylis-Hillman product.

Thus, treatment of 2-pyridinecarboxaldehyde **225** with methyl acrylate in the presence of the catalyst, DABCO, afforded the 2-pyridyl derivative **226**, which underwent thermal cyclisation to afford the indolizine **228** (Scheme 36).[90,91,92] It was found that use of the acetylated derivative **227**, obtained by acetylating the hydroxy group in the Baylis-Hillman product **226**, permitted moderation of the cyclisation conditions and an improvement in the yield of the indolizine product **228**. The generality of the reaction was demonstrated by Bode[91] and a kinetic-mechanistic study of the thermal cyclisation was undertaken.



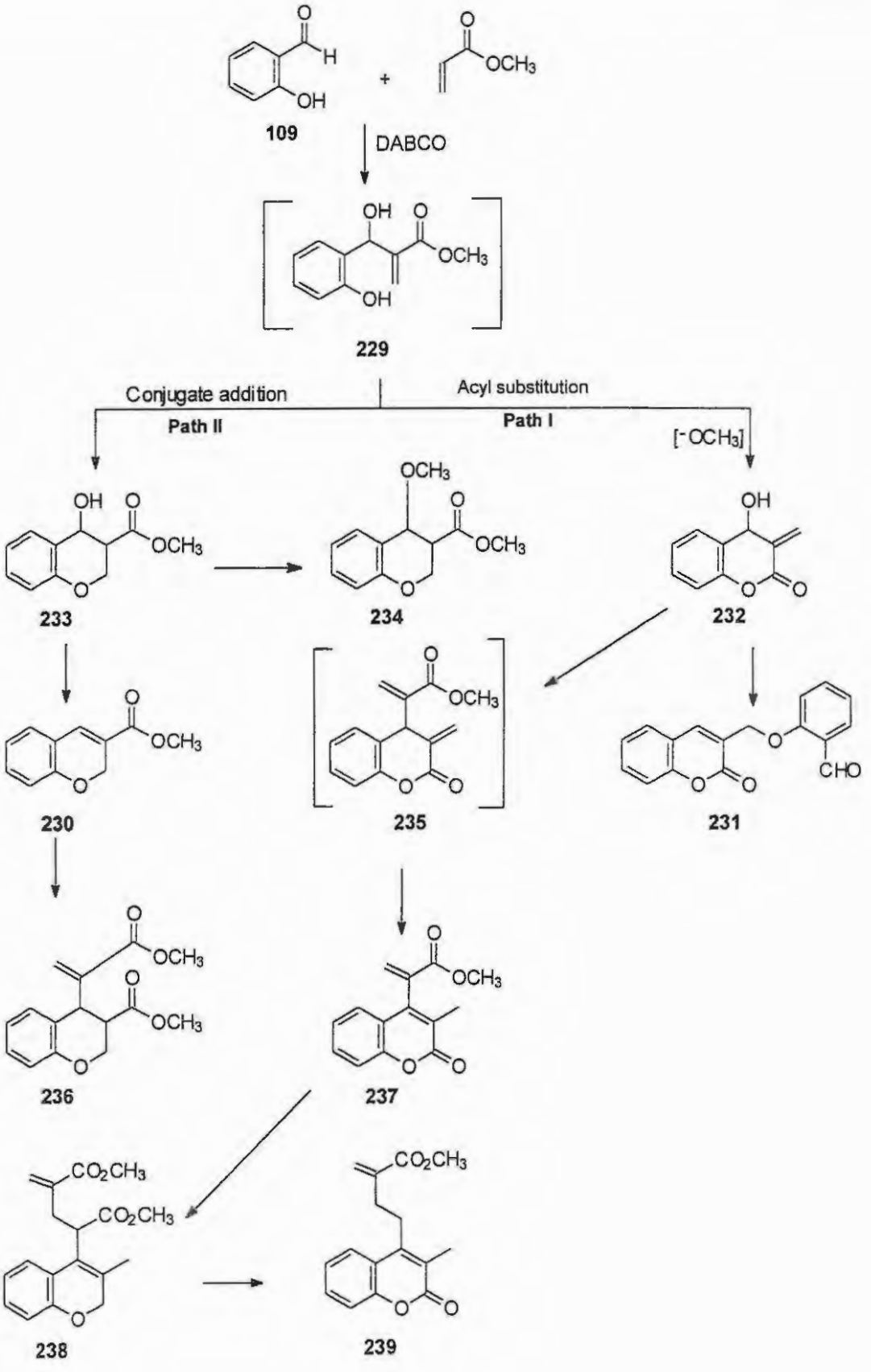
Scheme 36

Attempts were made to extend the methodology illustrated in Scheme 36 to the synthesis of chromene derivative **230** by treating salicylaldehyde with methyl acrylate in the presence of the catalyst, DABCO, but the only product to be isolated initially (in 19 % yield) was the unexpected coumarin derivative **231** (Scheme 37).[91,93]



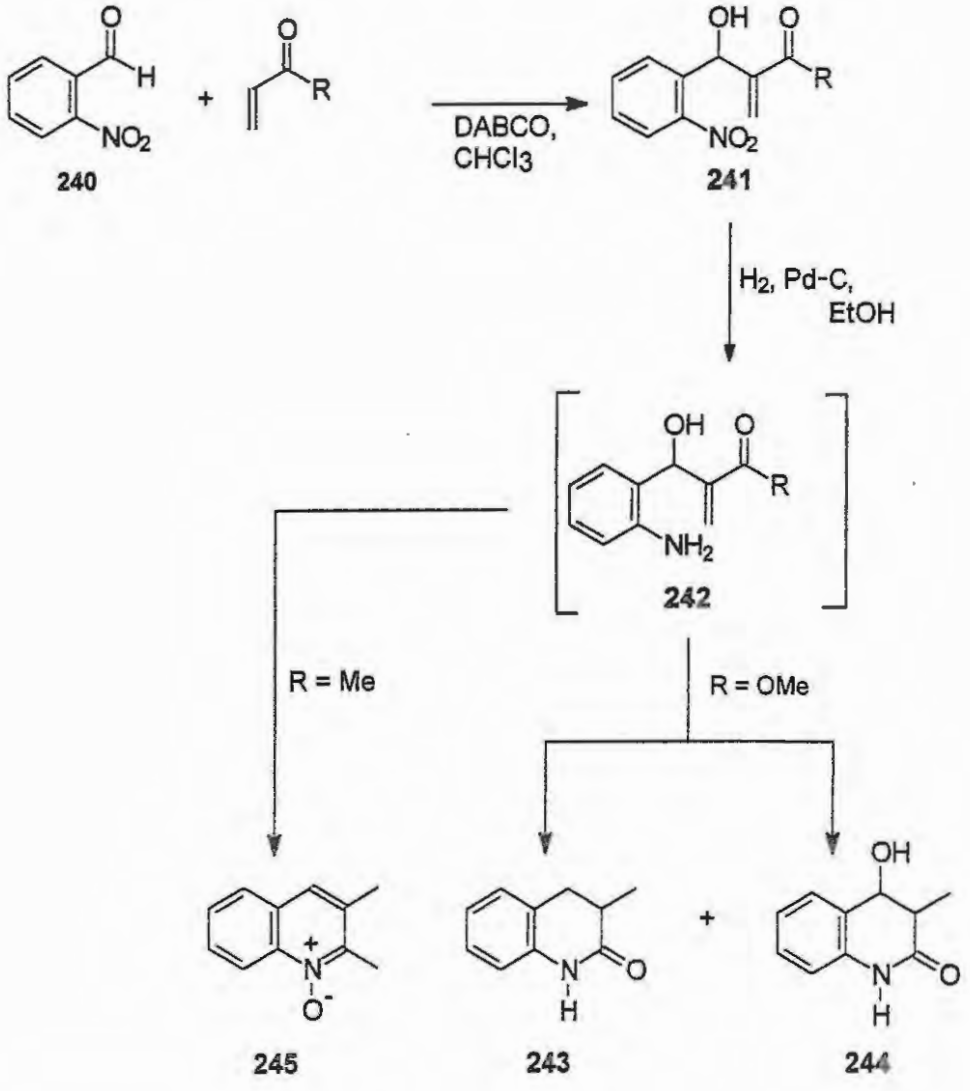
Scheme 37

The generality of the reaction resulting in the formation of coumarin **231** was further explored by Robinson,[94] and careful examination of the complex reaction mixtures revealed the presence of coumarin and chromene derivatives. In fact, compounds representing no less than eight types of chromene and coumarin derivatives (Scheme 38) were isolated and characterised.[94,95] The reaction was assumed to proceed *via* the formation of the Baylis-Hillman product **229**, which could not be isolated but was presumed to undergo immediate intramolecular cyclisation. Two, parallel, cyclisation pathways (I and II) were envisaged. In pathway I, acyl substitution, involving loss of the methoxy group, affords the coumarin **232**, while in pathway II, conjugate addition, followed by dehydration, affords the chromene **230**.[94,95,96] Once formed, these heterocyclic systems appeared to undergo a variety of further reactions.


109
DABCO
229
Conjugate addition
Path II
Acyl substitution
Path I
[-OCH3]
233
234
232
230
235
231
236
237
238
239

Scheme 38

Quinoline derivatives were obtained by Familoni and Klaas[97] following the reduction of Baylis-Hillman products, prepared by treating 2-nitrobenzaldehyde **240** with activated alkenes in the presence of the catalyst, DABCO. Use of methyl acrylate as the activated alkene afforded the quinolones **243** and **244** (Scheme 39), while the use of methyl vinyl ketone afforded 2,3-methyl quinoline *N*-oxide **245**. In all cases, cyclisation of the reduced intermediate **242** appeared to involve nucleophilic attack at the carbonyl carbon rather than the vinylic carbon. The generality of these approaches to quinoline has been demonstrated by Klaas.



Scheme 39

The potential of the Baylis-Hillman reaction for the formation of heterocyclic compounds, in general, and oxygen-containing systems, in particular, was thus clearly evident. However, the early the results (outlined in Scheme 38) posed significant challenges in chemoselectivity control. In a parallel study,[98] attention is being given to the chemoselective synthesis of coumarin derivatives, but the research reported in this thesis has focused on the chemoselective preparation and chemistry of chromene analogues. Consequently, the objectives of the current investigation have included the following:-

i) to control regioselectivity in the intramolecular cyclisation of salicylaldehyde derived Baylis-Hillman products to permit the selective formation of chromene derivatives;

ii) to optimise reaction conditions and thus improve the yields of the chromene products;

iii) to establish the generality of the reaction;

iv) to confirm the intermediacy of the Baylis-Hillman product in the formation of chromene and coumarin derivatives;

v) to extend the methodology to thiosalicylaldehyde (2-sulfanylbenzaldehyde) for the synthesis thiochromene analogues; and

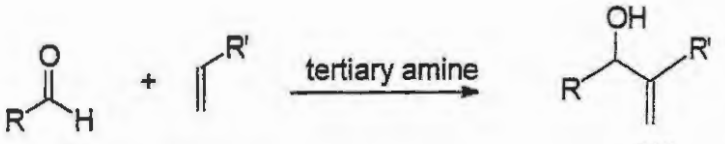
vi) to explore the use of chromenes and thiochromenes in the synthesis of potential HIV-1 protease inhibitors.

2. DISCUSSION

This investigation has been concerned, largely, with the application of Baylis-Hillman methodology in the synthesis of chromene derivatives. The discussion will cover :- the synthesis of chromene derivatives (Section 2.2); mechanistic considerations (Section 2.3); Michael-type addition reactions under Baylis-Hillman conditions (Section 2.4); attempted acceleration of the Baylis-Hillman reaction *via* intramolecular catalysis (Section 2.5); application of the Baylis-Hillman reaction in the synthesis of thiochromenes (Section 2.6); mass spectrometric studies of chromene and thiochromene derivatives (Section 2.7) and, finally, the synthesis of potential HIV-1 protease inhibitors containing chromene and thiochromene moieties.(Section 2.8).

2.1 THE BAYLIS-HILLMAN REACTION

The reaction between an aldehyde and an α,β-unsaturated ketone, ester or nitrile in the presence of a tertiary amine catalyst, such as DABCO, indolizine or quinuclidine, was first described in a German patent by Baylis and Hillman in 1972.[99] The reaction, which affords α-hydroxy vinylic products **246** usually called Baylis-Hillman products (Scheme 40),[99] is of great interest to Organic Chemists because it involves the formation of a new carbon-carbon bond. However, similar work had been reported five years previously by Morita,[100] who used tertiary phosphines as catalysts instead of tertiary amines; consequently, this reaction is sometimes referred to as the "Morita-Baylis-Hillman" reaction.[101] Reviews of the Baylis-Hillman reaction have been published by Drewes and Roos,[102] Basavaiah *et al.*[103] and Ciganek.[101]

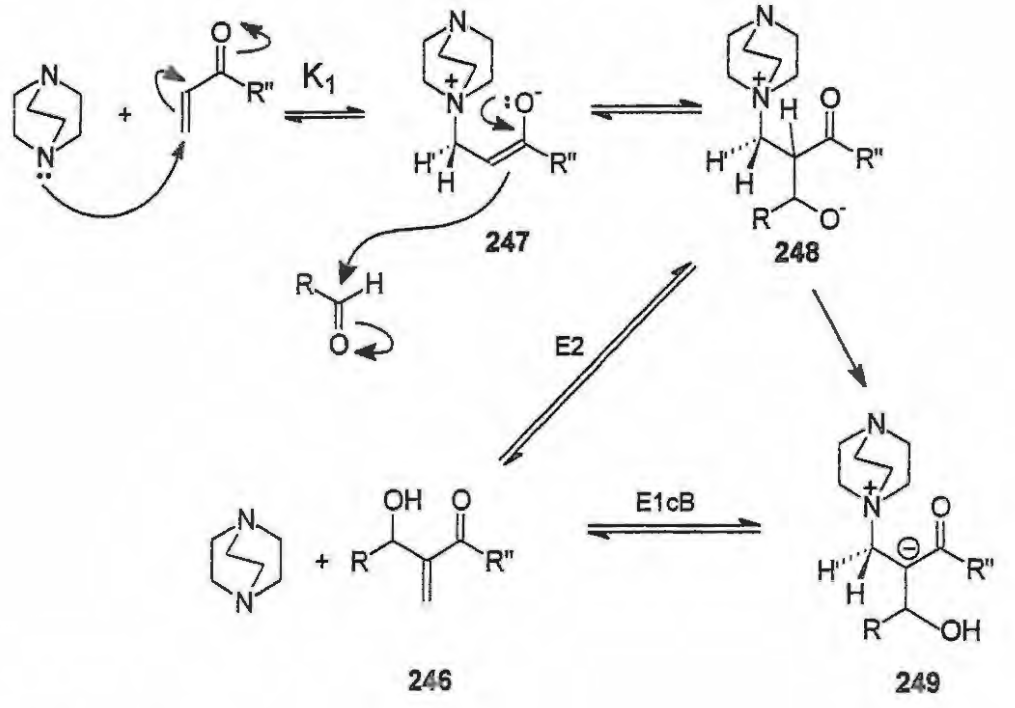


246

R' = COMe, CN, $CONEt_2$, CO_2Et, CO_2Ph, CO_2CH_2Ph

Scheme 40

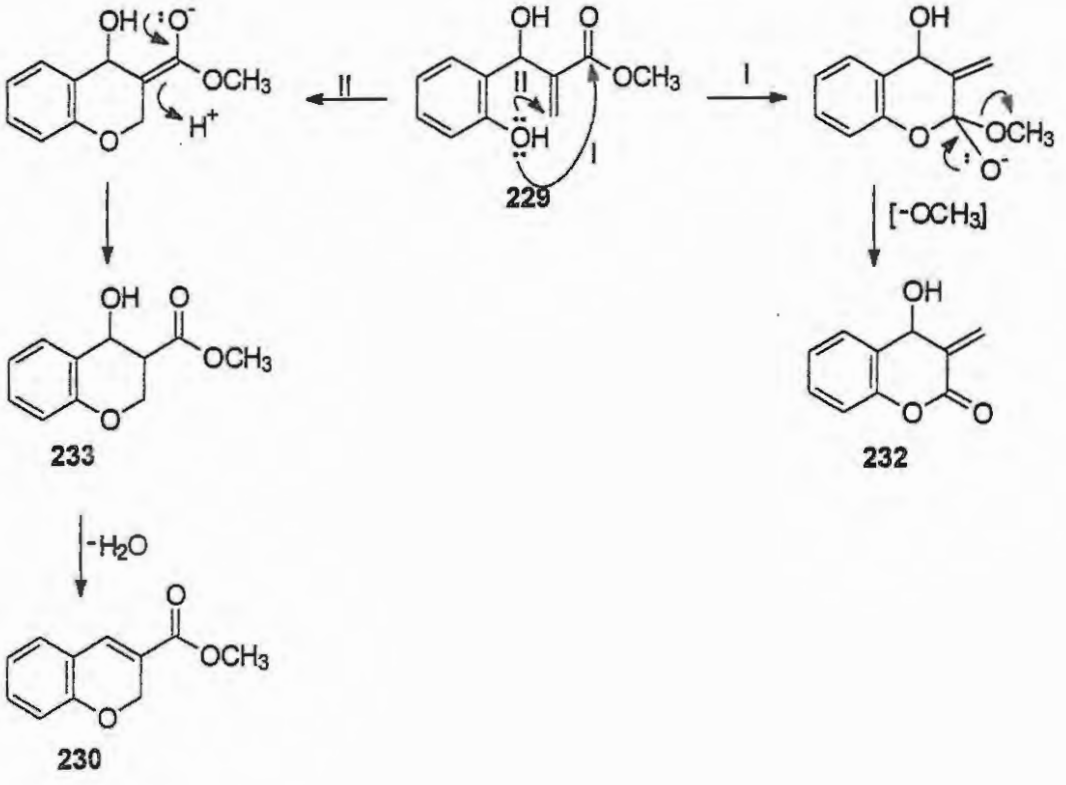
The generally accepted mechanism for the Baylis-Hillman reaction is illustrated in Scheme 41. The reaction is considered to involve initial conjugate addition of the catalyst to the vinyl system to form a zwitterionic intermediate **247**, which then attacks the carbonyl carbon of the aldehyde to afford a second zwitterion **248**. Base-assisted *anti*-E2 elimination of the catalyst, followed by protonation affords the Baylis-Hillman product **246**. Alternatively, the zwitterion **248** may undergo internal proton transfer to afford a resonance-stabilised intermediate **249**, which may undergo by E1cB elimination to afford the Baylis-Hillman product **246** a possibility supported by preliminary semi-empirical m.o. calculations (Scheme 41).[101,104,105,106,107] An indication that both pathways may operate is supported by a study of solvent and pressure dependence of the reaction of benzaldehyde with crotononitrile.[106] Protonation of the zwitterion **248** by an external donor is yet another possibility.[101]



Scheme 41

2.2 APPLICATION OF THE BAYLIS-HILLMAN REACTION IN THE SYNTHESIS OF CHROMENES

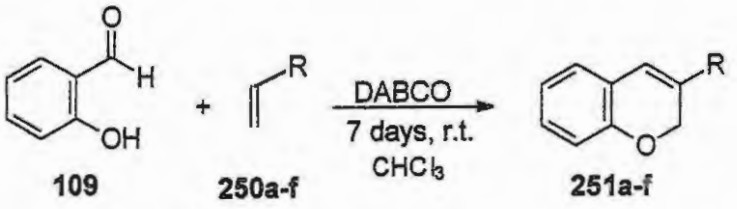
In his investigation of the Baylis-Hillman reaction of salicylaldehyde and methyl acrylate in the presence of the catalyst, DABCO, Robinson[94] obtained complex mixtures of chromene and coumarin derivatives (see Scheme 38, page 44). It was assumed that the Baylis-Hillman **229** product is, in fact, formed but immediately undergoes cyclisation to the chromene and coumarin derivatives. The isolation of these compounds suggests that the Baylis-Hillman product **229** undergoes two types of cyclisation, *viz.*, *conjugate addition* (pathway II, Scheme 42) resulting in the formation of the chroman-4-ol **233**, dehydration of which affords the chromene **230**, and *nucleophilic acyl substitution* (pathway I), loss of the alkoxy leaving group affording the coumarin **232**.



Scheme 42

It was considered likely that regiocontrol of the cyclisation could be achieved (with the selective formation of chromene derivatives) by replacing the good leaving group (*i.e.* the alkoxy group)

by a poor leaving group, thus inhibiting the acyl substitution pathway (I). This approach was explored using methyl vinyl ketone **250a** as the activated alkene component, and it was found that the conjugate addition pathway (II) dominated with the resultant formation of chromene **251a** in 42 % yield. This result was a significant improvement in terms of the yield and selectivity, and it was decided to explore the use of other vinyl derivatives in which the electron-withdrawing group (R) did not contain a good leaving group (*e.g.* R = CN, CHO, SO_3Ph, SO_2Ph, COEt). Using this approach, the chromenes **251a-f** were obtained from equimolar amounts of salicylaldehyde **109** and the corresponding α,β-unsaturated systems **250a-f** in poor (10 %) to fair yield (48 %) (Scheme 43). The products were readily identified by ^1H and ^{13}C NMR spectroscopy, and in none of these cases was any coumarin product isolated. The ^1H NMR spectrum of 3-acetylchromene **251a** is illustrated in Figure 2a, the 2-methylene protons resonating as a characteristic signal at 5.00 ppm and the methyl protons at 2.40 ppm. The ^{13}C NMR spectrum (Figure 2b) reveals the corresponding 2-methylene carbon signal at 64.2 ppm and the methyl carbon signal at 25.0 ppm.



109 **250a-f** **251a-f**

	R	Yield / %
a	COMe	42
b	COH	48
c	COEt	21
d	SO_2Ph	10
e	SO_3Ph	15
f	CN	20

Scheme 43

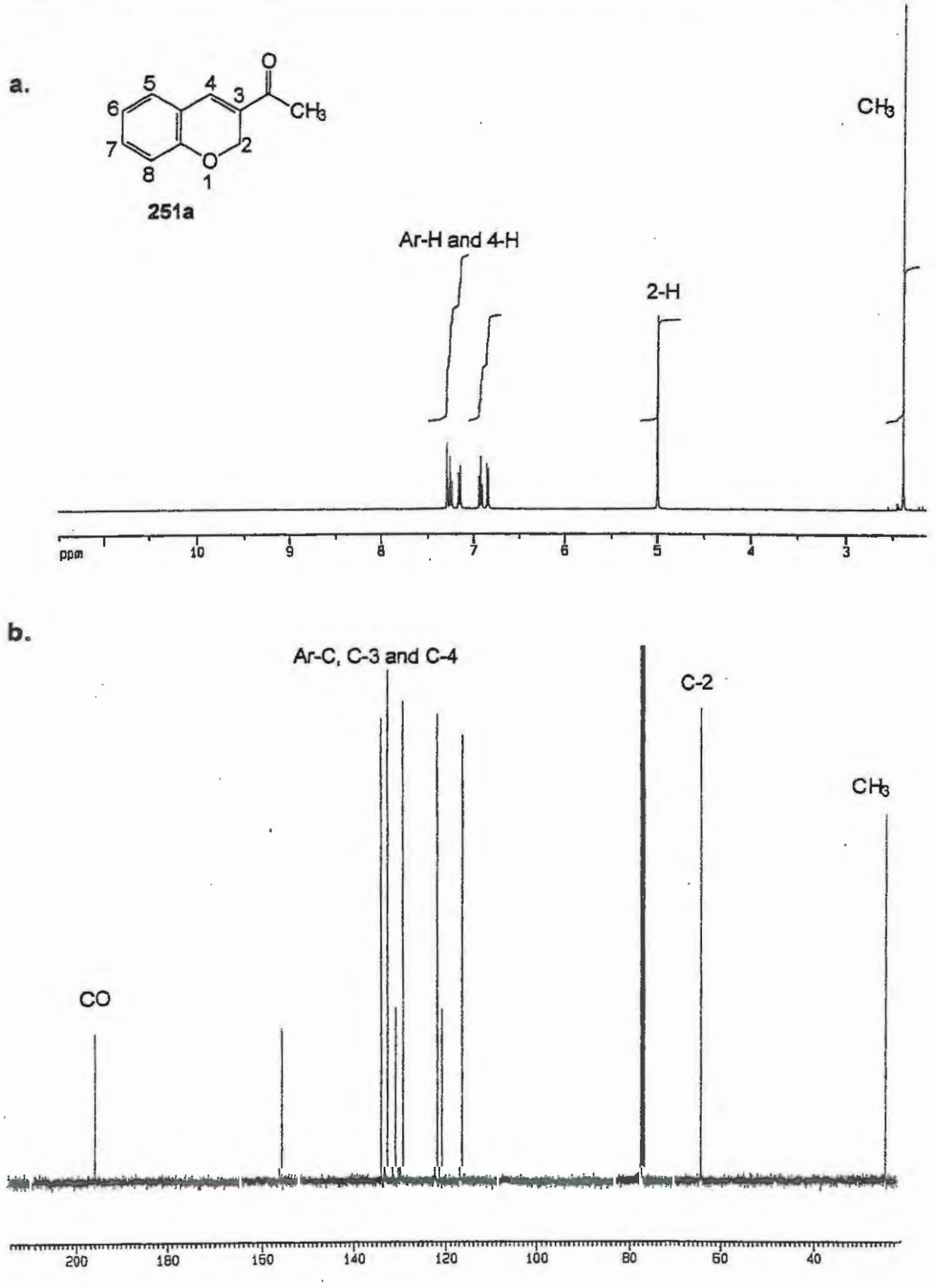
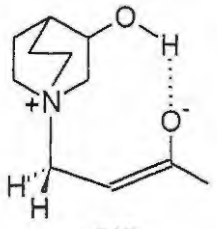


Figure 2 **(a)** 400 MHz ^{1}H NMR spectrum; and **(b)**100 MHz ^{13}C NMR spectrum of 3-acetyl-2*H*-1-chromene **251a** in $CDCl_3$.

2.2.1 Yield optimisation studies

The foregoing results clearly show that *regiocontrol* in the cyclisation step resulting in the selective formation of chromenes, had been achieved. The yields, however, were unsatisfactory. Attention was therefore given to improving the yields of the chromene products by varying the experimental conditions; the results of these optimisation studies are summarised in Table 3. The Baylis-Hillman reaction typically suffers from being very slow, and various attempts have been made to increase the rate of reaction. These attempts have included the use of microwave irradiation,[108] ultrasound[109] or high pressure,[110,106] but these methods require rather sophisticated equipment and, hence, were not used in the present study.

The preparation of 3-acetylchromene **251a** was repeated under the conditions used previously (Section 2.2, p. 50) in order to establish the reproducibility of the results and, in fact, the yield (Entry1; Table 3) was found to be consistent. Increasing the reaction time failed to produce a significant improvement in the yield; an increase of only 2 % was observed when the reaction time was doubled (Entry 2). No change was observed when the concentration of the reactants was "doubled" (Entry 3) and, surprisingly, when the concentration of DABCO was increased, the yield decreased (Entry 4). Earlier work has shown that use of 3-hydroxyquinuclidine as the catalyst leads to considerable rate enhancement of Baylis-Hillman reactions.[104,111] Such enhancement was initially rationalised in terms of hydrogen-bonding stabilisation (Figure 3) of the dipolar intermediate **247a** and, hence, a resultant increase in the equilibrium constant K_1 (Scheme 41). However, use of hydroxyquinuclidine as catalyst showed no improvement in the yield; instead, a decrease was observed (Entry 5).



247a

Figure 3

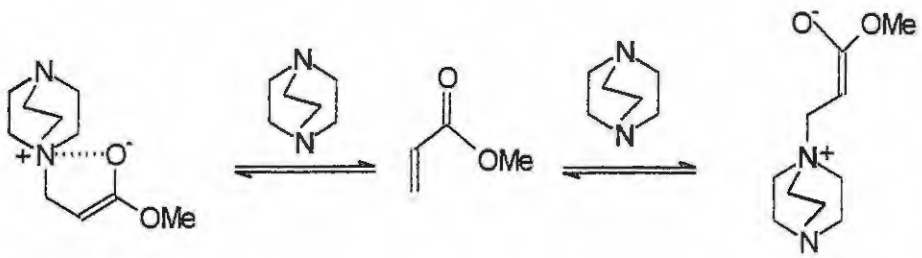
Table 3: Yield optimisation data for the Baylis-Hillman synthesis of 3-acetylchromene **251a** from salicylaldehyde[a] and methyl vinyl ketone.

Entry	MVK[b] / mmol	Catalyst used	Catalyst [c]/mmol	Period	Temp.	Solvent[d]	Yield [e] / %
1	9.6	DABCO	3.84	7 days	r.t.	$CHCl_3$	42
2	9.6	DABCO	3.84	14 days	r.t.	$CHCl_3$	44
3	9.6	DABCO	3.84	7 days	r.t.	$CHCl_3$[f]	42
4	9.6	DABCO	9.6	7 days	r.t.	$CHCl_3$	28
5	9.6	Hq[g]	3.84	7 days	r.t.	$CHCl_3$	31
6	9.6	PPh_3	3.84	7 days	r.t.	$CHCl_3$	28
7	9.6	DABCO	3.84	5 hours	60 °C	$CHCl_3$	36
8	9.6	DABCO	3.84	15 hours	60 °C	$CHCl_3$	33
9	9.6	DABCO	3.84	7 days	r.t.	-	36
10	9.6	DABCO	3.84	8 hours	0 °C	dioxane	16
11	9.6	DABCO	3.84	7 days	r.t.	$CHCl_3$-H_2O[h]	54
12	14.4	DABCO	3.84	5 hours	60 °C	$CHCl_3$	51
13	14.4	DABCO	3.84	7 days	r.t.	$CHCl_3$	64
14	19.2	DABCO	3.83	7 days	r.t.	$CHCl_3$	64
15	14.4	DABCO	7.68	7 days	r.t.	$CHCl_3$-H_2O[h]	66
16	14.4	DABCO	3.84	7 days	r.t.	EG[i]	63
17	14.4	DABCO	3.84	7 days	r.t.	$HCONH_2$	60
18	14.4	[j] mixture	-	7 days	r.t.	$CHCl_3$-H_2O[h]	60
19	14.4	[k] mixture	-	7 days	r.t.	$CHCl_3$-H_2O[h]	69

[a]In all the experiments, salicylaldehyde (9.6 mmol) was used. [b]Methyl vinyl ketone. [c] The amount of catalyst used. [d]1 ml of the indicated solvent was used. [e]Yield of chromene **251a** isolated following flash chromatography [elution with hexane:EtOAc (4:1)]. [f]0.5 ml of $CHCl_3$ was used. [g]3-Hydroxyquinuclidine. [h] H_2O:$CHCl_3$ (1:1; 2 ml). [i]Ethylene glycol. [j]Mixture of DABCO and triethanolamine (molar ratio 1:1.25). [k]Mixture of DABCO, triethanolamine and lanthanum triflate (molar ratio:- 20:10:1).

The early work by Morita,[100] Shojiro *et al.*[112,113] and Leahy *at al.*[114] has shown that tertiary phosphines could be used as catalysts in Baylis-Hillman reactions instead of DABCO. However this approach did not prove successful in the present study. When the catalyst, DABCO was replaced by triphenylphosphine, the chromene **251a** was isolated in only 28 % yield (entry 6). In an attempt to improve the yield by increasing the temperature, the reaction mixture was heated under reflux for 5 hours to afford the chromene **251a** in 36 % yield (entry 7), while extending the reaction time to 15 hours showed no improvement (entry 8), and such heating has been reported by Roos and Rampersadh[109] to result in the formation of side products and polymeric materials. When the reaction was carried out without a solvent (entry 9), the product was obtained in similar yield (36 %).

The work done by Leahy and Rafel [114] on the reaction between methyl acrylate and aryl or alkyl aldehydes demonstrated an unexpected rate acceleration when the reaction mixture was cooled to 0 °C. This was rationalised by assuming the formation of an equilibrium mixture of two intermediate conformers **247b** and **247c** (Figure 4), which are considered likely to react with the aldehyde at different rates. It was suggested that the relative concentrations of conformers **247b** and **247c** would be different at 0 °C, compared to their concentrations at elevated temperatures, and that this would be reflected in different overall rates of reaction. Furthermore, it was found that the reaction of acrylonitrile with benzaldehyde was not accelerated at low temperature-an observation attributed to the absence of effective dipolar stabilisation of the conformation corresponding to conformer **247b**. In the present study, however, when the synthesis of chromene **251a** was attempted at 0 °C, very low yields were obtained (entry 10).



247b **247c**

Figure 4

Water-promoted organic reactions have been reviewed by Lubineau *et al.*,[115] and Augé *et al.*[116] have reported that the Baylis-Hillman reaction between benzaldehyde and acrylonitrile is greatly accelerated in water. The activation volume of the Baylis-Hillman reaction has been found to be negative[101] and, hence, the reaction should be accelerated by hydrophobic effects. Moreover, water could stabilise the zwitterionic forms **247** and **248** (Scheme 41) through hydrogen-bond formation and, consequently, in our study, use of a solvent system comprising from equal volumes of water and chloroform was explored; the chloroform was used to dissolve the reactants while the water was expected to enhance the rate of reaction. Vigorous stirring was, of course, necessary and a significant improvement in the yield was observed (54 %; entry 11).

At the end of each reaction period, unreacted salicylaldehyde and a number of unknown products could typically be isolated, but no unreacted methyl vinyl ketone remained. This indicated that the methyl vinyl ketone might be involved in side reactions and, consequently, excess methyl vinyl ketone was added to the reaction mixture. In the first attempt using this approach, the mixture, containing a 0.5 molar excess of methyl vinyl ketone was heated under reflux at 60 °C for 5 hours. Under these conditions, the chromene **251a** was obtained in 51 % (entry 12). When a mixture, containing a 0.5 molar excess of methyl vinyl ketone, was stirred at room temperature the yield of the required chromene **251a** increased to 64 % (entry 13). Increasing the quantity of methyl vinyl ketone to a 2 molar excess showed no further improvement in the yield (entry 14), but a slight increase (66 %) was observed when the concentration of the catalyst, DABCO, was doubled (entry 15).

The rate of Baylis-Hillman reactions has been found to be greatly affected by the nature of solvent used. Drewes *et al.*[117,118] reported that the reaction rate could be enhanced by the use of methanol as solvent, while Augé *at al.*[116] suggest the use of solvents such as formamide or ethylene glycol. In the present study, use of ethylene glycol and formamide as solvents gave the chromene **251a** in yields of 63 % and 60 %, respectively (entries 16 and 17). Aggarwal *et al.*[120,121] have reported the use of Lewis acids such as $La(OTf)_3$ and $Sm(OTf)_3$ to enhance the rate of Baylis-Hillman reactions between aldehydes and *tert*-butyl acrylate. Because of its availability, these workers examined the use of lanthanide triflate in detail and found that at least 10 mol % of DABCO was needed for the reaction to occur. Some of the DABCO was considered to

associate with lanthanide triflate to form complex **252b**, which functions as a Lewis acid forming complex **253** with the zwitterionic intermediate (Figure 5).

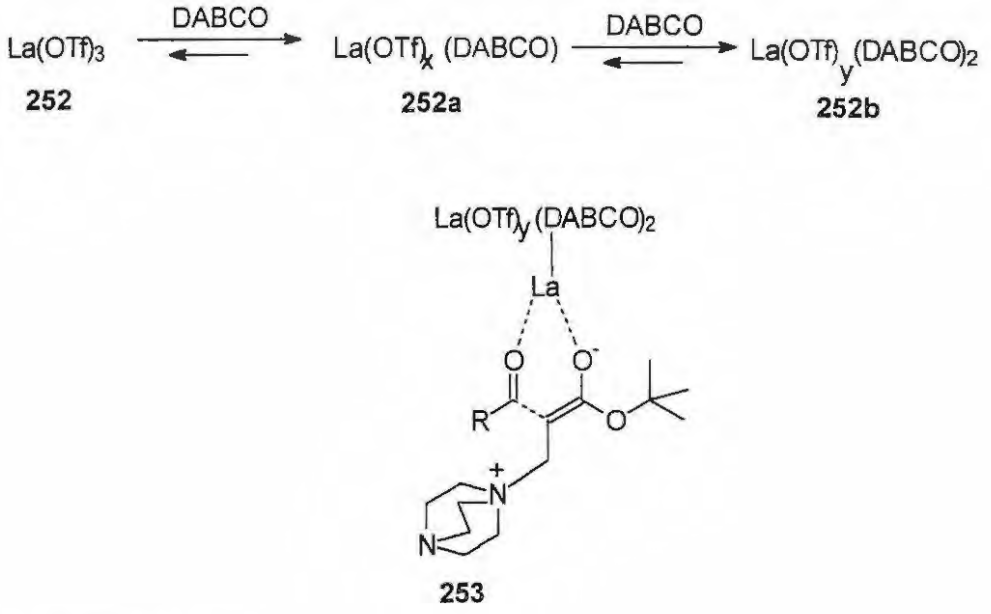


Figure 5

The same workers[120] also reported that the inclusion of ligands, such as triethanolamine, enhance the rate of reaction. These approaches were applied in our study and use resulted in a 60 % yield of the chromene **251a** (entry18); when 100 mol % DABCO, 50 mol % triethanolamine and 5 mol % lanthanide triflate were used, 3-acetylchromene **251a** was isolated in 69 % yield (entry 19).

The best two protocols at this stage corresponded to entries 15 and 19, with yields of 66 % and 69 %, respectively. Work-up of the reaction conducted following the protocol detailed in entry 15 revealed traces of unreacted salicylaldehyde. The reaction was then repeated using exactly the same protocol but, after 7 days, more methyl vinyl ketone and DABCO were added and the mixture stirred for a further seven days at room temperature. At the end of this reaction period, the product was purified by flash chromatography to afford the chromene **251a** in a yield of 75 %.

The rate of reaction was then followed by monitoring the disappearance of the salicylaldehyde aldehydic signal at *ca.* 9.9 ppm, and the appearance of the signal corresponding to the 2-

methylene protons in 3-acetylchromene **251a** at *ca.* 4.9 ppm. A plot of the percentage transformation to the product **251a** against time is illustrated in Figure 6.

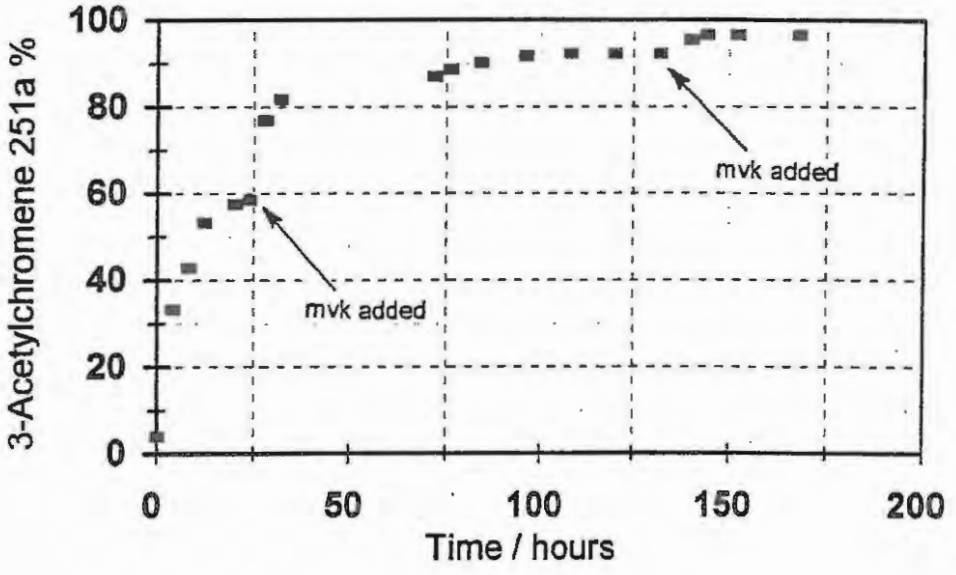


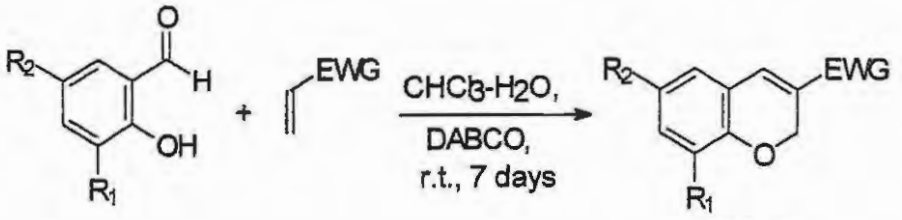
Figure 6: Data for the reaction of salicylaldehyde and methyl vinyl ketone in the presence of DABCO in $CDCl_3$-H_2O (equal amounts).

The reaction was started with 1 equivalent of salicylaldehyde, 1.5 equivalents of methyl vinyl ketone and 0.8 molar equivalents of the catalyst DABCO, while the solvent system comprised equal volumes of water and chloroform. The mixture was stirred vigorously at room temperature under nitrogen, and the reaction was monitored by ^{1}H NMR spectroscopy at regular intervals, as shown in Figure 6. The resulting graph revealed a decrease in the rate of formation of the chromene product between 20 and 24 hours. Consequently, after 24 hours, 0.5 equivalents methyl vinyl ketone and 0.3 molar equivalents of DABCO were added, resulting in a significant rate increase. After *ca.* 100 hours, reaction appeared to cease and more methyl vinyl ketone (0.25 equivalents) and DABCO (0.09 equivalents) were added, producing further product. The reaction was stopped after 168 hours and purification by flash chromatography afforded the expected 3-acetylchromene **251a** in 81 % yield.

2.2.2 Synthesis of chromenes under optimised conditions

The optimised protocol discussed in the foregoing section was then applied to the synthesis of chromenes **251b-f**. The isolated yields of these compounds were significantly better than our initially reported yields and these results were published in a preliminary communication.[125] The methodology was then extended to the synthesis of chromenes **251g-l** in average to good yield (Table 4).

Table 4: Yields of 3-substituted chromenes **251a-l** using the optimised protocol.



251a-l

Compound	R_1	R_2	EWG	Yield [a] / %
251a	H	H	COMe	81 (42)
251b	H	H	COH	54 (48)
251c	H	H	COEt	83 (21)
251d	H	H	SO_2Ph	70 (10)
251e	H	H	SO_3Ph	60 (15)
251f	H	H	CN	65 (20)
251g	OMe	H	COMe	79
251h	H	NO_2	COMe	54
251i	H	Cl	COMe	56
251j	OEt	H	COMe	84
251k	H	Br	COMe	87
251l	Br	Br	COMe	29

[a]Isolated yields following flash chromatography. The figures in parentheses refer to the yields reported initially (see Scheme 43)

The ^{1}H NMR spectra of the chromenes **251a-l** are characterised by the 2-methylene proton signal in the region δ 4.9 - 5.4 ppm; these signals typically appear as doublets (*J ca.* 1.2 Hz) due to long

range-allylic coupling with the vinylic 4-H nucleus, as illustrated in Figure 7. This coupling relationship was confirmed by ^{1}H-^{1}H correlation spectroscopy (COSY),as illustrated in Figure 9. Figure 7 also shows the 4-H signal at 7.70 ppm and the acetyl methyl singlet at 2.80 ppm. The ^{13}C NMR spectrum (Figure 8a) shows the acetyl methyl carbon signal at 24.9 ppm and the 2-methylene carbon signal at 64.6 ppm, the latter almost coinciding with the 1'-methylene signal. Assignment of the ^{13}C signal is supported by the distortionless Enhancement by Polarisation Transfer (DEPT) and ^{1}H-^{13}C Heteronuclear Multiple Quantum Coherence (HMQC) spectra which are illustrated in Figure 8b and 10 respectively.

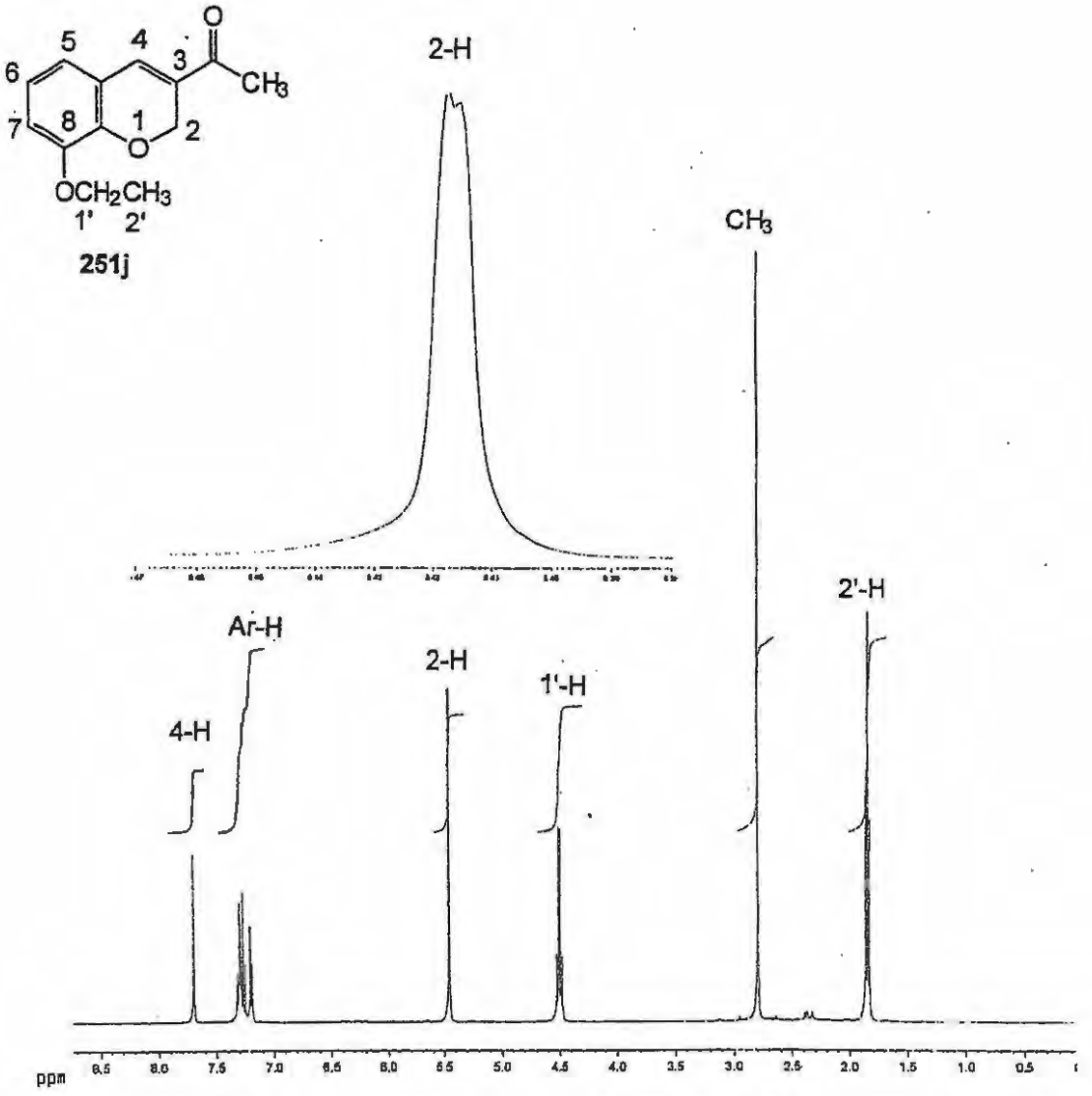
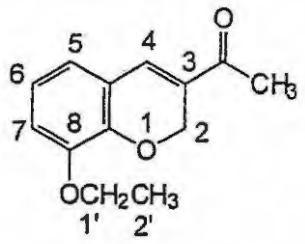
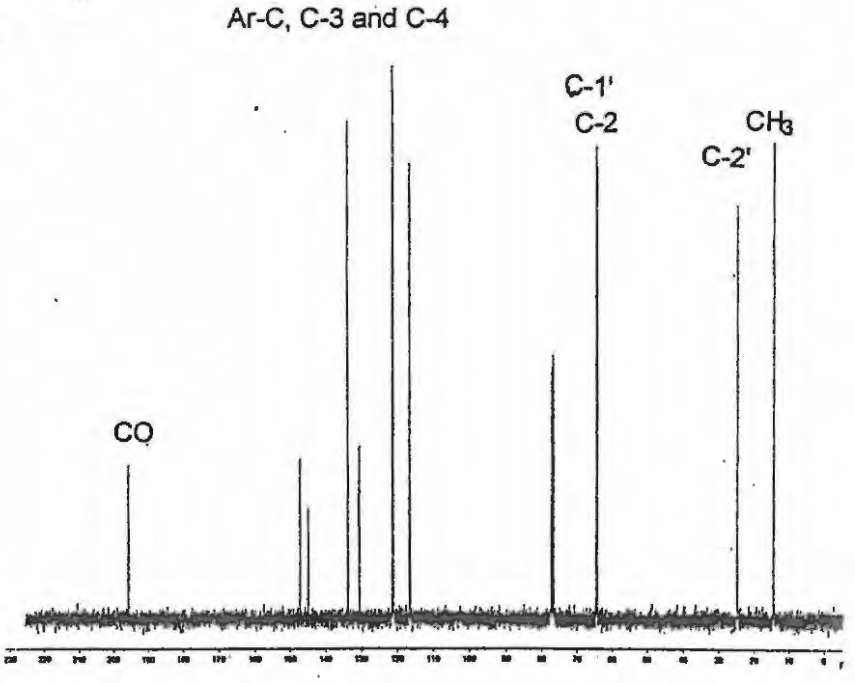


Figure 7. 400 MHz ^{1}H NMR spectrum of 3-acetyl-8-ethoxy-2*H*-1-chromene **251j** in $CDCl_3$.

a.



251j



b.

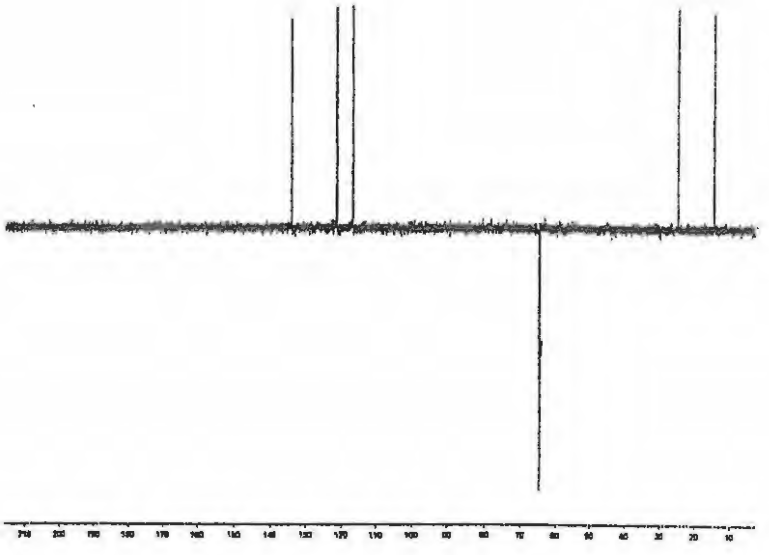
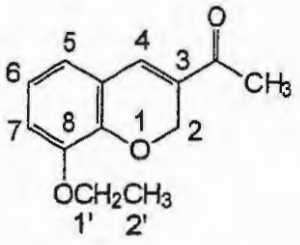


Figure 8 **(a)** 100 MHz ^{13}C NMR spectrum; and **(b)** DEPT spectrum of 3-acetyl-8-ethoxy-2*H*-1-chromene **251j** in $CDCl_3$.



251j

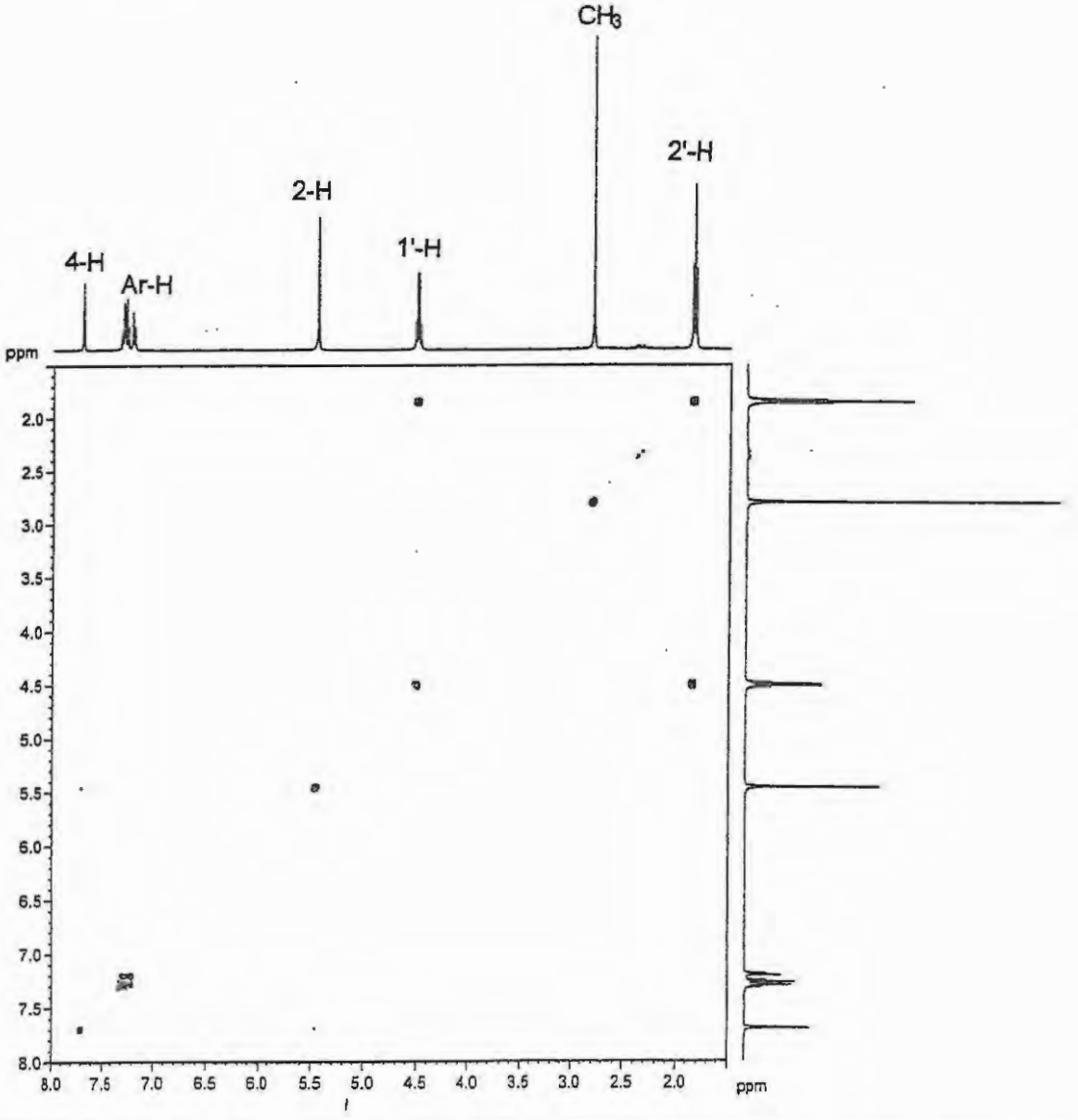


Figure 9. 400 MHz COSY spectrum of 3-acetyl-8-ethoxy-2*H*-1-chromene **251j** in $CDCl_3$.

