Synthetic Studies on Natural Coumarins

THESIS

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for the degree of Doctor of Philosophy

by

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Chemistry Department,

University of Glasgow.

Contents

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I would also like to thank the technical staff in the Chemistry Department for their assistance.

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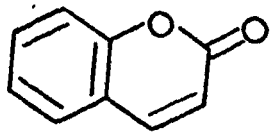
Summary

The biosynthesis of natural benzofurans, in particular, furanocoumarins, has long been the subject of speculation and investigation. It has been established that 2'-hydroxyisopropyldihydrofuranocoumarins are the biosynthetic precursors of the corresponding furanocoumarins. However, little is known about the details of this transformation. Part 1 of this thesis describes a variety of synthetic approaches to vaginidiol and vaginol, two naturally occurring coumarins which have been implicated as intermediates in furanocoumarin biosynthesis.

Recently, a new pyranocoumarin, avicennol, was isolated from Zanthoxylum avicennae, and the relative positions of the substituents on the fully substituted benzenoid ring established by a novel application of a spectroscopic technique in which several unsupported assumptions were made. The structure of avicennol has now been unambiguously confirmed by a synthetic sequence in which each substituent in this structurally complex coumarin is introduced in a regiospecific manner.

The structure of two new diterpenoids, isolated from the roots of Acacia jacqumontii, have been determined from chemical and spectroscopic evidence. Both diterpenoids possess the unique feature of a 7-membered hemi-acetal grouping in ring B of the cassane skeleton.

Introduction to Part 1, Including a Short Review of the Biosynthesis of Furanocoumarins.



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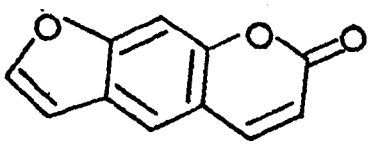


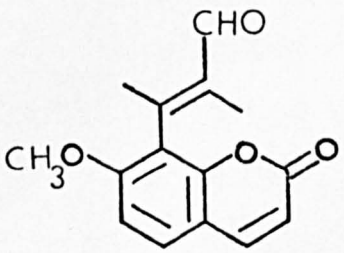
(2)

The history of coumarins can be traced back to 1820, when Vogel isolated the simplest member of this class of oxygen heterocycle, coumarin (1), from Coumarouna odorata[1]. Since then, its derivatives have been found to be widely distributed throughout the plant kingdom[2-5], as well as being present in some animals[6] and micro-organisms[7]. In 1963, Dean reported[4] that about ninety natural coumarins were known. By 1970, more than twice this number[8] had been isolated, with a current estimate[5] being over five hundred. These large increases represent advances in isolation and separation techniques[5], and in physical methods for structure determination[5].

Much interest has centred on the diversity of physiological effects which natural coumarins can exhibit[2,3]. These range from the contraceptive activity of psoralen (2)[9], and the well-established skin sensitising properties of many furanocoumarins[3], through anti-coagulant[3] and vasodilatory[3] activity, to behaviour as anti-tumour agents[10].

Although the synthesis of a wide range of naturally occurring coumarins has been accomplished[5], the synthesis of many such compounds has eluded the efforts of many research groups. To illustrate the problems facing the synthetic chemist, the structures of a few coumarins, chosen at random from the literature, but as yet unsynthesized, are shown in Scheme 1.1.

SCHEME 1.1



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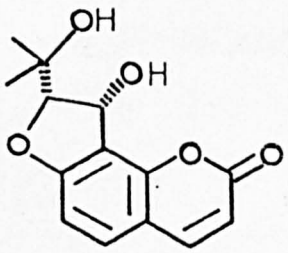

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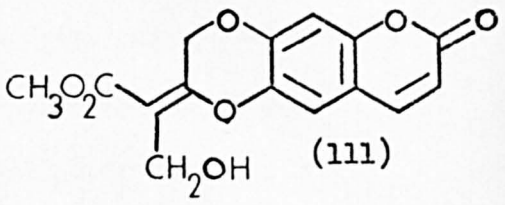

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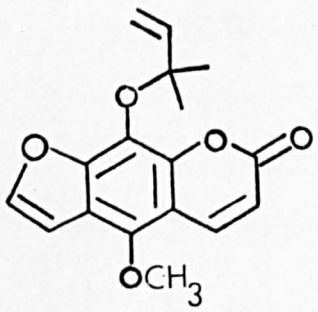

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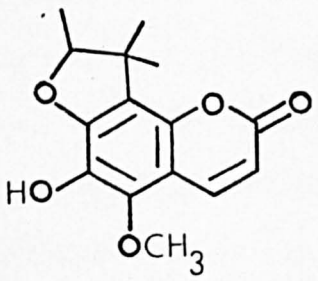

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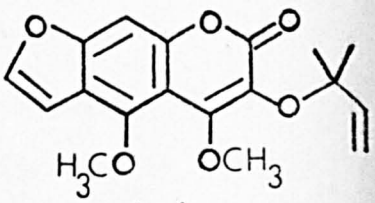

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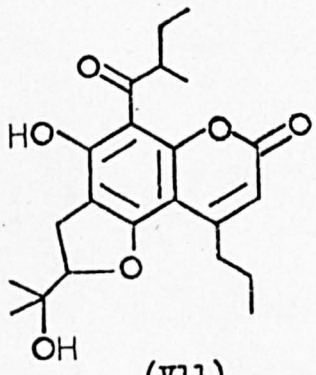

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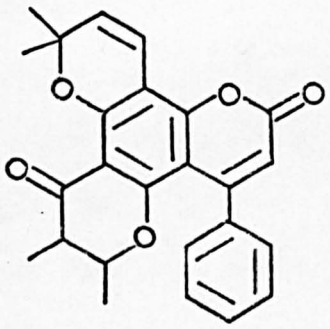

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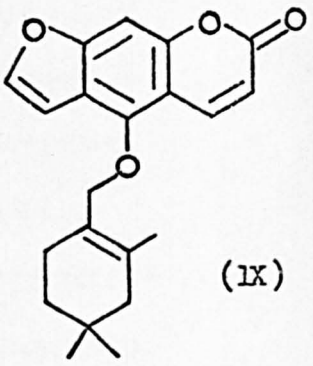

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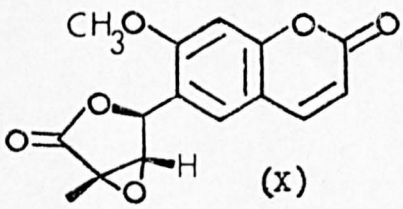

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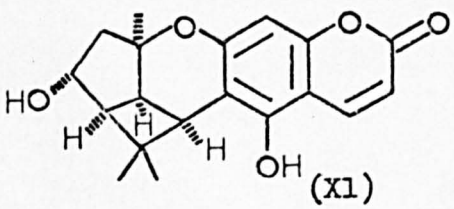

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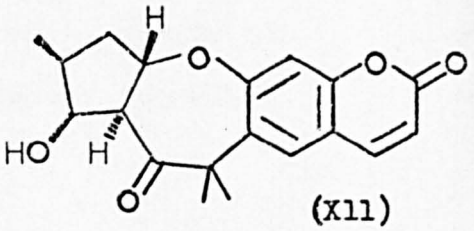

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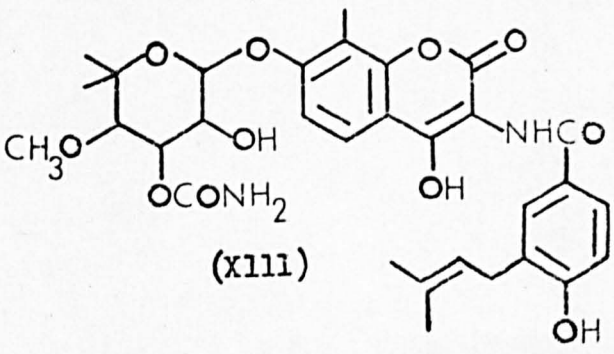
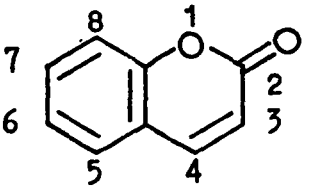


(XIII)

Index to Scheme 1.1

	Trivial Name	Reference
(I)	Murralongin	11
(II)	Vaginidiol	12
(III)	Bethancorol	13
(IV)	-	14
(V)	Nieshoutol	15
(VI)	Halfordinin	16
(VII)	-	17
(VIII)	Tomentolide A	18
(IX)	Archangelin	19
(X)	Micromelumin	20
(XI)	Hydroxyeriobrucinol	21
(XII)	Gynuron	22
(XIII)	Novobiocin	23



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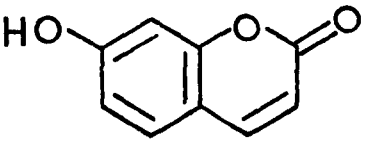


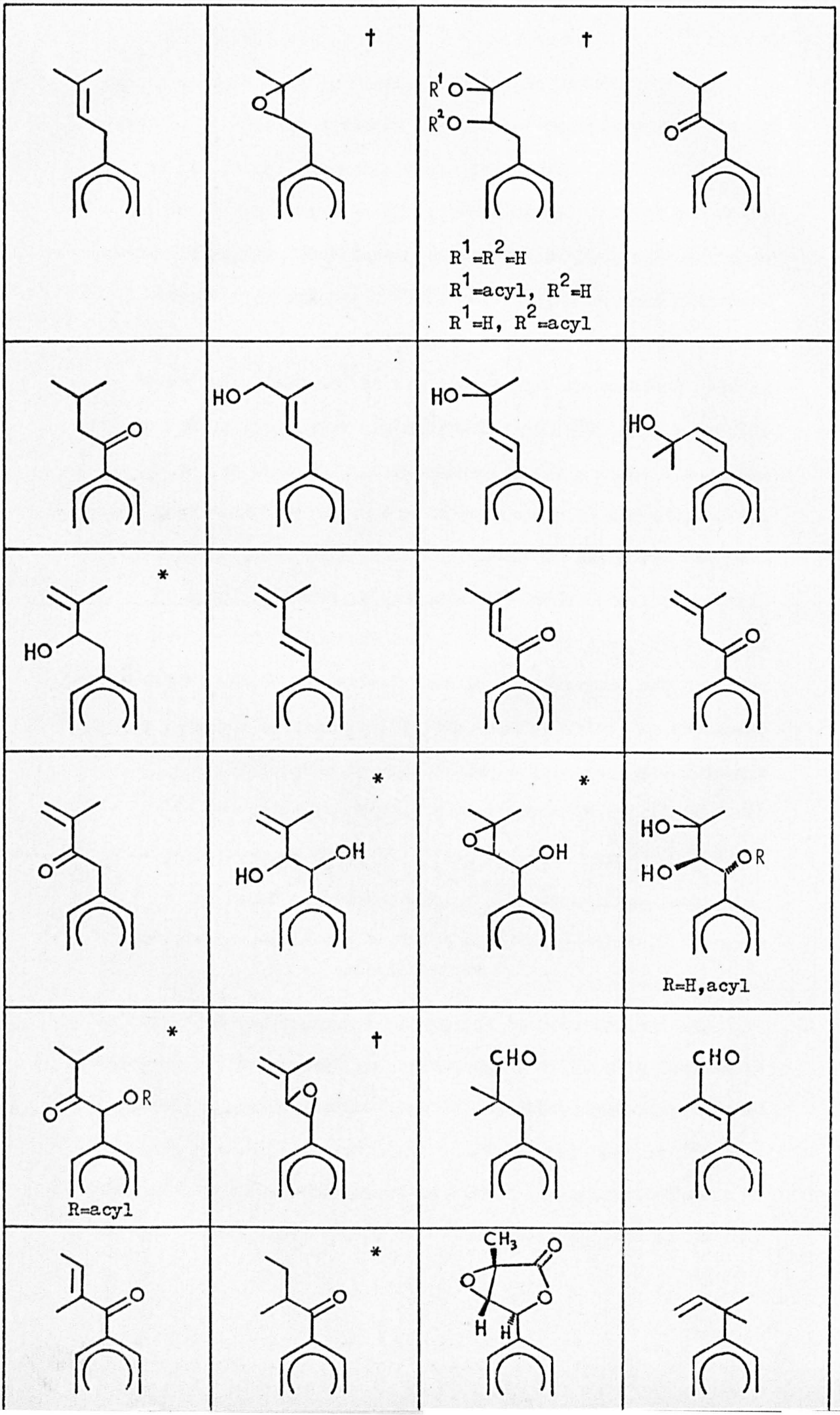
(3)

umbelliferone

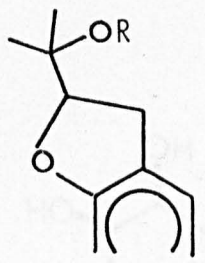
The most convenient classification of coumarins is based on the oxygenation pattern of the coumarin nucleus (1). There are six possible sites where oxygenation can occur, all of which are represented in Nature. These oxygen functions can be present as phenols, ethers or glycosides. Almost all known coumarins have an oxygen atom at C-7, and for this reason 7-hydroxycoumarin (3), more commonly known as umbelliferone, is best regarded as the parent natural compound. In common with many naturally occurring phenolic compounds, coumarins are frequently found with isoprenoid chains, of one, two or three units, attached to oxygen or to carbon, or to both. Many examples are known of coumarins carrying an isoprene derived unit on nuclear carbon. This moiety is normally found at C-6 or C-8, ortho to the C-7 oxygen function. This probably reflects the biosynthetic pathway leading to these prenylated coumarins, it being thought that the C_5 unit is inserted by direct C-alkylation of a phenolic precursor, with dimethylallyl pyrophosphate as a likely candidate for this purpose[24]. These isoprene units are often elaborated by oxidation, cyclisation and rearrangement, as shown in Scheme 1.2, which imparts an apparently endless variety to natural coumarins.

