Synthetic Approaches to Complex Natural Coumarins

A thesis submitted for the degree

of Doctor of Philosophy

by

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September, 1979

We shall not cease from exploration
And the end of all our exploring
Will be to arrive where we started
And know the place for the first time.

T.S. Eliot. (Little Gidding)

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Acknowledgements

I would like to thank my supervisor, Dr. R.D.H. Murray not only for the invaluable guidance he has rendered me throughout the period of this research, but also for his friendship which has helped make the last three years so pleasurable.

The assistance of the Technical Staff of the University of Glasgow Chemistry Department is also gratefully acknowledged.

Summary

The first example of a successful *para*-Claisen rearrangement of a 1,1-dimethylallyl aryl ether has been realised. The rearrangement product, a natural coumarin, on methylation gave another natural coumarin, furopinnarin.

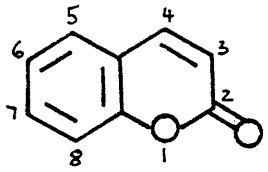
A technique for the formation of 2-isopropenylfurans, unusual amongst the furanocoumarins, has been developed *via* the coupling of the appropriate cuprous acetylide with an *ortho* iodophenol. By utilisation of this technique a number of approaches to the natural 2′-isopropenylfuranocoumarins, hortiolone and hortionone, have been investigated and the natural product oroselone synthesised.

A synthesis of the coumarin, *cis*-avicennol, recently isolated from *Zanthoxylum elephantiasis* has been attempted. The angular tricyclic framework of this molecule was readily prepared and the elaboration of the *cis*-3-methyl-3-hydroxybut-1-enyl side chain *via* a cuprous acetylide coupling investigated.

The naturally occurring coumarins vaginol and vaginidiol have been postulated as possible intermediates in the biosynthesis of the angular furanocoumarins. Syntheses of these compounds would be very valuable in that this would allow feeding experiments to be done in order that the actual role of these compounds be clarified. A number of synthetic approaches have thus been investigated.

Introduction

A Short Review of the Chemistry of the 5,7-Dioxygenated Coumarins and the Biogenesis of the Furanocoumarins.



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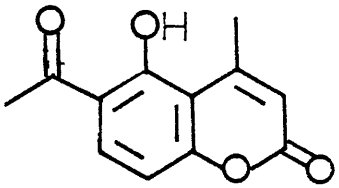

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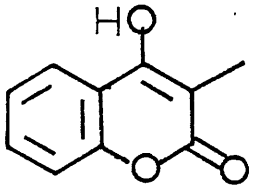

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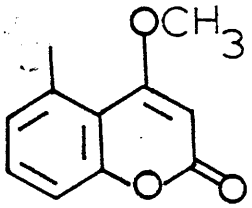

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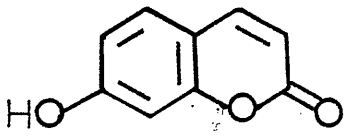

(5)

The position of the coumarins in the field of natural product chemistry is well established, for it was over a century and a half ago that Vogel isolated[1] the simplest member of the class, coumarin (1) from the tonka bean, Coumarouna odorata = Dipteryx odorata. Since then a great number of its derivatives have been shown to occur widely throughout the plant kingdom [2-5] as well as in certain animals[6] and micro-organisms[7]. Recently, improvements[5] in the techniques of isolation and structural analysis have led to a great increase in the number of known natural coumarins. Dean, in 1963[4] reported that around ninety were known, whilst the most recent review[5] (in 1978) lists over five hundred and a current estimate must run to well over seven hundred.

A convenient classification of coumarins is based upon the oxygenation pattern of the coumarin nucleus (1) and all six possible sites of oxygenation are represented in nature. These oxygen functions may be present as phenols, ethers or as glycosides. The presence of isoprenoid chains of one, two or three units, attached to carbon, oxygen or to both are also common features. Although coumarin (1) is the simplest representative of its class it is really atypical, as it lacks an oxygen at C-7. Only thirty or so of the known natural coumarins lack oxygenation at this position (e.g. (2), (3) and (4)) and thus it is best to consider umbelliferone, 7-hydroxycoumarin (5) as the parent compound. It is the intention to present here a short review of some of the chemistry of those 5,7-dioxygenated coumarins unsubstituted in the

Scheme 1

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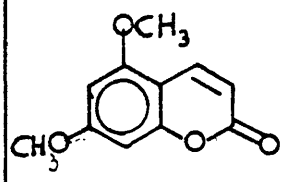

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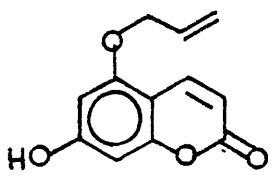

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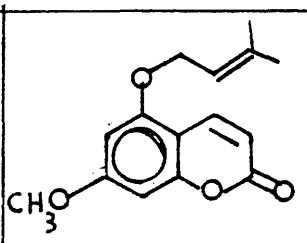

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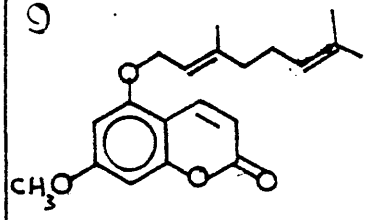

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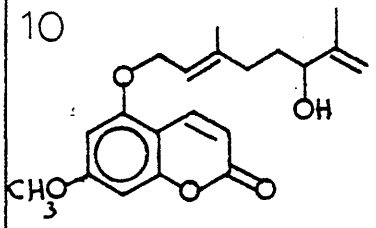

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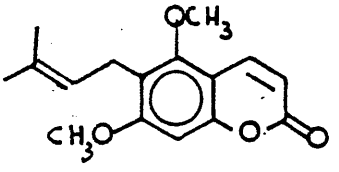

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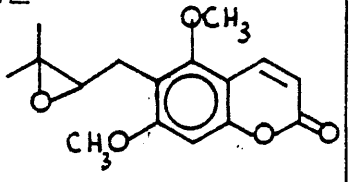

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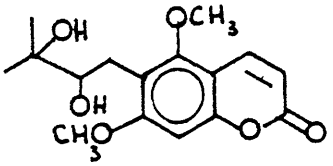

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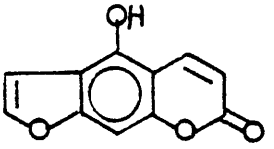

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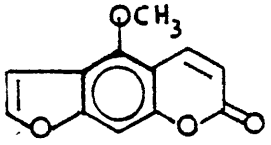

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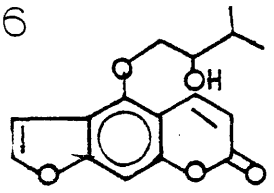

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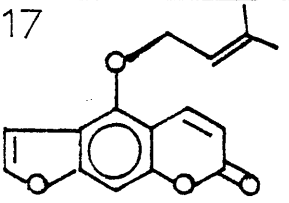

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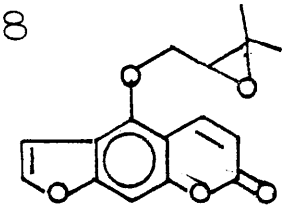

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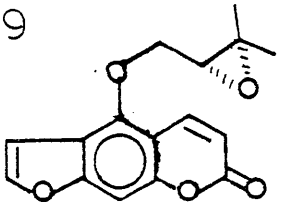

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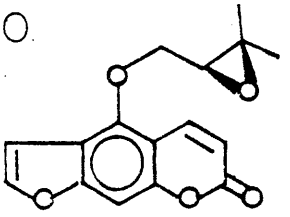

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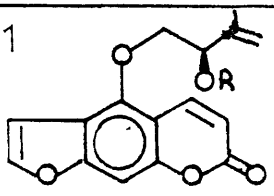

R = H

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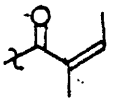
21: R =



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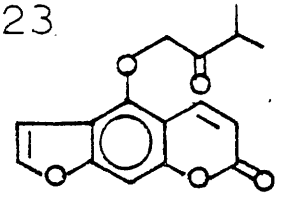

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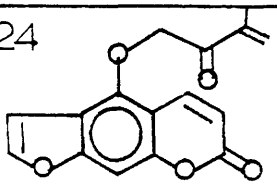

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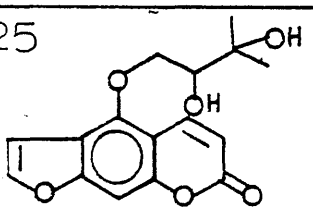

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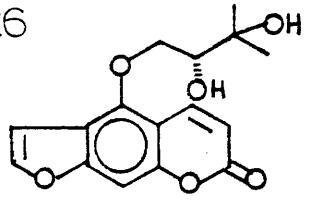

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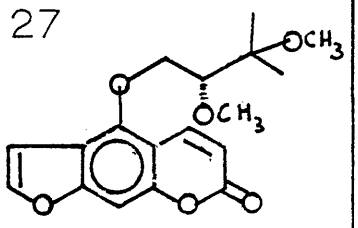
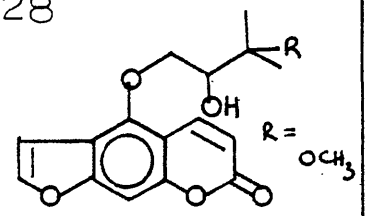
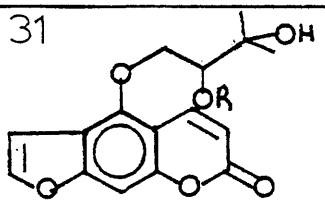
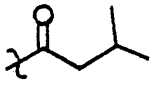
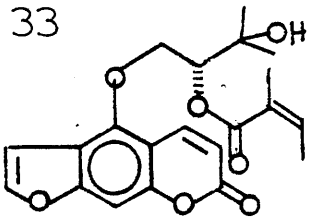
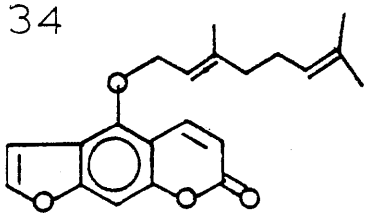
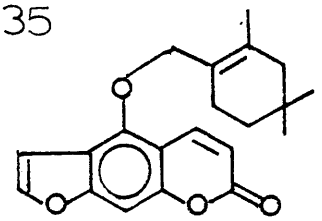
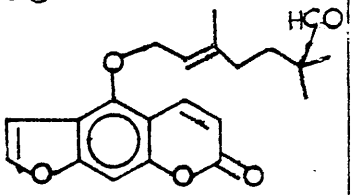
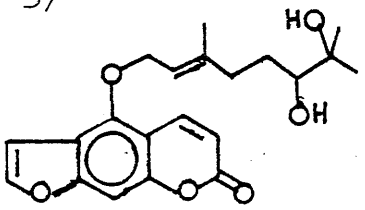
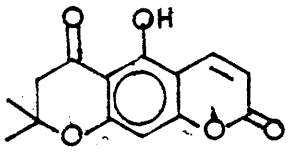
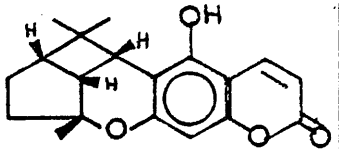
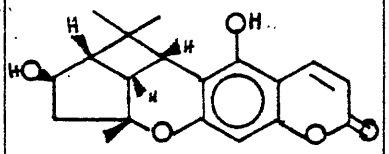
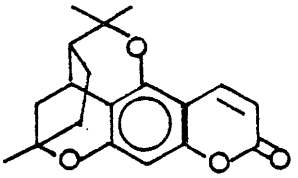
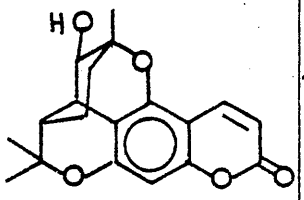
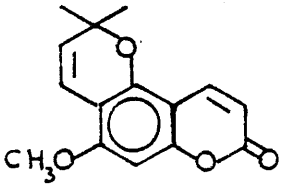
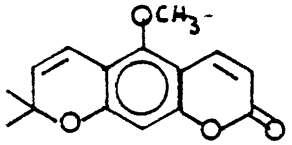
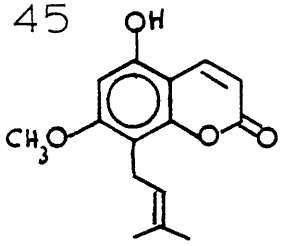
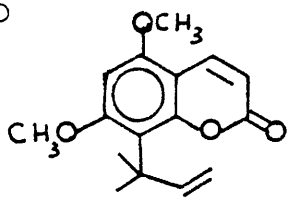
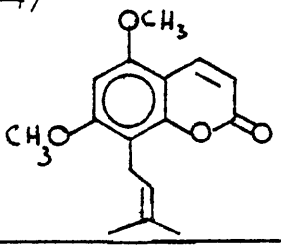
27 	28  R = OCH_3	29 28: R = OEt
30 28: R = Cl	31  R = D-glucosyl	32 31: R = 
33 	34 	35 
36 	37 	38 
39 	40 	41 
42 	43 	44 
45 	46 	47 

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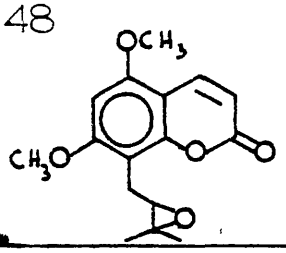

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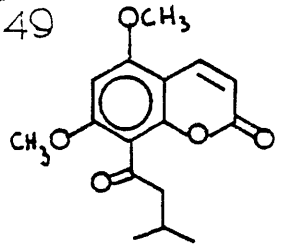

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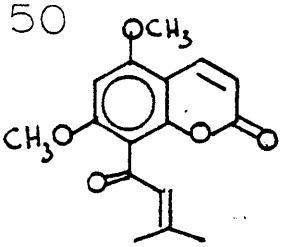

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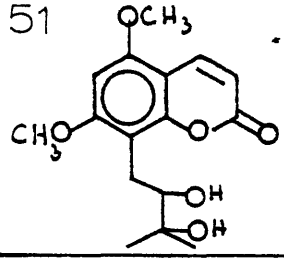

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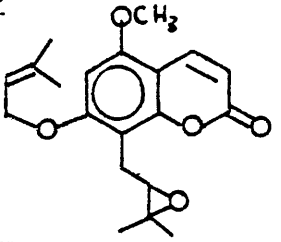

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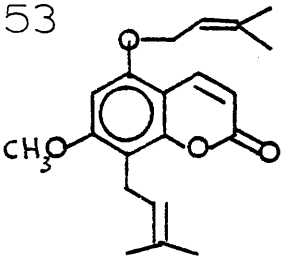

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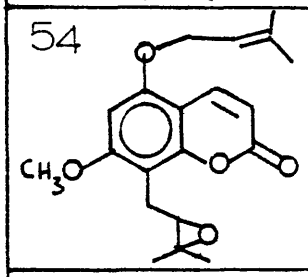

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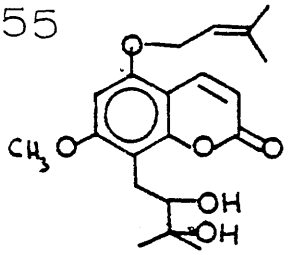

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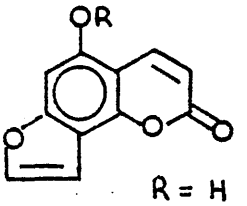


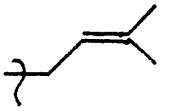
R = H

57

56: R = CH_3

58

56: R =



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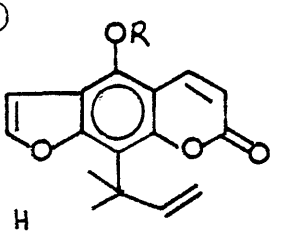

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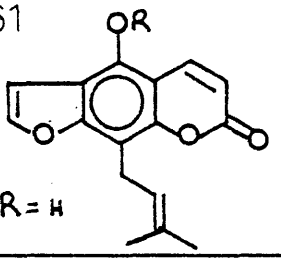
60

59: R = CH_3

61

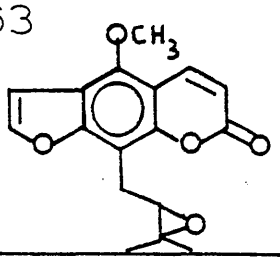


R = H

62

61: R = CH_3

63



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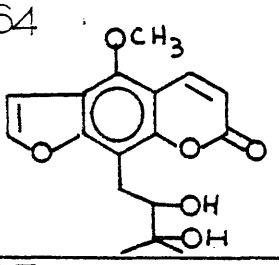

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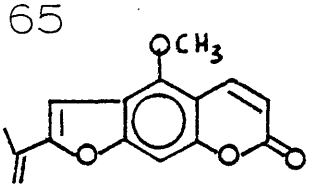

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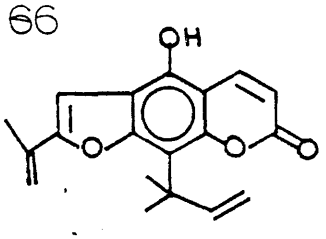

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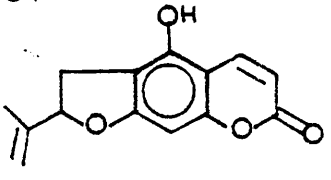

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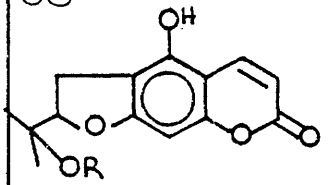


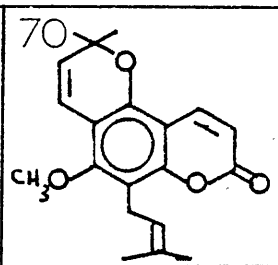
R = H

Scheme 1 (cont.)

69

68: R = D-glucosyl.

70



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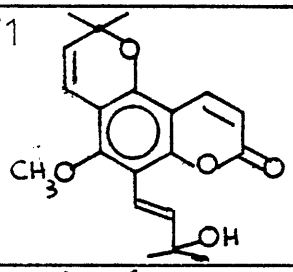

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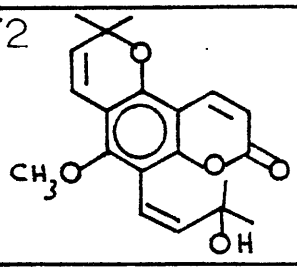

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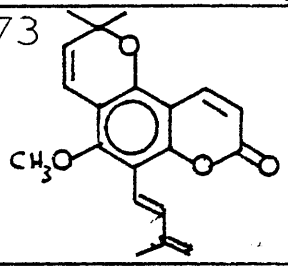

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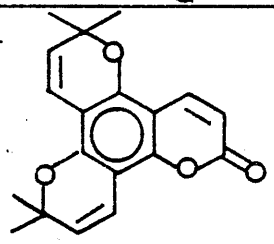

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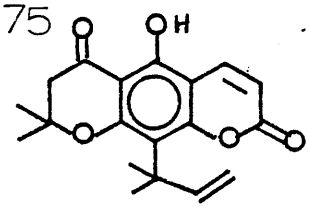

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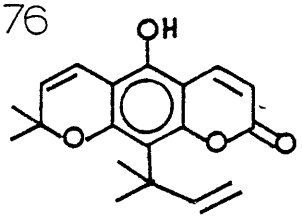

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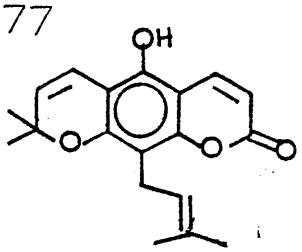

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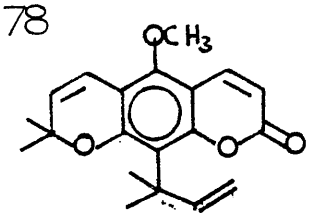
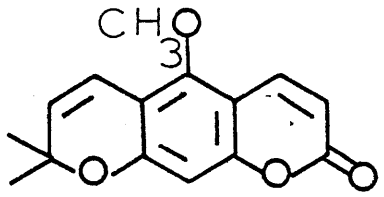


Index to Scheme 1

	Trivial Name
(6)	Citropten/Limettin*
(7)	Lacoumarin
(8)	-*
(9)	-
(10)	-
(11)	Toddaculin*
(12)	Aculeatin
(13)	Toddalolactone
(14)	Bergaptol*
(15)	Bergapten*
(16)	Pranferol*
(17)	Isoimperatorin*
(18)	(±) - Oxypeucidanin*
(19)	Prangolarin
(20)	(S)-(-)-Oxypeucidanin
(21)	Pangeline
(22)	Angeloylpangeline
(23)	Isoxypeucidanin
(24)	Pabulenone
(25)	Prangol
(26)	Aviprin
(27)	(+)-Oxypeucidanin hydrate
(28)	Tert-O-methyloxypeucidanin hydrate
(29)	-
(30)	Saxalin
(31)	Oxypeucidanin D-glucoside
(32)	-
(33)	Ostruthol
(34)	Bergammotin
(35)	Archangelin*
(36)	-
(37)	-
(38)	Clausenin*
(39)	Eriobrucinol*
(40)	Hydroxyeriobrucinol
(41)	Deoxybruceol*
(42)	Bruceol
(43)	Alloxanthoxyletin*
(44)	Xanthoxyletin*
(45)	Sibiricol*
(47)	Coumurrayin*
(48)	Sibiricin*
(49)	-
(50)	Glabralactone*
(51)	Mexoticin
(52)	-
(53)	Sesibiricin*
(54)	Sesebrin
(55)	Sesebrinol
(56)	Isobergaptol*
(57)	Isobergatpen*
(58)	Lanatin
(59)	-*
(60)	Furopinnarin*
(61)	Alloisoimperatorin*
(62)	Swietenocoumarin B
(63)	Swietenocoumarin D
(64)	Swietenocoumarin F
(65)	Hortionone
(66)	Hortiolone
(67)	Leptophyllidin
(68)	Leptophyllin
(69)	Leptophylloside
(70)	Dipetaline*
(71)	trans-Avicennol*
(72)	cis-Avicennol
(73)	Avicennin*
(74)	Dipetalolactone*
(75)	Clausenidin*
(76)	Nordentatin
(77)	Trachyphyllin
(78)	Poncitrin/Dentatin*

* - Coumarins subject to total synthesis



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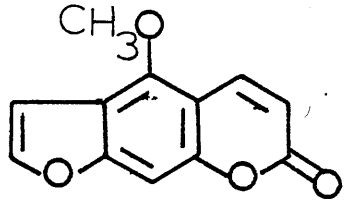

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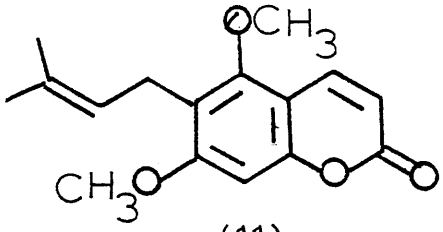

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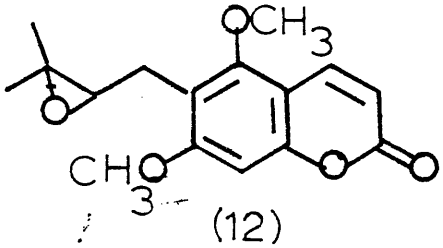

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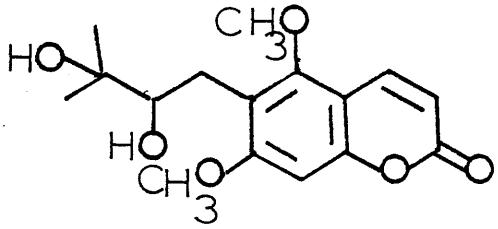
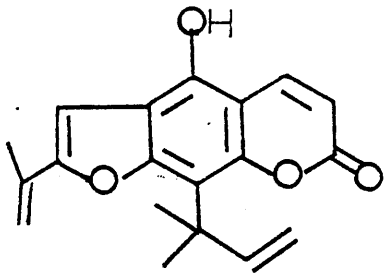


(13)

lactone ring (Scheme 1 lists all those known to date). A recent review[5] by Murray contains leading references to the majority of these compounds.

Xanthoxyletin (44) was the first of this series to be isolated[4] (in 1829) but until 1960 only eleven others were known. The recent great increase is again a reflection of the more refined modern techniques for isolation and structural determination. In the main, each compound has been found in only one plant source though a few such as bergapten (15) have been isolated from several[3]. Most commonly the 5,7-dioxygenated coumarins are found in the plant orders Umbelliferae, the Angelica species are particularly well represented and the Rutaceae of which the Citrus group predominates. It is interesting to note that in any one plant source, often structurally related compounds co-exist. In Toddalia aculeata[5] (11), (12) and (13) are all present and it is tempting to postulate that progressive enzymatic elaboration of the 3,3-dimethylallyl side chain may lead from the simplest to the most complex member of this series. (The biogenesis of the 5,7-dioxygenated coumarins and in particular the furanocoumarins will be discussed shortly).

Several common structural features can be readily seen from Scheme 1. Many of the compounds carry an isoprene derived unit on nuclear carbon or as an ether, though in most cases the 3,3-dimethylallyl group has been further elaborated in some way. Oxidation of this moiety is noticably prominent, with epoxides,



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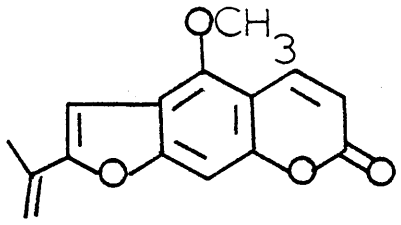

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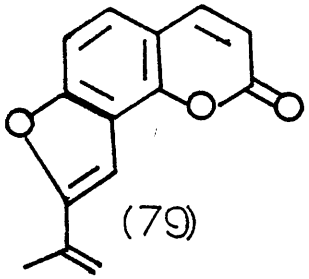

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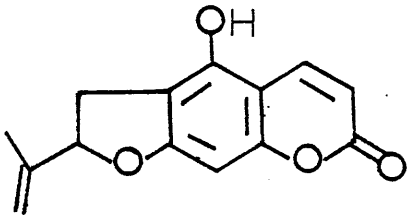

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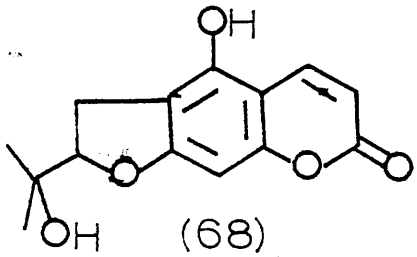

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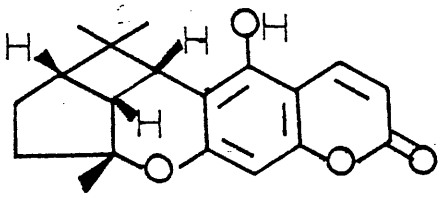

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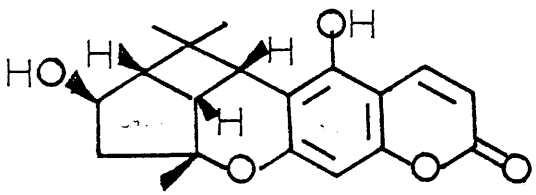

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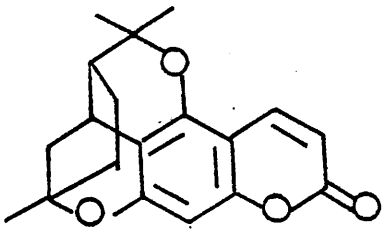

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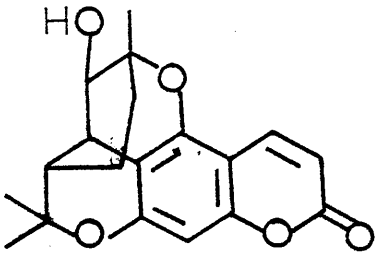
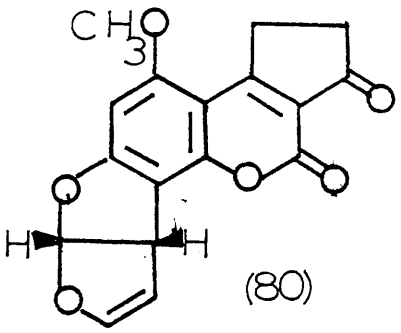


(42)

ketones, alchols and glycols all in evidence. The alcholic functions may be present as ethers, esters or as glycosides. Cyclisation to furans, chromenes etc., is also commonly observed. Coumarins containing an unsubstituted furan ring are particularly important, as almost half the known 5,7-dioxygenated coumarins possess this feature. It will be observed that the vast majority of these are linear furans, indeed only three angular furanocoumarins have to date been reported in this class. An exceedingly rare functionality is also exhibited by the 5,7-dioxygenated coumarins, that being a furan substituted in the 2-position with an isopropenyl group e.g. (65) and (66). Only one other such furanocoumarin is known, oroselone (79). Dihydrofurans (e.g. (67 and (68) are more commonly 2-substituted. Cyclisation in a different manner leads to the chromenes and chromanones. In a lesser number of cases a 1,1-dimethylallyl side chain is also present though never as an ether or in a further modified form. Perhaps this reflects a radically different biogenetic insertion to that of the 3,3-dimethylallyl unit. Also observed are geranyl ethers, again in various degrees of oxidation and cyclisation. Most noteworthy are the bruceols (39) - (42), which contain ten carbon tricyclic systems presumably of isoprenoid origin. It will now be clear from this short discussion and a perusal of Scheme 1, that the 5,7-dioxygenated coumarins exhibit a great diversity of structural types from only a few simple building blocks.

Although it is outwith the scope of this review to discuss



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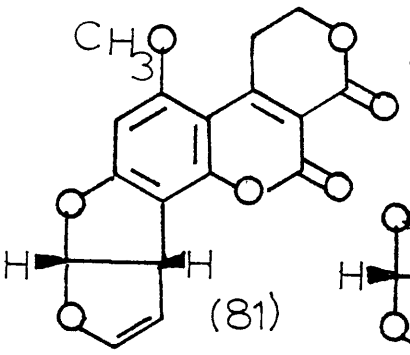

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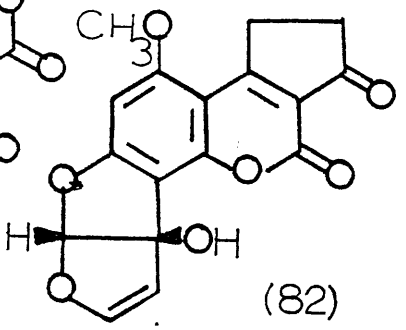

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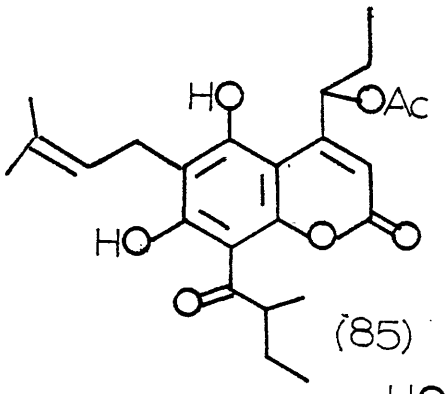

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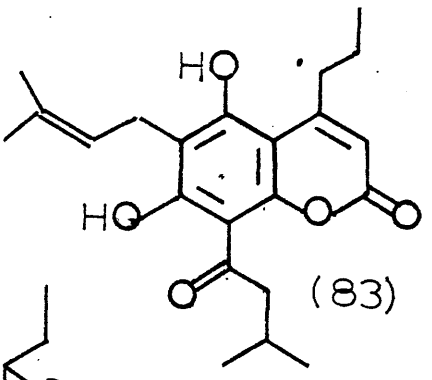

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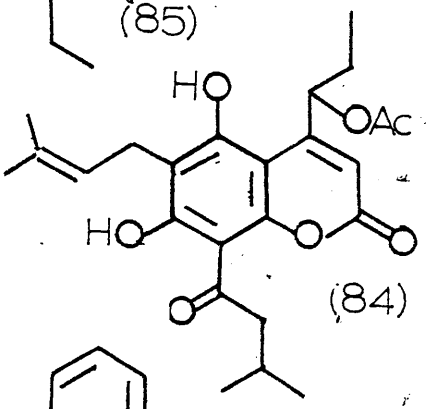

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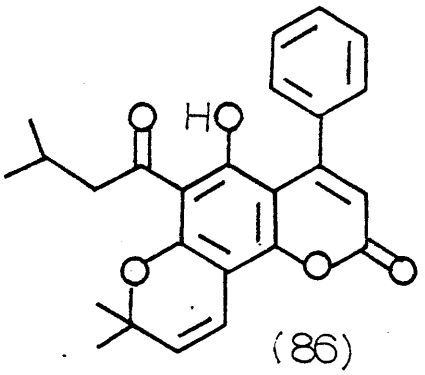

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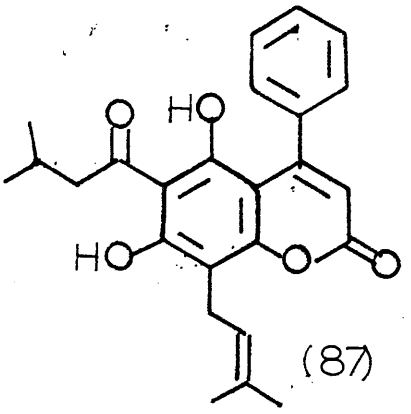
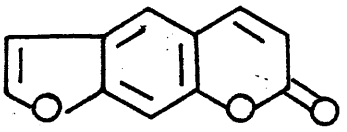


(87)

in any detail the chemistry of the 5,7-dioxygenated coumarins substituted in the lactone ring, the more important and interesting of these classes should be mentioned.

The most widely known are perhaps the highly carcinogenic liver poisons, the aflatoxins[8] of which a dozen or so have been isolated. Büchi has published[9] elegant syntheses of aflatoxins B_1 (80), G_1 (81) and M_1 (82). Of no lesser importance are the 4-alkyl coumarins which number around thirty five, the majority of which have been isolated[10-12] from the West Indian tree Mammea americana. The considerable recent interest in these compounds arises from their exciting biological potential. Mammein (83) has significant antitumor activity against Sarcoma 80[13], whilst (84) and (85) have shown insecticidal properties[12]. Not suprisingly much synthetic endeavour[14,15] has been directed toward the 4-alkyl coumarins, though with little success to date. The corresponding 4-aryl series is also well known, with Mammea americana[16,17] again the principal source. Compounds (86) and (87) are representative examples of this class of some twenty two coumarins.

The physiological behaviour of the natural coumarins is one of the most diverse and widely studied of their properties. Many papers appear every month on the subject of coumarin biological activity, though with the exception of the skin photosensitisation of the furanocoumarins, which will be discussed shortly, little is known about the underlying modes of action. Several excellent



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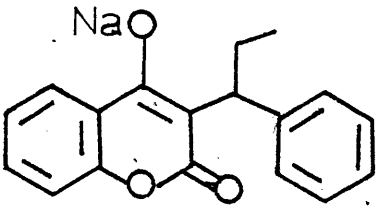

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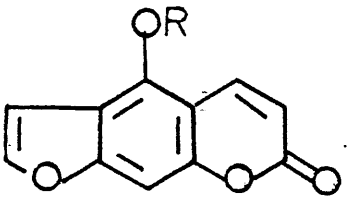
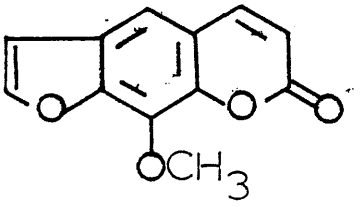
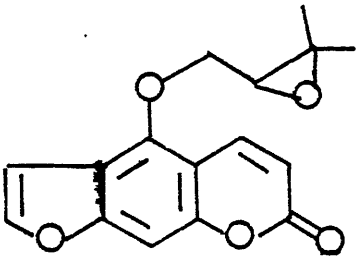


(14), R = H

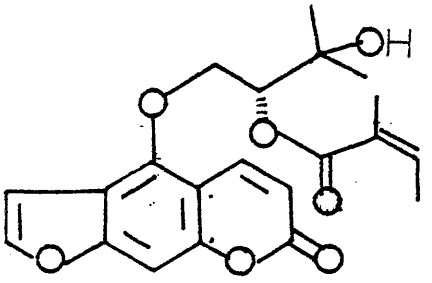
(15), R = CH_3



(90)



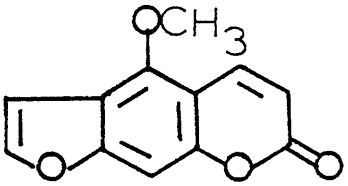
(18)



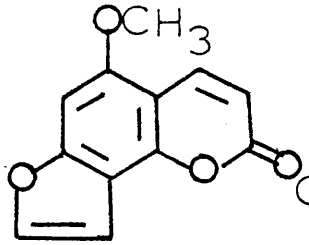
(33)

reviews are available on the subject[2,3,18,19]. These properties range from the contraceptive activity of psoralen[20] (88), through the anticoagulant behaviour of the rat poison warfarin[3] (89), to the antitumor activity[13] of the 4-alkyl coumarins. The 5,7-dioxygenated coumarins are amongst the least studied, but regardless of this, a considerable range of action has been discovered.