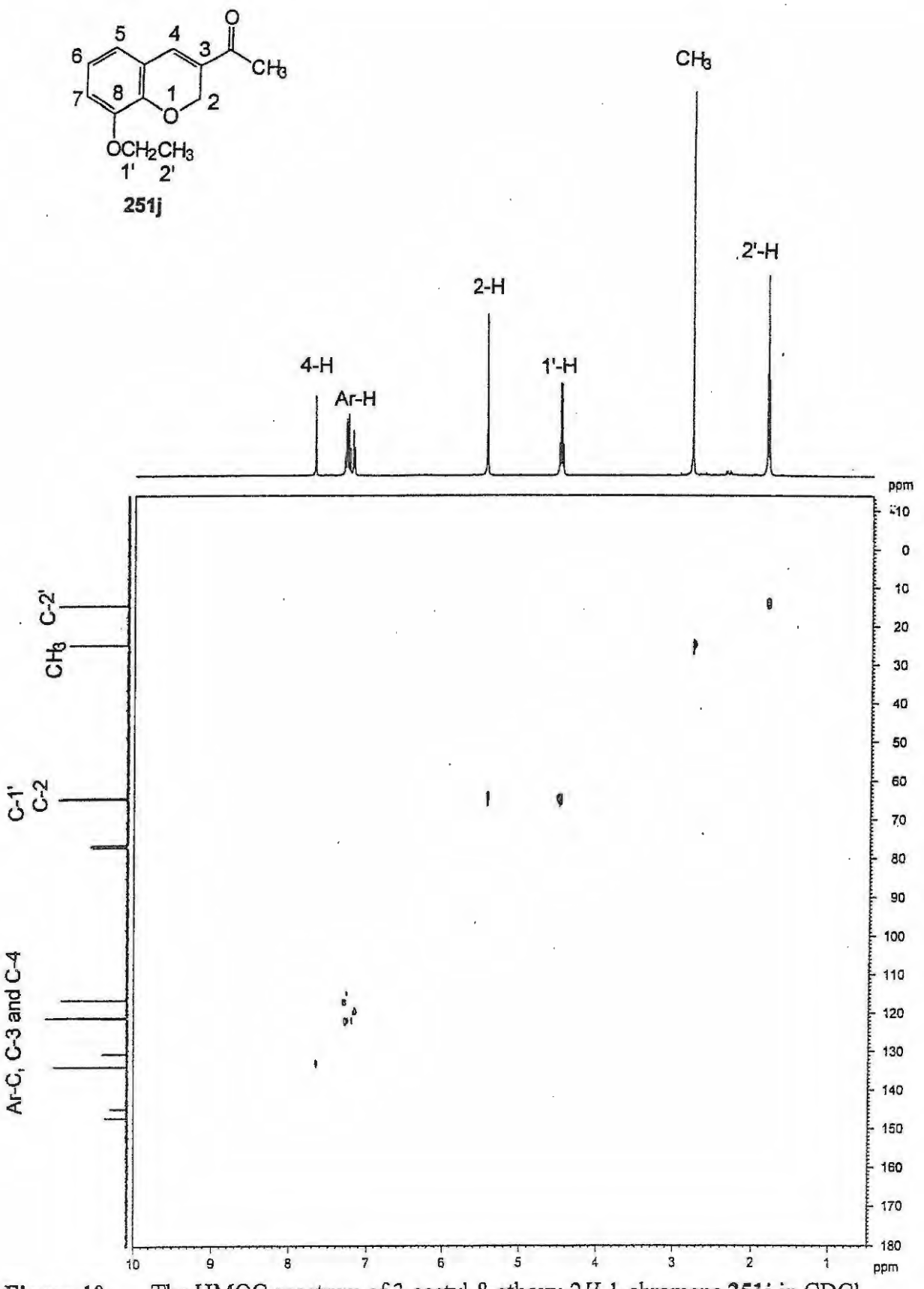
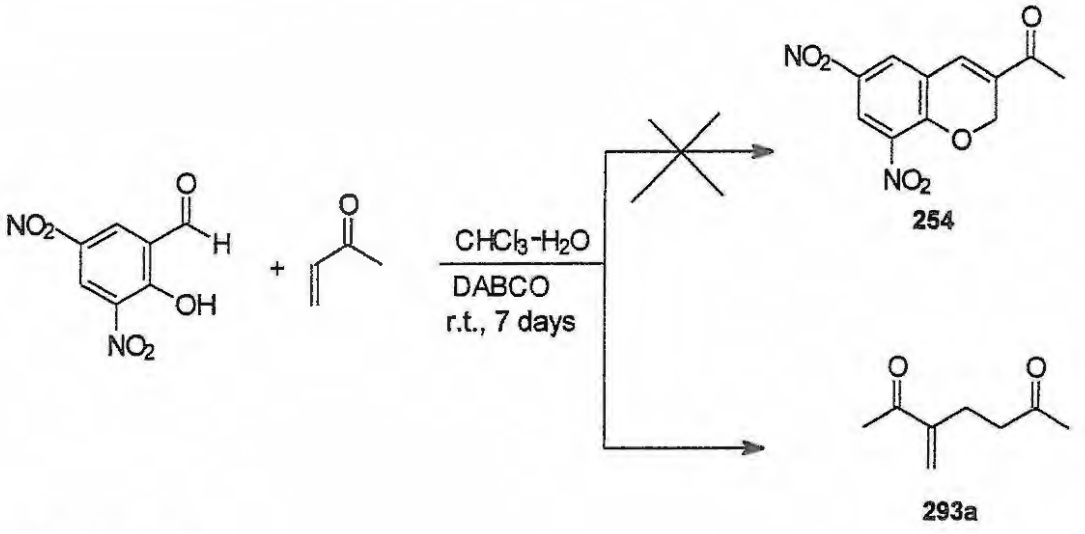


Figure 10. The HMQC spectrum of 3-acetyl-8-ethoxy-2*H*-1-chromene **251j** in $CDCl_3$.

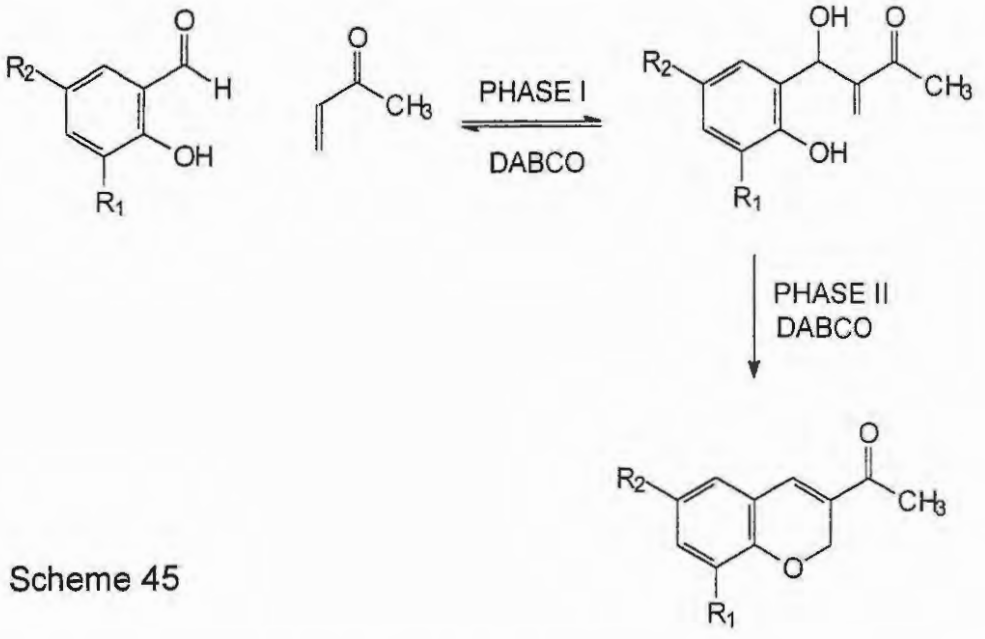
Although electron-releasing ring-substituents (*i.e.* the methoxy and ethoxy groups) are expected to reduce the electrophilicity of the salicylaldehyde carbonyl carbon and thus reduce the rate of the Baylis-Hillman reaction, the 8-methoxychromene **251g** and 8-ethoxychromene **251j** were isolated in good yields (79 % and 84 %, respectively; Table 4) after 7 days. The electron-withdrawing nitro group, on the other hand, is expected to increase the electrophilicity of the carbonyl carbon and hence increase the rate of reaction. However, 5-nitrosalicylaldehyde afforded 6-nitrochromene **251h** in only 54 % yield (Table 4) after 7 days, and when 3,5-dinitrosalicyladehyde was treated with methyl vinyl ketone under the same experimental conditions, the dimer **293a**, rather than the expected 6,8-dinitro-3-acetylchromene **254**, was isolated (Scheme 44).



Scheme 44

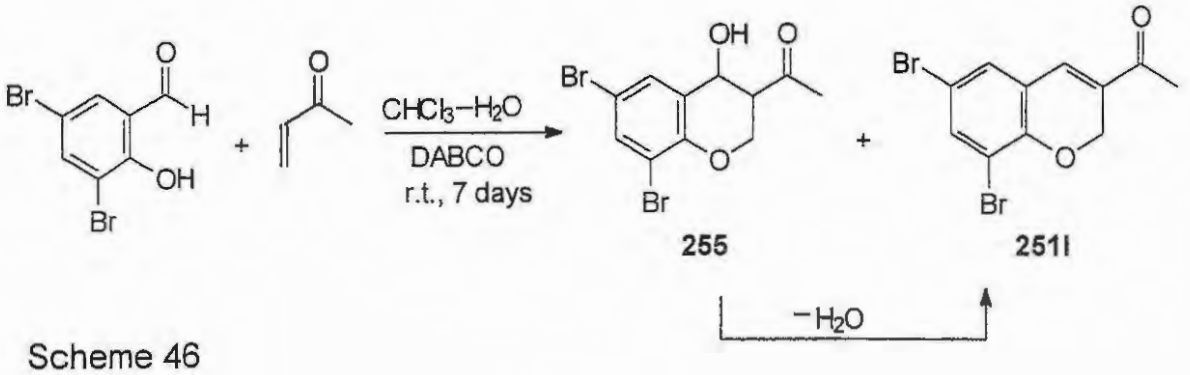
While caution should be exercised in drawing mechanistic conclusions from comparative yields, the observed data could be explained by considering the effect of substituents on the two distinct phases of the reaction. Thus, electron-withdrawing ring-substituents should enhance the Baylis-Hillman reaction by making the carbonyl carbon more electrophilic (Phase I; Scheme 45), but inhibit cyclisation (Phase II) by reducing nucleophilicity of the phenolic oxygen. The lower yield observed in the reaction of 5-nitrosalicylaldehyde may be associated with the unfavourable cyclisation in Phase II -a factor which may be exacerbated in the case of 3,5-dinitrosalicylaldehyde. Electron-releasing groups, however, would increase the nucleophilicity of the phenolic oxygen and, hence, enhance cyclisation *via* conjugate addition. The mechanistic

details of the reaction will be discussed further in Section 2.3.



Scheme 45

The halogenated salicylaldehydes gave average to good yields on treatment with methyl vinyl ketone. Thus, 5-chlorosalicylaldehyde afforded the expected 3-acetyl-6-chlorochromene **251i** in average yields of 56.1 %, while 5-bromosalicylaldehyde afforded 6-bromo-3-acetylchromene **251k** in 87 % yield. In the reaction of 3,5-dibromosalicylaldehyde with methyl vinyl ketone, the normally spontaneous dehydration was incomplete, and 6,8-dibromochroman-4-ol **255** was isolated as the major product (53 %) together with the chromene **251l** (29 %) (Scheme 46). This observation tends to support cyclisation *via* a conjugate addition-elimination sequence rather than S_N' displacement.



Scheme 46

Although the chroman-4-ol **255** contains two chiral centers, apparently only a single diastereoisomer was formed as evidenced by the absence of doubling of the ^{1}H and ^{13}C NMR signals. The small vicinal coupling constant ($J_{3,4}$ 3.5 Hz) between the 3- and 4-methine protons indicates a cis arrangement of the hydroxy and acetyl group.[122] In the ^{1}H NMR spectrum of this compound, illustrated in Figure12, the 3-methine proton resonates as a doublet of triplets, instead of the expected 4 doublets, due to overlap of signals. This is consistent with a large anti coupling with one of the 2-methylene protons and two (small) guache couplings with the 4-H nucleus and the second, methylene proton. The diastereotopic 2-methylene protons appear as double doublets at 4.43 ppm and 4.60 ppm, while the 4-methine proton appears as a multiplet at 5.04 ppm. The COSY spectrum (Figure 13) clearly confirms the expected coupling relationships, while the ^{13}C NMR, DEPT and HMQC spectra were all consistent with the structural assignment. The formation the of *cis*-isomer **255c** may be attributed to protonation of the methyl vinyl ketone intermediate **255a** at the less hindered face[123] (*i.e.* opposite the hydroxyl group) path I of Figure 11, while protonation at the more hindered face results in the *trans*-isomer **255b** path II of Figure 11.

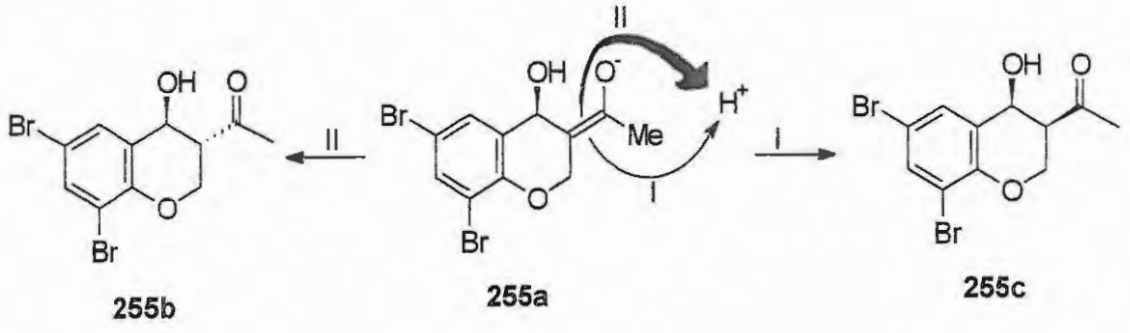
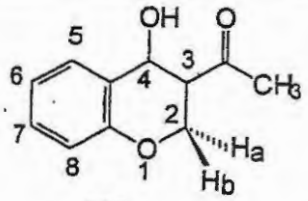


Figure 11: Two options for protonation of the intermediate **255a**.



255

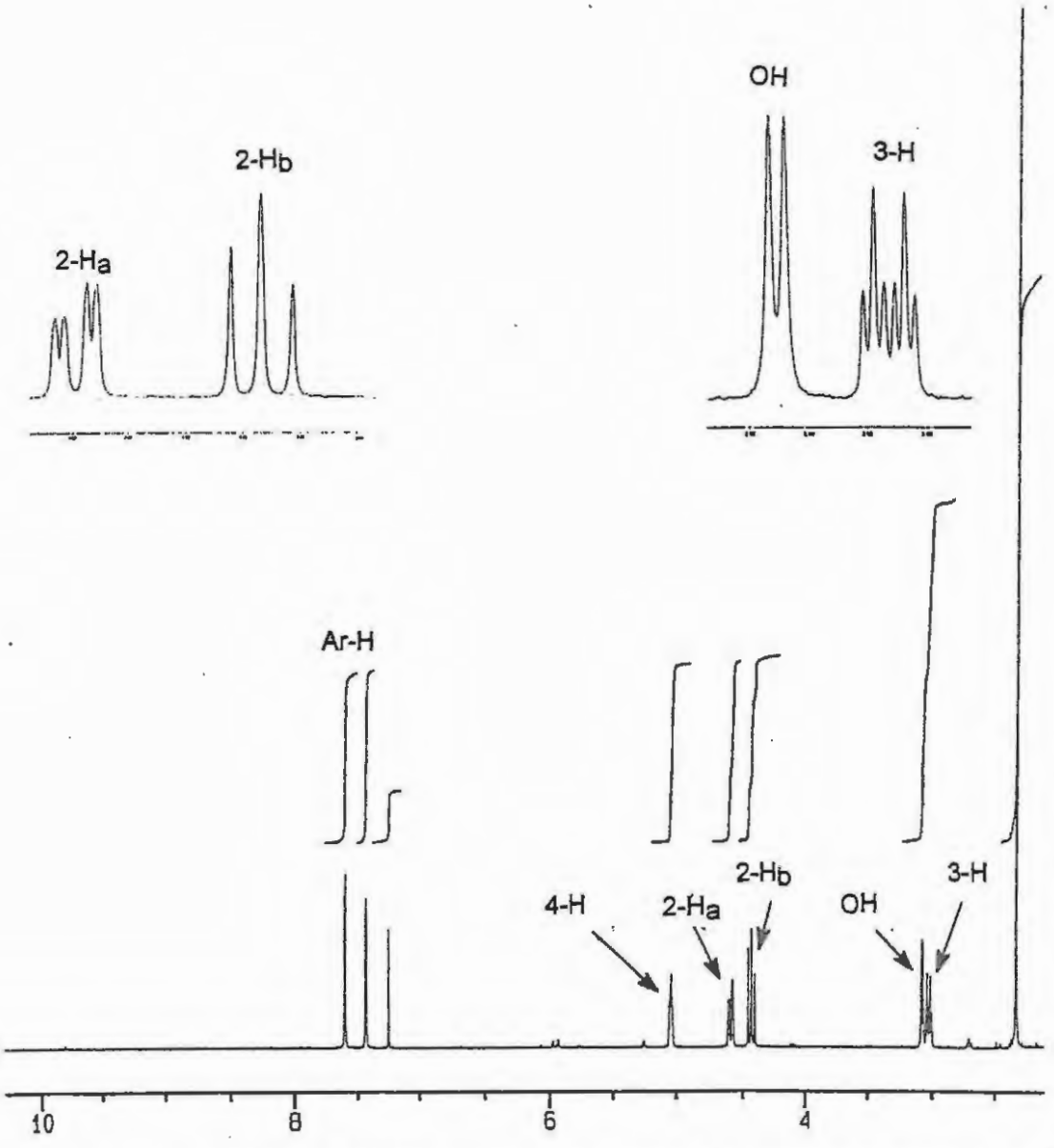
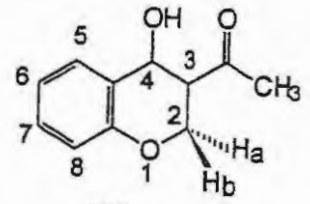


Figure 12. The 400 MHz ^{1}H NMR spectrum of 3-acetyl-6,8-dibromochroman-4-ol **255** in $CDCl_3$.



255

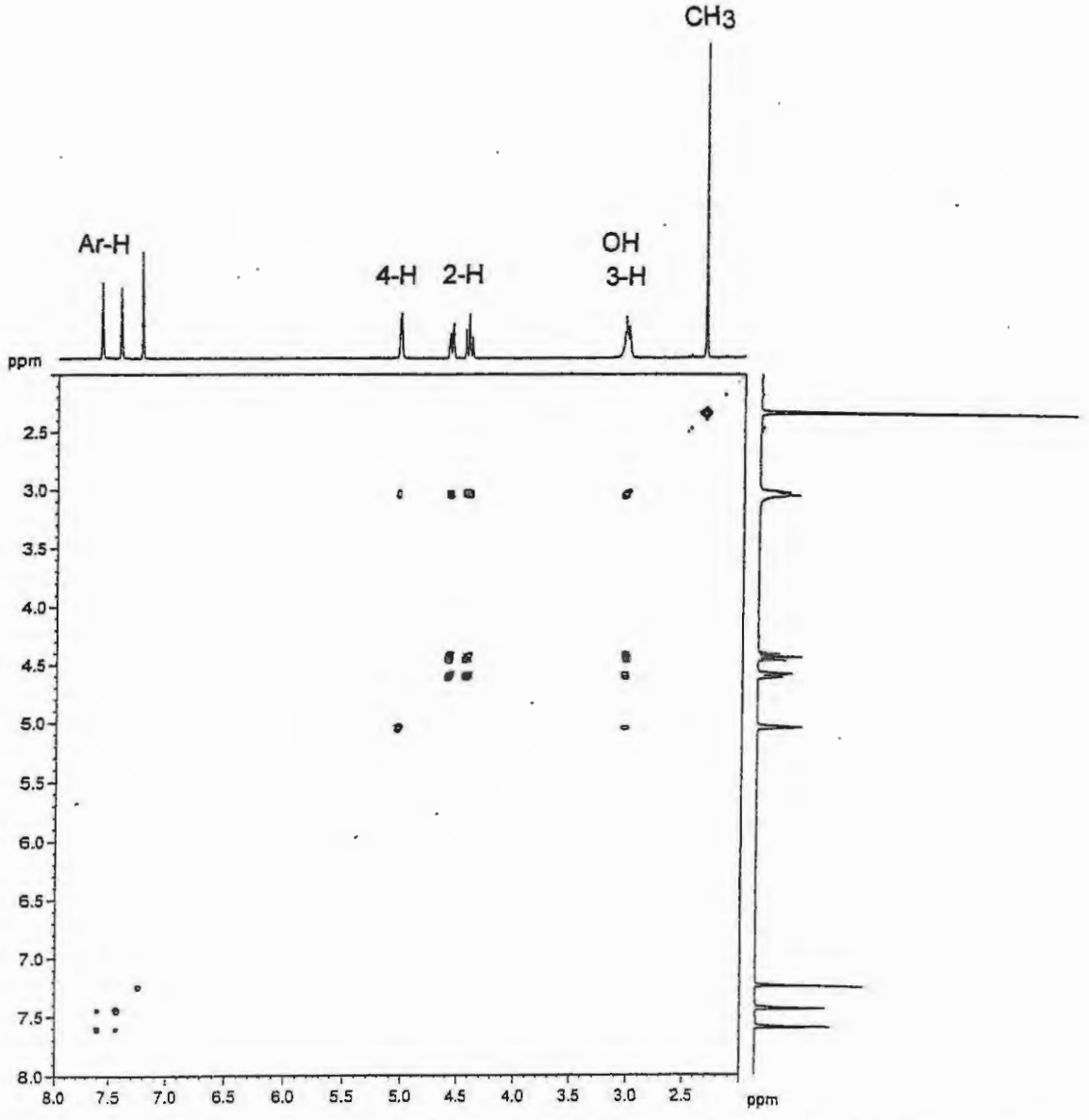
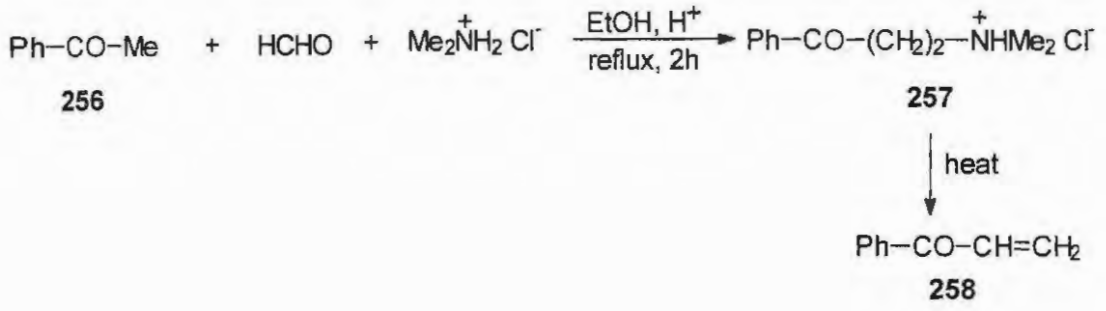
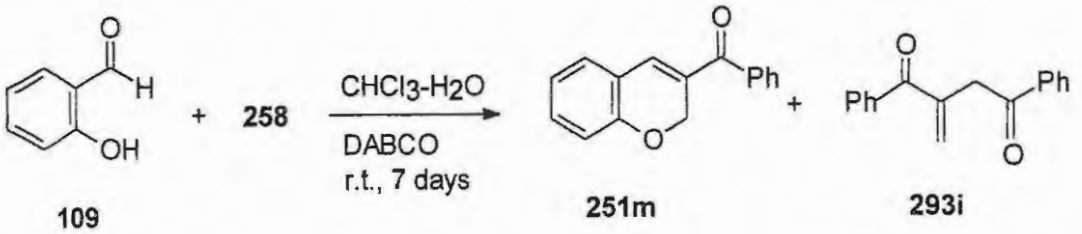


Figure 13. The COSY spectrum of 3-acetyl-6,8-dibromochroman-4-ol **255** in $CDCl_3$.

When phenyl vinyl ketone **258** was treated with salicylaldehyde under the same experimental conditions, the required chromene **251m** was isolated as the minor product (10 %), the dominant reaction being the dimerisation of the vinyl ketone **258** to afford the diketone **293i** (Scheme 47). The phenyl vinyl ketone **258** was obtained *via* a Mannich reaction;[124] acetophenone **256**, paraformaldehyde and dimethylamine hydrochloride were heated under reflux to obtain the hydrochloride salt **257**, which was converted to phenyl vinyl ketone **258** by heating vigorously under reduced pressure. (Attempts to synthesise *tert*-butyl vinyl ketone and isopropyl vinyl ketone using the same approach, however, were unsuccessful).





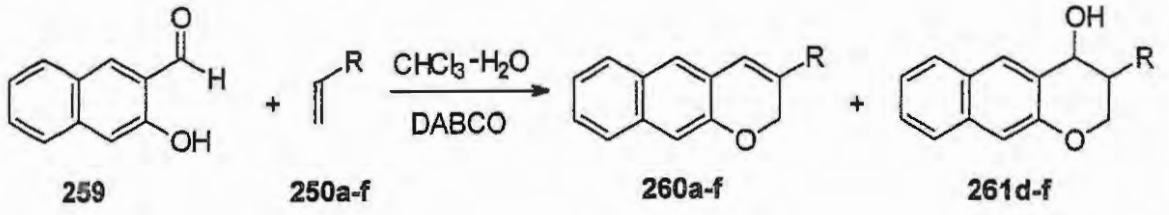
Scheme 47

Aggarwal and Mereu[120] have recently reported that 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) is a superior catalyst to DABCO in the Baylis-Hillman reaction of benzaldehyde and methyl acrylate. Consequently, DABCO was replaced by DBU as the catalyst in the reaction of salicylaldehyde and methyl vinyl ketone, using the experimental conditions developed previously (Section 2.2.2). The reaction was followed by ^{1}H NMR spectroscopy and, although the rate of disappearance of the aldehyde peak was faster than when DABCO was used as a catalyst, only 50 % of the 3-acetylchromene **251a** was isolated following flash chromatography.

2.2.3 The synthesis of fused-ring chromenes

The methodology developed for the synthesis of chromenes **251a-l** (Section 2.2.2) was extended to the synthesis of fused-ring chromenes in order to establish the generality of the reaction. 2-Hydroxynaphthaldehyde **259** was reacted with the α,β-unsaturated vinyl systems **250a-f** to afford the fused-ring chromenes **260a-f**, as crystalline solids; in some cases, dehydration was incomplete and the 4-hydroxy derivatives **261d-f** were isolated, as oils, in small amounts (Table 5).

Table 5: Data for the formation of 2*H*-Benzo[*g*]chromene derivatives.



259 **250a-f** **260a-f** **261d-f**

	% Yield[a]	% Ratio	m.p. / °C
R	**260 : 261**	**260 : 261**	**260**
a $COCH_3$	67 : 0	100 : 0	122 - 124
b CHO	17 : 0	100 : 0	144 - 146
c COEt	58 : 0	100 : 0	88 - 90
d SO_2Ph	20 : 2	91 : 9	186 - 188
e SO_3Ph	61 : 4	94 : 6	164 - 166
f CN	50 : 2	96 : 4	120 - 122

[a]Chromatographed material.

The chromene derivatives **260a-f** were all fully characterised by one- and two-dimensional NMR and high-resolution mass spectrometric analysis. Comparison of the ^{1}H NMR spectrum of compound **260a** (Figure14) with that of 3-acetylchromene **251a** (Figure 2a) reveals the expected similarities, the 2-methylene protons resonating at *ca.* 5.0 ppm for both **251a** and **260a**.

Additional signals are, of course, present in the aromatic region (δ 7 - 8 ppm) in the spectrum of compound **260a**. The hydroxy compounds **261d-f**, all contain two chiral centers but, in each case, the presence of only one diastereoisomer was indicated by the absence of signal doubling in the ^{1}H and ^{13}C NMR spectra. Assignment of cis stereochemistry to the substituents at C-3 and C-4 follows from the discussion in Section 2.2.2. The ^{1}H NMR spectrum of the phenylsulfonyl derivative **261d**, illustrated in Figure 15, exhibits a doublet of triplets at 3.65 ppm, due to the 3-methine proton, two double doublets at 4.56 ppm and at 4.65 ppm due to the diastereotopic 2-methylene protons, and multiplet at 5.83 ppm, due to the 4-methine proton. The yields obtained for some of benzo-fused chromenes were significantly less than those observed for the chromenes **251a-f** (Section 2.2.2). The extended conjugation in 2-hydroxynaphthaldehyde **259** (compared to salicylaldehyde **109**) may result in reduced electrophilicity of the carbonyl carbon, with consequent lowering of the reaction rate. The reaction with phenyl vinyl sulphone was particularly slow, and starting materials were isolated, together with the chromene **260d**, at the end of the reaction period.

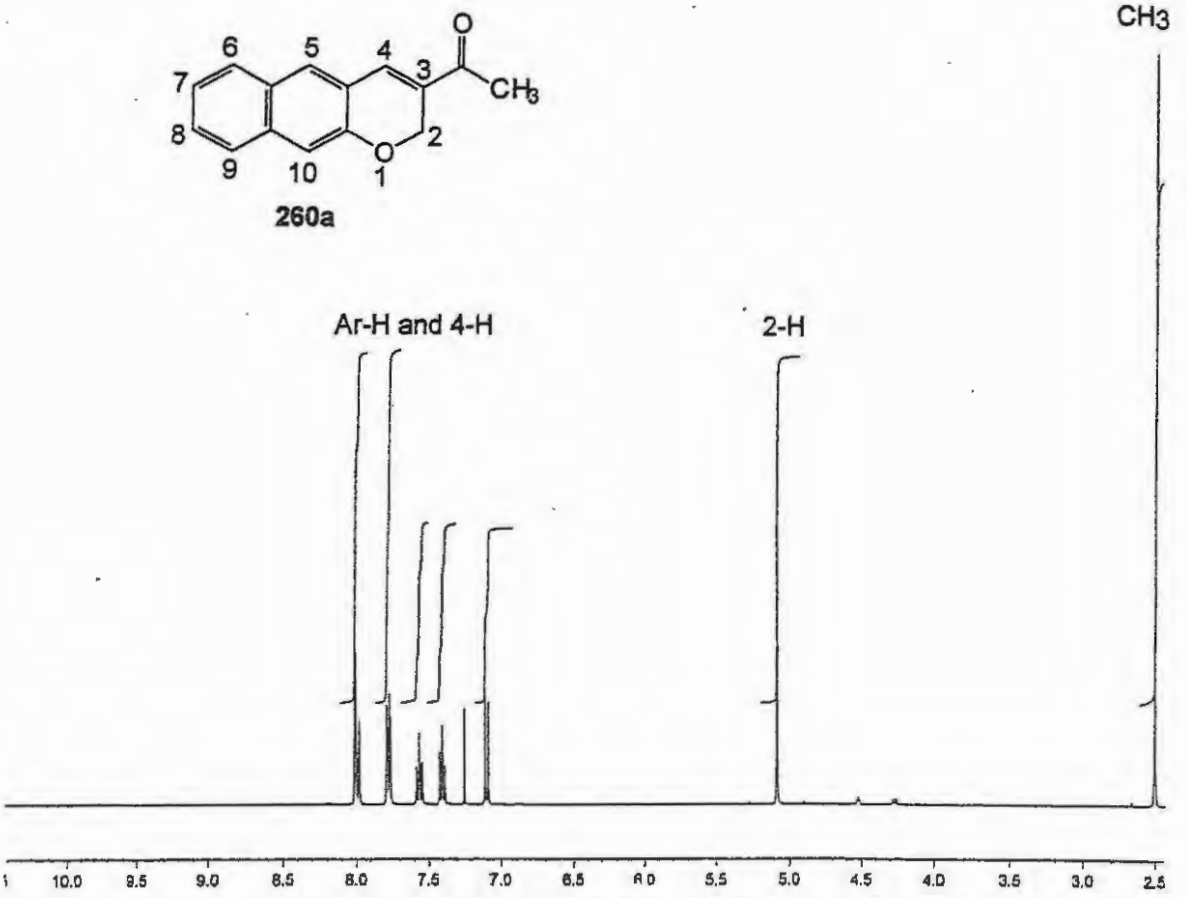
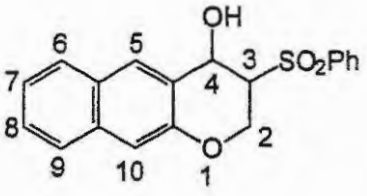


Figure 14. 400 MHz ^{1}H NMR spectrum of 3-acetyl-2*H*-1-benzo[*g*]chromene **260a** in $CDCl_3$.



261d

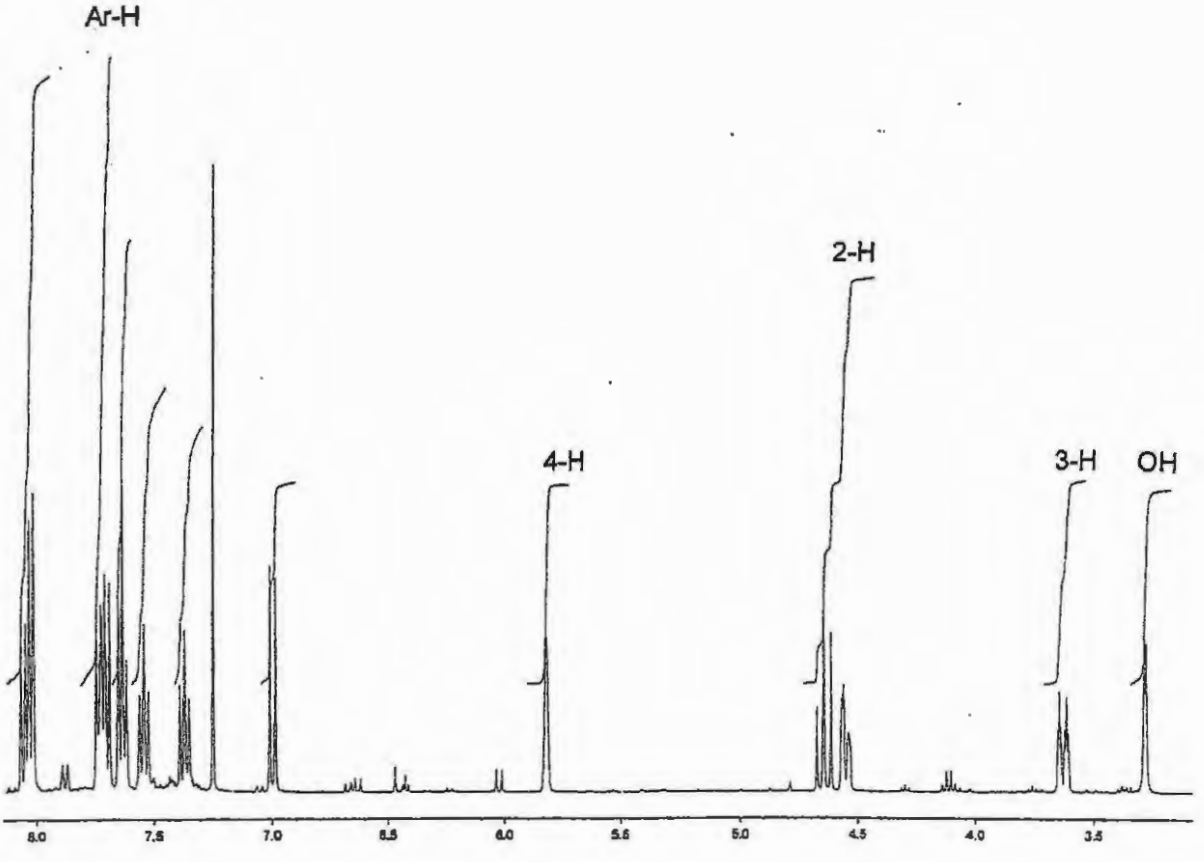
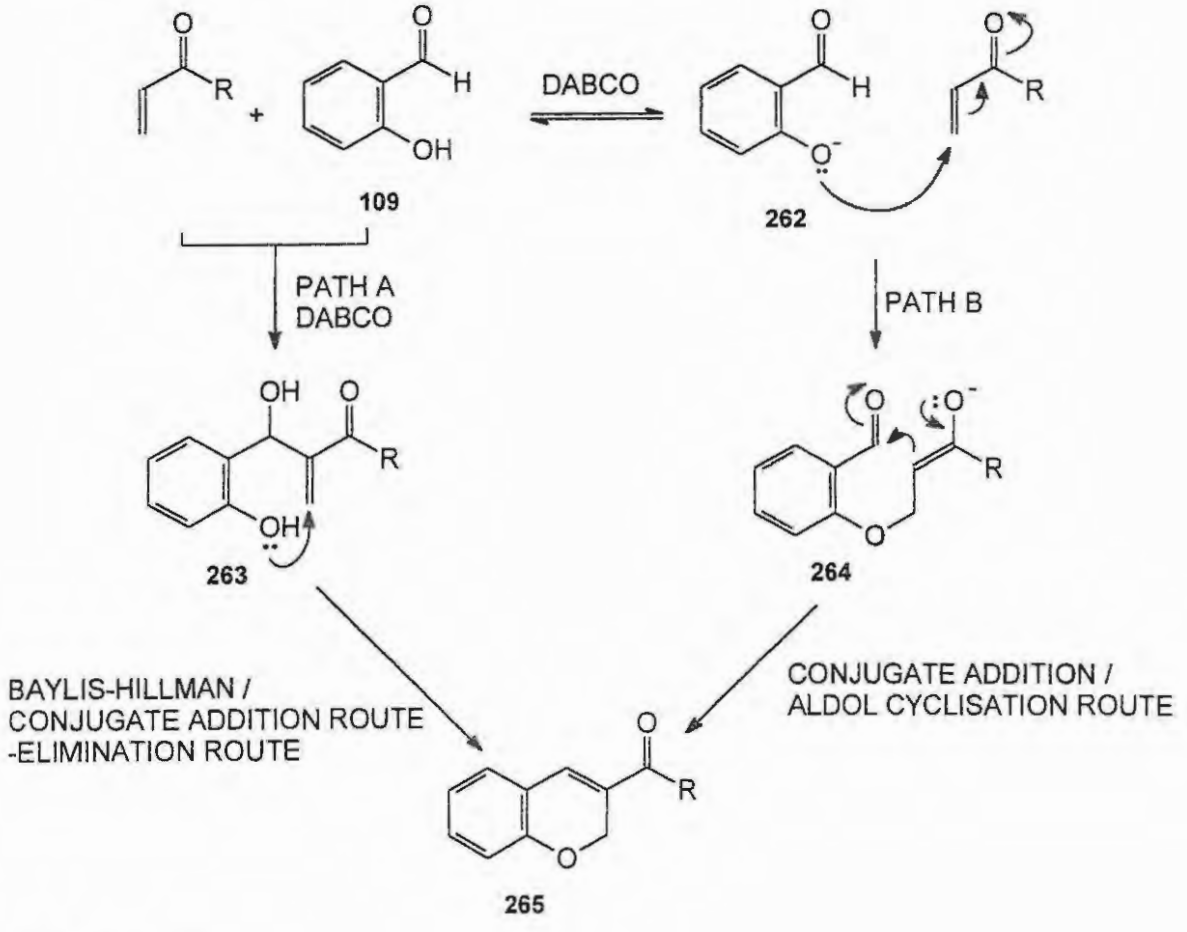


Figure 15. 400 MHz NMR spectrum of 3-phenylsulfonyl-2*H*-1-benzo[*g*]benzopyran-4-ol **261d** in $CDCl_3$.

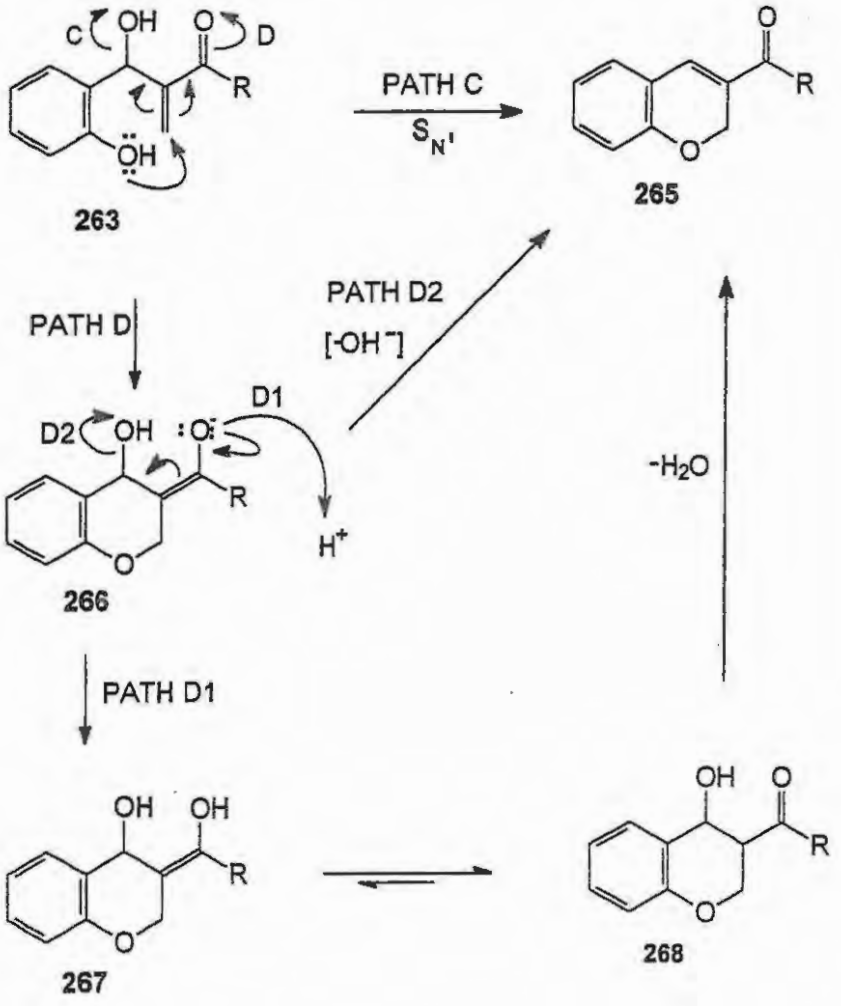
2.3 MECHANISTIC CONSIDERATIONS

As indicated earlier, formation of the chromenes is assumed to proceed *via* the Baylis-Hillman product, followed by a conjugate addition-elimination sequence (Path A, Scheme 48). However, other possible pathways need to be considered. The primary question relates to whether or not the Baylis-Hillman reaction is involved at all, since it could be argued that a conjugate addition-aldol cyclisation sequence (Path B) would also afford the chromene product. Réne and Royer[127] have reported synthesis of similar chromenes by treatment of salicylaldehyde with various acrylates in the presence of a base (K_2CO_3), the mechanism presumably involving formation of the phenoxide ion followed by the conjugate addition to the α,β-unsaturated system and cyclisation *via* an intramolecular aldol reaction (Path B).



Scheme 48

If Path A (Scheme 48) is, in fact, followed, the Baylis-Hillman product **263**, once formed, may undergo cyclisation *via* an S_N' process with the loss of the hydroxyl group to afford the chromene **265** (Path C; Scheme 49), or it may cyclise *via* conjugate addition (Path D) with the formation of an the enolate intermediate **266**. The enolate **266** may then undergo protonation at the enolate oxygen (Path D1) to afford the enol **267**, followed by tautomerism to the more favoured keto tautomer **268** and, finally, dehydration to afford the chromene **265**. Alternatively, elimination of hydroxide ion from the enolate **266** (Path D2) would afford the chromene **265** directly.



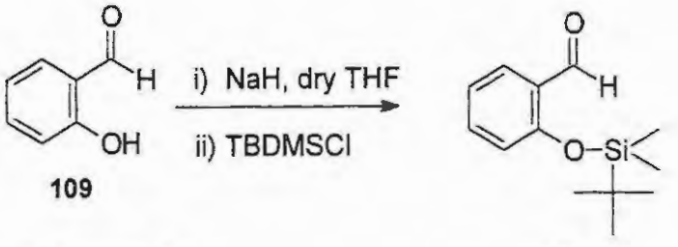
Scheme 49

2.3.1 Investigation of the intermediates

To prove that the formation of the chromenes prepared in the present study involves the Baylis-Hillman reaction, and that this is, in fact, the only mechanism taking place, three approaches were followed :- i) protection of the hydroxyl group of salicylaldehyde to inhibit cyclisation during reaction with methyl acrylate in the presence of the catalyst DABCO; ii) reaction of *para*-hydroxybenzaldehyde with vinyl systems under Baylis-Hillman conditions; and iii) treatment of salicylaldehyde with *tert*-butyl acrylate under Baylis-Hillman conditions.

2.3.1.1 Preparation and reactions of t-butyldimethylsilyl-protected salicylaldehyde

In the first approach, protection the hydroxyl group of salicylaldehyde as the *tert*-butyldimethylsilyl ether was expected to permit isolation of the Baylis-Hillman product and prevent the subsequent conjugate addition step to the chromene **230**. The intention was to complete and confirm the results of a preliminary study by Robinson.[94] The *tert*-butyldimethylsilyl protecting group was chosen because of its relative stability and its generally efficient introduction;[128,129] deprotection is typically achieved in high yield by treatment with *tetra*-butylammonium fluoride.[129] Silylation of salicylaldehyde was effected using the procedure developed by Robinson.[94] Salicylaldehyde was first reacted with sodium hydride in dry THF to generate the phenoxide ion, followed by treatment with *tert*-butydimethylsilyl chloride (TBDMSCl) to afford *O*-*t*-butyldimethylsilyl-protected salicylaldehyde **269** (Scheme 50).

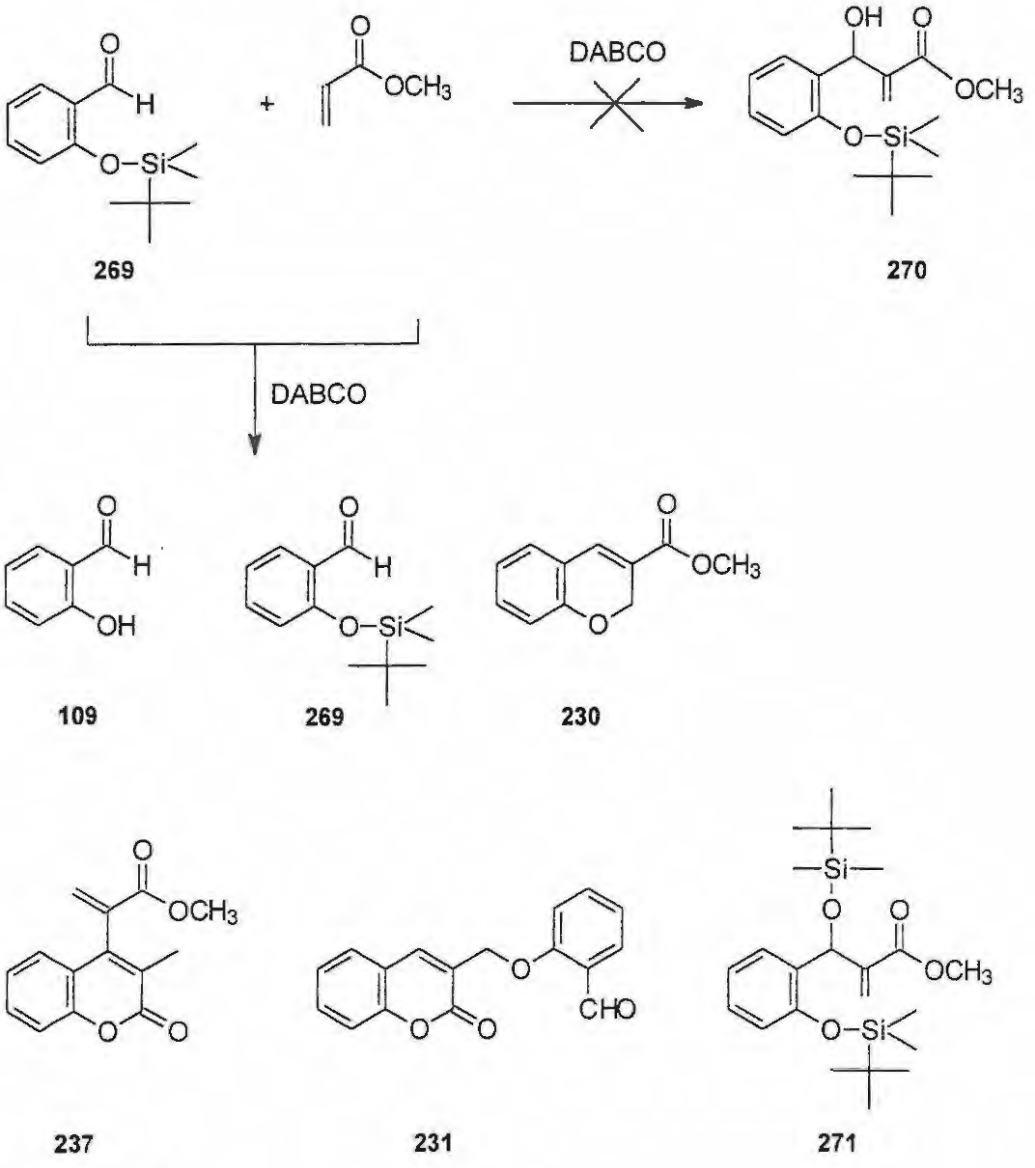


109 **269**

Scheme 50

The *O*-*t*-butyldimethylsilyl-protected salicylaldehyde **269** was treated with methyl acrylate in the presence of the catalyst, DABCO, to afford the disilylated Baylis-Hillman product **271**, the coumarins **237** and **231**, the chromene **230**, salicylaldehyde **109**, and starting material **269**, which

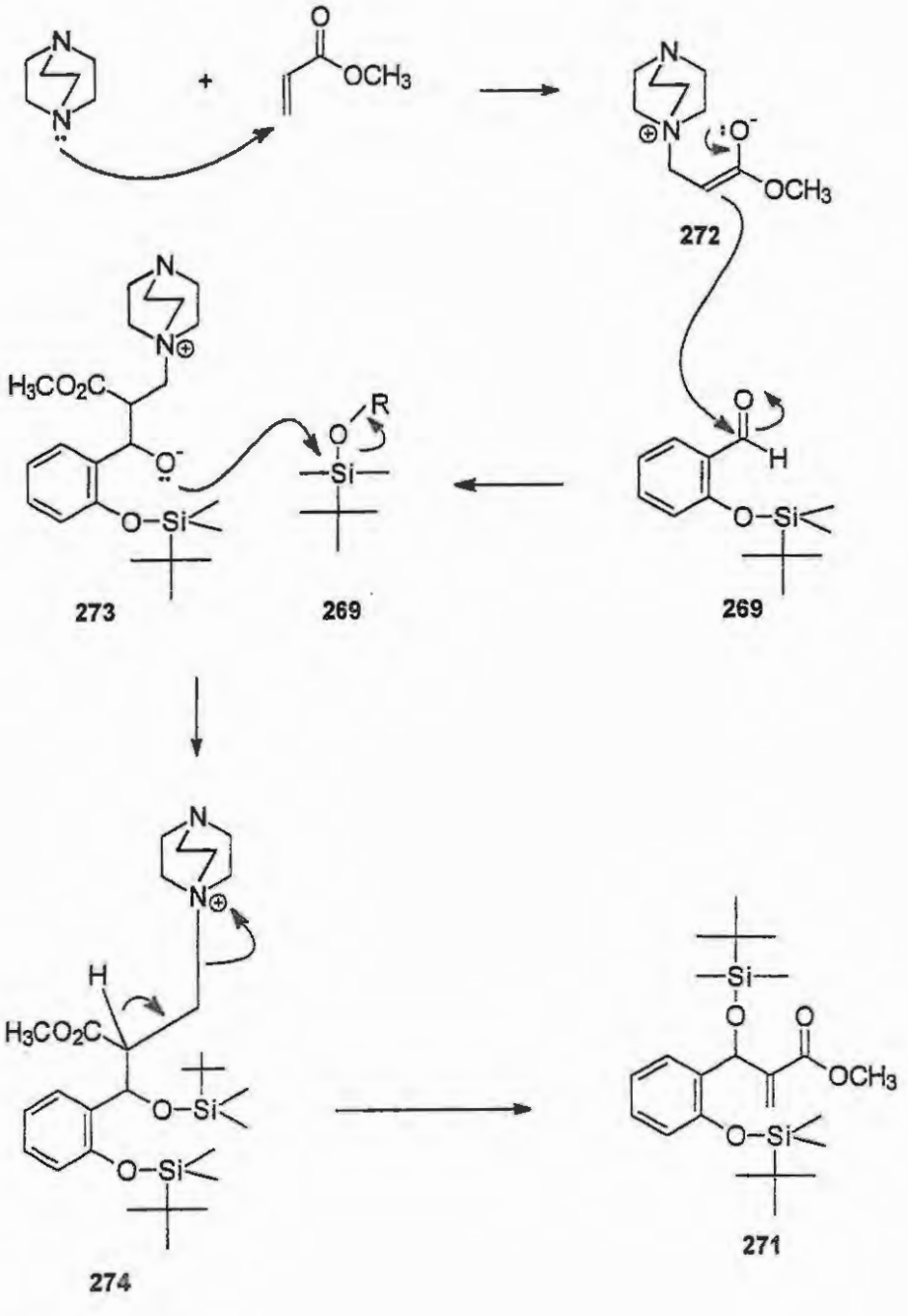
were isolated by flash chromatography and preparative layer chromatography (Scheme 51). The isolation of salicylaldehyde **109** indicates that, under the experimental conditions used, cleavage of the silyl group had occurred. The formation of salicylaldehyde may also account for the formation of the chromene **230**, and the coumarins **237** and **231**, following pathways reported earlier by Bode[91] and Robinson[94] (Schemes 37 and 38, respectively).