The biosynthesis of the coumarin nucleus has been studied by several groups[25,26]. In particular, Brown and his co-workers have shown[25] that coumarin (1) and 7-methoxycoumarin (herniarin,4) are both derived from shikimic acid (Scheme 1.3), but are formed by independent routes, resulting from a branch in the biosynthetic pathway at the trans-cinnamic acid stage. They found that in

S C H E M E 1.2

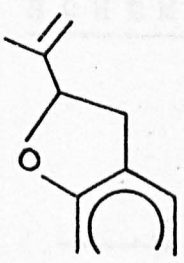


SCHEME 1.2



†

R=H,acyl,glycosyl



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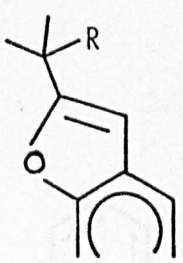
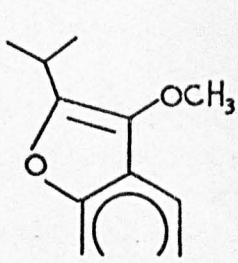
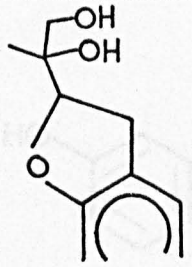


R=OH,OCH_3,NH_2





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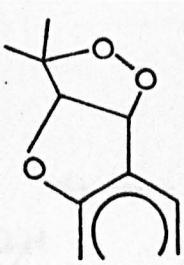

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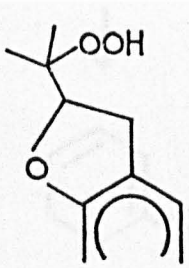

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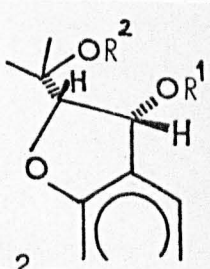
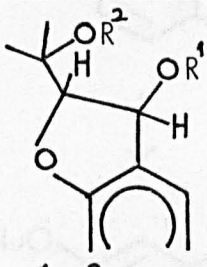
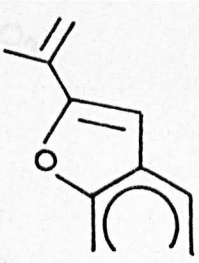


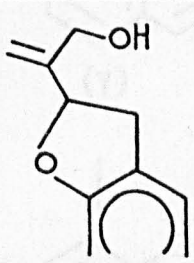
R^1=R^2=H
R^1=H,R^2=acyl
R^1=acyl, R^2=H
R^1,R^2=acyl
R^1=H, R^2=glycosyl



*

R^1=R^2=H
R^1=H, R^2=acyl





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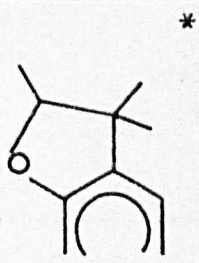

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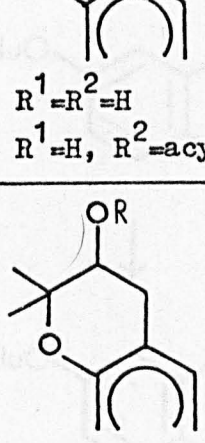

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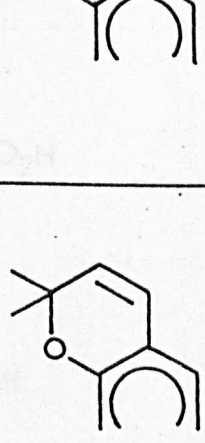
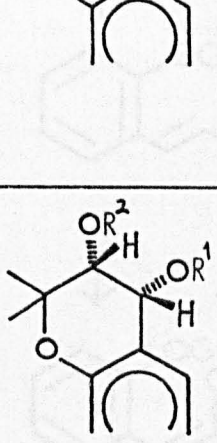
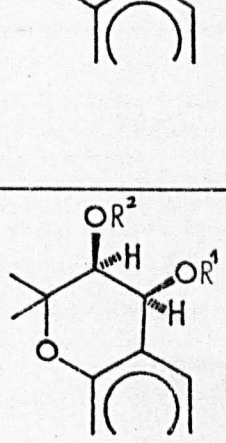
R=H,acyl

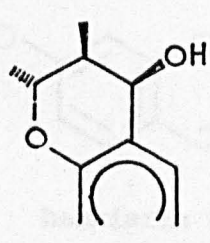


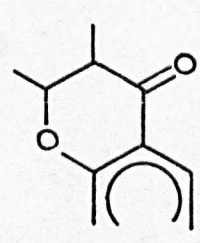


R^1=acyl, R^2=H
R^1,R^2=acyl



R^1,R^2=acyl





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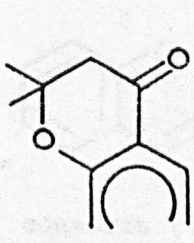
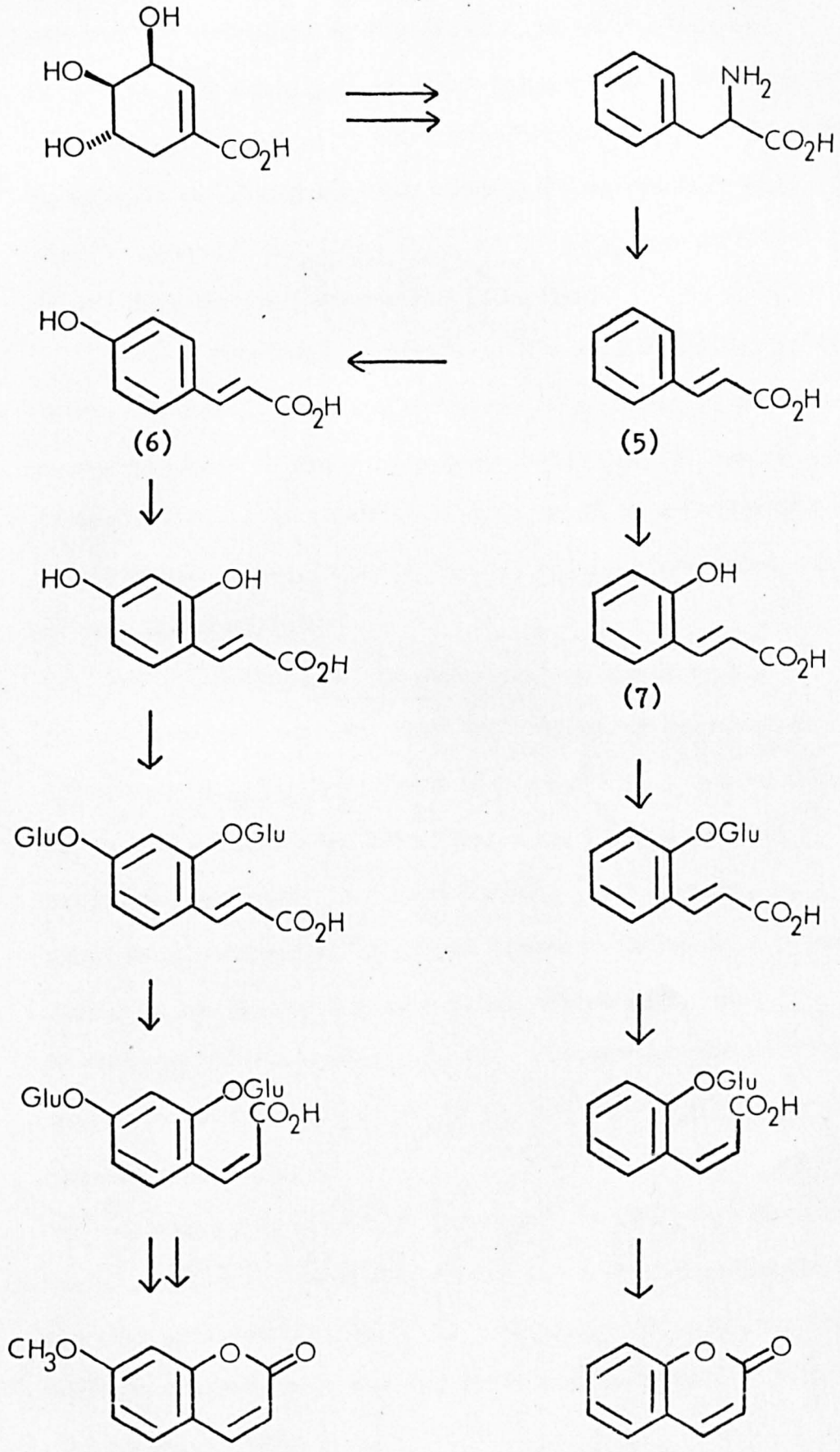


* = absolute stereochemistry not defined. † = both enantiomers known.

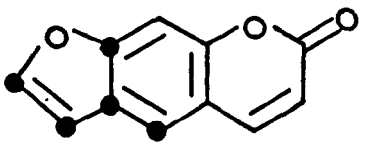
SCHEME 1.3



herniarin (4)

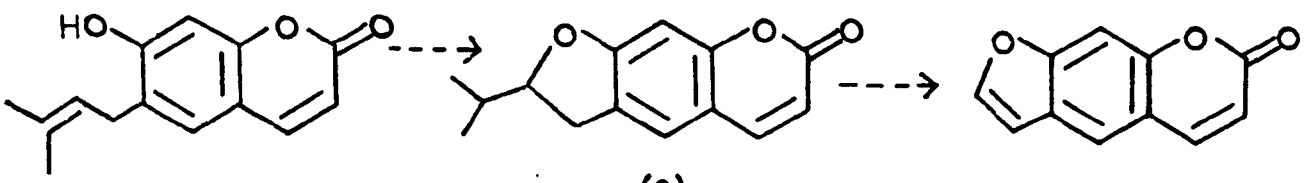
coumarin (1)

Glu = Glucose residue



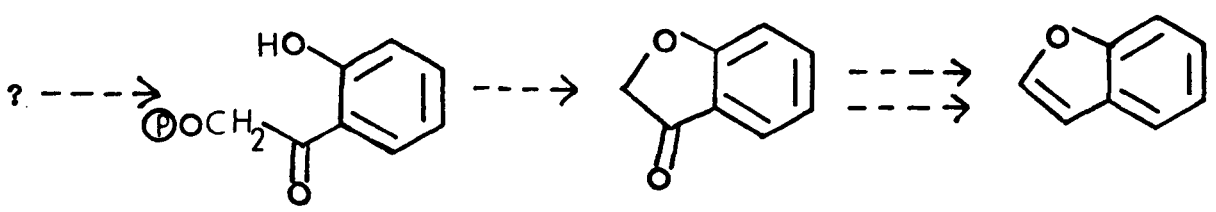
(8)

SCHEME 1.4



(9)

SCHEME 1.5



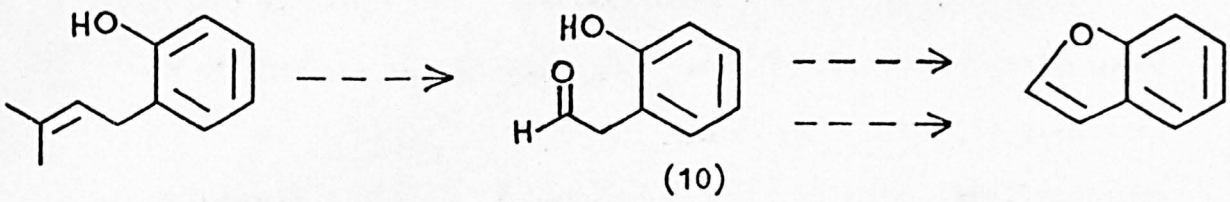
Lavandula officinalis, ortho-hydroxy-trans-cinnamic acid (7) was readily converted into coumarin (1), but not into herniarin (4), while para-hydroxy-trans-cinnamic acid (6) was converted with high efficiency into herniarin (4). Thus ortho-hydroxylation of cinnamic acid (5) leads to coumarin (1), whereas para-hydroxylation followed by ortho-hydroxylation leads to the more common 7-oxygenated coumarins.