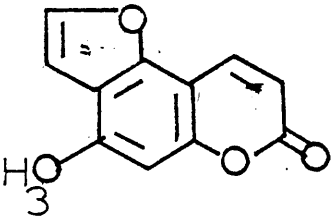
It has been known for many years that contact of the skin with the juices of certain plants[3] (e.g. parsley or figs) followed by exposure to sunlight can lead to pigmentation and blistering of the skin. This effect has been used clinically for the treatment of the skin diseases, leucoderma and psoriasis[21]. No such effects are observed in the absence of light. In the 1930's these effects were duplicated[3] by the direct application of the furanocoumarins psoralen (88), bergapten (15) and xanthotoxin (90) to the skin and it soon became clear that furanocoumarins were the active agents in plants. Since that time much work has elucidated the essential features of this process. The maximum activity is associated with psoralen[3] (88). Substitution of the aromatic nucleus with a C-5 hydroxyl (e.g. bergaptol (14)) removes all activity. The corresponding methyl ether, bergapten (15), however is second only to psoralen in photosensitising ability. Replacement of this methyl ether by increasingly bulky substituents diminishes the activity. (±)-Oxypeucidanin (18) has only very slight activity while ostruthol (33) has no photosensitising properties. A linear



(15)

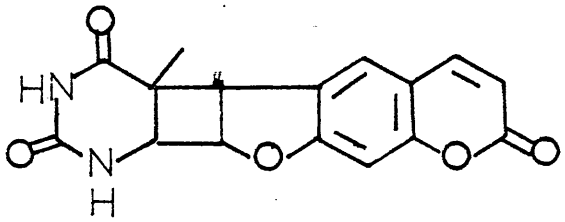


(57)

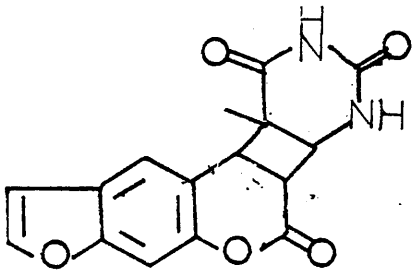


(91)

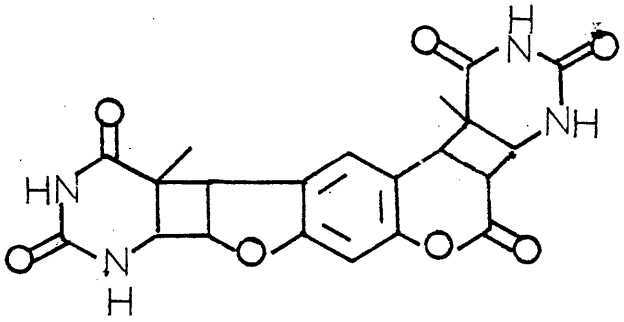
Figure 1



a 2',3'-photoadduct



a 3,4'-photoadduct

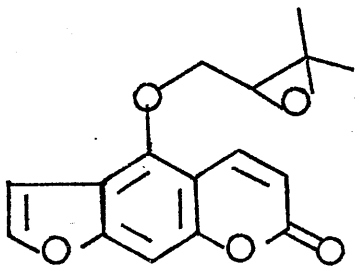


a 2',3'-3,4'-photoadduct

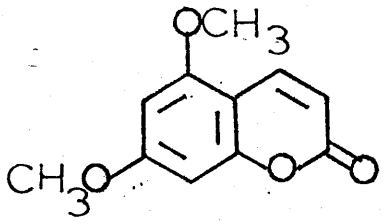
furan system is also necessary for high activity, as the angular isomers of bergapten (15), isobergapten (57) and the synthetic allobergapten (91) are very poor photodermal agents. Pathak and his co-workers[23] discovered that u.v. light of wavelengths between 320-400nm is required for photodermal activity.

Bergapten (15) (and the other simple furanocoumarins) exhibit other photobiological effects, for instance, the killing of bacteria, inactivation of tumor cells and mutagenesis[19]. This last phenomenon suggested that the site of action of the furanocoumarin could be at DNA. Much evidence[19] has since then been accumulated indicating that the flat furanocoumarin can intercalate between two stacked DNA base pairs[19] and that the active compounds then react further with DNA under the influence of light. The nature of this reaction[19] appears to be the formation of [2 + 2] photoadducts between the furanocoumarin and the pyrimidine bases, cystosine, uracil and thymine. The net result of this is to cross link two strands of DNA (see Figure 1). It has been assumed that the photobound furanocoumarin alters the normal functioning of DNA and this results in the observed photobiological effects[19].

A number of interesting biological properties of the furanocoumarins not mediated by light have also been observed. For many years it has been known that only very small quantities of bergapten (15) and other related compounds, act as efficient fish toxins[24]. Another interesting study has shown that bergapten (15)



(18)



(6)

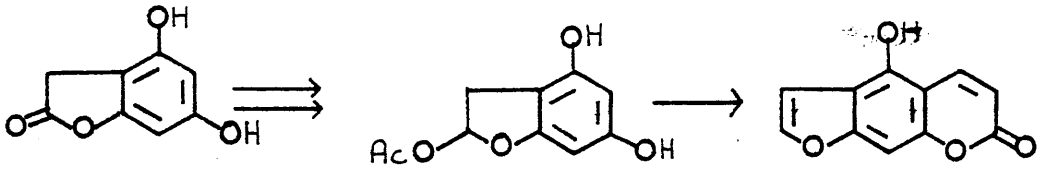
exhibits an extremely high molluscacidal activity[3] (only 5 p.p.m. are required for 100% snail fatality). Recently a number of papers have appeared from Russia (where there is intense interest in the biological properties of coumarins) dealing with coumarin-N-vinylpyrollidone co-polymers. Such a co-polymer with (±)-oxypeucidanin (18) possesses antiarrythmic activity[25].

Very little has been reported on the biological activity of the non-furanoid 5,7-dioxygenated coumarins. Citropten (6) is unique among non-furanocoumarins in that it photobinds to DNA and shows consequent anti-bacterial activity in addition to being a photo-mutagen[19]. The flat nature of this molecule is important in allowing it to intercalate with DNA in a manner analogous to the furanocoumarins. A number of dioxygenated coumarins have recently been discovered to act as antihypertensives[26] and citropten (6) is amongst them.

As can be seen from the short discussion above, the physiological properties of 5,7-dioxygenated coumarins and the class in general cover a wide and varied range and have, as a result, stimulated a great deal of basic research into this field of oxygen heterocycles.

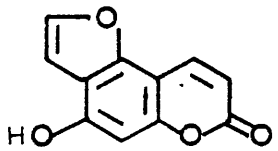
The synthetic chemist has found the 5,7-dioxygenated series a fruitful field as to date almost half of the class have been subject to total synthesis (those marked with * in the index to Scheme 1). Amongst the first to be synthesised were bergaptol (14) and the corresponding methyl ether bergapten[27] (15), though the

Scheme 2



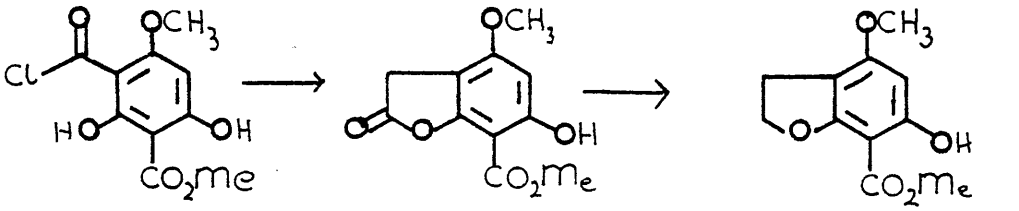
(14) minor

+

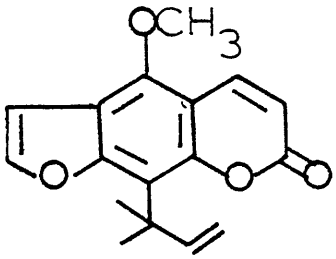


(92) major

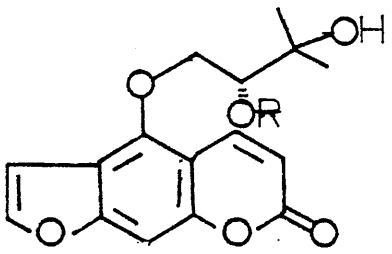
Scheme 3



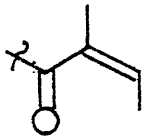
(15)



(62)

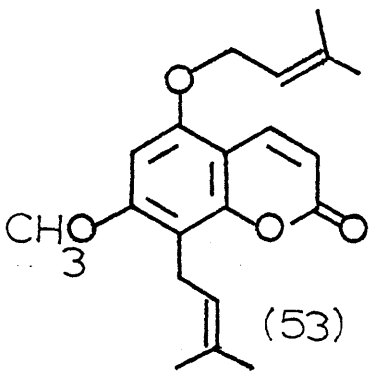


(26) R = H

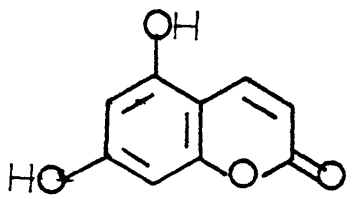
(33) R = 

efficiency of this early synthesis was low (Scheme 2). The angular isomer allobergaptol (92) (which is not known to occur naturally) was predominantly produced during the condensation to form the lactone ring. Caporale[28], by a similar route has overcome the problem of angular furan formation, in a synthesis of bergapten (15), by utilising a protected intermediate which on von Pechmann condensation can form only the linear system (Scheme 3). This synthesis, however, is still far from elegant. Despite this, to date no really satisfactory synthesis of bergaptol (14) has been reported. As a reflection of this, few total syntheses of 5,7-dioxygenated furanocoumarins have been achieved. Indeed, bergaptol (14) derived either by degradation or from natural sources has usually been used as the starting material for those syntheses that have been completed e.g. of furopinnarin[29] (62). Ostruthol (33) has been partially synthesised[30] from the optically active precursor aviprin (26) as a structure proof, simply by formation of the angelate ester, though the parent compound containing the glycolic function has not been made. It should be noted that angelate esters are fairly common structural features of the coumarins in general.

One of the most interesting and perennial challenges facing the synthetic chemist is that of regiospecifically introducing functionality. This problem is well illustrated by the 5,7-dioxygenated coumarins. In order to elaborate a particular molecule the 5-hydroxyl may have to be selectively functionalised

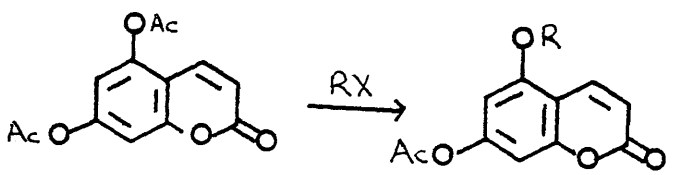


(53)

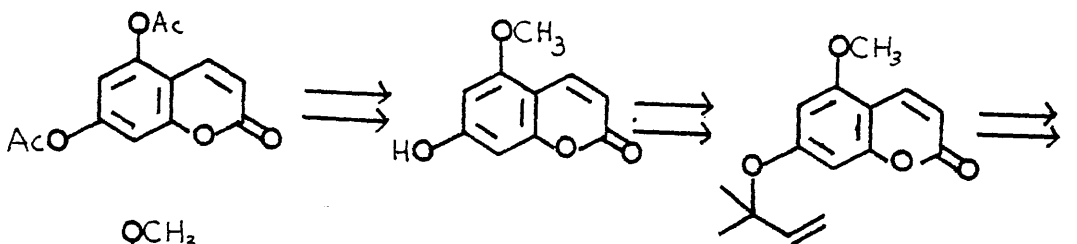


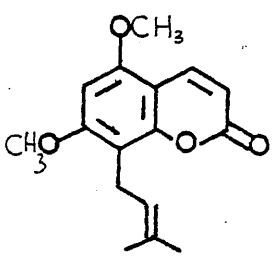
(93)

Scheme 4

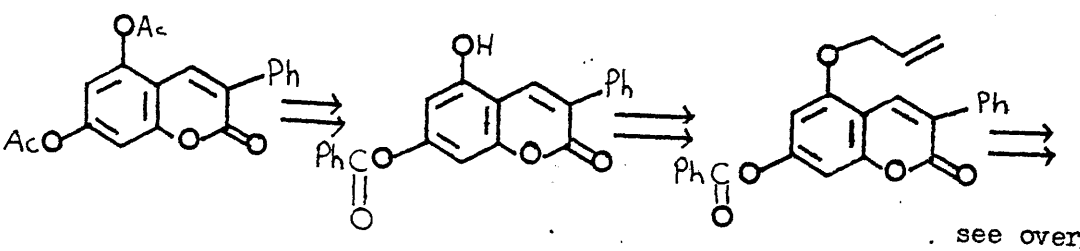


Soheme 5





(47)

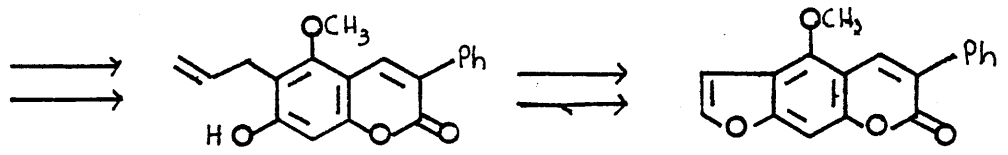


see over/

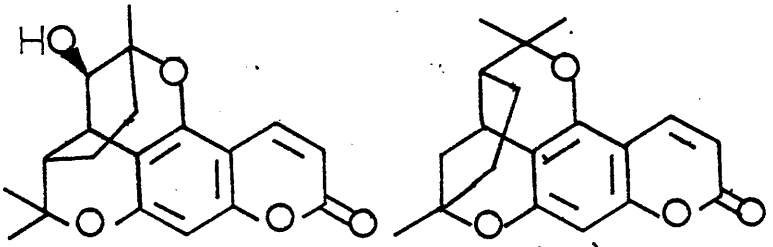
with respect to the 7-hydroxyl. Sesibiricin (53) for instance, has a 5-prenyl ether and a 7-methoxyl. Prenylation of a nuclear carbon at either C-6 or C-8 as desired, is another major hurdle which must be overcome if the task of synthesis is to be achieved. That these two problems have been substantially solved is borne witness to by the large number of the 5,7-dioxygenated coumarins that have been synthesised.

Unfortunately the two hydroxyl functions of 5,7-dihydroxycoumarin (93) show identical reactivity toward a number of alkylating agents[31]. This problem may be overcome however, by the simple precedent of acetylation. It has been shown[32] that 5,7-diacetoxycoumarin will react preferentially, under carefully controlled conditions, at the C-5 oxygen with a variety of alkylating agents, e.g. methyl iodide, 3,3-dimethylallyl bromide (Scheme 4). It is quite remarkable that radically different reactivity is shown by 3-phenyl-5,7-diacetoxycoumarin in that the oxygen at C-7 reacts the more readily[33]. Direct C-alkylation is very difficult synthetically and has rarely been achieved satisfactorily[34], therefore indirect techniques have generally been the most successful. The use of the Claisen rearrangement to introduce a variety of alkyl substituents on a nuclear carbon has often proved to be an efficient and regioselective method[5]. The usefulness of these two techniques is illustrated in two recent syntheses, that of coumurrayin[35] (47) (Scheme 5) and 3-phenylbergapten[33] (94) (Scheme 5).

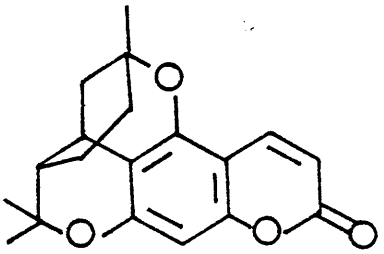
Scheme 5 (cont.)



(94)

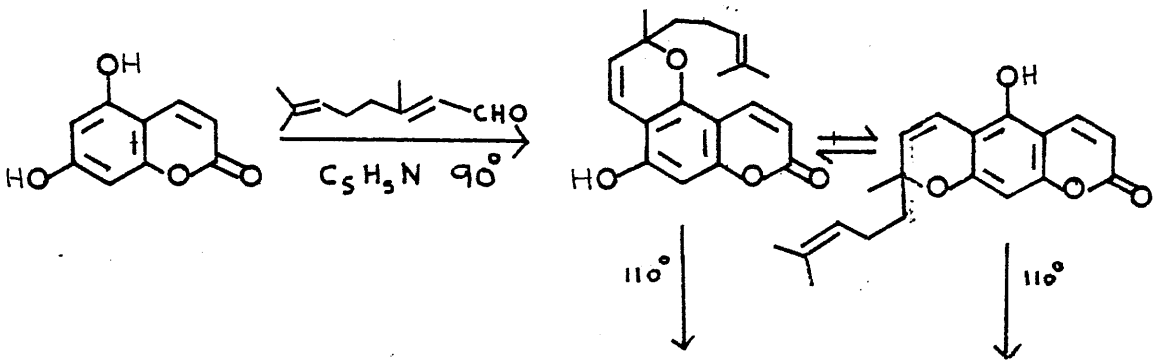


(42) (41)



(95)

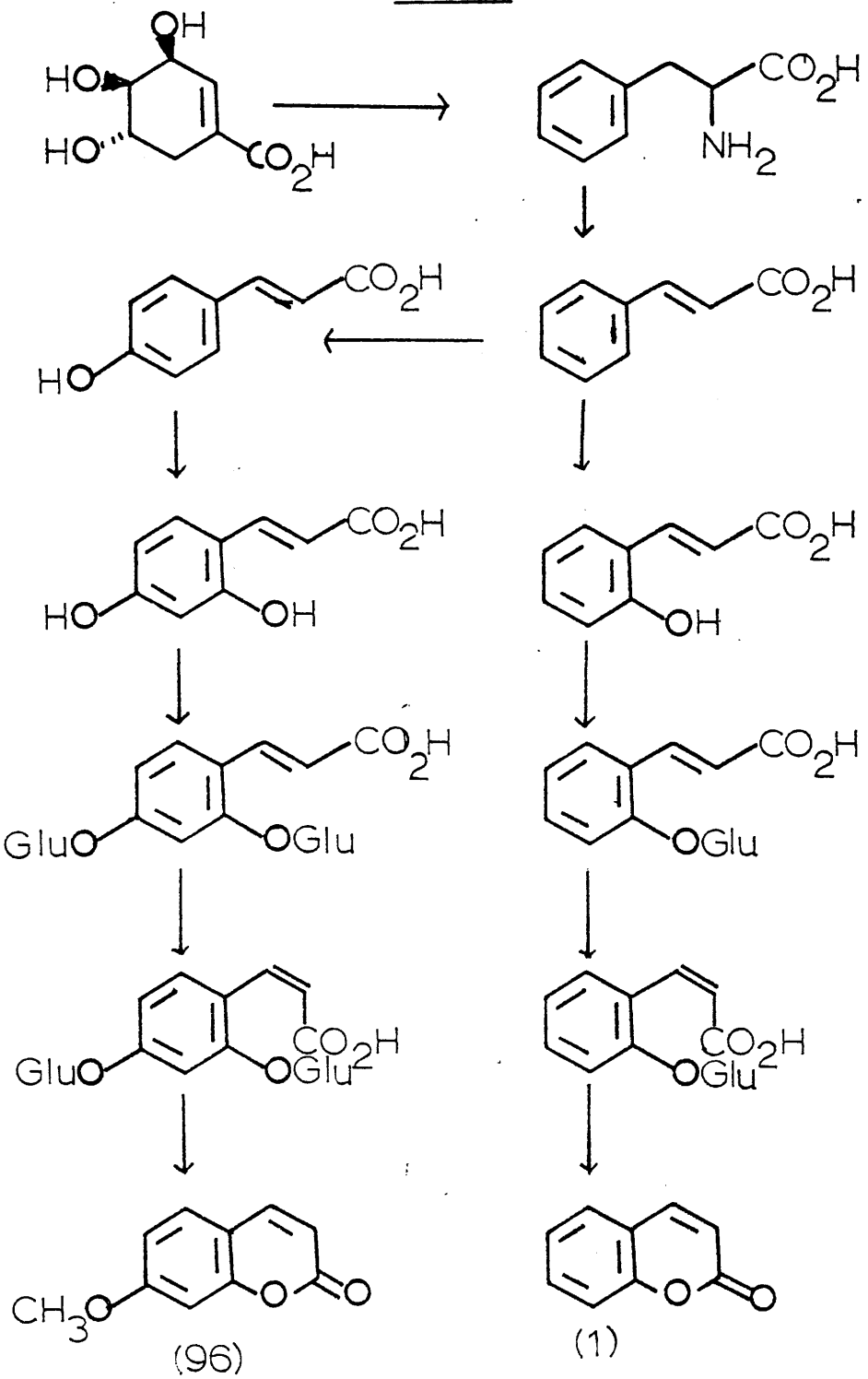
Scheme 6



(95) (41)

A particularly interesting recent synthesis was that of deoxybruceol (41). In 1963 bruceol[36] (42) was isolated from Eriostemon brucei and its structure assigned unequivocally by X-ray analysis. Eight years later deoxybruceol (41) was isolated from the same plant source and a synthesis published by Crombie[37] et al. The synthetic material was identical in all aspects to the natural and the structure was assigned that of the deoxy-isomer (95) of bruceol largely on spectral comparisons with bruceol (42). The synthesis involved prolonged pyrolysis of 5,7-dihydroxycoumarin with citral in the presence of pyridine, which appeared to produce a single citran. However, a re-examination of the reaction[38] in 1976 showed that two citrans were in fact formed. The major product (which was identical to that previously synthesised and consequently also to natural deoxybruceol[37]) was shown to have structure (41) from X-ray analysis of the 4-bromoderivative and not (95) as previously assigned on spectral grounds. The minor product was shown to have structure (95). Clearly spectral considerations cannot always be relied upon in distinguishing between closely related isomers. Mechanistically the reaction is believed to proceed via the isolable chromenes as shown in Scheme 6. The biogenesis is believed to follow an analogous mechanism. It is apparent that although deoxybruceol (41) and bruceol (42) occur side by side in the same plant, they do not possess the same citran orientation. No simple biosynthetic linkage via hydroxylation

Scheme 7


OH
HO
HO
CO2H
NH2
CO2H
CO2H
HO
CO2H
HO
OH
CO2H
OH
CO2H
GluO
OGlu
CO2H
OGlu
GluO
OGlu
CO2H
CO2H
OGlu
CH3O
O
O
O
O

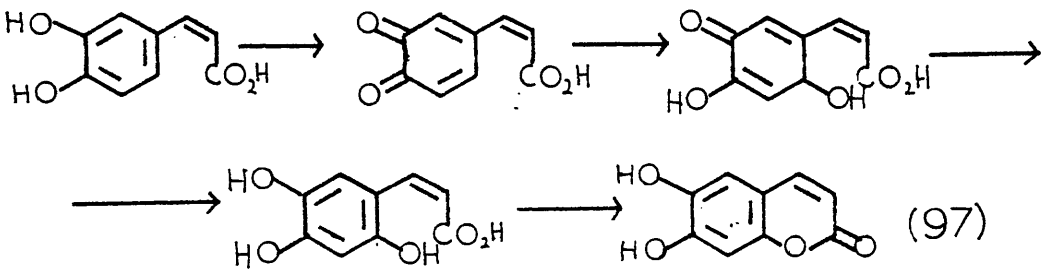
(96) (1)

can then exist. Their biosyntheses must diverge before the postulated chromene intermediates are formed, unless the coumarin ring is inserted at a late stage.

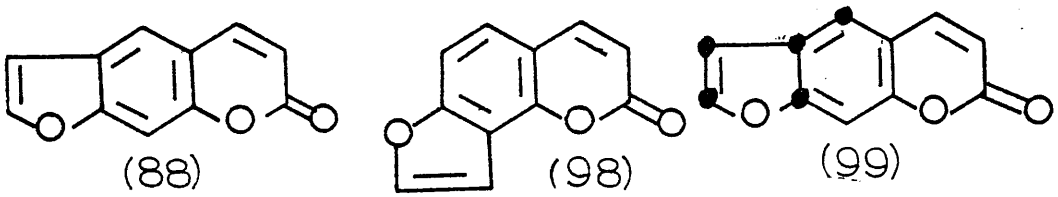
The biosynthesis of the coumarins has been subject to much study and it is appropriate at this juncture to describe some of this work laying particular emphasis on the furanocoumarins.

As coumarin (1) is a phenylpropanoid compound, it is reasonable in the light of earlier studies of phenylpropanoids to assume that it is shikimate derived. Much experimentation[39-41] has shown that both coumarin (1) and umbelliferone (5) are indeed shikimate derived (Scheme 7). The committed step in the formation of coumarins is the ortho-hydroxylation of a cinnamic acid. Brown[39] has shown that in lavender (Lavendula officinalis) trans-cinnamic acid is a good precursor of both coumarin (1) and herniarin (96). The same author has shown however, that the biosynthesis of coumarin (1) and the 7-oxygenated compounds diverge at cinnamic acid not at o-coumaric acid. In other words para-hydroxylation of cinnamic acid precedes the ortho-hydroxylation that is required to elaborate the coumarin ring. It is believed however that ortho-hydroxylation occurs prior to the isomerisation of the trans side chain double bond and this isomerisation is considered to be a photochemical one[42,43]. Apparently the full hydroxylation pattern of the benzene ring is established before lactonisation, at least in the compounds studied to date. No information is available currently on the biosynthesis of non-

Scheme 8

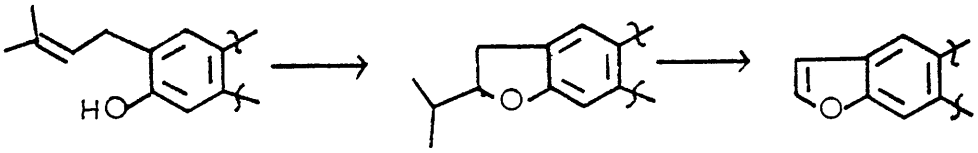


(97)

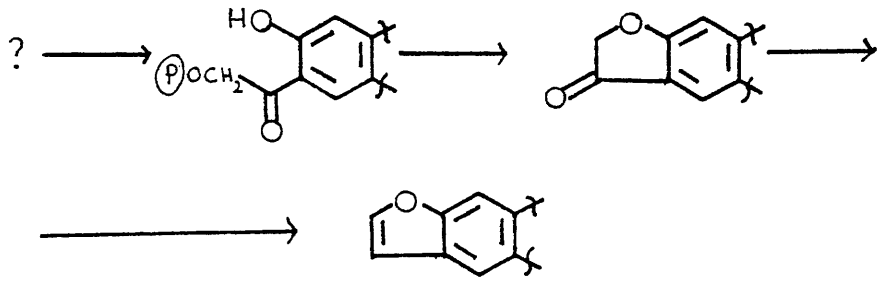


(88) (98) (99)

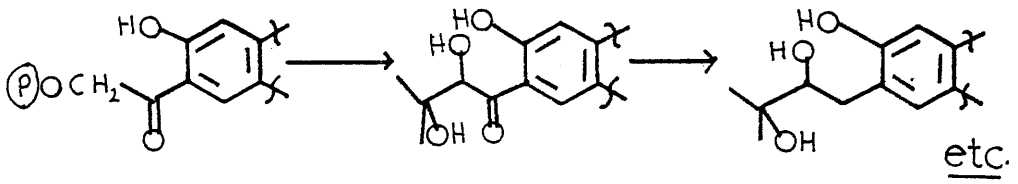
Scheme 9



Scheme 10



Scheme 11



etc.

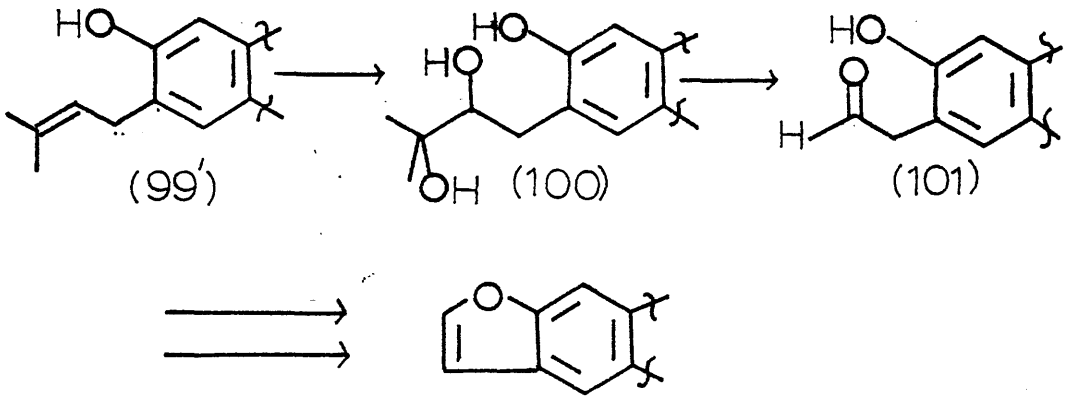
furanoid 5,7-dioxygenated compounds, consequently nothing is known about the position of hydroxylation on their biosynthetic pathway. However, 6,7-dihydroxycoumarin, aesculetin (97) has been studied[44] and this conforms to the above pattern, in that cis-caffeic acid has been shown to be a precursor (Scheme 8).

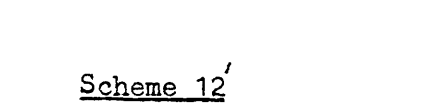
The biogenesis of the furanocoumarins has long been the subject of strenuous investigation. As has already been stated two categories of furanocoumarins exist, linear, psoralen (88) being the parent of these compounds and angular, with angelican (98) the parent furanocoumarin.

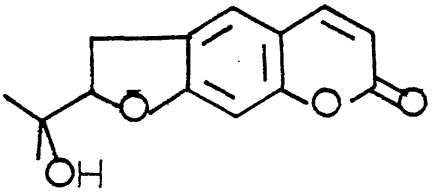
In 1937 Späth[45] suggested that all the carbon atoms of the furan ring were derived from an isopentane unit as illustrated in (99). In the same year Howarth[46] pointed out that furanocoumarins were theoretically derivable by elimination of propane from a 2-isopropyldihydrofuran (Scheme 9).

Geissman and Hinrainer proposed[47] in 1952 that unsubstituted furan rings could be formed from a two-carbon phosphorylated keto-alcohol precursor (Scheme 10). They gave no suggestions however, as to the means of attachment of this group to the aromatic ring. The authors did point out though, that it might be condensed with acetone, providing a system with potential for developing into many of the common modifications of an isopentenyl group (Scheme 11). This theory was extended to include hydrolysis of the phosphorylated hydroxyl and subsequent cyclis-

Scheme 12

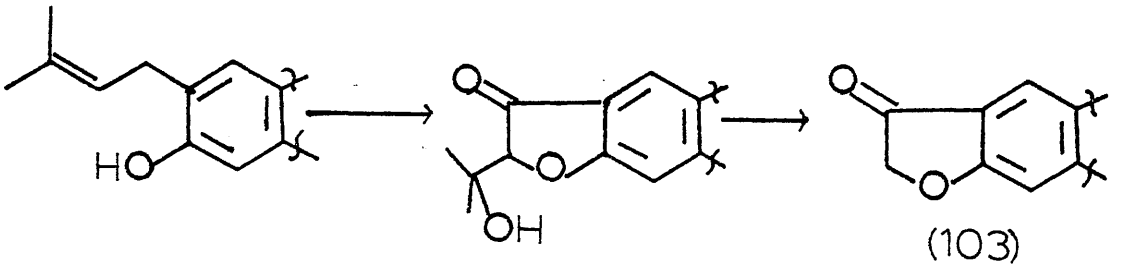


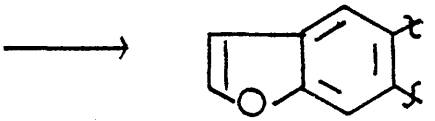




(102)

Scheme 12′



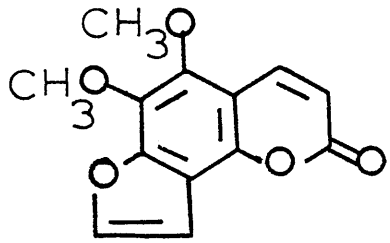


ation of the resultant glycol with an adjacent phenolic hydroxyl to account for the formation of hydroxyisopropyldihydrofurans and α,α-dimethylpyran moieties. The cleavage of the former as a possible route to unsubstituted furans was not considered.

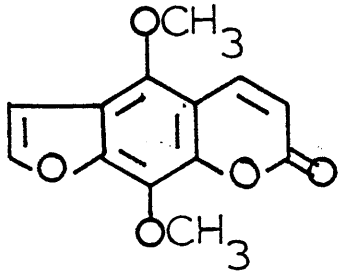
Two independant proposals were put forward in the late 1950's to the effect that a C-5 unit was the starting point for furan formation. Seshadri[48] postulated the removal of a three carbon unit prior to formation of the five membered ring. Scheme 12 illustrates his hypothesis. Oxidation of an ortho-isoprenylphenol of type (99'), possibly via an epoxide would lead to a glycol (100), which on oxidative cleavage to the aldehyde (101) followed by cyclisation and dehydration would generate a furan. Seshadri also noted that cyclisation of an oxygenated C-5 unit with an ortho phenolic hydroxyl, might give rise to an hydroxyisopropyldihydrofuran (102). In common with Geissman and Hinrainer however, he did not consider the possibility that the furanocoumarins could be derived by further elaboration of (102).

The second proposal, that of Birch and Smith[49], differed from that of Seshadri fundamentally, in that loss of the three carbon fragment was postulated to occur after cyclisation, the ketone (103) being a key intermediate (Scheme 12').

Despite all this early speculation it was not until the mid-sixties that any concrete evidence as to the biogenesis of furano-coumarins began to emerge.

