SYNTHETIC STUDIES

OF

NATURAL COUMARINS

THESIS

Presented to the University of Glasgow

for the degree of Master of Science

by

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Dedication

This thesis is dedicated to all members of my family, especially my dear father.

Also to the beloved people in Scotland and my homeland, Algeria.

Acknowledgements

I wish to thank my supervisor Dr. R.D.H. Murray for his constant guidance and the help he has rendered me throughout the period of this research.

I also would like to thank Professor G.W. Kirby for the opportunity of carrying out this work.

I also thank Dr. J.D. Connolly for his help during the period when Dr. Murray was in New Zealand.

The assistance of the technical staff of the University of Glasgow Chemistry Department is also gratefully acknowledged.

Finally, many thanks are due to the Algerian government for the financial support without which this work could not have been carried out.

Summary

The main emphasis of the work has been directed towards the synthesis of naturally occurring coumarins possessing the relatively rare trans-3-hydroxy-3-methylbut-1-enyl side chain.

Initially, work was undertaken to establish the structure of a possibly pharmacologically-active new natural coumarin, CM-c_2, isolated in Japan in 1965, for which two stereoisomeric structures were possible. From previous investigations it was believed that photo-oxygenation — reduction of osthol, 7-methoxy-8-(3-methylbut-2-enyl)coumarin, should give CM-c_2. After improvements were made to a previously reported synthesis of osthol, photo-oxygenation — reduction was found to proceed by a different pathway. However, this afforded a synthesis of a co-occurring natural coumarin, CM-c_1.

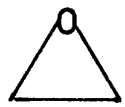
A method was successfully established for the introduction into a coumarin nucleus of a trans-3-hydroxy-3-methylbut-1-enyl side chain using the palladium acetate-catalysed Heck condensation of halocoumarins with 2-methylbut-3-en-2-ol. In this way a variety of 3- and 8-substituted coumarins were prepared including the naturally occurring coumarins, CM-c_2, swietenocoumarin G and seselin. Controlled dehydration of CM-c_2 provided a synthetic route to another natural coumarin, trans-dehydroosthol and established the stereochemistry of the former. The relationship of CM-c_2 to murraol, a coumarin first reported in mid-1987, has been clarified.

Epoxidation of trans-3-hydroxy-3-methylbut-1-enylcoumarins using meta-chloroperbenzoic acid gave the corresponding trans-1,2-epoxy-3-ols in good yields. Attempts were made to transform these epoxyalcohols into the corresponding 2,3-epoxy-1-ols by the Payne rearrangement but without success. However, a study of a non-coumarin model compound showed that the desired rearrangement could be brought about.

Heck reactions with 3-methylbut-2-en-1-ol were also studied and shown to give 1-hydroxy-3-methylbut-3-en-2-ylaryl compounds.

Synthetic Studies of Natural Coumarins

Introduction



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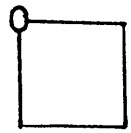

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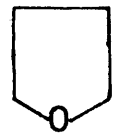

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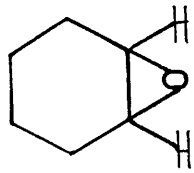

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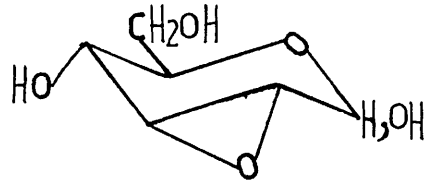

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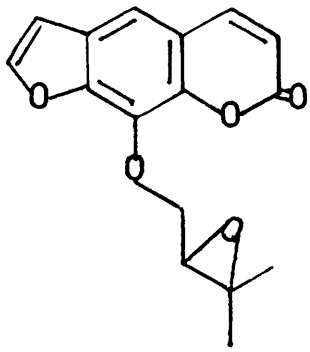

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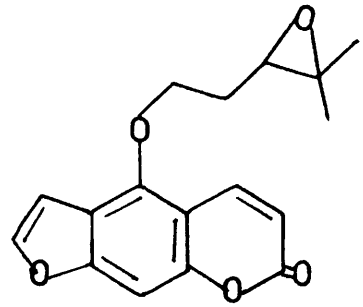

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Chemistry of Epoxides

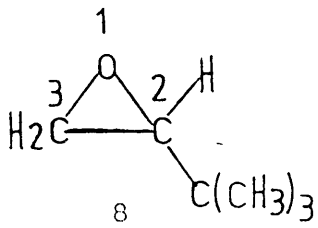
Although organic chemists have been fascinated by the three-dimensionality of their science for more than a century, it has been during the last few decades that the challenge of stereochemical control has come to the forefront of synthesis in some areas. The state of this art has become spectacularly sophisticated notably in the construction of rigid or conformationally well understood systems.

This review examines the recently developed methods currently available for controlling the stereochemistry of epoxides and for opening epoxides, with an emphasis on their application in natural coumarin synthesis.

This review is concerned only with three-membered ring or 1,2-oxides, all of which can be regarded as derivatives of ethylene oxide (1). It is not concerned with derivatives of trimethylene oxide (2) or of tetrahydrofuran (3), which are also termed 1,3- and 1,4-oxides, respectively.

The nomenclature of 1,2-epoxides or α-epoxides is somewhat confusing. Thus ethylene oxide (1) is also called "epoxyethane" or "oxirane", cyclohexene oxide (4) is also "1,2-epoxycyclohexane", "1,2-oxidocyclohexane", or "7-oxabicyclo[4.1.0] heptane", and when epoxides are regarded as derivatives of 1,2-glycols the prefix "anhydro" is used. The latter term is used particularly for sugar epoxides, thus (5) is 2,3-anhydro-D-allose. In addition, several natural coumarin epoxides have been given their own trivial names, e.g. (±)-heraclenin (6) and (±)-oxypeucedanin (7).

The I.U.P.A.C. system permits two alternative ways to name epoxides. In one of these, epoxides are named as epoxy



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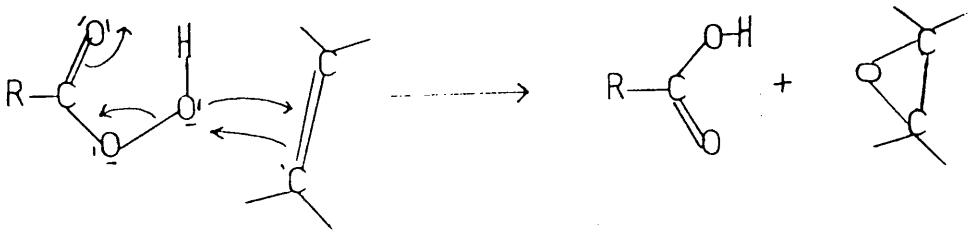
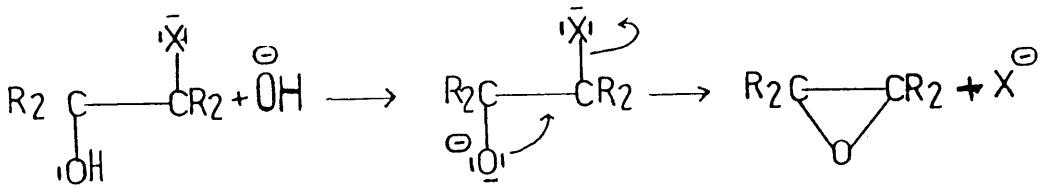
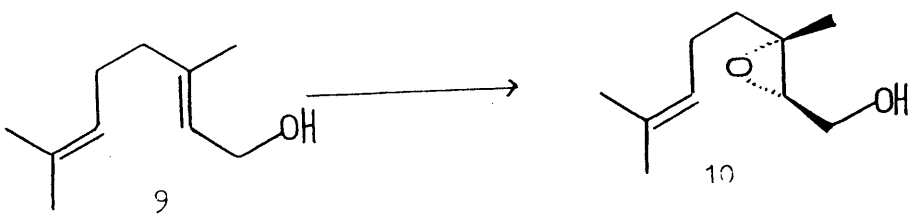


Scheme 1



Scheme 2



9 10

Scheme 3

derivatives of alkanes. According to this system, ethylene oxide (1) becomes epoxyethane and cyclohexene epoxide (4) becomes 1,2-epoxycyclohexane. The prefix "epoxy" always immediately precedes the alkane ending.

The second way that epoxides are named in the I.U.P.A.C. System is based on oxirane as the parent name of the simplest epoxide, ethylene oxide (1). Substituents are specified in the usual way and their positions identified by number. Numbering begins at the ring oxygen and goes in the direction that gives the lowest number to the substituent, in this system (8) is named 2-tert-butyloxirane, and (1) is named oxirane.

Many papers have reported the formation of three-membered rings[1-3] containing oxygen and their opening using different reagents and conditions. During last century, chemists observed that epoxides were the products of the reaction between an alkene and a peroxy acid. The peroxy acid acts as an electrophilic reagent towards the alkene, the mechanism being shown in Scheme 1. The weak oxygen-oxygen bond of the peroxy acid breaks as the hydroxyl group is transferred to the alkene.

Three-membered rings containing oxygen have been obtained from treatment of halohydrins with base. The latter brings the alcohol functional group into equilibrium with the corresponding alkoxide prior to ring closure (Scheme 2).

In recent years, Sharpless and his co-workers[4,5] have greatly extended the synthetic utility of epoxidation of allylic alcohols by controlling the regiochemistry and stereochemistry.

Selectivity has been achieved by reacting the allylic alcohol with tert-butylhydroperoxide (TBHP) in the presence of titanium tetraisopropoxide and either (-) or (+) dimethyl tartrate (DMT), shown in the conversion of (9) to (10) in Scheme 3.

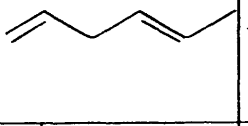
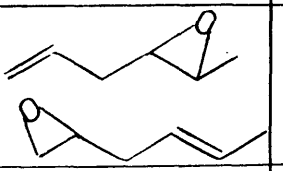
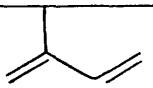
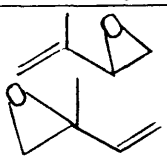
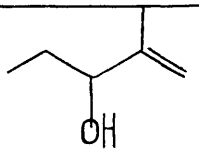
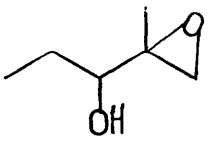
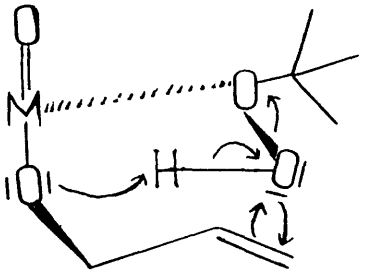
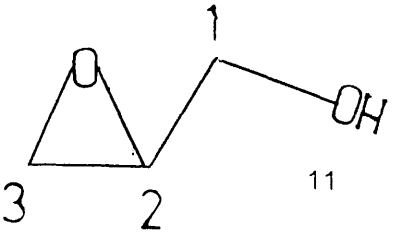
Alkene	Products	Catalyst	% yield
		$Mo(CO)_6$	90
		$Mo(CO)_6$	84
		$Mo(CO)_6$ $VO(acac)_2$	83 100

Table 1



Scheme 4



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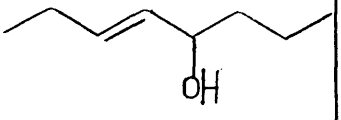
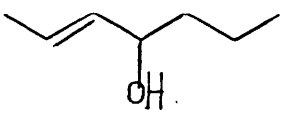
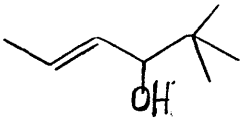
Allyl alcohol	MCPBA	Bu^tOOH	Bu^tOOH
		$VO(acac)_2$	$Mo(CO)_6$
	erythro/threo	erythro/threo	erythro/threo
	40:60	63:37	40:60
	37:63	60:40	37:63
	45:55	79:21	45:55

Table 2

In 1968, Sheng and Zajack[6] reported the epoxidation of monoalkenes with organic hydroperoxides catalysed by either vanadyl acetylacetonate or by molybdenum hexacarbonyl. Later,[7] this work was extended to a series of dialkenes, both conjugated and non-conjugated, and to functionalised alkenes such as allylic alcohols. It was found that molybdenum hexacarbonyl was the better catalyst for the epoxidation of most alkenes except allylic alcohols where vanadyl acetylacetonate was preferred (Table 1).

Chong and Sharpless[8] have proposed the following mechanism for oxidation of allylic alcohols by alkyl hydroperoxides involving co-ordination of the alkyl hydroperoxide by the oxygen adjacent to the alkyl group (Scheme 4). A key feature of this process is the hydrogen transfer from the hydroperoxide oxygen to the oxygen of the co-ordinated allylic alcohol.

More recently, Mihelich[9] has compared the stereochemistry of epoxidation of E-allylic secondary alcohols using m-chloroperbenzoic acid (MCPBA) and metal-catalysed organic hydroperoxides. It was found that the erythro-threo ratio of epoxyalcohols resulting from reaction with tert-butylhydroperoxide and vanadyl acetylacetonate was opposite to that obtained using either peracid or hydroperoxide catalysed by molybdenum hexacarbonyl (Table 2).

Vicinal Epoxyalcohols.

1,2-Epoxy-3-ols have not been studied until fairly recently. However, such systems can be obtained from the isomeric 2,3-epoxy-1-ols which have been found to undergo a number of interesting reactions.

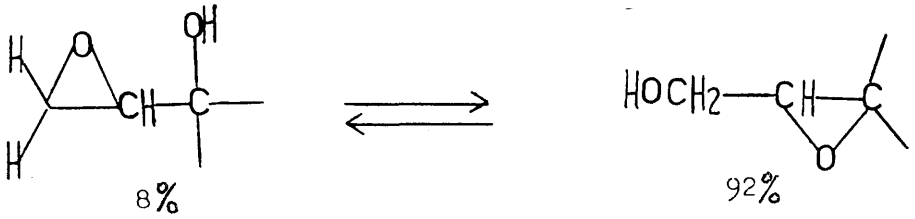
In principle, there are three reactive sites for nucleophilic substitution in a 2,3-epoxy alcohol (11).

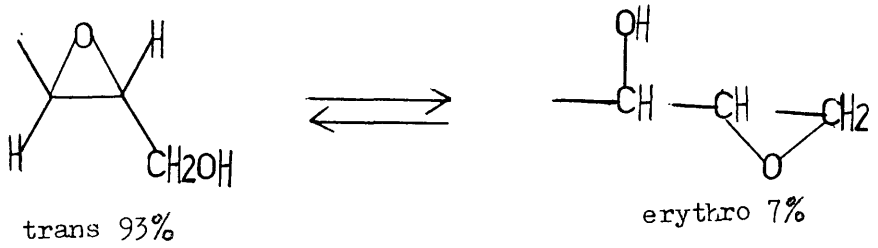
The reactivity of the C-2[10,11] and C-3[12] positions is immediately apparent; however, the reactivity at C-1 can be achieved in one step by means of the Payne rearrangement[13]. Payne was the first to make detailed observation of epoxide migration in simple acyclic 2,3-epoxyalcohols although such phenomena had been noted previously in sugars[14].

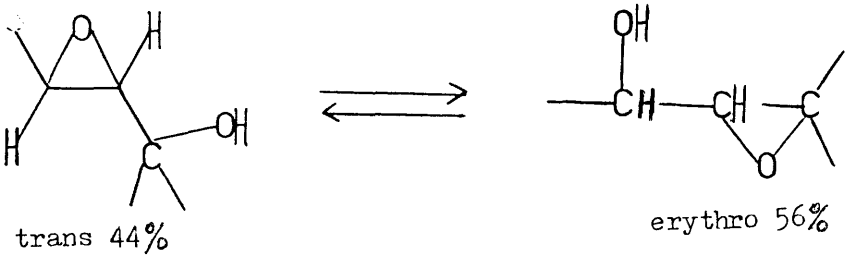
The opening of epoxides with nucleophiles occurs under an extremely wide range of conditions.

Good nucleophiles such as thiolate ions react with epoxides under neutral or alkaline conditions. In an acid medium even weak nucleophiles such as water react rapidly with epoxides. The resultant reaction provides one of the best methods for synthesis of two contiguous stereochemically defined sp^3 carbon centres.

The full mechanism is dependent on the conditions employed. Under neutral or alkaline conditions, ring opening can proceed by either an S_N2 mechanism or a borderline S_N2 mechanism in which the S_N2 transition state possesses substantial S_N1 character. Ring opening in an acidic medium can occur by either a borderline S_N2 mechanism or an S_N1 mechanism. The S_N1 mechanism does not intrude unless the epoxide bears at least one functional group (methoxyl, vinyl, phenyl) which has the capacity to stabilize an adjacent carbonium ion through resonance. The regioselectivity of epoxide opening is related to the mechanism of the reaction, and is therefore dependent on the reaction conditions. It has been observed that an epoxide cleavage reaction that is conducted in acid via an S_N1 mechanism will give ring opening at the more substituted epoxide terminus, whereas the opposite regioselectivity


8%
92%


trans 93%
erythro 7%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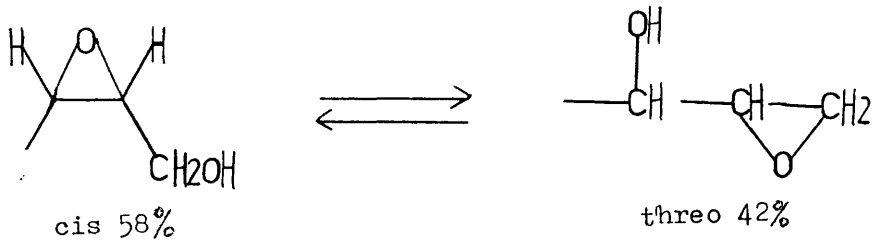
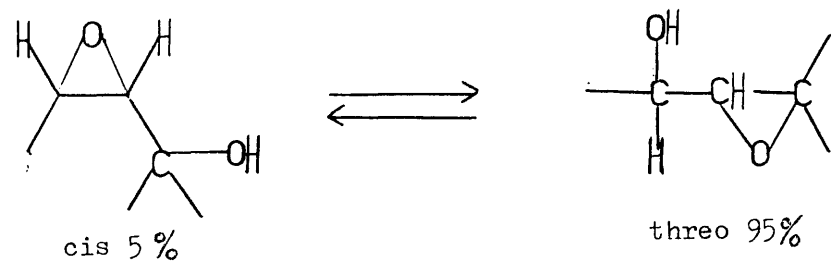
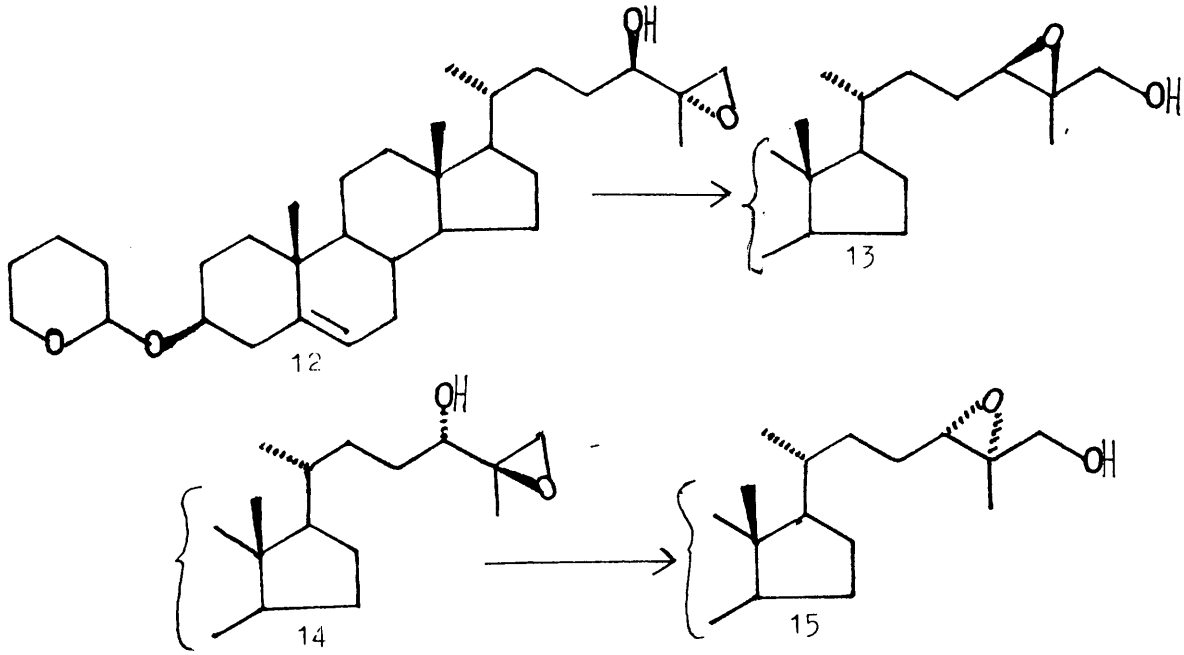
erythro 56%

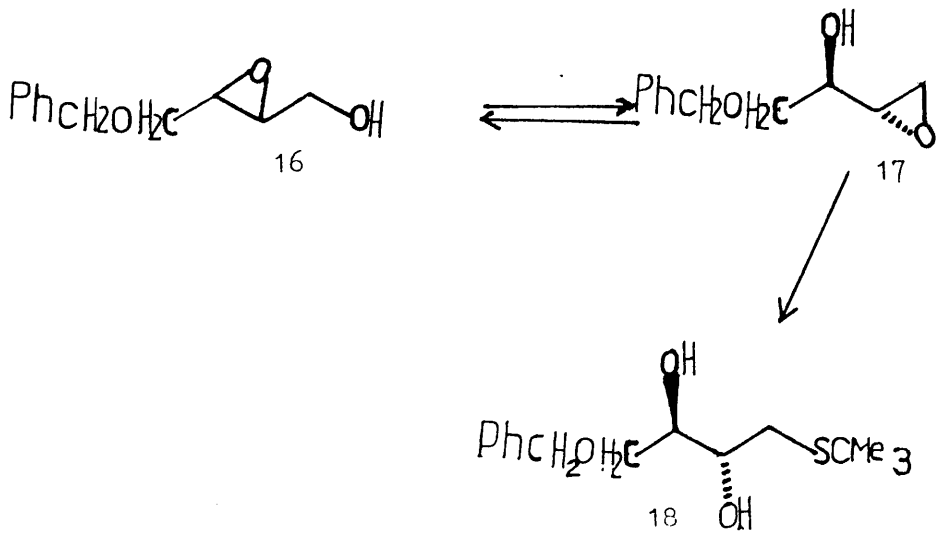

cis 58%
threo 42%


cis 5 %
threo 95%

Scheme 5



Scheme 6



Scheme 7

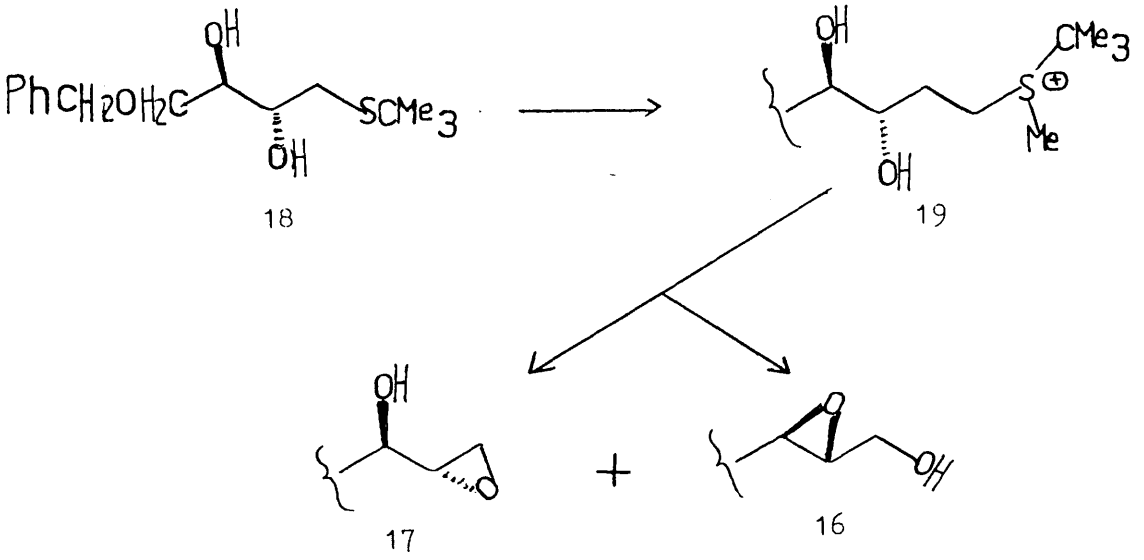
is found when the epoxide cleavage is conducted under basic conditions where an S_N2 mechanism will be operative.

The Payne rearrangement involves equilibration of a 2,3-epoxyalcohol with the isomeric 1,2-epoxyalcohol.

In general, this conversion of one epoxyalcohol into another is effected readily in 0.5M aqueous sodium hydroxide at room temperature. The results of Payne rearrangement of a series of model 2,3-epoxyalcohols in 0.5M aqueous sodium hydroxide are given in Scheme 5 with the percentage of each isomer present at equilibrium[15].

The rearrangement of epoxyalcohols using weaker bases such as potassium carbonate has also been observed and has proved to be very useful in the steroid series[16]. (24R,25R)-24,25-Epoxy-26-hydroxy-3β-tetrahydropyranyloxycholest-5-ene (13) was obtained in good yield from the corresponding epoxyalcohol (12). Similarly the 24S,25S isomer (15) was obtained, also in good yield, from the epoxyalcohol (14) as shown in Scheme 6. It can be seen from these results that the relative proportions of the 1,2- and 2,3- epoxyalcohols at equilibrium is very dependent on structure. It seems that epoxy primary alcohols are more stable than epoxy secondary alcohols and that the trans configuration is more favourable than the cis[13,17]. Since the Payne rearrangement usually produces a mixture of epoxy alcohols it is thus of limited preparative synthetic value. However, Payne rearrangements are known to occur rapidly, and an irreversible method for converting the 2,3-epoxyalcohol into its 1,2- isomer was developed using the differing rates of reaction of the isomeric terminal and internal epoxides with nucleophiles.

It seemed likely that the terminal epoxide (17) produced continually by the Payne rearrangement of (16) could be selectively and irreversibly captured by a nucleophile to give (18) (Scheme 7).



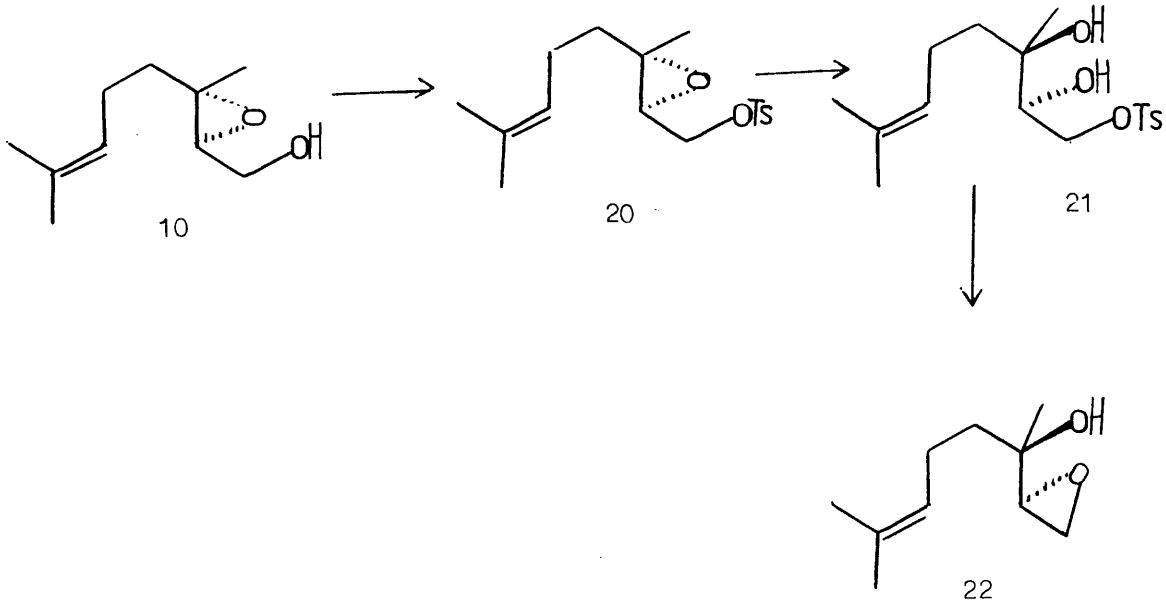
Scheme 8

The first choice of nucleophile for this Payne rearrangement opening sequence was sodium thiophenoxide but sodium tert-butylsulphide was later found to be even more selective in this application[18-20].

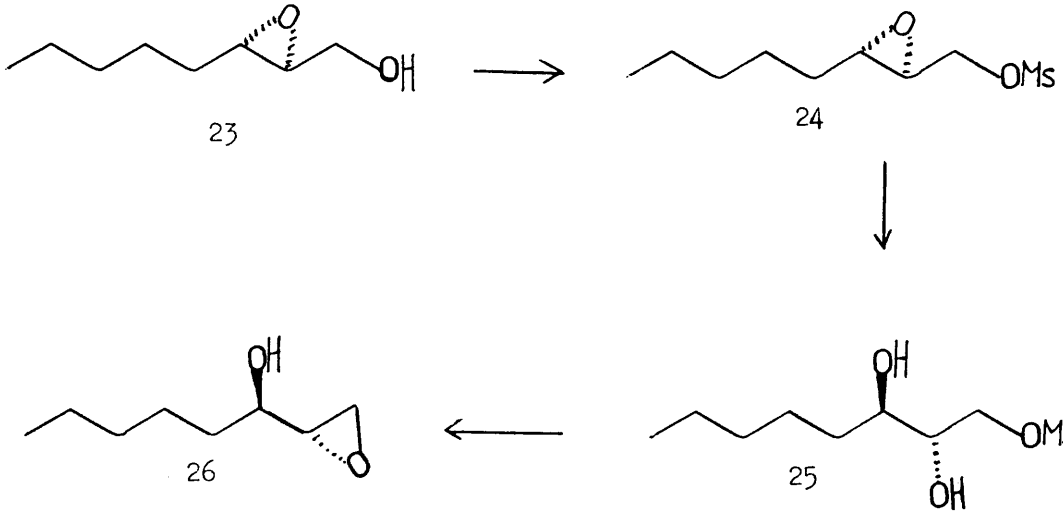
The 2,3-epoxyalcohol is heated to reflux in aqueous tert-butanol in the presence of sodium hydroxide, and the sulphide is then slowly added over a period of 1-2 hours. A faster rate of addition gave increased formation of C-2 and/or C-3 opened products. The Payne rearrangement opening sequence is limited in that many nucleophiles are incompatible with the reaction conditions, almost all organometallic reagents being too basic to survive.

An alternative route to increase the scope of the Payne rearrangement opening sequence has been achieved in three steps. First, a 2,3-dihydroxy-1-sulphide is prepared and then converted into its salt (19) using trimethyloxonium tetrafluoroborate (Meerwein's reagent) followed by base-mediated intramolecular elimination[15] as shown in Scheme 8.

