BAYLIS-HILLMAN DERIVED BENZOPYRANS AND RELATED SYSTEMS- A SYNTHETIC AND MECHANISTIC STUDY

THESIS

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ABSTRACT

The Baylis-Hillman reaction between substituted salicylaldehydes and various acrylate species has been shown to afford complex reaction mixtures, careful chromatography of which has led to the isolation of an extensive range of novel compounds. One- and two-dimensional NMR spectroscopic, mass spectrometric and X-ray crystallographic analysis of these compounds have permitted identification of no less than eight general classes of chromene and coumarin derivatives. The formation of the various product types is attributed to cascades of successive reactions stemming, in each case, from a Baylis-Hillman product as the common intermediate. The mechanistic sequence involved in the formation of the various chromene and coumarin derivatives have been elucidated by examining isolated or specifically prepared compounds as putative reaction intermediates.

Conjugate addition and acyl or allylic substitution by various nucleophiles appear to be common processes in the formation of the chromene and coumarin derivatives, and studies focussing on these processes have been undertaken. Reactions of Baylis-Hillman adducts have been carried out, using oxygen, sulfur and nitrogen nucleophiles, in order to explore stereoselectivity and regioselectivity trends. The results show that the reactions proceed with a very high degree of regioselectivity, affording conjugate addition rather than acyl substitution products. The diastereoselectivity observed for the addition products, however was typically low.

A kinetic study to explore the regioselectivity of the reaction between various Baylis-Hillman derived halogeno esters and the nucleophile, methyl 3-oxobutanolate enloate, in two different base-solvent systems at high dilution was also undertaken. The reactions were monitored by ^{1}H NMR spectroscopy, and the results revealed that the reaction kinetics are more complex than originally anticipated. A mechanistic rationalisation is offered which is consistent with both the kinetic data and the observed regioselectivity trends.

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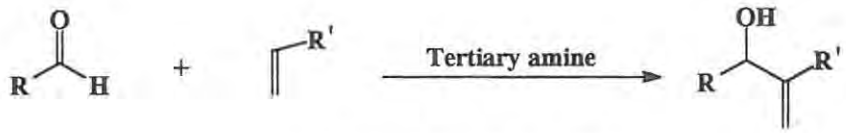
1. INTRODUCTION

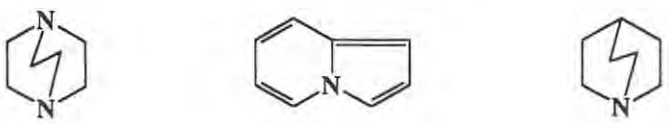
1.1 THE BAYLIS-HILLMAN REACTION

In 1972 A.D.Baylis and M.E.D. Hillman of the Celanese Corporation of New York were granted a patent[1] describing the catalytic formation of a multi-functional molecule from the reaction of an aldehyde with an α,β-unsaturated ester, amide, nitrile or ketone (**Scheme 1**). The catalysts described in the patent were all cyclic tertiary amines, *viz.*, DABCO {1,4-diazabicyclo[2.2.2]octane}(**1**), indolizine (**2**) and quinuclidine (**3**), with DABCO being the favoured base. Although the reactions were carried out at room temperature and atmospheric pressure, the transformation could also be carried out at 0°C or 200°C, under vacuum or at elevated pressure, and in the presence of solvents, *viz.*, chloroform, dioxane, ethanol and tetrahydrofuran; the use of solvents, however, is not essential.



e.g. R' = CN, CO_2Me, $CONH_2$

Scheme 1



(1) (2) (3)

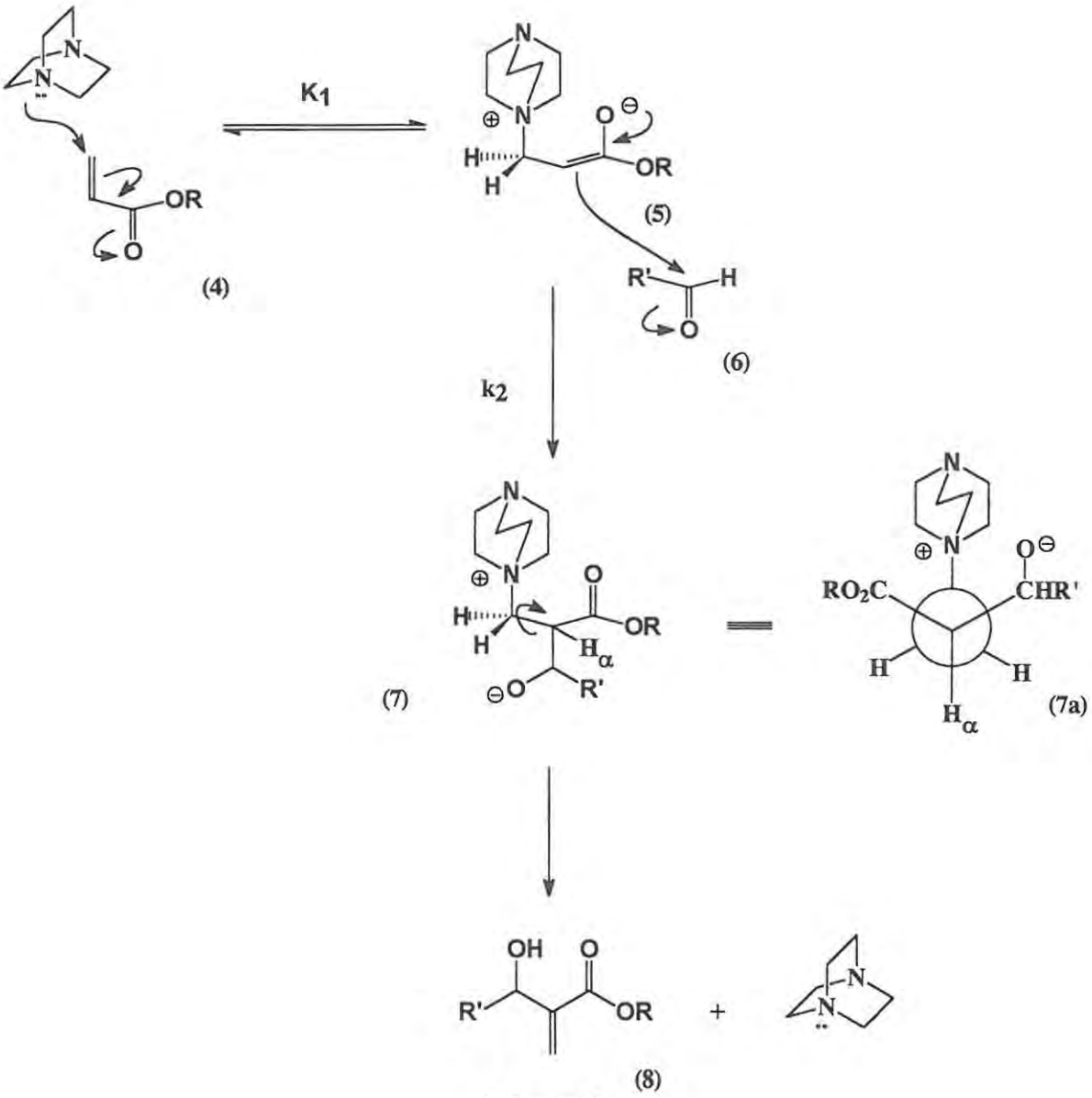
Initial interest in this reaction was slow in developing, and it was not until the early eighties that its use in studies directed towards the synthesis of necic acids highlighted its potential.[2,3] The Baylis-Hillman reaction, as it is now known, has found application in a steadily increasing number of studies, and two comprehensive reviews have been published by Drewes and Roos[4] and Basavaiah *et al.*[5]

The formation of a C-C bond in organic synthesis is of fundamental importance and many classic reactions exist for the formation of such bonds. Such reactions include:- the Robinson annulation, the Aldol reaction, the Michael reaction, the Stork enamine reaction and the Grignard reaction. The Baylis-Hillman reaction is particularly attractive as it requires mild conditions, utilizes all the carbon atoms, is chemo- and regioselective and yields versatile multi-functional compounds.
In the following section attention will be given to various aspects of the Baylis-Hillman reaction, such as mechanistic considerations, rate enhancement effects, stereoselectivity and applications in synthesis.

1.1.1 Mechanistic considerations

The mechanism for the formation of a C-C bond between the α,β-unsaturated system and the electrophile in the Baylis-Hillman reaction has been the subject of several investigations. The mechanism proposed by Isaacs[6] and by Bode and Kaye[7] involve an addition-elimination sequence (**Scheme 2**). From measurements of the rate of reaction at various pressures,[8,9,10] Isaacs showed the volume of activation ($\Delta V^{\neq}$) for these reactions to be *ca.* -70 $cm^3.mol^{-1}$. This value is considered too large to be associated with any single-step reaction and is indicative rather of a multi-step process possibly consisting of a series of equilibria. This sequence is initiated by nucleophilic attack of the tertiary amine on the activated α,β-unsaturated vinyl system in a Michael-type reaction, resulting in the formation of the zwitterionic enolate species (**5**). The pre-formed enolate subsequently attacks the electrophilic

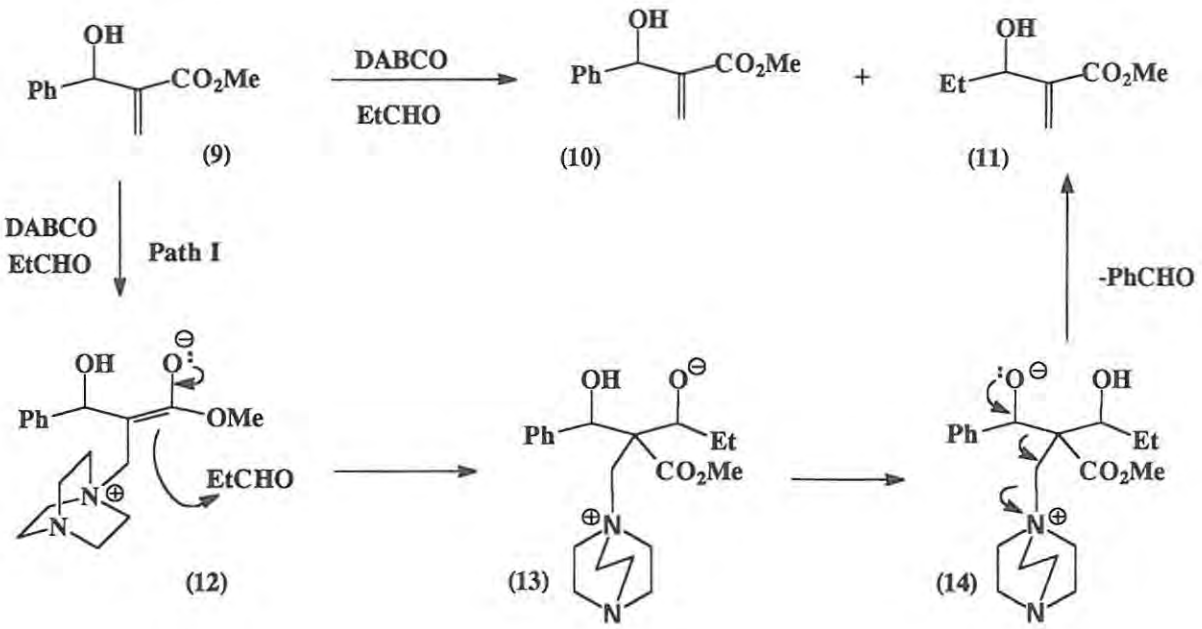
aldehyde (**6**), in a step considered to be the rate determining step of the reaction.[6,7] The resulting intermediate (**7**), according to Hoffmann *et al.*,[3] must rotate into an unfavourable gauche conformer (**7a**) for antiperiplanar elimination of the tertiary amine and the H_{α}-proton to afford the coupled Baylis-Hillman product (**8**). Bode and Kaye[7] showed experimentally that the Baylis-Hillman reaction obeys third-order reaction kinetics but, if the concentration of the tertiary amine catalyst remains constant, a pseudo second-order rate equation applies. Furthermore, there was no evidence to support the involvement of an electron transfer process involving the tertiary amine catalyst.[7]



Scheme 2

Fort *et al.*[11] have proposed that the overall Baylis-Hillman reaction must be equilibrated - a view supported by Roth *et al.*[12] and Roos and Manickum,[13] who observed a cross-over product (**11**) when the Baylis-Hillman product (**9**) was reacted with propanal in the presence of DABCO (**Scheme 3**). This observation may, however, also be rationalised in terms of the DABCO-catalysed sequence outlined in path I (**Scheme 3**). van Rozendaal *et al.*,[14] also

looked into the possibility of an equilibrated system, but noted that the system which they examined was not equilibrated (!), and cited steric hindrance for the lack of the retro-Baylis-Hillman reaction.



Scheme 3

1.1.2 Vinylic substrates

In the Baylis-Hillman reaction a wide variety of activated alkenes have been used to effect the transformation, the most common of which include acrylic acid esters, methyl vinyl ketone, acrylonitrile and substituted derivatives. A salient feature of the acryloyl derivatives is the presence of an electron-withdrawing group which enhances the electrophilicity of the alkene (**Figure 1**). This is also indicated by the relative reactivity order :-

for $X\text{-}CH{=}CH_2$: X= -CHO> $-COCH_3$> -CN> -COOR> $-CONH_2$

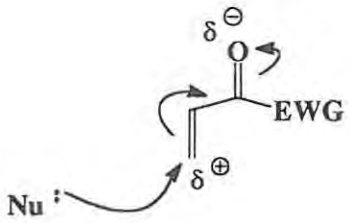


Figure 1

By appropriate choice of activated alkenes a wide range of multi-functional molecules have been synthesised (**Figure 2**), many of which have been used as precursors in the synthesis of other compounds.

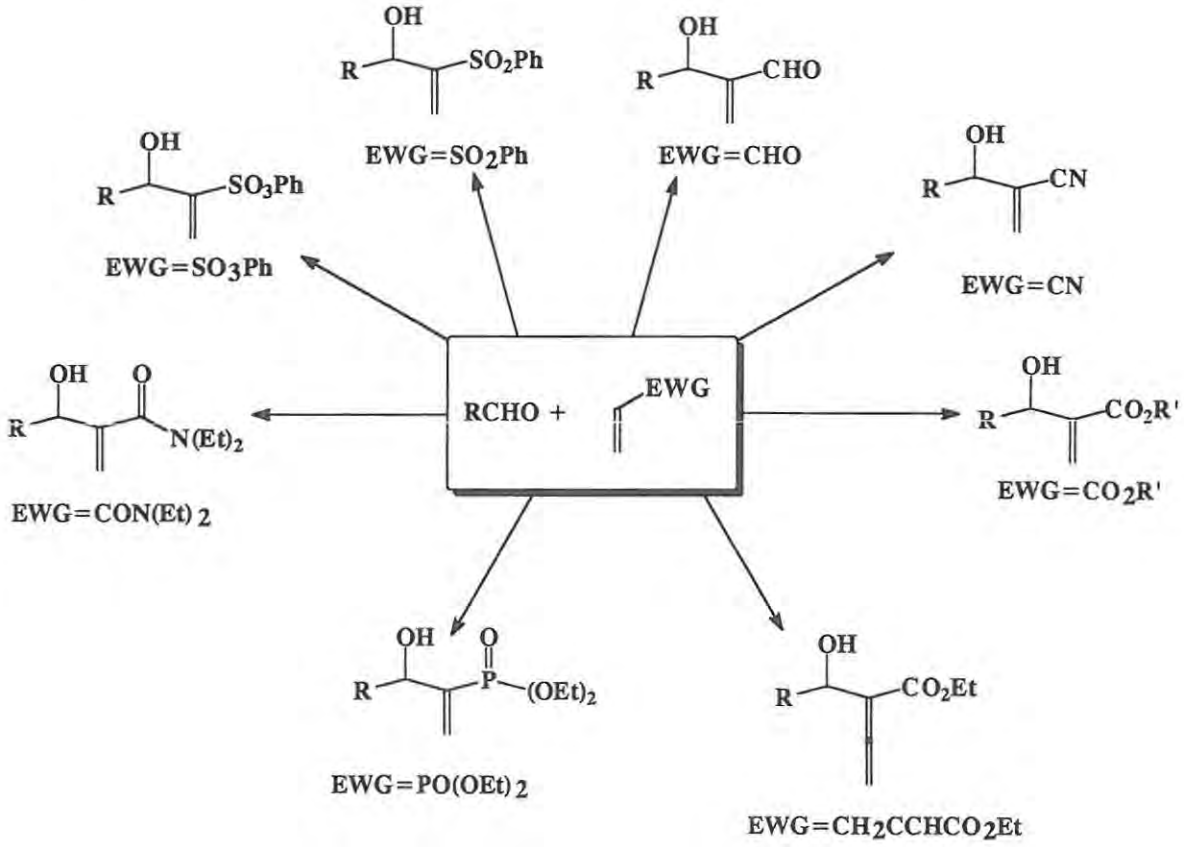
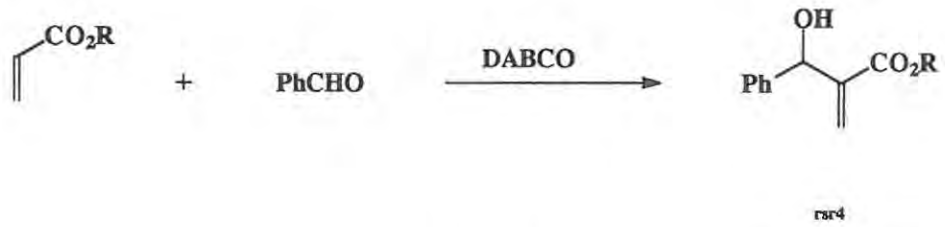


Figure 2

1.1.2.1 Acrylic acid derivatives

There has been much interest in α-substituted acrylic acid derivatives due to their wide-spread occurrence in natural products.[15,16] In fact, in their initial paper on the Baylis-Hillman reaction, Drewes and Emslie[2] used ethyl acrylate as a synthon in the preparation of integerrinecic acid, a commonly occurring necic acid component in various pyrrolizidine alkaloids.

Perlmutter *et al.*[17] noted that aryl acrylates react at significantly greater rates than alkyl acrylates, while Fort *et al.*[11] investigated the effect of varying the *O*-substituent (R; **Scheme 4**) on the reactivity of the acrylate esters in Baylis-Hillman type reactions. In their study they showed that the reaction between various aryl, benzyl and alkyl acrylate esters and benzaldehyde depended, to a large extent, on the electronic and steric effects of the R-group. Both electron-withdrawing and electron-releasing *O*-aryl substituents were studied and **Table 1** summarises their data for reactions of selected aryl acrylates.



Scheme 4

Table1. Selected data from the study by Fort *et al.*[11] of the DABCO catalysed condensation of aryl acrylates ($CH_2=CHCO_2R$) with benzaldehyde **(Scheme 4)**.

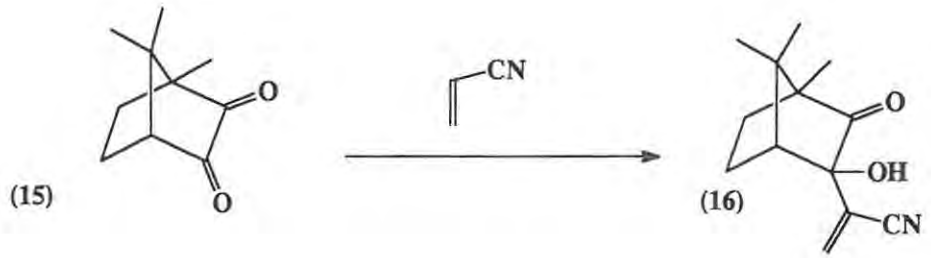
Entry	R	σ[a]	Time/ h	Product yield/%
1	*p*-$Me_2NC_6H_4$	-0.63	84	62
2	*p*-$MeOC_6H_4$	-0.28	8	54
3	*m*-MeC_6H_4	-0.06	36	54
4	C_6H_5	0	5	55
5	*p*-FC_6H_4	0	5	55
6	*m*-MeO-C_6H_4	0.10	24	43
7	*m*-FC_6H_4	0.34	5	43
8	*m*-$CF_3C_6H_4$	0.46	24	22
9	*p*-$NO_2C_6H_4$	0.81	24	-

[a] Hammett substituent constant.

From their results, Fort *et al.*[11] concluded that electron-donating *O*-alkyl and *O*-aryl substituents inhibit the condensation; Perlmutter *et al.*,[17] and Bode and Kaye[7] made similar observations. Bode and Kaye[7] suggested that the effect may be attributed to the relative destabilisation of the dipolar enolate **[(5); Scheme 1, page 4]**. Fort *et al.* noted that with very strongly electron-withdrawing groups only traces of the desired product were formed (*cf.* entry 9) and observed that the substituent constants (σ), reflecting the total resonance and field effects, were difficult to interpret. These authors also observed that an increase in the chain length of the *O*-alkyl groups leads to a decrease in reactivity- results which are supported by the earlier studies of Bode and Kaye[7] and Basavaiah *et al.*[18]

Struns and co-workers[19] investigated the possibility of carrying out Baylis-Hillman reactions

on some non-enolizable α-dicarbonyl compounds (**Scheme 5**) as possible leads to the synthesis of environmentally benign herbicides. In their study camphorquinone (**15**) was treated with methyl acrylate and acrylonitrile in the presence of various tertiary amines. However, only acrylonitrile appeared to react affording the corresponding Baylis-Hillman product (**16**).



Scheme 5

1.1.2.2 Masked acrylate systems

The introduction of the acrylate moiety can be achieved *via* either a vinyl carbanion, in an aldol type reaction, or a masked acrylate anion equivalent.[4,20] The direct vinyl anion approach (**Figure 3**) has the unfortunate drawback that vinyl carbanions generated with strong bases, such as lithium diisopropylamide (LDA), tend to undergo facile anionic polymerisation.[4]

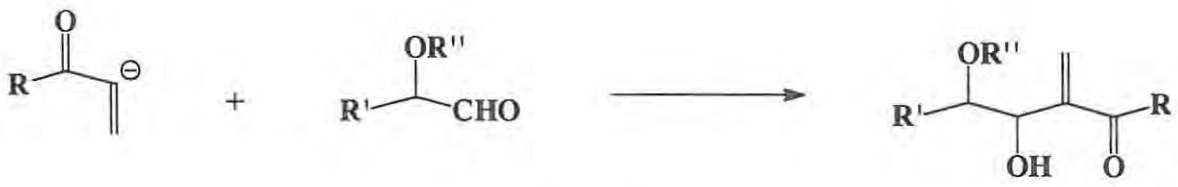


Figure 3

The masked acrylate approach avoids the problem of polymerisation and, consequently, a

wide range of masked acrylates have been synthesised and successfully used to introduce the acrylate moiety into particular systems. Hoffmann and Rabe[16] applied this method to the synthesis of terpenoid building blocks and listed several masked acrylate equivalents (**Figure 4**). The advantages of this approach include:- the use of simple precursors; the potential for stereocontrol; the mild reaction conditions; and the formation of multi-functional products capable of further elaboration.

Yu and Helquist[15] adopted an alternative approach and used synthons of the general structure Z-$CH_2CH_2CO_2R$ in which the Z-group, after appropriate modification, acts as a leaving group affording the unmasked acrylate system. Drewes *et al.*[21,22] extended this approach by making use of chiral Z-groups for the synthesis of chiral 2-hydroxyalkyl acrylates.

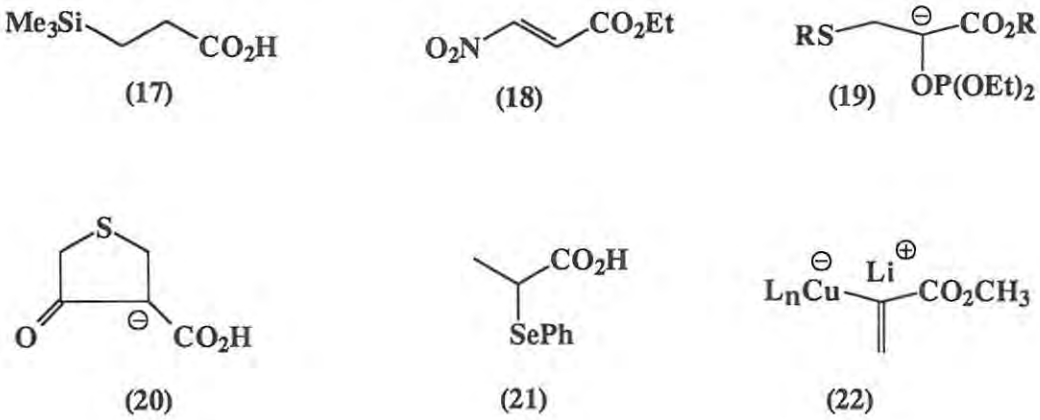
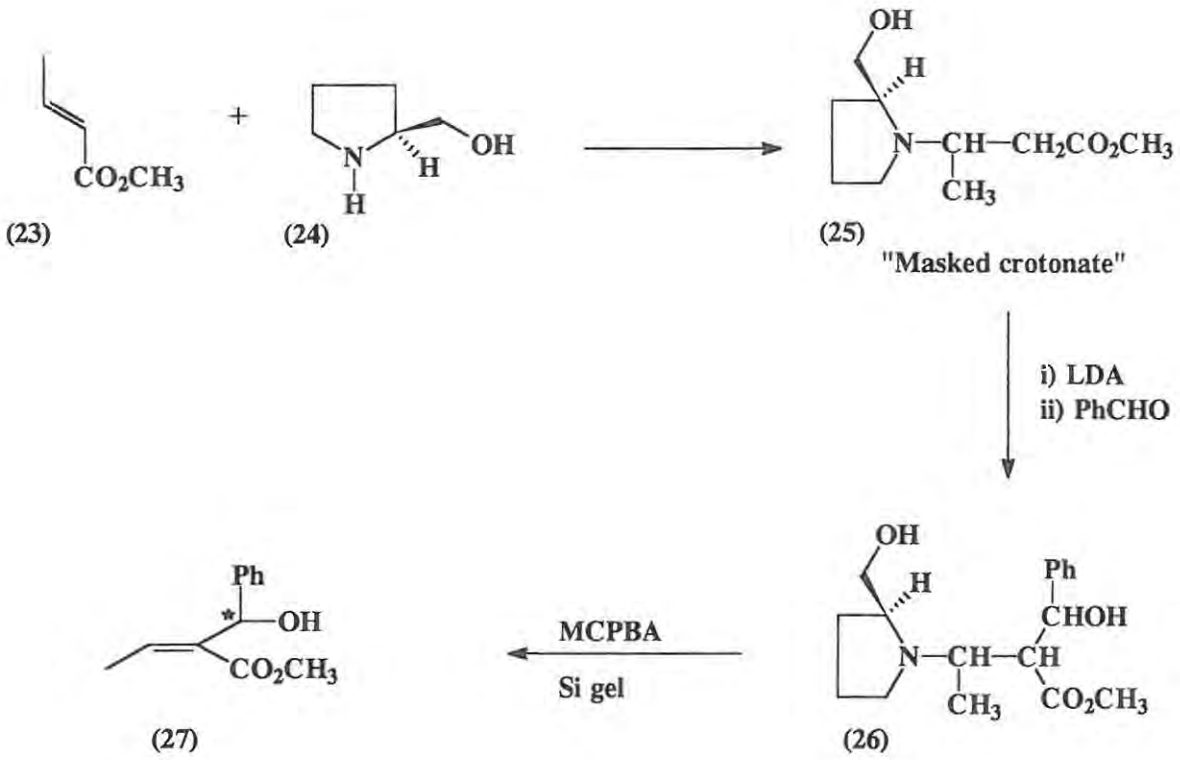


Figure 4

Many of the reactions involving masked acrylate equivalents have been directed towards the synthesis of new, chiral, Baylis-Hillman type products, or towards the synthesis of compounds not generally accessible *via* the Baylis-Hillman reaction. Drewes *et al.*[23] illustrated this point in a publication in which they synthesised a crotyl derivative (**Scheme 6**). The chiral auxiliary (+)-(*S*)-prolinol (**24**) was reacted with methyl crotonate (**23**) to generate the masked crotonate (**25**), use of which led to the α-hydroxy aryl derivative (**27**)

in 45% yield and 50% enantiomeric excess. Such products are not accessible under normal Baylis-Hillman conditions, but have been synthesised at high pressure (*ca.* 9 Kbar).[10]

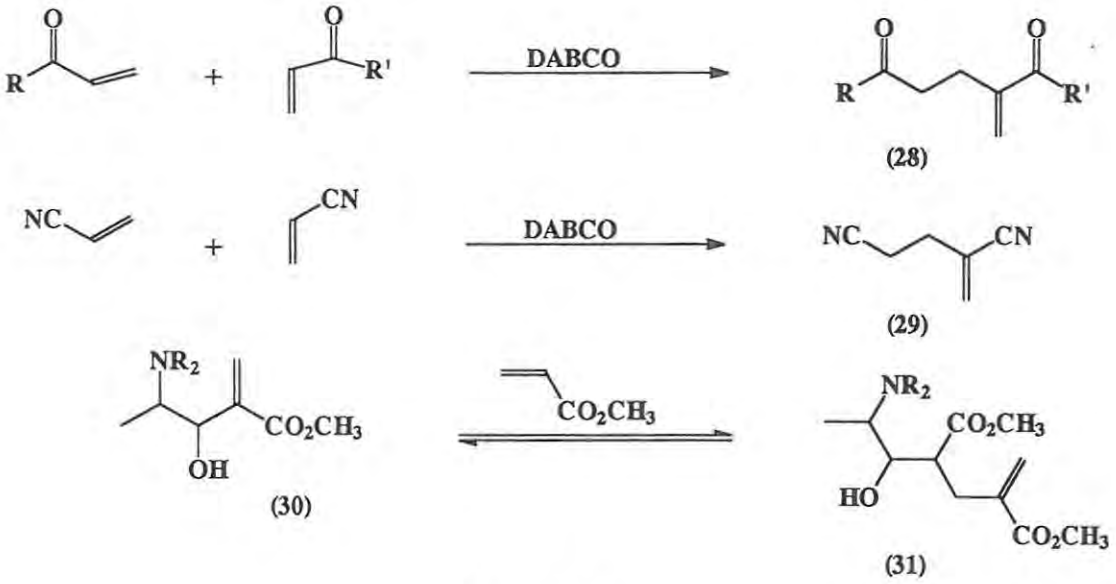


Scheme 6

1.1.2.3 Acrylate dimers

Basavaiah and co-workers[24] noted that, in the presence of catalytic amounts of DABCO (15 mol%), Michael-type dimerisation of α,β-unsaturated ketones or nitriles can occur (**Scheme 7**) yielding multi-functional molecules in yields of 40-60% in reaction periods ranging from 0.25 hours (for phenyl vinyl ketone) to 10 days (for acrylonitrile). Basavaiah[24] noted that such compounds may be useful synthons for the production of natural products. In terms

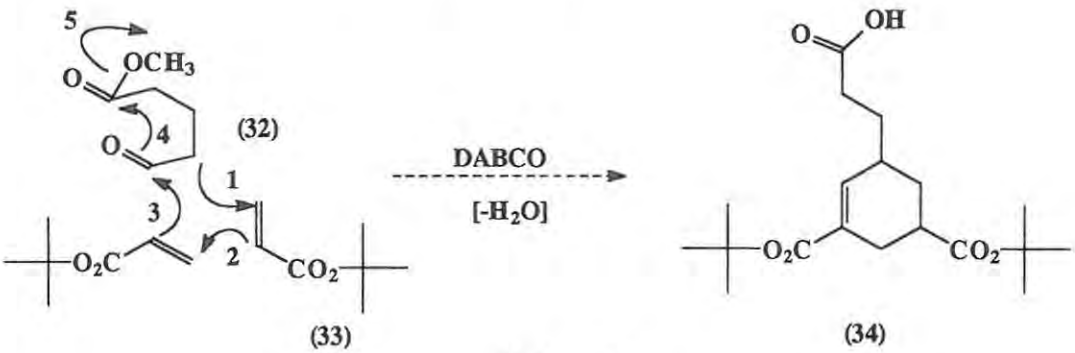
of the Baylis-Hillman reaction, the formation of such dimers is interesting as they have been shown, in some cases, to form concomitantly with the normal Baylis-Hillman products.[25] In most cases where both products are formed, the dimer is the minor product (usually less than 10% of the reaction yield).[26,27] Roos *et al.*[25] reported an interesting reaction in which they obtained the normal Baylis-Hillman product together with a secondary product **(31)**, which results from coupling between the Baylis-Hillman product **(30)** and a molecule of methyl acrylate.



Scheme 7

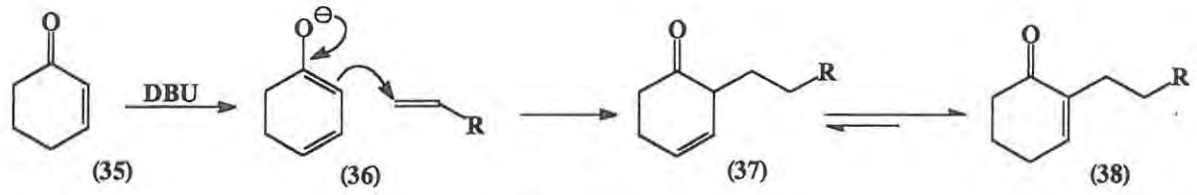
Drewes *et al.*[28] observed the dimerisation of various aryl and alkyl acrylates, under the influence of DABCO, to afford the dimers in high yield; esters bearing a good leaving group, such as 4-nitrophenyl or pantolactone, gave excellent yields in only 10 hours. The dimerisation mechanism proposed by Basavaiah *et al.*,[26] involves conjugate addition of DABCO to the acrylate species giving rise to a zwitterionic enolate, which subsequently attacks the vinyl carbon of another molecule of acrylate; this is followed by loss of the tertiary amine group to afford the dimer. Other researchers have demonstrated access to such dimers using other catalysts, such as $HRh(PPh_3)_4$,[27] Bu_3P,[29,30] $(C_6H_5)_3P$[31] and tris-dimethylaminophosphine (TDAP).[32]

Hoffmann *et al.*[33] have described the somewhat related formation of a [2+2+2] cyclisation product **(Scheme 8)** from the reaction of methyl 4-formylbutanoate **(32)** and *t*-butyl acrylate **(33)** in the presence of DABCO. The process involves a Michael addition, an intramolecular aldol reaction and a 6-*exo*-trig lactonisation to yield, after hydrolysis and dehydration, the cyclohexenecarboxylic acid **(34)** in 20% yield.



Scheme 8

Hwu *et al.*[34] have reported a method for the introduction of an alkyl group at the α-position of enones (illustrated for 2-cyclohexenone in **Scheme 9**), in a process which is superficially similar to the DABCO catalysed dimerisation of acrylates. These couplings were achieved by making use of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) as a catalyst and 1,3-dimethyl-2-imidazolidinone (DMEU) as a solvent. The reaction mixtures were heated at 185°C for 24 hours and the products were isolated, in most cases, in yields of 50 - 85%. The authors proposed, however, that the mechanism by which this process takes place differs from that of the Baylis-Hillman reaction in that an acidic γ-proton is removed by DBU and the resulting dienolate anion **(36)** , attacks the Michael acceptor. The carbon-carbon double bond in the intermediate adduct subsequently migrates to the thermodynamically more stable position giving the observed product **(38)**.



R=CO_2Et, SO_2Ph and CN

Scheme 9

1.1.3 Reactivity of aldehydes, ketones and other electrophiles

A wide variety of electrophiles have been utilised in the Baylis-Hillman reaction with varying success. In general, most aldehydes take between 5 and 10 days to react; however, in some cases, it has been noted that longer reaction times are required for satisfactory yields to be obtained. The following aldehyde reactivity order has been demonstrated: MeCHO> PhCHO> PrCHO.[8] Other compounds that have been used as electrophiles include:- imines, α-keto esters, dialdehydes,[35,36] aldimines and ketones.[10,37,38] It has been observed that ketones, unlike aldehydes, generally tend to be unreactive substrates, and this may be attributed to electronic and steric factors.[39] Ketones are more sterically hindered than aldehydes making transition states more crowded and, in addition, the electrophilicity of the carbonyl carbon is typically decreased by electron-releasing inductive or resonance effects. However the use of ketones in Baylis-Hillman reactions has been demonstrated at high pressure (*ca.* 5-10 Kbar) by Hill and Isaacs,[10] although alkyl aryl ketones and branched ketones fail to undergo addition even at 10 Kbar.

Basavaiah and Gowriswari[40] have reported an interesting reaction in which α-keto esters were employed as electrophiles in the Baylis-Hillman reaction (**Table 2**) to afford products in yields which ranged from moderate to good. These reactions proceed more rapidly than the reactions with aldehydes, but no explanation for this observed effect was offered by the authors. Hoffmann and Grundke[41] also observed that the α-ketoester, methyl pyruvate,

undergoes Baylis-Hillman type reactions in high yield, albeit slowly, and suggested that the keto group is activated by the adjacent ester functionality.

Table 2. Selected data from the studies of Hoffmann[41] and Basavaiah[40,42] on the use of α-keto esters as Baylis-Hillman electrophiles.

(39) (40)

Substrate	Ref	R	R'	Z	Time	Product Yield/%
39a	40	CH_3	CH_2CH_3	CN	24h	41
39b	42	OCH_2CH_3	CH_2CH_3	CN	3h	80
39c	42	OCH_2CH_3	CH_2CH_3	CO_2CH_3	4h	77
39d	42	OCH_2CH_3	CH_2CH_3	$CO_2CH_2CH_3$	6h	73
39e	40	Phenyl	CH_2CH_3	CN	5d	65
39f	41	CH_3	CH_3	CO_2CH_3	14d	95

The Baylis-Hillman reaction has also been extended to include imines[37] as electrophiles. Perlmutter and Teo[37] prepared a range of aryl tosylimines which, when reacted with ethyl acrylate in the presence of DABCO, afforded the analogous Baylis-Hillman products in yields ranging from 53 to 80% **(Scheme 10)**. Yamamoto *et al.*[38] made use of methyl benzylidenecarbamate as an electrophile in a Baylis-Hillman reaction to afford the corresponding product in 80% yield.

(41)

Z= tosyl, CO_2CH_3, PPh_2, SO_2Ph

R= aryl

Scheme 10

The effect of the substituents attached to the electrophile have been shown to influence the reaction rate significantly.[43,44] Basavaiah and Gowriswari[44] varied the length of the alkyl chain attached to the aldehyde (**Table 3**) and observed that with an increase in chain length there is a decrease in the rate of the reaction, an observation corroborated by Ollis *et al.*[45] This may be attributed either to increased steric interactions or to a change in the polarity of the medium due to increased alkyl chain length.

Table 3. Data for the preparation of Baylis-Hillman products from *n*-alkyl substituted aldehydes.[44]

R-CHO	Reaction Time	Product Yield/%
n-$C_5H_{11}CHO$	72h	65
n-$C_6H_{13}CHO$	80h	73
n-$C_7H_{15}CHO$	100h	63
n-$C_9H_{19}CHO$	10d	62
n-$C_{15}H_{31}CHO$	15d	51
C_6H_5CHO	9d	51
$C_6H_5CH_2CH_2CHO$	85h	65

1.1.4 Baylis-Hillman catalysts

A wide variety of nucleophiles have been employed as catalysts in the Baylis-Hillman reaction. These include tertiary amines, phosphines and rhodium catalysts. By far the most widely-used catalyst, however, has been the cyclic tertiary amine DABCO.

1.1.4.1 Tertiary amine catalysts

In Baylis and Hillman's original patent,[1] various cyclic tertiary amines were used to effect the reaction, *viz*, indolizine **(2)** and quinuclidine **(3)**. More recently, it has been shown that 3-hydroxyquinuclidine (3-HQ) not only catalyses the Baylis-Hillman reaction, but also leads to an enhancement of the reaction rate.[7,45,46] (This effect will be discussed in greater detail in **Section 1.1.6.1**). Hill and Isaacs[8] noted that, at high pressure, better control was obtained by making use of less reactive catalysts, such as triethylamine, rather than DABCO. In a bicyclic amine, such as DABCO, the alkyl groups are of course "tied back" resulting in a less-hindered nucleophile.[4,8,47] Drewes and Emslie[4] suggest that the basicity and reaction rate in the Baylis-Hillman reaction appear to run in parallel, and noted that the catalytic effect of the tertiary amines appears to follow the order:-

$$3\text{-HQ} > \text{DABCO} > \text{Quinuclidine} > Me_3N > Et_3N$$

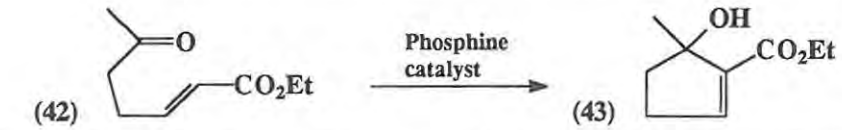
1.1.4.2 Phosphine catalysts

The use of phosphines as catalysts for the Baylis-Hillman reaction has been well documented. In fact, in 1968 Morita *et al.*[48] reported, for the first time, the preparation of 2-hydroxyalkyl derivatives of acrylate and related systems from acrylonitrile and various aldehydes in the presence of catalytic amounts of tricyclohexylphosphine. The fact that the yields obtained from this reaction were so low may account for the fact that not much notice was taken of this work, although, as Drewes *et al.*[4] point out, some credit is due to Morita for this

transformation.

Imagawa *et al.*[49] reported the use of tributylphosphine and triethylaluminium as catalysts for reactions between acrylonitrile and saturated aliphatic aldehydes, which afforded coupled products in 70 to 90% yield after 22 hours. Roth *et al.*,[12] in the course of preparing cyclopentenol derivatives *via* an intramolecular Baylis-Hillman reaction, made use of a variety of catalysts including phosphines. From their results **(Table 4)** it is apparent that tributylphosphine (entry 1) and dimethylphenylphosphine (entry 2) were the most effective catalysts. In contrast, DABCO was shown to have no activity in these reactions.

Table 4. Selected data from the study of Roth *et al.*[12] on the effect of various catalysts on intramolecular Baylis-Hillman reactions.

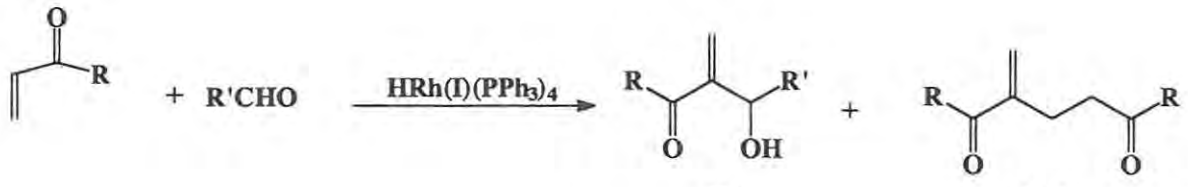


Entry	Catalyst	Reaction time	Reaction yield/%
1	$(n\text{-Bu})_3P$	1d	75
2	$(CH_3)_2(C_6H_5)P$	1d	65
3	$(i\text{-Bu}, CH_3, C_6H_5)P$	30d	50
4	$CH_3(C_6H_5)_2P$	40d	-
5	DABCO	32d	-

1.1.4.3 Rhodium(I) hydride catalysts

The use of metal catalysts for the introduction of an electrophile at the α-postion of an α,β-unsaturated system has been described by several authors.[50-52] Sato *et al.*[27] and Roos *et al.*[53] point out that such methods require equimolar amounts of catalyst, which would make their

application expensive. Sato *et al.*,[27] proposed the use of hydridotetrakis(triphenylphosphine)rhodium(I) [$HRh(PPh_3)_4$] as a more convenient rhodium catalyst since only catalytic amounts are required for the conversion (**Scheme 11**). The yields for these reactions have been shown to be fair with the dimeric product (**45**) being present only in low quantities (<*ca.*10%). The formation of compound (**45**) can be further retarded by making use of an excess of the aldehyde or, by conducting the reaction in the presence of a small quantity of alcohol.



(44) (45)

Scheme 11

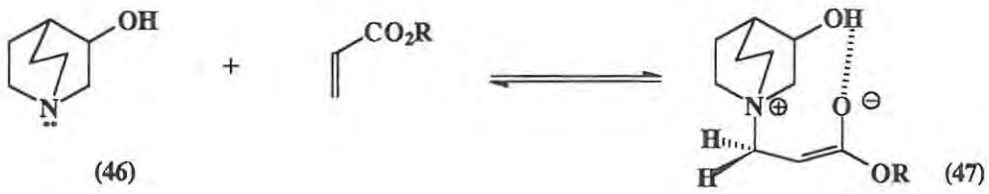
1.1.5 Rate enhancement effects

A considerable drawback of the Baylis-Hillman reaction has been the poor rate of product turnover. All but the most reactive aldehydes may take several days or weeks to react and, as a result, various methods have been employed to accelerate the transformations. Such methods include variation of the catalyst, solvent, pressure and temperature and the use of microwaves or ultrasound. As has been discussed earlier, the substrate structure plays an important role in determining the rate of the reaction and, hence, by taking note of the steric and electron-withdrawing or electron-donating effects of the substituents, one is able to predict the relative reactivity of a particular system. Varying the substrate structure, however, does not necessarily provide the desired product!

1.1.5.1 Catalytic effects

An obvious means of improving the rate of the Baylis-Hillman reaction would be to increase

the amount of catalyst in the reaction. This has been attempted on several occasions and, in fact, resulted in some lowering of $t_{½}$ values and an improvement in reaction yield.[43,54,55,56,74] Kaye *et al.*[7] showed that marked improvements in the rate of reaction can be achieved when 3-hydroxyquinuclidine **(46)** (3-HQ) is used as a catalyst instead of DABCO. This rate-enhancement can be attributed to hydrogen-bonding stabilization of the "Baylis-Hillman zwitterion" **(47)** as illustrated in **Scheme 12**. Drewes *et al.*[46] showed that when 3-hydroxyquinuclidine **(46)** was *O*-acetylated, the $t_{½}$ values were much greater indicating the importance of the alcohol moiety. Kaye *et al.*[7] also observed a small kinetic isotope effect with deuterated 3-hydroxyquinuclidine ($k_H/k_D=1.3$), lending additional support to hydrogen-bonding stabilisation of the intermediate zwitterion.



(46) (47)

Scheme 12

Table 5. Selected data from the study by Drewes *et al.*[46] on the influence of catalyst on the $t_{½}$ values for Baylis-Hillman reactions.

Entry	Aldehyde	Substrate	Catalyst	$t_{½}$(min)	Yield/ %
1	CH_3CHO	$CH_2=CHCO_2CH_3$	3-HQ-*O*-Ac[b]	9750	90
2	CH_3CHO	$CH_2=CHCO_2CH_3$	DABCO	3000	90
3	CH_3CHO	$CH_2=CHCO_2CH_3$	3-HQ	<900	90
4	CH_3CHO	$CH_2=CHCOCH_3$	3-HQ-*O*-Ac	223-229	69
5	CH_3CHO	$CH_2=CHCOCH_3$	DABCO	92.5-94.5	69
6	CH_3CHO	$CH_2=CHCOCH_3$	3-HQ	16-20	69
7	Pyr-4[a]	MVK[c]	3-HQ-*O*-Ac	2-3	85
8	Pyr-4[a]	MVK[c]	DABCO	1-2	85
9	Pyr-4[a]	MVK[c]	3-HQ	<0.37	85

[a]Pyr-4 is pyridine-4-carboxaldehyde. [b] *3*-HQ-*O*-Ac is *O*-acetylated 3-hydroxyquinuclidine. [c] MVK is methyl vinyl ketone

1.1.5.2 Pressure effects

Pressure has been identified as one of the more significant factors in determining the rate of Baylis-Hillman reactions. In their original patent,[1] Baylis and Hillman mentioned that the reaction may take place in a vacuum or under pressure and it has been shown, subsequently, that there is a significant increase in the rate of reaction at high pressure **(Table 6)**.[6,9,10,29,57] Hill and Isaacs[9] calculated the volume of activation ($\Delta V^{\ddagger}$) for Baylis-Hillman type reactions to be *ca.* -70 $cm^3.mol^{-1}$; such a large negative value indicates that the rate of the reaction will be sensitive to changes in pressure. Hill and Isaacs[6] point out that the volumes of activation for these reactions are greater than for any other reactions studied thus far, 15-fold increases in reaction rate being observed at only 1kbar. Many products that are not accessible at

atmospheric pressure have been obtained in good yield at high pressure (***cf.* Table 6: entries 7 and 8**). It has also been shown that even moderate pressures of 2-3 kbar, which are attainable in most laboratories,[9] can provide marked improvements in reaction yield and rate.

Table 6. Selected data from the study by Hill and Isaacs[10] on the effect of pressure on the Baylis-Hillman reaction.

Entry	Vinyl species	Electrophile	Catalyst[a]	Pressure/ kbar	Temp / °C	Time/ min	Yield /%
1	CH_2=CHCN	MeCHO	D	0.001	42	2900	76
2	CH_2=CHCN	MeCHO	E	5	20	5	78
3	CH_2=CHCN	MeCHO	E	8	20	5	96
4	CH_2=CHCN	EtCHO	D	0.001	20	7300	75
5	CH_2=CHCN	EtCHO	E	5	46	360	60
6	CH_2=CHCN	EtCHO	E	8	30	5	70
7	CH_3CH=CHCN	MeCHO	D	0.001	40	20160	-
8	CH_3CH=CHCN	MeCHO	D	9	50	1080	88
9	CH_2=CHCN	Me_2CO	D	0.001	40	20160	-
10	CH_2=CHCN	Me_2CO	D	5	40	240	76
11	CH_2=CHCN	Me_2CO	D	10	40	90	65

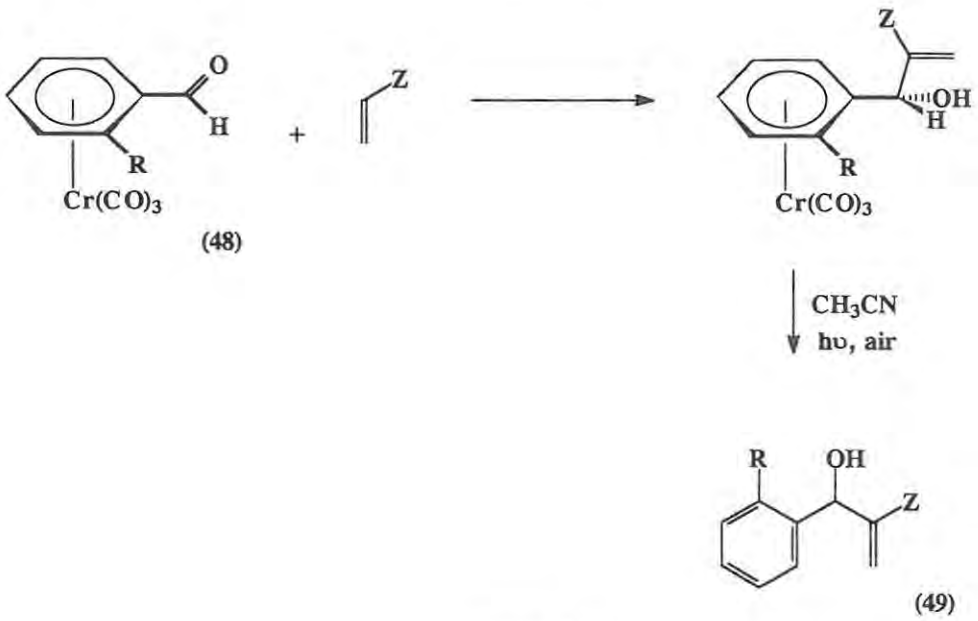
[a] D=DABCO; E= triethylamine.

1.1.5.3 Hydrogen bonding and chromium complexation effects

Several authors[4,7,46] have noted that the rate of Baylis-Hillman reactions may be enhanced by the addition of methanol as a solvent, and in a recent study by Augé and co-workers,[58] the effects of different solvents, including methanol, were studied. Augé *et al.*,[58] reacted acrylonitrile and benzaldehyde in the presence of DABCO in the various solvents, and the reaction was allowed to run at room temperature to between 90 and 98% completion.

The reactions in water, formamide and ethylene glycol took 7 hours, methanol 34 hours and DMSO and DMF 3-5 days; after 1 week the reaction in THF only afforded *ca.* 20% yield. The authors proposed that water and, to a lesser extent, ethylene glycol and formamide stabilise the zwitterionic Baylis-Hillman intermediate through hydrogen bonding, thus accounting for the enhancement of reaction rate. Several other papers on Baylis-Hillman reactions have been published[59-64] in which aqueous formaldehyde was used, and similar rate enhancement was observed.

Kündig *et al.*[65,66] demonstrated that the efficiency of Baylis-Hillman reactions of aromatic aldehydes could be significantly improved by complexation of the arene with the electron-withdrawing tricarbonylchromium complexing agent [$Cr(CO)_3$] (**Scheme 13**). The reactions afforded products in higher yields and in shorter reaction periods, compared with reactions run without the chromium complex. The authors also observed that complexation with $Cr(CO)_3$ afforded products with very high diastereoselectivity, subsequent decomplexation affording the Baylis-Hillman product in high yield.



Scheme 13

1.1.5.4 Effect of ultrasound, temperature and microwaves

Roos and Rampersadh[67] studied the effects of ultrasound and temperature as means of enhancing the rate of the Baylis-Hillman reaction. They showed that the use of ultrasound only effected a moderate improvement in the rate of the reaction, but that a moderate increase in temperature did, in fact, lead to a more marked improvement in the reaction rate. The use of elevated temperature is limited since, at higher temperatures, a larger number of side products, including acrylate dimers and polymers, tend to form.

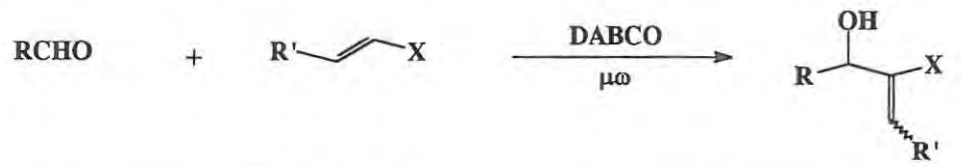
The use of microwave irradiation for organic synthesis, although only introduced relatively recently,[68a,b] has rapidly become widespread. Strauss *et al.*[64] have made use of a continuous microwave reactor (CMR) to effect a wide range of organic reactions, including Michael addition, Williamson's etherification, Hofmann degradation and Knoevenagel and Baylis-Hillman reactions. The authors prepared methyl 2-(hydroxymethyl)acrylate from methyl acrylate and aqueous formaldehyde in the presence of DABCO using CMR to obtain the product in 30% yield in 1.5 minutes. Kress *et al.*[70] attempted to prepare the same product utilizing a modified Baylis-Hillman reaction without the aid of microwave radiation, and only obtained product after several days making this method unsuitable for the preparation of kilogram quantities of product. In contrast, however, Strauss *et al.*[64] reported that CMR could be used for such a purpose, and that this and other applications of CMR were under investigation.

Bhat *et al.*[71] also studied the rate enhancement effects of microwave radiation on the Baylis-Hillman reaction and, from their results (**Table 7**), demonstrated that with simple aldehydes, the reaction rate was increased substantially. Under normal Baylis-Hillman conditions, acrylamides have been shown to be inert substrates and, even under high pressure (5 kbar), Isaacs *et al.*[8] only achieved a 5% yield from acrylamide after 16h. With microwave mediation, however, acrylamide has been shown to afford product in 40% yield

after 25 min (entry 8). Crotyl type systems, which are also unreactive even under high pressure, have similarly been synthesised, albeit in low yield (entry 7), by microwave mediation.

CMR techniques can also be applied under pressure (*ca.* 1.4 Kbar)[64] and, while such pressures are low compared to the pressures used by Isaacs *et al.*[10] this will still influence the rate of the reaction.

Table 7. Selected data from the study by Bhat *et al.*[71] on microwave mediated Baylis-Hillman reactions.



Entry	R	R'	X	Standard conditions		Microwave-mediated	
				Time/days	Yield/%	Time/min	Yield/%
1	C_6H_5	H	CO_2CH_3	2	25	10	34
2	2-HOC_6H_4	H	CO_2CH_3	3	10	10	70
3	3,4,5-$(CH_3O)_3C_6H_2$	H	CO_2CH_3	4	5	30	15
4	4-$NO_2C_6H_5$	H	CN	3	45	10	95
5	CH_3CH_2	H	CO_2CH_3	4	61	10	40
6	CH_3	H	CO_2CH_3	4	90	10	40
7	4-$NO_2C_6H_4$	CH_3	$CO_2C_2H_5$	–	–	40	10
8	3,4,5-$(CH_3O)_3C_6H_2$	H	$CONH_2$	3	–	25	40

1.1.5.5 Metal and ligand accelerated catalysis of the Baylis-Hillman reaction

Aggarwal *et al.*[69] showed that the rate of the Baylis-Hillman reaction could be greatly enhanced by the addition of lanthanide and group III metal triflates; this was especially marked with the use of $La(OTf)_3$ and $Sm(OTf)_3$. The authors also found that the use of diol ligands in conjunction with the triflates leads to even greater enhancement of the reaction rate by enhancing the oxophilicity of the metal **(Figure 5)**. Using this protocol, rate enhancement of the reaction was observed even with low DABCO concentrations (< 10 mol%).

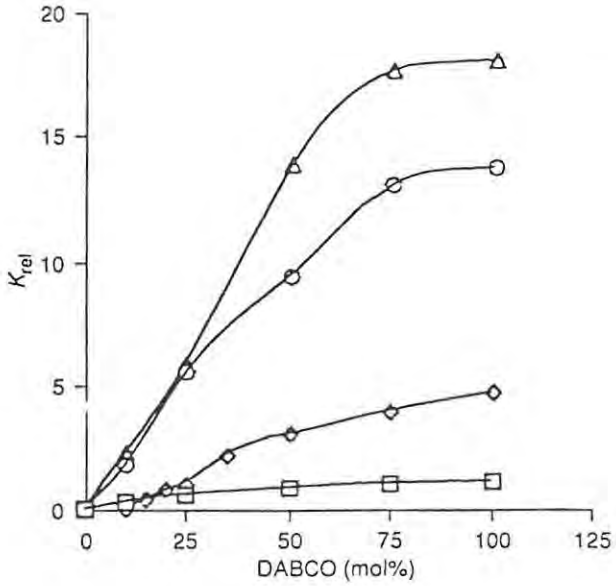
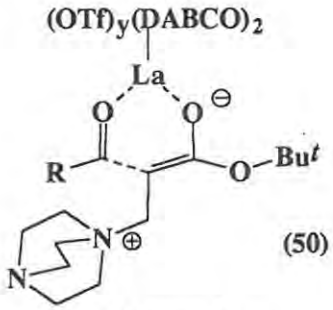


Figure 5 Relative rates of reaction as a function of DABCO concentration from the study by Aggarwal *et al.*[69] for the Baylis-Hillman reaction between *t*-butyl acrylate and benzaldehyde; (□) no metal or diol present, (◇) 5 mol% $La(OTf)_3$, (○) 5 mol% $La(OTf)_3$ and 5 mol% binol, (Δ) 5 mol% $La(OTf)_3$ and 10 mol% binol.

The enhancement is presumably due to co-ordination between the metal, the DABCO - enloate and the carbonyl oxygen of the aldehyde species during the formation of the new C-C bond **(50, Figure 6)**.



(50)

Figure 6

1.1.6 Asymmetric Baylis-Hillman reactions

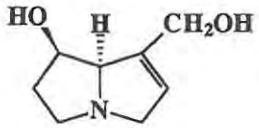
α-Hydroxyalkylation of activated alkenes with electrophiles in the Baylis-Hillman reaction results in the formation of a new chiral centre, and the potential exists for asymmetric induction. As a result, several groups have directed studies towards the development of asymmetric Baylis-Hillman reactions. Such studies have treated the problem from several angles, making use of different chiral catalysts, electrophiles, solvents and activated alkenes.

1.1.6.1 Chiral catalysts

It has been proposed that in the mechanism of the Baylis-Hillman reaction the tertiary amine catalyst participates throughout the development of the product, including the stage in which the new chiral centre is formed. It was thus speculated that a chiral base might, in fact, be able to induce asymmetric control in the formation of the product.

Drewes and Roos[4] studied a range of chiral bases including quinidine, retronecine (**51**) and (*S*)-(-)-*N*-methylprolinol (**52**). The chiral discrimination afforded by these bases was, however, very low with the greatest enantiomeric excess being only 12%. These authors

point out that, while the enantiomeric excesses obtained with these particular bases are low, there are still a vast number of naturally occurring chiral bases (e.g. alkaloids and amino acids), many containg hydroxyl groups, which have yet to be investigated.



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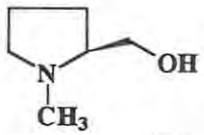
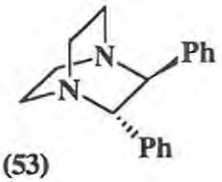


(52)

Sharpless *et al.*[72] synthesised *trans*-2,3 disubstituted 1,4-diazabicyclo[2.2.2]octane derivatives (***e.g.* 53**), and Soai *et al.*[73] prepared 2,5-disubstituted analogues (***e.g.* 54**). Both research groups reported that further studies would be undertaken to establish whether if, in fact, these chiral catalysts effect asymmetric induction in the Baylis-Hillman reaction. However, no such information has been reported to date.



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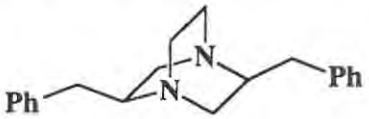

(54)

Hirama *et al.*[74] synthesised a range of chiral C_2-symmetric 2,3-disubstituted 1,4-diazabicyclo[2.2.2]octanes (**55**) as potential asymmetric Baylis-Hillman catalysts. Their use generally afforded Baylis-Hillman products in fair yield but with variable enantiomeric excess. However, the authors did show that, at elevated pressure, the rate and the enantioselectivity of the reaction between 4-nitrosalicylaldehyde and methyl vinyl ketone could be improved (**Table 8**). Isaacs *et al.*[75] have pointed out that a chiral catalyst attached to the β-carbon is too remote from the reaction centre to have any significant influence in the stereochemistry of the Baylis-Hillman reaction and, in addition, use of such catalysts tends to result in very low yields in many instances.

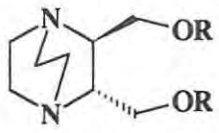

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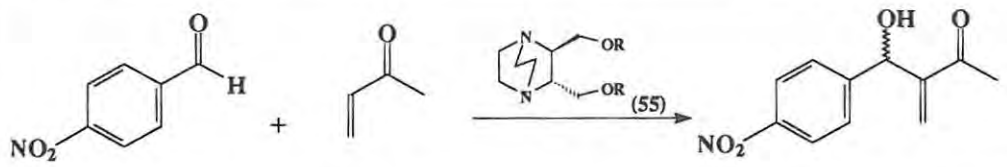
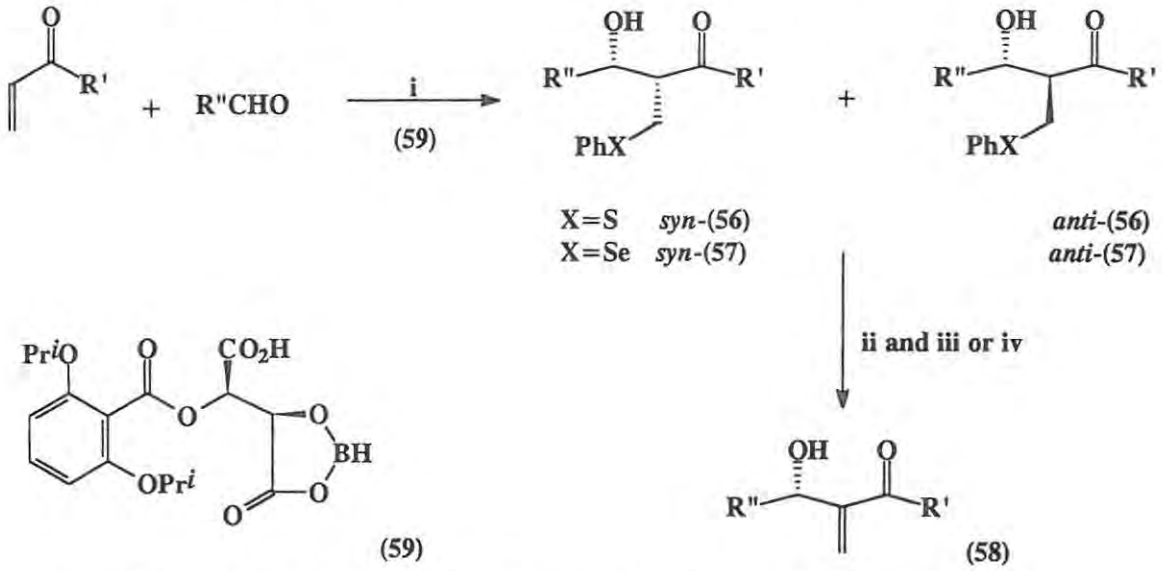
Table 8. Selected data from the study by Hirama *et al.*[74] on the effect of chiral catalysts and pressure on the Baylis-Hillman reaction.



Entry	R	Pressure/ kbar	Time/ h	Yield /%	e.e./ %
1	benzyl	0.001	504	66	12
2	*t*-butyldiphenylsilyl	0.001	504	42	15
3	benzyl	5	12	45	47
4	*t*-butyldiphenylsilyl	5	12	23	34
5	1-naphthyl	5	16	66	42
6	1-anthranyl	5	24	9	11

In a novel approach, Barrett *et al.*[76] have prepared asymmetric Baylis-Hillman type products, using organosulphur (or organoselenium) chemistry and a chiral borane catalyst. In their studies, these authors showed that, when the chiral borane **(59)** was used as a catalyst, methyl vinyl ketone, acetaldehyde and trimethylsilylphenyl sulphide **(Scheme 14)** all afforded the *syn*-diastereomeric adducts **(56)** predominantly (95:5) and in high

enantiomeric excess (93% e.e.); use of trimethylsilylphenyl selenide afforded the intermediate adducts **(57)** in higher yields but lower enantiomeric excess **(Table 9).** Reaction of the sulphides **(56)** with *m*-chlorobenzoic acid at -10°C, followed by thermolysis, afforded the Baylis-Hillman type products **(58),** while the selenides **(57)** were oxidised with hydrogen peroxide at room temperature to afford the same products.