Scheme 51

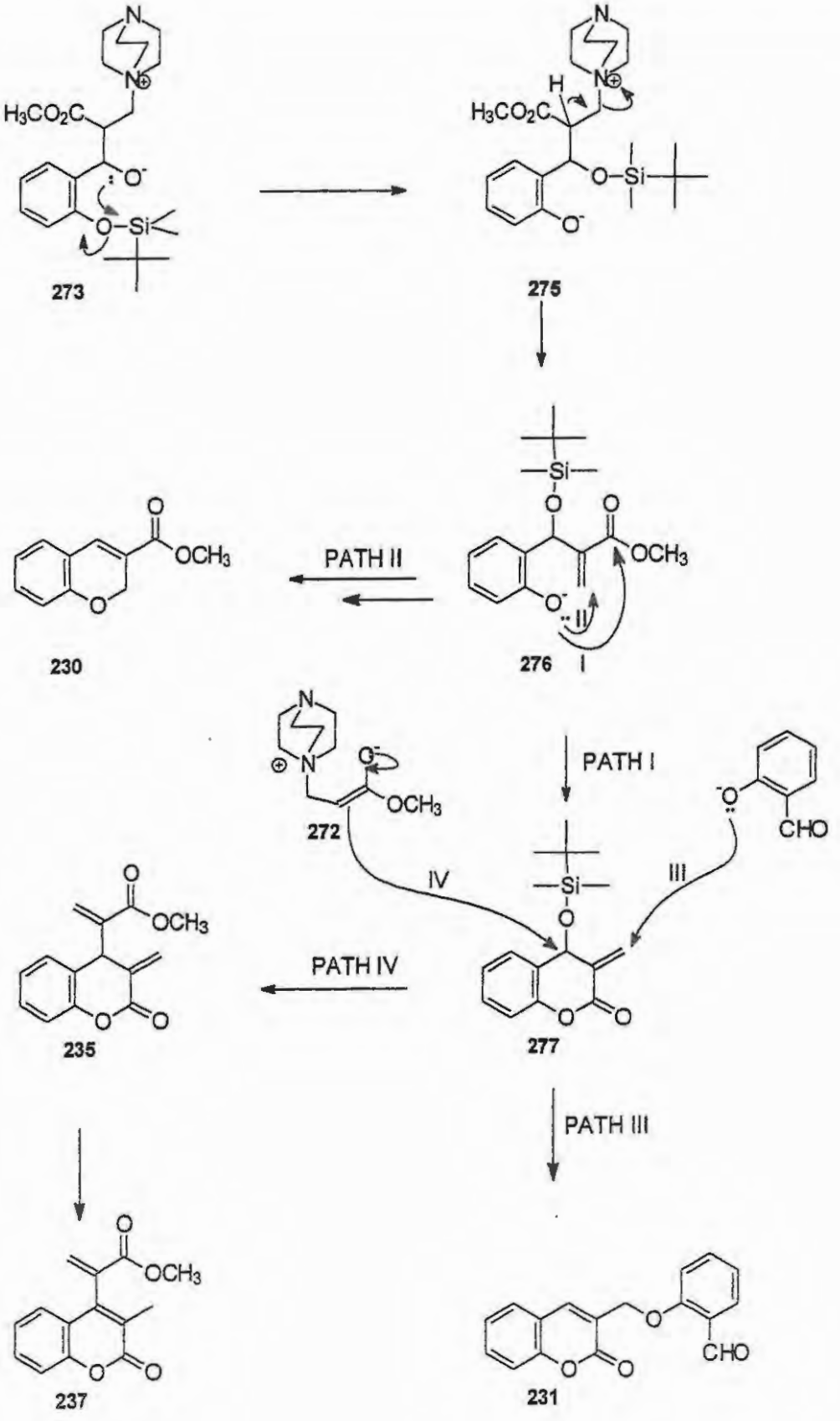
A possible mechanism for the formation of the disilylated Baylis-Hillman product **271** is outlined in Scheme 52. Nucleophilic attack by the Baylis-Hillman zwitterion **272** at the carbonyl carbon of the silylated salicylaldehyde **269** results in the formation of the dipolar adduct **273**, which then

attacks another molecule of the precursor **269** at the silicon centre displacing phenoxide ion and affording the disilylated adduct **274**. Subsequent elimination of the catalyst, DABCO, leads to the disilylated Baylis-Hillman product **271**.



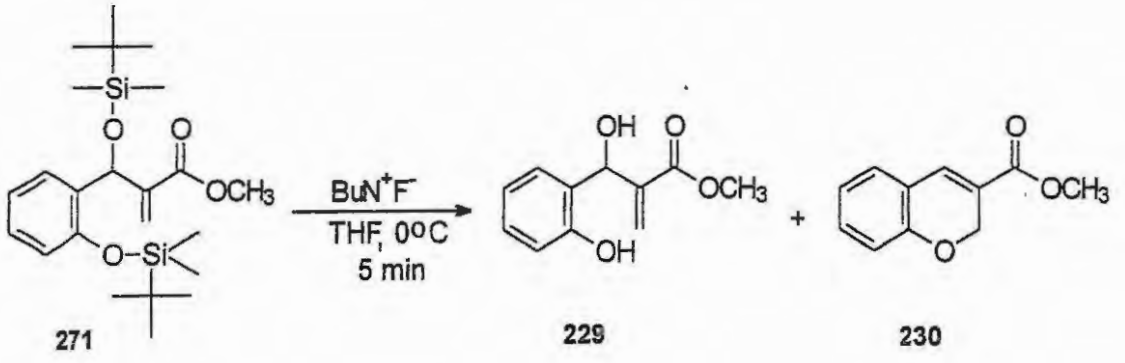
Scheme 52

The alkoxide **273**, once formed, may also undergo intramolecular migration of the TBDMS group to form the more stable phenoxide analogue **275** (Scheme 53). Elimination of DABCO may then lead to the phenoxide species **276** which is, is in fact, a mono-silylated Baylis-Hillman derivative. The phenoxide **276** may then undergo intramolecular cyclisation *via* conjugate addition (path II), and loss of the silyloxy group to afford the chromene **230**, or *via* acyl substitution (path I) to afford the coumarin intermediate **277**. The coumarin **277** may then undergo nucleophilic attack by the phenoxide anion [path III; generated in the sequence **273** + **269** → **274** (Scheme 52)], subsequent loss of silyloxy group affording the coumarin **231**. The silyloxy group may also be displaced by the Baylis-Hillman zwitterion **272** (path IV) to form the coumarin intermediate **235**, rearrangement of which affords the coumarin **237**.


273
275
276
230
235
237
231
272
277
PATH I
PATH II
PATH III
PATH IV
I
II
III
IV

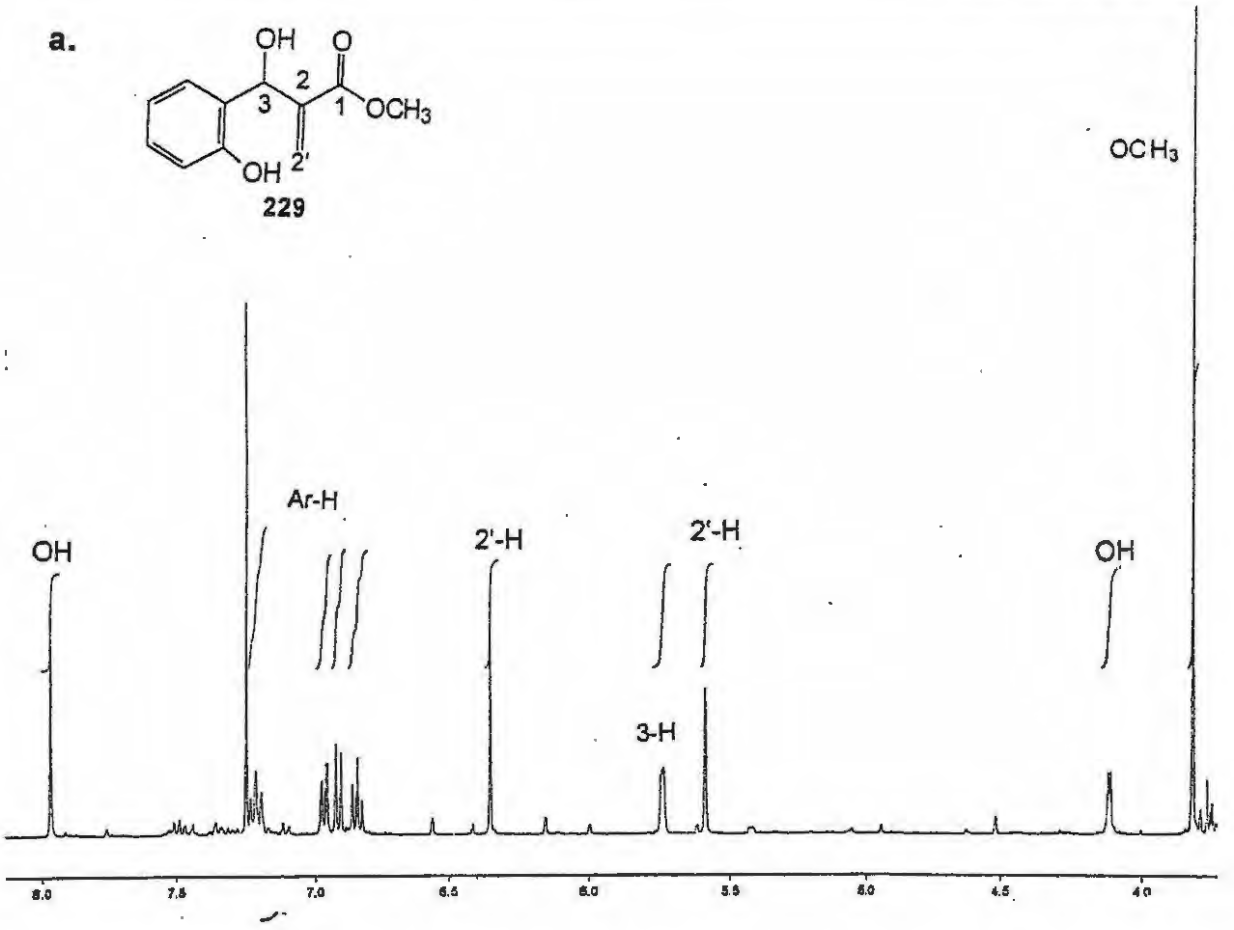
Scheme 53

In order to demonstrate the ability of Baylis-Hillman products to undergo intramolecular cyclisation, the disilylated derivative **271** was deprotected by treatment with tetrabutylammonium fluoride in tetrahydrofuran at 0 °C. Surprisingly, purification of the resulting mixture by preparative layer chromatography afforded the elusive Baylis Hillman product **229** in 70 % yield and the expected chromene **230** in 20 % yield (Scheme 54). The Baylis-Hillman product **229** was characterised by one- and two-dimensional NMR spectroscopy and high resolution mass spectrometry. The ^{1}H NMR spectrum of the Baylis-Hillman product **229**, illustrated in Figure 16a, reveals the two vinylic proton signals at 5.60 ppm and 6.35 ppm, the 3-methine proton signal 5.74 ppm and the methoxy singlet at 3.82 ppm. The ^{13}C NMR spectrum (Figure 16b) confirms the presence of the methoxy carbon (52.4 ppm), the 3-methine carbon (73.5 ppm), the vinylic methylene carbon (128.0 ppm) and the carbonyl carbon (167.7 ppm). The formation of the chromene **230** is undoubtedly due to intramolecular cyclisation of the Baylis-Hillman product **229** *via* conjugate addition as outlined in Scheme 42. Somewhat surprisingly, none of the coumarin **237** was isolated, suggesting that under these conditions (Scheme 54), the acyl substitution pathway is not favoured.



271 229 230

Scheme 54



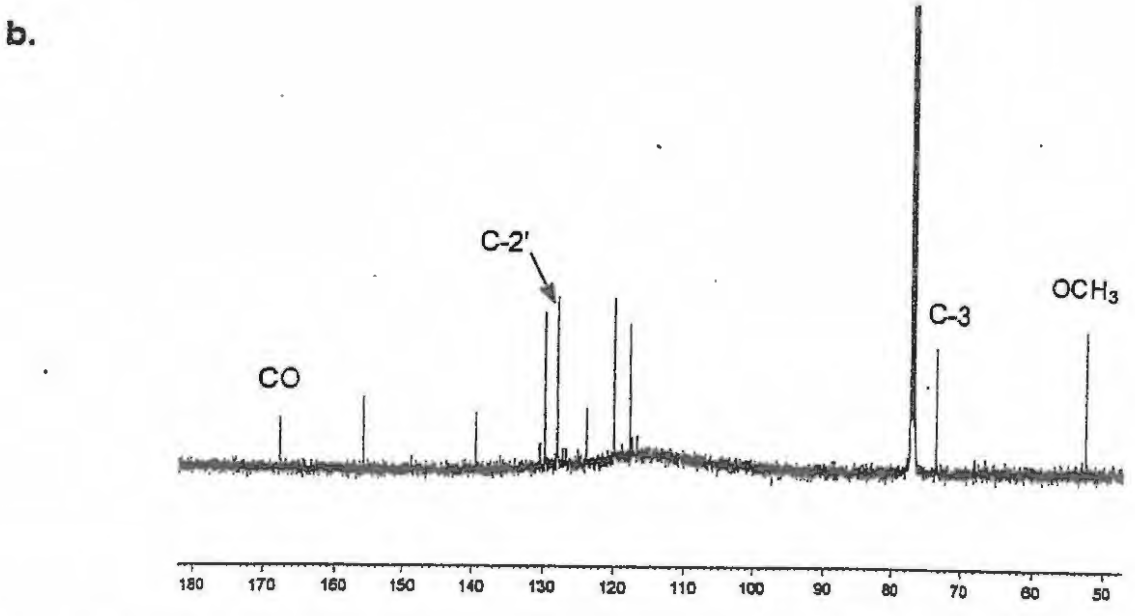


Figure 16. **(a)** 400 MHz ^{1}H NMR spectrum; and **(b)** 100 MHz ^{13}C NMR spectrum of methyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate **229** in $CDCl_3$.

The Baylis-Hillman product **229** was dissolved in $CDCl_3$, and the resulting solution left to stand in an NMR tube. After one week, no cyclisation of the Baylis-Hillman product **229** to the expected chromene and coumarin derivatives (Scheme 38) was apparent from the ^1H NMR spectrum of the solution. It was thought that the cyclisation process could be catalysed by DABCO and, consequently, DABCO was added to the NMR tube containing the $CDCl_3$ solution of the Baylis-Hillman product **229**. The ^1H NMR spectrum of the resulting mixture, shown in Figure 17, indicated the formation of :- methyl acrylate, identified by the vinylic proton signals between 5.7 ppm and 6.5 ppm; salicylaldehyde, identified by the aldehydic singlet at 9.89 ppm (confirmed by a ^{13}C NMR signal at 196.5 ppm); and, possibly, traces of methyl chromene-3-carboxylate **230**, tentatively identified by a singlet at 4.97 ppm, which is characteristic of the chromene 2-methylene protons.

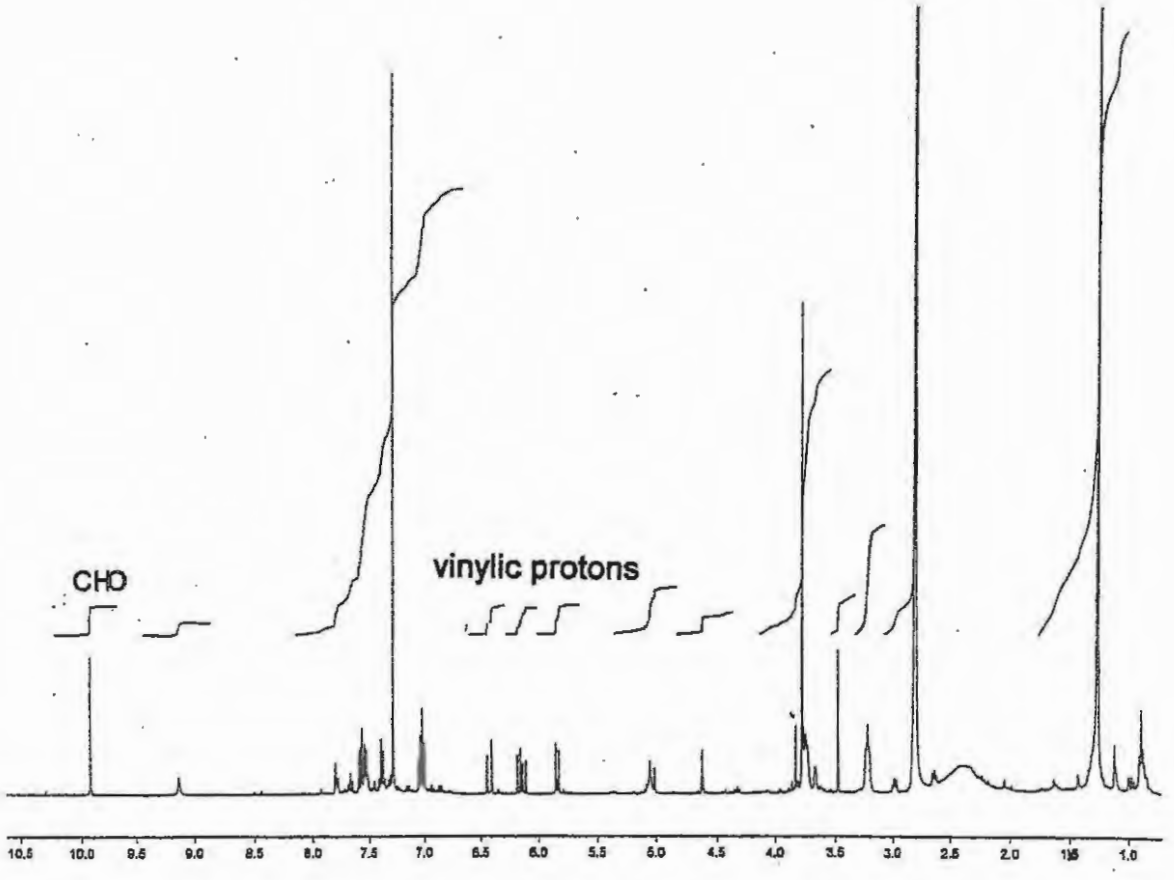
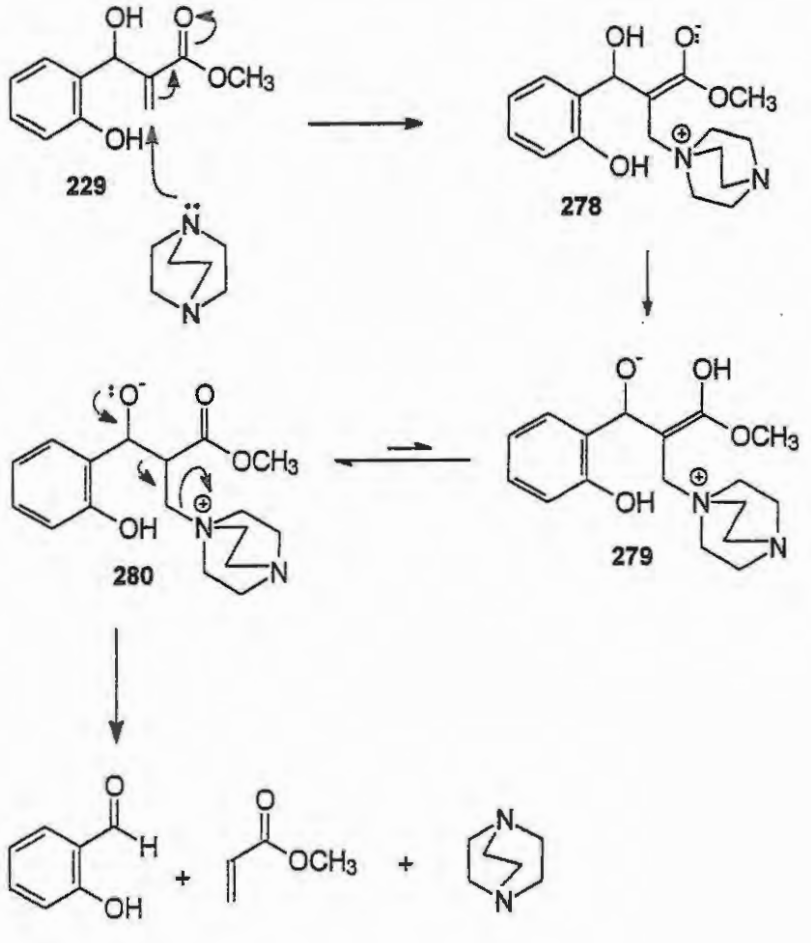


Figure 17. 400 MHz ^1H NMR spectrum of a crude mixture resulting from the reaction of methyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate **229** with DABCO in $CDCl_3$

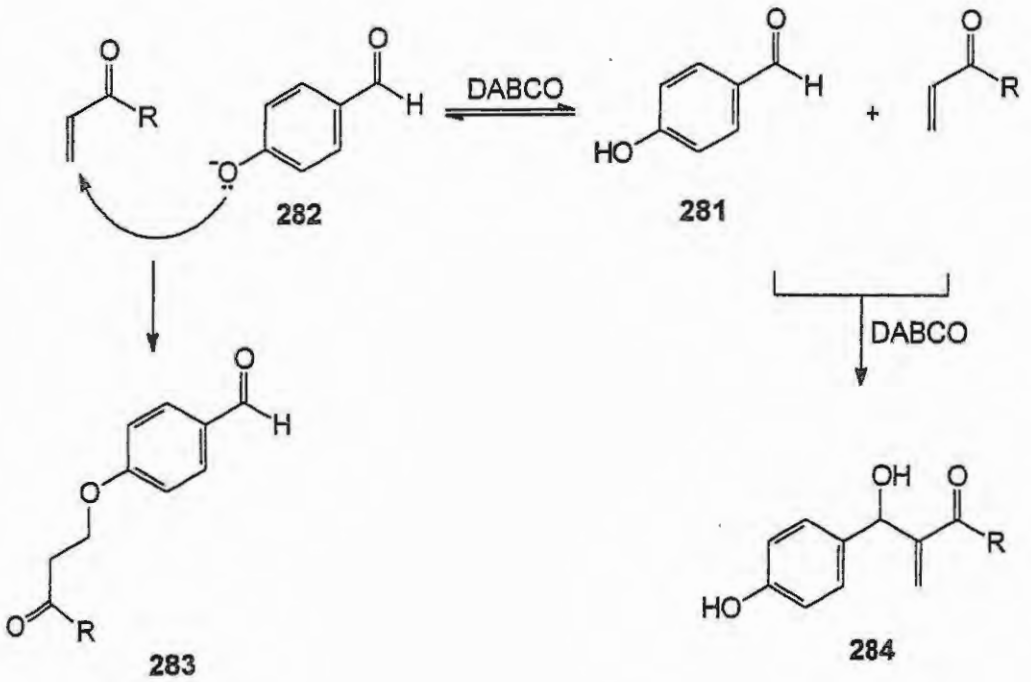
Clearly, the addition of DABCO to the solution of the Baylis-Hillman product **229** in $CDCl_3$ favours a *retro*-Baylis-Hillman reaction, and a proposed mechanism for this process is outlined in Scheme 55. Thus, the Baylis-Hillman product **229** undergoes conjugate addition by DABCO to afford the zwitterionic enolate **278**, followed by proton transfer to the enolate **279** and tautomerisation to the keto tautomer **280** - a putative intermediate in the forward reaction. Elimination of DABCO then results in the formation of salicylaldehyde and methyl acrylate.



Scheme 55

2.3.1.2 The Baylis-Hillman reaction of 4-hydroxybenzaldehyde

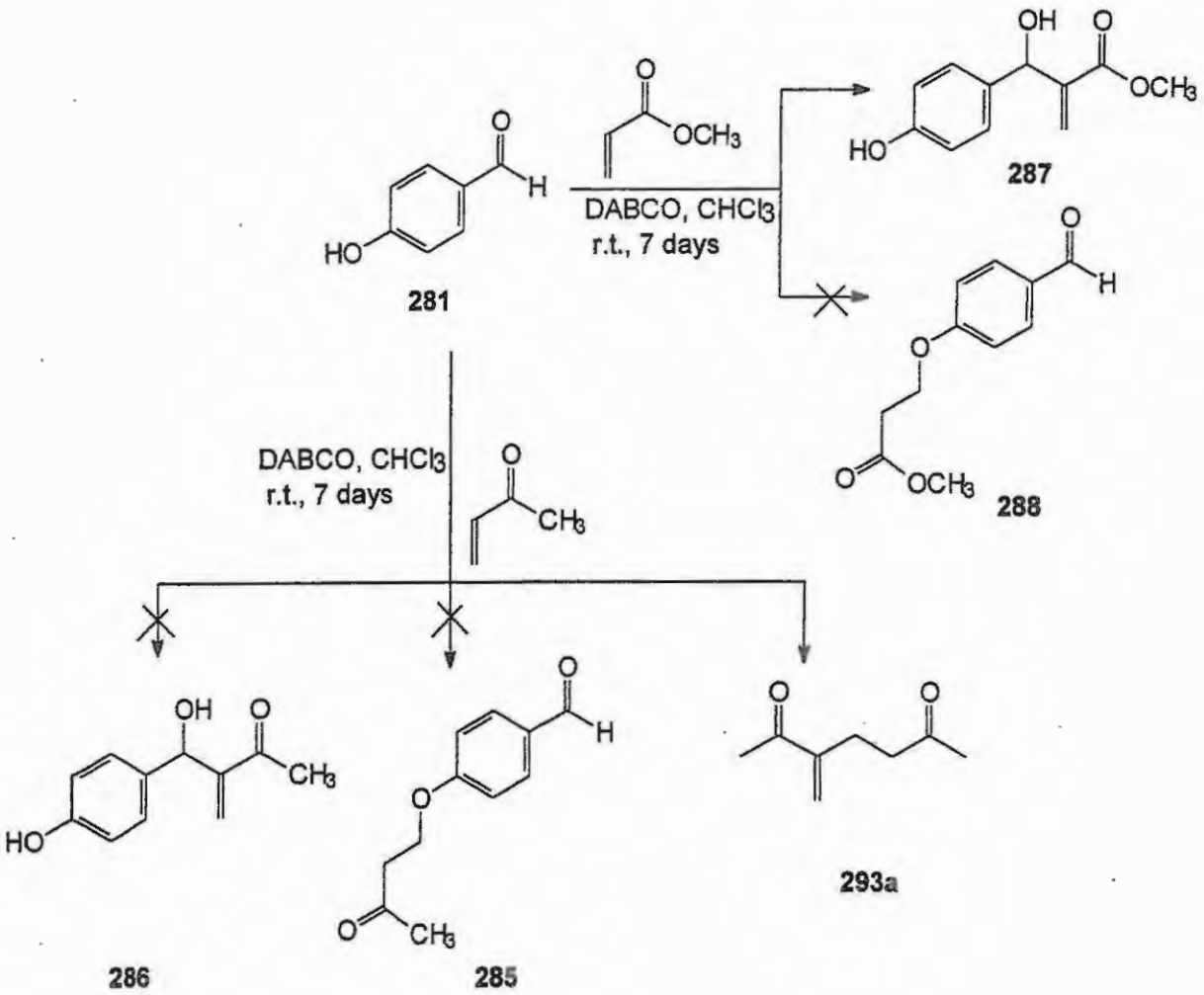
4-Hydroxybenzaldehyde was chosen as a model compound to explore possible competition between conjugate addition and the Baylis-Hillman reaction as the first step in the formation of chromene derivatives (Scheme 56). Thus, the Baylis-Hillman product **284** or the conjugate addition product **283** could be formed without the complication of intramolecular cyclisation.



Scheme 56

In the first attempt, 4-hydroxybenzaldehyde **281** was treated with methyl vinyl ketone in the presence of DABCO (Scheme 57). Neither of the expected reactions were observed; instead, the methyl vinyl ketone dimer **293a** (see Scheme 60) and the starting material 4-hydroxybenzaldehyde **281,** were isolated (Scheme 57). Methyl acrylate does not dimerise easily in presence of DABCO (see Section 2.4.2) and, consequently, was substituted for methyl vinyl ketone. A mixture of 4-hydroxybenzaldehyde **281**, 1.5 equivalents of methyl acrylate and DABCO were stirred at room temperature for seven days. Flash chromatography of the mixture afforded the starting material, 4-hydroxybenzaldehyde **281** and the Baylis-Hillman product **287**

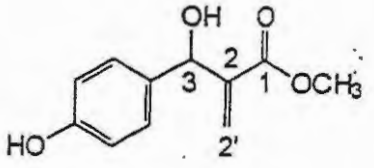
in 10 % yield. None of the conjugate addition product **288** was detected.



Scheme 57

The ^{1}H NMR spectrum of the Baylis-Hillman product **287** (Figure 18) reveals the characteristic vinylic proton signals at 5.85 ppm and at 6.31 ppm, and the 3-methine proton signal at 5.49 ppm. These assignments are supported by the HMQC spectrum (Figure 19), and the structure is also consistent with the ^{13}C NMR, DEPT and COSY NMR data. From these results, it seems that :-i) that the conjugate pathway is unlikely to compete with the Baylis-Hillman reaction (Scheme 57) as the first step in the construction of a chromene product; and ii) 4-hydroxybenzaldehyde is a far less reactive Baylis-Hillman substrate than salicylaldehyde. The latter observation may be

attributed to intramolecular hydrogen-bonding in salicylaldehyde,[130] which would increase the electrophilicity of the carbonyl carbon, thus enhancing its reactivity.



287

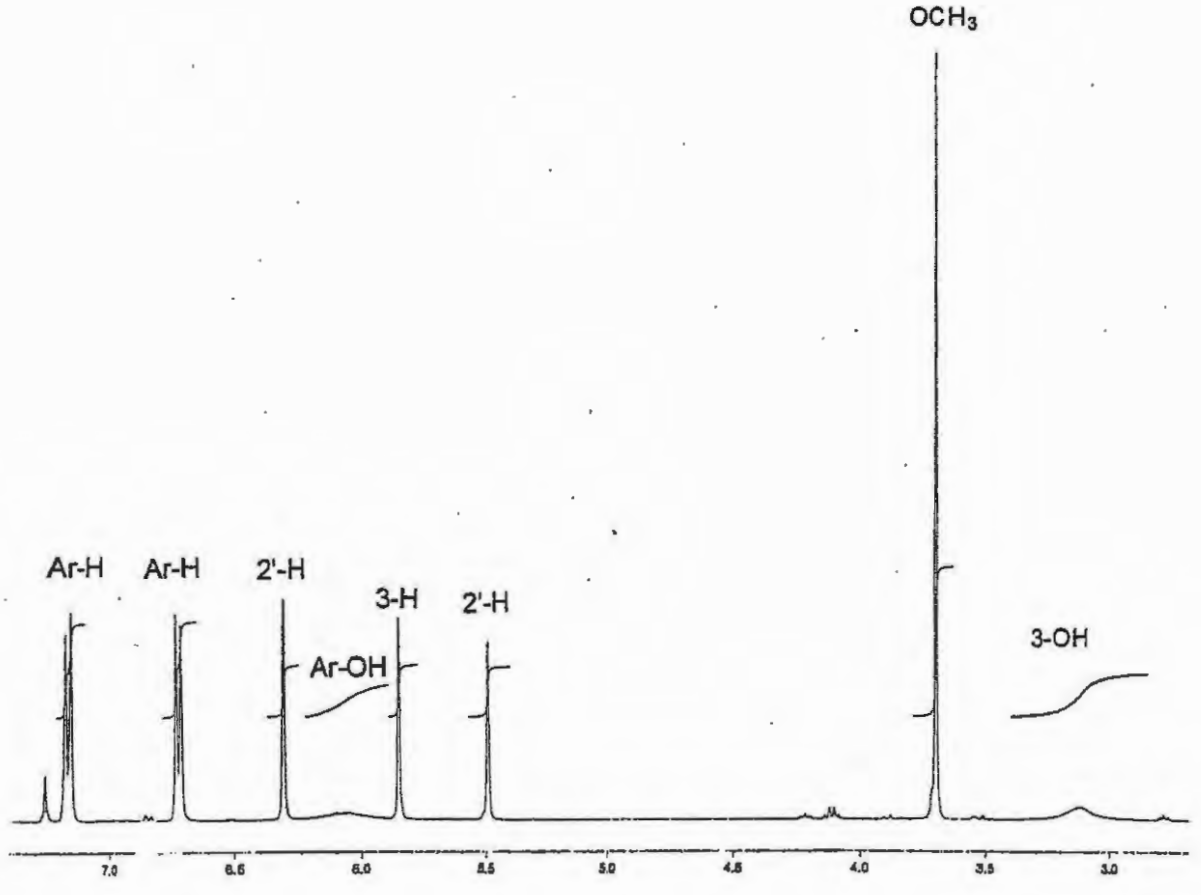
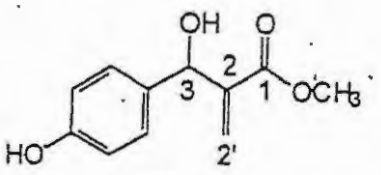


Figure 18. 400 MHz ^{1}H NMR spectrum of methyl 3-hydroxy-3(4-hydroxyphenyl)-2-methylenepropanoate **287** in $CDCl_3$.



287

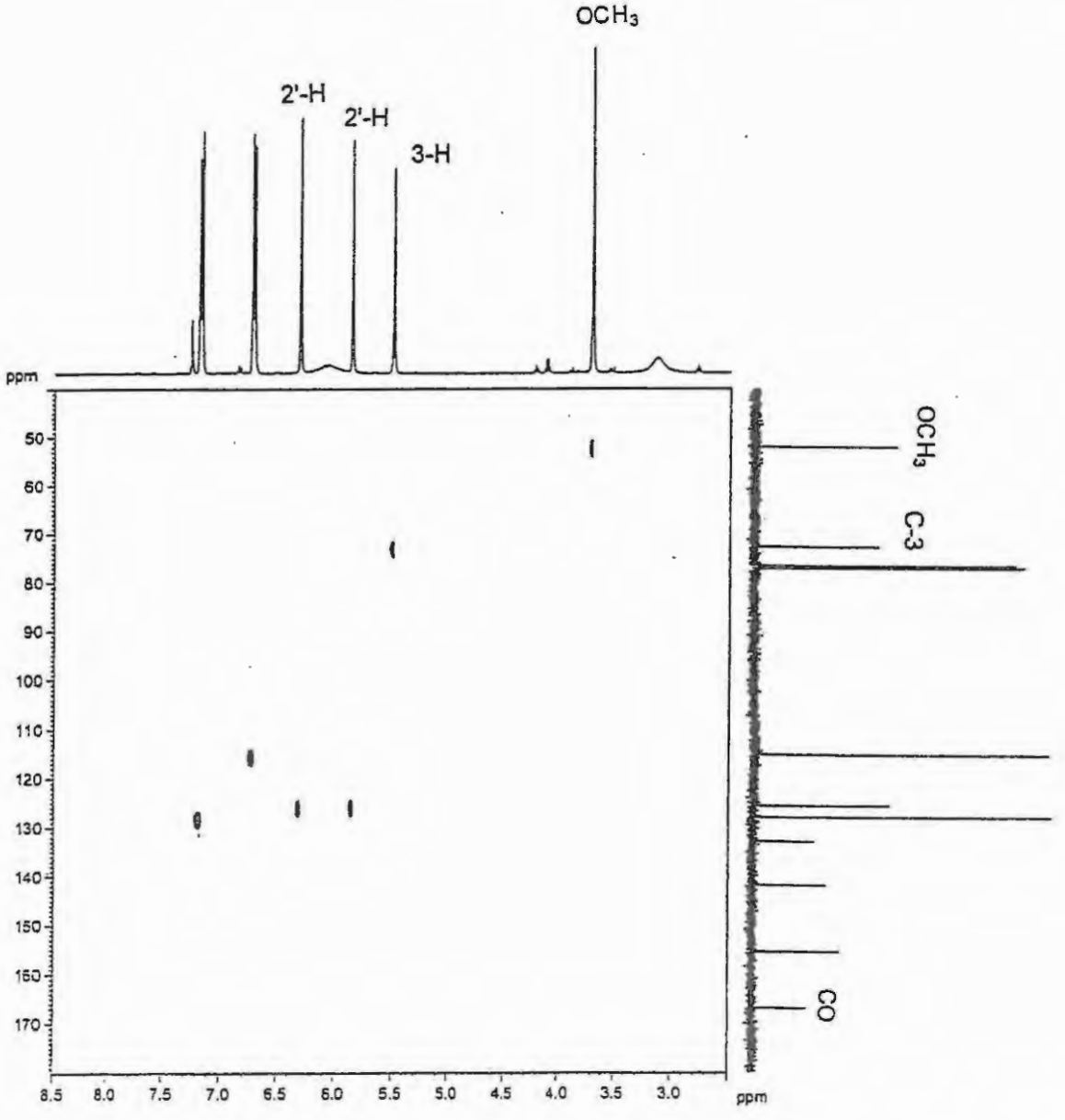


Figure 19. The HMQC spectrum of methyl 3-hydroxy-3(4-hydroxyphenyl)-2-methylene-propanoate **287** in $CDCl_3$.

2.3.1.3 The Baylis-Hillman reaction between salicylaldehyde and tert*-butyl acrylate*

In another attempt to explore competition between the conjugate addition and Baylis-Hillman pathways (Scheme 48), *tert*-butyl acrylate was used as the activated alkene instead of methyl acrylate. The electron-releasing inductive effect of the *tert*-butyl group was expected to reduce the electrophilicity of both the ester carbonyl carbon and the C-3 vinylic carbon (Figure 20), thus inhibiting cyclisation *via* either conjugate addition or acyl substitution. The steric bulk of the *tert*-butyl group was also considered likely to hinder cyclisation *via* acyl substitution and, hence, competitive formation of a coumarin product [In the computer-modelled structure of *tert*-butyl acrylate (Figure 21), it is apparent that the vinylic carbon is more accessible to the phenolic oxygen (Path II) than the carbonyl carbon (Path I)].

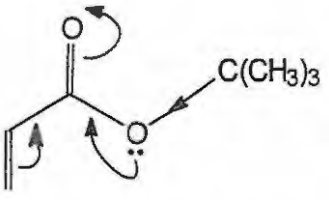


Figure 20. Electron-releasing inductive effect of the *t*-butyl group enhancing alkyl-oxygen lone-pair delocalisation and decreasing the electrophilicity of the carbonyl carbon.

Salicylaldehyde **109** was treated with excess *tert*-butyl acrylate in the presence of the catalyst, DABCO, and the reaction mixture was left to stir at room temperature for seven days. Work-up and flash chromatography afforded the starting material, salicylaldehyde **109** (50 %), and the Baylis-Hillman product **289** in 49 % yield (Scheme 58). The Baylis-Hillman product **289** was characterised by one- and two-dimensional NMR spectroscopy, and the ^{1}H NMR spectrum (Figure 22) reveals the two, characteristic vinylic proton signals at 5.54 ppm and 6.23 ppm, the 3-methine proton at 5.69 ppm, the alkyl hydroxy group resonating at 4.34 ppm and the *tert*-butyl protons at 1.50 ppm. The HMQC spectrum of compound **289** (Figure 23) confirms attachment of the two methylene protons to the same carbon. The isolation of the Baylis-Hillman product **289** clearly supports the expectation that the *initial* reaction between salicylaldehyde and an activated alkene favours the Baylis-Hillman (Path A; Scheme 48) over the conjugate addition pathway (Path B).

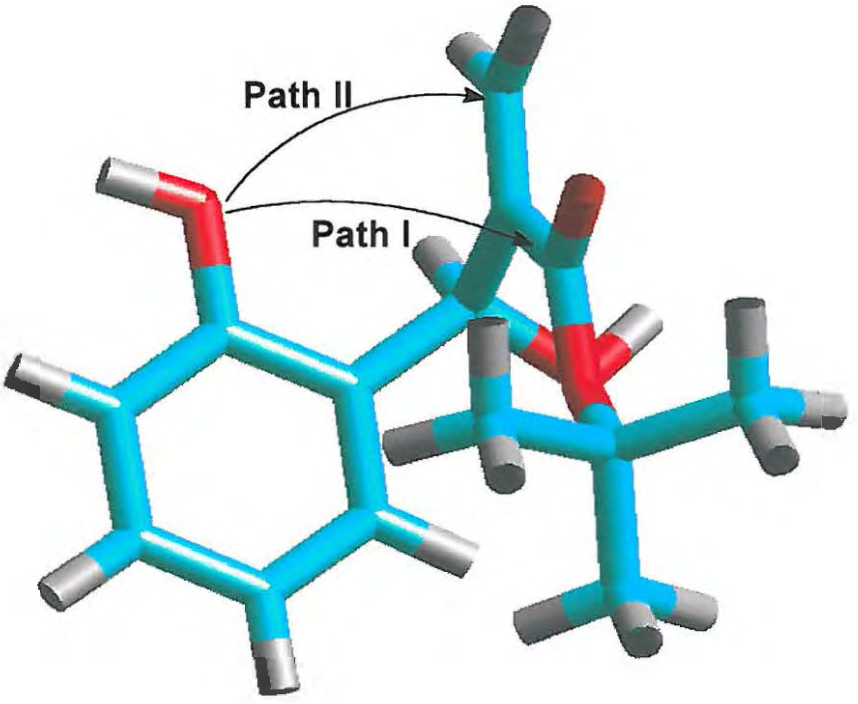
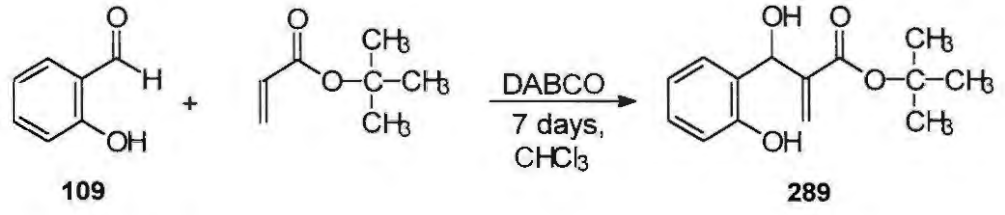


Figure 21. Energy-minimised structure of *tert*-butyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate **289** showing the steric crowding about the carbonyl group.



109 **289**

Scheme 58

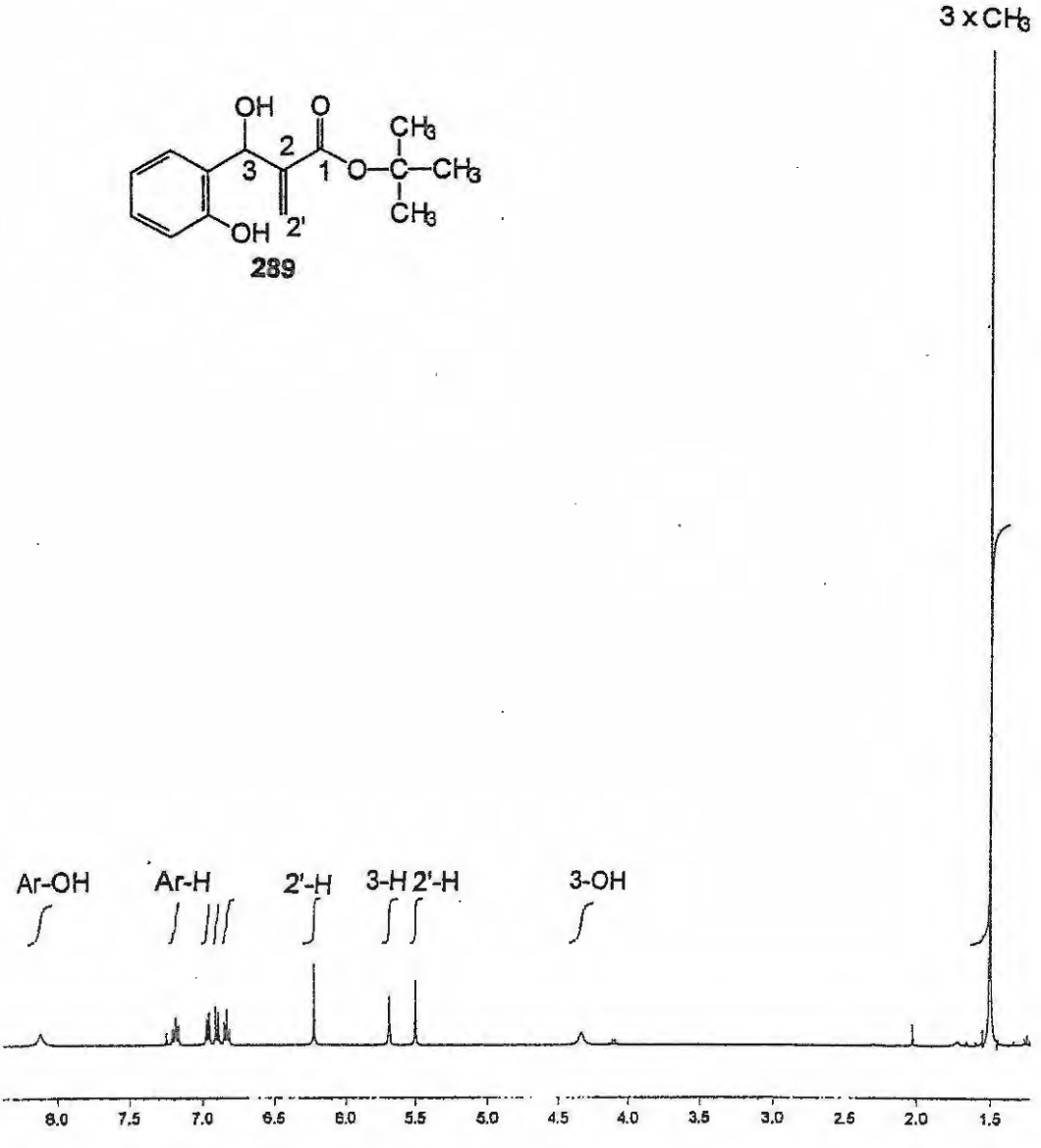
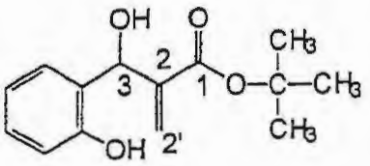


Figure 22. 400 MHz ^{1}H NMR spectrum of *tert*-butyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate **289** in $CDCl_3$.



289

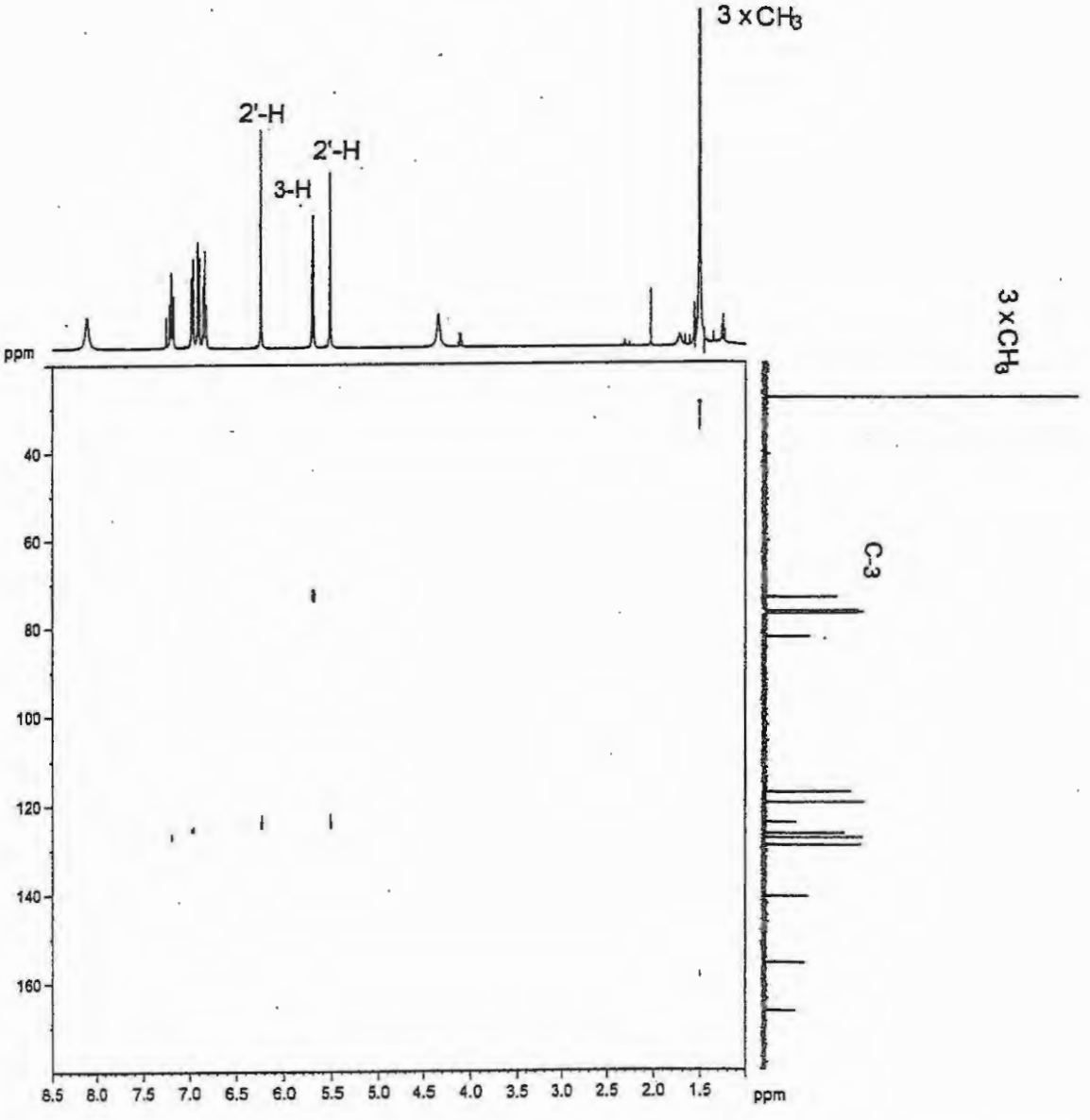
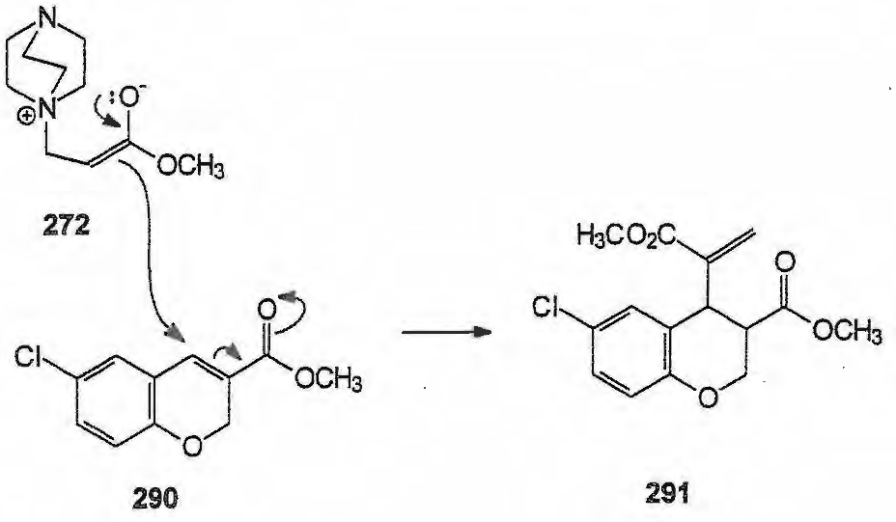


Figure 23. The HMQC spectrum of *tert*-butyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate **289** in $CDCl_3$.

2.4 MICHAEL-TYPE ADDITION REACTIONS UNDER BAYLIS-HILLMAN CONDITIONS.

2.4.1 Investigation of conjugate addition to 2H-chromene substrates

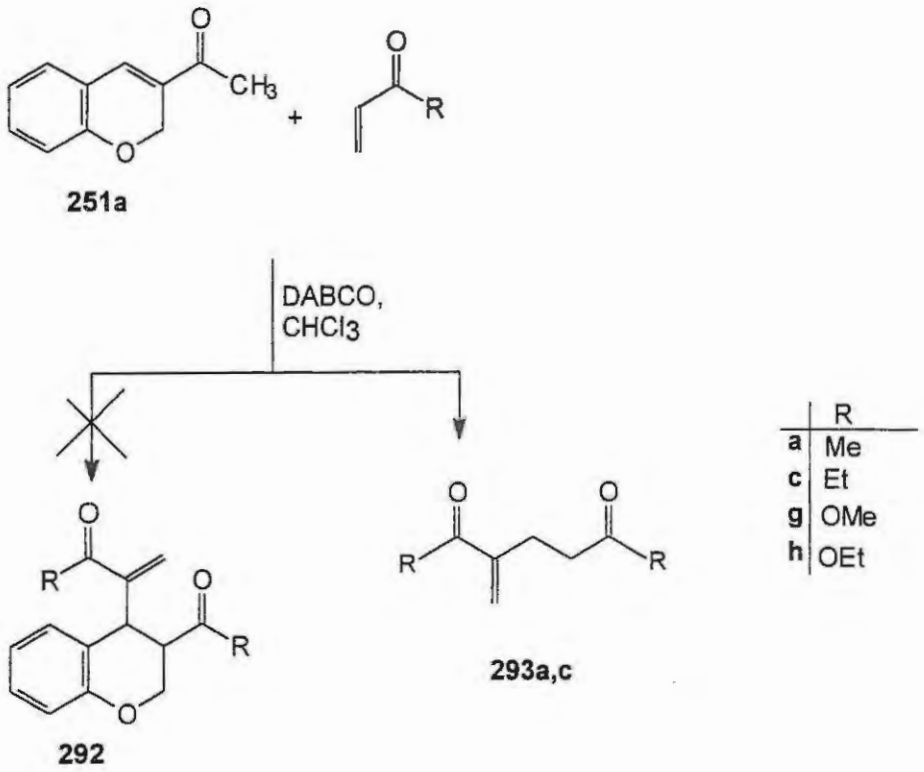
The 3,4-disubstituted chroman **291** was isolated by Robinson[94] from the reaction of 5-chlorosalicylaldehyde and methyl acrylate under Baylis-Hillman conditions. Its formation was attributed to nucleophilic attack by the Baylis-Hillman zwitterion **272** on the chromene precursor **290**, with the chromene **290** acting as a Michael-type acceptor (Scheme 59).



Scheme 59

Given the availability of various chromenes, analogous to compound **290**, it was thought to explore this reaction further. Methyl vinyl ketone, 3-acetylchromene **251a** and DABCO were dissolved in $CDCl_3$ and the resulting solution was analysed at intervals over 7 days by ^1H NMR spectroscopy. No evidence of the expected Michael addition product **292** was detected; instead, the formation of a dimer **293a** of methyl vinyl ketone (R = Me) was observed (Scheme 60). Similar results were obtained when ethyl vinyl ketone was (R = Et) used in place of methyl vinyl ketone. Attention was then turned to the use of acrylate esters rather than the vinyl ketones, and methyl acrylate (R = OMe) was treated with 3-acetylchromene **251a** in the presence of the catalyst DBU. However, ^1H NMR analysis of the solution indicated that neither the corresponding dimer nor the Michael addition product had formed; a similar lack of reactivity

was observed when ethyl acrylate (R = OEt) was used. It was concluded that, under these conditions, the desired conjugate addition to 2*H*-chromene substrates is not favoured.