An alternative route for the conversion of 2,3-epoxyalcohols such as (10) and (23) into the 1,2-epoxyalcohols(22 and 26) involves initial conversion of the C-1 hydroxyl group into a good leaving group such as tosylate or mesylate. Reaction of the tosylate (20) or mesylate (24) with nucleophiles generally results in the selective displacement of the sulphonate ester leaving the epoxide unit intact[21]. However, under acidic conditions the 2,3-epoxy-1-tosylate is regioselectively and stereospecifically opened at C-3 giving the corresponding diol (21). In the same way, the 2,3-epoxy-1-mesylate (24) reacts with a catalytic amount of perchloric acid in aqueous dimethylsulphoxide to give the diol (25). Treatment of these sulphonates with

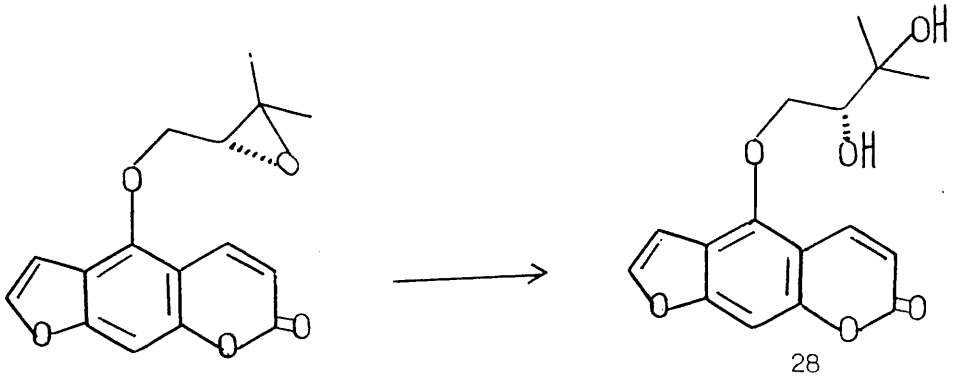


10 20 21 22



23 24 25 26

Scheme 9



27 28

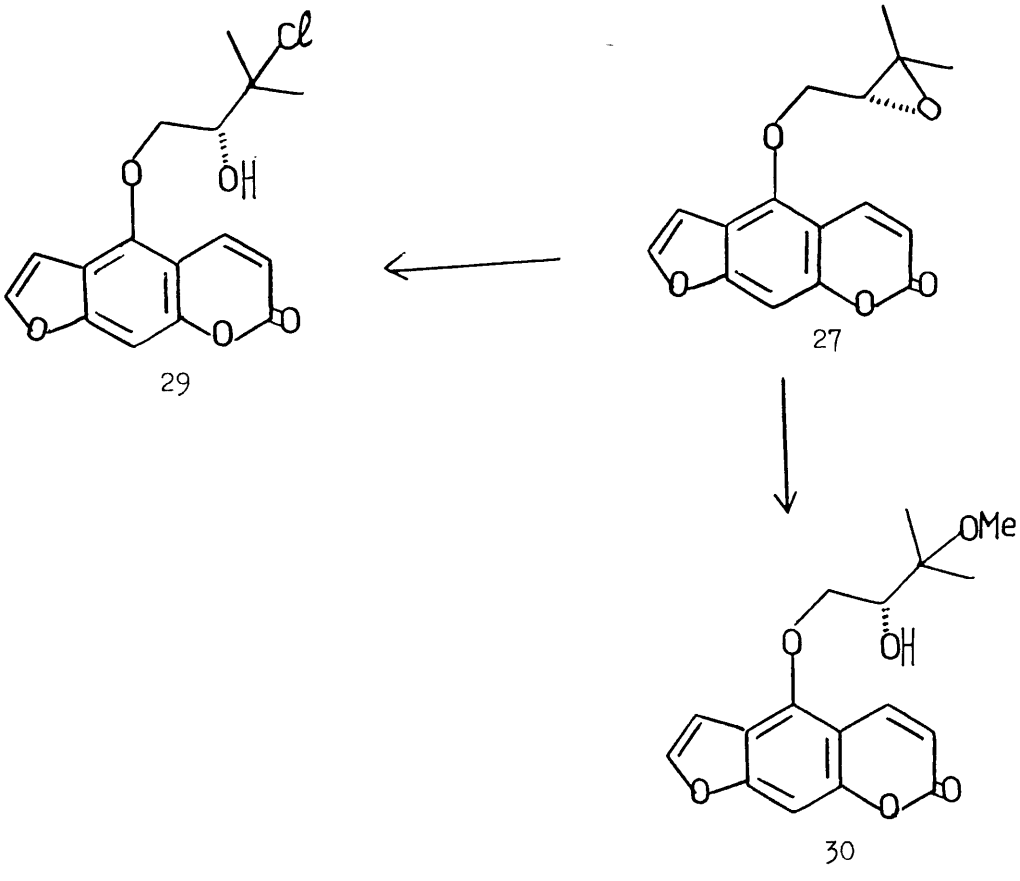
Scheme 10

mild base, such as potassium carbonate in methanol, leads to the 1,2-epoxy-3-alcohol by intramolecular displacement of the leaving group by the neighbouring hydroxyl group (Scheme 9).

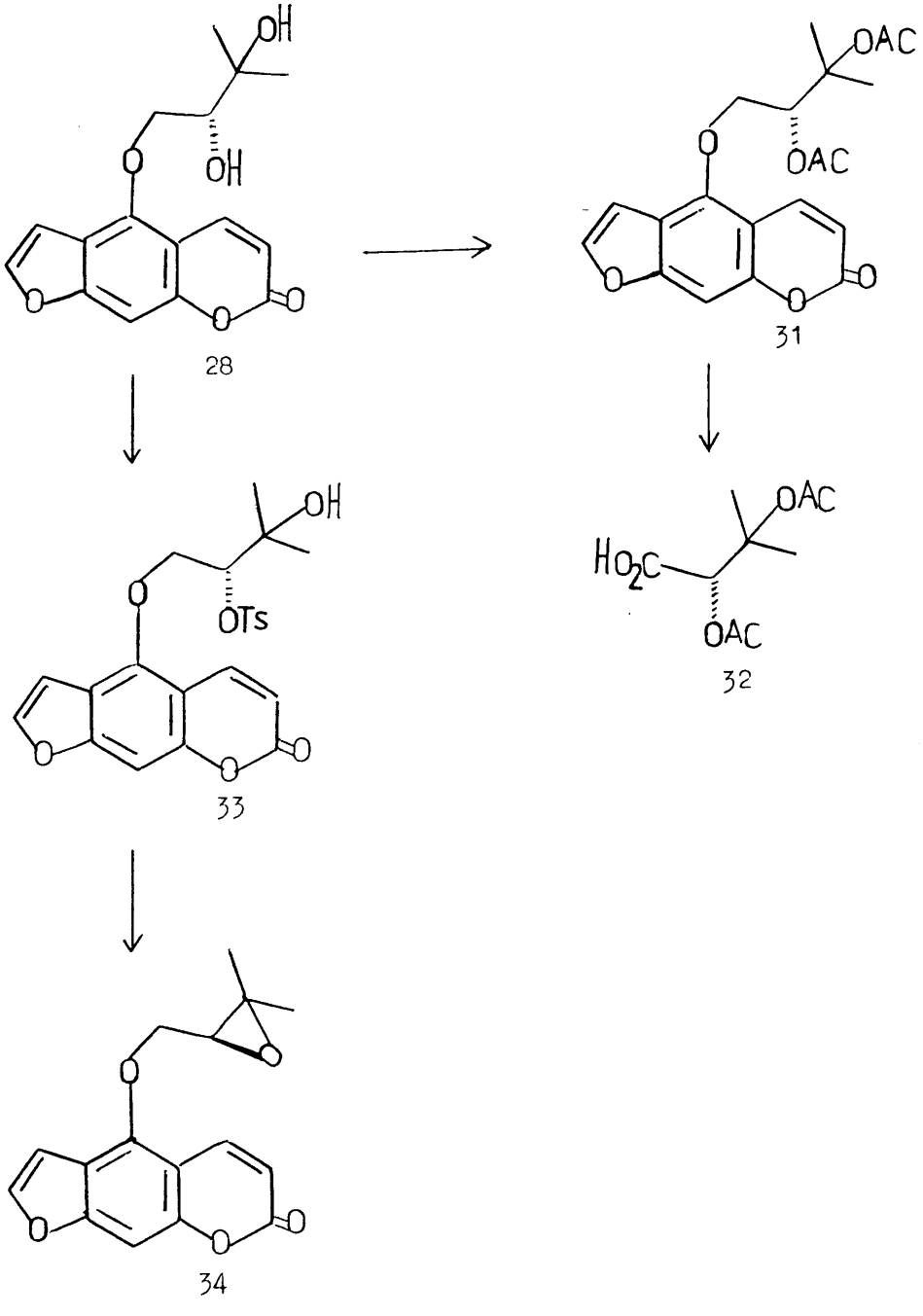
Coumarin Epoxides.

In the field of natural coumarins, Späth and Klager[22] in 1933 isolated the epoxide (±)-oxypeucedanin (7) from Imperatoria ostruthium, now known as Peucedanum ostruthium. This was hydrolyzed to the corresponding diol, oxypeucedanin hydrate using aqueous oxalic acid. Thirty years later, Nielsen and Lemmich [23,24] isolated (+)-oxypeucedanin (27) and (+)-oxypeucedanin hydrate (28) from the root of Peucedanum palustre (Scheme 10). Treatment of (+)-oxypeucedanin (27) in dry ether saturated with hydrogen chloride at 0° gave the chlorohydrin[25] (29) in good yield. In the acid conditions, opening of the protonated epoxide ring again proceeds via the more stabilised tertiary carbocation, giving overall retention of configuration. In a similar fashion, reaction of (+)-oxypeucedanin (27) with boron trifluoride in methanol gave (+)-oxypeucedanin methanolate[26] (30), a constituent of Skimmia japonica (Scheme 11).

The stereochemistry of (+)-oxypeucedanin (27) and (+)-oxypeucedanin hydrate (28) have been deduced to be R. Ozonolysis of the diacetate (31) of (+)-oxypeucedanin hydrate led to formation of (+)-2,3-diacetoxy-3-methylbutanoic acid (32), a compound of known absolute stereochemistry[24]. It has been noted that the formation of (+)-oxypeucedanin hydrate (28) from (+)-oxypeucedanin (27) presumably arises by a stereospecific process in which the configuration at the chiral centre is retained. Nielsen and Lemmich obtained additional confirmatory evidence by converting R-(+)-oxypeucedanin hydrate to (-)-oxypeucedanin (34)



Scheme 11

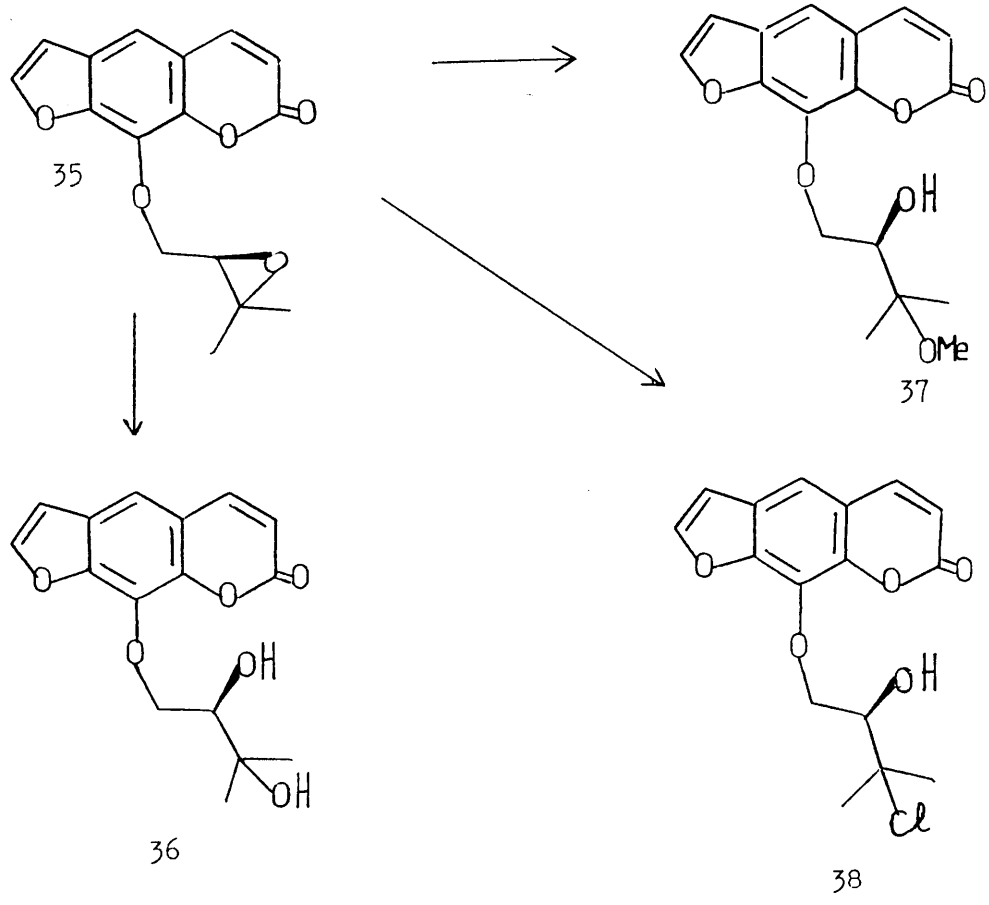


Scheme 12

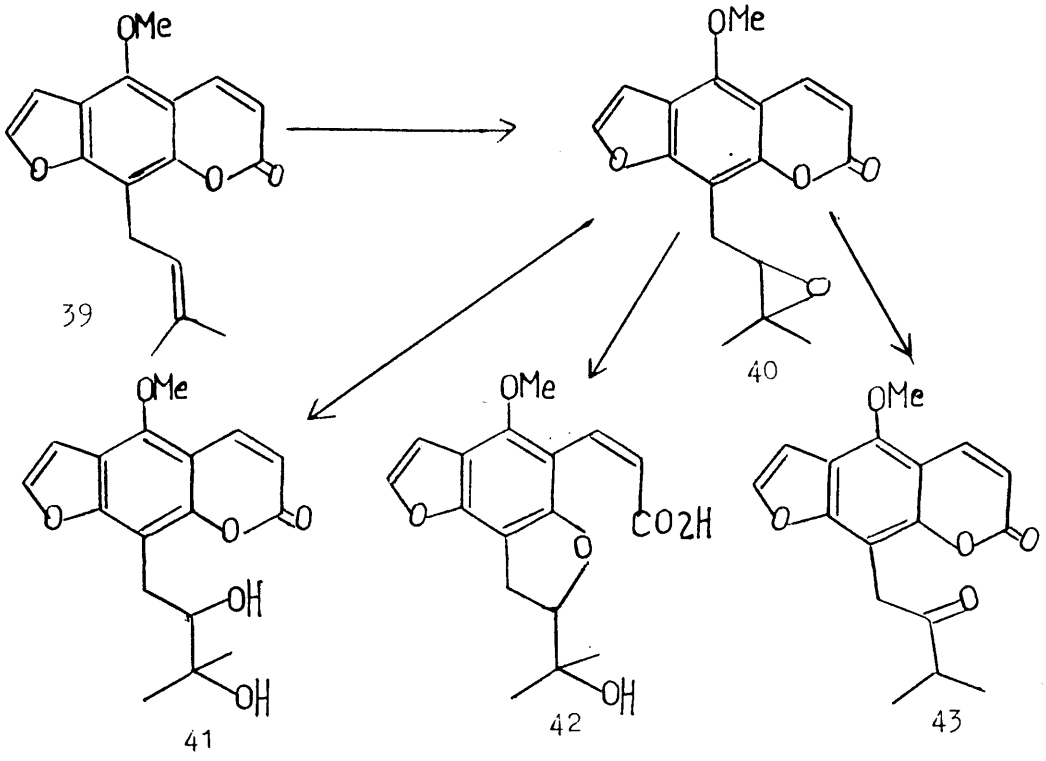
by sequential treatment with toluene-p-sulphonyl chloride and triethylamine. Monoesterification of the diol was expected to be much more likely to give the secondary toluene-p-sulphonate derivative (33), rather than the tertiary.

Subsequent intramolecular nucleophilic displacement of the tosyloxy group by the tertiary hydroxyl group, on treatment with triethylamine, would be expected to proceed with inversion of configuration. Thus (-)-oxypeucedanin (34) was deduced to have the S configuration[24] (Scheme 12). Interestingly, S-(-)-oxypeucedanin was found to occur naturally in Ligusticum seguieri[27] in 1971.

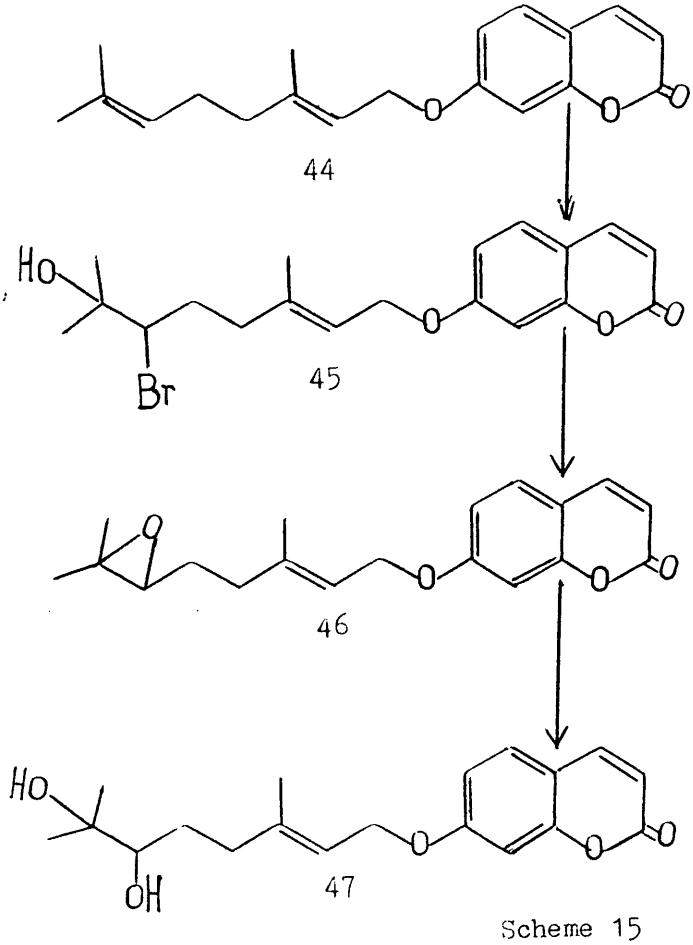
Sharma, Zaman and Kidwai[28] isolated the isomer (35) of (+)-oxypeucedanin having the chiral side chain at C-8 rather than at C-5. Since it was obtained from Heracleum candicans, they named it (+)-heraclenin and named the co-occuring diol, (+)-heraclenol (36). In a similar manner to that developed for oxypeucedanin, (+)-heraclenin (35) could be converted into (+)-heraclenol under mild aqueous acidic conditions. Similarly, two other natural coumarins, tert-O-methylheraclenol (37)[29] and the chlorohydrin (38)[25] were obtained from (+)-heraclenin by the action of oxalic acid in hot methanol and methanolic hydrogen chloride, respectively (Scheme 13). It is worthy of note that heraclenin has been found to occur in different plant species in dextrorotatory, laevoratatory and racemic forms. Natural sources have widely been used as the starting point[22,30] for epoxy coumarin syntheses. These are then mainly converted into the corresponding diols or isomerised to ketones. For example, swietenocoumarin B (39) was converted[30] in good yield into the epoxycoumarin (40) using peroxyacetic acid in chloroform



Scheme 13



Scheme 14

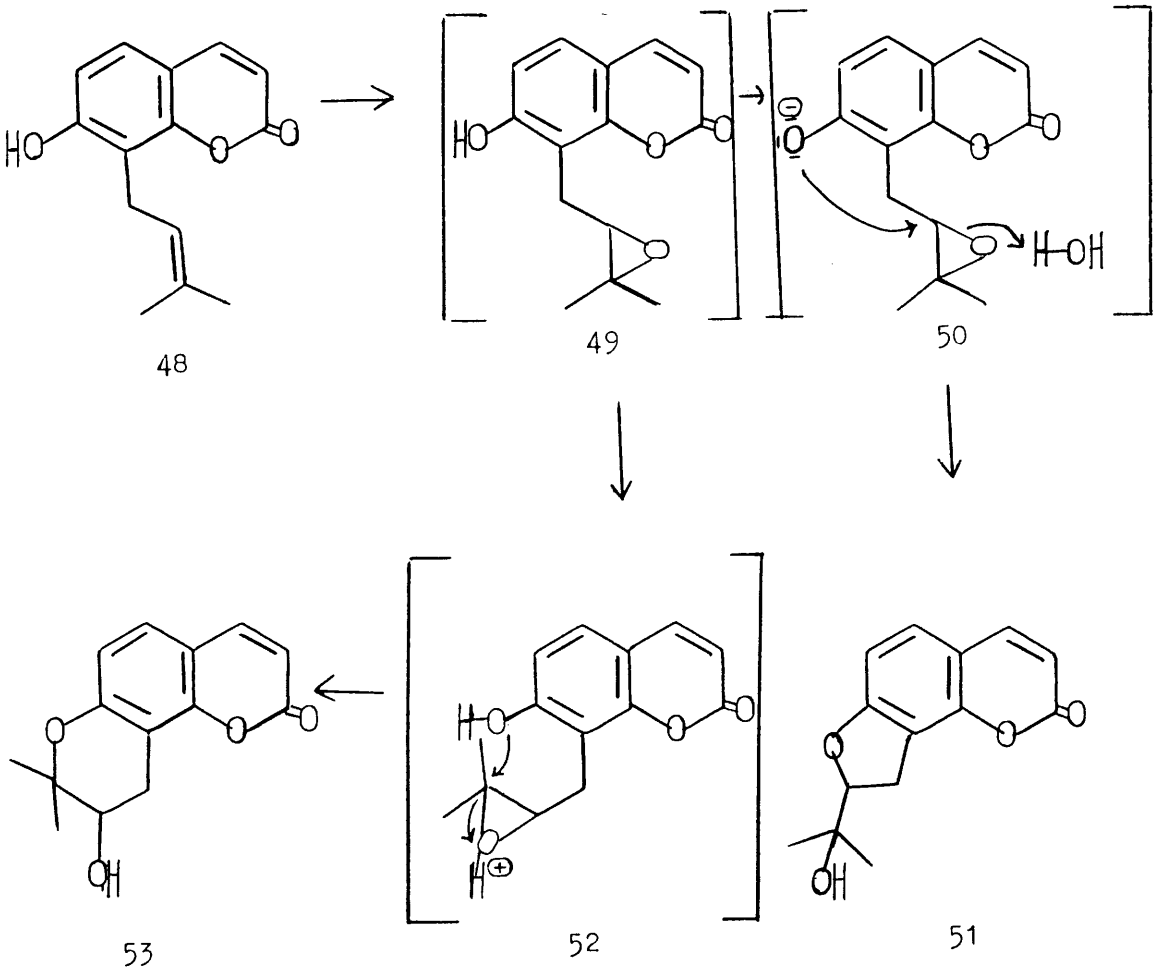


Scheme 15

at 0°. The epoxide was then hydrolysed using 1°/o oxalic acid to give the corresponding diol (41) in good yield. However treatment of the epoxide (40) with 10°/o aqueous sodium hydroxide resulted in initial opening of the lactone ring followed by intramolecular epoxide opening by the liberated phenoxide ion to give the acid (42). On the other hand, isomerisation of the epoxide (40) by action of boron trifluoride etherate at room temperature gave the ketone (43) in 50°/o yield. The older method using 10-20°/o mineral acid afforded only a 6°/o yield (Scheme 14).

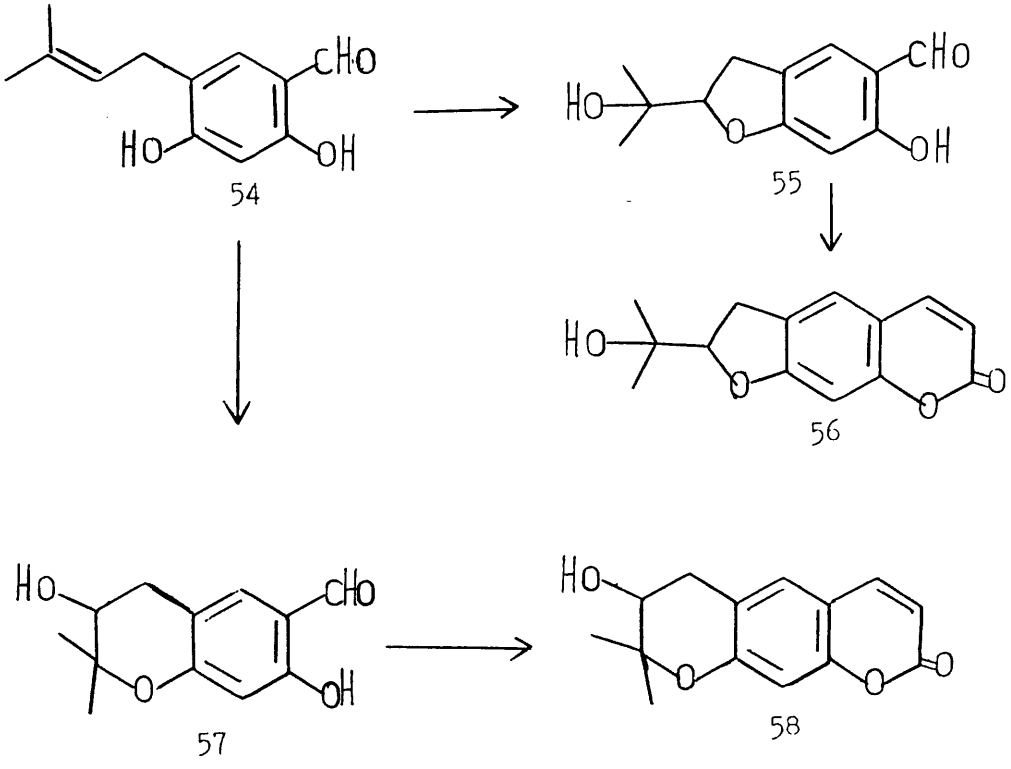
Many hydroxylated terpenyl coumarins have been isolated from the trunk bark of Aegle marmelos Correa[31] and grapefruit (Citrus paradisi Maef) peel oil[32] as epoxides or diols. (±)-Marmin (47) was synthesised[38] from 7-geranyloxycoumarin (44) by way of the corresponding epoxide (46) which was obtained in good yield by the action of potassium carbonate in ethanol on the corresponding bromohydrin (45) (Scheme 15).

Here at Glasgow University, Murray, Sutcliffe and McCabe[34] observed the controlled oxidation of o-prenylphenols to the corresponding hydroxyisopropyldihydrofuranocoumarins when m-chloroperbenzoic acid reacted quantitatively with osthenol (48) in ethyl acetate or ether to furnish only the dihydrofuranocoumarin (±)-columbianetin (51). When chloroform acidified with hydrochloric acid was used as solvent the major product was the isomeric dihydropyranocoumarin (±)-lomatin (53). Similar results were obtained by Bohlmann and Franke[35]. In slightly alkaline or neutral medium, the intermediate epoxide (49) would be expected to undergo nucleophilic epoxide ring opening at the less hindered secondary carbon atom(50) to give the dihydrofuran. In acidic

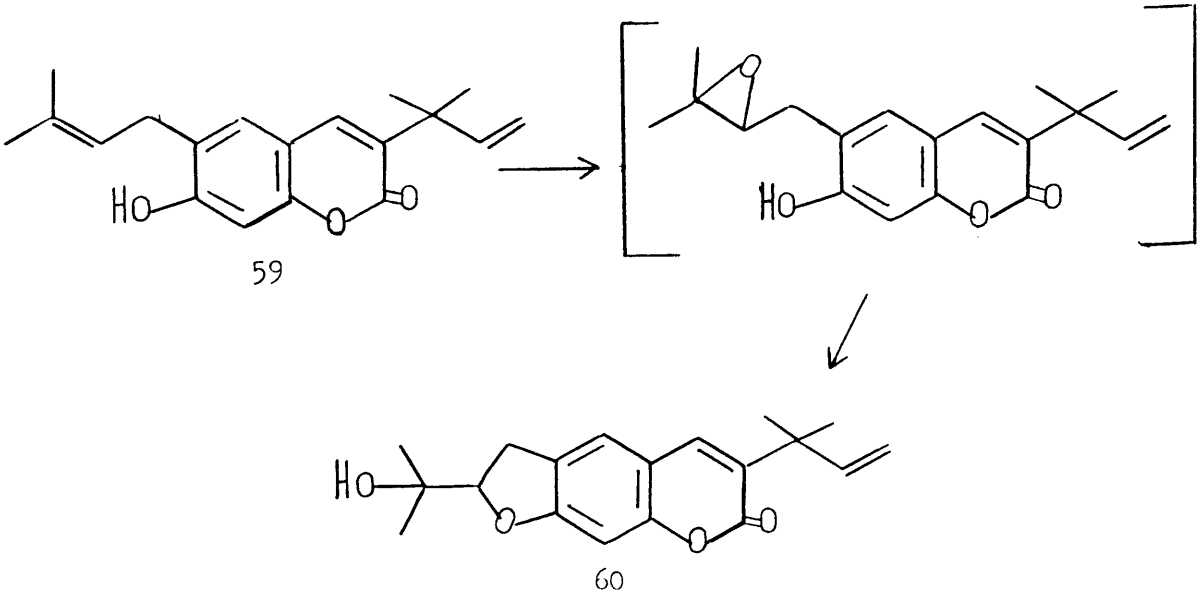


48 49 50 51 52 53

Scheme 16



Scheme 17



Scheme 18

medium , however the protonated epoxide intermediate (52) should open preferentially to a tertiary carbocation which would be trapped intramolecularly by the phenol to give the dihydropyran[34-36] (Scheme 16).

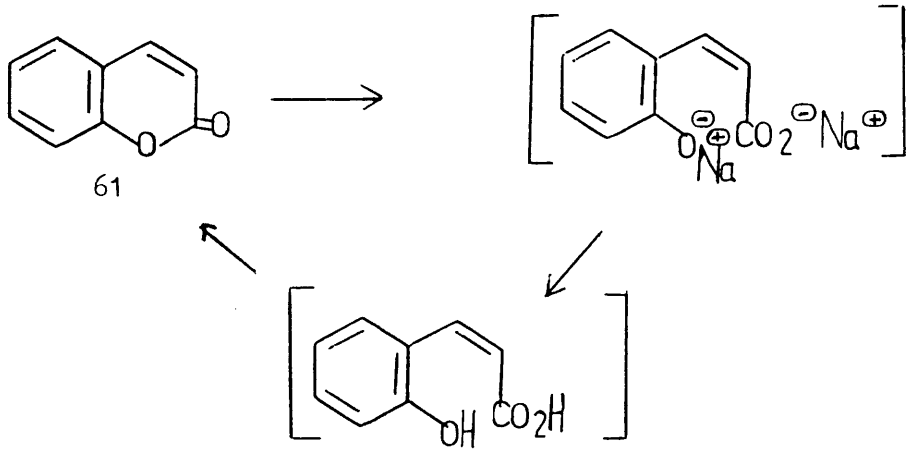
By similar reactions, demethylsuberosin, the linear isomer of osthenol, was converted into (±)-marmesin (56) and (±)-decursinol (58)[34]. Marmesin and decursinol were also synthesised from the dihydroxybenzaldehyde (54) by oxidative ring closure prior to pyrone-ring formation[36]. The dihydrofuran (55) required for marmesin was obtained by carrying out the reaction with m-chloroperbenzoic acid in acetone or in chloroform containing triethylamine. The isomeric dihydropyran (57) was obtained by carring out the oxidation in the presence of toluene-p-sulphonic acid (Scheme 17).

Recently[37], chalepin (60) was obtained by controlled oxidation of gravelliferone (59) using m-chloroperbenzoic acid in ether. Selectivity was obtained by preferential reaction of the peracid with the trisubstituted alkene rather than the monosubstituted double bond (Scheme 18).

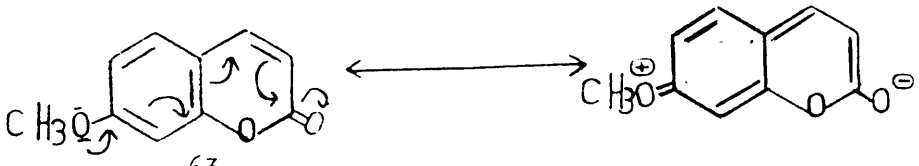
Characteristically all natural coumarins, being lactone rings, on treatment with hot dilute aqueous sodium hydroxide give a yellow solution containing sodium coumarinate derivatives in which the lactone ring has been opened[38].

Acidification normally leads to relactonisation and regeneration of the parent coumarin (Scheme 19). However the intermediate ortho-hydroxy-cis-cinnamic acid (coumarinic acid) (62) is too short-lived to be isolated.