Reagents and conditions: i, Me_3SiSPh or $Me_3SiSePh$, C_2H_5CN, -78 °C; ii, *m*-chloroperbenzoic acid, CH_2Cl_2, -10 °C; iii, 130- 150 °C; iv, H_2O_2, CH_2Cl_2, 25 °C

Scheme 14

Table 9. Preparation of chiral Baylis-Hillman type products from the study by Barrett *et al.*[76]

Compound	R'	R''	Intermediate **(56)/(57)**			Products **(58)**		
			Yield/ %	*Syn: anti*	e.e./ %	Compound	Yield/ %	e.e./ %
56a	Me	Me	50	95:5	93	**58a**	55	89
56b	Et	Me	38	93:7	92	**58b**	71	87
56c	Me	Et	41	98:2	97	**58c**	46	96
56d	Me	Bu	39	98:2	91	**58d**	51	90
57a	Me	Me	59	97:3	91	**58a**	88	87
57b	Et	Me	49	93:7	84	**58b**	72	79
57c	Me	Et	53	97:3	85	**58c**	85	73
57e	Me	Pr^i	37	97:3	63	**58e**	59	61

1.1.6.2 Chiral alkenes

Several studies directed towards the utilization of chiral alkenes for the synthesis of chiral Baylis-Hillman products have been reported in the literature, some of which offer high levels of stereoselectivity. The majority of activated alkenes studied for this purpose have been acrylate derivatives. This may be due to the fact that many of these derivatives are readily available and that removal of the chiral auxiliary, after the formation of the product, is readily achieved.

Basavaiah *et al.*[56] reacted the acrylate ester of (-)-menthol **(60)** **(Figure 7)** with various aldehydes in an attempt to achieve stereoselective Baylis-Hillman transformations. The diastereoselectivity proved variable, reactions with 2-methylpropanal and propanal affording products with a 2% and 70% d.e. respectively. Drewes *et al.*[77] made use of 8-phenylmenthol **(61)** as a chiral auxiliary, and the diastereomeric excesses obtained for reactions of the corresponding acrylate ester were, in all cases but one, appreciably higher than those obtained by Basavaiah *et al.*[56] This improvement in stereocontrol was attributed to the potential for π-stacking provided by the phenyl group.

Interestingly, Isaacs *et al.*[75] have reported that in the reaction between benzaldehyde and (-)-menthyl acrylate under high pressure (7.5 Kbar), only one diastereomer could be discerned (*i.e.* >99% d.e.) in a yield of 42%. However, when the reaction was carried out at atmospheric pressure, the stereoselectivity dropped to 22% d.e. but the yield increased to 93%.

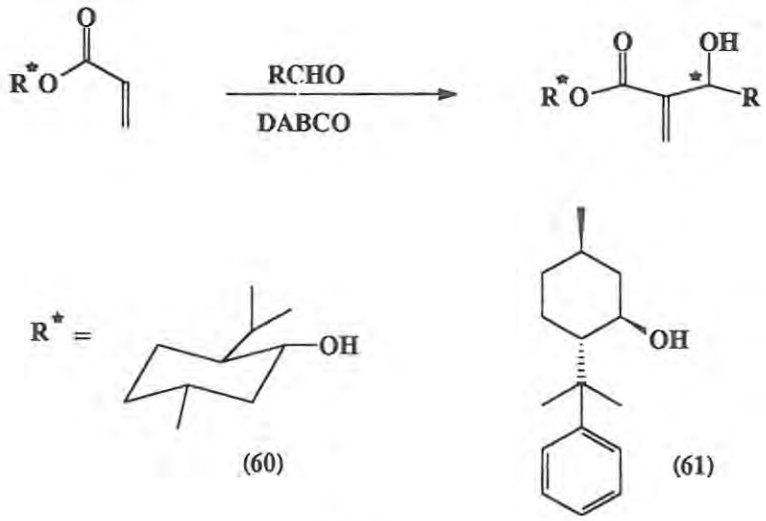
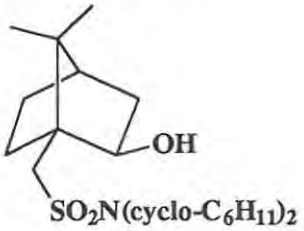


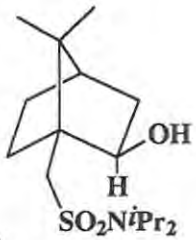
Figure 7

Basavaiah *et al.*[56] reported use of an acrylate ester derived from Oppolzer's chiral auxiliary **(62)** **(Figure 8)**, which afforded product with a diastereomeric excess of 70%. Roos *et al.*[78a] using the same chiral auxiliary were only able to obtain a diastereomeric excess of 7% but,

on recrystallisation, this rose to 70% d.e. Other chiral auxiliaries which have been examined include compounds **(63)** and **(64)**; however, neither of them provided significant chiral discrimination.



(62)



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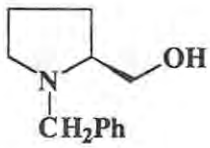
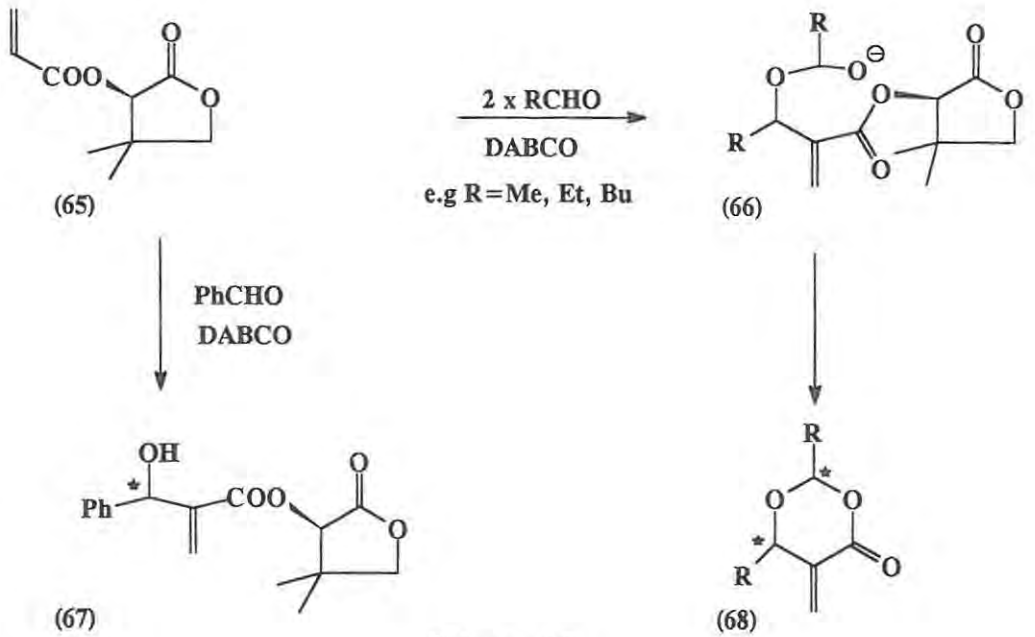


(64)

Figure 8

(*R*)-(+)-Pantolactoneacrylate **(65)(Scheme 15)** has been used as a chiral substrate by Drewes *et al.*[78b,79,80] in reactions with various aldehydes in the presence of DABCO. In most cases, the cyclic 2,6-dialkyl-5-methylene-1,3-dioxan-4-ones **(68)** are obtained in high yield and *ca.* 80% d.e. *via* intramolecular transesterification of the intermediates **(66)**. An exception was the reaction with benzaldehyde which afforded the 'normal' Baylis-Hillman product **(67)**.

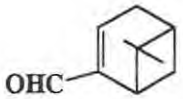


(65) **(66)** **(67)** **(68)**

Scheme 15

1.1.6.3 Chiral electrophiles

In studies conducted by Isaacs *et al.*,[75] the chiral aldehydes (*R*)-myrtenal **(69)** and isopropylidene-(*R*)-glyceraldehyde **(70)** were reacted with acrylonitrile and DABCO at elevated pressures (4.0- 5.5 kbar). The results, however, were somewhat disappointing both in terms of material yield and diastereoselectivity (*ca.* 16-23% d.e.).



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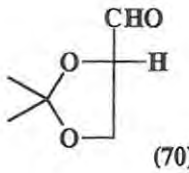
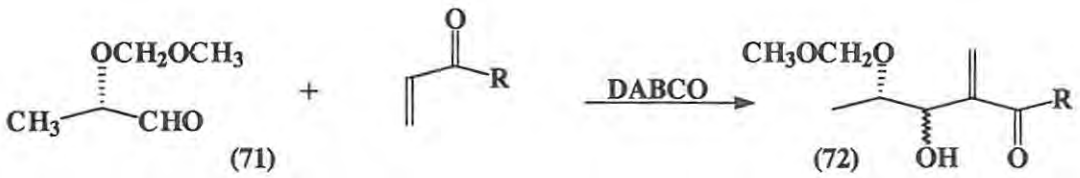


(70)

More promising results were reported by Drewes *et al.*[20] who reacted (*S*)-(-)-2-methoxymethoxy)propan-1-al **(71)** with various acrylates, in the presence of DABCO, to obtain mixtures of the *syn*- and *anti*- products **(72)** with the latter predominating **(Scheme 16)**.

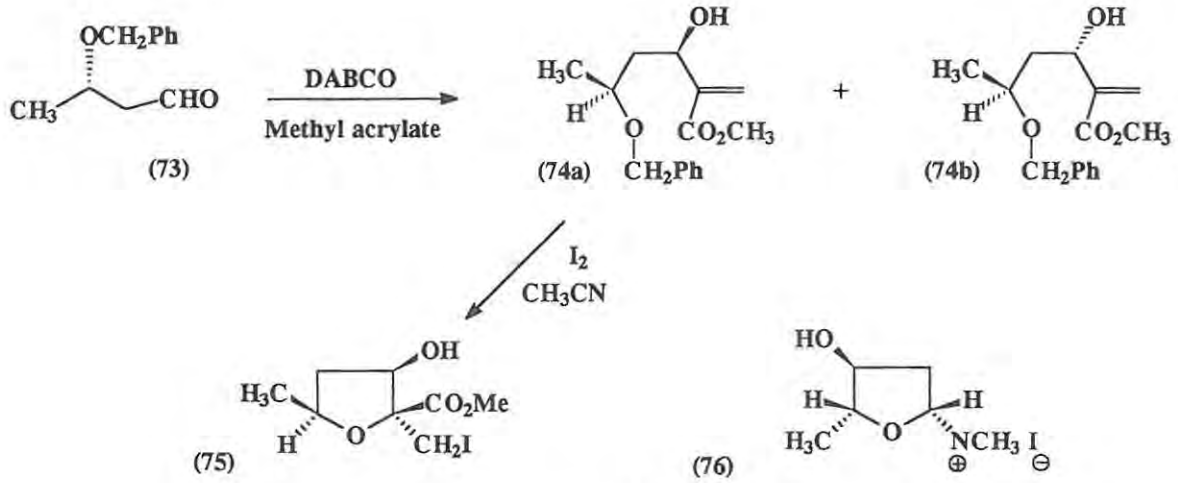


anti :*syn* *ca.* **70:3**

Scheme 16

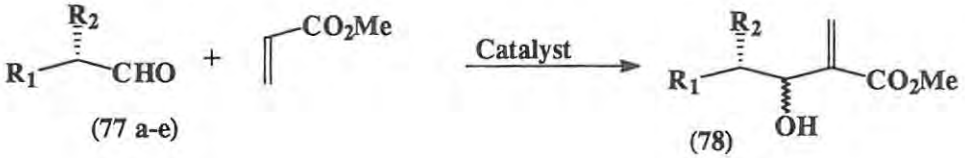
In a subsequent study, Drewes *et al.*[80] made use of the *O*-benzyl ether **(73)** derived from ethyl (3*S*)-3-hydroxybutanal **(Scheme 17)**. When this compound was reacted with methyl acrylate in the presence of DABCO, the diastereomeric Baylis-Hillman products **(74a,b)** were obtained in 70% yield. Compound **(74a)** was then cyclized using iodoetherification to the tetrahydrofuran derivative **(75)** in 60% yield and 95% d.e. [The configurational assignments shown in structure **(75)** are speculative, however, and must await final

confirmation].The authors drew attention to the similarity between the tetrahydrofuran (**75**) and the highly toxic compound, muscarine (**76**).

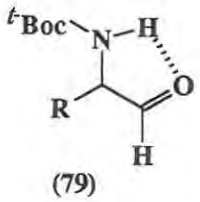


Scheme 17

Chiral amino aldehydes have also been employed in asymmetric Baylis-Hillman reactions. Roos *et al.*[54,55] reacted the α-dialkylamino and α-(*N*-acylamino)aldehydes (**77a-e**) with methyl acrylate to obtain the diastereomeric products (**78**) (**Scheme 18**). The reactivity of the aldehydes increased, as expected, with the introduction of electron- withdrawing *N*-substituents (**Table 10**), while molar equivalents of the tertiary amine catalysts DABCO and 3-hydroxyquinuclidine were used to expedite the reaction, following Basavaiah's[56] precedent. The authors noted that the diastereoselectivity was dependent on the *N*-substituent (**Table 10**), and rationalised the *anti*-selectivity in terms of the Felkin-Anh open chain model;[81,82] the *syn*-selectivity observed in the case of the *N*-*t*-Boc derivative (**77d**) was attributed to the involvement of the H-bonded chelate (**79**).



	R_1	R_2
a	Me	$N(CH_2Ph)_2$
b	CH_2Ph	$N(CH_2Ph)_2$
c	Me	N-phthaloyl
d	Me	*N*-*t*-Boc
e	$-(CH_2)_4N-SO_2Ph$	

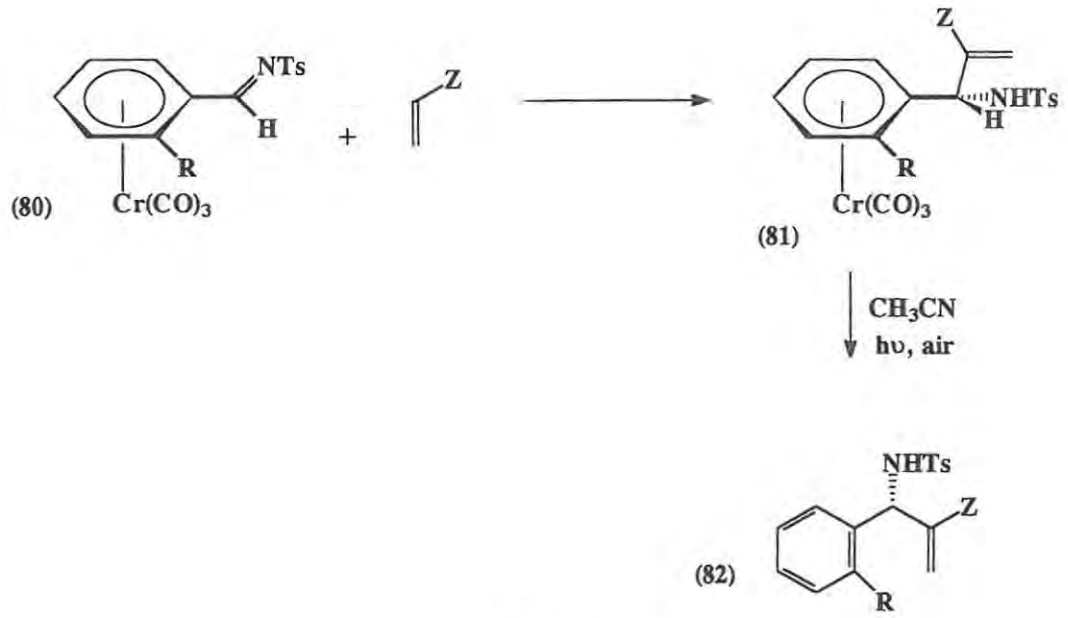


Scheme 18

Table 10. Reactions of *N*-protected α-amino aldehydes with methyl acrylate in the presence of DABCO from the study by Roos and Manickum[55] **(Scheme 18)**.

Aldehyde	Catalyst (Mol%)	Time/d	*Anti:syn* ratio	Product yield /%
77a	100	20	72:28	71
77b	100	31	70:30	80
77c	100	3.5	55:45	30
77d	10	7	26:74	80
77d	100	< 1.5	29:71	76
77e	100	< 0.5	88:12	55

In a very interesting approach, Kündig *et al.*[65,66] made use of tricarbonylchromium complexes **(Scheme 19)** to obtain Baylis-Hillman type products from various aryl aldehydes and aryl imines in high yield (> 80%) and in very high diastereomeric excess, typically greater than 95% d.e. The chromium complex is easily converted to the normal Baylis-Hillman type product and, in those cases where non-racemic aldehydes were utilized, decomplexation afforded products in high enantiomeric excess (> 98% d.e.).



Scheme 19

1.1.6.4 Chiral solvents

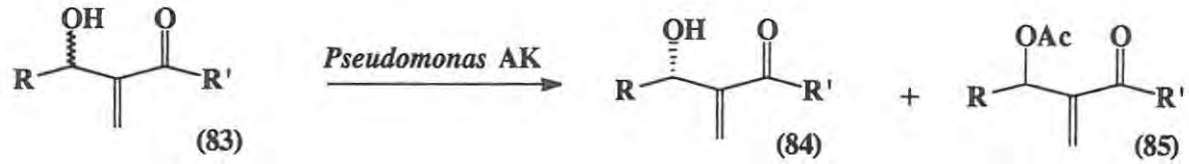
Very little appears to have been published on the use of chiral solvents in the Baylis-Hillman reaction. Isaacs *et al.*[75] investigated use of (+)-ethyl lactate as a chiral solvent, but with little success; in the reaction between acetaldehyde and acrylonitrile in the presence of 3-hydroxyquinuclidine, the product was obtained in high yield but only 3% e.e.

1.1.7 Optical resolution

α-Methylene-β-hydroxy esters and ketones afforded by the Baylis-Hillman reaction have found application in a multitude of synthetic transformations **(see Section 1.1.9)**. While these compounds are readily prepared in their racemic form, their potential in asymmetric synthesis has not been exploited effectively as no really convenient route to homochiral Baylis-Hillman type products has been developed. Owing to this, several authors have made use of resolution techniques as a means to enhance optical purity.

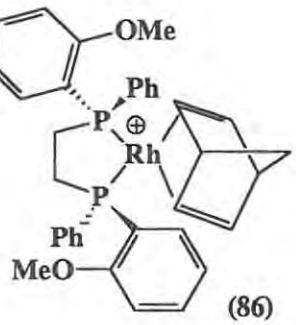
By far the most simple and inexpensive method developed for this purpose has involved the use of enzymes. Burgess and Jennings[83] used the enzyme, *Pseudomonas* AK lipase, to obtain the (*S*)-enantiomeric hydroxy products **(84)** in typically >95% e.e. **(Scheme 20)**, the (*R*)-enantiomers being selectively acetylated to afford the derivatives **(85).**

Pig liver acetone powder (PLAP) was used by Basavaiah and Darma Rao[84] to achieve enzymatic, enantioselective hydrolysis of acetates derived from Baylis-Hillman type products, and obtained the desired (+)-alcohols in 46-65% e.e. Adam *et al.*[85] made use of horseradish peroxidase to resolve hydroperoxides derived from Baylis-Hillman products, stereoselective reduction of the peroxides to the corresponding alcohols proceeding in >99% e.e.Drewes *et al.*[86] used diastereomeric crystallisation with the aid of a chiral amino diol to resolve a racemic acid mixture.



Scheme 20

Brown *et al.*[87,88] achieved kinetic resolution for a wide variety of racemic Baylis-Hillman products *via* homogeneous catalytic hydrogenation using chiral phosphine-rhodium catalysts, such as (*R,R*)-1,2-bis[(2-methoxyphenyl)phenylphosphino] ethane (dipamp) **(86)**, (*S,S*)-2,3-bis(diphenylphosphino)butane (chiraphos) **(87)** and (*R,R*)-4,5-bis(diphenylphosphino) -2,2-dimethyldioxolane (diop).



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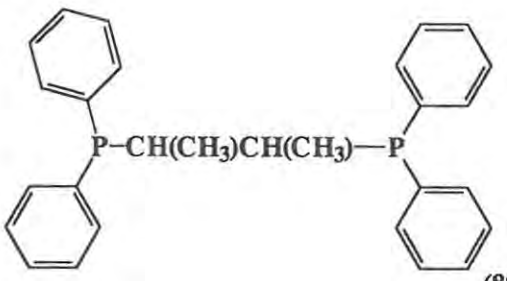
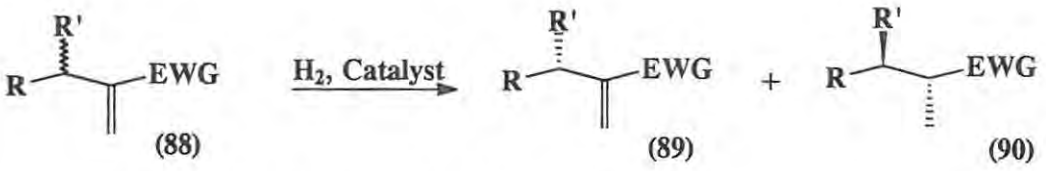


(87)

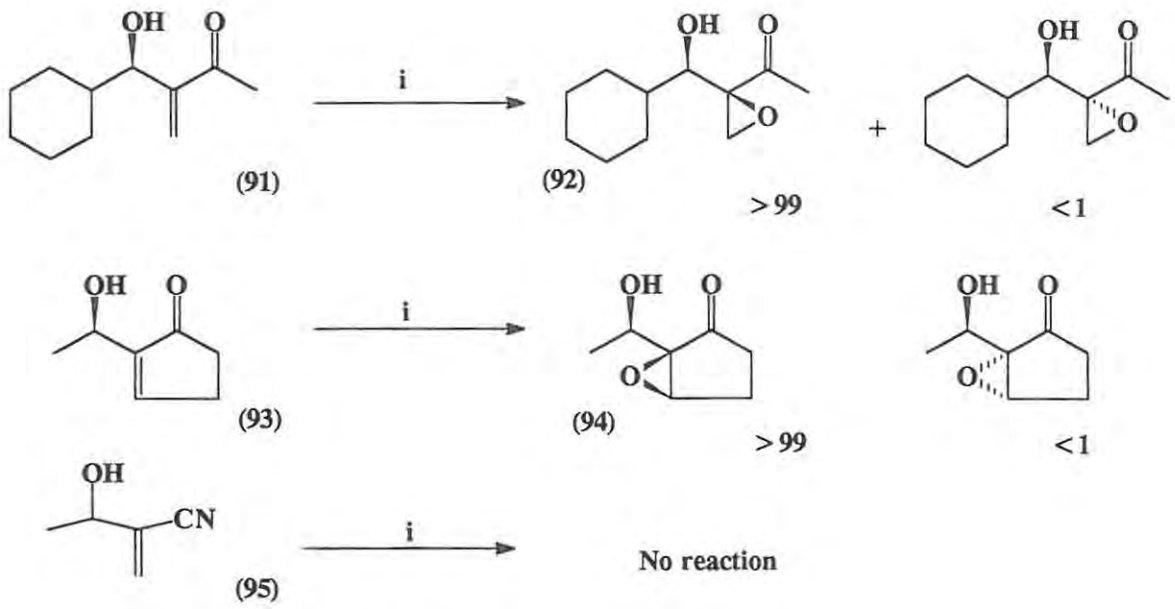
These reducing systems afforded the requisite products in high enantiomeric excess (typically >90% e.e.) and in high overall yield, thus providing a viable route to optically active α-(hydroxyalkyl)acrylates [with the *anti*-products **(90)** being the dominant species] **(Scheme 21)**. Noyori *et al.*[89] also found rhodium compounds to be highly effective for the stereoselective reduction of Baylis-Hillman products, and suggested that the dominance of the *anti*-product **(90)** could be due to the preferential chelation of the chiral catalyst at the *si*-face.



R' = OH, $NHCO_2{}^tBu$ EWG = CO_2Me, SO_2Ph

Scheme 21

Bailey *et al.*[45,90,91] explored the use of epoxides to resolve Baylis-Hillman type products. Sharpless epoxidation[92] of hydroxyenones **(Scheme 22)** afforded the *syn*-epoxides almost exclusively and in high yields; in contrast, Weitz-Scheffer[93] epoxidation of cyclic β-hydroxyenones **(93)** also afforded mostly the *syn*-epoxide, but with much lower stereoselectivity. However, the nitrile **(95)**, failed to react and, similarly, when the hydroxyl functionality was blocked, total inhibition of epoxidation was observed.

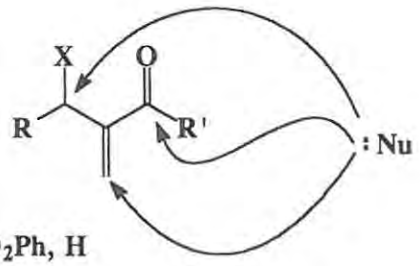


Reagents; i) $Ti(O^iPr)_4$ / TBHP / CH_2Cl_2 / -15°C

Scheme 22

1.1.8 Applications in synthesis

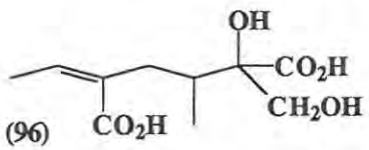
The products derived from Baylis-Hillman reactions have several centres where further elaboration may take place. Functional groups attached to the molecule (**X, C=C, C=O, R and R'; Figure 9)** may be modified and, in addition, the products are able to undergo nucleophilic addition or substitution at three different sites. Such susceptibility to subsequent transformation makes Baylis-Hillman products very versatile synthetic intermediates, and there have been many reports of their application in synthesis. These applications have been well covered in the review articles by Drewes and Roos[4] and Basavaiah *et al.*[5]



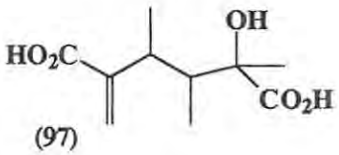
e.g. X = OH, NR_2
e.g. R' = CN, CO_2R, SO_2Ph, H

Figure 9

Many natural products contain the acrylate sub-unit, and a number of these also exhibit biological activity.[15] Some of the earliest natural products to be synthesised *via* the Baylis-Hillman approach were necic acids. These compounds constitute the acid portion of pyrrolizidine ester alkaloids, a class of hepatotoxic compounds which have been responsible for substantial stock losses around the world.[2] Retronecic acid **(96)**, senecivernic acid **(97)**, isolinecic acid **(98)** and mikanecic acid **(99)** are all examples of C_{10} -necic acids.



(96)



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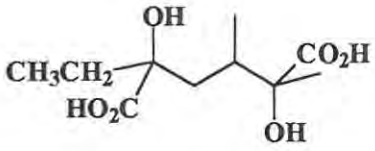

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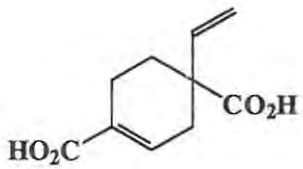
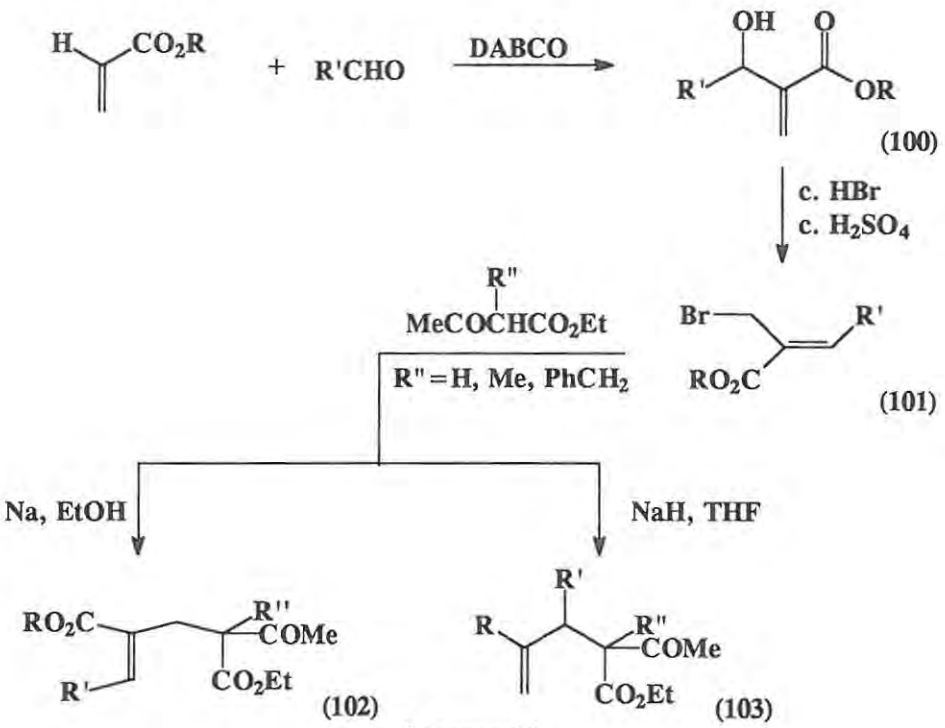


(99)

Drewes and co-workers have published several papers on the synthesis of various necic acids and analogues,[2,94-98] using the Baylis-Hillman approach **(Scheme 23)**. Intermediates of type **(102)** and **(103)** were readily converted into retronecic **(96)** and senecivernic acid **(97)**, respectively. This methodology proved to be very successful, when compared with alternative routes.[2]



Scheme 23

A significant aspect of the approach outlined in **Scheme 23** is the high degree of regiocontrol which may be achieved in S_N reactions of the allylic halide intermediates **(101).** Thus, two products **(102 or 103)** are available from the reaction depending on whether the nucleophile attacks the allylic carbon to afford a "normal" product (path I)**(Figure 10)** or the vinyl carbon to afford a rearranged product (path II). It has been observed that attack at the allylic carbon is enhanced by:- changing the base-solvent system from NaH-THF to NaOEt-EtOH, by increasing the steric bulk of the nucleophile or by the presence of an aryl substituent R'.[99]

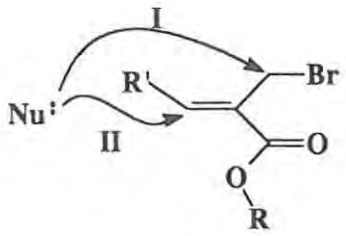
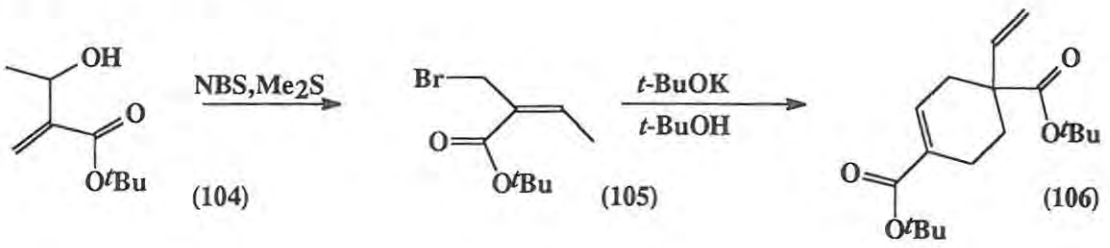


Figure 10

1.1.8.1 Cycloaddition reactions

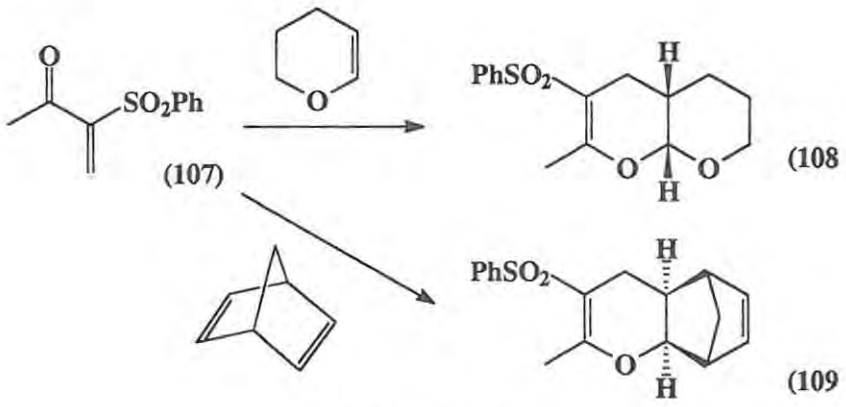
Several Baylis-Hillman products have been used either as dienes or dienophiles in Diels-Alder reactions.[100,101] Hoffmann and Rabe[102] synthesised mikanecic acid **(106)** *via* the Diels-Alder "dimerisation" of the allyl bromide **(105)** to obtain the required product in an overall yield of 40% **(Scheme 24)**.



(104) (105) (106)

Scheme 24

Hoffmann *et al.*,[100,101] used the mild Jones oxidation of Baylis-Hillman products to obtain α-methylene-β-keto esters and sulphones (***e.g.* 107**) **(Scheme 25)**. These compounds were then allowed to react under Diels-Alder conditions to afford products such as **(108)** and **(109)** in yields varying from 35 to 93%.

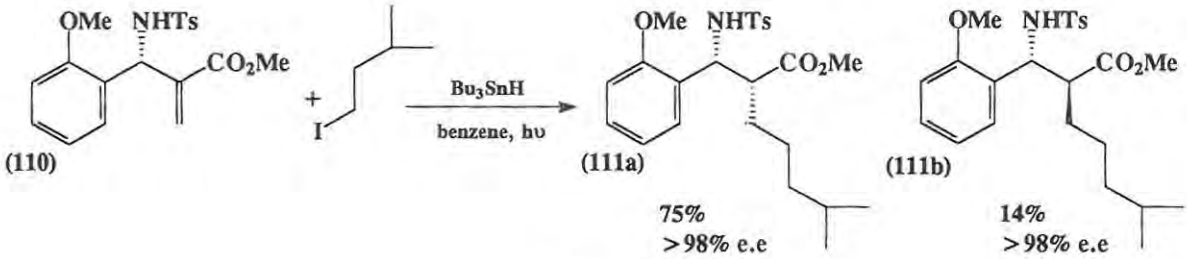


(107) (108) (109)

Scheme 25

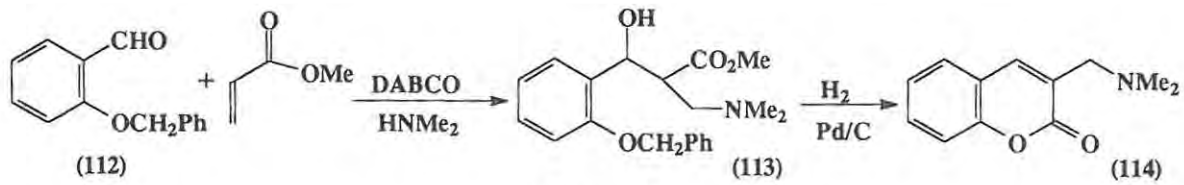
1.1.8.2 Nucleophilic reactions

Kündig *et al.*[103] studied diastereoselective addition to both racemic and enantiomerically pure Baylis-Hillman products. Reaction of the enantiomerically pure compound (*S*)-(+)-**(110)** and 1-iodo-3-methylbutane, in the presence of tributyltin hydride (Bu_3SnH), afforded the two diastereomeric β-amino acid derivatives **(111a)** and **(111b)**, with the *syn*-product being the major component **(Scheme 26)**.



Scheme 26

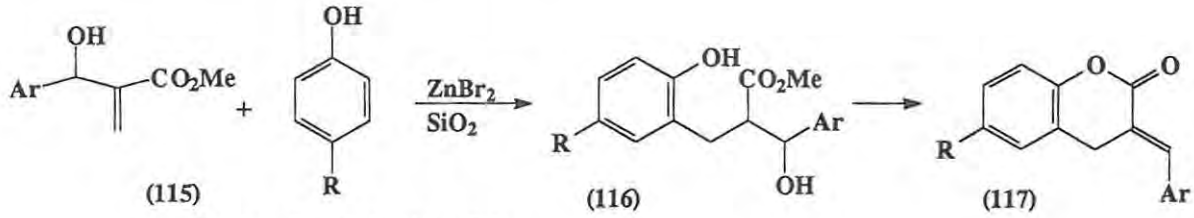
Drewes *et al.*[104] synthesised 3-(dimethylaminomethyl) coumarin **(114)** *via* a reaction between *O*-benzylsalicylaldehyde **(112)** and methyl acrylate, which was followed by conjugate addition of dimethylamine to the Baylis-Hillman product and catalytic hydrogenation, to afford the desired coumarin.



Scheme 27

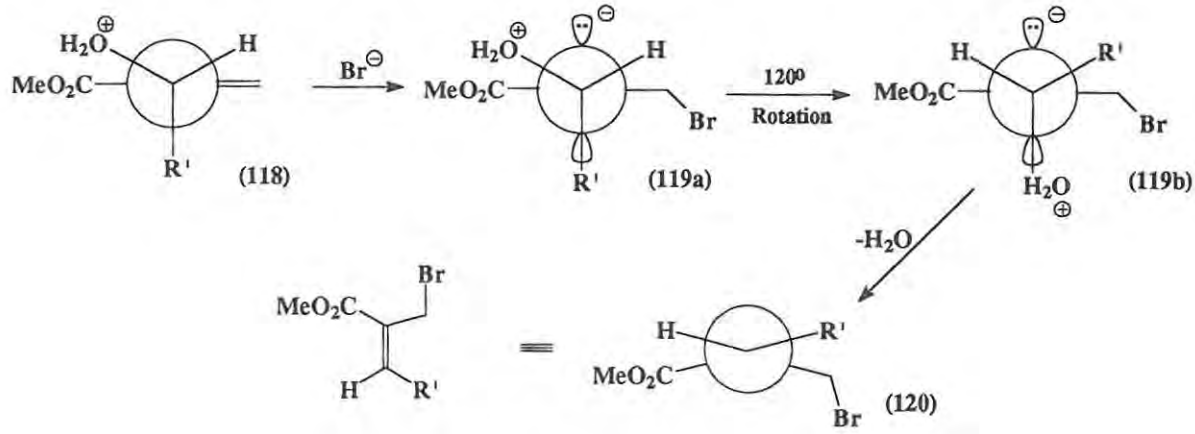
Foucaud and Brine[105] reported the simple and practical synthesis of 3-arylidene-3,4-dihydrocoumarins **(117)** using Baylis-Hillman products as precursors. In their study, a number of Baylis-Hillman products **(115)** were reacted with various *para*-substituted phenols in the presence of a Lewis acid and 1,2-dichloromethane to afford the desired products in

yields varying from 10 to 80% **(Scheme 28)**.



Scheme 28

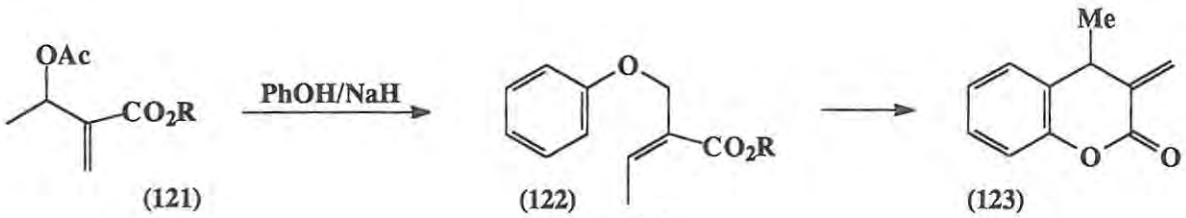
(*E*)-(*Z*)-Stereoselectivity in the synthesis of allyl halides by the action of reagents such as :- HBr-H_2SO_4, NCS-Me_2S, HCA-PPh_3, HI-H_3PO_4 and NBS-Me_2S has been extensively studied and is well documented in the literature.[2,3,16,97,106] Hoffmann and Bochholz[107] used molecular modelling to rationalise the formation of the (*Z*)-allyl bromides **(120)** from the reaction between HBr-H_2SO_4 and methyl 3-hydroxy-2-methylenealkanoates **(118)(Scheme 29).**



Scheme 29

They postulated that initial protonation of the hydroxyl group is followed by bromide attack at the less hindered face of the double bond in a Michael fashion with formation of intermediate **(119a)**. Anti-clockwise rotation of the "front" groups by 120° affords the conformer **(119b)**, in which the leaving group (H_2O) is anti to the carbanionic centre; elimination then leads to formation of a (*Z*)-double bond **(120)**.[107]

Drewes *et al.*[108] made use of an intramolecular Claisen-rearrangement of an allyl aryl ether precursor **(122)** in the synthesis of 4-methyl-3-methylene-3,4-dihydrocoumarin **(123)** **(Scheme 30)**. Such compounds have been synthesised previously *via* other routes, but according to Drewes *et al.*, this method provides a more efficient approach. The precursors **(122)** were prepared from the acetylated Baylis-Hillman products **(121)**, which were then cyclised in the presence of trifluoroacetic acid to afford the coumarin product **(123)** in a yield of 86%.

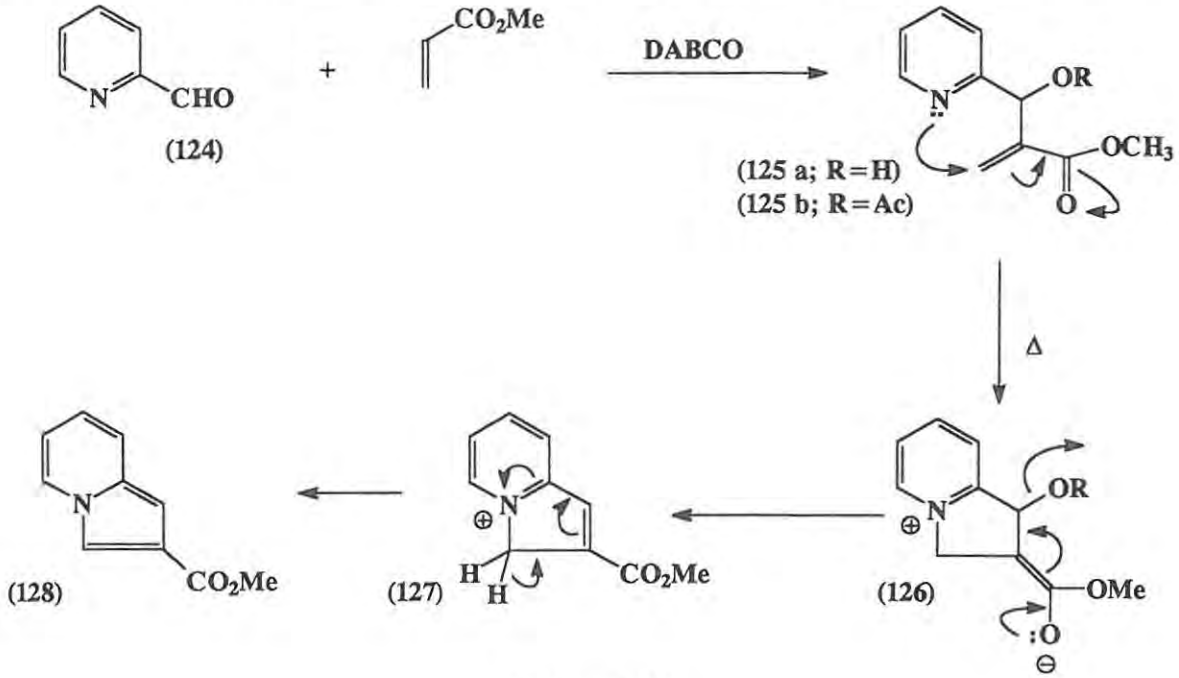


(121) (122) (123)

Scheme 30

1.2 EARLIER STUDIES AND AIMS OF THE INVESTIGATION

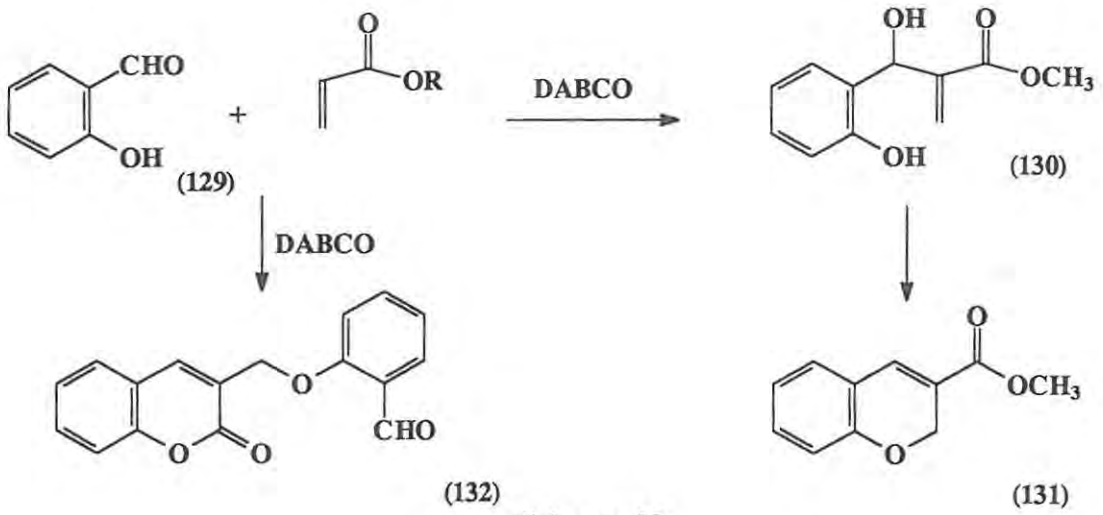
Previous work in the group has shown that indolizine derivatives may be synthesised in good yield by the thermal cyclisation of acetylated Baylis-Hillman products,[110] derived from pyridine-2-carboxaldehyde **(124)** and acrylate systems **(Scheme 31)**, and a kinetic study of the cyclisation has been undertaken to establish the mechanism of the reaction.[110]



Scheme 31

Attempts were also made to extend this methodology to the synthesis of chromene compounds **(131)**, from salicylaldehyde **(129)** and methyl acrylate, but a novel coumarin derivative **(132)** was obtained instead **(Scheme 32)**.[109,111]

Other work, directed towards the synthesis of necic acids,[94-99] had revealed that nucleophilic substitution reactions between halogenated Baylis-Hillman products and various nucleophiles, afforded regioisomeric products, the regioselectivity depending on the base-solvent system used.



Scheme 32

The present investigation was undertaken to address issues raised by these earlier studies, and specific objectives have included the following :-

i) to explore the generality of the Baylis-Hillman approach for the synthesis of coumarin derivatives from salicylaldehyde and to optimise the conditions for such reactions;

ii) to synthesise putative intermediates in this reaction, with a view to gaining a better understanding of the mechanism involved;

iii) to undertake a kinetic and mechanistic study of nucleophilic substitution reactions of Baylis-Hillman derived halogeno esters in order to rationalise the observed regioselectivity patterns; and

iv) to investigate the conjugate addition reactions of various nucleophiles with selected Baylis-Hillman products.

2. DISCUSSION

In the discussion which follows, attention will be focused on:- the use of the Baylis-Hillman reaction in the synthesis of oxygen-containing heterocycles **(Section 2.1)**; an investigation of the regio- and diastereoselectivity of the reaction of Baylis-Hillman products with various nucleophiles **(Section 2.2)**; and a mechanistic study of the regioselectivity of substitution reactions of Baylis-Hillman derived halogeno esters using the enolate anion of methyl 2-methyl-3-oxobutanoate as nucleophile **(Section 2.3)**.

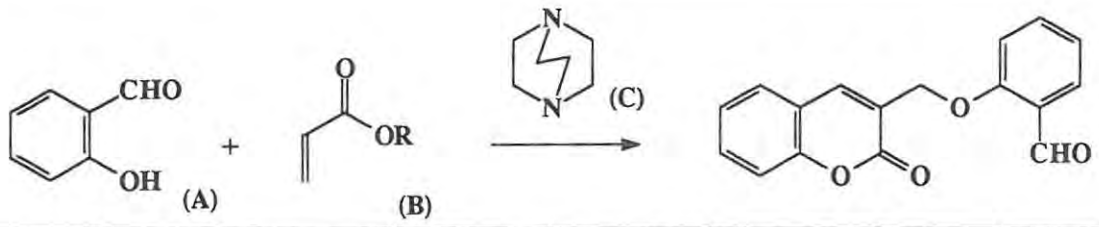
2.1 APPLICATION OF THE BAYLIS-HILLMAN REACTION IN THE SYNTHESIS OF OXYGEN-CONTAINING HETEROCYCLES

Previous attempts to obtain a chromene derivative *via* the Baylis-Hillman reaction of salicylaldehyde with methyl acrylate afforded, instead, the coumarin derivative 3-[(2-formylphenoxy)methyl]coumarin **(132a)** in a maximum yield of 10% **(Scheme 32)**.[109] Attempts to increase the yield of the coumarin and explore the generality and mechanistic details of the transformation have, surprisingly, led to the isolation of numerous, additional products, including chromene and coumarin derivatives.

2.1.1 Yield optimisation studies

Attention was given to improving the yield of the coumarin product in order to exploit the synthetic potential of the reaction. Several reaction variables were examined, including:- the concentration of the reagents, the catalyst, the temperature and the reaction time. The optimisation studies were conducted using salicylaldehyde and methyl or ethyl acrylate in the presence of DABCO or 3-hydroxyquinuclidine, and the results are summarised in **Table 11**.

Table 11. Optimisation of the Baylis-Hillman reaction of neat salicylaldehyde with acrylate esters in the presence of DABCO.



Entry	R	A/ mmol	B/ mmol	C/ mmol	Isolated yield/ %	Time	Temp./ °C
1	Me	21.0	19.9	5.0	24	5d	r.t
2	Me	21.0	19.9	5.0[a]	14	5d	r.t
3[c]	Me	21.0	20.0	1.0	19	3d	r.t
4[c]	Me	21.0	20.0	1.0[a]	3	14d	r.t
5	Me	19.97	21.02	5.13	30	13d	r.t
6	Me	19.97	21.02	1.99	10	8d	r.t
7	Me	19.97	21.02	0.99	5	8d	r.t
8	Me	6.66	7.01	1.67	54	19d	r.t
9	Me	39.9	21.02	0.99	4	11d	r.t
10	Et	13.3	8.2	1.67	37	14d	100[b]
11	Et	13.3	8.6	1.8	33	7hours	80
12	Et	12.0	7.4	1.78	32	9hours	100

[a] Reaction conducted with 3-hydroxyquinuclidine as the catalyst, [b] This reaction mixture was maintained at 100°C for 5h and thereafter allowed to react at room temperature. [c] Reaction carried out by M. L. Bode.[111]

From the results obtained it is apparent that increasing the concentration of the tertiary amine catalyst increases the rate of the reaction, with the highest yields being obtained with a

catalyst: acrylate mole ratio of 1:0.25. The highest yield (54%) was obtained following the protocol detailed in entry 8 (**Table 11**), *viz.*, using a DABCO: acrylate ester: aldehyde ratio of *ca.* 0.25:1:1 with a reaction period of 19 days.

3-Hydroxyquinuclidine has been shown to enhance the rate of the Baylis-Hillman reaction significantly.[7,45,46] Surprisingly, use of this catalyst in the reaction instead of DABCO failed to accelerate the transformation (see entries 1 and 2). This observation is supported by the work conducted by Bode,[111] who showed that the reaction carried out with 3-hydroxyquinuclidine as catalyst afforded the product in only 3% yield after 14 days compared to an identical reaction carried out with DABCO, which afforded a yield of 19% after only 3 days.

When the reaction temperature was elevated, the transformation proceeded much more rapidly than similar reactions carried out at ambient temperature; however, the yield could not be raised above 37% even when the duration of the reaction was increased. It was also observed that the product obtained from reactions at elevated temperatures was less pure and ^{1}H NMR spectroscopy indicated the crude reaction mixture to contain additional components.

2.1.2 Coumarin generality studies

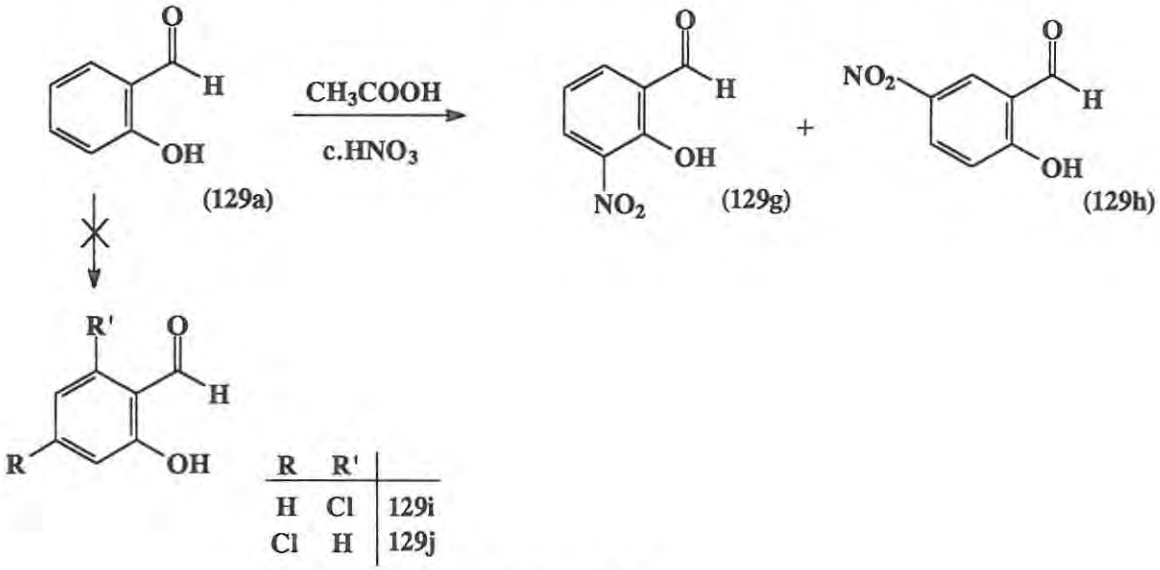
The next phase of the investigation involved exploring the generality of the transformation for the synthesis of coumarin derivatives, and for this purpose a range of substituted salicylaldehydes was required.

2.1.2.1 Synthesis of precursors

The range of commercially available substituted salicylaldehydes included:- 5-chloro-, 5-bromo-, 3,5-dibromo-, 3-methoxy-, 3-ethoxy- and 5-nitrosalicylaldehyde. These compounds were used as substrates but, in order to expand the range, attention was given to the synthesis

of several, additional, substituted salicylaldehydes.

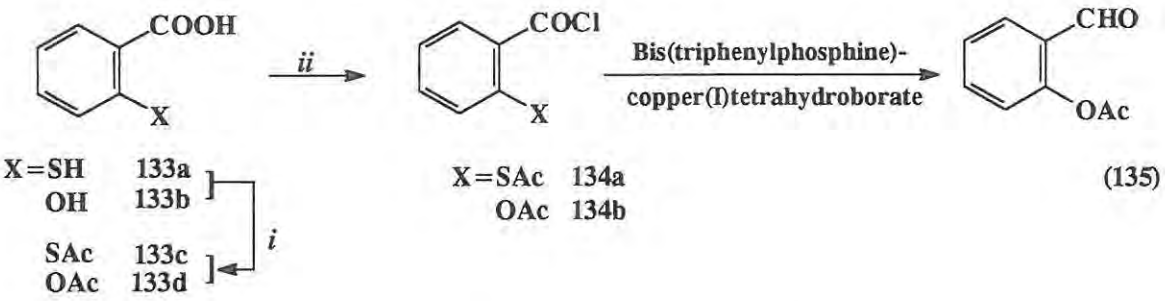
5-Nitro- **(129h)** and 3-nitrosalicylaldehyde **(129g)** were prepared using a procedure outlined in Beilstein,[113] in which salicylaldehyde **(129a)** is nitrated in a mixture of glacial acetic acid and fuming nitric acid **(Scheme 33)**. The reaction afforded, as expected, a mixture of 5-nitro- and 3-nitrosalicylaldehyde in a ratio of 2:1. Attempts to separate the two regioisomers using flash chromatography or by making the bisulphite addition compound of 5-nitrosalicylaldehyde, were unsuccessful and, as a result, the isomers were later used as a mixture. An attempt was also made to synthesise 6-chloro- **(129i)** and 4-chloro-salicylaldehyde **(129j)** following the method outlined by Casnati *et al.*,[114,118] using paraformaldehyde and $SnCl_4$; this method, however, did not afford any product.



R	R'	
H	Cl	129i
Cl	H	129j

Scheme 33

Attempts to synthesise acetylated thiosalicylaldehyde *via* reduction of the corresponding acid chlorides **(134a)** with the reducing agent,[115,116,117] bis(triphenylphosphine)copper(I)tetrahydro-borate proved unsuccessful, although this methodology was successfully used to reduce the acetylsalicylic acid chloride **(134b)** to the acetylated salicylaldehyde **(135)**.



Reagents: *i*) CH_3COCl, Pyridine, 60° C *ii*) $(COCl)_2$, benzene, 80° C.

Scheme 34

2.1.2.2 Reactions of substituted salicylaldehydes

The reactions were carried out under typical Baylis-Hillman conditions, in which the salicylaldehydes **[(129 a-h); Scheme 35 p.56)** were reacted with methyl acrylate[¶] in the presence of the tertiary amine catalyst, DABCO. The reactions were all conducted under an inert atmosphere of dry nitrogen in order to prevent oxidation of the aldehyde. The progress of the reactions was monitored by means of ^1H NMR spectroscopy, by observing the decrease in intensity of the distinctive aldehyde peak of the substrate. Some of the mixtures were left to react for several months, but coumarin formation was only evident in two cases, *viz.*, the reactions of salicylaldehyde (**129a**) and 5-chlorosalicylaldehyde (**129b**). What was evident in all cases was the formation of complex mixtures of different products.

The complex mixtures arising from these reactions were carefully chromatographed using a combination of flash chromatography and preparative layer chromatography. The purification of the components proved to be particularly difficult and, in some cases, repeated preparative layer chromatography was required in order to obtain compounds in sufficient purity for characterisation. It rapidly became apparent that the most common

[¶] The parent salicylaldehyde system (**129a**) was also reacted with acrylonitrile and with methyl vinyl ketone.

products were, in fact, the initially expected chromene derivatives **(131)** rather than the 3-substituted coumarins **(132)**. The only examples of the latter compounds to be isolated were the parent system **(132a)** and the 4',6-dichloro derivative **(132b)**.

In the reactions conducted with the nitrosalicylaldehyde **(129g,h)**, a precipitate was observed to form rapidly. The precipitates were shown to be the phenolate salts of DABCO and nitrosalicylaldehydes, the acidity of the phenolic protons being enhanced by the electron-withdrawing nature of the nitro group. In order to obviate this complication, protection of the phenolic group was explored **(see Section 2.1.6)**.

The influence of temperature on the product distributions was studied for the reactions involving 5-chlorosalicylaldehyde **(129b)**. It was found that at higher reaction temperatures (30°C) the chromene product **(131b)** was favoured (17%) but, even after several days, no coumarin product **(132b)** was detected. At room temperature (*ca.* 15-18°C), however, the formation of the 4',6-dichloro coumarin derivative **(132b)** was evident (*ca.*14%) after several hours, but at lower temperature (*ca.* 4°C) the reaction was noticeably slower and failed to afford any of the coumarin derivative.

In addition to the chromenes **(131 a-f)** and the coumarin derivatives **(132 a,b)**, numerous other products were obtained. In fact, representative examples of no less that *eight* classes of substituted heterocyclic systems were isolated and characterised. The product types **(II-V, VIII-XI)** are listed below[¶], their structures are depicted in the proposed reaction cascade outlined in **Scheme 36,** and the comparative yields are summarised in **Table 12 (p. 86)**.

i) Methyl 3,4-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylates (***II***)

ii) Methyl 2*H*-1-benzopyran-3-carboxylates (***III***)

iii) Methyl 2-(3-carbomethoxy-3,4-dihydro-2*H*-1-benzopyran-4-yl)propenoates (***IV***)

iv) Methyl 3,4-dihydro-4-methoxy-2*H*-1-benzopyran-3-carboxylates (***V***)

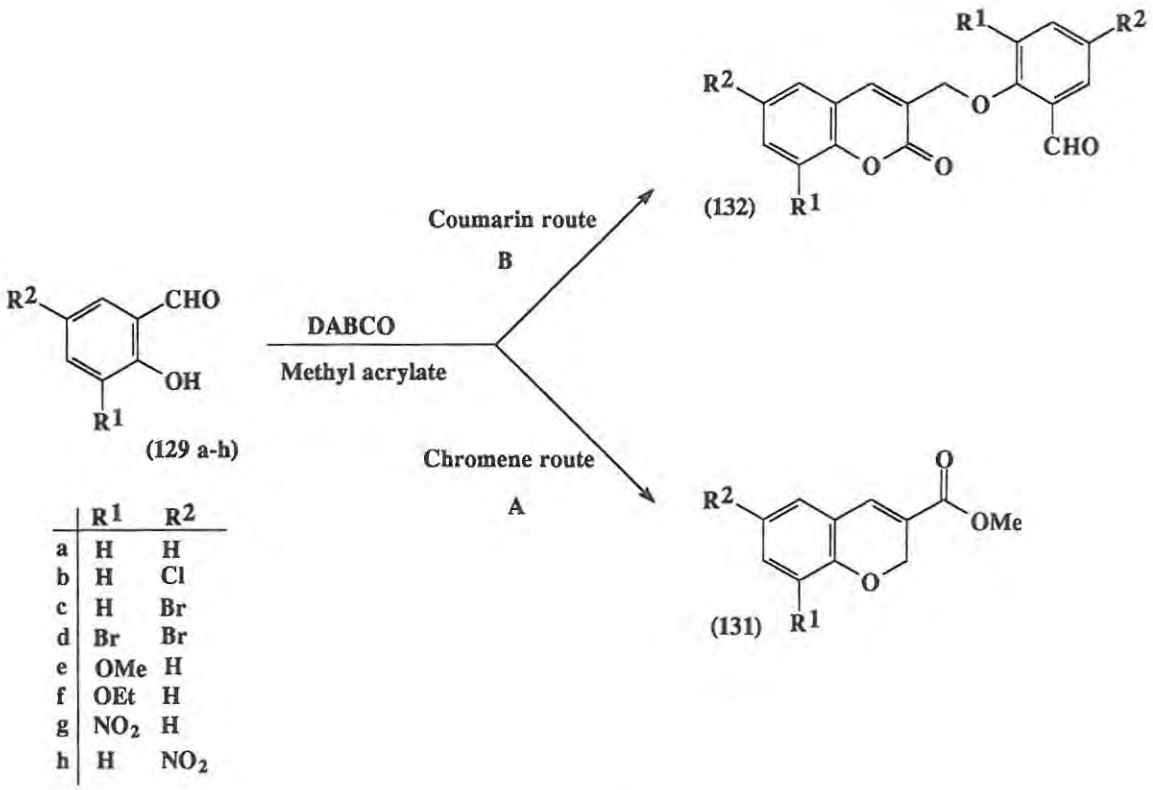
[¶] The names represent general product types.

v) Methyl 2-(3-methyl-1-benzopyran-2-on-4-yl)propenoates (***VIII***)

vi) Dimethyl 2-(3-methyl-1-benzopyran-2-on-4-yl)-4-methylenepentanedioates (***IX***)

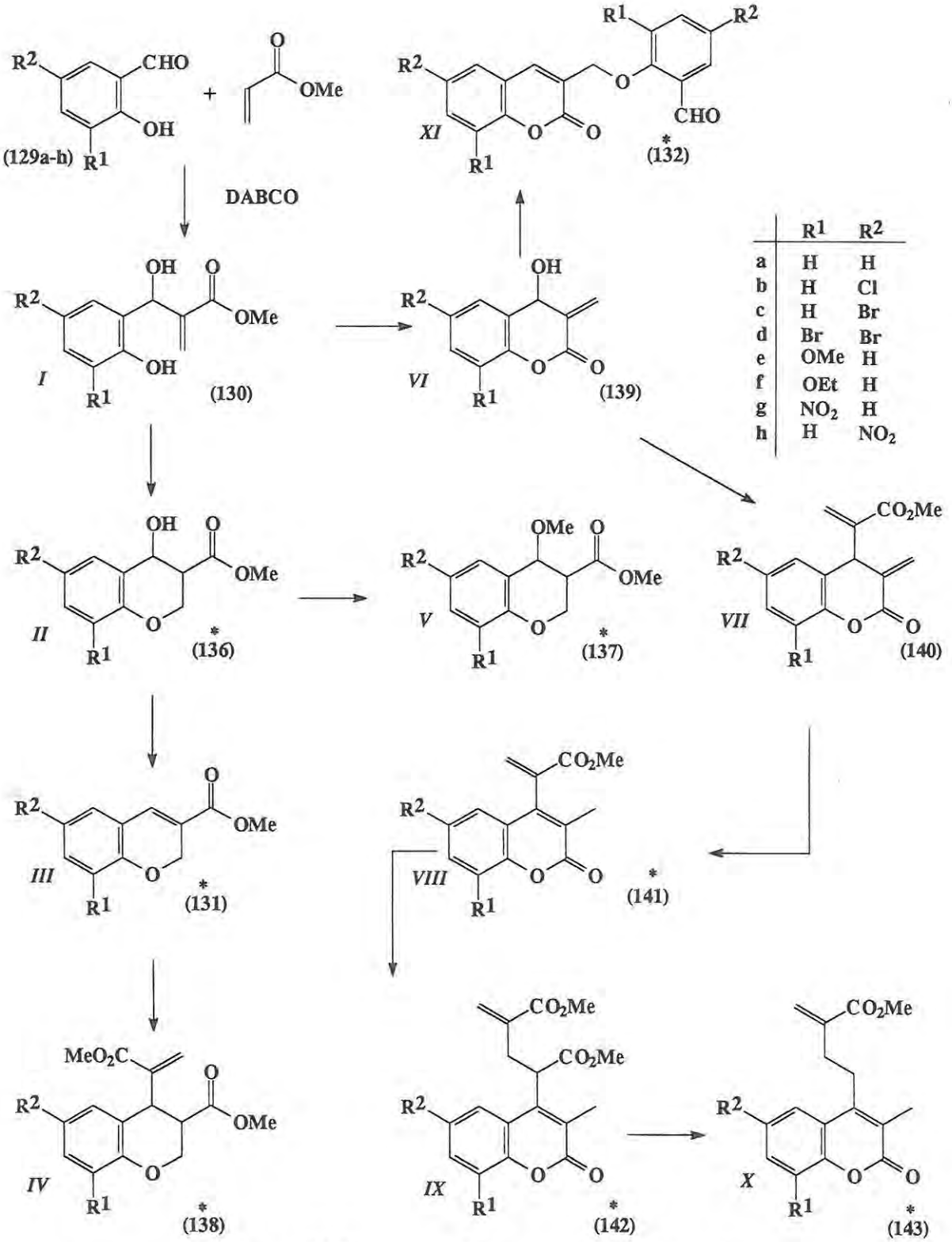
vii) Methyl 4-(3-methyl-1-benzopyran-2-on-4-yl)-2-methylenebutanoates (***X***)

viii) 3-[(2-Formylphenoxy)methyl]coumarins (***XI***)



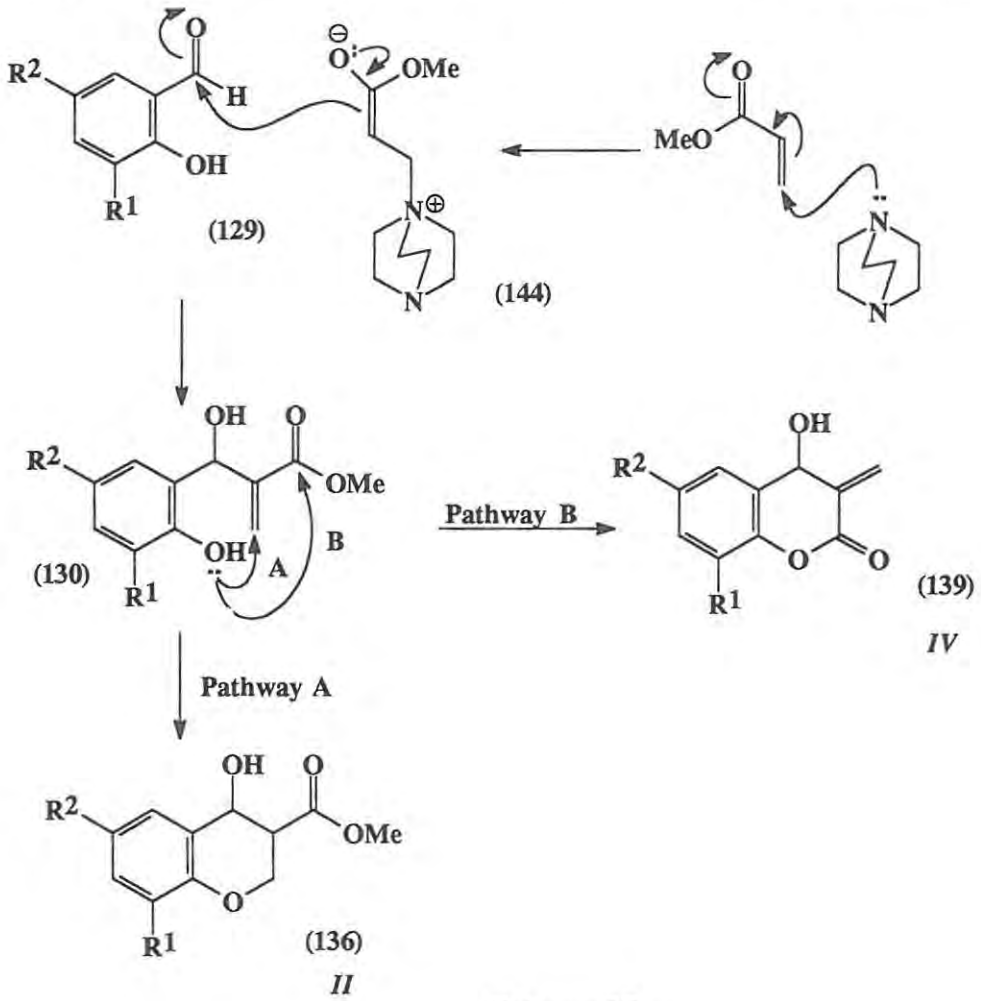
	R1	R2
a	H	H
b	H	Cl
c	H	Br
d	Br	Br
e	OMe	H
f	OEt	H
g	NO_2	H
h	H	NO_2

Scheme 35



Scheme 36 [*representitive example (s) isolated]

Pivotal to both product pathways is undoubtedly the formation of the Baylis-Hillman products **(130)** **(Scheme 37).** Whilst such intermediates were never isolated in *any* of the reactions using salicylaldehyde substrates, it seems very likely that such species are, in fact, the common precursors for the formation of both chromene and coumarin derivatives. The formation of the Baylis-Hillman product is expected to arise from attack by the zwitterionic enolate **(144),**[109] which will be subsequently described as the "Baylis-Hillman zwitterion".