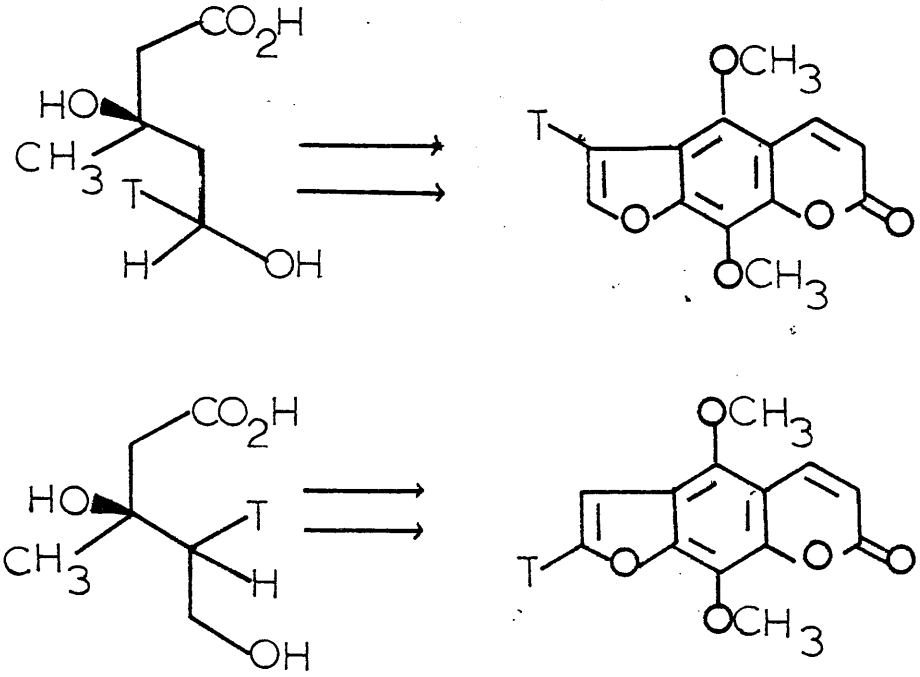


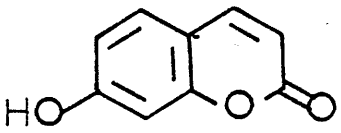
(104)



(105)

Scheme 13

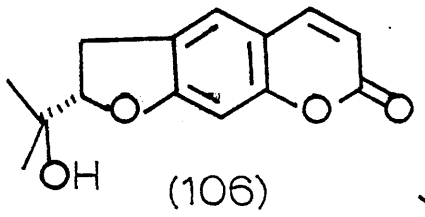




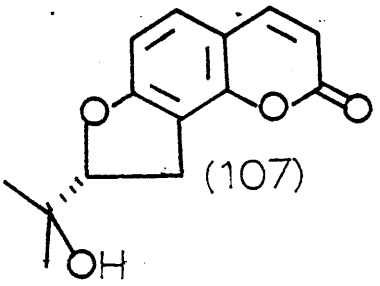
(5)

The first studies on the origin of furanocoumarins were carried out by Floss and Mothes[40] who established that umbelliferone (5) was a precursor of the furanocoumarins in Pimpinella magna. The precursor role of umbelliferone has since been established in a number of other plant species[50,51]. By a series of feeding experiments[52] they also established mevalonic acid as the source of the two carbon atoms of the furan ring in pimpinellin (104). It was thought that the furan ring was likely to be formed by prenylation at C-8 of a phenolic precursor followed by cyclisation and a loss of a three carbon unit. Extensive work by Kutneys' group[53] has firmly established the role of mevanolate in the elaboration of furanocoumarins. In separate experiments they fed 4-[^{3}H]-mevalonic acid and 5-[^{3}H] - mevalonic acid to tissue cultures of Thamnosma montana and after isolation of isopimpinellin (105), examined the distribution of the tritium label in this material. Their results which are shown in Scheme 13, clearly indicate that the C-2 and C-3 carbon atoms of the furan ring are derived from C-4 and C-5 of mevalonic acid respectively, in agreement with the results of Floss and Mothes.

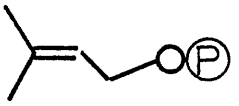
The results of Steck and Brown[54] in 1969, gave some of the first indications regarding the route from umbelliferone (5) to the furanocoumarins. They were able to show that labelled umbelliferone (5) when fed to the roots of Ruta graveolens (as the free phenol) and to Heracleum lanatium (as the glucoside),



(106)

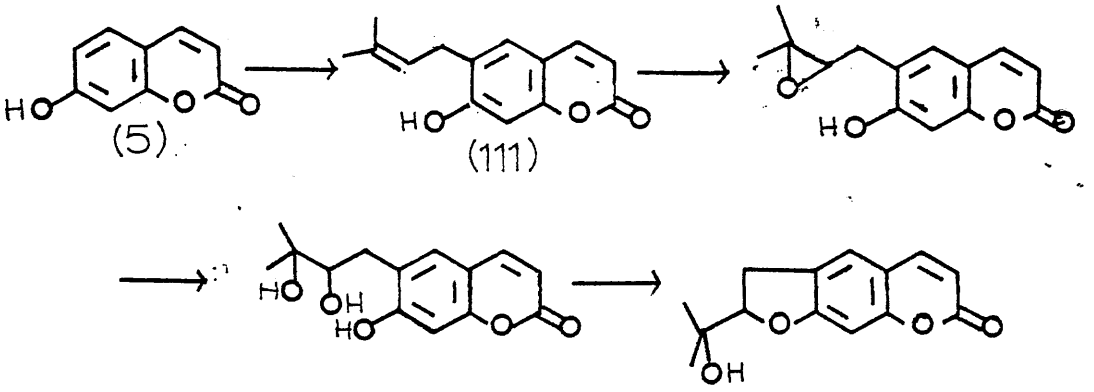


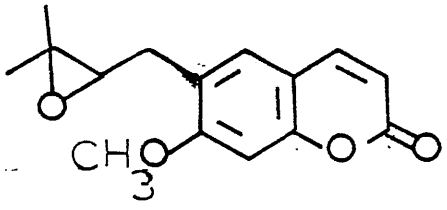
(107)



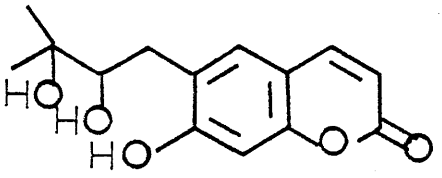
(108)

Scheme 14

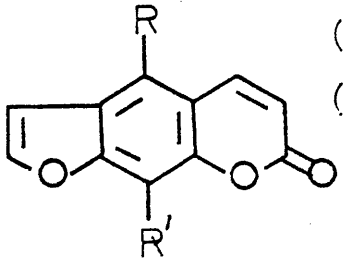




(109)



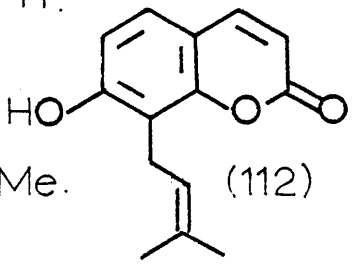
(110)



(15) R=OMe, R'=H.

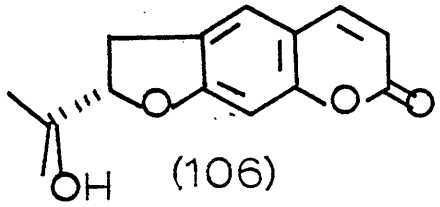
(88) R=R'=H.

(90) R=H, R'=OMe.

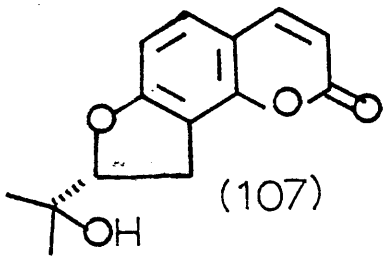


(112)

was incorporated into the dihydrofuranocoumarins marmesin (106) and columbianetin (107) respectively. On the basis of these results they proposed the pathway shown in Scheme 14 for umbelliferone (5) to marmesin (106), with an analogous scheme for columbianetin (107) biosynthesis. The direct introduction of a C-prenyl unit ortho to a phenol is believed to be a quite general method by which Nature introduces this group. Dimethylallyl pyrophosphate(108) is believed to be the alkylating agent and Brown[55] has recently isolated from Ruta graveolens the enzyme responsible for this transformation, umbelliferone-dimethylallyl-pyrophosphate-dimethylallyltransferase. It will be noted that compounds analogous to the epoxide (e.g. (109)) and the diol (e.g. (110)) intermediates postulated in Scheme 14 are known in Nature. Direct feeding[54] of tritiated marmesin (106) to the two plant species mentioned above, showed its incorporation into the furanocoumarins psoralen (88), bergapten (15) and xanthotoxin (90). Steck and Brown[56] have also shown that (+)-marmesin (106) is utilised for furanocoumarin biosynthesis, whilst its antipode is not. Columbianetin (107) was similarly shown to be incorporated[54] into a number of angular furanocoumarins. Steck and Brown[57] later showed conclusively that 7-demethylsuberosin (111) and osthenol (112) are precursors of the linear and angular furanocoumarins respectively, in a number of species.

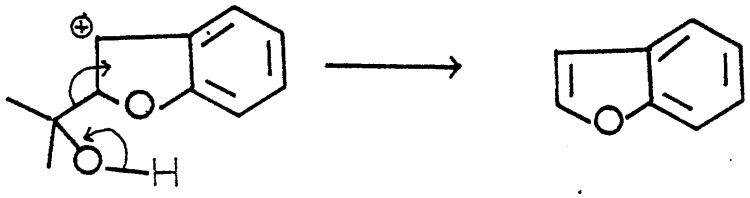


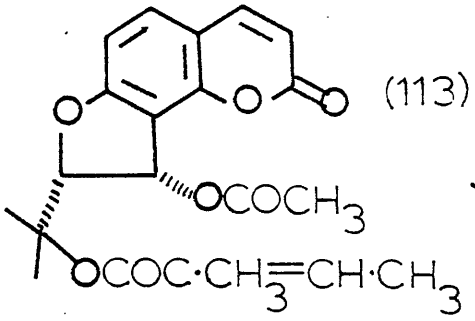
(106)



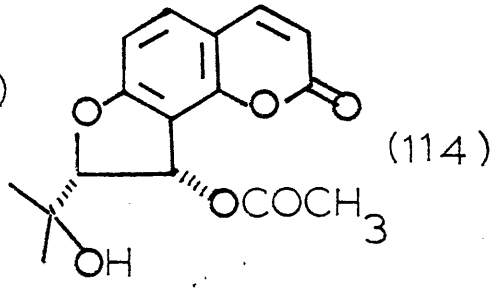
(107)

Scheme 15

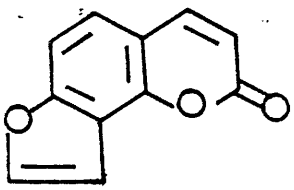




(113)



(114)



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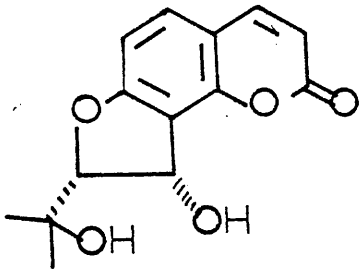
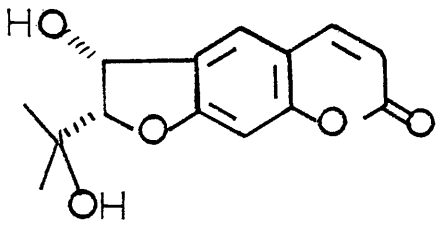


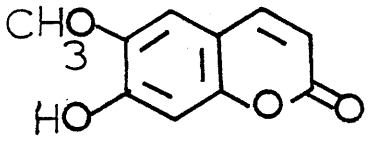
(115)



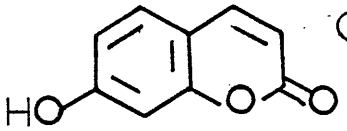
(116)

Birch, also in 1969, published a paper[58] which suggested an alternative to his earlier proposal (vide supra) for benzofuran formation which has relevance to the route from marmesin (106) and columbianetin (107) to the furanocoumarins. He pointed out that cleavage of an hydroxyisopropyldihydrofuran with concomitant loss of acetone (Scheme 15) required only a benzylic carbonium ion, however generated. Chemical evidence in support of this has been cited in a number of instances. It is known[58] that libanotin (113) on treatment with methanolic sodium hydroxide give angelican (98) and Seshadri[59] has found vaginidin (114) also furnishes angelicin (98) on alkali treatment.

Steck and Brown[60] have postulated the diol (115) as a probable intermediate on the pathway from columbianetin (107) to angelican (98) as it fits in well with the Birch hypothesis for benzofuran biogenesis. This diol, known as vaginidiol has since been isolated from Selinium vaginatum[61], though a number of its esters were known at the time of Steck and Brown's proposal. The absolute stereochemistry of natural vaginidiol (115) has been shown[61] to be 2'(S), 3'(R) and all its many known natural esters have this configuration. To account for this Steck proposed[60] that columbianetin (107) underwent a stereospecific hydroxylation at C-3 , followed by esterification as the probable biosynthesis of these compounds. The analogous diol (116) was also proposed to occupy a similar role in the biogenesis of the linear furanocoumarins. This diol has been isolated[62] in



(117)



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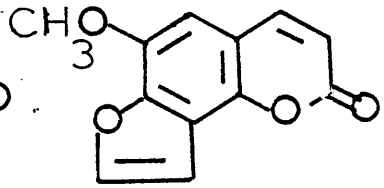
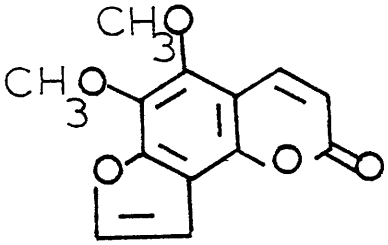


(118)



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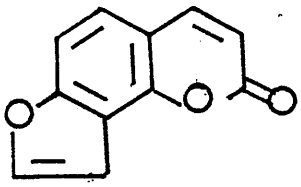

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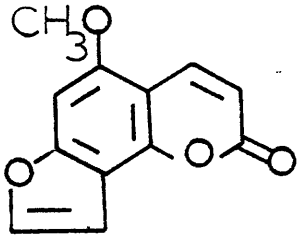
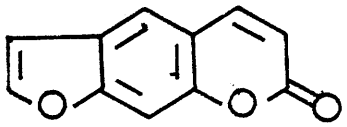


(57)

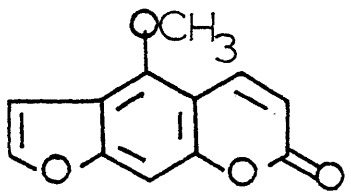


(88)

racemic form and a number of its esters are also known. It is not known, however, whether vaginidiol (115) or its linear analogue (116) are in fact intermediates on the biosynthetic pathways to the furanocoumarins.

Despite the fact that a number of hypotheses have been put forward to explain the conversions of marmesin (106) and columbianetin (107) to their respective furanocoumarins, little is really understood about the underlying mechanisms. Only negative mechanistic evidence is available. Kutney et al.[53] have deduced from experiments with specifically labelled mevalonic acid that furan formation cannot occur via any mechanism that involves loss of all the protons from either of the 2' or 3' positions of these intermediates. The proposals of Birch[58], i.e. that the three carbon fragment is lost, perhaps as acetone and the furan double bond is introduced in a concerted reaction involving a 1,3-cleavage are the most favoured however.

Much more information is available as to the position of further hydroxylation in the furanocoumarin biosynthetic pathway. In 1969 Floss deduced[63] on the basis that scopoletin (117) was a much poorer precursor than umbelliferone (5) of sphondin (118) and pimpinellin (104) that prenylation of umbelliferone (5) occurs before any further nuclear oxygenation. Indeed, it is known in a number of instances that further hydroxylation occurs after the furan ring has been formed. Brown[41] has shown that angelicin (98) is a precursor of isobergapten (57) and psoralen (88) is similarly



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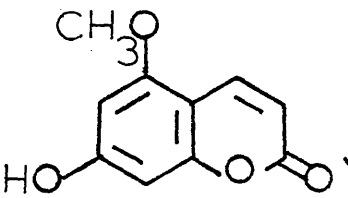
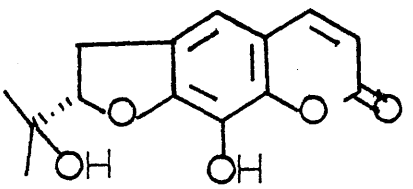
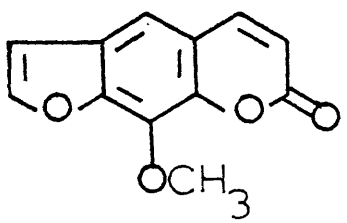


(119)



(120)



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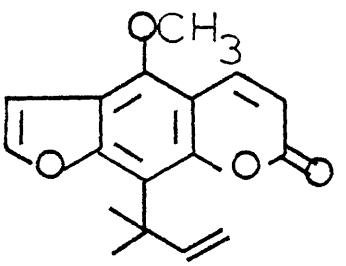
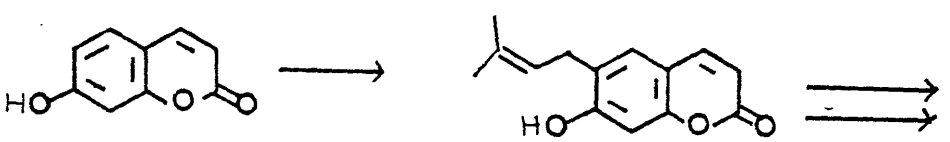
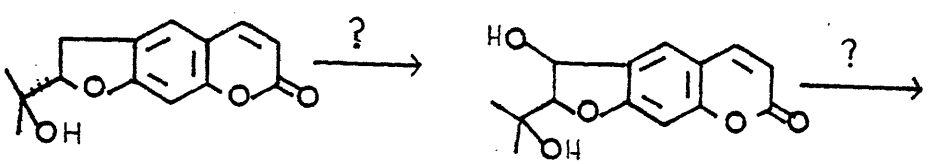
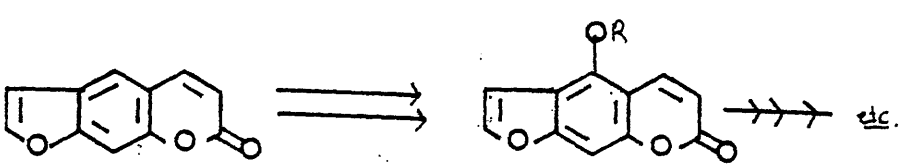


(62)

Scheme 16







a precursor of bergapten (15). In further confirmation of this Caporale[51] and his associates have shown that 5-methoxy-7-hydroxycoumarin (119) is not incorporated into bergapten (15) in Ruta graveolens. An exception to this general observation that hydroxylation occurs after cyclisation, is provided by the work of Caporale[64] and his associates who showed that 8-hydroxymarmesin (120) is elaborated to xanthotoxin (90) by Ruta graveolens. Presumably C-alkylation to yield such compounds as furopinnarin (62) proceeds at this late stage in the biogenesis also.

Scheme 16 summarises the biosynthetic pathways that lead from umbelliferone (5) to the furanocoumarins.

Introduction

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General Experimental and Abbreviations

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 Mrs. F. Lawrie and her staff. ^1H n.m.r. spectra were recorded on a Varian T-60 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 12 mass spectrometer. Ultra-violet spectra were recorded on a Unicam SP800 spectrophotometer. λ_{max} (base) refers to a solution to which two drops of 5N sodium hydroxide had been added.

Kieselgel GF_{254} (Merck) or HF_{254} (Merck) was used for preparative t.l.c.; Kieselgel G (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 and/or spraying the plates with a solution of ceric ammonium sulphate and then heating to 150°. The ceric ammonium sulphate solution was prepared by dissolving ceric ammonium nitrate (5g) in concentrated sulphuric acid (50ml) and making the volume up to 500 ml with water.

Petrol refers to the fraction of light petroleum b.p. 60-80°. All solutions, unless otherwise stated, were dried over anhydrous magnesium sulphate or anhydrous sodium sulphate.

The solvents used for chromatography are expressed in a volume ratio, e.g. $CHCl_3$/MeOH 2:1. The number of elutions required for separation by preparative t.l.c. are indicated with the solvent system. The compounds isolated from preparative t.l.c. of a mixture are given in order of decreasing mobility.

During the course of this research, crude reaction mixtures were often worked up by one of two methods. These have been referred to in the Experimental Sections as Work-up I and Work-up II.

Work-up I

O-Alkylation of a hydroxycoumarin was achieved by refluxing an acetone solution of the coumarin with the alkylating agent, in the presence of potassium carbonate. 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 5% w./v. aqueous potassium carbonate solution, to remove any starting material. Subsequent washing with brine, drying and evaporation of the solvent gave a residue which was treated as specified in each preparation.

Work-up II

This was employed for any reaction mixture containing pyridine. The reaction mixture was poured into a large

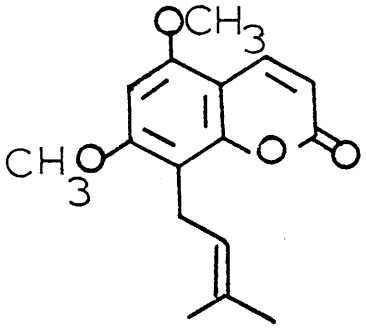
excess of iced water. The solution was then extracted with ethyl acetate and washed with a saturated copper sulphate solution, to remove the pyridine. The resultant solution was then washed with brine, dried and evaporated to give a residue which was treated as specified in each preparation.

The following abbreviations 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
sh.	shoulder
n.m.r.	nuclear magnetic resonance
t.l.c.	thin layer chromatography
w./v.	e.g. 5% w./v.; this refers to a solution of 5g. in 100ml of solvent.
*	e.g. 6.31*; this refers to a signal in an n.m.r. spectrum which disappears on addition of D_2O to the solution.
hr.	hour
Hz.	Hertz.

Part 1

Synthetic Studies on the 5,7-Dioxygenated Furanocoumarins



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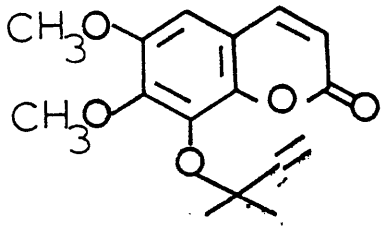

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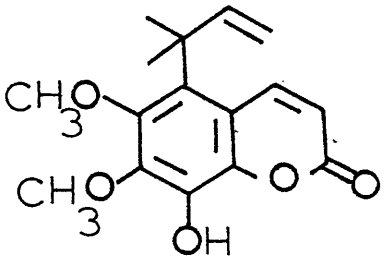

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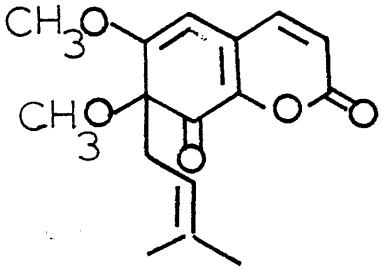

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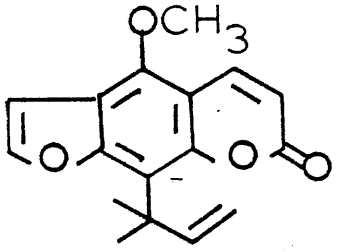

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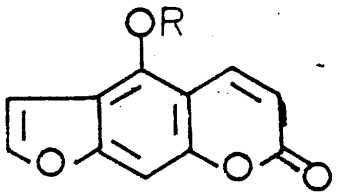


(6) R = H

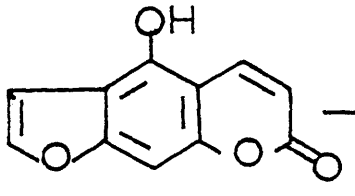
(7) R = Geranyl

The utility of the Claisen rearrangement in the synthesis of coumarins has already been alluded to. The pyrolysis of 1,1-dimethylallyl aryl ethers possessing a vacant ortho position has been shown to be a convenient method for the introduction of a prenyl moeity ortho to a phenol, as illustrated by the synthesis of coumurrayin[1](1) (vide supra). Although para-Claisen rearrangements of 3,3-dimethylallyl aryl ethers are well known[2], there was, when this work was initiated, no report of the successful para-Claisen rearrangement of an aryl 1,1-dimethylallyl ether. Indeed, the ether (2), which having both ortho positions blocked in the aryl moeity and the para position vacant, was expected to rearrange to (3), remarkably underwent rearrangement[3] solely to the ortho position furnishing the stable ortho-dienone (4). Suprisingly, no trace of the anticipated para-rearrangement product (3) could be detected, even on prolonged pyrolysis of (2). It is indeed unusual for an ortho-dienone to be the stable product of a Claisen rearrangement, especially when para-rearrangement and rearomatisation are possible[4].

Furopinnarin(5) was isolated[5] in 1970 from Ruta pinnata and the structure assigned largely on spectroscopic grounds. The synthetic route illustrated in Scheme 1 provided a method for further investigating the para-Claisen rearrangement of a 1,1-dimethylallyl aryl ether, as well as constituting a total synthesis of furopinnarin and thus a structure proof.

The starting material for this proposed synthesis, bergaptol (6), was readily available from the acid catalysed hydrolysis of bergammotin

Scheme 1



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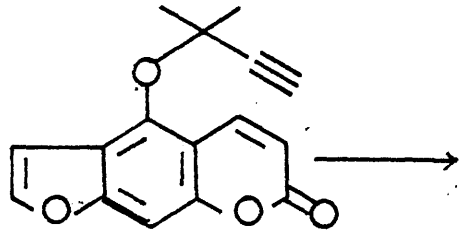

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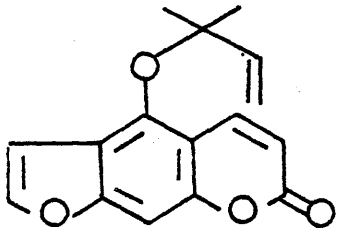

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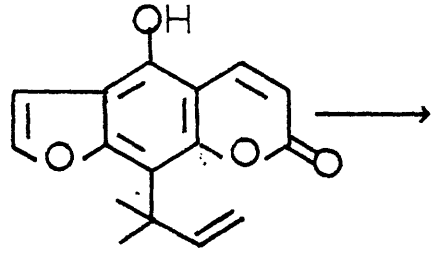

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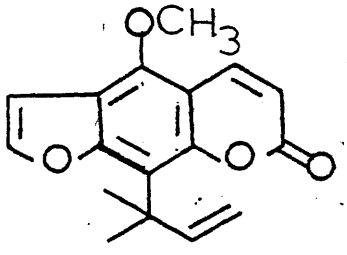

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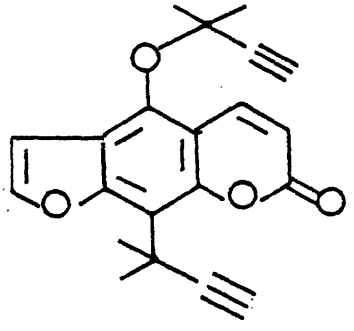

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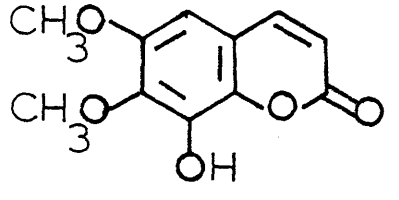
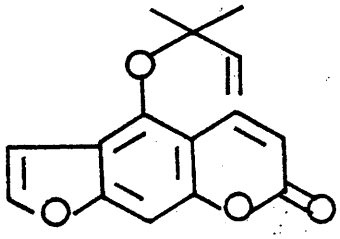


(11)

(7), a major component of the ether soluble portion of commercial bergamot oil[6]. Bergaptol (6), as described in the introduction, has itself been synthesised[7], though as this synthesis was a poor one, the natural material is much more readily accessible.

The 1,1-dimethylallyl ether (8) of bergaptol was prepared by the well established technique[1] of semi-hydrogenation of the corresponding 1,1-dimethylpropargyl ether (9). Etherification of bergaptol (6) with 3-chloro-3-methylbut-1-yne, gave two products, the required propargyl ether (9; 30%) and the C,O-bisalkylated analogue (10; 9%), though unreacted starting material remained even after prolonged reaction. The formation of a C,O-bisalkylated by-product has also been observed in the reaction[3] of tomentin (11) under similar circumstances. In neither instance could any C-monoalkylated products be detected. It would appear that if C-monoalkylation occurs, consequent O-alkylation becomes a very rapid process indeed, i.e. C-alkylated phenols are much more reactive than the parent compounds. Semi-hydrogenation of (9) proceeded cleanly over 5% palladium on barium sulphate to yield (8; 95%) though traces of hydrogenolysis and over-reduction were observed. These side-reactions can generally be eliminated by judicious poisoning of the catalyst. However, in this instance, the use of even tiny amounts of sulphur-quinoline poison[3] stopped all reaction.

Pyrolysis of the 1,1-dimethylallyl ether (8) at 120° did indeed result in the anticipated <u>para</u>-Claisen rearrangement affording demethylfuropinnarin (12) in 56% yield, as well as some cleavage to bergaptol (6). This rearranged product was readily characterised by its spectral



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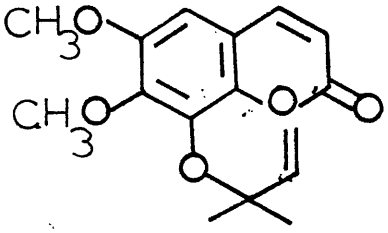

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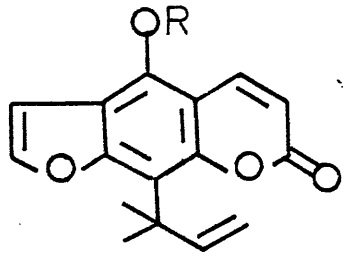


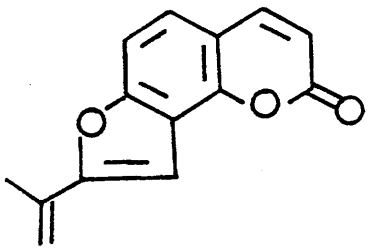
(5) R = H

(12) R = CH_3

properties. It was isomeric with the starting material, phenolic (u.v. base shift) and differed only in its n.m.r. spectrum in that the sole benzenoid proton in (8) was absent and a C-1,1-dimethylallyl group was present. This unequivocally indicated that a para-rearrangement had occurred. This constitutes the first example of a successful para-Claisen rearrangement of a 1,1-dimethylallyl aryl ether. No evidence for the formation of an ortho-dienone could be obtained. It is not clear why the 1,1-dimethylallyl ether (8) should undergo the para-Claisen rearrangement, while the structurally closely related coumarin (2) behaved in such an anomalous manner. Demethylfuropinnarin (12) has since been reported[8] as a constituent of Peucedanum stenocarpum and the spectral properties of the synthetic material were in complete agreement with those reported for the natural compound.

The phenol (12) on treatment with ethereal diazomethane afforded the corresponding methyl ether (5), the spectral properties of which were in complete accord with those of natural furopinnarin.

The work in this section of the thesis has been described in a recent publication[9].



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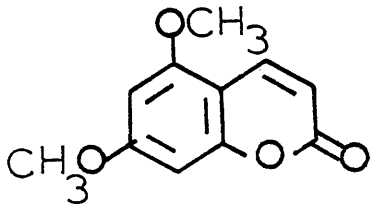

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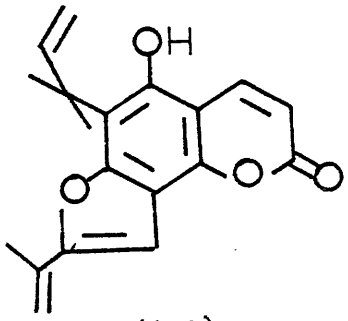

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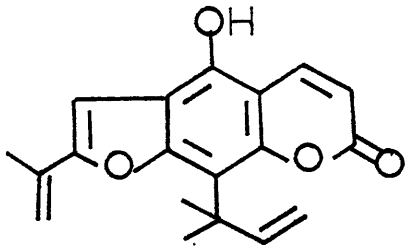

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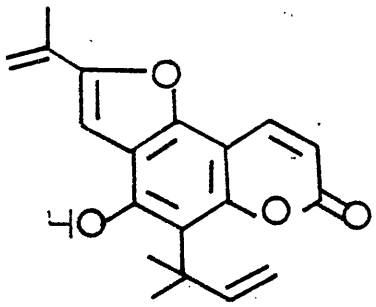
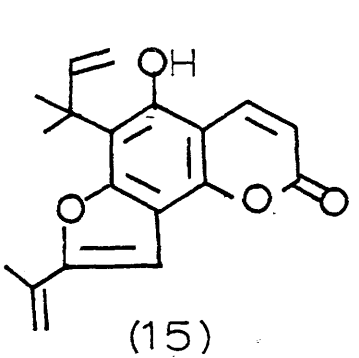


(17)

In 1976, Delle Monache *et al.* isolated[10] from the roots of *Hortia arborea* a new coumarin which they named hortiolone. The formula $C_{19}H_{18}O_4$ was attributed to this compound on the basis of analytical and mass spectral data. The presence of a phenolic hydroxyl group was deduced by the formation of a monoacetyl derivative. The gross structural features were readily determined from the proton n.m.r spectrum. The characteristic pair of doublets (J=10Hz) of the coumarin ring appeared at δ6.20 and 8.04. A 1,1-dimethylallyl side chain was deduced from the presence of a six proton singlet at δ1.75 and an ABX system with the AB part centred at 5.08 and the X at 6.45. The remaining features of the spectrum were a one proton singlet at δ7.25, a three proton singlet at 2.15 showing fine structure coupling, attributed to a methyl group on an olefinic linkage and a pair of broad singlets at δ5.30 and 5.73, which they assigned to the protons of a *gem*-disubstituted alkene. They inferred from these features that a 2-isopropenylfuran ring was present in the molecule. These spectral properties are very similar to those of the known[11] 2'-isopropenyl-furan, oroselone (13). Catalytic hydrogenation of hortiolone afforded a tetrahydro derivative, the u.v. spectra of which, both in ethanol and in 0.1N sodium hydroxide, were closely similar to those of 5,7-dimethoxycoumarin (14). This suggested a similar oxygenation pattern. The above data was consistent with three possible structures for hortiolone (15), (16) and (17).

In the following year, the same authors published a paper[12] in which they described how the actual structure of hortiolone was



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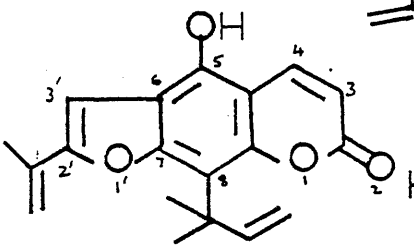

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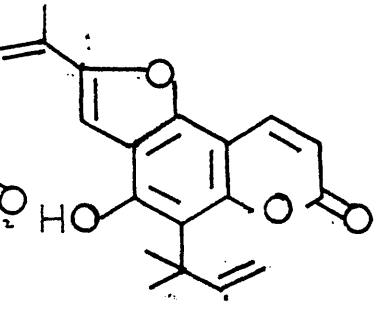
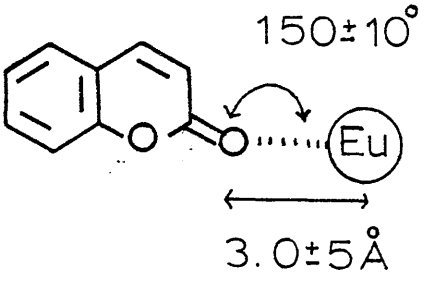


(17)

Table 1

Compound	Chemical Shift (δ)	
	H-3'	H-4
Hortiolone	7.25	8.40
Acetyl hortiolone	6.40	7.73

Figure 1



established. They firstly compared the n.m.r. spectrum of hortiolone and its monoacetate. If structure (15) was that of hortiolone, they argued, acetylation would cause a diamagnetic shift of H-4 in the n.m.r. spectrum. For structure (16) a diamagnetic shift of both H-4 and H-3' would be observed and for structure (17) a diamagnetic shift of H-3' only. The marked diamagnetic shift observed of both H-4 and H-3' in the acetyl derivative is consistent with structure (16) for hortiolone (Table 1).