It has been found that it is more difficult to convert 7-methoxycoumarin (63) to the corresponding sodium coumarinate



Scheme 19



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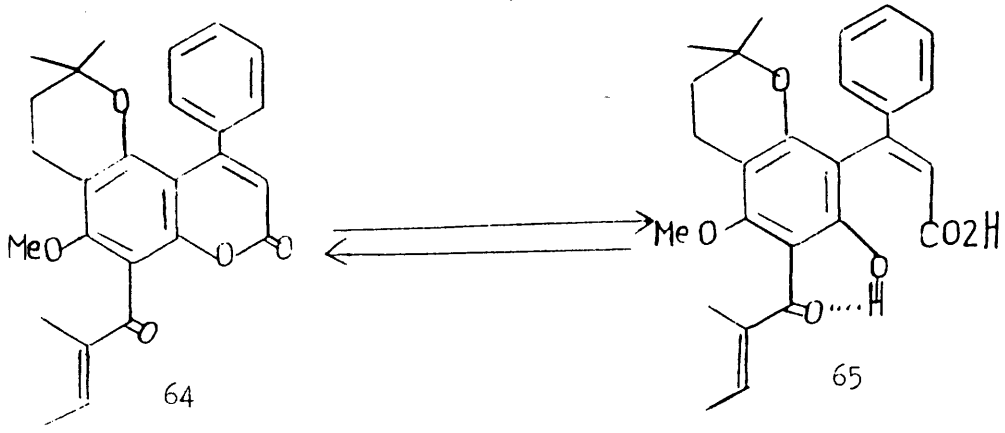
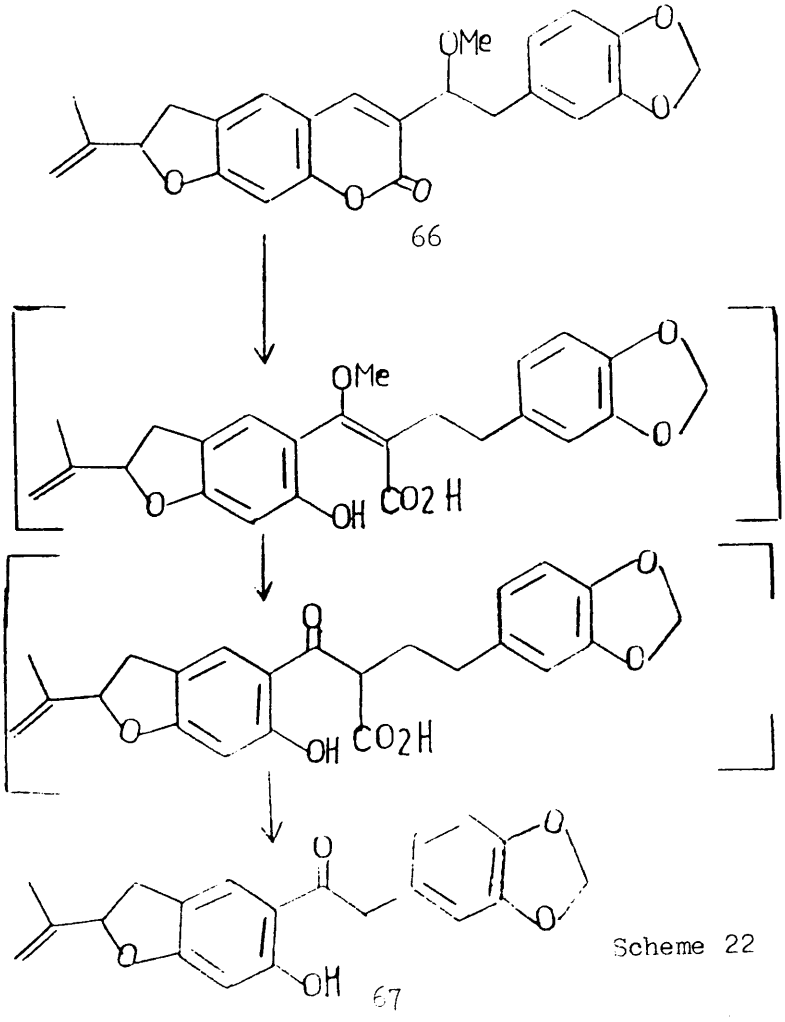
Scheme 20



64 65

Scheme 21



66 67

Scheme 22

with hot aqueous alkali than coumarin (61) presumably because electron delocalisation renders the carbonyl group in the former nucleus less sensitive to nucleophilic attack (Scheme 20).

It is even more difficult to form the sodium coumarinate from 7-hydroxycoumarin because of preferred formation of the phenolate.

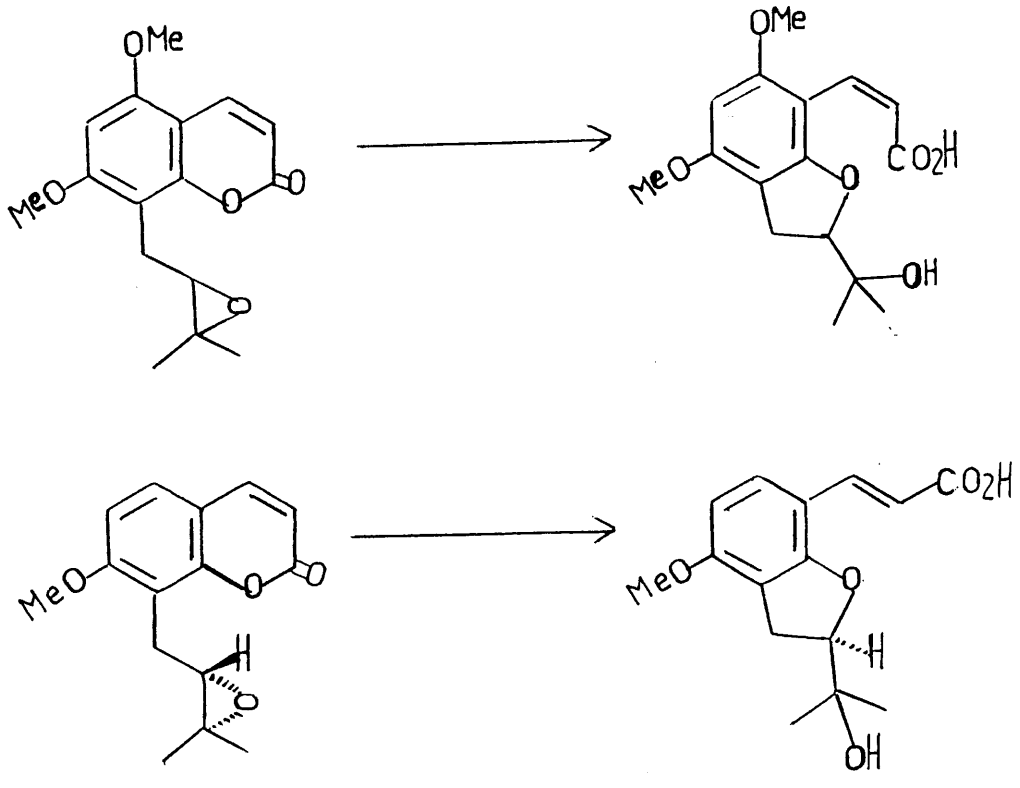
This "lactone-opening" behaviour towards dilute aqueous sodium hydroxide has been found useful to separate coumarins from other plant products. Regeneration of the original coumarin on acidification can be achieved even with carbon dioxide; however, this method should be used with caution since in some cases the original coumarin is not recovered by this process. Thus calophyllolide (64) was relactonised only when the derived coumarinic acid (65) was heated[39,40] (Scheme 21).

On the other hand, treatment of the 4-methoxy-3-arylcoumarin glabrescin (66) with hot dilute potassium hydroxide led to loss of the 4-methoxy group and carbon dioxide with formation of the desoxybenzoin[41] (67) (Scheme 22).

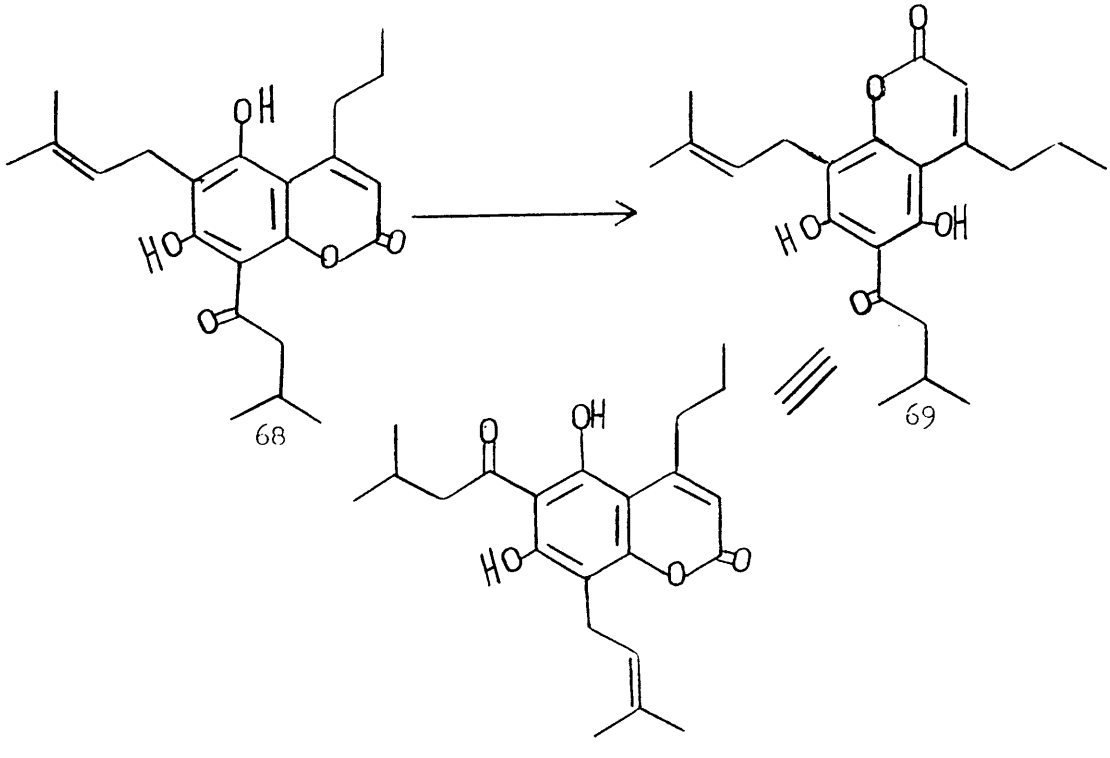
In coumarins where an epoxide group is contained in a side chain attached to C-8, treatment with hot dilute sodium hydroxide gives a product arising from phenolate anion interaction with the epoxide grouping[30,42,43]. Some examples are shown in Schemes 14 and 23.

When coumarins have a free phenolic group at C-5, cyclisation to this position on acidification of the coumarinate salt leads to the possibility of formation of a new coumarin. Mammein (68) for example afforded the isomer, isomammein[44] (69) (Scheme 24).

Knowledge of such isomerisation has been exploited in some recent syntheses of natural coumarins[45].



Scheme 23



Scheme 24

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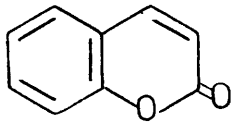
Results and Discussion



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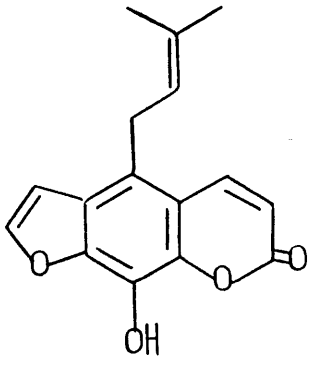

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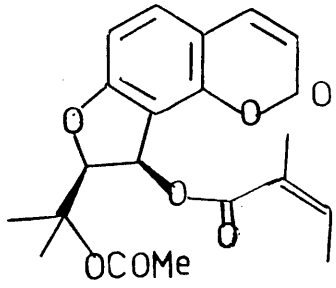

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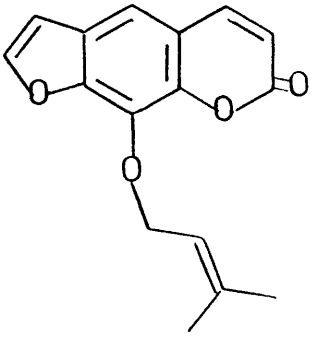

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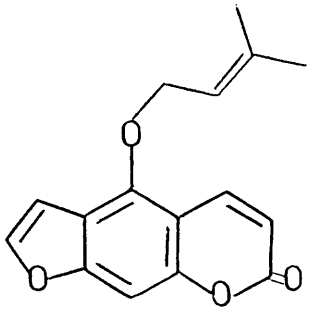

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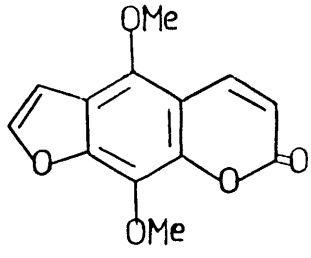

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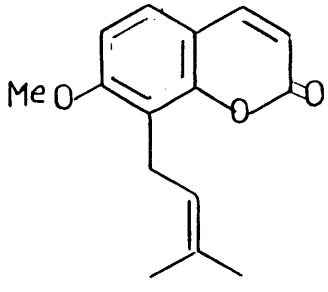

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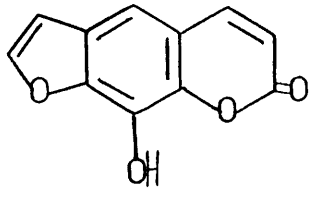

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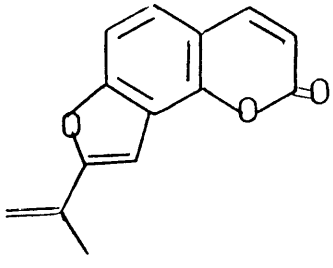
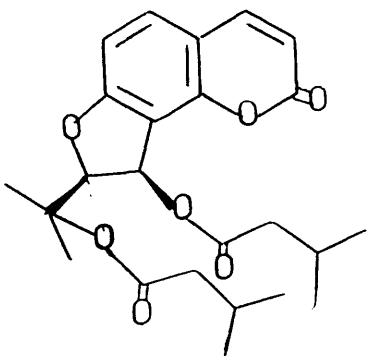


9

The well-established position of coumarins as natural products has its origin in 1920 when the simplest member, coumarin (1) was isolated by Vogel[1] from beans of the tonka tree, the Latin name for which, Coumarouna odorata Willd., gave rise to the trivial name. Over the past century and a half, its derivatives have been found to be widely distributed throughout the plant kingdom[2-5], especially in the Rutaceae and the Umbelliferae. In recent years, improvements in isolation techniques and structural analysis have led to a great increase in the number of natural coumarins identified, over one thousand different natural coumarins being known at present.

In 1964, Nikonov[6] studied the constituents of fruit of Selinum monnieri, also known as Cnidium monnieri, and isolated the following seven coumarins; alloimperatorin (2), edultin (3), imperatorin (4), isoimperatorin (5), isopimpinellin (6), osthol (7) and xanthotoxol (8). Two years later, Nakazaki and his co-workers[7] studied the seed constituents of Selinum monnieri and isolated osthol (7) and two other known coumarins, oroselone (9)[8] and edultin (3). They also established the absolute configuration of edultin and the related dihydrofuranocoumarin, athamantin (10) Two years ago, Yamahara and his colleagues[9], working at three Japanese universities, as part of a study of the biologically active principles of crude drugs, reported on the anti-allergic principles of Cnidii monnieri Fructus, the fruit of Cnidii monnieri Cusson (Umbelliferae). These fruits have been used as a natural medicine in China and Japan for such skin conditions as eczema and pruritis. The fruit was macerated in methanol and the filtered extract dried by evaporation under reduced pressure below 50°. The extract was then fractionated



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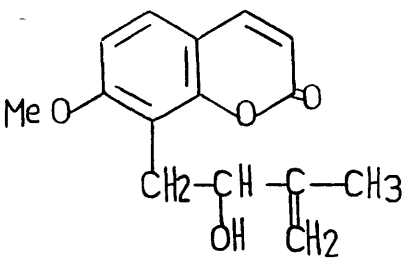

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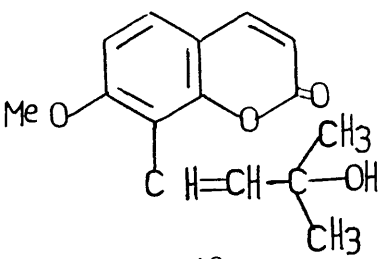

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into four fractions by silica gel column chromatography using as eluent a mixture of benzene and acetone (50:1 → 5:1). The second fraction was found to be effective in a screening procedure for contact dermatitis induced by picryl chloride in mice, used as an experimental model for a delayed allergic reaction. This fraction was then further fractionated by column chromatography using, as eluent, mixtures of hexane and ethyl acetate (4:1 → 3:1 → 2:1) into five fractions; CM-a, CM-b, CM-b′, CM-c_1 and CM-c_2. These five fractions, all coumarins, were characterised by measurements of melting points and their ^1H and ^{13}C n.m.r. spectra. CM-a, CM-b and CM-b′ were readily identified as osthol (7), imperatorin (4) and isopimpinellin (6), already known to be fruit constituents. The remaining two coumarins, CM-c_1, m.p. 119-122° and CM-c_2, m.p. 138-141°, were found to have the same molecular formula, $C_{15}H_{16}O_4$, on the basis of their mass spectra and elemental analyses. Structures (11) and (12), respectively, were proposed for these supposedly new coumarins[9].

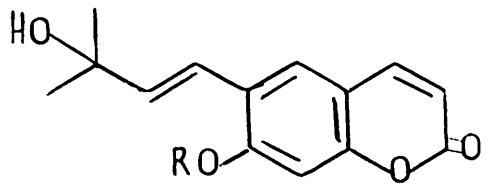
The spectroscopic evidence for CM-c_1 having structure (11) is sound, but the Japanese workers were obviously not aware that this coumarin had been isolated[10] in 1965 from bitter (Seville) orange oil (Citrus aurantium) and given the trivial name, auraptenol. Auraptenol was found to be optically active, $[\alpha]_D^{26}$ 14°, and have a melting point of 109-110°. There was no indication given in the paper on CM-c_1 concerning the chirality of the coumarin.

Structure (12) for CM-c_2 was based on the following evidence. Four pairs of doublets in the ^1H n.m.r. spectrum, recorded in $CDCl_3$, were assigned to the protons, H-3 (δ6.42, 1H, d, J 10Hz) and H-4 (7.60, 1H, d, J 10Hz), and two ortho-related aromatic protons, H-5 (6.84, 1H, d, J 8Hz) and H-6 (7.30, 1H, d, J 8Hz),

respectively. Thus CM-c_2 was a 7-methoxycoumarin, from the methyl quartet at δ56.4 in the ^{13}C n.m.r. spectrum, with a five-carbon side chain at C-8. Based on the presence of a six-proton singlet at 1.48 for two methyl groups (quartet at 24.7 in the ^{13}C n.m.r. spectrum) attached to a carbon bearing a hydroxyl group and two vinyl protons at 6.88, the nature of the side chain, and hence the structure (12), of CM-c_2 was deduced.

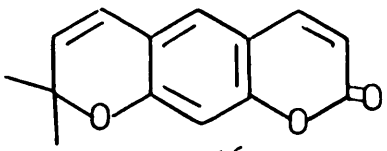
The results of the tests for possible anti-allergic effects of the five coumarins from Cnidii monnieri[9] showed that of the two major compounds, osthol (7) was ineffective but that imperatorin (4) showed significant anti-allergic activity. It was felt that this provided a pharmacological basis for one of the traditional medicinal effects of Cnidii monnieri which has been used as an ingredient of various tonics. Unfortunately, the remaining three coumarins, isopimpinellin (6), CM-c_1 (11) and CM-c_2 (12) were obtained in amounts too small for assay of their pharmacological effects.

Although it was claimed that CM-c_1 and CM-c_2 were new coumarins, only the latter has not been encountered in nature previously. However, the structure (12) assigned to CM-c_2 can represent two coumarins and not just one since two stereoisomers are possible differing in the orientation of the groups about the double bond. It is normally possible to assign the stereochemistry of such a disubstituted alkene from the coupling constant of the signals for the two coupled vinyl protons, being typically 7-10Hz for the cis (or Z) isomer and 14-16Hz for the trans (or E) isomer.



13 R= Me

14 R= H



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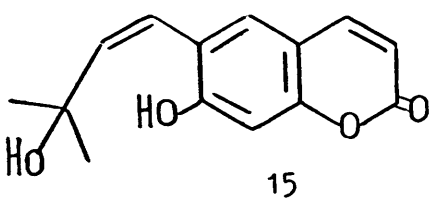

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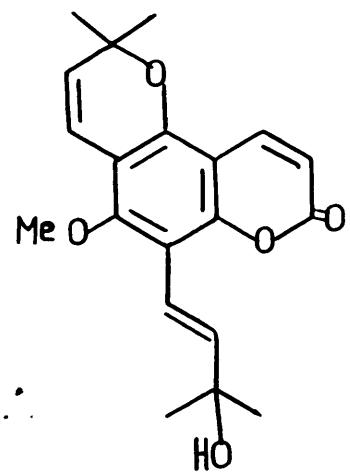

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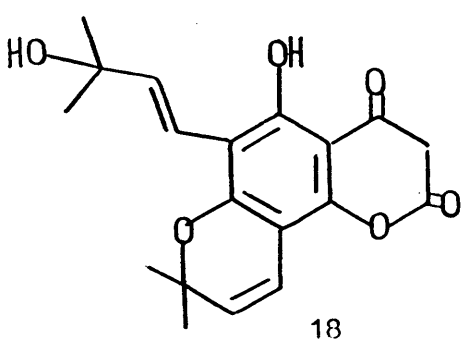

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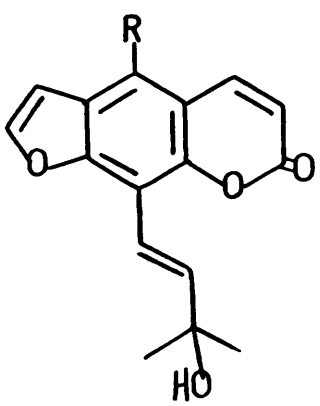


19 R = OCH_3

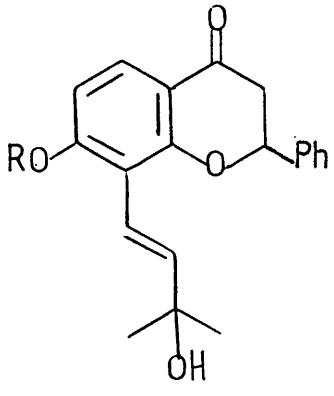
20 R = H

This approach is not possible in the present case for the two olefinic protons were found to resonate as a two-proton singlet at δ6.88[9].

The 3-hydroxy-3-methylbut-1-enyl unit is a relatively rare biogenetic modification of the common 3-methylbut-2-enyl (prenyl) group, but it has been encountered in the trans (or E) form in a number of naturally occurring oxygen heterocyclic compounds. The two olefinic protons appeared as an AB quartet at δ6.88 and 6.32 with a coupling constant of 16.5Hz in suberenol (13), the first coumarin found to contain this grouping when it was isolated[11] from Zanthoxylum suberosum in 1967. Ten years later, the corresponding phenol (14) was isolated[12] from the aerial parts of Boenninghausenia albiflora where it co-occurs with the cis isomer (15), the only natural coumarin known at present to contain this grouping. The trans isomer gave rise to an AB quartet centred at δ6.89 and 6.49 with a large coupling constant of 16Hz while the cis isomer showed its olefinic signals at 6.31 and 5.88 with a smaller coupling constant of 12.5Hz. Chemical support for the stereochemistry of the double bond in these two isomers was obtained by treatment with zinc chloride at room temperature which gave rise to dehydration and cyclisation. Thus each isomer gave xanthyletin (16), the trans isomer producing 18% after one hour, the cis isomer 52%.

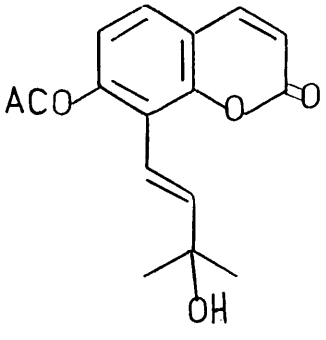
In 1975, avicennol was isolated[13] from the root-bark of Zanthoxylum avicennae and shown to have structure (17).

It was again clear from the ^{1}H n.m.r. spectrum that the double bond was trans from the coupling constant of 16Hz for the two



21 R = CH_3

22 R = $CH_2CH{=}C(CH_3)_2$



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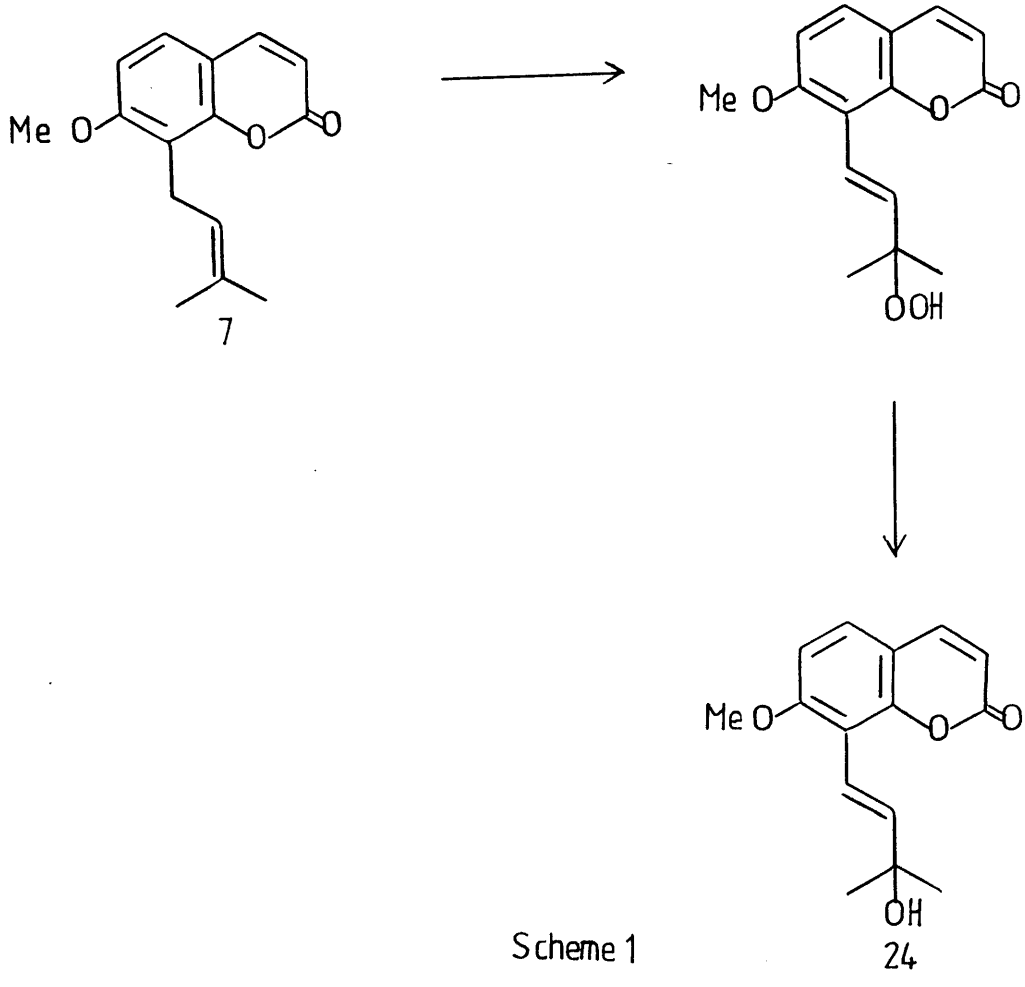
olefinic protons at δ6.95 and 6.81. At about the same time as suberenol (13) was discovered, the first chromone containing a 3-hydroxy-3-methylbut-1-enyl group was isolated[14] from Spathelia sorbifolia. The presence of a trans-disubstituted double bond in the side chain of sorbifolin (18) was revealed by the pair of doublets at δ6.95 and 6.80 with a coupling constant of 17Hz in its ^{1}H n.m.r. spectrum.

Recently, three new furanocoumarins were isolated[15] from the bark of Chloroxyon swietenia. Two of these, swietenocoumarin G and swietenocoumarin H were deduced to contain the trans-3-hydroxy-3-methylbut-1-enyl grouping in their structures (19) and (20), respectively. Dehydration of swietenocoumarin H with acetic anhydride in pyridine on a water bath for five hours gave the corresponding conjugated diene which showed signals at δ7.76 and 7.01 with a coupling constant of 16Hz in its ^{1}H n.m.r. spectrum. These two new natural coumarins were thus believed to possess the trans stereochemistry in their side chains. Significantly however the two vinyl protons appeared as a singlet at δ7.70 in the ^{1}H n.m.r. spectrum of swietenocoumarin G (19) and as a broad singlet at 7.18 in that of swietenocoumarin H (20). Similar accidental equivalence of the vinyl protons in a trans-3-hydroxy-3-methylbut-1-enyl side chain has also been observed very recently in falciformin (21), a flavanone from the seed pods of Tephrosia falciformis[16] and in a flavanone (22) from the seeds of Lonchocarpus costaricensis[17].

With the examples known to us in 1985 it seemed likely that coumarin CM-c_2 (12) would have the trans stereochemistry and



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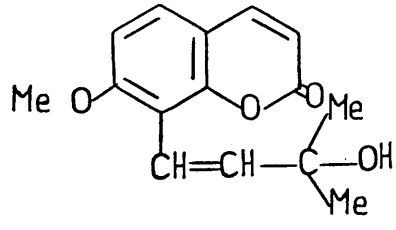
Scheme 1

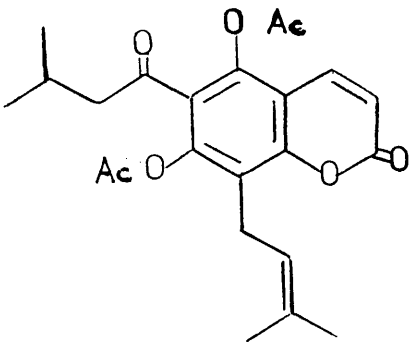


12

therefore structure (24). This view was reinforced by the information on the two flavanones which appeared after our work commenced. We also knew that the synthetic coumarin (23) prepared in this department[18] showed the vinyl protons as a singlet at δ6.73. A coupling constant of 17Hz between these two accidentally equivalent protons was only observed after addition of a small amount of the lanthanide-shift reagent $Eu(fod)_3$ to move these signals downfield and separate them. Since no sample of CM-c_2 was available to us we decided to try to resolve the stereochemical problem by a synthesis of the trans isomer (24) of coumarin CM-c_2 (12). The key compound in this approach was osthol (7) because we believed that it should be possible to convert it with singlet oxygen into an allylic hydroperoxide followed by reduction to (24) (Scheme 1).

In the first step, singlet oxygen abstracts an allylic hydrogen atom to form an allylic hydroperoxide in which the double bond has undergone a 1,2 shift. A cis cyclic ene-type mechanism was postulated by Nickon and Bagli[19] in 1961 in which the most favourable orientation of the carbon-hydrogen bond for the allylic hydrogen atom which is transferred to oxygen is perpendicular to the plane of the alkene. A 3-methylbut-2-enyl group attached to an aromatic ring possesses three sites at which hydrogen abstraction can occur. These are the benzylic position, which should be favoured mechanistically, or at either of the two terminal methyl groups.

A method for carrying out these transformations was devised by Polonsky and her co-workers[20] in 1970. They found that haematoporphyrin-sensitised photo-oxygenation of mammeisin acetate (25) followed by reduction gave a single allylic alcohol



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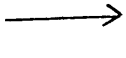

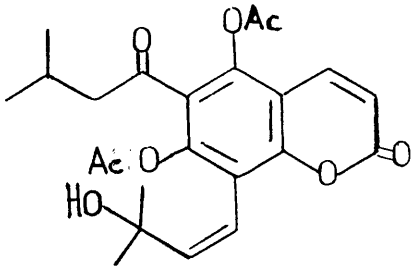

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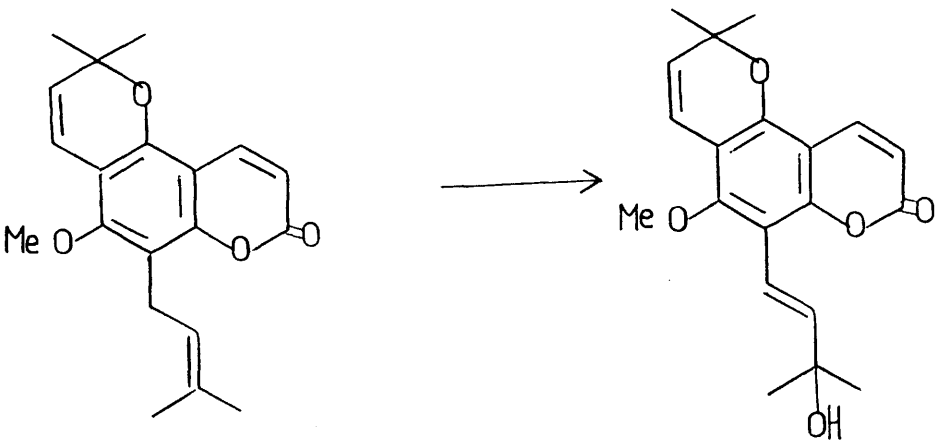
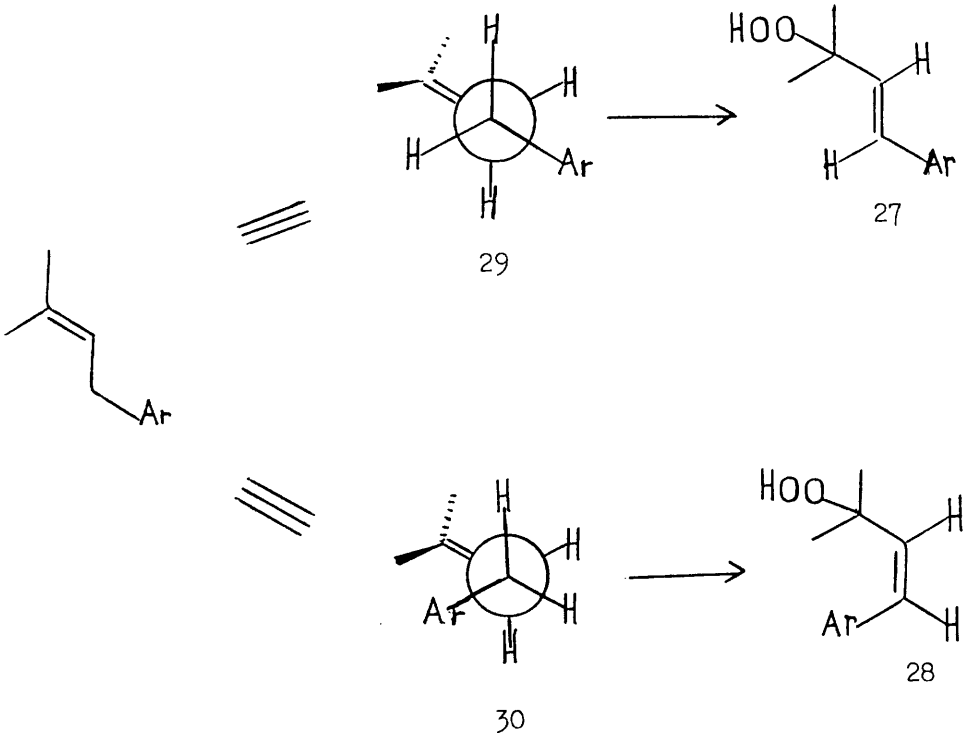
which was drawn as the cis isomer (26). It was found that the two vinyl protons of the side chain at C-8 were accidentally equivalent giving rise to a singlet at δ6.61.