Since a substantial portion of the work described in this thesis was directed to the synthesis of a number of natural coumarins, some of which have been implicated in furanocoumarin biosynthesis, it is relevant at this point to consider the biosynthesis of the furanocoumarins, an important sub-division of natural coumarins.

The biosynthesis of benzofurans, and specifically furanocoumarins, has long been the subject of speculation and investigation. In 1937, Spath suggested[27] in a review that all the carbon atoms of the furan ring were derived from an isopentane skeleton, as illustrated in (8). Hawarth, on the other hand, envisaged[28] that the furanocoumarins were potentially derivable by elimination of a three carbon unit from 2'-isopropyldihydrofurans e.g. (9). It was considered that this type of compound could arise by cyclisation of ortho- isoprenyl phenols (Scheme 1.4).

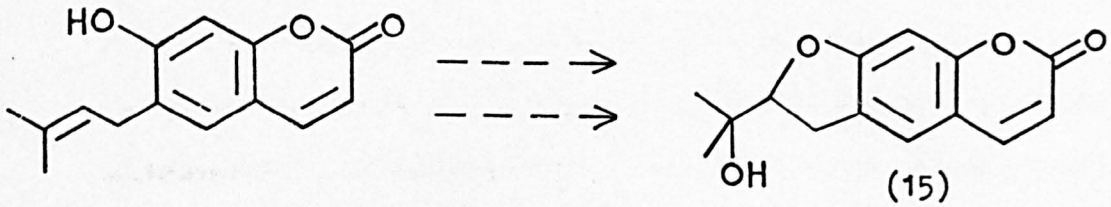
Geissman and Hinreiner proposed[29] in 1952 that unsubstituted furan rings could be formed from a two carbon phosphorylated α-ketol precursor (Scheme 1.5). Significantly perhaps, they made no comment as to how the ketol moiety became attached to the aromatic ring.

SCHEME 1.6



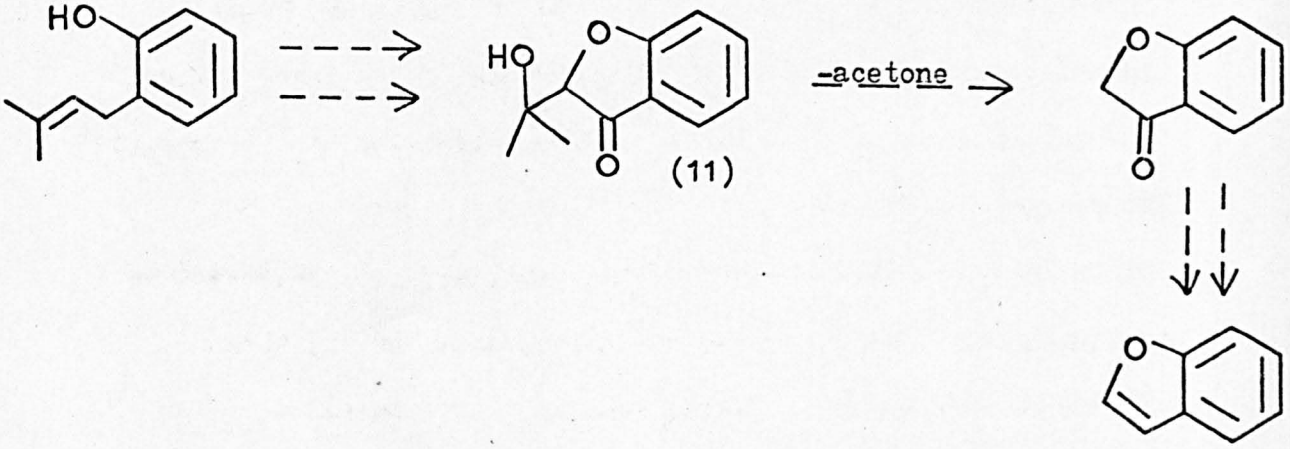
(10)

SCHEME 1.7



(15)

SCHEME 1.8



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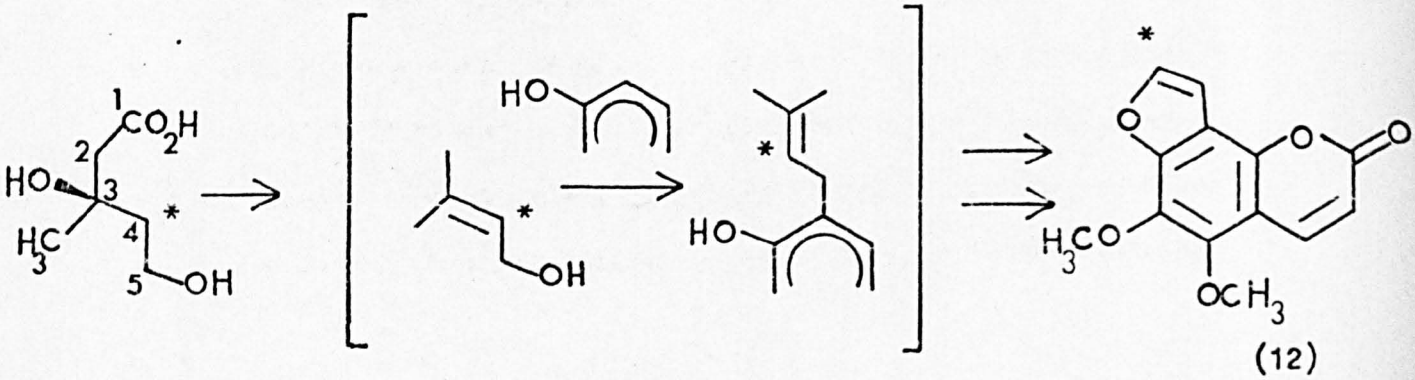


(12)

* = ^{14}C

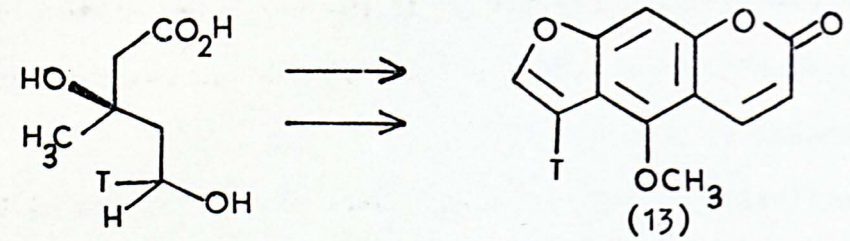
Six years later, two suggestions were independently put forward, each of which favoured a C_5 unit as the starting point for formation of the furan ring.

The first[30] (Scheme 1.6), by Seshadri, required removal of a three carbon fragment prior to formation of the furan ring. Starting with an ortho-isoprenyl phenol, he proposed that oxidative cleavage to the aldehyde (10) occurs, cyclisation and dehydration of which then leads to the benzofuran. It is interesting to note that in the same paper, Seshadri also postulated that coumarins possessing the 2'-hydroxyisopropyl-dihydrofuran ring system, e.g. (15), could arise by interaction of an ortho phenolic group with an oxygenated C_5 unit (Scheme 1.7), but he did not appreciate the possibility that furanocoumarins could be derived by further elaboration of this system.

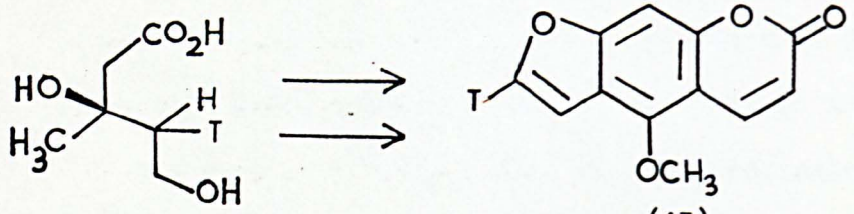
The second proposal[31] (Scheme 1.8), by Birch and Smith, differed from that of Seshadri in that loss of the three carbon fragment was considered to occur after cyclisation, the ketone (11) being a key intermediate.

Floss and Mothes[32] provided the first experimental evidence for the origin of the two 'extra' carbon atoms of the furan ring in furanocoumarins. After feeding $\left[4\text{-}^{14}C\right]$-mevalonic acid to the roots of Pimpinella magna, they isolated pimpinellin (12), and, by degradation, showed that it contained the label exclusively at C-2'. They had previously established[33] by labelling studies that umbelliferone (3) was also a precursor of pimpinellin (12) in this plant. 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 loss of a

SCHEME 1.10

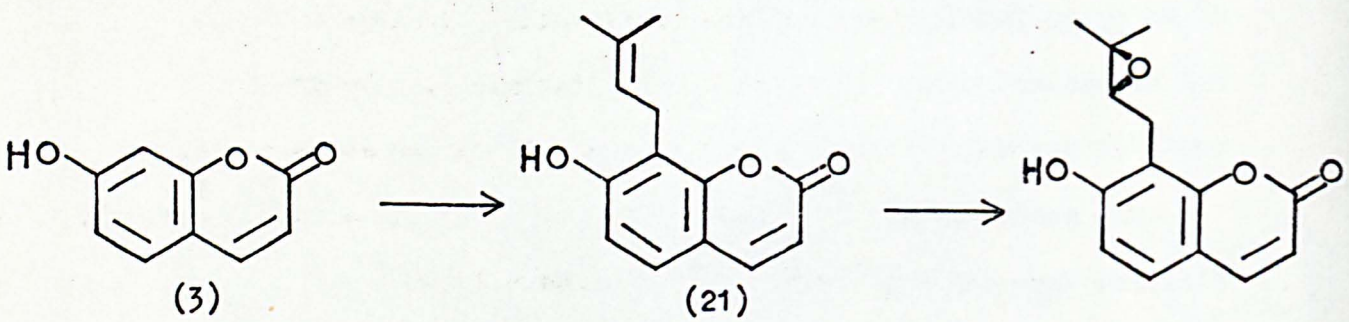


(13)

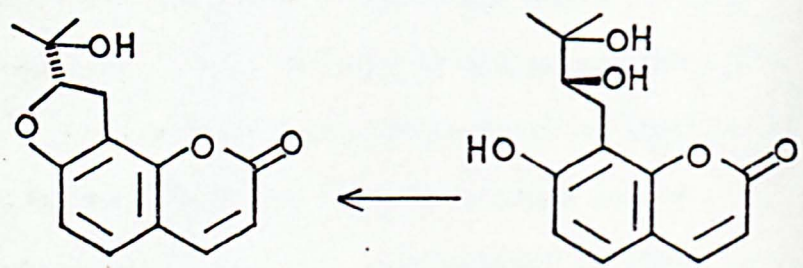


(13)