By utilisation of a lanthanide shift reagent further confirmation of the structure of hortiolone (16) was obtained. Gray, Waigh and Waterman have described[13,14] a simple technique whereby shift reagents may be used for the structural elucidation of coumarins. Normally the use of lanthanide shift reagents to differentiate structural isomers requires the three dimensional location of the lanthanide atom in the complex, a procedure usually necessitating the use of a computer to achieve a "best fit" with observed results. However by regarding the coumarin ring as planar and assuming coplanarity with the lanthanide atom in the coumarin-shift reagent complex, the problem may be reduced to one of two dimensions. Gray et al. have shown that $Eu(fod)_3$ complexes with the carbonyl oxygen atom of simple coumarins in such a way that all the proton shifts could be related to a fixed position of the europium atom in the plane of the ring (Figure 1). The H-3 proton is shifted most, and the shifts of the the other protons are most conveniently expressed relative to shift (3H)=1. The relative shifts may be calculated by

Equation 1

$$\Delta\nu = \frac{3\cos^2\theta - 1}{R^3} \times \text{constant}$$

θ = O ····· Eu ····· H bond angle

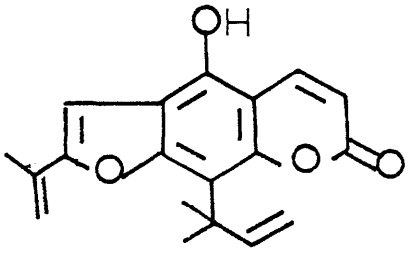
R = H ····· Eu distance

$\Delta\nu$ = relative shift

Table 2

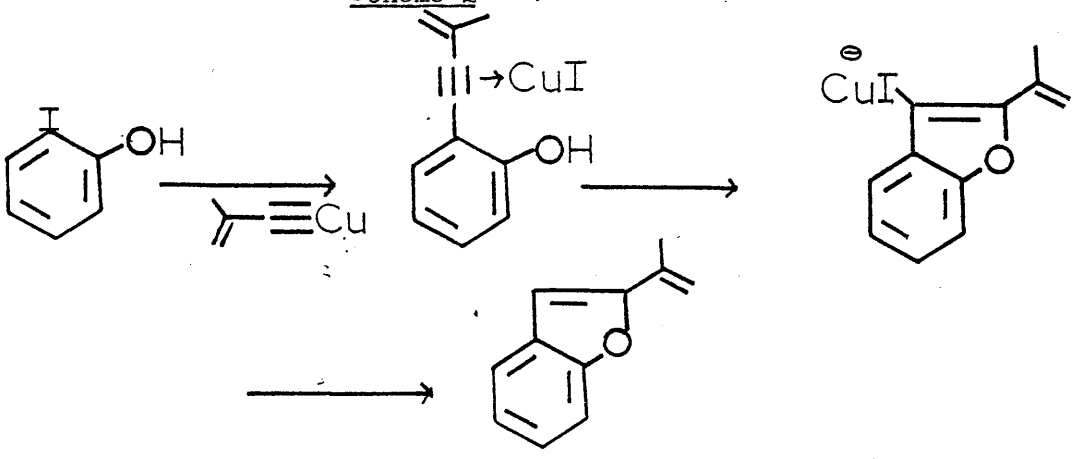
$Pr(fod)_3$ Induced Chemical Shifts

	H-4	OCH_3	$>C(CH_3)_2$
Methyl hortiolone	0.3	0.13	0.26



(16)

Scheme 2

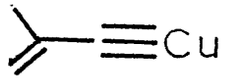


using the McConnell-Robertson equation[16] (Equation 1). Gray et al. have observed that in general the $Eu(fod)_3$-induced shifts could be expressed by the series 3>>4 =8>5=7>6, where the numbers represent the position of substituents in the coumarin skeleton. Delle Monache et al. considered the induced shifts of the methyl ether of hortiolone and observed that the gem-dimethyl of the isopropenyl group suffered a large shift relative to the methoxyl (Table 2), which is commensurate with structure (16) for hortiolone. Chemical evidence provided further confirmation of this structure, in that unmodified hortiolone could be recovered after mild acid treatment.

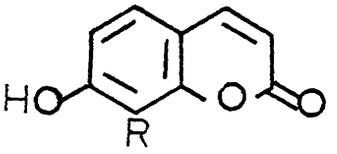
A total synthesis of hortiolone was thus initiated as a further structure proof.

The paucity of 2'-isopropenylfurans amongst the coumarins and, indeed, in the field of natural products in general, has meant that little synthetic attention has been directed toward them. Consequently, the development of an efficient synthetic approach to this functionality was of considerable interest.

The coupling of cuprous acetylides and aryl halides possessing an ortho hydroxyl group is known[17] to give a furan as sole product. By utilisation of this method, a simple one step synthesis of 2-isopropenylfurans was considered a distinct possibility (Scheme 2). To test this hypothesis the coupling of the cuprous acetylide (18) with 7-hydroxy-8-iodocoumarin was investigated. 7-Hydroxy-8-iodocoumarin (19) was prepared[18] in 90% yield by the regiospecific iodination of umbelliferone (20), using one equivalent of iodine/

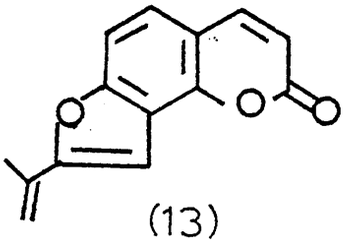


(18)



(19) R = I

(20) R = H



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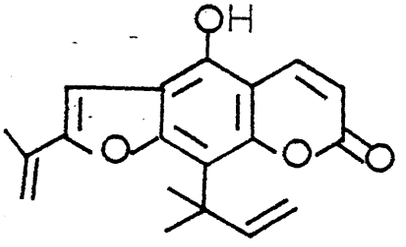

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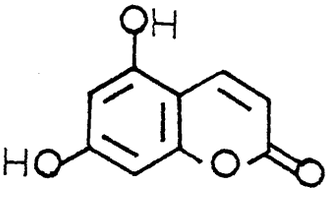


(21)

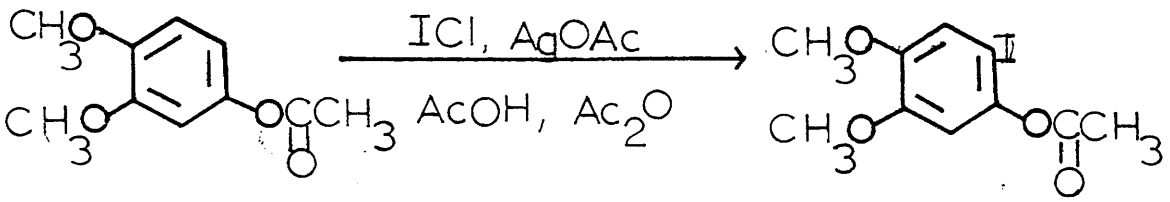
potassium iodide in 20% aqueous ammonia. That iodination had taken place exclusively at C-8 was indicated by the n.m.r. spectrum of the product, which showed the presence of two ortho aromatic protons (δ6.75 and 7.31 each 1H, d, J=8Hz).

Treatment of 7-hydroxy-8-iodocoumarin (19) with the cuprous acetylide (18) for two hours at 100° in pyridine under an inert atmosphere resulted in a smooth and clean coupling to produce the 2'-isopropenylfuran (13) in around 80% yield. This compound, oroselone, had been previosly isolated[11] from Peucedanum oroselone and the spectral properties of the synthetic material were in good agreement with those reported for the natural. Shortly after this work had been completed, Schreiber and Stevenson[19] published a similar synthesis of oroselone, though the conditions they employed for the coupling reaction were slightly different.

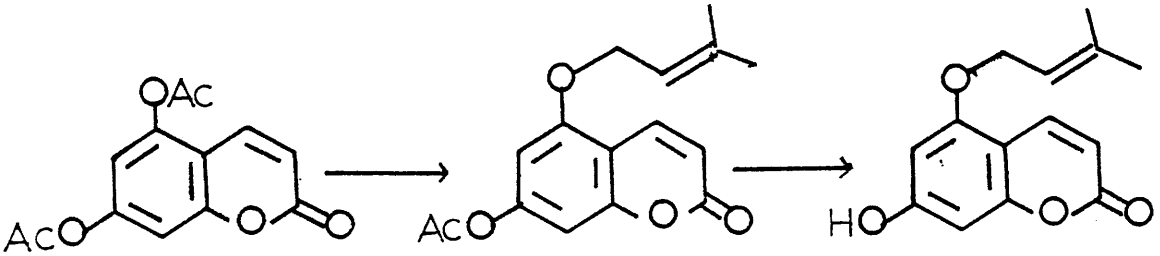
With the feasibility of the formation of the 2-isopropenylfuran moiety by this method established, attention was now directed toward the synthesis of an aryl iodide precursor suitable for elaboration into hortiolone (16). The starting material for this synthesis was 5,7-hydroxycoumarin (21) which was readily prepared[20] by the condensation of phloroglucinol with ethyl propiolate in the presence of zinc chloride.

All attempts to directly iodinate 5,7-dihydroxycoumarin selectively met with failure. Treatment of (21) with iodine/mercuric oxide[21] under a variety of conditions always produced mixtures. Unchanged starting material only, could be isolated when 5,7-diacetoxycoumarin

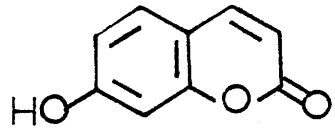
Scheme 3



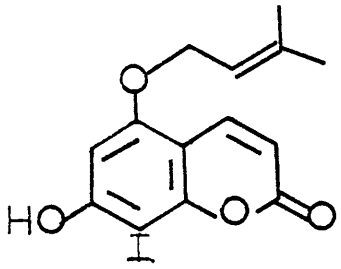
Scheme 4



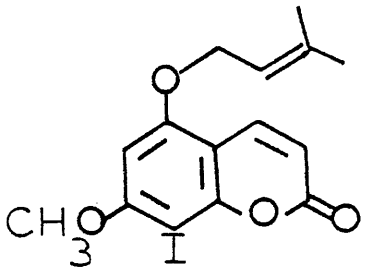
(22) (23) (24)



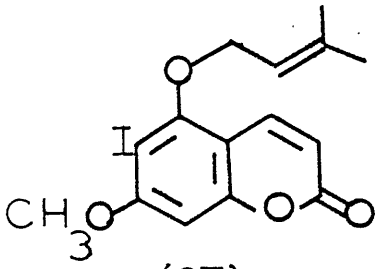
(20)



(25)



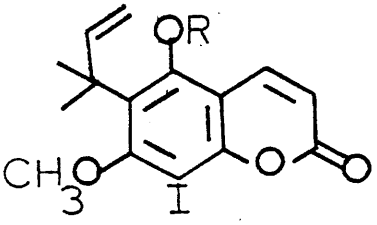
(26)



(27)

(22) was treated in this way. Schreiber and Stevenson[22] have recently reported conditions whereby phenolic acetates may be readily iodinated (Scheme 3). These involve treatment of the acetate with iodine monochloride and silver acetate in acetic acid. However, 5,7-diacetoxycoumarin (22) was stable to these conditions. It was thus considered that 5,7-dihydroxycoumarin (21) was too reactive to facilitate clean iodination, with a number of undesired reactions occurring, whilst 5,7-diacetoxycoumarin (22) was insufficiently reactive. Intermediate activity it was felt, might be exhibited by a 5-O-alkyl-7-hydroxycoumarin and a smooth iodination result. Mono-prenylation of 5,7-diacetoxycoumarin was readily achieved by refluxing[23] in glyme or acetone with 1.2 equivalents of 3,3-dimethylallyl bromide in the presence of potassium carbonate. 5-O-(3,3-Dimethylallyl)-7-hydroxycoumarin (24) was isolated in around 50-60% yield after the hydrolysis of the corresponding acetate (23) (Scheme 4).

By analogy with umbelliferone (20), 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (24) was anticipated to mono-iodinate selectively in the C-8 position to yield (25). On reaction with one equivalent of iodine and mercuric oxide in chloroform, (24) afforded cleanly one product. This compound analysed for $C_{14}H_{13}IO_4$ and showed only one aromatic singlet in its n.m.r. spectrum. At this stage, however, the position of iodination could not be assigned. A Claisen rearrangement of the corresponding methyl ether should, in principle, allow the two possible isomers (26) and (27) to be distinguished. If the iodine is at C-8 an ortho-Claisen rearrangement should result,



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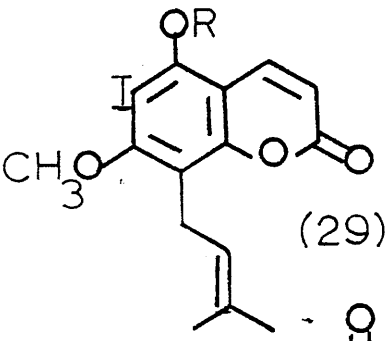
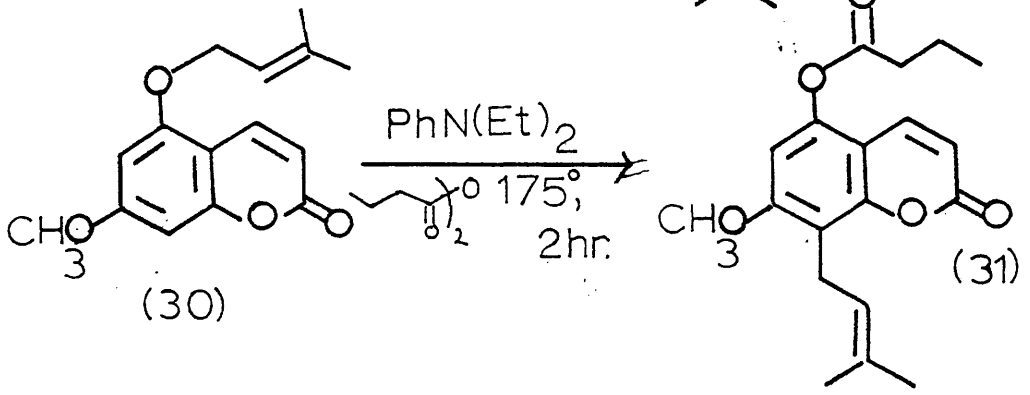


(29)

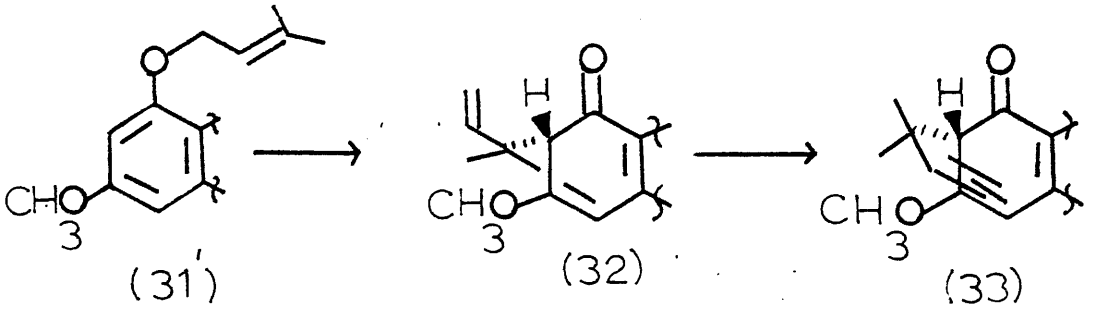
Scheme 5



(30)

(31)

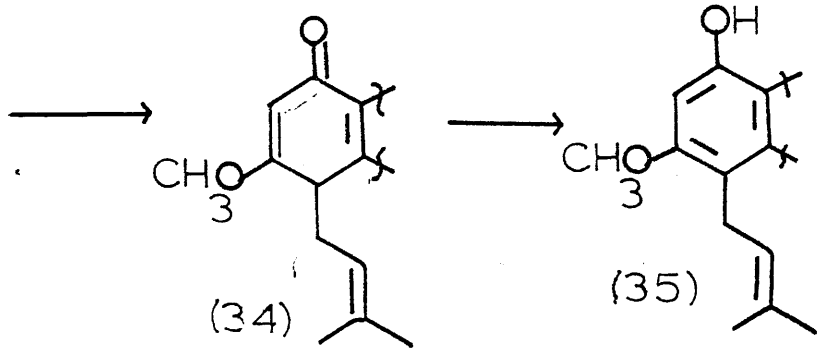
Scheme 6



(31′)

(32)

(33)

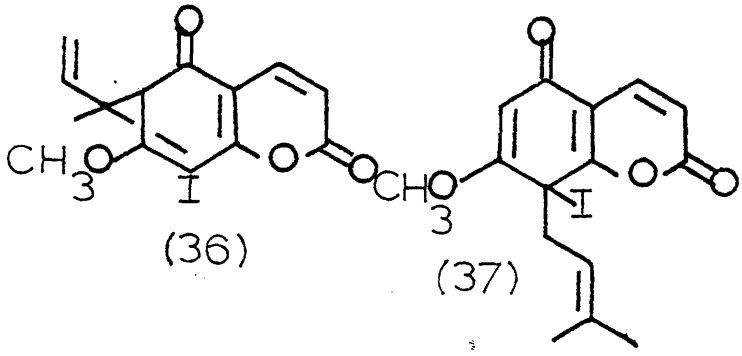


(34)

(35)

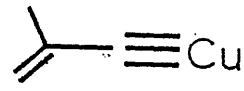
which will give rise to compound (28). In contrast, a para-rearrangement should be favoured in the instance of a C-6 iodine producing (29). (28) and (29) would be readily distinguishable on the basis of their n.m.r. spectra. 5-O-(3,3-dimethyallyl)-7-methoxycoumarin (30) is known[24] to readily undergo a para-rearrangement on pyrolysis at 175° to furnish (31) (Scheme 5). No ortho rearrangement is observed. Scheinmann[25] has suggested an explanation for this phenomena (Scheme 6). The "buttressing effect" of the gem-dimethyl group on the allyl side chain hinders enolisation to such an extent in the ortho-dienone intermediate that rearrangement to the para position becomes a competitive process. Thus, in Scheme 6, rearrangement of the prenyl ether (31) to the vacant ortho position gives the dienone (32) in which interaction of the dimethyl group with the neighbouring meta methoxyl hinders the formation of the pseudo-equatorial conformer (32). Free rotation of the side chain allows the formation of a conformer (33) which possesses the correct orientation for Cope rearrangement to the para position, to yield the thermodynamically more stable para-dienone (34) which enolises to the phenol (35).

The iodo-prenyl ether obtained above was recovered unchanged when pyrolysed under the same conditions which brought about the para-rearrangement of 5-O-(3,3-dimethylallyl)-7-methoxycoumarin (30). Increasing the temperature or the reaction time only brought about extensive decomposition. This evidence was interpretated as supporting the assumption that iodination had occurred at C-8. The ortho-dienone rearrangement product (36) would be disfavoured as



(36)

(37)



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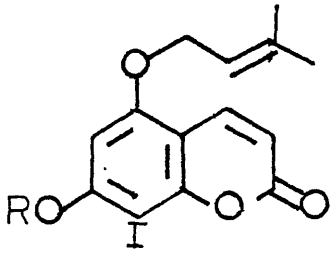
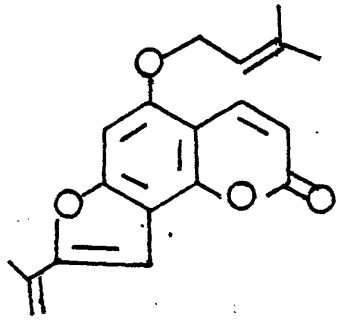


(25) R = H

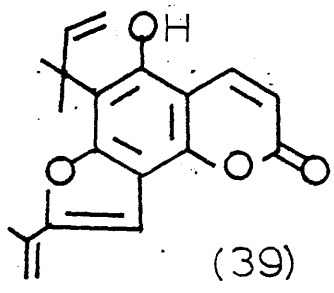
(26) R = CH_3



(38)

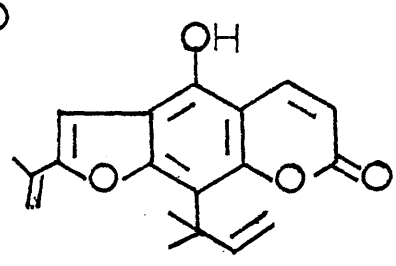
Scheme 7

(38) ⟶



(39)

⟶

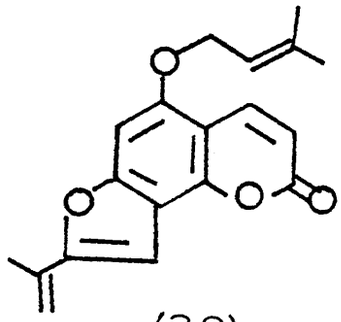


(16)

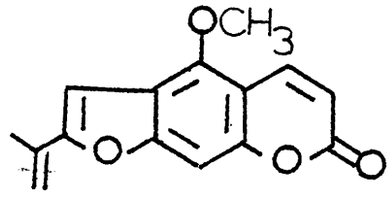
before, but the para product (37) could not, in this instance, readily aromatise. Thus the prenyl ether (26) may be thermodynamically more stable than either of the rearrangement products and consequently no rearranged product would be isolated. It was therefore assumed that iodination had taken place at C-8, an assumption which was to be later confirmed, by further experimental evidence.

5-O-(3,3-Dimethylallyl)-7-hydroxy-8-iodocoumarin (25) was readily elaborated into the corresponding 2'-isopropenylfuran (38) by reaction with the cuprous acetylide (18) in pyridine at 80°. The coupling was not as clean as in the case of 7-hydroxy-8-iodocoumarin (vide supra), but the desired product (38) could be isolated by chromatography in around 60% yield. This compound proved to be of only limited stability. If a pure sample of (38) were stored in a stoppered flask in the open laboratory, within ten days several new compounds were detectable on t.l.c., though present in only trace amounts. The n.m.r. spectrum of the material, at this stage, showed degradation principally of the resonances due to the olefinic protons of the isopropenyl moeity. Perhaps photochemical Diels Alder type processes were occurring here.

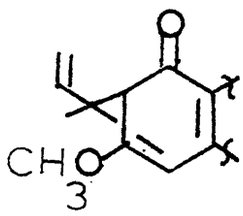
The synthetic strategy now envisaged for the elaboration of hortiolone (16), required firstly an ortho-Claisen rearrangement giving the phenol (39), followed by an isomerisation to produce the linear tricyclic system of hortiolone (Scheme 7). The availability of the key intermediate (38) also opened up a possible synthetic route to another 2'-isopropenylfuran hortionone (40), recently



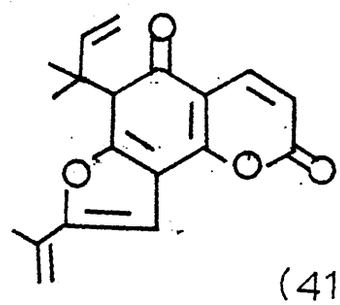
(38)



(40)



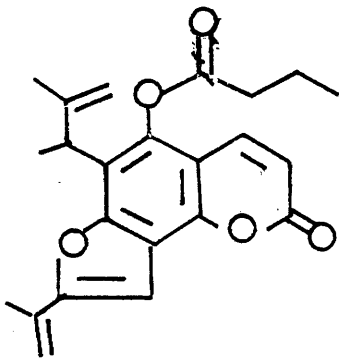
(33)



(41)

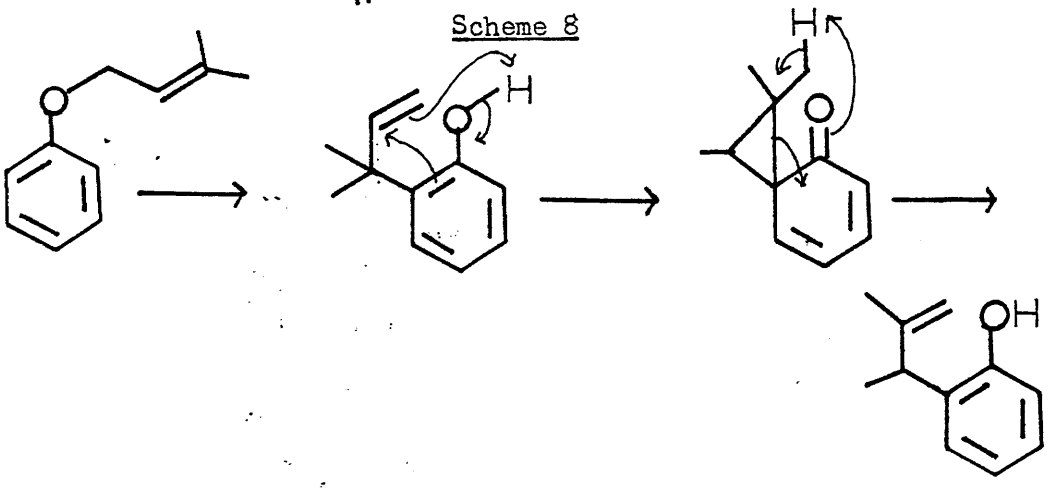
isolated[12] by Delle Monache and his collaborators. Deprenylation of (38), followed by isomerisation and methylation would yield hortionone (40).

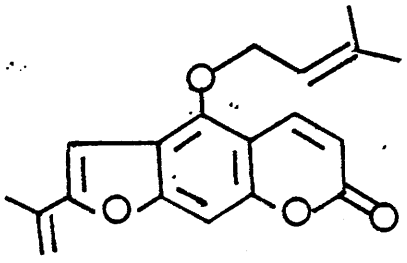
The steric interaction between the methoxyl group and the geminal methyl groups of 1,1-dimethylallyl moeity of ortho-dienones of type (33) has already been mentioned. In the case of the ortho-dienone (41) arising from Claisen rearrangement of the isopropenyl-furan (38), models show that the steric interaction should be considerably less, as the C-7 substituent is effectively "tied back" by its attachment at C-8. On this basis we predicted that the Claisen rearrangement of (38) would proceed even though (26) had been previously shown to be unreactive. Normally the Claisen rearrangement of 3,3-dimethylallyl ethers is brought about[24] by pyrolysis at 175$\pm$ 5° in N,N-diethylaniline containing butyric anhydride, which traps the phenol, as soon as it is formed, as its butyrate ester. This is intended to preclude any further reactions, such as the abnormal Claisen rearrangement, which are dependent upon a free phenolic hydroxyl. When the isopropenylfuran (38) was pyrolysed in this manner only one isolable compound resulted. Mass spectrum suggested a molecular weight of 380, which is consistent with a Claisen rearrangement having occurred. The n.m.r. spectrum clearly showed the presence of a butyrate ester, but the characteristic ABX system of the olefinic protons of a 1,1-dimethyl-allyl moiety were absent. However, a two proton multiplet at δ5.06 and a broad six proton singlet at 1.63 were attributed to a 1,2-dimethylallyl group. Thus, an abnormal Claisen rearrangement[4]



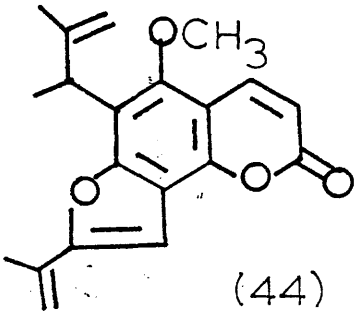
(42)

Scheme 8

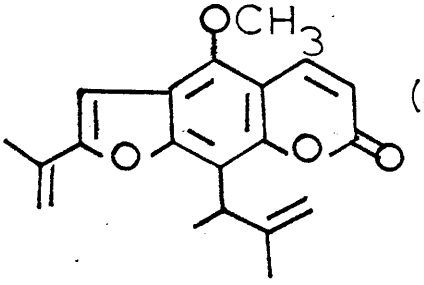




(43)



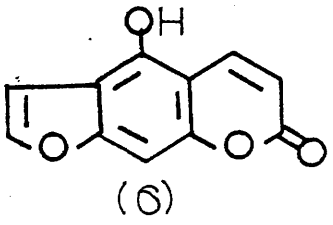
(44)



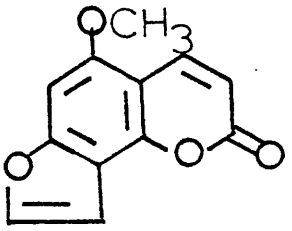
(45)

must have occurred, yielding (42) (Scheme 8), despite the presence of the trapping agent. The abnormal rearrangement must have been extremely rapid, for it could only have occurred before the trapping of the phenol. It is known[26], however, that the abnormal rearrangement of a 1,1-dimethylallyl phenol is often as fast, if not faster, than the rearrangement of the corresponding 3,3-dimethylallyl ether. That the 1,2-dimethylallyl group is thermodynamically more stable than the 1,1-dimethylallyl, in this system, is readily rationalised. Examination of models show that steric interaction between the side chain and the furan ring are appreciably less in the case of the 1,2-dimethylallyl group than in that of the 1,1-dimethylallyl moeity, thus favouring the former. The occurrence of this abnormal Claisen rearrangement confirmed the assignment of iodination of (24) at C-8. The abnormal rearrangement observed can only result where a 1,1-dimethylallyl group is ortho to a phenol (Scheme 8). If iodination had occurred at C-6 a linear furan system (43) would have been formed on coupling and consequently the Claisen rearrangement product would have contained a 3,3-dimethylallyl group para to a phenol.

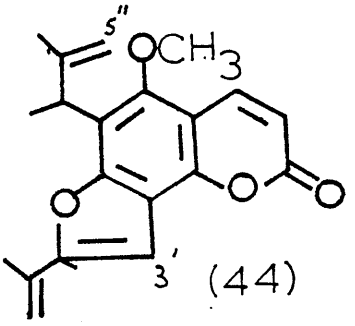
Hydrolysis of the butyrate (42) with 1% sodium hydroxide in methanol at reflux for 15 min., produced two isomeric compounds (which were isolated as their methyl ethers). On increasing the reaction time to 1hr. only one compound was produced (again isolated as a methyl ether). These compounds were shown to be the angular furan (44) and its linear analogue (45), the latter being formed exclusively from the longer hydrolysis. It is interesting to note that in the n.m.r. spectrum of the angular furans (42) and (44) the



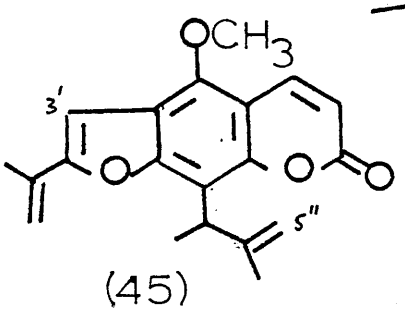
(6)



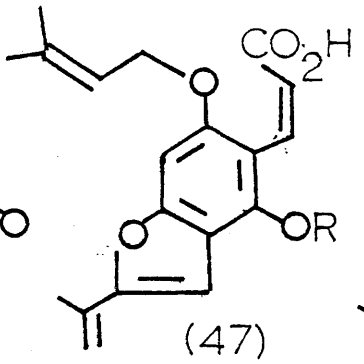
(46)



(44)



(45)



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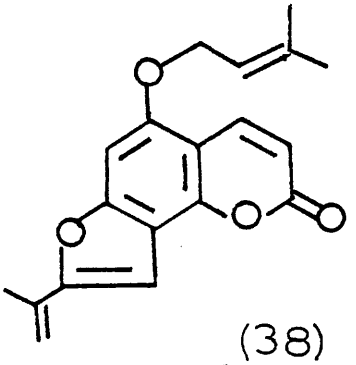
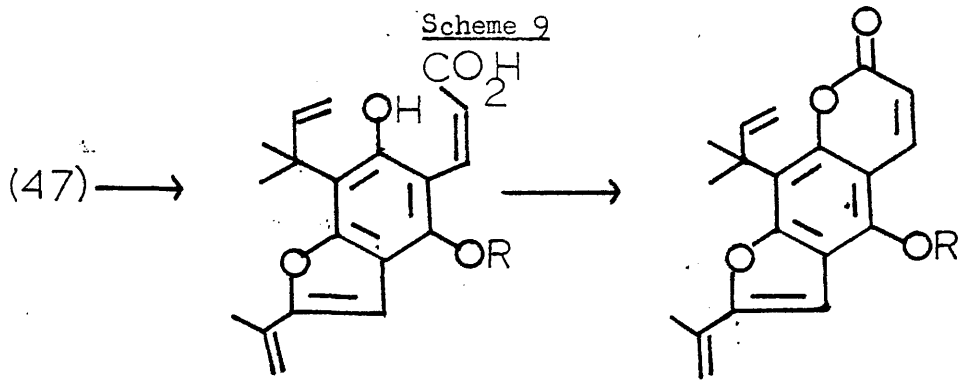


(38)

Table 3

Compound	$Eu(fod)_3$ Induced Shift (relative to H-3=1)	
	H-3'	H-5''
(44)	0.36	0.13
(45)	0.085	0.26

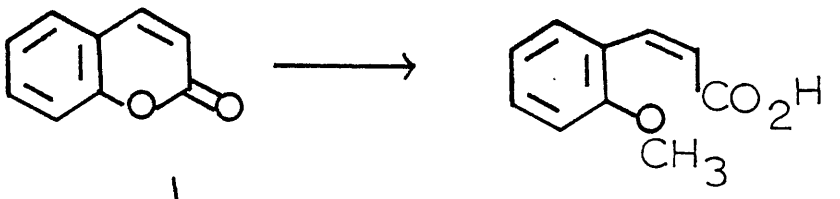
Scheme 9

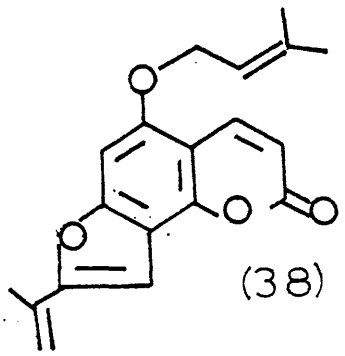


olefinic signals of the 1,2-dimethylallyl group appear as a two proton broad singlet, whilst in the linear compound (45) two broad singlets are observed. Base induced opening of the coumarin ring, followed by recyclisation in the alternative mode accounts for this isomerisation. That the linear isomer is favoured in this system is perhaps surprising, as treatment[27] of bergaptol (6) with alkaline dimethyl sulphate gives exclusively isobergapten (46). The isomers (44) and (45) were readily distinguished by the $Eu(fod)_3$ induced shifts of their respective n.m.r. spectra. Particularly characteristic were the shifts induced for the furan protons and the olefinic protons of the 1,2-dimethylallyl side chains (see Table 3). The relative magnitudes of these shifts were in agreement with those expected for the structures (44) and (45) as assigned.

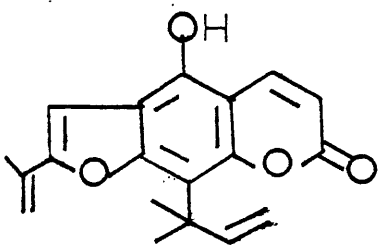
It was felt that an intramolecular trapping of the phenol formed on ortho-Claisen rearrangement may be more facile than the intermolecular method already utilised and this may eliminate the abnormal rearrangement. If the coumarinic acid (47), or equivalent, could be formed, then ortho-Claisen rearrangement should result in a rapid relactonisation, hopefully precluding the abnormal rearrangement, and bringing about the desired angular-linear isomerisation (Scheme 9). It has long been known that treatment of coumarins with alkaline dimethyl sulphate[28] can result in trapping of the ring opened product as its phenolic methyl ether (Scheme 10). Only starting material however, could be recovered when (38) was reacted with 1M sodium hydroxide and a large excess of dimethyl sulphate under a variety of conditions. The utilisation of

Scheme 10





(38)



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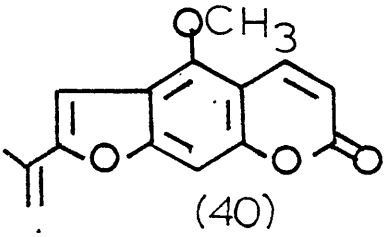

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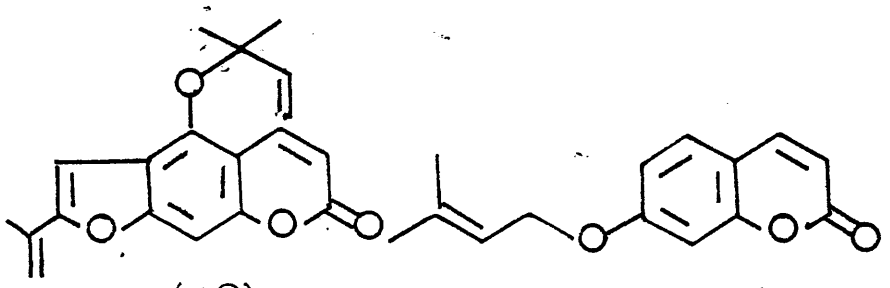
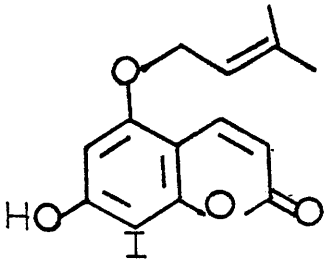


(48)

(49)



(25)

stronger base (e.g. 30% w./v. sodium hydroxide) or of extended reaction times led only to excessive decomposition. No ring opened products could be isolated from reaction of (38) with sodium methoxide in methanol. Thiophenoxide ring opening proved similarly fruitless. It would appear, in this system, that the closed chain form is so favoured, that when the lactone ring opens under the influence of base (or nucleophile) it closes again extremely rapidly.