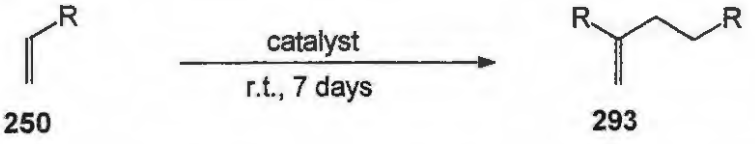
Scheme 60

2.4.2 Dimerisation of α,β-unsaturated vinyl systems

The dimerisation of α,β-unsaturated vinyl systems in the presence of a catalytic quantity of DABCO has been reported before by Drewes *et al.*[131] and Basavaiah *et al.*,[132,133,134] while other workers have demonstrated the synthesis of dimers using catalysts, such as triphenylphosphine,[135] trisdimethylaminophosphine,[136] $RhH(PPh_3)_4$[137] and DBU.[138] The isolation of the diketone **293a** during the investigation of 2*H*-chromenes as Michael acceptors (Section 2.4.1) prompted us to examine the synthesis of the dimeric systems more closely. The dimers **293a,c-i** were obtained in yields ranging from 5 to 65 % (Table 6) by treating the α,β-unsaturated vinyl systems **250a, c-i** with the catalyst, DABCO, in $CHCl_3$. The phenyl vinyl sulfone reaction (entry 4), however, proved to be very slow and at the end of the reaction period (7 days) only 20 % of the dimer was

isolated, while the reaction with acrylonitrile (entry 6) afforded the corresponding dimer in 12 % yield. Acrolein **250b**, methyl acrylate **250g** and ethyl acrylate **250h** were completely unreactive under these conditions, and none of the expected dimers was isolated. Dimerisation of methyl acrylate and ethyl acrylate was finally achieved using the catalyst, DBU, but the products (**293g** and **h**) were isolated in very low yields (10 % and 5 %, respectively; Table 6). The ^{1}H NMR spectrum of the diketone **293a**, illustrated in Figure 24, reveals the 1- and 7-methyl proton signals at 2.02 ppm and 2.22 ppm respectively and the two vinylic protons signals at 5.73 ppm and 5.93 ppm. The higher-order coupling between 4- and 5-methylene nuclei, which constitute an AA'BB' system is evident, as shown by the expanded insert in Figure 24. Similar coupling was observed for the analogous compounds **293c-h**. Assignment of the proton signals was facilitated by examination of HMQC spectrum (Figure 25), which confirms attachment of the two vinylic protons to the same carbon. This methodology clearly provides convenient access to certain 1,5-dicarbonyl compounds.

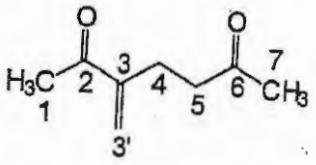
Table 6. Data for the formation of dimeric α,β-unsaturated vinyl systems.



250 **293**

Entry	Substrate	Catalyst	Product	R	Yield [a] / %
1	**250a**	DABCO	**293a**	$COCH_3$	59
2	**250b**	DABCO	**293b**	CHO	-
3	**250c**	DABCO	**293c**	COEt	55
4	**250d**	DABCO	**293d**	SO_2Ph	20
5	**250e**	DABCO	**293e**	SO_3PH	60
6	**250f**	DABCO	**293f**	CN	12
7	**250g**	DBU	**293g**	CO_2Me	10
8	**250h**	DBU	**293h**	CO_2Et	5
9	**250i**	DABCO	**293i**	COPh	65

[a] Chromatographed material.



293a

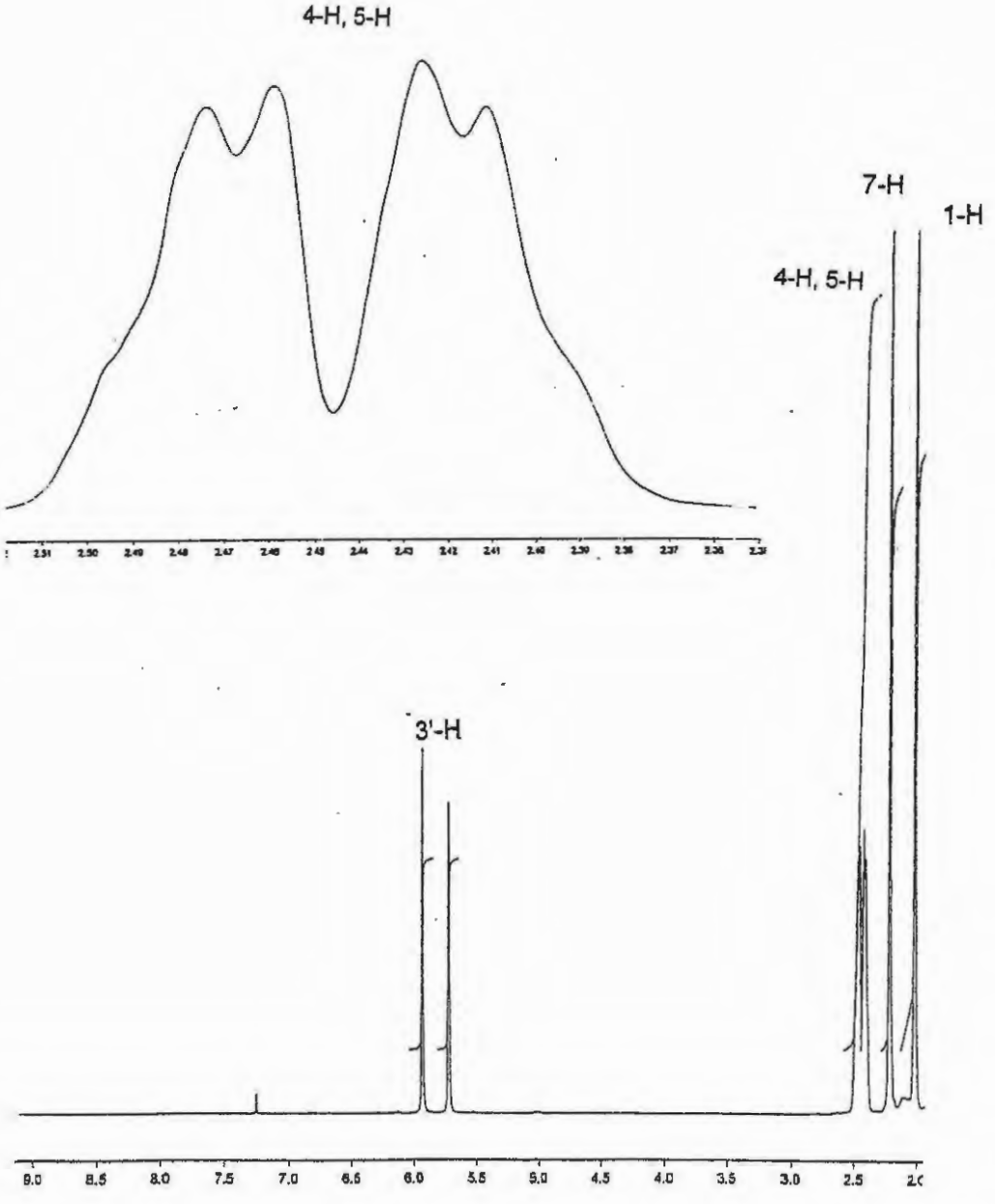
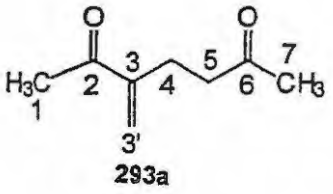


Figure 24. 400 MHz ^{1}H NMR spectrum of 3-methylene-2,6-heptanedione **293a** in $CDCl_3$.



293a

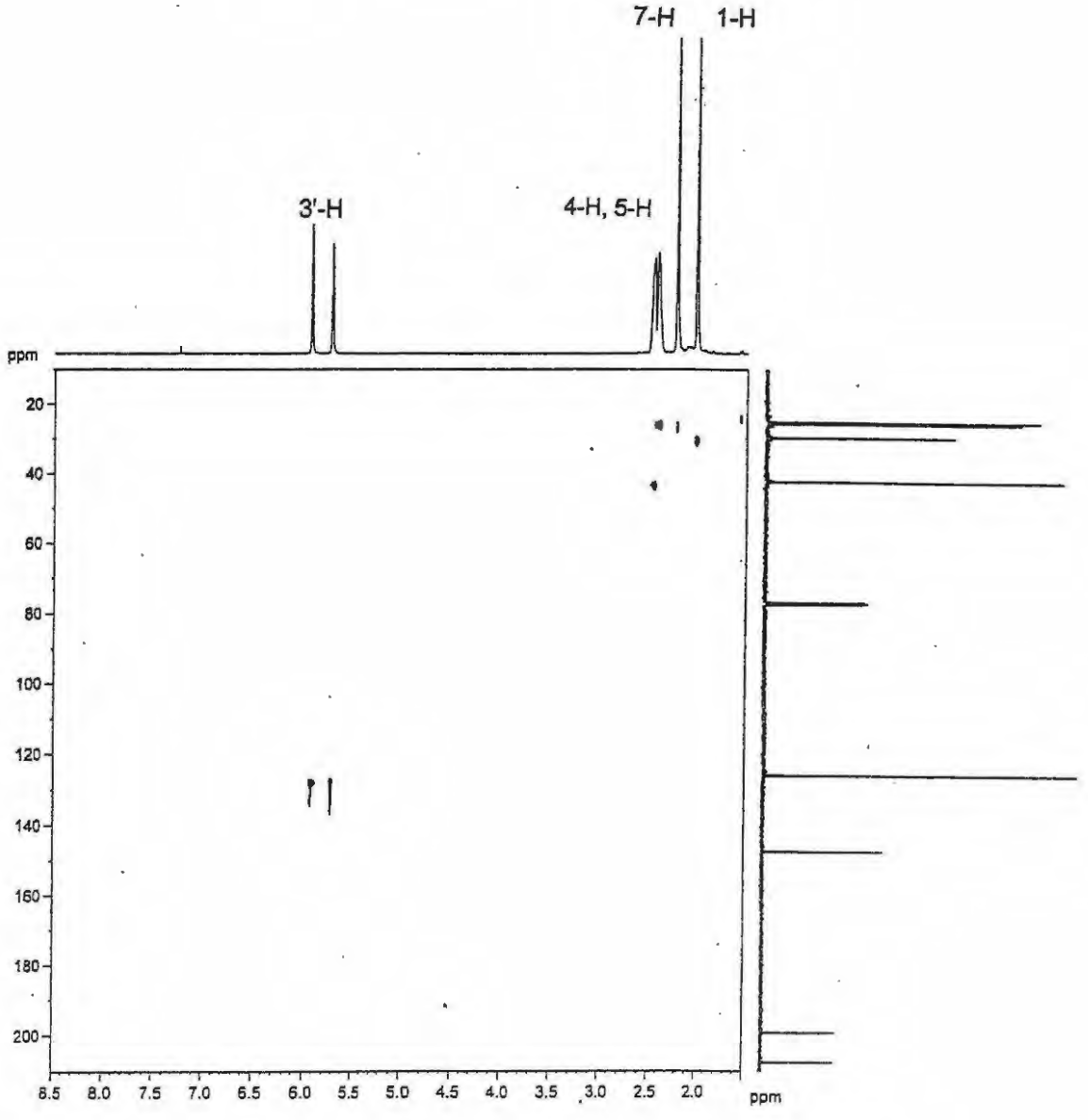
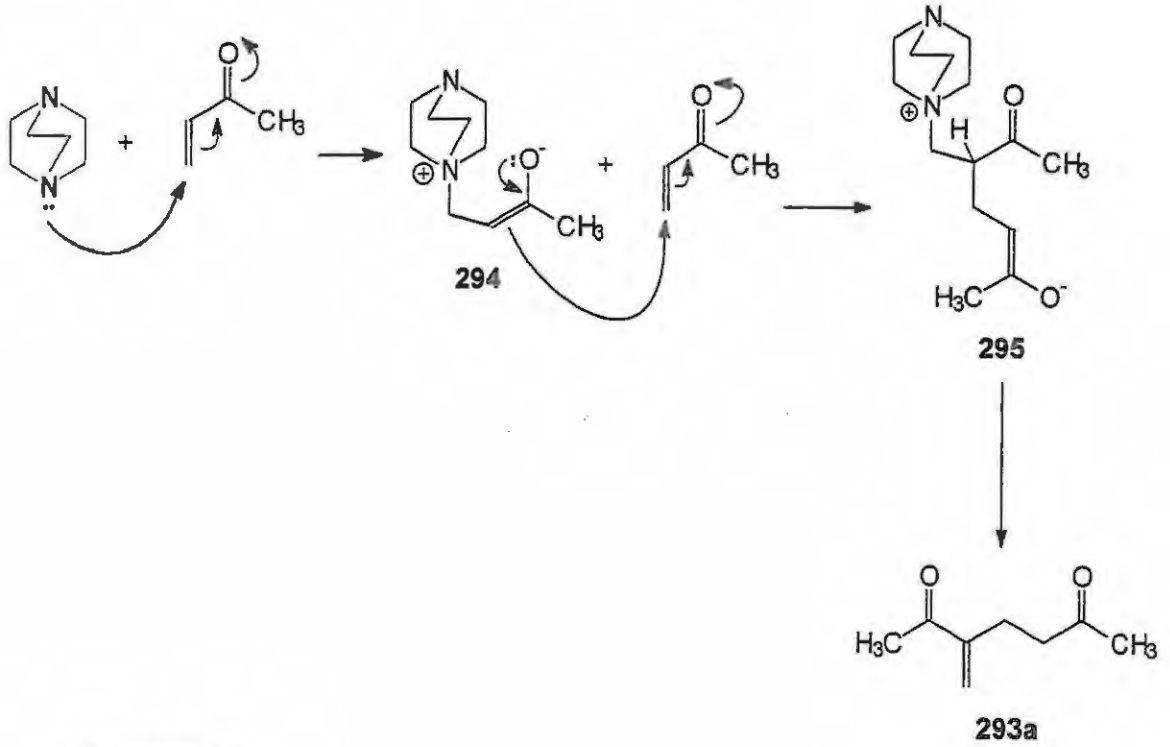


Figure 25. The HMQC spectrum of 3-methylene-2,6-heptanedione **293a** in $CDCl_3$.

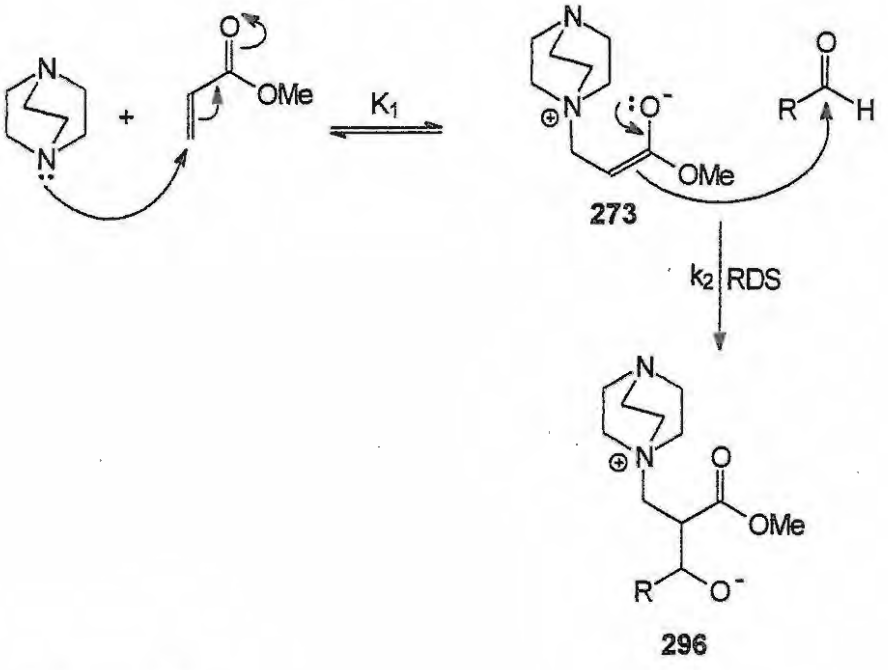
The mechanism suggested by Basavaiah[132] for the formation of the diketone **293a** (Scheme 61), is similar to that outlined in Scheme 41 (p.48). The reaction is initiated by conjugate addition of the catalyst to the vinyl system to form the zwitterion **294**; nucleophilic attack by the zwitterion on the vinylic carbon of a second molecule of the vinyl ketone gives the dipolar adduct **295**, the vinyl ketone acting as a Michael-type acceptor. Elimination of the catalyst then affords the dimer **293a**. A similar mechanism is assumed for the synthesis all the dimers listed in Table 6.



Scheme 61

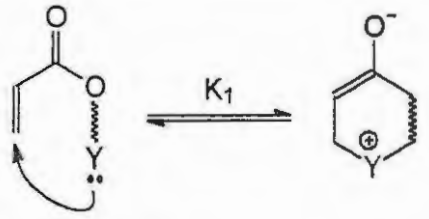
2.5 ATTEMPTED ACCELERATION OF THE BAYLIS-HILLMAN REACTION *via* INTRAMOLECULAR CATALYSIS

The first, reversible step in the Baylis-Hillman reaction has been proposed[104] to involve formation of the Baylis-Hillman zwitterion, which participates in the subsequent, rate determining step (as illustrated in Scheme 62).



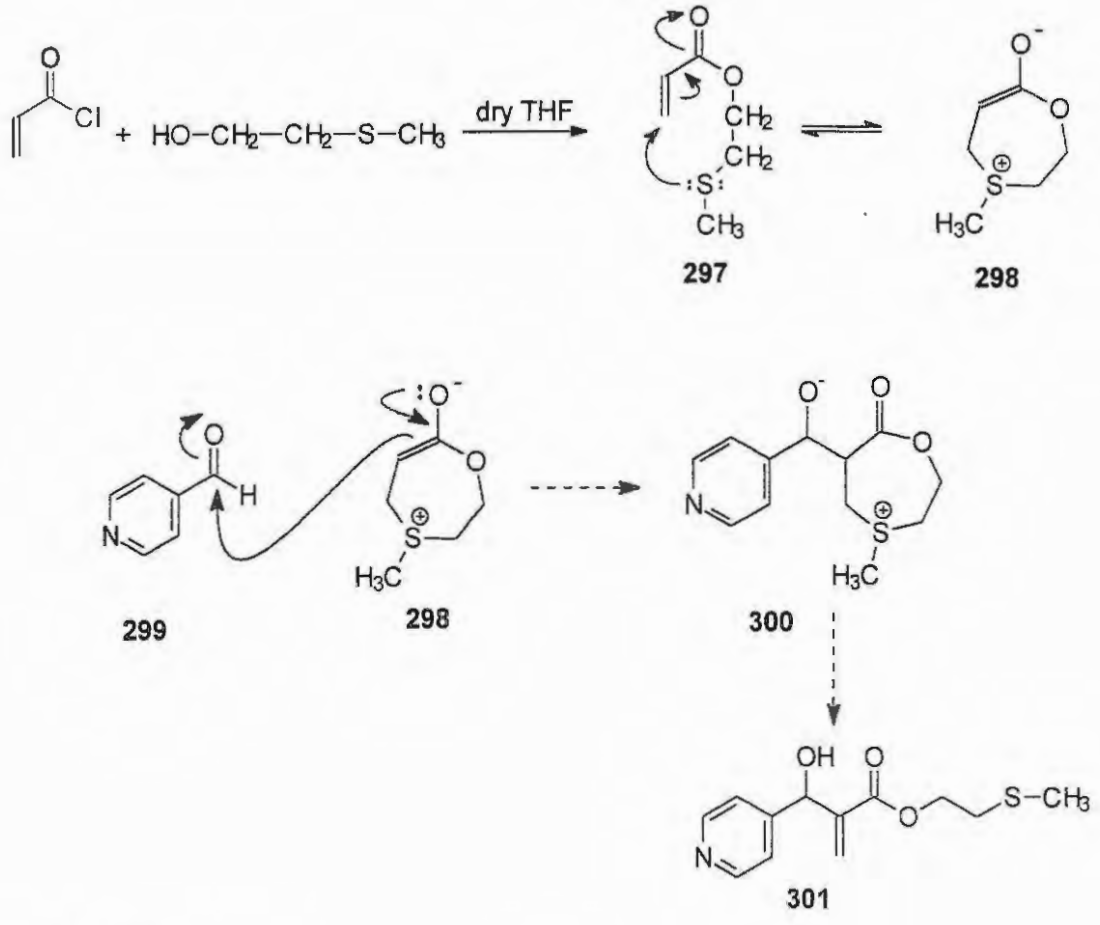
Scheme 62

Preliminary semi-empirical molecular orbital studies[139] have indicated, on the basis of heat of formation data, that the equilibrium constant K_1 is likely to be exceedingly small. Any increase in K_1 would increase the concentration of the Baylis-Hillman zwitterion **273** and, hence, increase the rate of reaction. It was anticipated that incorporation of the catalyst into the substrate would permit *intramolecular* catalysis, the resulting entropic advantage increasing K_1, as illustrated in Scheme 63.



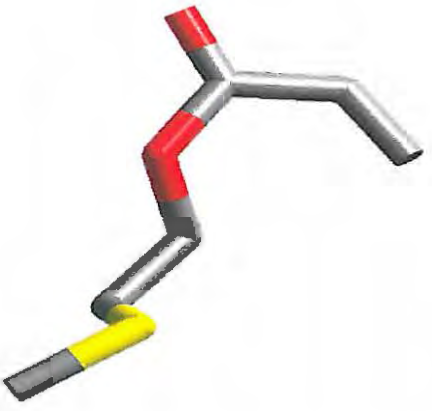
Scheme 63

The first step in exploring this approach was to synthesise the methylthioethyl acrylate ester **297**. This was achieved by treating acryloyl chloride with 2-(methylsulfanyl)ethanol in dry THF under nitrogen. The ester **297** was expected to be in equilibrium with its cyclic dipolar form **298** which, in the presence of pyridine-4-carbaldehyde **299**, would acts as a nucleophilic enolate to afford the zwitterion **300**. Proton transfer and subsequent ring-opening would then afford the Baylis-Hillman product **301** (Scheme 64). (Nitrogen and phosphorus analogues of the ester **297** were examined in cognate studies within the group).

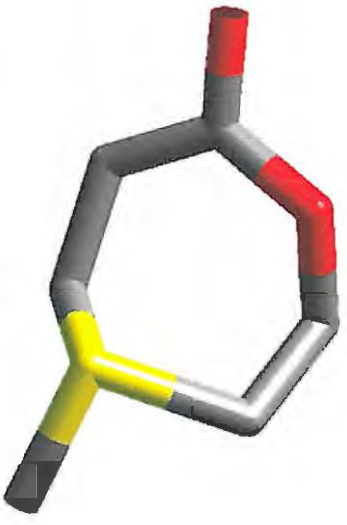


Scheme 64

When the ester **297** was treated with pyridine-4-carbaldehyde **299**, however, no reaction was observed, and an attempt to accelerate the reaction using the microwave irradiation was unsuccessful. In a further attempt, acetaldehyde was used instead of pyridine-4-carbaldehyde, but similar results were obtained. Formation of the cyclic, zwitterionic ester **298** would, of course involve formation of a 7-membered ring which is expected to be less stable due to conformational strain. Somewhat, surprisingly the computer modelling (Figure 26) indicated a global minimum of -59.5 kcal/ mol for compound **298**, and 4.13 kcal / mol for the acyclic system **297**.



297

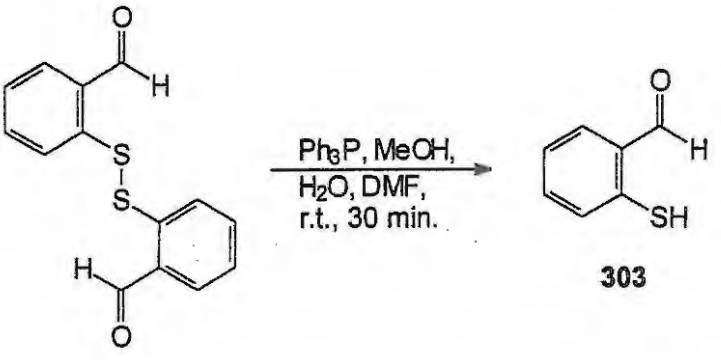


298

Figure 26. Energy-minimised structures of the ester **297** and the cyclic derivative **298**.

2.6 APPLICATION OF THE BAYLIS-HILLMAN REACTION IN THE SYNTHESIS OF THIOCHROMENES

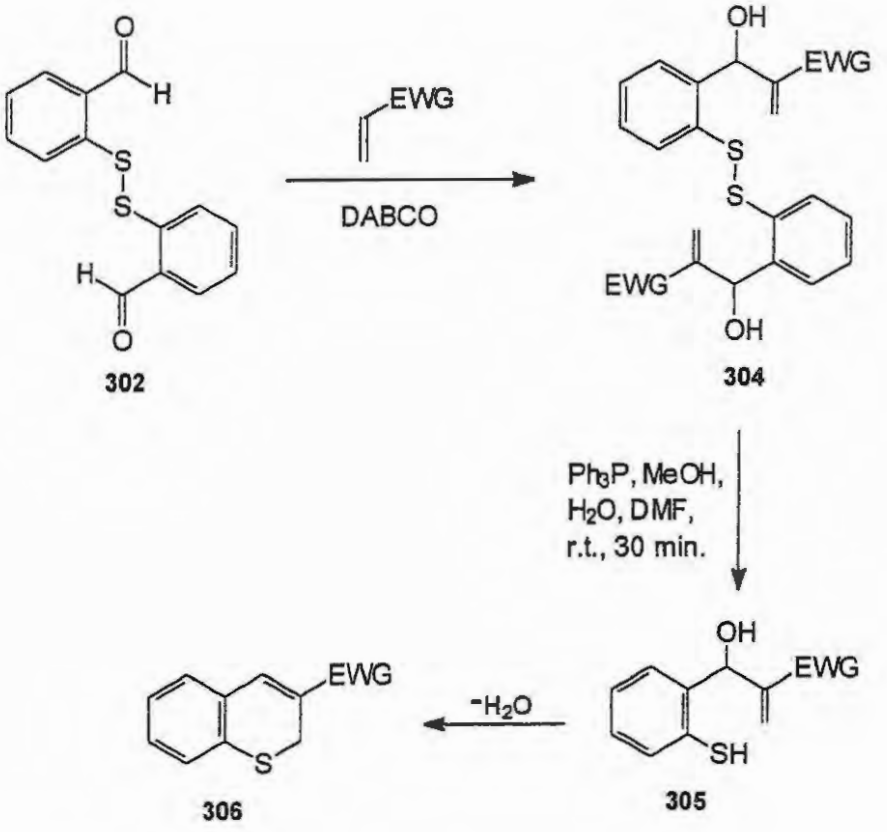
Following the successful application of the Baylis-Hillman reaction to the synthesis of chromene derivatives, the methodology was extended to the preparation of thiochromene analogues. The proposed synthesis was expected to involve treatment of 2-mercaptobenzaldehyde **303** with α,β-unsaturated vinyl systems in the presence of DABCO. A synthesis of 2-mercaptobenzaldehyde **303**, reported by Kasmai and Mischke,[140] proceeds *via* the formation of the disulphide intermediate, 2,2'-dithiobenzaldehyde **302**, which, upon reduction with triphenyl phosphine, affords the required 2-mercaptobenzaldehyde (Scheme 65).



302 **303**

Scheme 65

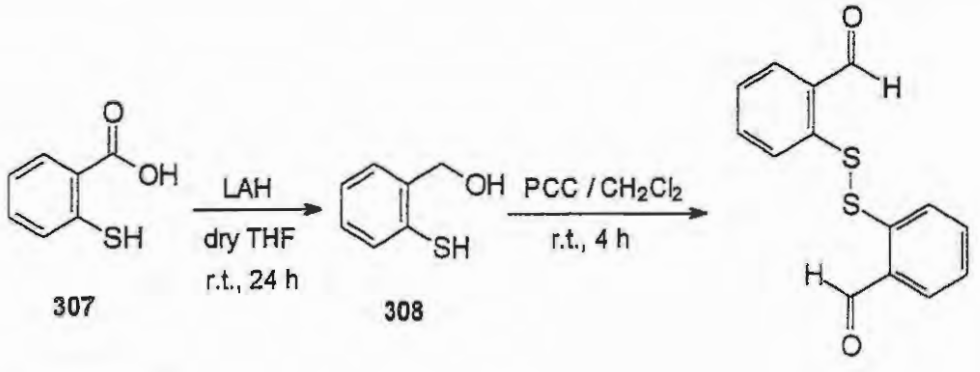
In our study, it was decided to use the disulphide **302**, instead of 2-mercaptobenzaldehyde, as the substrate, since this was expected to permit isolation of dimeric Baylis-Hillman products **304** in which the mercapto group is effectively protected (Scheme 66). Cleavage of the S-S bond using the method developed by Kasmai and Mischke[140] would then afford the monomeric Baylis-Hillman products **305**, which should undergo intramolecular cyclisation to afford the thiochromene derivatives **306**.



Scheme 66

2.6.1 Synthesis of 2,2'-dithiobenzaldehyde

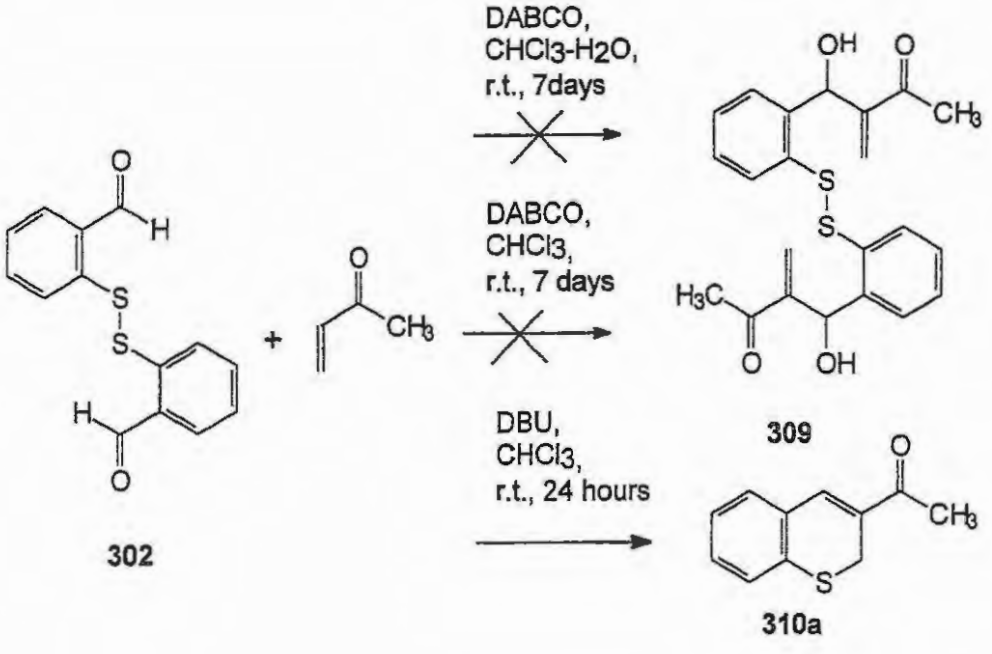
Commercially available thiosalicylic acid **307** was reduced, following the method reported by Arnoldi and Carughi,[89] which involves treatment with lithium aluminium hydride in dry THF, to afford the benzyl alcohol **308** in 72 % (Scheme 67). The alcohol **308** was then oxidised, following the method reported by Kasmai and Mischke;[140] this involved controlled oxidation using pyridinium chlorochromate (PCC) to afford 2,2'-dithiobenzaldehyde **302** in 54 % yield.



Scheme 67

2.6.2. Synthesis of thiochromene derivatives

In an attempt to synthesise the Baylis-Hillman dimer **309**, following the synthetic methodology established in Section 2.2.1, a mixture of methyl vinyl ketone, 2,2'-dithiobenzaldehyde **302** and DABCO in H_2O-$CHCl_3$ was stirred vigorously at room temperature for 7 days (Scheme 68). The resulting crude mixture was purified by flash- and preparative layer chromatography but none of the fractions appeared to contain the expected product. The reaction was repeated without water, but gave the same results. However, when 2,2'-dithiobenzaldehyde **302** was treated with methyl vinyl ketone in the presence of the catalyst, DBU, in chloroform, 3-acetylthiochromene **310a** was isolated in 59 % yield. The reaction was monitored by ^{1}H NMR spectroscopy and found to be complete within 24 hours, as evidenced by the disappearance of the aldehydic proton signal at *ca.* 10.2 ppm. Formation of the thiochromene **310a** was confirmed by one- and two-dimensional NMR spectroscopy and high-resolution mass spectrometry. The ^{1}H NMR spectrum of 3-acetylthiochromene **310a**, illustrated in Figure 27a, reveals the 2-methylene proton signal at 3.72 ppm and the methyl proton signal at 2.45 ppm, while in the ^{13}C NMR spectrum (Figure 27b) the C-2 nucleus resonates at 22.9 ppm and methyl carbon at 25.3 ppm. The HMQC spectrum (Figure 28) confirms the foregoing assignments.



Scheme 68

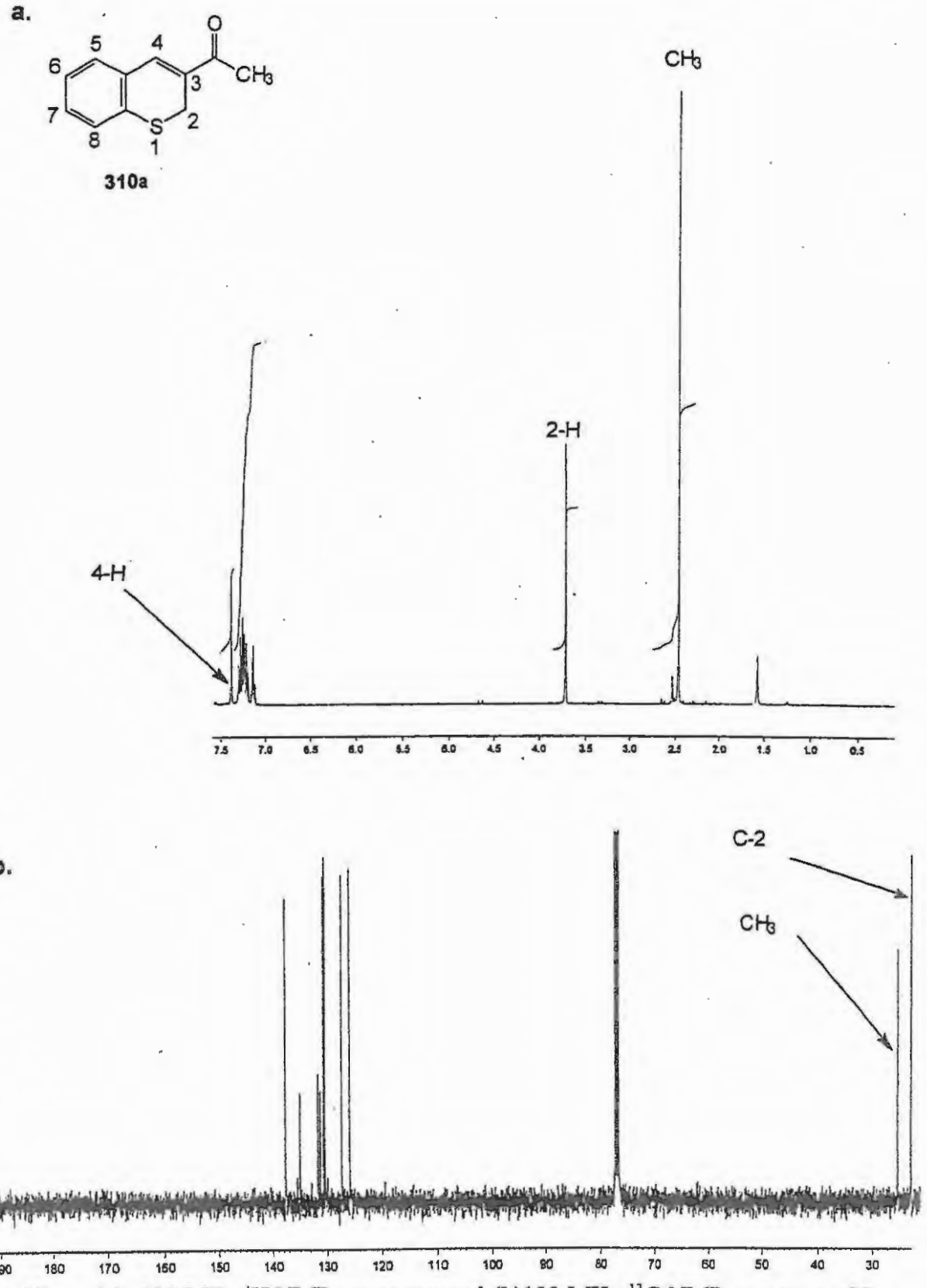


Figure 27. (**a**) 400 MHz ^{1}H NMR spectrum; and (**b**)100 MHz ^{13}C NMR spectrum of 3-acetyl-2*H*-1-thiochromene **310a** in $CDCl_3$.

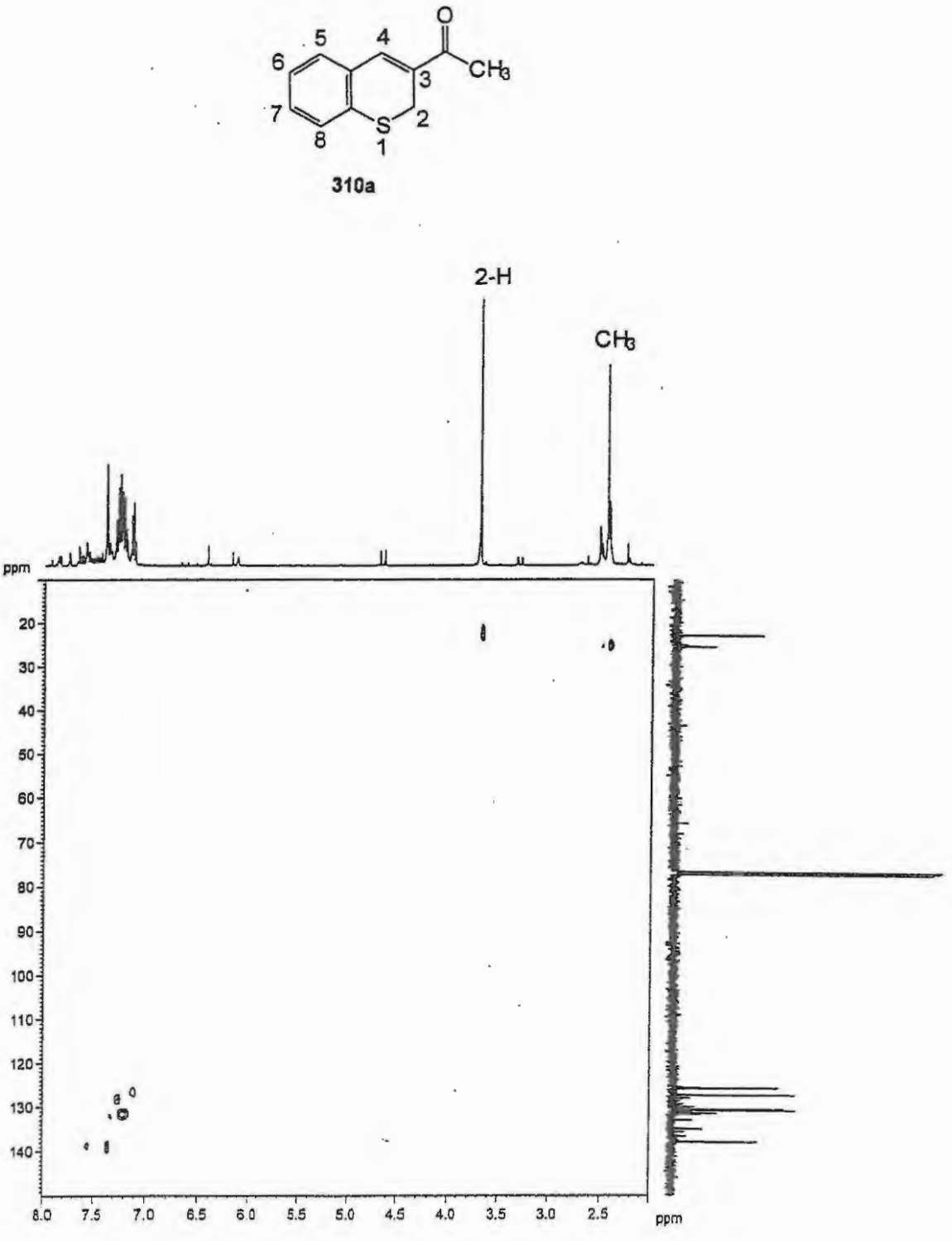
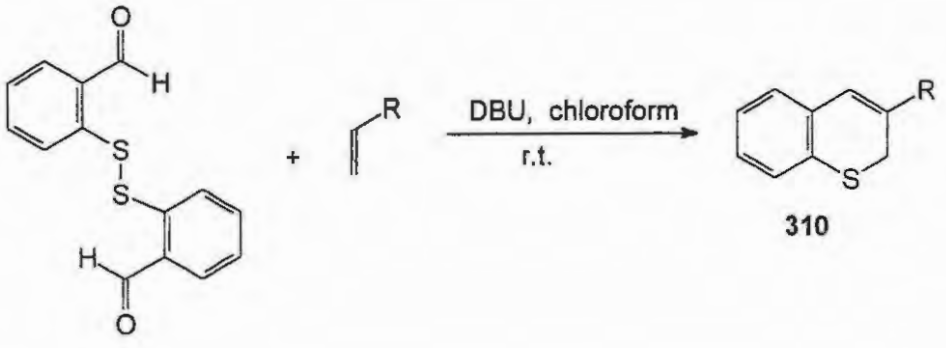


Figure 28. The HMQC spectrum of 3-acetyl-2*H*-1-thiochromene **310a** in $CDCl_3$.

The method was then extended by treating 2,2'-dithiobenzaldehyde **302** with a range of activated alkenes. In most of the reactions examined, the corresponding thiochromenes were obtained in moderate yields after 24 hours (Table 7), but the reaction with acrolein afforded an intractable mixture. In the case of ethyl vinyl ketone, a longer reaction time (48h) was necessary, while the reaction with ethyl acrylate failed to afford the expected product after 48 hours, and the mixture was stirred for a longer period (14 days) to give the thiochromene **310h** in 56 % yield. Surprisingly, the reactions between 2,2'-dithiobenzaldehyde and the esters, methyl acrylate and ethyl acrylate, afforded no traces of the thiocoumarins analogues. It may be that steric crowding with the larger sulfur atom (compared to oxygen) inhibits attack at the acyl carbon, and cyclisation *via* the less hindered vinylic centre is favoured.

Table 7. Data for the synthesis of 2*H*-thiochromene derivatives



302 **310**

Comp.	R	Reaction time	Yield [a]%
310a	COMe	24 hours	59
310b	CHO	24 hours	-
310c	COEt	48 hours	67
310d	SO_2Ph	24 hours	50
310e	SO_3Ph	24 hours	55
310f	CN	24 hours	52
310g	CO_2Me	24 hours	40
310h	CO_2Et	14 days	56

[a]Chromatographed material

It is apparent that, under the reaction conditions used, cleavage of the disulphide link occurs spontaneously, but it is not yet clear at what stage in the reaction this occurs. However, it seems likely that the mechanism of these reactions involves initial formation of the dimeric Baylis-Hillman products **304** (Scheme 66). Cleavage of the S-S bond and intramolecular cyclisation *via* the conjugate addition pathway would then account for the thiochromene product.

2.7 MASS SPECTROMETRIC STUDIES OF CHROMENE AND THIOCHROMENE DERIVATIVES

The electron-impact (EI) mass spectra of selected chromene and thiochromene derivatives were investigated, and the fragmentation patterns have been elucidated using high-resolution mass spectrometry and metastable peak analysis. Proposed fragmentation pathways for the chromene derivatives will be followed by an analysis of the thiochromene analogues. The analyses are not intended to be exhaustive but, rather, focus on major peaks in the various spectra.

The mass spectrum of 3-acetyl-2*H*-1-chromene **251a** is illustrated in Figure 29, and the proposed mass fragmentation patterns are outlined in Scheme 69.

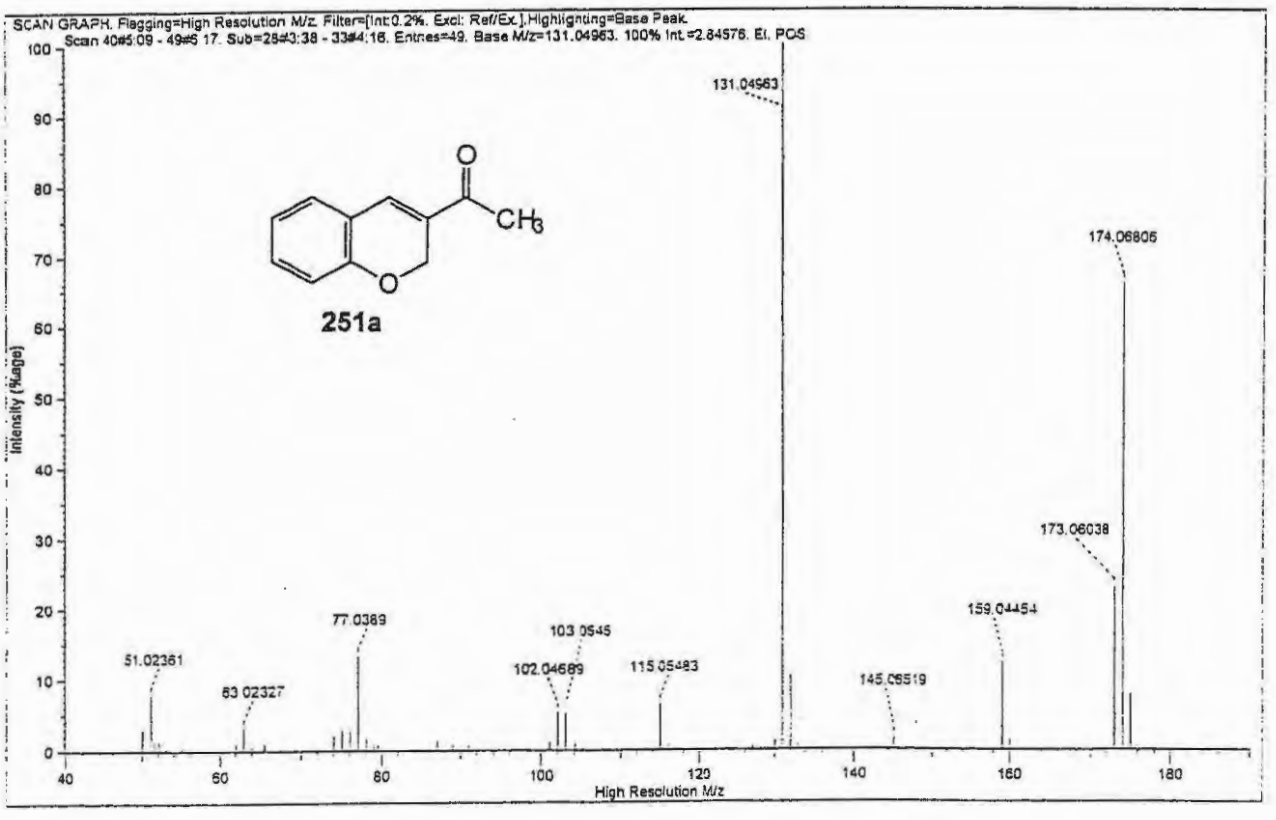
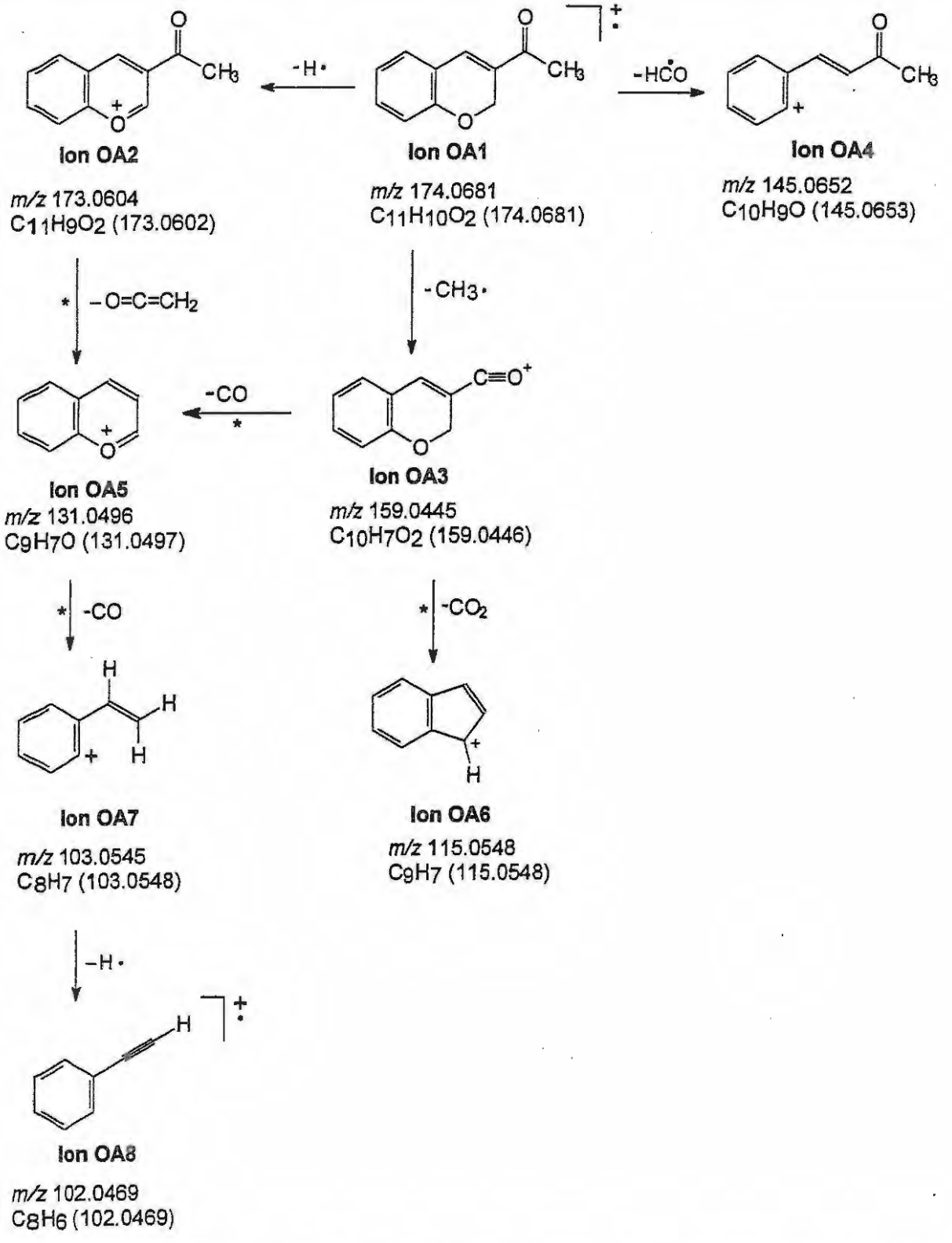


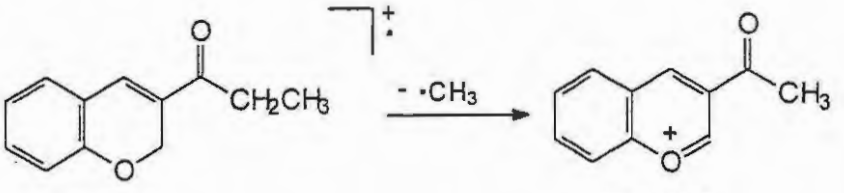
Figure 29. High-resolution EI mass spectrum of 3-acetylchromene **251a**.



Scheme 69. Proposed EI mass fragmentation pathways for 3-acetyl-2*H*-1-chromene **251a**; high-resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable peak data.

Loss of a hydrogen atom from the chromene ring of the molecular ion affords the benzopyrylium cation **OA2**[#] (Scheme 69)- a known fragmentation in 2*H*-1-chromene systems.[141,142,143] Loss of the neutral molecule, ketene, from ion **OA2** then accounts for the formation of ion **OA5**, which is responsible for the base peak, the fragmentation being supported by metastable peak data. Ion **OA5** also appears to be formed *via* decarbonylation of the resonance-stabilised acylium cation **OA3** (*i.e.* **OA1** → **OA3** → **OA5**). Elimination of carbon dioxide from the acylium ion **OA3** would account for the resonance-stabilised indanyl cation **OA6**, while loss of carbon monoxide from ion **OA5** to form the cation **OA7** has been reported previously[142] and is supported, in this case, by the metastable peak data; subsequent loss of a hydrogen atom then gives the radical cation **OA8**. The molecular ion may also lose a formyl radical to produce the cation **OA4**.

Not surprisingly, the mass fragmentation patterns observed for 3-acetyl-2*H*-1-chromene **251a** are very similar to those of its homologue, 3-propanoyl-2*H*-1-chromene **251c**. An additional fragmentation arising from loss of a methyl radical from the molecular ion **OC1** is observed at *m/z* 173 (Scheme 70). The proposed fragmentation patterns for the remaining chromene derivatives **251d-f, k** and thiochromene derivatives **310a, c-f** are outlined in Schemes 71 to 79.



Ion OC1
m/z 188.0835
$C_{12}H_{12}O_2$ (188.0837)

Ion OC2
m/z 173.0604
$C_{11}H_9O_2$ (173.0602)

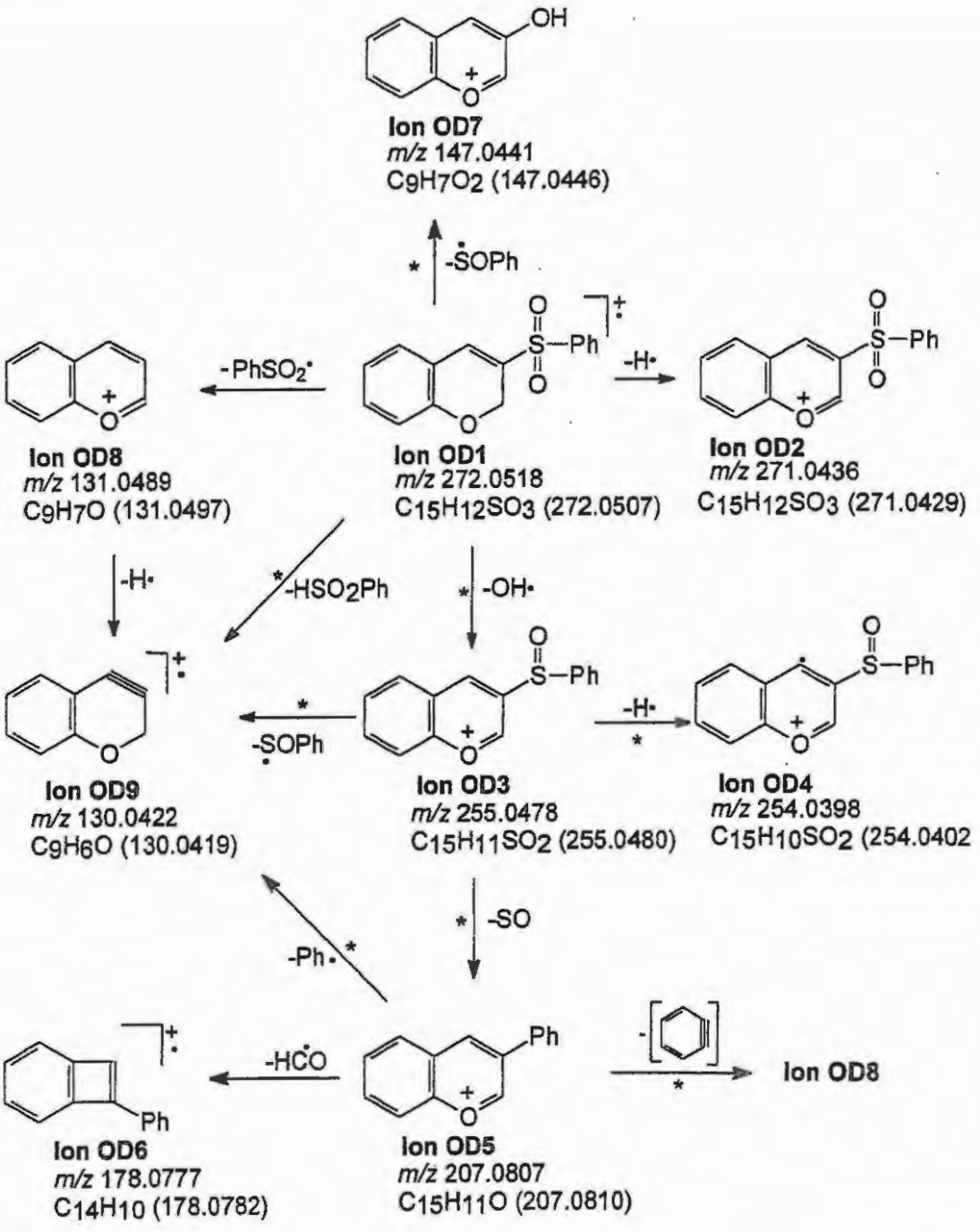
Scheme 70

[#]The prefix letter 'O' indicates a chromene system (as apposed to the use of 'S' for thiochromene analogues); the letter 'A' refers to the fact that this and other fragments in the Scheme arise from compound **251a**.