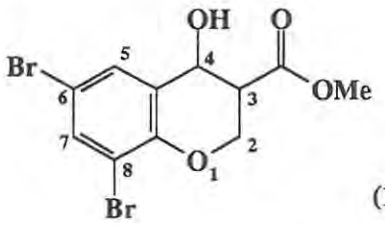
Scheme 37

Ring closure *via* conjugate addition **(pathway A; Scheme 37)** would afford access to the chromene systems, while acyl substitution **(pathway B)** would account for the formation of coumarin derivatives. In the following sections, the characterisation of the eight classes of

heterocyclic systems will be covered in detail.

2.1.3 Chromene derivatives

2.1.3.1 *Methyl 3,4-dihydro-4-hydroxy-*2H*-1-benzopyran-3-carboxylates* **(type *II* products).**



(136d)

The only compound representative of this class to be isolated was the 3,5-dibromo derivative ***methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2H-1-benzopyran-3-carboxylate*** **(136d)** which was obtained as colourless crystals. The most striking feature in the ^{1}H NMR spectrum of this compound **(Figure 11)** is the coupling observed between the protons attached to carbons 2, 3 and 4 which results in a complex splitting pattern for the 3-methine proton. The COSY spectrum **(Figure 12)** clearly confirms these coupling relationships, while the ^{13}C-, DEPT, and HETCOR spectra are all consistent with the structural arrangement. The formation of this compound is attributed to cyclisation of the corresponding Baylis-Hillman product *via* **(Pathway A, Scheme 37)** intramolecular conjugate addition.

Although the 4-hydroxychroman **(136)** has two chiral centres, its formation appears to be diastereoselective, [i] as evidenced by the absence of signal doubling in its ^{1}H and ^{13}C NMR spectra. The apparent stereoselectivity may be explained with the aid of computer modelling. Examination of the energy-minimised conformations of the *syn-* and *anti-* stereoisomers **(Figure 13)** of the 4-hydroxychroman **(136d)** reveals the respective 3-H, 4-H torsion angles to be :- ϕ_{syn} = 48° and ϕ_{anti} = 172.2°. Comparison of the *observed* vicinal coupling constant

[i] See also **Section 2.2 (p. 113)** for a discussion of the diastereoselectivity of conjugate addition reactions between Baylis-Hillman products and selected nucleophiles.

($J_{3,4}$= 7.7 Hz) with the values (J_{syn} = 6.7 Hz and J_{anti} = 9.9 Hz) estimated using the Karplus equation (J = 10 cos ϕ),[119] indicates preferential formation of the more sterically hindered *syn*-stereoisomer. The observed diastereoselectivity may be attributed to steric approach control,[120] in which protonation of the enolate (or enol) intermediate occurs at the less hindered face **(see Figure 13, path *I*)**.

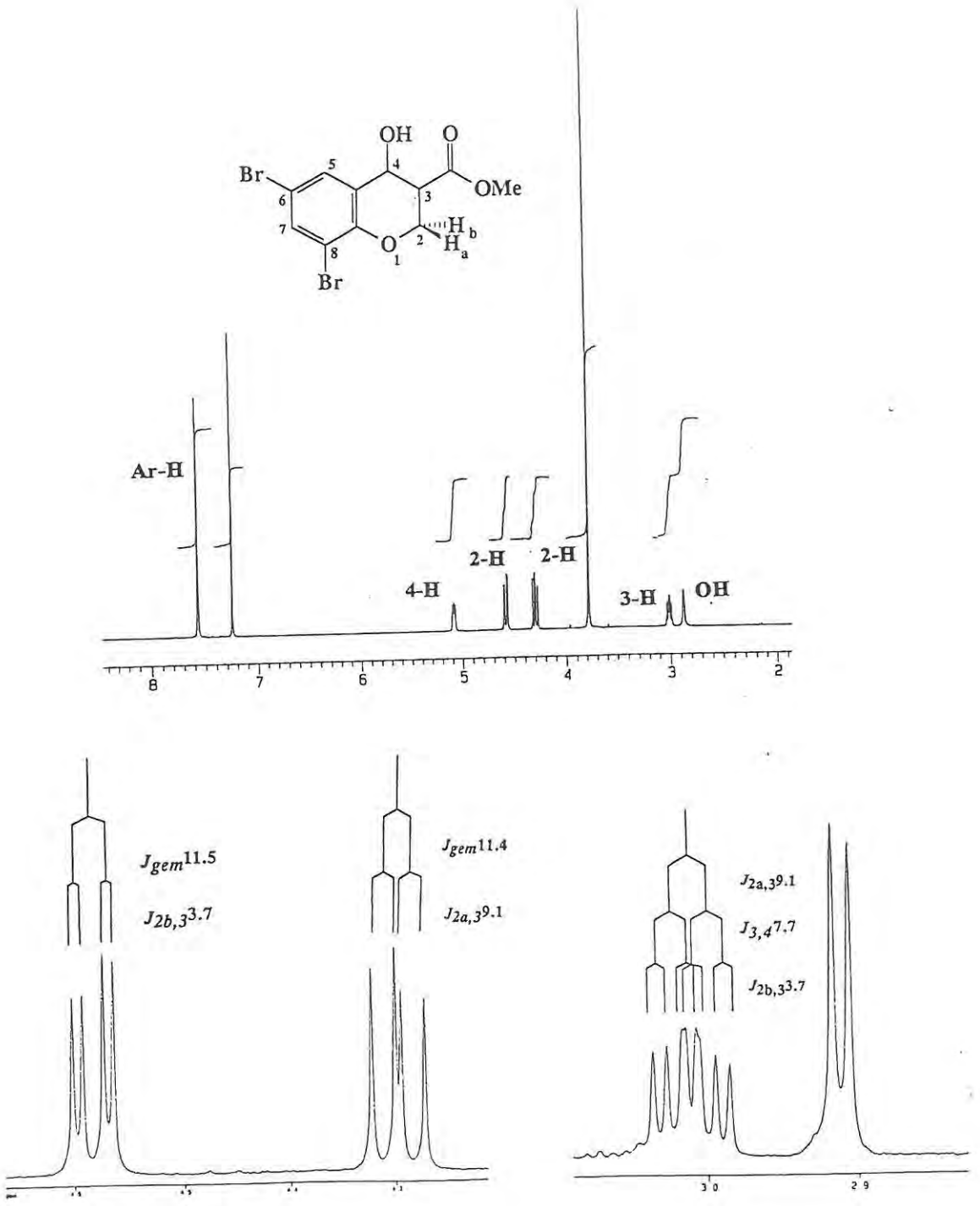


Figure 11 The 400 MHz ^{1}H NMR spectrum of methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylate (136d) in $CDCl_3$.

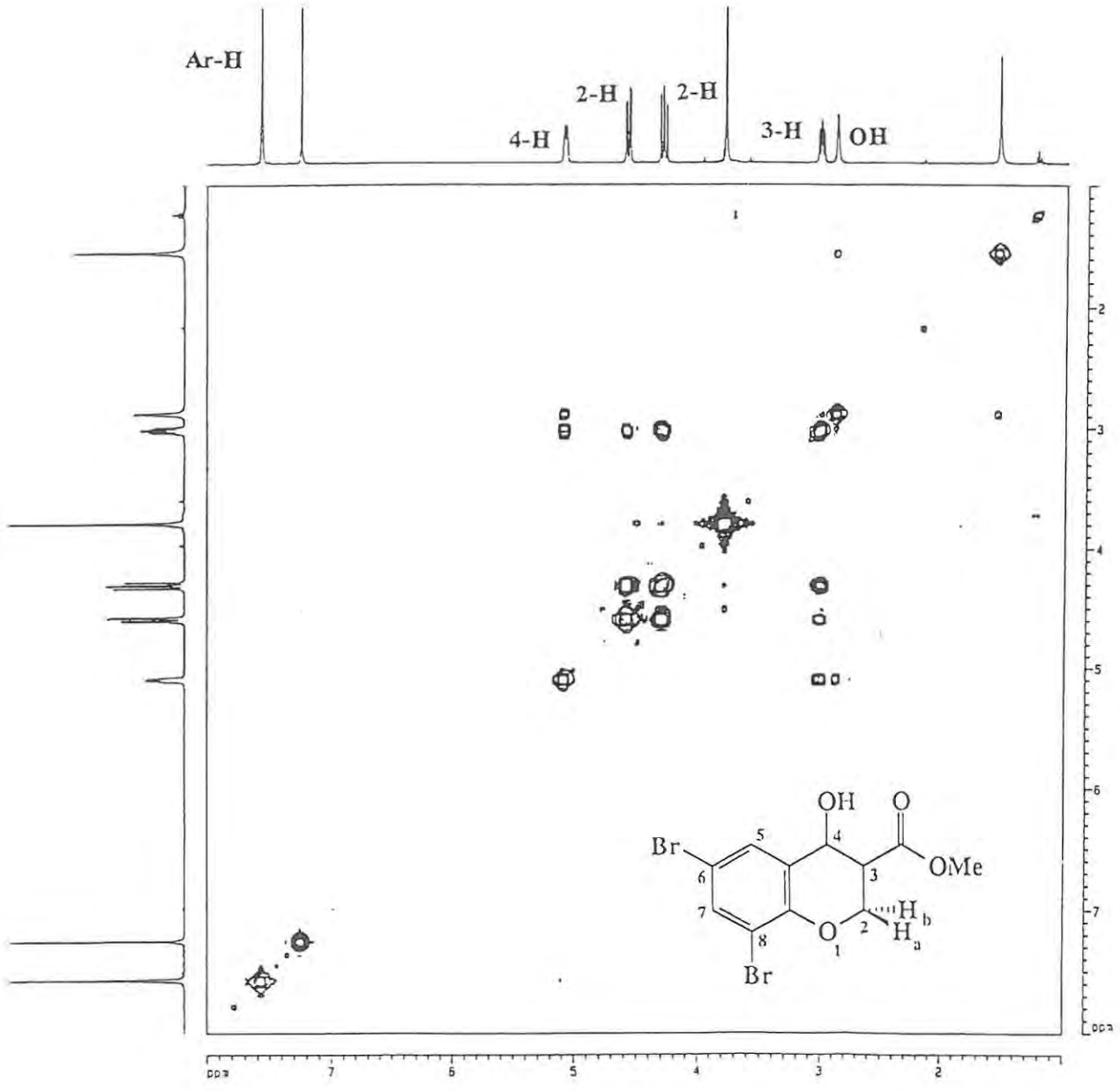


Figure 12 The 400 MHz COSY spectrum for methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylate (136d) in $CDCl_3$.

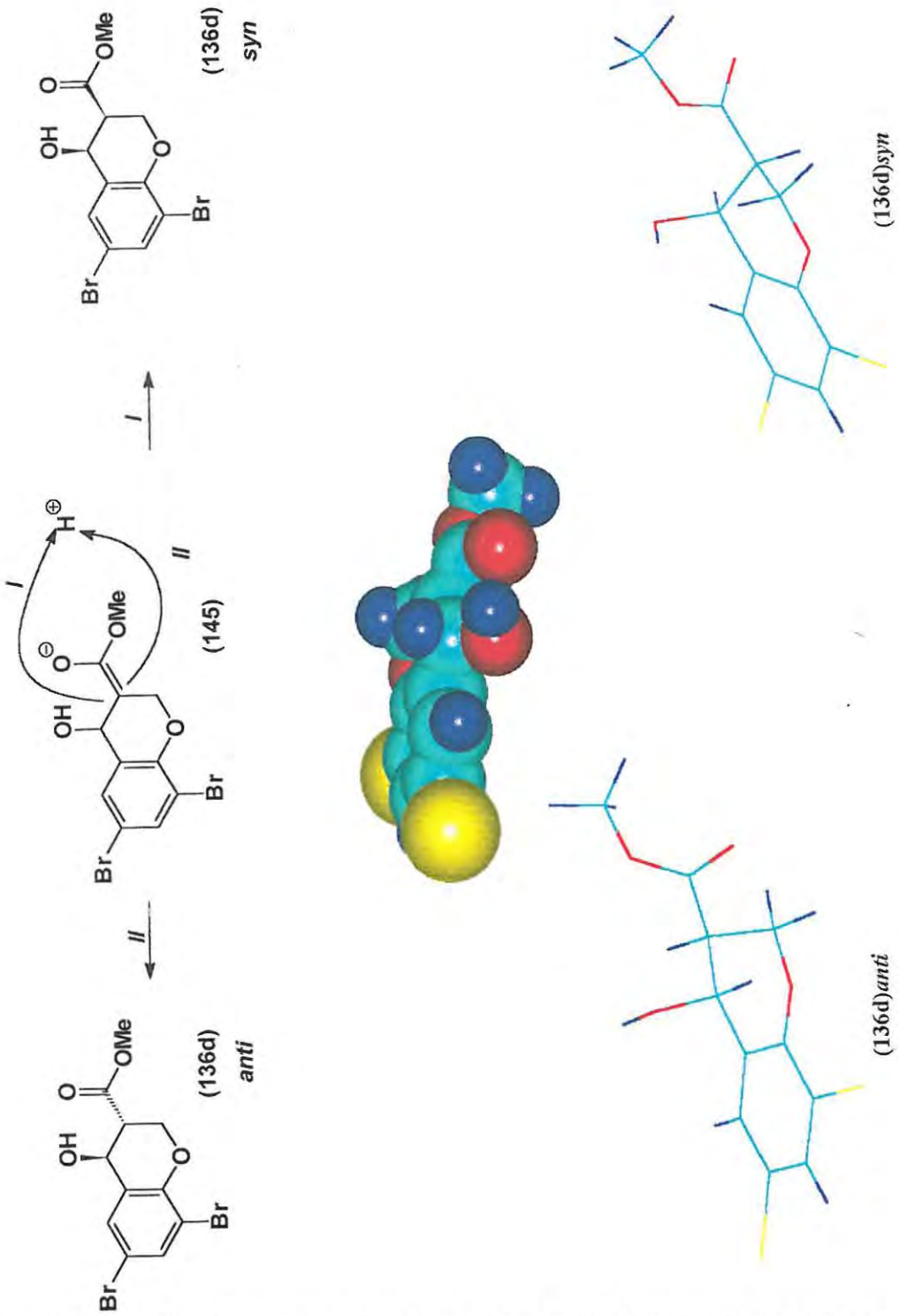
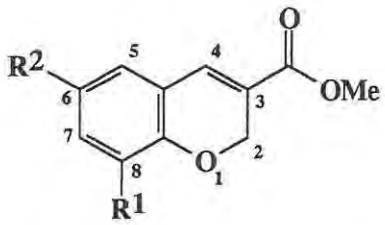


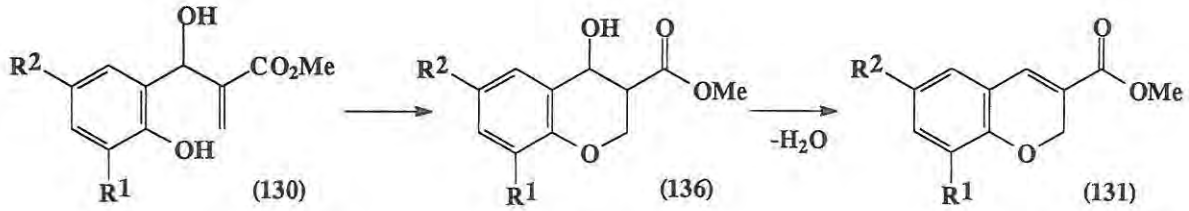
Figure 13 The two options for protonation of the intermediate (145), together with the respective energy minimised models.

2.1.3.2 *Methyl* 2H-*1-benzopyran-3-carboxylates* **(type *III* products)**



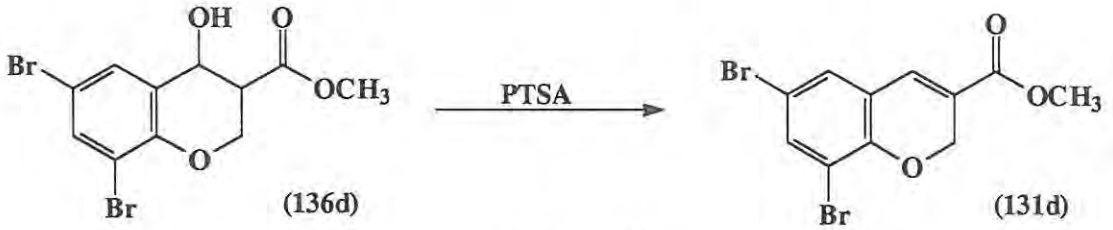
R^1	R^2	
H	H	131a
H	Cl	131b
H	Br	131c
Br	Br	131d
OMe	H	131e
OEt	H	131f

These derivatives were the most commonly isolated products, clearly vindicating the earlier expectation[109] that the Baylis-Hillman reaction could be extended to the synthesis of chromenes. Their formation is attributed to the dehydration of the 4-hydroxy-2*H*-1-benzopyran-3-carboxylate precursors **(136) (Scheme 38)**- an assumption supported by the acid-catalysed dehydration of methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylate **(136d) (Scheme 39)** to afford methyl 6,8-dibromo-3,4-dihydro-2*H*-1-benzopyran-3-carboxylate **(131d)** in quantitative yield.



Scheme 38

The ^{1}H NMR spectra of the chromenes **(131a-f)** are characterised by the magnetic equivalence of the 2-methylene protons (resonating at *ca.* 5.2 ppm) and their long range coupling (^4J *ca.* 1.5 Hz) to the vinylic 4-H nucleus **(see Figure 14)**.



Scheme 39

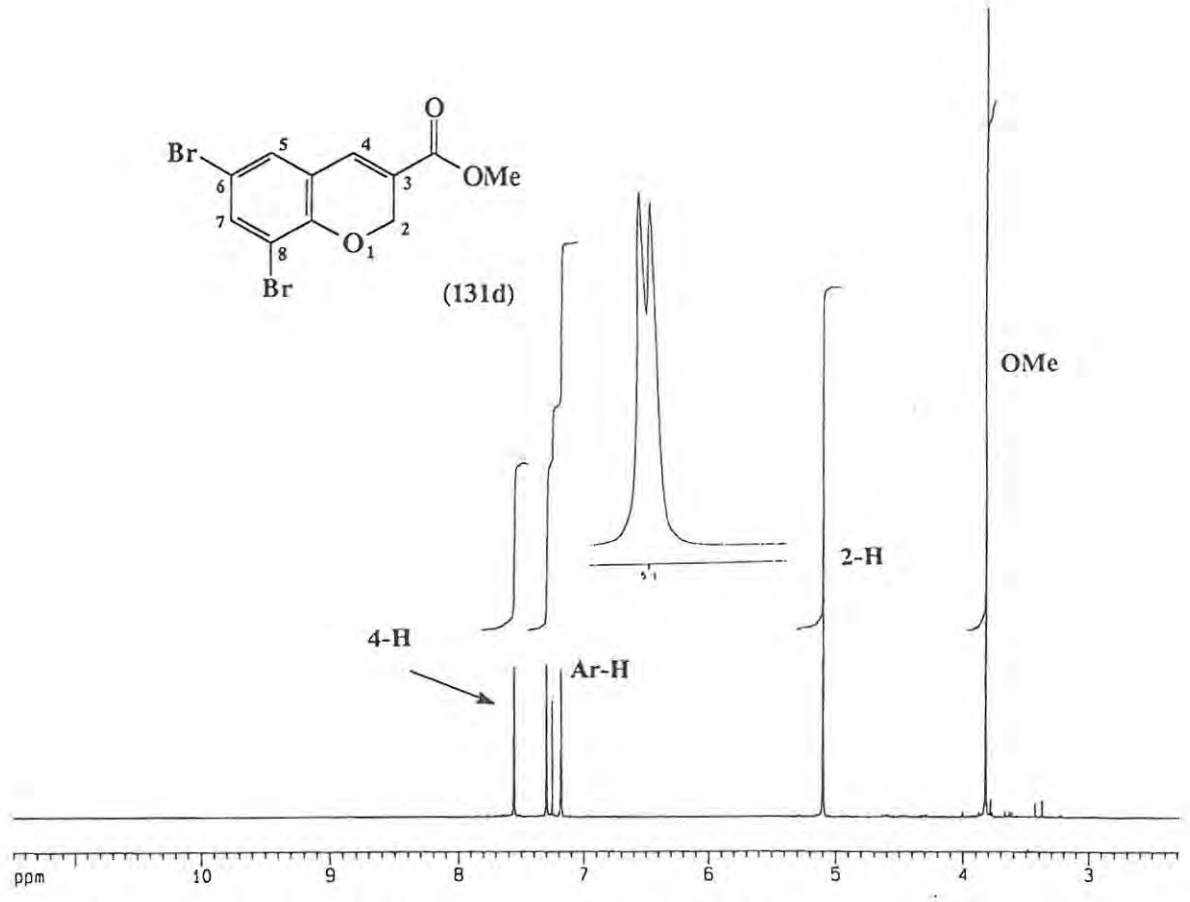


Figure 14 **400 MHz ^{1}H NMR spectrum of methyl 6,8-dibromo-2*H*-1-benzopyran-3-carboxylate (131d) in $CDCl_3$.**

René and Royer[121] have also prepared substituted chromenes by reacting various salicylaldehydes with acrylate derivatives in the presence of base, the mechanism presumably involving *initial* conjugate addition of the phenoxide ion to the α,β-unsaturated moiety **(Figure 15)** rather than cyclisation of a Baylis-Hillman product.

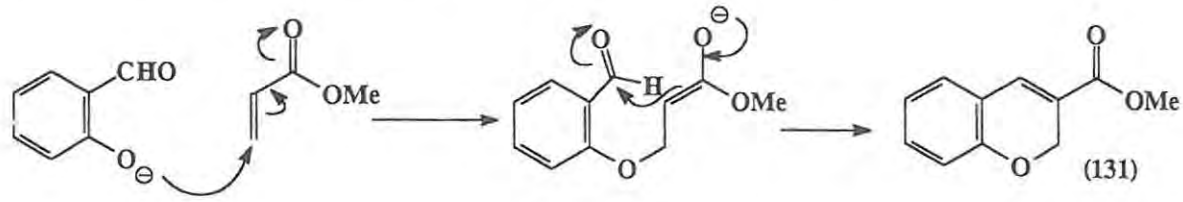
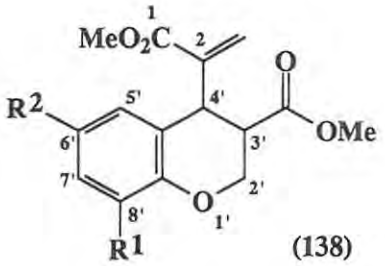


Figure 15

2.1.3.3 *Methyl 2-(3-carbomethoxy-3,4-dihydro-2H-1-benzopyran-4-yl)propenoates* **(type *IV* products)**



(138)

R1	R2	
H	Cl	138b
OMe	H	138e

Two representative examples of this class were isolated, *viz.*, compounds **(138b)** and **(138e).** Their formation is attributed to nucleophilic attack by the "Baylis-Hillman zwitterion" **(144)** on the chromene precursors **(131),** the latter acting as Michael acceptors **(Figure 16).** An analogous coupling between two acrylate molecules in the presence of DABCO has been discussed previously **(see Section 1.1.3.3).**[24,62]

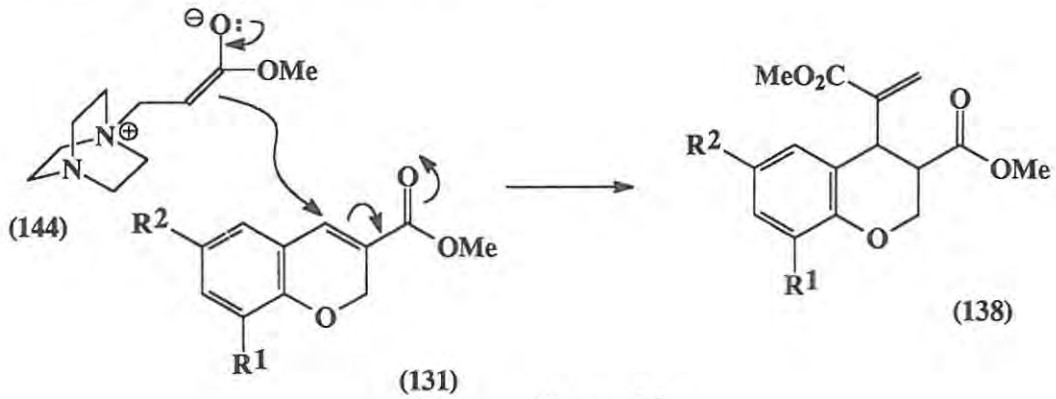


Figure 16

The ^{1}H NMR spectra for these compounds initially appeared to indicate the presence of some impurity. However, after careful examination of the ^{1}H and ^{13}C NMR spectra it became apparent that both *syn-* and *anti-* diastereomers were present as is clearly illustrated by the expansion of the δ 4.0- 4.6 ppm region in the ^{1}H NMR spectrum of compound **(138b)** **(Figure 17).**

The diastereomers were present in unequal quantities [52% d.e. for the chloro derivative

(138b) and 72% d.e. for the methoxy derivative **(138e)**]. Other significant features in the ^1H NMR spectra are the vinyl peaks at 5.4 and 6.5 ppm and the methyl singlets at *ca.* 3.8 ppm corresponding to the two carbomethoxy groups.

Since the substrates **(131)** in this case are achiral **(Figure 16)**, the observed stereoselectivity reflects "double stereodifferentiation"[122] rather than asymmetric induction. The identity of the dominant stereoisomer could not be determined by comparing the observed *vicinal* proton coupling constants ($J_{3'4'}$ = *ca.* 4.6 Hz) with those calculated[119] from the energy-minimised, computer-modelled structures as the two calculated coupling constants are very similar to each other but different to the observed value.

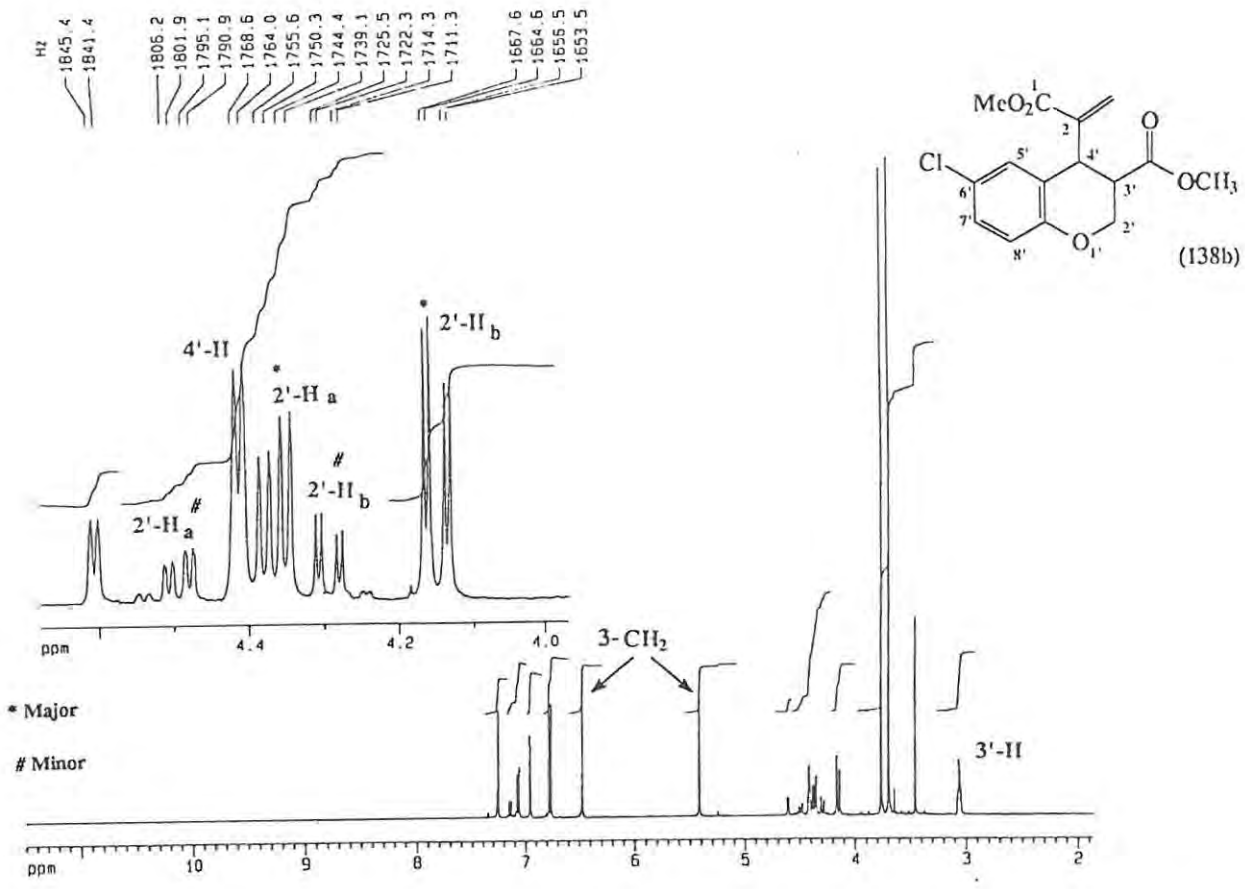
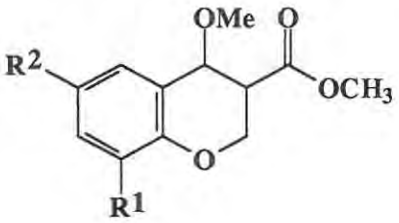


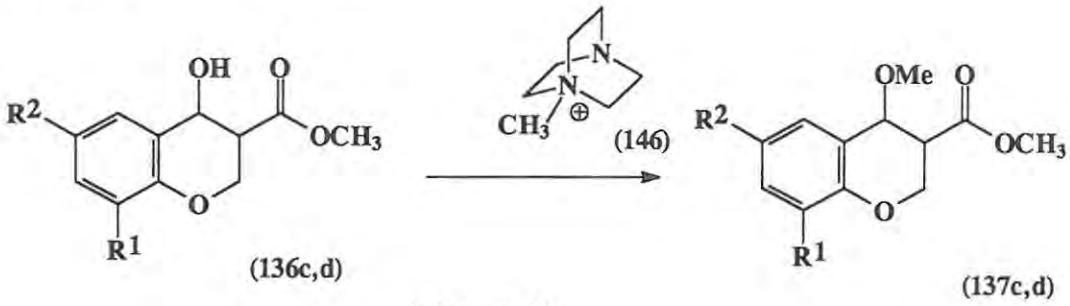
Figure 17 **400 MHz ^{1}H NMR spectrum for methyl 2-(3-carbomethoxy-6-chloro-3,4-dihydro-2*H*-1-benzopyran-4-yl)propenoate (138b) in $CDCl_3$.**

2.1.3.4 *Methyl 3,4-dihydro-4-methoxy-2H-1-benzopyran-3-carboxylates* **(type *V* products)**



R^1	R^2	
H	Br	137c
Br	Br	137d

The formation of the type *V* products, two of which were isolated [**(137c)** and **(137d)**] , is presumably due to methylation of the hydroxyl group by a methylated DABCO species **(146)** **(Scheme 40)**, which may act as a powerful methylating agent. It is apparent that DABCO may demethylate certain methyl esters[123] [see **Section 2.1.4.3** (p. 80) and **Section 2.1.9** (p. 107)] and the resulting methylated DABCO species **(146)** may, consequently, be expected to be present in the reaction mixture.



Scheme 40

The ^{1}H NMR spectra for these compounds clearly reveal the presence of the new methyl group, resonating as a 3-proton singlet at *ca.* 3.5 ppm, while the two diastereotopic 2-methylene protons resonate at *ca.* 4.3 and 4.5 ppm **(see Figure 18)**.Examination of the aliphatic region (*ca.*δ 4.2-4.6 ppm) indicates the presence of a single diastereomer† which given the diastereoselective formation of the proposed precursors **(136)**, is not unexpected.

†Presumably as *racemic* material.

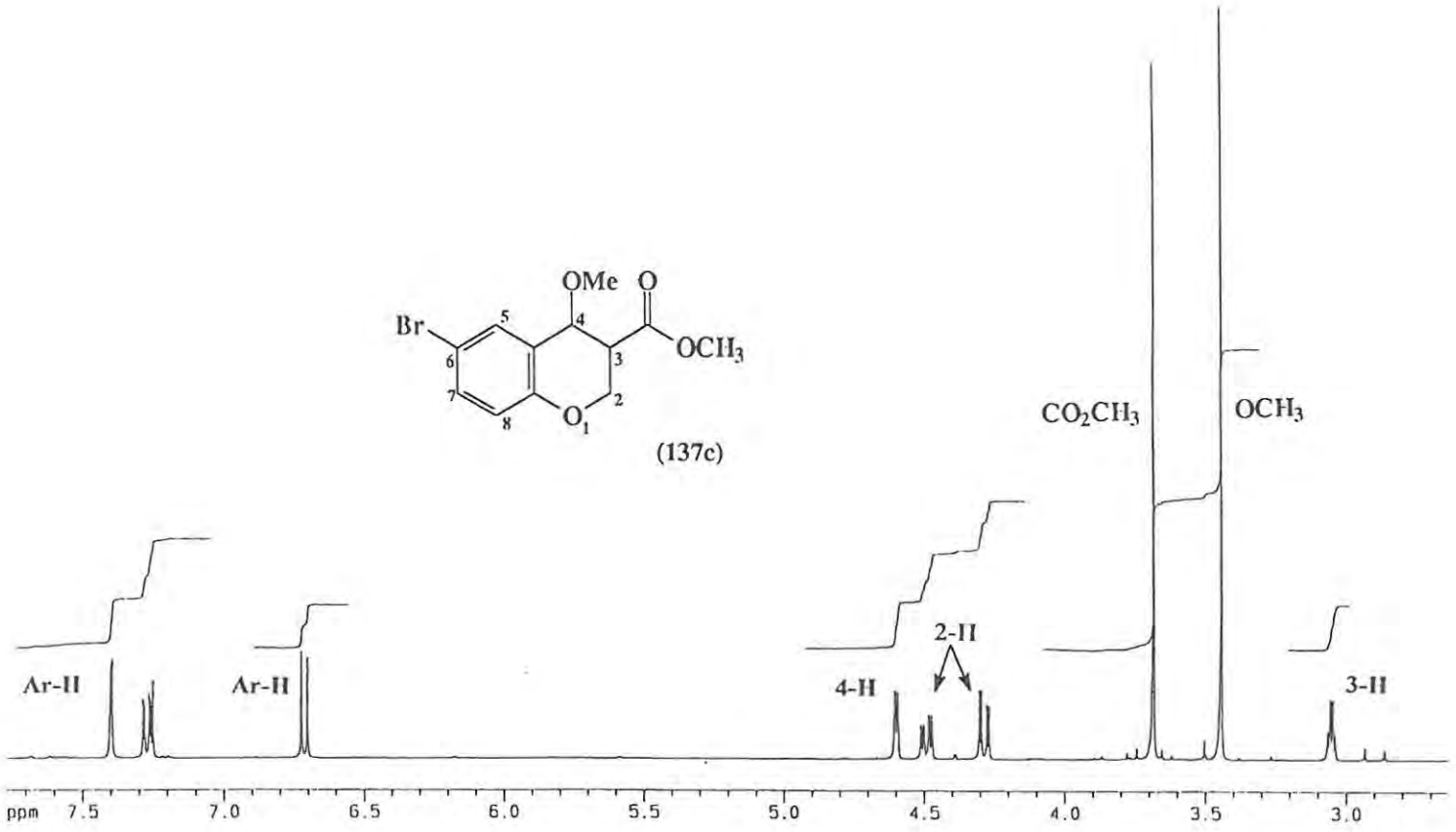
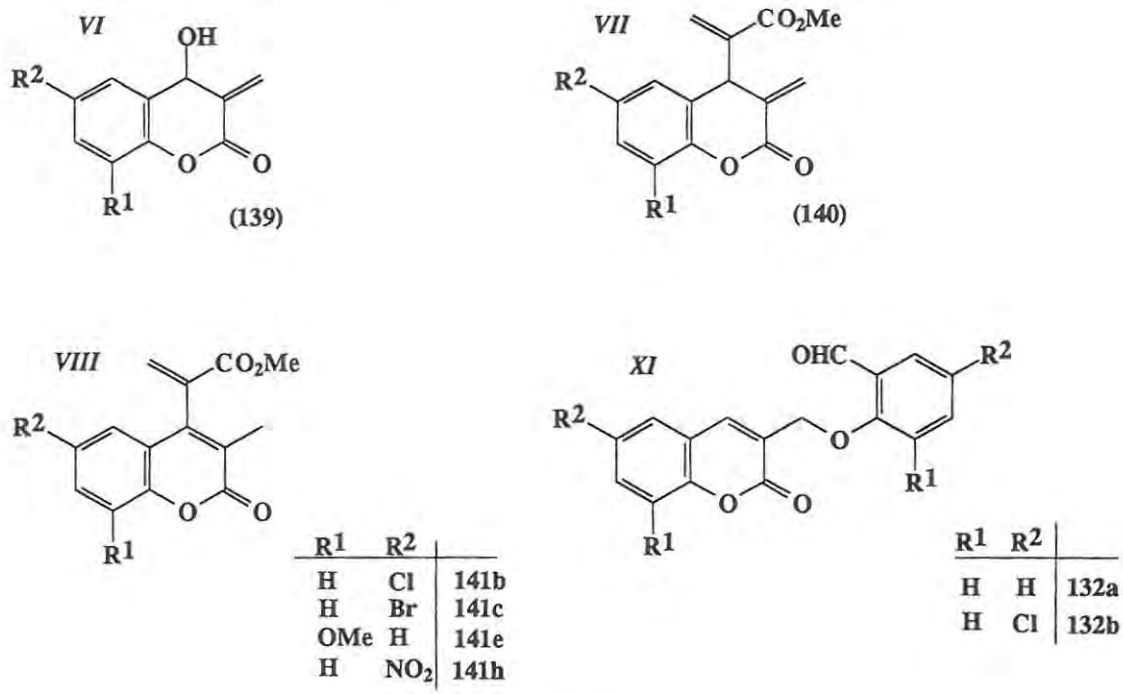


Figure 18 The 400 MHz H NMR spectrum of methyl 6-bromo-3,4-dihydro-4-methoxy-2*H*-1-benzopyran-3-carboxylate (137c) in $CDCl_3$.

2.1.4 Coumarin derivatives

2.1.4.1 Formation of product types *VI, VII, VIII* and *XI*



R1	R2	
H	Cl	141b
H	Br	141c
OMe	H	141e
H	NO_2	141h

R1	R2	
H	H	132a
H	Cl	132b

Figure 19

Whilst compounds of type *VI* and *VII* were never isolated in the reactions examined it seems likely that they act as key intermediates in the formation of both coumarin types *VIII* and *XI* **(Scheme 41).** The formation of the 4-substituted coumarins **(141)** may arise *via* "direct" (S_N) substitution of the hydroxyl group by the zwitterionic nucleophile **(144)**. The substitution is considered likely to occur *via* an intermolecular (S_N1) process involving an allylic-benzylic carbocation **(148)**; subsequent isomerisation of the double bond in the intermediate **(140)** results in the conjugated 3,4-disubstituted coumarins **(141)**. On the other hand, nucleophilic attack at the exocyclic double bond of the 4-hydroxy precursor **(139)** by salicylaldehyde *via* an allylic (S_N') process would account for the formation of the coumarins **(132)**.

The regioselectivity of the latter process may be rationalised in terms of a hydrogen-bonded, 6-membered transition state **(147)**, which directs nucleophilic attack to the exocyclic vinylic centre, resulting in a type *XI* product **(132)**. The identity of the coumarin derivative **(132a)** had been previously established by X-ray crystallography,[109] and its ^{1}H NMR spectrum is characterised by the presence of a singlet at *ca.* 5.2 ppm, corresponding to the two methylene protons, and a singlet at *ca.* 10.6 ppm resulting from the aldehyde proton [illustrated for the dichloro analogue **(132b)** in **Figure 20**].

The 5-nitro derivative **(141h)** afforded single crystals suitable for X-ray analysis, permitting its unambiguous identification as **methyl 2-(3-methyl-6-nitro-1-benzopyran-2-on-4-yl)propenoate (141h)(Figure 21a).** From the crystal structure the presence of a coumarin compound with its ether and carbonyl oxygens is evident, as well as the 3'-methyl group and the propenoate moiety at C-4'. These structural features are clearly evident in the ^{1}H NMR spectrum of this compound **(Figure 21b).** Thus, the methyl and methoxy groups resonating at 2.1 and 3.9 ppm respectively, and the vinyl proton signals at *ca.* 5.9 and 7.0 ppm, separated by *ca.* 1 ppm, are characteristic of this class of compounds. These compounds also tended to be highly lachrymatory, especially the 8-methoxy analogue **(141e)**.

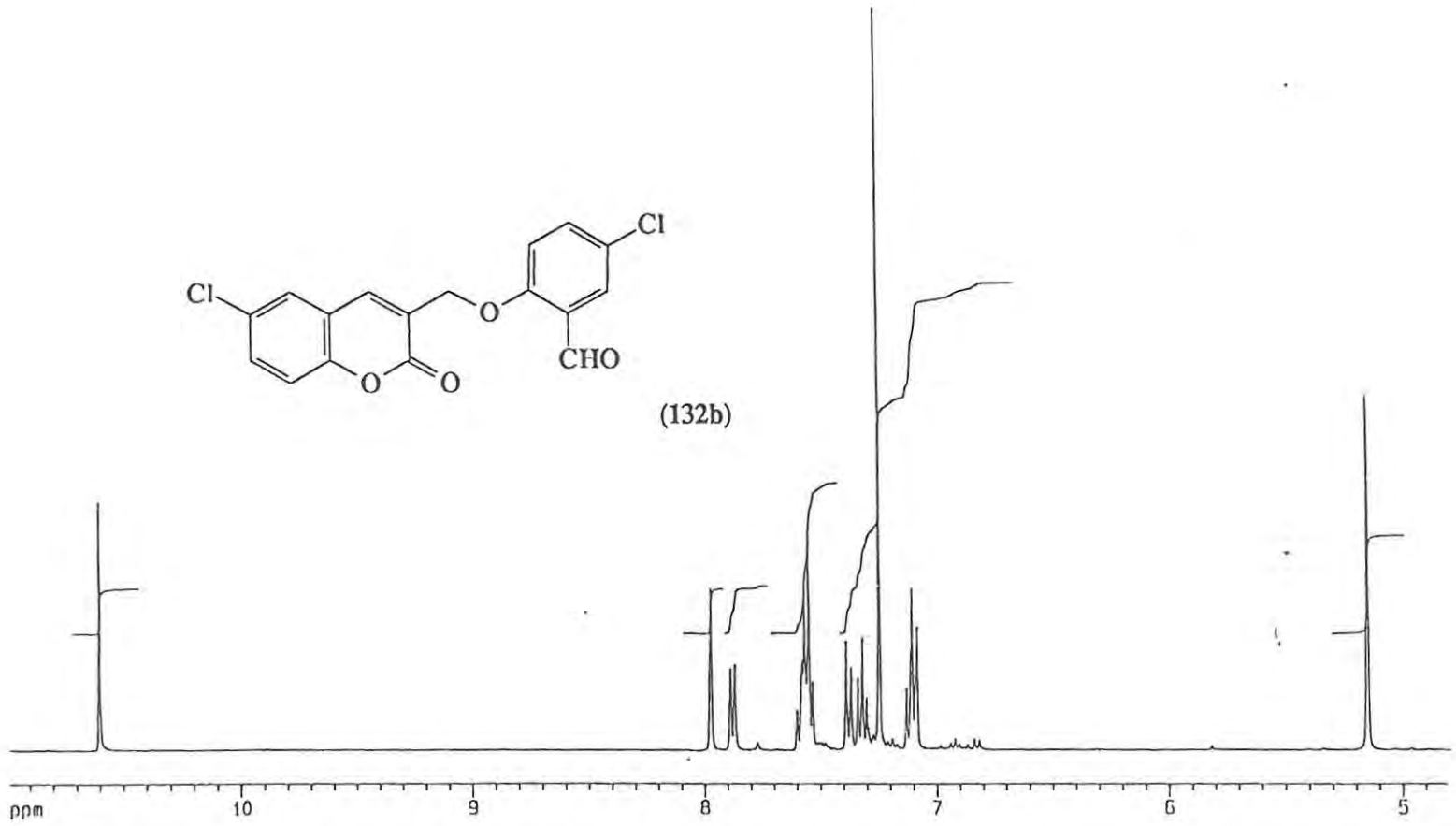
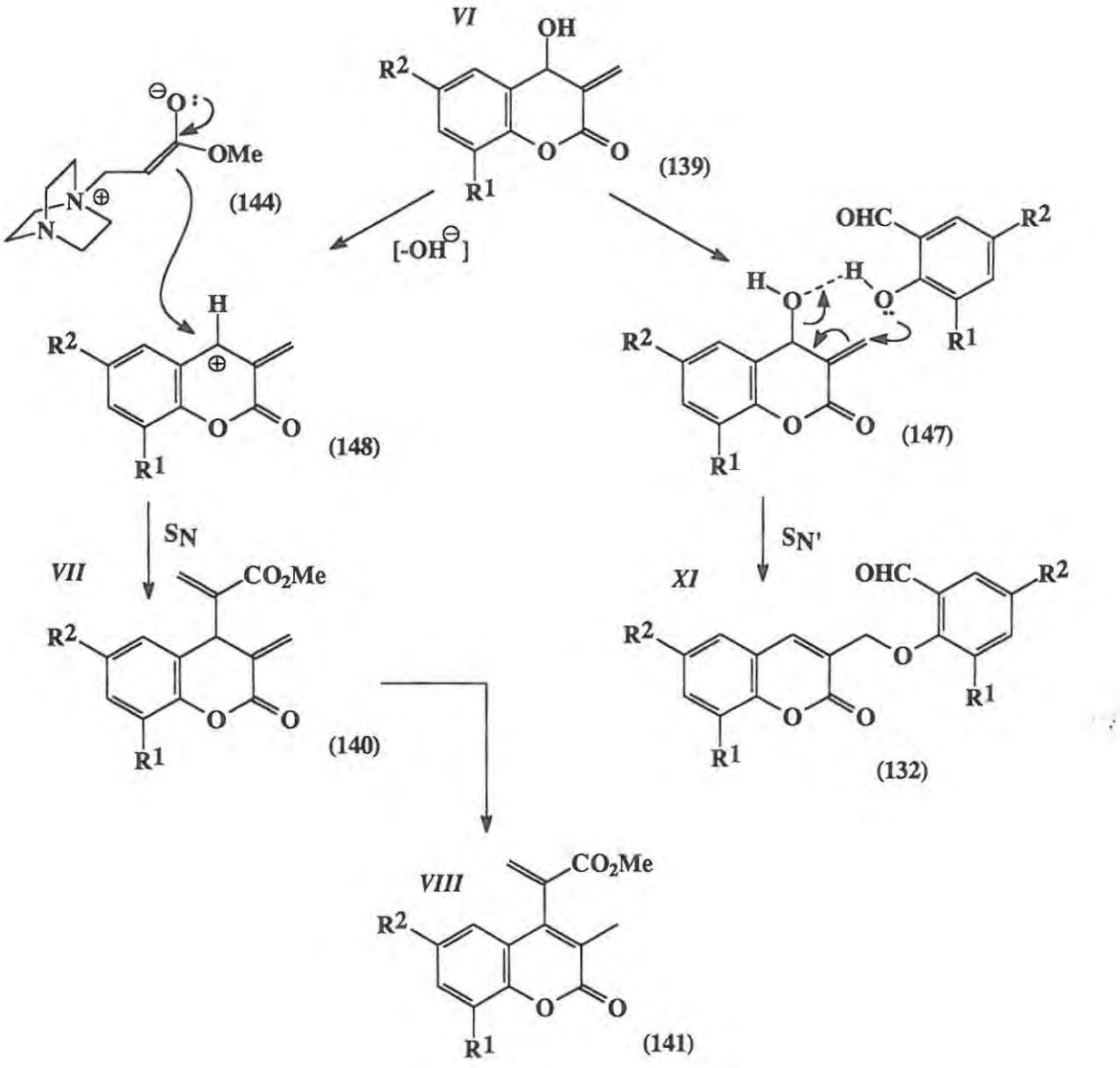
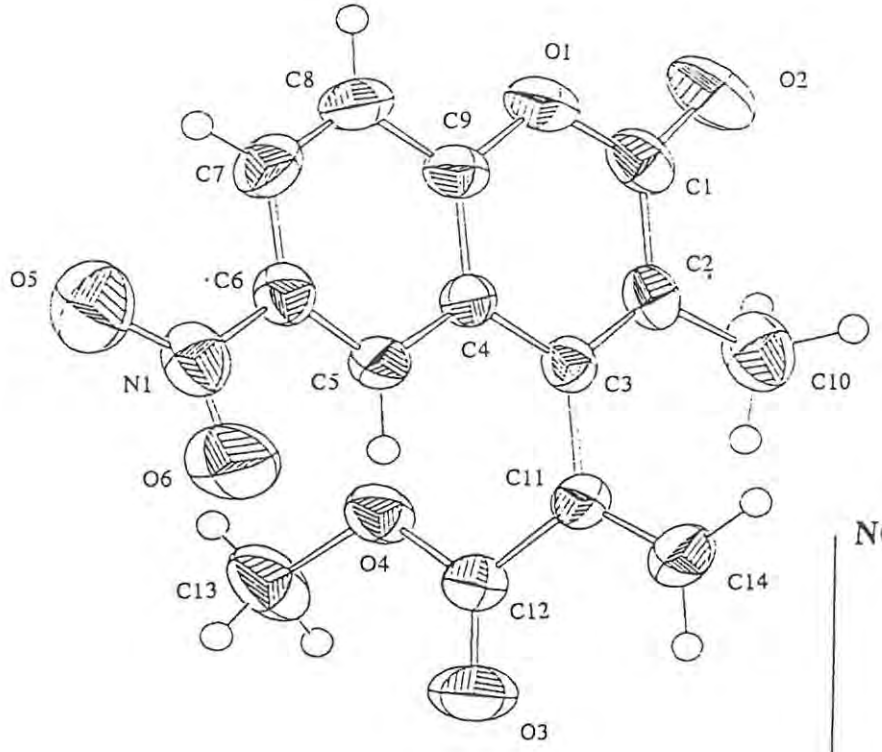


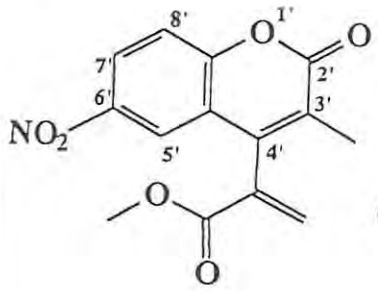
Figure 20 The 400 MHz ^{1}H NMR spectrum of 6-chloro-3-[(4-chloro-2-formylphenoxy)methyl] coumarin (132b) in $CDCl_3$.


VI
OH
R2
O
O
R1
(139)
[-OH⊖]
OMe
(144)
N⊕
N
H
R2
O
O
R1
(148)
OHC
R2
H
O
H
O
R2
O
O
R1
(147)
SN
VII
CO2Me
R2
O
O
R1
(140)
SN'
XI
OHC
R2
R2
O
O
R1
(132)
VIII
CO2Me
R2
O
O
R1
(141)

Scheme 41

a)





(141h)

b)

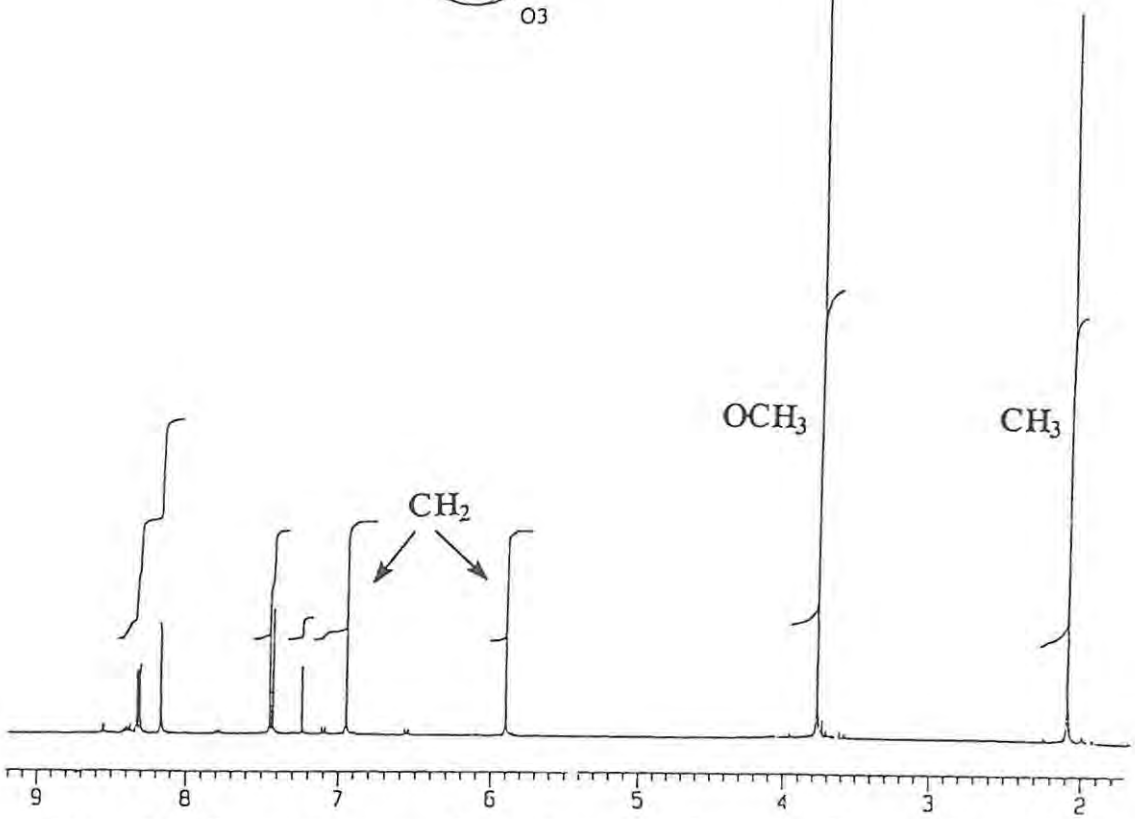
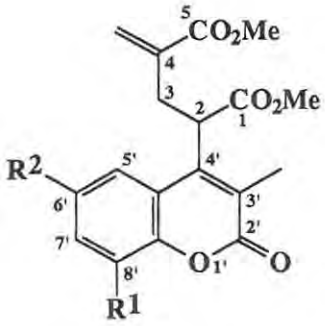


Figure 21 (a) The X-ray crystal structure, showing crystallographic numbering, and (b) the 400 MHz ^{1}H NMR spectrum of methyl 2-(3-methyl-6-nitrobenzopyran-2-on-4-yl)propenoate (141h).

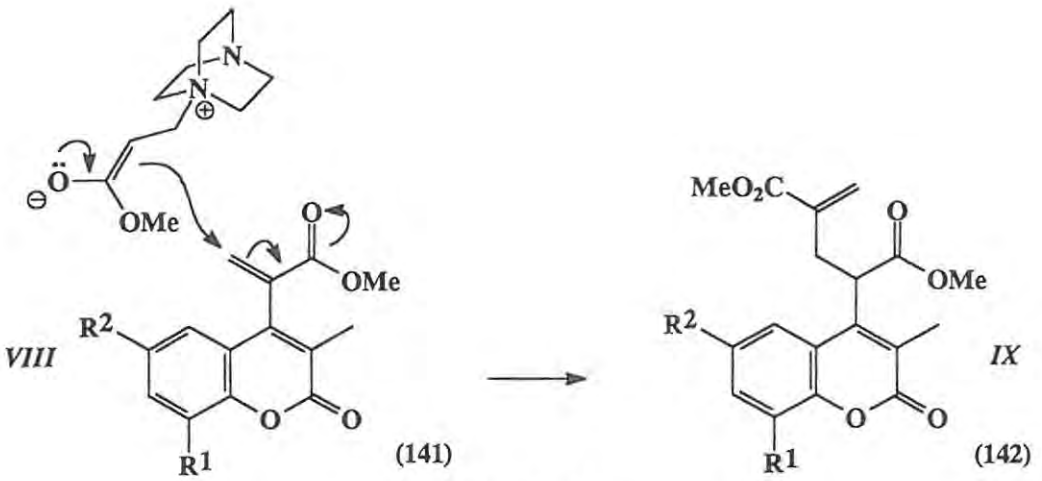
2.1.4.2 *Dimethyl 2-(3-methyl-1-benzopyran-2-on-4-yl)-4-methylenepentanedioates* **(type *IX* products)**



R1	R2	
H	Cl	142b
H	Br	142c
Br	Br	142d
H	OMe	142e
H	NO_2	142h

The type ***IX*** diesters **(142)** are presumed to arise from attack by the "Baylis-Hillman zwitterion" on type ***VIII*** precursors, which act as Michael acceptors, undergoing conjugate addition **(Scheme 42)** Five of these compounds have been isolated[♮] and their ^{1}H NMR spectra clearly indicate the presence of *two* methoxy groups at *ca.* 3.9 ppm and a single methyl group at *ca.* 2.2 ppm **(see Figure 22)**. The vinyl proton signals are closer than those of the type ***VIII*** precursors and appear at *ca.* 5.6 and 6.1 ppm separated by only *ca.* 0.5 ppm. The COSY spectrum for compound **(142b)(Figure 23)** clearly shows the coupling between the diastereotopic 3-methylene protons at 2.7 and 3.4 ppm and the 2-methine proton at 4.5 ppm, as well as coupling between the vinylic *exo*-methylene protons at 5.45 and 6.1 ppm. The elucidation of the structure of these type ***IX*** products was facilitated by the inverse HETCOR data **(see Figure 24)** which confirmed attachment of the diastereotopic 3-methylene protons to the C-3 nucleus resonating at 33 ppm. Interestingly, the C-2 signal was, typically, poorly defined and barely visible in the ^{13}C NMR spectra appearing as a broad peak, but its coupling to the 2-methine proton at *ca.* 4.5 ppm is clearly visible in the inverse HETCOR spectrum, as is the coupling between the 4''-methylene protons and the vinylic 4''-carbon at 129 ppm. The poor resolution of the C-2 peak is attributed to slow rotation of one of the attached groups resulting in the observed peak broadening.

[♮] The 5-nitro analogue was isolated from the *O*-acetylated salicylaldehyde see **Section 2.1.6**



Scheme 42

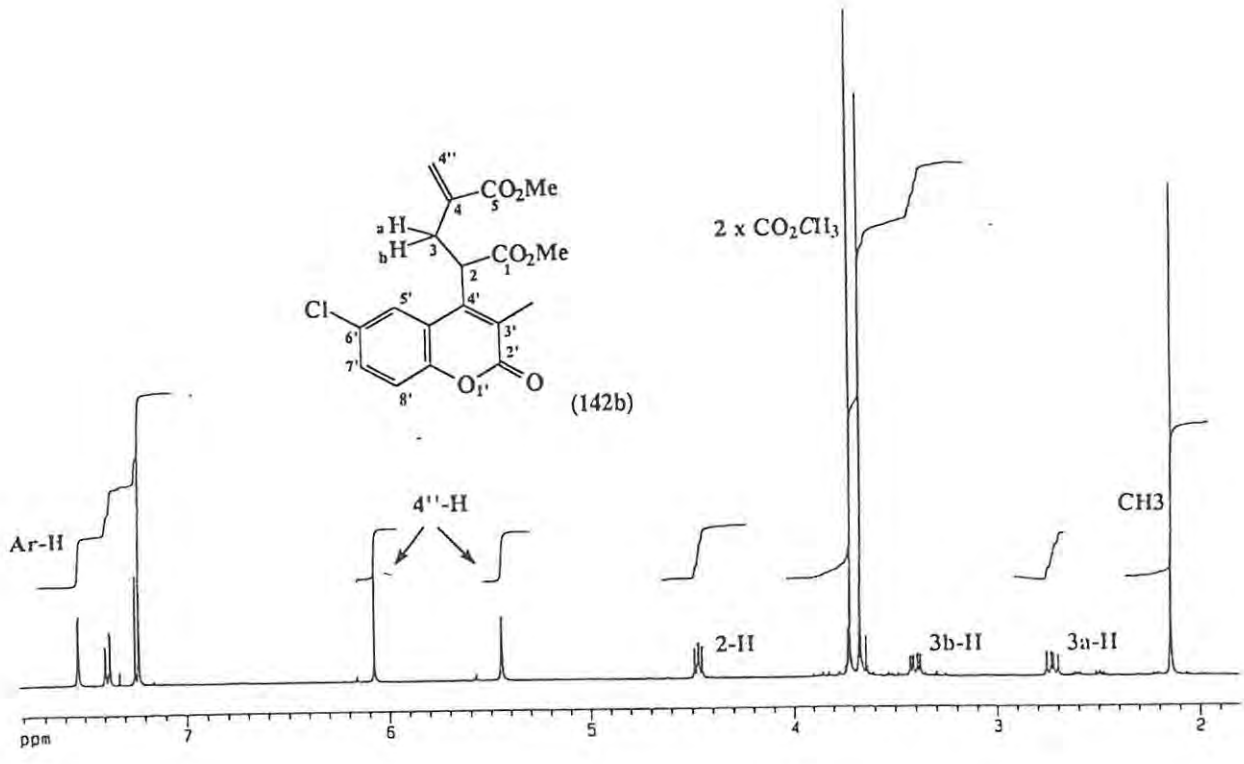


Figure 22 400 MHz ^1H NMR spectrum of dimethyl 2-(6-chloro-3-methyl-1-benzopyran-2-on-4-yl)-4-methylenepentanedioate (142b) in $CDCl_3$.