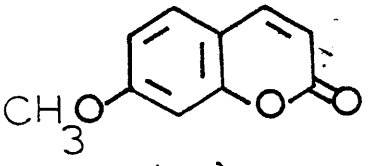
Attention was now turned toward the deprenylation of (38) with two objectives in mind; the proposed synthesis of hortionone (40) that has already been described and an alternative route to hortiolone (16). Para-Claisen rearrangement of the 1,1-dimethylallyl ether (48) would lead to the latter. The removal of prenyl ethers by reaction with dilute mineral acid is a well documented[29] process. Refluxing (38) in methanol containing one drop of conc. hydrochloric acid for 1hr., produced a complex mixture, the n.m.r. spectrum of which indicated that attack at the isopropenylfuran was a significant process. A smooth deprenylation was observed when the model system (49) was reacted with boron tribromide at -78°, in a process which is a direct analogy to the known demethylation[30] reaction. However, (38) gave only a complex mixture with attack at the isopropenylfuran moeity again observed. Clearly deprenylation must be achieved before the isopropenylfuran is constructed, if an acidic technique is to be used.

Although 5-O-(3,3-dimethylallyl)-7-hydroxy-8-iodocoumarin (25) can be readily deprenylated undesired side reactions occur in each

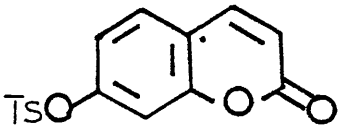
Table 4

Attempted Demethylations of Herniarin (50)

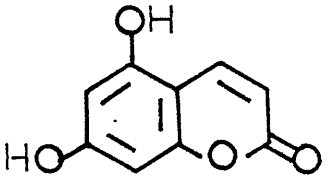
Reagent	Product	Reference
LiI/Collidine	Decomposition	32
NaCN/DMSO	" "	33
$EtS^{\ominus}$/DMF	" "	34
LiF/DMSO	Starting material	-
$(CH_3)_3SiCl/NaI$	" "	35



(50)



(51)



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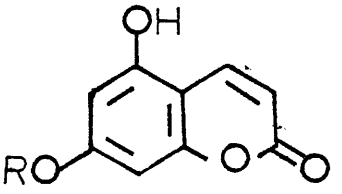


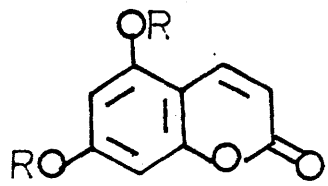
(52)

instance. Concomitant loss of iodine occurs on reaction with hydrochloric acid, whilst reaction with boron tribromide at -78° furnishes a mixture of at least three components, though deprenylation was clearly indicated from the n.m.r. spectrum of the crude product.

Selective iodination at the C-8 position requires that the C-5 hydroxyl be protected as an ether. A number of protecting groups other than the prenyl ether, which may be removed without the undesired side reactions mentioned above were now investigated.

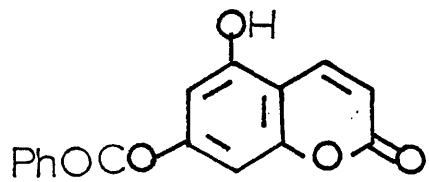
5-Methoxy-7-hydroxycoumarin is known in the literature[31] and a variety of non-acidic methods have been described for the removal of methyl ethers. 7-Methoxycoumarin (50) was used as a model to test some of these methods and the results are summarised in Table 4. The methyl ether is clearly not a suitable protecting group. Selective formation of either a THP or MEM ether at the 5-position proved impossible by standard techniques. A tosylate was also considered to be an unsuitable protecting group, as although it was anticipated that 5,7-diacetoxycoumarin could be selectively monotosylated, detosylation of the model system (51) required forcing acid conditions (refluxing with 5M hydrochloric acid in methanol). The coumarin double bond of umbelliferone benzyl ether proved more labile toward hydrogenation than the benzyl ether to hydrogenolysis.

It was felt that if selective functionalisation of 5,7-dihydroxy-coumarin (21) could be achieved at C-7, giving species of type (52)



(22) R = $COCH_3$

(53) R = COPh



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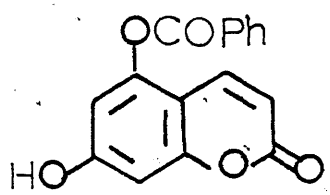

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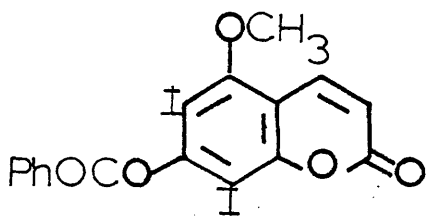

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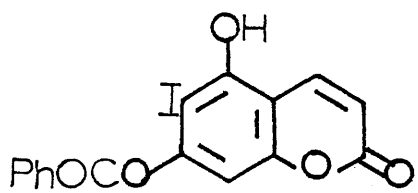
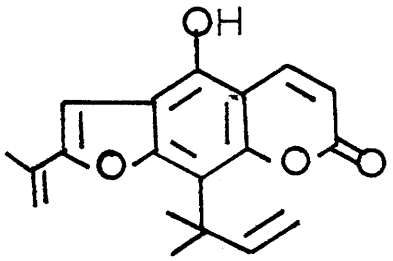


(57)

then iodination at C-6 might be possible. As alkylation occurs more readily at C-5 than at C-7 of 5,7-diacetoxycoumarin (22) it might be anticipated that the C-5 ester would be more susceptible to base hydrolysis. The dibenzoate (53) was chosen to test this hypothesis in preference to the diacetate (22) as benzoates are known[36] to hydrolyse more slowly than acetates and thus the reaction may be more controllable. Mono-hydrolysis of (53) could indeed by achieved by rigorous control of the amount of base used, and of the reaction time. 5-Hydroxy-7-benzyloxycoumarin (54) could be recovered in around 60% yield from this reaction, though traces (~5%) of the co-crystalline isomer, 5-benzyloxy-7-hydroxycoumarin (55) were detectable on t.l.c. These compounds were readily identified by methylation followed by hydrolysis of the benzoate, which yielded the two monomethyl ethers[31] identified by comparison with authentic samples.

On iodination of (54) with iodine/mercuric oxide only one compound could be isolated (as its methyl ether) in very low yield (22%). This was surprisingly the diiodo compound (56). No monoiodo compounds could be isolated.

Recently, Cambie et al have published conditions[37] whereby phenols may be selectively iodinated in the ortho position. These involve treatment with iodine in the presence of thallium (II) salts. (54), if reacted in this way should yield 5-hydroxy-6-iodo-7-benzyloxycoumarin (57) which is potentially an ideal intermediate for



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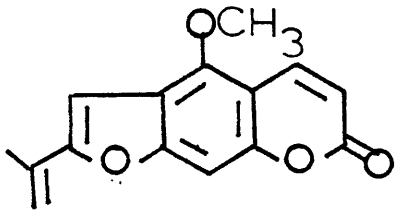

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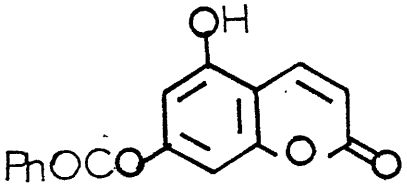

(54)

elaboration into hortiolone (16) and hortionone (40). However, (54) did not react cleanly to these conditions as a considerable amount of decomposition resulted and at least three compounds were formed. Diiodination was again observed.

Part 1

Experimental

5-O-(1,1-Dimethylpropargyl) bergaptol (9)

Potassium carbonate (4.4g) and potassium iodide (0.51g) were added to a stirred solution of bergaptol (6) (3g) in aqueous acetone (2% v./v.; 250ml) and stirred for 1hr. at r.t. 3-Chloro-3-methylbut-1-yne (4.4g) was added and the mixture refluxed for 20hr. Potassium carbonate (4.4g) and 3-chloro-3-methylbut-1-yne (4.4g) were then added and refluxing contined for a further 4hr. Work-up I gave a brown gum (5.1g). Purification by prep t.l.c. ($CHCl_3$x1) gave a yellow oily solid (2.03g). Trituration with ether/petrol followed by crystallisation of the solid residue from $CHCl_3$ afforded 5-O-(1,1-dimethylpropargyl) bergaptol (9) as yellow needles, m.p. 111-112° (1.25g,30%). Found: C,71.8; H, 4.6. $C_{16}H_{12}O_4$ requires C, 71.65; H, 4.45%); n.m.r. signals at δ1.75 (6H,s), 2.50 (1H,s), 6.30 and 8.17 (each 1H,d,J=9.5Hz), 6.68 and 7.56 (each 1H,d,J=2Hz) and 7.33 (1H,s); ν_{Max}^{KBr} 3290, 3130, 2100, 1730 and 1625cm^{-1}; mass spectrum peaks at m/e 268 (M^+, 15%), 202 (100). 174 (42) and 145 (21). Evaporation of the mother liquors of trituration gave a yellow oil (0.61g) which, after prep. t.l.c. ($CHCl_3$x1) and crystallisation from EtOAc/petrol gave 5-O-8-bis (1,1-dimethylpropargyl) bergaptol (10) as yellow needles m.p. 92-95° (0.41g, 9%), n.m.r. signals at δ2.01 (12H,s) 2.31 (1H,s), 2.50 (1H,s), 6.32 and 8.19 (each 1H,d,J=9.5Hz) and 6.68 and 7.56 (each 1H,d,J=2Hz); mass spectral peaks at m/e 334 (M^+, 14%), 268 (95), 253 (100), 202 (92) and 174 (38).

5-O-(1,1-Dimethyallyl)bergaptol (8)

5% Pd-$BaSO_4$ (40mg) was added to a solution of (9) (165mg) in ethyl acetate (15ml). After hydrogenation at r.t. for 0.5hr. the uptake of H_2 was 1 mole. Filtration through celite followed by evaporation of solvent gave (8) as a yellow solid, m.p. 115-116° (160mg. 95%); n.m.r. signals at δ 1,48 (6H,s), 4.98 (2H,AB part of ABX), 6.12 (1H,X part of ABX), 6.23 and 8.10 (each 1H,d,J=9.5Hz), 6.70 and 7.58 (each 1H,d,J=1Hz) and 7.15 (1H,s).

para-Claisen rearrangement

The ether (8) (160mg) was heated in a sublimation block at 120° for 1hr. On cooling, the yellow solid residue was purified by prep. t.l.c. (EtOAc/Petrol 7:3,X1) to give (6) (44mg,32%) and (12) which crystallised from EtOAc/Petrol as yellow needles, m.p. 231-235° (lit.[8] 213-215°) (89mg, 56%) (Found: C,71.0; H,5.3. $C_{16}H_{14}O_4$ requires C,71.1; H,5.2%); n.m.r. signals at δ1.73 (6H,s); 4.87 (2H,AB part of ABX), 6.10 and 8.23 (1H,d,J=9.5Hz); 6.31 (1H,X part of ABX) and 7.05 and 7.70 (each 1H,d,J=2Hz); ν_{max}^{KBr} 3150, 1690 and 1610cm^{-1}; λ_{max}^{MeOH} 253, 267 (sh), 274, 292 and 315nm (log 4.01, 4.22, 4.26, 4.02 and 3.95); λ_{max}^{MeOH} (in base) 237, 262(sh), 291, 332 and 402 nm (log 4.05, 3.91, 4.31, 3.85 and 3.53); mass spectral peaks at m/e 270 (M^+, 82%), 2.55 (100), 227 (79), 215(71) and 199 (44).

Furopinnarin (5)

A solution of (12) (200mg) in ether (100ml) was kept with a

10-fold excess of ethereal diazomethane for 24hr. Evaporation of the solvent and purification of the residue by prep. t.l.c. (EtOAc/Petrol 1:1,x1) afforded (5) which crystallised from benzene-hexane as yellow needles, m.p. 124-127° (lit.[5] 124-125°) (182mg, 90%) (Found: C,71.85; H,5.4 $C_{17}H_{16}O_4$ requires C,71.85; H,5.65%); n.m.r. signals at δ 1.78 (6H,s), 4.17 (3H,s), 5.00 (2H,AB part of ABX), 6.20 and 8.10 (each 1H,d,J=9.5Hz), 6.43 (1H,X part of ABX) and 6.96 and 7.49 (each 1H,d,J=2Hz); $\nu_{max}^{CCl_4}$ 2998, 1743, 1622 and 1478cm^{-1}; λ_{max}^{MeOH} 227, 254, 270 and 315nm (log 4.11, 3.94, 3.96 and 3.79); mass spectral peaks at m/e 284 (M^+, 95%), 269 (100), 241 (30), 229 (63). 202 (96) and 174 (61).

7-Hydroxy,- 8-iodocoumarin[18](19)

Umbelliferone (20) (10g) was dissolved in 20% aqueous ammonia (250ml) and to this solution was added dropwise, with stirring, a solution of iodine (16.7g) in 10% aqueous potassium iodide (200ml). After the addition was complete the solution was neutralised with 5M sulphuric acid. The resultant precipitate was filtered, washed with water, dried in vacuum and decolourised with charcoal. Crystallisation from ethyl acetate afforded 7-hydroxy,- 8-iodocoumarin (15.1g 84%) as colourless needles m.p. 266-268° (lit.[18] m.p. 268°); n.m.r. signals (d_6-dimethylsulphoxide) at δ 6.03 and 7.63 (each 1H, d,J=9.5Hz), and 6.75 and 7.31 (each 1H,d,J=8Hz); ν_{max}^{KBr} 3200, 1700, 1610 and 1600cm^{-1}.

Preparation of the cuprous acetylide (18)

To a stirred solution of $CuSO_4.5H_2O$ (1.87g) in 30% aqueous

ammonia (10ml) was added, under nitrogen, water (35ml). The solution was cooled to 0° and hydroxylamine hydrochloride (0.52g) was added. 2-Methyl-1-butene-3-yne (0.50g) in ethanol (7ml) was then added and the resultant yellow precipitate was filtered, washed with water, ethanol and ether, then dried in vacuum to furnish the cuprous acetylide (18; 0.91g).

Oroselone (13)

A solution of 7-hydroxy-8-iodocoumarin (19) (300mg) and the cuprous acetylide (18) (225mg) in pyridine (15ml) was stirred under argon at 100± 5° for 2hr. Work-up II furnished, after crystallisation from chloroform, oroselone as yellow needles (179mg, 79%) m.p. 187-189° (lit[11]. 188-189°); n,m. r. signals at δ 2.16 (3H,d,J= 1Hz), 5.29 (1H,m), 6.39 and 7.82 (each 1H,d,J=9.5Hz), 6.97 (1H,s) and 7.37 (2H,s); ν_{max}^{KBr} 1720, 1610, 1550, and 1295cm^{-1}; λ_{max}^{EtOH} 282 and 297nm (log ε 4.60 and 4.49); mass spectral peaks at m/e 226 (M^+; 50%), 225 (100), 200(33), 199 (98),198(30), and 184 (53).

Ethyl Propiolate[20]

A mixture of propiolic acid (20g), dry ethanol (60ml) and conc. sulphuric acid (3.3ml) was kept at r.t. for 40hr., then diluted with water (200ml) and extracted with ether. The combined organic layers were washed with dil. sodium carbonate, brine to neutrality and dried. Distillation afforded ethyl propiolate (14g, 50%), b.p. 117-118° (lit.[20] b.p. 119°/745mm).

5,7-Dihydroxycoumarin[20] (21)

Phloroglucinol dihydrate (8.10g), ethyl propiolate (7.35g) and zinc chloride (6.80g) were mixed together and heated in an oil bath at 115± 5° for 2hr. The resultant yellow solid on crstallisation from water afforded 5,7-dihydroxycoumarin as a light tan solid (6.58g, 74%) m.p. 267-270° decomp. (lit.[20] m.p. 280° decomp.).

5,7-Diacetoxycoumarin (22)

A solution of 5,7-dihydroxycoumarin (6.5g) in acetic anhydride (200ml) was stirred for 18hr. at r.t. in the presence of anhydrous sodium acetate (10g). The solution was then filtered and the solvent removed under reduced pressure. The residue on crystallisation from ethyl acetate, furnished (22) as colourless needles (8.89g, 93%) m.p. 139-140.5°(lit.[20] m.p. 139.5-141°); n.m.r. signals at δ2.37 (3H,s), 2.45 (3H,s), 6.38 and 7.70 (each 1H, d, J=9.5 Hz) and 7.00 (2H,m); $\nu_{max}^{CHCl_3}$ 1778, 1730 and 1630cm^{-1}; mass spectrum showed M^+ at m/e 262.

3,3-Dimethylallylbromide

Isoprene (100ml, 68g) and a solution of hydrogen bromide in glacial acetic acid (45% w./v. , 168ml) were cooled to 0° and then mixed. The solution was kept at -5° for 3 days, then diluted with iced water (1500ml). The yellowish oil which separated was washed with sat. sodium bicarbonate, brine and dried over anhydrous calcium chloride. Distillation of this oil at 65-68°/68mm yielded 3,3-dimethylallyl bromide (108g, 72%).

Prenylation of 5,7-diacetoxycoumarin

A mixture of 5,7-diacetoxycoumarin (3.3g), potassium carbonate (5.9g) and freshly distilled 3,3-dimethylallyl bromide (2.30g) in 1,2-dimethoxyethane (65ml) was refluxed for 1hr. Work-up I gave a yellow oil which after purification by column chromatography (Grade III neutral alumina) furnished;

i) 5-O,7-O-bis(3,3-dimethylallyl)coumarin (165mg, 7%) as colourless needles m.p. 78-80° (lit.[29] m.p. 79-80°); n.m.r. signals at δ 1.80 (12H,bs), 4.57 (4H, bd, J=6.5Hz), 5.50 (2H, bt, J=6.5Hz), 6.10 and 7.96 (each 1H, d, J=9.5Hz) and 6.30 and 6.40 (each 1H, d, J=2Hz).

ii) 5-O-(3,3-dimethylallyl)-7-acetoxy coumarin (23)(2.20g, 61%) as colourless needles (from ether-acetone) m.p. 127-129° (Found: C,66.88; H,5.58. $C_{16}H_{16}O_5$ requires:C, 66.66; H,5.59%); n.m.r. signals at δ 1.79 (6H,s), 2.35 (3H,s), 4.56 (2H, bd, J=6.5 Hz), 5.50 (1H, bt, J=6.5Hz), 6.23 and 8.06 (each 1H, d, J=9.5Hz) and 6.40 and 6.63 (each 1H, d, J=2Hz); $\nu_{max}^{CCl_4}$ 1773, 1749, 1623 and 1612cm^{-1}; mass spectral peaks at m/e 288 (M^+, 3%), 220 (20), 178 (34), 150 (36), 69 (100) and 41 (96).

5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (24)

The acetate (23) (2.20g) was dissolved in methanol (30ml) and sodium bicarbonate (1.3ml, 1%w./v.) added. The solution was refluxed for 0.75hr., allowed to cool, and carefully neutralised with 0.1M hydrochloric acid. The mixture was diluted with water and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated. The residue, on crystallisation from

ether, afforded (24) as colourless plates m.p. 142-144° (lit.[29] m.p. 143-145°); (Found: C,68.00; H,5.75. $C_{14}H_{14}O_4$ requires: C,68.30; H,5.75%); n.m.r. signals (d_6-acetone) at δ1.73 (3H, bs), 4.52 (2H, bd, J=6.5Hz), 5.47 (1H, bt, J=6.5Hz), 6.05 and 8.06 (each 1H, d, J=9.5Hz), 6.39 and 6.63 (each 1H, d, J=2Hz) and 7.70* (1H,s); $\nu_{max}^{CCl_4}$ 3600, 3330, 1745,1716 and 1705cm^{-1}; λ_{max}^{EtOH} 248, 256 and 330nm (log 3.71, 3.85 and 4.13); λ_{max}^{EtOH} (base) 236, 271 and 384nm; mass spectral peaks at m/e 246 (M^+, 8%), 231 (5), 191 (15), 179 (10), 178 (89), 150 (36) and 69 (100).

5-O-(3,3-dimethylallyl)-7-hydroxy-8-iodocoumarin (25)

To a solution of (24) (100mg) in chloroform (30ml) containing acetone (5ml) were added in portions, with shaking, iodine (105mg) and mercuric oxide (90mg) and shaking continued until all the iodine colour had dispersed. The solution was then filtered through celite, the filter pad thoroughly washed with chloroform and the solution washed with dil. sodium thiosulphate, brine and evaporated. The residue, on crystallisation from ethyl acetate/petrol, dinished (25) (107mg,71%) as yellow needles m.p. 163-165° . Found: C,45.16; H, 3.24; I, 34.19; $C_{14}H_{13}IO_4$ requires C, 45.1; H, 3.49; I, 34.13%); n.m.r. signals (d_6-acetone) at δ1.81 (6H,s), 4.76 (2H,bd, J=6.5Hz), 5.58 (1H,bt,J=6.5Hz) 6.18 and 8.00 (each 1H,d,J=9.5Hz) and 6.68 (1H,s); ν_{max}^{KBr} 3325, 1700, 1600, 157, 1386 and 1240cm^{-1}; mass spectral peaks at m/e 372 (M^+,11%), 305 (20), 304 (100), 280 (50), 279 (15) and 247 (10).

5-O-(3,3-dimethylallyl)-7-methoxy-8-iodocoumarin (26)

Potassium carbonate (200mg) and methyl iodide (1ml) were added to a solution of (25) (144mg) in acetone (15ml) and the mixture refluxed for 1hr. Work-up I furnished (26) as colourless needles m.p. 203-205° (from Et_2O/EtOAc) (133mg, 89%). (Found: C, 46.42; H, 3.92; I, 33.31. $C_{15}H_{15}IO_4$ requires C,46.63; H,3.89; I,32.90%); n.m.r. signals at 1.80 (6H,s), 4.00 (3H,s), 4.75 (2H,bd,J=6.5Hz), 5.57 (1H,bt,J=6.5Hz), 6.15 and 8.01 (each 1H,d,J=9.5Hz) and 6.58 (1H,s); υ_{max}^{KBr} 1720, 1595, 1350, 1335 and 1240cm^{-1}; mass spectral peaks at m/e 386 (M^+,9%), 319 (10), 318 (100), 317 (15), 290 (34), 289 (28), 162 (54) and 147 (49).

Pyrolysis of (26)

(26) (100mg) was stirred at 175±5° for 2hr. under argon, in N,N-diethylaniline (5ml) containing butyric anhydride (0.2ml). On cooling the mixture was diluted with water (30ml) and stirred at r.t. for 2hr. and then extracted with ethyl acetate. The organic layer was washed with dil. hydrochloric acid to pH2, 5% w./v. potassium carbonate to pH,11, brine to neutrality, dried and evaporated to yield only starting material (97mg,97%).

Preparation of (38)

A solution of 5-O-(3,3-dimethylallyl)-7-hydroxy-8-iodocoumarin (25) (180mg) and the curpous acetylide (18) (76mg) were stirred, under argon, in pyridine (20ml) at 80±5° for 2 hr. Work-up II furnished a brown oil which on purification by prep. t.l.c. ($CHCl_3$x1) gave (38)

(93mg,62%) as yellow needles (from Et_2O) m.p. 118-120° ; n.m.r. signals at δ1.88 (6H,bs), 2.12 (3H,bs), 4.63 (2H,bd,J=6.5Hz), 5.16 (1H,m), 5.51 (1H,bt,J=6.5Hz), 5.68 (1H,m), 6.21 and 8.10 (each 1H,bt,J=6.5Hz), 5.68 (1H,m), 6.21 and 8.10 (each 1H,d,J=9.5Hz) and 6.80 (2H,s); ν_{max}^{KBr} 1735, 1665, 1295, 1140 and 1110cm^{-1}; mass spectral peaks at m/e 310 (M^+,34%), 243 (62), 242 (100), 214 (52).

Claisen rearrangement of (38)

(38) (78mg) was stirred at 175±5° for 2hr. in diethylaniline (5ml) containing butyric anhydride (0.2ml). On cooling the mixture was diluted with water (30ml) and stirred at r.t. for 2hr. and then extracted with ethyl acetate. The combined organic layers were washed with dil. hydrochloric acid to pH2, 5% w./v. potassium carbonate to pH11, brine to neutrality, dried and evaporated to yield after purification by prep. t.l.c. ($EtOAc$/Petrol 1:3, x1) (42) (48mg;50%) as a colourless oil; n.m.r. signals at δ1.08 (3H,t,J=7Hz), 1.63 (6H,bs), 1.82 (2H,sextet,J=7Hz), 2.16 (3H,bs), 2.65 (2H,t,J=7Hz), 5.06 (2H,bs), 5.33 (1H,bs), 5.91 (1H,bs), 6.48 and 7.73 (each 1H,d, J=9.5Hz) and 7.08 (1H,s); ν_{max}^{CCl4} 1760, 1750, 1630, 1130 and 1100cm^{-1}; mass spectral peaks at m/e 380 (M^+,84%), 310 (100), 290 (98) and 267 (26).

Hydrolysis and isomerisation of (42)

i) A stirred solution of (42), 1% w./v. sodium hydroxide (1ml) in methanol (8ml) was refluxed for 0.25hr. On cooling the solution was carefully neutralised with 0.1M hydrochloric acid, diluted with water (30ml) and extracted with ethyl acetate. The combined organic

layers were washed with brine, dried and evaporated to yield a yellow solid (31mg). This material was then dissolved in acetone (10ml), potassium carbonate (100mg) and methyl iodide (o.5ml) added and the mixture refluxed for 1hr. Work-up I yielded after purification by prep. t.l.c. (EtOAc/Petrol 1:10,x3).

a) (44) (12mg,35%) as a colourless solid m.p. 92-95°, n.m.r. signals at δ1.83 (6H,bs), 2.18 (3H,bs), 3.93 (3H,s), 5.00 (2H,bs), 5.26 (1H,bs), 5.80 (1H,bs), 6.40 and 8.03 (each 1H,d,$J_{=}$9.5Hz) and 6.91 (1H,s); υ_{max}^{KBr} 1740, 1615, 1150 and 1130cm^{-1}; mass spectral peaks at m/e 324 (M^+,100), 309 (18), 293 (34), 283 (20) and 278 (16).

b) (45) (18mg,52%) as a colourless solid m.p. 110-112° ; n.m.r. signals at δ1.70 (6H,bs), 2.15 (3H,bs), 4.21 (3H,s), 4.95 (1H,bs), 5.04 (1H,bs), 5.17 (1H,bs), 5.80 (1H,bs), 6.28 and 8.15 (each 1H,s, J=9.5Hz) and 6.80 (1H,s); υ_{max}^{KBr} 1730, 1620, 1610, 1480 and 1140cm^{-1}; mass spectral peaks at m/e 324 (M^+,100), 314 (50), 283 (65), 278 (50) and 265 (40).

ii) (42) (25mg) when hydrolysed for 1hr., then treated as before gave (45) (15mg, 75%).

5-7-Dibenzyloxycoumarin (53)

5,7-dihydroxycoumarin (1g) and benzoyl chloride (5ml) were refluxed in pyridine (40ml) for 18hr. Work-up II yielded a yellow solid which on crystallisation from ether gave (53) (1.54g,71%) as colourless needles m.p. 171-2° ; (Found: C,72.43; H,3.68. $C_{23}H_{14}O_6$ requires C,72.25; H,3.78%); n.m.r. signals at δ6.40 and 8.01 (each

1H,d,J=9.5Hz), 7.22 (2H,s), 7.78 (6H,m) and 8.21 (4H,m); ν_{max}^{KBr} 1740, 1625, 1340 and 700cm^{-1}; mass spectral peaks at m/e (M^+,100%), 282 (80) and 173 (25).

5-Hydroxy-7-benzyloxycoumarin (34)

To a stirred solution of (53) (1g) in methanol (50ml) was added 1M sodium hydroxide (2.6ml,1.2eq.) and stirring continued for 0.5hr. The reaction mixture was then carefully acidified with 1M hydrochloric acid, diluted with water and extracted with ethyl acetate. The combined organic layers were washed with 1% sodium bicarbonate, brine, dried and evaporated to yield on fractional crystallisation from methanol.

i) starting material (53) (126mg,12.6%)

ii) 5-hydroxy-7-benzyloxycoumarin (54) (480mg,66%) m.p. 210-212°. (Found: C,68.15; H,3.28. $C_{16}H_{10}O_5$ requires C,68.08; H,3.57%), n.m.r. signals (d_6-acetone) at 6.31 and 7.91 (1H,d,J=9.5Hz), 6.83 (2H,bs), 7.80 (2H,m) and 8.22 (3H,m); ν_{max}^{KBr} 3050, 1740, 1680, 1340, 1130 and 700cm^{-1}; mass spectral peaks at m/e 282 (M^+,40%), 178 (30), 177 (260), 150 (100) and 149 (69).

iii) 5,7-dihydroxycoumarin (21), (110mg.24%)

Iodination of (54)

i) To a stirred solution of (54) (320mg) in chloroform (50ml) were added in portions iodine (290mg) and mercuric oxide (270mg). After the addition was complete the solution was filtered and the filter pad thoroughly washed with chloroform. The filtrate was then

washed with dilute sodium metabisulphate, brine, dried and evaporated to yield a brown oil (410mg). Without further purification this oil was dissolved in acetone (20ml) and refluxed for 1hr. with potassium carbonate (400mg) and methyl iodide (1ml). The product isolated by Work-up I was then purified by prep. t.l.c. (EtOAc/Petrol 2:3,x3) to afford on crystallisation from chloroform (56) (130mg,22%) as colourless plates m.p. 222° (decomp); (Found: C,37.12; H, 1.79; I, 46.78. $C_{17}H_{10}O_5I_2$ requires C,37.22; H,1.80; I,46.35%); n.m.r. signals at δ3.75 (3H,s), 6.25 and 7.75 (each 1H,d,J=9.5Hz), 7.50 (2H,m) and 8.16 (3H,m); ν_{max}^{KBr} 1740, 1615, 1570, 1340, 1070 and 700cm^{-1}; mass spectral peaks at m/e 548 (M^+,100), 421 (50), 406 (35), 316(75) and 301 (60).

ii) To a stirred solution of (54) (100mg) and thallium (II) formate (106mg) in methylene chloride (25ml) was added dropwise a solution of iodine (90mg) in methylene chloride (10ml) and the mixture stirred at r.t. for 48hr., when potassium iodide (200mg) were added and stirring continued for 1hr. The solution was then filtered, washed with sodium thiosulphate, brine, dried and evaporated to yield a yellow oil (132mg) which t.l.c. and n.m.r. showed to be a complex mixture.

Part 1

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Introduction to Part 2.

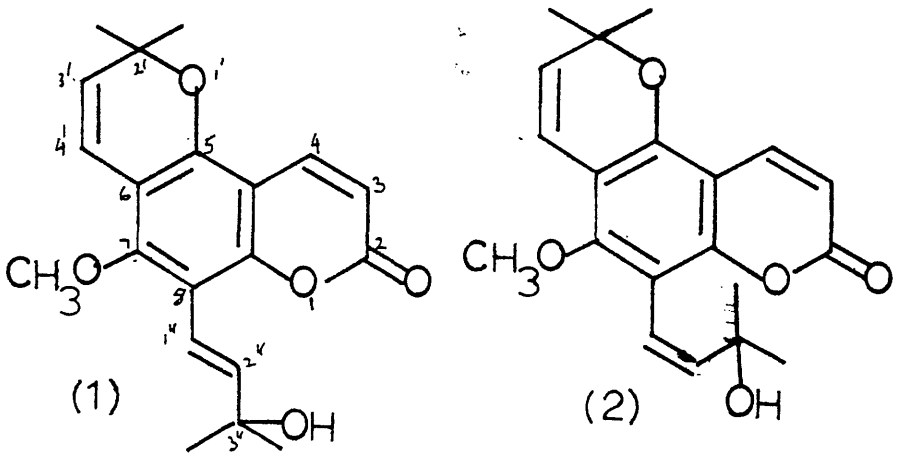
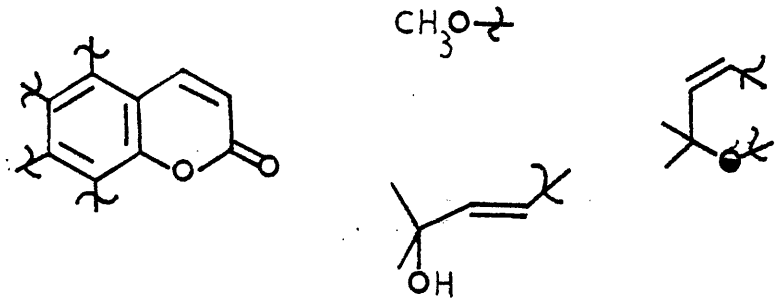


Table 1

N.m.r. Spectrum of trans-Avicennol

Signal (δ)	Integration	Multiplicity
1.59	6	s
1.60	6	s
2.58*	1	s
3.80	3	s
5.69	1	d, J=10Hz
6.27	1	d, J=10Hz
6.65	1	d, J=10Hz
6.81	1	d, J=16Hz
6.95	1	d, J=16Hz
8.06	1	d, J=10Hz

Figure 1



In 1975 Gray, Waigh and Waterman isolated the coumarin, trans-avicennol (1) from Zanthoxylum avicennae[1] and two years later the isomeric cis-avicennol (2) from Zanthoxylum elephantiasis[2]. The i.r. and u.v. spectra of trans-avicennol indicated an extensively conjugated and substituted coumarin which analysed for $C_{20}H_{22}O_5$. The gross structural features were readily determined from the proton n.m.r. spectrum (see Table 1.). The characteristic resonances for the C-3 and C-4 protons of the coumarin ring appeared at δ6.27 and 8.06 respectively (each 1H, d, J = 10Hz.) and the presence of a three proton singlet at 3.80 indicated a methoxyl group. A 2,2-dimethyl-chromene moiety was suggested by the presence of an AB quartet at δ5.69 and 6.65 (each 1H, d, J =10Hz) and a six proton singlet at 1.60. At this point, the signals left unassigned were two trans olefinic protons at 6.81 and 6.95 (each 1H, d, J = 16 Hz.), a six proton singlet at 1.59 and an hydroxyl group at 2.58* (1H,s). As there was now only one position on the coumarin nucleus unaccounted for, these signals must arise from a single moiety and were thus attributed to a trans-3-hydroxy-3-methylbut-1-enyl group.

Clearly however, although the functionality had been determined, a number of isomeric structures of trans-avicennol could exist arising from varying the position of substitution on the benzene ring. (See Figure 1). In fact there are twelve such possible isomers. The absolute structure of trans-avicennol was then elucidated largely by the application of a lanthanide shift reagent, namely tris-(7,7-dimethyl-1,1,1,2,2,3,3-heptafluoro-octene-4,6-dionato) europium III

Table 2

	Shifts Calculated for Attachment of Side Chain at:				Observed Value
	C-5	C-6	C-7	C-8	
H_A	0.12	0.11	0.11	0.33	0.40
H_B	0.15	0.14	0.15	0.45	0.52

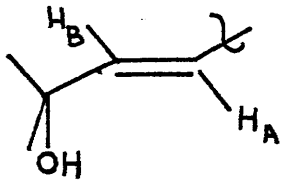
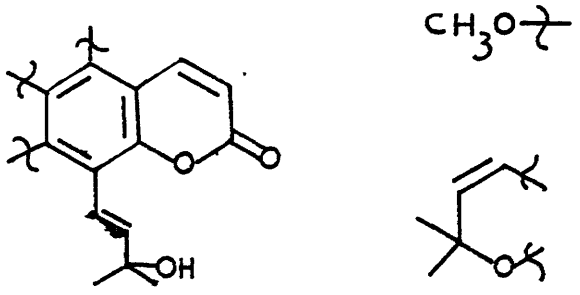


Figure 2



$(Eu(fod)_3)^3$. For a fuller discussion of the use of $Eu(fod)_3$ for coumarin structure determination see Part 1, page 37.