In 1978, Murray and Forbes[18] in this department suggested that reaction of singlet oxygen at the benzylic position of a 3-methylbut-2-enyl group attached to an aromatic system could lead, in principle, to two stereoisomeric allylic hydroperoxides, (27) and (28) in Scheme 2. This is because two conformations of the 3-methylbut-2-enyl group attached to the aromatic ring are possible (29) and (30) which meet the mechanistic requirements of Nickon and Bagli for the reaction with singlet oxygen. The anti conformation (29) would lead stereospecifically to the trans allylic hydroperoxide (27) whereas the gauche conformer (30) would give the cis isomer (28). From molecular models it could be seen that in the transition state leading to the trans hydroperoxide (27) there should be significantly less steric congestion than that from the gauche conformer (30) to the cis isomer (28). In the second case there is unfavourable interaction between the aromatic portion and one of the methyl groups attached to the double bond. Consequently Murray and Forbes predicted that photo-oxygenation of 3-methylbut-2-enylaryl compounds should, when undergoing abstraction of the benzylic hydrogen atom, give stereoselectively and possibly stereospecifically the trans-hydroperoxide (Scheme 2).

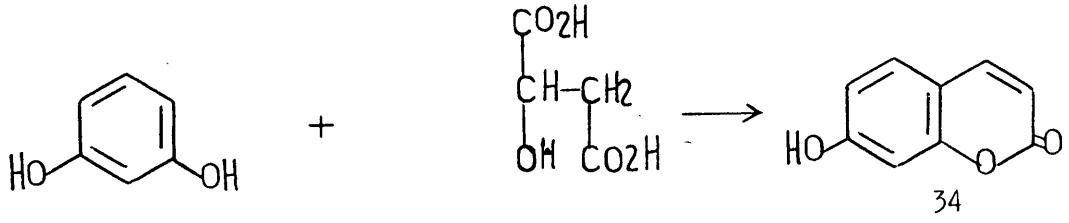
Murray and Forbes[18] then carried out a synthesis of avicennol (17). Haematoporphyrin-sensitised photo-oxygenation of the precursor, dipetaline (31) which they had synthesised, produced a single hydroperoxide which, after reduction with triphenylphosphine, afforded only the trans allylic alcohol (17), in 50°/o yield, which was found to be completely identical with a sample of natural avicennol. Before starting work on the synthesis of



31 17



Scheme 2



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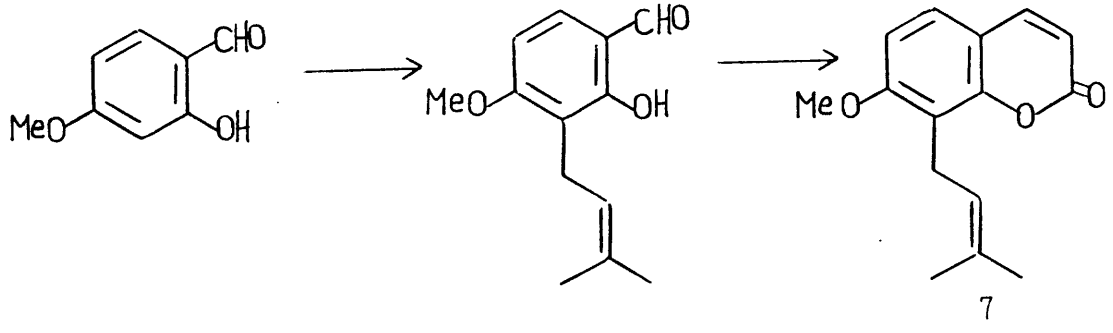
Scheme 3



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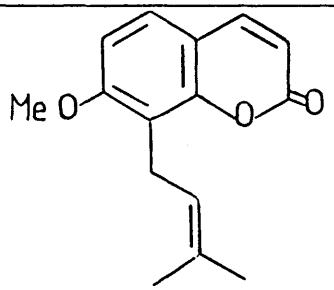
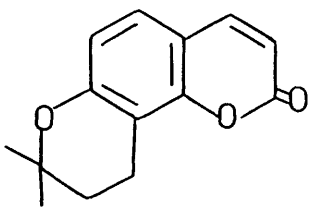
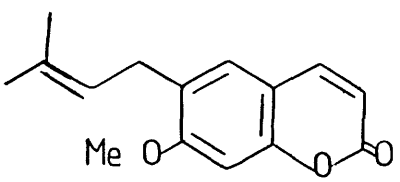
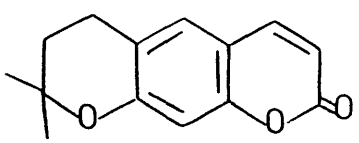
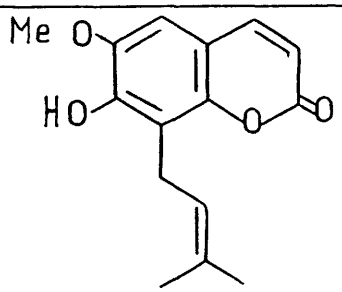
Scheme 4

the avicennol precursor, dipetaline, an investigation had been carried out on the photo-oxygenation of a model compound, osthenol acetate (32). Photo-oxygenation in pyridine using haematoporphyrin as sensitiser proceeded cleanly to give, after sodium iodide reduction, a single product in 52°/o yield which was identified as the trans allylic alcohol (23). The probability that a mistake had been made by Polonsky et al.[20] in assigning the cis stereochemistry to the product (26) was reached independently and almost simultaneously by Taylor and his colleagues[21]. They carried out a synthesis of sorbifolin (18) by the same method, but no details are given in their paper on the yield or method of purification of the products. The synthesis of coumarin CM-c_2 (12) therefore required osthol (7) as a starting material for the photo-oxygenation process. Osthol (7) was eventually prepared by a variation of a method developed in this department from the simpler coumarin, 7-hydroxycoumarin (34) which is often referred to by its trivial name of umbelliferone. The recommended method[22] of preparation of umbelliferone in the literature is by Pechmann condensation of resorcinol with malic acid and sulphuric acid (Scheme 3). However, umbelliferone is available commercially and is relatively cheap.

Two methods have been developed[22] for the synthesis of ortho-(3,3-dimethylallyl)-hydroxycoumarins, such as osthenol (33). In the first method the prenyl group is introduced into a benzene derivative followed by formation of the lactone ring, while in the second method the prenyl group is introduced into a pre-formed coumarin nucleus. The first method (Scheme 4) developed by Späth 50 years ago involves C- alkylation of a

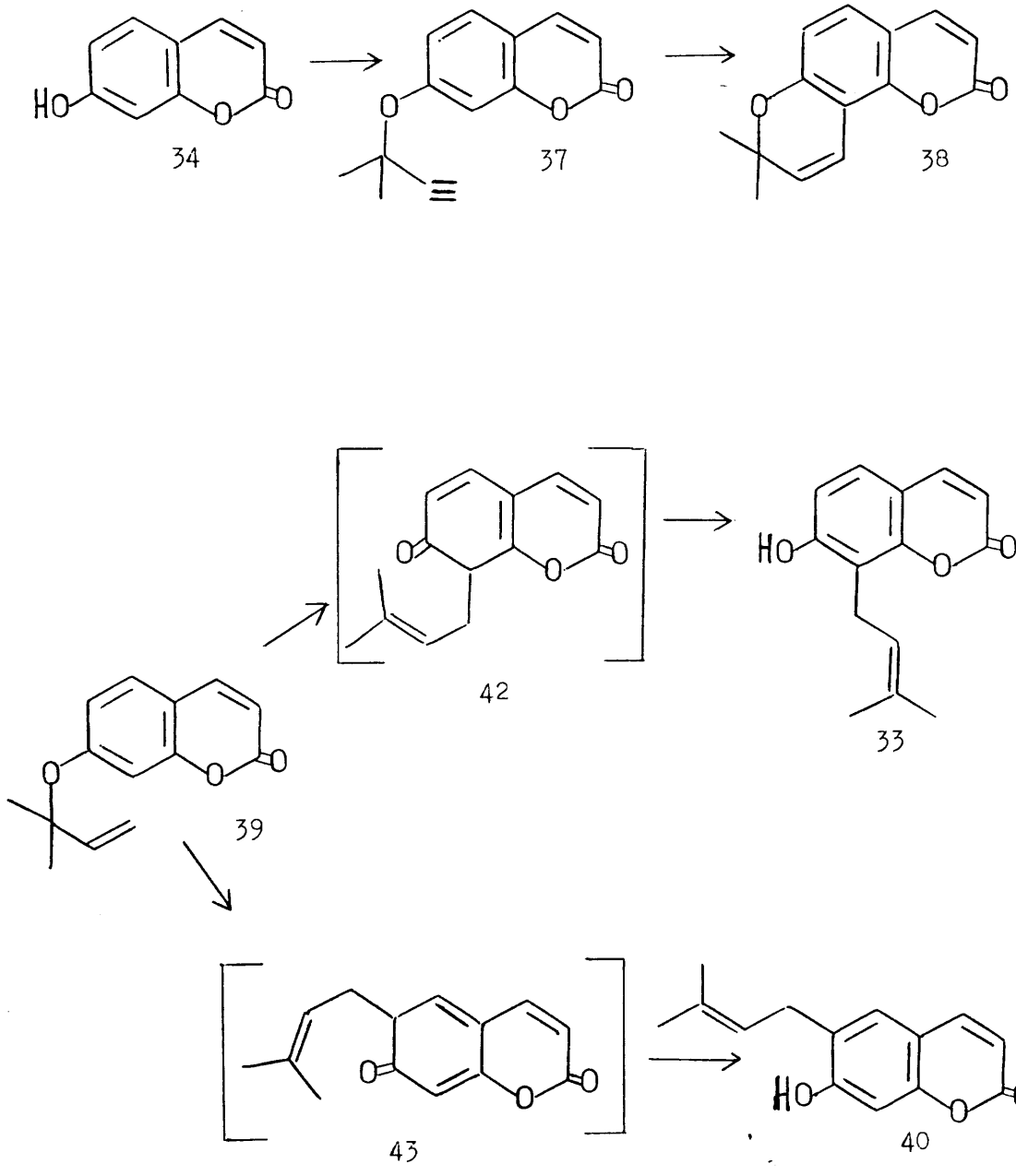
Product	Method A C-Alkylation of salicylaldehyde B C-Alkylation of hydroxycoumarin
 7	A 1%o from 4-methoxy-2-hydroxy-benzaldehyde
	B 5%o from 7-hydroxycoumarin
 35	A 3%o from 2,4-dihydroxy-benzaldehyde
	B 5%o from 7-hydroxycoumarin
 36	B 50%o from scopoletin (7-hydroxy-6-methoxycoumarin)

substituted salicylaldehyde and then formation of the pyrone ring. This method suffers from the necessity of preparing a correctly substituted salicylaldehyde.

Two variations of the second method are known[22]. The first of these involves direct C- alkylation of a pre-formed hydroxycoumarin nucleus and yields from this method are generally very poor, the greatest difficulty being at the C- alkylation stage. Poor overall yields are obtained using direct C- alkylation either of a pre-formed hydroxycoumarin or of a substituted salicylaldehyde (Table 1). Only the conversion of scopoletin (7-hydroxy-6-methoxycoumarin) to cedrelopsin (36) was found to proceed in an acceptable yield. The expected products from 7-hydroxycoumarin would be osthenol (33) and 7-demethylsuberosin (40). Since only the cyclic ethers were obtained, the first-formed C- alkylated hydroxycoumarin must be unstable to the vigorous reaction conditions. A much more reliable and efficient synthetic method was therefore required.

In 1971, Murray, McCabe and Ballantyne[23] in this department investigated the Claisen rearrangement of 3-methylbut-2-enyl aryl ethers and found the reaction to be suitable for introducing the then relatively uncommon 1,1-dimethylallyl unit into a coumarin nucleus. It occurred to them that if the corresponding 1,1-dimethyl-allyl (2-methylbut-3-en-2-yl) ethers could be prepared, their pyrolyses might result in the introduction of a 3-methylbut-2-enyl (prenyl) unit ortho to the phenolic hydroxyl group.

The procedure developed[24] has been found to be extremely useful for the synthesis of many natural coumarins in good overall



Scheme 5

yields and circumvents the necessity for C- prenylation of a phenol either before or after formation of the pyrone ring. Initially 2-chloro-2-methylbut-3-yne is required. This is readily prepared[25] from 2-methylbut-3-yn-2-ol (the condensation product of acetone and acetylene) with calcium chloride and concentrated hydrochloric acid. The chloroalkyne is easily decomposed and should be distilled under reduced pressure from a flask containing solid potassium carbonate into a flask containing solid potassium carbonate.

7-Hydroxycoumarin (34) was treated with 2-chloro-2-methylbut-3-yne in refluxing 2% aqueous acetone in the presence of potassium carbonate and a catalytic amount of potassium iodide for 24 hours. The desired propargyl ether (37) can be obtained in reproducible yields of 75-77% but these depend on the quality of the 2-chloro-2-methylbut-3-yne which can deteriorate on standing, even in the cold.

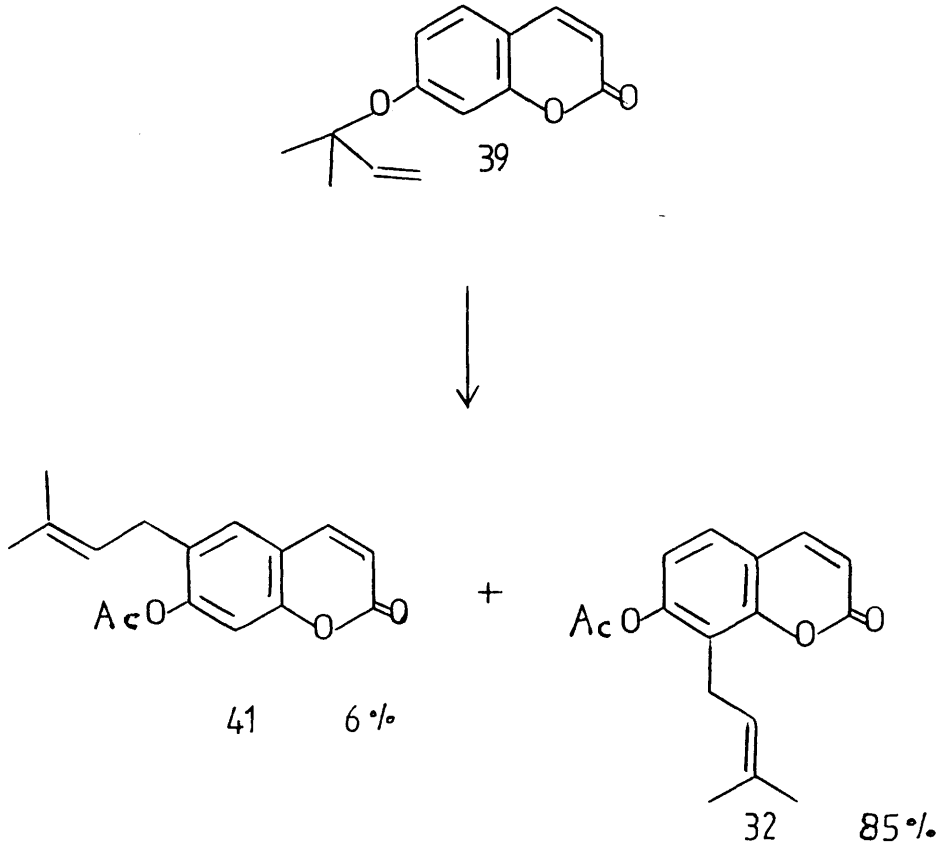
Partial hydrogenation of the propargyl ether (37) can be effected rapidly in ethyl acetate over a Lindlar catalyst at room temperature, one mole of hydrogen being absorbed in 15-20 minutes. Removal of the catalyst by filtration through celite and evaporation gave the desired 1,1-dimethylallyl ether (39) in almost quantitative yield as colourless needles, m.p. 75-78° from ethyl acetate-light petroleum. Elemental analysis, the mass spectrum and the ^{1}H n.m.r. spectrum confirmed the structure.

The next step involved the thermal rearrangement of the ether (39) into the isomeric phenol, osthenol (33). Since there are two ortho positions available for rearrangement, demethylsuberosin (40) is also a possible reaction product (Scheme 5). In the original

paper Murray, Ballantyne and Mathai[24] pyrolysed the ether (39) in a sublimation block. This gave osthenol (33) (74°/o) and demethylsuberosin (40) (14°/o) which had to be separated by preparative silica gel thin-layer chromatography. Although this method is acceptable for small-scale preparation, for larger scale work the rearrangement was carried out in refluxing N,N-diethylaniline. It is often difficult to remove all traces of this solvent and the problem of chromatographic separation still remains.

Since reasonable amounts of osthenol were required for the present work, a variation of the simple thermal rearrangement was used. In this method, a solution of the ether (39) in acetic anhydride containing sodium acetate was refluxed for two hours. Under these conditions, the first formed phenol is converted into its acetate ester. An aqueous work up gave osthenol acetate (32) containing a small amount of demethylsuberosin acetate (41) which was observed from the ^1H n.m.r. spectrum. Pure osthenol acetate could be obtained by crystallisation of the mixture from ethyl acetate and light petroleum giving needles, m.p. 94-95°.

The structure was confirmed by elemental analysis, mass spectroscopy (molecular ion at m/z 272 as expected for $C_{16}H_{16}O_4$) and from the infra-red bands in chloroform at 1764 cm^{-1} for the acetate and 1735 for the coumarin carbonyl group. The ^1H n.m.r. spectrum showed a pair of doublets at δ6.37 and 7.63, J 9.5 Hz for H-3 and H-4, respectively, and a pair of ortho-related protons at 6.98 and 7.33, J 9 Hz for H-5 and H-6, respectively with an acetoxy methyl singlet at 2.35. The side chain, which had to



Scheme 6

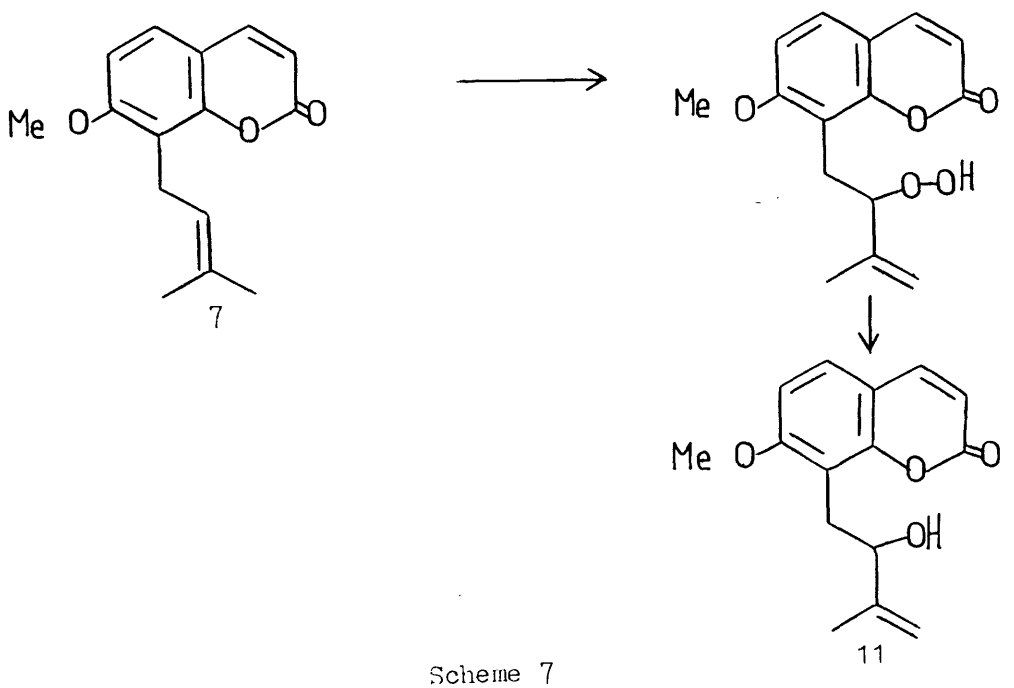
be attached to C-8, gave rise to signals characteristic of a 3-methylbut-2-enyl group, a pair of broadened three-proton singlets at 1.68 and 1.82 for the two methyl groups, a broadened two-proton doublet at 3.49, J 7 Hz for the protons of the methylene group attached to a benzene ring, the latter being coupled to the single olefinic proton which appeared as a broadened triplet at 5.5, J 7 Hz.

Hydrolysis of osthenol acetate (32) with 2°/o aqueous sodium carbonate in methanol at room temperature for 30 minutes gave the corresponding phenol, osthenol (33) in 90°/o yield. The ^{1}H n.m.r. spectrum was similar to that of the ester except for the absence of the acetoxy methyl singlet at δ2.35. The infra-red spectrum in CCl_4 showed the disappearance of the aromatic ester band at 1764 cm^{-1} and the presence of a hydroxyl group at 3501 cm^{-1}. Methylation of the phenol osthenol (33) was carried out in refluxing acetone for four hours with methyl iodide and potassium carbonate. Osthol (7) was obtained in 85°/o yield, m.p. 82-83°. Like osthenol it was readily purified by crystallisation from ethyl acetate and light petroleum. Its ^{1}H n.m.r. spectrum showed a new signal at δ3.92 corresponding to a methoxyl group attached to an aromatic ring. In the Claisen rearrangement of the substituted allylic ether (39) to osthenol (32) and demethylsuberosin (40), or their acetates, it has been observed that significantly more rearrangement takes place to C-8 than to the alternative C-6 position. A possible reason for this preference for rearrangement to C-8 is that in the transition state leading to the cyclohexadienone intermediate (42), delocalisation of the pyrone ring is retained.

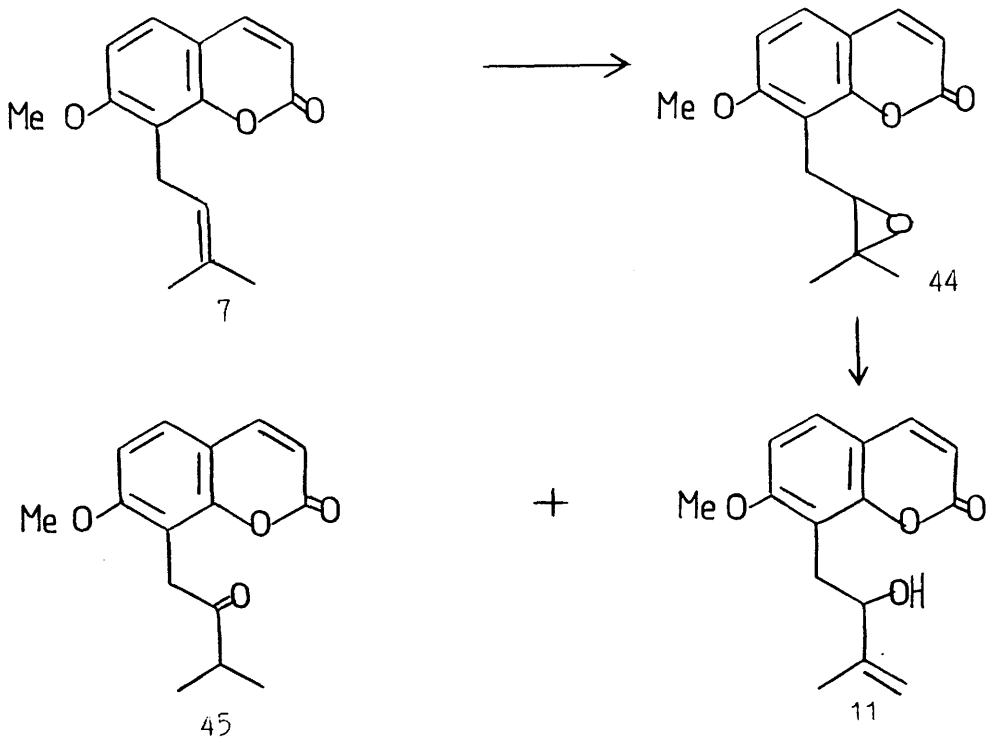
On the other hand, in the transition state leading to rearrangement to the C-6 intermediate (43), the electron delocalisation in the pyrone ring is lost[22].

It should also be noted that the preparation of the acetylenic precursor (37) of the allyl ether (39) was first reported[26] by Hlubucek, Ritchie and Taylor in 1969, who showed that on pyrolysis it afforded the chromene, seselin (38). Their independent paper which reported[27] that it could be semi-hydrogenated to the allyl ether (39) and rearranged thermally to osthenol (33) was published shortly after the first report[28] from this department had been accepted for publication.

Now that osthol (7) was available, it was possible to attempt the photo-oxygenation followed by reduction process as a method for the synthesis of coumarin CM-c_2 (12). Osthol (7) was dissolved in dry pyridine and haematoporphyrin added as sensitiser for the production of singlet oxygen. A continuous stream of oxygen was bubbled upwards through the solution using a glass sinter placed in the centre of the round-bottomed flask. The flask and its contents were irradiated by a 60 watt lamp situated approximately 10cm from the flask. After irradiation for 17 hours most of the pyridine had evaporated and thin-layer chromatography indicated the disappearance of the starting material and the production of a more polar compound. Work up gave an allylic hydroperoxide as a brown oil which was immediately dissolved in dry ethanol containing a few drops of glacial acetic acid. Sodium iodide was added and after 24 hours the reaction was worked up. The crude product was purified by preparative t.l.c. eluting three times with an



Scheme 7



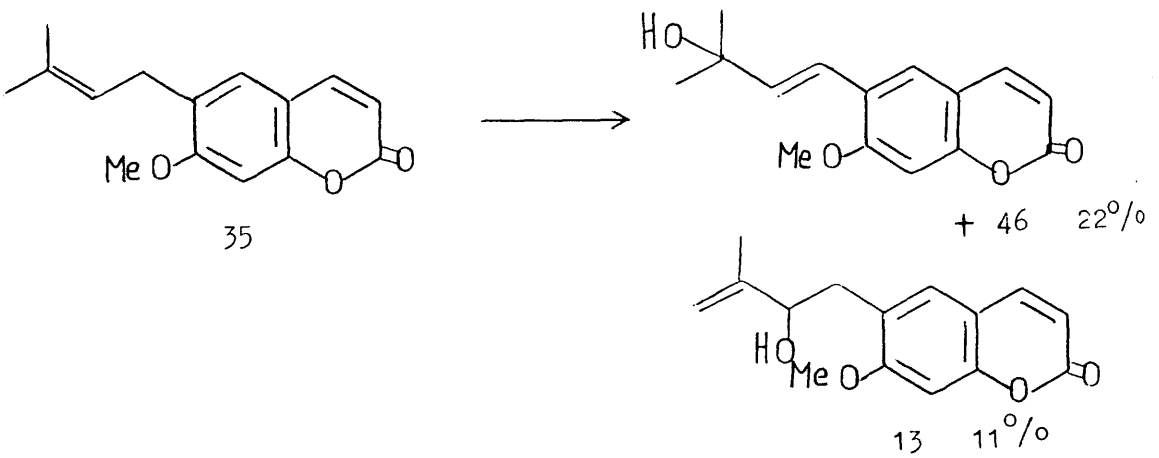
Scheme 8

eluent mixture of ethylacetate and light petroleum (2:3).

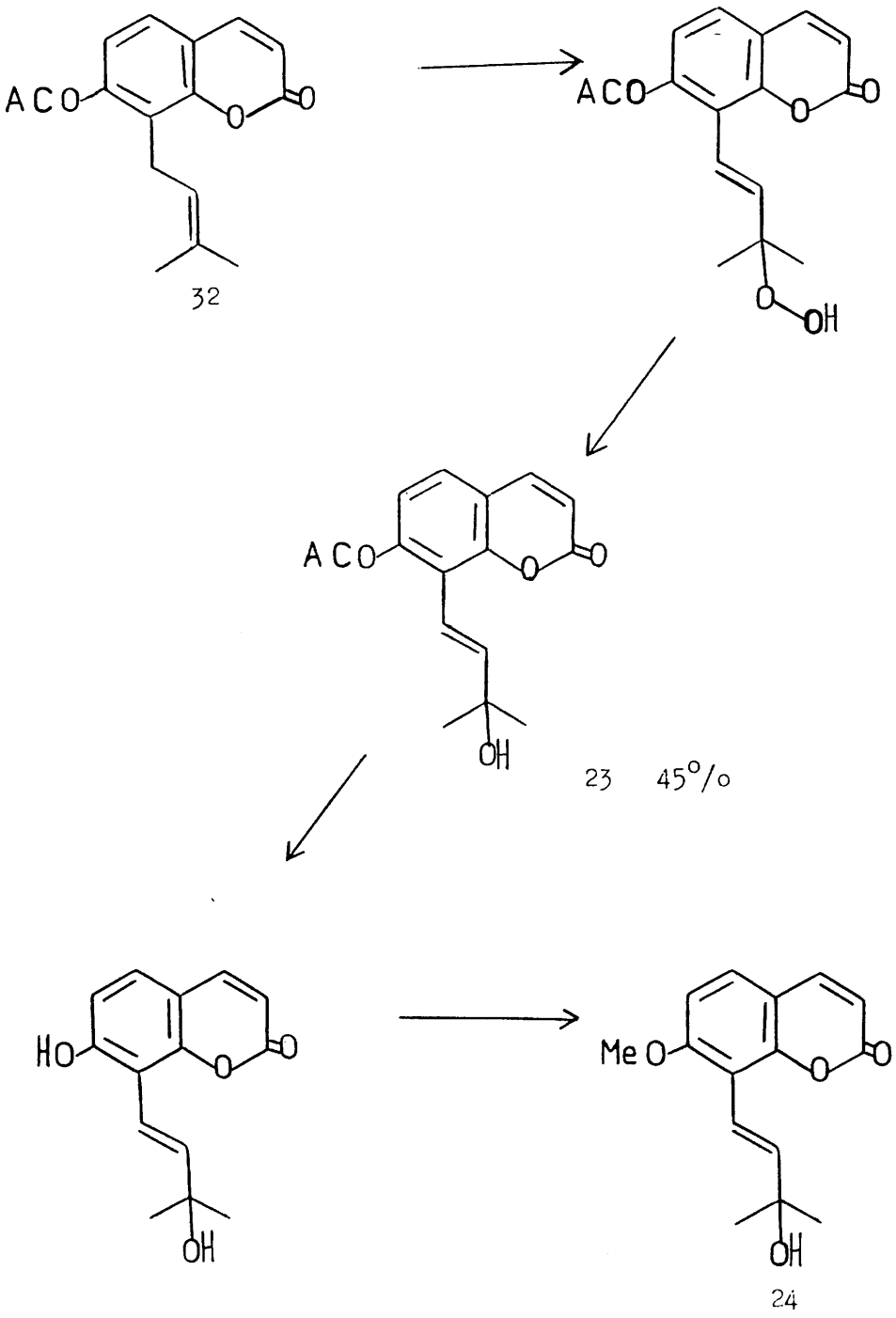
The only product which could be obtained pure was a colourless solid which crystallised from ethyl acetate-light petroleum. The melting point, 123-124°, though sharp was significantly lower than that reported[9] for coumarin CM-c_2 (12) m.p. 138-141°. However, it was almost identical with that reported for the isomer CM-c_1, m.p. 119-122° (11). Confirmation came from the ^{1}H n.m.r. spectrum which showed signals corresponding to a 2-hydroxy-3-methylbut-3-enyl side chain; a three-proton singlet at δ1.88 for the vinyl methyl group with the two vinyl protons as broadened singlets at 4.8 and 4.9, and the benzylic protons as a two-proton multiplet at 3.15 with the proton on the carbon bearing the hydroxyl group as a broadened triplet at 4.38. This corresponds to a second synthesis of auraptenol (11) (Scheme 7), the first being achieved[29] when the epoxide, (±)-meranzin (44) derived from osthol (7) was treated with boron trifluoride etherate in dimethylsulphoxide at 100°. Racemic auraptenol (11) was obtained in 40°/o yield along with the isomeric ketone isomeranzin (45) (Scheme 8).