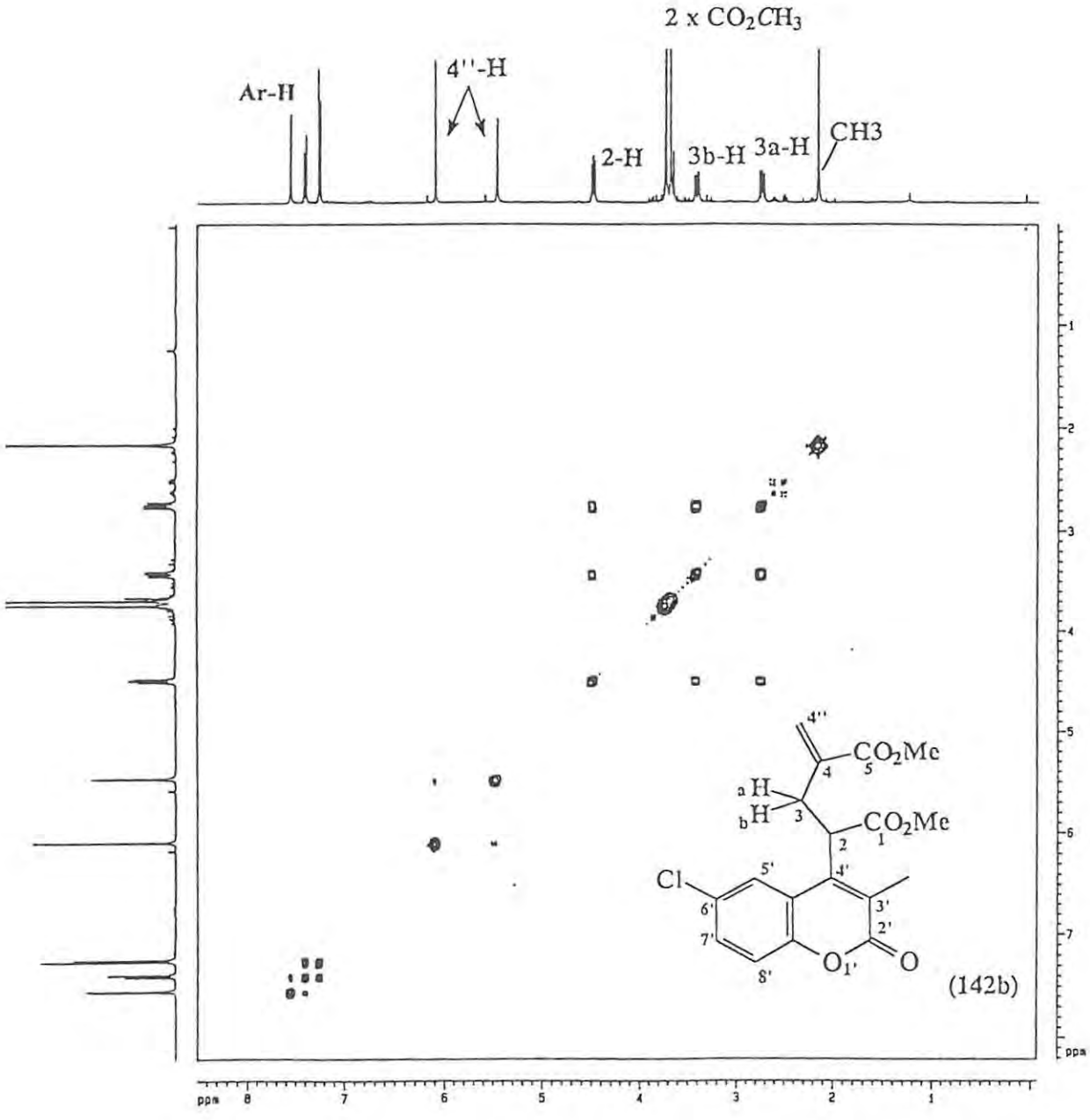


Figure 23 **400 MHz COSY spectrum of dimethyl 2-(6-chloro-3-methyl-1-benzopyran-2-on-4-yl)-4-methylenepentanedioate (142b) in $CDCl_3$.**

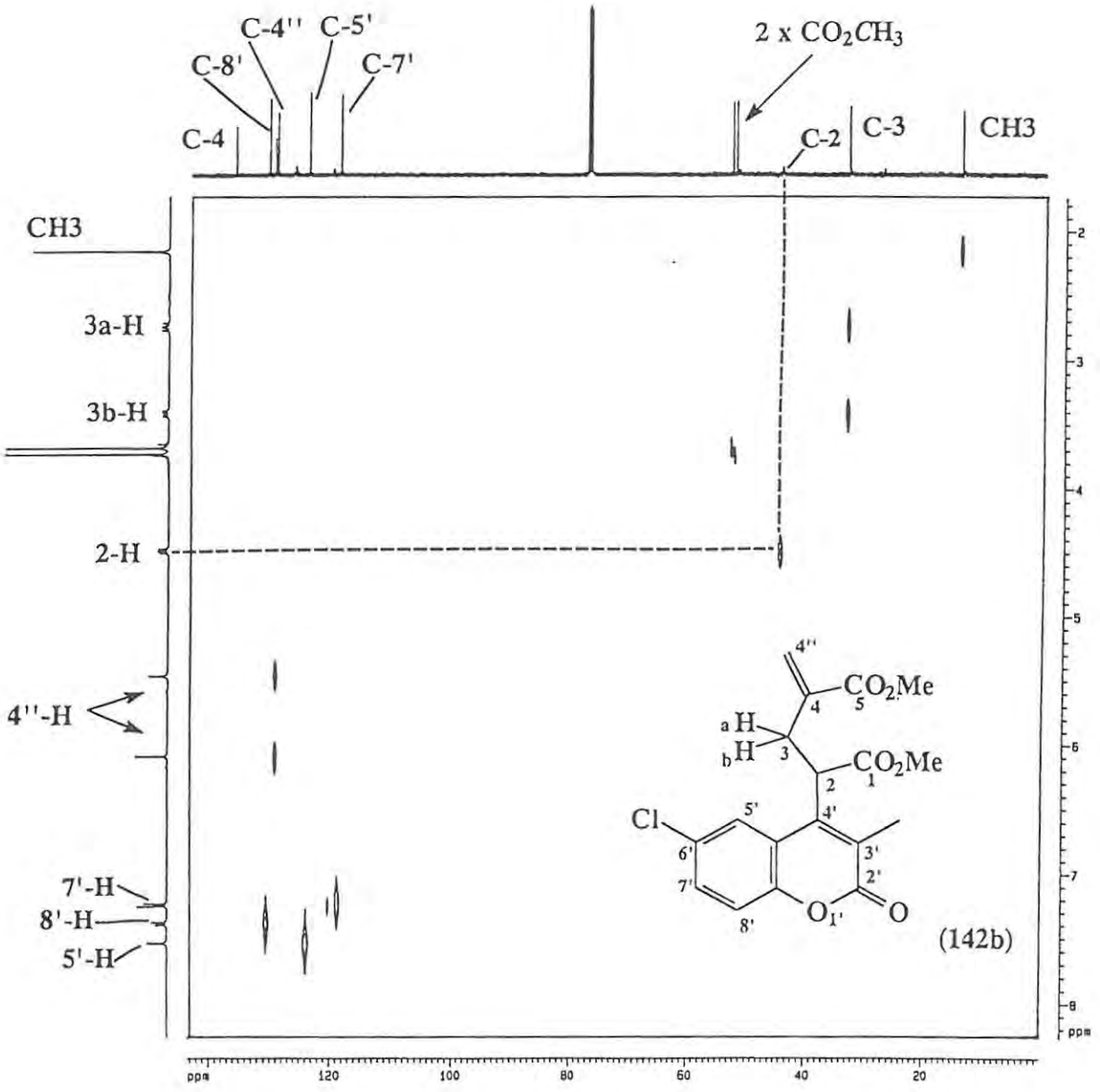
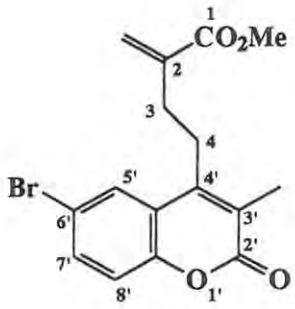


Figure 24 The inverse HETCOR spectrum of dimethyl 2-(6-chloro-3-methylene-1-benzopyran-2-on-4-yl)-4-methylenepentanedioate (142b) in $CDCl_3$.

2.1.4.3 *Methyl 4-(3-methyl-1-benzopyran-2-on-4-yl)-2-methylenebutanoates* **(type *X* products)**

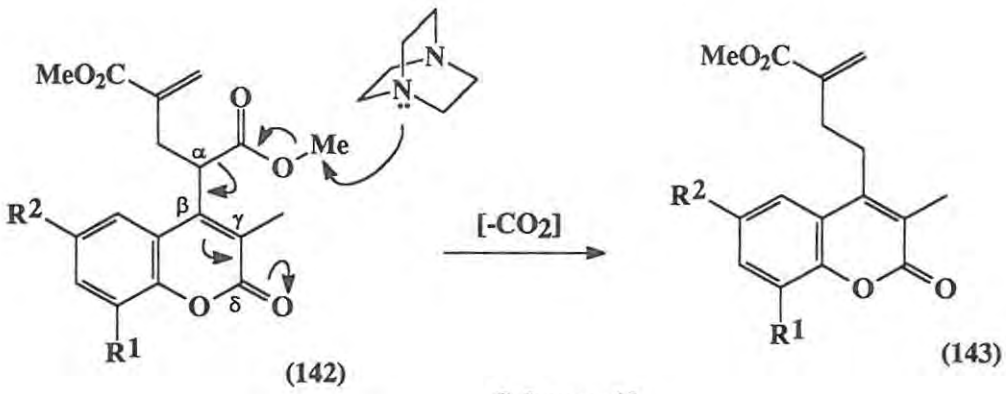


(143)

The only example of this compound to be isolated was **methyl 4-(6-bromo-3-methyl-1-benzopyran-2-on-4-yl)-2-methylenebutanoate (143c)**. The ^{13}C NMR spectrum of this compound indicates the presence of 16 different carbons, while the ^{1}H NMR spectrum **(Figure 25b)** clearly indicates the presence of a methyl group (resonating at 2.3 ppm), a single methoxy group (resonating at 3.85 ppm) and a pair of adjacent methylene groups, responsible for the multiplets at 2.55 and 2.95 ppm. The remaining ^{1}H NMR signals were similar to those observed for the dimethyl esters **(142)**.

Crystals of this compound were obtained, which were suitable for X-ray analysis. The X-ray crystal structure **(Figure 25a)** permitted unambiguous identification of the product as the coumarin derivative **(143c)**. The X-ray structure shows the coumarin substructure with the presence of the ether oxygen and the carbonyl group. In addition the presence of the 3'-methyl group and the butanoate moiety, with the two adjacent methylene groups, is evident.

The formation of this compound is presumed to occur *via* the selective decarbmethoxylation described by Miles *et al.*,[123] in which DABCO selectively cleaves "δ-keto-β,γ-unsaturated esters". This grouping is present in the diesters **(142)**, and the formation of the type *X* product **(143c)** is attributed to such decarbmethoxylation of the corresponding diester **(142c)** **(Scheme 43)**.



Scheme 43

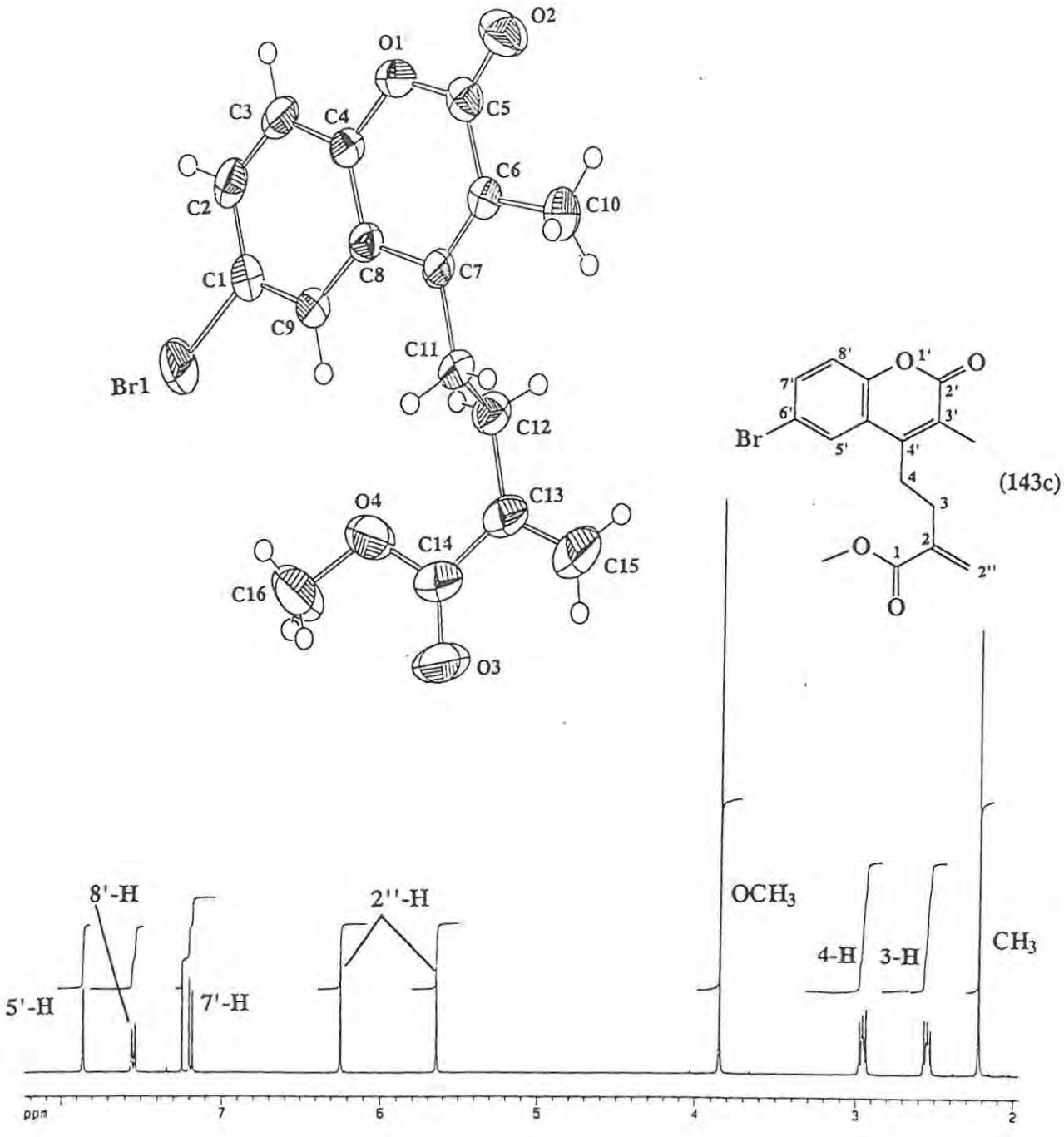


Figure 25 a) The X-ray crystal structure, showing crystallographic numbering, and b) the 400 MHz ^{1}H NMR spectrum of methyl 4-(6-bromo-3-methyl-1-benzopyran-2-on-4-yl)-2-methylenebutanoate (143c).

2.1.5 Reaction yield determination

As indicated in the foregoing sections, a wide range of the chromene and coumarin compounds were isolated from various reaction mixtures. However, the yields of the products could seldom be determined from isolated material because of the steps required for the purification of some of the components. Yields were initially determined by comparing the ^{1}H NMR integrals of the components in the crude reaction mixtures with the DABCO 12- proton singlet at 2.9 ppm, the concentration of DABCO being assumed to remain constant. However, from the relative integrals it became apparent that the DABCO peak was in many cases significantly smaller than expected, indicating that the DABCO "catalyst" was being consumed in the reaction. Consequently an internal standard was introduced to calculate the relative percentages of the reaction components. The internal standard chosen was mesitylene (1,3,5-trimethylbenzene), which exhibits a 9-proton methyl singlet at 2.15 ppm - conveniently out of the way of the peaks of interest. The reactions were carried out in an NMR tube, and from the results, it was immediately apparent that the DABCO was indeed being consumed in the reaction. Two intense peaks, at 3.15 and 3.60 ppm, were identified as being significant, and these were attributed to the methylene protons in a quaternary DABCO species.[§§] The two peaks had similar intergrals and, when the sum of these integrals was added to the integral for the free DABCO (**Figure 26**), the total matched the value expected for the amount of DABCO added. The yields could thus be determined by taking into account both the quaternised and free DABCO species, without having to make use of an internal reference standard. In many of the reactions studied *ca.* 80-90% of the DABCO was present as a quaternary ammonium species.

[§§] Support for this assignment is provided by the chemical shift values for the endocyclic methylene protons in the quaternary DABCO derivatives **(156)** and **(173)**.

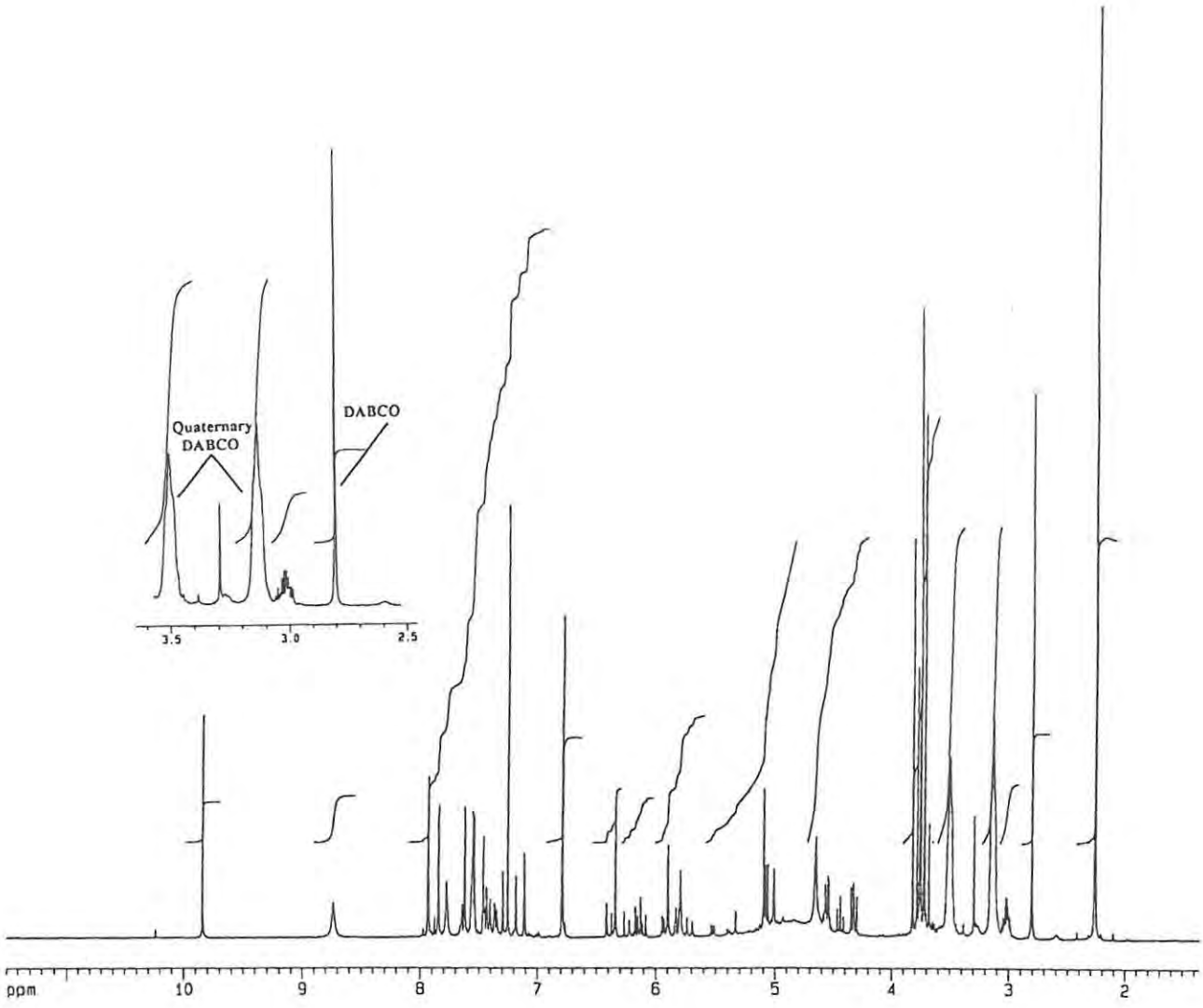
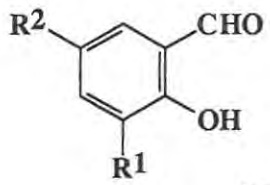


Figure 26 400 MHz ^{1}H NMR spectrum of crude reaction mixture for the reaction between 5-chlorosalicylaldehyde (129b) and methyl acrylate, showing the quaternarised DABCO species.

When this method of calculating reaction yields was applied, it was found that the product distributions for equivalent reactions varied somewhat. Consequently, the product distributions quoted in **Table 12** should be treated as illustrative rather than definitive. The observed fluctuations of the reaction yields may be accounted for by the large number of consecutive reactions and common intermediates implicated in the reactions.

Table 12. % Product distributions[a] for DABCO-catalysed reactions of salicylaldehyde derivatives **(129)** with methyl acrylate **(see Scheme 36)**.



(129)

Substrate			Product types							
Compd	**R^1**	**R^2**	**131**	**132**	**136**	**137**	**138**	**141**	**142**	**143**
129a	H	H	13	18(50[b])	-	-	-	-	-	-
			28[c]	-	-	-	-	-	-	-
			12[d]	-	-	-	-	-	-	-
			14[e]	-	-	-	-	-	-	-
129b	H	Cl	17	14[f]	-	-	13	17	23	-
129c	H	Br	17(6[g])	-	-	7	-	13	5	4(35[g])
129d	Br	Br	15	-	47	14	-	-	24	-
129e	OMe	H	7	-	-	-	10	9	5	-
129f	OEt	H	9	-	-	-	-	-	-	-

[a] Percentage yields determined by ^{1}H NMR spectroscopy of reaction mixtures prior to chromatography. [b] Maximum isolated yield. [c] Analogous product **(131k)** obtained using methyl vinyl ketone in place of methyl acrylate. [d] Analogous product **(131l)** obtained using acrylonitrile in place of methyl acrylate. [e] Analogous product **(131m)** obtained using ethyl acrylate in place of methyl acrylate. [f] Reaction conducted at *ca.* 14-18 °C. [g] Isolated yield after 1 month.

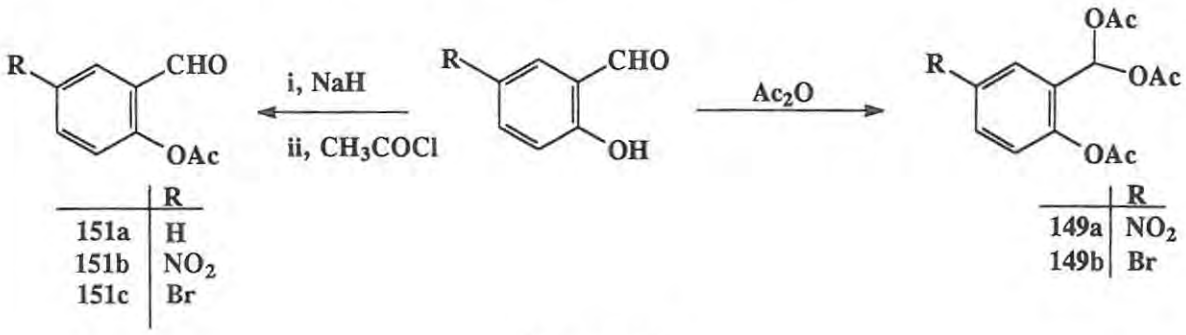
2.1.6 Reactions of protected salicylaldehydes

As mentioned earlier **(see Section 2.1.2.2)** the formation of a phenolate salt between DABCO and 5-nitrosalicylaldehyde was unexpected and undesirable and, in order to

overcome this problem, it was decided to *O*-acetylate selected salicylaldehydes. In addition to protecting the hydroxyl functionality, it was expected that acetylation would prevent subsequent cyclisation to the chromene and coumarin type products, thus allowing isolation of the elusive Baylis-Hillman intermediate **(130)**.

2.1.6.1 Preparation of *O*-acetylated salicylaldehydes

In order to prepare the *O*-acetylated salicylaldehyde derivatives, 5-bromo- and 5-nitro-salicylaldehyde were treated with acetic anhydride, but this procedure afforded the corresponding tri-acetates, *O*-acetyl-2-(diacetoxymethyl)-4-nitrophenol **(149a)** and *O*-acetyl-2-(diacetoxymethyl)-4-bromophenol **(149b)** **(Scheme 44)**. Consequently an alternative approach was adopted in order to obtain the mono-acetates. The respective phenoxide ions, generated *in situ* using NaH, were treated with acetyl chloride to afford the desired mono-acetylated products **(151a-c)**.[§§] Both the mono- and tri-acetates were reacted further in the same manner as the non-acetylated salicylaldehydes in order to establish what products would be formed under Baylis-Hillman reaction conditions.

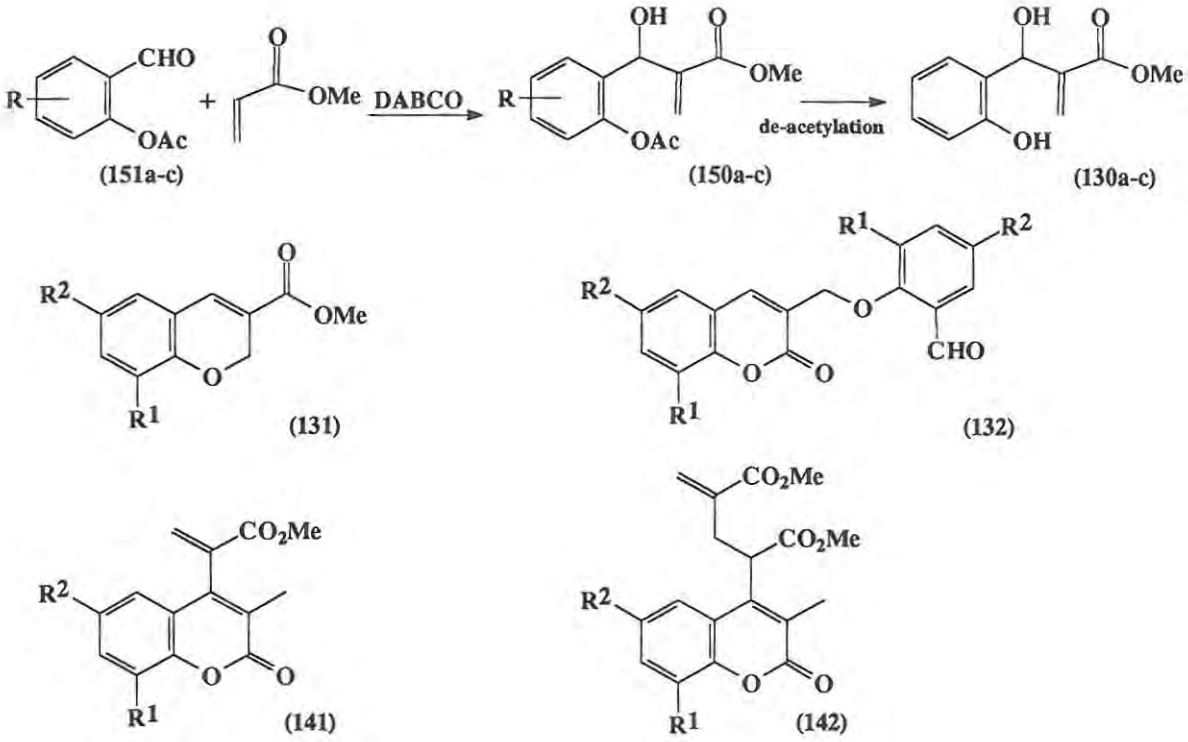


Scheme 44

[§§] Purification of *O*-acetyl-5-nitrosalicylaldehyde proved difficult due to deacetylation during chromatography

2.1.6.2 Baylis-Hillman reactions of *O*-acetylated salicylaldehydes

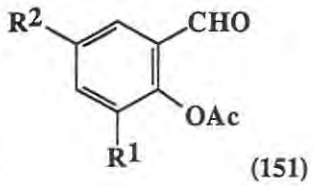
Reaction of the *O*-acetylated salicylaldehydes **(151)** with methyl acrylate in the presence of DABCO was expected to afford the corresponding coupled products **(150)**, de-acetylation of which would lead to the phenolic systems **(130)** and, hence, to cyclised products.



Scheme 45

However, when the *O*-acetylated salicylaldehydes **(151a-c)** were reacted with methyl acrylate and DABCO, neither the Baylis-Hillman products **(150)** nor the de-acetylated analogues **(130)** were isolated; instead products of the type afforded by the non-acetylated salicylaldehydes were obtained, *viz.*, **(131)**, **(132)**, **(141)** and **(142)** **(see Table 13)**. These observations clearly indicate deacetylation of the substrates **(151)** or the Baylis-Hillman products **(150)** under the conditions of the reaction, followed by swift cyclisation. Due to the problem of de-acetylation, the use of an *O*-silylated system was investigated.

Table 13 % Product distributions for the DABCO-catalysed reactions of *O*-acetylated salicylaldehyde derivatives with methyl acrylate



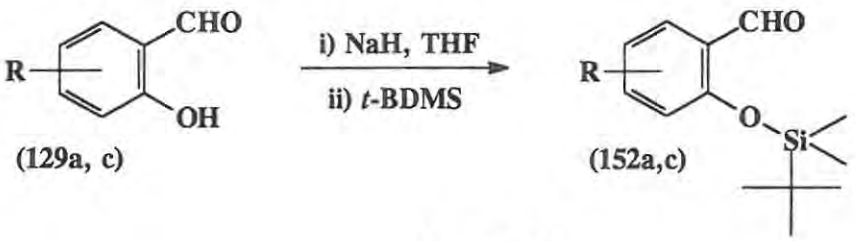
(151)

Substrate			Product types /%			
Compd.	**R^1**	**R^2**	**131**	**132**	**141**	**142**
151a	H	H	13	22	-	-
151b	H	NO_2	2	-	20	21
151c	H	Br	23	-	-	-

2.1.6.3 Preparation and Baylis-Hillman reactions of *t*-butyldimethylsilyl-protected salicylaldehydes

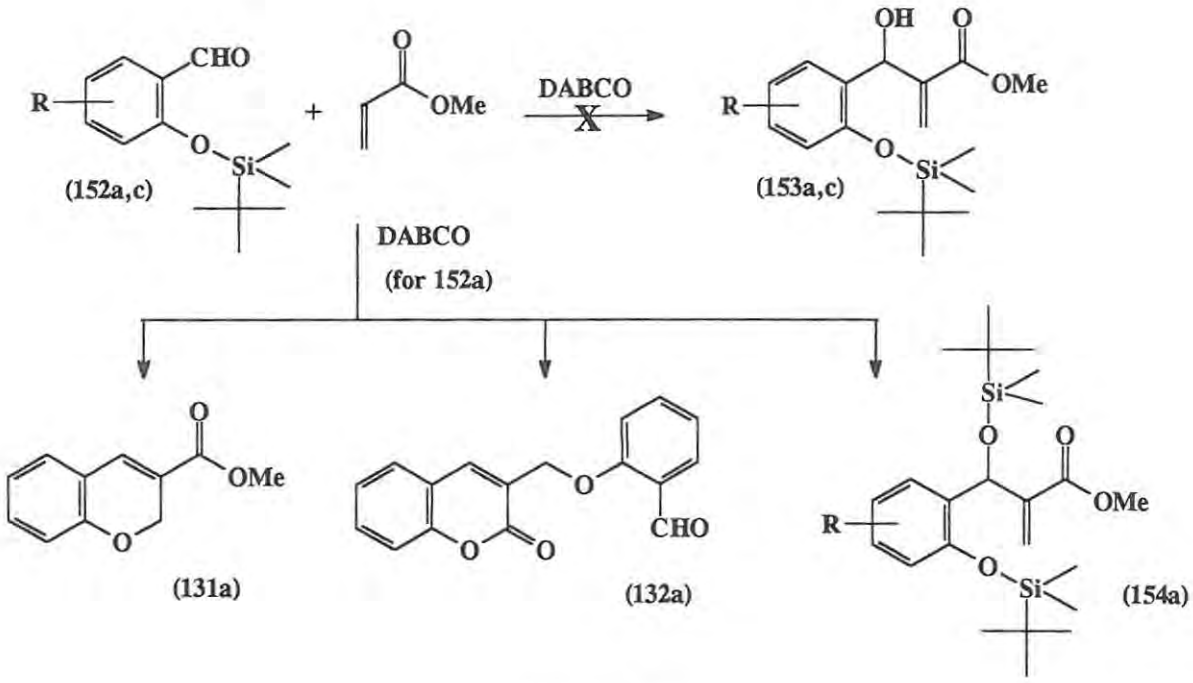
The *t*-butyldimethylsilyl protecting group was chosen due to its greater stability (relative to other silyl protecting groups) and the fact that the protected ethers may typically be obtained in high overall yield (>90%). Moreover, the protecting group may be selectively removed, in high yield, using reagents such as $Bu_4N^+F^-$ in THF or aq. HF in CH_3CN.[124,125]

Initial attempts to synthesise *O*-*t*-butyldimethylsilyl-protected salicylaldehyde following the method outlined by Green,[124] utilizing imidazole and *t*-butyldimethylsilyl chloride, failed to afford the required product. An alternative approach was then adopted, using NaH as base, to ensure generation of the nucleophilic phenoxide ion, followed by the addition of *t*-butyldimethylsilyl chloride. This approach afforded the desired products, **(152a)** and **(152c)**, in high yields (typically >90%)**(Scheme 46)**.



Scheme 46

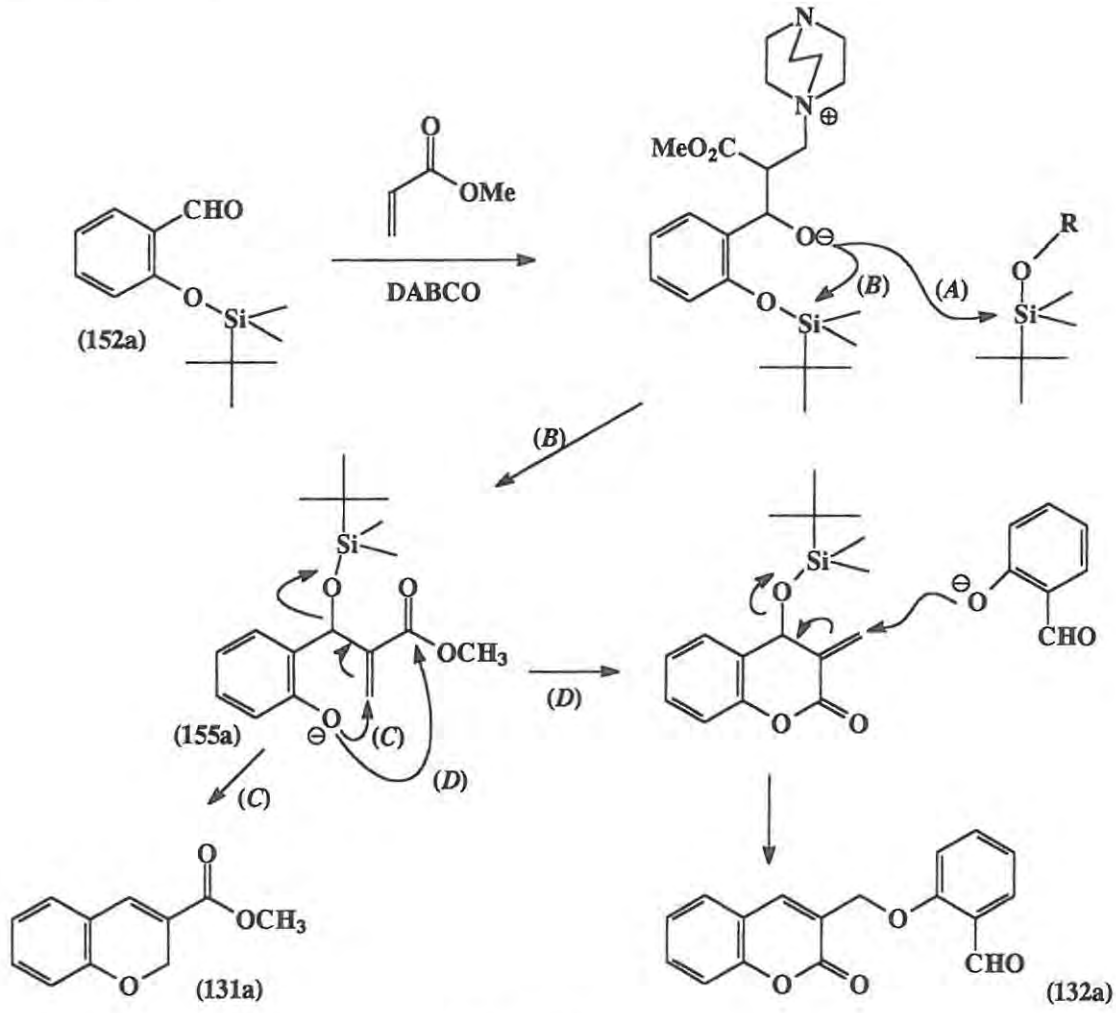
The *O*-*t*-butyldimethysilyl-protected salicylaldehydes were subsequently reacted with methyl acrylate in the presence of DABCO in expectation of obtaining the Baylis-Hillman products **(153; Scheme 47)**. When this reaction was carried out with the salicylaldehyde derivatives **(152a)**, a significant amount of crystalline material was observed to precipitate out of the reaction medium. This material was shown, by ^{1}H NMR spectroscopy, to be 3-[(2-formylphenoxy)methyl]coumarin **(132a)**, while the supernatant liquid was shown to contain the chromene derivative, methyl 2*H*-1-benzopyran-3-carboxylate **(131a).** The reaction conditions again appeared to facilitate deprotection of the salicylaldehyde derivative **(152a)**-somewhat unexpectedly, given the relative inertness of the *t*-butyldimethylsilyl protecting group.[124,125] Deprotection was also evident in the reaction of the 5-bromo derivative**(152c)**, which was shown to afford the chromene **(131c)** but none of the corresponding coumarin. On repeating the reaction with the protected salicylaldehyde **(152a)**, a small quantity of a protected Baylis-Hillman product was, in fact, isolated and characterised. This product was shown, by ^{1}H NMR spectroscopy, to be the disilylated compound **(154a)**, not the expected mono-protected product **(153a) (Scheme 47)**.



Scheme 47

The formation of the disilylated compound **(154a)**, and its possible implication in the generation of the cyclised chromene **(131a)** and coumarin **(132a)** may be rationalised in terms of the pathways illustrated in **Scheme 48.**The alkoxide intermediate, formed during the Baylis-Hillman reaction, could act as a nucleophile attacking silicon either *intermolecularly* **(pathway *A*)**, to afford the disilylated compound **(154a)**, or *intramolecularly* **(pathway *B*)** to afford the phenoxide species **(155a)** with concomitant migration of the silyl moiety to the more reactive alkoxide oxygen. The latter species **(155a)** could then lead to the formation of the chromene **(131a)** and coumarin **(132a)** *via* **pathway *C* and *D*** respectively. Thus, attack by the phenoxide oxygen at the vinyl carbon with migration of the double bond and subsequent loss of the silyloxy group, would result in the chromene **(131a)**. On the other hand, acyl substitution at the ester carbonyl carbon **(pathway *D*)**, followed by conjugate attack by a second molecule of salicylaldehyde at the newly formed *exo*-methylene carbon and loss of the silyloxy group would afford coumarin **(132a)**. With such a variety of plausible reaction options available for the "protected" salicylaldehyde

it is, perhaps, not surprising that difficulty was experienced in isolating the corresponding Baylis-Hillman product.



Scheme 48

The disilylated Baylis-Hillman product **(154a)** was then subjected to deprotection using the method described by Green,[124] in which the silylated compound in THF is reacted with tetrabutylammonium fluoride at 0°C for five minutes. The ^{1}H NMR spectrum of the mixture, obtained after work-up, confirmed formation of the 4-hydroxychroman **(136a)** and the conjugated chromene **(131a)** and the presence of a third component, tentatively identified as the 4-hydroxy-3-methylenecoumarin **(139a)** [previously proposed as an intermediate in

the cascade detailed in **Scheme 37 (p.58)**] . The relative percentages of the three products **(Figure 27)** were determined by integration, and their formation from the disilylated derivative **(154a)** lends support to the intermediacy of both the Baylis-Hillman products **(130)** and the 4-hydroxy-3-methylenecoumarin **(139)** in the reactions being examined. Unfortunately, due to the limitations of time and the quantity of crude material available, isolation of the individual reaction components was not possible.

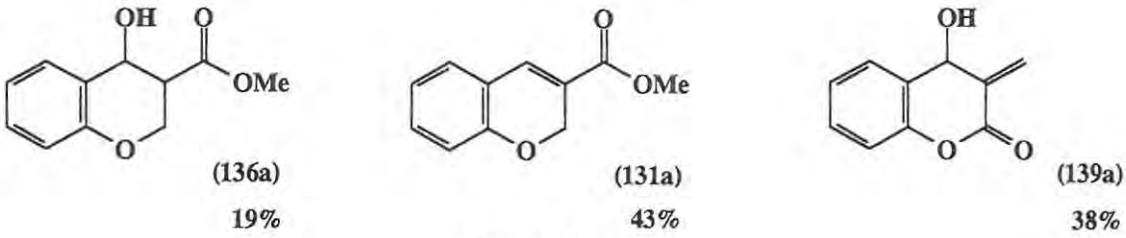
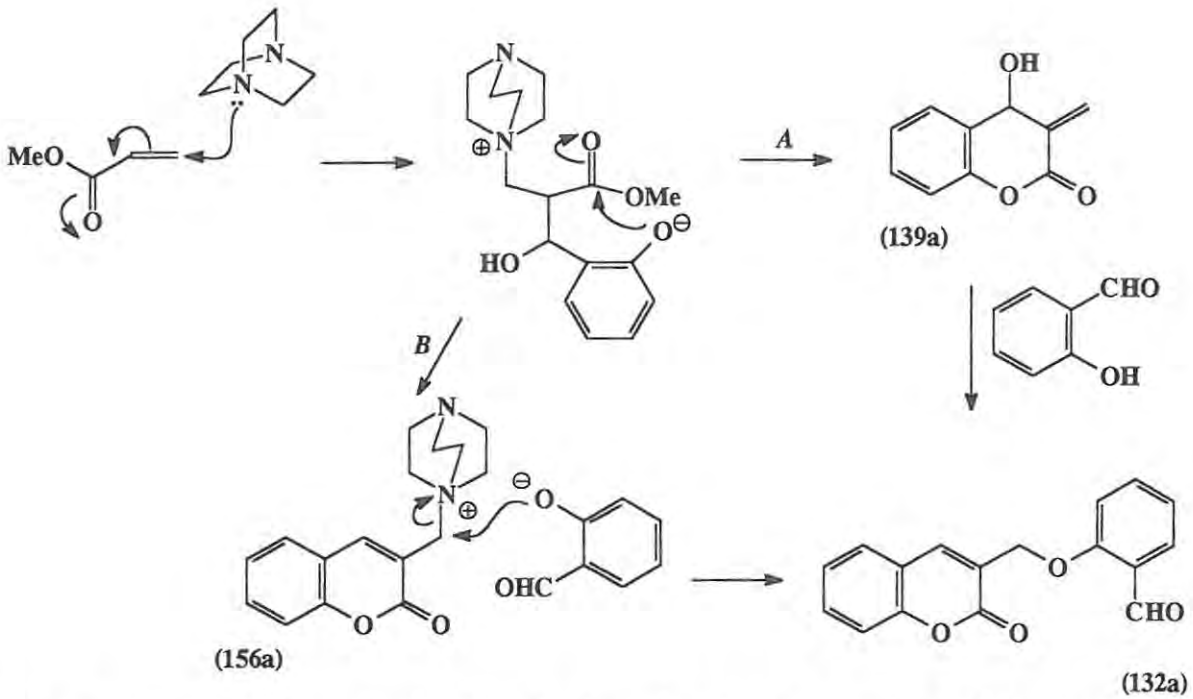


Figure 27

2.1.7 4-Hydroxy-3-methylenecoumarin as a reaction intermediate

As indicated above, a further intermediate of importance in the "Baylis-Hillman cascade" **(Scheme 36, p.57)** is the 4-hydroxy-3-methylenecoumarin **(139).** The possible role of this compound in the formation of the **type *XI*** coumarin **(132a)** **(Scheme 49 , path *A*)** was first proposed by Bode *et al.*;[109] however, it has now been further implicated in the formation of *both* classes of coumarin products (type ***XI*** and type ***VII;*** **see Scheme 41, p.74).** Bode *et al.*[109] also noted that the DABCO salt **(156a)** could afford the coumarin **(132a)** *via* nucleophilic substitution **(path *B*).**



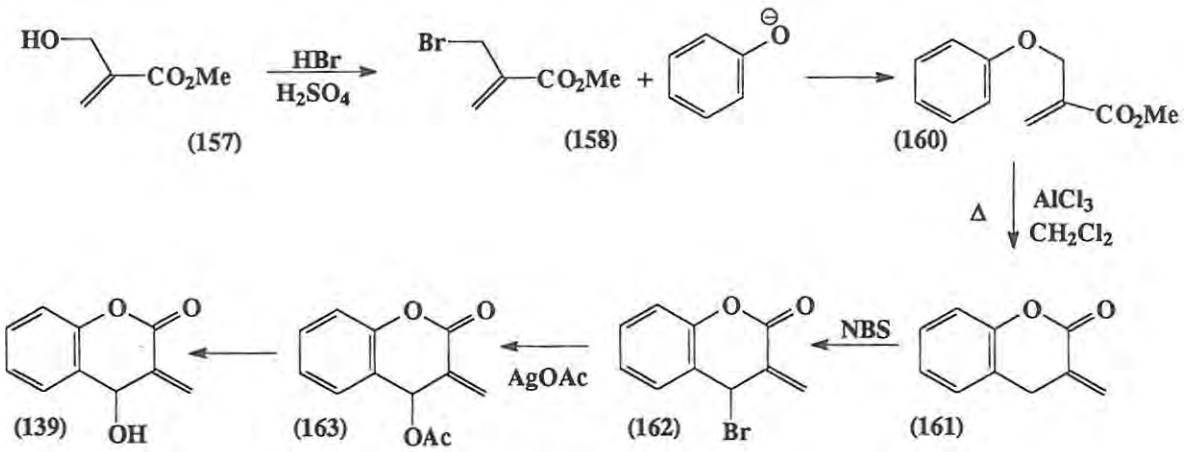
Scheme 49 **Possible mechanism for the formation of the coumarin (132a) as proposed by Bode *et al.*[109]**

With both of the proposed pathways being plausible, further evidence was required to establish which pathway is responsible for the formation of the coumarin products **(132)**. Thus, the synthesis of 3-methylene-4-hydroxycoumarin **(139a)** was undertaken, with the intention of monitoring its reaction with salicylaldehyde under controlled conditions. Such a study was expected to provide a better understanding of the reaction mechanism involved. Furthermore, this compound would lend itself to an extension of our study of conjugate addition reactions, having a rigid, cyclic α,β-unsaturated carbonyl group unlike the flexible, acyclic substrates discussed in **Section 2.3.**

2.1.7.1 Synthesis of 4-hydroxy-3-methylenecoumarin

In order to prepare 4-hydroxy-3-methylenecoumarin **(139)**, the approach outlined in **Scheme 50** was explored. This required formation and Claisen rearrangement of the allyl aryl ether

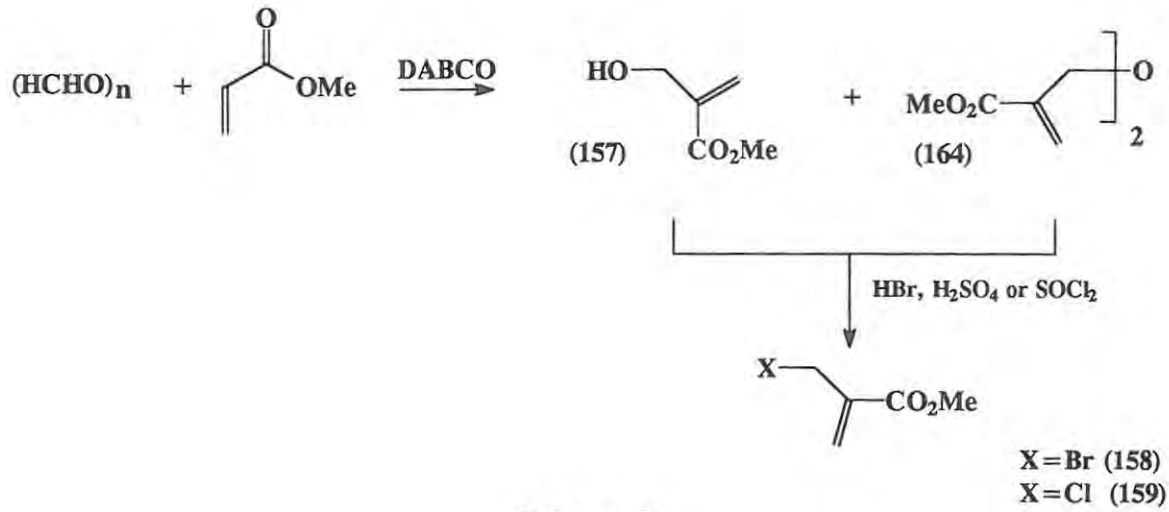
(**160**) to afford the 3-methylenecoumarin (**161**), Wohl Ziegler bromination[126] of which was expected to give the allyl bromide (**162**) which, in turn, could be reacted with silver acetate to afford 4-acetoxy-3-methylene coumarin (**163**). The acetylated compound would then be carefully de-acetylated (so as not to cleave the lactone) and thus afford compound (**139**).



Scheme 50

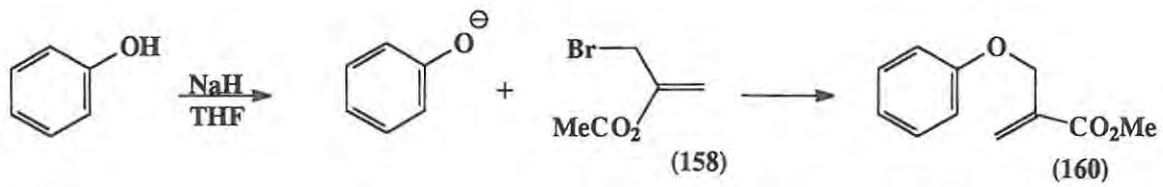
The hydroxy ester (**157**) was synthesised using the Baylis-Hillman approach described by Roos *et al.*[127] In this method, paraformaldehyde and methyl acrylate are coupled together in the presence of DABCO, in an autoclave, to afford methyl 2-(hydroxymethyl)acrylate (**157**) together with its symmetrical dimer (**164**) in good yield (**Scheme 51**). Separation of these two compounds was not necessary as Roos *et al.*[127] have shown that both compounds may be converted to the stable bromide, methyl 2-(bromomethyl)acrylate (**158**)[¥¥] under standard mineral acid conditions and in good yield.

[¥¥]Methyl 2-(chloromethyl)acrylate (**159**) was also prepared and used in these reactions.



Scheme 51

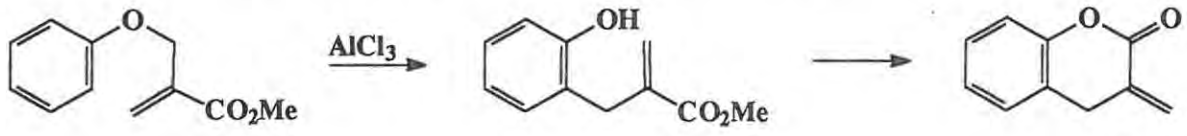
The formation of the allyl aryl ether **(160)** proceeded smoothly in *ca.* 50% yield when sodium phenoxide was reacted with methyl 2-(bromomethyl)acrylate **(158)(Scheme 52).** However, the formation of the phenolic compound **(165)** *via* Claisen rearrangement of the allyl aryl ether **(160)** and thermal cyclisation to the 3-methylene-3,4-dihydrocoumarin **(161)** proved unexpectedly difficult.



Scheme 52

Rajagopalan *et al.*[128] have reported use of the Lewis acid, aluminium trichloride, to effect Claisen rearrangement of the allyl aryl ether **(160)** to obtain, methyl 2-methylene-3-(2-hydroxyphenyl)propanoate **(165)** in 66% yield **(Scheme 53).** Drewes and Roos[4] have also reported that this transformation occurs in good overall yield. In our hands, however, the desired 3-methylene-3,4-dihydrocoumarin **(161)** could only be obtained *once* (!) In this reaction, a mixture of the allyl aryl ether **(160)** and *p*-toluenesulfonic acid in dry toluene was boiled under reflux for 5 hours, using a Dean-Stark trap charged with 3Å molecular sieves.

Chromatography afforded the coumarin **(161)** in 90% yield together with the dimer, 1,2-bis(1-benzopyran-2-on-3-yl)ethane **(168)**. Repetition of the reaction using the same or different quantities of the reagents failed to afford the required product.



(160) **(165)** **(161)**

Scheme 53

Numerous, alternative approaches were then explored. These included heating the allyl aryl ether **(160)**:-

i) with varying amounts of aluminium trichloride in dichloromethane under dry nitrogen for varying periods;

ii) with aluminium trichloride or *p*-toluenesulfonic acid in higher boiling solvents (toluene and xylene);

iii) to 170°C under vacuum (0.02 mmHg) for 5 hours in a cold finger apparatus;

iv) with aluminium trichloride to 150°C, as in (iii) above; and

v) with 10 equivalents of trifluoroacetic acid at 32°C for 6 day, following the method described by Loizou[129] for the synthesis of 4-methyl-3,4-dihydrocoumarin.

Reagents were checked for purity, solvents were dried and reactions were conducted under dry nitrogen but, inexplicably, none of these reactions afforded the required coumarin **(161)**. In some cases, the Claisen rearrangement product **(165)** was obtained and its identity was confirmed by 1- and 2-D NMR spectroscopy and mass spectrometry. The ^{1}H NMR spectra of the allyl aryl ether precursor **(160)**, the Claisen rearranged product **(165)** and the desired coumarin **(161)** are given in **Figure 28**.

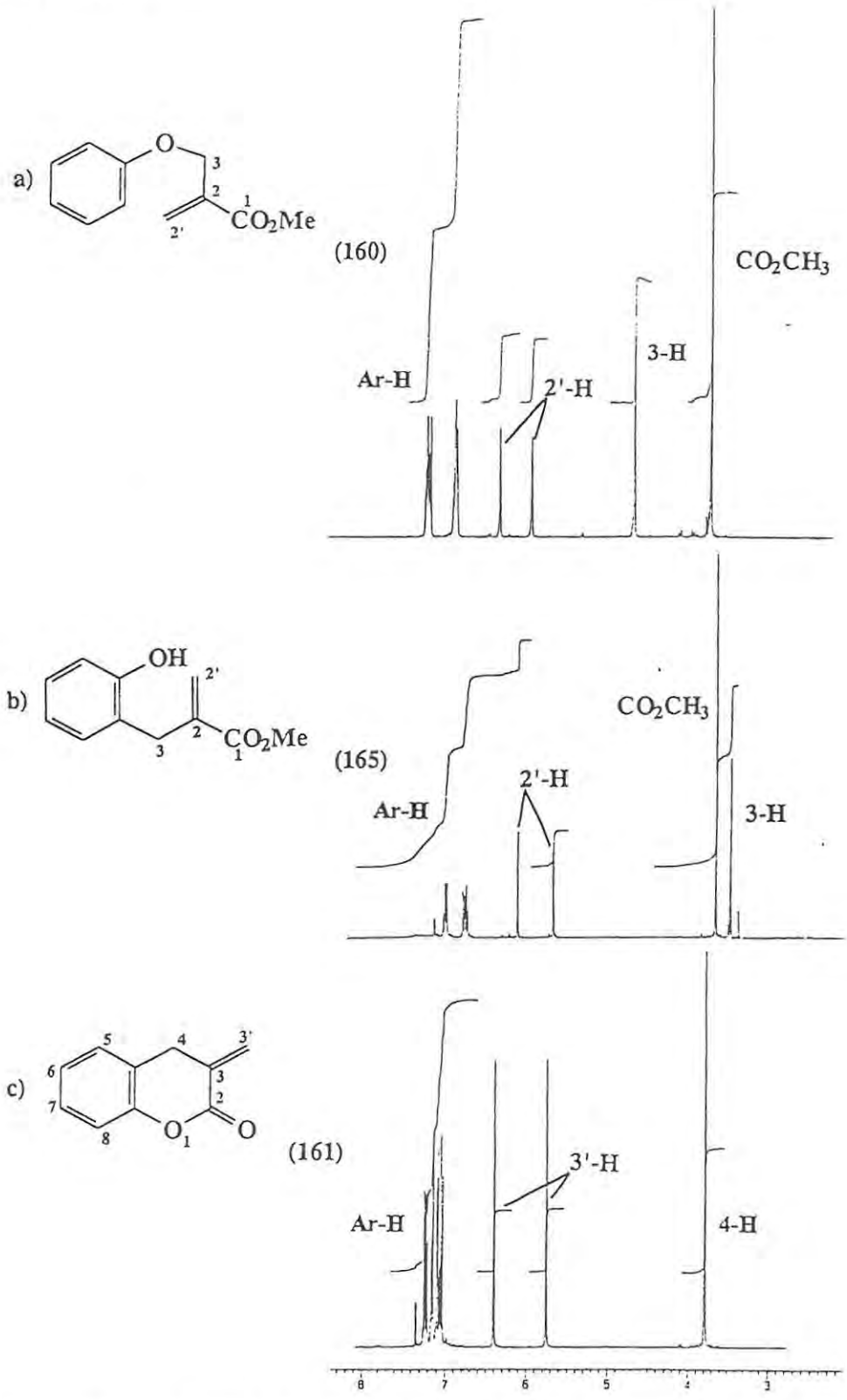
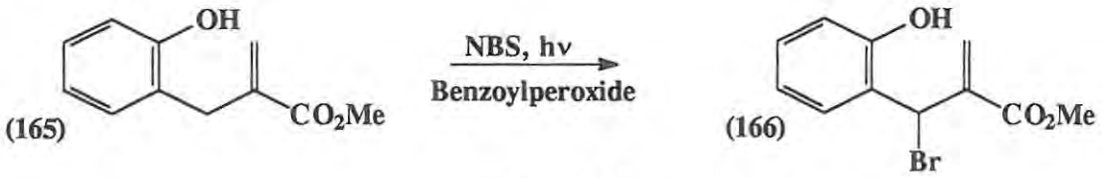


Figure 28 400 MHz ^{1}H NMR spectra of a) methyl 2-methylene-3-phenoxypropanoate (160); b) methyl 2-methylene-3-(2-hydroxyphenyl)propanoate (165); c) 3-methylene-3,4-dihydrocoumarin (161).

Isa *et al.*[130] have described a preparation of α-benzylacrylic acid, which could possibly be adapted to obtain α-[(2-hydroxyphenyl)methyl]acrylic acid; the latter compound has been cyclised by Hutchinson,[131] albeit on a 100 milligram scale, to the 3-methylenecoumarin **(161)**. However, time constraints did not permit this approach to be explored.

Wohl-Ziegler bromination[126] of the Claisen rearrangement product **(165)** afforded, as one of the products, the allyl bromide **(166)** **(Scheme 54)** but, under similar conditions, the coumarin **(161)** gave a complex mixture. Given the difficulties in obtaining further supplies of the coumarin **(161)**, the subsequent transformations detailed in **Scheme 50** could not be investigated.



Scheme 54

The dimer **(168)**, which was isolated in low yield (3%) together with the coumarin **(161)**, has been reported previously by Rajagopalan and Gopalan.[132] These authors have pointed out that the dimer **(168)** could be formed *via* either an ene reaction, involving the 6-membered transition state complex illustrated in **Figure 29**, or an acid-catalysed process initiated by the glassware. Groutas *et al.*[133] have shown that 3-methylene-5-valerolactones, on storage for long periods or when heated in the presence of acid, afford similar dimers.

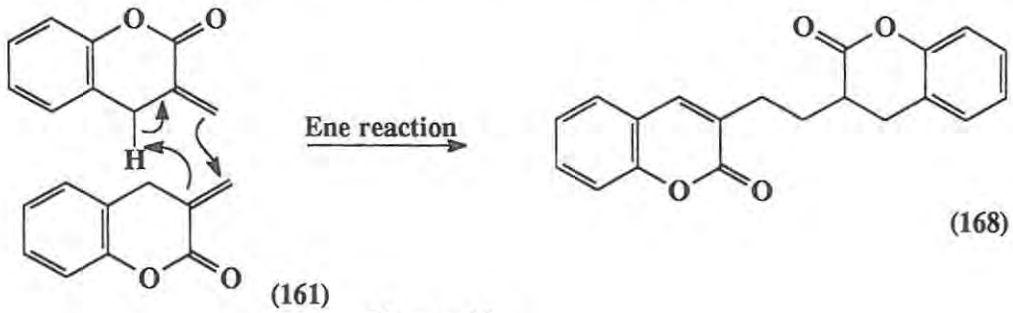


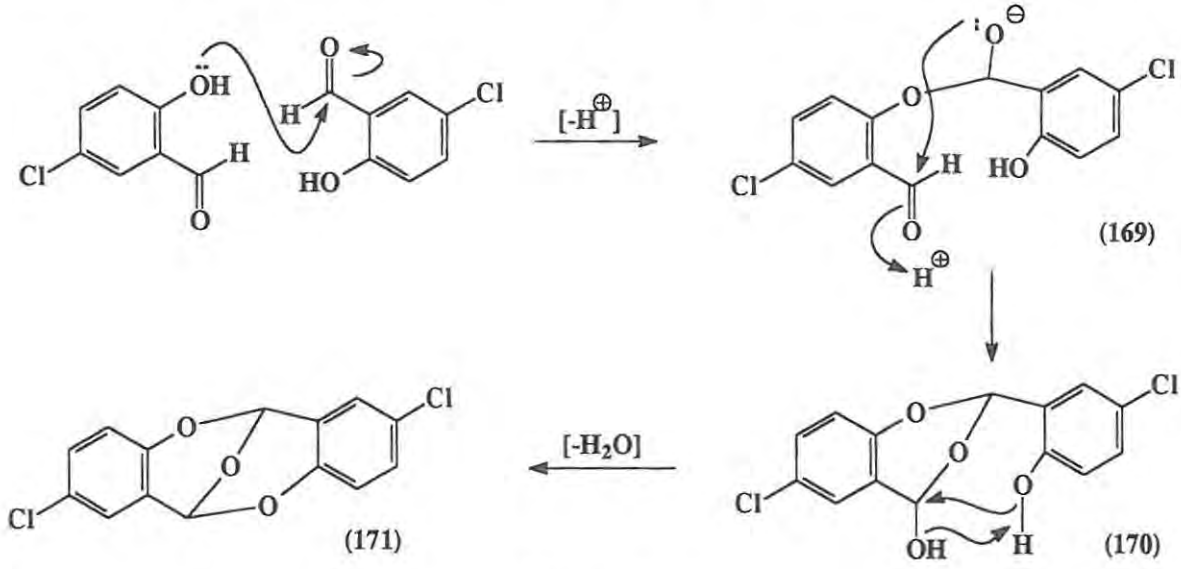
Figure 29

2.1.8 Other compounds isolated from Baylis-Hillman reactions of substituted salicylaldehydes

In addition to the coumarin and chromene derivatives discussed earlier, several other compounds were isolated from the Baylis-Hillman reactions carried out with substituted salicylaldehydes.

2.1.8.1 The salicylaldehyde dimer **(171)**

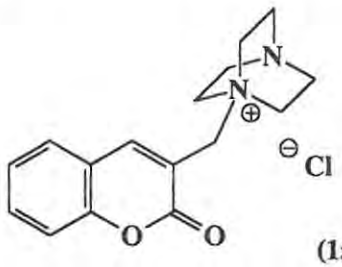
Isolated in 13% yield from the reaction conducted with 5-chlorosalicylaldehyde was a white crystalline compound identified (by 1- and 2-D ^{1}H NMR spectroscopy, high resolution mass spectrometry and combustion analysis) as the salicylaldehyde dimer, 3,4;7,8 bis(4-chloro-benzo)-2,6,9-trioxabicyclo[3.3.1]nonane **(171).** The formation of this compound is presumed to occur *via* the mechanism outlined in **Scheme 55**, in which nucleophilic addition involving two molecules of salicylaldehyde is followed by intramolecular nucleophilic addition and substitution steps - the overall process being, in effect, an intramolecular diacetalisation.



Scheme 55

When 5-chlorosalicylaldehyde was left for several months in a stoppered vial together with DABCO in chloroform the reaction afforded the dimer **(171)** in *ca.* 14% yield, but attempts to extend the transformation to other salicylaldehydes, *viz.*, 5-nitro- and 3-methoxy-salicylaldehyde, failed to afford any of the corresponding dimers, even after several months.

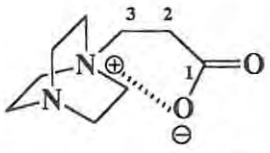
2.1.8.2 The quaternary (3-coumaryl)methyl DABCO salt **(156)**



(156)

In many of the Baylis-Hillman reactions undertaken, an insoluble precipitate was observed to form. The crystals were shown to be insoluble in many organic solvents but did dissolve in methanol. The crystals were, however, highly soluble in water and ^{1}H NMR spectroscopy of the compound showed it to be the DABCO salt **(156)**. This compound has, in fact, been isolated previously by Drewes *et al.*,[104] who suggested that its formation proves the intermediacy of an elusive "Michael" adduct in the Baylis-Hillman reaction - an intermediate postulated by all researchers in the area, but not yet isolated.

2.1.8.3 The zwitterionic 3-(DABCO)propanoate salt **(172)**



(172)

A second, water-soluble salt was isolated from the reactions of certain salicylaldehydes, *viz.*, salicylaldehyde and its 5-bromo-, 5-chloro-, 3-methoxy- and 3,5-dibromo derivatives. The salt **(172)** was identified by 1- and 2-dimensional NMR spectroscopy **(Figure 30)** as the betaine **(172)**. The resonance frequencies observed in the ^{1}H NMR spectrum for the

quaternised DABCO moiety are the same as those for the quaternary DABCO salt (**156**). The vicinal coupling between adjacent, DABCO methylene protons is also clearly evident in the ^{1}H NMR spectrum. The ^{13}C NMR spectrum for the betaine also only shows the five signals expected for this compound.