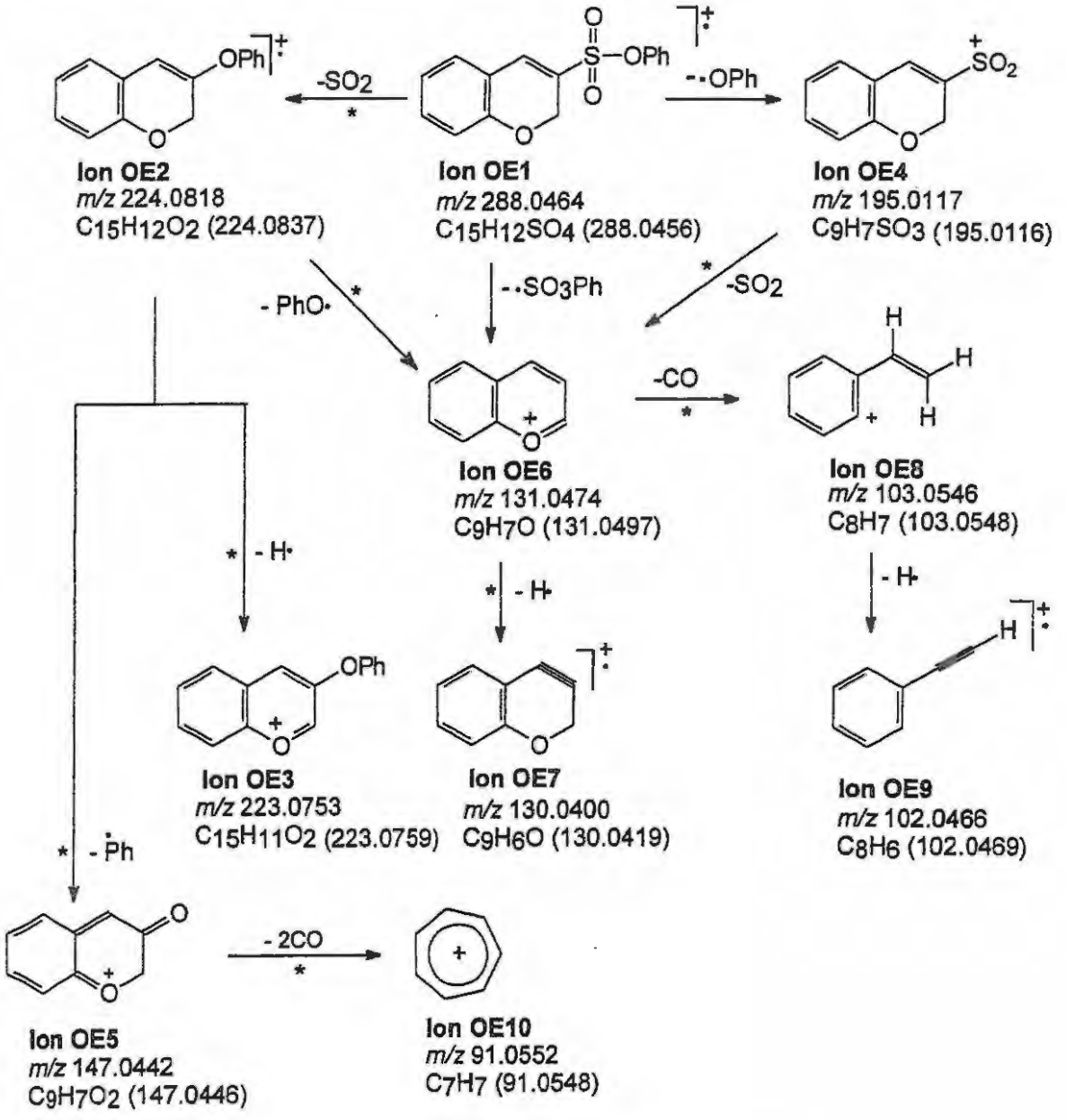
Scheme 71 illustrates the proposed fragmentation patterns for 3-phenylsulfonylchromene **251d**, some of which appear to be rather different from those proposed for 3-acetylchromene (Scheme 69). Such fragmentations include loss of a hydroxyl group from the molecular ion **OD1** to afford the benzopyrilium cation **OD3**, and loss ·SOPh to afford the 3-hydroxybenzopyrilium cation **OD7**. The benzopyrilium motif appears to be common, and is also present in fragments **OD2**, **OD5** and **OD8**.

In the case of phenyl chromene-3-sulphonate **251e** (Scheme 72), the loss of the neutral molecule, sulphur dioxide, from the molecular ion affords the radical cation **OE2**. The characteristic benzopyrilium species **OE3** and **OE6** are evident, as are two fragments observed in the spectrum of 3-acetylchromene **251a** (Scheme 69), *viz.*, the vinylbenzene cation **OE8** and the phenylacetylene radical cation **OE9**. Also of significance are the benzyne radical cation **OE7** [present as ion **OD9** in the spectrum of 3-phenylsulfonylchromene **251d** (Scheme 71)] and the tropylium cation **OE10**, which is proposed to arise from the ketonic cation **OE5**.

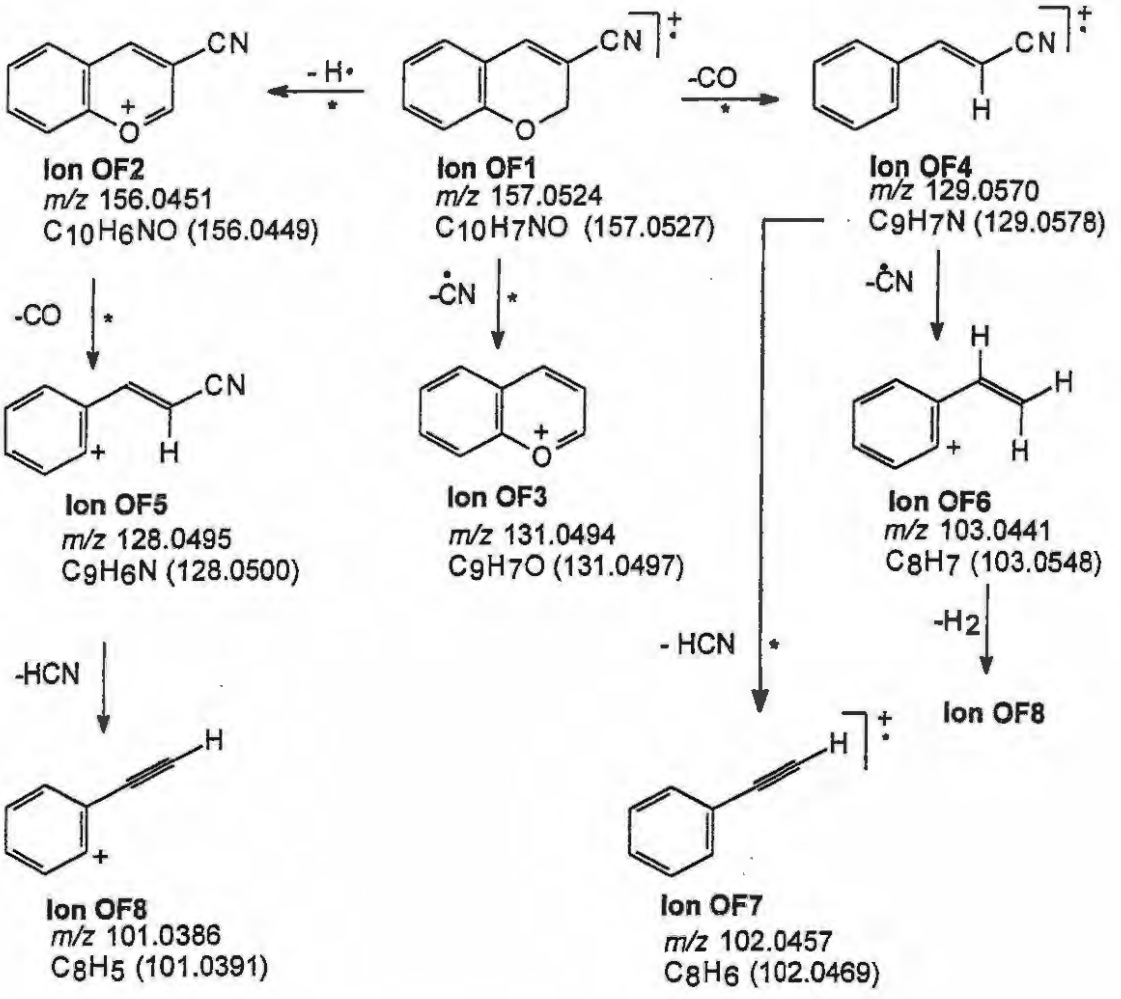
The fragments proposed for 3-cyanochromene **251f** are illustrated in Scheme 73, and appear to be rather similar to those observed for 3-acetylchromene **251a**. In the case of 3-cyanochromene **251f**, however, additional, decarbonylation processes appear to account for the formation of fragments **OF4** and **OF5**, while loss of ·CN leads to the even-electron species **OF3** and **OF6**. Not surprisingly, some of the fragmenation patterns observed for 3-acetyl-6-bromochromene **251k** (Scheme 74) appear to parallel those of 3-acetylchromene **251a**; however, elimination of the 6-bromo substituent leads to the formation of cation **OK4**.



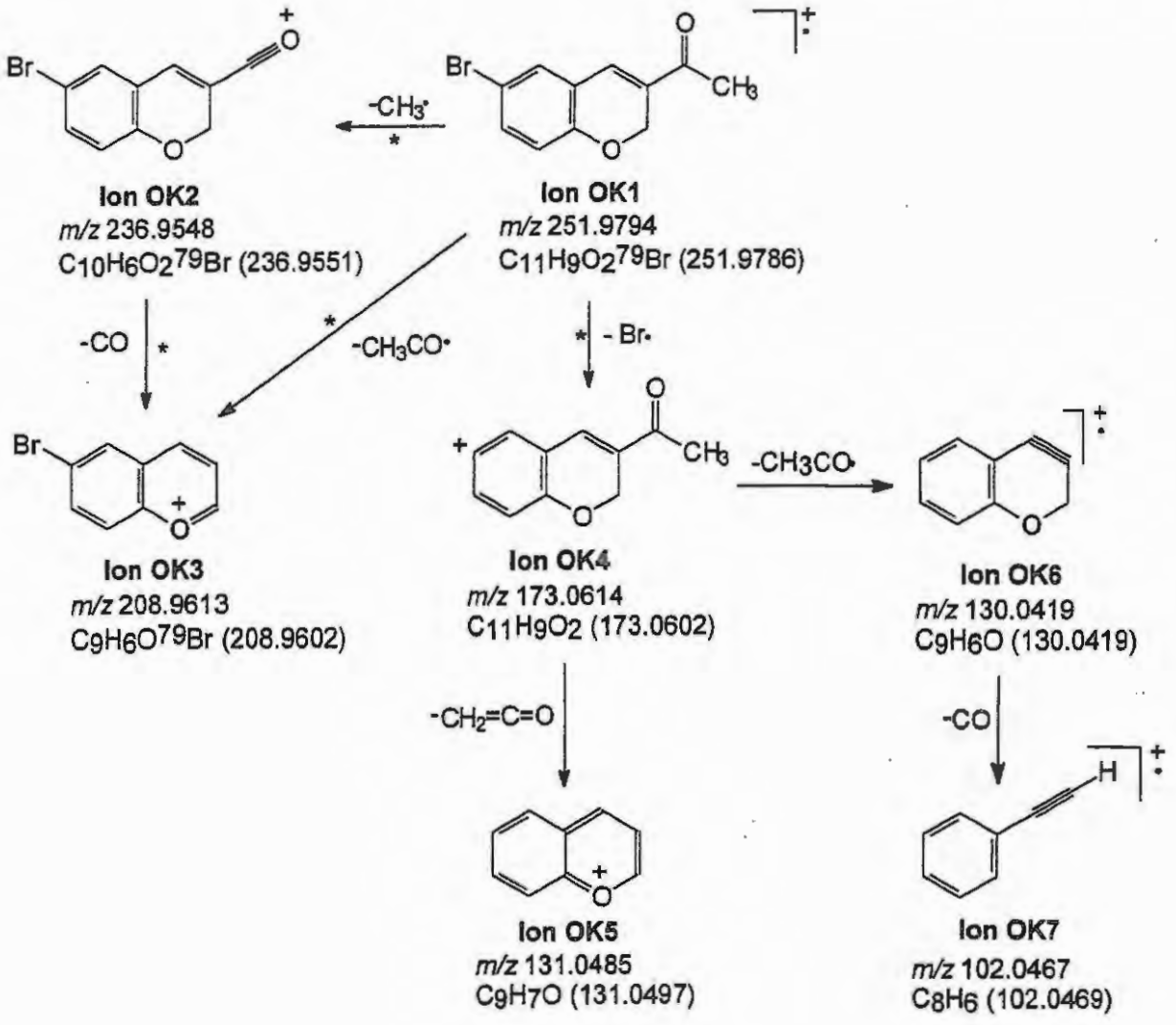
Scheme 71. Proposed EI mass fragmentation pathways for 3-phenylsulfonyl-2*H*-1-chromene **251d**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.



Scheme 72. Proposed EI mass fragmentation pathways for phenyl 2*H*-1-chromene-3-sulfonate **251e**, high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.



Scheme 73. Proposed EI mass fragmentation pathways for 3-cyano-2*H*-1-chromene **251f**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.

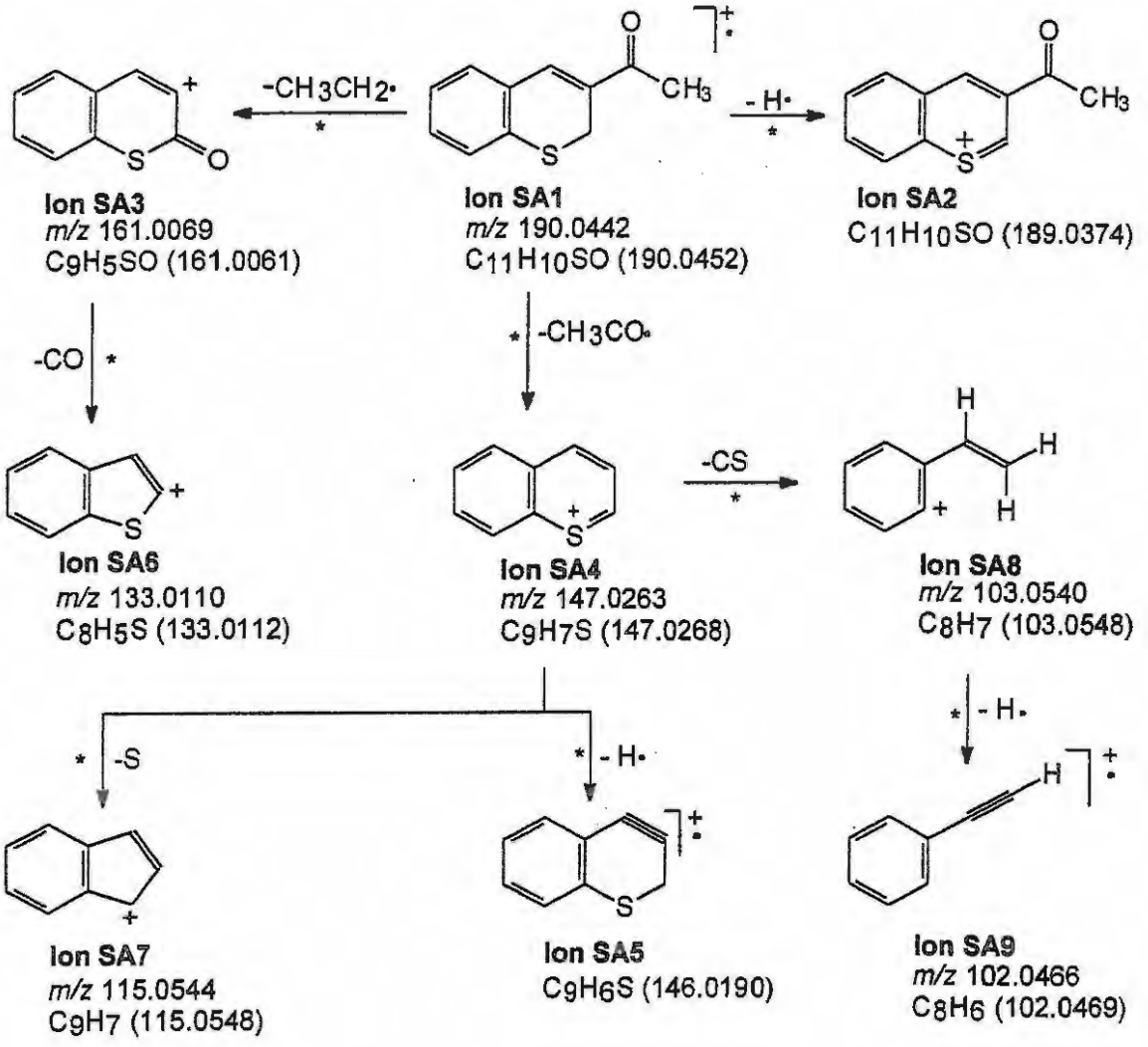


Scheme 74. Proposed EI mass fragmentation pathways for 3-acetyl-6-bromo-2*H*-1- chromene **251k**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.

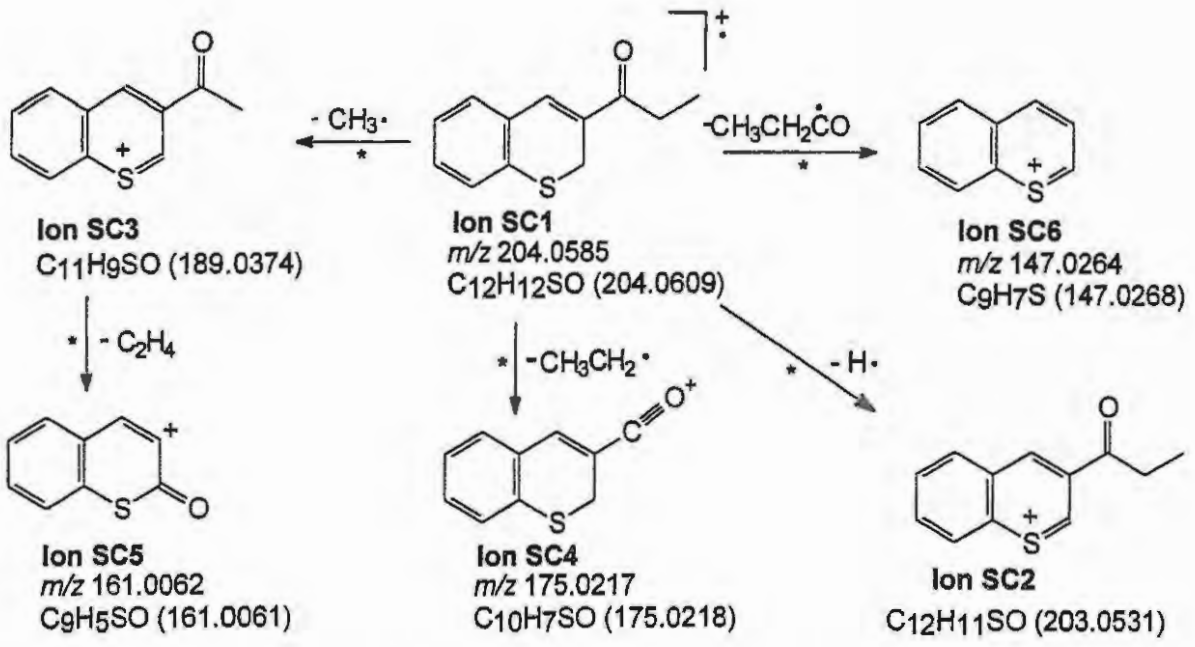
Almost all of the fragments proposed for 3-acetylthiochromene **310a** (Scheme 75) find parallels with those observed in the mass spectra of the various chromenes examined. Two exceptions involve the apparent loss of C_2H_5· (as an ethyl radical ?) from the molecular ion **SA1** to afford an ion formulated as the thiocoumarin species **SA3**, and the subsequent extrusion of CO to give ion **SA6**. Like its oxygen-containing analogue **251c**, 3-propanoylthiochromene **310c** exhibits loss of a methyl radical to afford the corresponding benzo(thio)pyrilium cation **SC3** and loss of an ethyl radical to afford the corresponding acylium ion **SC4** (Scheme 76). The thiocoumarin species **SC5** is also apparent in the mass spectrum of the 3-acetyl analogue **310a**.

Scheme 77 illustrates the proposed fragmentation patterns for 3-phenylsulfonythiochromene **310d**, some of which are analogous to those proposed for 3-phenylsulfonylchromene **251d** (Scheme 71). Similarly for phenyl thiochromene-3-sulfonate **310e** (Scheme 78), many of the fragments correspond to those proposed for the oxygen-containing analogue **251e** (Scheme 72). The fragment formulated as the ring-contracted cation **SE7** is also evident in the mass spectrum of the sulfone **310d** (Scheme 77), while the indanyl cation **SE6**, generated in this case, by extrusion of sulfur from the cation **SE4**, also appears to be produced in the mass spectra of some of the chromene derivatives.

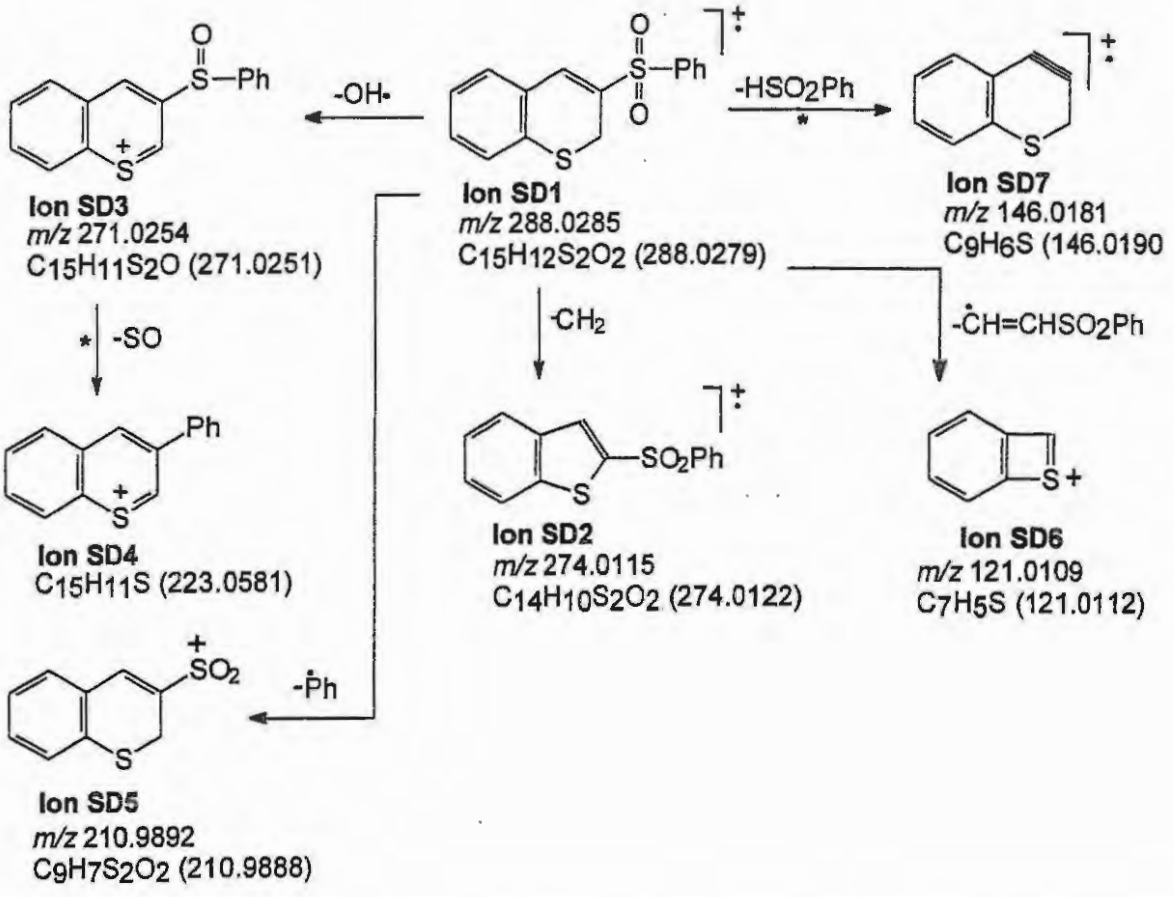
In Scheme 79, the fragmentation patterns proposed for 3-cyanothiochromene **310f** show some similarities to those of 3-cyanochromene **251f** and other chromene derivatives; however, loss of an SH· radical to afford the indanyl cation **SF6** does not appear to be paralleled by loss of OH· in the case of the chromene **251f**.



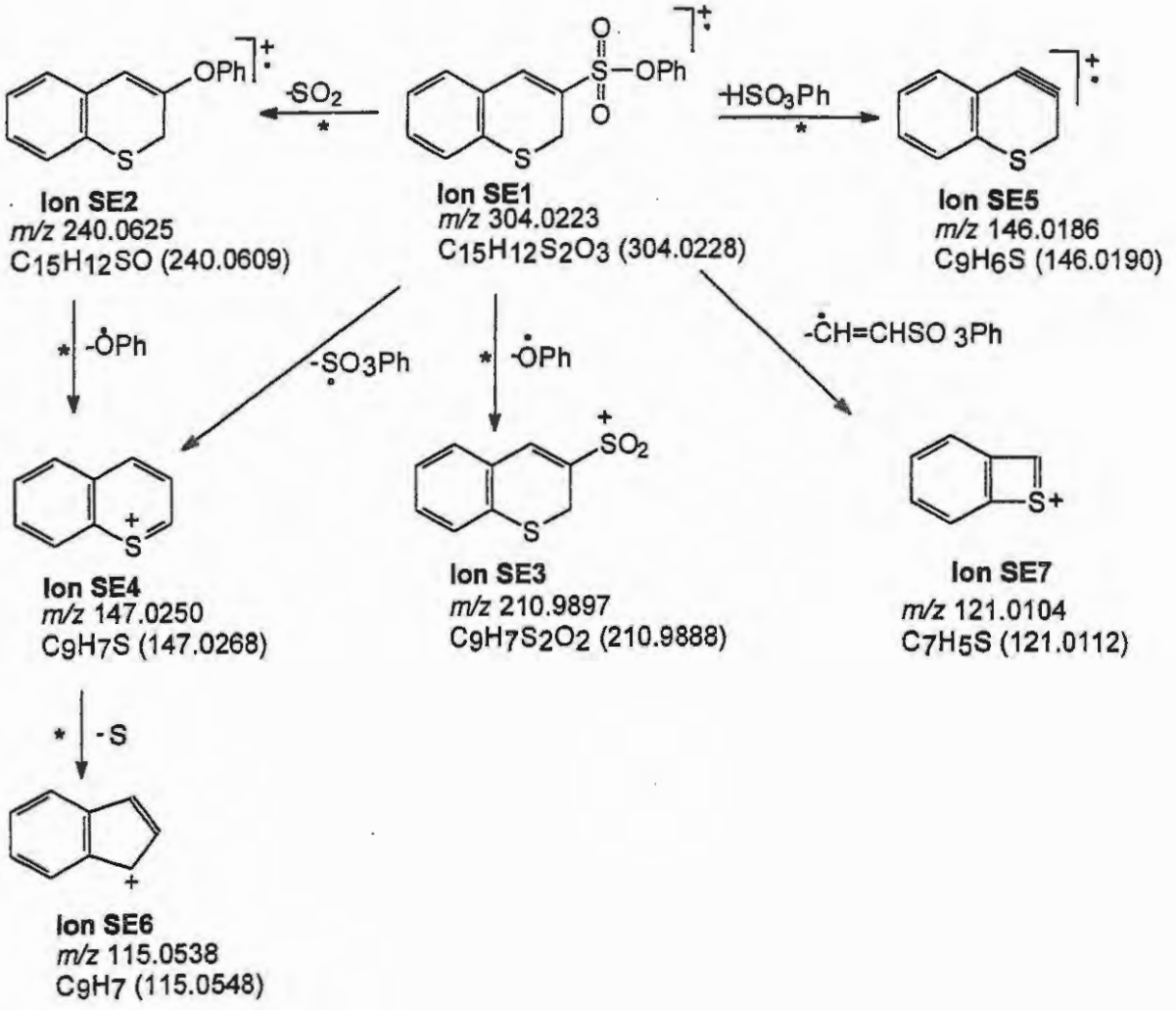
Scheme 75. Proposed EI mass fragmentation pathways for 3-acetyl-2*H*-1-thiochromene **310a**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses, an asterisk indicates a pathway supported by metastable data.



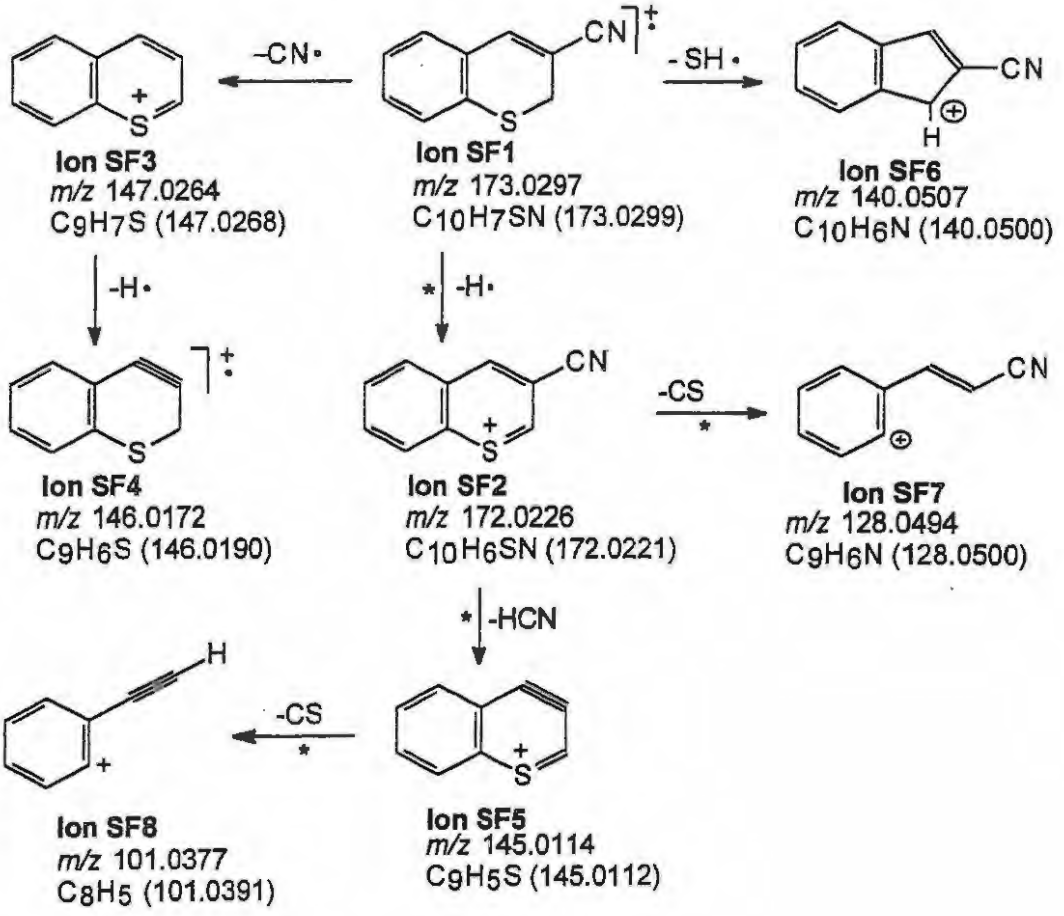
Scheme 76. Proposed EI mass fragmentation pathways for 3-propanoyl-2*H*-1- thiochromene **310c**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.



Scheme 77. Proposed EI mass fragmentation pathways for 3-phenylsulfonyl-2*H*-1-thiochromene **310d**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.

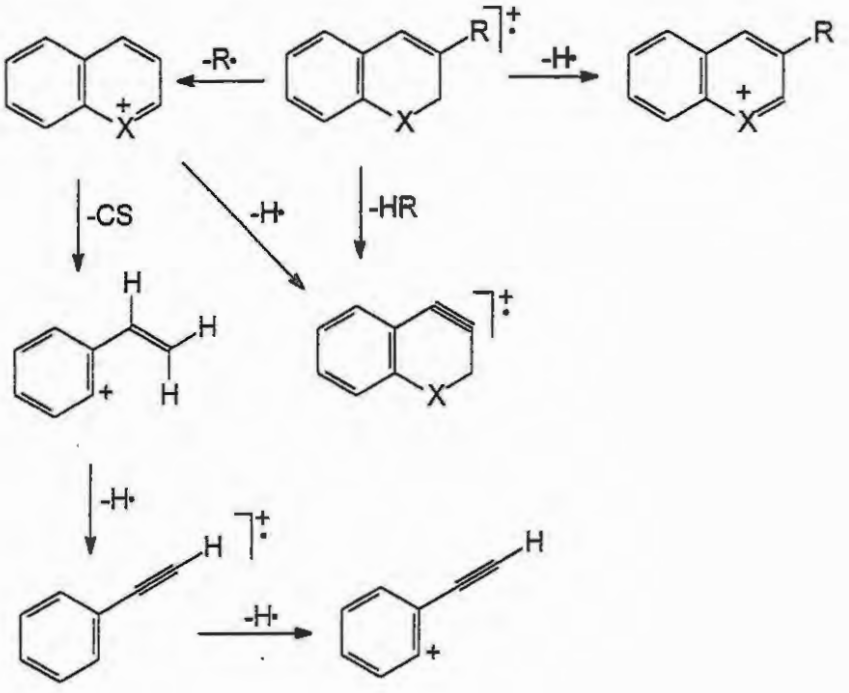


Scheme 78. Proposed EI mass fragmentation pathways for phenyl 2*H*-1-thiochromene-3-sulfonate **310e**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.



Scheme 79. Proposed EI mass fragmentation pathways for 3-cyano-2*H*-1-thiochromene **310f**; high resolution data (*m/z*) are followed, in parentheses, by calculated formula masses; an asterisk indicates a pathway supported by metastable data.

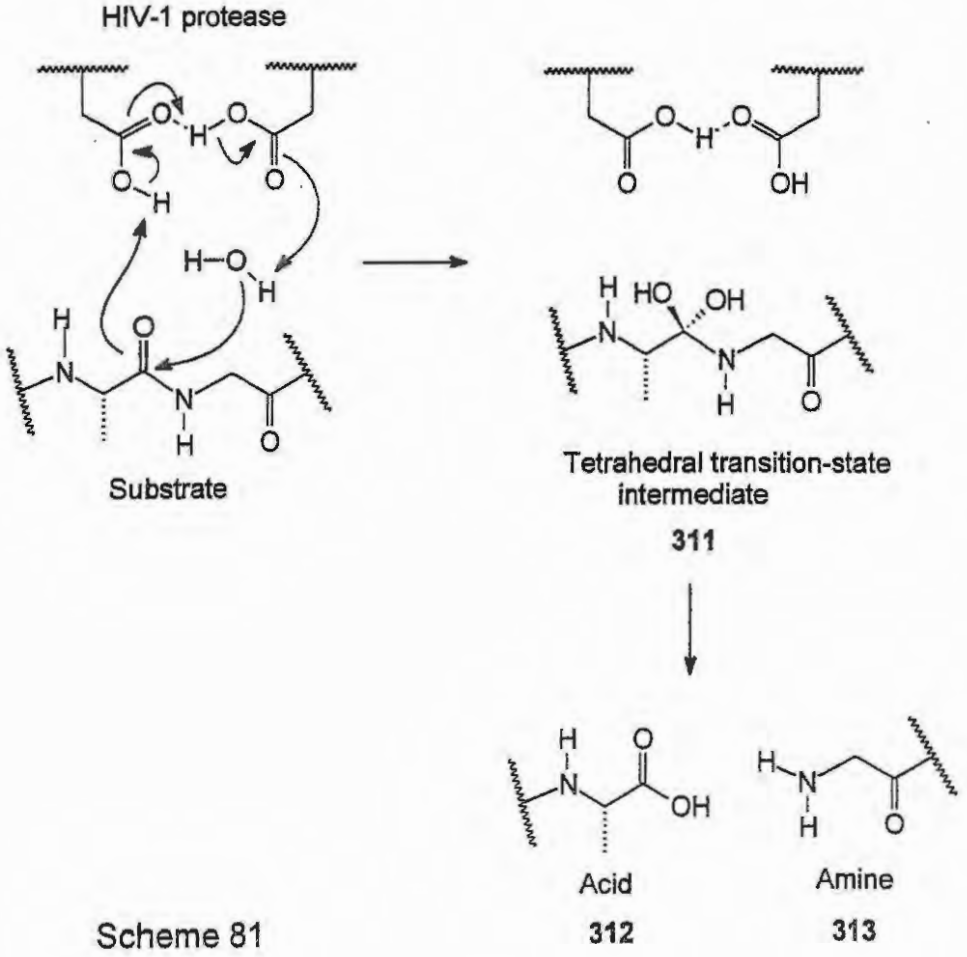
Examination of the fragmentation pathways proposed in Schemes 69 - 75 reveals a number of close correlations between the patterns observed for the chromene and their thiochromene analogues. Not surprisingly, however, certain fragmentations appear to be heteroatom-specific. Fragmentation patterns which appear to be common for both chromene and thiochromene derivatives are outlined in Scheme 80. Loss of a hydrogen atom or the 3-substituent (as R·) affords resonance-stabilised benzopyrilium or benzothiopyrilium cations, while loss of CX (X = O, S) appears to provide access to vinylic and acetylenic fragments.



Scheme 80. Common EI mass fragmentations observed for the chromene and thiochromene derivative (X = O, S).

2.8 HIV-1 PROTEASE INHIBITORS

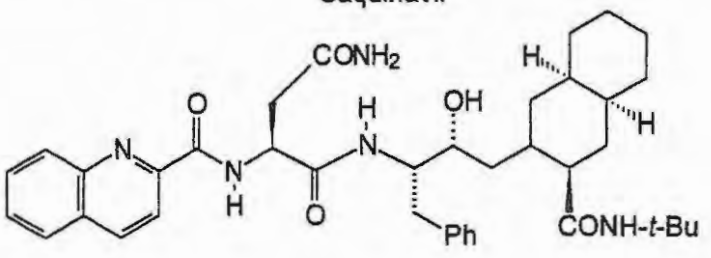
Since the human immunodeficiency virus (HIV) was identified as the cause of the acquired immune deficiency syndrome (AIDS), efforts have been made to elucidate its replication process and, hence, identify a suitable target for antiviral therapy. HIV is known to be a member of the *Lentiviridae*, a subfamily retroviruses.[144] Like other retroviruses it consists of 3 major genes, *viz*, *gag*, *pol* and *env*.[145,146,147] The *gag* and *pol* genes are expressed as polyproteins and are processed by a virally encoded aspartic acid protease (HIV-1 protease).[148,149,150,151] The HIV-1 protease acts as a "molecular pair of scissors" cutting the protein substrate; at a molecular level, it acts as a catalyst in the hydrolysis of the *gag* and *pol* precursor proteins to produce viral structural proteins.[145] Scheme 81 illustrates the proposed mechanism by which the HIV-1 protease hydrolyses and cleaves the protein substrate.[145]



Scheme 81

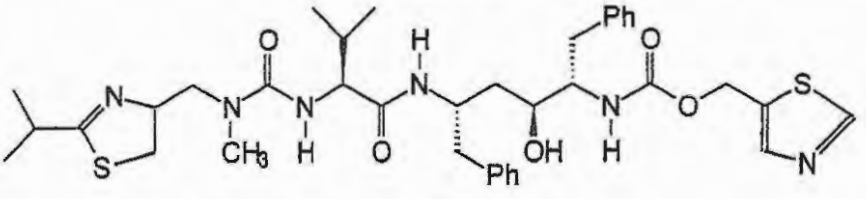
The catalytic hydrolysis of the protein substrate affords the transition state intermediate **311**, which subsequently undergoes fission to afford fragments with carboxylic acid and an amine termini. These fragments are used by the virus to build up its structural core. The disruption of this process results in the production of virions which are immature and non-infectious[152,153] and, consequently, the HIV-1 protease enzyme has been a major target for AIDS chemotherapy. Several HIV-1 protease inhibitors have been based on the transition state (**311**) mimetic concept, which is to incorporate a non-hydrolysable isostere at the P_1-P_1' cleavage site.[154,155,156] The currently approved HIV-1 protease inhibitors include saquinavir **314**, ritonavir **315**, indinavir **316** and nelfinavir **317**.[145]

Saquinavir



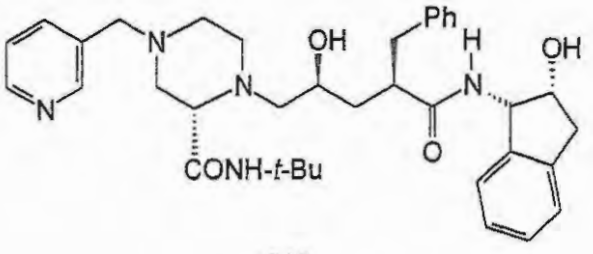
314

Ritonavir

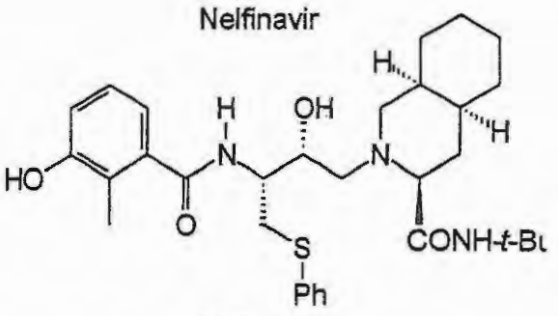


315

Indinavir



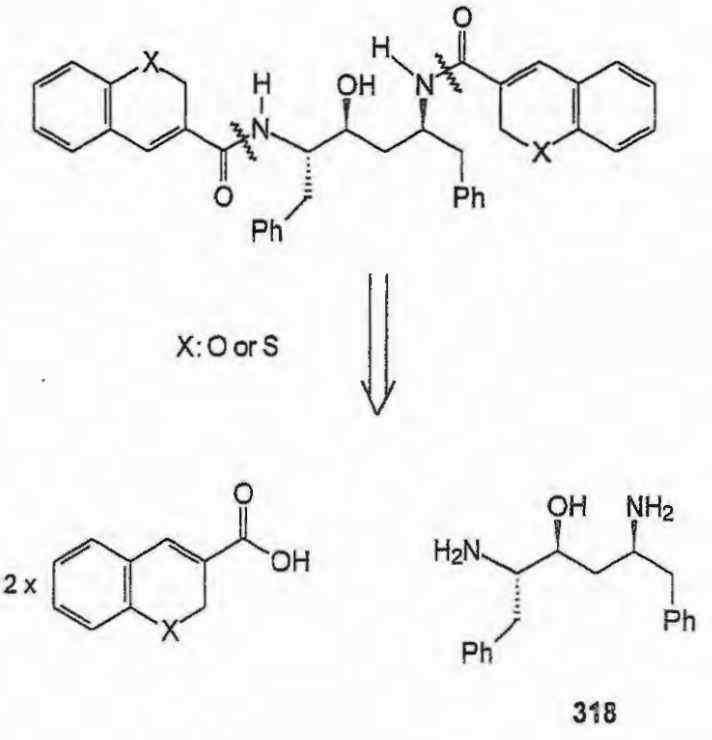
316



317

Some workers have reported that an *S*-configuration at the asymmetric carbon bearing the hydroxy group is crucial for optimum activity as an HIV-1 protease inhibitor.[157,158]

In this study, the synthesis of ritonavir analogues, containing chromene and thiochromene termini was investigated. Ritonavir and its clinically useful analogues contain a hydroxyethylene dipeptide "back-bone". The strategy which we adopted was to synthesise the hydroxyethylene dipeptide isostere **318**, which could then be coupled to carboxylic acid derivatives of chromene and thiochromene systems to afford the required ritonavir analogues as illustrated in the retrosynthetic analysis (Figure 30).

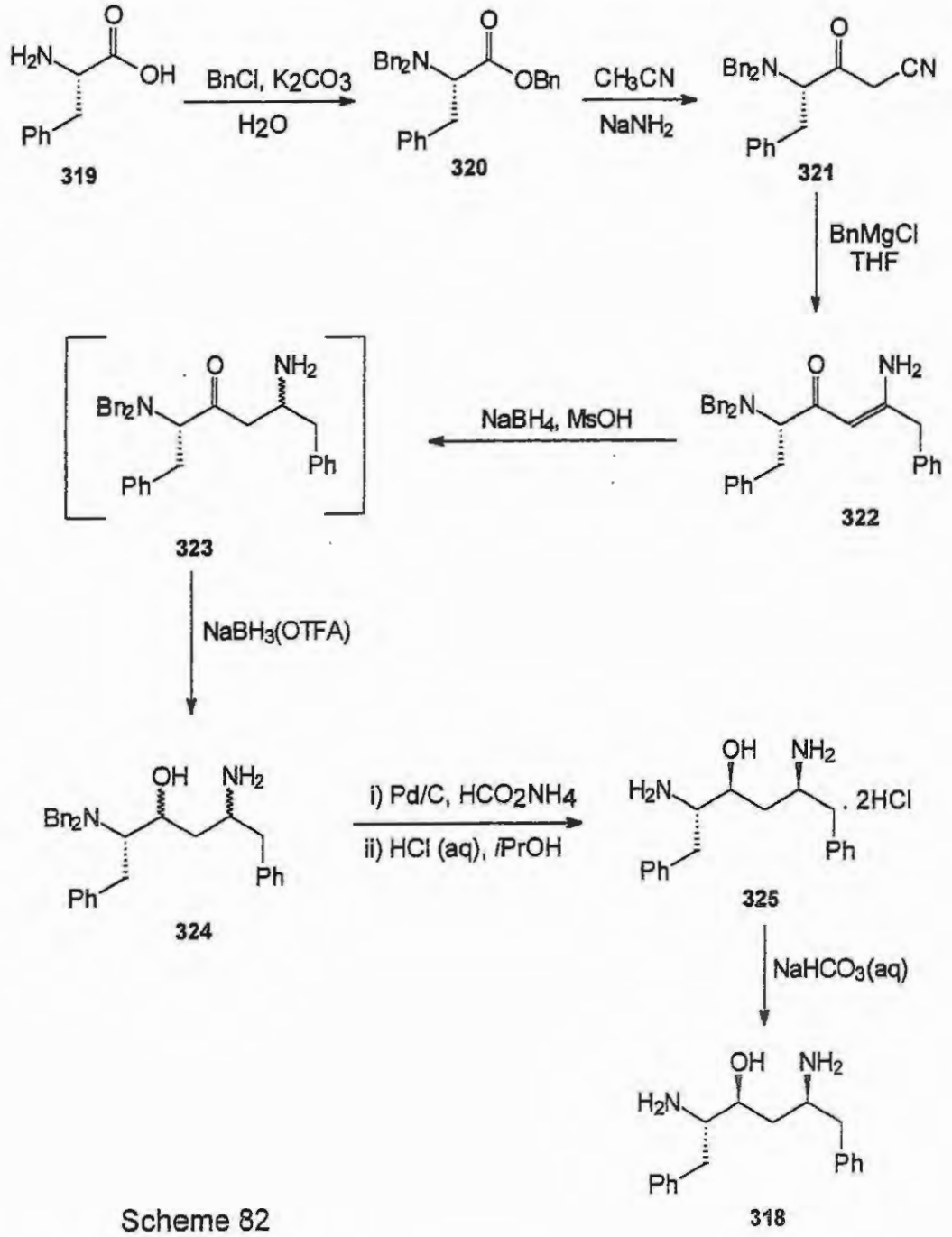


318

Figure 30

2.8.1 Synthesis of the hydroxyethylene dipeptide isostere

The synthetic methodology reported by Stuk *et al.*[159] was used to synthesise the hydroxyethylene dipeptide isostere **318** (Scheme 82). The synthesis begins with commercially available L-phenylalanine **319**. In order to ensure that the reduction of the carbonyl group would afford the required alcohol, it was necessary to protect the adjacent amino group as to inhibit chelation-controlled addition. Such protection was achieved by treating L-phenylalanine **319** with benzyl



319 **320** **321** **322** **323** **324** **325** **318**

Scheme 82

chloride under basic conditions to give the tribenzylated derivative **320**. The cyanomethyl ketone **321** was obtained by acyl substitution using the acetonitrile-derived anion in THF at - 40 °C. (The temperature and mode of addition are important in minimising racemisation). The Grignard reagent, benzyl magnesium chloride, reacted cleanly with the nitrile **321** in dry THF at 20 °C, to afford the enaminone **322**. The next step, which is crucial for the stereoselective generation of the C-2 and C-4 centres, involves reduction of the enaminone **322** using excess sodium borohydride in the presence of methanesulphonic acid. Enaminones, existing predominantly in the carbonyl form, are presumed to favour a hydrogen-bonded cisoid conformation,[133] and the resulting rigidity of the system apparently controls the observed 1,4-stereo-induction. Reduction of the ketone **323** was achieved using $NaBH_3(OTFA)$, generated *in situ* from trifluoroacetic acid and sodium borohydride. The resulting mixture was de-benzylated by treatment with a 5 % palladium on carbon catalyst in the presence of ammonium formate. Purification was achieved by precipitating the product from isopropyl alcohol and concentrated HCl to afford the hydrochloride salt **325**, which was easily converted to the free diamine **318** by treatment with saturated aqueous sodium hydrogen carbonate (Scheme 82).

Compounds **318 - 325** were all characterised by one- and two-dimensional NMR spectroscopy, the ^1H NMR and ^{13}C NMR data being consistent with those reported by Stuk *et al.*[159] and were found to be the same. The ^1H NMR spectrum of the diamine **318** (illustrated in Figure 31a) reveals the 3-methine proton signal at *ca.* 3.71 ppm, the 5-methine proton signal at *ca.* 3.10 ppm and the 1-methylene proton signals as multiplets at 1.54 ppm and 1.64 ppm. The ^{13}C NMR spectrum reveals the 3-methine carbon resonating at 74.4 ppm, the 2-methine carbon at 57.5 ppm and the 5-methine carbon at 54.0 ppm (Figure 31b). The assigned structure is supported by the HMQC data (Figure 32) which confirms attachment of the three pairs of diastereotopic methylene protons to the corresponding upfield carbon nuclei, C-1, C-4 and C-6.

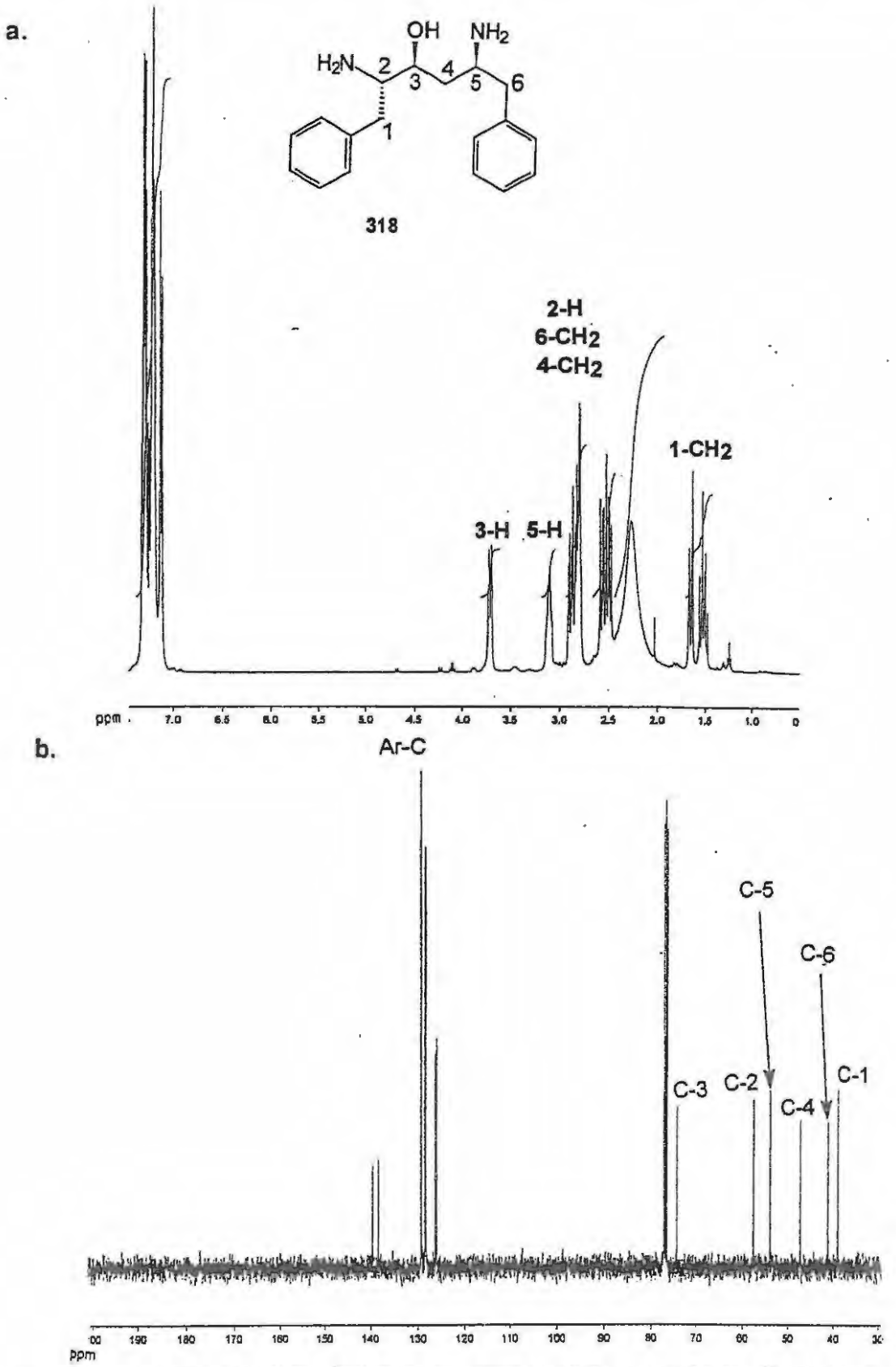
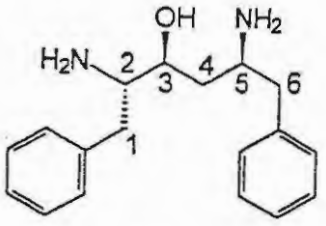


Figure 31. **(a)** The 400 MHz ^{1}H NMR spectrum; and **(b)** the 100 MHz ^{13}C NMR spectrum of (2*S*, 3*S*, 5*S*)-2,5-diamino-1,6-diphenylhexane **318** in $CDCl_3$.