In the photo-oxygenation process, it is evident from this result that the hydrogen atom abstracted by the singlet oxygen must have come from a methyl group rather than from the benzylic position. It has been reported that Rose Bengal-sensitised photo-oxygenation of suberosin (35), the isomer of osthol (7) having the prenyl group at C-6, gave a 2:1 mixture of the allylic alcohols (46) and (13), but in poor yield, 22°/o and 11°/o respectively (Scheme 9).

Earlier in this discussion it was stated that photo-oxygenation of osthenol acetate (32) followed by reduction of the first-formed



Scheme 9



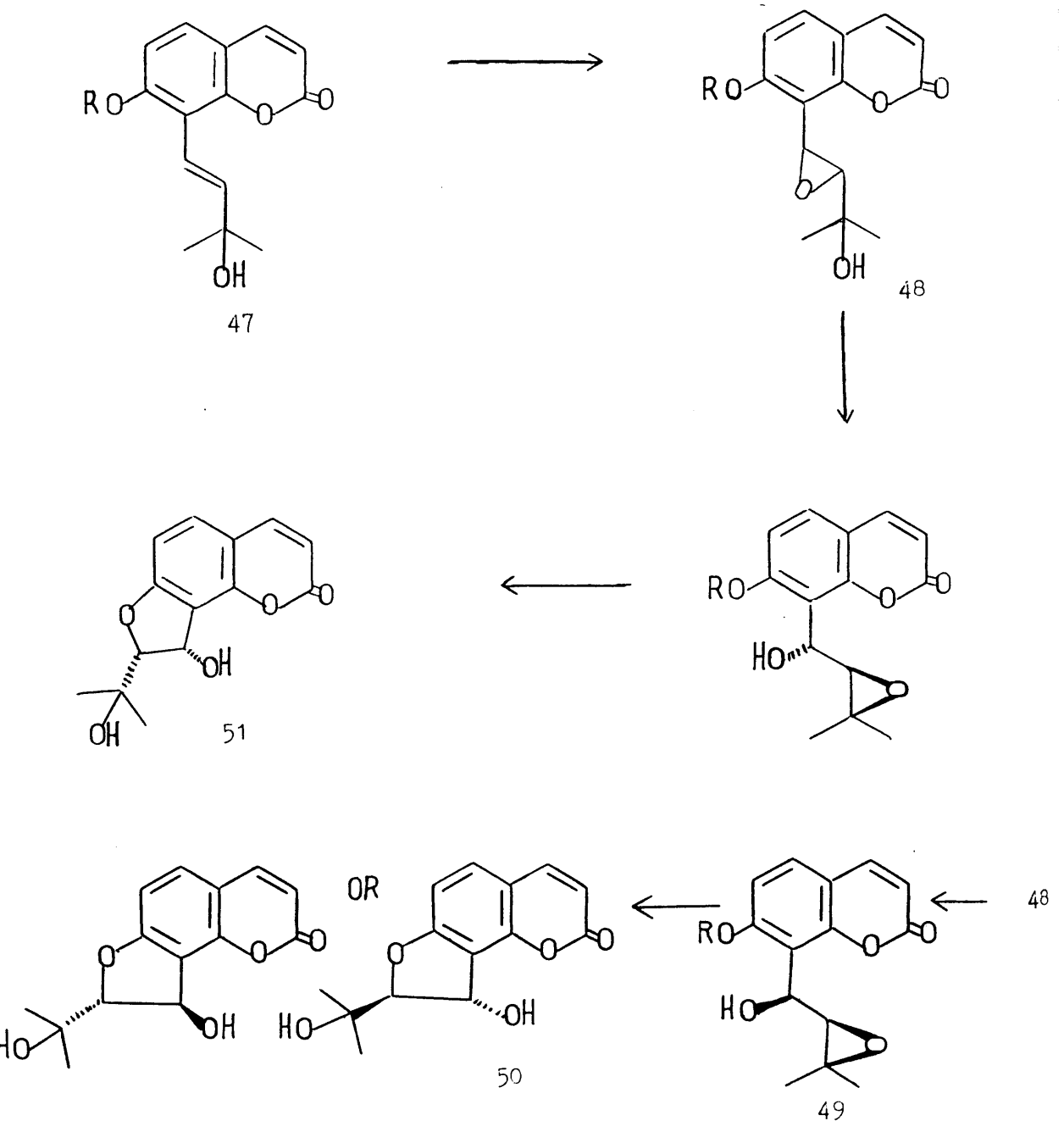
Scheme 10

hydroperoxide had given the trans allylic alcohol (23) in 51°/o yield. Osthol and osthenol acetate each have a 3-methylbut-2-enyl side chain at C-8 of the coumarin nucleus and differ only in the nature of the group attached to the oxygen atom at C-7. In osthol this is a methyl group, in osthenol acetate (32) it is an acetyl group. It is difficult to understand why these groups should have such an influence on the course of the photo-oxygenation reaction.

It is clear from the results however that when a methoxyl group is attached to C-7, the singlet oxygen must abstract a hydrogen atom from one of the terminal methyl groups of the side chain rather than from the benzylic position. On the other hand, with an acetoxyl group at C-7, singlet oxygen preferentially abstracts a hydrogen atom from the benzylic position.

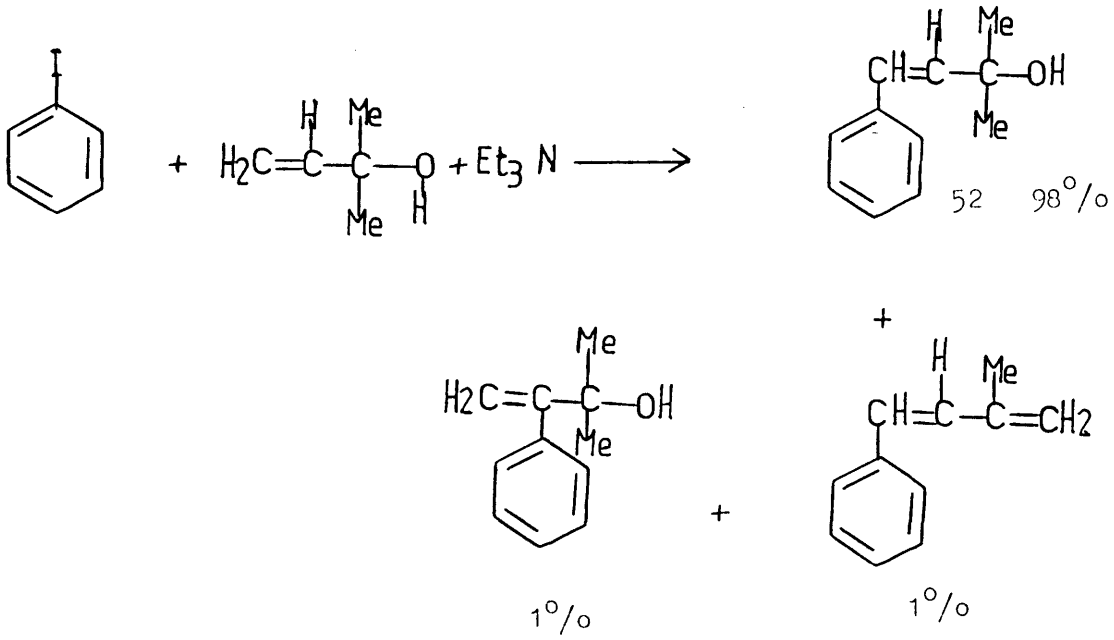
A synthesis of CM-c_2 (24) therefore required carrying out the photo-oxygenation on osthenol acetate, then converting the product (23) to the phenol, then preparing the methyl ether (24) (Scheme 10). The photo-oxygenation process was carried out on osthenol acetate (32) and the desired product (23) obtained in 45°/o yield. This product however was an oil which was not easy to purify even by preparative t.l.c.

At this point it was decided to look for a simpler method involving fewer steps for introducing a trans-3-hydroxy-3-methylbut-1-enyl residue into C-8 of a 7-oxygenated coumarin nucleus. Apart from the difficulties encountered at the photo-oxygenation stage, there are other problems which made it difficult to carry out the sequence reproducibly.

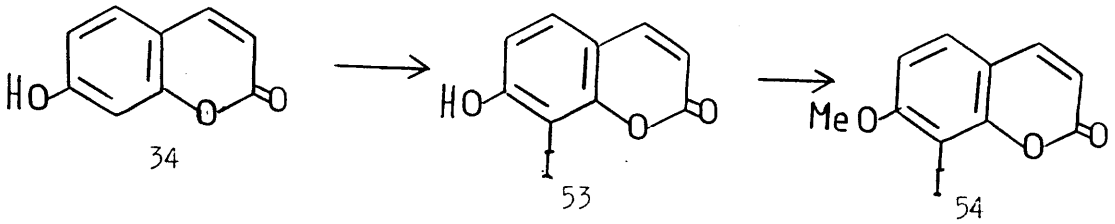


Scheme 11

The alkylation of 7-hydroxycoumarin (34) depended on the quality of the 2-choro-2-methylbut-3-yne. Control of semi-hydrogenation of the acetylenic ether (37) proved very difficult. Sometimes semi-hydrogenation was complete in less than 15 minutes and over-hydrogenation had begun, other times semi-hydrogenation was far from complete after 30 minutes and starting material remained. In either case there were difficulties in obtaining the required ether (39) in a pure state. Again, in the Claisen rearrangement step, some rearrangement to C-6 always occurs and fractional crystallisation is never an efficient method for obtaining reasonable quantities of a pure product. Apart from a synthesis of CM-c_2, we were hoping to be able to produce a synthetic route to coumarins like vaginol (50) or vaginidiol (51) many esters of which occur naturally (Scheme 11). The idea was to be able to prepare a number of compounds (47) having different R groups. In coumarin CM-c_2 R would be a methyl group. Epoxidation of the double bond should give an epoxy alcohol (48) which should undergo Payne rearrangement to (49). Removal of the protecting group R and conversion to hydroxide ion should lead to nucleophilic ring opening of the epoxide at the secondary rather than the tertiary position, leading to the dihydrofuranocoumarins (50) or (51) (Scheme 11). The second approach to the synthesis of CM-c_2 again involved 7-hydroxycoumarin as starting material and a direct insertion of the required side chain into C-8 by an alkylation. It is known from the work of Melpolder and Heck[31] that iodobenzene will arylate an allylic alcohol in the presence of a palladium catalyst. When the alkene is 2-methylbut-3-en-2-ol,


I
+ H2C=C(H)-C(Me)(Me)-O-H + Et3 N
CH=C(H)-C(Me)(Me)-OH
52 98%
H2C=C(Me)-C(Me)(Me)-OH
1%
+
CH=C(H)-C(Me)=CH2
1%

Scheme 12



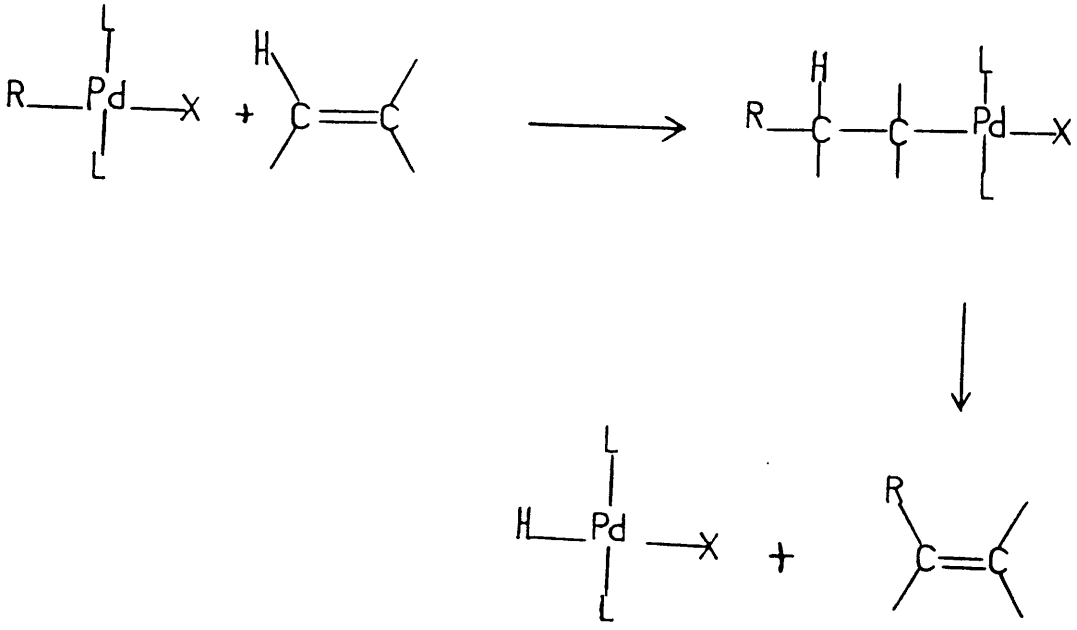
Scheme 13

the three products shown in Scheme 12 are formed, the yield of (52) being reported as 98°/o when the catalyst was palladium acetate-triphenylphosphine.

It was therefore of interest to discover if a similar Heck reaction could be carried out on an iodocoumarin. 7-Hydroxy-8-iodocoumarin (53) was prepared in 90°/o yield by the regiospecific iodination of 7-hydroxy-coumarin (34) using one mole equivalent of iodine and potassium iodide in 20°/o aqueous ammonia. That iodination had taken place exclusively at C-8 was indicated by the ^{1}H n.m.r. spectrum of the product which showed the presence of two ortho aromatic protons at δ6.75 and 7.31 as a pair of doublets, J 8 Hz. Methylation of 7-hydroxy-8-iodocoumarin (53) using methyl iodide and potassium carbonate in refluxing acetone overnight gave the desired compound,7-methoxy-8-iodocoumarin (54) in 85°/o yield (Scheme 13). The methoxy group was evident from a three-proton singlet at δ4.01 in the ^{1}H n.m.r. spectrum, while the mass spectrum showed the molecular ion at m/z 302 which was also the parent ion, with an important fragment ion at m/z 274 (50°/o) due to loss of carbon monoxide from the pyrone ring, followed by loss of the methyl group giving an ion at m/z 259 (66°/o).

When 7-methoxy-8-iodocoumarin was treated with 2-methylbut-3-en-2-ol in the presence of a catalytic amount of palladium acetate and triphenylphosphine in triethylamine at 100° under nitrogen, the only product which could be isolated was triphenylphosphine oxide.

In 1984, Jeffery[32] reported that Heck-type reactions involving organic halides proceed readily at or near room temperature

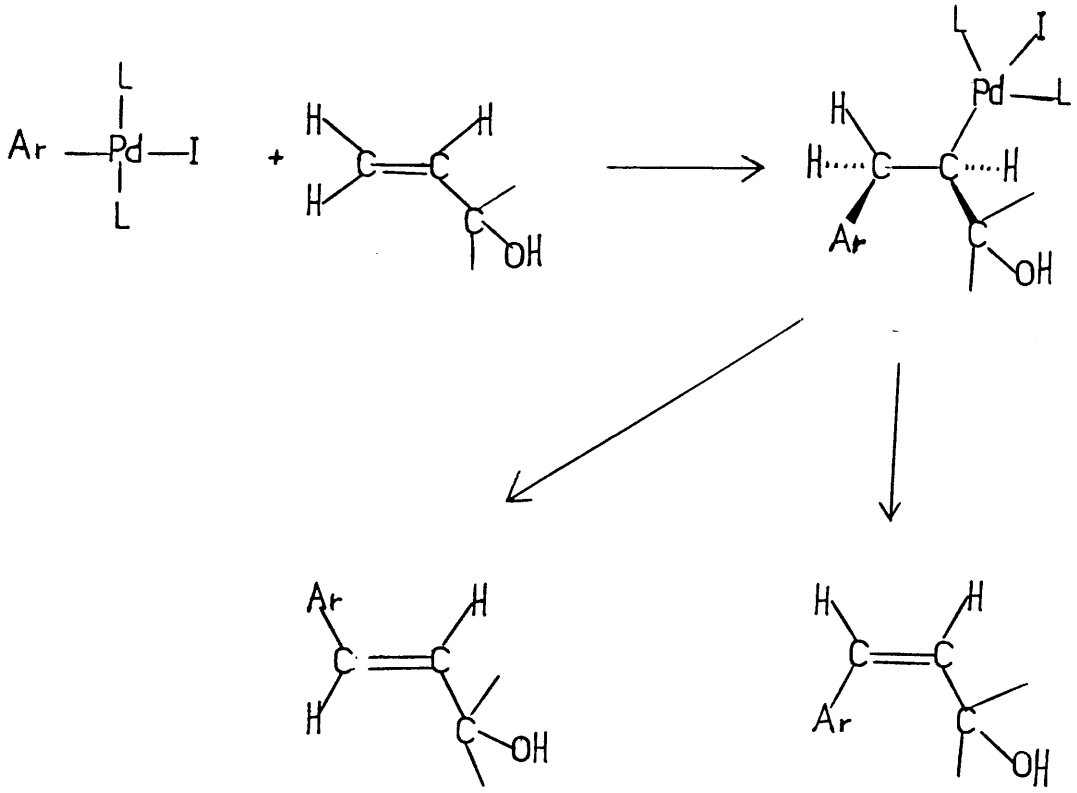


X = halide

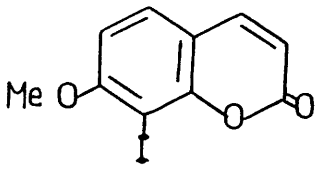
L = ligand

Scheme 14

under solid-liquid phase-transfer conditions, using tetrabutylammonium chloride as phase transfer reagent and sodium hydrogen carbonate as base. In the general reaction, Heck[33-35] had concluded that an organopalladium complex is involved which undergoes a syn addition to the double bond of an alkene, the organic group preferring the less substituted carbon atom of the double bond. This is followed by a syn elimination of a palladium hydride (Scheme 14). Using Jeffery's procedure, a solution of 7-methoxy-8-iodocoumarin (54) in dimethylformamide was treated with excess 2-methylbut-3-en-2-ol, tetrabutylammonium bromide (the chloride not being readily available), sodium hydrogen carbonate and a catalytic amount of palladium acetate under argon. There was no detectable reaction until the reaction mixture was warmed in an oil bath held at about 90°. After 24 hours, t.l.c. showed no starting material left. Work up followed by silica gel column chromatography gave in 83°/o yield a colourless solid. Crystallisation from ethylacetate-light petroleum gave needles, m.p. 138-142° which analysed for $C_{15}H_{16}O_4$. The molecular ion in the high-resolution mass spectrum was in complete agreement with this formula. The melting point reported for CM-c_2 is 138-141°, therefore it was probable that a synthesis of CM-c_2 had been achieved. The ^{1}H n.m.r. spectrum was also very similar to that reported for CM-c_2, two pairs of doublets at δ 6.25 and 7.60, $\underline{J}$ 10 Hz for H-3 and H-4 respectively, and at 6.84 and 7.30, $\underline{J}$ 8 Hz for H-5 and H-6 respectively, indicated an 8- substituted 7-methoxy coumarin. There were also signals for a 3-hydroxy-3-methylbut-1-enyl side chain, two identical methyl groups as a six-proton singlet at 1.48, one hydroxyl singlet at 1.82, exchangeable with D_2O, and two vinyl protons as a two-proton singlet at 6.88. Although a synthesis of CM-c_2 appeared to be complete, it was not possible immediately

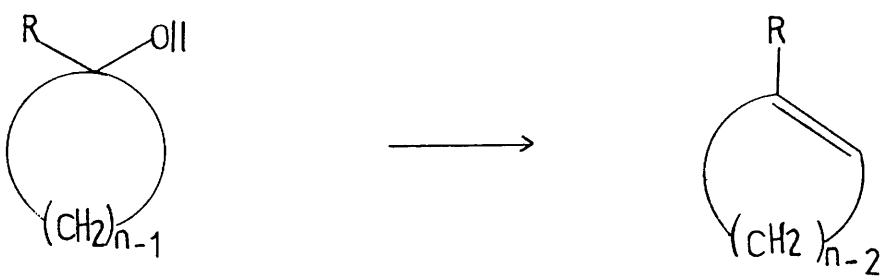


Ar =



Scheme 15

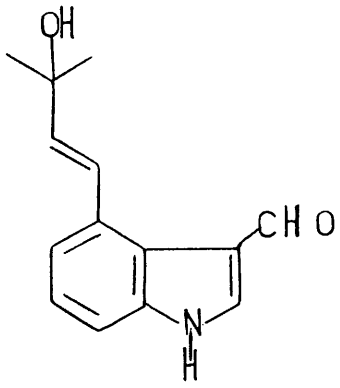
to assign the stereochemistry which we believed to be trans. On mechanistic grounds, the trans double bond would be expected. In Scheme 15, it can be seen that the organopalladium intermediate can adopt two conformations from which syn elimination of palladium hydride can occur. In that giving rise to the cis alkene, the coumarin portion would have an eclipsed interaction with the 1-hydroxy-1-methylethyl substituent. This high energy conformation should be much less favoured than that leading to the trans alkene where each bulky substituent has an eclipsing interaction with hydrogen. It is interesting that in a recent synthesis[36] of the ergot alkaloid (±)-6,7-secoagroclavine, a key step was the condensation of 3-formyl-4-iodoindole with 2-methylbut-3-en-2-ol in the presence of a catalytic amount of palladium acetate in dimethylformamide and triethylamine. The product (55), obtained in 83°/o yield, was found to have the trans stereochemistry from the large coupling constant, 16 Hz, of the olefinic protons at δ 6.19 and 7.78. In order to confirm that the synthetic coumarin from the modified Heck reaction which had the same melting point and ^{1}H n.m.r. spectral data as CM-c_2 (12) was indeed the trans isomer (24), it was decided to dehydrate it to the corresponding diene (56). Trans-dehydroosthol, m.p. 84°, was isolated by Bohlmann and his co-workers[37] in 1972 from Choisya ternata. The stereochemistry was revealed from the coupling constant of 15 Hz between H-1 and H-2 . Very recently[38], trans-dehydroosthol and its cis isomer, a new natural coumarin, were isolated from fresh leaves of Murraya exotica. The cis stereochemistry was revealed from the coupling constant of 12 Hz between H-1 and H-2 .



R = $CH{=}CH_2$, C_6H_5

n = 5, 6, 7

Scheme 16

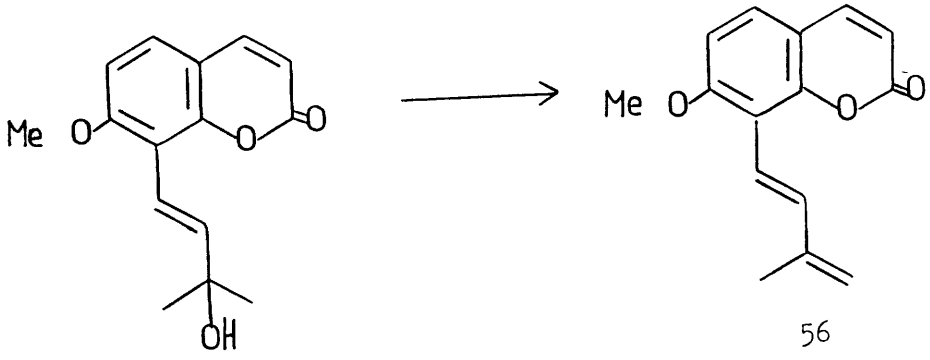


55

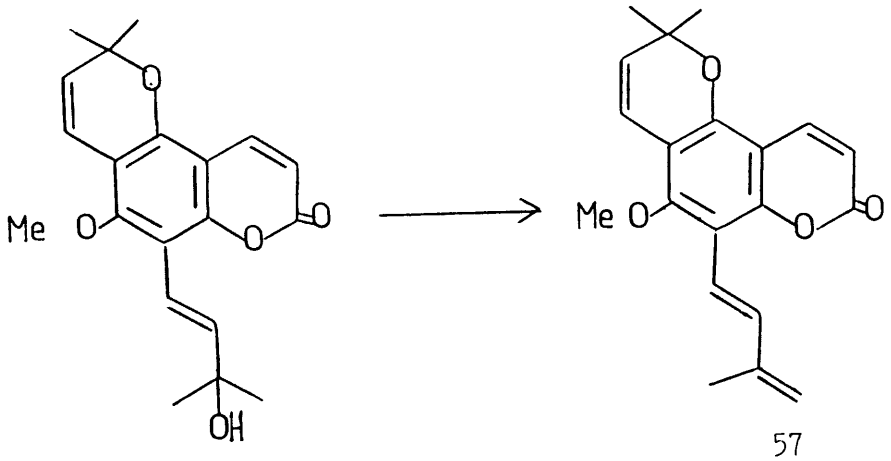
For the synthesis of trans-dehydroosthol (53), Bohlmann et al. first carefully brominated osthol (7) in chloroform at 0° then carried out a double dehydromination with diazabicyclo-[5.4.0] undec-5-ene.

During their studies on avicennol (17), Gray, Waigh and Waterman[13] observed changes in the ^{1}H n.m.r. spectrum after a solution of avicennol in deuteriochloroform had been allowed to stand for some time. They concluded that traces of phosgene were helping to carry out a dehydration. They then showed that avicennol (17) could be cleanly dehydrated to avicennin (57) using a solution of phosgene in toluene. When the synthetic coumarin from the Heck reaction was treated with phosgene in toluene, t.l.c. indicated that a mixture of compounds was produced.

In 1984, J. Hodge Markgraf and his co-workers[39] were interested in preparing 1,3-dienes[40] in connection with studies of the Diels-Alder reaction. They found that dehydration of 1-vinyl- and 1-phenylcycloalkanols could be effected quantitatively at room temperature using molecular sieves (Scheme 16). In connection with our attempts to assign the stereochemistry of CM-c_2 by dehydration under mild conditions to trans-dehydroosthol (56), a solution of CM-c_2 in dry benzene was stirred at room temperature with 5Å molecular sieves which had been stored in a warm oven for two days. T.l.c. showed only starting material after two days and even after five days no trace of any dehydration product could be detected. Attempted dehydration was thus repeated by refluxing the allylic tertiary alcohol in dry pyridine with one mole of toluene-p-



24 56

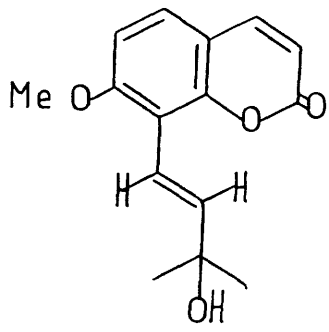


17 57

sulphonyl chloride for two hours. Work up and separation by preparative t.l.c. gave trans-dehydroosthol (56), m.p. 81-82° in 33°/o yield. The high resolution mass spectrum confirmed the molecular formula $C_{15}H_{14}O_3$ while the large coupling constant of 15 Hz for two of the vinyl protons at δ 7.42 and 6.80 confirmed the trans stereochemistry. It therefore follows that the tertiary alcohol (24) from the Heck reaction has the trans stereochemistry and coumarin CM-c_2 is therefore the trans isomer (24).

In the July 1987 issue of the Japanese journal, Heterocycles, Ito and Furukawa[38] reported the isolation of three new coumarins from leaves of Murraya exotica. One of these, which they named murraol had m.p. 105-107° and was deduced to have the structure (24) which we had assigned to our synthetic coumarin, m.p. 138-142° from the Heck reaction and had also assigned to CM-c_2, m.p. 138-141°. The u.v. and i.r. data for murraol were in agreement with the proposed structure. The fragment ions in the mass spectrum were identical to those we had observed, and the ^1H n.m.r. signals were almost identical to ours except that the two olefinic protons gave rise to an AB quartet at δ 7.02 and 6.93 having a coupling constant of 16.4 Hz.

Our synthetic coumarin (24) and murraol should have been completely identical but had significantly different melting points and differed slightly in their ^1H n.m.r. spectra. Professor Furukawa was not able to provide us with a sample of natural murraol as so little had been obtained from the natural source. He did, however, send copies of its i.r., u.v., ^1H and ^{13}C n.m.r., and mass spectra. There was no doubt that the two compounds gave rise to virtually identical spectra (apart from the olefinic signals) but differed by over 30° in their respective melting points.



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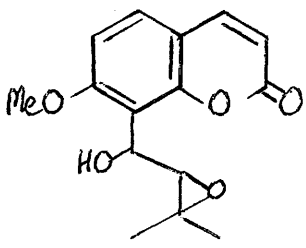

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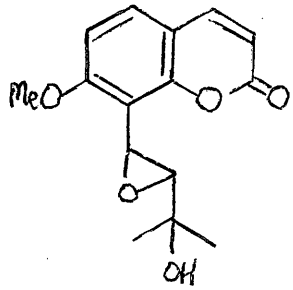

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A sample of our synthetic coumarin was then sent to Professor Furukawa. Its solution i.r. spectrum in chloroform was completely identical with that of murraol, as were the ^{13}C and, significantly, the ^{1}H n.m.r. spectra. The last was recorded in $CDCl_3$ on a 270 MHz machine and at the higher field than we had used (90 MHz) the pair of doublets for the vinyl protons was clearly visible. Very careful re-examination of our spectrum revealed that the outer limbs of the doublets were just visible and not background noise as had previously been supposed.

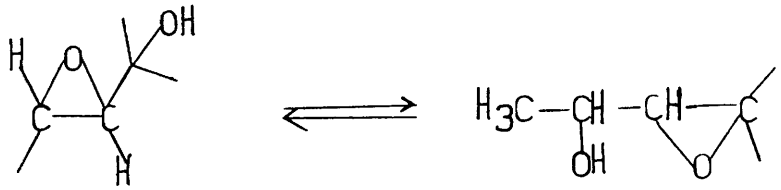
The problem of the melting points still remained until Professor Furukawa isolated murraol from a different source, Murraya paniculata leaves. This time the murraol was found to show the same higher melting point of our synthetic sample. The possibility of bimorphism of these crystalline forms was then considered. Professor Furukawa tried a seeding experiment for the different crystals in acetone. He then discovered that by recrystallising his lower melting form of murraol and seeding it with one of our synthetic crystals, the higher melting form was obtained.

Thus there is now little doubt that murraol, CM-c_2 and our synthetic coumarin all have structure (24).

In 1980, two Russian chemists, Gantimur and Semenov[41], in a study of Phlojodicarpus sibiricus, which is used in folk medicine for the treatment of tumours, isolated coumarins from the biologically active portion of the alcoholic extract of the epigeal parts. The two coumarins were named phlojodicarpin (58) and isophlojodicarpin (59), respectively and although these

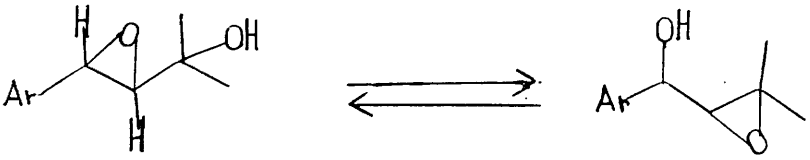
were the main components of the biologically active fraction, neither coumarin when pure possessed cytotoxic properties. The structures of the two isomers were deduced from spectroscopic evidence, but no attempt was made to interconvert them chemically. The Z configuration for the substituents attached to the oxirane ring in isophojodicarpin (59) followed from the coupling constant of 5 Hz for the protons at H-1 and H-2 . In such systems J cis is normally found to be between 2.5 and 4.5 Hz with J trans 0.5 - 2.5 Hz[42].

Although it is not easy to synthesise isophlojodicarpin (59), it was felt that synthesis of the isomer (60) of isophlojodicarpin having the E stereochemistry should be possible and it was of interest to examine the behaviour of this coumarin towards alkali in the hope of effecting a Payne rearrangement to (61). Synthetic murraol was subjected to epoxidation with m-chloroperbenzoic acid in ethyl acetate at 0°. Work up after 17 hours gave a single product in 95°/o yield which crystallised as needles, m.p. 145-146° from chloroform and light petroleum. The molecular ion at m/z 276 in the mass spectrum, which was also the parent ion, supported the molecular formula $C_{15}H_{16}O_5$. The i.r. spectrum showed bands at 1250 and 937 cm^{-1} indicative of an epoxide while the signals in the ^1H n.m.r. spectrum of the side chain were as follows; two tertiary methyl groups in different environments as three-hydrogen singlets at δ 1.42 and 1.48, a hydroxyl singlet at 2.39 exchangeable with D_2O, and a pair of doublets at 3.42 and 4.09, the coupling constant of only 2 Hz indicating the trans stereochemistry of the epoxide (60).