The position of attachment of the trans-3-hydroxy-3-methylbut-1-enyl group was determined by calculating the expected shifts for the four possible sites of attachment of this group to the benzenoid ring. These calculations used the average values for the Eu⋯H distance and the O⋯Eu⋯H angle over the two possible conformations of the side chain double bond in the plane of the ring and are consequently only approximate, as the actual conformation in solution is unknown. The resultant calculated values were then compared with the observed shifts of the two olefinic protons in question (see Table 2). (The observed shifts were measured on the trimethylsilyl (TMS) ether of trans-avicennol to avoid complexation of the shift reagent with the alcohol function). It was clear from these results, that the trans-3-hydroxy-3-methylbut-1-enyl moiety must be at C-8, as only in this position is there a close agreement between the observed and calculated shifts of the olefinic protons. The number of possible isomers for trans-avicennol was now reduced from twelve to four. (see Figure 2).

By utilisation of the nuclear Overhauser effect it was possible to distinguish between these isomers. Irradiation at the methoxyl signal resulted in an enhancement in intensity of both sets of side chain olefinic protons, indicating that the methoxyl group was adjacent to both these sets of protons. Now, as the trans-3-hydroxy-3-methylbut-1-enyl side chain had already been assigned to

Table 3

N.m.r. Spectrum of cis-Avicennol

Signal (δ)	Integration	Multiplicity
1.31	6	s
1.49	6	s
2.85*	1	s
3.85	3	s
5.69	1	d, J=10Hz
6.01	1	d, J=13Hz
6.25	1	d, J=13Hz
6.29	1	d, J=10Hz
6.65	1	d, J=10Hz
8.05	1	d, J=10Hz

C-8, this unequivocally determined the structure of trans-avicennol as (1).

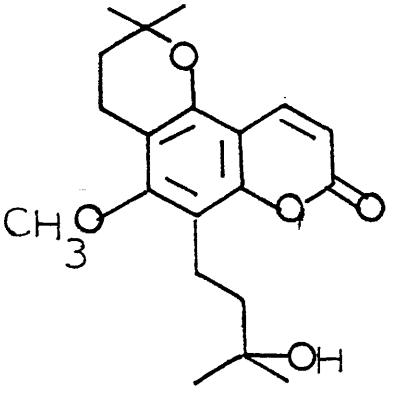
That this structure, based largely on a novel application of a lanthanide shift reagent was in fact that of trans-avicennol, was later confirmed by Murray and Forbes[4] by an unambiguous total synthesis.

Some two years after the isolation of trans-avicennol, Gray et al. reported[2] the isolation of cis-avicennol. This compound differed only in possessing a cis rather than trans configuration of the 3-hydroxy-3-methylbut-1-enyl side chain. Mass measurement of cis-avicennol gave a molecular ion M^+ 342.1453 ($C_{20}H_{22}O_5$) with fragmentation pattern showing only relative abundance variations from that of trans-avicennol. The i.r. spectrum was also in close accord with that of trans-avicennol. However, the u.v. spectrum of cis-avicennol (236, 275 and 294 nm. cf. 250, 257 and 301 for trans-avicennol) and the proton n.m.r. spectrum (see Table 3) showed distinct differences. In regard to the n.m.r. spectrum, although the signals indicated a compound with similar substituents to trans-avicennol, chemical shift differences in the signals derived from the 3-hydroxy-3-methylbut-1-enyl moiety and in the olefinic coupling constant (J=13Hz. cf. J=16Hz.) were clearly seen. Since a 13Hz. coupling constant cannot be unambiguously assigned to either a cis or trans configuration, then in principle this new coumarin could be any one of the twenty three possible isomers of trans-avicennol. The actual structure was once again elucidated with the aid of

Table 4

Comparison of Induced Shift Value (Relative to 3H=1.00) for trans-Avicennol and cis-Avicennol TMS Ethers with $Eu(fod)_3$.

	C-3	C-4	C-3	C-4	C-2	OMe	C-1	C-2	C-3	TMS
trans-Avicennol	1.00	0.31	0.08	0.13	0.08	0.15	0.40	0.52	0.13	0.11
cis-Avicennol	1.00	0.32	0.09	0.51	0.08	0.16	0.32	0.32	0.25	0.19



(3)

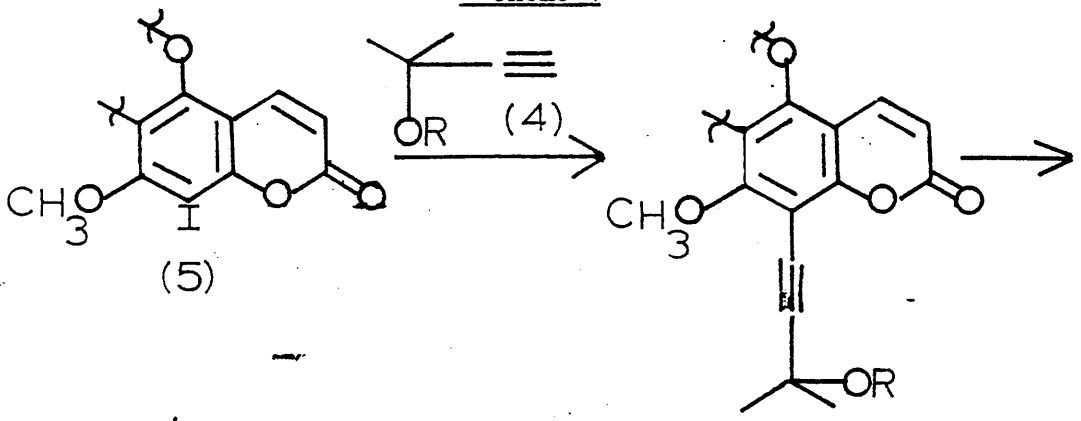
$Eu(fod)_3$- induced shifts of the TMS derivative of *cis*-avicennol and by comparison of those with that of the TMS derivative of *trans*-avicennol (see Table 4). There was little significant difference in the shift ratios of the protons of the lactone ring, chromene ring and methoxyl group while those of the olefinic protons on the side chain were again of such magnitude as to limit side chain attachment to C-8. However, the shifts of the *gem*-dimethyl and TMS signals were considerably larger than those of the corresponding *trans* side chain indicating that these groups were closer to the site of complexation. These results are in accord with those expected for *cis*-avicennol. The substitution pattern was further confirmed by hydrogenation to give the previously synthesised[1] tetrahydroavicennol (3).

It was felt that a regiospecific total synthesis of *cis*-avicennol would be itself of considerable interest whilst further constituting a structural proof and such a project was thus initiated.

Part 2

Synthetic Approaches to the Coumarin cis-Avicennol

Scheme 1



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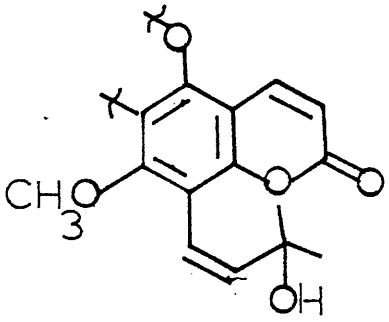

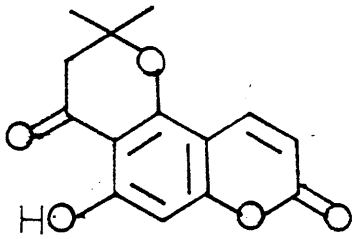

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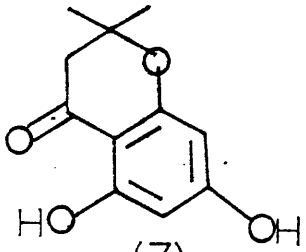

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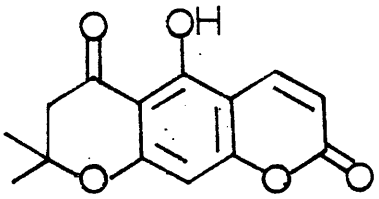
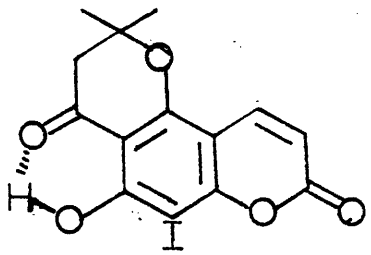


(8)



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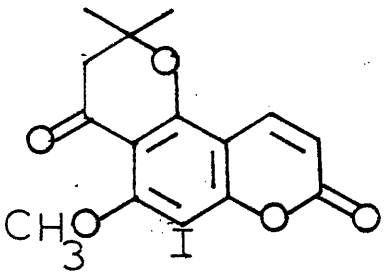


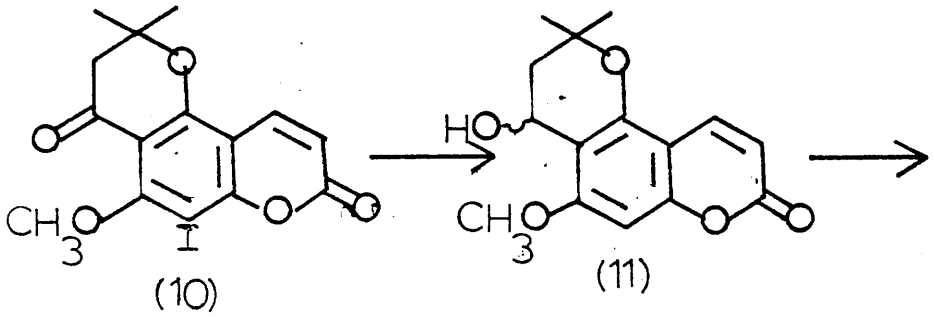
(10)

It was considered that the key step in the synthesis of cis-avicennol (2) was the introduction of the cis-3-hydroxy-3-methylbut-1-enyl side chain. A plausible approach for this would be by coupling[5] the cuprous acetylide (4) with the aryl iodide (5), followed by semi-hydrogenation of the resultant acetylene to a cis-olefin (Scheme 1). Given the above considerations the problem now reduced to the synthesis of a substrate suitable for the coupling reaction, namely a coumarin regiospecifically substituted with iodine at C-8, a methoxyl at C-7 and a 2,2-dimethylchromene, or its equivalent attached angularly through oxygen at C-5.

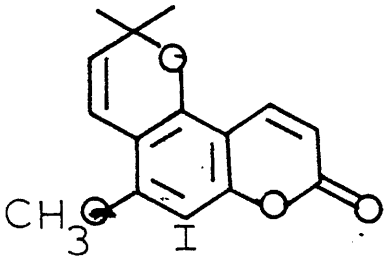
The chromano-coumarin (6) which exhibits the necessary angular tricyclic framework may be readily prepared[6], albeit in 27% yield, simply by crystallisation of the crude product resulting from a von Pechmann condensation of 2,2-dimethyl-5,7-dihydroxychroman-4-one[8] (7) with malic acid and conc. sulphuric acid. Small amounts (7%) of the naturally occuring coumarin clausenin[7] (8) may also be recovered from this reaction by repeated chromatography of the mother liquors of crystallisation[9] of (6). The chromanone starting material[8] (7) may itself be prepared by reaction of phloroglucinol with 3,3-dimethylacrylic (senecoic) acid in the presence of zinc chloride in reasonable yield (40%).

Iodination of the phenol (6) with iodine and mercuric oxide[10] proceeded smoothly and in high yield, at the only unsubstituted site on the benzenoid ring (C-8) to give (9). Methylation of the iodophenol (9) with methyl iodide/potassium carbonate to give the corresponding ether (10) went cleanly, if somewhat slowly, possibly as a consequence of the

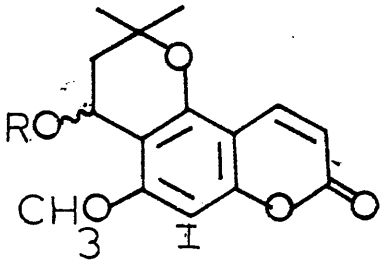
Scheme 2



(10) (11)



(12)

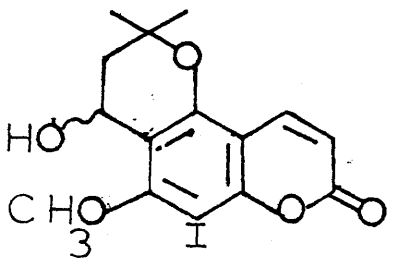


(13)

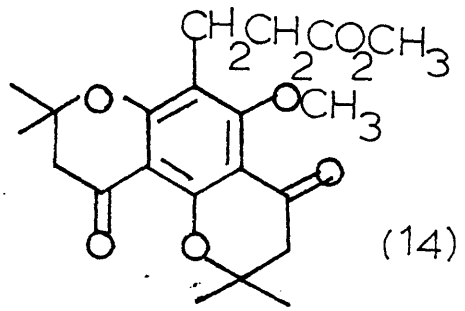
R = CH_3, C_2H_5

chelated nature of the phenolic hydroxyl.

It was felt that before any coupling reactions were to be attempted the feasibility of the elaboration of the 2,2-dimethylchroman-4-one ring into the corresponding chromene should be investigated. The simplest approach for accomplishing this transformation would appear to be the reduction/dehydration sequence shown in Scheme 2. This procedure did indeed give the chromene (12), though the reactions proved much less facile than had been originally anticipated. The major problems were associated with the reduction step which transpired to be very slow, with the nature of the solvent and the stoichiometry of reducing agent ($NaBH_4$) to substrate proving to be the critical factors. When the reaction was attempted in methanol (in which $NaBH_4$ has a short lifetime[11]), or in ethanol (in which the lifetime of $NaBH_4$ is considerably longer[11]), this proved none too successful, since competition for reagent by substrate and solvent meant that a large excess of reducing agent (approximately tenfold) was required for chromanone reduction. As a consequence of this, the side reactions, de-iodination and reduction of the lactone became important, in addition to the expected ether formation generating species of type (13). The use of isopropanol (in which $NaBH_4$ is indefinately stable[11]) as solvent provided the answer to this problem, since this allowed carefully controlled amounts of reducing agent to be employed. It was found, after much experimentation that treatment of the chromanone (10) with 0.5-0.7 equivalents of $NaBH_4$ in isopropanol/chloroform(the cosolvent is required to increase substrate solubility) for 24 hours at room temperature, limited the over-reduction and



(11)



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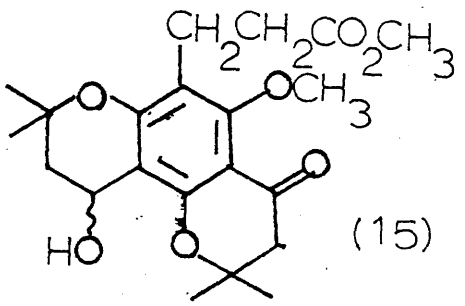

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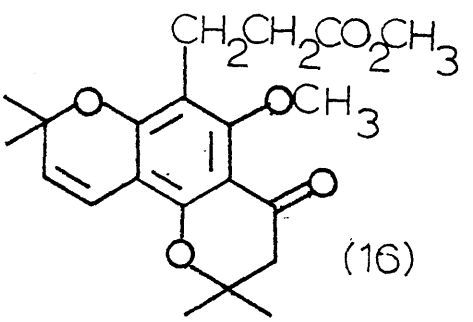

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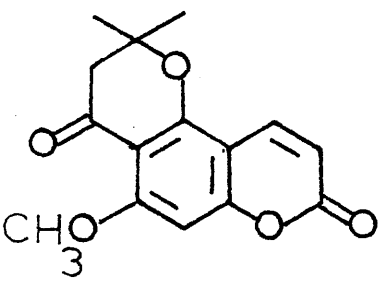
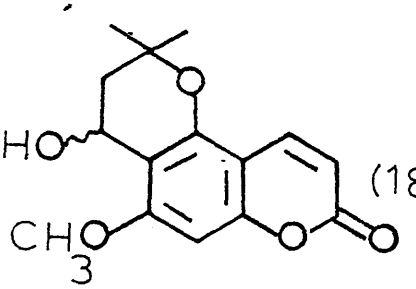


(17)

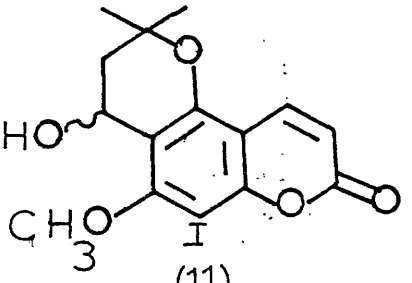


(18)

allowed the chromanol (11) to be prepared reproducably in 60-70% yield.

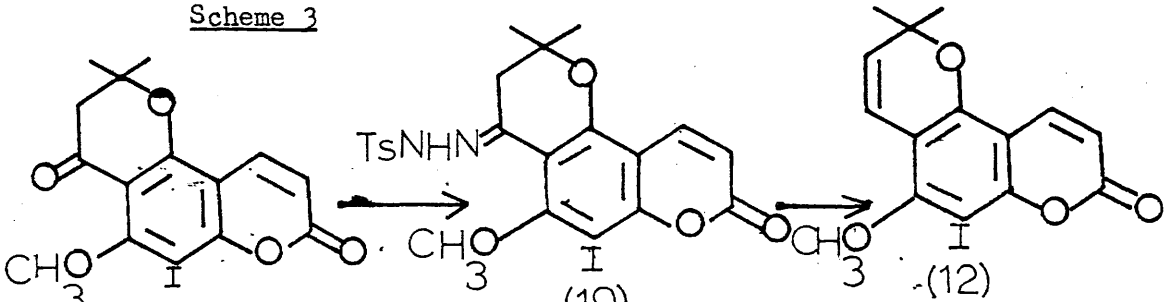
Slow reduction of the carbonyl group in angular chromanones such as (10) has been observed in other cases. For instance, treatment[12] of the dichromanone (14) with Raney Nickel/H_2 resulted in the reduction of only the linear chromanone carbonyl to produce (15). The carbonyl in the angular chromanone (16) can be reduced[12], but it necessitates the use of fairly forcing conditions i.e. a sixfold excess of $NaBH_4$ in refluxing tetrahydrofuran. A more direct analogy with the reduction of (10) was provided by Joshi[13], with his work on the de-iodo derivative (17). The formation of the chromanol (18) again required forcing conditions, in this case treatment of (17) with a threefold excess of $NaBH_4$ in pyridine/H_2O at 70°, with (18) being produced in less than 10% yield by this method.

That the reduction of angular chromanones such as (10) and (17) is slow, is thus well established and a possible explanation of this may well be steric congestion at the carbonyl group. Examination of models of (10) and (17) does indeed show that the C-7 methoxyl and the carbonyl group of the chromanone are in close proximity. In that event the carbonyl of the 2,2-dimethylchroman-4-one residue may well be shielded to some extent from the attacking reducing agent, thus making reduction a slow process. The effect of the bulky iodine at C-8 in (10) may also compound the situation with respect to the de-iodo derivative (17). Steric interactions between the methoxyl group and the iodine may force the methoxyl to take up a conformation which increases the steric



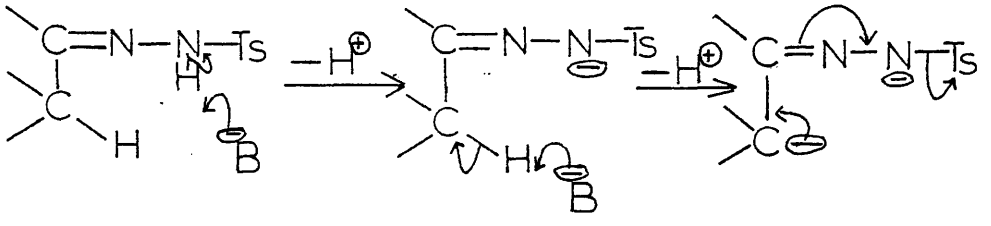
(11)

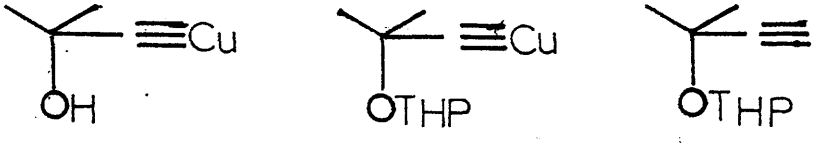
Scheme 3



(10) (19) (12)

Scheme 4





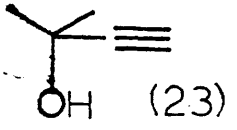
(20) (21) (22)

compression about the chromanone carbonyl with respect to the unsubstituted case (17).

In contrast, the dehydration of the chromanol (11) to the chromene (12) was readily achieved in about 50% yield by refluxing in toluene over $KHSO_4$[12].

In an effort to improve upon the yield of the reduction/dehydration sequence (25-35% overall), an alternative approach, that of the Bamford-Stevens[14] reaction, was investigated (see Scheme 3). This reaction is known to produce olefins from tosylhydrazones in a wide variety of cases[14] and is believed to proceed via the mechanism shown in Scheme 4. Treatment of the tosylhydrazone (19), derived[15] in 80% yield from the chromanone (10) with n-butyllithium (2.8eq.) under a variety of conditions produced only complex mixtures from which the chromene (12) could not be isolated. Nucleophilic attack of the alkylithium reagent on the coumarin ring may be an important process here. Decomposition products were obtained from the reaction and it was obvious from n.m.r. that these lacked the characteristic pair of doublets indicative of coumarins.

With substrates (10), (11) and (12) to hand it now became possible to investigate the feasibility of the elaboration of the 3-hydroxy-3-methylbut-1-enyl side chain, by the proposed cuprous acetylide coupling. The cuprous acetylide (20) could be prepared but due to its solubility in the reaction medium isolation proved difficult. However, the cuprous acetylide (21) of the tetrahydropyranyl ether (22) of 3-hydroxy-



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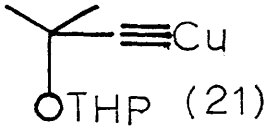

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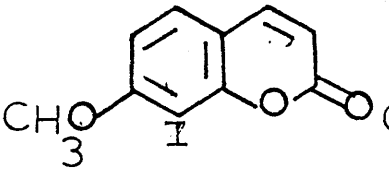

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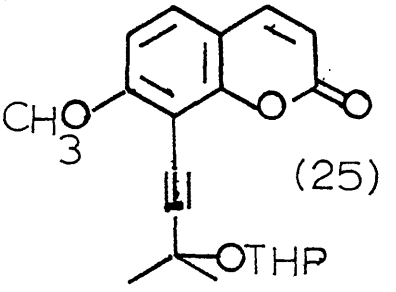

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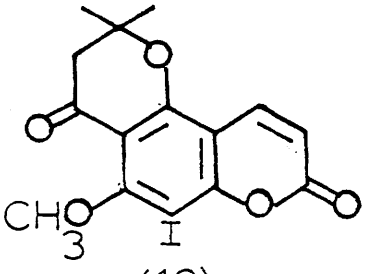

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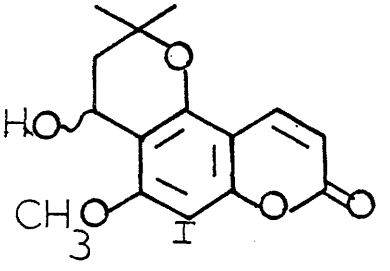

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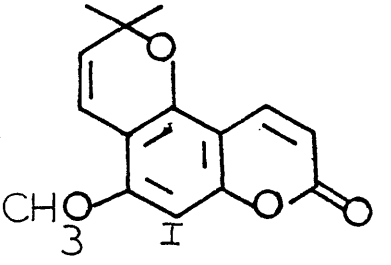
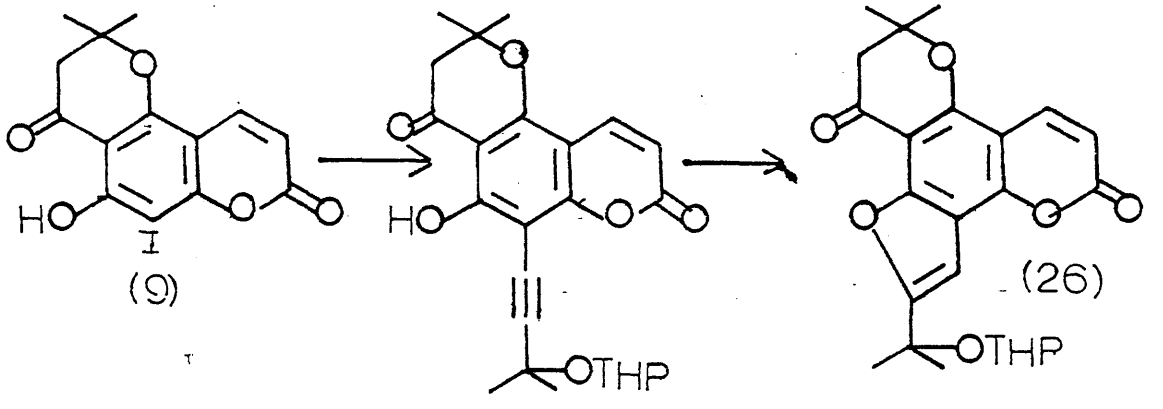
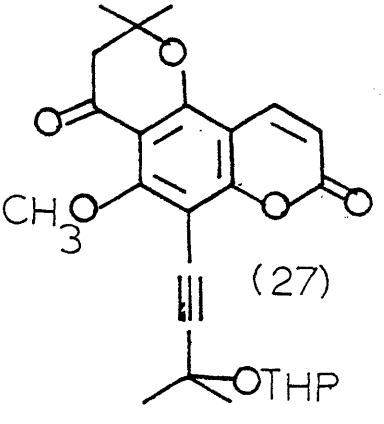


(12)

Scheme 5



(9) (26)



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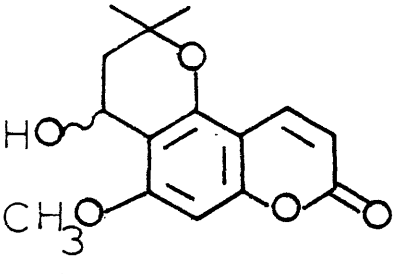
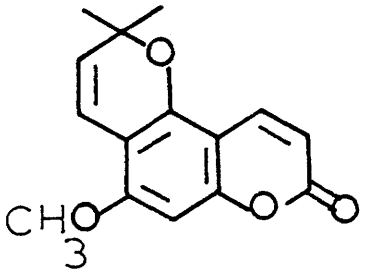


(1-8)

3-methylbut-1-yne (23) could be readily prepared and isolated and was used for coupling reactions. It had been previously shown[16] that treatment of (24) with (21) in refluxing pyridine, under an inert atmosphere for 18hr., produced the coupled compound (25) in around 50% yield. Consequently those conditions were initially used for the following reactions. Treatment of the chromanone (10) in this manner produced a complex mixture from which two compounds could be isolated and identified. The major product (30%) was the de-iodinated compound (17), de-iodination is a well documented side reaction of cuprous acetylide couplings[17]. The only other isolable compound proved to be the furan (26), which was readily identified by the characteristic aromatic singlet in the n.m.r. at δ7.34. Its genesis has to be from traces of the iodophenol (9) (Scheme 5), which may have arisen by an *in situ* demethylation of the methyl ether (10). As it seems likely that only small amounts of the phenol (9) could have been produced, then the coupling of the phenol is a quite efficient process. No evidence could be obtained for the formation of the desired product (27).

Similar results were observed on repeating the reaction on the chromanol (11). The de-iodinated product (18) was formed in low yield (14%), though on this occasion no evidence for the formation of any furan could be obtained as the starting material had been rigorously purified to remove any phenolic impurities. The chromene (12) when treated with the cuprous acetylide (21) under the above conditions produced only a complex mixture from which no identifiable compounds



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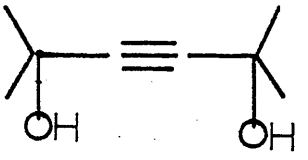

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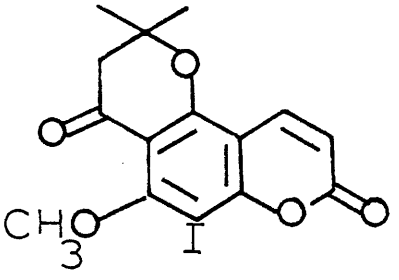

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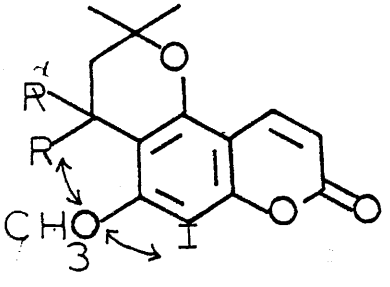


R=R'=H,O

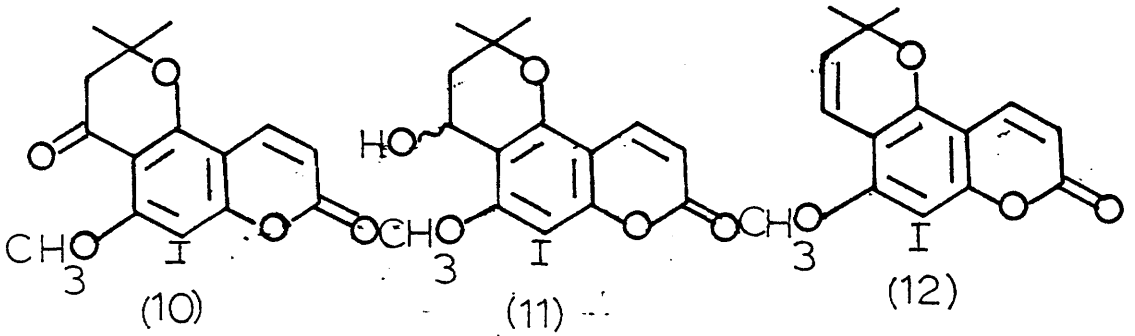
R=OH, R'=H

Figure 3

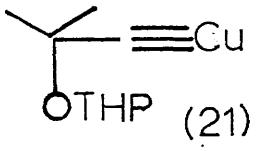
could be isolated.

It was noted that in all the above reactions, a great deal of decomposition took place and it was felt that if the reaction were repeated under milder conditions it might prove more profitable. Recently[18] Songashira et al. have reported new mild conditions for cuprous acetylide couplings with aromatic iodides. These involve treatment of the aryl iodide with the acetylene in the presence of catalytic amounts of $(Ph_3P)_2PdCl_2$[19] and cuprous iodide[20] in diethylamine at r.t. for several hours. However, when the reaction was repeated under these conditions again disappointingly no indication of any coupled compound could be found. As observed in previous cases the only coumarin isolated proved to be the de-iodinated product (29), though in this case the dimerised acetylene (30) was isolated in 62% yield as the major reaction product.

It was felt that the lack of success of the attempted coupling reactions could be attributed to the high degree of steric congestion present in the fully substituted benzene ring, previously mentioned in connection with the slow reduction of the chromanone (10). Examination of models shows a high degree of steric interation between the three positions indicated in Figure 3, namely the C-8 iodine, the C-7 methoxyl and the substituent at C-6. The interaction between the C-7 methoxyl and the C-8 iodine being aggravated by the interaction between the C-7 methoxyl and C-4' of the angular ring and vice versa,



(10) (11) (12)



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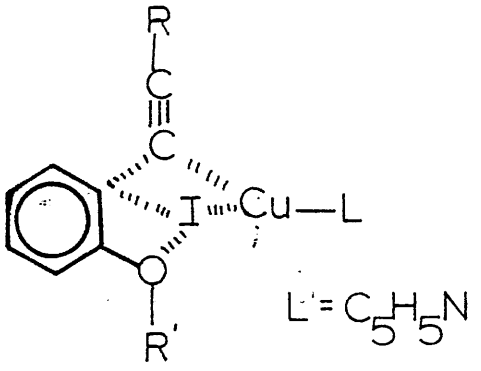
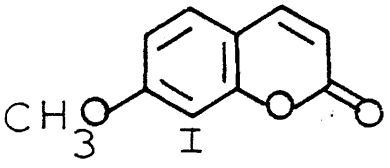


Figure 4



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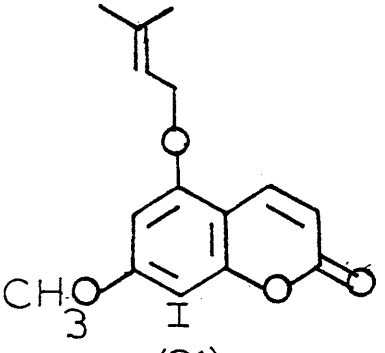
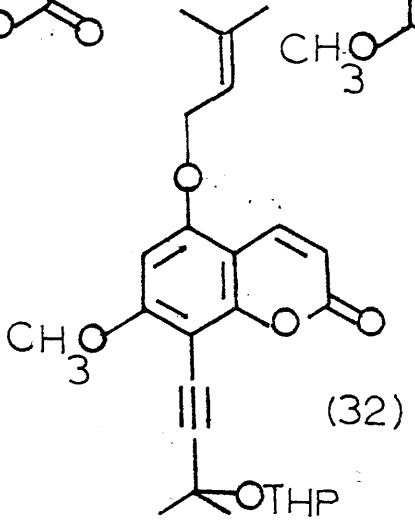


(31)



(32)

i.e. a kind of steric buttressing effect exists along that face of the molecule, the mutual interactions of these three substituents producing a high degree of steric compression. Because of this, it will be difficult for the bulky cuprous acetylide reagent (21) to approach the system close enough to effect reaction. Castro et al.[21] have postulated a four-centre transition state for cuprous acetylide couplings (Figure 4) and it might be anticipated that the steric demands on such a transition state would be too great in the sterically constrained system under consideration.

It has already been stated that 7-methoxy-8-iodocoumarin (24) will couple[16] quite readily with reagent (21). Though steric hindrance was felt to be the cause of the non-coupling of compounds (10), (11) and (12) it was conceivable that electronic effects present in the 5,7-dioxygenated instances, but not present in the 7-oxygenated case, might play an important role. Coupling of the compound (31), available from the hortiolone work, resolved this problem. This compound should have very similar electronic properties to (10), (11) and (12), though as the C-6 position is unsubstituted a lesser degree of steric congestion would exist between the critical positions C-6, C-7 and C-8. On treatment as before with the cuprous acetylide (21), this compound did indeed couple to produce (32), albeit in rather low yield (15%). This evidence supports the hypothesis that steric congestion due to the interactions of the substituents of a fully substituted benzene ring was the principal reason for the the failure of compounds (10), (11) and (12) to undergo the desired coupling. It now became clear from the above considerations

that the proposed synthesis of cis-avicennol by this route was not feasible and was consequently discontinued.

Part 2

Experimental

2,2 -Dimethyl-5,7-dihydroxychroman-4-one (7)

This was prepared by the method of Miyano and Matsui[8] using phloroglucinol (3.2g), zinc chloride (2.0g) and senecoic acid (2.0g). This gave the required chromanone (1.6g , 38%), m.p. 196-197°.

Preparation of the chromano-coumarin (6)

2,2-Dimethyl-5,7-dihydroxychroman-4-one (3g), malic acid (2g) and conc. H_2SO_4 (8ml) were heated at 125±5° for 1hr[6] to give (6) (1g, 27%), needles, m.p. 215-220° (from EtOAc), (lit.[6] m.p. 218-220°); $\nu_{max}^{CHCl_3}$ 1740, 1650, 1632 and 1595cm^{-1}; λ_{max} 278 and 323nm (log 4.38 and 4.02); n.m.r. (d_6-acetone) signals at δ1.60 (6H,s), 2.84 (2H,s), 6.25 and 7.90 (each 1H,d,J=9.5Hz.), 6.44 (1H,s), and 12.10* (1H,s).