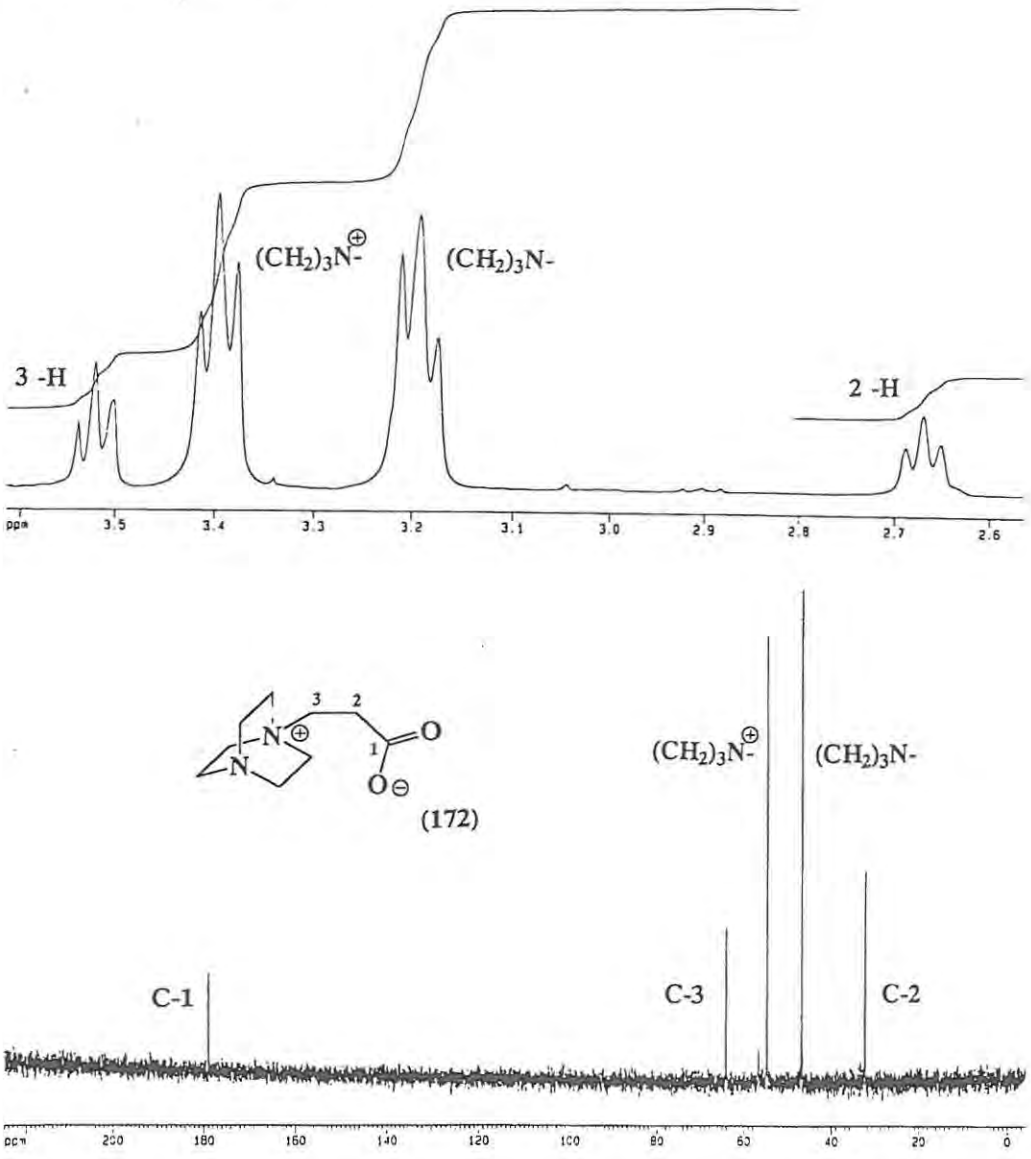


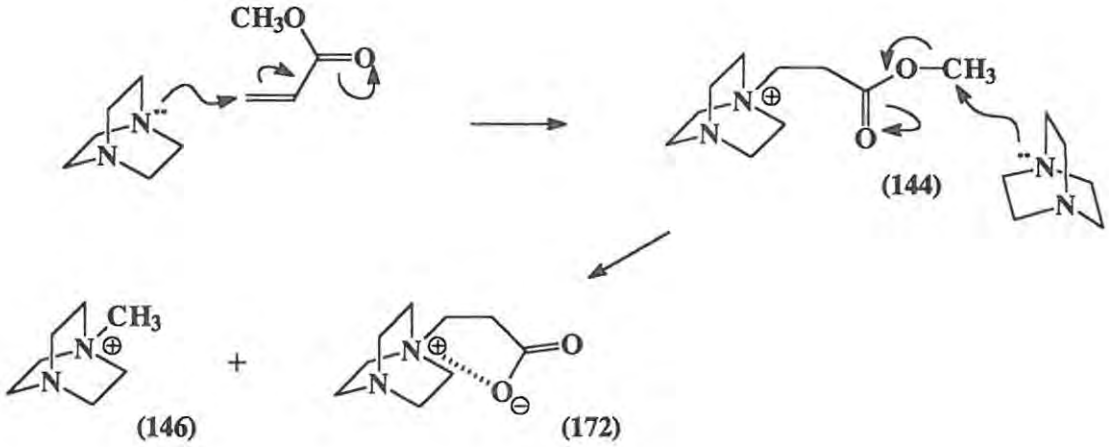
Figure 30 400 MHz ^{1}H and 100 MHz ^{13}C NMR spectra of the zwitterionic 3-(DABCO)propanoate salt (172) in D_2O.

Many years ago Hammett *et al.*[134,135] showed that methyl esters may readily be demethylated

in the presence of a tertiary amine base resulting in the formation of salts **(Equation 1)**.

$$RCOOCH_3 + N(CH_3)_3 \rightarrow RCOO^- + {}^+N(CH_3)_4 \qquad \textbf{(Equation 1)}$$

In the mechanism proposed to account for the formation of the betaine **(172)** **(Scheme 56)**, methyl acrylate undergoes initial conjugate addition by DABCO to afford the quaternary salt **(144)**. Subsequent attack by a second DABCO molecule, acting as a powerful demethylating agent results in the formation of the betaine **(172)**. We have already noted the demethylation of δ-keto-β,γ-unsaturated methyl esters by DABCO **(see Scheme 43, p. 81)**; the driving force for demethylation of the methyl ester **(144)**, however, is attributed to the resulting electrostatic attraction in the zwitterionic product **(172)**.



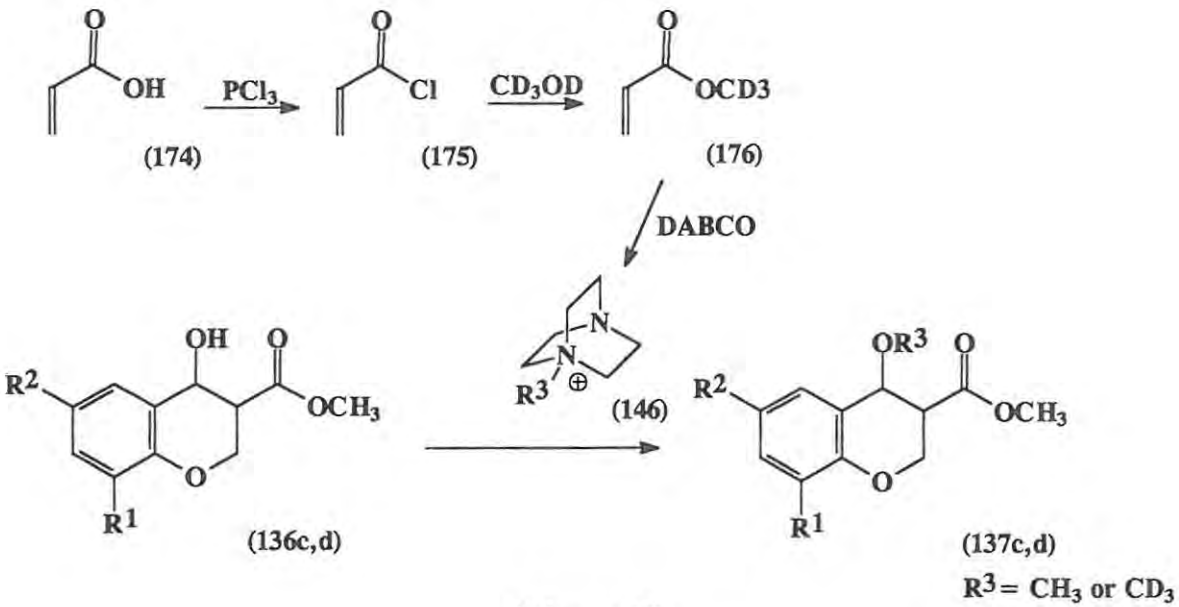
Scheme 56

2.1.9 Studies conducted with compounds isolated from the Baylis- Hillman reactions of substituted salicylaldehydes

Some of the compounds isolated from the reactions of substituted salicylaldehydes were recognised as possible intermediates in the reaction cascade (see **Scheme 36, p. 57**). Consequently, these compounds were reacted further to establish if, in fact, the expected products could be synthesised from them.

2.1.9.1 Attempted preparation of methyl 6,8-dibromo-4-methoxy-3,4-dihydro-2*H*-1-benzopyran-3-carboxylate (**137d**)

The isolated 4-methoxychromans (**137c,d**) are considered to arise by methylation of methyl 3,4-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylates (**136**) by a reactive, methylated DABCO species (**146**)(**Scheme 57; R^3= CH_3**), which is thought likely to arise from the de-methylation of methyl acrylate by DABCO (see **Scheme 56**). In order to substantiate this, methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylate (**136d**) was reacted in the presence of deuterated methyl acrylate (**176**) and DABCO.



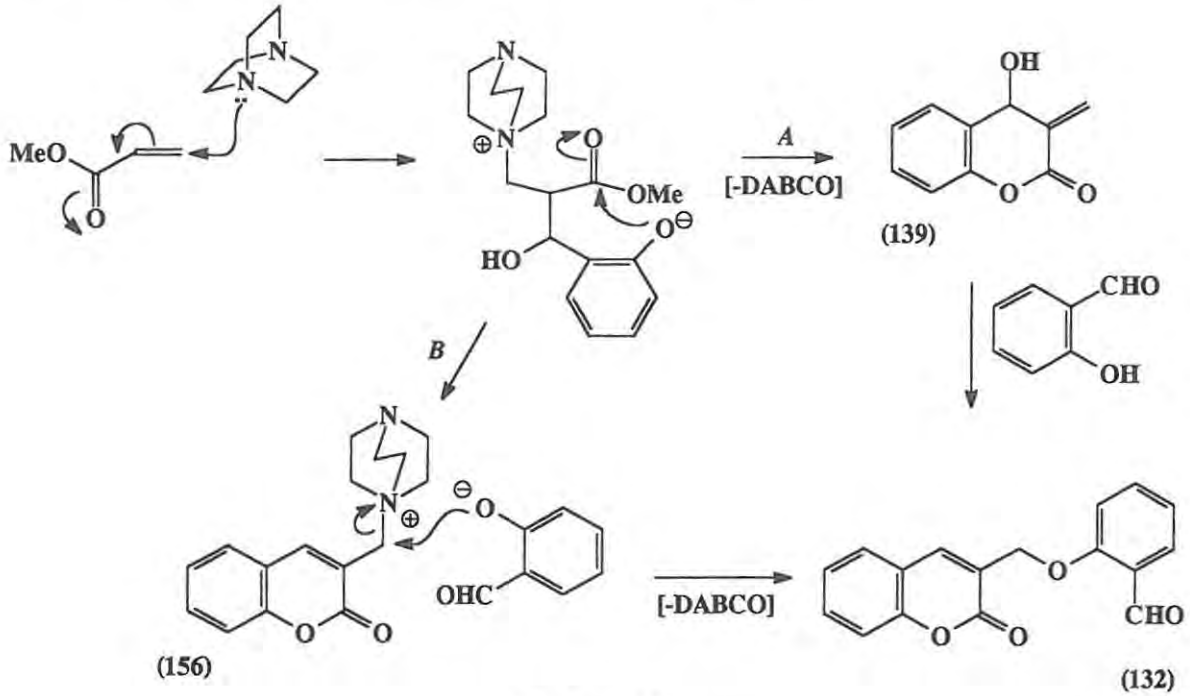
Scheme 57

The deuterated methyl acrylate **(176)** was prepared by methylating the acid chloride **(175)**, prepared from acrylic acid **(174)**, with methanol-d_4 **(173)** **(Scheme 57)**. The deuterated methyl acrylate was then placed in an NMR tube together with deuterated chloroform; to this solution was added methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2H-1-benzopyran-3-carboxylate **(136d)** together with a catalytic amount of DABCO, and the tube was sealed with a septum. The progress of this reaction was monitored over a period of 30 days by ^{1}H NMR spectroscopy. However, after this period, none of the expected product could be detected and starting material was still present together with some unidentified side products. Failure to form the 4-methoxychromans **(137c,d)** is possibly due to the fact that the methylated DABCO species **(146)** was not formed in the reaction or that *O*-methylation occures *via* another process.

2.1.9.2 The quaternary (3-coumaryl)methyl DABCO salt (156) as a possible intermediate in the Baylis-Hillman reaction of salicylaldehyde

The quaternary (3-coumaryl)methyl DABCO salt **(156)** isolated previously in this study had,

in fact, been proposed by Bode *et al.*[109] as a possible intermediate in the reaction leading to the formation of 3-[(2-formylphenoxy)methyl]coumarin **(132a) path *B* (Scheme 58)**, as opposed to the 4-hydroxy-3-methylenecoumarin **(139) (path *A*)**.

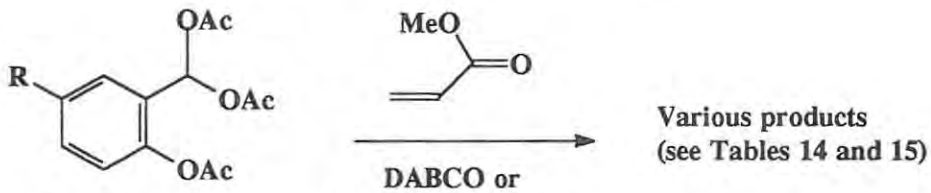


Scheme 58

The quaternary salt **(156)** was mixed with salicylaldehyde in an NMR tube, and the course of the reaction was monitored by ^{1}H NMR spectroscopy over several weeks, after which time none of the desired coumarin was detected in the reaction mixture. DABCO was added to the mixture in the NMR tube; this too failed to afford any coumarin product **(132)**. A stronger base, sodium methoxide, was then employed in order to generate the salicylaldehyde phenoxide ion; the ^{1}H NMR spectrum of the reaction mixture indicated that some changes had taken place, but the expected coumarin had clearly not been formed. It thus seems unlikely that the quaternary salt **(156)** acts as an intermediate in the formation of 3-[(2-formylphenoxy)methyl]coumarin **(132a)**. The alternative route **(pathway *A*)** involves the intermediacy of the 3-methylenecoumarin **(139)** and its consumption would explain why this particular compound could not be isolated.

2.1.10 Baylis-Hillman reactions conducted with salicylaldehyde triacetate derivatives

During the attempted preparation of *O*-acetylated salicylaldehydes (**Section 2.1.6.1, p. 87**), two triacetates were isolated, *viz.*, *O*-acetoxy- 2-(diacetoxymethyl)-4-nitrophenol (**149a**) and its bromo-analogue (**149b**). Both these compounds were also treated with methyl acrylate in the presence of DABCO or 3-hydroxyquinuclidine (**Scheme 59**).



R = NO_2 (149a)
R = Br (149b)

Scheme 59

^{1}H NMR Spectroscopy of the crude reaction mixtures, after one week, revealed the formation of complex mixtures of products. The best method for separating the reaction components proved to be preparative layer chromatography using a solvent which afforded low R_f values for most of the compounds, permitting the plate to be eluted several times and thus affording better resolution. Both reactions afforded some interesting products. Formation of the compounds detailed in **Tables 14** and **15** clearly requires deacetylation of the 5-nitro and 5-bromo substrates. Work by Miles *et al.*,[123,136] is of particular relevance in this connection. These authors showed that tertiary amine bases such as DABCO and 3-hydroxyquinuclidine are capable of cleaving geminal diesters, thus affording the corresponding mono-esters in good yield, the process being essentially a decarbmethoxylation. In the present study, however, deacetylation presumably takes place *via* tandem demethylation and decarboxylation and deacetylation resulting in the formation of the enol acetate, which in turn undergoes deacylation resulting in the unprotected salicylaldehyde.

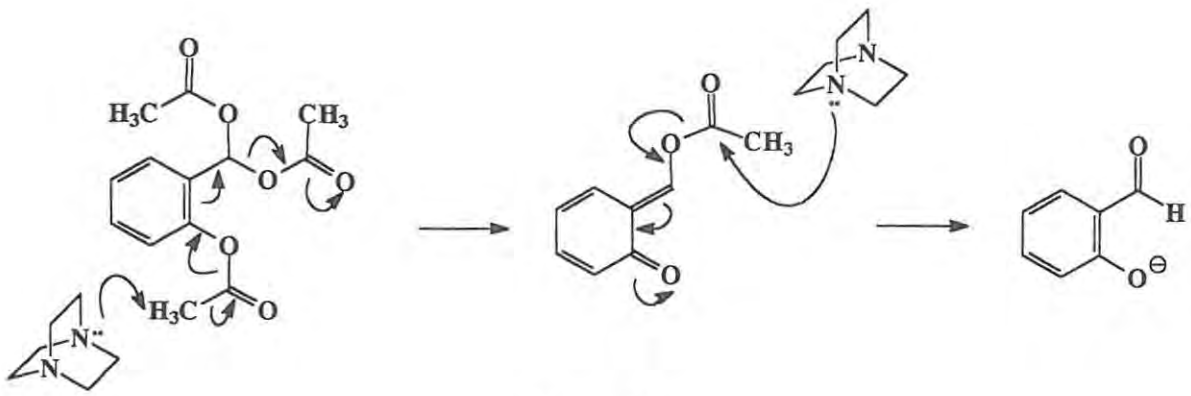
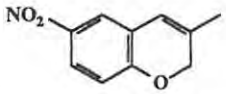
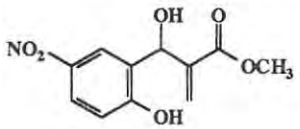
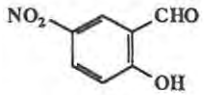
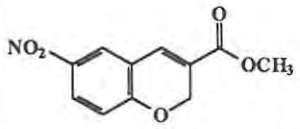


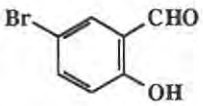
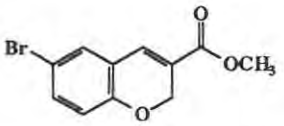
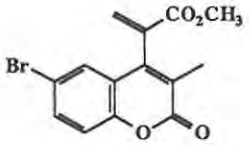
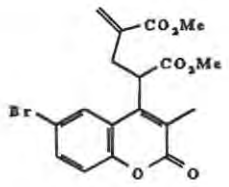
Figure 31

Table 14. Product distributions for the DABCO-catalysed reaction of the 5-nitro triacetate **(149a)** with methyl acrylate

Compound	Cpd. Number	Yield[a] /%
	**177h**	**11**
	**130h**	**21**
	**129h**	**42**
	**131h**	**22**

[a] As determined by ^{1}H NMR spectroscopy of the crude reaction mixture prior to chromatography

Table 15. Product distributions for the 3-hydroxyquinuclidine-catalysed reaction of the 5-bromo triacetate **(149b)** with methyl acrylate

Isolated product	Compd. No.	Yield[a]/ %
	**129c**	**22**
	**131c**	**10**
	**141c**	**12**
	**142c**	**19**

[a] As determined by ^{1}H NMR spectroscopy of the crude reaction mixture prior to chromatography

In the reaction carried out with the 5-nitro triacetate **(149a)**, two new products were isolated and characterised, *viz.*, compounds **(177h)** and **(130h)**.The chromene **(177h)** was readily identified by ^{1}H NMR spectroscopy **(Figure 32)**, the spectrum being very similar to that obtained for the type *III* products discussed previously **(see Section 2.1.3.2, p. 64)**. However, a striking difference is the presence of a *methyl* singlet at *ca.* 2.1 ppm, instead of a methoxy singlet at *ca.* 4.0 ppm. The mechanism by which this compound arises is, as yet, not understood.

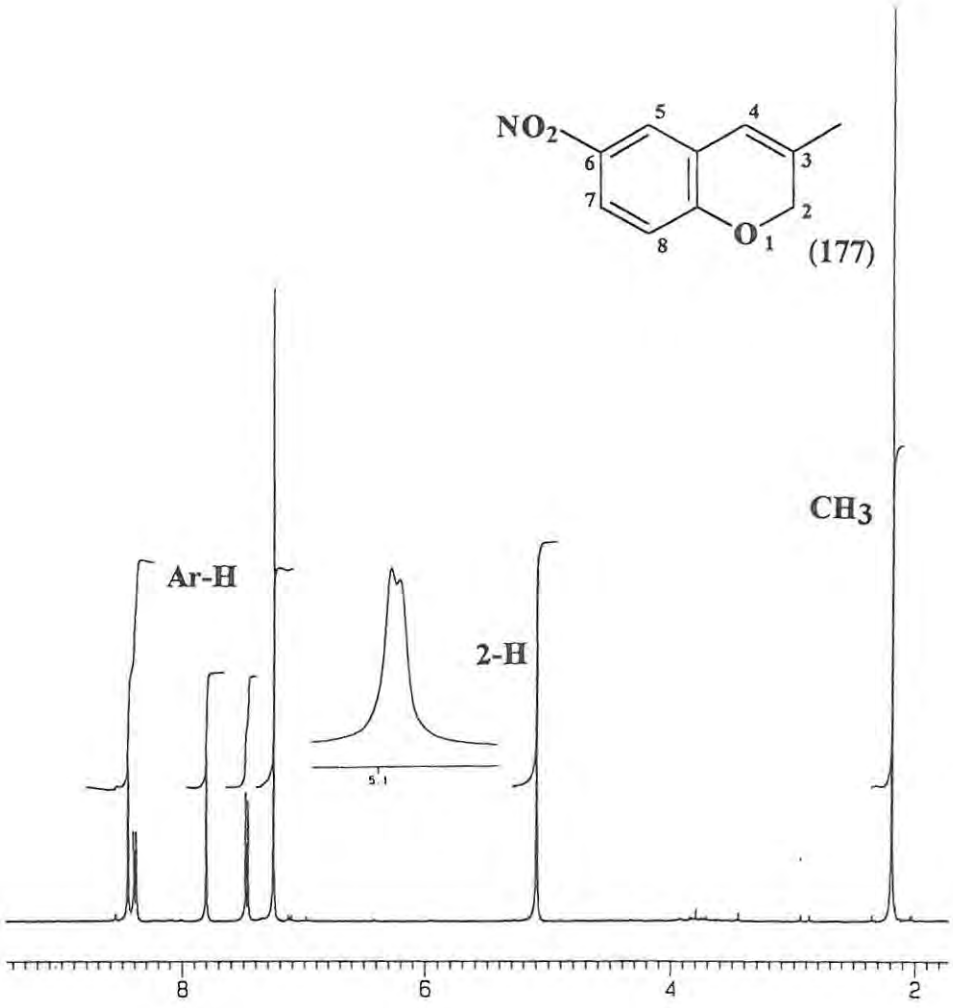


Figure 32 400 MHz ^{1}H NMR spectrum of *3*-methyl-6-nitro-2*H*-1-benzopyran (177)

The second, new nitro compound to be isolated was, in fact, methyl 3-hydroxy-3-(2-hydroxy-5-nitrophenyl)-2-methylenepropanoate **(130h)**- the elusive Baylis-Hillman product! The ^{1}H NMR spectrum for this compound **(Figure 33)** shows the expected *exo*-methylene protons [confirmed by the HETCOR **(Figure 34)** as being attached to the same carbon] and the methoxy singlet at 3.8 ppm. The ^{13}C NMR, COSY and DEPT spectra, as well as the high resolution mass spectral data all support the proposed structure. The isolation of the Baylis-Hillman product **(130h)** from the reaction mixture clearly provides further support for

its pivotal role in the formation of both coumarin and chromene derivatives (**Scheme 37, p. 58**).

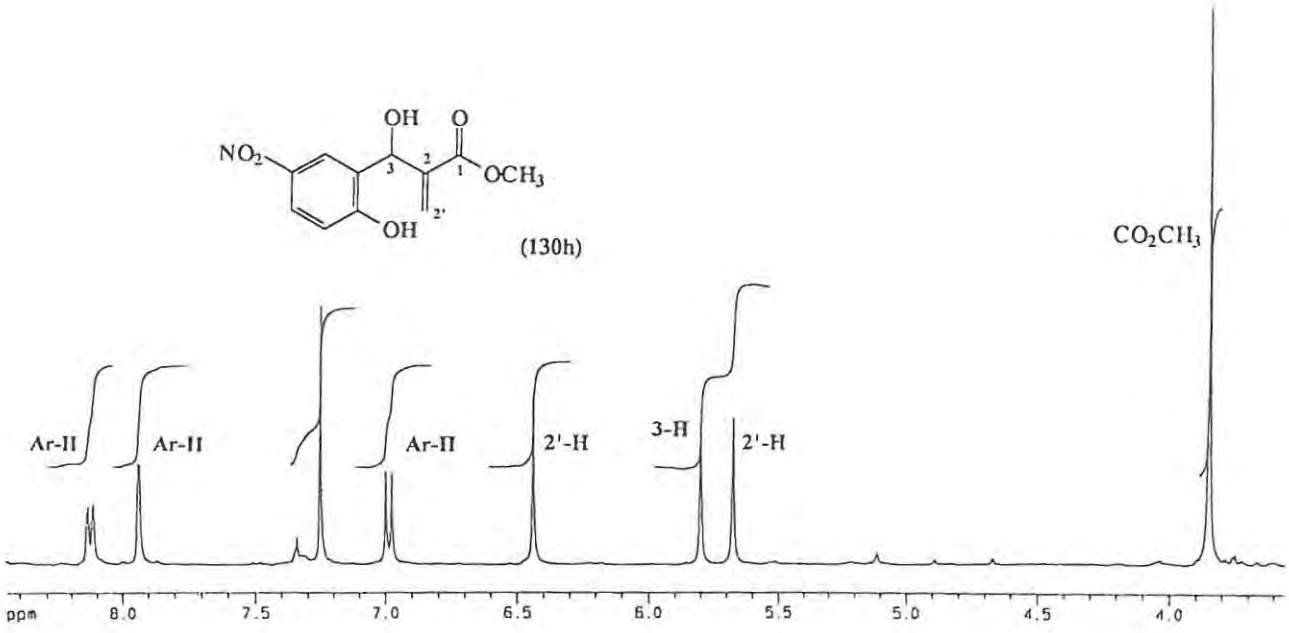


Figure 33 **400 MHz ^{1}H NMR spectrum for methyl 3-hydroxy-3-(2-hydroxy-5-nitrophenyl)-2-methylenepropanoate (130h) in $CDCl_3$.**

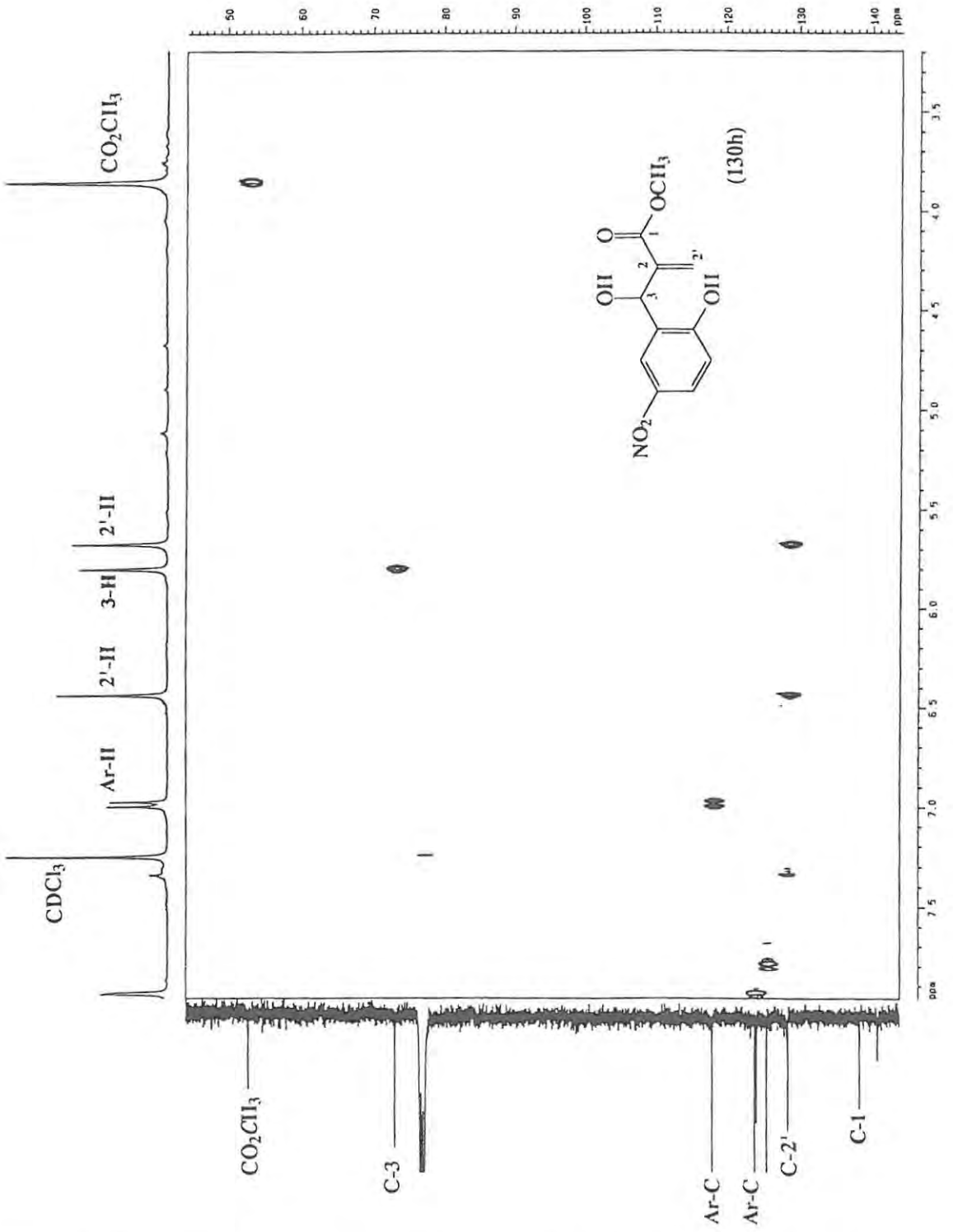


Figure 34 **The inverse HETCOR spectrum of methyl 3-hydroxy-3-(2-hydroxy-5-nitrophenyl)-2-methylenepropanoate (130h) in $CDCl_3$.**

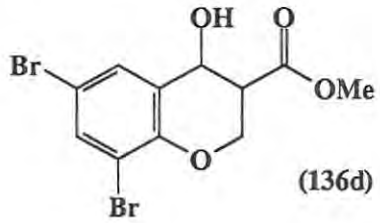
2.1.10.1 Attempted cyclisation of methyl 3-hydroxy-3-(2-hydroxy-5-nitrophenyl)-2-methylenepropanoate **(130h)**

In order to cyclise this compound a small quantity of DABCO was added to the NMR tube containing a $CDCl_3$ solution of compound **(130h)** and the reaction was monitored by ^1H NMR spectroscopy. Somewhat expectedly a precipitate rapidly formed in the NMR tube due to the formation of the DABCO salt with the acidic phenol group. In addition, both methyl acrylate and 5-nitrosalicylaldehyde were observed in the reaction mixture, indicating the existence of an equilibrated system in the formation of the Baylis-Hillman product **(130h)(Figure 35)**. The possibility of a retro- Baylis-Hillman reaction has been discussed earlier **(Section 1.1.2)**, and the apparent formation of the precursors for the Baylis-Hillman product **(130h)** is essentially consistent with an equilibrium process.

Figure 35

2.2 CONJUGATE ADDITION REACTIONS OF BAYLIS-HILLMAN PRODUCTS

In the previous sections attention has been drawn to the expected ability of the Baylis-Hillman products, to undergo cyclisation *via* either an intramolecular conjugate addition involving attack at the vinyl carbon or intramolecular acyl substitution (involving attack at the carbonyl carbon). Attention has consequently been focused on analogous *intermolecular* reactions between similar substrates. Furthermore, conjugate addition results in the formation of two new chiral centres and the potential thus exists for a level of stereocontrol. This is of course also reflected in the formation of 4-hydroxychroman **(136d)** as a single diastereomer *via intramolecular* cyclisation **(see Section 2.1.3.1)**



(136d)

In the choice of the nucleophiles, oxygen, nitrogen and sulfur nucleophiles were used for the intermolecular reactions, the latter two types being chosen to assess the potential for generating N-, and S- heterocyclic analogues of the chromene and coumarins studied earlier **(Figure 36)**.

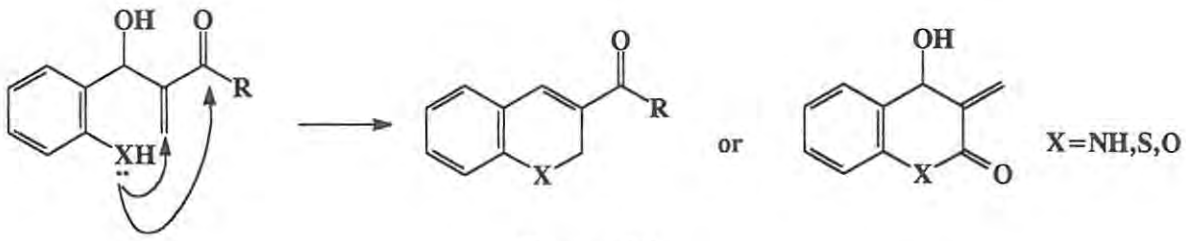
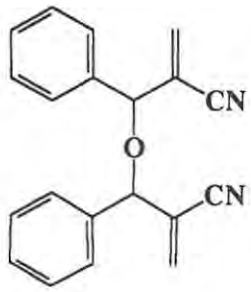


Figure 36

In order to examine the potential for regio- and stereocontrol in such systems a range of Baylis-Hillman products were synthesised and reacted with various nucleophiles. The diastereomeric excesses for the various reaction systems were determined from ^{1}H NMR spectroscopy of the crude reaction mixtures.

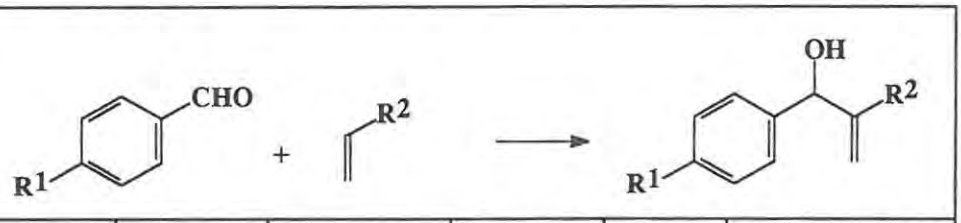
2.2.1 Preparation of Baylis-Hillman products as substrates

The preparation of the Baylis-Hillman products was carried out using standard reaction conditions, in which the substituted aldehyde was stirred together with methyl acrylate or acrylonitrile in the presence of the catalyst, DABCO. The reactions were monitored by TLC and ^{1}H NMR spectroscopy. The crude product was then purified using chromatographic techniques to afford the desired products **(Table 16)**. In the case of the reaction between acrylonitrile and benzaldehyde the reaction afforded the dimeric ether **(182)**, present in both diastereomeric forms in 72% yield.



(182)

Table 16 Data for the preparation of Baylis-Hillman products as conjugate addition substrates.



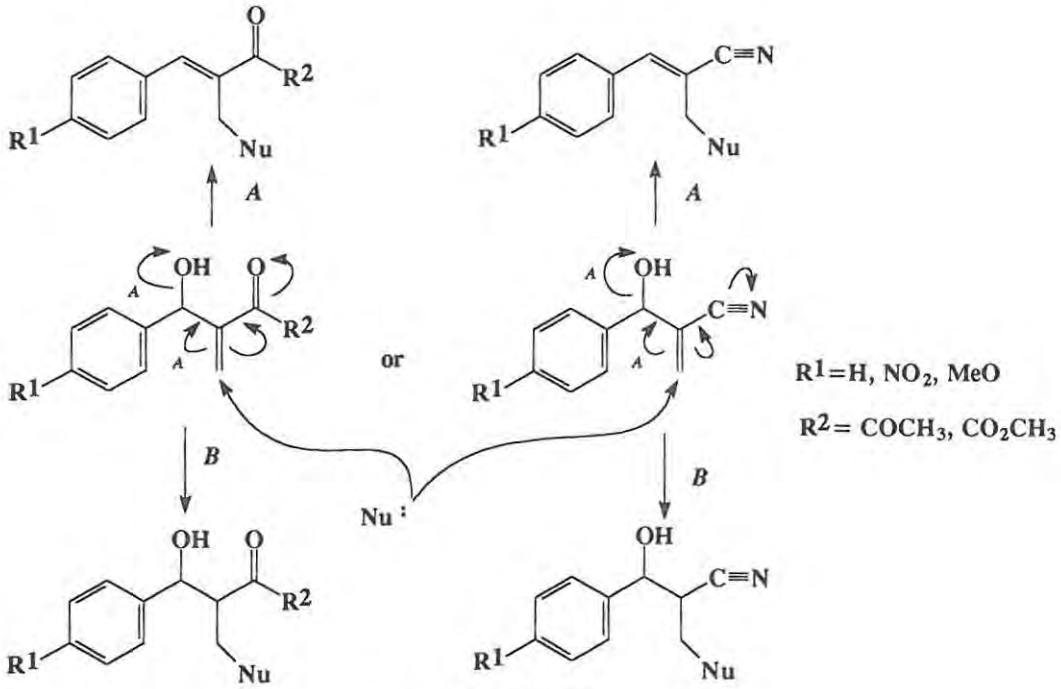
Entry	R^1	R^2	Product No.	Time/ days	Reaction yield/ %
1	NO_2	CN	**178**	21	58
2	H	$COCH_3$	**179**	14	18
3	OCH_3	CO_2CH_3	**180**	30	41
4	H	CO_2CH_3	**181**	30	48

2.2.2 Conjugate addition reactions

The Baylis-Hillman products were then reacted with molar equivalents of the respective nucleophiles, *viz.*, phenol, thiophenol, pyrrolidine and piperidine.

Initially, in the reactions conducted with the nucleophiles, phenol and thiophenol, aqueous NaOH was used to generate the respective anions before carrying out the conjugate addition reactions. However, in some cases, this protocol gave an unidentified product and, thus, NaH was used instead to generate the anions in some cases. The reactions were conducted in THF except when NaOH was used, in which cases the solvent was water. The reactions using the nitrogen nucleophiles all tended to afford the expected conjugate addition products **(pathway B; Scheme 60)** in high yield, but, some of the reactions carried out using phenol or thiophenol as the nucleophile were less successful. However, in none of the reactions

examined was competition evident from either of substitution modes [S_N' **(pathway A; Scheme 60)** or acyl substitution].



Scheme 60

After the reactions were complete, and the solvent had been removed *in vacuo,* the crude reaction mixtures were analysed using ^{1}H and ^{13}C NMR spectroscopy, and the diastereomeric excess was determined from the integrals of the distinctive H-α protons resonating at *ca.* 4.9 and 5.1 ppm for the respective diastereomers, as illustrated in **Figure 37**.

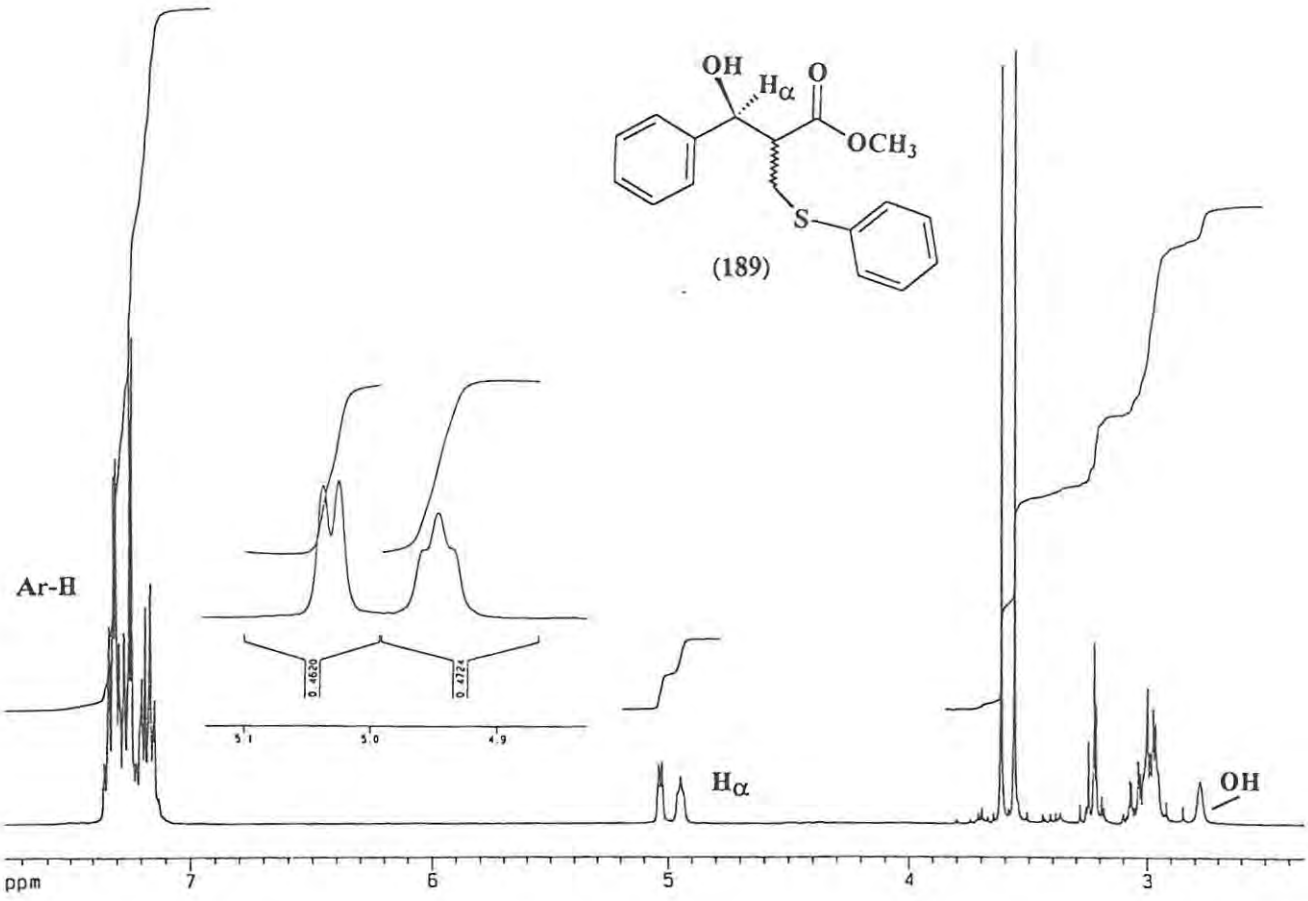
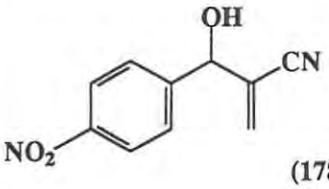
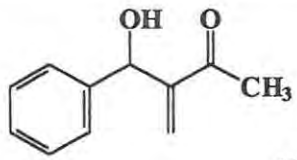
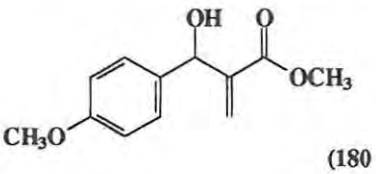
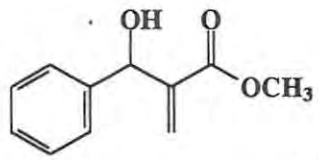
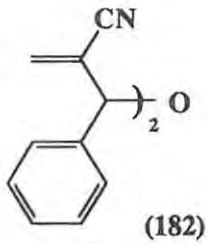


Figure 37 **400 MHz ^{1}H NMR spectrum of the crude reaction mixture for the reaction between methyl 3-hydroxy-2-methylene-3-phenylpropanoate (181) and benzenethiolate in D_2O.**

The yields and percentage diastereomeric excesses for all the conjugate addition reactions are summarised in **Table 17,** and it is apparent that there is a wide variation in the observed diastereoelectivities.

Table 17 Data for conjugate addition of various nucleophiles to Baylis-Hillman products.

Substrate	Entry	Nucleophile	Reaction yield /%	d.e. /%	Product No.
 (178)	1	ArS^-	-	-	-
	2	ArO^-	-	-	-
	3	Pyrrolidine	97	16	183
	4	Piperidine	84	31	184
 (179)	5	ArS^-	-	-	-
	6	ArO^-	-	-	-
	7	Pyrrolidine	83	10	185
	8	Piperidine	86	36	186
 (180	9	ArS^-	-	-	-
	10	ArO^-	-	-	-
	11	Pyrrolidine	89	28	187
	12	Piperidine	78	31	188
 (181)	13	ArS^-	88	5	189
	14	ArO^-	30	57[a]	190
	15	Pyrrolidine	66	29	191
	16	Piperidine	98	16	192
 (182)	17	ArS^-	-	-	-
	18	ArO^-	-	-	-
	19	Pyrrolidine	82	25	193
	20	Piperidine	77	34	194

[a] Product was contaminated with an unidentified impurity.

In the analogous *intramolecular* conjugate addition discussed in **Section 2.1.3** (p. 60), preferential formation of the *syn*-product was attributed to protonation of the *cyclic* enolate at the face opposite to the hydroxyl group (*i.e. steric approach control*). In the *intermolecular* reactions considered here, protonation may occur at either face of the enolate intermediate **(Figure 37).** The energy-minimised conformations obtained by computer modelling the *syn*- and *anti*- stereoisomers showed the 2-H, 3-H torsion angles to be :- ϕ_{syn} = 65.8° and ϕ_{anti} = 176.9°. Comparison of the measured coupling constants for the two diastereomers (J = 5.3 Hz and 8.9 Hz, with J= 5.3 Hz corresponding to the dominant species) with the values (J_{syn} = 4.1 Hz and J_{anti} = 9.9 Hz) estimated using the Karplus equation,[119] indicates that the dominant stereoisomer is likely to be the *syn*-product. This is consistent with the trend observed earlier, and is attributed to *steric approach control.*[120]

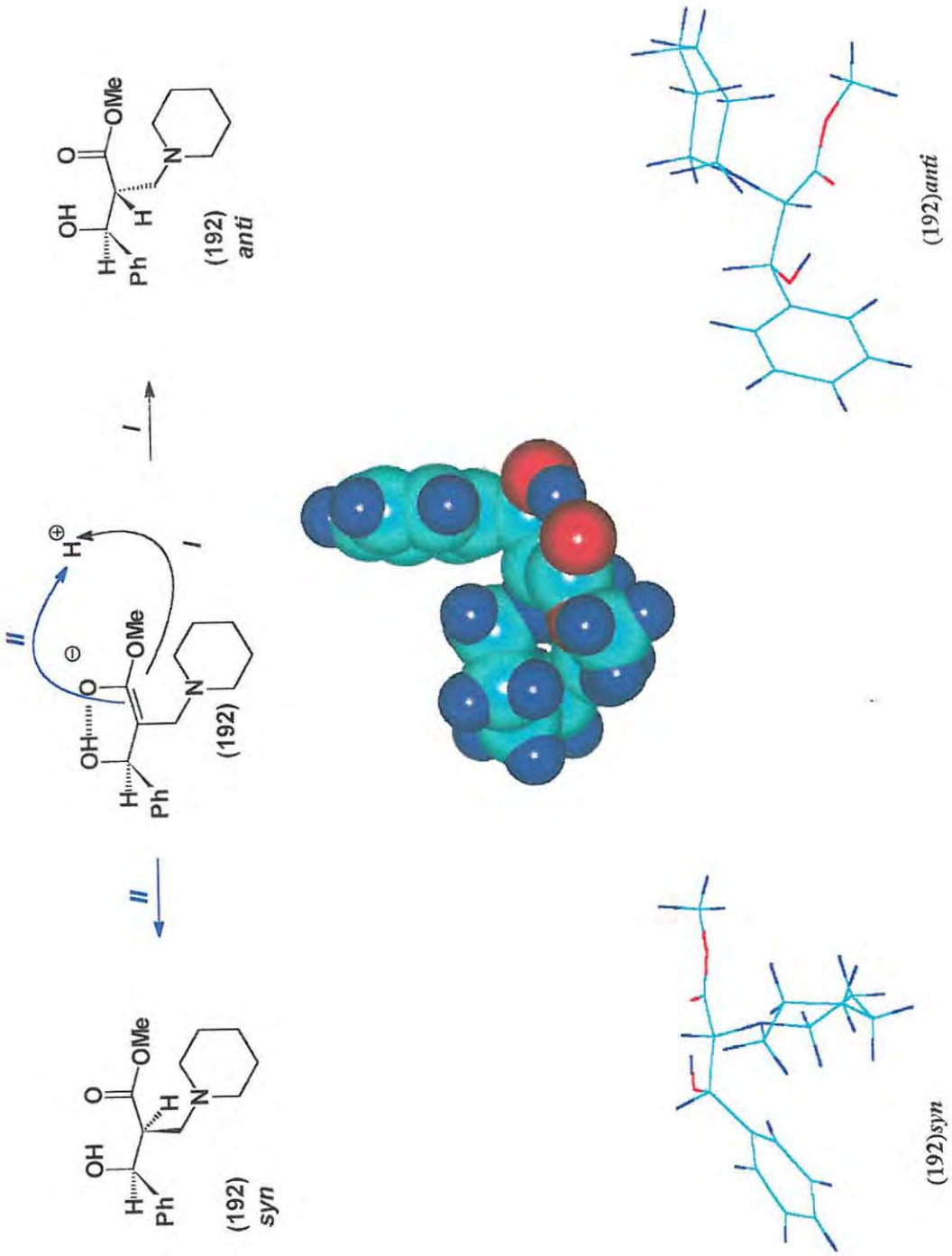
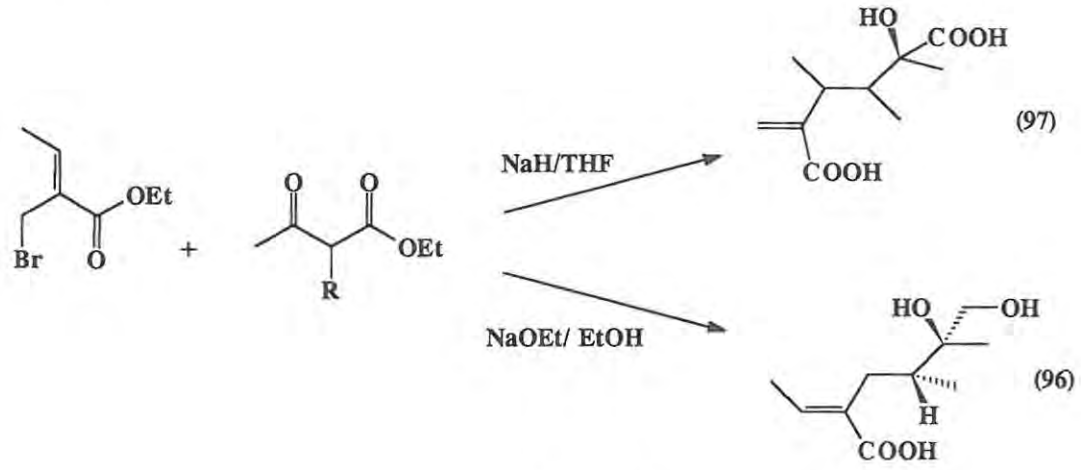


Figure 37 Energy minimised conformations showing electrophilic attack on the enolate species (192) to afford the *syn*- and *anti*- products.

From the results of the study, it can be seen that the diastereoselectivities ranged from as low as 5% d.e. **(entry 13, Table 17)** to 57% d.e. (entry 14). In the latter case, the yield was substantially lower than in the other reactions. The exclusive formation of the conjugate addition products rather than the S_N' products may be attributed to the fact that the hydroxyl group is generally a poor leaving group in these reactions. This was well illustrated by the work of Bode *et al.*[110] who showed that the cyclisation of 2-pyridylcarboxaldehyde-derived Baylis-Hillman products to indolizines could be accelerated by *O*-acetylating the hydroxy compounds and thus providing acetate as the leaving group. Certain reactions carried out with phenol and thiophenol failed to afford any product, the exception being the reaction with methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(181) (entries 13 and 14; Table 17)**. However, the reactions with phenol and thiophenol also gave complex mixtures, which based on the ^{1}H NMR spectra appear to be polymers. On the strength of the high yields obtained for the reactions conducted with piperidine and pyrrolidine it seems likely that nitrogen heterocycles may be accessible *via* the Baylis-Hillman methodology.

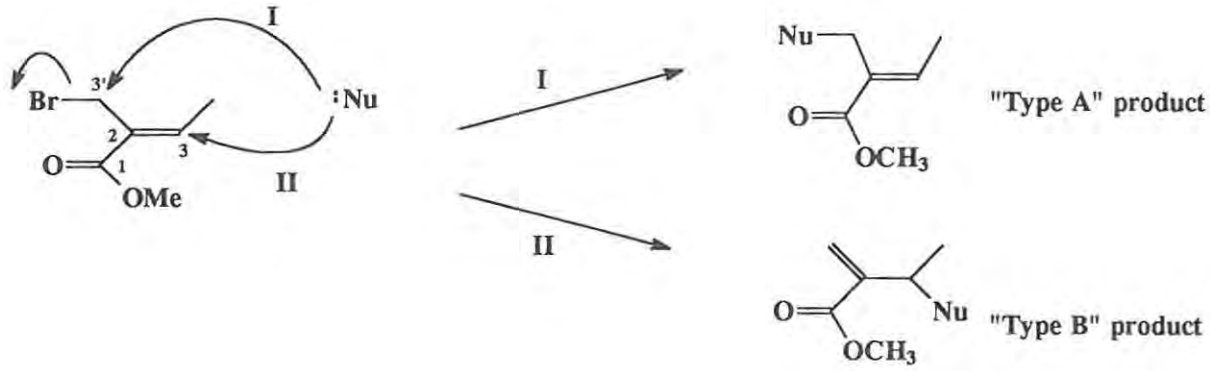
2.3 ALLYLIC DISPLACEMENT STUDIES

In research directed towards the synthesis of necic acids, Ameer *et al.*[94] explored the regioselectivity of reactions between a range of Baylis-Hillman derived alkenoate esters and alkylacetoacetate nucleophiles. It was observed that by varying the base-solvent system, used to generate the nucleophile, two different products could be obtained. This approach was successfully used in the synthesis of the necic acids, retronecic **(96)** and senecivernic acid **(97)**, from common precursors **(Scheme 61)**[137], and has been extended to the synthesis of a range of necic acids.[99]



Scheme 61

If nucleophilic attack takes place at the allylic carbon, C(3') **(Path I; Scheme 62)**, the resulting product contains a non-terminal double bond (a "type A" product), while attack at the vinylic carbon, C(3), proceeds with allylic rearrangement to afford a product containing a terminal double bond (a "type B" product) **(Path II)**.



Scheme 62

Ameer[99] studied the effects of varying the substituents, the leaving group and the base-solvent system on the relative distributions of the "type A" and "type B" products (**Table 18**) . From the results of this study it was apparent that:- i) "type A" products are favoured in ethanol, "type B" in THF; ii) changing the leaving group from I→Br →Cl results in an enhancement of the "type A" products; and iii) increasing the bulk of the alkyl substituent in the nucleophile leads to a relative increase in "type A" products. It was suggested that these trends could be accommodated by assuming that formation of the "type A" product follows a unimolecular S_N1 mechanism and that the "type B" products arise from a bimolecular S_N2' type process.[99]

Table 18. Selected data from the study by Drewes *et al.*[94] on substituent and solvent effects on the relative product distributions of "type A" and "type B" products.

Entry	R	R'	X	Base/ solvent	R'' = H		R'' = CH_3	
					Type A	Type B	Type A	Type B
a	CH_3	CH_3	Br	A	80	20	83	17
				B	14	86	17	83
b	CH_2CH_3	CH_3	Br	A	72	28	90	10
				B	22	78	30	70
c	$CH(CH_3)_2$	CH_3	Br	A	66	34		
				B	44	56		
d	CH_2CH_3	CH_3	Cl	A			100	0
				B			44	56
e	CH_2CH_3	CH_3	I	A			85	15
				B			64	36

A= NaOEt/ EtOH; B= NaH/ THF

In an attempt to establish the mechanistic basis of these allylic displacements, McMillan[112] followed selected reactions by HPLC but, unfortunately, use of this technique failed to monitor the formation of intermediates and to afford definitive kinetic data.

Consequently, the displacement reaction has been re-investigated, using ^1H NMR spectroscopy. The main advantages in using NMR spectroscopy for studying such systems include :-

i) continuous monitoring of the consumption of reactants, the formation of possible

intermediates and the development of products within a single sample;

ii) elimination of the need to regularly remove and quench aliquots of the reaction mixture; and

iii) elimination of the need for internal concentration standards.

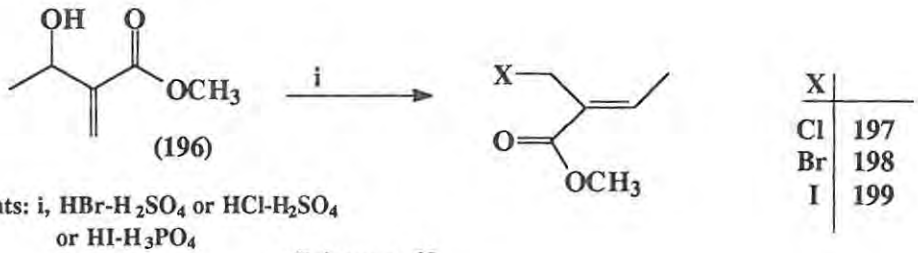
2.3.1 Preparation of substrates

The methyl (*Z*)-2-halogenomethyl-2-butenoate systems used as substrates in the studies were prepared from the Baylis-Hillman product, methyl-3-hydroxy-2-methylenebutanoate (**196**) in moderate yields (**Scheme 63**), following the methods reported by Ameer[99] and McMillan.[112] Thus, the Baylis-Hillman product (**196**) was brominated with a mixture of concentrated HBr and concentrated H_2SO_4 to afford the (*Z*)-regioisomer (**198**) *via* nucleophilic attack at the primary vinylic carbon. Attack at the secondary allylic carbon is presumed to be less likely due to the steric bulk of the bromide ion.[112] The (*Z*)-geometrical assignment is based on the ^{13}C chemical shift data.[98,99]

The preparation of the chloro analogue (**197**) was achieved by using a mixture of HCl and H_2SO_4 as the chlorinating agent. However, unlike the bromo esters, the (*Z*)-chloro ester contained some of the (*E*)-isomer (as much as 18% was present in some cases). Attempted purification of the mixture using flash chromatography, preparative layer chromatography, preparative gas liquid chromatography and distillation *in vacuo* only afforded marginal improvements in the purity of the sample. Further purification of this compound was not possible and, consequently, the compound was used with a small amount of (*E*)-isomer present.

Initial attempts to synthesise the iodo analogue (**199**), utilizing the method described by Mc-Millan[138] [in which concentrated H_3PO_4 was added dropwise to a stirred solution of methyl 2-hydroxy-2-methylenebutanoate (**196**) and HI in water], failed to afford the desired product.

A second approach[97] was therefore used in which concentrated HI and then concentrated H_3PO_4 were added dropwise to the unsaturated ester, methyl 2-hydroxy-2-methylene-butanoate (**196**); after stirring for several days, work up afforded the desired product in high purity in 30% yield.



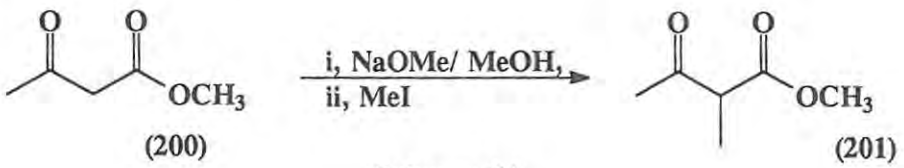
Reagents: i, $HBr-H_2SO_4$ or $HCl-H_2SO_4$ or $HI-H_3PO_4$

Scheme 63

2.3.2 Preparation of the nucleophile

Methyl 2-methyl-3-oxobutanoate (**201**) was prepared from commercially available methyl acetoacetate (**200**) (**Scheme 64**) by treating the sodium salt of methyl acetoacetate with methyl iodide. The product was obtained in sufficient purity by fractional distillation, the purity being confirmed by gas liquid chromatography and NMR spectroscopy.

In the preparation of the substrates and the nucleophile, yields were sacrificed in favour of sample purity as the quantities of reagent needed for the kinetic runs were minimal. All the samples were stored under dry N_2 in a desiccator at 5°C.



Scheme 64

The sodium enolate of methyl 2-methyl-3-oxobutanoate **(201)**, used as the nucleophile in the kinetic study, was generated using either NaH/THF-d_8 or NaOMe/CD_3OD as base-solvent systems. Ameer[99] noted that a problem associated with the use of NaOMe was the ability of the base to act as a nucleophile in the reaction, affording the ether **(202)** **(Scheme 65)**. Such a situation may be prevented, however, by using stoichiometric quantities of the base and by allowing sufficient time for the nucleophile to be generated prior to addition of the halogeno ester substrate.

Scheme 65

2.3.3 Kinetic studies

Reactions between the unsaturated halogenoesters **(197-199)** and the nucleophile methyl 2-methyl-3-oxobutanoate **(201)** were conducted using both base-solvent systems, *viz.*, NaH-THF-d_8 or NaOMe-CD_3OD, and followed by ^1H NMR spectroscopy at 303 K. The kinetic runs were carried out in an NMR tube as described in the experimental section **(Section 3.2.10)**, and NMR spectra were acquired at set time intervals using an automatic acquisition programme (as illustrated in **Figure 38**). The data were collected for each of the successive kinetic runs and the regions of interest were integrated individually since automatic integration tended to include baseline noise resulting in some scatter of the data points. The resulting data is summarised in the experimental section.

At preparative concentrations (*ca.* 0.3 **M**) the reactions are too fast to be efficiently monitored by ^{1}H NMR spectroscopy, but the relative insensitivity of the technique precludes excessive dilution. It was found that, at concentrations of *ca.* 0.02 **M**, the reaction could be conveniently monitored by ^{1}H NMR spectroscopy. While the range of substrates studied included the chloro-, bromo- and iodomethyl esters, reactions involving the bromomethyl substrate **(198)** were explored extensively in order to optimise the reaction conditions, before extending the study to include the other substrates.

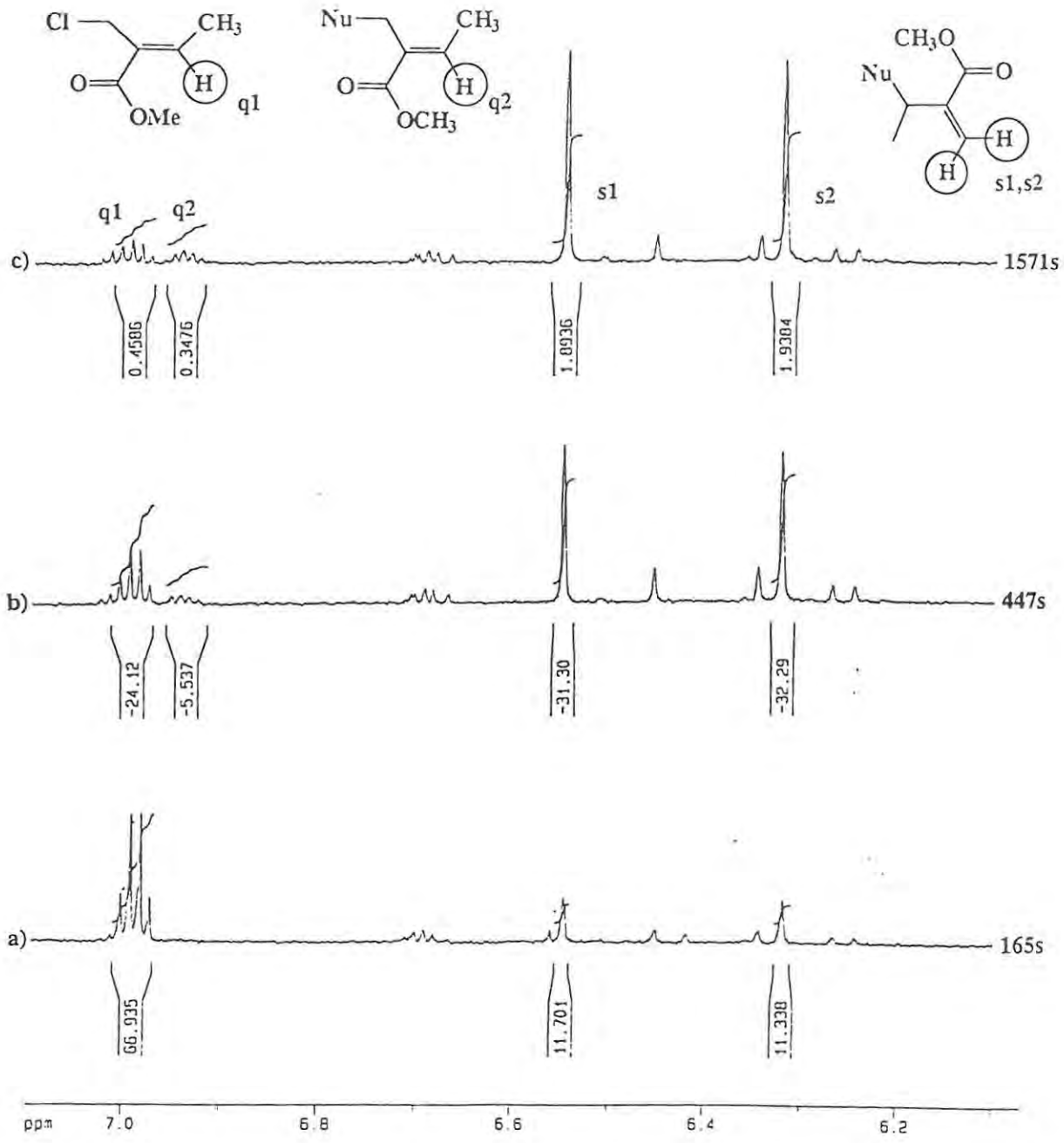


Figure 38 **Partial 400 MHz ^{1}H NMR spectra for the reaction between methyl (*Z*)-2-(chloromethyl)-2-butenoate (197) (0.02324 M) and methyl 2-methyl-3-oxobutanoate (201) (0.07024 M) in methanol-d_4 after the indicated reaction times.**

2.3.4 Kinetic studies of reactions in methanol

The reactions were followed by integrating the relevant signals in the region, δ 6.0-7.2 ppm. The signals in this region are due to the vinyl hydrogen of the unsaturated halogenoester [a quartet at *ca.*, 7.15 ppm **(q1)**], the corresponding signal for the "type A" product [a quartet at *ca.*, 7.0 ppm **(q2)**] and vinyl protons of the "type B" [broad singlets at *ca.*, 5.9 and 6.3 ppm **(s1 and s2)**], as illustrated in **Figure 39**.