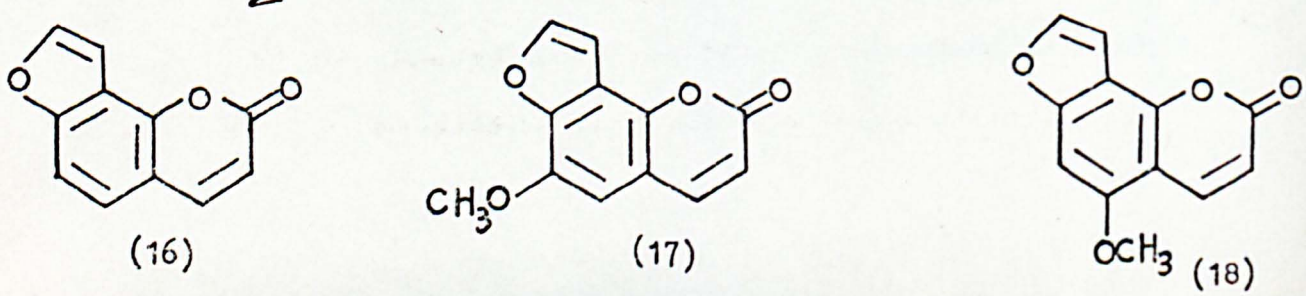
SCHEME 1.11



(3) (21)



(14)



(16) (17) (18)

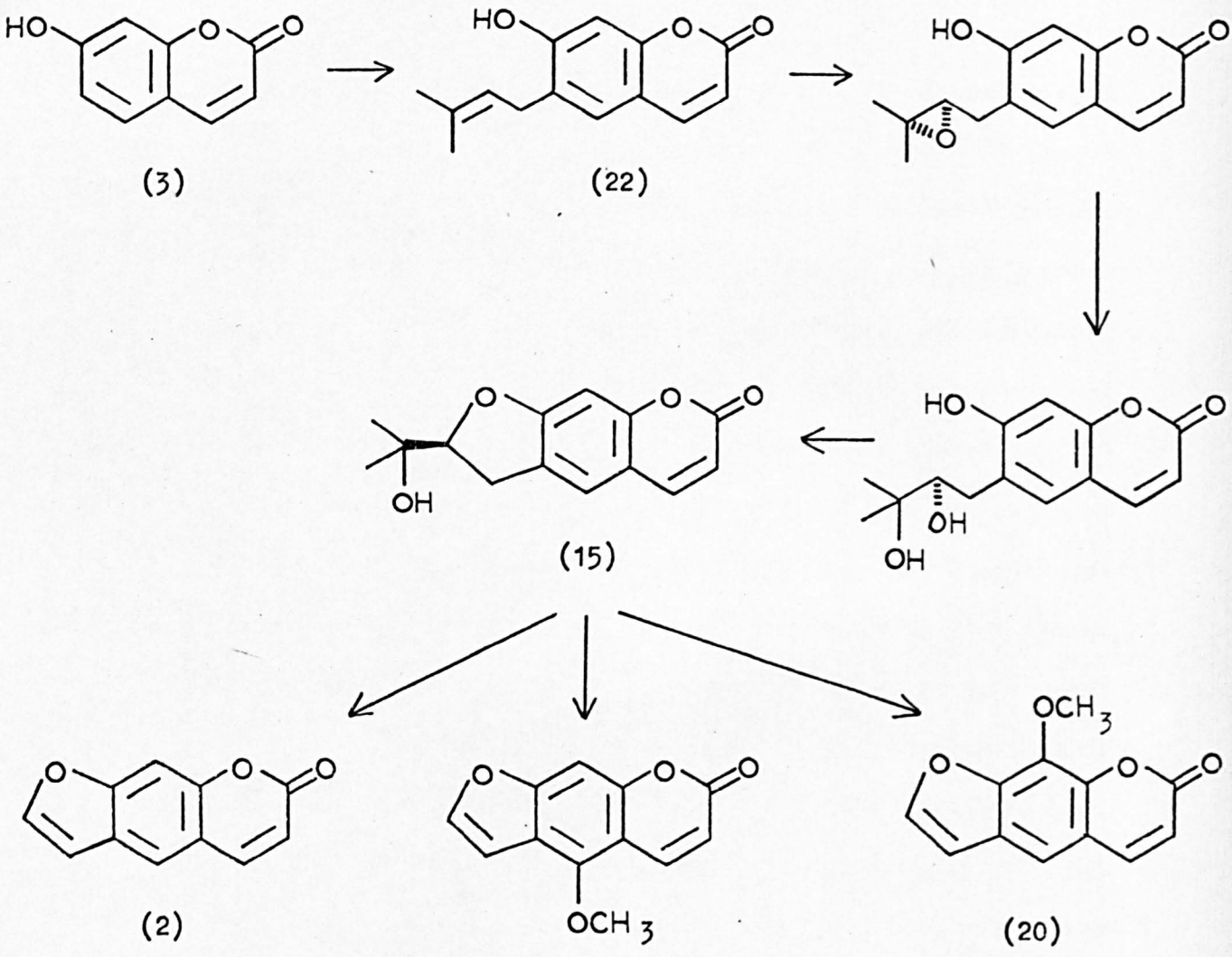
three carbon unit (Scheme 1.9). It was not known at what stage in the biosynthesis of pimpinellin (12) the two methoxyl groups were introduced.

More recently, Kutney et al[34] have also investigated the role of mevalonic acid in furanocoumarin biosynthesis. They found, in Thamnosma montana plants, that the level of incorporation of mevalonic acid was very low. However, by using Thamnosma montana tissue cultures, a higher level of incorporation was obtained. In separate experiments, they fed [4-^{3}H]-mevalonic acid and [5-^{3}H]-mevalonic acid to Thamnosma montana tissue cultures, and after isolation of isopimpinellin (13), examined the distribution of the tritium label in this furanocoumarin. Their results, shown diagrammatically in Scheme 1.10, 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.

In 1969, Steck[35] showed that labelled umbelliferone (3), when fed to the roots of Heracleum lanatum and Ruta graveolens, was incorporated into the dihydrofuranocoumarins columbianetin (14) and marmesin (15) respectively. From these results, Steck proposed Scheme 1.11 as the route from umbelliferone (3) to columbianetin (14), with an analogous scheme for the biosynthesis of marmesin (15) (Scheme 1.12). In addition, feeding experiments with labelled columbianetin (14) and marmesin (15), strongly indicated their conversion into angelicin (16), sphondin (17) and isobergapten (18), and psoralen (2), bergapten (19) and xanthotoxin (20) respectively.

The role of osthenol (21) and 7-demethylsuberosin (22) in the biosynthetic pathways was later established by Steck

SCHEME 1.12


HO
O
O
(3)
HO
O
O
(22)
HO
O
O
O
HO
O
O
OH
OH
OH
O
O
O
(15)
O
O
O
(2)
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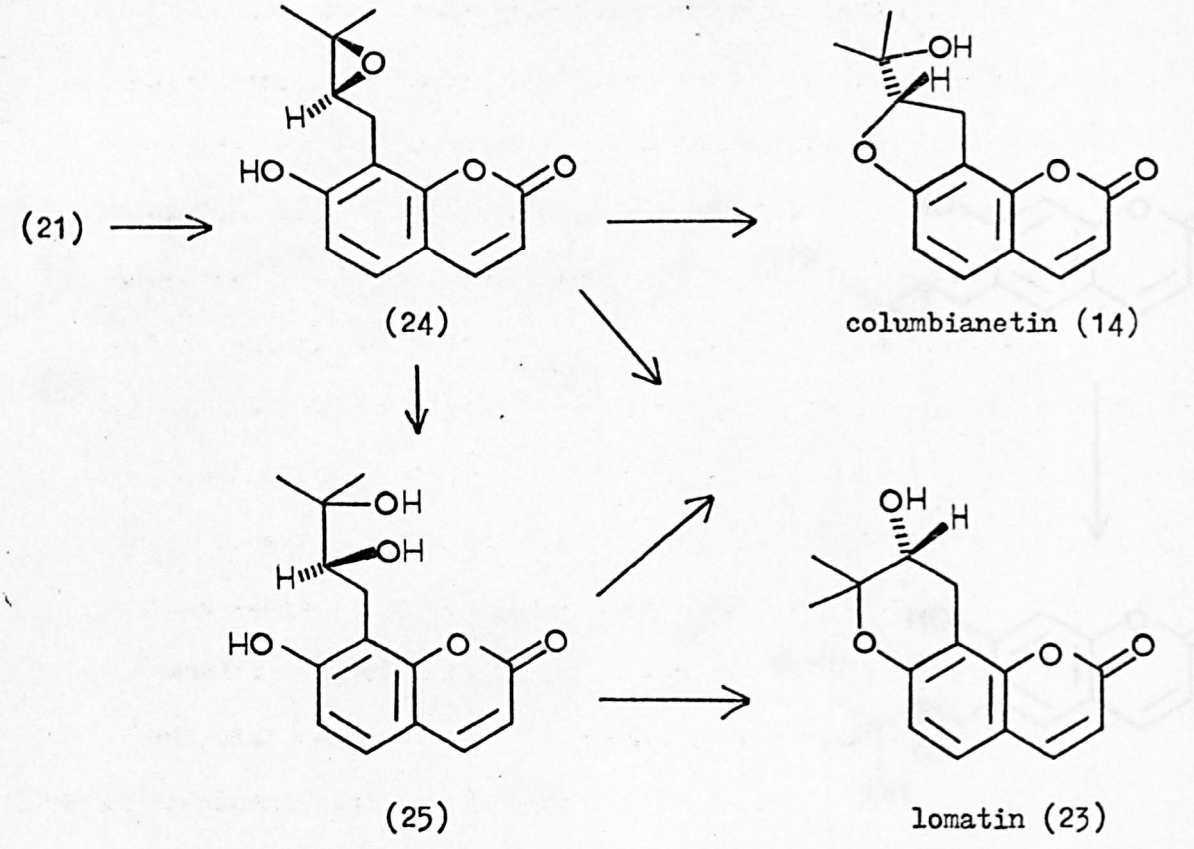
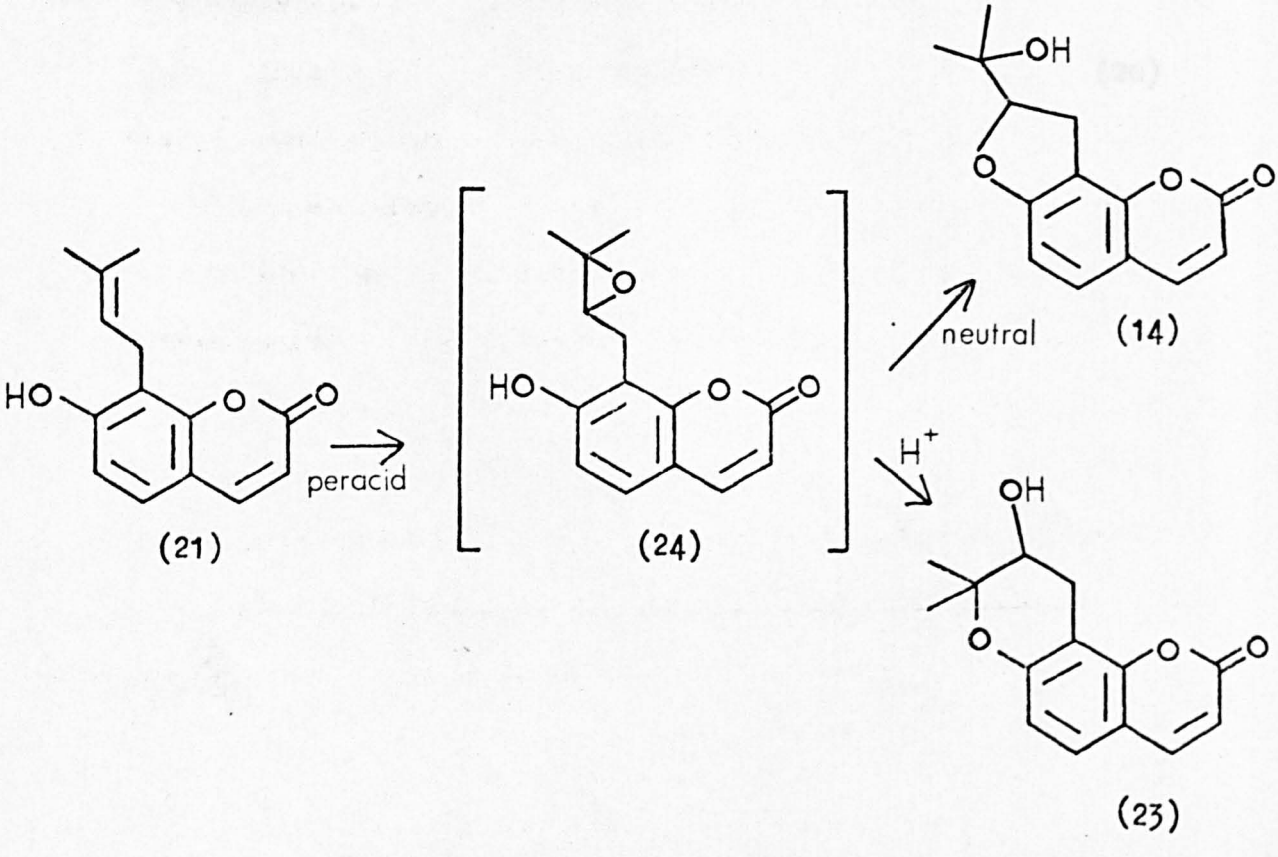
O
O
OCH 3
(19)
OCH 3
O
O
O
(20)