318

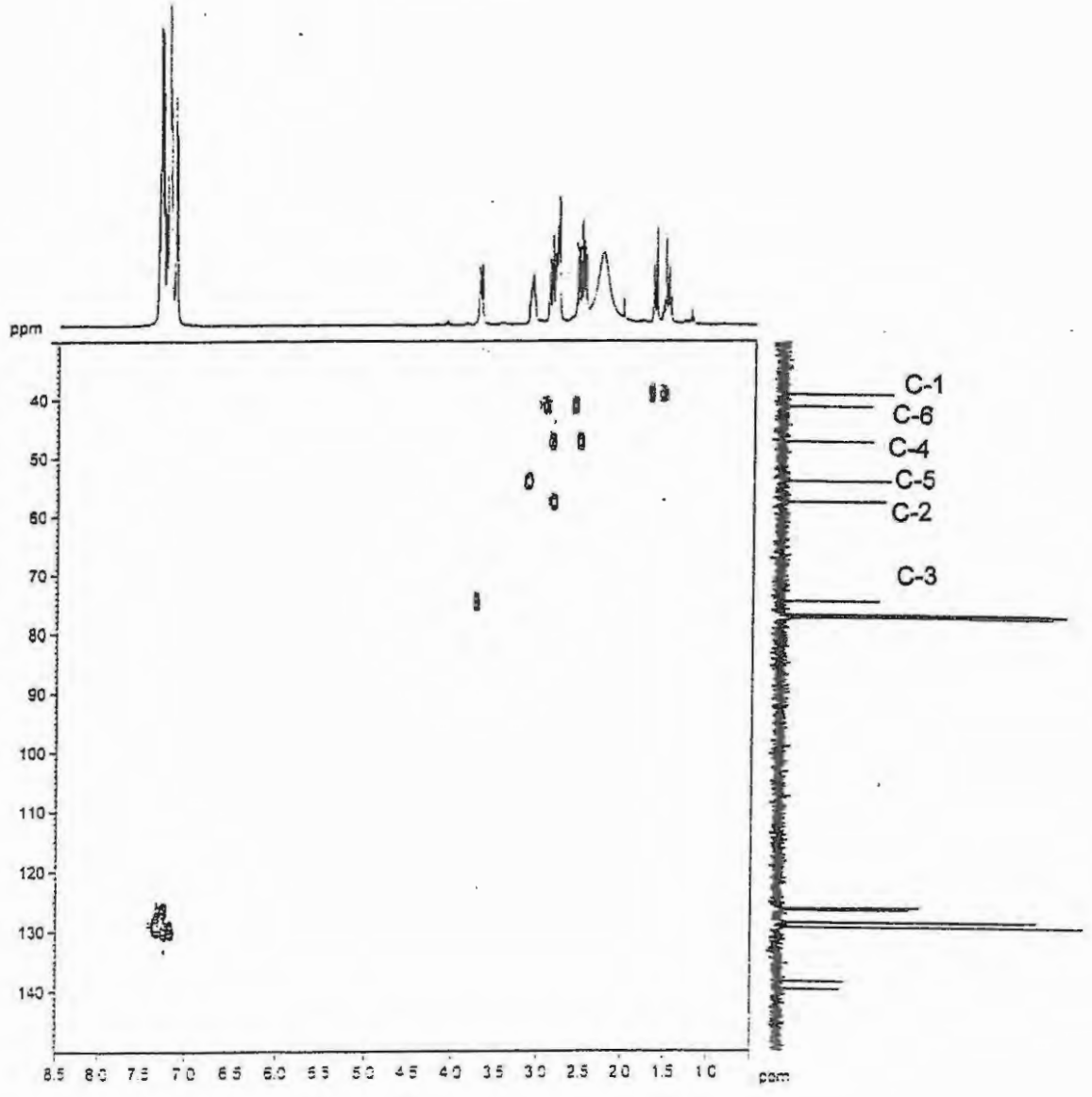
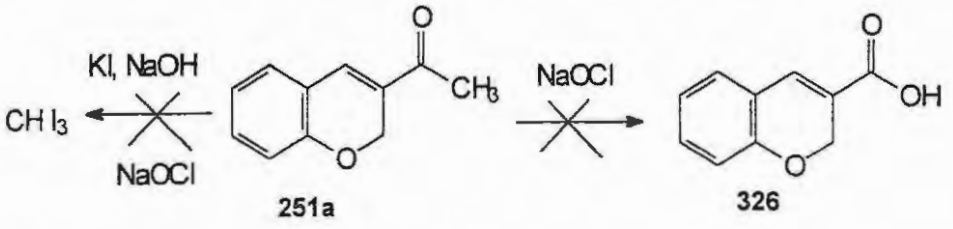


Figure 32. The HMQC spectrum of (2*S*, 3*S*, 5*S*)-2,5-diamino-1,6-diphenylhexane **318** in $CDCl_3$.

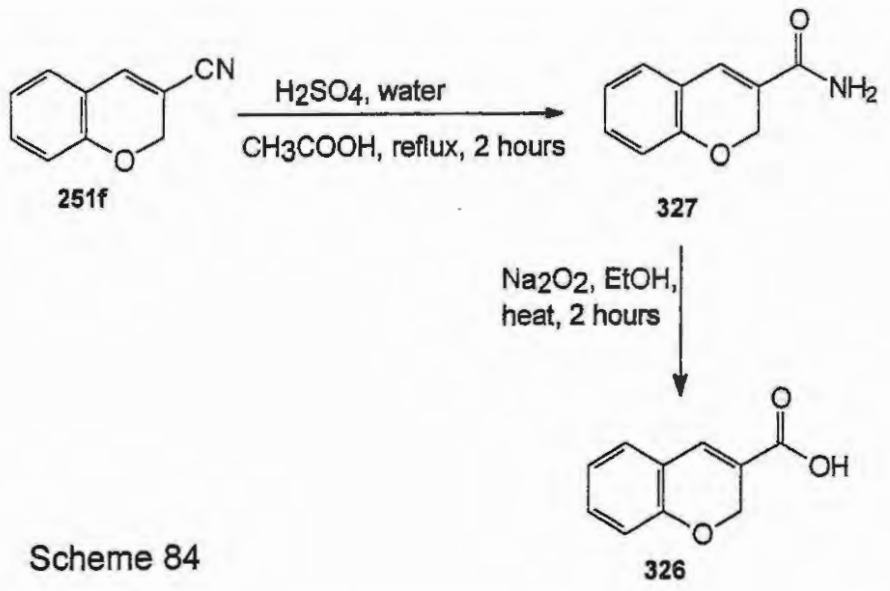
2.8.2 Synthesis of chromene and thiochromene carboxylic acid derivatives

The chromene and thiochromene carboxylic acid derivatives were required for coupling with the diamine **318** to obtain the ritonavir analogues **329** and **330**. It is well known that oxidation of methyl ketones to carboxylic acids can be effected by the haloform reaction. This approach was applied in an attempt to convert the methyl ketone, 3-acetylchromene **251a**, to its carboxylic acid derivative **326** (Scheme 83). 3-Acetylchromene **251a** was treated with 15% sodium hypochlorite,[160] but no reaction was apparent. Using an alternative method, 3-acetylchromene **251a** was treated with potassium iodide, sodium hydroxide and sodium hypochlorite,[163] but none of the expected iodoform was precipitated; the aqueous solution was acidified using concentrated HCl and extracted with an organic solvent to afford an intractable mixture.



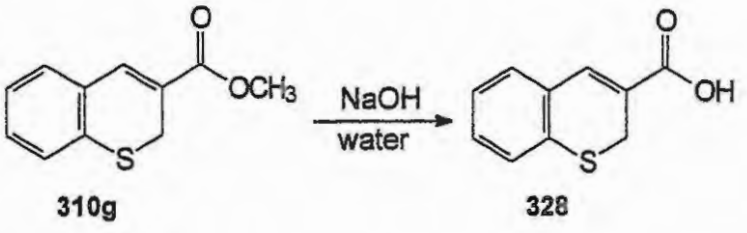
Scheme 83

Using an alternative approach to the carboxylic acid derivative **326**, the carbonitrile **251f** was hydrolysed using a mixture of sulphuric acid, acetic acid and water to afford the amide **327**, but an attempt to effect hydrolysis of the amide by heating the mixture under reflux for a longer period was unsuccessful. The amide was successfully hydrolysed, however, following a method reported by Robbins and Vuaghan;[161] this involved treating the amide **327** with excess sodium peroxide in ethanol to afford the carboxylic acid **326** (Scheme 84).



Scheme 84

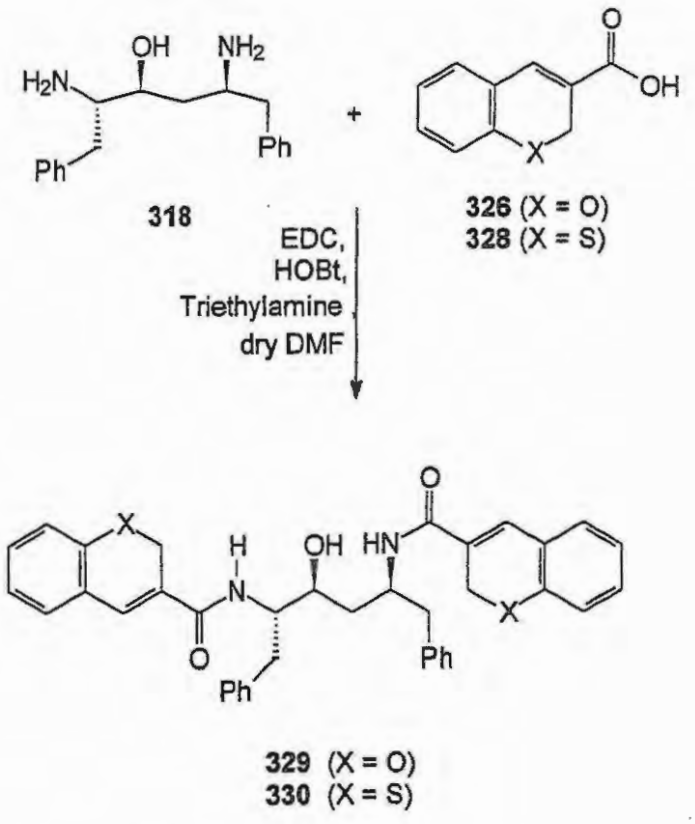
Esters are known to be readily hydrolysed to carboxylic acids by treatment with aqueous sodium hydroxide, and the methyl ester **310g** was readily converted to thiochromene-3-carboxylic acid **328** by this means (Scheme 85).



Scheme 85

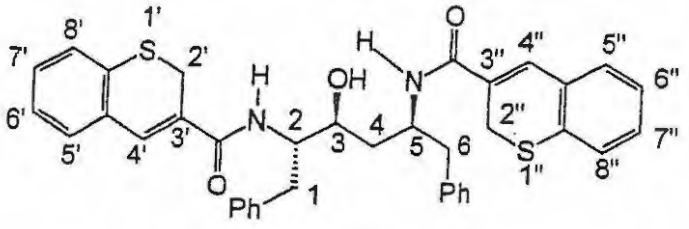
2.8.3 Synthesis of ritonavir analogues

The diamine **318** was coupled with chromene-3-carboxylic acid **326** and with thiochromene-3-carboxylic acid **328** using a standard peptide coupling procedure,[162] involving use of *N*-ethyl-*N'*-(dimethylaminopropyl)carbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole hydrate (HOBt) in the presence of triethylamine in dry DMF, to afford (*ca.*60 % yield) the ritonavir analogues **329** and **330**, respectively (Scheme 86).



Scheme 86

Both ritonavir analogues (**329** and **330**) were fully characterised by one- and two-dimensional NMR analysis and by high-resolution mass spectroscopy. The ^{1}H NMR spectrum of compound **330** (illustrated in Figure 33) reveals the 4-methylene proton signal at 1.78 ppm, the 6-methylene proton signal at 2.88 ppm and the 1-methylene proton signal at 3.00 ppm. The 5-methine, 2-methine and 3-methine protons resonate at 4.34 ppm, 4.21 ppm and 3.84 ppm respectively. The ^{13}C NMR spectrum (Figure 34a) shows the three methine carbons resonating at 69.4 ppm (C-3), 55.7 ppm (C-2) and 49.3 ppm (C-5), while the methylene carbons resonate at 24.5 ppm and 24.6 ppm (C-2',2"), 38.0 ppm (C-1), 39.6 ppm (C-4) and 40.6 ppm (C-6). The methylene and the methine signal assignments were confirmed by the DEPT spectrum (Figure 34b). The COSY spectrum (Figure 35) shows the coupling of the 4-methylene protons to both the 5-methine and 3-methine protons, the 1-methylene protons to the 2-methine proton and the 6-methylene protons to 5-methine proton. Both compounds (**329** and **330**) are to be submitted for testing as potential HIV-1 protease inhibitors.



330

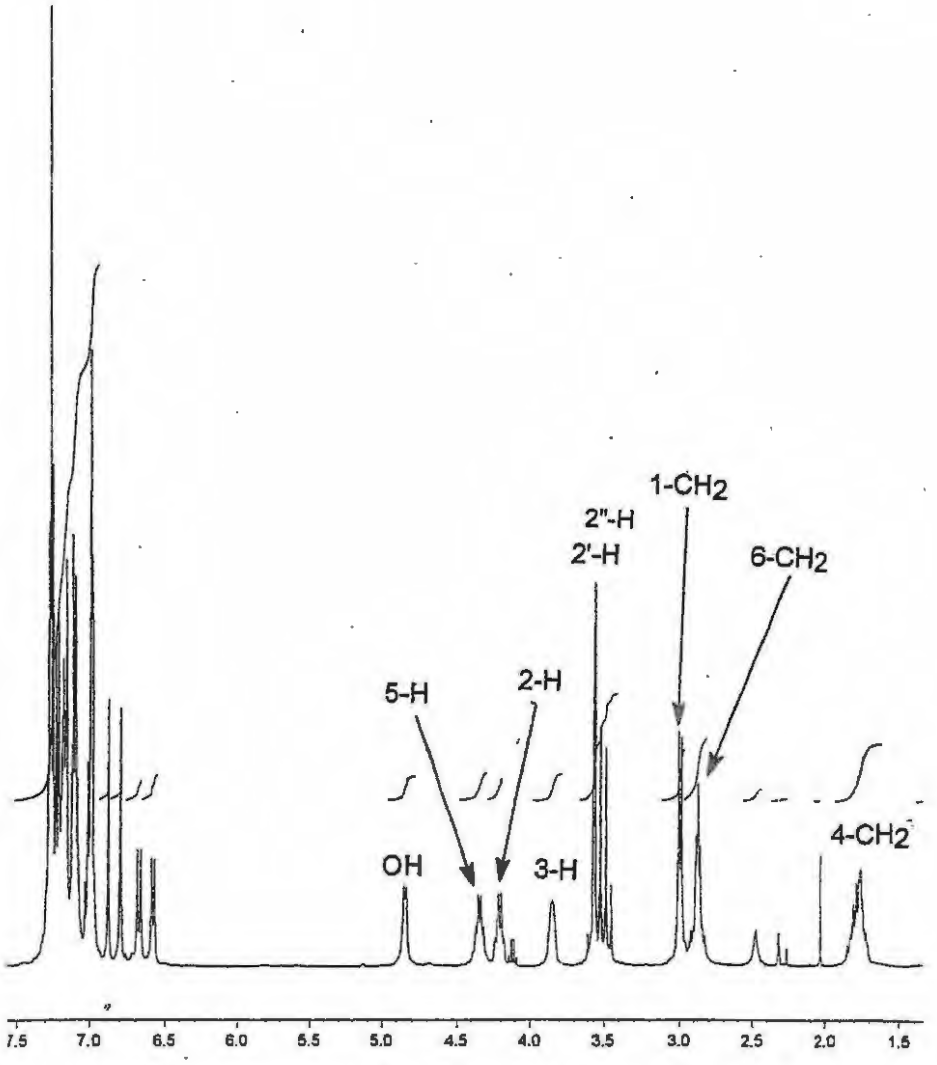
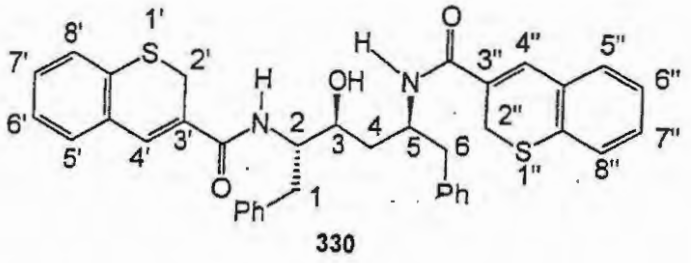


Figure 33. ^{1}H NMR spectrum of (2*S*, 3*S*, 5*S*)-2,5-bis(2*H*-1-chromene-3-carbamoyl)-3-hydroxy-1,6-diphenylhexane **330** in $CDCl_3$.



330

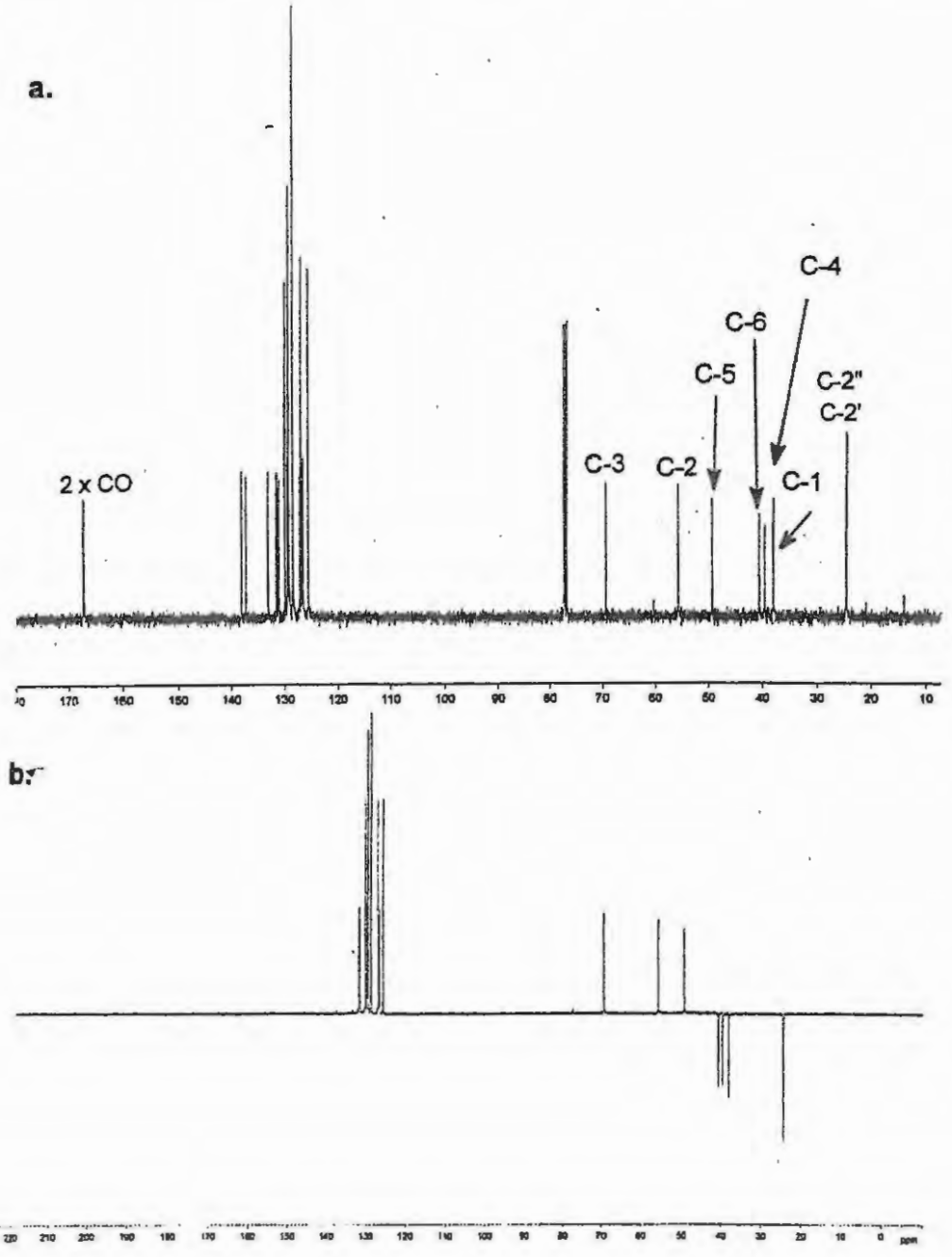


Figure 34. (**a**) ^{13}C NMR spectrum, and (**b**) DEPT spectrum of (2*S*, 3*S*, 5*S*)-2,5-bis(2*H*-1-chromene-3-carbamoyl)-3-hydroxy-1,6-diphenylhexane **330** in $CDCl_3$.

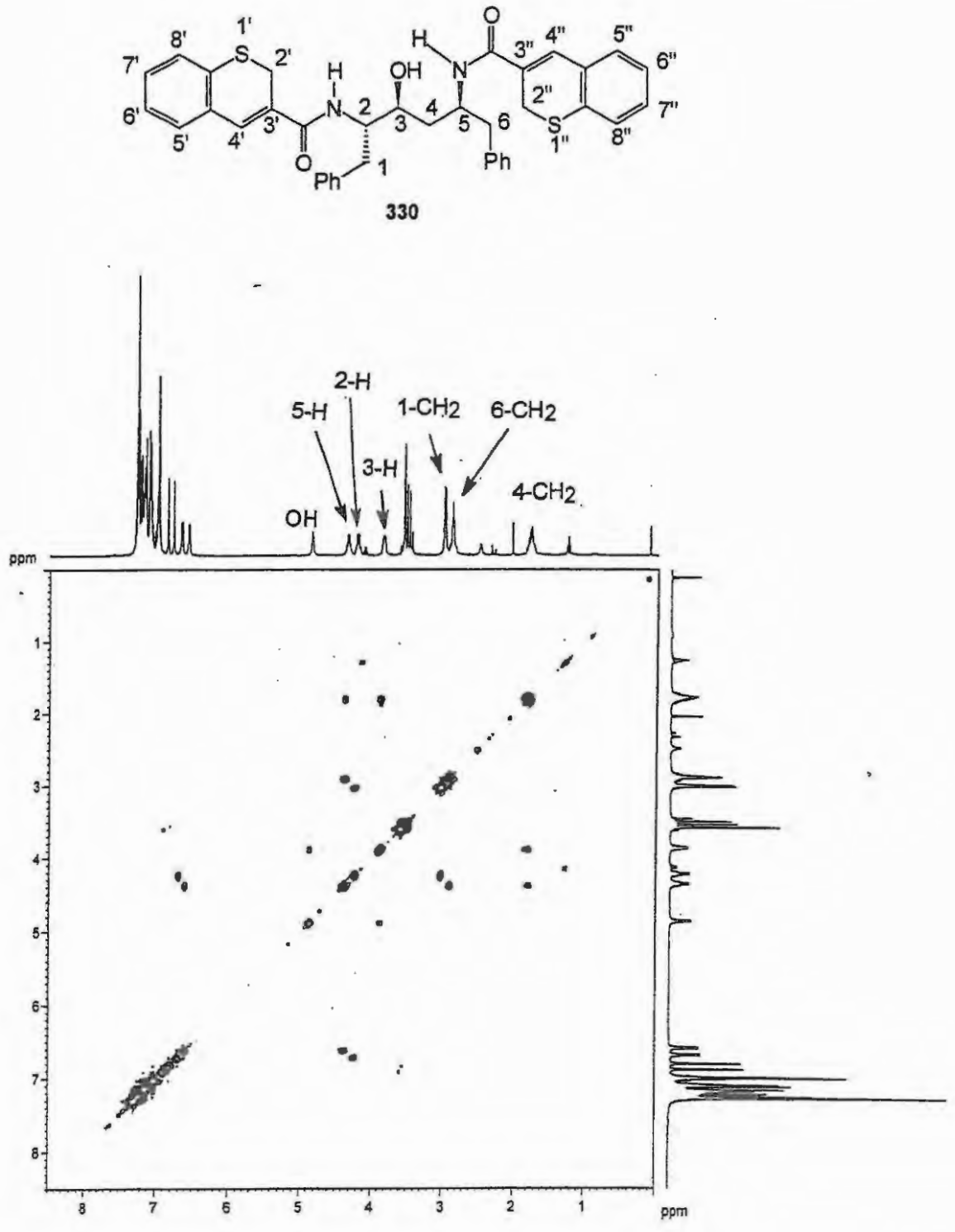


Figure 35. COSY spectrum of (2S, 3S, 5S)-2,5-bis(2*H*-1-thiochromene-3-carbamoyl)-3-hydroxy-1,6-diphenylhexane **330** in $CDCl_3$

2.9 CONCLUSIONS

Earlier work in the research group had demonstrated that the Baylis-Hillman reaction between salicylaldehyde and methyl acrylate results in the formation of complex mixture of chromene and coumarin derivatives. This project was aimed at controlling the regioselectivity of the reaction to achieve exclusive formation of chromenes. Regiocontrol of the cyclisation has been successfully achieved by replacing the α,β-unsaturated carboxylate ester substrate by vinyl ketones thus inhibiting cyclisation *via* acyl substitution, which would have resulted in the formation of coumarin derivatives. Using this approach, salicylaldehyde was treated with a series of α,β-unsaturated vinyl systems, including vinyl ketones, acrolein, acrylonitrile, phenyl vinyl sulfone and phenyl vinylsulfonate, to afford the corresponding chromene derivatives in yields ranging from 10 to 48 %. The reaction conditions were then optimised in order to improve the yields, optimum conditions being obtained when 1.5 molar equivalents of the activated alkene and a water-chloroform solvent system were used and additional activated alkene and DABCO were added during the course of the reaction. Using this methodology, a series of chromene derivatives have been obtained from various salicylaldehydes in moderate to good yields (up to 87 %). The generality of the methodology has been further demonstrated by the synthesis of a series of fused-ring chromenes, using naphthaldehyde in place of salicylaldehyde.

The formation of chromene derivatives had been assumed to proceed *via* initial formation of an intermediate Baylis-Hillman product, which had not been isolated previously. Efforts were consequently made to isolate such an intermediate; these included treatment of *tert*-butyldimethylsilyloxybenzaldehyde with methyl acrylate under Baylis-Hillman conditions to afford, as one of the products, the disilylated Baylis-Hillman product. Deprotection of the disilylated product yielded the Baylis-Hillman product which, upon treatment with DABCO, underwent a retro-Baylis-Hillman reaction. In another approach, 4-hydroxybenzaldehyde was treated with methyl acrylate in the presence of DABCO, to afford the Baylis-Hillman product, as the sole product - an indication that the Baylis-Hillman pathway is followed in preference to conjugate addition under these conditions. Even more significantly, treatment of salicylaldehyde with *tert*-butyl acrylate in the presence of DABCO afforded the Baylis-Hillman product (in 49 % yield), but none of the conjugate addition product, providing compelling evidence for the

earlier assumption that cyclisation is initiated by a Baylis-Hillman reaction.

The synthetic methodology developed for the preparation of chromene derivatives has been successfully adapted for the synthesis of thiochromenes by treating 2,2'-dithiobenzaldehyde with activated alkenes, but using DBU rather than DABCO as the catalyst. Using this approach, a series of 3-substituted thiochromenes has been obtained in 40 - 67 % yields. Surprisingly, the reaction with methyl acrylate gave none of the thiocoumarin derivative.

Michael-type addition reactions under Baylis-Hillman conditions have also been explored and the dimerisation of α,β-unsaturated vinyl systems in the presence of the catalyst, DABCO, confirmed. The EI mass fragmentation patterns of selected chromene and thiochromene derivatives have been investigated using high resolution mass spectrometry and metastable peak data, and certain common fragmentations have been identified.

Two, potential HIV-1 protease inhibitors, designed as ritonavir analogues, have been obtained by treating a specially prepared, hydroxyethylene dipeptide isostere with chromene- and thiochromene-3-carboxylic acids in the presence of the coupling agent, EDC. The thiochromene-3-carboxylic acid derivative was obtained by simple saponification of the methyl ester, while chromene-3-carboxylic acid was finally obtained by step-wise hydrolysis of 3-cyanochromene.

The various aims of the project have thus been successfully addressed; and future research in this area is expected to include:-

i) use of *tert*-butyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate as a model for studying the kinetics and mechanism of the cyclisation pathways;

ii) computational analyses of the competing reaction pathways;

iii) biological testing of the ritonavir analogues and the development of structural derivatives as potential HIV-1 protease inhibitors; and

iv) Wittig reactions of 3-acetylchromenes with *para*-substituted benzyl bromide derivatives to afford biologically active styrylchromenes.

3. EXPERIMENTAL

3.1 GENERAL

All melting points were determined using a Kofler hot-stage apparatus and are uncorrected. NMR spectra were recorded on a Bruker AMX400 spectrometer at 303 K in $CDCl_3$ or DMSO-d_6. Spectra recorded in $CDCl_3$ were calibrated on the chloroform signal at 7.25 ppm for ^1H and 77.00 ppm for ^{13}C; spectra recorded in DMSO-d_6 were calibrated using the signals at 2.5 ppm for ^1H and 39.4 ppm for ^{13}C. Infrared spectra were recorded on a Perkin Elmer FT-IR spectrum 2000 spectrometer, the samples being analysed using hexachlorobutadiene or nujol mulls as thin films or NaCl discs. Low-resolution mass spectroscopy was carried out on a Finnigan GCQ mass spectrometer using the electron ionisation (EI) mode and high-resolution mass spectra on a Kratos MS 80RF double focusing magnetic sector spectrometer (Cape Technikon Mass Spectrometry unit). Computer-modelled, energy-minimised structures were obtained using the MSI Ceruis 2 platform on a Silicon Graphics O^2 computer.

Flash chromatography was[119] carried out using Merck silica gel 60 (particle size 0.040 - 0.063 mm) and preparative layer chromatography was effected on glass plates coated with Merck silica gel 60 PF_{254}. Thin layer chromatography (TLC) was performed using precoated Merck silica gel F_{254} plates, with visualisation of the components by inspection under UV light (254/365 nm) and/or by exposure to iodine vapour.

Solvents were dried under dry N_2 using procedure described by Perrin and Armarego.[126] Thus, THF and Et_2O were dried over sodium wire, and distilled from sodium using benzophenone as an indicator; DMF was distilled from 3A molecular sieves under reduced pressure; CH_2Cl_2 was pre-dried over $CaCl_2$ and distilled from P_2O_5.

3.2 SYNTHESIS OF CHROMENE DERIVATIVES

3.2.1 Synthesis of 3-acetyl-2*H*-1-chromene

Method 1 (optimised conditions)

Salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in $CHCl_3$ (1.0 ml) and H_2O (1.0 ml) was stirred vigorously under N_2 in a stoppered flask at room temperature. After stirring the reaction mixture for 24 hours, additional methyl vinyl ketone (0.4 ml, 5 mmol) and DABCO (0.29g, 2.6 mmol) were added and stirring was continued for 24 hours before adding further quantities of methyl vinyl ketone (0.20 ml, 2.4 mmol) and DABCO (0.10g, 0.85 mmol) and stirring for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as yellow crystals, 3-acetyl-2*H*-1-chromene **251a** (1.4g, 81 %), m.p. 39 - 40 °C (Found: $\mathbf{M}^+$,174.06708. $C_{11}H_{10}O_2$ requires: *M*, 174.06808); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 3058 and 2852 (CH and CH_3) and 1655 (CO); δ_H (400 MHz; $CDCl_3$) 2.39 (3H, s, CH_3), 4.99 (2H, s, CH_2), 6.83 (1H, d, ArH), 6.95 (1H, t, ArH), 7.16 (1H, d, ArH), 7.23 (1H, t, ArH) and 7.29 (1H, s, 4-CH); δ_C(100 MHz, $CDCl_3$) 25.0 (CH_3), 64.2 (CH_2), 116.3, 120.7, 121.8, 129.1, 130.8, 132.4, 133.9 and 155.6 (ArC and C=CH) and 195.9 (CO); *m/z* 174 ($\mathbf{M}^+$, 62.3) and 131 (100 %).

The reaction was followed by ^{1}H NMR spectroscopy, monitoring the disappearance of the salicylaldehyde aldehydic signal at *ca.* 9.9 ppm and the appearance of the 2-methylene signal of 3-acetylchromene **251a** at *ca.*4.9 ppm. The progress of the reaction was determined at intervals from the relative integrals of these signals and the resulting graph is illustrated in Figure 6 (p. 57) and the data is tabulated below.

Table 8. Relative percentage of 3-acetylchromene **251a** as a function of time in the DABCO-catalysed reaction between salicylaldehyde and methyl vinyl ketone (optimised conditions).

Time in hours	Relative %
0	4
4	33.3
8	42.9
12	53.3
20	57.6
24	58.6
28	76.9
32	81.8
72	87
76	88.6
84	90.2
96	91.7
108	92.3
120	92.3
132	92.3
140	95.5
144	96.6
152	96.6
168	96.6

The Baylis-Hillman reaction between salicylaldehyde and methyl vinyl ketone to afford 3-acetylchromene **251a** was studied in detail, varying the experimental parameters in order to determine the optimum conditions. The results are discussed in Section 2.2.1.

Experiment 1

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and DABCO (0.43g, 3.84 mmol) in chloroform (1.0 ml) was stirred in a stoppered reaction flask at room temperature under N_2 for 7 days. The resulting oily mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1- chromene **251a** (0.70g, 42 %);

Experiment 2

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) was stirred in a stoppered flask at room temperature under N_2 for 14 days. The resulting oily mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.73g, 44 %);

Experiment 3

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (0.5 ml) was stirred in a stoppered flask at room temperature under N_2 for 7 days. The resulting oily mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.70g, 42 %);

Experiment 4

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and DABCO (1.1g, 9.6 mmol) in chloroform (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting oily mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.47g, 28 %);

Experiment 5

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and 3-hydroxyquinuclidine (0.49g, 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature under N_2 for 7days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.35g, 31 %);

Experiment 6

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and triphenylphosphine (1.0g, 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature for under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.47g, 28 %);

Experiment 7

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80ml, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) was heated at 60 °C under reflux for 5 hours, with stirring. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.60g, 36 %);

Experiment 8

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80ml, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml). The reaction mixture was heated under reflux at 60 °C for 15 hours with stirring. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.55g, 33 %);

Experiment 9

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and DABCO (1.1g, 9.6 mmol) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.60g, 36 %);

Experiment 10

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol) and methyl vinyl ketone (0.80 ml, 9,6 mmol) in dioxane (1.0 ml) was cooled to 0 °C in an ice bath and DABCO (0.43g, 3.8 mmol) was added. The reaction mixture was kept at 0 °C for 8 hours, and then chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.26g, 16 %);

Experiment 11

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (0.80 ml, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.90g, 54 %);

Experiment 12

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) was heated at 60 °C for 5 hours with stirring. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (0.85g, 51 %);

Experiment 13

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.1g, 64 %);

Experiment 14

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.6 ml, 19 mmol) and DABCO (0.43g 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.1g, 64 %);

Experiment 15

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.1g, 66 %);

Experiment 16

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in ethylene glycol (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.1g, 63 %);

Experiment 17

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.0g, 60 %);

Experiment 18

Triethanolamine (0.64 ml, 4.8 mmol) was added to a mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) and water (1.0 ml). The reaction mixture was stirred vigorously at room temperature in a stoppered flask under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.0g, 60 %);

Experiment 19

To a stirred mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) in chloroform (1.0 ml) and water (1.0 ml), was added DABCO (1.1g, 9.6 mmol),

lanthanum triflate (0.28g, 0.48 mmol) and triethanolamine (0.64 ml, 4.8 mmol). The reaction mixture was stirred vigorously at room temperature for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.2g, 69 %);

Experiment 20

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously under N_2 for 7 days. After this period, methyl vinyl ketone (0.63 ml, 4.8 mmol) and DABCO (0.29g, 2.6 mmol) were added. The stirring was continued for another 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 3-acetyl-2*H*-1-chromene **251a** (1.3g, 75 %).

3.2.2 Synthesis of other chromene derivatives

***2H-1-chromene-3-carbaldehyde* 251b**

Method 1 (Optimised conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), acrolein (0.95 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in $CHCl_3$ (1.0 ml) and water (1.0 ml) was stirred vigorously under N_2 in a stoppered flask at room temperature. After stirring for 24 hours, acrylonitrile (0.32 ml, 4.8 mmol) and DABCO (0.29g, 26 mmol) were added and stirring was continued for 72 hours; thereafter, acrylonitrile (0.16 ml, 2.4 mmol) and DABCO (0.10 g, 0.85 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as a yellow oil, 2*H*-1-chromene-3-carbaldehyde **251b** (0.82 g, 54 %) (Found: M^+, 160.0532. $C_{10}H_8O_2$ requires: *M*, 160.0524); ν_{max} (hexachlorobutadiene mull/cm^{-1})1680 (CO); δ_H (400 MHz; $CDCl_3$) 5.02 (2H, s, CH_2), 6.85 (1H, d, ArH), 6.93 (1H, t, ArH), 7.18 (1H, d, ArH), 7.28 (1H, t, ArH), 7.23 (1H, s, 4-CH) 9.57 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 63.3 (CH_2), 116.6, 120.5, 121.9, 129.4, 131.8, 133.2, 141.2 and 156.1 (ArC and CH=C) and 189.8 (CO); *m/z* 160 (M^+, 100) and 131 (99.2 %).

Method 2 (Initial conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), acrolein (0.63 ml, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature in a stoppered flask under N_2 for 7 days. The reaction mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford 2*H*-1-chromene-3-carbaldehyde **251b** (0.74g, 48 %).

3-*Propanoyl-2*H-*1-chromene* 251c

Method 1 (Optimised conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), ethyl vinyl ketone (1.4 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in $CHCl_3$ (1.0 ml) and water (1.0 ml) was stirred vigorously under N_2 in a stoppered flask at room temperature. After stirring for 24 hours, ethyl vinyl ketone (0.50ml, 4.8 mmol) and DABCO (0.29g, 2.6 mmol) were added and stirring was continued for 72 hours; thereafter, more ethyl vinyl ketone (0.24 ml, 2.4 mmol) and DABCO (0.1g, 0.9 mmol) were added and stirring for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-benzene (2:3)] to afford, as a yellow oil, *3-propanoyl-2*H-*1-chromene* **251c** (1.5g, 83 %) (Found: M^+,188.0835. $C_{12}H_{12}O_2$ requires: *M*, 188.0837); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 3076 and 3060 (C=*C-H*), 2987 and 2911 (CH_2 and CH_3) and 1656 (CO); δ_H (400 MHz; $CDCl_3$) 1.16 (3H, t, *J* 7.3 Hz, CH_3), 2.76 (2H, q, *J* 7.4 Hz, CH_2), 5.00 (2H, s, CH_2), 6.84 (1H, d, ArH), 6.92 (1H, t, ArH), 7.13 (1H, d, ArH), 7.24 (1H, t, ArH) and 7.30 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 8.4 (CH_3), 30.2 (CH_2), 64.4 (CH_2), 116.3, 120.8, 121.7, 129.1, 130.2, 130.3, 132.6 and 155.6 (ArC and C=CH) and 198.8 (CO); *m/z* 188 (M^+, 37.1) and 173 (100 %).

Method 2 (Initial conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), ethyl vinyl ketone (0.96 ml, 9.6 mmol) and DABCO (0.43 g, 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with benzene-hexane (3:2)] to afford *3-propanoyl-2*H-*1-chromene* **251c** (0.38g, 21 %).

***3-phenylsulfonyl-2*H-*1-chromene* 251d**

Method 1 (Optimised conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), phenyl vinyl sulfone (2.4g, 14 mmol) and DABCO (0.86g, 7.7 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, phenyl vinyl sulfone (0.81g, 4.8 mmol) and DABCO (0.29g, 2.6 mmol) were added and stirring was continued for 72 hours; thereafter, more phenyl vinyl sulfone (0.40g, 2.4 mmol) and DABCO (0.10g, 0.85 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as white crystals, *3-phenylsulfonyl-2H-1-chromene* **251d** (1.0g, 70 %), m.p.122-123 °C (Found: M^+, 272.0510. $C_{15}H_{12}O_3S$ requires: *M*, 272.0506); ν_{max} (hexachlorobutadiene mull/cm^{-1}); 3077 and 3058 (C=*C-H*) and 1311 (S=O); δ_H (400 MHz; $CDCl_3$) 4.85 (2H, s, CH_2) 6.81 - 7.91 (10H, m, ArH and C=CH); δ_C (100 MHz; $CDCl_3$) 63.11 (CH_2), 116.3, 119.9, 122.3, 127.9, 129.4, 129.5, 131.06, 132.6, 132.8, 133.8, 139.3 and 154.1 (ArC and CH=C); *m/z* 130 (M^+, 100) and 272 (90.9 %).

Method 2 (Initial conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), phenyl vinyl sulphone (1.6g, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford *3-phenylsulphonyl-2H-1-chromene* **251d** (0.26g, 10 %).

***Phenyl 2H-1-chromene-3-sulfonate* 251e**

Method 1 (Optimised conditions)

A mixture of salicylaldehyde (0.50 ml, 4.8 mmol), phenyl vinylsulfonate (1.4g, 7.2 mmol), DABCO (0.43g, 3.8 mmol) in chloroform (0.5 ml) and water (0.5 ml) was stirred vigorously in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, phenyl vinylsulfonate (0.30g, 1.6 mmol) and DABCO (0.14g, 1.3 mmol) were added and stirring was continued for 72 hours; thereafter phenyl vinylsulfonate (0.15g, 0.80 mmol) and DABCO (0.05g, 0.4 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as white crystals, *phenyl 2H-1-Chromene-3-sulfonate* **251e** (0.83g, 60 %), m. p. 82 - 84 °C (Found: M^+, 288.0444. $C_{15}H_{12}O_4S$ requires: *M*, 288.0455); ν_{max} (hexachlorobutadiene mull/cm^{-1})

3065 (C=*C-H*) 2922 (CH_2) and1487 (C=C; δ_H (400 MHz; $CDCl_3$) 5.21 (2H, d, *J* 1.0, CH_2) 6.92 - 7.57 (10H, m, ArH and CH=C); δ_C (100 MHz; $CDCl_3$) 63.3 (CH_2) 116.7, 119.7, 122.3, 122.5, 125.1, 127.4, 129.6, 129.9, 133.3, 135.8, 149.4 and 154.7 (ArC and C=CH); *m/z* 288 (M^+, 61.8) and 131 (100 %).

Method 2 (Initial conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), phenyl vinyl sulphonate (1.8g, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford *phenyl 2H-1-chromene-3-sulphonate* **251e** (0.42g 15 %).

***3-Cyano-2H-1-chromene* 251f**

Method 1 (Optimised conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), acrylonitrile (0.95 ml, 14 mmol) and DABCO (0.86g, 7.7 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously at room temperature under N_2. After stirring for 24 hours, acrylonitrile (0.32 ml, 4.8 mmol) and DABCO (0.29g, 2.6 mmol) were added and stirring was continued for 72 hours; thereafter, acrylonitrile (0.16 ml, 2.4 mmol) and DABCO (0.10 g, 0.85 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as pink crystals, 3-cyano-2*H*-1-chromene **251f** (0.96g, 65 %), m.p. 42-43 °C (Found: M^+, 157.0520. $C_{10}H_7NO$ requires: *M*, 157.0527); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 2214 (CN); δ_H (400 MHz; $CDCl_3$) 4.80 (2H, s, CH_2) 6.85 (1H, d, ArH), 6.94 (1H, t, ArH), 6.98 (1H, d, ArH), 7.28 (1H, t, ArH) and 7.16 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 64.3 (CH_2) 103.4, 116.4, 116.6, 120.0, 122.4, 128.4,132.7 and 138.8 (ArC and C=CH) and 154.3 (CN); *m/z* 157 (M^+, 71.9) and 156 (100 %).

Method 2 (Initial conditions)

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), acrylonitrile (0.63 ml, 9.6 mmol) and DABCO (0.43g, 3.8 mmol) in chloroform (1.0 ml) was stirred at room temperature under N_2 for 7 days. The resulting mixture was chromatographed [flash chromatography; elution with hexane-EtOAc (9:1)] to afford 3-cyano-2*H*-1-chromene **251f** (0.24g, 20 %).

***3-Acetyl-8-methoxy-2H-1-chromene* 251g**

A mixture of *o*-vanillin (1.0g, 6.6 mmol), methyl vinyl ketone (0.82 ml, 9.9 mmol) and DABCO (0.59g, 5.3 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, methyl vinyl ketone (0.27ml, 3.3 mmol) and DABCO (0.20g, 1.8 mmol) were added and stirring was continued for 72 hours; thereafter, methyl vinyl ketone (0.14 ml, 1.7 mmol) and DABCO (0.07g, 0.6 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (7:3)] to afford, as yellow crystals, 3-acetyl-8-methoxy-2*H*-1-chromene **251g** (1.1g, 79 %), m.p.100-101 °C (Found: M^+, 204.0788. $C_{12}H_{12}O_3$ requires: *M*, 204.0786); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 3055 and 3019 (C=*C-H*) 2968 and 2868 (CH_2 and CH_3) and 1661 (CO); δ_H (400 MHz; $CDCl_3$) 2.39 (3H, s, CH_3) 3.87 (3H, s, OCH_3) 5.05 (2H, s, CH_2) 6.77 - 6.90 (3H, m, ArH) and 7.28 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 25.0 (CH_3), 56.1 (OCH_3) 64.6 (CH_2)114.9, 121.1, 121.4, 121.4, 130.8, 133.8, 144.6 and 148.1 (ArC and C=CH) and 195.83 (CO); *m/z* 204 (M^+, 65.7) and 161 (100 %).

***3-Acetyl-6-nitro-2H-1-chromene* 251h**

A mixture of2-hydroxy-5-nitrobenzaldehyde (1.0g, 6.0 mmol), methyl vinyl ketone (0.74 ml, 9.0 mmol) and DABCO (0.54g, 4.8 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously under N_2 at room temperature. After stirring for 24 hours, methyl vinyl ketone (0.25 ml, 3.0 mmol) and DABCO (0.18g, 1.6 mmol) were added and stirring was continued for 72 hours; thereafter, methyl vinyl ketone (0.12 ml, 1.5 mmol) and DABCO (0.06g, 0.53 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford, as yellow crystals, *3-acetyl-6-nitro-2*H-*1-chromene* **251h** (0.70g, 54%), m.p.132-134 °C (Found: M^+, 219.0516. $C_{11}H_9NO_4$ requires: *M*, 219.0532); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 2924 and 2850 (CH_2 and CH_3); δ_H (400 MHz; $CDCl_3$) 2.42 (3H, s, CH_3) 5.13 (2H, s, CH_2) 6.90 (1H, d, ArH), 8.07 (1H, s, ArH), 8.11 (1H, d, ArH) and 7.29 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 25.1 (CH_3) 65.5 (CH_2)116.7, 120.2, 124.6, 127.8, 131.3, 131.9, 142.1 and 160.4 (ArC and C=CH) and 195.5 (CO); *m/z* 219 (M^+, 70.7) and 176 (100 %).

***3-Acetyl-6-chloro-2H-1-chromene* 251i**

A mixture of 5-chlorosalicylaldehyde (0.5g, 3 mmol), methyl vinyl ketone (0.39 ml, 4.8 mmol) and DABCO (0.29g, 2.6 mmol) in chloroform (0.5 ml) and water (0.5 ml) was stirred vigorously under N_2 at room temperature. After stirring for 24 hours, methyl vinyl ketone (0.13 ml, 1.6 mmol), DABCO (0.10g, 0.85 mmol) were added and stirring was continued for 72 hours; thereafter, methyl vinyl ketone (0.07 ml, 0.8 mmol), DABCO (0.03g, 0.3 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as yellow crystals, *3*-acetyl-6-chloro-2*H*-1-chromene **251i** (0.37g, 56%), m.p. 47-48 °C (Found: M^+, 208.0296. $C_{11}H_9{}^{35}ClO_2$ requires: *M*, 208.0291); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 2925, 2856 (CH_2 and CH_2) and 1666 (CO); δ_H (400 MHz; $CDCl_3$) 2.39 (3H, s, CH_3) 4.98 (2H, s, CH_2), 6.79 -7.17 (3H, m, ArH) and 7.20 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 25.1 (CH_3), 64.4 (CH_2), 117.6, 122.0, 126.5, 128.3, 131.7, 131.9, 132.5 and 154.0 (ArC and C=CH) 195.7 (CO); *m/z* 208 (M^+, 100) and 165 (77.1%).

***3-Acetyl-8-ethoxy-2H-1-chromene* 251j**

A mixture of 3-ethoxysalicylaldehyde (1.0g, 6.0 mmol), methyl vinyl ketone (0.74 ml, 9.0 mmol) and DABCO (0.54g, 4.8 mmol) in chloroform (1.0 ml) and water (1.0 ml)was stirred at vigorously in stoppered flask under N_2 at room temperature. After stirring for 24 hours, methyl vinyl ketone (0.25 ml, 3.0 mmol) and DABCO (0.18g, 1.6 mmol) were added and stirring was continued for 72 hours; thereafter, methyl vinyl ketone (0.10 ml, 1.5 mmol) and DABCO (0.06g, 0.5 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford, as yellow crystals, 3-acetyl-8-ethoxy-2*H*-1-chromene **251j** (1.1g, 84 %), m.p. 68 -70 °C (Found: M^+, 218.0945. $C_{13}H_{14}O_3$ requires: *M*, 218.0943); ν_{max} (nujol mull/cm^{-1})1665 (CO) and 1574 (C=C); δ_H (400 MHz; $CDCl_3$) 1.84 (3H, t, *J* 7.0 Hz, CH_3), 2.80 (3H, s, CH_3), 4.50 (2H, q, *J* 7.0 Hz, CH_2), 5.45 (2H, d, *J* 1.2 Hz,CH_2), 7.19 - 7.32 (3H, m, ArH) and 7.70 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 14.7 (CH_3), 24.9 (CH_3), 64.3 (CH_2), 64.6 (CH_2), 116.6, 121.1, 121.3, 121.5, 130.6, 133.9, 144.9 and 147.2 (ArC and C=CH) and 195.67 (CO); *m/z* 218 (M^+, 100) and 175 (44.4 %).

***3-Acetyl-6-bromo-2H-1-chromene* 251k**

A mixture of 5-bromosalicylaldehyde (1.0g, 5.0 mmol), methyl vinyl ketone (0.61 ml, 7.4 mmol) and DABCO (0.44g, 4.0 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, methyl vinyl ketone (0.20 ml, 2.5 mmol) and DABCO (0.15g, 1.3 mmol) were added and stirring was continued for 72 hours; thereafter, methyl vinyl ketone (0.10 ml, 1.2 mmol) and DABCO (0.05g, 0.5 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford, as yellow crystals, 3-acetyl-6-bromo-2*H*-chromene **251k** (1.1g, 87 %), m.p. 59-60 °C (Found: M^+, 251.9795. $C_{11}H_9O_2{}^{79}Br$ requires: *M*, 251.9786); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 2855 (CH_3) and 1668 (CO); δ_H (400 MHz; $CDCl_3$) 2.38 (3H, s, CH_3), 4.97 (2H, s, CH_2), 6.72 (1H, d, ArH), 7.21 (1H, s, ArH), 7.29 (1H, d, ArH) and 7.18 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 25.0 (CH_3), 64.4 (CH_2), 113.6, 118.0, 122.5, 131.3, 131.6, 132.3, 134.7 and 154.5 (ArC and C=CH) 195.74 (CO); *m/z* 251 (M^+, 74.8) and 208 (100 %).

3-*Acetyl-6,8-dibromo-2H-1-chromene* 251l

A mixture of 3,5-dibromosalicylaldehyde (1.0g, 3.6 mmol), methyl vinyl ketone (0.44 ml, 5.4 mmol) and DABCO (0.32g, 2.9 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, methyl vinyl ketone (0.15 ml, 1.8 mmol) and DABCO (0.11g, 0.95 mmol) were added and stirring was continued for 72 hours; thereafter, methyl vinyl ketone (0.08 ml, 0.9 mmol) and DABCO (0.04g, 0.3 mmol) were added and stirring was continued for a further 72 hours. The resulting reaction mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford two fractions,

i) as yellow crystals, *3-acetyl-6,8-dibromo-2*H-*1-chromene* **251l** (0.34g, 29 %), m.p.59-60 °C (Found: M^+, 329.8881. $C_{11}H_8O_2{}^{79}Br_2$ requires: *M*, 329.8891); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 3066 (C=*C-H*) 2926 and 2864 (CH_2 and CH_3) and 1666 (CO); δ_H (400 MHz; $CDCl_3$) 2.40 (3H, s, CH_3), 5.10 (2H, s, CH_2), 7.16 (1H, s, 4-CH), 7.22 (1H, s, ArH) and 7.58 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 25.2 (CH_3), 65.3 (CH_2), 111.2, 123.2, 130.5, 131.5, 132.1, 137.4 and 151.4 (ArC and CH=C) 195.3 (CO); *m/z* 332 (M^+, 64.3) and 289 (100 %); and

ii) as pale yellow crystals, *3-acetyl-6,8-dibromobenzopyran-4-ol* **255** (0.66g, 53 %), m.p. 132-134 °C (Found: M^+, 347.8990. $C_{11}H_{10}O_3{}^{79}Br_2$ requires: *M*, 347.8997); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3444 (OH), 3083 (C=*C-H*), 2985 and 2952 (CH_2 and CH_3) and 1696 (CO); δ_H (400 MHz; $CDCl_3$), 2.34 (3H, s, CH_3), 3.02 (1H, d, *J* 5.3 Hz, OH), 3.04 (1H,dt, *J* 3.5 Hz and 13.8 Hz, 3-H) 4.43 (1H, dd, *J* 11.0 Hz and 11.0 Hz, 2-H_b) 4.60 (1H, dd, *J* 3.5 and 11.4 Hz, 2-H_a) 5.04 (1H, m, 4-CH) 7.44 (1H, s, ArH) and 7.60 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 29.0 (CH_3), 50.6 (CH), 63.2 (CH_2), 64.2 (CH), 111.7, 112.9, 126.1, 131.8, 135.7 and 150.1 (ArC) and 206.82 (CO); *m/z* 350 (M^+, 30.2) and 289 (100 %).

Attempted preparation of 3-acetyl-6,8-dinitrochromene 254

A mixture of 3,5-dinitrosalicylaldehyde (1.0g, 4.7 mmol), methyl vinyl ketone (0.58ml, 7.1 mmol) and DABCO (0.42g, 3.8 mmol) in chloroform (2.0 ml) and water (2.0 ml) was stirred vigorously at in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, methyl vinyl ketone (0.19 ml, 2.4 mmol) and DABCO (0.14g, 1.3 mmol) were added and stirring was continued for 72 hours; and thereafter, methyl vinyl ketone (0.1 ml, 1 mmol) and DABCO (0.14g, 1.3 mmol) were added and stirring was continued for a further 72 hours. No 3-acetyl-6,8-dinitrochromene **254** could be detected in the ^1H NMR spectrum of the reaction mixture.