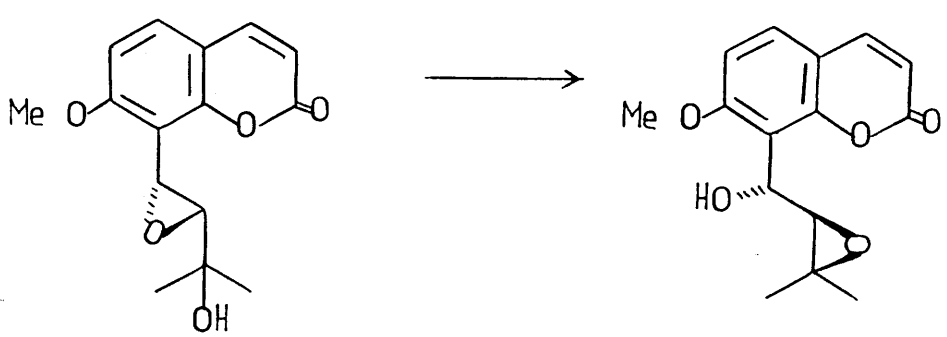
trans 62 erythro 63

Scheme 18



trans 60 erythro 61

Ar = 7-Methoxycoumarin-8-yl.



60 61

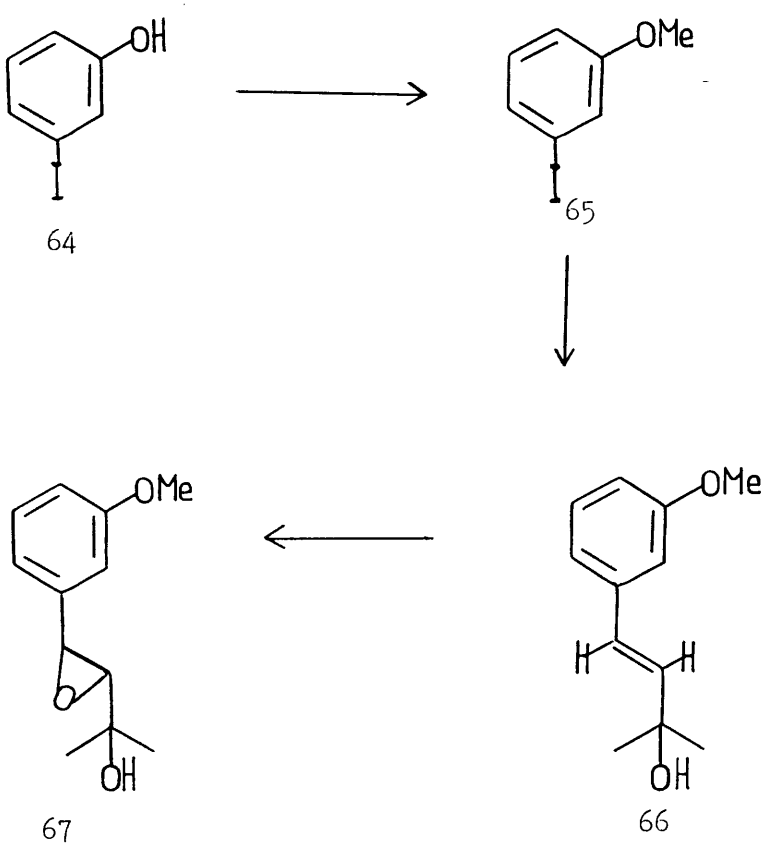
Scheme 17

The next step was attempted Payne rearrangement. In general, such a rearrangement is carried out by treating the epoxy alcohol with 0.5M aqueous sodium hydroxide, as has been discussed earlier. In this way, the trans epoxide (62) was found to give an equilibrium mixture containing 56°/o of the erythro isomer (63) (Scheme 18). Thus it was anticipated that it might be possible to convert (60) to (61) (Scheme 17) to the extent of about 50°/o, and Gantimur and Semenov[41] had shown that it was possible to separate1.04g of phlojodicarpin from 92mg of isophlojodicarpin by preparative t.l.c. on silica gel using the solvent system chloroform-methanol (10:1).

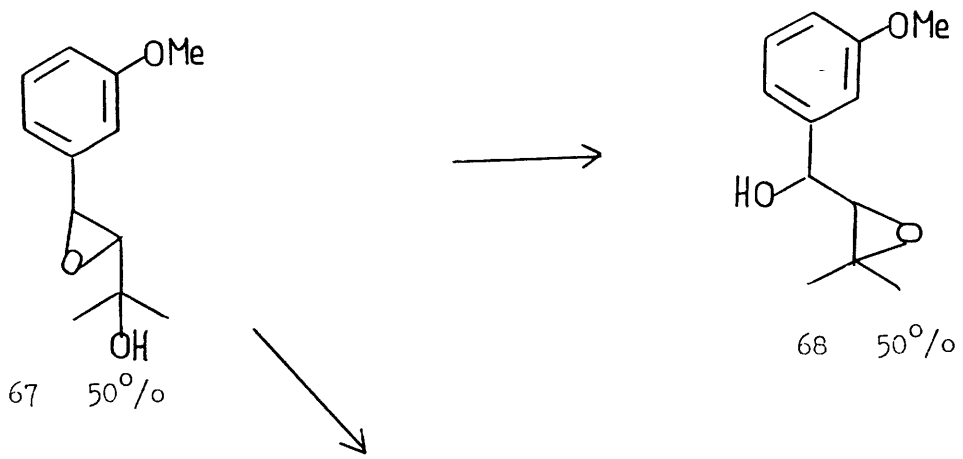
The epoxy alcohol (60) was stirred with 0.5M aqueous sodium hydroxide in the cold for one hour. After careful acidification and extraction into ether, the recovered organic material was found to be very polar on t.l.c. It was obvious from the streaking that a complex mixture of compounds had been produced. In addition, when the t.l.c. plate was placed under a u.v. lamp the spots did not fluoresce. It had to be concluded that there were no coumarins in the product and that under the alkaline conditions the lactone ring had opened and the liberated phenoxide ion had interacted with the side chain functional groups.

The pair of doublets with the characteristic coupling constant of about 9.5 Hz for H-3 and H-4 of the coumarin nucleus were totally absent.

Many attempts were made in an endeavour to use milder conditions and to try to carry out only the Payne rearrangement and avoid the opening of the lactone ring. However, complex mixtures of products, none of which fluoresced, were obtained when the epoxy alcohol (60) was treated with 0.5M aqueous sodium hydroxide



Scheme 19



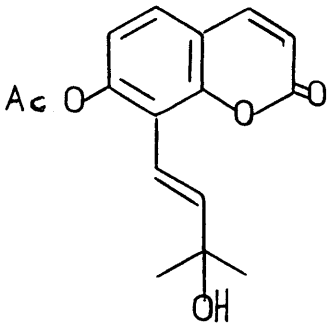
Scheme 20

in methanol, with 0.1M and 0.01M aqueous sodium hydroxide. Treatment with warm potassium carbonate also gave a complex mixture and when water was avoided, no reaction took place with sodium hydride in refluxing tetrahydrofuran, the starting material being recovered unchanged.

It was felt to be of interest to prepare a model compound to study the rearrangement of a 1-aryl-1,2-epoxy-alcohol (Scheme 20) having an aryl substituent which could not interact with the rearranging system. A sample of 3-iodophenol (64) was available so it was converted into its methyl ether (65), a colourless oil. This methyl ether was subjected to the modified Heck reaction conditions. Treatment with 2-methylbut-3-en-2-ol in the presence of palladium acetate, tetrabutylammonium bromide and sodium hydrogen carbonate in dimethylformamide at 90 $\pm$ 5° under argon overnight gave the allylic alcohol (66) as a colourless oil in 85°/o yield. The structure was confirmed by the ^{1}H n.m.r. spectrum which showed a six-proton singlet at δ 1.42 for two methyl groups attached to the carbon atom bearing the hydroxyl group, a methoxyl three-proton singlet at 3.69 and four benzenoid protons as a multiplet between 6.70 and 7.00. The two vinyl protons resonated at 6.28 and 6.58, each as one-proton doublets, the large coupling constant of 16 Hz confirming their trans relationship.

Epoxidation of the trans allylic alcohol (66) with m-chloroperbenzoic acid in ethyl acetate at room temperature gave the corresponding epoxy alcohol (67) as a colourless oil in 95°/o yield (Scheme 19). Compared with the allylic alcohol (66), the molecular ion in the mass spectrum had

increased by 16 atomic mass units from m/z 192 to 208. In the ^{1}H n.m.r. spectrum, the two tertiary methyl groups were now in different environments and appeared as two three-proton singlets at δ 1.28 and 1.33, while the pair of doublets for the two vinyl protons had been replaced by a new pair of doublets at 2.95 and 3.92 showing a coupling constant of 3.5 Hz. When the epoxy alcohol (67) was stirred for one hour with 0.5M aqueous sodium hydroxide and the mixture acidified, t.l.c. of the product indicated it to be a 1:1 mixture of starting material and a slightly more polar product. Careful preparative t.l.c., with six elutions using a mixture of chloroform and light petroleum (1:1) was required for the separation. The less polar of the two products was identified as starting material from its spectral data. The new compound was deduced to be the isomer (68) resulting from a Payne rearrangement. As expected, it showed a molecular ion at m/z 208 in its mass spectrum, but a different fragmentation pattern from that of (67). Its i.r. spectrum showed bands at 3425 cm^{-1} for a hydroxyl group and bands at 1150 and 1040 which could be due to the oxirane ring. The ^{1}H n.m.r. spectrum in $CDCl_3$ was similar to, but in no way identical with, that of its precursor. Thus the two tertiary methyl groups, attached to a carbon bearing an oxygen atom, appeared as singlets at δ 1.21 and 1.33, and there were two-proton doublets at 3.35 and 4.95 showing a coupling constant of 3.5 Hz for the two protons attached to carbon atoms bearing oxygen.



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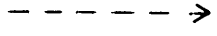

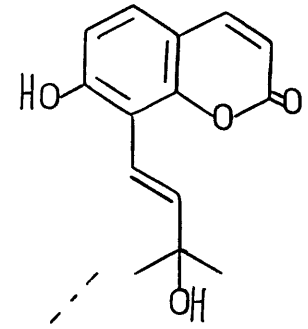

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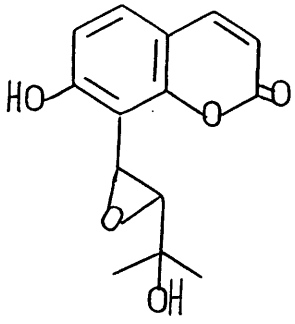


71

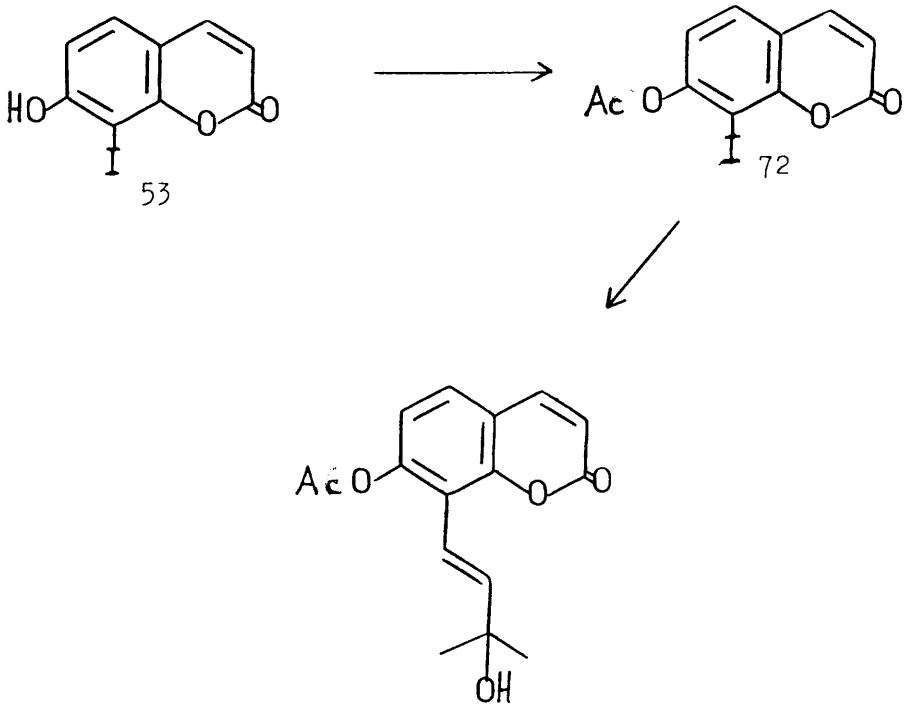
Scheme 21

It was thus clear that the desired Payne rearrangement had taken place here, and would have also probably occurred in the reaction of (60) with aqueous sodium hydroxide if only the coumarin lactone ring had not also opened under the alkaline reaction conditions and led to products from further intramolecular reaction.

Since we had now shown that the Payne rearrangement shown in Scheme 20 was possible using 0.5M aqueous sodium hydroxide, it was of interest to discover the mildest conditions possible for carrying it out. With this in mind, the epoxy alcohol (67) was treated with 0.1M aqueous sodium hydroxide, and when the reaction was worked up after one hour, t.l.c. indicated the disappearance of all the starting material and none of the expected rearrangement product. Instead a very polar compound was produced, the i.r. spectrum of which showed very strong absorption in the hydroxyl region. The conclusion was reached that decreasing the concentration of the alkali had resulted in complete hydrolysis of the epoxide ring and produced the triol (69) (Scheme 20).

It was next decided to see if it was possible to carry out the modified Heck reaction on 7-acetoxy-8-iodocoumarin to give (23) then convert the acetoxyl group to the phenol (70), epoxidise the double band and treat the product (71) with base (Scheme 21).

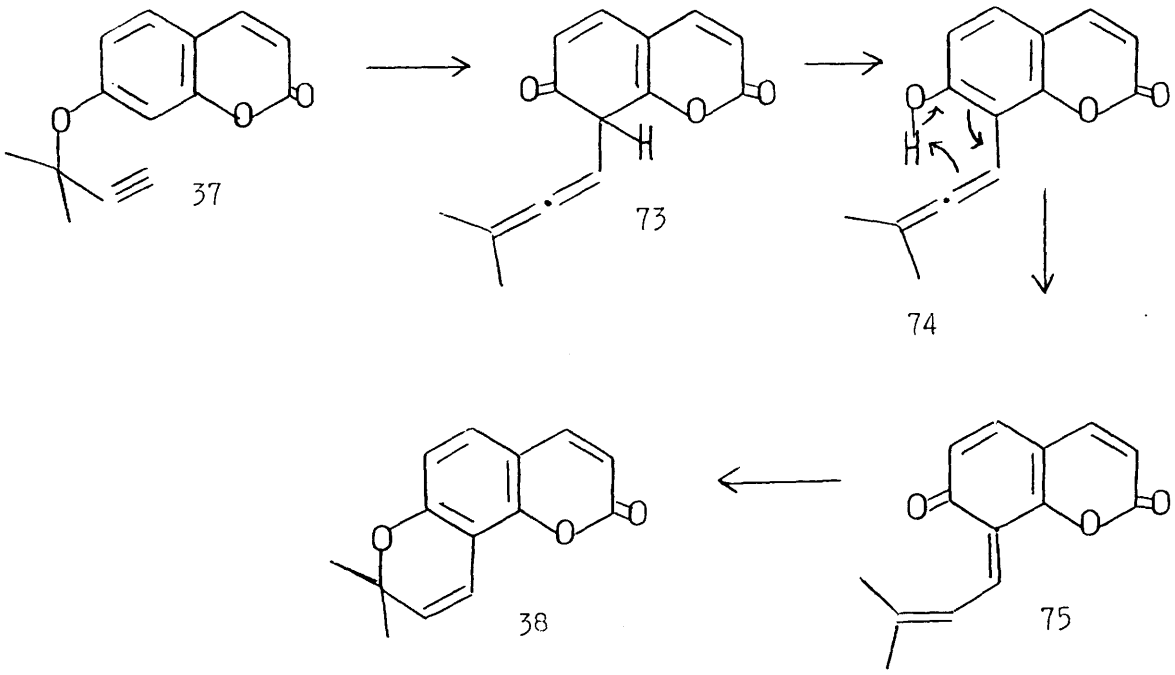
7-Hydroxy-8-iodocoumarin (53) was converted into its acetate (72) (Scheme 22) in 85°/o yield by reacting it with refluxing acetic anhydride containing sodium acetate for two hours.



Scheme 22

A solution of 7-acetoxy-8-iodocoumarin in dimethylformamide was treated with 2-methylbut-3-en-2-ol in the presence of palladium acetate, tetrabutylammonium bromide and sodium hydrogen carbonate in an oil bath held at 90 ± 5° for 24 hours. Work up gave a single product in good yield which crystallised from methanol as needles, m.p. 122-123°. The ^{1}H n.m.r. spectrum of this compound was interesting. It was clear from the complete absence of a three-proton singlet at about δ 2.4 that the acetoxyl group had disappeared. The expected condensation product (23) contains a tertiary hydroxyl group, but there was no D_2O exchangeable proton in the spectrum of the product. Two equivalent tertiary methyl groups were present, giving rise to a six-proton singlet at δ 1.50. The remaining six protons in the spectrum appeared as six doublets. It was also clear that three pairs of protons were present with each proton in each pair coupled only to the other proton in the pair and to no other. The pair of doublets at δ 6.26 and 7.63, J 9.5Hz could be attributed to H-3 and H-4, respectively of the pyrone ring; 6.75 and 7.25, J 9Hz to the ortho-related benzenoid protons at H-5 and H-6, respectively; and 5.85 and 6.93, J 10Hz to two adjacent protons on a chromene ring. The structure was therefore deduced to be that of seselin (38), m.p. 120-121° (from ethanol), lit.[5] m.p. 119-120°.

This was confirmed by preparing seselin by pyrolysis of 7-O-(1,1-dimethylprop-2-ynyloxy)-coumarin (37) in N,N-diethylaniline at 220° for two hours. This useful method for making a dimethylchromene ring referred to earlier[26] is believed to occur[43] as shown in Scheme 23.



Scheme 23

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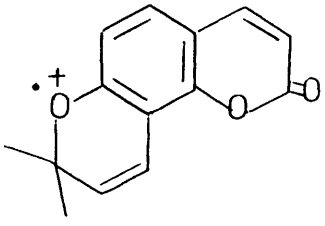
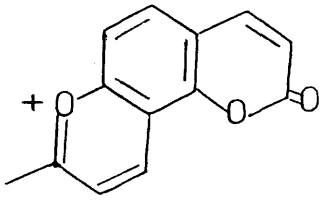


m/z 228

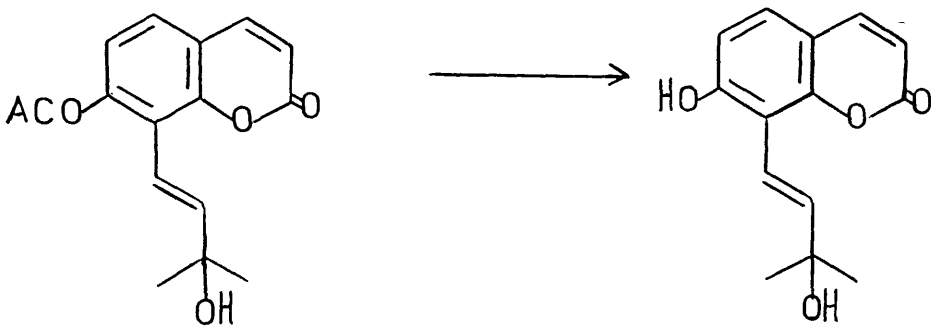
$-\dot{C}H_3$



76 m/z 213

Scheme 24

The first-formed ortho-dienone intermediate (73), formed by a variation of the Claisen rearrangement, is thought to tautomerise to the ortho-allenylphenol (74). A 1,5-hydride transfer is followed by an electrocyclic ring closure of (75). Additional support for the structure of seselin came from its mass spectrum which was dominated by the loss of a methyl radical and generation of a stable benzopyrylium ion (76) as the base peak[44] (Scheme 24). Since seselin (38) was confirmed to be the product of the attempted Heck reaction on 7-acetoxy-8-iodocoumarin (72), it was clear that a five-carbon unit had been introduced at C-8. Since no trace of the anticipated product (23) could be detected, it seemed possible that it had been formed but was unstable under the reaction conditions used for its production. The Heck reaction with 2-methylbut-3-en-2-ol was therefore repeated at room temperature. After 24 hours completely unreacted starting material was recovered. However, when the reaction mixture was kept in an oil bath at $65 \pm 5^{\circ}$ for 24 hours, t.l.c. showed formation of a new polar product. Work up gave, in $70^{\circ}/o$ yield, the trans-allylic alcohol (23), the i.r. and ^{1}H n.m.r. spectra of which were completely identical with those of the product previously obtained by photo-oxygenation of osthenol acetate(32). Significantly, the pure trans-allylic alcohol (23) was converted smoothly into seselin (38) when heated in N,N-diethylaniline at 220° for two hours. It is possible that thermal loss of acetic acid occurs, possibly aided by the slightly basic reaction conditions, to give the immediate precursor (75) of seselin (38).



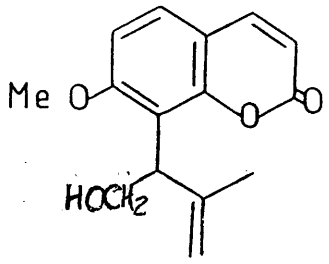
23 70

This three-step method for preparing (23) from 7-hydroxy-coumarin is much more efficient and much more convenient than the method used originally.

Hydrolysis of 7-acetoxy-8-(trans-3-hydroxy-3-methylbut-1-enyl)-coumarin (23) in methanol in the presence of 2°/o w/v aqueous sodium carbonate at room temperature for 30 minutes cleanly afforded the corresponding phenol (70) in 90°/o yield as colourless needles, m.p. 159-161°. Microanalysis confirmed the structure $C_{14}H_{14}O_4$. The ^1H n.m.r. spectrum in dimethyl-sulphoxide-d_6 showed a six-proton singlet at δ 1.32 for the two side-chain methyl groups with the two vinyl protons appearing as a pair of doublets at 6.78 and 6.90, J 16Hz. Additionally the expected signals for the coumarin nucleus were present.

It was hoped that it might be possible to convert (70) into its epoxide but treatment with m-chloroperbenzoic acid in ethyl acetate led only to a complex mixture of compounds separation of which proved impossible. Presumably the phenolic hydroxyl group must interact immediately with the epoxide ring as soon as it is formed.[45]

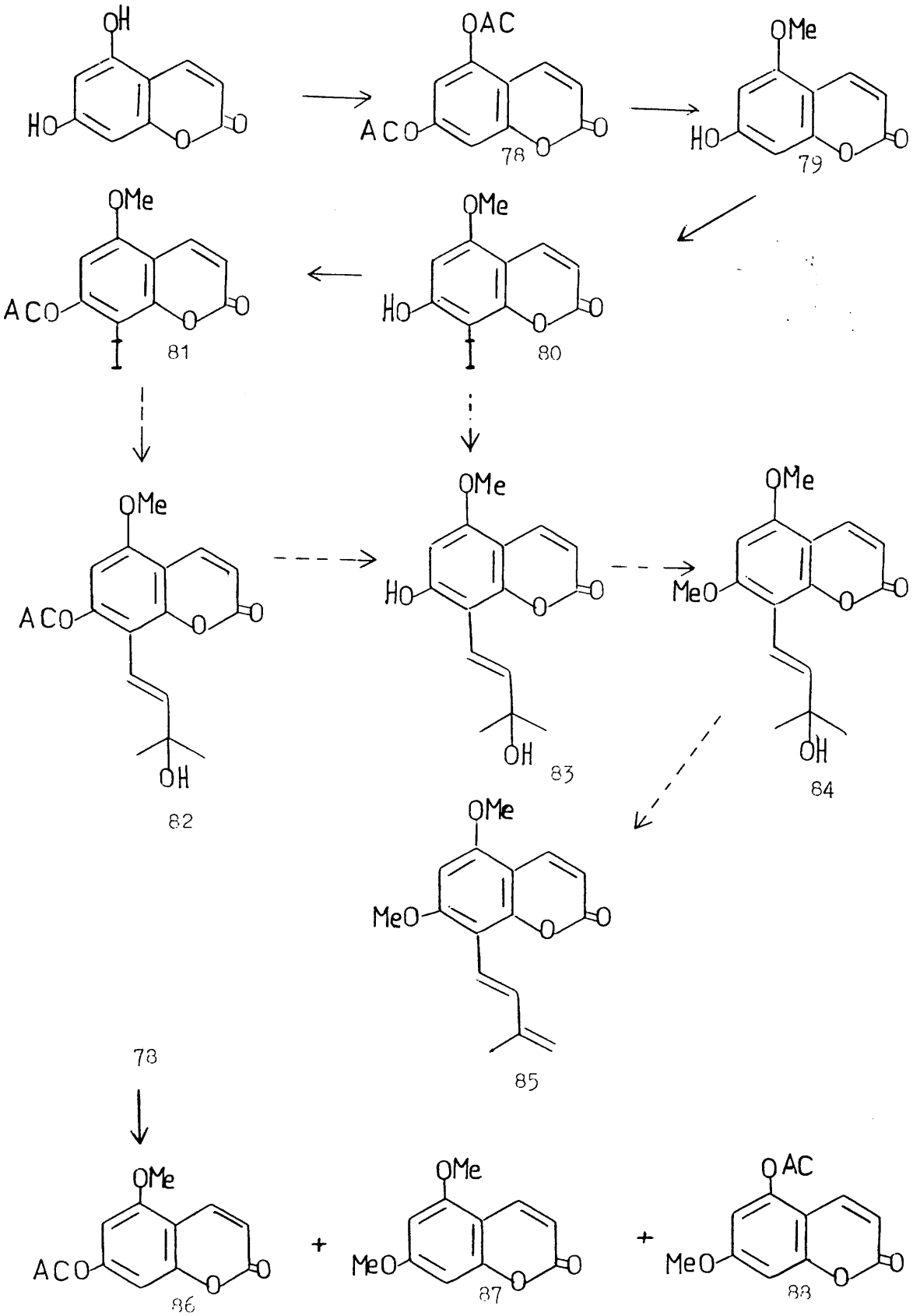
Since we had shown that 7-methoxy- and 7-acetoxy-8-iodocoumarin could undergo a Heck-type reaction with 2-methylbut-3-en-2-ol (1,1-dimethylallyl alcohol), it was of interest to examine the course of the reaction with 3-methylbut-2-en-1-ol (3,3-dimethylallyl alcohol), the isomeric alcohol having the two methyl groups at the other end of the allyl group. Thus 7-methoxy-8-iodocoumarin was treated with 3-methylbut-2-en-1-ol in the presence of palladium acetate, tetrabutylammonium bromide and sodium hydrogen carbonate in dimethylformamide at 65 ± 5°



77

overnight. Extensive preparative thin-layer chromatography of the product gave two main bands, the more polar of which could not be obtained sufficiently pure to be identified. The major product, obtained in 40°/o yield as colourless crystals, m.p. 113-114° from ethyl acetate-light petroleum, was found to have the formula $C_{15}H_{16}O_4$ by high-resolution mass spectrometry. The ^1H n.m.r. spectrum showed two pairs of doublets at δ 6.25 and 7.55, J 9.5Hz, for H-3 and H-4, respectively, and 6.85 and 7.30, J 8Hz for H-5 and H-6 respectively. The methoxyl group was also still present as a three-proton singlet at 3.85. Thus, as in the previous Heck reaction using the isomeric allylic alcohol, the iodine atom at C-8 had been replaced by a C_5H_9O unit. The oxygen atom was present as a hydroxyl group, ν_{max} (KBr) 3450 cm^{-1} with the broad singlet at δ 1.90 exchangeable with D_2O. The single unit of unsaturation in the five-carbon side chain was present as an alkene. Two olefinic protons were present as a methylene group from the two-proton broad singlet at 4.89 and a methyl group was also attached to the double bond as shown by the three-proton singlet at 1.65. The signals for the remaining three protons appeared as a multiplet at 4.25. These were accounted for by assuming that a $-CH_2OH$ group was present, attached to a carbon carrying one proton which was both allylic and benzylic.

Structure (77) is therefore proposed for the new compound. The formation of (77) can be rationalised in terms of syn addition of the organopalladium intermediate in such a way that the coumarin moiety adds to the less substituted position


OH
HO
O
OAC
ACO
78
OMe
HO
79
OMe
ACO
81
OMe
HO
80
OMe
ACO
OH
82
OMe
HO
OH
83
OMe
MeO
OH
84
OMe
MeO
85
78
OMe
ACO
86
+
OMe
MeO
87
+
OAC
MeO
88

Scheme 25

of the double bond of the allylic alcohol. Syn elimination of palladium hydride can then take place with one of the six possible hydrogen atoms from the two terminal methyl groups. In the February 1987 issue of Phytochemistry, the structure of a new coumarin, gleinadiene (85) from Murraya gleinei roots was reported[46]. The structure of gleinadiene is the same as that of trans-dehydroosthol (56) except that it has an additional methoxyl group at C-5. A possible synthetic route to gleinadiene is shown in Scheme 25. The key reaction in the sequence appeared on paper to be the Heck reaction of 5-methoxy-7-acetoxy-8-iodocoumarin (81) with 2-methylbut-3-en-2-ol. If the allylic alcohol (82) could be formed, it should be possible to hydrolyse the acetoxyl group to the phenol (83) and then prepare the methyl ether (84). Dehydration should then give gleinadiene (85).

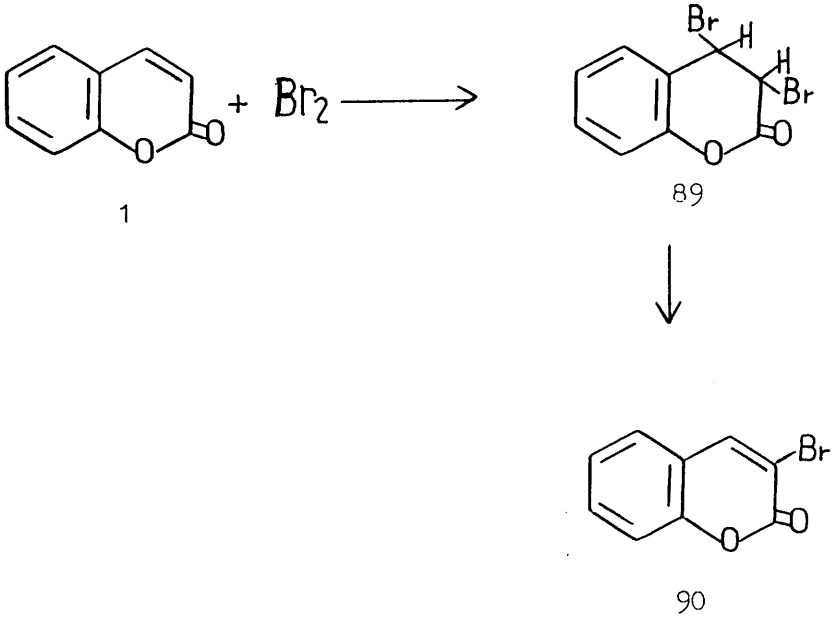
The problem therefore was how to prepare 5-methoxy-7-acetoxy-8-iodocoumarin (81). In 1969, Ahluwalia et al.[47] had shown that partial methylation of 5,7-diacetoxycoumarin (78) using methyl iodide and potassium carbonate in refluxing acetone resulted in a readily separable mixture of 7-acetoxy-5-methoxycoumarin (86) and 5,7-dimethoxycoumarin (87), better yields of which were obtained[48] when the crude methylation product was hydrolysed prior to separation.

A sample of 5,7-dihydroxycoumarin was available and this was converted into the crystalline diacetate (78) in 88% yield by refluxing in acetic anhydride containing sodium acetate overnight. A solution of 5,7-diacetoxycoumarin in acetone was refluxed with a slight excess of methyl iodide in the

presence of solid potassium carbonate overnight. T.l.c. of the solution showed the disappearance of all the starting material. The acetone solvent was then removed by evaporation and the residue dissolved in 50°/o aqueous methanol and heated on a steam bath for 15 minutes. The products from this hydrolysis were then separated into a base-soluble fraction and a base-insoluble fraction using 0.5°/o w/v aqueous sodium hydroxide.