SCHEME 1.13

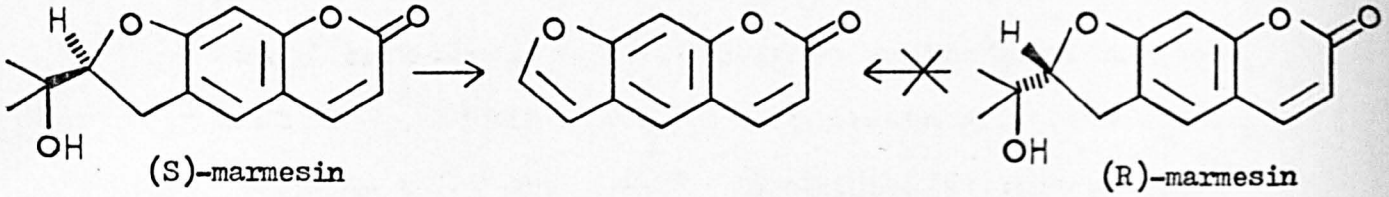


SCHEME 1.14



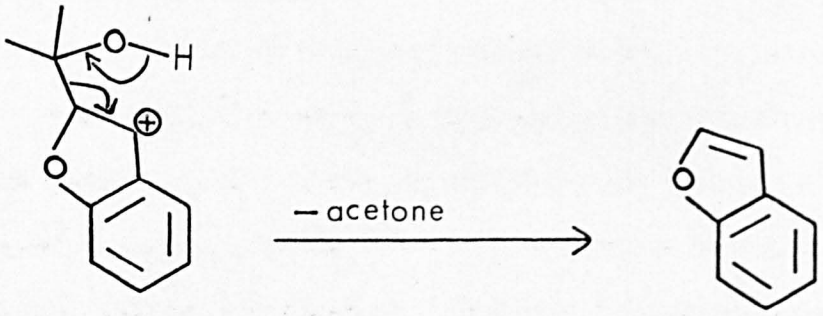
and Brown[36]. They showed conclusively that these compounds were indeed precursors of angular and linear furanocoumarins respectively, in various species. The co-occurrence of columbianetin (14) and lomatin (23) derivatives, in certain plants, was used by Steck as support for the idea of a common biogenetic precursor, which could undergo ring closure in two possible ways. The known configurations of columbianetin (14) and lomatin (23) place stereochemical constraints on the configuration of any intermediate in their biosynthesis. In principle, either the epoxy-phenol (24) or the vicinal diol (25) could produce the five or six-membered ring system (Scheme 1.13). Steck proposed that the epoxide (24) was converted into the diol (25), and that this latter compound was the immediate precursor of (14) and (23), giving as his reason the fact that such 1,2-diols frequently co-occur with the related epoxide. More recently, Murray and Sutcliffe[37] have obtained _in vitro_ results which cast doubt on Steck's proposal. They found that epoxidation of osthenol (21) with _meta_-chloroperbenzoic acid under effectively neutral conditions gave only columbianetin (14) as product, whereas the same reaction under acidic conditions gave exclusively lomatin (23) (Scheme 1.14). In both cases, no evidence for an intermediate epoxide was obtained, indicating that cyclisation of the epoxy-phenol (24) must be relatively fast. Alternatively, the substrate-peracid complex may undergo cyclisation with the _ortho_ hydroxyl, before disocciation, in which case (24) as such may never be formed. These results suggest the epoxy-phenol (24) is the immediate biosynthetic precursor of columbianetin (14) and lomatin (23), rather than the analogous diol (25) (see Scheme 1.13).

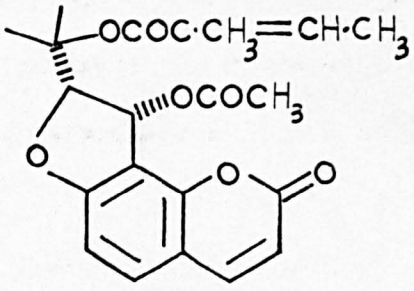
S C H E M E 1.15



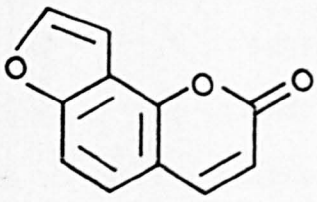
(S)-marmesin (R)-marmesin

S C H E M E 1.16



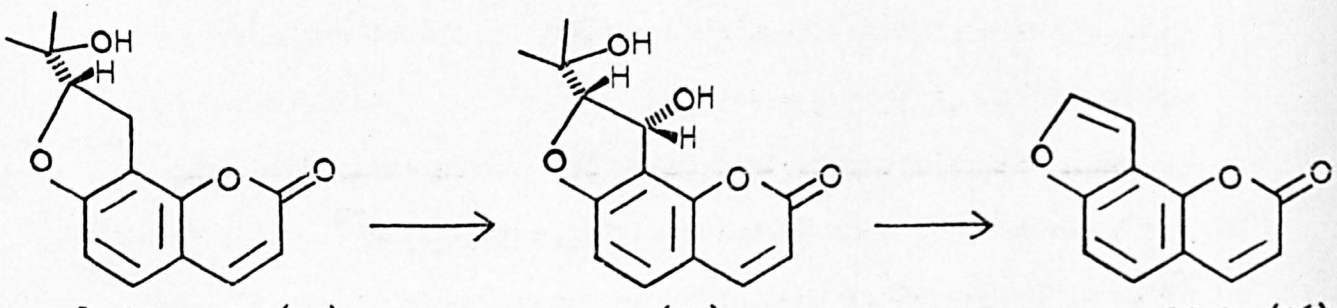


(26)



(16)

S C H E M E 1.17



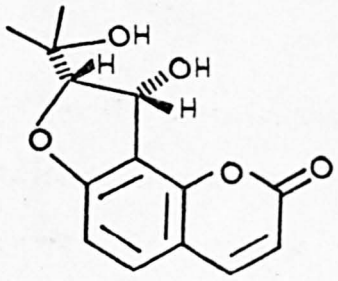
columbianetin (14) (27) angelicin (16)

It is interesting to note that whereas columbianetin (14) has only been found naturally in the (S)-configuration[38], its linear isomer, marmesin (15), is known in both antipodal forms[39]. Steck and Brown[40] have recently investigated the relative efficiencies of these enantiomers as furanocoumarin precursors in Ruta graveolens, Heracleum lanatum and Angelica archangelica. Their results clearly demonstrated that in each of these species, only (S)-marmesin was incorporated (Scheme 1.15).

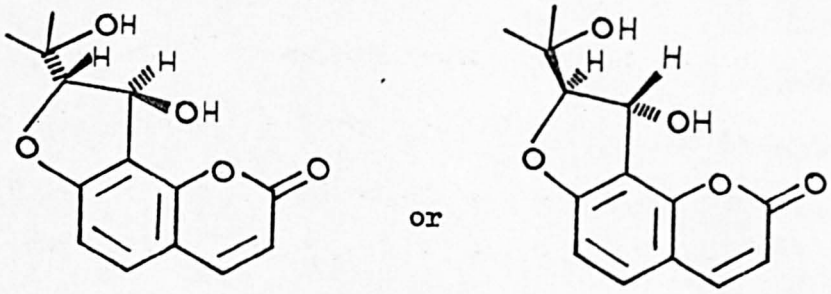
Also in 1969, Birch and his co-workers[41] published a paper in which they suggested an alternative to their earlier proposal (vide supra) regarding the formation of benzofurans. They pointed out that cleavage of the hydroxyisopropyldihydrofuran moiety, with concomitant loss of acetone (Scheme 1.16), required only a carbonium ion in the benzylic position, however generated. In support of this, they quoted the example of libanotin (26)[42], one of many di-esters of this structural type which, on treatment with dilute sodium hydroxide, underwent a facile fragmentation, to give angelicin (16).

In considering the pathway from columbianetin (14) to angelicin (16), Steck suggested that the diol (27) could well be a biogenetic intermediate[43] (Scheme 1.17). Although the diol itself was unknown at that time, a number of its esters had been recognised as constituents of various Umbelliferous plants e.g. libanotin (26). Moreover, the intermediacy of such a diol would fit in well with Birch's mechanism for the biosynthesis of benzofurans (vide supra).

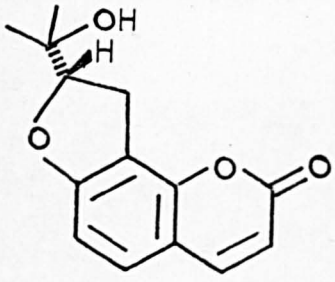
Since Steck's paper, this diol (27), named vaginidiol, has been reported as a constituent of Selinum vaginatum[12]. It was assigned the cis stereochemistry, as shown, on the basis of the



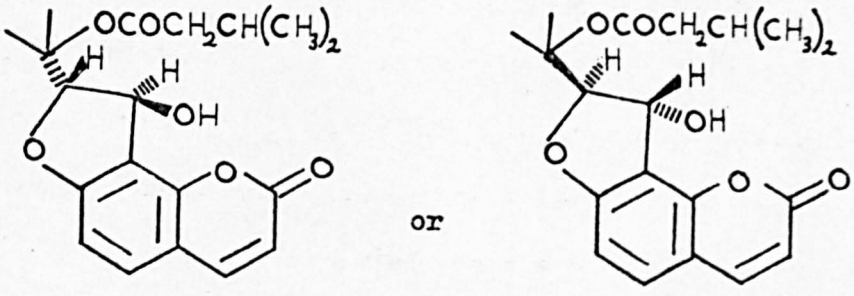
vaginidiol (27)



vaginol (28)



(14)

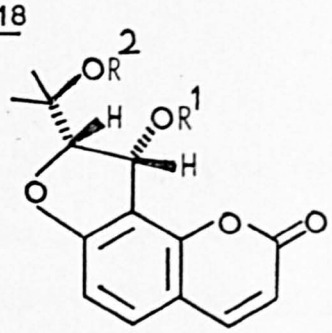


(29)

magnitude of the coupling constant (6Hz) between the two dihydrofuran ring protons. This assignment was possible because a diastereomer, vaginol (28), previously isolated from Selinum vaginatum[44], exhibited a coupling constant of 3.5Hz between the dihydrofuran ring protons. Thus the allocation of cis stereochemistry to vaginidiol (27) and trans stereochemistry to vaginol (28) could be made, since Bothner-by[45] and others had previously observed that in five-membered rings, $J_{cis} > J_{trans}$. 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 (27) was shown[12] to be 2'(S), 3'(R) by correlation, through hydrogenolysis, with optically active columbianetin (14). It is interesting to note that until recently, vaginol (28) was the only known naturally occurring coumarin of this type which had trans stereochemistry in the dihydrofuran ring. However, in 1976, a second example was reported by Gonzalez et al[46]. They isolated a new coumarin from the roots of Peucedanum bourgaei, which was assigned structure (29). The coupling constant of 4Hz between the dihydrofuran ring protons was decisive in assigning trans stereochemistry. In comparison, there are many natural esters of vaginidiol (27) (Scheme 1.18). All have cis stereochemistry, and in every case, the absolute configuration has been shown to be 2'(S), 3'(R). Vaginidiol (27) and its esters are found in a wide variety of plants, which contrasts markedly with vaginol (28) and (29), each of which have been isolated from one plant source only[44,46].