Methylation of (6)

Potassium carbonate (80mg) was added to a solution of (6) (125mg) in acetone (25ml) and the mixture stirred at r.t. for 0.5hr. Methyl iodide (0.75ml) was then added and the mixture refluxed for 20hr. Work-up procedure I gave the methyl ether (17) (100mg, 76%) as colourless plates, m.p. 190-191° (from $CHCl_3$-ether), (lit.[13] m.p. 193-194°); ν_{max} 1732, 1682 1614 and 1594cm^{-1}; λ_{max} 230 (sh), 273 and 318nm (log 3.80, 4.15 and 3.87); n.m.r. signals at δ1.52 (6H,s), 2.76 (2H,s), 4.05 (3H,s), 6.23 and 8.01 (each 1H,d,J=9.5Hz.) and 6.45 (1H,s).

Iodination of (6)

To a stirred solution of (6) (200mg) in $CHCl_3$ (30ml) were added

in portions over a period of 0.5 hr, iodine (280mg) and mercuric oxide (175mg) whilst maintaining vigorous stirring. The solids were then filtered off and washed thoroughly with $CHCl_3$. The combined organic layers were then washed with dilute aqueous sodium thiosulphate, dried over Na_2SO_4 and evaporated to dryness. Crystallisation of the resultant solid from EtOAc-petrol yielded (9) (250mg, 67%) as yellow needles, m.p. 232-236°; (Found: C,43.23; H,3.10; I,33.05. $C_{14}H_{11}O_5I$ requires: C,43.52; H,2.84; I,32.90%); n.m.r. (d_6-acetone) signals at δ 1.53 (6H,s), 2.87 (2H,s), 6.15 and 7.82 (each 1H,d,J = 9.5Hz.) and 12.31* (1H,s); $\nu_{max}^{CHCl_3}$ 1765, 1650, 1625, 1450, 1400 and 1380cm^{-1}; mass spectral peaks at m/e 386 (91% M^+), 369 (22), 368 (100), 327 (73), 326 (70) and 299 (81).

Methylation of (9)

Potassium carbonate (250mg) was added to a stirred solution of (9) (500mg) in acetone (50ml) and stirred for 0.5hr at r.t. Methyl iodide (2.1ml) was then added and the mixture refluxed for 20hr. Work-up procedure I yielded (10) (420mg, 79%) as light yellow needles (from methanol) m.p. 185-186°; (Found: C,44.81; H,3.14; I,32.01. $C_{15}H_{13}O_5I$ requires: C,45.00; H,3.25; I,31.75%); n.m.r. signals at δ1.50 (6H,s), 2.75 (2H,s), 4.05 (3H,s), 6.21 and 7.83 (each 1H,d,J = 9.5Hz.); ν_{max}^{KBr} 1760. 1695, 1615, 1575, 1390 and 1220cm^{-1}; mass spectral peaks at m/e 400 (51% M^+), 386 (95), 371 (100), 344 (40), 331 (27), 330 (26), 321 (33) and 302 (27).

Reduction of (10)

To a stirred solution of (10) (100mg) in isopropanol/$CHCl_3$ (4:1

25ml) was added $NaBH_4$ (7.5mg) and the mixture stirred at r.t. for 24hr. The solution was then diluted with water (50ml) and extracted with ethyl acetate. The combined organic layers were washed with dilute HCl, brine to neutrality, dried over Na_2SO_4 and evaporated to dryness. The resultant solid on crystallisation from EtOAc-Petrol gave (11) as white needles (75mg, 74%) m.p. 154-158°; n.m.r. signals at δ1.41 (3H,s), 1.46 (3H,s), 2.10 (2H,d,J = 6Hz), 3.98 (3H,s), 5.03 (1H,t,J = 6Hz) and 6.20 and 7.91 (each 1H,d,J =9.5Hz); ν_{max}^{KBr} 3500, 1740, 1610, 1590, 1140 and 830 cm^{-1}; mass spectral peaks at m/e 402 (11% M^+), 400 (59), 385 (29), 384 (18), 374 (76), 344 (100) and 316 (52).

Dehydration[12] of (11)

To a stirred solution of (11) (120mg) in toluene (20ml) was added potassium hydrogen sulphate (650mg) and the mixture refluxed for 7hr. The solids were then filtered off, the toluene removed in vacuum and the resultant yellow oil purified by prep. t.l.c. (EtOAc/Petrol 1:2) to yield (12) (54mg,50%) as colourless needles (from Et_2O) m.p. 135-137°. (Found: C, 46.91; H, 4.21; I 32.76. $C_{15}H_{16}O_4I$ requires C, 46.63; H, 4.15; I, 32.90); n.m.r. signals at δ1.45 (6H,s), 3.83 (3H,s), 5.65 (1H,d,J = 10Hz), 6.23 (1H,d,J = 9.5Hz), 6.57 (1H,d,J = 10Hz) and 7.95 (1H,d,J = 9.5Hz); ν_{max}^{KBr} 2900, 1735, 1625, 1615, 1580, 1555 and 1230 cm^{-1}; mass spectral peaks at m/e 384 (39% M^+), 369 (100) and 354 (18).

Formation[15] of the tosylhydrazone (19)

To a stirred solution of (10) (200mg) in dry THF (15ml) was added

NH_2NHTs[15] (100mg) and 2 drops of conc. HCl and the mixture refluxed for 2.5hr. After cooling dry benzene (50ml) was added and the solution placed in a Dean and Stark apparatus and refluxing continued until all the H_2O had been removed. Evaporation of the solvent gave the crude tosylhydrazone (19) (280mg,82%) as a yellow solid. This compound was used without further purification. n.m.r. signals at δ 1.03 (6H,s), 2.06 (3H,s), 2.70 (2H,s), 3.73 (3H,s), 6.23 (1H,d,J =9.5Hz.), 6.91 (2H,d,J = 8Hz), 7.80 (2H,d,J = 8Hz) and 7.94 (1H,d,J = 9.5Hz); ν_{max}^{KBr} 3120, 1740, 1625, 1610, 1575, 1320, 1300, 1280 and 1130cm^{-1}; mass spectral peaks at m/e 604 (15%M^+), 450 (68), 386 (100), 371 (91), 340 (26) and 330 (13).

Attempted formation of chromene (12) from (19)

To a stirred solution of (19) (100mg) in dry ether (2oml) under argon at r.t. was added 0.6ml (0.28eq) of n-butyllithium (1.58M solution in hexane) and stirring continued for 3.5hr. when t.l.c. indicated no remaining starting material. Water (10ml) was then added, the layers separated and the aqueous layer extracted with Et_2O (x4). The combined organic layers were dried over Na_2SO_4 and evaporated to yield a light yellow oil (76mg), which TLC showed to be a complex mixture from which (12) could not be isolated.

Preparation of the tetrahydropyranyl ether of 3-hydroxy-3 methylbut-1-yne (22)

3-Hydroxy-3-methylbut-1-yne (8.4g) and dihydropyran (16g) were mixed and a few crystals of p-toluenesulphonic acid added. The solution was stirred for 0.5hr, when K_2CO_3 (200mg) were added and stirring continued for a further 0.5hr. Distillation of the

filtered solution gave the required tetrahydropyranyl ether (22) (15.2g, 90%), b.p. 60-65°/8mm (lit[22] b.p. 65.5°/8mm); n.m.r. signals at δ 1.50 (3H,s), 1.57 (3H,s), 1.70 (6H,bm), 2.43 (1H,s), 3.80 (2H,bm) and 5.13 (1H,bs).

Preparation of the cuprous acetylide (21)

Sodium sulphite (7.5g) in water (25ml) was added to a solution of cupric chloride (5g) in water (5ml). The resultant white precipitate was washed with water (3x20ml) after decanting the supernatant liquid. The following operations were carried out under an argon atmosphere. Sufficient saturated aqueous ammonium chloride was added to dissolve the white precipitate obtained above and sodium acetate (~2g) was added to make the solution slightly alkaline. To this solution was added 3-hydroxy-3-methylbut-1-yne tetrahydropyranyl ether (1.3g) in ethanol (30ml). Addition of water to the resultant bright yellow solution precipitated the cuprous acetylide (21) as a bright yellow solid. This precipitate was filtered on a sintered glass funnel, washed with water, ethanol and ether and dried in vacuum.

Attempted coupling of the chromanone (10) and (21)

A solution of (10) (250mg) and (21) (150mg) was refluxed in dry pyridine (20ml) under argon for 20hr. Work-up II gave a brown oil (200mg) which t.l.c. showed to be a complex mixture. Prep. t.l.c. (EtoAC/Petrol 1:1) yielded only the following identifiable materials;

i) the de-iodinated product (17) (51mg,31%) identified by

comparison with an authentic sample (t.l.c.,n.m.r,m.p.) and

ii) the furan (26), (11mg) as a yellow oil, n.m.r. signal at δ1.49 (6H,s), 1.56 (6H,bm), 1.67 (3H,s), 1.75 (3H,s), 2.87 (2H,s), 3.67 (2H,bm), 4.71 (1H,bm), 6.21 and 7.91 (each 1H,d,J = 9.5Hz) and 7.34 (1H,s).

Attempted coupling of the chromanol (11) with (21)

A solution of (11) (250mg) and (21) (160mg) was refluxed in dry pyridine (20ml) under argon for 20hr. Work-up II gave a brown oil (290mg) which t.l.c. showed to be a complex mixture. Prep. t.l.c. (EtOAc/Petrol 1:1) facilitated the isolation of only one identifiable product, the de-iodinated product (28) (25mg,14%); n.mr. signals at δ1.47 (3H,s), 1.50 (3H,s), 2.10 (2H,d,J, = 6Hz), 4.01 (3H,s), 5.03 (1H,t,J = 6Hz), 6.21 and 7.91 (each 1H,d,J = 9.5Hz) and 6.50 (1H,s).

Attempted coupling of (12) with (21)

i) (12) (200mg) and (21) (100mg) were refluxed in dry pyridine (15ml) under argon for 20hr. Work-up II gave a brown oil (170mg) which t.l.c. showed to be a complex mixture from which no useful information could be obtained.

ii) A stirred solution[18] of (12) (100mg), 3-hydroxy-3-methylbut-1-yne (23)(50mg), $(Ph_3P)_2PdCl_2$[19] (5mg) and cuprous iodide[20] (5mg) in dry diethylamine (25ml) was kept under argon for 24hr. at r.t. Most of the solvent was then removed under reduced pressure and the residues diluted with water, carefully acidified, extracted with EtOAc, the combined organic layers were washed to neutrality with

brine, dried over Na_2SO_4 and evaporated to yield a yellow oil (100mg) which on purification by prep. t.l.c. (EtOAc/Petrol 1:1) gave

i) the de-iodinated compound (29) (25mg,32%) m.p. 113-115°(lit[13] 115-116°); n.m.r. signals at δ1.45 (6H,s), 3.91 (3H,s), 5.67 and 6.58 (each 1H,d,J = 10 Hz), 6.23 and 8.00 (1H,d,J = 9.5Hz) and 6.49 (1H,s) and

ii) the dimerised acetylene (30) (31mg,62%) identified by comparison with authentic sample (t.l.c.,m.p. and n.m.r.).

Coupling of (31) with (21)

A solution of (31) (100mg) and (21) (50mg) were refluxed in dry pyridine (20ml) under argon for 18hr. Work-up II gave a brown oil (105mg) which on purification by prep. t.l.c. (EtOAc/Petrol 2:3) yielded (32) (14mg,15%) as colourless needles (ether/petrol) m.p. 124-126°; n.m.r. signals at δ 1.66 (3H,s), 1.70 (3H,s), 1.75 (6Hbm), 180 (3H,s), 1.85 (3H,s), 3.73 (2H,bm), 4.01 (3H,s), 4.70 (2H,bd,J = 6.5Hz), 5.37 (1H,bs), 5.54 (3H,bt,J = 6.5Hz), 6.16 and 8.06 (each 1H,d,J = 9.5Hz) and 6.40 (1H,s), mass spectrum shows molecular ion M^+ at m/e 428.

Part 2

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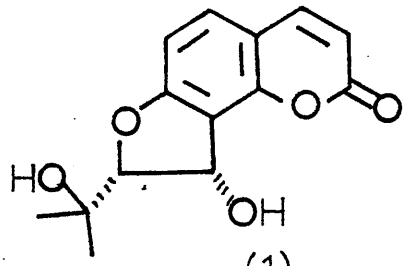
Part 3

Synthetic Approaches to the Coumarins Vaginidiol and Vaginol



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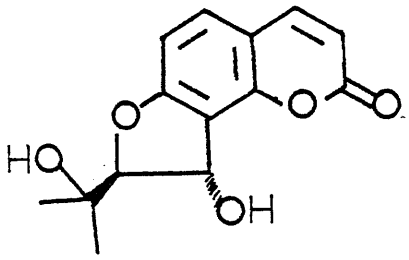

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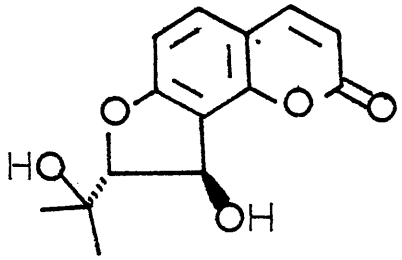

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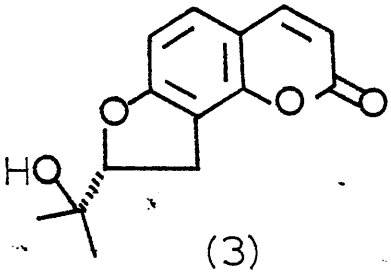
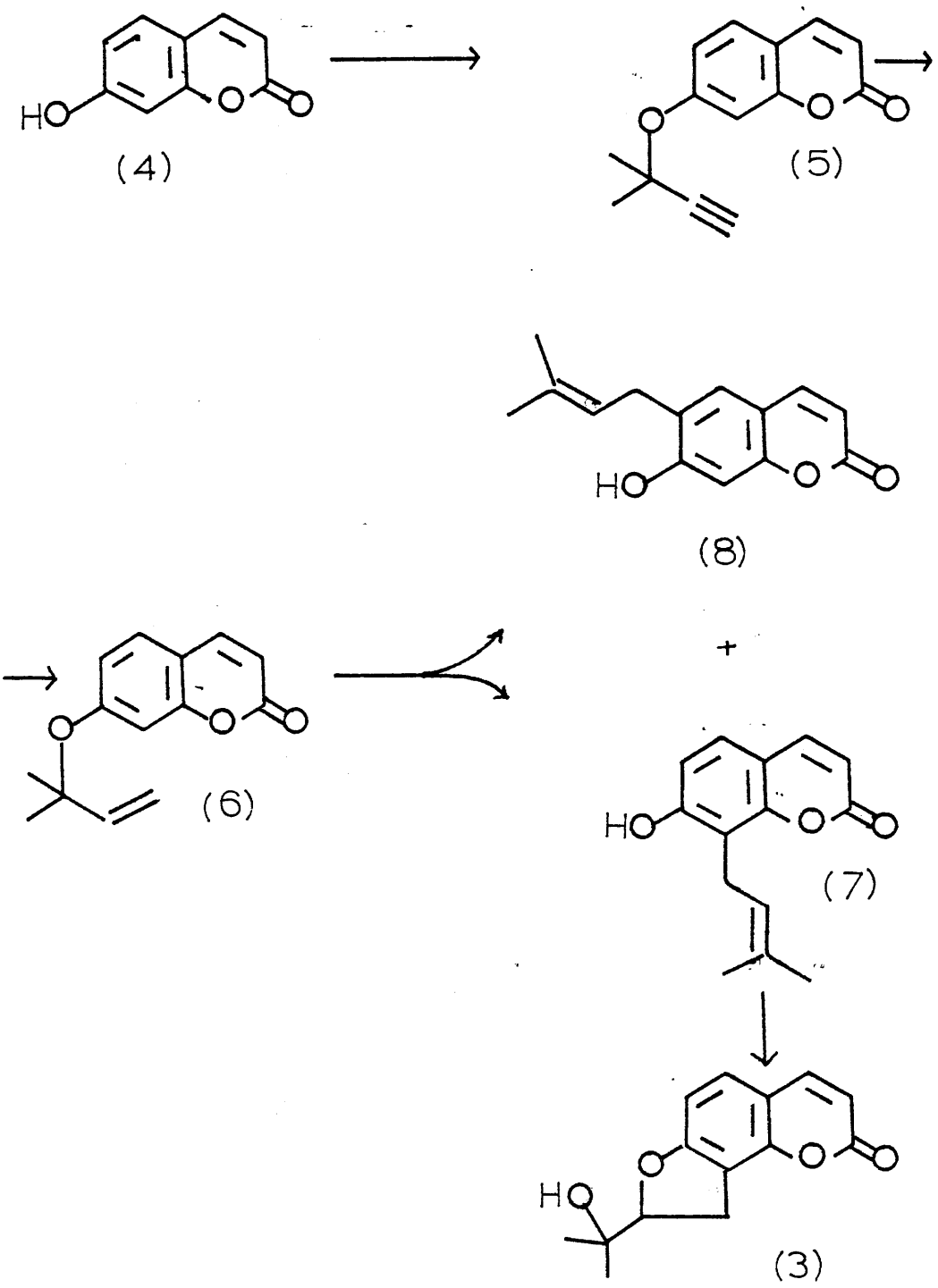


(3)

In 1971 the diol (1), named vaginidiol, was isolated[1] from Selinium vaginatium, just one year after it was proposed[2] as an intermediate in the biosynthesis of angular furanocoumarins (vide supra). It was assigned the cis stereochemistry, as shown, on the basis of the magnitude of the coupling constant (6Hz) between the two dihydrofuran ring protons. This assignment was only possible, as a diastereoisomer, vaginol (2), which exhibited a 3.5Hz coupling constant, had been previously isolated from the same plant source[3]. Bothner-by[4] had previously shown that in five-membered rings, $J_{cis} > J_{trans}$, thus a cis and trans stereochemistry could be assigned to vaginidiol (1) and vaginol (2) respectively. This is in agreement with the values predicted by the Karplus curve, assuming dihedral angles of 0° and 120° between the cis and trans protons respectively. Then the expected values for the coupling constant are 7Hz (cis) and 4Hz (trans). The absolute stereochemistry of vaginidiol (1) was shown to be 2'(S), 3'(R), by correlation, through hydrogenolysis, with optically active columbianetin[1] (3). The absolute stereochemistry of vaginol (2) is not known. At present, it is unclear whether either, or both, of these diols are involved in furanocoumarin biosynthesis. Thus, a synthesis of these diols would be of great value, in that labelling experiments could then be carried out in order that this problem be resolved.

A number of approaches to the synthesis of vaginidiol (1) and vaginol (2) have been previously investigated in this depart-

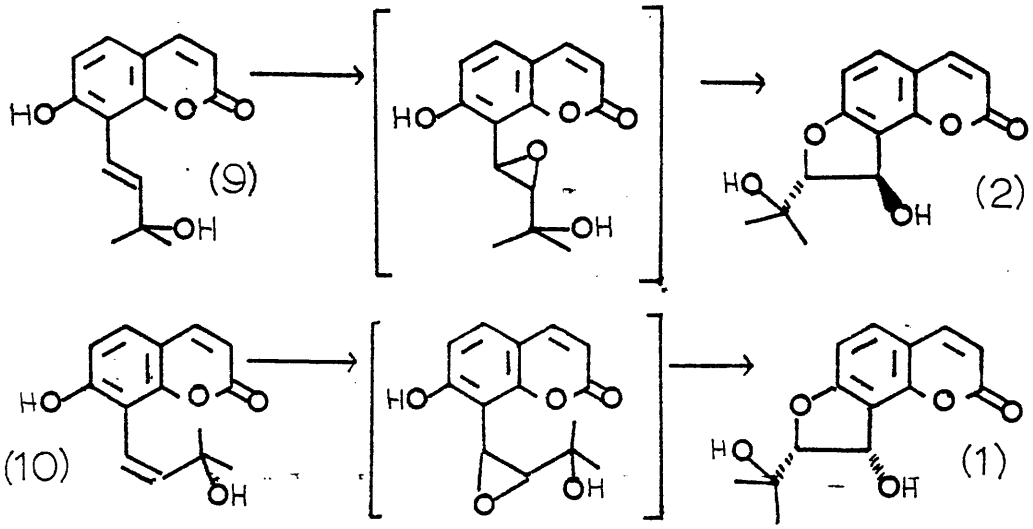
Scheme 1



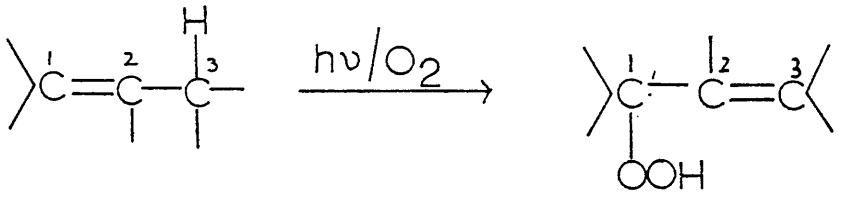
ment. The first involved a biomimetic type synthesis[5], in that benzylic hydroxylation of columbianetin (3) was attempted. A synthesis of columbianetin was readily achieved as illustrated in Scheme 1. Umbelliferone (4) was treated with 3-chloro-3-methylbut-1-yne[6], in refluxing 2% aqueous acetone in the presence of potassium carbonate and a catalytic amount of potassium iodide. This facilitated the preparation of the desired propargyl ether (5) in 70% yield. Semi-hydrogenation over 5% palladium on barium sulphate with a carefully controlled amount of sulphur-quinoline poison yielded 7-O-(1,1-dimethylallyl)umbelliferone(6) almost quantitively. Pyrolysis of this ether at 130° for 1 hour gave a three component mixture. The two major products were osthenol (7) and 7-demethylsuberosin (8) in the ratio of 5:1, the third compound being umbelliferone (4) which was formed in only trace amounts. Separation of this mixture was achieved by prep. t.l.c.

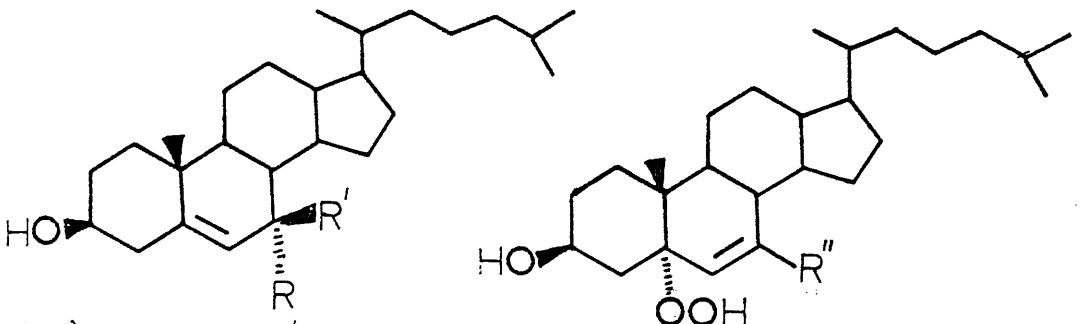
Osthenol (7), on reaction with meta-chloroperbenzoic acid gave only columbianetin (3). The opening of the presumed epoxide intermediate at the less substituted carbon was anticipated, under the effectively neutral conditions employed. The proposed benzylic oxidation of columbianetin (3) was then attempted, employing a variety of oxidising agents, each of which was known to facilitate benzylic oxidation. However, no useful oxidation could be achieved. Benzylic bromination proved similarly unsuccessful.

Scheme 2



Scheme 3





(11) R = H, R' = D

(12) R = D, R' = H

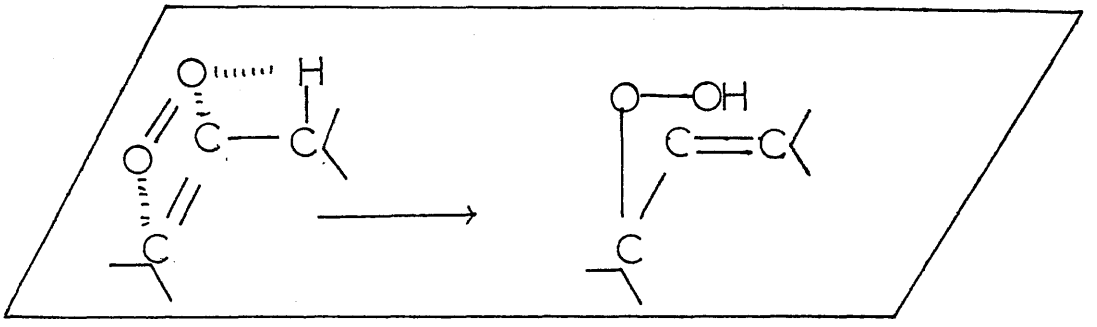
(13) R'' = D

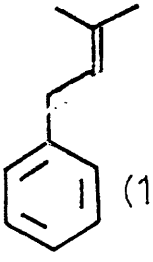
(14) R'' = H

It was now clear that any successful route to vaginidiol (1) and vaginol (2) would require that the benzylic position be functionalised prior to cyclisation. Two such approaches have been investigated in this department[7]. The first required the allylic alcohols (9) and (10) as illustrated in Scheme 2. The trans allylic alcohol (9) was readily synthesised from osthenol (7). The dye sensitised photo-oxygenation of olefins[8,9], which leads to allylic hydroperoxides (Scheme 3) is a convenient method for the introduction of oxygen at a specific site in a molecule. Nickon and Bagli[9] have shown that photo-oxygenation of cholesterols labelled at the 7α and 7β positions, (11) and (12), led exclusively to the formation of the 5α hydroperoxides, (13) and (14) respectively. Thus, they deduced that hydrogen abstraction at C-7 occurred on the same side of the molecule as that on which the new carbon-oxygen bond was formed. Consequently, they postulated a cis cyclic "ene-type" mechanism (Scheme 4), in which the most favourable orientation for reaction had an allylic hydrogen atom perpendicular to the olefinic plane.

It is known that hydrogen abstraction during photo-oxygenation of an aromatic 3,3-dimethylallyl group (14) occurs at the doubly activiated benzylic position[8]. Nickon and Bagli[9] have shown that there are two distinct conformations of the 3,3-dimethylallyl group in (14) that could react with singlet oxygen, i.e. (15) and (16), which possess an allylic hydrogen atom perpendicular to the olefinic plane. As shown in

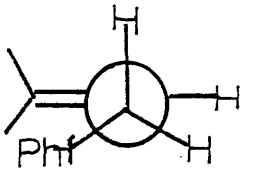
Scheme 4





(14)

Scheme 5



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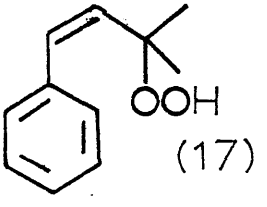

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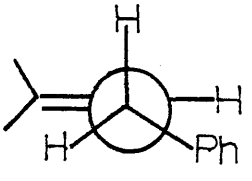

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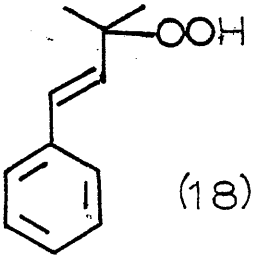
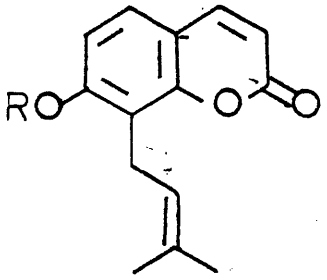


(18)

Scheme 5, reaction of (15) with singlet oxygen would lead stereospecifically to the cis allylic hydroperoxide (17), whereas (16) would yield the trans hydroperoxide (18). As a result of steric interactions, conformation (16) should be greatly favoured over (15) and on this basis Murray and Forbes[7] predicted that dye sensitised photo-oxygenation of osthenol (7) should yield stereoselectively the trans allylic hydroperoxide (19).

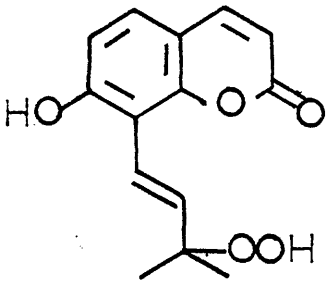
They, indeed, showed this to be the case, as treatment of osthenol acetate (20) (for some reason osthenol (7) would not react) in pyridine, with oxygen and haemotoporphyrin as sensitiser, followed by reduction with sodium iodide/acetic acid yielded the trans allylic alcohol (21) in 50% yield. The n.m.r. signals of the two olefinic protons on the 3-hydroxy-3-methylbut-1-enyl side chain in (21) were accidentally equivalent, but were separated by the addition of small amounts of $Eu(fod)_3$, which enabled the trans coupling constant of 17Hz to be determined. Epoxidation of (21) proceeded cleanly to give (22) which on mild basic hydrolysis produced a complex mixture which did not contain the desired product (2). Treatment of the phenol (9) with peracid yielded a similar complex mixture.

The key compound in the second approach (Scheme 6) of Murray and Forbes was the allylic alcohol (23). The cyclisation proposed here was a direct analogy to the oxidative cyclisation of osthenol (7) which gives rise to columbianetin (3) (Scheme 1).



(7) R=H

(20) R=COCH$_3$



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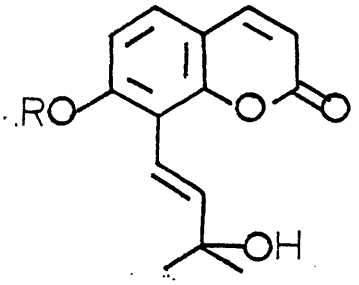
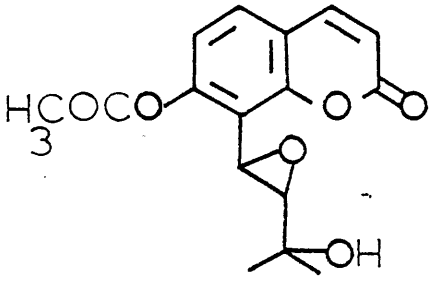


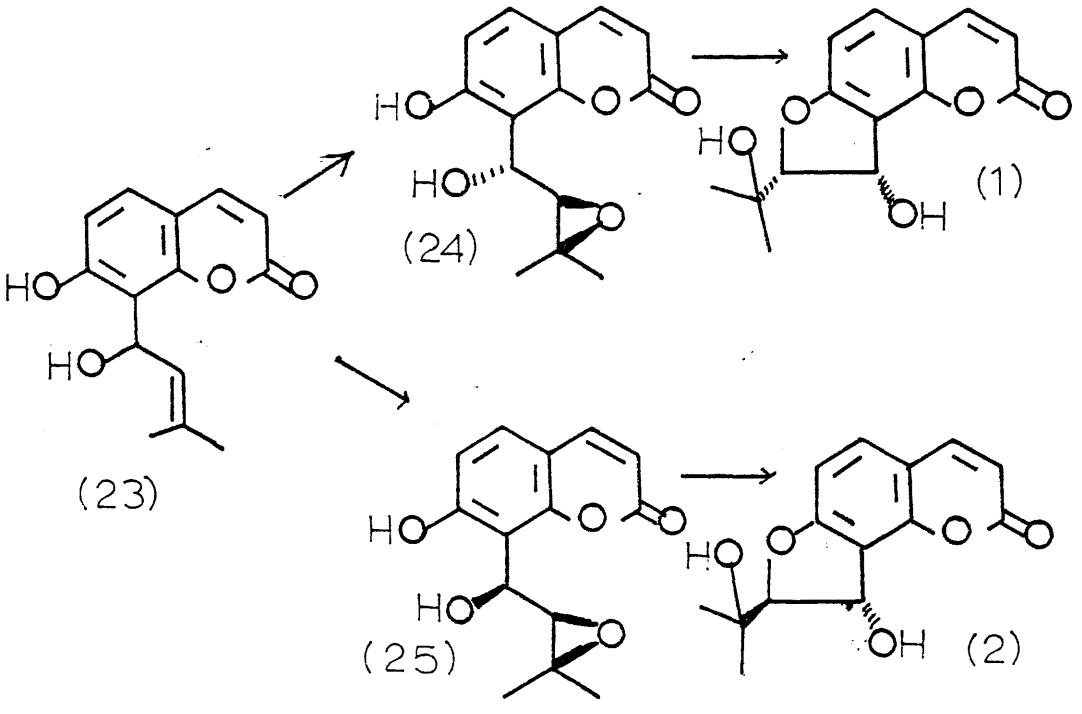
(9) R=H

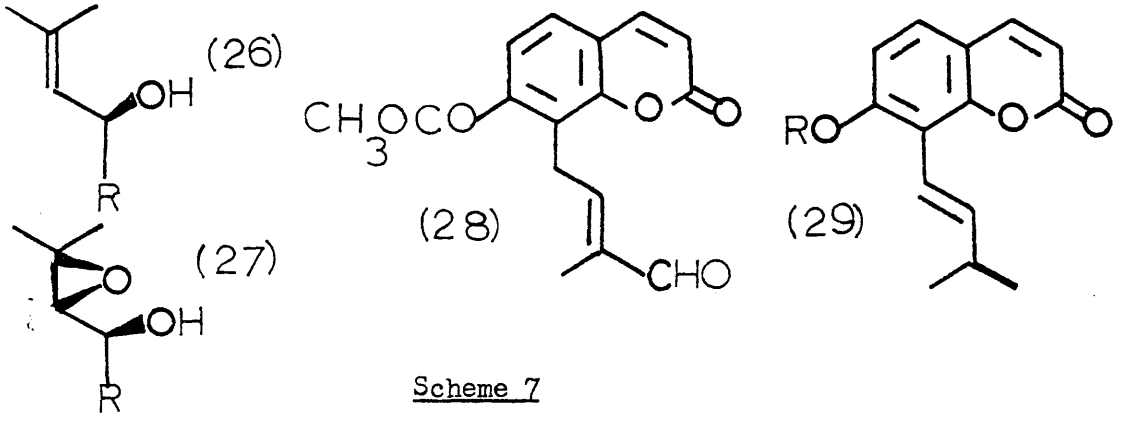
(21) R=COCH$_3$



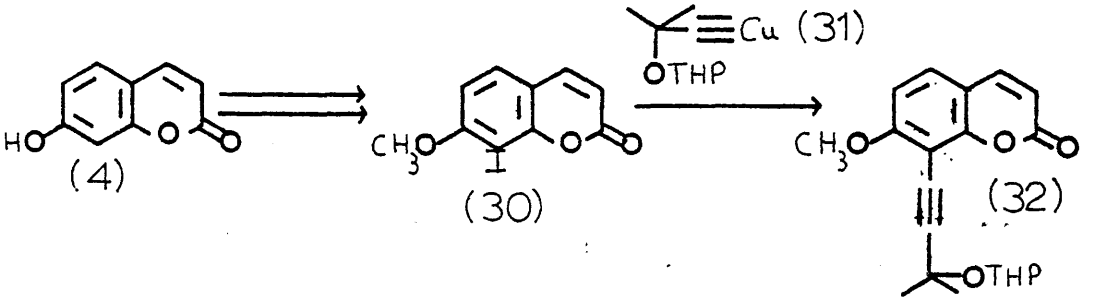
(22)

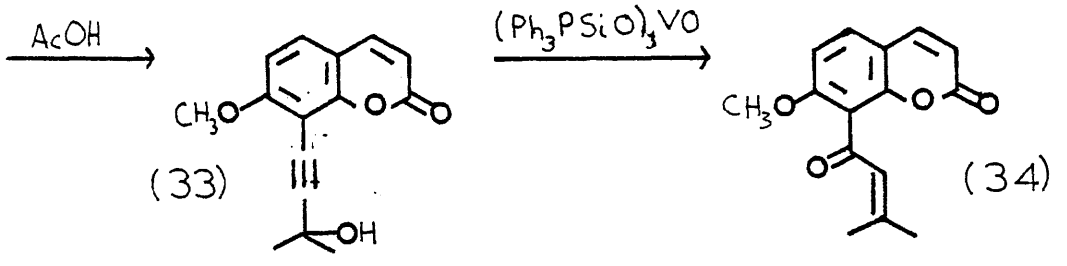
Scheme 6



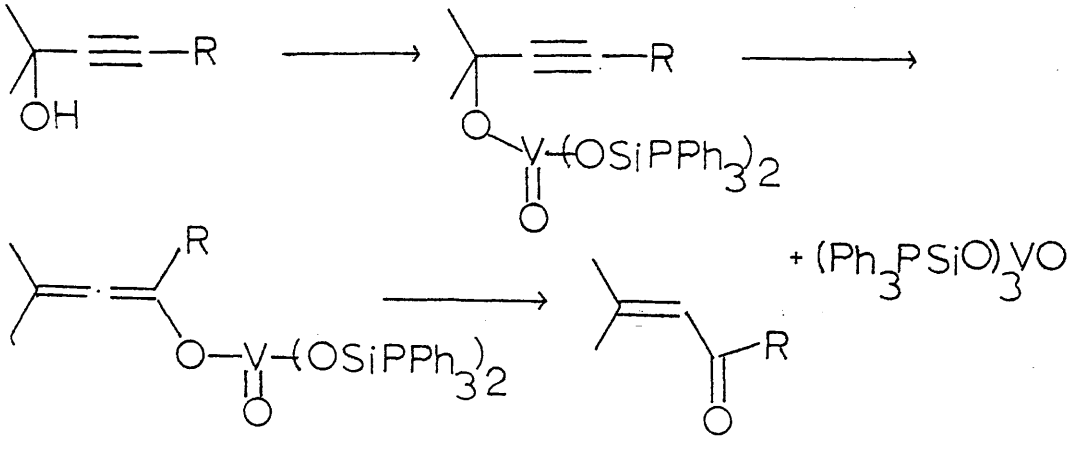


Scheme 7



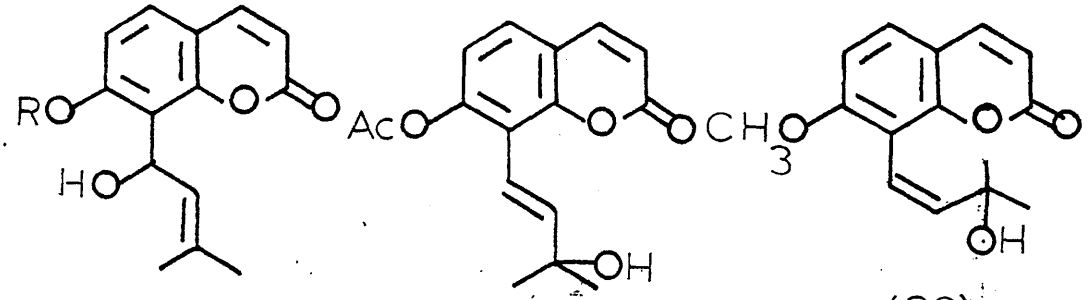


Scheme 8



With this approach, however, a mixture of vaginidiol (1) and vaginol (2) should be produced, the ratio depending upon the stereochemistry of epoxidation. It is known that the hydroxyl group in allylic alcohols of type (26) has a directing effect on the stereochemistry of epoxidation[10]. Such allylic alcohols, with peracid, form the threo epoxide (27) preferentially. Consequently epoxidation of (23) should lead to a stereo-selective formation of the epoxy phenol (25) and hence a predominance of vaginol (2).