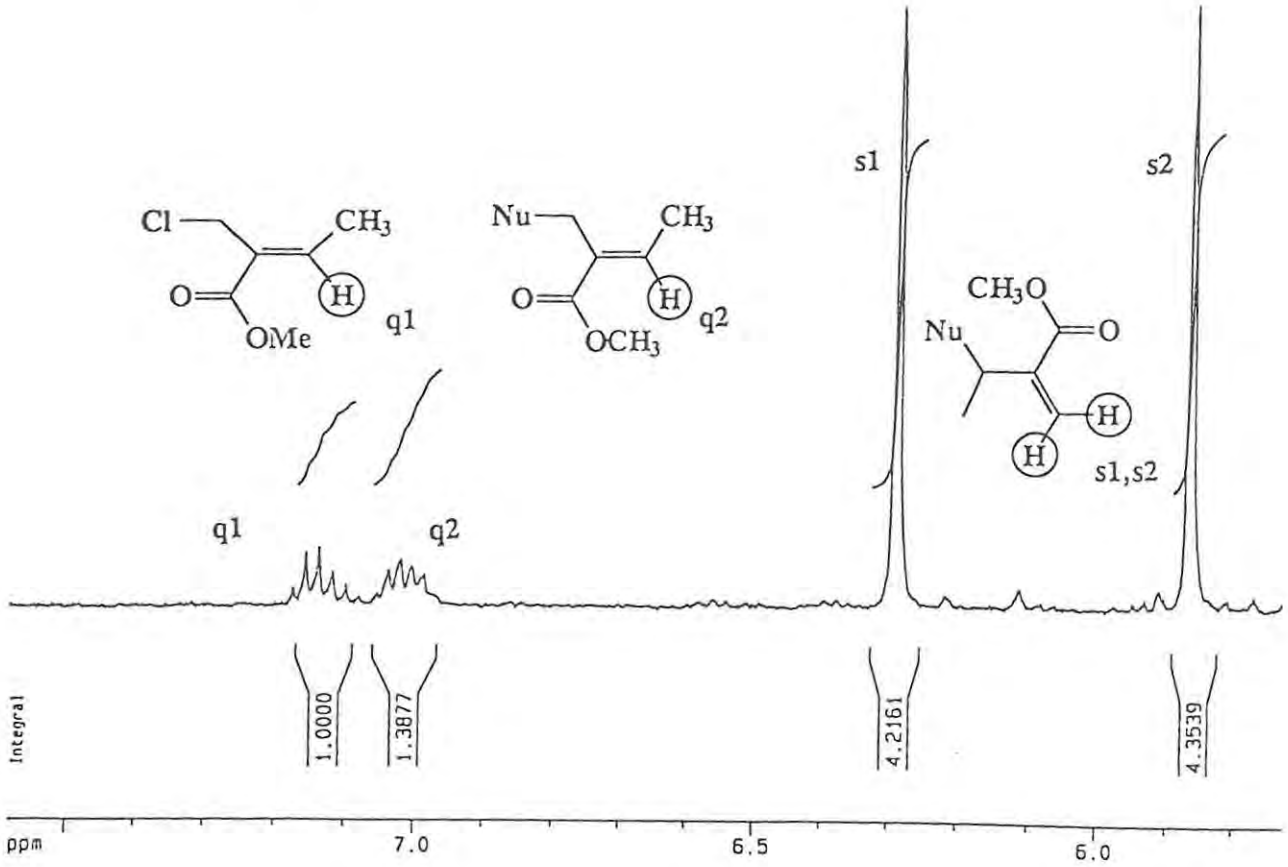


Figure 39 **Partial ^{1}H NMR spectrum showing the product spread for the reaction between methyl (Z)-2-(chloromethyl)-2-butenoate (197) (0.02324 M) and methyl 2-methyl-3-oxobutanoate (201) (0.07024 M) in methanol-d_4.**

The data collected from a typical kinetic run is illustrated in **Table 19**. The integrals for **s1** and **s2** were averaged and the individual integral ratios, *viz.*, **Q1**, **Q2** and **S** were calculated as proportions of the sum of the integrals, for example,

$$Q_1 = \frac{q1}{q1 + q2 + (s1 + s2)/2}$$

The reaction profile corresponding to the data in Table 19 is illustrated in **Figure 41**.

Table 19. Kinetic data for the reaction of methyl (*Z*)-2-(bromomethyl)-2-butenoate **(198)**(0.00544 M) and methyl 2-methyl-3-oxobutanoate **(201)** (0.02167 M) in CD_3OD at 303 K (Experiment M-5)

Run	q1	q2	s1	s2	Mean (s1,s2)	Time/s	Total	Q1	Q2	S
100	1	0	0.1748	0.1694	0.1721	238	1.1721	0.8532	0	0.1491
101	1	0	0.5623	0.5757	0.569	766	1.569	0.6374	0	0.3584
102	1	0.1164	0.9857	0.9915	0.9886	1294	2.105	0.4756	0.5529	0.4683
103	1	0.2241	1.3005	1.3005	1.3248	1822	2.5489	0.3923	0.0879	0.5102
104	1	0.2355	1.7502	1.7621	1.7561	2350	2.9917	0.3343	0.0787	0.5851
105	1	0.3467	2.1568	2.2101	2.1835	2878	3.5301	0.2833	0.0982	0.6109
106	1	0.3986	2.5157	2.5932	2.5544	3406	3.9535	0.2529	0.1008	0.6364
107	1	0.4895	2.8523	2.9352	2.8937	3934	4.3833	0.2281	0.1117	0.6507
108	1	0.5791	3.2993	3.3808	3.3400	4462	4.9192	0.2033	0.1178	0.6707
109	1	0.7061	3.6535	3.7386	3.6960	4990	5.4022	0.1851	0.1307	0.6763
110	1	0.7579	4.1288	4.2265	4.1777	5518	5.9355	0.1685	0.1277	0.6956
111	0.419	0.329	1.9523	1.9523	1.9428	6046	2.6908	0.1557	0.1223	0.7185

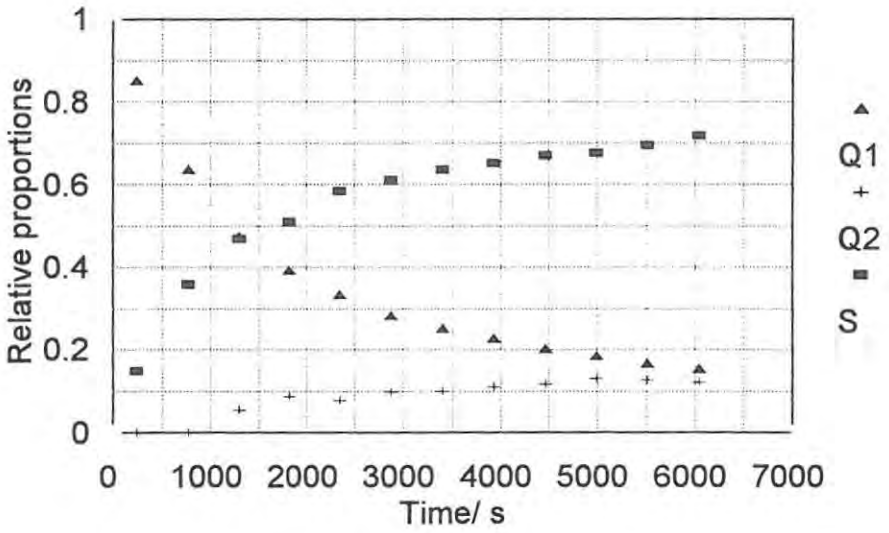
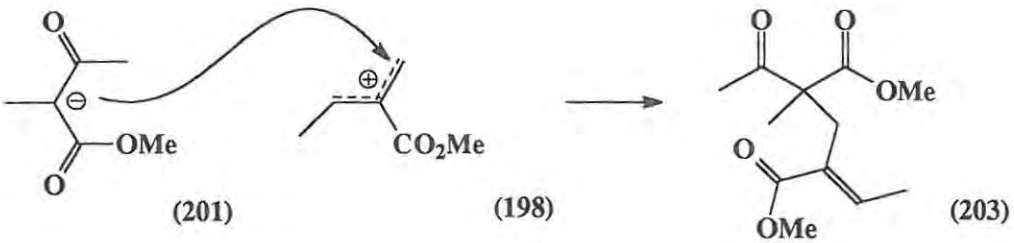


Figure 40 **Kinetic data for the reaction of methyl (*Z*)-2-(bromomethyl)-2-butenoate (198)(0.00544 M) and methyl 2-methyl-3-oxobutanoate (201) (0.02167 M) in CD_3OD at 303 K (Experiment M-5).**

Since reactions involving the base-solvent system, NaOMe-CD_3OD favour "type A" products, it was assumed that an S_N1 type mechanism would be followed[99] **(Scheme 66)** However when a first-order graph was plotted using the kinetic data, a curved line was obtained (!) Zero- and second- order plots also failed to afford straight lines, indicating a more complex reaction pathway than anticipated. A number of kinetic runs using different substrates afforded similar results.



Scheme 66

In order to establish initial rates, more data points in the early stages of the reaction were

required. This necessitated reducing the reaction rate and, to this end, the reactant concentrations were lowered still further by decreasing the concentration of the nucleophile by 50% At these low nucleophile concentrations (*ca.* 0.0077 **M**), however, it was noted that the reaction became unpredictable, and in some cases, ceased after a short period. This pattern has been observed on occasions, even at higher concentrations, but was much more marked in more dilute solutions. It was assumed that this was due to small quantities of moisture in the reaction mixture. Consequently, in addition to ensuring that all the glassware, NMR tubes and syringes were oven dried and stored in desiccators prior to use, all the reagents were stored over molecular sieves (3Å) and the deuterated methanol was freshly distilled, prior to use, from a small quantity of sodium metal in a small, flame/ vacuum dried cold-cup apparatus. These precautions were marginally successful, but it was found that some of the reactions were still being quenched prematurely (see, for example, **Figure 41**).

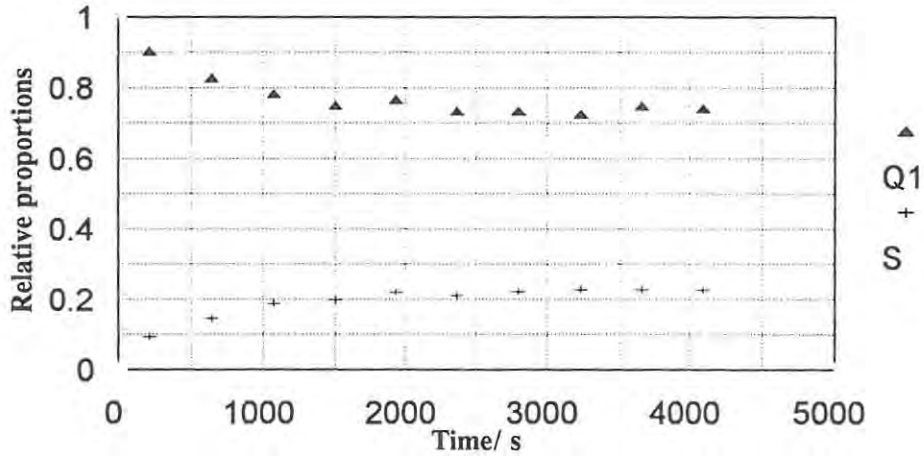


Figure 41 **Kinetic data for the reaction of methyl (*Z*)-2-(bromomethyl)-2-butenoate (198) (0.01544 M) and methyl 2-methyl-3-oxobutanoate (0.01625 M) in methanol-d_4 (Experiment M-7).**

Given the time constraints, the difficulties in obtaining reproducible, quantitative data for dilute solutions and the obvious complexity of the transformations involved, it was decided to follow a qualitative approach. From earlier studies[99] it had been established that, in ethanol, the "type A" product is favoured. However, from our NMR data the formation of a product with two vinyl protons was evident (resonating at *ca.*, 5.9 and 6.3 ppm), while the vinyl quartet corresponding to the "type A" product appeared to be still minimal. In certain kinetic experiments, the NMR tube was placed back into the NMR probe on the following day, and it was observed that the product distribution had changed dramatically (**Figure 42**), with the expected "type A" product being predominant. In fact, the relative proportions of the products were comparable to those obtained by Ameer[99] (*i.e.* type A: type B:: 83:17). The change in product distribution with time is graphically illustrated in **Figure 42**.

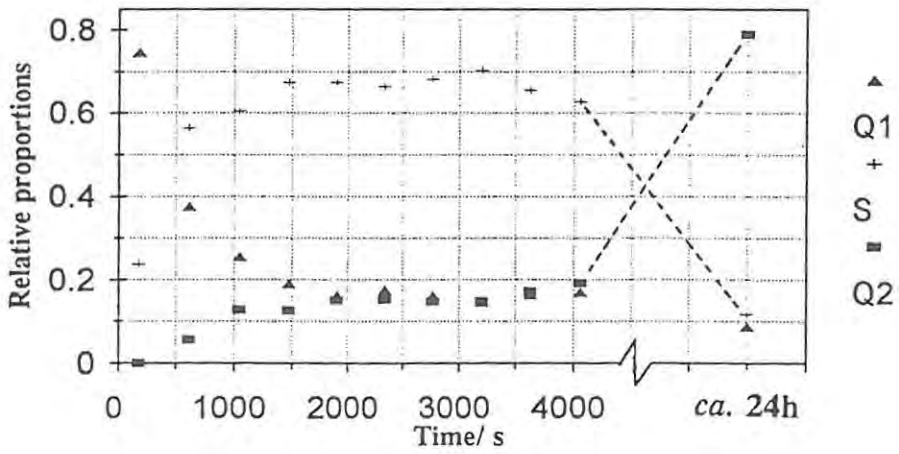


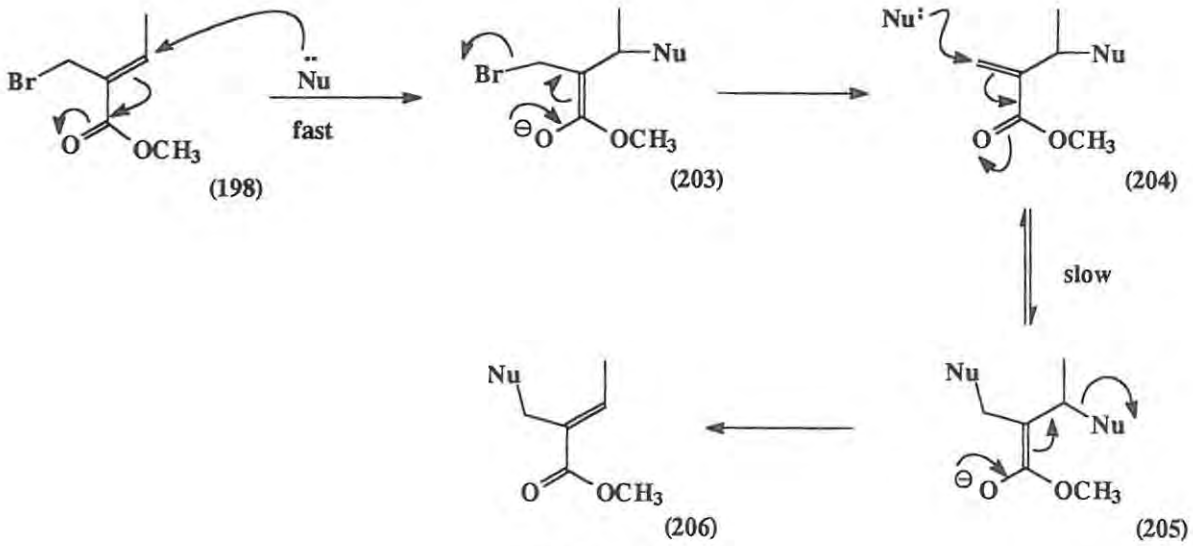
Figure 42 **Graph of the reaction between methyl (*Z*)-2-(bromomethyl)-2-butenoate (198) (0.0039 M) and methyl 2-methyl-3-oxobutanoate (201) (0.02167 M) in methanol-d_4, showing the change in product ratios after *ca.* 24h (Experiment M-9).**

For elucidating the initial rates of reaction the initial stages of the reaction are, obviously, of crucial importance. However, even at low concentrations, the reaction is still rather fast and the techniques used did not permit further dilution of the reagents.

These observations may be tentatively accommodated by the mechanism outlined in **Scheme 67,** involving two addition-elimination sequences. In the first, which is considered to be rapid, a "type B" product **(204)** is formed, which is characterised by *two* vinyl proton signals. In the second, and much slower, addition-elimination sequence, a further molecule of the nucleophile attacks the intermediate **(204)**, with subsequent formation of the expected "type A" product **(206)**. This mechanism, which involves consecutive reactions, would clearly account for :- i) initial formation of a "type B" product **(204)**,

ii) final predominance of the "type A" product **(206)**; and

iii) the observed complexity of the reaction kinetics.



Scheme 67

2.3.5 Kinetic studies of reactions in THF

The data acquired from the kinetic runs in THF were treated in the same fashion as the data for reactions in methanol, and a typical reaction profile is illustrated in **Figure 43**. Although the reactions were characterised by smooth transformation to the "type A" and "type B" products, the data again failed to give zero-, first-, or second-order kinetic plots. Nucleophilic attack is more likely at the less hindered sp^2 vinylic carbon, C(3), as opposed to the more sterically hindered sp^3 allylic carbon, C(3'). If such attack at C(3) is concomitant with loss of the halide ion, the reaction would be bimolecular (*i.e.* S_N2'), which is more likely in THF than in the more polar methanol. However, the fact that second-order kinetics are not followed suggests a more complex mechanism, such as the addition-elimination sequence outlined in **Scheme 68**, in which both steps are kinetically significant.

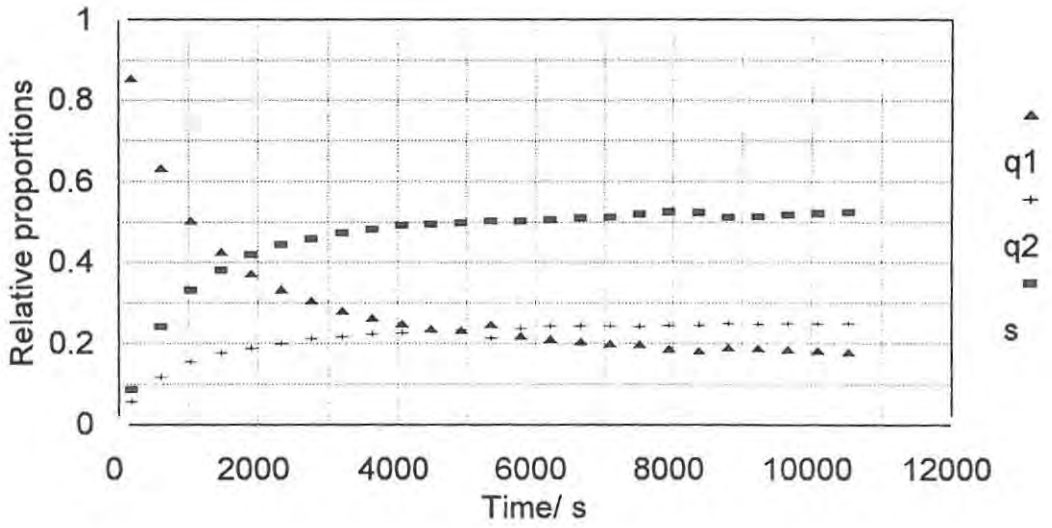
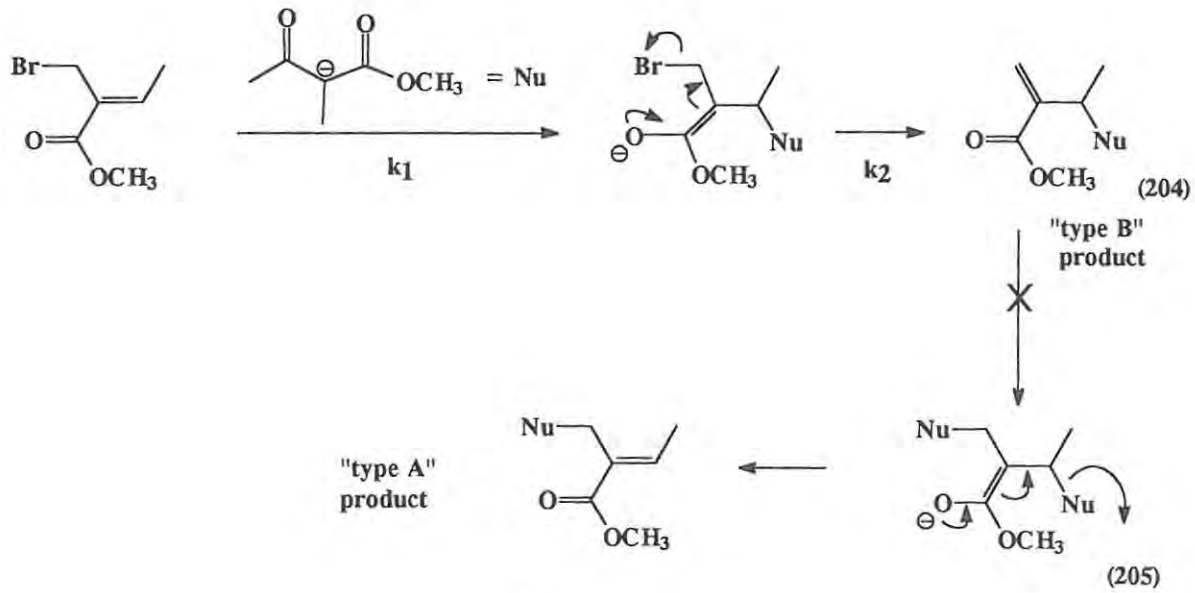


Figure 43 **Graph of the reaction between methyl (*Z*)-2-(bromomethyl)-2-butenoate (198) (0.0232 M) and methyl 2-methyl-3-oxobutanoate (201) (0.03657) in THF (Experiment T-3).**

In the less polar solvent (THF) and in the absence of the halide leaving group, the second

addition-elimination sequence observed in methanol is inhibited and the "type B" product **(204)** predominates.

From our kinetic studies, it is thus apparent that, irrespective of whether the solvent is THF or CD_3OD, the reactions do not follow a simple S_N1 or S_N2' mechanism as postulated previously. In fact, it appears that the "type B" product is formed in *both* solvents but, *in the more polar CD_3OD*, subsequent allylic displacement of the nucleophile results in predominance of the "type A" product in this solvent. Thus, we propose that the regioselectivity switch observed when the solvent is changed does not reflect a change in mechanism, but rather inhibition of the second addition-elimination sequence in the less polar solvent, THF **(Scheme 68)**.



Scheme 68

2.4 CONCLUSION

The initial aims of the study, *viz.*, to explore the generality of the Baylis-Hillman approach to the synthesis of coumarin derivatives, and to elucidate the mechanistic basis of this transformation and the regioselective nucleophilic substitution reactions of Baylis-Hillman derivatives have all been achieved.

It was found that reaction of salicylaldehydes with methyl acrylate in the presence of DABCO gave 3-[(2-formylphenoxy)methyl]coumarins with only two substrates, 5-chlorosalicylaldehyde and salicylaldehyde itself; optimisation of the reaction conditions permitted isolation of the parent coumarin in up to 50% yield. In all cases, however, complex mixtures were obtained, careful chromatography of which revealed the formation of *eight* distinct product types including *both* coumarin and chromene type compounds, and mechanistic pathways have been proposed to account for the formation of all these compounds.[139a,b] In addition to the coumarin and chromene derivatives, a number of quaternary DABCO "salts" were also isolated; these "salts" are believed to play an important role in the formation of many of the compounds isolated from the reactions, with DABCO acting as a demethylating and deacetylating agent. High field one- and two-dimensional NMR spectroscopy and X-ray crystallography were used to elucidate the structures of the various products.

The research into the synthesis of coumarin and chromene derivatives, *via intramolecular* cyclisation, was extended to an *intermolecular* study in which "free" nucleophiles (pyrrolidine, piperidine, thiophenol and phenol) were reacted with Baylis-Hillman products to assess the regioselectivity and stereoselectivity of nucleophilic attack. The results show that the reactions are, in fact, highly regioselective, affording only conjugate addition products; however, only modest levels of stereoselectivity (5-57% d.e.) were realised. This study has also indicated the possibilities of incorporating other heteroatoms, such as nitrogen and sulfur, in Baylis-Hillman approaches to thia- and aza- coumarin and chromene

analogues.

The kinetic study of the regioselectivity of the reaction between various halogenoesters and the nucleophile, methyl 2-methyl-3-oxobutanoate, was carried out using two different solvent/base systems, *viz*, NaOMe-CD_3OD and NaH-THF-d_8. The results from these studies show that the reaction mechanism is, in fact, considerably more complex than anticipated as the data do not fit the expected unimolecular or bimolecular kinetics. In addition isomerisation also appears to be taking place. The observed regioselectivity can be explained, however, in terms of an inhibition of the second addition-elimination sequence in the less polar THF.

While the initial and developing objectives have been addressed various possibilities for future research have been identified; these include the following:-

i) the potential for DABCO as a more general demethylating agent;

ii) the Baylis-Hillman zwitterion as a possible Michael nucleophile;

iii) control of chromene and coumarin product formation with the aim of establishing synthetically useful procedures; and

iv) application of the Baylis-Hillman approach to the synthesis of aza and thia analogues of chromene and coumarin derivatives.

3. EXPERIMENTAL

3.1 GENERAL

Melting points were determined using a Kofler hot-stage apparatus and are uncorrected. NMR spectra were run on a Bruker AMX400 or a Perkin-Elmer R12A spectrometer, and chemical shifts (δ) are expressed in parts per million (ppm). NMR samples were, in most cases, dissolved in $CDCl_3$, CD_3OD or THF-d_8. Spectra recorded in $CDCl_3$ were calibrated using the solvent signal at 7.25 ppm for ^1H and 77.0 ppm for ^{13}C, while ^1H spectra run in THF-d_8 and in CD_3OD were calibrated using the solvent signals at 1.72 ppm and 3.31 ppm respectively. IR spectra were recorded on a Perkin-Elmer 180 spectrometer using KBr disks or liquid films. Low resolution mass spectra were obtained on a Hewlett Packard 5988A mass spectrometer and high-resolution mass spectra on a Kratos MS 80RF double focusing magnetic sector spectrometer (Cape Technikon Mass Spectrometry Unit).

Semi-preparative GLC separations were achieved on a Perkin-Elmer 900 gas chromatograph using flame ionisation detection and a 1 x 250 cm semi-preparative column packed with 10% OV-225. Semi-preparative HPLC separations were achieved using a Spectra-Physics P100 HPLC with a Spectra Physics UV100 detector set to 275 nm, and a 250 x 10 mm Spherisorb S5W normal phase column. Flash chromatography[140,141] was carried out using Merck Silica gel 60 [particle size 0.040-0.063 mm (230-400 mesh)], while preparative layer chromatography[142] was effected on glass plates coated with Merck Silica gel PF_{254}. Thin layer chromatography (TLC) was performed using precoated Merck Silica gel F_{254} plates, with visualization 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 the procedures described by Perrin and Armarego.[143] Thus, THF was dried over sodium wire, and distilled from the sodium using benzophenone

as an indicator; DMF was distilled under N_2 from 3Å molecular sieves;[144,145] dichloromethane was distilled from CaH_2; and methanol was distilled from magnesium methoxide, generated *in situ* by reacting methanol with magnesium turnings in the presence of iodine.

3.2 PREPARATIVE PROCEDURES

3.2.1 Optimisation of 3-[(2-formylphenoxy)methyl]coumarin (132a) formation

Methyl acrylate or ethyl acrylate was reacted with freshly distilled salicylaldehyde and DABCO under an atmosphere of dry N_2, in ten different reactions, under a variety of molar ratio's and and reaction conditions as shown in **Table 11, p. 50**, following which 3-[(2-formylphenoxy)methyl]coumarin **(132a)** was purified by filtration or flash chromatography (elution with $CHCl_3$), and the reaction yields were determined from the mass of the isolated components.

3.2.2 Preparation of salicylaldehyde derivatives

Preparation of 5-nitrosalicylaldehyde (129h) and 3-nitrosalicylaldehyde (129g)[113]

Fuming HNO_3 (4.0 ml) was added dropwise, to a stirred solution of salicylaldehyde (4.93 ml, 150 mmol) and glacial acetic acid (18.9 ml) in a round-bottomed flask, fitted with a thermometer, a reflux condenser and a pressure equalising dropping funnel, keeping the reaction temperature below 15°C by cooling, when necessary, in ice. After addition of the fuming HNO_3, the temperature of the reaction mixture was allowed to rise to 40-45°C and the mixture was then left to cool to room temperature. The mixture was then poured on to crushed ice (*ca.* 20 g), and the resulting slurry filtered to yield a yellow powder, which was shown by ^1H NMR spectroscopy to be a mixture of 5-nitrosalicylaldehyde **(129h)** [δ_H (400 MHz; $CDCl_3$) 7.12 (1H, d, Ar-H), 8.39 (1H, dd, Ar-H), 8.56 (1H, d, Ar-H), 10.02 (1H, s, CHO) and 11.60 (1H, s, Ar-OH)] and 3-nitrosalicylaldehyde **(129g)** {δ_H (400 MHz; $CDCl_3$) 7.12 [(overlapping)1H, d, Ar-H], 8.11 (1H, dd, Ar-H), 8.33 (1H, dd, Ar-H), 10.40 (1H, s, CHO) and 11.42 (1H, s, Ar-OH)} in a ratio of 2:1 (7.32 g, 93%). Attempts to separate the regioisomers using flash chromatography or by

forming the bisulfite addition product[113] with the 5-nitrosalicylaldehyde **(129h)** isomer proved unsuccessful.

Attempted preparation of 6-chlorosalicylaldehyde (129i) and 4-chlorosalicylaldehyde(129j)[114]

3-Chlorophenol (5.0 g, 39 mmol), $SnCl_4$ (1.02 g, 3.9 mmol) and tributylamine (2.10 g, 15.6 mmol) in dry *N,N*-dimethylformamide (8.0 ml) were stirred in a two-necked flask fitted with a thermometer and a reflux condenser attached to an N_2 line for 20 min. Paraformaldehyde (2.64 g, 86.0 mmol) was then added, and the resulting mixture heated at 100°C for 8h. On cooling, the reaction mixture was poured into water and the pH adjusted to pH 2 with 2N HCl, before extracting with diethyl ether. The ethereal extract was washed with saturated brine and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded only starting material.

Attempted preparation of salicylaldehyde (129a)[114]

Phenol (0.376 g, 4.0 mmol), $SnCl_4$ (1.25 g, 5.54 mmol) and tributylamine (2.96 g, 15.9 mmol) in dry toluene (8 ml) were stirred for 20 minutes in a flask fitted with a reflux condenser attached to an N_2 line. Paraformaldehyde (2.64 g, 88.0 mmol) was then added to the reaction mixture which was heated at 100°C for 8h. On cooling, the reaction mixture was poured into water and the pH adjusted to 2 with 2N HCl, before extracting into diethyl ether. The ethereal extract was washed with saturated brine and dried ($MgSO_4$). Removal of the solvent *in vacuo* afforded only starting material.

Preparation of acetylthiosalicylic acid (133c)[146]

Acetyl chloride (0.64 ml, 9.0 mmol) was added dropwise to a stirred solution of thiosalicylic acid (1.0 g, 6.5 mmol) and dry pyridine (0.63 ml), maintaining the temperature of the mixture between 50-60°C by cooling, when necessary, in ice. The mixture was then heated for 5 min on a water bath and then allowed to cool, following

which the mixture was quenched with water (30 ml), which resulted in the precipitation of pale yellow crystals. The crystals were filtered off and washed with cold water (3 x 10 ml). The crude product was then recrystallised [glacial acetic acid and water (1:1)] to afford acetylthiosalicylic acid **(133c)** (1.0 g, 79%); ν_{max}(KBr)/cm^{-1} 1647, 1708 and 3000 br; δ_H (400 MHz; $CDCl_3$) 2.44 (3H, s, $COCH_3$), 7.50 (1H, m, Ar-H), 7.58 (2H, m, Ar-H) and 8.08 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 30.3 ($COCH_3$), 129.4, 131.8, 132.6, 132.7 and 136.7 (Ar-C) and 170.9 (*C*OOH); *m/z* 196 (M^+, 3.8%) and 136 (100%).

Preparation of acetylsalicylic acid (133d)[146]

Salicylic acid (2.0 g, 14.5 mmol) was dissolved in dry pyridine (1.4 ml), followed by the dropwise addition of acetyl chloride (1.5 ml, 21.0 mmol). The resulting mixture was then heated on a waterbath for 5 min, cooled to room temperature with vigorous stirring and water (30 ml) was added, during which a white precipitate formed. Filtration of the reaction mixture afforded, as a white solid acetyl salicylic acid **(133d)** (2.21 g, 85%); ν_{max}(thin film)/cm^{-1} 1689 and 3500; δ_H (400 MHz; $CDCl_3$) 2.44 (3H, s, $COCH_3$), 7.45-7.6 (3H, m. Ar-H) and 8.1 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 30.1 ($COCH_3$), 129.4, 131.8, 132.6 and 136.7 (Ar-C), 170.9 ($COCH_3$) and 193 (*C*OOH).

Preparation of acetylthiosalicylic acid chloride (134a)[147]

Method 1: Oxalyl chloride (2.67 ml; 30.6 mmol) was added dropwise *via* a pressure equalising dropping funnel to a stirred solution of acetylthiosalicylic acid **(133c)** (3.0 g, 15 mmol) in dry benzene (45 ml), in a round-bottomed flask fitted with a reflux condenser attached to an N_2 line. The resulting mixture was gently boiled under reflux for 1.5h. The benzene and unreacted oxalyl chloride were removed *in vacuo* to afford a crude product (2.5 g), which was shown by ^{1}H NMR and infrared spectroscopy to contain some starting material. The starting material was removed by eluting the mixture through a silica bed (5 cm bed; elution with chloroform). The solvent was then removed from the eluant *in vacuo* to afford acetylthiosalicylic acid chloride **(134a)** (1.7g, 52%);

ν_{max}(thin film)/cm^{-1} 1726 and 1877.[¶]

Method 2:[148] Thionyl chloride (0.88 ml, 12 mmol) was added dropwise to a stirred mixture of acetylthiosalicylic acid **(133c)** (1.5g, 0.76 mmol), 1,2-dichloroethane (12.0 ml) and *N,N*-dimethylformamide (0.18 ml, 2.3 mmol) in a three-necked flask fitted with a thermometer, a pressure equalising dropping funnel and a reflux condenser attached to an N_2 line. The resulting mixture was boiled under reflux for 1h, following which the solvents were removed *in vacuo* to afford acetylthiosalicylic acid chloride**(134a)** (1.4 g, 86%).

Preparation of bis(triphenylphosphine)copper(I) tetrahydroborate (135)[115-117] Hydrated $CuSO_4$ (16.0 g, 64.0 mmol) was added to a stirred solution of triphenyl phosphine (54.0 g, 200 mmol) in ethanol (1.4 L) in a 2 litre round-bottomed flask attached to an N_2 line. After 1h, sodium borohydride (12.0 g,0.31 mol) was added resulting in a milky-white dispersion. The precipitate was collected by filtration and re-dissolved in chloroform (400 ml).Insoluble material was filtered off and the product was precipitated from the filtrate by the addition of diethyl ether (*ca.* 500 ml) and filtered off to afford bis(triphenylphosphine)copper(I) tetrahydroborate **(135)** (34.2 g, 89%); m.p. 175-177 °C (lit.[116] 174-176 °C); ν_{max}(KBr)/cm^{-1} 2375 and 2010.

Attempted preparation of acetylthiosalicylaldehyde (151d)

Bis(triphenylphosphine)copper(I) tetrahydroborate **(135)** (4.82 g, 8.0 mmol) was added to a stirred solution of acetylthiosalicylic acid chloride **(134a)** (1.71 g, 8.0 mmol) and triphenyl phosphine (4.19 g, 16.0 mmol) in dry acetone (100 ml; distilled from 4Å molecular sieve) under an atmosphere of dry N_2. After stirring for 2h, the reaction

[¶] Rapid decomposition of the acid chloride did not permit NMR spectroscopy of the product; however, product formation was supported by the loss of the acid hydroxyl band and the presence of a carbonyl band at 1786 cm^{-1} in the infrared spectrum.

mixture was filtered and washed several times with diethyl ether. The combined organic extracts were concentrated *in vacuo* and re-dissolved in chloroform. Finely powdered copper(I) chloride (1.2 g) was added to the solution and the mixture was stirred for 30 min, before being filtered and concentrated *in vacuo* to afford a thick dark oil, which was shown by ^{1}H NMR spectroscopy to be a complex mixture of products not containing any of the desired product.[§]

Preparation of acetyl salicylaldehyde (151a)[115,116]

Bis(triphenylphosphine)copper(I) tetrahydroborate **(135)** (4.28 g, 8.0 mmol) was added to a stirred solution of acetylsalicylic acid chloride **(134b)** (1.41g, 7.1 mmol) and triphenyl phosphine (3.73 g, 14 mmol) in dry acetone (*ca.* 40 ml; distilled from 4Å molecular sieve). After 1h, the resulting precipitate was filtered, washed with diethyl ether and the combined washings were concentrated *in vacuo* and the resulting residue was redissolved in methanol (60 ml). Diethyl ether was then added to the methanolic solution resulting in the formation of a precipitate which was subsequently filtered to afford acetyl salicylaldehyde **(151a)** (0.26 g, 22%); ν_{max}(thin film)/cm^{-1} 1700; δ_H (400 MHz; $CDCl_3$) 2.30 (3H, s, $COCH_3$), 7.17 (1H, d, Ar-H), 7.37 (1H, t, Ar-H), 7.60 (1H, t, Ar-H), 7.86 (1H, d, Ar-H) and 10.1 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 20.7 ($COCH_3$), 123.4, 126.4, 128.0, 131.2, 135.2 and 151.4 (Ar-C), 169.1 ($COCH_3$) and 188.7 (CHO).

[§]Repeated attempts to obtain the desired product by this method proved unsuccessful.

3.2.3 Baylis-Hillman reactions of substituted salicylaldehydes

3.2.3.1 General procedure

A mixture of the substituted salicylaldehyde, the α,β-unsaturated system and DABCO were left to stand at room temperature, under an atmosphere of dry N_2, for a period of between 1 week and 1 month. The progress of the reaction was monitored by ^{1}H NMR spectroscopy and TLC and after consumption of the substituted salicylaldehyde was complete, the reaction products were separated using flash chromatograpy. Further purification was, when necessary, carried out using preparative layer chromatography. Reaction yields were determined by ^{1}H NMR spectroscopy prior to chromatography (see **Section 2.1.5**).

3.2.3.1.1 Reactions with salicylaldehyde

Following the general procedure, salicylaldehyde (0.70 ml, 6.6 mmol), methyl acrylate (0.63 ml, 7.0 mmol) and DABCO (0.187 g, 1.67 mmol) afforded, after flash chromatography (elution with $CHCl_3$), the following four products :-

i) Methyl 2*H*-1-benzopyran-3-carboxylate[149] (131a) (13%)

(Found: M^+, 190.0618. Calc. for $C_{11}H_{10}O_3$ *M*, 190.0630); ν_{max}(thin film)/cm^{-1} 2840 and 1700; δ_H (400 MHz; $CDCl_3$) 3.98 (3H, s, OCH_3), 4.99 (2H, d, 2-CH_2), 6.83 (1H, d, 8-H), 6.91 (1H, dd, 6-H), 7.12 (1H, m, 5-H), 7.22 (1H, dd, 7-H) and 7.42 (1H, br s, 4-H); δ_C (100 MHz; $CDCl_3$) 51.9 (OCH_3), 64.5 (C-2), 116.1 (C-6), 120.9 (C-4a), 121.8 (C-7), 122.4 (C-3), 128.9 (C-5), 132.0 (C-8), 133.7 (C-4). 115.2 (C-8a) and 165.0 (C=O); *m/z* 190 (M^+, 0.33%) and 136 (100%).

ii) 3-[(2-Formylphenoxy)methyl]coumarin (132a)[109](18%)

ν_{max}(thin film)/cm^{-1} 1715 and 1670; δ_H (400 MHz; $CDCl_3$) 5.15 (2H, s, CH_2O), 7.08-7.11 (2H, m, Ar-H), 7.32-7.39 (2H, m, Ar-H), 7.53-7.58 (3H, m, Ar-H), 7.87 (1H, dd, Ar-H), 7.97 (1H, s, Ar-H) and 10.60 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 65.2 (CH_2O), 112.8, 116.8, 118.7, 121.6, 124.0, 124.9, 125.2, 128.1, 129.6, 131.8, 136.2, 139.4, 153.3 and 160.1 (Ar-C), 160.2 (C=O) and 189.4 (CHO).

iii) The quaternary (3-coumaryl)methyl DABCO salt (156)[104]

δ_H (400 MHz; D_2O) 3.22 [6H, m, $(CH_2)_3N$], 3.54 [6H, m, $(CH_2)_3N^+$], 4.47 (2H, s, CH_2), 7.48 (2H, m, Ar-H), 7.76 (2H, m, Ar-H) and 8.39 (1H, s, 4-H); δ_C (100 MHz; D_2O) 46.9 (CH_2N), 54.9 (CH_2N^+), 65.3 (CH_2), 116.7, 119.2, 120.9, 128.2, 132.0, 136.9 and 155.2 (Ar-C, C-3 and C-4) and 165.9 (C=O); *m/z* 271 (M^+, 3.2%) and 159 (100%).

iv) ***The zwitterionoic 3-(DABCO)propanoate salt*** **(172)**

δ_H (400 MHz; D_2O) 2.78 (2H, t, 2-CH_2), 3.29 [6H, m, $(CH_2)_3N$], 3.50 [6H, m, $(CH_2)_3N^+$] and 3.62 (2H, t, 3-CH_2); δ_C (100 MHz; D_2O) 32.6 (C-2), 46.9 [$(CH_2)_3N$], 54.8 [$(CH_2)_3N^+$], 64.2 (C-3) and 179.1 (C=O); *m/z* 184 (M^+, 0.24%) and 57 (100%).

Following the general procedure, salicylaldehyde (1.75 g, 14.3 mmol), methyl vinyl ketone (1.01 g, 14.3 mmol) and DABCO (0.32 g, 2.9 mmol) afforded, after flash chromatography (elution with $CHCl_3$), the following product :-

3-Acetoxy-2*H*-1-benzopyran (131k)[121,150](28%)

(Found: M^+, 174.0670. Calc. for $C_{11}H_{10}O_2$ *M*, 174.0681); ν_{max}(thin film)/cm^{-1} 1698; δ_H (400 MHz; $CDCl_3$) 2.34 (3H, s, $COCH_3$), 4.97 (2H, d, CH_2), 6.82 (1H, d, 8-H), 6.91 (1H, dd, Ar-H), 7.13 (1H, m, Ar-H) 7.21 (1H, m, Ar-H) and 7.22 (1H, br s, 4-H); δ_C (100 MHz; $CDCl_3$) 24.9 (CH_3), 64.1 (C-2), 116.2 (C-6), 120.6 (C-4a), 121.7 (C-7),

129.1 (C-5), 130.6 (C-3), 132.4 (C-8), 133.9 (C-4), 155.5 (C-8a) and 195.9 (C-1'); *m/z* 174 (M^+, 67.6%) and 131 (100%).

Following the general procedure, salicylaldehyde (1.75 g, 14.3 mmol), acrylonitrile (0.76 g, 14 mmol) and DABCO (0.32 g, 2.9 mmol) afforded after, flash chromatography (elution with dichloromethane), the following product :-

3-Cyano-2*H*-1-benzopyran (131l)[121,150](12%)
(Found: M^+, 157.0541. Calc. for $C_{10}H_7ON$ ***M***, 157.0526); δ_H (400 MHz; $CDCl_3$) 4.90 (2H, d, CH_2), 6.97 (1H, d, 8-H), 7.07 (1H, dd, 6-H), 7.19 (1H, dd, 5-H), 7.25 (1H, br s, 4-H) and 7.38 (1H, dd, 7-H); δ_C (100 MHz; $CDCl_3$) 64.1 (C-2), 103.2 (C-4a), 116.2 (C-3), 116.4 (C-8), 119.9 (C≡N), 122.3 (C-5), 128.3 (C-7), 132.6 (C-6), 138.6 (C-4) and 154.1 (C-8a); *m/z* 157 (M^+, 89%) and 156 (100%).

3.2.3.1.2 Reaction with 5-chlorosalicylaldehyde:-

Following the general procedure, 5-chlorosalicylaldehyde (1.0 g, 6.4 mmol), methyl acrylate (3.0 ml, 33 mmol) and DABCO (0.27 g, 2.6 mmol) afforded, after flash chromatography (elution with $CHCl_3$), the following seven products :-

i) Methyl 6-chloro-2*H*-1-benzopyran-3-carboxylate (131b)[151](17%)
(Found: M^+, 224.0239. Calc. for $C_{11}H_9O_3{}^{35}Cl$: ***M***, 224.0230); ν_{max}(KBr)/cm^{-1} 1712 and 2350; δ_H (400 MHz; $CDCl_3$) 3.79 (3H, s, OCH_3), 4.96 (2H, d, CH_2), 6.74 (1H, d, 8-H), 7.06 (1H, d, 5-H), 7.13 (1H, dd, 7-H) and 7.31 (1H, br s, 4-H); δ_C (100 MHz; $CDCl_3$) 52.0 (OCH_3), 64.6 (C-2), 117.4 (C-8), 122.1 (C-4a), 123.6 (C-3), 126.5 (C-6), 128.1 (C-5), 131.4 (C-7), 132.3 (C-4), 153.6 (C-8a) and 164.6 (C=1); *m/z* 224 (M^+, 7%) and 149 (100%).

ii) ***6-Chloro-3-[(4-Chloro-2-formylphenoxy) methyl]coumarin*** **(132b)** (14%) (Found: M^+, 347.9949 $C_{17}H_{10}O_4{}^{35}Cl_2$ requires *M*, 347.9956); ν_{max}(KBr)/cm^{-1} 1725 and 1640; δ_H (400 MHz; $CDCl_3$) 5.12 (2H, s, CH_2), 7.04 (1H, d, Ar-H), 7.32 (1H, d, Ar-H), 7.49-7.56 (3H, m, Ar-H), 7.83 (1H, d, Ar-H), 7.88 (1H, s, 4-H) and 10.49 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 65.4 (CH_2), 105.0, 114.5, 118.2, 119.7, 124.9, 126.1, 127.4, 127.6, 129.4, 130.3, 131.9, 125.6, 138.1 and 151.6 (C-3, C-4 and Ar-C), 158.2 (C=O) and 187.8 (CHO); *m/z* 348 [$M^+(^{35}Cl_2)$, 2.5%] and 193 (100%).

iii) ***Methyl 2-(3-carbomethoxy-6-chloro-3,4-dihydro-2H-benzopyran-4-yl)propenoate*** **(138b)** (13%)

(Found: M^+, 310.0613. $C_{15}H_{15}{}^{35}ClO_5$ requires *M*, 310.0608); ν_{max} (thin film)/cm^{-1} 1730 and 1712; δ_H (400 MHz; $CDCl_3$) 3.07 (1H, m, 3'-H), 3.70 and 3.76 (2 x 3H, 2 x s, 2 x CO_2CH_3), 4.15 and 4.38 (2H, 2 x dd, 2'-CH_2), 4.41 (1H, d, 4'-H), 5.41 (1H, br s, C=CH) and 6.47 (1H, s, C=CH), 6.77 (1H, d, Ar-H), 6.95 (1H, d, Ar-H) and 7.07 (1H, dd, Ar-H); δ_C (100 MHz; $CDCl_3$) 39.1 (C-4'), 42.6 (C-3'), 52.2 and 52.3 (2 x CO_2CH_3), 63.7 (C-2'), 130.6 (C-3), 118.3, 122.9, 125.8, 128.2, 129.4, 142.3 and 153.0 (Ar-C and C-2), 166.1 (CH_2=C-CO_2 CH_3) and 171.5 (CO_2 CH_3); *m/z* 310 [$M^+(^{35}Cl)$, 28%] and 250 (100%).

iv) ***Methyl 2-(6-chloro-3-methyl-1-benzopyran-2-on-4-yl)propenoate*** **(141b)** (17%)

(Found: M^+, 278.0340. $C_{14}H_{11}{}^{35}Cl\ O_4$ requires *M*, 278.0346); ν_{max} (thin film)/cm^{-1} 1722; δ_H (400 MHz; $CDCl_3$) 2.02 (3H, s, CH_3), 3.78 (3H, s, CO_2CH_3), 5.85 and 6.88 (2H, 2 x d, C=CH_2), 7.23 (1H, d, 5'-H), 7.26 (1H, d, 7'-H) and 7.40 (1H, dd, 8'-H); δ_C (100 MHz; $CDCl_3$) 14.7 (CH_3), 52.8 (OCH_3), 118.2, 120.9, 120.5, 125.2, 129.4, 129.6, 134.7 and 150.8 (C-3', C-4' and Ar-C), 130.7 (C-3), 144.7 (C-2), 161.2 (C-1) and 164.6 (C-2') ; *m/z* 278 [$M^+(^{35}Cl)$, 62%] and 128 (100%).

v) ***Dimethyl 2-(6-chloro-3-methyl-1-benzopyran-2-on-4-yl)-4-methylenepentanedioate*** **(142b)** (23%)

(Found: M^+, 364.0787. $C_{18}H_{17}{}^{35}ClO_6$ requires *M*, 364.0714); ν_{max} (thin film)/cm^{-1} 1715; δ_H (400 MHz; $CDCl_3$) 2.16 (3H, s, CH_3), 2.73 (1H, dd, 3-H), 3.40 (1H, ddd, 3-H), 3.68 (3H, s, 1-CO_2CH_3), 3.72 (3H, s, 5-CO_2CH_3), 4.47 (1H, dd, 2-H), 5.46 (1H, br s, C=CH) and 6.08 (1H, d, C=CH), 7.26 (1H, d, 7'-H), 7.39 (1H, dd, 8'-H) and 7.55 (1H, d, 5'-H); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 33.1 (C-3), 44.2 (C-2), 52.1 (5-$CO_2\mathit{C}H_3$), 52.7 (1-$CO_2\mathit{C}H_3$), 118.7 (C-7'), 120.0 (C-4'a), 123.8 (C-5'), 126.3 (C-3'), 129.2 (C=$\mathit{C}H_2$), 129.6 (C-8'a), 130.5 (C-8'), 135.9 (C-4), 144.9 (C-4'), 150.6 (C-6'), 161.1 (C-2'), 166.9 (5-$\mathit{C}O_2CH_3$) and 171.8 (1-$\mathit{C}O_2CH_3$); *m/z* 364 [M^+(^{35}Cl), 4.5%] and 278 (100%).

vi) ***3,4;7,8-Bis(4'-chlorobenzo)-2,6,9-trioxabicyclo[3.3.1]nonane*** **(171a)** (13%[ϕ])

(Found: C, 56.9; H, 2.6; M^+, 293.9867. $C_{14}H_8O_3{}^{35}Cl_2$ requires C, 56.9; H, 2.7%; *M*, 293.9850); ν_{max}(KBr)/cm^{-1} 1470; δ_H (400 MHz; $CDCl_3$) 6.27 (2H, s, 1-H), 6.82 (2H, d, Ar-H), 7.21 (2H, dd, Ar-H) and 7.26 (2H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 89.6 (C-1), 118.2 (C-4'), 120.9 (Ar-C), 126.8 (Ar-C), 127.2 (Ar-C), 131.3 (Ar-C) and 149.0 (C-7); *m/z* 294 [M^+(^{35}Cl), 25.8%] and 153 (100%).

vii)The zwitterionic 3-(DABCO)propanoate salt (172)

3.2.3.1.3 Reaction with 5-bromosalicylaldehyde

Following the general procedure given above, 5-bromosalicylaldehyde (1.0 g, 5.0 mmol), methyl acrylate (0.43 g, 5.0 mmol) and DABCO (0.40 g, 3.6 mmol) afforded,

[ϕ]Isolated yield.

after flash chromatography (elution with $CHCl_3$), the following six products :-

i) ***Methyl 6-bromo-2H-1-benzopyran-3-carboxylate*** **(131c)** (17%)
(Found: M^+, 267.9739. $C_{11}H_9O_3{}^{79}Br$ requires *M*, 267.9735); ν_{max}(KBr)/cm^{-1} 1700; δ_H (400 MHz; $CDCl_3$) 3.80 (3H, s, CH_3), 4.97 (2H, d, CH_2), 6.70 (1H, d, 8-H), 7.21 (1H, d, 5-H), 7.28 (1H, dd, 7-H) and 7.31 (1H, br s, 4-H); δ_C (100 MHz; $CDCl_3$) 52.0 (CH_3), 64.6 (C-2), 113.6, 117.9, 112.6, 123.5, 131.0, 132.1, 134.3 and 154.1 (C-3, C-4 and Ar-C) and 164.5 (C=O); *m/z* 268 [M^+(^{79}Br), 43%] and 253 (100%).

ii) ***Methyl 6-bromo-3,4-dihydro-4-methoxy-2H-1-benzopyran-3-carboxylate*** **(137c)** (7%)
(Found: M^+, 299.9979. $C_{12}H_{13}O_4{}^{79}Br$ requires *M*, 299.9997); ν_{max}(thin film)/cm^{-1} 1696; δ_H (400 MHz; $CDCl_3$) 3.05 (1H, m, 3-H), 3.44 (3H, s, OCH_3), 3.68 (3H, s, CO_2CH_3), 4.28 and 4.49 (2H, 2 x dd, CH_2), 4.60 (1H, d, 4-H), 6.72 (1H, d, Ar-H), 7.28 (1H, dd, Ar-H) and 7.40 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 42.8 (C-3), 52.3 (CO_2CH_3), 56.5 (OCH_3), 63.3 (C-2), 72.7 (C-4), 112.6, 118.9, 122.5, 132.6, 132.8 and 153.3 (Ar-C) and 170.6 (C=O); *m/z* 300 [M^+(^{79}Br), 49%] and 199 (100%).

iii) ***Methyl 2-(6-bromo-3-methyl-1-benzopyran-2-on-4-yl)propenoate*** **(141c)** (13%)
(Found: M^+, 321.9848. $C_{14}H_{11}{}^{79}BrO_4$ requires *M*, 321.9841); ν_{max}(thin film)/cm^{-1} 1716; δ_H (400 MHz; $CDCl_3$) 2.05 (3H, s, CH_3), 3.76 (3H, s, CO_2CH_3) 5.81 and 6.87 (2H, 2 x s, C=CH_2), 7.17 (1H, d, 5'-H), 7.35 (1H, d, 7'-H) and 7.51 (1H, dd, 8'-H); δ_C (100 MHz; $CDCl_3$) 14.6 (CH_3), 52.7 (CO_2CH_3), 116.9, 118.4, 121.3, 125.1, 127.9, 133.4, 134.6, 144.5 and 151.2 (C-2, C-3', C-4' and Ar-C), 131.9 (C-3), 160.9 (C-1) and 164.5 (C-2'); *m/z* 322 [M^+(^{79}Br),17.0%] and 57 (100%).

iv) ***Dimethyl 2-(6-bromo-3-methyl-1-benzopyran-2-on-4-yl)-4-methylene-pentanedioate*** **(142c)** (5%)

(Found: M^+, 408.0217. $C_{18}H_{17}{}^{79}BrO_6$ requires *M*, 408.0208); ν_{max}(thin film)/cm^{-1} 1722; δ_H (400 MHz; $CDCl_3$) 2.15 (3H, s, CH_3), 2.74 (1H, dd, 3-H), 3.41 (1H, ddd, 3-H), 3.65 and 3.70 (6H, 2 x s, 2 x CO_2CH_3), 4.49 (1H, dd, 2-H), 5.46 (1H, br s, C=CH), 6.09 (1H, s, C=CH), 7.19 (1H, d, Ar-H), 7.53 (1H, dd, Ar-H) and 7.69 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 13.9 (CH_3), 33.2 (C-3), 44.1 (C-2), 52.2 and 52.8 (2 x CO_2CH_3), 129.1 (C=CH_2), 144.7 (C-4'), 116.9, 118.9, 120.5, 126.2, 126.9, 133.4, 135.9 and 151.1 (C-3', C-4 and Ar-C), 161.1 (C-2') and 166.9 and 171.8 (2 x CO_2CH_3); *m/z* 408 [M^+(^{79}Br), 1.3%] and 59 (100%).

v) ***Methyl 4-(6-bromo-3-methyl-1-benzopyran-2-on-4-yl)-2-methylene-pentanoate*** **(143c)** (35%)

(Found: M^+, 350.0158. $C_{16}H_{15}{}^{79}BrO_4$ requires *M*, 350.0154); ν_{max}(KBr)/cm^{-1} 1712; δ_H (400 MHz; $CDCl_3$) 2.22 (3H, s, CH_3), 2.55 (2H, m, 3-CH_2), 2.95 (2H, m, 4-CH_2), 3.85 (3H, s, CO_2CH_3), 5.65 and 6.24 (2H, 2 x br s, C=CH_2), 7.19 (1H, d, 7'-H), 7.55 (1H, dd, 8'-H) and 7.86 (1H, d, 5'-H); δ_C (100 MHz; $CDCl_3$) 13.2 (CH_3), 28.4 (C-4), 31.2 (C-3), 52.1 (CO_2CH_3), 117.1, 118.7, 121.2, 123.8, 127.0, 133.2, 138.6, 147.6 and 151.3 (C-3', C-4', C-2 and Ar-C), 126.9 (C=CH_2) and 161.4 and 167.0 (C-1 and C-2'); *m/z* 350 [M^+(^{79}Br), 8.7%] and 115 (100%).

vi) The zwitterionic 3-(DABCO)propanoate salt (172)

3.2.3.1.4 Reaction with 3,5-dibromosalicylaldehyde

Following the general proceedure, reaction of 3,5-dibromosalicylaldehyde (0.40 g, 1.4 mmol), methyl acrylate (0.47 g, 5.6 mmol) and DABCO (0.06 g, 0.54 mmol) afforded,

after flash chromatography (elution with $CHCl_3$) the following five products :-

i) ***Methyl 6,8-dibromo-2H-1-benzopyran-3-carboxylate*** **(131d)** (15%)

(Found: M^+, 345.8847. $C_{11}H_8{}^{79}Br_2O_3$ requires ***M***, 345.8840); ν_{max}(KBr)/cm^{-1} 1700; δ_H (400 MHz; $CDCl_3$) 3.15 (3H, s, CH_3), 5.10 (2H, d, CH_2), 7.18 (1H, d, Ar-H), 7.30 (1H, t, Ar-H) and 7.56 (1H, d, 4-H); δ_C (100 MHz; $CDCl_3$) 52.2 (CH_3), 64.5 (C-2), 111.0, 113.6, 123.3, 124.3, 130.3, 131.6, 137.0 and 151.0 (C-3, C-4 and Ar-C) and 164.2 (C=O); *m/z* 346 [$M^+(^{79}Br)$, 18.3%] and 333 (100%).

ii) ***Methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2H-1-benzopyran-3-carboxylate*** **(136d)** (47%[e])

(Found: M^+, 363.8933. $C_{11}H_{10}{}^{79}Br_2O_4$ requires ***M***, 363.8946); ν_{max}(KBr)/cm^{-1} 3400 and 1700; δ_H (400 MHz; $CDCl_3$) 2.87 (1H, d, $J_{4,OH}$ 4.5, OH[y]), 3.01 (1H, ddd, $J_{2a,3}$ 9.1, $J_{3,4}$ 7.7 and $J_{2b,3}$ 3.8, 3-H), 3.80 (3H, s, CH_3), 4.29 (1H, dd, J_{gem} 11.5 and $J_{2a,3}$ 9.1, 2_a-H) and 4.58 (1H, dd, J_{gem} 11.5 and $J_{2b,3}$ 3.7, 2_b-H), 5.08 (1H, dd, $J_{3,4}$ 7.7 and $J_{4,OH}$ 4.5, 4-H) and 7.57 (2H, s, Ar-H); δ_C (100 MHz; $CDCl_3$) 45.7 (C-3), 52.6 (CH_3), 64.8 (C-2), 65.3 (C-4), 113.0, 113.3, 126.4, 130.3, 135.2 and 149.7 (Ar-C) and 170.9 (C=O); *m/z* 364 [$M^+(^{79}Br)$, 22.8%] and 306 (100%).

iii) ***Methyl 6,8-dibromo-3,4-dihydro-4-methoxy-2H-1-benzopyran-3-carboxylate*** **(137d)** (14%)

(Found: M^+, 377.9111. $C_{12}H_{12}O_4{}^{79}Br_2$ requires ***M***, 377.9102); ν_{max}(thin film)/cm^{-1} 1712; δ_H (400 MHz; $CDCl_3$) 2.96 (1H, m, 3-H), 3.38 (3H, s, OCH_3), 3.79 (3H, s, CO_2CH_3), 4.43 (1H, t, CH_2), 4.50 (1H, m, 4-H), 7.28 (1H, m, Ar-H) and 7.62 (1H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 42.8 (C-3), 52.1 ($CO_2\underline{C}H_3$), 56.9 (OCH_3), 62.5 (C-2), 72.8 (C-4),

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[e]Isolated yield. [y]D_2O exchange

111.6, 112.0, 122.8, 132.2, 136.0 and 150.3 (Ar-C) and 169.6 (C=O); *m/z* 378 [$M^+(^{79}Br)$, 14%] and 83 (100%)

iv) ***Dimethyl 2-(6,8-dibromo-3-methyl-1-benzopyran-2-on-4-yl)-4-methylene-pentanedioate*** **(142d)** (24%)

(Found: M^+, 485.9312. $C_{18}H_{16}{}^{79}Br_2O_6$ requires *M*, 485.9314); ν_{max}(thin film)/cm^{-1} 1722; δ_H (400 MHz; $CDCl_3$) 2.24 (3H, s, CH_3), 2.71 and 3.38 (2H, 2 x dd, 3-CH_2), 3.68 and 3.74 (6H, 2 x s, 2 x CO_2CH_3), 4.47 (1H, dd, 2-H), 5.48 (1H, br s, C=CH), 6.11 (1H, s, C=CH), 7.67 (1H, d, Ar-H) and 7.82 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.0 (CH_3), 33.2 (C-3), 44.3 (C-2), 52.2 and 52.9 (2 x $CO_2\mathit{C}H_3$), 111.9, 116.8, 126.2, 127.0, 132.2, 135.8, 136.3, 144.5, 148.1 (C-3', C-4, and Ar-C), 129.4 (C=$\mathit{C}H_2$), 160.1 (C-2') and 166.9 and 171.6 (2 x $\mathit{C}O_2CH_3$); *m/z* 486 [$M^+(^{79}Br)$, 1.3%] and 59 (100%).

v) The zwitterionic 3-(DABCO)propanoate salt (172)

3.2.3.1.5 Reaction with 3-methoxysalicylaldehyde

Following the general procedure, reaction of 3-methoxysalicylaldehyde (1.07 g, 7.0 mmol), methyl acrylate (0.96 g, 11 mmol) and DABCO (0.20 g, 1.8 mmol) afforded, after flash chromatography [elution with $CHCl_3$-EtOAc (8:2)], the following four products:-

i) ***Methyl 8-methoxy-2H-1-benzopyran-3-carboxylate*** **(131c)** (14%)

(Found: M^+, 220.0735. $C_{12}H_{12}O_4$ requires *M*, 220.0736); ν_{max}(KBr)/cm^{-1} 1710; δ_H (400 MHz; $CDCl_3$) 3.81 (3H, s, OCH_3), 3.87 (3H, s, CO_2CH_3), 5.05 (2H, d, CH_2), 6.77 (1H, dd, Ar-H), 6.87 (2H, m, Ar-H) and 7.42 (1H, m, 4-H); δ_C (100 MHz; $CDCl_3$)

51.7 (OCH_3), 56.0 (CO_2CH_3), 64.6 (C-2), 114.5, 120.8, 121.3, 121.5, 122.4, 133.5, 144.0 and 148.7 (C-3, C-4 and Ar-C) and 164.8 (C=O); *m/z* 220 (M^+, 65.2%) and 205 (100%).

ii) ***Methyl 2-(3-carbomethoxy-8-methoxy-3,4-dihydro-2H-1-benzopyran-4-yl)propenoate*(138c)** (10%)

(Found: M^+, 306.1112. $C_{16}H_{18}O_6$ requires *M*, 306.1103); ν_{max}(thin film)/cm^{-1} 1718 and 1710; δ_H (400 MHz; $CDCl_3$) 3.06 (1H, m, 3'-H), 3.69, 3.76 and 3.85 (9H, 3 x s, OCH_3 and 2 x CO_2CH_3), 4.23 and 4.51 (2H, 2 x dd, 2'-CH_2), 4.46 (1H, m, 4'-H), 5.39 (1H, t, C=CH) and 6.44 (1H, d, C=CH), 6.58 (1H, m, Ar-H), 6.72 (1H, dd, Ar-H) and 6.80 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 39.0 (C-4'), 43.0 (C-3'), 52.1, 52.2 and 55.8 (3 x OCH_3), 64.0 (C-2'), 130.3 (C-3), 109.6, 120.5, 121.7, 122.0, 142.8, 143.9 and 148.2 (C-2 and Ar-C) and 166.4 and 171.6 (2 x *C*O.CH_3); *m/z* 306 (M^+, 62.5%) and 246 (100%).

iii) ***Methyl 2-(8-methoxy-3-methyl-1-benzopyran-2-on-4-yl)propenoate*** **(141c)** (9%)

(Found: M^+, 274.0830. $C_{15}H_{14}O_5$ requires *M*, 274.0841); ν_{max}(thin film)/cm^{-1} 1710; δ_H (400 MHz; $CDCl_3$) 2.08 (3H, s, CH_3), 3.75 (3H, s, OCH_3), 3.95 (3H, s, CO_2CH_3), 5.79 (1H, d, C=CH) and 6.84 (2H, m, C=CH and Ar-H), 7.01 (1H, d, Ar-H) and 7.11 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.6 (CH_3), 52.6 (OCH_3), 56.3 (CO_2CH_3), 112.7, 117.0, 120.4, 123.8, 124.1, 135.5, 142.2, 145.9 and 147.3 (C-2, C-3', C-4' and Ar-C), 130.3 (C-3) and 161.2 and 165.0 (C-1 and C-2'); *m/z* 274 (M^+, 88.5%) and 215 (100%).

iv) ***Dimethyl 2-(8-methoxy-3-methyl-1-benzopyran-2-on-4-yl)-4-methylenepentanedioate*** **(142c)** (5%)

(Found: M^+, 360.1207 $C_{19}H_{20}O_7$ requires *M*, 360.1208); ν_{max}(thin film)/cm^{-1} 1705; δ_H (400 MHz; $CDCl_3$) 2.16 (3H, s, CH_3), 2.78 and 3.45 (2H, 2 x dd, 3-CH_2), 3.64 and

3.71 (6H, 2 x s, 2 x CO_2CH_3), 3.93 (3H, s, OCH_3), 4.49 (1H, dd, 2-H), 5.38 (1H, br s, C=CH), 6.06 (1H, d, C=CH), 6.99 (1H, dd, Ar-H) and 7.13 (2H, m, 2 x Ar-H); δ_C (100 MHz; $CDCl_3$) 13.8 (CH_3), 33.2 (C-3), 44.7 (C-2), 52.0 and 52.6 (2 x CO_2CH_3), 56.2 (OCH_3), 112.3, 115.6, 115.8, 123.8 and 147.7 (Ar-C), 125.4 (C-3'), 128.9 ($C=CH_2$), 136.1 (C-4), 142.2 (C-8a), 145.9 (C-4'), 161.2 (C-2') and 166.9 and 172.3 (2 x CO_2CH_3); *m/z* 360 (M^+, 36.5%) and 241 (100%).

3.2.3.1.6 Reaction with 3-ethoxysalicylaldehyde

Following the general procedure, reaction of 3-ethoxysalicylaldehyde (2.0 g, 12.0 mmol), methyl acrylate (2.86 g, 34.4 mmol) and DABCO (0.27 g, 2.4 mmol) afforded, after flash chromatography [elution with hexane-EtOAc (9:1)], the following product :-

Methyl 8-ethoxy-2H-1-benzopyran-3-carboxylate **(131e)**(9%)
(Found: M^+, 234.0878. $C_{13}H_{14}O_4$ requires ***M***, 234.0892); ν_{max}(thin film)/cm^{-1} 1718; δ_H (400 MHz; $CDCl_3$) 1.44 (3H, t, OCH_2CH_3), 3.80 (3H, s, OCH_3), 4.00 (2H, q, OCH_2CH_3), 5.04 (2H, d, CH_2), 6.75-6.89 (3H, m, Ar-H) and 7.42 (1H, s, 4-H); δ_C (100 MHz; $CDCl_3$) 14.8 (CH_2CH_3), 51.8 (OCH_3), 64.68 (C-2), 64.71 (CH_2CH_3), 116.3, 121.0, 121.4, 121.8, 122.4, 123.7, 133.8 and 147.4 (C-3, C-4 and Ar-C) and 165.0 (C=O); *m/z* 234 (M^+, 7.0%) and 147 (100%).