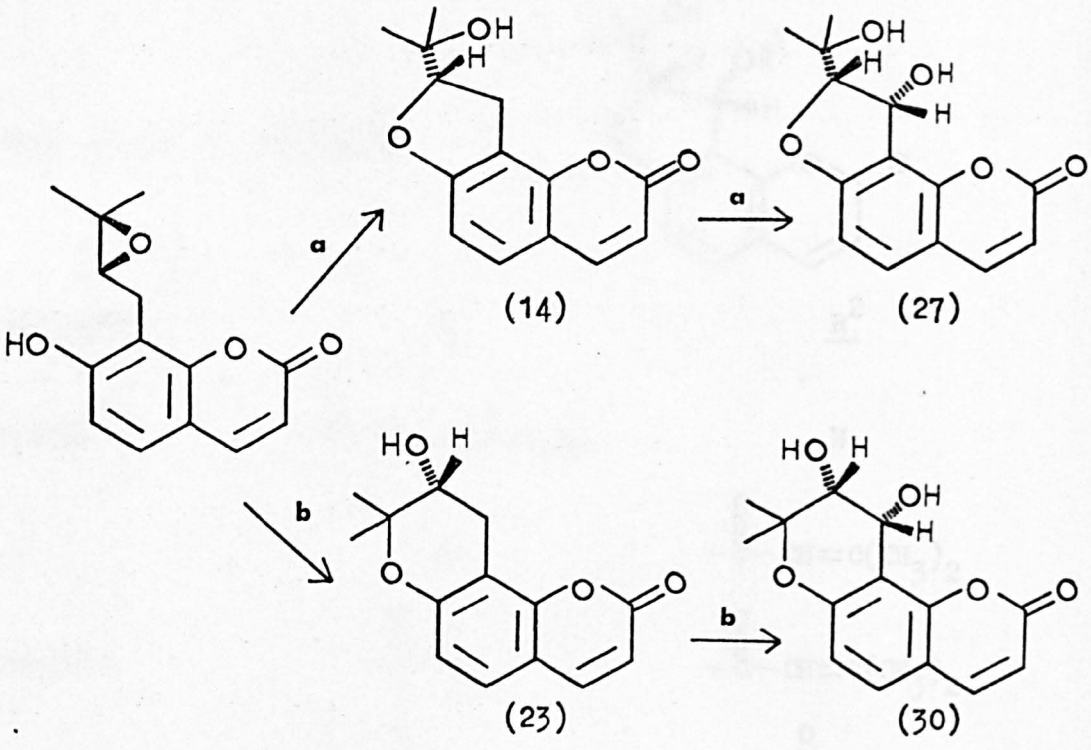
S C H E M E 1.18

Natural esters of vaginidiol

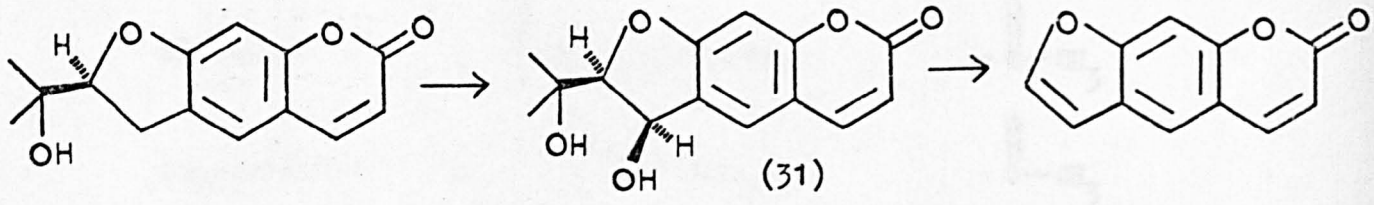


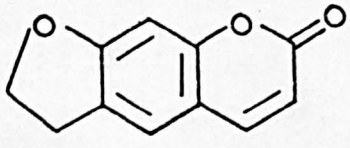
Trivial Name	R^1	R^2
Vaginidin	$-C(=O)-CH_2-CH(CH_3)_2$	H
-	H	$-C(=O)-CH=C(CH_3)_2$
Peucenidin	$-C(=O)-CH_3$	$-C(=O)-CH=C(CH_3)_2$
-	$-C(=O)-CH_3$	$-C(=O)-CH_3$
-	$-C(=O)-CH(CH_3)_2$	$-C(=O)-CH_3$
Libanotin	$-C(=O)-C(CH_3)\overset{t}{=}CH(CH_3)$	$-C(=O)-CH_3$
Isopeucenidin	$-C(=O)-CH=C(CH_3)_2$	$-C(=O)-CH_3$
-	$-C(=O)-C_6H_5$	$-C(=O)-CH_3$
-	H	$-C(=O)-CH_2-CH(CH_3)_2$
-	$-C(=O)-CH_3$	$-C(=O)-CH_2-CH(CH_3)_2$
Athamantin	$-C(=O)-CH_2-CH(CH_3)_2$	$-C(=O)-CH_2-CH(CH_3)_2$
Isoedultin	$-C(=O)-CH_3$	$-C(=O)-C(CH_3)\overset{t}{=}CH(CH_3)$
Archangelicin	$-C(=O)-C(CH_3)\overset{t}{=}CH(CH_3)$	$-C(=O)-C(CH_3)\overset{t}{=}CH(CH_3)$
Angeladin	$-C(=O)-CH\overset{t}{=}CH-C_6H_4OH$	$-C(=O)-C(CH_3)\overset{t}{=}CH(CH_3)$

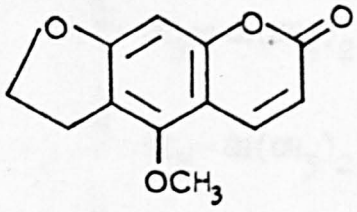
SCHEME 1.19

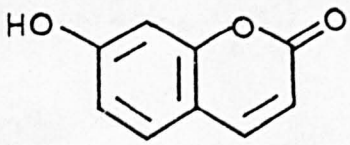


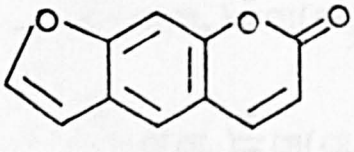
SCHEME 1.20




(32)


(33)

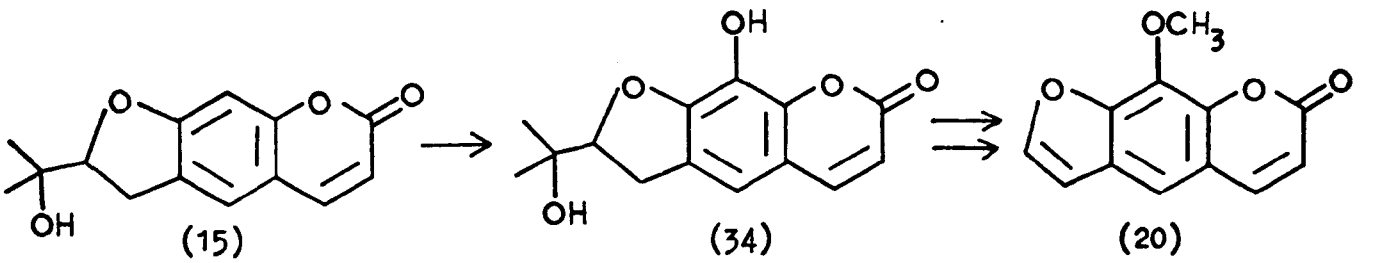

(3)

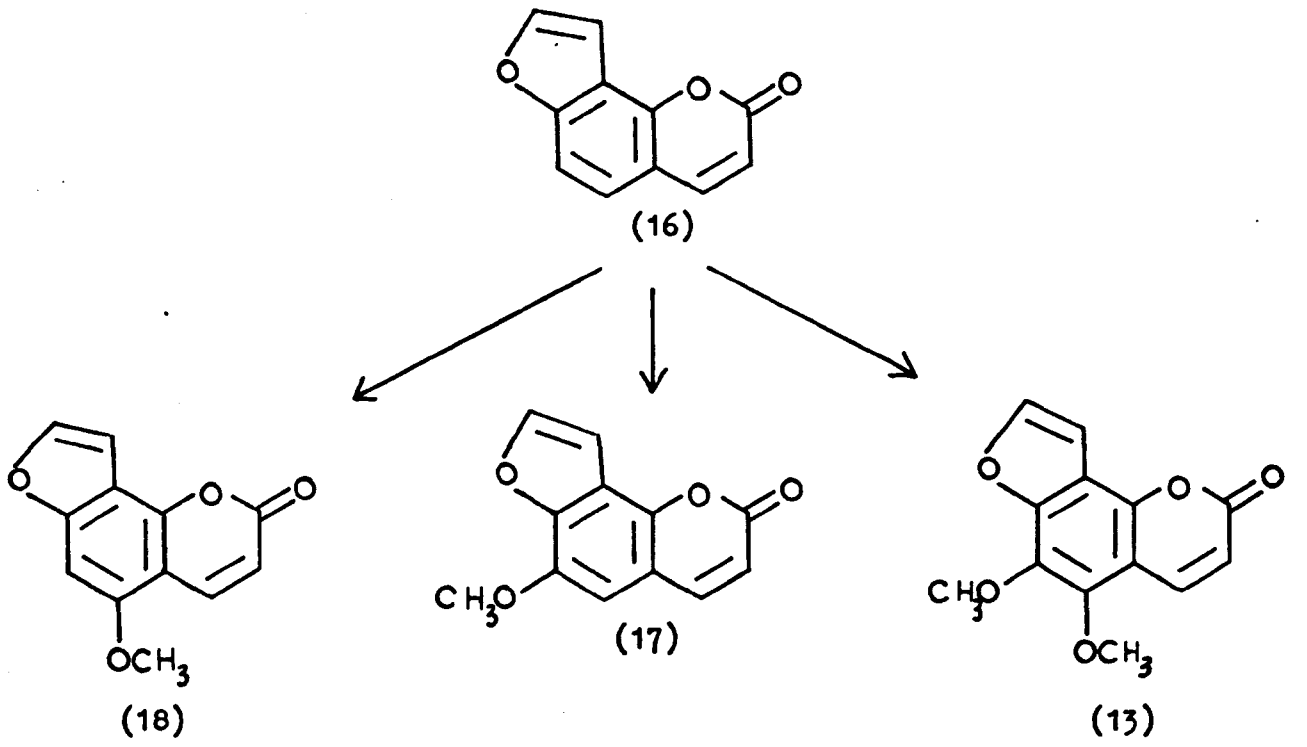

(2)