Murray and Forbes attempted a number of unsuccessful routes to the key allylic alcohol (23). Direct oxidation of osthenol acetate (20) they found, yielded only the aldehyde (28), whilst photo-oxygenation of species of type (29) proved to be impossible. Another approach, they considered, was the reduction of the enone (34) which was readily synthesised as in Scheme 7. This isomerisation of α-acetylenic alcohols to the corresponding α,β-unsaturated ketones has been known for many years (the Meyer-Schuster reaction[11]). This reaction was originally accomplished by heating the alcohol in the presence of an acid catalyst, recently, however, the use of tris (triphenylsilyl)vanadate[12] in refluxing xylene allows the transformation to proceed under much milder conditions (Scheme 8). However, despite the use of a number of reducing agents known to bring about 1,2-reduction[13] (e.g. 9-BBN, di-isobutylaluminium hydride etc.), it proved impossible to selectively reduce the ketone carbonyl to yield

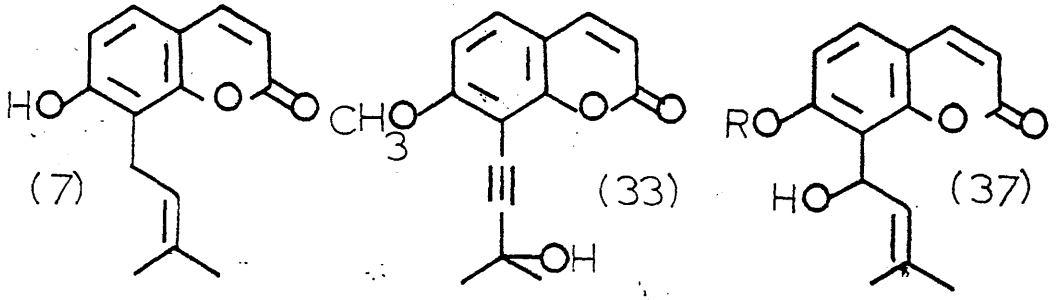


(23) R = H

(35) R = CH_3

(21)

(36)



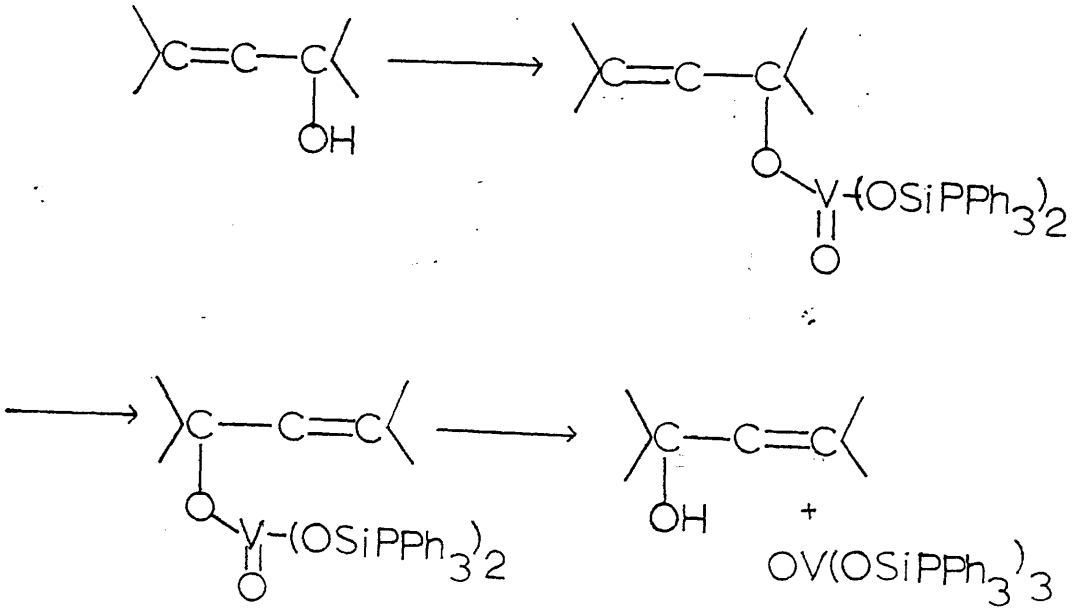
(7)

(33)

(37)

R = Me, Ac

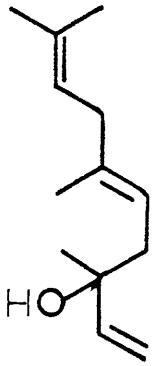
Scheme 9



the allylic alcohol (35).

In the following discussion some new approaches to the allylic alcohol (23) and some related studies will be described.

The allylic alcohols (21) and (36) were available from the photo-oxygenation of osthenol (7) and the semi-hydrogenation of the acetylenic alcohol (33) respectively. This suggested a possible route to the target allylic alcohol (37) via an allylic isomerisation of one or other of these compounds. The use of tris(triphenylsilyl)vanadate as a catalyst for the isomerisation of α-acetylenic alcohols has already been referred to. Further to this, it was considered that the isomerisation of an allylic alcohol by a similar mechanism (Scheme 9), was a possibility worth exploring. Initially, nerolidol (38) was used as a model system to test the feasibility of this hypothesis. By refluxing nerolidol (38) in toluene in the presence of catalytic amount of tris(triphenylsilyl)vanadate for 3hr. allylic isomerisation did indeed result. This was readily determined from the n.m.r. spectrum of the crude product. The characteristic doublet at δ4.14 of the methylene protons α to the hydroxyl in the isomerised product (39) was clearly seen. From the integration of the spectrum it was clear that the extent of conversion was only around 25%, i.e. the equilibrium lies heavily on the side of starting material. Similar results were observed on repeating the reaction with one equivalent of tris(triphenylsilyl)vanadate, or on



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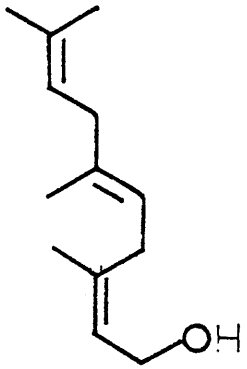
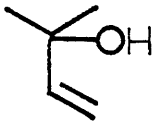
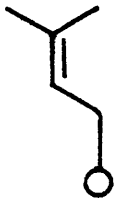


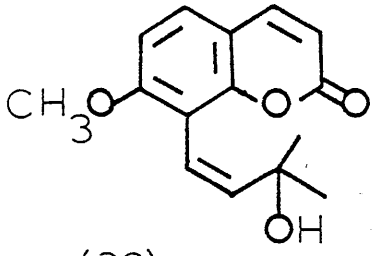
(39)



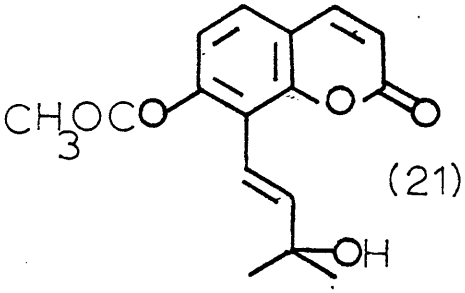
(40)



(41)



(36)



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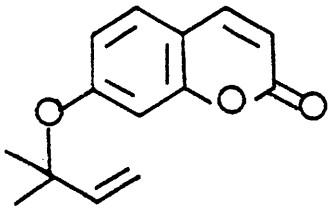

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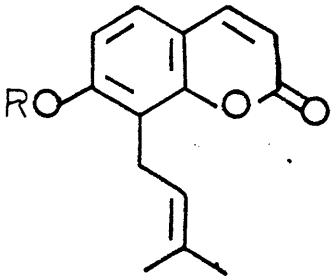
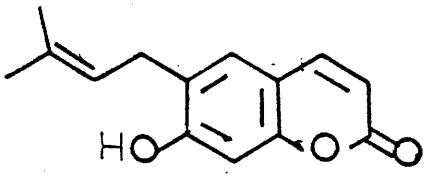


(7) R =H

(20) R= $\rightarrow COCH_3$

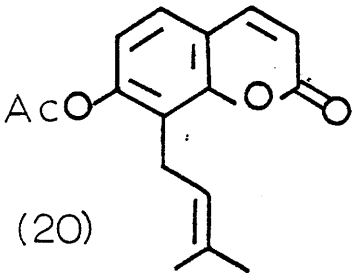


(8)

increasing the reaction time to 24hr. Chabardes[14] et al. have independently published similar results. They have shown that 3-hydroxy-3-methylbut-1-ene (40) when treated at 150° with catalytic amounts of tetrahydrolinalyl orthovanadate for 7hr. yielded an equilibrium mixture of (40) and(41) in a ratio of 3:1. A number of analogous compounds reacted similarly.

The possibility of the desired allylic isomerisation occurring by this technique was thus established, but first the required demethylation of the cis allylic alcohol (36) was investigated. The preferred method for demethylation of coumarin phenolic methyl ethers that has been used in this department is by treatment with boron tribromide[15] at -78° in methylene chloride. Reaction of (36) under these conditions however, gave a mixture of at least six products. Attention was thus turned to the trans allylic alcohol (21).

Osthenol acetate (20) was synthesised by a modified, and improved route to that previously described (vide supra). 7-O-(1,1-dimethylallyl)umbelliferone (6) was prepared as before[6]. Previously, the Claisen rearrangement required to produce osthenol (7) had been achieved either by pyrolysing the neat ether[6] or its N,N-diethylaniline solution[16]. Both these methods produced 7-demethylsuberosin (8) in around 10-15% yield, as a by-product, and a difficult chromatographic separation was required, in order that osthenol (7) could be isolated pure. Kishi[17] has recently published new conditions for the Claisen rearrange-



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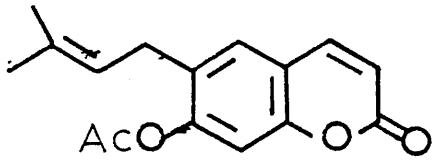
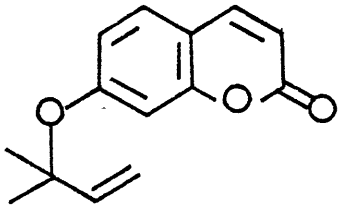


(42)

Scheme 10



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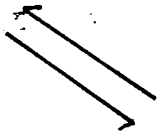

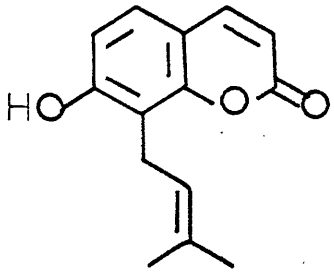

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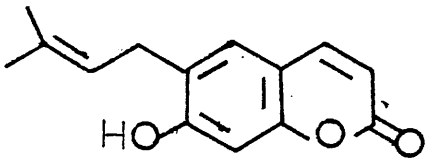
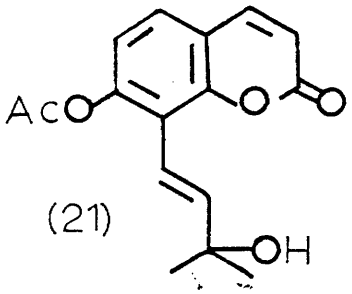


(8)

ment of 1,1-dimethylallyl ethers. These involve refluxing the ether for 1-2hr. in acetic anhydride in the presence of sodium acetate. The first formed phenol is thus trapped as its acetate and further undesired reactions, such as the abnormal Claisen rearrangement, are consequently eliminated. 7-O-(1,1-dimethylallyl)umbelliferone (6), when treated in this manner, produced osthenol acetate (20) contaminated with only ~5% 7-demethylsuberosin acetate (42), (estimated from n.m.r.) which could be readily removed by fractional crystallisation. The yield of pure osthenol acetate from this reaction was 85%. That rearrangement to the 6-position is disfavoured, by this technique, with respect to the earlier ones, may be due to a number of reasons. The rate of the Claisen rearrangement is known to depend upon the polarity of the solvent[18]. It may be that on changing from N,N-diethylaniline to acetic anhydride the rate of rearrangement into the 8-position is altered differentially to that of rearrangement into the 6- position. Alternatively, as the Claisen rearrangement is known to be a reversible process[19], an equilibrium, as illustrated in Scheme 10, may be set up during the pyrolysis of 7-O-(1,1-dimethylallyl)umbelliferone (6). If the first formed phenol is osthenol (7), then trapping of (7) as the acetate will eliminate the retro-Claisen rearrangement and thus disfavour the formation of (8). Photo-oxygenation of osthenol acetate (20) then proceeded as before.

The allylic alcohol (21) was now refluxed with one equivalent



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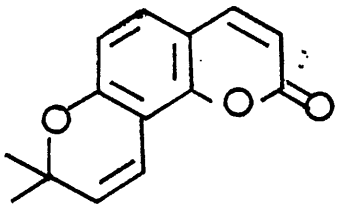
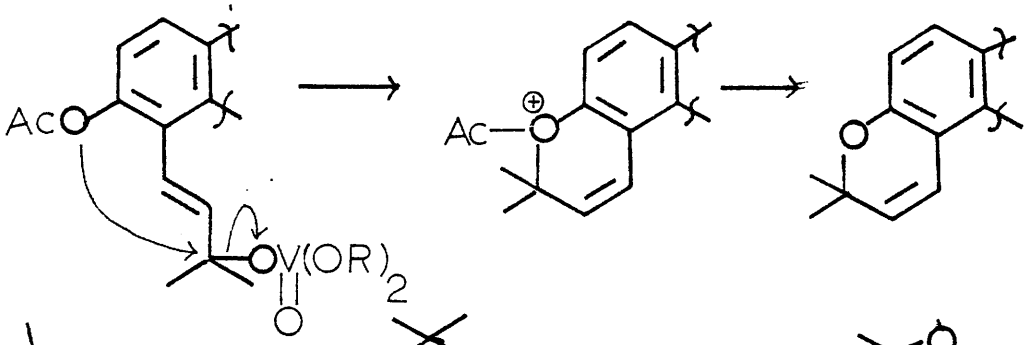
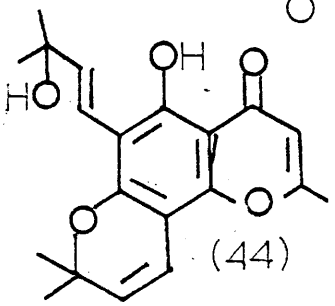


(43)

Scheme 11





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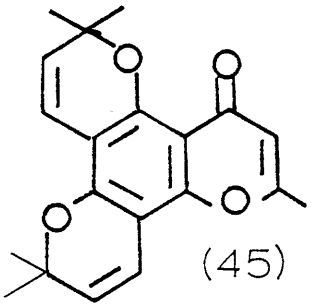

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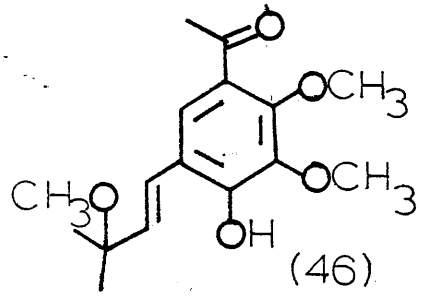
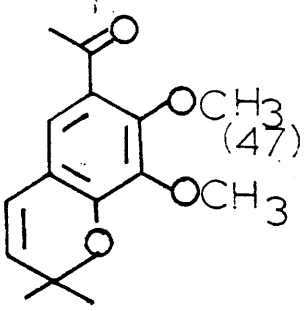


(46)

Scheme 12



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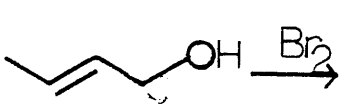
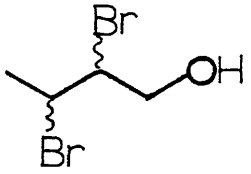
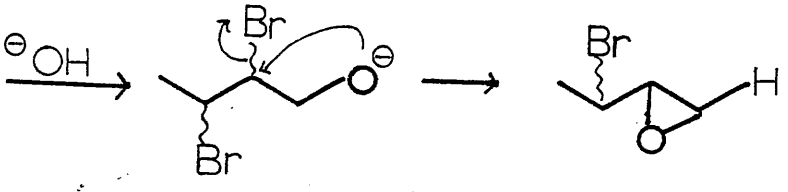


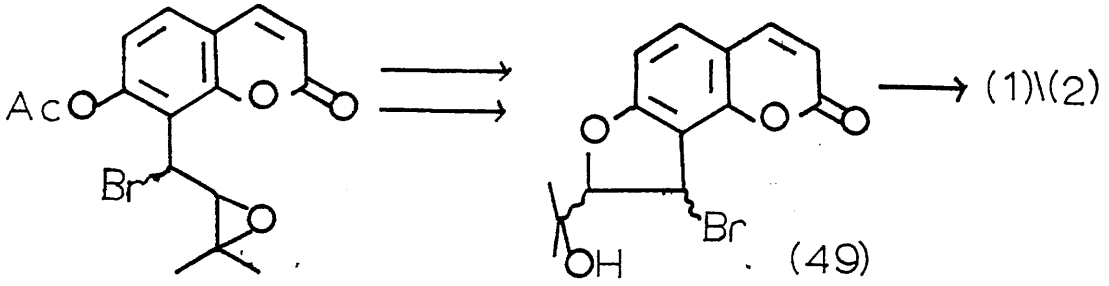




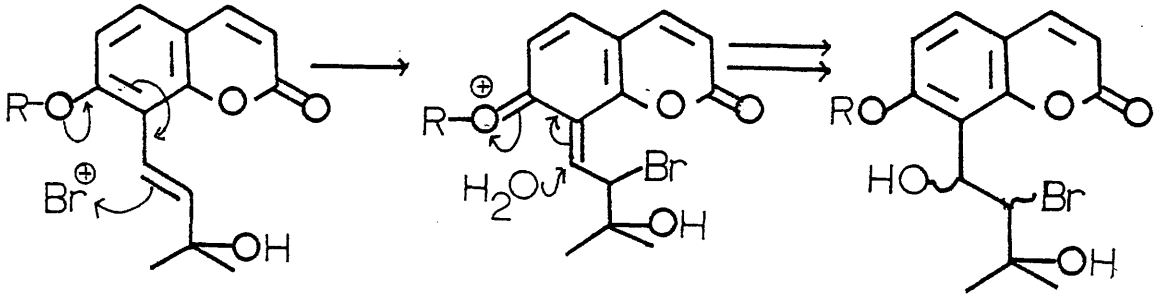
of tris(triphenylsilyl)vanadate in xylene under an inert atmosphere for 5hr. in an attempt to bring about the desired allylic isomerisation. On work-up and purification by chromatography only one product could be isolated and identified, that being the chromene, seselin (43) in 27% yield. This must arise by a cyclisation of the trans-3-hydroxy-3-methylbut-1-ene side chain on to the ortho oxygen, which may be aided by the formation of the vanadate ester of the alcoholic function, thus producing a better leaving group (Scheme 11). The cyclisation of this moiety with ortho phenolic hydroxyls is well known. Sorbifolin (44) cyclises[20] slowly to the dichromene (45) at r.t. and the alcoholic methyl ether (46) reacts to form (47) even in the dark.

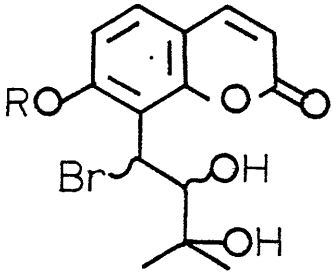
Santell and Viala[21] have recently reported a method for the formation of β-bromoepoxides from allylic alcohols (Scheme 12). This formally brings about the desired isomerisation, for reaction of the allylic alcohol (21) in this manner would produce the benzylic bromide (48), which on further elaboration could yield vaginidiol (1) and vaginol (2) (Scheme 13). A solution of (21) in THF/Na_2CO_3 was treated with bromine at 0°, which on work-up yielded a three component mixture. Cyclisation to produce seselin (43) was again observed, though the major products were starting material (21) and the corresponding phenol (22). No evidence could be obtained for the formation of the desired bromoepoxide (48), or of the corresponding dihydrofuran (49).

Scheme 13



Scheme 14

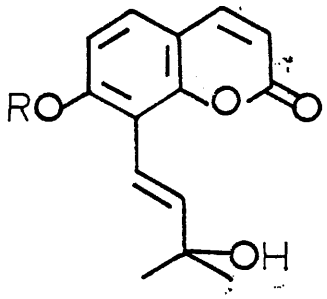




It is clear from the above results that cyclisation of the trans-3-hydroxy-3-methylbut-1-enyl group to the corresponding chromene is a very facile process in these systems.

Another precursor which contains the necessary benzylic functionalisation and the potential for cyclisation to the elusive dihydrofuran systems is the bromohydrin (50). Scheme 14 rationalises that the addition of HOBr across the trans-3-hydroxy-3-methylbut-1-enyl side chain double bond should occur in the required mode to produce species of type (50) and not in the opposite manner, which would lead to (51). Feed-in of electrons from the C-7 oxygen through the aromatic ring to the side chain double bond will control the site of $Br^{\oplus}$ attack, i.e. at the 2'-position.

A convenient method for the formation of bromohydrins from olefins, which has been reported[22] to proceed quickly, cleanly and in high yield with a number of simple olefins, is by treatment with N-bromosuccinimide in aqueous dimethylsulphoxide. The acetate (21) when subject to these conditions proved rather unreactive, the recovery of starting material from this reaction being in the region of 80%. However, at least three other unidentified products were formed in very low yield. It is possible that these arose from attack of $Br^{\oplus}$ at the aromatic nucleus or the coumarin double bond. Addition of Br_2 across the 3-4 double bond[23] of the lactone ring followed by elimination of the elements of HBr to yield a 3-bromocoumarin is a well



(9) R = H

(21) R = $\rightarrow COCH_3$

documented reaction. A similar process may be operating here.

Hydrolysis of the acetate (21) with 2% w./v. aqueous sodium carbonate in methanol gave the phenol (9), which, it was considered, might be more reactive toward bromohydrin formation. The phenol (9), however, on treatment with N-bromosuccinamide produced a complex mixture from which no identifiable compounds could be isolated. Presumably, attack of $Br^{\oplus}$ at the aromatic ring or coumarin double bond are important processes here.

Part 3

Experimental

Preparation of osthenol acetate (20)

To a stirred solution of 7-O-(1,1-dimethylallyl) umbelliferone[6] (6) (3g) in acetic anhydride (30ml) was added anhydrous sodium acetate (5g) and the mixture refluxed, under an inert atmosphere, for 2hr. On cooling the solution was poured on to ice and stirred for a further 2hr., then extracted with ethyl acetate, washed thoroughly with sat. sodium bicarbonate solution, brine to neutrality, dried, and evaporated to yield, on crystallisation from EtOAc/Petrol osthenol acetate (20), (3.02g, 85%) as colourless needles m.p. 94-95° ; (Found: C,70,56; H,5.85; $C_{16}H_{16}O_4$ requires C,70.57; H, 5,92%); n.m.r. signals at δ 1.68 (3H,bs), 1.82 (3H,bs). 2.35 (3H,s), 3.49 (2H,bd, J = 7Hz), 5.15 (1H,bt,J=7Hz), 6.37 and 7.63 (each 1H,d,J=9.5Hz) and 6.98 and 7.33 (each 1H,d,J=9Hz); $\nu_{max.}^{CHCl_3}$ 1764, 1735 and 1605 cm^{-1}; mass spectral peaks at m/e 272 (M^+,11%) 230 (87), 215 (32), 201 (18), 187 (43) and 175 (100).

Photo-oxygenation of osthenol acetate (20)

Oxygen was bubbled, via a glass sinter, upwards through a solution of osthenol acetate (20) (500mg) in pyridine (70ml) containing haematoporphyrin (20mg). This solution was irradiated by a 60 watt lamp, positioned approximately 10cm. from the centre of the reaction flask, for 24hr. Most of the pyridine was then evaporated, and work-up II gave a brown oil (520mg). This brown oil was then dissolved in dry ethanol (70ml) containing glacial

acetic acid (1.8ml) and sodium iodide (5g). After 18hr., the ethanol was evaporated, the residue dissolved in ethyl acetate, washed with 0.1M sodium thiosulphate, brine to neutrality, dried, and evaporated to yield a dark brown oil (470mg) which, after purification by prep. t.l.c. ($CHCl_3$x1), furnished the allylic alcohol (21) (270mg, 52%) as a colourless oil; n.m.r. signals at δ1.43 (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) and 7.03 and 7.38 (each 1H,d,J=9Hz). On addition of a small amount of Eu(fod)$_3$ the signal at δ6.73 separated into 9.15 and 9.60 (each 1H,d,J=17Hz), $\nu_{max}^{CHCl_3}$ 3500, 1740, 1600, 1114 and 970 cm^{-1}; mass spectral peaks at m/e 288 (M^+,4%), 246 (12), 231 (14), 228 (20), 213 (100) and 149 (74).

7-Hydroxy-8-(trans-3-hydroxy-3-methylbut-1-enyl)coumarin (9)

A solution of (21) (220mg) in methanol (8ml) was stirred with 2% w./v. aqueous sodium carbonate (2ml) for 0.25hr, at r.t. The solution was then carefully neutralised with 0.1M hydrochloric acid, diluted with water and extracted with ethyl acetate. The combined organic layers were then washed with brine, dried and evaporated to give the phenol (9) (170mg,90%) as needles (from EtOAc/Petrol) m.p. 158.5-160°; (Found: C,68.29, H,5.69. $C_{14}H_{14}O_4$ requires C,67.99; H,5.81%); n.m.r. signals (d_6-dimethylsulphoxide) at δ1.32 (6H,s), 4.64* (1H,bs), 6.18 and 7.90 (each 1H,d,J=9.5Hz), 6.78 and 6.96 (each 1H,d,J=16Hz), 6.94 and 7.35 (each 1H,d,J=8Hz) and 10.91* (1H,s); $\nu_{max}^{CHCl_3}$ 3600, 2980, 1735, 1620 and

1610 cm^{-1}; mass spectral peaks at m/e 246 (M^+, 0.13%), 228 (24), 213 (100) and 185 (22).

7-Methoxy-8-iodocoumarin (30)

Potassium carbonate (9.4g) was added to a solution of 7-hydroxy-8-iodocoumarin (6g) and methyl iodide (8g) in acetone (300ml) and the solution refluxed for 1.5hr. Work-up I gave 7-methoxy-8-iodocoumarin (30) (5.50g,87%) as colourless needles (from EtOAc/Petrol) m.p. 153-154°; (Found: C,39.53, H,2.52, I,41.6, $C_{10}H_7O_3I$ requires C,39.76; H,2.34; I,42.01%) n.m.r. signals at δ4.01 (3H,s), 6.30 and 7.63 (each 1H,d,J=9.5Hz) and 6.83 and 7.48 (each 1H,d,J=8Hz); $\nu_{max}^{CHCl_3}$ 1750, 1290, 1141 and 1081cm^{-1}, λ_{max}^{EtOH} 213, 265 and 316nm (log ε 4.3, 4.07 and 4.24); mass spectral peaks at m/e 302.(M^+,100%), 274 (51) and 259 (66).

Coupling of (30) and (31)

A solution of (30) (5g) and (31) (4.26g) in pyridine (120ml) was refluxed under argon for 18hr. Work-up II gave a brown oil (7.2g) which, after purification by prep. t.l.c. ($CHCl_3$ x 1) furnished;

i) 7-methoxycoumarin (0.57g,21%) as white needles m.p. 116-118° (lit.[24] m.p.118°). This compound was identical to an authentic sample.

ii) the acetylene (32) (2.89g,51%) as a yellow solid m.p. 99-101°; n.m.r. signals at δ1.65 (3H,s), 1.70 (3H,s), 1.74 (6H, bm), 3.73 (2H,bm), 3.97 (3H,s), 5.37 (1H,bs), 6.28 and 7.51 (each

1H,d,J=9.5Hz) and 6.83 and 7.40 (each 1H,d,J=8Hz); $\nu_{max}^{CCl_4}$ 1750, 1600, 1276 and 1114 cm^{-1}; mass spectral peaks at m/e 342 (M^+, 3%), 258 (45), 243 (91) and 201 (100).

7-Methoxy-8-(3-hydroxy-3-methylbut-1-ynyl)coumarin (33)

A solution of the tetrahydropyranyl ether (32) (2g) in 60% aqueous acetic acid (120ml) was stirred at r.t. for 2hr. The solution was then diluted with water, and extracted with ethyl acetate. The combined organic layers were washed with 5% sodium carbonate solution, brine, dried and evaporated to give (33) as a yellow solid which on crystallisation from ethyl acetate gave colourless needles (1.20g, 86%) m.p. 100-102°; (Found: C, 69.72; H,5.39; $C_{15}H_{14}O_4$ requires C,69.76; H,5.46%); n.m.r. signals at δ1.70 (6H,s), 4.00 (3H,s), 6.27 and 7.60 (each 1H, d,J=9.5Hz) and 6.83 and 7.21 (each 1H,d,J=8Hz); $\nu_{max}^{CHCl_3}$ 3610, 1735, 1604 and 1117 cm^{-1}; mass spectral peaks at m/e 258 (M^+, 43%), 243 (87), 227 (29), 215 (26) and 201 (100).

7-Methoxy-8-(cis -3-hydroxy-3-methylbut-1-enyl)coumarin (36)

A solution of (33) (200mg) in ethyl acetate (20ml) containing 10% palladium on barium sulphate catalyst (130mg) was stirred under a hydrogen atmosphere until the uptake of hydrogen was 1 mole. The solution was then filtered through celite and evaporated to dryness. The resultant yellow solid was purified by prep. t.l.c. ($CHCl_3$ x 2) and crystallised from ether to yield (36) (170mg, 83%) as colourless needles m.p. 118-120°; (Found:

C,68.95; H, 5.95; $C_{15}H_{16}O_4$ requires C, 69.21; H, 6.20%); n.m.r. signals at δ 1.22 (6H,s), 2.00* (1H,s), 3.86 (3H,s), 6.00 (2H,s), 6.16 and 7.56 (each 1H,d,J=9.5Hz) and 6.83 and 7.37 (each 1H,d, J=8Hz); ν_{max}^{KBr} 3480, 1715, 1600, 1290 and 1095 cm^{-1}; mass spectral peaks at m/e 260 (M^+, 33%) 245 (84), 217 (100) and 203 (74).

Allylic Isomerisation[12] of nerolidol

i) Nerolidol (38) (5g), tris(triphenylsilyl)vandate (0.58g), triphenylsilanol (1.16g) and benzoic acid (90mg) were refluxed in toluene (30ml) for 3hr. with stirring. On cooling, the solvent was evaporated, the residue taken up in hexane, filtered and evaporated to yield 4.41g of a yellow oil. N.m.r. clearly showed the presence of a new doublet at δ 4.14.

ii) identical results were obtained on repeating the reaction in the absence of triphenylsilanol and benzoic acid.

Attempted demethylation of (36)

To a stirred solution of (36) (50mg) in dry methylene chloride (15ml) at -78° was added boron tribromide (0.2ml) and after 1hr. the solution was allowed to warm to -20° when it was poured on to ice and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated to dryness to furnish a brown solid (41mg). N.m.r. showed extensive decomposition had taken place and t.l.c. indicated that at least six compounds were present.

Attempted rearrangement of the allylic alcohol (21)

A solution of (21) (280mg) in xylene (10ml) containing tris(triphenylsilyl)vandate (70mg) was stirred at reflux for 5hr. On cooling the solution was filtered through celite and the xylene removed under reduced pressure, furnishing a complex mixture. Prep. t.l.c. ($CHCl_3$ x 1) facilitated the isolation of only one identifiable compound, seselin (43) (60mg,27%), identified by comparison with an authentic sample (i.r.,n.m.r. and m.p.).

Attempted formation[21] of the bromoepoxide (18)

To a stirred solution of (21) (90mg) in THF (10ml) containing 1.5N sodium bicarbonate solution (5ml) was added at 0°, bromine (two drops) and the mixture stirred at r.t. for 18hr. Water (30ml) was then added and the solution carefully neutralised and extracted with ethyl acetate. The combined organic layers were washed with brine, dried and evaporated to yield a brown oil (62mg) which t.l.c. and n.m.r. showed to be a mixture of starting material (21), the corresponding phenol (9) and seselin (43).

Attempted formation of the bromohydrin of (21)

To a stirred solution of N-bromosuccinimide (50mg) in dimethylsulphoxide (5ml) containing water (0.1ml) was added dropwise *via* a syringe (21) (70mg) in dimethylsulphoxide (2ml), under argon, and stirring continued for 14hr. Water (10ml) was then added and the solution extracted with ethyl acetate, dried

and evaporated to yield a brown oil (126mg). Purification by prep. t.l.c. (EtOAc/Petrol 3:2) facilitated the isolation of only starting material (21) (40mg, 80%).

Attempted formation of the bromohydrin of (9)

To a stirred solution of N-bromosuccinimide (25mg) in dimethylsulphoxide (5ml) containing water (0.1ml) was added dropwise, via a syringe (9) (40mg) in dimethylsulphoxide (1ml), under argon, and continued for 1hr. Water (15ml) was then added and the solution extracted with ethyl acetate, dried and evaporated to yield a brown oil (65mg). T.l.c. showed this to be a complex mixture from which no useful compounds could be isolated.

Part 3

References

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