3.2.3.1.7 Reaction with *O*-acetylsalicylaldehyde (151a) :-

Following the general procedure, reaction of *O*-acetylsalicylaldehyde **(151a)** (2.03 g, 12.4 mmol), methyl acrylate (1.27 g, 14.72 mmol) and DABCO (0.374 g, 3.34 mmol) afforded, after flash chromatography [elution with $CHCl_3$-hexane (9:1)], the following product :-

Methyl 2*H*-1-benzopyran-3-carboxylate (131a) (13%)

3.2.3.1.8 Reaction with *O*-acetyl-5-bromosalicylaldehyde **(151c)**

Reaction of *O*-acetyl-5-bromosalicylaldehyde **(151c)** (1.0 g, 3.6 mmol), methyl acrylate (1.91 g, 22.1 mmol) and DABCO (0.089 g, 0.79 mmol) in chloroform (0.2 ml) afforded, after flash chromatography [elution with $CHCl_3$-hexane (7:3)], the following two products :-

i) Methyl 6-bromo-2*H*-1-benzopyran-3-carboxylate (131c)(23%)

ii) The zwitterionic 3-(DABCO)propanoate salt (172)

3.2.3.1.9 Reaction with *O*-acetyl-5-nitrosalicylaldehyde **(151b)**

Following the general procedure, reaction of *O*-acetyl-5-nitrosalicylaldehyde **(151b)** (2.0 g, 9.6 mmol), methyl acrylate (1.65 g, 19.2 mmol) and DABCO (0.78 g, 7.0 mmol) in chloroform (1.0 ml) afforded, after flash and preparative layer chromatography (elution with dichloromethane), the following three products:-

i) *Methyl 6-nitro-2H-1-benzopyran-3-carboxylate* (131h) (2%)
(Found: M^+, 235.0482. $C_{11}H_9O_5N$ requires *M*, 235.0481); ν_{max}(KBr)/cm^{-1} 1700; δ_H (400 MHz; $CDCl_3$) 3.80 (3H, s, CH_3), 4.97 (2H, d, CH_2), 6.70 (1H, d, 8-H), 7.21 (1H, d, 5-H), 7.28 (1H, dd, 7-H) and 7.31 (1H, br s, 4-H); δ_C (100 MHz; $CDCl_3$) 52.0 (CH_3), 64.6 (C-2), 113.6, 117.9, 112.6, 123.5, 131.0, 132.1, 134.3 and 154.1 (C-3, C-4 and Ar-C) and 164.5 (C=O); *m/z* 235 (M^+, 36%) and 220 (100%).

ii) *Methyl 2-(3-methyl-6-nitro-1-benzopyran-2-on-4-yl)propenoate* (141h)(20%)

(Found: M^+, 289.0574. $C_{14}H_{11}O_6N$ requires *M*, 289.0568); ν_{max}(thin film)/cm^{-1} 1730; δ_H (400 MHz; $CDCl_3$) 2.12 (3H, s, CH_3), 3.87 (3H, s, CO_2CH_3), 5.92 (1H, br s, C=CH) and 6.96 (1H, s, C=CH), 7.45 (1H, d, Ar-H), 8.17 (1H, d, Ar-H) and 8.32 (1H, dd, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.9 (CH_3), 52.9 (CO_2CH_3), 117.9, 120.0, 121.7, 125.5,126.4, 134.2, 144.1, 144.7 and 155.9 (C-2, C-3', C-4' and Ar-C), 132.6 (C-3) and 160.2 and 164.3 (C-1 and C-2'); *m/z* 289 (M^+, 77%) and 272 (100%).

iii) ***Dimethyl 2-(3-methyl-6-nitro-1-benzopyran-2-on-4-yl)-4-methylenepentane-dioate*** **(142h)** (21%)

(Found: M^+, 375.0950. $C_{18}H_{17}O_8N$ requires *M*, 375.0954); ν_{max}(thin film)/cm^{-1} 1715; δ_H (400 MHz; $CDCl_3$) 2.21 (3H, s, CH_3), 2.78 and 3.46 (2H, 2 x dd, 3-CH_2), 3.71 and 3.74 (6H, s, 2 x CO_2CH_3), 4.58 (1H, dd, 2-H), 5.53 (1H, br s, C=CH) and 6.12 (1H, d, C=CH), 7.43 (1H, d, Ar-H), 8.32 (1H, dd, Ar-H) and 8.58 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 14.1 (CH_3), 33.3 (C-3), 44.4 (C-2), 52.2 and 53.0 (2 x CO_2CH_3), 118.4, 120.7, 125.4, 127.3, 132.7, 144.0, 145.2 and 155.8 (Ar-C, C-4' and C-3'), 129.4 ($C=CH_2$), 135.9 (C-4), 160.2 (C-2') and 168.8 and 171.3 (2 x CO_2CH_3).

3.2.4 Preparation of O-acetylated salicylaldehydes.

Preparation of 2-acetoxybenzaldehyde (151a).[146]

Salicylaldehyde (4.0 g, 33 mmol) and pyridine (3.5 ml) were stirred at 0°C in a two-necked flask fitted with a pressure equalising dropping funnel and a condenser attached to an N_2 line. Acetyl chloride (3.75 ml, 52.7 mmol) was then added dropwise to the stirred solution, following which the resulting mixture was heated on a water bath (*ca.* 70°C) for 5 min. The reaction mixture was cooled, diluted with water (30 ml) and then extracted with diethyl ether. The ethereal extract was washed with saturated brine and dried ($MgSO_4$) and the solvent was removed *in vacuo*. Distillation *in vacuo* yielded, as a

yellow oil, 2-acetoxybenzaldehyde **(151a)** (2.50 g, 46%); ν_{max}(thin film)/cm^{-1} 3100, 1770 and 1702; δ_H (400 MHz; $CDCl_3$) 2.36 (3H, s, $COCH_3$), 7.16 (1H, d, Ar-H), 7.37 (1H, t, Ar-H), 7.59 (2H, d, Ar-H) and 10.12 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 20.7 ($COCH_3$), 123.4 (Ar-C), 126.4 (Ar-C), 128.0 (C-1), 131.3 (Ar-C), 135.2 (Ar-C), 151.4 (C-2), 169.1 ($COCH_3$) and 188.7 (CHO).

Preparation of 2-acetoxy-5-bromobenzaldehyde (151c)

NaH (50% suspension in oil; 0.86 g, 18 mmol) was placed in a three-necked flask fitted with a pressure equalising dropping funnel, a thermometer and a condenser attached to an N_2 line. Dry THF (15 ml) was then added, followed by 5-bromosalicylaldehyde (2.76 g, 13.7 mmol). The resulting mixture was boiled under reflux for 1h to generate the phenoxide ion, following which the reaction mixture was allowed to cool. A solution of acetyl chloride (1.27 ml, 17.9 mmol) in THF (15 ml) was then added dropwise, with stirring, and the reaction mixture was boiled under reflux for 3h. The reaction was quenched by addition of H_2O (20 ml) and the resulting mixture extracted with diethyl ether. The ethereal solution was washed with saturated brine, dried ($MgSO_4$) and concentrated *in vacuo* to afford a crude product together with the mineral oil from the NaH, which was removed by adding a small quantity of diethyl ether (*ca.* 1 ml) and freezing the sample in liquid N_2. On warming the mixture, a precipitate formed which was filtered off and dried to afford 2-acetoxy-5-bromobenzaldehyde **(151c)** (1.42 g, 43%); ν_{max}(thin film)/cm^{-1} 1765 and 1700; δ_H (400 MHz; $CDCl_3$) 2.38 (3H, s, OCH_3), 7.09 (1H, d, Ar-H), 7.72 (1H, dd, Ar-H), 7.99 (1H, d, Ar-H) and 10.01 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 20.8 ($COCH_3$), 119.7 (Ar-C), 125.3 (Ar-C), 129.3 (Ar-C), 133.5 (Ar-C), 137.9 (Ar-C), 150.6 (C-2), 168.8 ($COCH_3$) and 187.1 (CHO); *m/z* 202 (M^+, 100%) and 43 (31%).

Preparation of 2-acetoxy-5-nitrobenzaldehyde (151b)[152]

NaH (50% suspension in oil; 1.38 g, 28.8 mmol) was placed in a three-necked flask fitted with a thermometer, a pressure equalising dropping funnel and a condenser attached to an N_2 line. In order to remove the mineral oil, dry THF (15 ml) was added and after stirring for several minutes the NaH was allowed to settle, and the supernatant decanted off *via* a cannula. Fresh THF (40 ml) was added, and a solution of 5-nitrosalicylaldehyde (4.0 g, 24 mmol) in THF (10 ml) was added dropwise, and the resulting mixture boiled under reflux for 1h. The reaction mixture was allowed to cool, and then acetyl chloride (2.05 ml, 28.8 mmol) was added dropwise with stirring, and the resulting mixture was boiled under refluxed for 2h. After cooling, the mixture was filtered and the solvent removed *in vacuo* to afford *2-acetoxy-5-nitrobenzaldehyde* **(151b)** (4.02 g, 80%) (Found: M^+, 209.0331. $C_9H_7NO_5$ requires *M*, 209.0324); ν_{max}(KBr)/cm^{-1} 1710 and 1655; δ_H (400 MHz; $CDCl_3$) 2.46 (3H, s, $COCH_3$), 7.43 (1H, d, 3-H), 8.46 (1H, dd, 4-H), 8.74 (1H, d, 6-H) and 10.39 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) 20.8 ($COCH_3$), 124.9, 126.1, 128.5, 129.5, 145.7 and 155.6 (Ar-C), 168.1 ($COCH_3$) and 186.4 (CHO); *m/z* 209 (M^+, 8.2%) and 145 (100%).

Attempted preparations of 2-acetoxy-5-nitrobenzaldehyde (151b) :-

Method 1.[146]– 5-Nitrosalicylaldehyde **(129h)** (1.0 g, 6.0 mmol) and dry pyridine (1.55 ml; dried over 4Å molecular sieves) were stirred together at 0°C in a two-necked flask fitted with a pressure equalising dropping funnel and a condenser attached to an N_2 line. Acetyl chloride (0.71 ml, 10.0 mmol) was then added dropwise, and the resulting mixture was heated on a water bath (70°C) for 5min. The mixture was cooled and the reaction quenched with water (30 ml). The resulting mixture was extracted with diethyl ether, and the ethereal layer was washed with saturated brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to yield a compound shown to be the pyridinium salt of 5-nitrosalicylaldehyde.

Method 2.[110]– A mixture of 5-nitrosalicylaldehyde **(129h)** (1.48 g, 8.88 mmol) and acetic anhydride (5.0 ml, 53 mmol) was boiled under reflux 0.5h. The cooled reaction mixture was washed with 10% aqueous NaOH (20 ml), resulting in the formation of a precipitate which, after filtration, was shown to be the sodium salt of 5-nitrosalicylaldehyde.[ϕ]

Preparation of *O*-acetyl-2-(diacetoxymethyl)-4-bromophenol (149b)[110]

A mixture of 5-bromosalicylaldehyde (4.0 g, 20 mmol) and acetic anhydride (24.0 ml, 0.25 mol) was boiled under reflux for 1h. After cooling, diethyl ether (20 ml) was added and the mixture basified with aqueous $NaHCO_3$ and extracted with diethyl ether (2 x 40 ml). The ethereal solution was washed with saturated brine, dried ($MgSO_4$) and concentrated *in vacuo* to yield a yellow oil which, on standing, crystallised to yield *O*-acetyl-2-(diacetoxymethyl)-4-bromophenol **(149b)** (3.96 g, 58%) m.p. 90-92 °C (from $CHCl_3$) (lit.,[153] 88°C) (Found: M^+, 343.9883. Calc. for $C_{13}H_{13}{}^{79}BrO_6$: *M*, 343.9893); ν_{max}(thin film)/cm^{-1} 1692 and 1685; δ_H (400 MHz; $CDCl_3$) 2.03 (6H, s, 2 x $COCH_3$), 2.41 (3H, s, 4-$COCH_3$), 6.96 (1H, d, 5-H), 7.46 (1H, dd, 6-H), 7.70 (1H, d, 2-H), 7.81 (1H, s, CH); δ_C (100 MHz; $CDCl_3$) 20.7 (2 x $COCH_3$), 20.8 (4-$COCH_3$), 84.4 (CH), 119.3, 124.9, 129.8, 130.8, 133.7 and 147.2 (Ar-C), 168.2 (2 x $COCH_3$) and 169.0 (4-$COCH_3$); *m/z* 344 [M^+(^{79}Br), 1.1%] and 202(100%).

Preparation of *O*-acetyl-2-(diacetoxymethyl)-4-nitrophenol (149a)[110]

A mixture of 5-nitrosalicylaldehyde (2.0 g, 12 mmol) and acetic anhydride (7.0 ml) was boiled under reflux for 2h, following the procedure used in the synthesis of *O*-acetyl-2-(diacetoxymethyl)-4-bromophenol **(149b)**, workup afforded, as yellow crystals, *O*-acetyl-

[ϕ]Acidification of the salt followed by extraction, yielded starting material.

2-(diacetoxymethyl)-4-nitrophenol **(149a)** (1.31 g, 37%) [m.p. 110-112°C (from $CHCl_3$) (lit.,[154] 114-115°C) (Found: M^+, 311.0633. Calc. for $C_{13}H_{13}NO_8$: *M*, 311.0637); ν_{max}(thin film)/cm^{-1} 1692 and1685; δ_H (400 MHz; $CDCl_3$) 2.13 (6H, s, 2 x $COCH_3$), 2.37 (3H, s, 4-$COCH_3$), 7.34 (1H, d, 5-H), 7.93 (1H, s, CH), 8.29 (1H, dd, 6-H) and 8.52 (1H, d, 2-H); δ_C (100 MHz; $CDCl_3$) 20.6 (2 x $COCH_3$), 20.8 (4-$COCH_3$), 83.9 (CH), 123.8, 125.8, 129.6, 131.9, 145.6 and 152.7 (Ar-C), 168.1 (2 x $COCH_3$) and 168.3 (4-$COCH_3$); *m/z* 311 (M^+, 0.05%) and 145 (100%)] and 2-acetoxy-5-nitrobenzaldehyde **(151b)** (1.36 g, 54%) as a yellow oil, which was separated by filtration.

3.2.5 Preparation of *t*-butyldimethylsilyl-protected Baylis-Hillman products

Preparation of 2-(*t*-butyldimethylsiloxy)benzaldehyde (152a)

Dry THF (25 ml) was added to a three-necked flask fitted with a condenser attached to an N_2 line containing washed NaH (0.47 g, 9.95 mmol).[¶¶] Salicylaldehyde (0.87 ml, 8.89 mmol) was then added dropwise *via* a syringe and the mixture was allowed to stir for 30 min to generate the phenoxide ion. *t*-Butyldimethylsilyl chloride (1.5 g, 10 mmol) was then added and the resulting mixture stirred for 12h. The reaction was quenched by the addition of aq. $NaHCO_3$ (20 ml) and extracted into diethyl ether. The ethereal extract was dried ($MgSO_4$), and the solvent removed *in vacuo* to give the crude product (2.4 g), which was subsequently purified by flash chromatography [elution with hexane; ethyl acetate (9:1)] to afford 2-(*t*-butyldimethyl siloxy)benzaldehyde **(152a)** (1.32 g, 62%); ν_{max}(thin film)/cm^{-1} 1705 and 1495; δ_H (400 MHz; $CDCl_3$) 0.26 [6H, s, $Si(CH_3)_2$], 1.02 [9H, s, $SiC(CH_3)_3$], 6.85-7.05 (4H, m, Ar-H) and 10.49 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) -4.3 [$Si(CH_3)_2$], 18.32 [$SiC(CH_3)_3$], 25.7 [$SiC(CH_3)_3$], 120.2, 121.4, 127.3, 128.4, 135.7 and 158.9 (Ar-C) and 190.2 (CHO); *m/z* 236 (M^+, 1.3%) and 73 (100%).

¶¶ The NaH was washed with dry THF, and the washings were removed *via* a cannula.

Attempted preparation of 2-(*t*-butyldimethylsiloxy)benzaldehyde (152a)[124,125]

Salicylaldehyde (0.873 g, 8.9 mmol), imidazole (1.39 g, 20.5 mmol) and *t*-butyldimethylsilyl chloride (1.5 g, 9.8 mmol) were stirred together in dry DMF (*ca.* 100 ml) in a three-necked flask fitted with a condenser attached to an N_2 line. The reaction was maintained at 30°C for 8h, after which time no apparent reaction had taken place. The reaction mixture was then heated to 80-90°C for a further 5h under dry N_2, after which time the absence of product was confirmed by ^1H NMR spectroscopy.

Preparation of 5-bromo-2-(*t*-butyldimethyl siloxy)benzaldehyde (152c)

Dry THF (100 ml) was added to a three-necked flask fitted with a condenser attached to an N_2 line containing washed NaH (0.47 g, 9.95 mmol).[§§] 5-Bromosalicylaldehyde (2.0 ml, 9.9 mmol) was then added dropwise *via* a syringe and the mixture was allowed to stir for 30 min to generate the phenoxide ion. *t*-Butyldimethylsilyl chloride (1.65 g, 10.9 mmol) was added and the resulting mixture stirred for 12h, after which the reaction mixture was diluted with diethyl ether (60 ml) and washed with 10% aq. $NaHCO_3$ (20 ml) and then with brine (40 ml). The ethereal layer was separated and dried ($MgSO_4$), and the solvent removed *in vacuo* to afford the crude product (3.38 g). Flash chromatography [elution with hexane; EtOAc (9:1)] afforded, as white crystals, 5-bromo-2-(*t*-butyldimethylsiloxy)benzaldehyde **(152c)**[155] (2.48g, 84%) m.p. 48-50°C (from $CHCl_3$); ν_{max}(thin film)/cm^{-1} 1695 and 1480; δ_H (400 MHz; $CDCl_3$) 0.27 [6H, s, $Si(CH_3)_2$], 1.02 [9H, s, $SiC(CH_3)_3$], 6.77 (1H, d, Ar-H), 7.53 (1H, dd, Ar-H), 7.98 (1H, d, Ar-H) and 10.35 (1H, s, CHO); δ_C (100 MHz; $CDCl_3$) -4.4 [$Si(CH_3)_2$], 18.3 [$SiC(CH_3)_3$], 25.6 [$SiC(CH_3)_3$], 114.2, 122.1, 128.5, 130.1, 138.3 and 157.8 (Ar-C) and 188.6 (CHO); *m/z* 257 (M^+- $Si(CH_3)_2$, 26%) and 149 (100%).

[§§] The NaH was washed with dry THF, and the washings were removed *via* a cannula.

Preparation of methyl 3-(*t*-butyldimethylsiloxy)-3-[2-(*t*-butyldimethylsiloxy)phenyl]-2-methylenepropanoate (154a)

2-(*t*-Butyldimethylsiloxy)benzaldehyde **(152a)** (1.32 g, 5.59 mmol), methyl acrylate (0.6 ml, 7 mmol) and DABCO (0.05 g, 0.5 mmol) were stirred together in a stoppered round-bottomed flask flushed with dry N_2. After 48h a red precipitate started to form together with fine crystals. The crude reaction mixture was separated using flash chromatography (elution with $CHCl_3$) to afford 3-[(2-formylphenoxy)methyl]coumarin **(132a)** (0.102g, 7%), salicylaldehyde (0.40g, 58%) and *methyl 3-(t-butyldimethylsiloxy)-3-[2-(t-butyldimethylsiloxy)phenyl]-2-methylenepropanoate* **(154a)** (0.113g, 5%) [Found: 322.1010: M^+ - $Si(CH_3)_2Bu^t$, $C_{17}H_{25}O_4Si$ requires *M*, 321.1522]; ν_{max}(thin film)/cm^{-1} 1710; δ_H (400 MHz; $CDCl_3$) -0.11, 0.04, 0.22, 0.29 [12H, 4 x s, 2 x $Si(CH_3)_2$], 0.86 and 1.16 [2 x 9H, 2 x s, 2 x $SiC(CH_3)_3$], 3.71 (3H, s, $COCH_3$), 5.45 and 6.14 (2H, 2 x s, $C=CH_2$), 6.06 [1H, s, C*H*(OH)], 6.77 (1H, d, Ar-H), 6.94 (1H, dd, Ar-H), 7.12 (1H, dd, Ar-H) and 7.42 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) -5.1, -4.8, -4.2, -4.15 [2 x $Si(CH_3)_2$], 25.7 [2 x $SiC(CH_3)_3$], 51.4 (CO_2CH_3), 124.8 ($C=CH_2$), 18.1, 66.6, 117.8, 120.7, 128.0, 128.7, 132.0, 143.9 and 152.3 [Ar-C, $C=CH_2$, CH(OH) and $SiC(CH_3)_3$] and 166.9 (C=O); *m/z* 380 [M^+- $Si(CH_3)_2$, 9.4%] and 73 (100%).

Attempted preparation of the methyl 3-hydroxy-3-[2-(*t*-butyldimethylsiloxy)-5-bromophenyl]-2-methylenepropanoate (153c)

5-Bromo-2-(*t*-butyldimethylsiloxy)benzaldehyde **(152c)** (1.0 g, 3.2 mmol), methyl acrylate (1.0 ml, 11 mmol) and 3-hydroxyquinuclidine (0.04 g, 0.3 mmol) were stirred together in a stoppered round-bottomed flask flushed with dry N_2 for 14 days. ^1H NMR spectroscopy of the crude reaction mixture showed that none of the desired product had formed.

Deprotection of methyl 3-(*t*-butyldimethylsiloxy)-3-[2-(*t*-butyldimethyl siloxy)phenyl]-2-methylenepropanoate (154a)[124]

Tetrabutylammonium fluoride (0.18 g, 0.57 mmol) was added to a stirred solution of methyl 3-(*t*-butyldimethylsiloxy)-3-[2-(*t*-butyldimethylsiloxy)phenyl]-2-methylene-propanoate **(154a)** (0.021 g, 0.048 mmol) in dry THF (1.0 ml) at 0°C for 5min. Water was then added (0.2ml), followed by dilute HCl until the sample was just acidic, and the sample was then extracted with diethyl ether. The ethereal layer was dried ($MgSO_4$), and the solvent removed *in vacuo* to afford an orange oil (0.031 g) which was shown by ^1H NMR spectroscopy to contain:-

i) Methyl 3,4-dihydro-4-hydroxy-2*H*-1-benzopyran-3-carboxylate **(136a)** (19%)

ii) Methyl 2*H*-1-benzopyran-3-carboxylate **(131a)** (43%)

iii) 4-Hydroxy-3-methylenecoumarin **(139a)** (38%)

3.2.6 3-Methylene-3,4-dihydrocoumarin synthesis.

Preparation of methyl 2-(hydroxymethyl)acrylate (157) and dimethyl 4-oxahept-1,6-diene-2,6-dicarboxylate (164)

Methyl acrylate (18.0 ml, 0.20 mol), paraformaldehyde (9.04 g, 0.30 mol) and DABCO (1.12 g, 10 mmol) were stirred in an autoclave at 95°C for 4 h, to afford, on cooling, a mixture of methyl 2-(hydroxymethyl)acrylate **(157)** (25.9 g) [ν_{max} (thin film)/cm^{-1} 3400 and 1712; δ_H (400 MHz; $CDCl_3$) 3.29 (1H, s, OH), 3.70 (3H, s, OCH_3), 4.22 (2H, m, CH_2) and 5.85 and 6.22 (2H, 2 x s, $C=CH_2$)], and dimethyl 4-oxahept-1,6-diene-2,6-dicarboxylate **(167)** [δ_H (400 MHz; $CDCl_3$) 3.81 (6H, s, 2 x OCH_3), 4.31 (4H, m, 2 x CH_2) and 5.94 and 6.32 (4H, m, 2 x CH_2)], which was used without further purification.

Preparation of methyl 2-(chloromethyl)acrylate (159)[127]

Methyl 2-(hydroxymethyl)acrylate **(157)** (10 g, 86 mmol), *N*,*N*-dimethylformamide (57

μl) and dry benzene (3 ml) were stirred together at 0°C in a three-necked flask fitted with a thermometer, dropping funnel and a reflux condenser attached to both an N_2 line and an aqueous NaOH scrubber. Thionyl chloride (2.3 ml, 32 mmol) was added dropwise to the stirred reaction mixture, after which the resulting mixture was heated at 60°C for 1h. The reaction was quenched by the gradual addition of crushed ice and the resulting mixture was then extracted with diethyl ether. The ethereal layer was washed with saturated brine and dried ($MgSO_4$), and the solvent removed *in vacuo* to yield methyl 2-(chloromethyl)acrylate **(159)** (6.84 g, 60%) ν_{max} (thin film)/cm^{-1} 1722; δ_H (60MHz; $CDCl_3$) 3.80 (3H, s, CO_2CH_3), 4.32 (2H, s, CH_2), 5.95 and 6.40 (2H, 2 x s, $C=CH_2$).

Preparation of methyl 2-(bromomethyl)acrylate (158)[127]

Dilute H_2SO_4 (8%; 22 ml) was added dropwise to a stirred solution of methyl 2-(hydroxymethyl)acrylate **(157)** (10 g, 86 mmol) in conc.HBr (47% aqueous solution; 24 ml) at 0°C. The reaction mixture was then stirred at room temperature for 16h, during which time the mixture separated into two layers. The upper layer was isolated and extracted into diethyl ether (75 ml) and the ethereal solution was washed with saturated aqueous $NaHCO_3$ (3 x 50 ml) and with saturated brine. The organic layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford, as a colourless oil, methyl 2-(bromomethyl)acrylate **(159)** (8.33 g, 55%); ν_{max} (thin film)/cm^{-1} 1710; δ_H (60MHz; $CDCl_3$) 3.75 (3H, s, CO_2CH_3), 4.10 (2H, s, CH_2), 5.92 and 6.29 (2H, 2 x s, $C=CH_2$).

Preparation of methyl 2-methylene-3-phenoxypropanoate (160)[128]

Dry THF (50 ml) was added to a three-necked flask fitted with a condenser attached to an N_2 line containing washed NaH (3.36 g, 70.0 mmol).[ω] Phenol (6.80 g, 72 mmol) dissolved in THF (20 ml) was then added dropwise *via* a syringe and the mixture was

[ω] The NaH was washed with dry THF, and the washings were removed *via* a cannula.

allowed to stir for 1h to generate the phenoxide ion. To the resulting mixture, a solution of methyl 2-(bromomethyl)acrylate (**158**)[cc] (8.34 g, 46.6 mmol) in dry THF (20 ml) was added dropwise. After stirring vigorously for 3 days, the reaction was quenched by adding H_2O (50 ml), and the resultant mixture was extracted with diethyl ether. The ethereal solution was washed with saturated brine, dried ($MgSO_4$) and concentrated to afford the crude product, flash chromatography (elution with $CHCl_3$), of which afforded methyl 2-methylene-3-phenoxypropanoate (**160**) (4.33 g, 48.8%); ν_{max} (thin film)/cm^{-1} 1750 and 1700; δ_H (400 MHz; $CDCl_3$) 3.70 (3H, s, CO_2CH_3), 4.66 (2H, m, CH_2), 5.91 and 6.30 (2H, 2 x dd, C=CH_2), 6.85 (3H, m, Ar-H) and 7.18 (2H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 51.8 (CH_3), 66.0 (CH_2), 135.8 (C=*C*H_2), 114.8, 121.1, 126.4, 129.4 and 158.3 (Ar-C and C-2) and 165.9 (*C*O_2CH_3).

Preparation of 3-methylene-3,4-dihydrocoumarin (161)[128,131] and the coumarin dimer (168)

A mixture of methyl 2-methylene-3-phenoxypropanoate (**160**) (1.00 g, 5.18 mmol) in dry toluene (200 ml) and *p*-toluenesulfonic acid (0.204 g) was refluxed for 5h in a round-bottomed flask fitted with a Dean-Stark apparatus containing 3Å molecular sieves. The solvent was removed *in vacuo* and the crude mixture flash chromatographed [elution with benzene-EtOAc (8:1)], to afford both a crystalline product and an ether insoluble product. Recrystallisation of the ether soluble product from diethyl ether and pentane afforded 3-methylene-3,4-dihydrocoumarin (**161**) [(0.748 g, 90%) [m.p. 65-67°C (lit.,[128] 66-68°C); ν_{max} (KBr)/cm^{-1} 1735 and 1630; δ_H (400 MHz; $CDCl_3$) 3.79 (2H, br s, CH_2), 5.76 and 6.40 (2H, 2 x m, C=CH_2), 7.03-7.25 (4H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 32.0 (CH_2), 128.5 (C=*C*H_2), 117.0, 121.2, 124.6, 127.7, 128.2, 128.5 and150.9 (Ar-C and C-3) and 163.2 C-2; *m/z* 160 (M^+, 31.2 %) and 131 (100)], while filtration of the

[cc]Methyl 2-(chloromethyl)acrylate (**159**) (7.99 g, 59.4 mmol) was also used, affording the required product methyl 2-methylene-3-phenoxypropanoate (**160**) (3.52 g, 46%).

ether insoluble product afforded the coumarin dimer **(168)** [(0.0491 g, 3%) [(Found: M^+, 320.1047. $C_{20}H_{16}O_4$ requires *M*, 320.1048); ν_{max}(thin film)/cm^{-1} 1745 and 1695; δ_H (400 MHz; $CDCl_3$) 1.98 and 2.20 (2H, 2 x m, 2'-H), 2.69-2.92 (3H, m, 1'-CH_2 and 3'-H), 2.88 and 3.09 (2H, 2 x dd, 4'-H), 7.00-7.51 (8H, m, Ar-H) and 7.59 (1H, br s, 4-H); δ_C (100 MHz; $CDCl_3$) 28.3 (C-2'), 28.4 (C-1'), 29.5 (C-4'), 38.6 (C-3'), 116.4, 116.5, 119.4, 122.5, 124.35, 124.37, 127.3, 128.1, 128.3, 128.4, 138.8, 151.5 and 153.2 (Ar-C), 139.5 (C-4),161.6 (C-2) and 170.5 (C-10'); *m/z* 320 (M^+, 0.18%) and 41 (100%)].

Attempted preparations of 3-methylene-3,4-dihydrocoumarin (161):-

Method 1.- Methyl 2-methylene-3-phenoxypropanoate **(160)** (2.50 g, 13 mmol) and aluminium trichloride (3.47 g, 26 mmol) and dry dichloromethane (260 ml) were placed in a three-necked flask, fitted with a thermometer and a reflux condenser attached to an N_2 line. The mixture was boiled under reflux for 45h, during which the colourless solution became dark brown. The reaction was quenched by the addition of ice (*ca.* 20 g) and the resulting mixture extracted with diethyl ether. The ethereal solution was dried ($MgSO_4$) and the solvent was removed *in vacuo*. Flash chromatography of the residue [elution with benzene-EtOAc (8:1)] of this material afforded, as an orange oil, methyl 3-(2-hydroxyphenyl)-2-methylenepropanoate **(165)**[131] (1.59 g, 61.2 %); ν_{max} (thin film)/cm^{-1} 3400 and 1695; δ_H (400 MHz; $CDCl_3$) 3.58 (2H, s, CH_2), 3.77 (3H, s, CO_2CH_3), 5.79 and 6.22 (2H, 2 x s, C=CH_2), 6.90 (2H, m, Ar-H), 7.12 (2H, m, Ar-H) and 7.48 (1H, br s, Ar-OH); δ_C (100 MHz; $CDCl_3$) 32.8 (CO_2CH_3), 52.5 (CH_2), 127.1 (C=CH_2), , 117.4, 120.8, 125.4, 128.2, 130.6, 139.0 and 154.1 (Ar-C and C=CH_2) and 169.3 (CO_2CH_3); *m/z* 192 (M^+, 2.2%) and 131 (100%).

Method 2.- A mixture of methyl 2-methylene-3-phenoxypropanoate **(160)** (0.50 g, 2.6 mmol) and aluminium trichloride (0.74 g, 5.5 mmol) in dry 1,2-dichloromethane (30 ml) was boiled under refluxed for 5h following the procedure described in method 1. The orange oil recovered after work-up was shown to be starting material (0.45 g, 90%).

Method 3.– A solution of methyl 2-methylene-3-phenoxypropanoate (**160**) (4.33 g, 22.6 mmol) in dry toluene (400 ml) was boiled under reflux together with *p*-toluenesulfonic acid monohydrate (1.77 g, 9.3 mmol) in a 500 ml three-necked flask fitted with a condenser and a drying tube. After boiling the mixture for 28h, the work-up procedure, described in method 1, yielded starting material.

Method 4.[129] – A mixture of methyl 2-methylene-3-phenoxypropanoate **(160)** (0.510 g, 2.62 mmol) and trifluoroacetic acid (2.0 ml, 26 mmol) was stirred in a stoppered flask, in a water-bath at 32 °C. The progress of the reaction was monitored by ^{1}H NMR spectroscopy; however, after 10 days only starting material was present in the reaction mixture.

Method 5.– A solution of methyl 2-methylene-3-phenoxypropanoate **(160)** (1.0 g, 5.2 mmol) in xylene (80 ml) was boiled under reflux for 12h in a round-bottomed flask fitted with a Dean-Stark trap filled with 3Å molecular sieves. The reaction was monitored by ^{1}H NMR spectroscopy; however, none of the expected product was detected in the reaction mixture.

Method 6.– Methyl 2-methylene-3-phenoxypropanoate **(160)** (1.0 g, 5.2 mmol) was heated at 160-170°C in a cold-finger apparatus under vacuum (0.02 mmHg) for 5h, after which ^{1}H NMR spectroscopy showed only starting material to be present.

Method 7.– A mixture of methyl 2-methylene-3-phenoxypropanoate **(160)** (1.0 g, 5.2 mmol) and aluminium trichloride (0.113 g, 0.840 mmol) was heated in a cold-finger apparatus at 140-150°C for 5h. ^{1}H NMR spectroscopy showed the formation of a complex mixture which contained none of the desired product.

Method 8.– A solution of methyl 2-methylene-3-phenoxypropanoate **(160)** (0.50 g, 2.6 mmol) in diethyl ether (20 ml) was washed with dilute HCl. The ethereal layer was washed with brine and dried ($MgSO_4$) and the solvent removed *in vacuo* to afford, as an orange oil 3-(2-hydroxyphenyl)-2-methylene propanoic acid **(165a)** (0.42 g, 91%); ν_{max} (thin film)/cm^{-1} 3475 br and 1640 ; δ_H (400 MHz; $CDCl_3$) 3.62 (2H, s, CH_2), 5.60 and 6.40 (2H, 2 x s, C=CH_2), 6.90 (2H, m, Ar-H), 7.15 (2H, m, Ar-H) and 9.00 (1H, br s, Ar-OH); δ_C (100 MHz; $CDCl_3$) 31.9 (CH_2), 128.2 (C=*C*H_2), 116.8, 121.0, 125.1, 129.3, 130.7, 138.3 and 153.6 (Ar-C and *C*=CH_2) and 173.0 (*C*O_2H).

Method 9.- A mixture of methyl 3-(2-hydroxyphenyl)-2-methylenepropanoate **(165a)** (3.29 g, 17.22 mmol) and aluminium trichloride (4.85 g, 36.4 mmol) was boiled under reflux for 64h, after which time the reaction was quenched with water (*ca.* 70 ml) and the resulting extracted into diethyl ether. The ethereal layer was dried ($MgSO_4$) and the solvent removed *in vacuo* yielding an orange oil, which was shown by ^{1}H NMR spectroscopy not to be the desired compound.

Preparation of methyl 3-bromo-3-(2-hydroxyphenyl)-2-methylene-propanoate (166)

N-Bromosuccinimide (1.22 g, 6.85 mmol) and dibenzoyl peroxide (0.076 g, 0.31 mmol) were placed in a round-bottomed flask fitted with a thermometer, a pressure equalising dropping funnel and a condenser attached to an N_2 line. Carbon tetrachloride (*ca.* 20 ml) was added and the resulting mixture was stirred. A solution of methyl 3-(2-hydroxy-phenyl)-2-methylenepropanoate **(165)** (1.0 g, 5.21 mmol) in carbon tetrachloride (*ca.* 10 ml) was then added dropwise. The resulting mixture was boiled under reflux and irradiated with two Philips 375W incandescent lamps for 2.5 hours. The resulting slurry was filtered through a sintered glass funnel and the solvent removed *in vacuo* to yield a dark oil (1.93 g) flash chromatography [elution with benzene-EtOAc (8:1)] of which, followed by semi-preparative gas chromatography afforded *methyl 3-bromo-3-(2-*

hydroxyphenyl)-2-methylenepropanoate **(166)** (Found: M^+, 269.9880. $C_{11}H_{11}O_3{}^{79}Br$ requires *M*, 269.9891); δ_H (400 MHz; $CDCl_3$) 3.75 (3H, s, CO_2CH_3), 5.60 and 6.23 (2H, 2 x s, CH_2), 6.54 (1H, br s, OH), 6.73 (1H, t, Ar-H), 7.13 (2H, dd, Ar-H) and 7.34 (1H, dd, Ar-H); δ_C (100 MHz; $CDCl_3$) 32.9 (CHBr), 52.4 (CO_2CH_3), 121.4, 126.7, 128.5, 130.2, 130.8, 132.7, 138.5 and 150.6 (Ar-C and $C=CH_2$) and 168.2 (C=O); *m/z* 270 [$M^+(^{79}Br)$, 19.4%] and 159 (100%).

3.2.7 Miscellaneous reactions

3.2.7.1 Preparation of substituted salicylaldehyde dimers

Preparation of *3,4;7,8-bis(4-chlorobenzo)-2,6,9-trioxabicyclo[3.3.1]-nonane* (171a)

5-Chlorosalicylaldehyde **(129b)** (0.5 g, 3.2 mmol) was placed in a round-bottomed flask together with DABCO (0.0179g, 0.16 mmol) and $CHCl_3$ (1 ml) and the flask was stoppered. The course of the reaction was monitored by ^1H NMR spectroscopy and, after several weeks, the formation of *3,4;7,8-bis(4-chlorobenzo)-2,6,9-trioxabicyclo[3.3.1]-nonane* **(171a)**(14%) was evident from the ^1H NMR spectrum.

Attempted preparation of *3,4;7,8-bis(4-bromobenzo)-2,6,9-trioxabicyclo[3.3.1]nonane* (171b)

5-Bromosalicylaldehyde (0.5 g, 2.5 mmol) was treated with DABCO (0.028 g, 0.25 mmol) in $CHCl_3$ (2.0 ml) and the course of the reaction was monitored by ^1H NMR spectroscopy. After several days, at room temperature, none of the desired product was evident in the reaction mixture. The reaction was then boiled under reflux for 2h, but none of the desired product could be detected.

Attempted preparation of *3,4;7,8-bis(3-methoxybenzo)-2,6,9-trioxabicyclo[3.3.1]nonane* (171c)

o-Vanillin (0.50 g, 3.3 mmol) was treated with DABCO (0.11 g, 0.98 mmol) in $CHCl_3$ (2.0 ml). After a month, however, no product was detected by ^1H NMR spectroscopy.

3.2.7.2 Attempted preparation of methyl 6,8-dibromo-3,4-dihydro-4-(methoxy-d_3)-2H-1-benzopyran-3-carboxylate (137d)

Preparation of acryloyl chloride (175)[156]

Acrylic acid (**174**) (8.0 g, 95 mmol) and PCl_3 (5.1 g, 3.7 mmol) were placed in a three-necked flask fitted with a condenser attached to an N_2 line. The mixture was maintained at 60°C for 20 min, following which the reaction mixture separated into two layers. The upper layer was removed, placed in another reaction vessel [to which Cu(I)Cl (0.054 g) was added] and distilled to afford acryloyl chloride (**175**) (3.56 g, 54%) b.p. 72-75°C (lit.[156] 73-75).

Preparation of methyl acrylate-d_3 (176)

Method 1: CD_3OD (1.2 ml) was added dropwise, *via* a syringe to stirred acryloyl chloride (**175**) (3.0 g, 29 mmol) in a cold cup apparatus at 0°C, and the resulting mixture stirred for 20 min. The mixture was made just basic by the addition of a 20% solution of KOH made up in ethylene glycol. The mixture was heated on a waterbath and the deuterated methyl acrylate was collected in the cold cup (*ca.* 600 μl, 22%). Further purification of the sample using preparative gas liquid chromatography afforded methyl acrylate-d_3 (**176**) δ_H (400 MHz; $CDCl_3$) 5.79 and 6.38 (2H, 2 x dd, $CH{=}CH_2$) and 6.09 (1H, dd, $CH{=}CH_2$); δ_C (100 MHz; $CDCl_3$) 49.6 (CD_3), 128.1 and 130.7 ($CH{=}CH_2$) and 166.7 (C=O).

Method 2: CD_3OD (0.4 ml) was added dropwise, under N_2, to stirred acryloyl chloride **(175)** (1.0 g, 9.8 mmol) and the resulting solution stirred for 30 min. Water (1 ml) was added and the resulting mixture was basified with aqueous $NaHCO_3$, and the sample transferred to a small narrow test tube. The acrylate layer was removed with a Pasteur pipette and further dried over molecular sieve (4Å) to yield methyl acrylate-d_3 **(176)** (0.332 g, 54%). This sample was still contaminated with methanol, which proved difficult to remove.

Attempted preparation of *methyl 6,8-dibromo-3,4-dihydro-4-methoxy-2H-1-benzopyran-3-carboxylate* (137d)

A small quantity of *methyl 6,8-dibromo-3,4-dihydro-4-hydroxy-2H-1-benzopyran-3-carboxylate* **(136d)** together with DABCO (0.0030 g, 0.03 mmol) and $CDCl_3$ (500 μl) were added to methyl acrylate-d_3 contained in an NMR tube and the reaction was followed by ^1H NMR spectroscopy for a month, after which period, only starting material and some unidentified side products were observed.

3.2.8 Baylis-Hillman reactions with triacetate derivatives

Reaction with *O*-acetyl-2-(diacetoxymethyl)-4-bromophenol (149b)

4-Acetoxy-2-(diacetoxymethyl)bromobenzene **(149b)**(1.084 g, 3.15 mmol) was placed in a round-bottomed flask together with methyl acrylate (3.0 ml) and 3-hydroxyquinuclidine (0.110 g, 0.866 mmol) and the resulting mixture boiled under reflux for 3h, and stirred at room temperature for 7d. The crude reaction sample was then chromatographed by PLC [elution with hexane-EtOAc (9:1)] to afford the following five components :-

i) 5-Bromosalicylaldehyde (129c) (22%)

ii) Methyl 6-bromo-2*H*-1-benzopyran-3-carboxylate (131c) (10%)

iii) Dimethyl 2-(6-bromo-3-methyl-1-benzopyran-2-on-4-yl)-4-

methylenepentanedioate (142c) (19%; isolated yield)

iv) **Methyl 2-(6-bromo-3-methyl-1-benzopyran-2-on-4-yl) propenoate (141c)** (12%)

v) ***O*-acetyl-2-(diacetoxymethyl)-4-bromophenol (149b)** (32%)

Reaction with *O*-acetyl-2-(diacetoxymethyl)-4-nitrophenol (149a)

A mixture of 4-acetoxy-2-(diacetoxymethyl)-4-nitrophenol **(149a)** (0.814 g, 2.6 mmol), methyl acrylate (0.5 ml) and DABCO (0.0717 g, 0.64 mmol) was stirred in chloroform (1.0 ml) for 1 week in a stoppered flask. The reaction mixture was separated using PLC [elution with hexane-EtOAc (9:1)] to afford the following four products :-

i) **3-Methyl-6-nitro-2*H*-1-benzopyran (177h)** (11%)

δ_H (400 MHz; $CDCl_3$) 2.19 (3H, s, CH_3), 5.09 (2H, d, CH_2), 7.47 (1H, d, Ar-H), 7.80 (1H, br s, CH), 8.39 (1H, dd, Ar-H) and 8.45 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 20.8 (CH_3), 60.7 (CH_2), 98.2, 117.9, 118.9, 123.8, 126.5, 144.3, 156.8 and 158.5 (Ar-C, C-3 and C-4).

ii) ***Methyl 3-hydroxy-3-(2-hydroxy-5-nitrophenyl)-2-methylenepropanoate*** **(130h)** (21%) (Found: M^+, 253.0539. $C_{11}H_{11}O_6N$ requires *M*, 253.0528); δ_H (400 MHz; $CDCl_3$) 1.42-1.81 (2H, br m, 2 x OH), 3.86 (3H, s, CO_2CH_3), 5.67 and 6.44 (2H, 2 x s, CH_2), 5.80 (1H, s, C*H*OH), 6.98 (1H, d, Ar-H), 7.93 (1H, d, Ar-H) and 8.14 (1H, dd, Ar-H); δ_C (100 MHz; $CDCl_3$) 52.7 (CO_2CH_3), 73.1 (CHOH), 118.2, 124.1, 124.4, 125.7, 138.5, 140.9 and 161.9 (Ar-C and $C{=}CH_2$), 128.7 ($C{=}CH_2$) and 167.5 (C=O); *m/z* 253 (M^+,17%) and 220 (100%).

iii) **5-Nitrosalicylaldehyde (129h)** (42%)

iv) **Methyl 6-nitro-2*H*-1-benzopyran-3-carboxylate (131h)** (22%)

3.2.8.1 Attempted cyclisation of methyl 3-hydroxy-3-(2-hydroxy-5-nitrophenyl)-2-methylenepropanoate **(130h)**

To an NMR tube containing a small amount of methyl 3-hydroxy-2-methylene-3-(2-hydroxy-5-nitrophenyl)propanoate **(130h)** in $CDCl_3$ (500 μl), DABCO (0.012 g, 0.1 mmol) was added and the tube shaken. The reaction mixture immediately turned a bright orange yellow and ^1H NMR spectroscopy of the mixture indicated the formation of methyl acrylate and 5-nitrosalicylaldehyde together with the expected DABCO salt of the nitrosalicylaldehyde.

3.2.9 Conjugate addition reactions

3.2.9.1 Preparation of Baylis-Hillman products

Preparation of 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile (178)
4-Nitrobenzaldehyde (5.0 g, 33 mmol), acrylonitrile (1.59 g, 30.1 mmol) and 3-hydroxyquinuclidine (0.45 g, 3.53 mmol) were placed in a round-bottomed flask, which was flushed with dry N_2 and stoppered. The reaction was left for *ca.* 21 days during which time the reaction's progress was monitored by TLC and ^1H NMR spectroscopy, and when sufficient consumption of the starting material was evident, the reaction was worked up by the addition of diethyl ether (*ca.* 50 ml) followed by washing with dilute HCl (10 ml). The organic extract was washed with dilute NaOH (15 ml) and then brine and dried ($MgSO_4$). The solvent was removed *in vacuo* to afford a crude oil, flash chromatography (elution with $CHCl_3$) of which afforded 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile **(178)**[10] (3.94 g, 58.4%); ν_{max}(thin film)/cm^{-1} 3455; δ_H (400 MHz; $CDCl_3$) 2.70 (1H, br s, OH), 5.44 (1H, s, CH), 6.09 and 6.18 (2H, 2 x s, C=CH_2) and 7.59 and 8.26 (4H, 2 x d, Ar-H); δ_C (100 MHz; $CDCl_3$) 73.3 [CH(OH)], 116.2, 124.1, 125.4, 127.4, 145.9 and 148.1 (*C*=CH_2, Ar-C and CN) and 130.9

(C=CH_2); *m/z* 204 (M^+, 15%) and 152 (100%).

Preparation of methyl 3-hydroxy-2-methylene-3-phenylpropanoate (181)

Benzaldehyde (5.0 g, 47 mmol), methyl acrylate (4.24 ml, 47 mmol) and 3-hydroxy-quinuclidine (0.60 g, 4.7 mmol) were allowed to react for 30d in a stoppered flask. Work-up, following the procedure described for the preparation of 3-hydroxy-2-methylene-3-(4-nitrophenyl)-propanenitrile **(178)** afforded methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(181)**[1,157] (3.57 g, 47.6 %); ν_{max}(thin film)/cm^{-1} 3455 and1690 ; δ_H(400 MHz; $CDCl_3$) 3.11 (1H, d, OH), 3.75 (3H, s, CO_2CH_3), 5.55 (1H, d, CH), 5.83 and 6.32 (2H, 2 x s, C=CH_2) and 7.22-7.40 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 51.9 (CO_2CH_3), 67.6 (*C*HOH), 107.9 (C=*C*H_2), 125.8, 126.6, 127.7, 128.3 and 141.4 (*C*=CH_2 and Ar-C) and 166.7 (C=O); *m/z* 192 (M^+, 52%) and 105 (100%).

Preparation of bis(2-cyano-3-phenyl-1-propen-3-yl)ether (182)

Benzaldehyde (5.0 g, 47 mmol), acrylonitrile (2.50 g, 47 mmol) and 3-hydroxy quinuclidine (0.599 g, 4.71 mmol) were allowed to react for 30 days in a stoppered flask. Work-up, following the procedure outlined for the preparation of 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile **(178)** afforded bis(2-cyano-3-phenyl-1-propen-3-yl)ether **(182)**(7.48 g, 71%); ν_{max}(thin film)/cm^{-1} 2238; δ_H (400 MHz; $CDCl_3$) 4.84/4.93 (2H, 2 x s, 2 x CH_2), 5.79/6.02 and 6.18 (4H, 2 x d and br s, 2 x CH_2) and 7.3-7.5 (10H, m, 2 x Ar-H); δ_C (100 MHz; $CDCl_3$) 78.1/78.7 (CH), 116.3/116.5 (*C*=CH_2), 124.0/124.4, 126.8/127.4, 128.8/128.9, 129.0/129.5 and 135.6/136.2 (Ar-C and C≡N) and 130.7/131.3 (C=*C*H_2); *m/z*[§] 301 (M+1, 100%) and 142 (35%).

Preparation of methyl 3-hydroxy- 3-(4-methoxyphenyl)-2-methylene-

[§] Chemical ionisation (CI) using methane.

Preparation of methyl 3-hydroxy- 3-(4-methoxyphenyl)-2-methylene-propanoate (180)

p-Anisaldehyde (5.00 g, 36.7 mmol), methyl acrylate (3.31 ml, 36.7 mmol) and 3-hydroxyquinuclidine (0.47 g, 3.67 mmol) were allowed to react for 30d in a stoppered flask, following the proceedure described for the synthesis of 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile **(178).** Work-up afforded methyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylene propanoate **(180)**[1] (3.31 g, 41%); ν_{max}(thin film)/cm^{-1} 3510 and 1700; δ_H(400 MHz; $CDCl_3$) 2.85 (1H, d, OH), 3.71 and 3.79 (6H, 2 x s, 2 x OCH_3), 5.52 (1H, d, CH), 5.83 and 6.30 (2H, 2 x s, C=CH_2), 6.87 and 7.25 (4H, 2 x d, Ar-H); δ_C (100 MHz; $CDCl_3$) 51.8 and 55.2 (2 x OCH_3), 72.6 (CHOH), 114.3, 125.4, 127.9, 131.9, 133.6 and 142.3 (Ar-C and *C*=*C*H_2) and 166.7 (C=O); *m/z* 222 (M^+, 18%) and 135 (100%).

Preparation of 4-hydroxy-3-methylene-4-phenyl-2-butanone (179)

Benzaldehyde (5.0 g, 47 mmol), methyl vinyl ketone (3.92 ml, 47 mmol) and DABCO (0.53 g, 0.47 mmol) were allowed to react for 14d in a stoppered flask, following the procedure described for the synthesis of 3-hydroxy-2-methylene-3-(4-nitrophenyl)-propanenitrile **(178)**. Work-up afforded 4-hydroxy-3-methylene-4-phenyl-2-butanone **(179)**[1,71] (1.48 g, 18%); ν_{max}(thin film)/cm^{-1} 3400 and 1694; δ_H(400 MHz; $CDCl_3$) 2.29 (3H, s, $COCH_3$), 3.20 (1H, br s, OH), 5.58 and 5.99 (2H, 2 x s, C=CH_2), 6.34 (1H, s, C*H*OH) and 7.22-7.35 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 26.4 (CO*C*H_3), 72.7 (CHOH), 126.2, 126.5, 127.6, 127.9, 128.3, 129.7, 141.6 (Ar-C and C=*C*H_2), 150.1 (*C*=CH_2) and 200.0 (C=O); *m/z* 176 (M^+, 100%) and 43 (1.0%).

3.2.9.2 Conjugate addition reactions with piperidine

Reaction with 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile (178)

Piperidine (28.7μl, 0.29 mmol) was added to a solution of 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile **(178)** (0.055 g, 0.289 mmol) in dry THF (150 μl), in a stoppered vial. After 12 hours, unreacted piperidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (31% d.e.) of *3-hydroxy-3-(4-nitrophenyl)-2-[(piperidin-1-yl)methyl]propanenitrile* **(184)** (0.0704 g, 84%) (Found: M^+, 289.1426 $CH_2(CH_2)_4N$ requires *M*, 289.1426); ν_{max}(thin film)/cm^{-1} 3450, 1735 and 1510; δ_H (400 MHz; $CDCl_3$) 1.41- 1.71 and 2.42- 3.11 [12H, 2 x m, $\overline{CH_2(CH_2)_4N}$, C*H*CN, and CH(O*H*)], 3.71 (2H, br s, CH_2), 5.03/5.18[e] (1H, 2 x d, C*H*OH) and 7.63 and 8.21 (4H, 2 x m, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.5/23.56, 25.51/25.67 and 54.6/55.3 ($\overline{CH_2(CH_2)_4N}$), 36.0/36.3 (*C*HCH_2), 58.5/60.4 (CH_2), 73.3/75.9 (CHOH), 117.6/118.2 (CN), 123.6, 123.9, 126.9/127.5, 147.7/147.9 (Ar-C); *m/z* 289 (M^+, 0.35%) and 98 (100%).

Reaction with 4-hydroxy-3-methylene-4-phenyl-2-butanone (179)

Piperidine (0.0485 g, 0.569 mmol) was added to a solution of 4-hydroxy-3-methylene-4-phenyl-2-butanone **(179)** (0.1002 g, 0.569 mmol) in dry THF (100 μl), in a stoppered vial. After 12 hours, unreacted piperidine was removed *in vacuo* to afford, as a dark brown oil, a diastereomeric mixture (36% d.e.) of 3-hydroxy-4-phenyl-2-[(piperidin-1-yl)methyl]-2-butanoate **(186)** (0.1281 g, 86%); ν_{max}(thin film)/cm^{-1} 3495 and 1690; δ_H (400 MHz; $CDCl_3$) 2.13/2.11 (3H, s, $COCH_3$), 1.30 -1.65 and 2.11-2.74 [13H, 2 x m, $\overline{CH_2(CH_2)_4N}$, CH_2 and CH(O*H*)], 2.95/3.10 (1H, 2 x m, C*H*CH_2), 4.84/5.06 (1H, 2 x d, C*H*OH), 7.15-7.35 (5H, m, Ar- H); δ_C (100 MHz; $CDCl_3$) 25.87/25.97 (CH_3), 23.65/24.12, 31.01/31.74, 54.40, 54.88 ($\overline{CH_2(CH_2)_4N}$), 40.9/41.0 (*C*HCH_2), 60.6/61.2

[e] Chemical shift values quoted in this format, here and elsewhere, refer to diastereomeric nuclei; the combinations, in some cases, being necessarily tentative.

(CH_2), 125.9/126.6, 127.5/127.8, 128.2, 142.1/142.3 (Ar-C) and 208.7/210.1 (C=O).

Reaction with bis(2-cyano-3-phenyl-1-propen-3-yl)ether (182)

Piperidine (0.057 g, 0.67 mmol) was added to a solution of bis(2-cyano-3-phenyl-1-propen-3-yl)ether **(182)** (0.1064 g, 0.67 mmol) in dry THF (100 μl), in a stoppered vial. After 12 hours, unreacted piperidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (34% d.e.) of 3-hydroxy-3-phenyl-2-[(piperidin-1-yl)methyl]propanenitrile**(194)** (0.132 g, 77%); ν_{max}(thin film)/cm^{-1} 2990; δ_H (400 MHz; $CDCl_3$) 1.32-1.70 and 2.41-3.14 (13H, m, $\overline{CH_2(CH_2)_4N}$, CH_2 and CHO*H*), 4.94 and 5.07 (2H, 2 x d,C*H*OH and C*H*CN) and 7.32-7.48 and 8.71-8.85 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.7/24.2, 25.8/25.9 and 54.1/55.3 ($\overline{CH_2(CH_2)_4N}$), 36.5 (*C*HCN), 63.1 (CH_2), 74.1 (CHOH), 108.9, 118.8/118.9, 126.0/125.5, 128.4/128.5, 128.8/130.2, 140.2/140.7 and 144.9 (Ar-C and CN); *m/z* 226 (M^+ -H_2O, 1.2%) and 98 (100%).

Reaction with methyl 3-hydroxy-2-methylene-3-phenylpropanoate (181)

Piperidine (0.184 g, 2.16 mmol) was reacted with methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(181)** (0.415 g, 2.16 mmol) in a stoppered vial. After 12h, the unreacted piperidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (16% d.e.) of methyl 3-hydroxy-3-phenyl-2-[(piperidin-1-yl)methyl]propanoate **(192)** (0.586 g, 98%); ν_{max}(thin film)/cm^{-1} 3420 and 1715; δ_H (400 MHz; $CDCl_3$) 1.30-1.70 and 2.30- 3.15 (13H, 3 x m, $\overline{CH_2(CH_2)_4N}$, CH_2 and CHO*H*), 3.37/3.61 (3H, 2 x s, CO_2CH_3), 4.97/5.27 (1H, 2 x d, C*H*OH) and 7.20- 7.41 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.9/24.1, 25.9/26.0 and 54.7/56.2 ($\overline{CH_2(CH_2)_4N}$), 47.2 (*C*HCH_2), 49.9 (CO_2CH_3), 61.2 (CH_2), 75.1/78.0 (*C*HOH), 126.0/126.5, 127.4/127.7, 128.1 and 141.6/142.2 (Ar-C) and 171.9/172.4 (C=O); *m/z* 277 (M^+, 0.5%) and 98 (100%).

Reaction with methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate

(180)

Piperidine (22.2μl, 0.224 mmol) was reacted with methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate **(180)** (0.052 g, 0.224 mmol) in a stoppered vial. After 12h, unreacted piperidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (31% d.e.) of *methyl 3-hydroxy-3-(4-methoxyphenyl)-2-[(piperidin-1-yl)methyl]propanoate* **(188)** (0.0538 g, 78%) (Found: M^+, 307.1788. $C_{17}H_{25}O_4N$ requires *M*, 307.1783); ν_{max}(thin film)/cm^{-1} 3430 and 1705; δ_H (400 MHz; $CDCl_3$) 1.40-1.71 and 2.31-3.11 [14H, 2 x m, $\overline{CH_2(CH_2)_4N}$, C*H*CO_2CH_3, CH_2 and CH(O*H*)], 3.70 (6H, br s, 2 x OCH_3), 4.89/5.17 (1H, 2 x d, C*H*OH), 6.82 (2H, m, Ar-H) and 7.14-7.27 (2H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.9/24.0, 25.8/25.9 and 54.7 ($\overline{CH_2(CH_2)_4N}$), 50.0 (CO_2CH_3), 51.8 ($CHCO_2CH_3$), 55.1 (OCH_3), 174.7/177.4 (*C*HOH), 113.5/113.6, 127.2/127.7, 133.6 and 158.9 (Ar-C) and 172.3/172.5 (C=O); *m/z* 307 (M^+, 12%) and 98 (100%).

3.2.9.3 Conjugate addition reations with pyrrolidine

Reaction with methyl 3-hydroxy-2-methylene-3-phenylpropanoate (181)

Pyrrolidine (0.189 g, 2.66 mmol) was added to a solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(181)** (0.510g, 2.66 mmol) in dry THF (250 μl) in a stoppered vial. After 12h, the unreacted pyrrolidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (29% d.e.) of *methyl 3-hydroxy-3-phenyl-2-[(pyrrolidin-1-yl)methyl]propanoate* **(191)** (0.517 g, 66%) (Found: M^+, 263.1510. $C_{15}H_{21}O_3N$ requires *M*, 263.1521); ν_{max}(thin film)/cm^{-1} 3400 and 1725; δ_H (400 MHz; $CDCl_3$) 1.62-1.80 and 2.30-3.25 (14H, 2 x m, $\overline{CH_2(CH_2)_3N}$, CH_2, C*H*CO_2CH_3 andCHO*H*), 3.29/3.54 (3H, 2 x s, CO_2CH_3), 4.89/4.98 (1H, 2 x d, C*H*OH) and 7.14-7.35 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.48/23.49 and 53.9/54.1 ($\overline{CH_2(CH_2)_3N}$), 51.6/51.7 ($CHCO_2CH_3$), 57.9 (CH_2), 75.0/78.1 (*C*HOH), 126.1/126.4, 122.5/128.1,

127.1 and 141.7/142.3 (Ar-C) and 172.0/172.8 (C=O); *m/z* 263 (M^+, 1.3%) and 84 (100%).

Reaction with 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile (178)

Pyrrolidine (0.0225 g, 0.316 mmol) was added to a solution of 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile **(178)** (0.060g, 0.32 mmol) in dry THF (150 μl) in a stoppered vial. After 12h, unreacted pyrrolidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (16% d.e.) of *3-hydroxy-3-(4-nitrophenyl)-2-[(pyrrolidin-1-yl)methyl]propanenitrile* **(183)** (0.0843 g, 97%) (Found: M^+, 275.1282. $C_{14}H_{17}O_3N_3$ requires *M*, 275.1270); ν_{max}(thin film)/cm^{-1} 3190, 1735 and 1350; δ_H (400 MHz; $CDCl_3$) 1.72-1.95 and 2.56-3.42 [12H, 2 x m, $\overline{CH_2(CH_2)_3N}$, CH_2, CH(O*H*) and CHCN], 5.08/5.21 (1H, d and br s, C*H*OH) and 7.66-7.79 and 8.23- 8.34 (4H, 2 x d, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.5/23.6 and 54.2/54.9 ($\overline{CH_2(CH_2)_3N}$), 37.1/37.7 (*C*HCN), 56.5 and 56.6 (CH_2 and CO_2CH_3), 74.0/76.3 (*C*HOH) and 117.7/117.1, 123.7, 126.9/127.5 and 147.6 and 147.8 (Ar-C and C≡N); *m/z* 275 (M^+, 0.4%) and 84 (100%).

Reaction with methyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylene-propanoate (180)

Pyrrolidne (0.0172 g, 0.241 mmol) was added to a solution of methyl 3-hydroxy-3-(4-methoxyphenyl)-2-methylenepropanoate **(180)** (0.056 g, 0.241 mmol) in dry THF (100 μl) and left to react for 12h, following which unreacted pyrrolidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (28% d.e.) of *methyl 3-hydroxy-3-(4-methoxyphenyl)-2-[(pyrrolidin-1-yl)methyl]propanoate* **(187)** (0.0624 g, 89%) (Found: M^+, 293.1619. $C_{16}H_{23}O_4N$ requires *M*, 293.1627); ν_{max}(thin film)/cm^{-1} 3490, 1690 and 1520; δ_H (400 MHz; $CDCl_3$) 1.77-1.91 and 2.45-3.49 (12H, $\overline{CH_2(CH_2)_3N}$, CH_2 , C*H*CO_2CH_3 and CHO*H*), 3.63 (3H, s, OCH_3), 3.76 (3H, s, CO_2CH_3), 4.93/5.10 (1H, 2 x d, C*H*OH), 6.76 (2H, m, Ar-H), 7.14 (1H, d, Ar-H) and

7.24 (1H, d, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.4 and 54.1/54.19 ($\overline{CH_2(CH_2)_3N}$), 49.8 (*C*HCO_2CH_3), 55.1 and 58.1 (CH_2 and CO_2CH_3), 74.7/77.8 (*C*HOH), 113.5/113.52, 127.5/127.6, 133.7/134.5 and 158.9/159.1 (Ar-C) and 172.1/172.8 (C=O); *m/z* 293 (M^+, 13%) and 84 (100%).

Reaction with bis(2-cyano-3-phenyl-1-propen-3-yl)ether (182)

Pyrrolidine (0.0489 g, 0.688 mmol) was added to a solution of bis(2-cyano-3-phenyl-1-propen-3-yl)ether **(182)**(0.1101 g, 0.688 mmol) in dry THF (100 μl) in a stoppered flask. After 12h, unreacted pyrrolidine was removed *in vacuo* to afford, as a dark brown oil, a diastereomeric mixture (25% d.e.) of *3-hydroxy-3-phenyl-2-[(pyrrolidin-1-yl)methyl]propanenitrile* **(193)** (0.129 g, 82%) (Found: M^+, 229.1333. $C_{14}H_{18}ON$ requires *M*, 229.1341); ν_{max}(thin film)/cm^{-1} 3400 and 2995; δ_H (400 MHz; $CDCl_3$) 1.72-1.92 and 2.48-3.40 (11H, 2 x m, $\overline{CH_2(CH_2)_3N}$, CH_2 and CHO*H*), 4.98 and 5.07 (2H, 2 x d,C*H*OH and CHCN) and 7.10-7.51 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.5/23.6 and 53.7/53.8 ($\overline{CH_2(CH_2)_3N}$), 54.2/54.8 (*C*HCN), 60.0 (CH_2) and 126.0/126.4, 128.3, 128.4/128.5, 128.8/129.8,133.5 and 144.5 (Ar-C and CN); *m/z* 211 (M^+ -H_2O, 2.2%) and 84 (100%).

Reaction with 4-hydroxy-3-methylene-4-phenyl-2-butanone (179)

Pyrrolidine (0.0445 g, 0.626 mmol) was added to a stirred solution of 4-hydroxy-3-methylene-4-phenyl-2-butanoate **(179)** (0.1102, 0.626 mmol) in dry THF (100 μl) in a stoppered flask. After 12h, unreacted pyrrolidine was removed *in vacuo* to afford, as a yellow oil, a diastereomeric mixture (10% d.e.) of 4-hydroxy-4-phenyl-3-[(1-pyrrolidinyl)methyl]-2-butanone **(185)** (0.128 g, 83%); ν_{max}(thin film)/cm^{-1} 3360 and 1720; δ_H (400 MHz; $CDCl_3$) 2.66-3.35 (15H, m, $\overline{CH_2(CH_2)_3N}$, CH_2, C*H*COC*H*$_3$ and CHO*H*), 4.90/5.06 (1H, 2 x d, C*H*OH) and 7.10-7.40 (5H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 23.4/23.5 (CH_3), 31.8 and 54.3/53.6 ($\overline{CH_2(CH_2)_3N}$), 54.2 and 56.5/56.6 (CH_2 and *C*H$COCH_3$), 78.7 (*C*HOH), 126.0, 126.6, 127.6 and 128.4 (Ar-C) and 209.0

(C=O); *m/z* 247 (M^+, 1.0%) and 84 (100%).