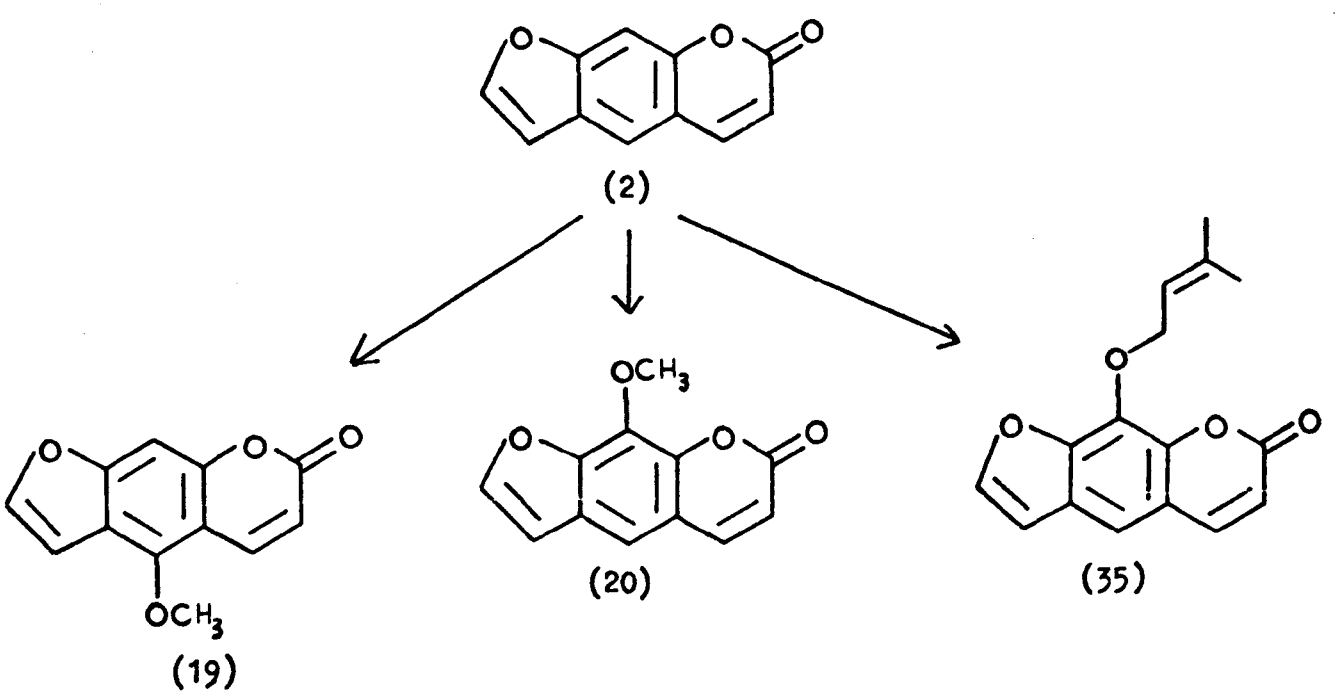
To account for the observed consistency in the configuration of both asymmetric centres (2'S,3'R) in the natural esters of vaginidiol (27), Steck[43] proposed that columbianetin (14) underwent a stereospecific hydroxylation at C-3', followed by esterification as the probable biosynthesis of these compounds (Scheme 1.19a). If the same stereospecific hydroxylation were to obtain in the biosynthesis of the angular pyranocoumarins, then this would lead to the diol (30), with the absolute configuration 3'(R),4'(R) (Scheme 1.19b). The diol (30) is not a known natural product, but a number of its esters are, and significantly, all have the absolute configuration 3'(R),4'(R).

The analogous diol (31) was also proposed by Steck[47] to occupy a similar role in the biosynthesis of linear furanocoumarins (Scheme 1.20).

Since 1970, a series of papers concerning furanocoumarin biosynthesis has been published by Caporale and his co-workers. They tested the efficiency of the unsubstituted dihydrofurano-coumarins (32) and (33) as possible furanocoumarin precursors, in Ficus carica[48]. Good incorporation into the corresponding furanocoumarins was obtained, consequently dehydrogenation was proposed as the probable final step in furanocoumarin biosynthesis. This conclusion was questioned by Brown[49]. He fed labelled umbelliferone (3) to the roots of Ruta graveolens and was thereafter able to extract labelled dihydropsoralen (32) and labelled psoralen (2). No matter what time had elapsed before extracting the plant, he found that the dihydropsoralen (32) activity was always two orders of magnitude lower than the psoralen (2) activity. He concluded that dihydropsoralen (32)


OH
OCH3
O
(15)
(34)
(20)


(16)
OCH3
CH3O
(18)
(17)
(13)

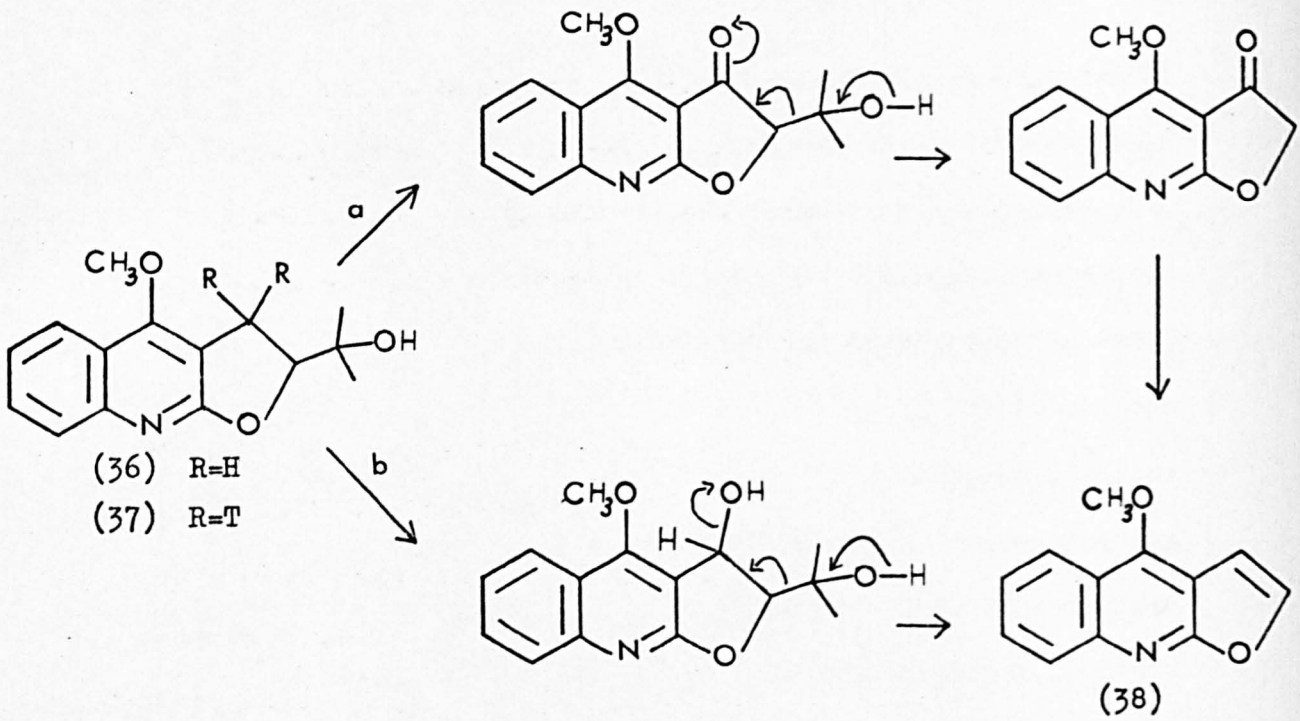

(2)
OCH3
(19)
(20)
(35)

is not on the main biosynthetic pathway, but is in a possible equilibrium with psoralen (2).

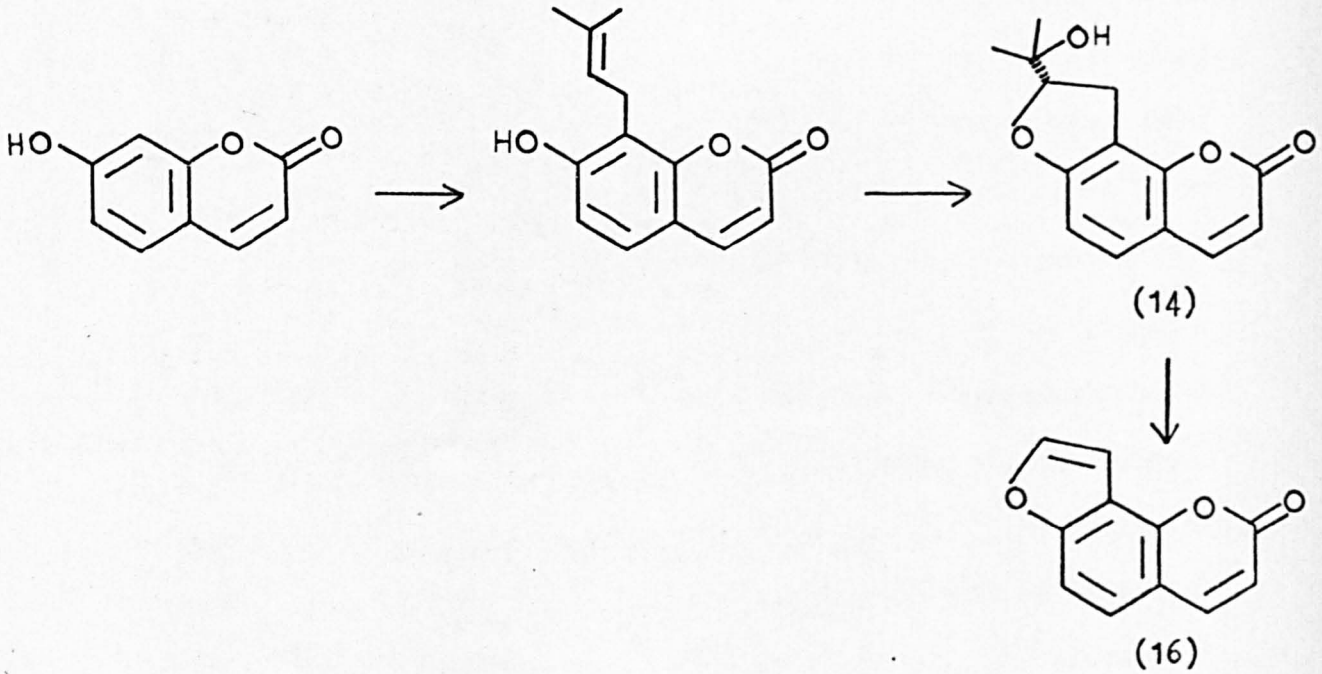
Caporale also observed[50] good incorporation of rutaretin (34) into xanthotoxin (20) in Ruta graveolens, suggesting that, at least in this plant, further hydroxylation of the aromatic nucleus occurs prior to cleavage of the C_5 unit. In a later paper[51], he established the sequential roles of marmesin (15) and rutaretin (34), by showing that (15) was a highly efficient precursor of (34). Steck, however, has shown that in Heracleum lanatum, angelicin (16) is converted with high efficiency into the furanocoumarins (13), (17) and (18)[43], and that in various species, psoralen (2) is converted into (19), (20) and (35)[47]. These results, taken in conjunction with those of Caporale, imply that further hydroxylation of the aromatic nucleus can take place either at the 2'-hydroxyisopropyldihydrofuran stage, or after cleavage of the C_5 unit to form the furan ring.

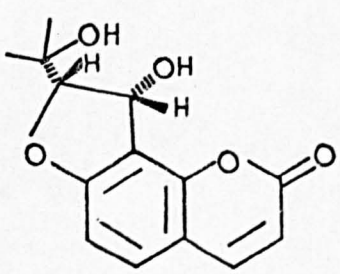
A very similar sequence of events to those described earlier, has been shown to operate in the biosynthesis of furanochromones[52] and furanoquinoline alkaloids[53]. In particular, Grundon and his co-workers[54] have recently published a paper in which they distinguish between two proposed mechanisms for formation of the furan ring in furanoquinoline alkaloids (Scheme 1.21). The difference in these mechanisms concerns the benzylic methylene group of (36), in that both hydrogens are lost in pathway (a), but only one hydrogen is lost in pathway (b). In order to investigate this, they synthesized the hydroxyisopropyldihydrofuran precursor with both benzylic positions labelled with tritium (37). After administration of this compound to plant shoots of Choisya ternata, the

SCHEME 1.21

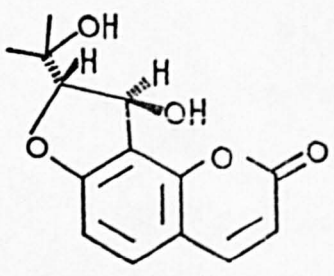


SCHEME 1.22





vaginidiol (27)



or enantiomer

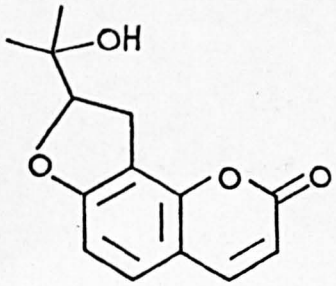
vaginol (28)

furanoquinoline (38) was isolated, and shown to have approximately half the tritium content of (37). Consequently, they concluded that their results are only consistent with mechanism (b), in which one benzylic hydrogen is retained during formation of the furan ring.