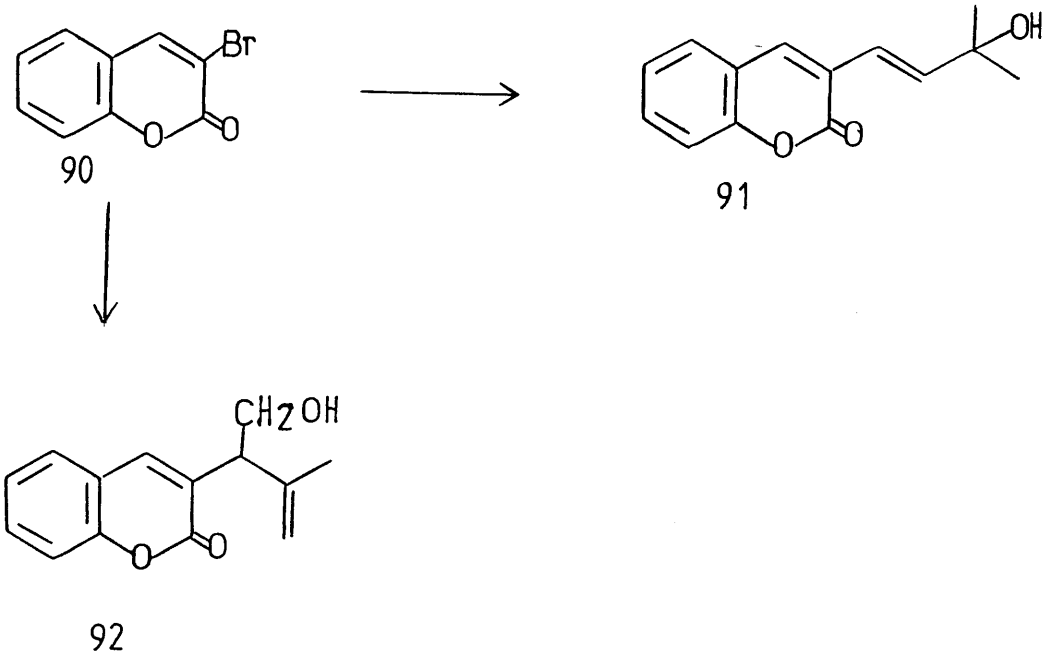
The base-insoluble fraction yielded 5,7-dimethoxycoumarin (87) in 20°/o yield, two methoxyl reasonances at δ 3.85 and 3.88 being observed in the ^{1}H n.m.r. spectrum. The base-soluble fraction contained two compounds which could be separated by fractional crystallisation into 7-hydroxy-5-methoxycoumarin (79) obtained in 41°/o yield and a mixture of (87) and the isomer, 5-hydroxy-7-methoxycoumarin.

7-Hydroxy-5-methoxycoumarin (79) was iodinated regiospecifically at C-8 using one molar equivalent of iodine in the presence of morpholine at room temperature for 48 hours. The m.p., 232-235°, of 7-hydroxy-5-methoxy-8-iodocoumarin (80) obtained in 56°/o yield by this method agreed with the literature value[55], 235-237°. Treatment with 2-methylbut-3-en-2-ol in dimethylformamide, palladium acetate, tetrabutylammonium bromide and sodium hydrogen carbonate in an oil bath held at 90 $\pm$ 5° for 24 hours gave a complex mixture and no trace of the signals expected for the desired condensation product could be detected in the ^{1}H n.m.r. spectrum. It was therefore decided to carry out the reaction on the corresponding acetate since it was felt that the presence of the



1 89 90

Scheme 26



Scheme 27

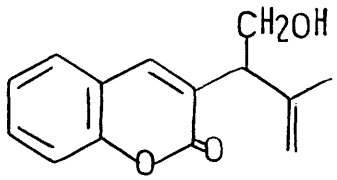
phenolic hydroxyl group might be responsible for the poor result. 7-Acetoxy-5-methoxy-8-iodocoumarin (81) was obtained in good yield as needles, m.p. 204-206°, when the phenol (80) was refluxed for three hours in acetic anhydride containing sodium acetate. The microanalysis, ^{1}H n.m.r. spectrum with the single H-6 aromatic proton as a singlet at δ 6.60 and the mass spectrum, which showed a molecular ion at m/z 360 and the base peak for loss of the acetyl group at m/z 317, confirmed the structure. Unfortunately and unexpectedly, when 7-acetoxy-5-methoxy-8-iodocoumarin was subjected to the Heck reaction with 2-methylbut-3-en-2-ol at 90 ± 5° for 24 hours, the starting material was recovered completely unchanged.

It has been reported[33] that the Heck reaction is less successful when there are electron-donating groups on the aromatic ring and the presence of the additional methoxyl group at C-5 must have been sufficient to prevent the reaction. The attempted synthesis of gleinadiene had therefore to be abandoned.

Earlier we had shown that 7-methoxy-8-iodocoumarin (54) and 7-acetoxy-8-iodocoumarin (72) underwent the Heck reaction with 2-methylbut-3-en-2-ol and its isomer 3-methylbut-2-en-1-ol.

In recent years a number of natural coumarins have been discovered[22] in which the C-3 position is substituted by a five-carbon fragment such as 1,1-dimethylallyl and 3,3-dimethylallyl. It was therefore of interest to discover if the Heck reaction could be used to prepare functionalised 3-alkylcoumarins. Coumarin (1) was chosen as starting material because it is relatively cheap and available commercially. A solution of coumarin in chloroform was stirred with a solution of bromine

in chloroform at room temperature for two hours. Evaporation gave 3,4-dibromo-3,4-dihydrocoumarin (89) in 76°/o yield which crystallised from chloroform as colourless needles, m.p. 103 - 105°. Dehydrobromination was effected by warming this product in dry pyridine for 15 minutes on a water bath. The desired compound, 3-bromocoumarin (90) was obtained in 95°/o yield as long prismatic needles, m.p. 107 - 108° from ethanol (Scheme 26). 3-Bromocoumarin (90) was condensed with 2-methylbut-3-en-2-ol at 70 ± 5° using the conditions previously used for the Heck reaction. The desired product, 3-(3-hydroxy-3-methylbut-1-enyl)-coumarin (91) was obtained in 85°/o yield after column chromatography of the crude product on silica gel followed by recrystallisation from ethyl acetate-light petroleum as needles, m.p. 96 - 98°. The structure followed from the microanalytical and mass spectral data which gave the molecular formula $C_{14}H_{14}O_3$. The trans configuration of the double bond in the side chain followed from the pair of one-proton doublets at δ 6.61 and 6.91, J 16Hz in the ^1H n.m.r. spectrum in $CDCl_3$. When 3-bromocoumarin was treated with 3-methylbut-2-en-1-ol under the same conditions, another Heck reaction took place. On this occasion it was not possible to purify the product completely by column chromatography, and preparative thin-layer chromatography was required. The major product was obtained in 75°/o yield as colourless needles, m.p. 95 - 97°. Microanalysis and high resolution mass spectrometry showed the product to be an isomer of (91) and in view of the structure (77) of the similar reaction product from 7-methoxy-8-iodocoumarin, the structure was likely to be (92). This was confirmed by



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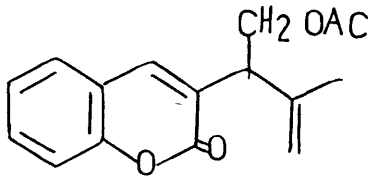

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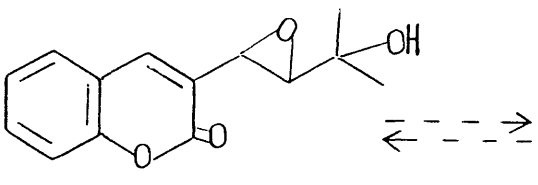

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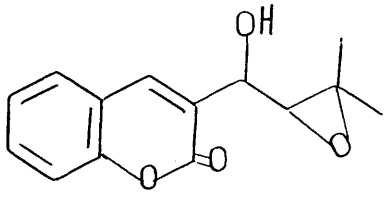
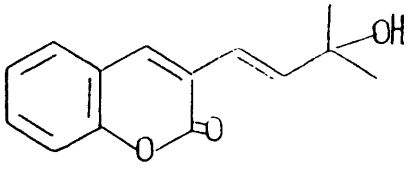


95

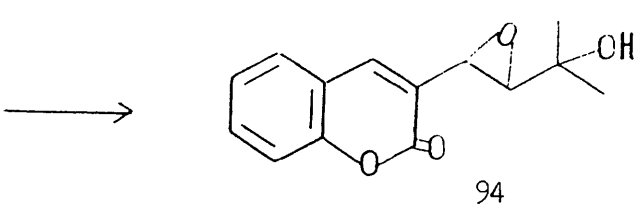
the ^{1}H n.m.r. spectrum which showed signals for a 1-hydroxy-3-methylbut-3-en-2-yl side chain attached to C-3. The vinyl methyl group resonated as a three-proton singlet at δ 1.80, the two vinyl protons as broadened singlets at 4.97 and 5.11, the benzylic proton as a broadened triplet at 3.82 with the hydroxymethylene protons as a two-proton multiplet centred at 3.92, the hydroxyl proton appearing as a broadened singlet at 2.25.

3-(1-Hydroxy-3-methylbut-3-en-2-yl)coumarin (92) was refluxed in acetic anhydride in the presence of sodium acetate for two hours. Aqueous work up gave the corresponding acetate 3-(1-acetoxy-3-methylbut-3-en-2-yl)coumarin (93) in 88°/o yield as a colourless oil. The i.r. spectrum in chloroform showed the presence of a new carbonyl band for the acetoxyl group at 1740 cm^{-1} and the absence of a hydroxyl group. The molecular formula $C_{16}H_{16}O_4$ was confirmed by high resolution mass spectrometry.

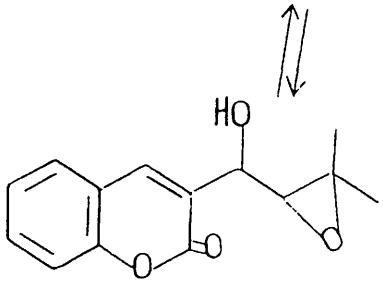
Epoxidation of 3-(trans-3-hydroxy-3-methylbut-1-enyl)coumarin (91) was achieved smoothly using m-chloroperbenzoic acid in ethyl acetate at room temperature for 17 hours. Work up gave the epoxide (94) in 90°/o yield which crystallised from ethyl-acetate-light petroleum as colourless long prismatic needles, m.p. 98 - 99°. The structure (94) of the epoxide was confirmed by microanalysis and high resolution mass spectrometry. A hydroxyl group was observed in the i.r. spectrum (KBr) at 3420 cm^{-1}, the coumarin ring at 1720 and 1610, and the epoxide ring at 1180 and 755 cm^{-1}. The ^{1}H n.m.r. spectrum confirmed the nature of the side chain with two methyl



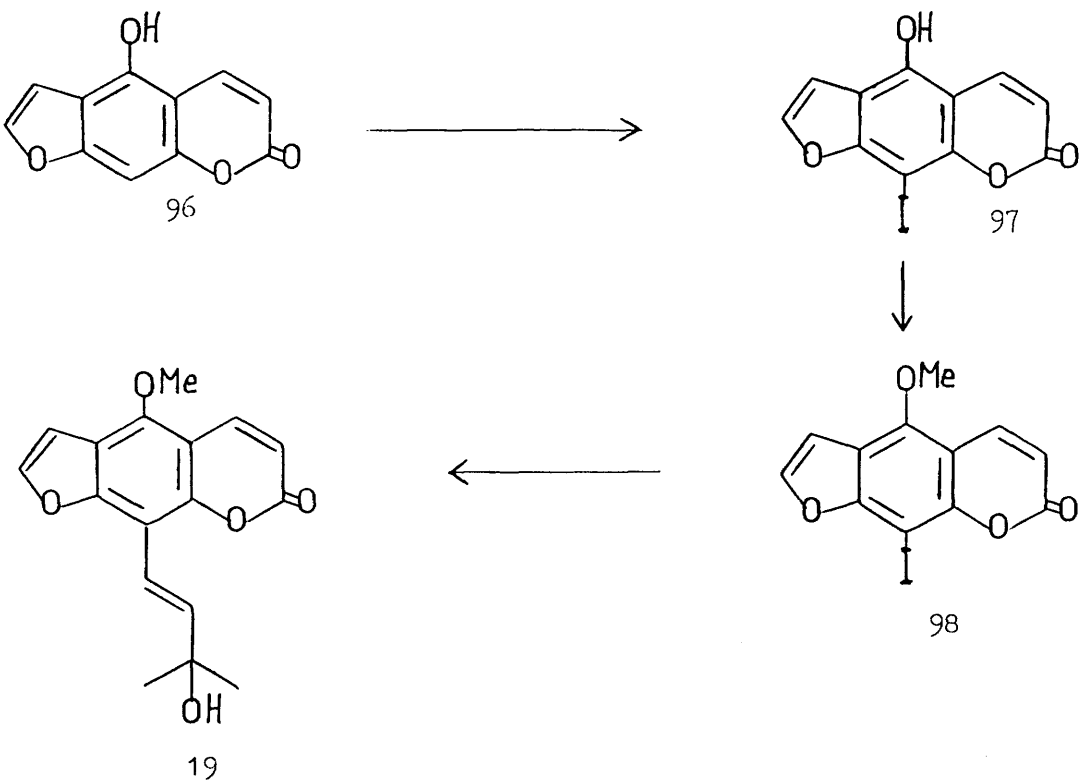
91



94



95



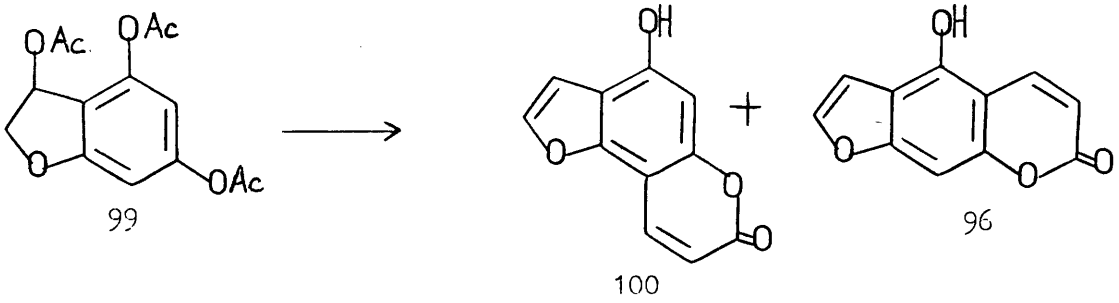
Scheme 29

signals at δ 1.85 and 1.87, a hydroxyl group at 2.15, with one proton downfield at 4.12 coupled only to another at 2.15, the coupling constant of 3.5Hz indicating the trans stereochemistry for the structure (94).

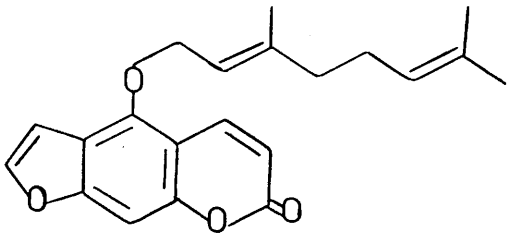
Having achieved the synthesis of the trans-epoxy alcohol (94), it was felt that it should be possible to isomerise it to (95) at least to the extent of about 50°/o as we had found for the model compound (66). However, this proved not to be the case. The trans-epoxyalcohol (94) was stirred with 0.5M aqueous sodium hydroxide in the cold for one hour. After careful neutralisation with 0.4M hydrochloric acid and extraction into ether, the recovered organic material was found to be a complex mixture, the ^{1}H n.m.r. spectrum of which showed the absence of both the starting material and the signals anticipated for the expected Payne rearrangement product (95). When the attempted rearrangement was repeated using 0.1M aqueous sodium hydroxide or with sodium hydride in refluxing tetrahydrofuran, starting material was recovered intact. Treatment with hot aqueous potassium carbonate also led to a complex mixture.

During the preparation of this thesis, consideration was given to the possibility of synthesising swietenocoumarin G (19). It was felt that if the single benzenoid proton in the furocoumarin bergaptol (96) could be replaced by iodine, a Heck reaction with 2-methylbut-3-en-2-ol on the corresponding methyl ether (98) should lead directly to swietenocoumarin G (Scheme 29).

Only one synthesis of bergaptol is recorded in the literature (Scheme 30). In 1937, Späth and his co-workers[58] condensed



Scheme 30



101

the triacetate (99) with the sodium salt of ethyl 3-oxopropanoate in a sealed tube. The major product was the unnatural isomer allobergaptol (100), only a small amount of the desired linear isomer bergaptol (96) being obtained.

The geranyl ether of bergaptol, known as bergamottin (101) was shown to be a major constituent of bergamot oil, Citrus bergamia Risso, by Späth and Gocias[59] in 1934. Commercial bergamot oil was available in the department and bergamottin had been isolated and the geranyl side chain removed by acid hydrolysis to give bergaptol.

Iodination of bergaptol was carried out in acetone-chloroform by the portionwise addition alternately of yellow mercuric oxide and iodine. After refluxing for 24 hours, thin-layer chromatography revealed partial conversion to a more polar product, the slow conversion presumably reflecting the low solubility of bergaptol in the solvent mixture. Because of the low solubility of bergaptol and its iodination product (97), the crude product was alkylated using methyl iodide and potassium carbonate. Purification by silica gel column chromatography gave 8-iodopergapten (98) though only in 24% yield. Lack of time prevented reinvestigation of this reaction sequence in order to obtain a more efficient overall conversion. The structure of 8-iodobergapten was confirmed from the molecular ion at m/z 342 in the mass spectrum and the absence of any benzenoid proton in the ^{1}H n.m.r. spectrum. The Heck reaction of 8-iodobergapten with 2-methylbut-3-en-2-ol was carried out using the modified conditions established

earlier. The melting point, 187 - 188° of the product was close to the 190° reported[15] for swietenocoumarin G. The mass spectrum with the molecular ion at m/z 300 was in agreement with the proposed structure (19) as was the ^{1}H n.m.r. spectrum the signals of which were identical with those reported[15] for the natural coumarin. Although it has not yet been possible to obtain a sample of natural swietenocoumarin G for direct comparison, the identity of the two samples is likely for the synthetic material gave an ultra-violet spectrum virtually identical with that reported.

General Experimental

Abbreviations

Abbreviations

The following abbreviation and symbols have been used in this thesis.

b	broad
d	doublet
m	multiplet
q	quartet
s	singlet
t	triplet
i.r.	infra-red
u.v.	ultra-violet
n.m.r.	nuclear magnetic resonance
t.l.c.	thin-layer chromatography
w/v	weight per volume
v/v	volume per volume
Hz	Hertz
hr	hour
min	minute
lit.	literature
m.p.	melting point
m/z	mass to charge ratio

Experimental

General Experimental

Melting points which are uncorrected, were determined on a Kofler hot stage apparatus. Microanalyses were performed by Mrs. W. Harkness and her staff. Infra-red spectra were recorded on a Perkin Elmer 225 spectrophotometer by Mr. G. McCulloch and his staff. ^1H n.m.r. spectra were recorded on a Varian T90 spectrometer. Unless otherwise stated n.m.r. spectra were recorded with $CDCl_3$ as solvent and TMS as internal standard. Mass spectra were recorded by Mr. A. Ritchie with an AEI-GEC MS 9 mass spectrometer. Ultra-violet spectra were recorded on a Unicam SP800 spectrophotometer.

Kieselgel GF_{254} (Merck) or HF_{254} (Merck) was used for preparative t.l.c.; Kieselgel (Merck) was used for analytical t.l.c. Analytical and preparative t.l.c. plates were viewed under an ultra-violet lamp (254 or 350 nm). Analytical plates were developed by iodine vapour.

Light petroleum refers to the fraction having b.p. 60 - 80°. All solutions, unless otherwise stated, were dried over anhydrous magnesium sulphate. The solvents used for chromatography are expressed in a volume ratio, e.g. ethyl acetate-light petroleum (2:1). The number of elutions required for separation by preparative t.l.c. are indicated with the solvent system.

Preparation of 2-chloro-2-methylbut-3-yne[25]

A mixture of 2-methylbut-3-yn-2-ol (84 g, 1 mole) calcium chloride (10 g, 1 mole), hydroquinone (1 g) and concentrated hydrochloric acid (420 ml, 5 mole) was shaken in a separating funnel at 20° for 45 min . The separated organic layer was dried over anhydrous potassium carbonate and distilled at 33-35°/175mm to give 2-chloro-2-methylbut-3-yne (52.9 g, 52°/o).

7-(1,1-Dimethylprop-2-ynyloxy)coumarin (37)

Umbelliferone (8 g) was dissolved in aqueous acetone (2°/o v/v) (100 ml). Potassium carbonate (8.5 g) and potassium iodide (1.5 g) were added and the mixture stirred at room temperature for 1 hr. 2-Chloro-2-methylbut-3-yne (10 g) was added and the mixture refluxed for 5 hr. More potassium carbonate (8.5 g) and 2-chloro-2-methylbut-3-yne (10 g) were added and the reflux continued for a further 24 hr. The reaction mixture was filtered off and the filtrate evaporated. The residue was then dissolved in a mixture of ethyl acetate and brine, and the organic layer washed with aqueous potassium carbonate solution (5°/o w/v) to remove any starting material. Subsequent washing with brine, drying and evaporation gave a yellow solid which on crystallisation from ethyl acetate-light petroleum yielded 7-(1,1-dimethylprop-2-ynyloxy)coumarin (37) as pale yellow needles (7.84 g, 70°/o), m.p. 139-140° (lit.[28] 136-139°).

7-(1,1-Dimethylprop-2-enyloxy)coumarin (39)

7-(1,1-Dimethylprop-2-ynyloxy)coumarin (1.1 g) was dissolved in ethyl acetate (80 ml) and Lindlar catalyst (0.116 g) added.

After hydrogenation at room temperature for 30 min. the uptake of hydrogen was 1 mole. Filtration over celite followed by evaporation of the solvent gave 7-(1,1-dimethylprop-2-enyloxy)-coumarin (39) as a colourless solid (1.1 g) which crystallised from ethyl acetate-light petroleum as needles (0.99 g, 90°/o), m.p. 79-80° (lit.[28] m.p. 76-78°); n.m.r. signals at δ 1.55 (6H, s), 5.23 (1H, d, J 18Hz), 5.23 (1H, d, J 10Hz), 6.15 (1H, dd, J 18 and 10Hz), 6.23 (1H, d, J, 9.5Hz), 6.85 (1H, dd, J 10 and 2Hz), 6.93 (1H, bs), 7.28 (1H, d, J 10Hz) and 7.60 (1H, d, J 9.5Hz); mass spectral peaks at m/z 230 (M^+, 14°/o), 162 (12), 134 (100) and 169 (60).

Osthenol acetate (32)

A solution of the allyl ether (39) (1.1 g) in acetic anhydride (14 ml) and sodium acetate (3.3 g) was refluxed under nitrogen for 2.5 hr. The reaction mixture was cooled in an ice bath, water (20 ml) added and stirring continued for 2 hr. After extraction with ethyl acetate, the organic layer was washed thoroughly with saturated sodium hydrogen carbonate solution, brine to neutrality and dried over magnesium sulphate. Evaporation of the solvent gave osthenol acetate (32) (1.03 g, 84°/o) which crystallised from ethyl acetate-light petroleum as colourless needles, m.p. 94-95° (lit.[49] 94-95°); (Found: C, 70.57; H, 5.88. $C_{16}H_{16}O_4$ requires: C, 70.57; H, 5.92°/o); n.m.r. signals at δ 1.68 (3H, bs), 1.82 (3H, bs), 2.35 (3H, s), 3.49 (2H, bd, J 7Hz), 5.5 (1H, bt, J 7Hz), 6.37 and 7.63 (each 1H, d, J 9.5Hz), 6.98 and 7.33 (each 1H, d, J 9Hz); ν max ($CHCl_3$) 1764, 1735 and 1605 cm^{-1};

mass spectral peaks at m/z 272 (M^+, 11%), 230 (186), 215 (32), 201 (18), 187 (43) and 175 (100).

Photo-oxygenation of osthenol acetate

Osthenol acetate (500 mg) was dissolved in dry pyridine (70 ml) and haematoporphyrin (20 mg) was added. A steady stream of oxygen was bubbled through the solution via a sinter and the solution irradiated by a 60 watt lamp positioned approximately 10 cm from the reaction flask for 17 hr. Most of the pyridine had by then evaporated and the residue was poured into a large excess of ice water (500 ml) and extracted with ethyl acetate. The organic layer was washed with saturated copper sulphate solution (4 x) to remove the excess pyridine, brine to neutrality, dried over magnesium sulphate and evaporated to give a brown oil (520 mg). This brown oil was then dissolved in dry ethanol (70 ml) containing glacial acetic acid (2 ml) and sodium iodide (5 g). The mixture was kept at room temperature for 24 hr. The ethanol was evaporated, the residue dissolved in ethyl acetate (50 ml) washed with sodium thiosulphate (0.1 M), brine to neutrality, dried and the solvent evaporated to yield a dark brown oil (450 mg, 85%) as a mixture which after purification by preparative t.l.c. (ethyl acetate-light petroleum, 1:4 then 2:3) furnished the allylic alcohol[16] (23) as a colourless oil (237 mg, 45%); n.m.r. signals at δ 1.43 (6H, s); 2.33 (3H, s); 2.63 (1H, bs), 6.38 and 7.70 (each 1H, d, J 9.5Hz), 6.73 (2H, s), 7.03 and 7.38 (each 1H, d, J 9Hz); ν_{max} ($CHCl_3$) 3500, 1740, 1600, 1114 and 970 cm^{-1}; mass spectral peaks at m/z 288 (M^+, 4%), 246 (12), 231 (14), 288 (20), 213 (100) and 149 (74).

Osthenol (33)

Osthenol acetate (32) (1 g) was dissolved in methanol (40 ml) and aqueous sodium carbonate (2°/o w/v) (10 ml) added. The mixture was stirred at room temperature for 0.5 hr. The solution was then carefully neutralised with hydrochloric acid (0.1 M), diluted with water, and extracted with ethyl acetate. The ethyl acetate layer was washed with brine, dried over magnesium sulphate, evaporated to give the crude phenol (0.76 g, 90°/o), which crystallised from ethyl acetate-light petroleum as colourless needles, m.p. 123-126° (lit.[50] m.p. 124-125°); n.m.r. signals at δ 1.73 (3H, bs), 1.82 (3H, bs), 3.58 (2H, d, J 7Hz), 5.28 (1H, bt, J 7Hz); 6.25 (1H, d, J 9.5Hz), 6.87 (1H, d, J 9Hz), 7.18 (1H, d, J 9Hz) and 7.65 (1H, d, J 9.5Hz); ν^{max} (CCl_4) 3501, 1745 and 1610 cm^{-1}; mass spectral peaks at m/z 230 (M^+, 68°/o), 215 (27), 187 (100) and 175 (24).

Osthol (7)

Potassium carbonate (115 mg) was added to a solution of osthenol (33) (200 mg) in acetone (35 ml), and the mixture stirred at room temperature for 30 min. Methyl iodide (1.1 ml) was added and the mixture was refluxed under argon for 4 hr. The reaction mixture was filtered, and the acetone solution evaporated. The residue was dissolved in a mixture of ethyl acetate and brine. The organic layer was washed with aqueous potassium carbonate (0.5 w/v) to remove any starting material, brine to neutrality, dried, filtered, and evaporated to give osthol (7) (180 mg, 85°/o), which crystallised from

ethyl acetate-light petroleum as colourless needles, m.p. 82-83° (lit.[51] m.p. 83-84°); n.m.r. signals at δ 1.68 (3H, bs), 1.85 (3H, bs), 3.50 (2H, bd, J 6.5Hz), 3.92 (3H, s), 5.30 (1H, bt, J 7Hz), 6.20 (1H, d, J 9.5Hz), 6.80 (1H, d, J 9Hz), 7.30 (1H, d, J 9Hz) and 7.60 (1H, d, J 9.5Hz); ν_{max} ($CHCl_3$) 1720 and 1610 cm^{-1}; mass spectral peaks at m/z 244 (M^+, 98%), 229 (100), 213 (82), 201 (65), 184 (53) and 131 (44).

Photo-oxygenation of osthol

Oxygen was bubbled, via a glass sinter upwards through a solution of the methyl ether (7) (108 mg) in dry pyridine (30 ml) containing haematoporphyrin (7 mg). This solution was irradiated by a 60 watt lamp, positioned approximately 10 cm from the centre of the reaction mixture flask, for 24 hr. By then most of the pyridine had evaporated. The residue was poured into a large excess of ice-water (300 ml) and extracted with ethyl acetate. The organic layer was washed with saturated copper sulphate solution to remove the pyridine, brine to neutrality, dried over magnesium sulphate and evaporated to give a brown oil (128 mg). This brown oil was dissolved in dry ethanol (17 ml) containing glacial acetic acid (0.4 ml) and sodium iodide (1.3 g). After 24 hr the ethanol was evaporated and the residue dissolved in ethyl acetate, washed with sodium thiosulphate (0.1 M) several times, brine to neutrality, dried over magnesium sulphate and evaporated to yield a dark brown oil (75 mg), which after purification by prep. t.l.c. plate (ethylacetate-light petroleum, 2:3, 3x) furnished auraptenol (11) (34 mg, 30%) which crystallised

from ethyl acetate-light petroleum as needles, m.p. 122-123° (lit.[9] m.p. 119-122°); n.m.r. signals at δ 1.88 (3H, s), 2.20 (1H, bs), 3.15 (2H, m), 3.92 (3H, s), 4.38 (1H, bt), 4.80 (1H, bs), 4.90 (1H, bs), 6.22 (1H, d, J 9.5Hz), 6.82 (1H, d, J 9Hz); 7.32 (1H, d, J 9Hz) and 7.62 (1H, d, J 9.5Hz).

7- Hydroxy-8-iodocoumarin (53)

7-Hydroxycoumarin (34) (10 g) was dissolved in 20°/o aqueous ammonia (250 ml) and to this solution was added dropwise, with stirring, a solution of iodine (16.7 g) in aqueous potassium iodide (10°/o w/v) (200 ml). After 6 hr the solution was neutralised with sulphuric acid (5 M). The resultant precipitate was filtered, washed several times with water until the precipitate was colourless and oven dried at 50° overnight to give 7-hydroxy-8-iodocoumarin (53) (16.3 g, 91°/o), m.p. 266-267° (lit.[52] m.p. 268°); ν_{max} (KBr) 3200, 1700, 1610 and 1600 cm^{-1}; n.m.r. signals (DMSO-d_6) at δ 6.03 (1H, d, J 9.5Hz), 7.63 (1H, d, J 9.5Hz), 6.75 (1H, d, J 8Hz) and 7.31 (1H, d, J 8Hz).

7-Methoxy-8-iodocoumarin (54)

Potassium carbonate (2.3 g) was added to a solution of 7-hydroxy-8-iodocoumarin (53) (1.5 g) in acetone (50 ml). The solution was stirred at room temperature for 0.5 hr, then methyl iodide (2 g) was added and the mixture refluxed overnight. The reaction mixture was allowed to cool, filtered, and the acetone solution evaporated. The residue was dissolved in a mixture of ethyl acetate and brine. The organic layer was washed with aqueous potassium carbonate (0.5 w/v), brine to neutrality, dried over magnesium sulphate, filtered, and evaporated to give 7-methoxy-8-iodocoumarin (54)

(1.3 g, 87°/o) as colourless needles (from ethyl acetate-light petroleum), m.p. 154-156° (lit.[53] m.p. 153-154°); ν max ($CHCl_3$) 1740, 1620, 1140 and 1090 cm^{-1}; n.m.r. signals at δ 4.01 (3H, s), 6.30 (1H, d, J 9.5Hz), 7.63 (1H, d, J 9.5Hz), 6.83 (1H, d, J 8Hz) and 7.48 (1H, d, J 8Hz); mass spectral peaks at m/z 302.0699 (M^+, 100°/o) ($C_{10}H_7IO_3$ requires M^+, 302.0439), 274 (50) and 259 (66).

Attempted condensation of 7-methoxy-8-iodocoumarin with 2-methylbut-3-en-2-ol.

1. With triphenylphosphine

To a 50 ml three-necked round-bottomed flask equipped with a condenser and a thermometer was added a solution of 7-methoxy-8-iodocoumarin (60 mg) in triethylamine (8 ml). To this solution, 2-methylbut-3-en-2-ol (21 mg), triphenylphosphine (150 mg) and palladium acetate (10 mg) were added and the mixture refluxed under argon overnight. The reaction mixture was cooled, diluted with water and extracted with ethyl acetate, the organic layer washed with brine, dried over magnesium sulphate, filtered and evaporated to give a colourless solid (70 mg) which the ^1H n.m.r., mass and i.r. spectra indicated was triphenylphosphine oxide.