3.2.9.4 Conjugate addition reations with thiophenol

Reaction with methyl 3-hydroxy-2-methylene-3-phenylpropanoate (181)

NaOH (0.208 g, 5.2 mmol) was added to thiophenol (0.573 g, 5.2 mmol) in water (2.0 ml), and the resulting mixture allowed to stand for 10 minutes to generate the benzenethiolate anion. The benzenethiolate solution was then added dropwise, *via* a pressure equalising dropping funnel, into a solution of methyl 3-hydroxy-2-methylene-3-phenylpropanoate **(181)**(1.00 g, 5.2 mmol) in THF (10 ml), contained in a three-necked flask fitted with a thermometer and a condenser attached to an NaOH scrubber. During the addition of the thiophenol the temperature rose from 19 to 23°C. After 1 hour brine was added to the solution, which was then extracted with ethyl acetate. The extract was dried ($MgSO_4$), and the solvent removed *in vacuo* to afford, as a colourless oil, a diastereomeric mixture (5% d.e.) of *methyl 3-hydroxy-3-phenyl-2-[(phenylthio)methyl]-propanoate* **(189a)** (1.34 g, 88%) (Found: M^+, 302.0974. $C_{17}H_{18}O_3S$ requires ***M***, 302.0976); ν_{max}(thin film)/cm^{-1} 3495 and 1720; δ_H (400 MHz; $CDCl_3$) 2.77 (1H, br s, OH), 2.95-3.24 (4H, m, C*H*CO_2CH_3, CH_2 and CHO*H*), 3.56/3.66 (3H, 2 x s, CO_2CH_3), 4.96/5.04 (1H, 2 x d, C*H*OH) and 7.15- 7.40 (10H, m, Ar-H); δ_C (100 MHz; $CDCl_3$) 30.8/33.2 (*C*HCO_2CH_3), 51.9/51.95 and 52.7/53.1 (CH_3 and CH_2), 73.9/74.3 (*C*HOH), 125.9/126.2, 126.6, 127.9, 128.2, 128.5/128.6, 128.8/128.9, 129.4, 130.1, 135.0/135.4 and 140.8/141.1 (Ar-C) and 173.5/173.8 (C=O); *m/z* 302 (M^+, 3.4%) and 87 (100%); Flash chromatography (elution with $CHCl_3$) of the crude material afforded the dehydration product, *methyl 3-phenyl-2-[(phenylthio)methyl]-2-propenoate* **(189b)** (Found: M^+, 284.0861. $C_{17}H_{16}O_2S$ requires ***M***, 284.0870); ν_{max}(thin film)/

cm^{-1} 1710; δ_H (400 MHz; $CDCl_3$) 3.80 (3H, s, CO_2CH_3), 4.04 (2H, s, CH_2), 7.1-7.4 (10H, m, Ar-H) and 7.75 (1H, s, C=CH); δ_C (100 MHz; $CDCl_3$) 32.3 (CO_2CH_3), 52.3 (CH_2), 126.8, 128.4, 128.6, 128.9, 128.94, 129.4, 130.9, 134.8, 135.9 and 141.5 (Ar-C, and *C*=*C*H) and 167.7 (C=O); *m/z* 284 (M^+, 7.2%) and 115 (100%)].

Following procedures similar to that described for the preparation of methyl 3-hydroxy-3-phenyl-2-[(phenylthio)methyl]propanoate **(189)** a solution of sodium benzenethiolate was added to solutions of :-

i) **3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile (178)** in water;

ii) **methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate (180)** in water;

iii) **4-hydroxy-3-methylene-4-phenyl-2-butanoate (179)** in THF (the benzenethiolate anion generated with NaH); and

iv) **bis(2-cyano-3-phenyl-1-propen-3-yl)ether (182)** in THF (the benzenethiolate anion generated with NaH).

In each of the four cases, ^1H NMR spectroscopy indicated that the material isolated after work-up contained none of the expected product.

3.2.9.5 Conjugate addition reations with phenol

Reaction with 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile (178)

Phenol (0.178 g, 1.89 mmol) was added to a stirred suspension of washed NaH (0.1088 g, 2.27 mmol) in dry THF (3.0 ml) in a two-necked flask fitted with a condenser attached to an N_2 line. After *ca.* 10 minutes,3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile **(178)** (0.359 g, 1.89 mmol) was added and the resulting mixture stirred overnight. The mixture was then diluted in chloroform (20 ml) and washed with brine. Evaporation of the solvent *in vacuo* afforded a residue, shown by ^1H NMR spectroscopy to contain none of the expected product.

Following the procedure described for the reaction of 3-hydroxy-2-methylene-3-(4-nitrophenyl)propanenitrile **(178)**, a solution of sodium phenoxide in THF was treated with:-

i) **methyl 3-hydroxy-2-methylene-3-phenylpropanoate (181) (30% yield);**

ii) **4-hydroxy-3-methylene-4-phenyl-2-butanoate (179)**;

iii) **di(2-cyano-3-phenyl-1-propen-3-yl)ether (182)**;

iv) **methyl 3-hydroxy-2-methylene-3-(4-methoxyphenyl)propanoate (180)**.

In each of the four cases, ^{1}H NMR spectroscopy indicated that the material isolated after work-up contained none of the expected product.

3.2.10 Preparation of compounds used for the kinetic study

Preparation of methyl 3-hydroxy-2-methylenebutanoate (196)

A solution of methyl acrylate (12.9 ml, 140 mmol), acetaldehyde (20.0 g, 400 mmol) and DABCO (1.8 g, 16 mmol) were stirred in a sealed flask for 7d. The reaction was extracted with diethyl ether, washed sequentially with HCl (6M), NaOH (2M) and brine. The ethereal layer was dried ($MgSO_4$) and the solvent removed *in vacuo* to afford a crude product (16.3 g) which was distilled to afford methyl 3-hydroxy-2-methylenebutanoate **(196)** (6.27 g, 35%) b.p. 40 °C/ 0.3 mmHg (lit.,[156] 45°C/ 0.5 mmHg); ν_{max}(thin film)/cm^{-1} 3450; δ_H (400 MHz; $CDCl_3$) 1.28 (3H, d, CH_3), 3.08 (1H, d, OH)[ŧ], 3.68 (3H, s, CO_2CH_3), 4.50 [1H, q, C*H*(CH_3)] and 5.75 and 6.12 (2H, 2 x s, C=CH_2).

Preparation of methyl (*Z*)-2-(chloromethyl)but-2-enoate (197)

To a stirred solution of methyl 3-hydroxy-2-methylenebutanoate **(196)** (10.0 g, 76.9 mmol) in HCl (23 ml; 47%) at 0°C, was added, conc. H_2SO_4 (20 ml) and the reaction stirred at room temperature for 24 h, following which the mixture was poured over crushed ice, neutralised ($NaHCO_3$) and extracted with diethyl ether. The ethereal extract was washed with brine, separated and dried ($MgSO_4$) and the solvent removed *in vacuo*. The crude product was distilled under reduced pressure (further purification using preparative gas chromatography to afford a purer product was carried out) to afford methyl (*Z*)-2-(chloromethyl)but-2-enoate **(197)** (3.13 g, 28%) b.p. 94°C/15mmHg; ν_{max}(thin film)/cm^{-1} 1716; δ_H (400 MHz; $CDCl_3$) 1.89 [3H, d, CH(C*H*$_3$)], 3.71 (3H, s, CO_2CH_3), 4.29 (2H, s, CH_2) and 7.07 [1H, q, C*H*(CH_3)]; δ_C (100 MHz; $CDCl_3$) 14.5 (CH_3), 36.9 (CH_2), 52.1 (CO_2CH_3), 130.1 [*C*=CH(CH_3)], 143.6 [*C*H(CH_3)] and 166.0 (C=O).

[ŧ] D_2O exchange

Preparation of methyl (*Z*)-2-(bromomethyl)but-2-enoate (198)

To a stirred solution of methyl 3-hydroxy-2-methylenebutanoate **(196)** (6.27g, 48.23 mmol) in HBr (17.6 ml; 48%) at 0°C, was added conc. H_2SO_4 (10.7 ml) dropwise and the resulting mixture stirred for 24h at room temperature. The reaction mixture was then poured over crushed ice (100 ml), and neutralised ($NaHCO_3$) and extracted into diethyl ether. The ethereal extract was washed with brine, separated and dried ($MgSO_4$), and the solvent removed *in vacuo*. The resulting oil was distilled under reduced pressure to afford methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (4.77 g, 51.5%) b.p. 40°C/0.4 mmHg (lit.,[112] 52°C/2.5 mmHg); ν_{max}(thin film)/cm^{-1} 1720 and 1642; δ_H (400 MHz; $CDCl_3$) 1.85 (3H, d, $CHCH_3$), 3.73 (3H, s, OCH_3), 4.17 (2H, s, CH_2) and 7.0 (1H, q, $CHCH_3$); δ_C (100 MHz; $CDCl_3$) 14.3 (CH_3), 23.8 (CH_2), 51.8 ($COCH_3$), 130.1 (C=$CHCH_3$), 143.1 ($CHCH_3$) and 165.7 (C=O).

Preparation of methyl (*Z*)-2-(iodomethyl)but-2-enoate (199)[97]

Conc. H_3PO_4 (23 ml) was added dropwise *via* a pressure equalising funnel to a stirred solution of methyl 3-hydroxy-2-methylenebutanoate **(196)** (8.97 g, 69 mmol) and conc. HI (26.5 ml; 57%). The resulting mixture was stirred for 12h after which it was poured over crushed ice (100 ml) and neutralised ($NaHCO_3$). The mixture was extracted into diethyl ether, washed with brine and dried ($MgSO_4$). The solvent was removed *in vacuo* and the resulting oil was distilled under reduced pressure to afford methyl (*Z*)-2-(iodomethyl)but-2-enoate **(199)** (3.41 g, 21%) b.p. 64°C/ 0.6 mmHg; δ_H (400 MHz; $CDCl_3$) 1.75 [3H, d, $CH(CH_3)$], 3.76 (3H, s, CO_2CH_3), 4.09 (2H, s, CH_2) and 6.95 [1H, q, $CH(CH_3)$]; δ_C (100 MHz; $CDCl_3$) 14.5 (CH_3), 51.96 (CH_2), 51.99 (CO_2CH_3), 131.3 [C=$CH(CH_3)$], 141.3 [$CH(CH_3)$] and 165.7 (C=O).

Attempted preparation of methyl (*Z*)-2-(iodomethyl)but-2-enoate (199)[112]

Conc. H_3PO_4 (27 ml) was added dropwise to a stirred mixture of methyl 3-hydroxy-2-methylenebutanoate **(196)** (9.4 g, 72.3 mmol) and HI (9.8 g, 77 mmol) in water (15 ml)

at 0°C. The resulting mixture was stirred at room temperature for 5d, followed by the workup described above. ^{1}H NMR showed that no product had been formed.

Preparation of methyl 2-methyl-3-oxobutanoate (201)[99]

Na (1.84 g, 80 mmol) was added slowly to a stirred solution of dry methanol (20 ml) in a three-necked flask fitted with a condenser attached to an N_2 line and a pressure equalising dropping funnel. Methyl acetoacetate **(200)** (7.55 ml, 70 mmol) was added dropwise and the resulting mixture was heated to 50°C. Methyl iodide (4.6 ml, 74 mmol) was then added dropwise and boiled under reflux for 5h to afford a clear yellow solution. After cooling, the solvent was removed *in vacuo* and the resulting mixture filtered through a sintered glass funnel. The resulting oil was distilled under reduced pressure to afford methyl 2-methyl-3-oxobutanoate **(201)** (4.34 g, 48%) b.p. 82°C/ 15 mmHg; ν_{max}(thin film)/cm^{-1} 1708 and 1715; δ_H (400 MHz; $CDCl_3$) 1.30 (3H, m, CH_3), 2.18 (3H, s, CH_3O), 3.47 (1H, q, CH) and 3.68 (3H, s, CO_2CH_3); δ_C (100 MHz; $CDCl_3$) 12.6 (CH_3), 21.8 (C-H), 49.7 and 53.3 ($COCH_3$ and CO_2CH_3), 170.9 and 173.9 (2 x C=O).

Preparation of sodium methoxide

Sodium (*ca.* 2 g) was added portion-wise to stirred dry methanol (*ca.* 100 ml) in a round-bottomed flask fitted with a condenser and an N_2 line. After the addition was complete, the solvent was removed *in vacuo* to afford sodium methoxide as a white powder which was stored under an atmosphere of dry N_2, in a stoppered vial in a desiccator.

3.3 KINETIC STUDY OF NUCLEOPHILIC SUBSTITUTION REACTIONS OF 2-HALOGENOMETHYL ESTERS

3.3.1 Kinetic procedure for reactions in methanol-d_4

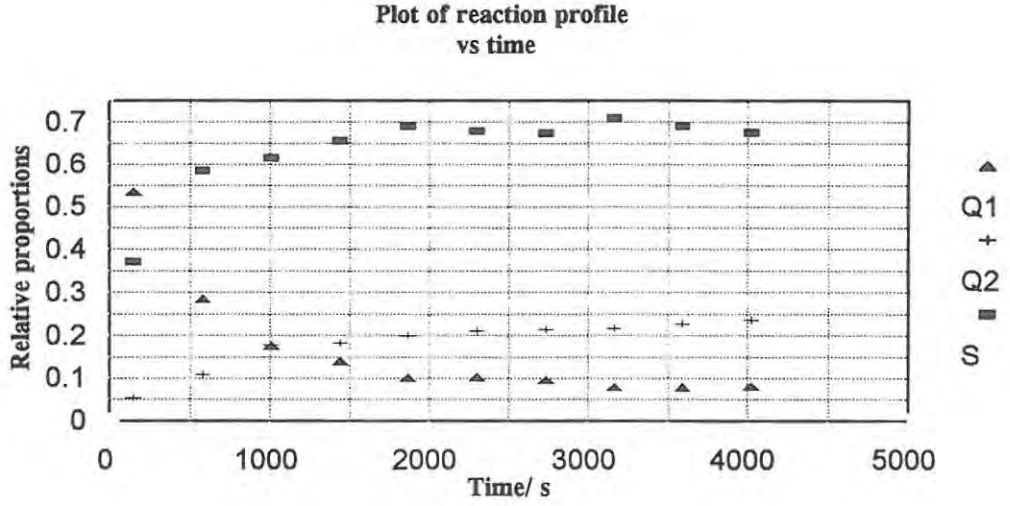
Approximately 1.7 mg of NaOMe was accurately weighed (to five decimal figures) into the dry reaction flask and CD_3OD (Merck, Uvasol; 99.5%D) was added to achieve a concentration of 0.02167 mol.L^{-1}. To the resulting solution was added the nucleophile, in sufficient quantity to afford a nucleophile concentration of 0.02167 mol.L^{-1}. The resulting mixture was stirred under dry N_2 for 1h to generate the nucleophilic anion, after which the sample was divided into three equal aliquots of ≥500 μl and each aliquot was injected into a separate, dry, N_2-flushed NMR tube *via* a septum. The NMR tube was inserted into the NMR spectrometer to allow equilibration to the probe temperature (303 K) and the instrument was tuned and locked for that sample. The tube was removed and the required amount of unsaturated halogenoester was injected *via* the septum into the NMR tube, which was then shaken to mix the sample. At the same time a stop-watch was started (T_o) to measure the delay from injection to first pulse. The tube was then re-inserted into the probe and data acquisition commenced using an automatic programme. After a suitable number of data points had been collected, the kinetic run was terminated and the data analysed. In some cases the nucleophile was diluted further by adding deuteriated solvent to the NMR tube.

3.3.1.1 Kinetic data and graphs for kinetic studies carried out in methanol-d_4.

Experiment M-1

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.03873 mol.L^{-1}) **[a]** and the enolate of nucleophile methyl 2-methyl-3-oxobutanoate **(201)** (0.07024 mol.L^{-1}) **[b]** in methanol-d_4.

Expt. No.	Time/ s	x	[a]	[b]
100	147.5	0.01798	0.02075	0.05226
101	578.5	0.02767	0.01105	0.04257
102	1009.5	0.03191	0.00681	0.03833
103	1440.5	0.03329	0.00544	0.03695
104	1871.5	0.03482	0.00390	0.03542
105	2302.5	0.03472	0.00401	0.03552
106	2733.5	0.03499	0.00374	0.03525
107	3164.5	0.03563	0.00310	0.03461
108	3595.5	0.03568	0.00304	0.03456
109	4026.5	0.03559	0.00314	0.03465

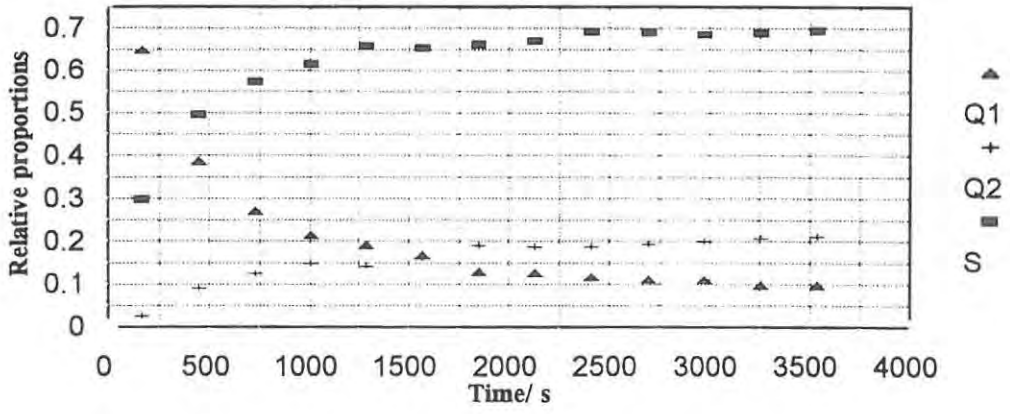


Experiment M-2

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(chloromethyl)but-2-enoate **(197)** (0.02324 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.07024 mol.L^{-1}) **[b]** in methanol-d_4.

Expt. No.	Time/ s	x	[a]	[b]
100	165.5	0.00815	0.01509	0.06209
101	446.5	0.01423	0.00901	0.05601
102	727.5	0.01695	0.00629	0.05329
103	1008.5	0.01825	0.00499	0.05199
104	1289.5	0.01880	0.00444	0.05144
105	1570.5	0.01934	0.00390	0.05090
106	1851.5	0.02022	0.00302	0.05002
107	2132.5	0.02027	0.00297	0.04997
108	2413.5	0.02052	0.00272	0.04972
109	2694.5	0.02063	0.00261	0.04961
111	2975.5	0.02065	0.00259	0.04959
112	3256.5	0.02096	0.00228	0.04928
113	3537.5	0.02094	0.00230	0.04930

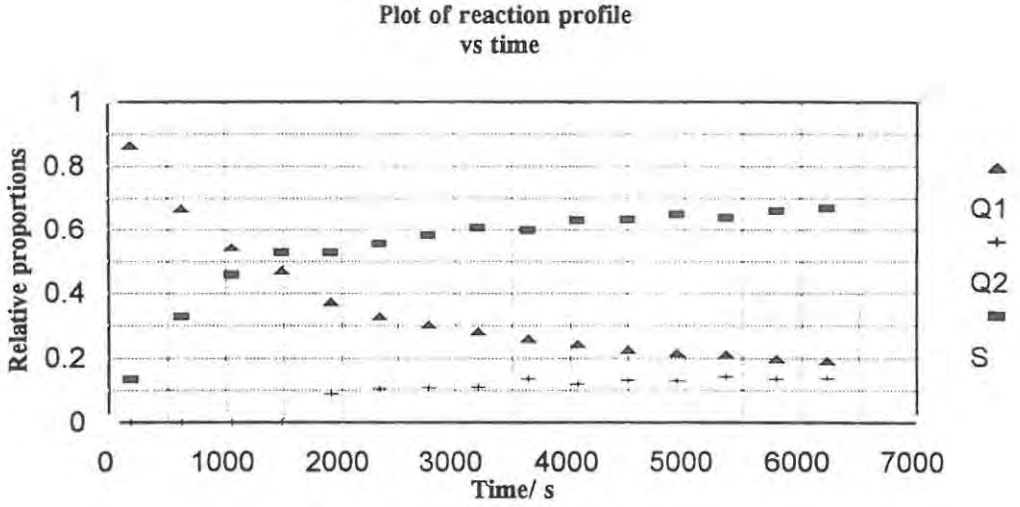
Plot of reaction profile vs time



Experiment M-3

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.003859 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.02289 mol.L^{-1}) **[b]** in methanol-d_4.

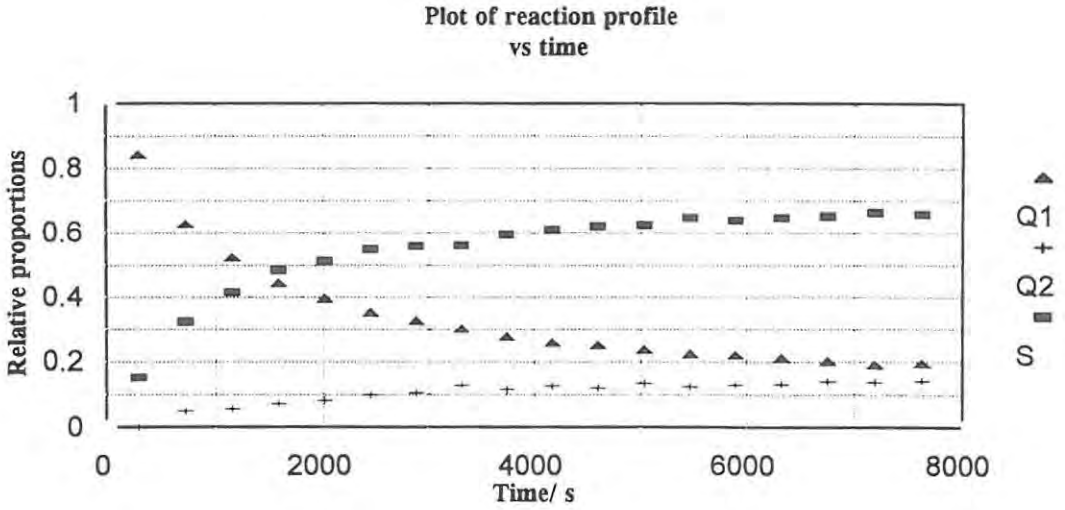
Expt. No.	Time/ s	x	[a]	[b]
100	188.5	0.00051	0.00335	0.02238
101	619.5	0.00128	0.00258	0.02161
102	1050.5	0.00175	0.00210	0.02114
103	1481.5	0.00203	0.00183	0.02086
104	1912.5	0.00241	0.00145	0.02048
105	2343.5	0.00258	0.00128	0.02031
106	2774.5	0.00269	0.00117	0.02020
107	3205.5	0.00277	0.00109	0.02012
108	3636.5	0.00285	0.00101	0.02004
109	4067.5	0.00291	0.00095	0.01998
111	4498.5	0.00298	0.00088	0.01991
112	4929.5	0.00302	0.00084	0.01987
113	5360.5	0.00304	0.00082	0.01986
114	5791.5	0.00309	0.00077	0.01980
115	6222.5	0.00311	0.00075	0.01978



Experiment M-4

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.008159 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.02167 mol.L^{-1}) **[b]** in methanol-d_4.

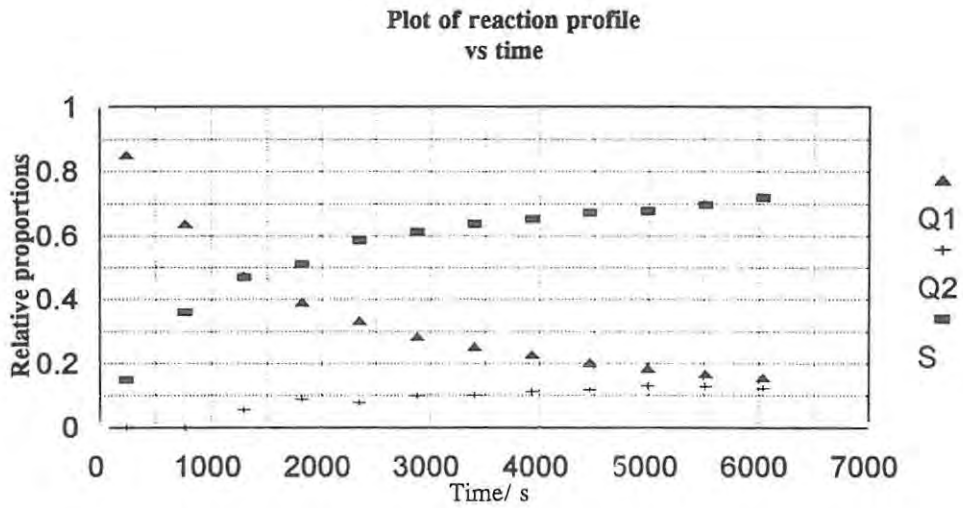
Expt. No.	Time/ s	x	[a]	[b]
100	293.5	0.00127	0.00689	0.02040
101	724.5	0.00303	0.00513	0.01864
102	1155.5	0.00388	0.00428	0.01779
103	1586.5	0.00453	0.00363	0.01714
104	2017.5	0.00492	0.00324	0.01675
105	2448.5	0.00528	0.00288	0.01639
106	2879.5	0.00549	0.00267	0.01618
107	3310.5	0.00569	0.00247	0.01598
108	3741.5	0.00588	0.00228	0.01579
109	4172.5	0.00604	0.00212	0.01563
111	4603.5	0.00610	0.00206	0.01557
112	5034.5	0.00621	0.00195	0.01546
113	5465.5	0.00632	0.00184	0.01535
114	5896.5	0.00634	0.00182	0.01533
115	6327.5	0.00641	0.00175	0.01526
116	6758.5	0.00649	0.00167	0.01518
117	7189.5	0.00659	0.00157	0.01508
118	7620.5	0.00655	0.00161	0.01512



Experiment M-5

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.005439 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.02167 mol.L^{-1}) **[b]** in methanol-d_4.

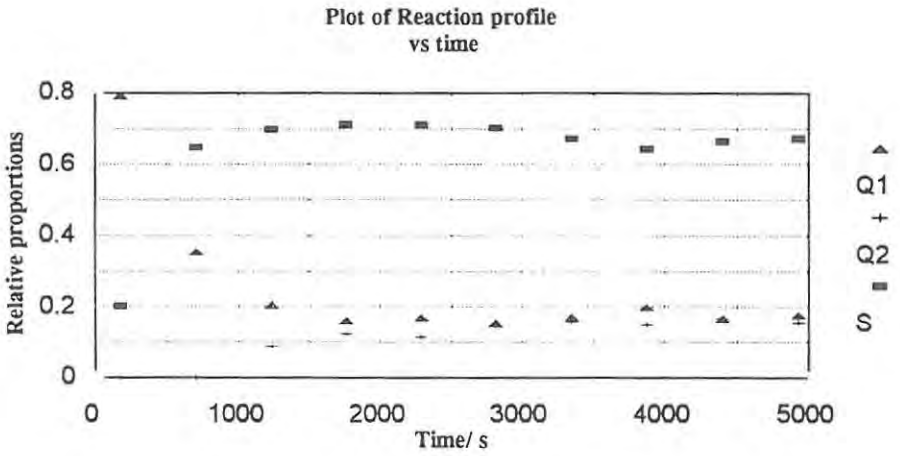
Expt. No.	Time/ s	x	[a]	[b]
100	238	0.00080	0.00464	0.02087
101	766	0.00197	0.00347	0.01970
102	1294	0.00286	0.00258	0.01881
103	1822	0.00331	0.00213	0.01836
104	2350	0.00362	0.00182	0.01805
105	2878	0.00390	0.00154	0.01777
106	3406	0.00406	0.00138	0.01761
107	3934	0.00420	0.00124	0.01747
108	4462	0.00433	0.00111	0.01734
109	4990	0.00443	0.00101	0.01724
111	5518	0.00452	0.00092	0.01715
112	6046	0.00459	0.00085	0.01710



Experiment M-6

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.00193 Mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.02167 Mol.L^{-1}) **[b]** in methanol-d_4.

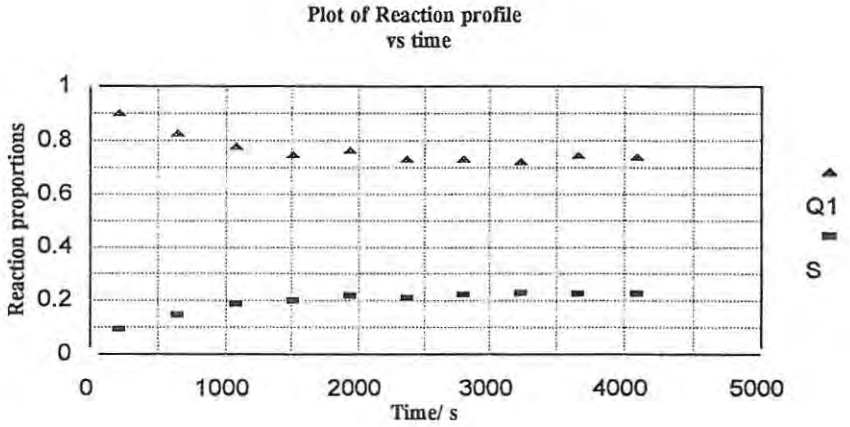
Expt. No.	Time/ s	x	[a]	[b]
100	179	0.00040	0.00153	0.02127
101	707	0.00124	0.00069	0.02043
102	1235	0.00153	0.00040	0.02014
103	1763	0.00162	0.00031	0.02005
104	2291	0.00160	0.00033	0.02007
105	2819	0.00163	0.00030	0.02004
106	3347	0.00160	0.00033	0.02007
107	3875	0.00155	0.00038	0.02012
108	4403	0.00161	0.00032	0.02006
109	4931	0.00159	0.00034	0.02008



Experiment M-7

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)**(0.01544 Mol.L^{-1})**[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.01625 Mol.L^{-1})**[b]** in methanol-d_4.

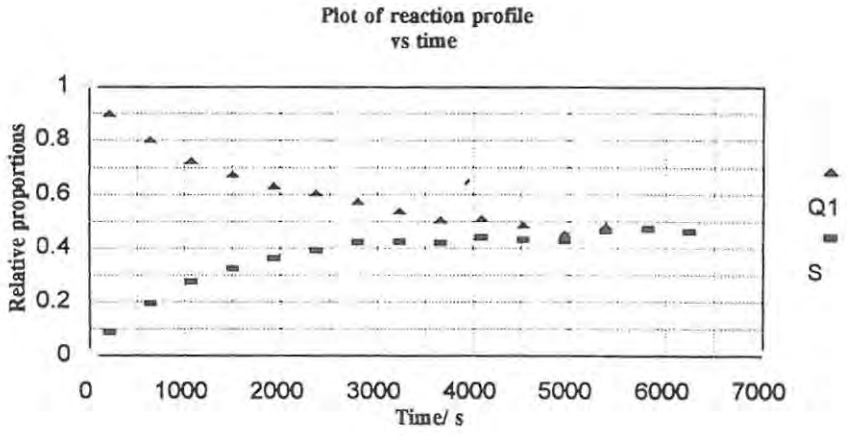
Expt. No.	Time/ s	x	[a]	[b]
100	214.5	0.00149	0.01395	0.01476
101	645.5	0.00264	0.01280	0.01361
102	1076.5	0.00336	0.01208	0.01289
103	1507.5	0.00385	0.01159	0.01240
104	1938.5	0.00359	0.01185	0.01266
105	2369.5	0.00410	0.01134	0.01215
106	2800.5	0.00411	0.01133	0.01214
107	3231.5	0.00426	0.01118	0.01199
108	3662.5	0.00389	0.01155	0.01236
109	4093.5	0.00400	0.01144	0.01225
111	4524.5	0.00399	0.01145	0.01226
112	4955.5	0.00361	0.01183	0.01264
113	5386.5	0.00404	0.01140	0.01221
114	5817.5	0.00362	0.01182	0.01263
115	6248.5	0.00417	0.01127	0.01208



Experiment M-8

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.007719 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.01625 mol.L^{-1}) **[b]** in methanol-d_4.

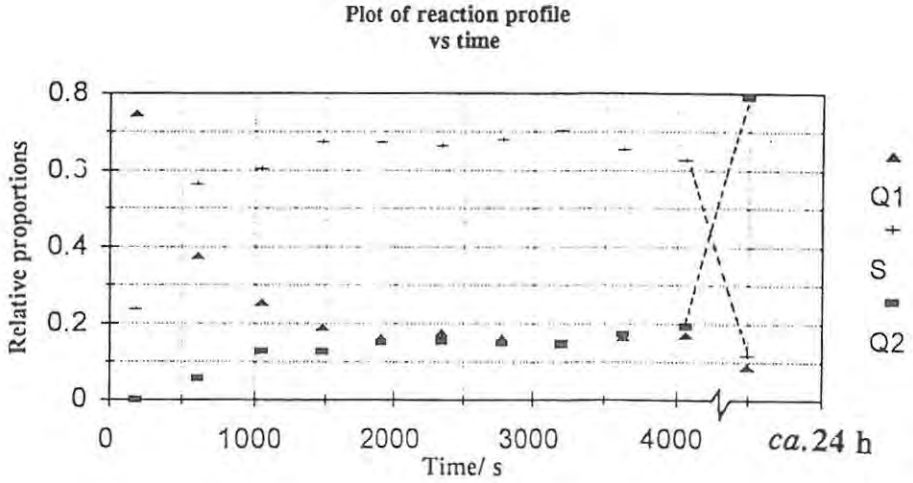
Expt. No.	Time/ s	x	[a]	[b]
100	214.5	0.00076	0.00696	0.01549
101	645.5	0.00151	0.00621	0.01474
102	1076.5	0.00213	0.00559	0.01412
103	1507.5	0.00250	0.00522	0.01375
104	1938.5	0.00283	0.00489	0.01342
105	2369.5	0.00301	0.00471	0.01324
106	2800.5	0.00327	0.00445	0.01298
107	3231.5	0.00354	0.00418	0.01271
108	3662.5	0.00380	0.00392	0.01245
109	4093.5	0.00375	0.00397	0.01250
111	4524.5	0.00394	0.00378	0.01231
112	4955.5	0.00421	0.00351	0.01204
113	5386.5	0.00398	0.00374	0.01227
114	5817.5	0.00406	0.00366	0.01219
115	6248.5	0.00413	0.00359	0.01212



Experiment M-9

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.003895 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.02167 mol.L^{-1}) **[b]** in methanol-d_4.

Expt. No.	Time/ s	x	[a]	[b]
100	184.5	0.00097	0.00289	0.02070
101	615.5	0.00240	0.00146	0.01927
102	1046.5	0.00288	0.00098	0.01879
103	1477.5	0.00312	0.00074	0.01855
104	1908.5	0.00323	0.00063	0.01844
105	2339.5	0.00318	0.00068	0.01849
106	2770.5	0.00323	0.00063	0.01844
107	3201.5	0.00329	0.00057	0.01838
108	3632.5	0.00322	0.00064	0.01845
109	4063.5	0.00320	0.00066	0.01847
111	*ca.* 24h	0.00352	0.00034	0.01815

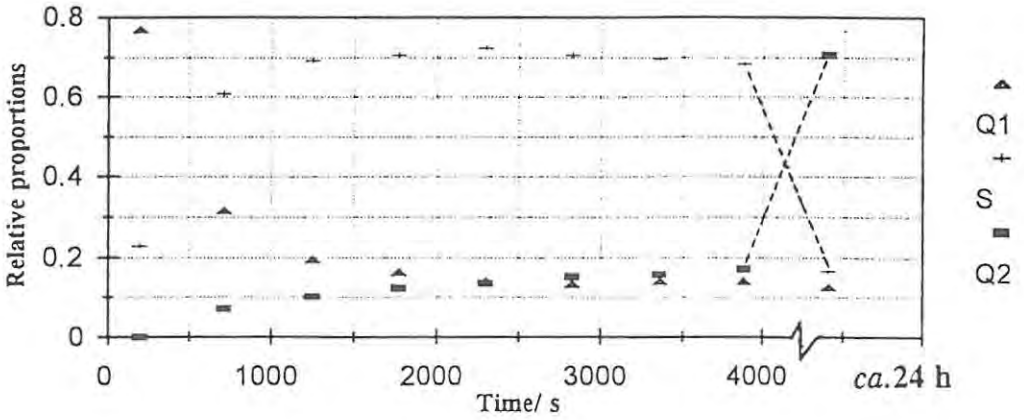


Experiment M-10

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.003895 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.02167 mol.L^{-1}) **[b]** in methanol-d_4.

Expt. No.	Time/ s	x	[a]	[b]
100	188	0.00089	0.00297	0.02078
101	716	0.00264	0.00122	0.01903
102	1244	0.00310	0.00076	0.01857
103	1772	0.00322	0.00064	0.01845
104	2300	0.00331	0.00055	0.01836
105	2828	0.00334	0.00052	0.01833
106	3356	0.00331	0.00055	0.01836
107	3884	0.00331	0.00055	0.01836
108	4412	0.00337	0.00049	0.01830

Plot of reaction profile vs time



3.3.2 Kinetic procedure for reactions in THF-d_8

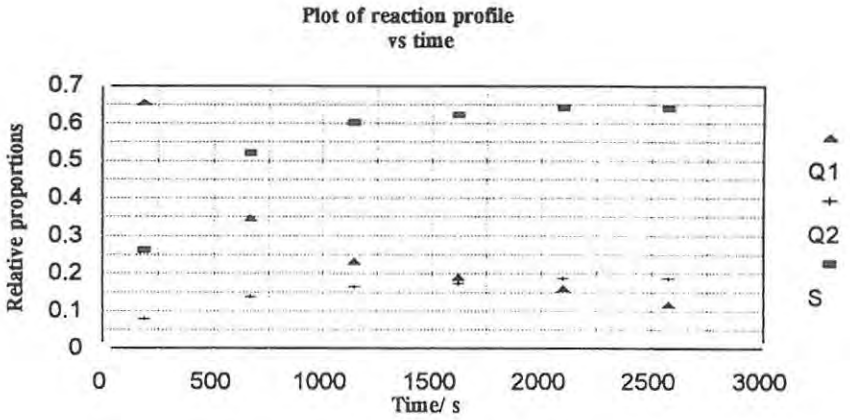
Approximately 16.1 mg of NaH (60%; dispersion in oil) was accurately weighed (to five decimal figures) into a dry reaction flask. Depending on the amount of NaH, THF-d_8 was added ($\geq$ 1000 μl) to achieve a standard concentration (0.04022 mol.L^{-1}). The nucleophile was then added in sufficient quantity to achieve the required concentration. The sample was left to stand for an hour to generate the nucleophilic anion, after which the sample was divided into two equal aliquots and each injected *via* a septum into a separate dry, N_2 flushed NMR tube. The introduction of the substrate and the NMR data collection were as described for the kinetic runs in methanol-d_4.

3.3.2.1 Kinetic data and graphs for kinetic studies carried out in THF-d_8

Experiment T-1

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.03873 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.07128 mol.L^{-1}) **[b]** in THF-d_8.

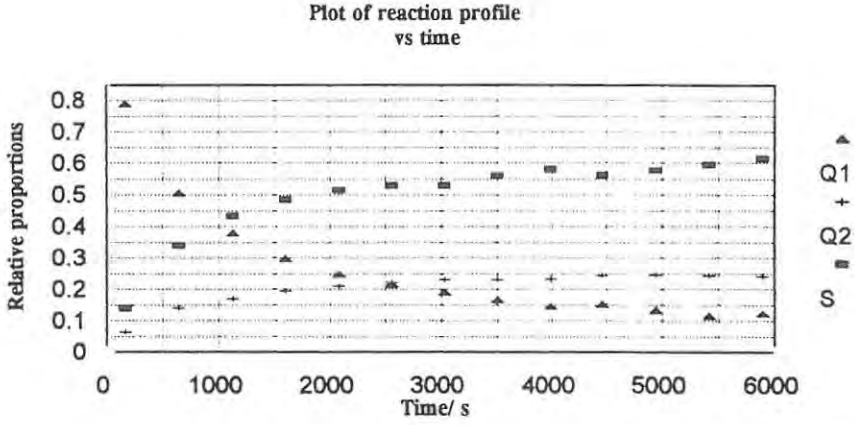
Expt. No.	Time/ s	x	[a]	[b]
100	190.5	0.01332	0.02541	0.05796
101	667.5	0.02526	0.01347	0.04602
102	1144.5	0.02970	0.00903	0.04158
103	1621.5	0.03135	0.00738	0.03993
104	2098.5	0.03246	0.00627	0.03882
105	2575.5	0.03412	0.00461	0.03716



Experiment T-2

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.02324 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.03657 mol.L^{-1}) **[b]** in THF-d_8.

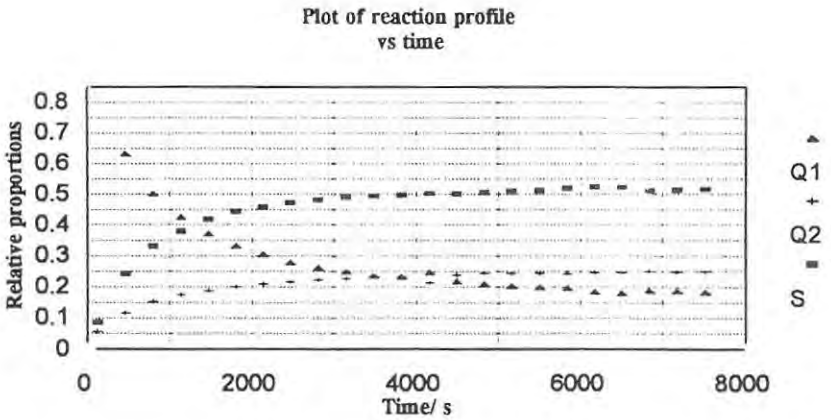
Expt. No.	Time/ s	x	[a]	[b]
100	172.5	0.00485	0.01839	0.03172
101	649.5	0.01147	0.01177	0.02510
102	1126.5	0.01439	0.00885	0.02218
103	1603.5	0.01632	0.00692	0.02025
104	2080.5	0.01746	0.00578	0.01911
105	2557.5	0.01821	0.00503	0.01836
106	3034.5	0.01877	0.00447	0.01780
107	3511.5	0.01933	0.00391	0.01724
108	3988.5	0.01983	0.00341	0.01674
109	4465.5	0.01965	0.00359	0.01692
111	4942.5	0.02009	0.00315	0.01648
112	5419.5	0.02052	0.00272	0.01605
113	5896.5	0.02034	0.00290	0.01623
114	6373.5	0.02061	0.00263	0.01596
115	6850.5	0.02049	0.00275	0.01608
116	7327.5	0.02073	0.00251	0.01584
117	7804.5	0.02063	0.00261	0.01594
118	8281.5	0.02094	0.00230	0.01563
119	8758.5	0.02088	0.00236	0.01569



Experiment T-3

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(bromomethyl)but-2-enoate **(198)** (0.02324 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.03657 mol.L^{-1}) **[b]** in THF-d_8.

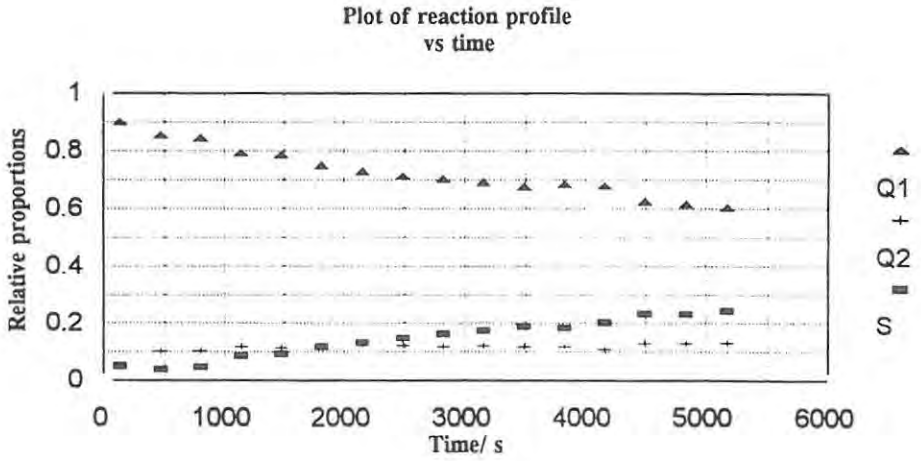
Expt. No.	Time/ s	x	[a]	[b]
100	128	0.00338	0.01986	0.03319
101	464	0.00852	0.01472	0.02805
102	800	0.01153	0.01171	0.02504
103	1136	0.01332	0.00992	0.02325
104	1472	0.01459	0.00865	0.02198
105	1808	0.01548	0.00776	0.02109
106	2144	0.01614	0.00710	0.02043
107	2480	0.01672	0.00652	0.01985
108	2816	0.01712	0.00612	0.01945
109	3152	0.01745	0.00579	0.01912
111	3488	0.01773	0.00551	0.01884
112	3824	0.01780	0.00544	0.01877
113	4160	0.01747	0.00577	0.01910
114	4496	0.01813	0.00511	0.01844
115	4832	0.01832	0.00492	0.01825
116	5168	0.01848	0.00476	0.01809
117	5504	0.01858	0.00466	0.01799
118	5840	0.01862	0.00462	0.01795
119	6176	0.01889	0.00435	0.01768
120	6512	0.01901	0.00423	0.01756



Experiment T-4

Kinetic data acquired for the nucleophilic substitution reaction between methyl (*Z*)-2-(chloromethyl)but-2-enoate **(197)** (0.02324 mol.L^{-1}) **[a]** and the enolate of methyl 2-methyl-3-oxobutanoate **(201)** (0.03657 mol.L^{-1}) **[b]** in THF-d_8.

Expt. No.	Time/ s	x	[a]	[b]
100	134	0.00229	0.02095	0.03428
101	470	0.00335	0.01989	0.03322
102	806	0.00359	0.01965	0.03298
103	1142	0.00480	0.01844	0.03177
104	1478	0.00494	0.01830	0.03163
105	1814	0.00580	0.01744	0.03077
106	2150	0.00627	0.01697	0.03030
107	2486	0.00664	0.01660	0.02993
108	2822	0.00689	0.01635	0.02968
109	3158	0.00713	0.01611	0.02944
111	3494	0.00749	0.01575	0.02908
112	3830	0.00730	0.01594	0.02927
113	4166	0.00743	0.01581	0.02914
114	4502	0.00869	0.01455	0.02788
115	4838	0.00888	0.01436	0.02769
116	5174	0.00914	0.01410	0.02743



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5.APPENDICES

5.1 CRYSTALLOGRAPHIC DATA FOR METHYL 2-(3-METHYL-6-NITROBENZOPYRAN-2-ON-4-YL)PROPENOATE (141h)

Table 20.

Identification code	*141h*
Empirical formula	*C28 H22 N2 O12*
Formula weight	*578.48*
Temperature	*293(2) K*
Wavelength	*.71070 A*
Crystal system	*Monoklinik*
Space group	*C 2/c*
Unit cell dimensions	*a = 16.600(4) A alpha = 90 deg.*
	b = 16.994(7) A beta = 124.24 deg.
	c = 11.086(2) A gamma = 90 deg.
Volume	*2585.3(1) A^3*
Z	*8*
Density (calculated)	*1.486 Mg/m^3*
Absorption coefficient	*0.118 mm^{-1}*
F(000)	*1200*
Theta range for data collection	*2.21 to 29.96 deg.*
Index ranges	*-23<=h<=20, -1<=k<=23, -1<=l<=15*
Reflections collected	*4559*
Independent reflections	*3768 [R(int) = 0.0145]*
Refinement method	*Full-matrix least-squares on F^2*
Data / restraints / parameters	*3768 / 0 / 223*
Goodness-of-fit on F^2	*0.917*
Final R indices [I>2sigma(I)]	*R1 = 0.0677, wR2 = 0.2095*
R indices (all data)	*R1 = 0.0932, wR2 = 0.2280*
Largest diff. peak and hole	*.332 and -.242 $e.A^{-3}$*

Table 21. Atomic coordinates (x 104) and equivalent isotropic displacement parameters (A2 x 103) for methyl 2-(3-methyl-6-nitrobenzopyran-2-on-4-yl)propenoate (141h)a,b. U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
O(1)	3749(1)	7124(1)	492(2)	48(1)
C(1)	3648(1)	6716(1)	2845(2)	34(1)
O(5)	1976(1)	6914(1)	2665(2)	45(1)
C(8)	3690(1)	7536(1)	2512(2)	33(1)
C(7)	3715(2)	8163(1)	3344(2)	36(1)
C(6)	3755(2)	8918(1)	2935(3)	40(1)
C(9)	3726(2)	7710(2)	1315(2)	38(1)
C(2)	3664(2)	6141(1)	2018(3)	41(1)
C(11)	3598(2)	6533(1)	4115(2)	37(1)
C(12)	2667(2)	6659(1)	3989(3)	41(1)
C(4)	3740(2)	8477(2)	894(3)	47(1)
C(5)	3750(2)	9087(2)	1710(3)	48(1)
N	3824(2)	9566(1)	3859(3)	54(1)
O(2)	3790(2)	5877(2)	35(3)	69(1)
C(3)	3737(2)	6342(2)	800(3)	45(1)
O(6)	2560(2)	6543(2)	4956(2)	70(1)
C(10)	3618(3)	5277(2)	2245(4)	61(1)
C(13)	4353(2)	6253(2)	5355(3)	55(1)
O(3)	4062(2)	9417(1)	5086(3)	78(1)
O(4)	3643(2)	10229(1)	3356(4)	88(1)
C(14)	1033(2)	7041(3)	2399(4)	66(1)

[a]*For atom labelling, see Fig.1.* [b]*Estimated standard deviations in parenthesis*

Table 22. Bond lengths [A] and angles [deg] for methyl 2-(3-methyl-6-nitrobenzopyran-2-on-4-yl)propenoate (141h).[a,b]

O(1)-C(9)	1.366(3)
O(1)-C(3)	1.376(4)
C(1)-C(2)	1.351(3)
C(1)-C(8)	1.453(3)
C(1)-C(11)	1.488(3)
O(5)-C(12)	1.327(3)
O(5)-C(14)	1.438(3)
C(8)-C(9)	1.394(3)
C(8)-C(7)	1.394(3)
C(7)-C(6)	1.374(3)
C(6)-C(5)	1.385(4)
C(6)-N	1.465(3)
C(9)-C(4)	1.389(4)
C(2)-C(3)	1.462(4)
C(2)-C(10)	1.499(4)
C(11)-C(13)	1.322(3)
C(11)-C(12)	1.489(3)
C(12)-O(6)	1.197(3)
C(4)-C(5)	1.369(4)
N-O(3)	1.210(4)
N-O(4)	1.217(3)
O(2)-C(3)	1.199(3)
C(9)-O(1)-C(3)	121.9(2)
C(2)-C(1)-C(8)	120.0(2)
C(2)-C(1)-C(11)	121.5(2)
C(8)-C(1)-C(11)	118.5(2)
C(12)-O(5)-C(14)	116.0(2)
C(9)-C(8)-C(7)	117.8(2)
C(9)-C(8)-C(1)	118.6(2)
C(7)-C(8)-C(1)	123.6(2)
C(6)-C(7)-C(8)	119.0(2)
C(7)-C(6)-C(5)	122.9(2)
C(7)-C(6)-N	118.1(2)
C(5)-C(6)-N	119.0(2)
O(1)-C(9)-C(4)	116.5(2)
O(1)-C(9)-C(8)	121.0(2)
C(4)-C(9)-C(8)	122.5(2)
C(1)-C(2)-C(3)	120.1(2)
C(1)-C(2)-C(10)	124.9(2)
C(3)-C(2)-C(10)	115.0(2)
C(13)-C(11)-C(12)	118.4(2)
C(13)-C(11)-C(1)	122.3(2)
C(12)-C(11)-C(1)	119.3(2)
O(6)-C(12)-O(5)	125.0(2)
O(6)-C(12)-C(11)	124.2(2)
O(5)-C(12)-C(11)	110.8(2)
C(5)-C(4)-C(9)	119.0(2)

Table 22. Continued

C(4)-C(5)-C(6)	118.8(2)
O(3)-N-O(4)	123.4(3)
O(3)-N-C(6)	118.4(2)
O(4)-N-C(6)	118.2(3)
O(2)-C(3)-O(1)	116.4(2)
O(2)-C(3)-C(2)	125.3(3)
O(1)-C(3)-C(2)	118.4(2)

[a]For atom labelling, see Fig.1. [b]Estimated standard deviations in parenthesis

Table 23. Anisotropic displacement parameters (A^2 x 10^3) for methyl 2-(3-methyl-6-nitrobenzopyran-2-on-4-yl)propenoate (141h).[a,b] *The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$*

	U11	U22	U33	U23	U13	U12
O(1)	45(1)	66(1)	38(1)	-6(1)	27(1)	-2(1)
C(1)	29(1)	37(1)	34(1)	1(1)	16(1)	3(1)
O(5)	35(1)	59(1)	41(1)	-2(1)	22(1)	3(1)
C(8)	29(1)	38(1)	32(1)	3(1)	17(1)	2(1)
C(7)	35(1)	38(1)	38(1)	2(1)	22(1)	1(1)
C(6)	37(1)	37(1)	49(1)	2(1)	25(1)	2(1)
C(9)	28(1)	54(1)	31(1)	1(1)	16(1)	1(1)
C(2)	33(1)	43(1)	44(1)	-5(1)	21(1)	2(1)
C(11)	41(1)	34(1)	38(1)	3(1)	23(1)	1(1)
C(12)	42(1)	44(1)	41(1)	0(1)	26(1)	0(1)
C(4)	42(1)	62(2)	40(1)	12(1)	25(1)	1(1)
C(5)	42(1)	46(1)	56(1)	15(1)	28(1)	3(1)
N	57(1)	38(1)	77(2)	-5(1)	43(1)	-3(1)
O(2)	71(1)	81(2)	71(1)	-31(1)	49(1)	-9(1)
C(3)	33(1)	58(1)	44(1)	-11(1)	22(1)	-2(1)
O(6)	64(1)	104(2)	57(1)	15(1)	43(1)	7(1)
C(10)	66(2)	41(1)	79(2)	-10(1)	43(2)	-1(1)
C(13)	51(1)	62(2)	48(1)	18(1)	27(1)	12(1)
O(3)	116(2)	57(1)	80(2)	-17(1)	66(2)	-4(1)
O(4)	122(2)	36(1)	127(2)	5(1)	82(2)	6(1)
C(14)	39(1)	94(3)	64(2)	-7(2)	29(1)	9(1)

[a]*For atom labelling, see Fig. 1.* [b]*Estimated standard deviations in parenthesis*

Table 24. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$ x 10^3) for methyl 2-(3-methyl-6-nitrobenzopyran-2-on-4-yl)propenoate (141h).[a,b]

	x	y	z	U(eq)
H(7)	3707(20)	8080(17)	4170(31)	43
H(4)	3760(24)	8570(19)	65(36)	56
H(5)	3745(23)	9633(20)	1496(34)	58
H(10A)	4284(33)	5020(27)	2741(47)	91
H(10B)	3195(31)	5003(28)	1278(49)	91
H(10C)	3372(32)	5159(26)	2862(47)	91
H(13A)	4975(27)	6150(21)	5466(37)	66
H(13B)	4297(25)	6127(21)	6153(39)	66
H(14A)	656(33)	7191(28)	1448(51)	99
H(14B)	1086(33)	7426(29)	3066(51)	99
H(14C)	804(36)	6560(28)	2572(51)	99

[a]*For atom labelling, see Fig. 1.* [b]*Estimated standard deviations in parenthesis*

5.2 CRYSTALLOGRAPHIC DATA FOR METHYL 4-(6-BROMO-3-METHYLBENZOPYRAN-2-ON-4-YL)-2-METHYLENEBUTANOATE (143c)

Table 25.

Identification code	rr256
Empirical formula	C8 H7 Br.50 O2
Formula weight	175.09
Temperature	293(2) K
Wavelength	.71069 A
Space group	P1
Unit cell dimensions	a = 7.7312(13) A alpha = 103.81 deg. b = 10.112(4) A beta = 103.58 deg. c = 11.404(3) A gamma = 111.90 deg.
Volume	749.5(4) A^3
Z	2
Density (calculated)	1.552 Mg/m^3
Absorption coefficient	2.754 mm^{-1}
F(000)	354
Theta range for data collection	2.33 to 29.96 deg.
Index ranges	-10<=h<=10, -14<=k<=13, -1<=l<=16
Reflections collected	4963
Independent reflections	4355 [R(int) = 0.0180]
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	4355 / 0 / 246
Goodness-of-fit on F^2	1.186
Final R indices [I>2sigma(I)]	R1 = 0.0488, wR2 = 0.1138
Largest diff. peak and hole	.553 and -.434 $e.A^{-3}$

Table 26. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (A^2 x 10^3) for methyl 4-(6-bromo-3-methyl benzopyran-2-on-4-yl)-2-methylenebutanoate (143c).[a,b] U(eq) is defined as one third of the trace of the orthogonalized Uij tensor.

	x	y	z	U(eq)
Br(1)	3635(1)	1033(1)	2353(1)	64(1)
O(1)	9273(3)	6968(2)	6714(2)	46(1)
C(12)	7961(5)	6714(4)	2034(3)	46(1)
C(11)	9630(4)	6559(3)	2940(3)	39(1)
C(9)	6776(4)	4061(3)	3451(3)	38(1)
C(1)	5462(4)	2916(3)	3711(3)	42(1)
C(3)	6722(5)	4478(3)	5938(3)	43(1)
C(7)	9525(4)	6756(3)	4264(2)	35(1)
O(2)	11550(4)	9358(3)	7528(2)	70(1)
C(5)	10577(4)	8227(3)	6574(3)	45(1)
O(4)	6837(4)	3832(3)	414(2)	62(1)
C(6)	10675(4)	8081(3)	5289(3)	40(1)
C(13)	8028(5)	6428(4)	695(3)	50(1)
C(4)	8030(4)	5635(3)	5679(2)	36(1)
O(3)	7712(6)	4512(4)	-1152(3)	93(1)
C(8)	8106(4)	5467(3)	4452(2)	33(1)
C(14)	7530(5)	4858(4)	-122(3)	55(1)
C(10)	12171(6)	9512(4)	5243(5)	57(1)
C(15)	8506(7)	7514(6)	214(4)	72(1)
C(16)	6332(10)	2272(6)	-285(6)	85(1)
C(2)	5421(5)	3113(3)	4946(3)	46(1)

[a]*For atom labelling, see Fig. 2.* [b]*Estimated standard deviations in parenthesis*

Table 27. Bond lengths [A] and angles [deg] for methyl 4-(6-bromo-3-methylbenzopyran-2-on-4-yl)-2-methylenebutanoate (143c).[a,b]

Br(1)-C(1)	1.891(3)
O(1)-C(5)	1.370(4)
O(1)-C(4)	1.370(3)
C(12)-C(13)	1.502(4)
C(12)-C(11)	1.536(4)
C(12)-H(12A)	1.01(4)
C(12)-H(12B)	.92(4)
C(11)-C(7)	1.499(4)
C(11)-H(11A)	.88(3)
C(11)-H(11B)	.98(3)
C(9)-C(1)	1.375(4)
C(9)-C(8)	1.402(4)
C(9)-H(9)	.98(3)
C(1)-C(2)	1.385(4)
C(3)-C(2)	1.371(4)
C(3)-C(4)	1.379(4)
C(3)-H(3)	.94(4)
C(7)-C(6)	1.352(4)
C(7)-C(8)	1.459(3)
O(2)-C(5)	1.198(4)
C(5)-C(6)	1.460(4)
O(4)-C(14)	1.333(4)
O(4)-C(16)	1.439(5)
C(6)-C(10)	1.500(4)
C(13)-C(15)	1.314(5)
C(13)-C(14)	1.485(5)
C(4)-C(8)	1.386(4)
O(3)-C(14)	1.200(4)
C(10)-H(10A)	.72(4)
C(10)-H(10B)	.74(6)
C(15)-H(15A)	.88(5)
C(15)-H(15B)	.96(5)
C(16)-H(16A)	.98(7)
C(16)-H(16B)	.86(7)
C(16)-H(16C)	.90(10)
C(2)-H(2)	.90(3)
C(5)-O(1)-C(4)	121.6(2)
C(13)-C(12)-C(11)	111.9(2)
C(13)-C(12)-H(12A)	110(2)
C(11)-C(12)-H(12A)	110(2)
C(13)-C(12)-H(12B)	107(2)
C(11)-C(12)-H(12B)	111(2)
H(12A)-C(12)-H(12B)	107(3)
C(7)-C(11)-C(12)	112.8(2)
C(7)-C(11)-H(11A)	111(2)
C(12)-C(11)-H(11A)	110(2)
C(7)-C(11)-H(11B)	109(2)
C(12)-C(11)-H(11B)	113(2)

Table 27. Continued

H(11A)-C(11)-H(11B)	101(3)
C(1)-C(9)-C(8)	119.6(2)
C(1)-C(9)-H(9)	122(2)
C(8)-C(9)-H(9)	118(2)
C(9)-C(1)-C(2)	121.5(3)
C(9)-C(1)-Br(1)	119.6(2)
C(2)-C(1)-Br(1)	118.9(2)
C(2)-C(3)-C(4)	119.2(3)
C(2)-C(3)-H(3)	119(2)
C(4)-C(3)-H(3)	122(2)
C(6)-C(7)-C(8)	118.4(2)
C(6)-C(7)-C(11)	123.0(2)
C(8)-C(7)-C(11)	118.6(2)
O(2)-C(5)-O(1)	116.7(3)
O(2)-C(5)-C(6)	125.6(3)
O(1)-C(5)-C(6)	117.8(2)
C(14)-O(4)-C(16)	117.3(3)
C(7)-C(6)-C(5)	121.7(2)
C(7)-C(6)-C(10)	124.7(3)
C(5)-C(6)-C(10)	113.6(3)
C(15)-C(13)-C(14)	118.5(3)
C(15)-C(13)-C(12)	122.5(4)
C(14)-C(13)-C(12)	119.0(3)
O(1)-C(4)-C(3)	115.9(2)
O(1)-C(4)-C(8)	121.6(2)
C(3)-C(4)-C(8)	122.5(3)
C(4)-C(8)-C(9)	117.7(2)
C(4)-C(8)-C(7)	118.8(2)
C(9)-C(8)-C(7)	123.5(2)
O(3)-C(14)-O(4)	122.3(4)
O(3)-C(14)-C(13)	125.3(4)
O(4)-C(14)-C(13)	112.4(3)
C(6)-C(10)-H(10A)	114(4)
C(6)-C(10)-H(10B)	113(5)
H(10A)-C(10)-H(10B)	132(6)
C(13)-C(15)-H(15A)	114(4)
C(13)-C(15)-H(15B)	118(3)
H(15A)-C(15)-H(15B)	128(5)
O(4)-C(16)-H(16A)	109(4)
O(4)-C(16)-H(16B)	113(5)
H(16A)-C(16)-H(16B)	104(5)
O(4)-C(16)-H(16C)	106(6)
H(16A)-C(16)-H(16C)	92(6)
H(16B)-C(16)-H(16C)	130(7)
C(3)-C(2)-C(1)	119.5(3)
C(3)-C(2)-H(2)	122(2)
C(1)-C(2)-H(2)	119(2)

[a]*For atom labelling see, Fig. 2.* [b]*Estimated standard deviations in parenthesis*

Table 28. Anisotropic displacement parameters (A^2 x 10^3) for methyl 4-(6-bromo-3-methylbenzopyran-2-on-4-yl) -2-methylenebutanoate (143c).[a,b] The anisotropic displacement factor exponent takes the form: $-2\pi^2 [h^2 a^{*2} U11 + ... + 2 h k a^* b^* U12]$

	U11	U22	U33	U23	U13	U12
Br(1)	65(1)	37(1)	66(1)	9(1)	15(1)	10(1)
O(1)	54(1)	45(1)	32(1)	11(1)	17(1)	17(1)
C(12)	56(2)	51(2)	39(2)	21(1)	19(1)	31(2)
C(11)	39(1)	46(1)	36(1)	19(1)	18(1)	19(1)
C(9)	43(1)	36(1)	37(1)	14(1)	16(1)	20(1)
C(1)	44(1)	32(1)	47(2)	14(1)	16(1)	17(1)
C(3)	52(2)	51(2)	41(2)	27(1)	25(1)	26(1)
C(7)	38(1)	37(1)	34(1)	16(1)	15(1)	18(1)
O(2)	74(2)	52(1)	48(1)	-1(1)	17(1)	8(1)
C(5)	45(2)	41(1)	41(2)	11(1)	13(1)	15(1)
O(4)	70(2)	54(1)	49(1)	7(1)	27(1)	19(1)
C(6)	42(1)	38(1)	40(1)	16(1)	16(1)	17(1)
C(13)	52(2)	68(2)	38(2)	26(1)	16(1)	34(2)
C(4)	42(1)	38(1)	34(1)	15(1)	16(1)	20(1)
O(3)	146(3)	119(3)	44(1)	34(2)	47(2)	80(2)
C(8)	36(1)	34(1)	34(1)	14(1)	16(1)	18(1)
C(14)	56(2)	81(2)	34(2)	20(2)	15(1)	37(2)
C(10)	60(2)	41(2)	56(2)	18(2)	22(2)	7(2)
C(15)	87(3)	87(3)	55(2)	42(2)	28(2)	43(2)
C(16)	97(4)	59(2)	74(3)	-4(2)	29(3)	27(2)
C(2)	50(2)	44(2)	59(2)	30(1)	29(1)	22(1)

[a]*For atom labelling, see Fig. 2.* [b]*Estimated standard deviations in parenthesis*

Table 29. Hydrogen coordinates (x 10^4) and isotropic displacement parameters (A^2 x 10^3) for methyl 4-(6-bromo-3-methylbenzopyran-2-on-4-yl)-2-methylenebutanoate (143c).[a,b]

	x	y	z	U(eq)
H(15A)	8514(74)	7206(58)	-570(52)	98(17)
H(15B)	8750(72)	8513(60)	724(47)	97(16)
H(9)	6826(46)	3922(35)	2581(31)	47(9)
H(3)	6751(50)	4583(40)	6782(35)	54(9)
H(2)	4498(48)	2348(38)	5072(31)	46(8)
H(12A)	6615(55)	5975(42)	1996(33)	56(10)
H(12B)	8066(52)	7683(43)	2339(33)	57(10)
H(11A)	10808(50)	7207(39)	2986(30)	46(9)
H(11B)	9653(47)	5581(39)	2584(30)	46(8)
H(10A)	12116(70)	9497(51)	4598(44)	73(15)
H(10B)	12737(88)	10136(69)	5882(58)	112(21)
H(16A)	7276(94)	2265(71)	-732(62)	135(22)
H(16B)	5182(103)	1800(78)	-900(64)	125(24)
H(16C)	6894(137)	1945(102)	300(90)	204(42)

[a]*For atom labelling, see Fig. 3.* [b] *Estimated standard deviations in parenthesis*