Preparation of 3-(dimethylamino)propiophenone hydrochloride* 257[124] *(via the Mannich reaction)

Dry dimethylamine hydrochloride (27g, 0.33 mol), powdered paraformaldehyde (10g,0.33 mol) and acetophenone (29 ml, 0.25 mol) were placed in 250 ml round-bottomed flask fitted with a reflux condenser. A mixture of ethanol (40ml) and concentrated hydrochloric acid (0.5 ml) was added, and the mixture boiled under reflux on a water bath for 2 hours. The reaction mixture ultimately became a clear yellow solution, which was transferred to a conical flask and, while the solution was still warm, acetone (200 ml) was added. The mixture was allowed to cool to room temperature and left to stand in the refrigerator overnight. The precipitated crystals were filtered off and washed with cold acetone to afford, as white crystals, 3-(dimethylamino)propiophenone hydrochloride **257** (36g, 70 %), m.p.154 - 156 °C (lit.[124] 155 - 156 °C); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 1678 (CO); δ_H (400 MHz; $CDCl_3$) 2.84 (6H, s, 2 x CH_3) 3.51 (2H, t, *J* 7.0 Hz, CH_2)

3.74 (2H, t, *J* 7.0 Hz, CH_2) 7.47 (2H, t, ArH), 7.60 (1H, t, ArH) and 7.98 (2H, d, ArH), δ_C (100 MHz; $CDCl_3$) 33.8 (CH_2), 43.3 (2 x CH_3), 52.7 (CH_2), 128.3, 128.9, 134.2 and 135.4 (ArC) and 195.7 (CO).

***Phenyl vinyl ketone* 258**[124]

3'-(Dimethylamino)propiophenone hydrochloride **258** (10.0g, 46.8 mmol) and hydroquinone (0.10g) were placed in a 100 ml round-bottomed flask. The apparatus was arranged for distillation under vacuum, and a few crystals of hydroquinone were placed in the receiving flask. The amine hydrochloride was pyrolysed by heating the reaction flask in an electric mantle and the phenyl vinyl ketone was distilled off as a yellow oil (3.6g, 55 %); ν_{max} (hexachlorobutadiene mull/cm^{-1}) 1686 (CO); δ_H (400 MHz; $CDCl_3$) 5.90 (1H, dd, *J* 1.6 Hz and 10.6 Hz, CH), 6.40 (1H, dd, *J* 1.6 Hz and 17.1 Hz, CH), 7.13 (1H, dd, *J* 10.5 Hz and 17.1 Hz, CH) 7.45 (2H, t, ArH), 7.53 (1H, t, ArH) and 7.92 (2H, d, ArH); δ_C (100 MHz; $CDCl_3$) 128.5, 128.6, 130.0, 132.3, 132.9 and 137.2 (ArC and CH=CH_2) and 191.0 (CO).

Attempted preparation of 1-dimethyl-3-pentanone hydrochloride

Dry dimethylamine hydrochloride (13g, 0.16 mol) powdered formaldehyde (5.0g, 0.17 mol) and 3,3-dimethyl-2-butanone (16 ml, 0.13 mmol) were placed in a 250 ml round-bottomed flask fitted with a reflux condenser. A mixture of ethanol (20 ml) and concentrated HCl (0.5 ml) was added, and the mixture was boiled under reflux on a water bath for 2 hours. While the mixture was still warm, acetone (100 ml) was added, the resulting mixture allowed to cool to room temperature and then left to stand in the cold room overnight. No crystals were precipitated and ^1H NMR analysis indicated the absence of the expected product.

***3-Benzoyl-2H-1-Chromene* 251m**

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), phenyl vinyl ketone (1.9g, 14 mmol) and DABCO (0.86g, 7.7 mmol) in chloroform (1.0 ml) and water (1.0 ml) was stirred vigorously in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, phenyl vinyl ketone (0.64g, 4.8 mmol) and DABCO (0.29g, 2.6 mmol) were added and stirring was continued for 72 hours; thereafter, phenyl vinyl ketone (0.32g, 2.4 mmol) and DABCO (0.1g, 0.9 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was

chromatographed [flash chromatography on silica; elution with benzene-hexane (4:1)] to afford, as yellow oil, 3-phenyl-2*H*-1-chromene **251m** (0.15g, 10 %), (Found: M^+, 236.0835. $C_{16}H_{12}O_2$ requires: *M*, 236.08373); ν_{max} (hexachlorobutadiene mull/cm^{-1})1750 (CO); δ_H (400 MHz; $CDCl_3$) 5.16 (2H, s, CH_2) 6.90 - 7.73 (10H, m, ArH and C=CH); δ_C (100 MHz; $CDCl_3$) 65.3 (CH_2), 116.4, 121.0, 121.8, 128.4, 129.0, 129.3, 129.8, 132.0, 132.5, 137.0, 137.6 and 155.6 (ArC and C=CH) and 194.1 (CO); *m/z* 236 (M^+, 24.0) and 105 (100 %).

3.2.3 Synthesis of 2*H*-benzo[*g*]chromenes

***3-Acetyl-2H-1-benzo[g]chromene* 260a**

A mixture of 2-hydroxy-1-naphthaldehyde (1.6g 9.6 mmol), DABCO (0.86g, 7.7 mmol) and methyl vinyl ketone (1.2 ml, 14 mmol) in $CHCl_3$ (1.0 ml) and H_2O (1.0 ml) was stirred vigorously under N_2 in a stoppered flask at room temperature. After stirring for 24 hours, additional methyl vinyl ketone (0.40 ml, 4.8 mmol) and DABCO (0.29g, 2.6 mmol) were added and stirring was continued for a further 24 hours; further quantities of methyl vinyl ketone (0.20 ml, 2.4 mmol) and DABCO (0.10g, 0.85 mmol) were then added and was stirring continued for a further 72 hours. The resulting mixture was chromatophed [flash chromatography on silica gel; elution with hexane-EtOAc(4:1)] to afford, as yellow crystals, *3-acetyl-2*H-*1-benzo[g]chromene* **260a** (1.4g, 67 %), m.p.122-124 °C (Found: M^+, 224.0832. $C_{15}H_{12}O_2$ requires: *M*, 224.0837); ν_{max} (hexachlorobutadiene mull / cm^{-1}) 3066 (C=*C-H*) 2857 (CH_3) and 1660 (CO); δ_H (400 MHz; $CDCl_3$) 2.51 (3H, s, CH_3), 5.09 (2H, s, CH_2), 7.10 (1H, d, ArH), 7.41 (1H, t, ArH), 7.55 (1H, t, ArH), 7.77 (1H, d, ArH), 7.80 (1H, s, ArH), 7.99 (1H, s, ArH) and 8.01 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 25.1 (CH_3), 64.0 (CH_2), 113.9, 117.6, 120.9, 124.4, 127.7, 128.4, 128.9, 129.4, 130.1, 130.8, 133.2 and 155.2 (ArC and C=C) 195.6 (CO); *m/z* 224 (M^+, 62.8) and 181 (100 %).

***2H-1-Benzo[g]chromene-3-carbaldehyde* 260b**

A mixture of 2-hydroxy-1-naphthaldehyde (1.0 g, 5.8 mmol), acrolein (0.58 ml, 8.7 mmol), DABCO (0.52 g, 4.7 mmol) in $CHCl_3$ (1.0 ml) and water (1.0 ml) was stirred vigorously under N_2 in a stoppered flask at room temperature. After stirring for 24 hours, acrolein (0.19 ml, 2.9 mmol) and DABCO (0.17 g, 1.55 mmol) were added and stirring was continued for 72 hours; thereafter, acrolein (0.10 ml, 1.5 mmol) and DABCO (0.06 g, 0.5 mmol) were added and stirring

was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with EtOAc-hexane (1:4)] to afford, as yellow crystals, *2H-1-benzo[g]chromene-3-carbaldehyde* **260b** (0.21g 17 %), m.p.144 - 146 °C (Found: M^+, 210.0678. $C_{14}H_{10}O_2$ requires: *M*, 210.0681); ν_{max} (in chloroform /cm^{-1}) 1630 (CO); δ_H (400 MHz; $CDCl_3$) 5.1 (2H, s, CH_2) 7.13 (1H, d, ArH), 7.41(1H, t, ArH), 7.58 (1H, t, ArH), 7.79 (1H, d, ArH), 7.80 (1H, d, ArH), 8.00 (1H, d, ArH), 7.95 (1H, s, 4-CH) and 9.7 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 63.2 (CH_2), 114.0, 117.7, 121.0, 124.6, 128.1, 129.0, 129.4, 129.5, 131.1, 130.7, 134.2 and 137.6 (ArC and C=CH) and 189.5 (CO); *m/z* 210 (M^+, 65.5) and 181 (100 %).

***3-Propanoyl-2H-1-benzo[g]chromene* 260c**

A mixture of 2-hydroxy-1-naphthaldehyde (0.20g, 2.9 mmol), ethyl vinyl ketone (0.43 ml, 4.4 mmol) and DABCO (0.26g, 2.3 mmol) was stirred vigorously in a stoppered flask under N_2 at room temperature. After stirring for 24 hours, ethyl vinyl ketone (0.14 ml, 1.5 mmol) and DABCO (0.09g, 0.8 mmol) were added and stirring was continued for 72 hours; thereafter, ethyl vinyl ketone (0.07 ml, 0.7 mmol) and DABCO (0.03g, 0.3 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with benzene-Hexane (4:1)] to afford, as yellow crystals, *3-propanoyl-2H-1-benzo[g]chromene* **260c** (0.40g, 58 %), m.p.88 - 90 °C (Found: M^+, 238.0994. $C_{16}H_{14}O_2$ requires :*M*, 238.1005); ν_{max} (in chloroform/cm^{-1}) 2923 and 2848 (CH_2 and CH_3) and 1653.6 (CO); δ_H (400 MHz; $CDCl_3$) 1.22 (4H, t, *J* 7.3, CH_3) 2.89 (3H, q, *J* 7.3, CH_2) 5.10 (2H, s, CH_2)7.11(1H, d, ArH), 7.42 (1H, t, ArH), 7.54 (1H, t, ArH), 7.76 (1H, s, ArH), 7.78 (1H, s, ArH) 7.80 (1H, d, ArH) and 8.02 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 8.6 (CH_3), 30.4 (CH_2), 64.3 (CH_2), 114.0, 117.6, 120.9, 124.3, 127.6, 127.9, 128.8, 128.9, 129.4, 130.8, 133.0 and 155.1 (ArC and C=CH) and 198.6 (CO); *m/z* 238 (M^+, 100) and 181 (95.3 %).

***3-Phenylsulfonyl-2H-1-benzo[g]chromene* 260d**

A mixture of 2-hydroxy-1-naphthaldehyde (1.0 g, 5.8 mmol), phenyl vinyl sulfone (1.5g, 8.7 mmol) and DABCO (0.52 g, 4.7 mmol) in $CHCl_3$ (1.0 ml) and water (1.0 ml) was stirred vigorously at room temperature under N_2. After stirring for 24 hours, phenyl vinyl sulfone (0.5 g, 2.9 mmol) and DABCO (0.17 g, 1.6 mmol) were added and stirring was continued for 72 hours; thereafter, phenyl vinyl sulphone (0.25 g, 1.5 mmol) and DABCO (0.06 g, 0.5 mmol) were

added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford two fractions :-

i) as dark yellow crystals, *3-phenylsulfonyl-2H-1-Benzo[g]chromene* **260d** (0.37g, 20 %), m.p.186 - 188 °C (Found: M^+, 322.0674. $C_{19}H_{14}O_3S$ requires: *M*, 322.0664); ν_{max} (in chloroform /cm^{-1}) 3020 (C=*C-H*) and 2918 (CH_2); δ_H (400 MHz; $CDCl_3$) 4.9 (2H, s, CH_2), 7.1 - 8.0 (11 H, m, ArH) and 8.2 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 63.1 (CH_2), 113.4, 117.2, 121.3, 124.6, 127.8, 128.1, 128.3, 128.8, 129.3, 129.5, 130.6, 133.6, 133.7, 139.7 and 153.6 (ArC and C=CH); *m/z* 322 (M^+, 65.6) and 180 (100 %); and

ii) *3-Phenylsulfonyl-2H-1-benzo[g]benzopyran-4-ol* **261d**, as an oil, (0.04g, 2 %) (Found: M^+ 340.0769. $C_{19}H_{16}O_4S$ requires: *M*, 340.0779); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3023 (OH); δ_H (400 MHz; $CDCl_3$) 3.3 (1H, d, *J* 3.5 Hz, OH), 3.6 (1H, dt, *J* 3.2 Hz and 11.8 Hz, 3-H), 4.6 (1H, dd, *J* 2.8 Hz and 10.6 Hz, 2-H), 4.7 (1H, dd, *J* 11.2 Hz and 11.7 Hz, 2-H), 5.8 (1H, m, 4-CH) 7.0 - 8.0 (6H, m, ArH); δ_C (100 MHz; $CDCl_3$) 59.0 (CH_2), 59.5 (CH), 63.2 (CH), 113.5, 118.2, 121.8, 124.2, 127.6, 128.5,128.6, 129.3, 129.6, 131.3, 132.3, 134.5, 138.6 and 151.5 (ArC); *m/z* 340 (M^+, 90.3) and 169 (100 %).

***Phenyl 2H-1-benzo[g]chromene-3-sulfonate* 260e**

A mixture of 2-hydroxy-1-naphthaldehyde (0.5g, 2.9 mmol), phenyl vinylsulfonate (0.80g, 4.4 mmol) and DABCO (0.26g, 2.3 mmol) in $CHCl_3$ (1.0 ml) and water (1.0 ml) was stirred vigorously at room temperature in stoppered flask under N_2. After stirring for 24 hours, phenyl vinyl sulphonate (0.27g, 1.5 mmol) and DABCO (0.09g, 0.8 mmol) were added and stirring was continued for 72 hours; thereafter, phenyl vinylsulfonate (0.1g, 0.7 mmol) and DABCO (0.03g, 0.3 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford

i) as yellow crystals, *phenyl 2H-1-benzo[g]chromene-3-sulfonate* **260e** (0.60g, 61 %), m.p.164 -166 °C, (Found: M^+, 338.0617. $C_{19}H_{14}O_4S$ requires: *M*, 338.0613); ν_{max} (in chloroform /cm^{-1})

3022 (C=*C-H*) 2923 (CH_2); δ_H (400 MHz; $CDCl_3$) 5.06 (2H, s, CH_2), 7.10 - 7.80 (1H, m, ArH) and 7.88 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 63.2 (CH_2), 113.2, 117.3, 121.3, 122.0, 122.3, 124.9, 127.4, 128.2, 128.8, 129.5, 129.9, 130.6, 132.4, 134.2, 149.4 and 154.4 (ArC and C=CH); *m/z* 338 (M^+, 100) and 181 (91.7 %); and

ii) *phenyl 4-hydroxy-2*H*-1-benzo[g]benzopyran-3-sulfonate* **261e**, as an oil, (0.04g, 4 %) (Found: M^+, 356.0722. $C_{19}H_{16}O_5S$ requires: *M*, 356.0718); ν_{max} (in chloroform /cm^{-1}) 3328.8 (OH) 3018 (C=*C-H*) 2854.6 (CH_2); δ_H (400 MHz; $CDCl_3$) 2.74 (1H, d, *J* 4.4 Hz, OH), 4.02 (1H, q, *J* 3.5 Hz, 3-H), 4.60 (1H, dd, 3.4 Hz and 12.2 Hz, 2-H), 4.80 (1H, dd, *J* 3.5 Hz and 10.4 Hz, 2-H), 5.93 (1H, m, 4-CH), 7.12 - 8.12 (11H, m, ArH); δ_C (100 MHz; $CDCl_3$) 60.6 (CH), 60.8 (CH_2), 61.3 (CH), 112.9, 118.5, 121.9, 122.3, 124.3, 127.4, 127.6, 128.9, 129.8, 130.0, 131.2, 132.2, 148.8 and 152.2 (ArC); *m/z* 356 (M^+, 59.1) and 198 (100 %).

***3-Cyano-2H-1-benzo[g]chromene* 260f**

A mixture of 2-hydroxy-1-naphthaldehyde (1.0g, 5.8 mmol), acrylonitrile (0.57 ml, 8.7 mmol) and DABCO (0.52g, 4.7 mmol) in $CHCl_3$ (1.0 ml) and water (1.0 ml) was stirred vigorously at room temperature under N_2. After stirring for 24 hours, acrylonitrile (0.19 ml, 2.9 mmol) and DABCO (0.17g, 1.6 mmol) were added and stirring was continued for 72 hours; thereafter, acrylonitrile (0.10 ml, 1.5 mmol) and DABCO (0.06g, 0.5 mmol) were added and stirring was continued for a further 72 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with Hexane-EtOAc (4:1)] to afford two fractions :-

i) *3-cyano-2*H *-1-Benzo[g]chromene* **260f**, as yellow crystals, (0.6g, 50 %), m.p. 120-122 °C (Found: M^+, 207.0675. $C_{14}H_9NO$ requires: *M*, 207.0684); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 2851 (CH_2) and 2210 (CN); δ_H (400 MHz; $CDCl_3$) 4.88 (2H, s, CH_2), 7.10 (1H, ArH), 7.42 (1H, t, ArH), 7.57 (1H, t, ArH) , 7.77 (1H, d, ArH) 7.81 (1H, d, ArH) 7.86 (1H, d, ArH) 7.85 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 64.2 (CH_2), 100.3, 113.8, 117.0, 117.3, 121.0, 124.8, 128.2,128.9, 129.5, 129.9, 133.5 and 135.3 (ArC) and 154.0 (CN); *m/z* 207 (M^+, 73.4) and 206 (100 %); and

ii) *3-cyano-4-hydroxy-2*H*-1-benzo[g]benzopyran* **261f**, as an oil, (0.03g, 2 %) (Found: M^+, 225.0788. $C_{14}H_{11}NO_2$ requires: *M*, 225.0790); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3421 (OH)

and 2249 (CN); δ_H (400 MHz; $CDCl_3$) 2.75 (1H, br s, OH), 3.24 (1H, dt, *J* 3.6 Hz and 11.8 Hz, 3-CH), 4.42 (1H, dd, *J* 10.9 Hz and 11.2, 2-H), 4.53 (1H, dd, *J* 3.6 Hz and 10.7 Hz, 2-H) 5.5 (1H, m, 4-CH) 705 (1H, d, ArH), 7.41 (1H, t, ArH), 7.56 (1H, t, ArH), 7.76 (1H, d, ArH), 7.79 (1H, d, ArH), 8.02 (1H, s, ArH); δ_C (100 MHz; $CDCl_3$) 32.3 (CH), 59.7 (CH), 60.7 (CH_2), 112.4, 116.8, 118.4, 121.6, 124.4, 127.8, 128.8, 129.4, 131.5 and 132.2 (ArC) and 151.6 (CN); *m/z* 225 (M^+, 65.8) and 172 (100 %).

3.2.4 Investigation of the intermediates

***Preparation of 2-(t-butyldimethylsilyloxy)benzaldehyde* 269**

Dry THF (50 ml) was added to a two-necked flask (fitted with a condenser attached to a N_2 line) containing washed NaH (50 % dispersion in oil; 0.94 g, 20 mmol). Salicylaldehyde (1.9 ml, 18 mmol) was then added dropwise, with stirring, *via* a syringe, and the mixture was stirred at room temperature for 30 minutes to generate the phenoxide species. *t*-Butyldimethylsilyl chloride (3.0g, 20 mmol) in dry THF was then added and the resulting mixture was stirred at room temperature for 12 hours. The reaction was quenched by the addition of aq. $NaHCO_3$ (20 ml) and extracted into diethyl ether (3 x 20 ml). The ethereal extracts were washed with satd. brine (50 ml) and dried over anhydrous $MgSO_4$. The solvent was removed *in vacuo* to give a crude product (6.4 g), which was purified by flash chromatography [elution with hexane-EtOAc (9:1)] to afford *2-(t-butyldimethylsilyloxy)benzaldehyde* **269** [§] (2.7g, 65 %) (Found: M^++1, 237.1310. $C_{13}H_{21}SiO_2$ requires *M*+1, 237.1311), ν_{max} (hexachlorobutadiene mull /cm^{-1})1742 (CO); δ_H (400 MHz; $CDCl_3$) 0.26 [6H, s, $Si(CH_3)_2$] 1.02 [9H, s, $Si(CH_3)_3$] 6.86 (1H, d, ArH), 7.01 (1H, d, ArH), 7.43 (1H, t, ArH), 7.80 (1H, d, ArH) and 10.46 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) -4.4 [$Si(CH_3)_2$], 18.3 [$SiC(CH_3)_3$], 25.6 [$SiC(CH_3)_3$], 120.2, 121.4, 127.3, 128.3, 135.6 and 158.8 (ArC) and 189.9 (CHO); *m/z* 236 (M^+, 0.9) and 179 (100 %).

Attempted preparation of methyl 3-hydroxy-3-[2-(*t*-butyldimethylsilyloxy)phenyl]-2-methylenepropanoate 270

A solution of 2-(t-butyldimethylsilyloxy)benzaldehyde **269** (1.5 g, 6.4 mmol), methyl acrylate

[§]Previously isolated by Robinson[94] but not fully characterised.

(0.72 ml, 7.9 mmol) and DABCO (0.07 g, 0.6 mmol) in chloroform (1.0 ml) was stirred in a closed two-necked round-bottomed flask under N_2 for 3 days. The crude mixture was purified by flash chromatography followed by preparative layer chromatography (elution with chloroform) to afford six fractions :-

i) salicylaldehyde (0.30g, 39 %);

ii) 2-(t-butyldimethylsilyloxy)benzaldehyde **269** (0.22g, 15 %);

iii) *methyl 3-(t-butyldimethylsilyloxy)-3-[2-(t-butyldimethylsilyloxy)phenyl]-2-methylenepropanoate* **271**[5], as light yellow oil, (0.33g, 12 %) Found: M^++1, 437.2544. $C_{23}H_{41}Si_2O_4$ requires *M*+1, 437.2543), ν_{max} (hexachlorobutadiene mull /cm^{-1}) 1727 (CO); δ_H (400 MHz; $CDCl_3$) -0.020, 0.067, 0.23 and 0.26 [12H, 4 x s, 2 x $Si(CH_3)_2$], 0.86 and 0.99 [18H, 2 x s, 2 x $C(CH_3)_3$], 3.71 (3H, s, OCH_3), 5.44 and 6.14 (2H, 2 x s, $C=CH_2$), 6.05 (1H, s, OCH), 6.75 (1H, d, ArH), 6.93 (1H, t, ArH), 7.12 (1H, t, ArH) and 7,42 (1H, d, ArH); δ_C (100 MHz; $CDCl_3$) -4.76, -4.17, -4.11 and -4.12 [2 x $Si(CH_3)_2$], 18.2 [$C(CH_3)_3$], 25.8 [2 x $C(CH_3)_3$], 51.5 (OCH_3), 66.7 (OCH), 117.8, 120.7, 124.8, 124.9, 128.1, 132.4, 143.9 and152.3 (ArC and $C=CH_2$) and 166.9 (CO); *m/z* 436 (M^+, 0.05) and 179 (100 %);

iv) 3-[(2-formylphenoxy)methyl]coumarin **231**, as white crystals, (0.05g, 3 %), m.p.178 - 180 °C (lit.[123]180 - 182 °C); (Found: M^+, 280.0749. $C_{17}H_{12}O_4$ requires: *M*, 280.0736); ν_{max} (nujol mull /cm^{-1}) 1715 and 1676 (2 x CO); δ_H (400 MHz; $CDCl_3$) 5.15 (2H, s, CH_2) 7.09 - 7.97 (9H, m, ArH) and 10.60 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 65.1 (CH_2), 112.9, 116.7, 118.9, 121.7, 124.0, 125.2, 128.1, 129.7, 131.8, 136.1, 139.2, 153.2 and 160.0 (ArC), 160.1 (CO) and 189.3 (CHO);

v) *methyl 2-(3-methyl-1-benzopyran-2-on-4-yl)propenoate* **237**, as white crystals, (0.03g, 2 %), m.p. 104 - 106 °C (Found: M^+, 244.0745. $C_{14}H_{12}O_4$ requires: *M*, 244.0736); ν_{max} (nujol mull /cm^{-1}) 1707 and 1667 (2 x CO); δ_H (400 MHz; $CDCl_3$) 2.09 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 5.82 and 6.87 (2H, 2 x s, $C=CH_2$), 7.21 - 7.46 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 14.6 (CH_3), 52.7 (OCH_3), 116.8, 119.7, 123.9, 124.2, 125.6, 130.7, 131.4, 135.3, 145.8 and 152.4 (ArC, C=C and

[5]Previously isolated by Robinson[94] but not fully characterised.

(OCH_3), 116.8, 119.7, 123.9, 124.2, 125.6, 130.7, 131.4, 135.3, 145.8 and 152.4 (ArC, C=C and $C=CH_2$) 161.8 (CO_2CH_3) and 165.0 (CO); and

vi) methyl 2H-1-chromene-3-carboxylate **230** (0.08g, 6.6 %); δ_H (400 MHz; $CDCl_3$) 3.81 (3H, s, CH_3) 4.99 (2H, s, CH_2) 6.84 (1H, d, ArH) 6.91 (1H, t, ArH), 7.11 (1H, d, ArH) 7.24 (1H, d, ArH) and 7.43 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 51.9 (CH_3), 64.5 (CH_2), 116.1, 120.9, 121.8, 122.1, 128.9, 132.0, 133.7 and 155.0 (ArC and C=CH) and 165.3 (CO).

***Deprotection of methyl 3-(t-butyldimethylsilyloxy)-3-[2-(t-butyldimethylsilyloxy)phenyl]-2-methylenepropanoate* 271**

Tetrabutylammonium fluoride (1.0g, 3.2 mmol) was added to a stirred solution of methyl 3-(*t*-butyldimethylsiloxy)-3-[2-(*t*-butyldimethylsiloxy)phenyl]-2-methylenepropanoate **271** (0.12 g, 0.27 mmol) in dry THF (1.0 ml) at 0 °C. After 5 minutes, water was added (0.2 ml), followed by dilute HCl until the solution was just acidic, and the sample was then extracted with diethyl ether. The ethereal extracts were combined, dried using anhydrous $MgSO_4$, and the solvent was removed in *vacuo* to afford a crude mixture (0.10 g), which was purified by preparative layer chromatography [elution with hexane-EtOAc (3:2)] to afford, two fractions :-

i) *methyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate* **229**, as a colourless oil, (0.04g, 71 %) (Found: M^+, 208.0733. $C_{11}H_{12}O_4$ requires: *M*, 208.0736); δ_H (400 MHz; $CDCl_3$) 3.82 (3H, s, OCH_3), 4.12 (1H, br s, CH*OH*), 5.59 and 6.35 (2H, 2 x s, $C=CH_2$), 5.74 [1H, s, C*H*(OH)], 6.85 (1H, t, ArH), 6.93 (1H, d, ArH), 6.96 (1H, d, ArH), 7.21 (1H, t, ArH), 7.97 (1H, s, ArOH); δ_C (100 MHz; $CDCl_3$) 52.4 (OCH_3), 73.5 [CH(OH)], 117.6, 120.0, 123.8, 127.8, 128.0, 129.7, 139.4 and 155.9 (ArC and $C=CH_2$) and 167.7 (CO); and

ii) Methyl 2H-1-chromene-3-carboxylate **230**

Attempted cyclisation of methyl 3-hydroxy-3(2-hydroxyphenyl-2-methylenepropanoate 229

To a solution of methyl 3-hydroxy-3(2-hydroxyphenyl)-2-methylenepropanoate **229** in $CDCl_3$ was added a few crystals of DABCO. The ^1H NMR spectrum of the crude mixture indicated the formation of methyl acrylate and salicylaldehyde; other signals tentatively attributed to the

presence of methyl 2*H*-1-chromene-3-carboxylate **230.**

Attempted preparation of 4-hydroxy-4-(4-hydroxyphenyl)-2-methylenebutan-2-one 286

The mixture of 4-hydroxybenzaldehyde (1.2 g, 9.6 mmol), methyl vinyl ketone (1.2 ml, 14 mmol), DABCO (0.86 g, 7.7 mmol) in $CHCl_3$ (1.0 ml) in stoppered flask under N_2 was stirred at room temperature for 7 days. The resulting mixture was purified by flash chromatography [elution with hexane-EtOAc (3:2)] to afford the dimer 3-methylene-2,6-heptanedione **293a** and the starting material, 4-hydroxybenzaldehyde.

***Methyl 3-hydroxy-3-(4-hydroxyphenyl)-2-methylenepropanoate* 287**

A mixture of 4-hydroxybenzaldehyde (0.20 g, 1.6 mmol), methyl acrylate (0.22 ml, 2.5 mmol) and DABCO (0.07 g, 0.7 mmol) in $CHCl_3$ (0.5 ml) in a stoppered reaction flask under N_2 was stirred at room temperature for 7 days. The resulting mixture was purified by flash chromatography [elution with hexane-EtOAc (3:2)], to afford, 4-hydroxybenzaldehyde (0.12 g, 60 %), and as colourless oil, *methyl 3-hydroxy-3-(4-hydroxyphenyl)-2-methylenepropanoate* **287** (0.03 g, 10 %) (Found: M^+, 208.0743. $C_{11}H_{12}O_4$ requires: *M*, 208.0736; ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3407 (br, OH) and 1710 (CO); δ_H (400 MHz; $CDCl_3$) 3.13 [1H, br s, CH(*OH*)], 3.70 (3H, s, OCH_3), 5.49 [1H, s, C*H*(OH)], 5.85 and 6.31 (2H, 2 x s, C=CH_2), 6.10 (1H, s, ArOH), 6.72 (2H, d, ArH) and 7.17 (2H, d, ArH). δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 72.8 [CH(OH)] 115.8, 125.8, 128.1, 133.0, 142.0 and 155.6 (ArC and C=CH_2) and 167 (CO).

tert-*Butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate* 289

A mixture of salicylaldehyde (1.0 ml, 9.6 mmol), *tert*-butyl acrylate (2.1 ml, 14 mmol) and DABCO (0.86 g, 7.7 mmol) in $CHCl_3$ (3.0 ml) was stirred at room temperature in a stoppered flask under N_2 for 7 days. The resulting mixture was purified by flash chromatography [elution with hexane-EtOAc (4:1)] to afford the starting material, salicylaldehyde (0.60 g), and *tert-Butyl 3-hydroxy-3-(2-hydroxyphenyl)-2-methylenepropanoate* **289** (1.10 g, 48.9 %) as a colourless oil which later crystalised, m.p.104 - 106 °C (Found: M^+, 250.1203. $C_{14}H_{18}O_4$ requires: *M*, 250.1205); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3351 (br, OH) and 1691 (CO); δ_H (400 MHz; $CDCl_3$) 1.50 [9H, s, $C(CH_3)_3$], 4.34 [1H, br s, CH(*OH*)], 5.50 and 6.23 (2H, 2 x s, C=CH_2), 5.69 (1H, s, CH), 6.81(1H, t, ArH) 6.87 (1H, d, ArH), 6.96 (1H, d, ArH) 7.15 (1H, t, ArH) and 8.11

3.3 MICHAEL-TYPE ADDITION REACTIONS UNDER BAYLIS-HILLMAN CONDITIONS

Attempted preparation of 2-(3-acetylchromen-4-yl)-1-buten-3-one 292.

3-Acetylchromene **251a** (0.10g, 0.57 mmol), methyl vinyl ketone (0.06ml, 0.7 mmol) and DABCO (0.05g, 0.5 mmol) in $CDCl_3$ (0.50 ml) were placed in an NMR tube. The mixture was shaken and the reaction was monitored by ^1H NMR spectroscopy. After 7 days, there was no evidence of the formation of the expected 2-(3-acetylchromen-4-yl)-1-buten-3-one **292**; instead, the formation of diketone **293a** was observed.

Attempted preparation of 2-(3-acetylchromen-4-yl)-1-penten-3-one

3-Acetylchromene **251a** (0.10g, 0.57 mmol), ethyl vinyl ketone (0.07 ml, 0.7 mmol) and DABCO (0.05g, 0.5 mmol) in $CDCl_3$ (0.5 ml) were placed in an NMR tube. The mixture was shaken and the reaction was monitored by the ^1H NMR spectroscopy. After 7 days, there was no evidence of the formation of the expected 2-(3-acetylchromen-4-yl)-1-penten-3-one; instead a diketone **293c** was observed.

Attempted preparation of ethyl 2-(3-acetylchromen-4-yl)-2-propenoate (method 1)

3-Acetylchromene **251a** (0.10g, 0.57 mmol), ethyl acrylate (0.08ml, 0.7 mmol) and DABCO (0.05g, 0.5 mmol) in $CDCl_3$ (0.5 ml) were placed in an NMR tube. The mixture was shaken and the reaction was monitored by the ^1H NMR spectroscopy. After 7 days, there was no evidence of the formation of ethyl 2-(3-acetylchromen-4-yl)-2-propenoate.

Attempted preparation of ethyl 2-(3-acetylchromen-4-yl)-2-propenoate (method 2)

3-Acetylchromene **251a** (0.10g, 0.57 mmol), ethyl acrylate (0.08ml, 0.7 mmol) and DBU (0.07ml, 0.5 mmol) were placed in an NMR tube. The mixture was shaken and the reaction was monitored by ^1H NMR spectroscopy. After 7 days there was no evidence of the formation of the expected ethyl 2-(3-acetylchromen-4-yl)-2-propenoate.

Attempted preparation of methyl 2-(3-acetylchromen-4-yl)-2-propenoate

3-Acetylchromene **251a** (0.10g, 0.57 mmol), methyl acrylate (0.06 ml, 0.7 mmol) and DBU (0.07ml, 0.5 mmol) in $CDCl_3$ (0.5 ml) were placed in an NMR tube. The mixture was shaken and the reaction was monitored by ^1H NMR spectroscopy. After 7 days, there was no evidence of the formation of the expected methyl 2-(3-acetylchromen-4-yl)-2-propenoate.

3.3.1 Preparation of dimers of α,β-unsaturated vinyl systems

***3-Methylene-2,6-heptanedione* 293a**

A mixture of methyl vinyl ketone (1.0 ml, 12 mmol) and DABCO (0.45g, 4.0 mmol) in chloroform (1.0 ml) was stirred at room temperature in a stoppered reaction flask for 7 days. The resulting mixture was purified by flash chromatography [elution with hexane - EtOAc (3:2)] to afford, as a dark yellow oil, 3-methylene-2,6-heptadione **293a** (0.50g, 59 %). ν_{max} (thin film /cm^{-1}) 1709 and 1670 (CO); δ_H (400 MHz; $CDCl_3$) 2.02 (3H, s, CH_3), 2.22 (3H, s, CH_3), 2.43 (2H, m, CH_2), 2.47 (2H, m, CH_2), 5.73 and 5.93 (2H, 2 x s, C=CH_2); δ_C (100 MHz; $CDCl_3$) 25.0 (CH_3), 25.6 (CH_2), 29.6 CH_2), 42.2 (CH_3) 125.9 (C=*C*H_2) 147.5 (*C*=CH_2) 199.2 (CO) and 207.5 (CO).

Attempted preparation of 2-methylenedipentanal 293b

A mixture of acrolein (1.0 ml, 15 mmol) and DABCO (0.56g, 5.0 mmol) in chloroform (1.0 ml) was stirred at room temperature for 7 days to form intractable mixture.

***4-Methylene-3,7-nonanedione* 293c**

A mixture of ethyl vinyl ketone (0.50 ml, 5.0 mmol) and DABCO (0.19g, 1.7 mmol) in chloroform (0.5 ml) was stirred at room temperature in a stoppered reaction flask for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane - EtOAc (4:1)] to afford, as a yellow oil, 4-methylene-3,7-nonanedione **293c** (0.23g, 55 %); ν_{max} (thin film /cm^{-1}) 1713 and 1677 (CO); δ_H (400 MHz; $CDCl_3$) 0.94 (3H, t, *J* 7.3 Hz, CH_3), 0.99 (3H, t, *J* 7.3 Hz, CH_3), 2.33 (2H, q, *J* 7.3 Hz, CH_2), 2.46 (4H, m, 2 x CH_2), 2.62 (2H, q, *J* 7.3 Hz, CH_2), 5.69 and 5.92 (2H, 2 x s, C=CH_2); δ_C (100 MHz; $CDCl_3$) 7.7 (CH_3), 8.3 (CH_3), 25.6 (CH_2), 30.7 (CH_2), 35.8 (CH_2), 41.0 (CH_2), 124.7 (C=*C*H_2) 147.2 (*C*=CH_2), 202.1 (CO) and 210.5 (CO).

***2,4-(Diphenylsulfonyl)but-1-ene* 293d**

A mixture of phenyl vinyl sulfone (0.50g, 3.0 mmol) and DABCO (0.11g, 0.99 mmol) in chloroform (1 ml) was stirred at room temperature in a stoppered reaction flask for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as a colourless oil, 2,4-(diphenylsulfonyl)but-1-ene **293d** (0.10g, 20 %); ν_{max} (thin film/cm^{-1}) 3038 (C=*C-H*) and 2929 (CH_2); δ_H (400 MHz; $CDCl_3$) 2.64 (2H, m, CH_2), 3.32 (2H, m, CH_2), 5.80 and 6.38 (2H, 2 x s, C= CH_2) 7.49 - 7.88 (10H, m, ArH); δ_C (100 MHz; $CDCl_3$) 23.6 (CH_2), 54.4 (CH_2), 126.2, 128.1, 128.2, 129.4, 129.5, 133.9, 134.0, 137.8, 138.4 and 146.7 (ArC and C=CH_2).

***Diphenyl butene-2,4-disulfonate* 293e**

A mixture of phenyl vinylsulfonate (0.20g, 1.1 mmol) and DABCO (0.04g, 0.4 mmol) in chloroform (0.5 ml) was stirred at room temperature in a stoppered reaction flask for 7 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane - EtOAc (4:1)] to afford, as colourless oil, 2,4-diphenyl butene-2,4-disulfonate **293e** (0.12g, 60 %); ν_{max} (thin film /cm^{-1}) 2922 (CH_2) and 1588 (*C*=*C*H_2); δ_H (400 MHz; $CDCl_3$) 3.21 (2H, m, CH_2) 3.63 (2H, m, CH_2) 6.01 and 6.02 (2H, 2 x s, C=CH_2) 7.18 - 7.43 (10H, m, ArH); δ_C (100 MHz; $CDCl_3$) 25.8 (CH_2), 48.6 (CH_2),121.8, 121.9, 127.5, 130.0, 130.1, 130.2, 130.3, 141.1, 148.9 and 149.1 (ArC and C=CH_2).

***2,4-Dicyanobut-1-ene* 293f**

A mixture of acrylonitrile (1.0 ml, 15 mmol) and DABCO (0.56g, 5.1 mmol) in chloroform (1.0 ml) was stirred in stoppered reaction flask at room temperature for 7 days. The resulting mixture was chromatographed (elution with EtOAc) to afford, as colourless oil, 2,4-dicyanobut-1-ene **293f** (0.10g, 12 %); ν_{max} (thin film / cm^{-1}) 2867 (CH_2) 2250 and 2224 (2 x CN); δ_H (400 MHz; $CDCl_3$) 2.62 (2H, m, CH_2), 2.74 (2H, m, CH_2), 5.91 and 6.02 (2H, 2 x s, C=CH_2); δ_C (100 MHz; $CDCl_3$) 30.3 (CH_2), 46.9 (CH_2), 117.0, 117.4, 119.0 (2 x CN and *C*=CH_2) and 133. 4 (C=*C*H_2).

Attempted preparation of dimethyl 2-methylenepentenoate 293g

A mixture of methyl acrylate (1.0 ml, 11 mmol) and DABCO (0.41g, 3.7 mmol) in chloroform (1.0 ml) was stirred in a closed reaction flask for 7 days. The ^{1}H NMR spectroscopy indicated an

unreacted methyl acrylate

***Dimethyl 2-methylenepentanoate* 293g**

A mixture of methyl acrylate (1.0 ml, 11 mmol) and DBU (0.55 ml, 3.7 mmol) in chloroform (1.0 ml) was stirred in a stoppered reaction flask for 7 days. The resulting mixture was chromatographed. (flash chromatography on silica; elution with EtOAc) to afford, as yellow oil, dimethyl 2-methylenepentanoate **293g** (0.08g, 10 %); ν_{max} (thin film / cm^{-1}) 1739 and 1733 (2 x CO); δ_H (400 MHz; $CDCl_3$) 2.49 (2H, m, CH_2), 2.61 (2H, m, CH_2), 3.64 (3H, s, CH_3), 3.71 (3H, s, CH_3), 5.57 and 6.15 (2H, 2 x s, C=CH_2); δ_C (100 MHz; $CDCl_3$) 27.3 (CH_2), 32.9 (CH_2), 51.5 (CH_3), 51.8 (CH_3), 125.9 (C=*C*H_2), 138.8 (*C*=CH_2), 167.1 (CO) and 171.0 (CO).

***Diethyl 2-methylenepentanoate* 293h**

A mixture of ethyl acrylate (1.0 ml, 9.2 mmol) and DBU (0.46 ml, 3.1 mmol) in chloroform (1.0 ml) was stirred in stoppered reaction flask for 7 days. The resulting mixture was chromatographed (flash chromatography on silica; elution with EtOAc) to afford, as a yellow oil, diethyl 2-methylenebutanoate **293h** (0.05g, 5 %); ν_{max} (thin film / cm^{-1}); 1724 and 1715 (2 x CO); δ_H (400 MHz; $CDCl_3$) 1.23 (3H, t, *J* 7.1 Hz, CH_3), 1.28 (3H, t, *J* 7.1 Hz, CH_3), 2.49 (2H, m, CH_2) 2.62 (2H m, CH_2), 4.11 (2H, q, *J* 7.1 Hz, CH_2), 4.20 (2H, q, *J* 7.1 Hz, CH_2), 5.56 and 6.17 (2H, 2 x s, C=CH_2); δ_C (100 MHz; $CDCl_3$) 14.2 (2 x CH_3) 27.3 (CH_2) 33.1 (CH_2) 60.4 (CH_3CH_2) 60.7 (CH_3CH_2), 125.5 (C=*C*H_2) 139.2 (*C*=CH_2) 166.7 (CO) and 172.7 (CO).

***1,5-Diphenyl-2-methylene-1,5-pentanedione* 293i**

A mixture of phenyl vinyl ketone (0.50g, 3.8 mmol) and DABCO (0.15g, 1.3 mmol) in chloroform (1.0 ml) was stirred in a closed stoppered flask for 7 days. The resulting reaction mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc(3:2)] to afford, as white crystals, 1,5-diphenyl-2-methylene-1,5-pentanedione **293i**, (0.32g, 65 %) m.p.52 °C; ν_{max} (in chloroform /cm^{-1}) 1684 and 1650 (2 x CO); δ_H (400 MHz; $CDCl_3$) 2.91 (2H, t, *J* 7.2 Hz, CH_2), 3.24 (2H, t, *J* 7.24 Hz, CH_2), 5.67 and 5.96 (2H, 2 x s, C=CH_2) 7.40 - 7.98 (10H, m, ArH). δ_C (100 MHz; $CDCl_3$) 27.3 (CH_2), 37.2 (CH_2), 127.3, 128.1, 128.2, 128.6, 129.5, 132.2, 133.1, 136.7, 137.7 and 146.7 (ArC and C=CH_2) 198.1 (CO) and 199.2 (CO).

3.4 ATTEMPTED INTRAMOLECULAR CATALYSTS

***Methylthioethyl-2-propenoate* 297**

A solution of 2-methythioethanol (1.0 ml, 12 mmol) and triethanolamine (1.6 ml, 12 mmol) in dry THF (1.0 ml) was placed in two-necked flask under N_2. To the solution, acryloyl chloride (0.93 ml, 12 mmol) was added slowly with stirring, the reaction mixture was stirred at room temperature for 2 hours. The resulting mixture was extracted with EtOAc (3 x 50 ml) and the combined extracts were dried over $MgSO_4$. The solvent was evapourated in *vacuo* to afford, as a light yellow oil, methylthioethyl-2-propenoate **297** (1.35g, 80.4 %); ν_{max} (thin film /cm^{-1}) 1727 (CO); δ_H (400 MHz; $CDCl_3$) 2.06 (3H, s, CH_3), 2.67 (2H, t, *J* 7.2 Hz, CH_2S) 4.23 (2H, t, *J* 7.2 Hz, CH_2O) 5.75 (1H, dd, *J* 1.2 Hz and 10.4 Hz, CH), 6.04 (1H, dd, *J* 10.4 Hz and 17.2 Hz, CH), 6.31 and (1H, dd, 1.6 Hz and 17.2 Hz); δ_C (100 MHz; $CDCl_3$) 15.5 (CH_3), 32.3 (CH_2S), 63.0 (CH_2O), 128.0 (*C*H=CH_2), 130.7 (CH=*C*H_2) and 165.6 (CO).

Attempted preparation of methylthioethyl 3-hydroxy-2-methylene-3-(pyridin-4-yl)propanoate 301

Methylthioethyl 2-propenoate **297** (0.20g, 1.4 mmol) and pyridine-4-carboxaldehyde (0.13ml, 1.4 mmol) were dissolved in $CDCl_3$ (0.3 ml), and the solution was stirred at room temperature for 2 hours. ^{1}H NMR analysis gave no evidence of the formation of methylthioethyl 3-hydroxy-2-methylene-3-(pyridin-4-yl)propanoate **301**. Microwave irradiation of the mixture for 5 minutes failed to effect any change.

Attempted preparation of methylthioethyl 3-hydroxy-2-methylenebutanoate

Acetaldehyde (0.080 ml, 1.4 mmol) and methylthioethyl-2-propenoate **297** (0.20g, 1.4 mmol) were dissolved in $CDCl_3$ (0.3 ml). The reaction mixture was stirred at room temperature for 2 hours, but ^{1}H NMR analysis gave no evidence of the formation of methylthioethyl 3-hydroxy-2-methylenebutanoate.

3.5 SYNTHESIS OF THIOCHROMENES

***Sulfanylbenzyl alcohol* 308**[89]

A solution of thiosalicylic acid (4.4g, 28 mmol) in dry THF (50 ml) was added dropwise to a stirred slurry of lithium aluminium hydride (2.0g, 52 mmol) in THF (80 ml) under N_2, and the resulting mixture was stirred for 24 hours. Ethyl acetate (10 ml) and 10 % sulphuric acid (40 ml) were added dropwise, the mixture was filtered and the aqueous layer extracted with ethyl acetate (2 x 30 ml). The combined organic layer was washed with satd. brine, dried over anhydrous Na_2SO_4, and the solvent was evaporated under vacuum to afford sulfanylbenzyl alcohol **308** (2.80g, 72 %); δ_H (400 MHz; $CDCl_3$) 2.64 (1H, br s, OH), 3.65 (1H, s, SH), 4.71 (2H, s, CH_2), 7.17 - 7.32 (4H, m, ArH); δ_C (100 MHz; $CDCl_3$) 64.2 (CH_2), 126.3, 128.3, 128.7, 130.1, 131.3 and 138.8 (ArC).

***2,2'-Dithiodibenzaldehyde* 302**[140]

In a 100 ml round-bottomed flask, fitted with a reflux condenser and a magnetic stirrer and filled with N_2, pyridiniumchlorochromate (9.6g, 45 mmol) was dispersed in deoxygenated and dry dichloromethane (40ml). A solution of sulfanylbenzyl alcohol **308** (2.50g, 17.8 mmol) in deoxygenated and dry dichloromethane (8 ml) was added, *via* a syringe through a septum, to the stirred mixture. After stirring the reaction mixture for 4 hours at room temperature, dichloromethane (40 ml) was added and the supernatant liquid was decanted from the black gum which had formed. The black gum was washed with dichloromethane (3 x 15 ml) and dry diethyl ether (20 ml)and the combined washings were passed through a florisil pad. The solvent evaporated under vacuum and the residual solid was recrystallised from ethanol to afford 2,2'-dithiodibenzaldehyde **302** as white crystals (1.30g, 53 %), m.p. 142 - 144 °C (lit. [147] 144 °C); δ_H (400 MHz; $CDCl_3$) 7.38 (1H, t, ArH), 7.48 (1H, t, ArH), 7.78 (1H, d, ArH), 7.86 (1H, d, ArH) and 10.22 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 126.3, 126.8, 133.9, 134.2, 134.5 and 140.0 (ArC) and 191.7 (CO).

***3-Acetyl-2H-1-thiochromene* 310a**

To a stirred solution of 2,2'-dithiodibenzaldehyde **302** (0.25g, 0.91 mmol), methyl vinyl ketone (0.22ml, 2.7 mmol) in chloroform (1.0 ml) under N_2 was slowly added DBU (0.22ml, 1.5 mmol).

The reaction mixture was stirred vigorously in a stoppered reaction flask under N_2 at room temperature for 24 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with EtOAc-hexane (2:3)] to afford, as yellow oil, *3-acetyl-2*H-*1-thiochromene* **310a** (0.20g, 59 %) (Found: M^+, 190.0447. $C_{11}H_{10}OS$ requires: *M*, 190.0452); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3053 (C=*C-H*) and 1667.6 (CO); δ_H (400 MHz; $CDCl_3$) 2.46 (3H, s, CH_3), 3.71 (2H, s, CH_2), 7.13 - 7.27 (4H, m, ArH) and 7.38 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 22.9 (CH_3), 25.3 (CH_2), 125.7, 127.3, 130.5, 130.8, 131.4, 131.8, 135.0 and 137.8 (ArC and C=CH) and 196.6 (CO); *m/z* 190 (M^+, 22.7) and 163 (100 %).

Attempted preparation of 2*H*-1-thiochromene-3-carbaldehyde 310b

To a stirred solution of 2,2'-dithiodibenzaldehyde **302** (0.10g, 0.36 mmol), acrolein (72.5 µl, 1.10 mmol) in chloroform (1.0 ml) under N_2, was slowly added DBU (0.09 ml, 0.6 mmol). The mixture was stirred in a stoppered reaction flask under N_2 for 24 hours. The resulting oily mixture was chromatographed [flash chromatography on silica; elution with benzene-EtOAc (4:1)] to afford material, ^{1}H NMR analysis of which failed to reveal the presence of the expected product.

***3-Propanoyl-2*H-*1-thiochromene* 310c**

To a stirred solution of 2,2'-dithiodibenzaldehyde **302** (0.10g, 0.36 mmol), ethyl vinyl ketone (0.11ml, 1.1 mmol) in chloroform (0.50 ml) under N_2, was slowly added DBU (0.09 ml, 0.6 mmol). The mixture was stirred in a stoppered reaction flask under N_2 at room temperature for 48 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford, as a yellow oil, *3-propanoyl-2*H-*1-thiochromene* **310c** (0.10g, 67 %) (Found: M^+, 204.0590. $C_{12}H_{12}OS$ requires: *M*, 204.0609); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 2924, 2853 (CH_2 and CH_3) and 1674 (CO); δ_H (400 MHz; $CDCl_3$) 1.18 (3H, t, *J* 7.3 Hz, CH_3), 2.84 (3H, q, *J* 7.3, CH_2), 3.72 (2H, s, CH_2), 7.13 - 7.27 (4H, m, ArH) and 7.39 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 8.6 (CH_3), 23.1 (CH_3CH_2), 30.4 (CH_2), 125.7, 127.3, 130.4, 130.7, 131.2, 131.4, 134.9 and 136.6 (ArC and C=CH) and 199.5 (CO); *m/z* 204 (M^+, 19.9) and 203 (100 %).

***3-Phenylsulfonyl-2*H-*1-thiochromene* 310d**

To a stirred solution of 2,2'-dithiodibenzaldehyde **302** (0.20g, 0.73 mmol), phenyl vinyl sulfone

(0.87g, 2.19 mmol) in chloroform (1.0 ml) under N_2 was slowly added DBU (0.18 ml, 1.2 mmol). The reaction mixture was stirred in a stoppered reaction flask under N_2 at room temperature for 24 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford, as a yellow oil, *3-phenylsulfonyl-2H-1-thiochromene* **310d** (0.21g, 50 %); (Found: M^+, 288.0278. $C_{15}H_{12}O_2S_2$ requires: *M*, 288.0279); ν_{max} (hexachlorobutadiene mull /cm^{-1})3066 (C=*C-H*) and 1444 (C=C); δ_H (400 MHz; $CDCl_3$) 3.56 (2H, s, CH_2), 7.11 - 7.93 (10H, m, ArH and 4-CH); δ_C (100 MHz; $CDCl_3$) 23.3 (CH_2), 125.8, 126.9, 127.7, 129.2, 129.3, 129.6, 131.0, 132.1, 132.6, 133.6, 135.7 and 139.1 (ArC and C=CH); *m/z* 288 (M^+, 37.2) and 146 (100 %).

***Phenyl 2H-1-thiochromene-3-sulfonate* 310e**

To a stirred solution of 2,2'-dithiodibenzaldehyde **302** (0.20g, 0.73 mmol), phenyl vinylsulfonate (0.40g, 2.2 mmol) in chloroform (1.0 ml) under N_2 was slowly added DBU (0.18 ml, 1.2 mmol) The reaction mixture was stirred in stoppered reaction flask under N_2 at room temperature for 24 hours. The resulting oily mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford, as a yellow oil, *phenyl 2H-1-thiochromene-3-sulfonate* **310e** (0.22g, 55 %); (Found: M^+, 304.0244. $C_{15}H_{12}O_3S_2$ requires: *M*, 304.0228); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 2923 and 2853 (CH_2 and CH_3) and 1488.8 (C=C); δ_H (400 MHz; $CDCl_3$) 3.84 (2H, s, CH_2), 7.18 - 7.40 (10H, m, ArH and 4-CH); δ_C (100 MHz; $CDCl_3$) 115.3, 122.3, 126.3, 126.4, 127.3, 127.4, 129.8, 131.3, 131.5, 133.3, 138.6 and 149.4 (ArC and C=CH); *m/z* 304 (M^+, 35.2) and 146 (100 %).

***3-Cyano-2H-1-thiochromene* 310f**

To a stirred solution of 2,2'-dithiodibenzaldehyde **302** (0.20g, 0.73 mmol), acrylonitrile (0.14ml, 2.2 mmol) in chloroform (1.0 ml) under N_2, was slowly added DBU (0.18 ml, 1.2 mmol). The mixture was stirred in stoppered reaction flask under N_2 at room temperature for 24 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as yellow crystals, *3-cyano-2H-1-thiochromene* **310f** (0.13g, 52 %), m.p.78 - 80 °C; (Found: M^+, 173.0298. $C_{10}H_7NS$ requires: *M*, 173.0299); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 2924 and 2851 (CH_2 and CH_3) and 2211 (CN); δ_H (400 MHz; $CDCl_3$) 3.57 (2H, s, CH_2), 7.14 - 7.24 (5H, m, ArH and C=CH); δ_C (100 MHz; $CDCl_3$) 25.9

(CH_2), 103.9, 118.2, 126.3, 127.5, 130.1, 130.9, 132.8 and 142.1 (ArC and C=CH) and 152.8 (CN); *m/z* 173 (M^+, 60.3) and 172 (100 %).