2. With phase transfer reagent

7-Methoxy-8-iodocoumarin (0.53 g) was dissolved in dimethylformamide (10 ml) then 2-methylbut-3-en-2-ol (1.164 g) was added with stirring. Tetrabutylammonium bromide (1.932 g), sodium hydrogen carbonate (0.5 g) and palladium acetate (0.04 g) were added. The mixture was heated in an oil bath at 90±5°

under argon for 24 hr. When t.l.c. showed no starting material left the reaction was cooled and filtered through celite. The filtrate was dissolved in ethyl acetate (30 ml) and washed several times with brine, dried and evaporated to give impure allylic alcohol (24) (0.501 g) which was purified by silica gel column chromatography. Elution with chloroform-light petroleum (1:4 → 4:1) gave 7-methoxy-8-(trans-3-hydroxy-3-methylbut-1-enyl)coumarin (24) (0.4 g, 83°/o) which crystallised from ethyl acetate-light petroleum as colourless needles, m.p. 138-142° (lit.[9], m.p. 138-141°); (Found: C, 68.95; H, 6.19. $C_{15}H_{16}O_4$ requires: C, 69.21; H, 6.19°/o); n.m.r. signals at δ 1.48 (6H, s), 3.88 (3H, s), 6.25 (1H, d, J 9.5Hz), 6.84 (1H, d, J 8Hz), 6.88 (2H, s), 7.30 (1H, d, J 8Hz) and 7.6 (1H, d, J 9.5Hz); ν max (KBr) 3420, 1720, 1600, 1250, 1050 and 837 cm^{-1}; mass spectral peaks at m/z 260.1047 (M^+, 15°/o) ($C_{15}H_{16}O_4$ requires M^+ 260.1029), 242 (90), 227 (27), 211 (100), 183 (52), 155 (36), 128 (32) and 115 (30).

Dehydration of the allylic alcohol (24)

The allylic alcohol (24) (65 mg) was dissolved in dry pyridine (2 ml) and toluene-p-sulphonyl chloride (54 mg) was added and the solution refluxed under argon for 2 hr. The reaction mixture was poured into iced water (300 ml) and extracted with ethyl acetate. The organic layer was washed with saturated copper sulphate solution, brine, dried and evaporated to give a mixture (66 mg) which was separated by preparative t.l.c. using ethyl acetate-light petroleum (1:4 then 2:3) to give trans-dehydroosthol (56) (20 mg, 33°/o) which crystallised

from ether-light petroleum as needles, m.p. 81-82° (lit.[37] m.p. 84°); n.m.r. signals at δ 2.00 (3H, t, J 1Hz), 3.82 (3H, s), 4.90 (2H, m), 6.15 (1H, d, J 9.5Hz), 6.77 (1H, d, J 8.5Hz), 6.80 (1H, d, J, 15Hz), 7.18 (1H, d, J 8.5Hz), 7.42 (1H, d, J 15Hz) and 7.50 (1H, d, J 9.5Hz); ν max ($CHCl_3$) 1735, 1605, 1500 and 835 cm^{-1}; mass spectral peaks at 242.0899 (M^+, 14°/o) ($C_{15}H_{14}O_3$ requires M^+ 242.0897), 228 (24), 212 (52), 187 (15), 183 (16), 155 (24), 131 (34), 115 (47) and 91 (100).

Epoxidation of the allylic alcohol (24)

A solution of m-chloroperbenzoic acid (43 mg) in ethyl acetate (1 ml) and a solution of the allylic alcohol (24) (44 mg) in ethyl acetate (2 ml) were mixed at 0° then sodium hydrogen carbonate (44 mg) was added. After 20 min stirring at 0° the ice bath was removed and stirring continued at room temperature for a further 17 hours. When t.l.c. showed no starting material left, the reaction mixture was diluted with ethyl acetate (10 ml) washed with aqueous sodium sulphite (10°/o w/v) (10 ml), brine to neutrality, dried over magnesium sulphate, filtered, and evaporated. 8-(Trans-1,2-epoxy-3-hydroxy-3-methylbutyl)-7-methoxycoumarin (60) (46 mg, 95°/o) crystallised from chloroform-light petroleum as needles, m.p. 145-146° (Found: C, 65.21; H, 5.82. $C_{15}H_{16}O_5$ requires: C, 65.20; H, 5.83°/o); ν max (KBr) 3420, 1720, 1610, 1250, 1050 and 937 cm^{-1}; n.m.r. signals at δ 1.42 (3H, s), 1.48 (3H, s), 2.39 (1H, bs, exchangeable with D_2O), 3.42 (1H, d, J 2Hz), 3.87 (3H, s,), 4.09 (1H, d, J 2Hz), 6.21 (1H, d, J 9.5Hz), 6.85 (1H, d, J 8Hz), 7.39 (1H, d, J 8Hz) and

7.61 (1H, d, J 9.5Hz); mass spectral peaks at m/z 276.1008 (M^+, 100%) ($C_{15}H_{16}O_4$ requires M^+, 276.1023), 218 (95), 189 (13), 160 (40), 131 (66) and 103 (14).

Attempted isomerisation of the epoxide (60)

The epoxide (60) (64 mg) was mixed at 0° with aqueous sodium hydroxide (0.5 M) (2 ml). After 15 min the solution was allowed to warm to room temperature for 1 hr with stirring. The solution was acidified with dilute hydrochloric acid (0.5 M), diluted with water, extracted with ether, the organic layer washed with brine, dried, filtered and evaporated to give a mixture (60 mg) of polar non-coumarin products.

This reaction was repeated using aqueous sodium hydroxide (0.1 M). After the workup, t.l.c. and ^1H n.m.r. showed formation of a complex mixture with opening of the lactone ring of the coumarin. The same result was obtained with aqueous sodium hydroxide (0.01 M). Using aqueous potassium carbonate, this also gave a complex mixture from which no useful compound was obtained.

7-Acetoxy-8-iodocoumarin (72)

Sodium acetate (4.1 g) was added to a stirred solution of 7-hydroxy-8-iodocoumarin (2.88 g) in acetic anhydride (30 ml). The reaction mixture was refluxed under nitrogen for 3 hr, then the reaction was cooled down in an ice bath, water (24 ml) was added and the mixture stirred for a further 2 hr. After extraction with ethyl acetate, the organic layer was washed with saturated sodium hydrogen carbonate solution, brine, dried over magnesium sulphate and evaporated to give 7-acetoxy-8-iodocoumarin (72) (1.95 g, 95%) which crystallised

from ethyl acetate-light petroleum as colourless needles, m.p. 142-144° (lit.[53] 143-144°); ν_{max} (CCl_4) 1740, 1710, 1600 and 1120 cm^{-1}; n.m.r. signals at δ 2.43 (3H, s), 6.39 (1H, d, J 9.5Hz), 7.05 (1H, d, J, 8Hz), 7.48 (1H, d, J 8Hz) and 7.65 (1H, d J 9.5Hz); mass spectral peak at m/z 330 (M^+, 30%), 287 (100), 160 (70), 132 (20) and 104 (15).

Condensation of 7-acetoxy-8-iodocoumarin with 2-methylbut-3-en-2-ol

1. At 105°

To a solution of 7-acetoxy-8-iodocoumarin (72) (0.12 g) in dimethylformamide (5 ml) was added 2-methylbut-3-en-2-ol (0.2 g), tetrabutylammonium bromide (0.42 g), sodium hydrogen carbonate (0.1 g) and palladium acetate (7.4 mg) and the mixture was stirred and heated at 105 ± 5° under argon for 24 hr. The reaction mixture was cooled down and filtered through celite, ethyl acetate (50 ml) was added and the organic layer washed three times with water (30 ml), dried over magnesium sulphate, filtered, and evaporated to give a mixture (0.08 g) which after short silica gel column chromatography and dilution with chloroform-light petroleum (1:4 → 4:1) gave seselin (38) (48 mg, 58%) as colourless needles (from methanol), m.p. 120-121° (lit.[26] m.p. 119-120°); n.m.r. signals at δ 1.50 (6H, s), 5.85 (1H, d, J 10Hz), 6.26 (1H, d, J 9.5Hz), 6.75 (1H, d, J 9Hz), 6.93 (1H, d, J 10Hz), 7.25 (1H, d, J 9Hz) and 7.63 (1H, d, J 9.5Hz); mass spectral peaks at m/z 228 (M^+, 13%), 213 (100), 185 (25) and 128 (16).

This product was also prepared by rearrangement of 7-(1,1-dimethylprop-2-ynyloxy)coumarin (37) in N,N-diethylaniline at 220° for 2 hr and the samples of seselin found to be identical.

2. At 65°

2-Methylbut-3-en-2-ol (1.16 g) was added to a stirred solution of 7-acetoxy-8-iodocoumarin (0.531 g) in dimethylformamide (10 ml). Tetrabutylammonium bromide (1.932 g), sodium hydrogen carbonate (0.53 g) and palladium acetate (0.08 g) were added and the mixture heated at 65 ± 5° under argon for 24 hr. The mixture was cooled, filtered through celite and washed with ethyl acetate (100 ml). The filtrate was washed several times with brine, dried over magnesium sulphate and evaporated to give a brown oil (0.50 g) which was purified by column chromatography. Elution with ethyl acetate-light petroleum gave 7-acetoxy-8-(trans-3-hydroxy-3-methylbut-1-enyl)-coumarin (23) as a colourless oil (0.368 g, 80°/o); n.m.r. signals at δ 1.43 (6H, s), 2.33 (3H, s), 2.63 (1H, bs), 6.38 (1H, d, J 9.5Hz), 6.73 (2H, s), 7.03 (1H, d, J 9Hz), 7.38 (1H, d, J 9Hz) and 7.70 (1H, d, J 9.5Hz); ν_{max} ($CHCl_3$) 3500, 1740, 1600, 1114 and 970 cm^{-1}; mass spectral peaks at m/z (288, M^+, 4°/o), 246 (15), 231 (114), 228 (20), 213 (100) and 149 (74).

7-Hydroxy-8-(trans-3-hydroxy-3-methylbut-1-enyl)coumarin (70)

A solution of the acetate (23) (288 mg) in methanol (10 ml) was stirred with aqueous sodium carbonate (2°/o w/v) (3.6 ml) for 15 min at room temperature. The solution was then carefully neutralised with dilute hydrochoric acid (0.2 M), diluted with water and extracted with ethyl acetate. The organic layer was washed with brine and dried over magnesium sulphate to give 7-hydroxy-8-(trans-3-hydroxy-3-methylbut-1-enyl)coumarin (70) (222 mg, 90°/o) as colourless needles (from ethyl acetate-light

petroleum), m.p. 159-160° (Found: C, 68.29; H, 5.68. $C_{14}H_{14}O_4$ requires: C, 67.99; H, 5.81°/o); n.m.r. signals (DMSO-d_6) at δ1.32 (6H, s), 4.64 (1H, bs), 6.18 (1H, d, J 9.5Hz), 6.78 (1H, d, J 16.4Hz), 6.90 (1H, d, J 16.4Hz), 6.94 (1H, d, J 8Hz), 7.35 (1H, d, J 8Hz), 7.90 (1H, d, J 9.5Hz) and 10.91 (1H, bs, OH); ν_{max} ($CHCl_3$) 3600, 2980, 1735, 1620 and 1610 cm^{-1}; mass spectral peaks at m/z 246 (M^+, 0.13°/o), 228 (24), 213 (100) and 183 (22).

Attempted epoxidation of 7-hydroxy-8-(trans-3-hydroxy-8-methylbut-1-enyl)coumarin

To a solution of the allylic alcohol (70) (144 mg) in ethyl acetate (6 ml) was added sodium hydrogen carbonate (144 mg) and a solution of m-chloroperbenzoic acid (140 mg) in ethyl acetate (3 ml) at 0°. After 20 min the ice bath was removed and stirring continued for 17 hr at room temperature. The mixture was then diluted with ethyl acetate and washed with an equal volume of sodium sulphite solution (10°/o w/v), brine to neutrality, dried over magnesium sulphate, filtered and evaporated to give a mixture (144 mg) of many products from which no useful compound could be separated.

3-Iodomethoxybenzene (65)

Potassium carbonate (4.6 g) was added to a solution of 3-iodophenol (64) (3 g) in acetone (100 ml). The solution was stirred at room temperature for 30 min then methyl iodide (4 g) was added and the reaction mixture refluxed for 3 hr under argon. When the reaction was complete all solid material was removed by filtration and the filtrate evaporated.

The residue was then dissolved in a mixture of ethyl acetate and water, and the organic layer washed with 0.5°/o w/v aqueous potassium carbonate solution. Subsequent washing with brine, drying and evaporation gave 3-iodomethoxybenzene (65) (2.7 g, 85°/o); n.m.r. signals at δ 3.7 (3H, s) and 6.2 - 7.2 (4H, m).

Condensation of 3-iodomethoxybenzene with 2-methylbut-3-en-2-ol

To a solution of 3-iodomethoxybenzene (234 mg) in dimethylformamide (10 ml) was added with stirring 2-methylbut-3-en-2-ol (129 mg), tetrabutylammonium bromide (809 mg), sodium hydrogen carbonate (210 mg) and palladium acetate (4.8 mg). The reaction mixture was heated at (90 ± 5°) under argon overnight after which t.l.c. showed no starting material left. The reaction mixture was cooled, filtered and the filtrate dissolved in ethyl acetate (50 ml), washed with brine, dried over magnesium sulphate, filtered and evaporated to give the allylic alcohol (66) as an oil (249 mg, 82°/o); n.m.r. signals at δ 1.42 (6H, s), 1.89 (1H, bs), 3.69 (3H, s), 6.28 (1H, d, J 16Hz), 6.58 (1H, d, J 16Hz) and 6.7 - 7.20 (4H, m); mass spectral peaks at m/z 192 (M^+, 51°/o), 177 (65), 174 (44), 159 (77), 149 (93), 121 (66) and 43 (100).

Epoxidation of the allylic alcohol (66)

A solution of m-chloroperbenzoic acid (86 mg) in ethyl acetate (2 ml) and a solution of the allylic alcohol (66) (88 mg) in ethyl acetate (4 ml) were mixed at 0° then sodium hydrogen carbonate (88 mg) was added. After 20 min stirring at 0° the ice bath was removed and the stirring continued at room temperature for a further 17 hr when t.l.c. showed no starting material left.

The solution was diluted with ethyl acetate (20 ml) and washed with aqueous sodium sulphite solution (10°/o w/v), brine to neutrality, dried over magnesium sulphate, filtered and evaporated to give the epoxide (67) (90 mg, 95°/o) as an oil; n.m.r. signals at δ 1.28 (3H, s), 1.33 (3H, s), 2.35 (1H, bs), 2.95 (1H, d, J 3.5Hz), 3.78 (3H, s), 3.92 (1H, d, J 3.5Hz) and 6.71 - 7.20 (4H, m); mass spectral peaks at m/z 208 (M^+, 9°/o), 150 (32), 135 (74), 122 (39), 107 (37), 72 (100), 59 (53) and 52 (41).

Payne rearrangement of the epoxyalcohol (67)

Aqueous sodium hydroxide (0.5 M) (2 ml) was cooled at 0° then the epoxide (67) (358 mg) added with stirring. After 15 min the solution was allowed to warm to room temperature for 1 hr, then acidified with dilute hydrochloric acid (0.5 M), diluted with water, extracted with chloroform, washed with brine, dried, and evaporated to give a brown oil which, after purification by preparative silica gel t.l.c. (chloroform-light petroleum, 1:1, 6x) furnished -

i. the epoxyalcohol (68) (154 mg, 43°/o); n.m.r. signals at δ 1.21 (3H, s), 1.31 (3H, s), 2.75 (1H, bs), 3.35 (1H, d, J 3.5Hz), 3.81 (3H, s), 4.95 (1H, d, J 3.5Hz) and 6.21 - 7.25 (4H, m); mass spectral peaks at m/z 208 (M^+, 11°/o), 150 (31), 137 (39), 109 (40) and 72 (100); ν max (KBr) 3425, 1600, 1150 and 1040 cm^{-1}.

ii. the epoxyalcohol (67) (154 mg, 43°/o).

5,7-Diacetoxycoumarin (78)

A solution of 5,7-dihydroxycoumarin (1.78 g) in acetic anhydride (14 ml) and sodium acetate (8.2 g) was refluxed for 24 hr.

The reaction mixture was cooled in an ice bath, water (24 ml) was added and the mixture stirred at room temperature for 2 hr then extracted with ethyl acetate. The organic layer was washed with brine, dried and evaporated. The residue on crystallisation from ethyl acetate-light petroleum yielded 5,7-diacetoxycoumarin (78) as colourless needles (2.3 g, 88°/o), m.p. 139 - 141° (lit.[54] m.p. 139 - 141°); n.m.r. signals at δ 2.33 (3H, s), 2.40 (3H, s), 6.36 (1H, d, J 9.5Hz), 6.95 (1H, d, J 1.5Hz), 7.01 (1H, d, J 1.5Hz) and 7.69 (1H, d, J 9.5Hz); ν_{max} ($CHCl_3$) 1778, 1730 and 1630 cm^{-1}.

5-Methoxy-7-hydroxycoumarin (79)

Potassium carbonate (3.5 g) was added to a solution of 5,7-diacetoxycoumarin (1.75 g) in dry acetone (170 ml) and the mixture stirred for 0.5 hr at room temperature. Methyl iodide (7 ml) was added and the mixture refluxed for 48 hr. The reaction mixture was allowed to cool then the solvent was evaporated and the residue dissolved in aqueous methanol (50°/o v/v) (100 ml). The solution was heated on a steam bath for 15 min, allowed to cool and neutralised with dilute hydrochloric acid. Most of the solvent was then evaporated and the residue dissolved in a mixture of ethyl acetate and aqueous sodium hydroxide (0.5°/o w/v). The organic layer was washed with aqueous sodium hydroxide (0.5°/o w/v) until the basic washings were colourless. The combined washings were carefully acidified with dilute hydrochloric acid, diluted with water and extracted with ethyl acetate. The organic layer was washed with brine to neutrality, dried over magnesium

sulphate and evaporated to give 5-methoxy-7-hydroxycoumarin (79) as colourless needles (from methanol) (0.502 g, 41°/o), m.p. 240 - 244° (lit.[47] m.p. 243 - 245°).

5-Methoxy-7-hydroxy-8-iodocoumarin (80)

To a solution of 5-methoxy-7-hydroxycoumarin (1 g) in dry ethanol (40 ml), iodine (1.9 g) was added at 0° and morpholine (1.3 ml) was added with stirring. After 30 min the ice bath was removed and the stirring continued at room temperature for 48 hr. The solvent was removed and the residue dissolved in ethyl acetate and brine. The organic layer was washed with a solution of sodium thiosulphate, brine, dried over magnesium sulphate and evaporated to give 5-methoxy-7-hydroxy-8-iodocoumarin (80) (0.91 g, 56°/o) which crystallised from ethanol as colourless needles, m.p. 232 - 235° (lit.[55] m.p. 235 - 237°).

5-Methoxy-7-acetoxy-8-iodocoumarin (81)

Sodium acetate (1 g) was added to 5-methoxy-7-hydroxy-8-iodocoumarin (80) (318 mg) in acetic anhydride (5 ml). The mixture was refluxed for 3 hr. On cooling, the solution was poured on to ice and stirred for a further 3 hr, then extracted with ethyl acetate (3 x 30 ml), washed thoroughly with saturated sodium hydrogen carbonate solution, brine to neutrality, dried, filtered, and evaporated to give 5-methoxy-7-acetoxy-8-iodocoumarin (81) (320 mg, 90°/o). Crystallisation from ethyl acetate-light petroleum gave colourless needles, m.p. 204 - 206° (Found: C, 40.09; H, 2.35; I, 35.31. $C_{12}H_9IO_5$ requires: C, 40.0; H, 2.50; I, 35.20°/o); n.m.r. signals at δ 2.15 (3H, s), 3.90 (3H, s), 6.28 (1H, d, J 9.5Hz),

6.60 (1H, s) and 7.95 (1H, d, J 9.5Hz); mass spectral peaks at m/z 360 (M^+, 26%), 317 (100), 289 (20), 274 (68), 189 (53) and 131 (41).

Attempted condensation of 5-methoxy-7-acetoxy-8-iodocoumarin with 2-methylbut-3-en-2-ol

2-Methylbut-3-en-2-ol (116 mg), sodium hydrogen carbonate (500 mg), and palladium acetate (90 mg) were added to a solution of 5-methoxy-7-acetoxy-9-iodocoumarin (530 mg) in dimethylformamide (10 ml) and the reaction mixture was heated at 90 ± 5° under argon for 24 hr. The reaction mixture was cooled, filtered, and the filtrate dissolved in ethyl acetate, washed with brine, dried, filtered and evaporated to give only starting material (500 mg). The same conditions were repeated using 5-methoxy-7-hydroxy-8-iodocoumarin but no reaction took place, ^1H n.m.r. indicating only starting material.

3-Bromocoumarin (90)

In a three-necked flask, equipped with a dropping funnel and condenser fitted with a trap for hydrogen bromide, were placed coumarin (10 g) and chloroform (700 ml). A solution of bromine (10.9 g) in chloroform (5.8 ml) was added dropwise to the well stirred solution at room temperature over 2 hr. After t.l.c. showed no starting material left, the excess of bromine was removed by adding aqueous sodium sulphite (20% w/v) (25 ml) through the dropping funnel. The chloroform layer was separated and washed with water several times, dried over magnesium sulphate and evaporated to give 3,4-dibromo-3,4-dihydrocoumarin (89) (16 g, 76%) as colourless

needles (from chloroform), m.p. 101 - 105° (lit.[56] m.p. 103 - 105°). A solution of 3,4-dibromo-3,4-dihydrocoumarin (16 g) in dry pyridine (8ml) was warmed on a water bath for 15 min until a dark brown precipitate of pyridinium bromide was observed. Most of the solvent was evaporated and the residue was poured into iced water, extracted with ethyl acetate and the organic layer washed with saturated copper sulphate solution to remove the pyridine. The resultant solution was then washed with brine, dried over magnesium sulphate and evaporated to give 3-bromocoumarin (90) (15.2 g, 95°/o) which crystallised from ethanol as colourless long prismatic needles, m.p. 107 - 108° (lit.[57] m.p. 110°); ν_{max} (CCl_4), 1750, 1610 and 960 cm^{-1}; n.m.r. signals at δ 8.8 (1H, s) and 6.2 - 6.65 (4H, m); mass spectral peaks at m/z 225 (M^+, 79°/o), 89 (100) and 63 (33).

Condensation of 3-bromocoumarin with 2-methylbut-3-en-2-ol.

To a solution of 3-bromocoumarin (2.19 g) in dimethylformamide (10 ml), 2-methylbut-3-en-2-ol (1.72 g) was added with stirring followed by tetrabutylammonium bromide (4.17 g), sodium hydrogen carbonate (2.1 g) and palladium acetate (214 mg). The mixture was heated at 70 ± 5° for 24 hr. The reaction was cooled and filtered. The filtrate was diluted with ethyl acetate (100 ml) and washed several times with water, dried over magnesium sulphate, and evaporated to give the crude allylic alcohol (91) (2.00 g) which was purified by column chromatography on silica gel. Elution with ethyl acetate-light petroleum (1:4→3:2) gave 3-(trans-3-hydroxy-3-methylbut-1-enyl)coumarin (91) (1.9 g, 85°/o) as colourless needles (from ethyl acetate-light petroleum), m.p. 96 - 98° (Found: C, 73.06; H, 5.99.

$C_{14}H_{14}O_3$ requires: C, 73.02; H, 6.10°/o); n.m.r. signals at δ 1.42 (6H, s), 6.61 (1H, d, J 16Hz), 6.91 (1H, d, J 16Hz), 7.2 - 7.5 (4H, m), 7.63 (1H, s) and 2.15 (1H, bs, exchangeable with D_2O); mass spectral peaks at m/z 230 (M^+, 40°/o), 187 (100), 159 (36), 173 (51), 115 (37) and 43 (31); ν max (KBr) 3420, 1720, 1610 and 769 cm^{-1}.

Epoxidation of the allylic alcohol (91)

A solution of m-chloroperbenzoic acid (0.23 g) in ethyl acetate (5 ml) and a solution of (91) (0.23 g) in ethyl acetate (9 ml) were mixed at 0°, and sodium hydrogen carbonate (0.23 g) added. After 30 min the ice bath was removed and the reaction mixture kept at room temperature for 17 hr, then diluted with ethyl acetate (25 ml), and washed with sodium sulphite (10°/o w/v) brine, dried over magnesium sulphate, and evaporated to give the epoxide (94) (0.22 g, 90°/o) as colourless needles (from ethyl acetate-light petroleum), m.p. 98 - 99° (Found: C, 68.37; H, 6.00. $C_{14}H_{14}O_4$ requires: C, 68.28; H, 6.1°/o); n.m.r. signals at δ 1.87 (3H, s), 1.85 (3H, s), 2.15 (1H, bs), 2.5 (1H, d, J 3.5Hz), 4.12 (1H, d, J 3.5Hz), 7.26 - 7.57 (4H, m) and 7.61 (1H, s); mass spectral peaks at m/z 246 (M^+, 4°/o), 175 (100), 160 (31), 131 (25), 77 (17), 59 (31) and 43 (27); νmax (KBr) 3420, 1720, 1610, 1180 and 755 cm^{-1}.

Condensation of 3-bromocoumarin with 3-methylbut-2-en-1-ol

To a solution of 3-bromocoumarin (0.531 g) in dimethylformamide (10 ml), 3-methylbut-2-en-1-ol (1.164 g) was added with stirring. Tetrabutylammonium bromide (2.0 g), sodium hydrogen carbonate (0.50 g), and palladium acetate (0.08 g) were added, and the reaction mixture was heated in an oil bath at 70° under argon for 24 hr. The reaction mixture was cooled, filtered, and the filtrate diluted with ethyl acetate (50 ml), washed several times with water, brine, dried over magnesium sulphate, filtered,

and evaporated to give a mixture (0.60 g). Column chromatography on silica gel and elution with ethyl acetate-light petroleum (1:4 → 4:1) gave two main fractions. The less polar fraction had to be purified using preparative silica gel t.l.c. using chloroform-light petroleum (2:3, 8x). This gave 3-(1-hydroxy-3-methylbut-3-en-2-yl)coumarin (92) (0.38 g, 74°/o) which crystallised from ethyl acetate-light petroleum as colourless needles, m.p. 95 - 97° (Found: C, 72.79; H, 6.27. $C_{14}H_{14}O_3$ requires: C, 73.02; H, 6.10°/o); ν_{max} ($CHCl_3$) 3020, 1720, 1610 and 1100 cm^{-1}; n.m.r. signals at δ 1.80 (3H, s) 2.25 (1H, bs), 3.82 (1H, bt), 3.92 (2H, m), 4.97 (1H, bs), 5.11 (1H, bs), 7.15 - 7.60 (4H, m) and 7.67 (1H, s); mass spectral peaks at m/z 230 (M^+, 2°/o), 200 (100), 185 (15), 157 (11) and 128 (21).

3-(1-Acetoxy-3-methylbut-3-en-2-yl)coumarin (93)

To a solution of the allylic alcohol (92) (140 mg) in acetic anhydride (2 ml), sodium acetate (190 mg) was added and the reaction mixture refluxed under nitrogen for 3 hr, then the reaction was cooled in an ice bath, water (10 ml) was added and the mixture stirred at room temperature for 2 hr. The mixture was extracted with ethyl acetate and the organic layer washed with saturated sodium hydrogen carbonate solution, brine to neutrality and dried over magnesium sulphate. Evaporation gave 3-(1-acetoxy-3-methylbut-3-en-2-yl)coumarin (93) (130 mg, 88°/o) as a colourless oil; ν_{max} ($CHCl_3$), 1700, 1740 and 1610 cm^{-1}; n.m.r. signals at δ 1.80 (3H, bs), 1.98 (3H, s), 3.95 (1H, bt, J 7Hz), 4.43 (2H, m), 4.94 (1H, bs), 5.07 (1H, bs), 7.25 - 7.55 (4H, m) and 7.58 (1H, s); mass spectral peaks at m/z 272.3028 (M^+, 5°/o) ($C_{16}H_{16}O_4$ requires

M^+ 272.3008), 212 (94), 200 (52), 199 (33) and 43 (100).

Iodination of bergaptol (96)

Yellow mercuric oxide (1.16 g) and iodine (1.36 g) were added alternately portionwise with stirring over 20min to a solution of bergaptol (96) (1.32 g) in acetone (80 ml) and chloroform (20 ml) and the mixture refluxed for 24 hr. The cooled mixture was filtered through celite and the filtrate evaporated under reduced pressure. The residue was extracted with ethyl acetate, washed with aqueous sodium thiosulphate, brine, dried over magnesium sulphate, filtered, and evaporated to give a yellow solid (1.80 g). Without further purification this solid was dissolved in acetone (50 ml) and refluxed for 6 hr with potassium carbonate (1.70 g) and methyl iodide (4.4 ml). The reaction mixture was filtered and the filtrate evaporated. The residue was dissolved in a mixture of ethyl acetate and water, and the organic layer washed with 5°/o w/v aqueous potassium carbonate solution. Subsequent washing with brine, drying over magnesium sulphate and evaporation of the solvent yielded a solid (1.90 g). Purification by silca gel column chromatography and elution with ethyl acetate-light petroleum (1:4→ 4:1) gave 8-iodobergapten (98) (0.53 g, 24°/o) as yellow needles (from ethyl acetate-light petroleum) m.p. 197 - 199°; ν_{max} (KBr) 1732, 1610 and 1350 cm^{-1}; n.m.r. signals at δ 4.30 (3H, s), 6.25 (1H, d, J 9.5Hz), 7.06 (1H, d, J 2Hz), 7.50 (1H, d, J 2Hz) and 8.20 (1H, d, J 9.5Hz); mass spectral peaks at m/z 342 (M^+, 39°/o), 216 (100), 201 (35), 173 (75) and 145 (39).

Condensation of 8-iodobergapten with 2-methylbut-3-en-2-ol

To a solution of 8-iodobergapten (98) (50 mg) in dimethylformamide (4 ml), 2-methylbut-3-en-2-ol (103 mg), tetrabutylammonium bromide (172 mg), sodium hydrogen carbonate (50 mg), and palladium acetate (9 mg) were added. The mixture was heated in an oil bath at 95 ± 5° for 24 hr under argon. The reaction mixture was cooled and filtered. The filtrate was diluted with ethyl acetate (20 ml) and washed several times with brine, dried over magnesium sulphate, filtered, and evaporated to give swietenocoumarin C (19) (37 mg, 85°/o) as yellow needles (from ethyl acetate light petroleum) m.p. 187 - 188° (lit.[15] m.p. 190°); λmax (EtOH) (log ε) 224 (4.35), 238 (4.35), 245 (4.30), 277 (4.38), 287 (4.45) and 312 (4.10)nm (lit.[15] 2.35 (4.35, 244 (4.33, 276 (4.41), 285 (4.43) and 3.12 (4.11); n.m.r. signals at δ 1.50 (6H, s), 4.20 (3H, s), 6.30 (1H, d, J 9.5Hz), 7.05 (1H, d, J 2Hz), 7.10 (2H, s), 7.65 (1H, d, J 2Hz) and 8.10 (1H, d, J 9.5Hz); mass spectral peaks at m/z 300 (M^+, 26 °/o), 285 (67), 282 (53), 257 (41), 243 (29) and 229 (100).

Condensation of 7-methoxy-8-iodocoumarin with 3-methylbut-2-en-1-ol

To a solution of 7-methoxy-8-iodocoumarin (54) (0.531 g) in dimethylformamide (10 ml), 3-methylbut-2-en-1-ol (1.164 g) was added with stirring. Tetrabutylammonium bromide (2.0 g), sodium hydrogen carbonate (0.50 g) and palladium acetate (0.80 g) were added and the reaction mixture was heated in an oil bath at 70° under argon for 24 hr. The reaction mixture was cooled, filtered and the filtrate diluted with ethyl acetate (50 ml),

washed several times with brine, dried over magnesium sulphate, filtered, and evaporated to give a mixture (0.60 g). Column chromatography on silica gel and elution with ethyl acetate-light petroleum (1:4 → 4:1) gave three main fractions. The least polar fraction had to be purified using preparative silica gel t.l.c. using chloroform-light petroleum (2:3, 10x). This gave 7-methoxy-8-(1-hydroxy-3-methylbut-3-en-2-yl)coumarin (77) (0.182 g, 40%) which crystallised from ethyl acetate-light petroleum as colourless needles, m.p. 113 - 114°; ν_{max} (KBr) 3450, 1720, 1610 and 1100 cm^{-1}; n.m.r. signals at δ 1.65 (3H, s), 1.90 (1H, bs), 3.84 (3H, s), 4.25 (3H, m), 4.89 (2H, bs), 6.25 (1H, d, J 9.5Hz), 6.85 (1H, d, J 8.5Hz), 7.30 (1H, d, J 8.5Hz) and 7.55 (1H, d, J 9.5Hz); mass spectral peaks at m/z 260 (M^+, 4%), 230 (100), 215 (15), 187 (11) and 159 (21).

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