***Methyl 2H-1-thiochromene-3-carboxylate* 310g**

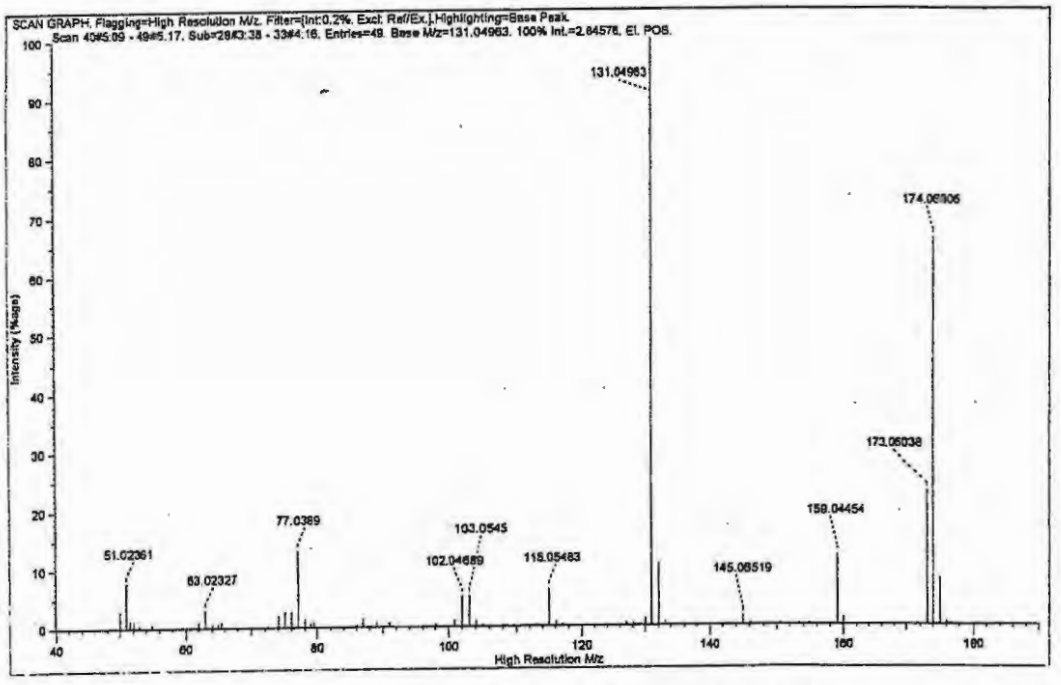
To a stirred solution of 2,2'-dithiodibenzaldehyde **302** (0.20g, 0.73 mmol), methyl acrylate (0.20 ml, 2.2 mmol) in chloroform (1.0 ml) under N_2, was slowly added DBU (0.18 ml, 1.2 mmol). The mixture was stirred in a stoppered reaction flask under N_2 at room temperature for 24 hours. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (3:2)] to afford, as yellow oil, *methyl 2H-1-thiochromene-3-methanoate* **310g** (0.12g, 40 %) (Found: M^+, 190.0447. $C_{11}H_{10}OS$ requires: *M*, 190.0452); ν_{max} (hexachlorobutadiene mull / cm^{-1}) 2949 and 2846 (CH_2 and CH_3) and 1713 (CO); δ_H (400 MHz; $CDCl_3$) 3.75 (2H, s, CH_2), 3.86 (3H, s, CH_3), 7.11 - 7.26 (4H, m, ArH) and 7.56 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 24.0 (CH_2), 52.1 (CH_3), 123.0, 125.7, 127.1, 130.1, 130.6, 131.3, 134.0 and137.3 (ArC and C=CH) and 166.3 (CO); *m/z*190 (M^+,15.8) and 161 (100 %).

***Ethyl 2H-1-Thiochromene-3-carboxylate* 310h**

To a solution of 2,2'-dithiodibenzaldehyde **302** (0.10g, 0.36 mmol), ethyl acrylate (0.12ml, 1.1 mmol) in chloroform (1.0 ml) under N_2, was slowly added DBU (0.09 ml, 0.6 mmol). The mixture was stirred in a stoppered reaction flask under N_2 at room temperature for 14 days. The resulting mixture was chromatographed [flash chromatography on silica; elution with hexane-EtOAc (4:1)] to afford, as yellow oil, *ethyl 2H-1-thiochromene-3-carboxylate* **310h** (0.09g, 56 %) (Found: M^+, 220.0542. $C_{12}H_{12}O_2S$ requires: *M*, 220.0558); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 2928 and 2852 (CH_2 and CH_3) and 1715 (CO); δ_H (400 MHz; $CDCl_3$) 1.37 (4H, t, *J* 7.1 Hz, CH_3), 3.72 (2H, s, CH_2), 4.28 (2H, q, *J* 7.1 Hz, CH_3CH_2) 7.12 - 7.26 (4H, m, ArH) and 7.53 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 14.3 (CH_3), 24.0 (CH_2), 61.1 (CH_3CH_2) 123.4, 125.7, 127.1, 130.1, 130.5, 131.4, 134.0 and 137.0 (ArC and C=CH) and 165.9 (CO); *m/z* 220 (M^+, 19.1) and 219 (100 %).

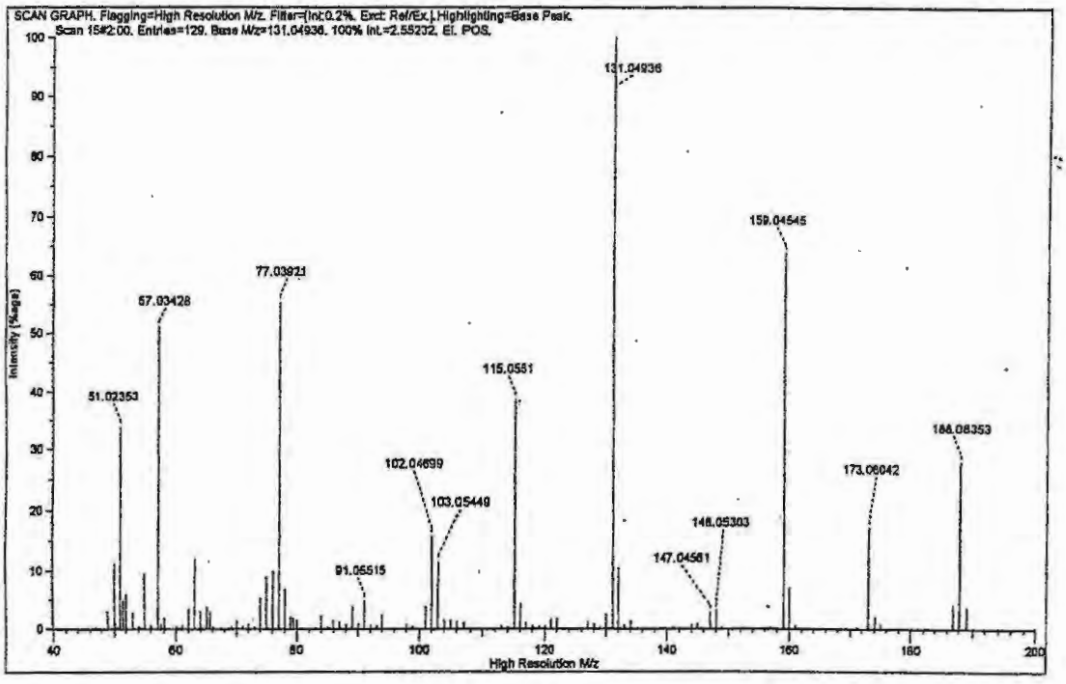
3.6 DATA FOR THE ELECTRON-IMPACT MASS SPECTROMETRIC ANALYSIS OF THE CHROMENE AND THIOCHROMENE DERIVATIVES

3-Acetyl-2H-1-chromene 251a



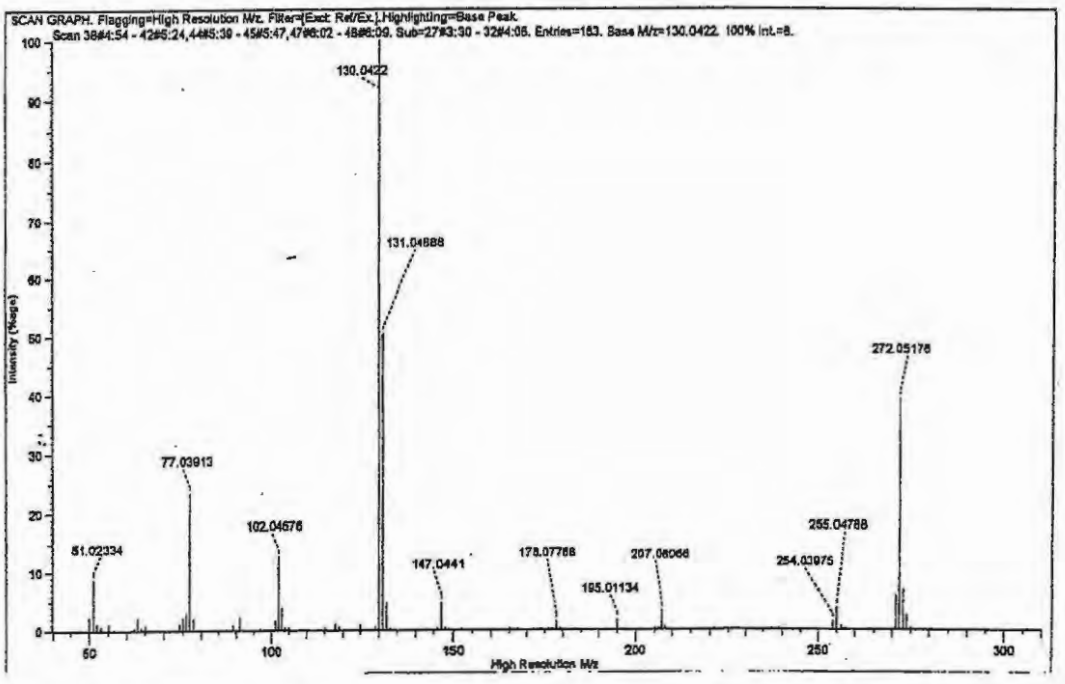
Formula	Observed Mass	Calculated Mass
$C_{11}H_{10}O_2$	174.0681	174.0681
$C_{11}H_9O_2$	173.0604	173.0603
$C_{10}H_7O_2$	159.0445	159.0446
$C_{10}H_9O$	145.0652	145.0653
C_9H_7O	131.0496	131.0497
C_9H_7	115.0548	115.0548
C_8H_7	103.0545	103.0548
C_8H_6	102.0469	102.0469
C_6H_5	77.0389	77.0391
C_5H_3	63.0233	63.0235

3-Propanoyl-2H-1-chromene 251c



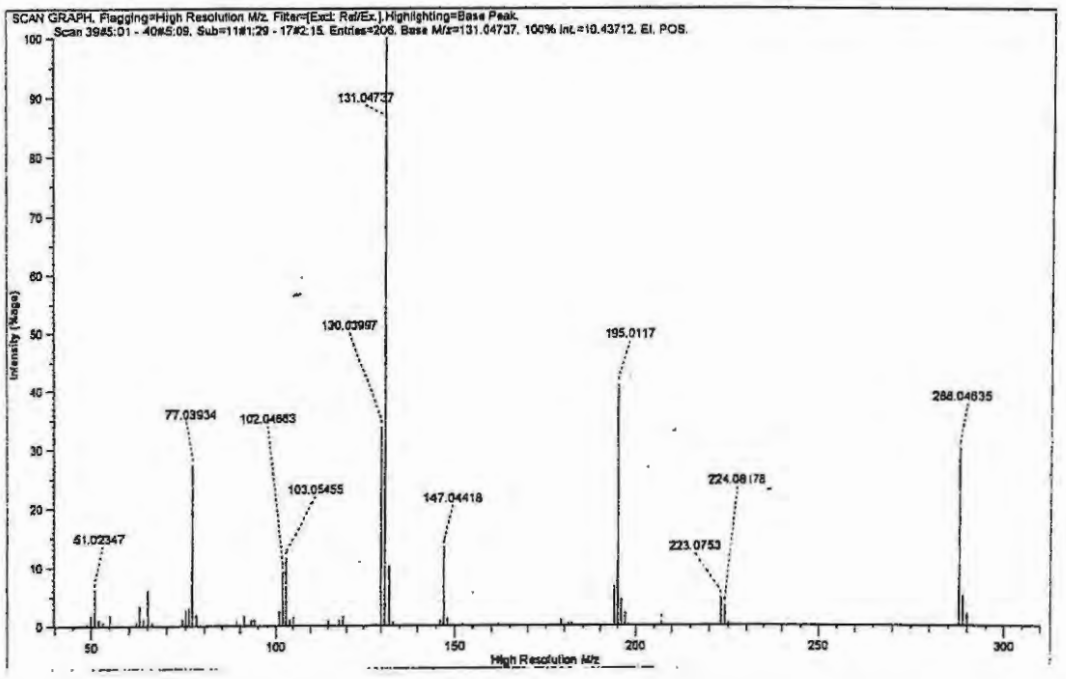
Formula	Observed Mass	Calculated Mass
$C_{12}H_{12}O_2$	188.0835	188.0837
$C_{11}H_9O_2$	173.0604	173.0602
$C_{10}H_7O_2$	159.0454	159.0446
C_9H_7O	131.0494	131.0497
C_9H_7	115.0551	115.0548
C_8H_7	103.0545	103.0548
C_8H_6	102.0470	102.0469
C_6H_5	77.0392	77.0391
C_3H_5O	57.0343	57.0340

3-Phenylsulfonyl-2H-1-chromene 251d



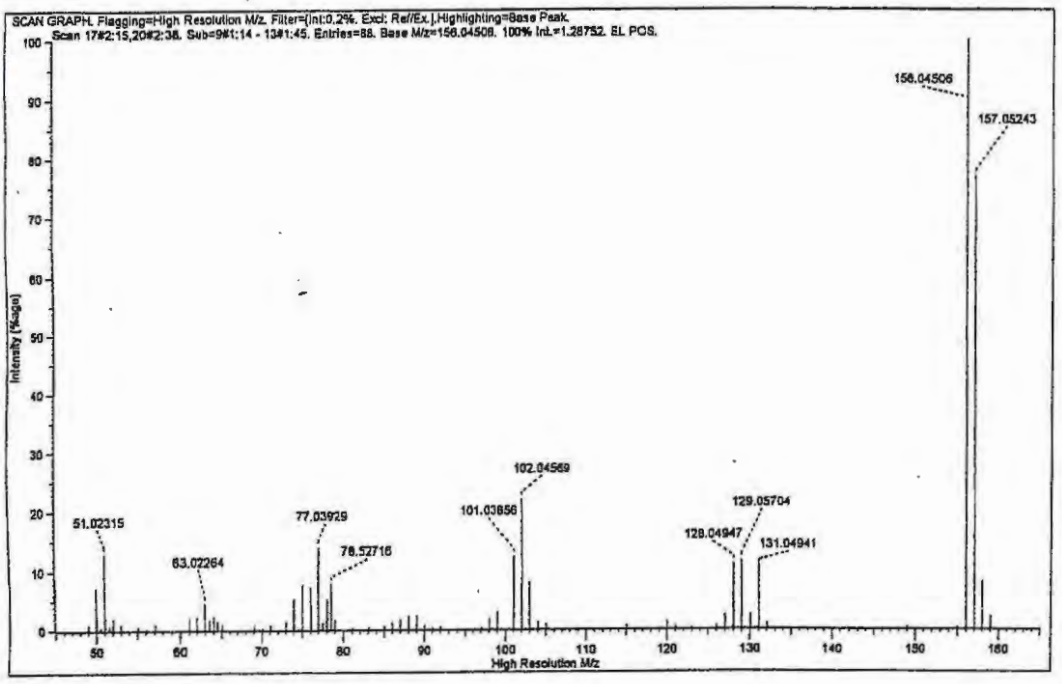
Formula	Observed Mass	Calculated Mass
$C_{15}H_{12}SO_3$	272.0518	272.0507
$C_{15}H_{11}SO_2$	255.0479	255.0480
$C_{15}H_{11}SO_2$	254.0397	254.0402
$C_{15}H_{11}SO$	239.0516	239.0531
$C_{15}H_{11}O$	207.0807	207.0810
$C_9H_7SO_3$	195.0113	195.0116
$C_{14}H_{10}$	178.0777	178.0782
$C_9H_7O_2$	147.0441	147.0446
C_9H_7O	131.0489	131.0497
C_9H_6O	130.0422	130.0419
C_8H_6	102.0468	102.0469
C_6H_5	77.0391	77.0391

***Phenyl 2H-1-chromene-3-sulfonate* 251e**



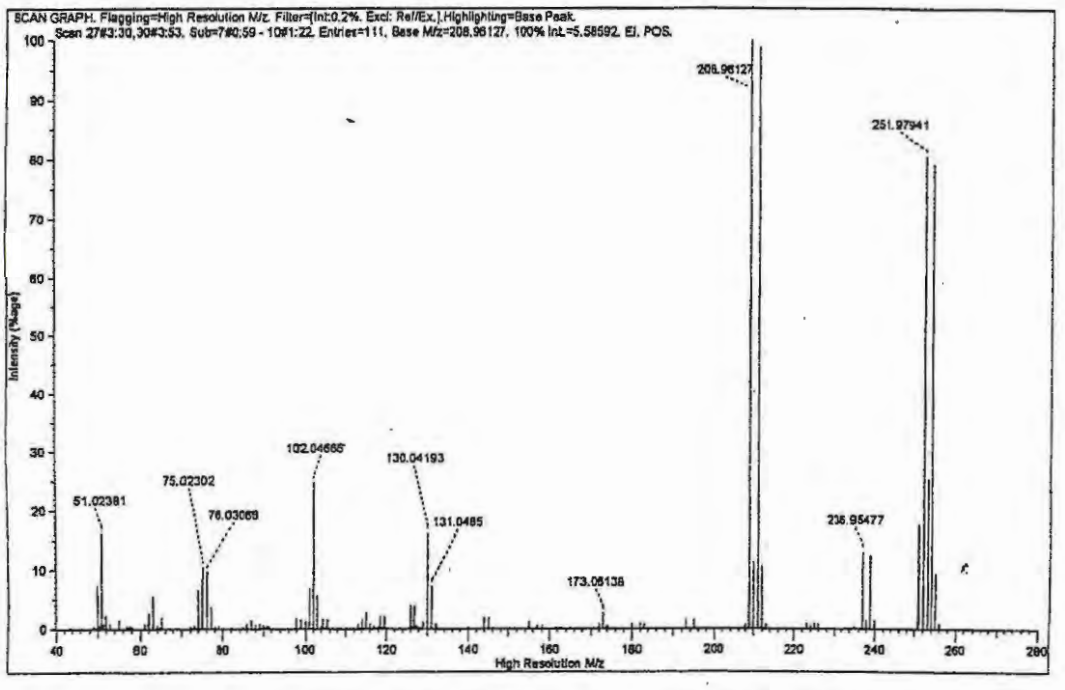
Formula	Observed Mass	Calculated Mass
$C_{15}H_{12}SO_4$	288.0464	288.0456
$C_{15}H_{12}O_2$	224.0818	224.0837
$C_{15}H_{11}O_2$	223.0753	223.0759
$C_9H_7SO_3$	195.0117	195.0116
$C_9H_7O_2$	147.0442	147.0446
C_9H_7O	131.0474	131.0497
C_9H_6O	130.0400	130.0419
C_8H_7	103.0546	103.0548
C_8H_6	102.0466	102.0469
C_7H_7	91.0552	91.0548
C_6H_5	77.0393	77.0391

3-Cyano-2H-1-chromene 251f



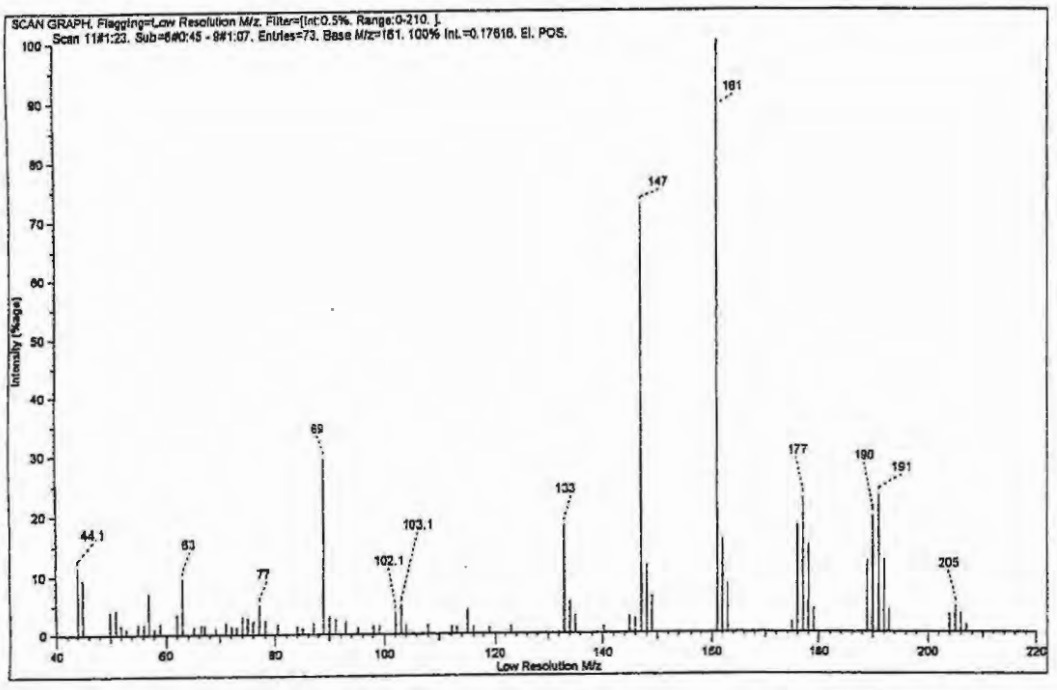
Formula	Observed Mass	Calculated Mass
$C_{10}H_7NO$	157.0524	157.0528
$C_{10}H_6NO$	156.0451	156.0449
C_9H_7O	131.0494	131.0497
C_9H_7N	129.05	129.0578
C_9H_6N	128.0495	128.0500
C_8H_6	102.0457	102.0469
C_8H_5	101.0386	101.0391
C_6H_5	77.0393	77.0391
C_6H_3	75.0230	75.0235

3-Acetyl-6-bromo-2H-1-chromene 251k



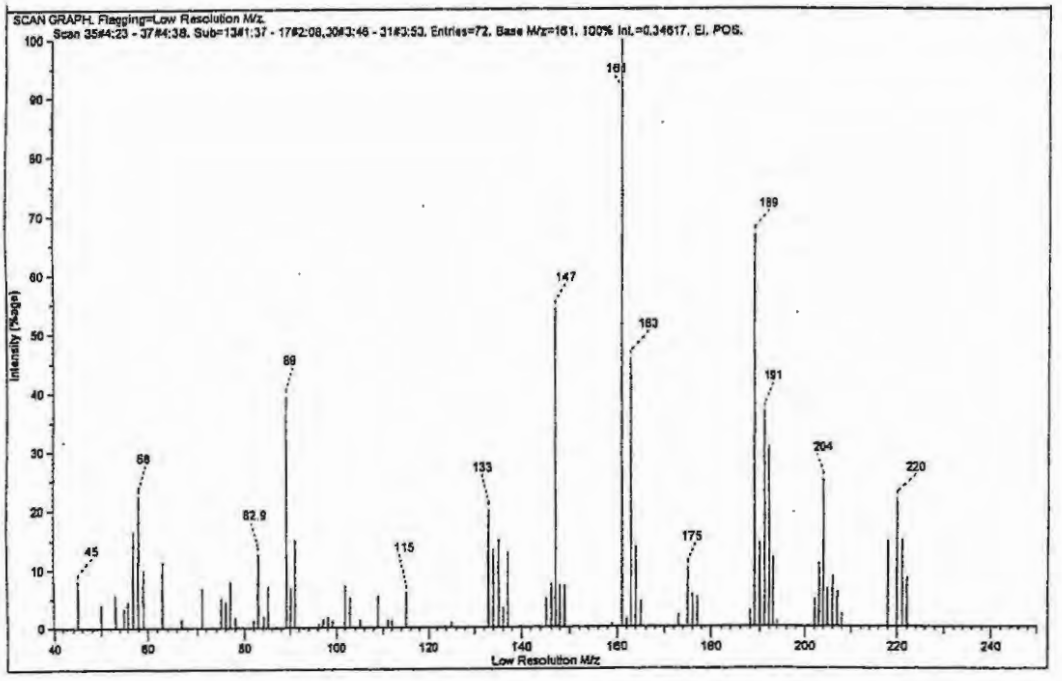
Formula	Observed Mass	Calculated Mass
$C_{11}H_9O_2{}^{79}Br$	251.9794	251.9786
$C_{10}H_6O_2{}^{79}Br$	236.9548	236.9551
$C_9H_6O^{79}Br$	208.9613	208.9602
$C_{11}H_9O_2$	173.0614	173.0602
C_9H_7O	131.0485	131.0497
C_9H_6O	130.0419	130.0419
C_8H_6	102.0467	102.0469
C_6H_4	76.0307	76.0313
C_6H_3	75.0230	75.0235
C_5H_3	63.0232	63.0235

3-Acetyl-2H-1-thiochromene **310a**



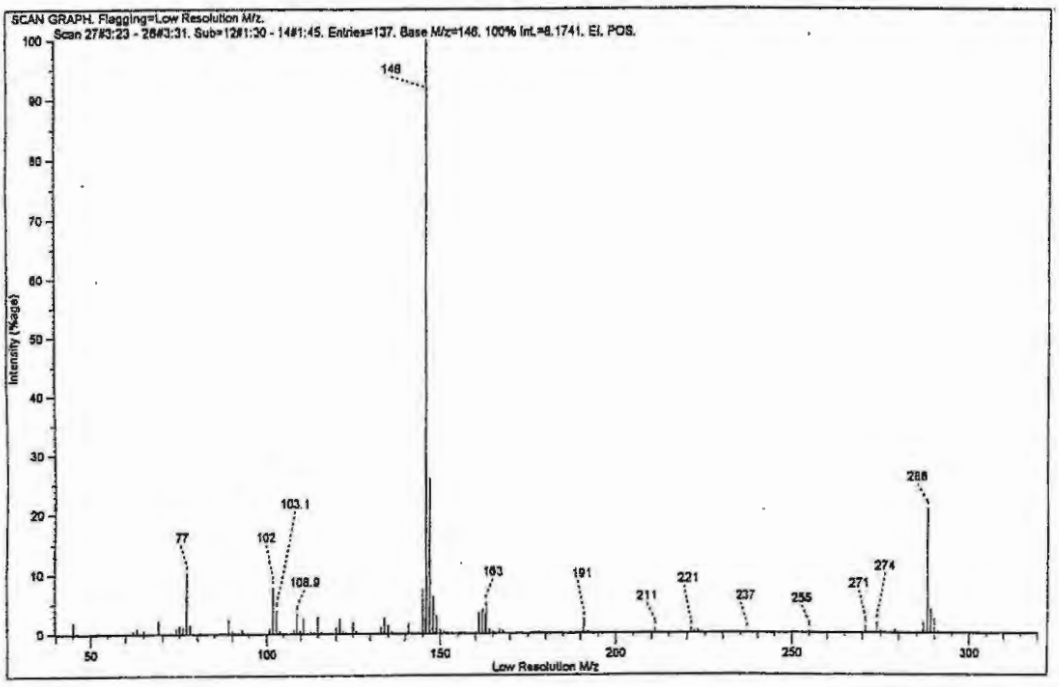
Formula	Observed Mass	Calculated Mass
$C_{11}H_{10}SO$	190.0442	190.0452
C_9H_5SO	161.0069	161.0061
C_9H_7S	147.0263	147.0268
C_8H_7S	135.0255	135.0268
C_8H_6S	134.0183	134.0190
C_8H_5S	133.0110	133.0112
C_9H_7	115.0544	115.0548
C_8H_7	103.0548	103.0548
C_8H_6	102.0466	102.0469

3-Propanoyl-2H-1-thiochromene **310c**



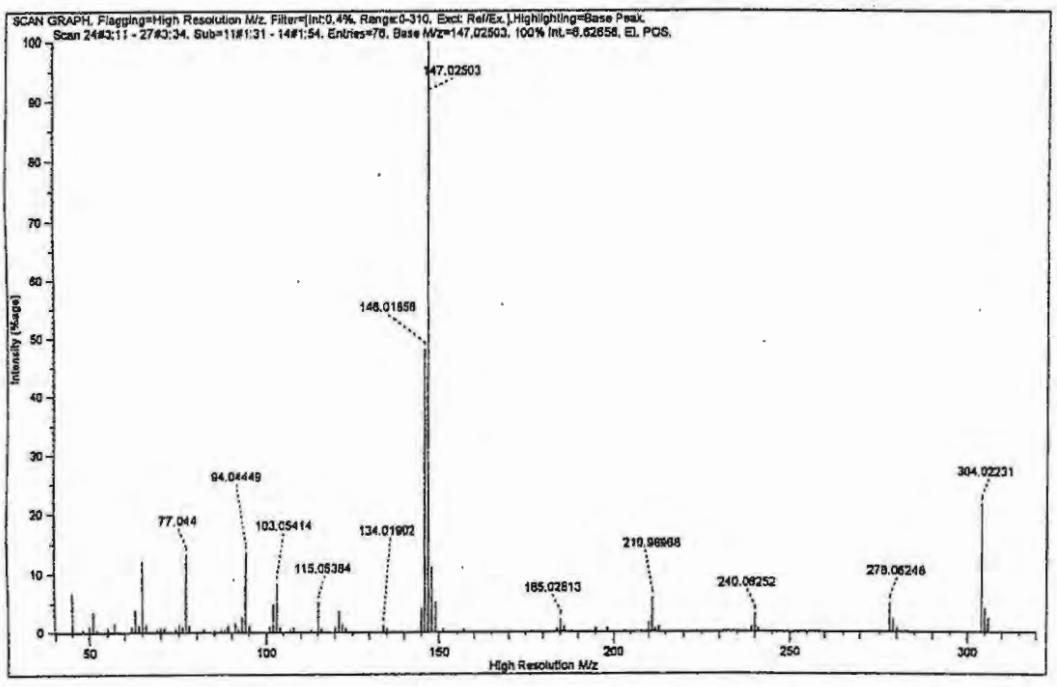
Formula	Observed Mass	Calculated Mass
$C_{12}H_{12}SO$	204.0585	204.0609
$C_{11}H_{11}SO$	191.0504	191.0531
$C_{11}H_{10}SO$	190.0440	190.0452
$C_{10}H_7SO$	175.0217	175.0218
C_9H_5SO	161.0062	161.0061
C_9H_7S	147.0264	147.0268
C_8H_6S	134.0168	134.0190
C_8H_5S	133.0109	133.0112

3-Phenylsulfonyl-2H-1-chromene 310d



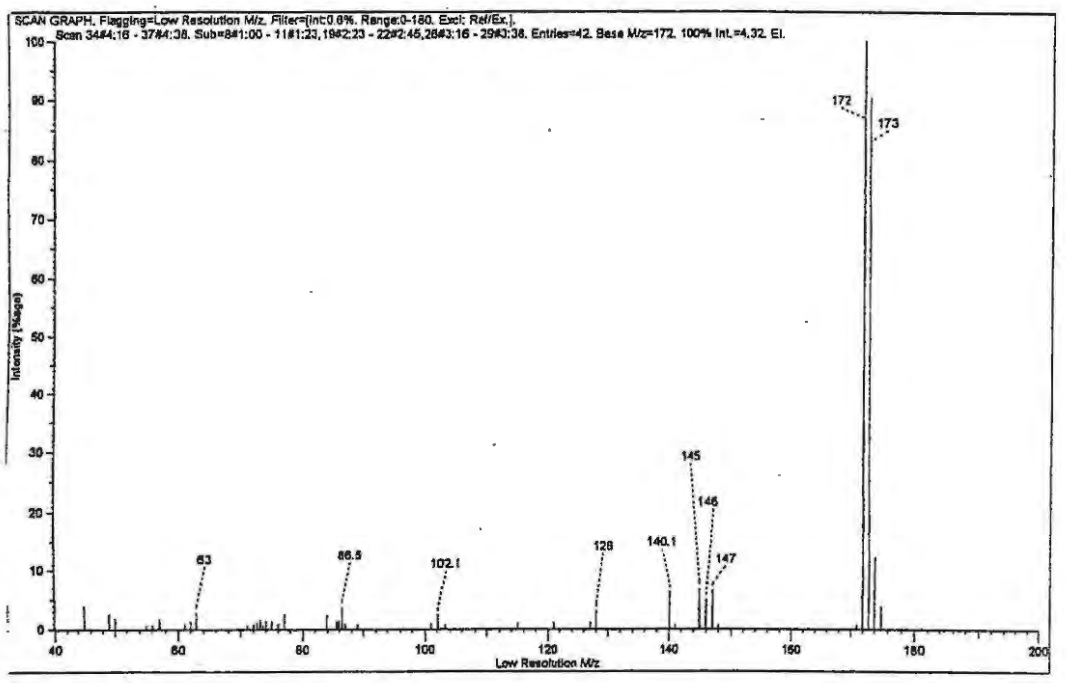
Formula	Observed Mass	Calculated Mass
$C_{15}H_{12}S_2O_2$	288.0285	288.0279
$C_{14}H_{10}S_2O_2$	274.0115	274.0122
$C_{15}H_{11}S_2O$	271.0254	271.0251
$C_{15}H_9SO$	237.0369	237.0374
$C_{15}H_9S$	221.0421	221.0425
$C_9H_7S_2O_2$	210.9892	210.9887
$C_{11}H_{11}SO$	191.0534	191.0531
C_9H_6S	146.0181	146.0190
C_8H_6S	134.0188	134.0190
C_7H_5S	121.0109	121.0112
C_8H_6	102.0462	102.0469

***Phenyl 2H-1-thiochromene-3-sulfonate* 310e**



Formula	Observed Mass	Calculated Mass
$C_{15}H_{12}S_2O_3$	304.0223	304.0228
$C_{15}H_{12}SO$	240.0625	240.0609
$C_9H_7S_2O_2$	210.9897	210.9887
$C_8H_9SO_3$	185.0281	185.0272
C_9H_7S	147.0250	147.0268
C_9H_6S	146.0186	146.0190
C_8H_6S	134.0190	134.0190
C_7H_5S	121.0104	121.0112
C_9H_7	115.0538	115.0548
C_8H_7	103.0541	103.0548
C_8H_6	102.0462	102.0469

3-Cyano-2H-1-thiochromene 310f



Formula	Observed Mass	Calculated Mass
$C_{10}H_7SN$	173.0298	173.0299
$C_{10}H_6SN$	172.0226	172.0221
C_9H_7S	147.0264	147.0268
C_9H_6S	146.0172	146.0190
C_9H_5S	145.0114	145.0112
$C_{10}H_6N$	140.0507	140.0500
C_9H_6N	128.0494	128.0500
C_8H_5	101.0377	101.0391

3.7 HIV-1 PROTEASE INHIBITORS

3.7.1 Synthesis of hydroxyethylene dipeptide isostere

***(L)-N,N-Dibenzylphenylalanine benzyl ester* 320**[159]

To a solution of L-phenylalanine (15g, 91 mmol), K_2CO_3 (40g, 0.29 mmol)and water (60 ml) was added benzyl chloride (33 ml, 0.29 mmol). The solution was heated under reflux for 16 hours. Heptane (40 ml) and water (30 ml) were added to the cooled reaction mixture; the organic solution was separated and washed with water- methanol (2:1; 2 x 30ml), and concentrated in *vacuo* to afford (L)-N,N-dibenzylphenylalanine benzyl ester **320** as a pale yellow oil (37g, 98 %); ν_{max} (nujol mull /cm^{-1}) 1732 (CO); δ_H (400 MHz; $CDCl_3$) 3.18 and 3.32 (2H, 2 x dd,CH_2) 3.77 (2H, d, CH_2) 3.93 (1H, t, CH), 4.12 (2H, d, CH_2), 5.38 (2H, dd, CH_2) 7.17 - 7.52 (20H, m, ArH); δ_C (100 MHz; $CDCl_3$) 31.8 (CH_2), 54.3 (2 x CH_2), 62.3 (CH), 65.9 (CH_2), 126.1, 126.7, 128.0, 128.1, 128.2, 128.3, 128.4, 128.6, 129.3, 135.9, 138.0 and 139.1 (ArC) and 171.9 (CO).

***(4S)-4-Dibenzylamino-3-oxo-5-phenyl-pentanonitrile* 321**[159]

A solution of the crude benzyl ester **320** (20g, 46 mmol) in dry THF (54 ml) was cooled to -45 °C under N_2. A separate flask was charged with sodium amide 95 %; (4.0g, 99.0 mmol) under N_2 followed by THF (44.7 ml). The slurry was cooled to -45 °C and CH_3CN (5.5 ml, 110 mmol) was added over 15 minutes and the resulting solution was then added to the ester solution over 15minutes. After stirring the mixture at -45 °C for 2 hours, the reaction was quenched with 25 % aqueous citric acid (95 ml). The organic layer was separated, washed with 20 % brine (95 ml), filtered and concentrated *in vacuo*. The residue was crystallised from ethanol (denatured with toluene; 50 ml) to afford (4*S*)-4-dibenzylamino-3-oxo-5-phenylpentanonitrile **321** as white crystals (11 g, 64 %), m.p.132 - 134 °C (lit.[159] 84 - 85 °C); ν_{max} (nujol mull /cm^{-1}) 2265 (CN) and 1739 (CO); δ_H (400 MHz; $CDCl_3$) 2.98 (1H, dd, CH), 3.0 (1H, d, CH), 3.21 (1H,dd, CH), 3.54 (1H, dd, CH), 3.57 (2H, d, CH_2), 3.81 (2H, d, CH_2), 3.86 (1H, d, CH) and 71.14 - 7.38 (15H, m, ArH); δ_C (100 MHz; $CDCl_3$) 28.5 (CH_2), 30.0 (CH_2), 54.8 (2 x CH_2), 68.6 (CH), 113.8, 126.5, 127.8, 128.6, 128.8, 129.0, 129.5 and 138.1 (ArC), 183.4 (CN) and 196.9 (CO).

***(5S)-2-Amino-5-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene* 322**[159]

To a solution of nitrile **321** (4.0g, 11 mmol) in dry THF (12 ml) at 10 °C was added a solution of benzylmagnesium chloride in dry THF (2.0 M;16.5 ml, 113 mmol). The solution was warmed to 25 °C and stirred for 16 hours. The reaction was cooled to 5 °C and quenched by the slow addition of 10 % aqueous citric acid (60 ml). The organic layer was separated and washed with 0.5 saturated brine (39 ml), dried over Na_2SO_4 and was concentrated *in vacuo*. The residue was crystalised from EtOH (denatured with toluene; 12 ml) to afford (5*S*)-2-amino-5-dibenzylamino-4-oxo-1,6-diphenylhex-2-ene **322**, as white crystals (4.5 g, 87 %) m.p. 100 - 102 °C (lit.[159] 101 - 102); ν_{max} (nujol mull /cm^{-1}) 3433 and 3324 (NH_2)1597 (CO); δ_H (400 MHz; $CDCl_3$) 2.96 and 3.14 (2H, 2 x dd, CH_2), 3.48 (3H, m, CH_2 and CH), 3.65 (2H, d, CH_2), 3.77 (2H, d, CH_2), 4.91 (1H, br s, NH), 3.51 (1H, s, CH), 7.10 - 7.41 (20H, m, ArH) and 9.79 (1H, br s, NH); δ_C (100 MHz; $CDCl_3$) 32.4 (CH_2), 42.3 (CH_2), 54.5 (2 x CH_2), 66.6 (CH), 96.9, 125.6, 126.7, 127.3, 128.0, 128.1, 128.7, 128.9, 129.3,129.5,135.8,140.1, 140.2 and 162.8 (ArC and CH=C) and 198.1 (CO).

***(2S, 3S, 5S)-5-Amino-2-(dibenzylamino)-3-hydroxy-1,6-diphenylhexane* 324**[159]

A suspension of sodium borohydride (0,80g, 21 mmol) in dry THF (14 ml) was cooled to -5 °C. Methanesulfonic acid (3.5 ml, 53 mmol) was added at a rate such that the temperature remained below 5 °C. The reaction was cooled to 0 °C and a solution of enaminone (4.0g, 8.7 mmol) in THF (10 ml)and *i*PrOH (5 ml) was added, and the resulting mixture stirred for 14 hours at 10 °C. In a separate flask, a dispersion of sodium borohydride (1.31g, 34.7 mmol) in THF (17 ml) was cooled to 0 °C and trifluoroacetic acid (3.3 ml, 43 mmol) was added slowly. The resulting solution was stirred for 30 minutes at 10 °C and then added slowly to the enaminone solution maintaining the temperature below 15 °C. The mixture was stirred for 4 hours , cooled to 10 °C, and quenched with 3 M NaOH (30 ml). *tert*-Butyl methyl ether (32 ml) was added and the organic layer was separated and was washed sequentially with NaOH (33 ml), 20 % aqueous NH_4Cl (32 ml) and 6 % aqueous NaCl (2 x 32 ml). The organics solution was dried over Na_2SO_4 and concentrated *in vacuo* to afford a mixture of diastereomers (4.11g); δ_H (400 MHz; $CDCl_3$) 1.25 (1H, m, CH) 1.60 (1H, m, CH) 2.45 (1H, dd, CH) 2.65 (2H, m, CH_2) 3.00 (3H, m, CH and CH_2) 3.45 (2H, d, CH_2) 3.65 (1H, m, CH) 4.15 (2H, d, CH_2) 7.02 - 7.29 (20H, m, ArH); δ_C (100 MHz; $CDCl_3$) 30.7 (CH_2), 39.2 (CH_2), 44.9 (CH_2), 53.5 (CH), 54.7 (2 x CH_2), 63.9 (CH_2), 71.9

(CH_2), 125.9, 126.4, 127.0, 128.1, 128.3, 128.4, 128.5, 129.3, 129.4, 138.0, 139.7 and 140.5 (ArC).

***(2S, 3S, 5S)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane dihydrochloride* 325**[159]

A mixture of the crude dibenzylamine **324** (4.0g, 8.6 mmol), methanol (64 ml) and aqueous ammonium formate (2.7g in 4.6 ml of water) and 5 % palladium on carbon (50 - 60 % water by weight; 0.80g) was heated under reflux for 6 hours. The cooled suspension was filtered through a bed of diatomaceous earth and the cake was washed with methanol (2 x 60 ml). The filtrate was concentrated *in vacuo* to afford an oil, which was dissolved in EtOAc (35 ml) and was washed sequentially with 1M NaOH (40 ml), 20 % aqueous brine (39 ml) and water (194 ml). The organic layer was concentrated *in vacuo* and, to the residue, was added *i*PrOH (24 ml) and conc. HCl (3.4 ml). The resulting suspension was heated under reflux for 1h, cooled to 25 °C and then stirred for 12 hours. The slurry was filtered and the cake washed with *i*PrOH to afford, as white crystals, the diamine dihydrochloride **325** (1.65 g, 55 %), m.p.302 - 304 °C (lit.[159] > 300 °C); ν_{max} (nujol mull /cm^{-1}) 3189 - 2360 (br, OH) and 1596 (C=C); δ_H (400 MHz; DMSO-d_6)1.62 and 1.79 (2H, 2 x m, CH_2), 2.90 (4 H, m, 2 x CH_2), 3.19 (1H, m, CH), 3.46 (1H, m, CH), 3.72 (1H, m, CH) 7.18 - 7.34 (10H, m, ArH) and 8.12 (4H, br s, 2 x NH_2); δ_C (100 MHz; DMSO-d_6) 34.9 (CH_2), 35.2 (CH_2), 37.8 (CH_2), 50.5 (CH), 56.4 (CH), 66.1 (CH) 126.6, 126.7, 128.5, 129.3, 129.4, 136.0 and 136.5 (ArC).

***(2S, 3S, 5S)-2,5-Diamino-3-hydroxy-1,6-diphenylhexane* 318**

A solution of the dihydrochloride salt **325** (0.50g, 1.4 mmol) in water (2.0 ml) was basified with a saturated solution of $NaHCO_3$ (monitored by pH indicator paper). The resulting solution was extracted with EtOAc (3 x 50 ml). The combined extracts were dried over Na_2SO_4 and the solvent was evaporated *in vacuo* to afford (2*S*, 3*S*, 5*S*)-2,5-diamino-3-hydroxy-1,6-diphenylhexane **318** as a yellow oil (0.30g, 77 %); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3467 - 3090 (br, OH and NH_2), 3038 (C=*C-H*) and 2922 and 2850 (CH_2 and CH); δ_H (400 MHz; $CDCl_3$) 1.60 (2H, m, CH_2), 2.54 and 2.85 (5H, m, CH and 2 x CH_2), 3.11 (1H, m, CH), 3.74 (1H, m, CH), 7.12 - 7.32 (10H, m, ArH); δ_C (100 MHz; $CDCl_3$) 39.1 (CH_2), 41.3 (CH_2), 47.3 (CH_2), 54.0 (CH), 57.5 (CH), 74.5 (CH), 126.1, 126.5, 128.4, 128.6, 129.3, 129.3, 138.3 and139.7 (ArC).

3.7.2 Synthesis of chromene- and thiochromene-carboxylic acid derivatives

***2H-1-Chromene-3-carboxylic acid* 326**[161]

(method 1)

Sodium peroxide (0.67g, 8.6 mmol) was added slowly with care to a stirred solution of the amide **327** (1.0g, 5.7 mmol) in ethanol (25 ml). The evolution of the ammonia was detected by mens of moist pH paper. After heating the mixture for 2 hours, the resulting solution was cooled to 0 °C and carefully acidified by the dropwise addition of concentrated HCl. The resulting solid was filtered off to afford *2H-1-chromene-3-carboxylic acid* **326** (0.93, 93 %) as yellow crystals, m.p. 184 - 186 °C (Found: $\mathbf{M}^+$,176.0473. $C_{10}H_9NO_2$ requires: *M*, 176.0469); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3440 (br, OH) 1679 (CO); δ_H (400 MHz; $CDCl_3$) 5.08 (2H, s, CH_2), 6.24 (1H, br, OH), 6.86 (1H, d, ArH), 6.91 (1H, t, ArH), 7.16 (1H, d, ArH) and 7.27 (1H, t, ArH) and 7.56 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 64.2 (CH_2), 116.3, 120.7, 121.5, 121.9, 129.3, 132.5, 136.0 and 155.5 (ArC and C=CH) and 169.7 (CO).

***Chromene-3-carboxylic acid* 326**[161]

(method 2)

The amide **327** (1.0g, 5.7 mmol) was dispersed in water (25 ml), and the mixture was warmed on a steam bath. Sodium peroxide (0.44g, 5.7 mmol) was then added cautious in portions. After heating the mixture for 2 hours, the resulting solution was cooled to 0 °C and carefully acidified by the dropwise addition of concentrated HCl. The resulting solid was separated by filtration and purified by flash chromatography [elution with EtOAc-methanol (4:1)] to afford the chromene-3-carboxylic acid **326** (0.20g, 20 %).

Method 3. Attempted preparation chromene-3-carboxylic acid 326[160]

3-Acetylchromene (1.0g, 5.7 mmol) and dioxane (1.5 ml) were added to a cold (*ca.* 10 °C) solution of sodium hypochlorite in 17.2 ml of water in a two-necked flask, fitted with a condenser and a magnetic stirrer. The mixture was stirred for 2 hours at room temperature, but no reaction had occurred.

Method 4. Attempted preparation of chromene-3-carboxylic acid 326[163]

To 3-acetylchromene (1.0g, 6.9 mmol), 10 % aqueous potassium iodide (20 ml) and 10 % sodium hydroxide solution (8ml) in a 50 ml conical flask, was added 15 % sodium hypochlorite solution (20 ml). The mixture was stirred at room temperature for 2 hours but no precipitation of iodoform was observed.

***2H-1-Chromene-3-carboxamide* 327**[164]

A mixture of 3-cyanochromene **251f** (0.5g, 4 mmol), water (0.4 ml), concentrated H_2SO_4 (0.4 ml) and glacial acetic acid (0.4 ml) was heated under reflux for 2 hours. The reaction mixture was poured into crushed ice with stirring, and the resulting solid was filtered off and dissolved in EtOAc. The solution was then filtered by gravitational filtration, evaporated *in vacuo* to afford *2H-1-chromene-3-carboxamide* **327** as white crystals (0.48g, 86 %), m.p.142 - 144 °C (Found: M^+, 175.0633. $C_{10}H_9NO_2$ requires: *M*, 175.0632); ν_{max} (in $CHCl_3$ /cm^{-1}) 3500 and 3411 (NH_2) and 1668 (CO); δ_H (400 MHz; $CDCl_3$) 5.00 (2H, s, CH_2), 5.65 (2H, br s, NH_2), 6.86 (1H, d, ArH), 6.91 (1H, t, ArH), 7.01 (1H, d, ArH), 7.10 (1H, t, ArH) and 7.21 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 64.71 (CH_2), 116.2, 120.8, 121.8, 125.6, 128.4, 128.6, 131.7 and 154.9 (ArC and C=CH) and 166.9 (CO).

***2H-1-Thiochromene-3-carboxylic acid* 328**[165]

3-Acetylthiochromene **310g** (0.30g, 1.45 mmol) and a solution of sodium hydroxide (0,12g) in water(0.5 ml) were placed in 50 ml round-bottomed flask equipped with a reflux condenser. The mixture boiled under reflux for 5 - 10 minutes (until the oily ester had disappeared), and then diluted with an equal volume of water before pouring, with vigorous stirring, into concentrated HCl (0,5 ml). The reaction mixture was allowed to cool to room temperature and the resulting solid was filtered off and washed with a little water to afforded, as yellow crystals, *2H-1-thiochromene-3-carboxylic acid* **328** (0.27g, 96.4 %), m.p. 150 - 152 °C (Found: M^+, 192.0244. $C_{10}H_8O_2S$ requires: *M*, 192.0245); ν_{max} (in $CHCl_3$ /cm^{-1}) 3500 (br, OH) and 1681 (CO); δ_H (400 MHz; $CDCl_3$) 3.78 (2H, s, CH_2), 6.50 (1H, br s, OH), 7.18 - 7.28 (4H, m, ArH) and 7.69 (1H, s, 4-CH); δ_C (100 MHz; $CDCl_3$) 23.7 (CH_2), 122.1, 125.8, 127.2, 130.6, 131.0, 131.1, 134.5 and 139.4 (ArC and C=CH) and 170.6 (CO); *m/z* 192 (M^+, 37.5) and 147 (100 %).

3.7.3 Isostere coupling to thiochromene and chromene carboxylic acid derivatives

***(2S, 3S, 5S)-2,5-Bis(2H-1-chromene-3-carbamoyl)-3-hydroxy-1,6-diphenylhexane* 329**[162]

To a solution of the amine **318** (0.15 g, 0.53 mmol) in dry DMF (5 ml) were added 1-hydroxybenzotriazole hydrate (HOBt) (0.48g, 3.5 mmol), *N*-ethyl-*N'*-(dimethylaminopropyl) carbodiimide hydrochloride (EDC) (0.68g, 3.5 mmol) and chromene-3-carboxylic acid **326** (0.16g, 0.91 mmol). Triethylamine was then added to adjust the pH of the solution to 8.5. The resulting mixture was stirred at room temperature for 12 hours, and then poured into water (6 ml) and extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed, sequentially, with 10 % citric acid , saturated aq. $NaHCO_3$ solution, and satd. brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to afford *(2S, 3S, 5S)-2,5-bis(2H-1-chromene-3-carbomyl)-3-hydroxy-1,6-diphenylhexane* **329** as a light yellow powder (0.26g, 81 %), m.p. 154 - 156 °C (Found: M^+, 600.2624. $C_{38}H_{36}N_2O_3$ requires: *M* 600.2634); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3328 (br, OH), 1651 and 1645 (2 x CO), δ_H (400 MHz; $CDCl_3$) 1.73 (2H, m, CH_2), 2.86 (2H, m, CH_2), 2.94 (2H, m, CH_2), 3.75 (1H, s, CH), 4.10 (1H, m, CH), 4.22 (1H, m, CH), 4.84 (2H, d, *J* 4.6 Hz, CH_2), 4.89 (2H, d, *J* 2.9 Hz, CH_2), 6.08 (1H, d, *J* 7.20 Hz, NH), 6.21 (1H, d, *J* 8.8 Hz, NH), 6.74 - 7.30 (20H, m, ArH, 4'-and 4"-CH); δ_C (100 MHz; $CDCl_3$) 38.1 (CH_2), 40.3 (CH_2), 41.4 (CH_2), 49.6 (CH), 55.5 (CH), 64.6 (CH_2), 64.8 (CH_2), 69.9 (CH), 116.1, 120.8, 120.9, 121.8, 126.2, 126.5, 126.6, 127.3, 127.7, 128.3, 128.4, 128.6, 128.7, 129.2, 129.3, 131.3, 131.4, 137.2, 138.0 and 154.7 (ArC and C=CH), 165.5 (CO) and 165.6 (CO); *m/z* 600 (M^+, 12.8) and 159 (100 %).

***(2S, 3S, 5S)-2,5-bis(2H-1-thiochromene-3-carbamoyl)-3-hydroxy-1,6-diphenylhexane* 330**[162]

To a solution of the amine **318** (0.10g, 0.35 mmol) in dry DMF (5 ml) were added 1-hydroxybenzotriazole hydrate (0.48g, 3.5 mmol), *N*-ethyl-*N'*-(dimethylaminopropyl)carbodiimide hydrochloride (0.68g, 3.5 mmol) and thiochromene-3-carboxylic acid **328** (0.18g, 0.91 mmol) Triethylamine was added to adjust the pH of the solution to 8.5. The resulting mixture was stirred at room temperature for 12 hours, and then poured into water (6 ml) and extracted with EtOAc (2 x 25 ml). The combined organic extracts were washed, sequentially, with 10 % citric acid, saturated aq. $NaHCO_3$ solution, satd. brine and then dried over anhydrous Na_2SO_4. The solvent was evaporated *in vacuo* to afford *(2S, 3S, 5S)-2,5-bis(2H-1-thiochromene-3-carbamoyl)-3-*

hydroxy-1,6-diphenylhexane **330** as a yellow powder (0.14g, 64 %), m.p.112 - 114 °C (Found: M^+, 632.2167. $C_{38}H_{36}N_2O_3S_2$ requires: *M*, 632.2167); ν_{max} (hexachlorobutadiene mull /cm^{-1}) 3267 (br, OH), 1650 and 1643 (2 x CO); δ_H (400 MHz; $CDCl_3$) 1.78 (2H, m, CH_2), 2.88 (2H, m, CH_2), 3.00 (2H, m, CH_2), 3.88 (1H, br s, CH), 3.52 (4H, m, 2 x CH_2), 4.21 (1H, m, CH), 4.34 (1H, m, CH), 4.84 (1H, d, *J* 5.2 Hz, OH), 6.58 (1H, d, *J* 7.8 Hz, NH), 6.69 (1H, d, *J* 8.8 Hz, NH), 6.80 - 7.30 (20H, m, ArH, 4'- and 4"-CH); δ_c (100 MHz; $CDCl_3$) 24.5 (CH_2) 24.6 (CH_2) 38.0 (CH_2) 39.6 (CH_2) 40.6 (CH_2) 49.3 (CH) 55.7 (CH) 69.4 (CH_2) 125.6, 126.5, 126.7, 126.9, 127.1, 127.2, 128.5, 129.3, 129.5, 129.9, 131.0, 131.1, 131.5, 131.6, 133.2, 133.2, 137.3 and 138.1 (20H, ArC and C=CH) 167.1 and 167.2 (2 x CO); *m/z* 632 (M^+, 5.5) and 147 (100 %).

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