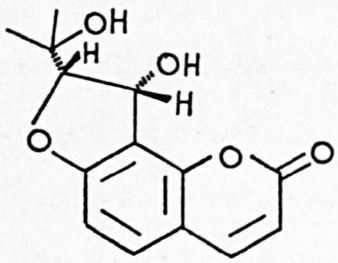
To summarise, much work has been done on the biosynthesis of the furan ring in benzofurans. With coumarins, it has been conclusively established that Scheme 1.22 operates in various plants, however little is known about the details of the route from columbianetin (14) to angelicin (16). It has been proposed that vaginidiol (27) is an intermediate, itself arising from a stereospecific hydroxylation of columbianetin (14). A number of natural esters of vaginidiol (27) are known, all of which have the same cis stereochemistry, and are known to give angelicin (16) on mild hydrolysis. Vaginol (28), the trans diol, has also been isolated from a plant source. At present, it is not known which, if either, or both, of these diols is the 'missing' intermediate in furanocoumarin biosynthesis. Clearly, a synthesis of these diols would be of great value, in that labelling experiments could be carried out to investigate this biosynthetic problem. Part 1 of this thesis describes synthetic approaches to these compounds.

Part 1

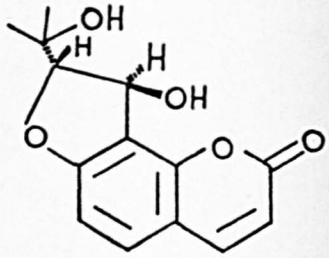
Synthetic Approaches to the Coumarins Vaginidiol and Vaginol.



(14)

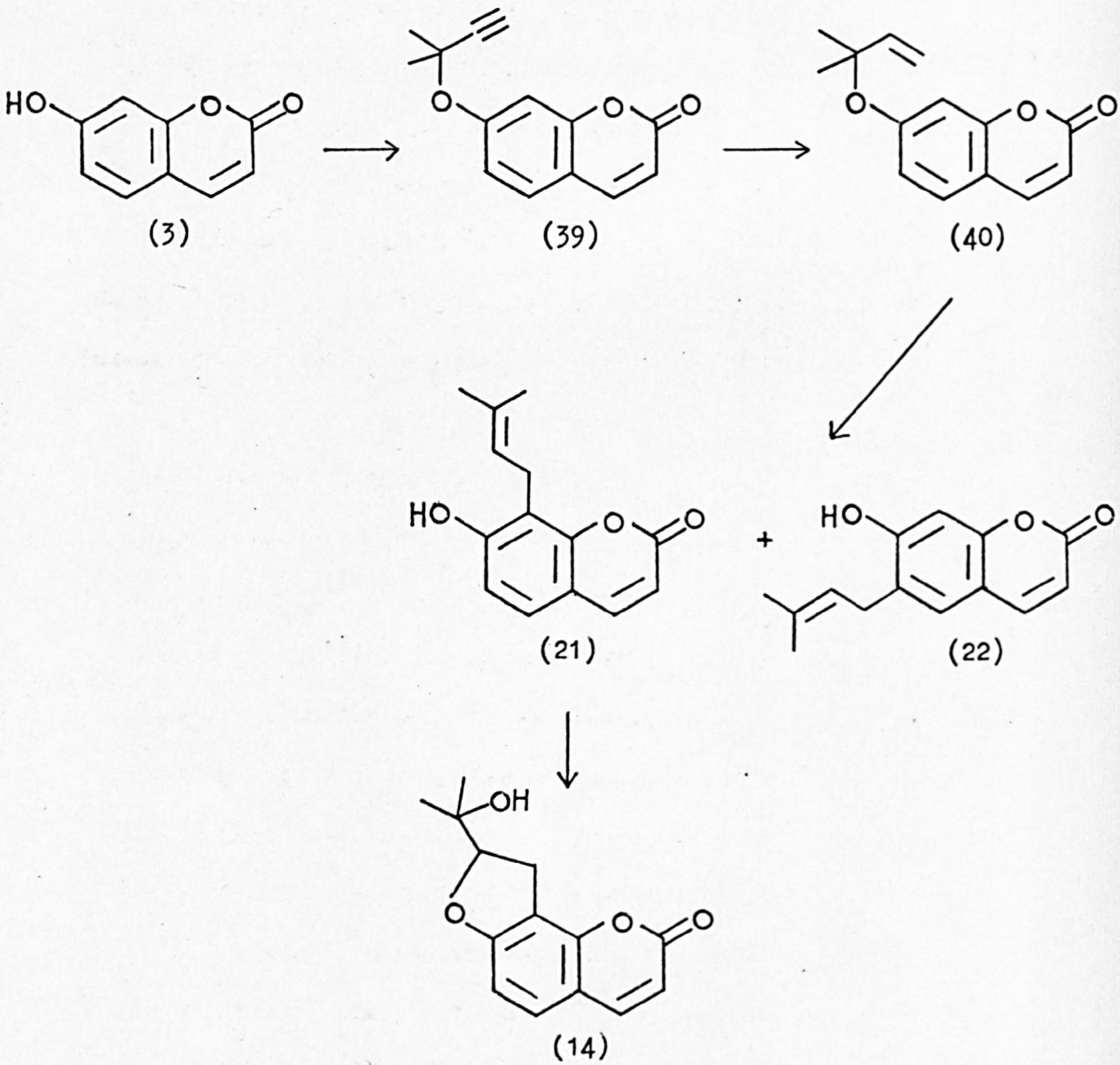


(27)



(28)

SCHEME 1.23



In this section of the thesis, all racemic compounds are illustrated by one enantiomer only.

One approach to the synthesis of vaginidiol (27) and vaginol (28) has previously been investigated in this department[55]. This route involved preparation of the dihydrofuranocoumarin columbianetin (14), followed by its benzylic hydroxylation. The synthesis of columbianetin (14) (Scheme 1.23) was achieved as follows : Umbelliferone (3) was treated with 3-chloro-3-methyl-but-1-yne in refluxing 2% aqueous acetone, in the presence of potassium carbonate and potassium iodide. The required propargyl ether (39) was thus obtained in 70% yield. Hydrogenation of (39) over 5% palladium on barium sulphate with a carefully determined amount of sulphur-quinoline poison afforded 7-O-(1,1-dimethylallyl) umbelliferone (40) almost quantitatively. Pyrolysis of this ether at 130° for 1 hour gave a mixture of three compounds. Umbelliferone was present in trace amounts, but the two major components were osthenol (21) and 7-demethylsuberosin (22) , in the ratio ~ 5:1. Separation of these compounds was achieved by careful preparative t.l.c.

Osthenol (21), on reaction with meta-chloroperbenzoic acid in ether, gave a single product which was identified as columbianetin (14), from spectroscopic evidence. The opening of the presumed epoxide ring at the less substituted carbon atom was anticipated, under the effectively neutral conditions employed.

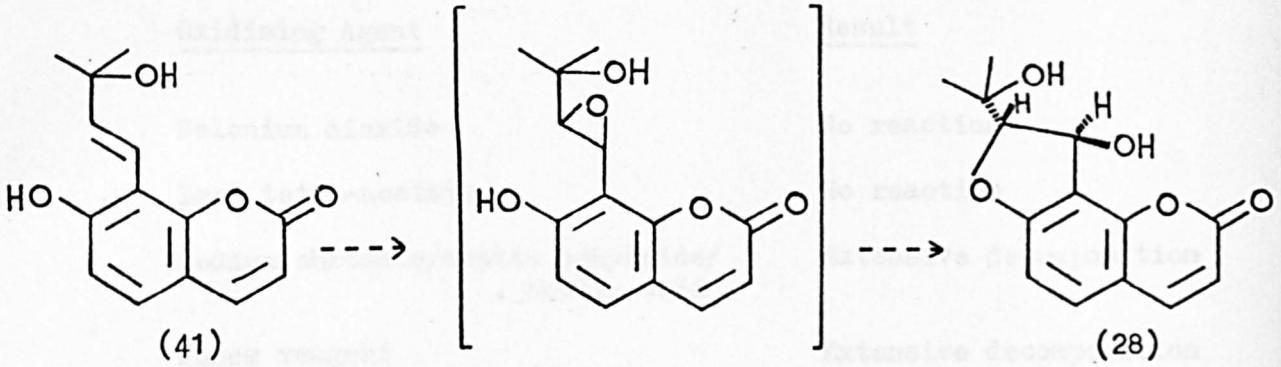
Murray and Sutcliffe[55] then attempted the benzylic oxidation of columbianetin (14). Although nine different oxidising agents were used, each of which was known to be capable of specifically effecting a benzylic oxidation, no useful oxidation of columbianetin (14) was achieved. Table 1.1 summarises their results.

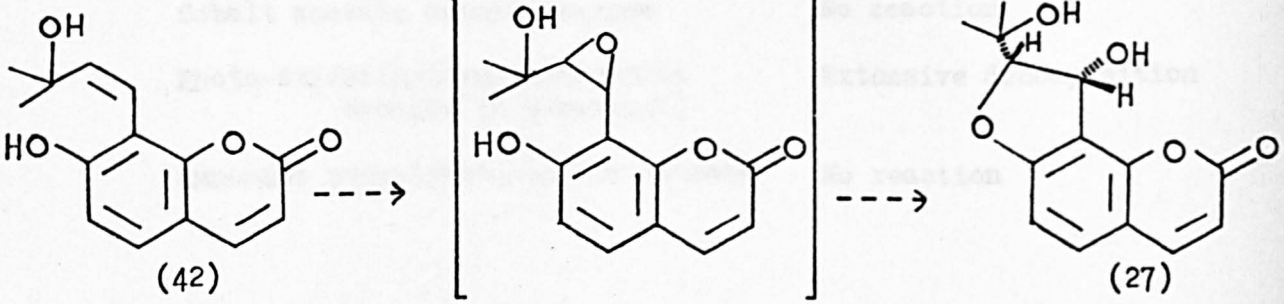
Consequently, it was apparent to us that any successful route to vaginidiol (27) and vaginol (28) would require the benzylic

TABLE 1.1

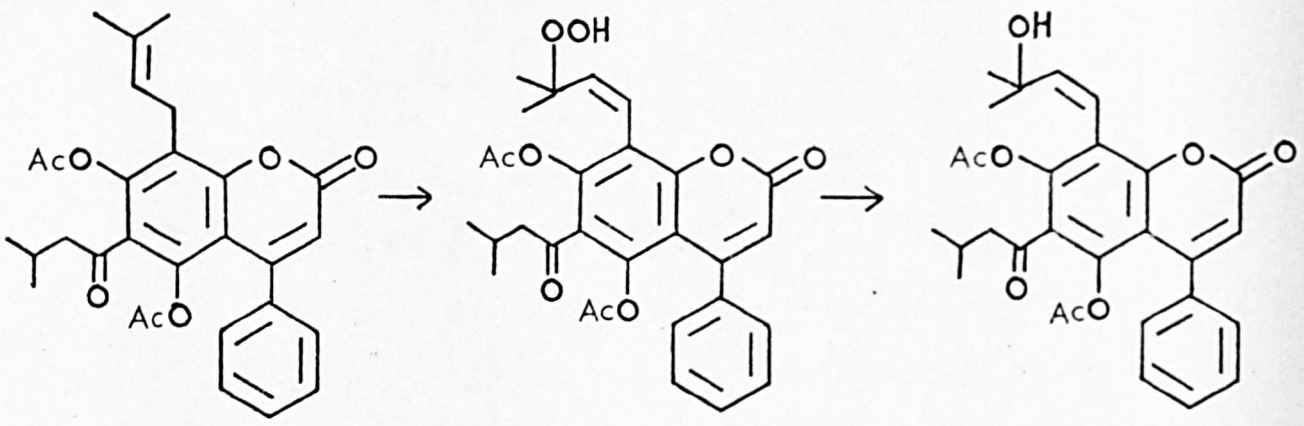
Oxidising Agent	Result
Selenium dioxide	No reaction
Lead tetra-acetate	No reaction
Sodium chromate/acetic anhydride/ acetic acid	Extensive decomposition
Jones reagent	Extensive decomposition
Chromyl chloride	No reaction
N-Bromosuccinimide	Bromination at C-3
Cobalt acetate bromide/oxygen	No reaction
Photo-oxidation(oxygen/mercuric bromide in t-butanol)	Extensive decomposition
Ammonium persulphate/silver nitrate	No reaction

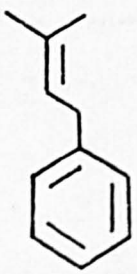
S C H E M E 1.24





S C H E M E 1.25





(45)

position to be functionalised prior to formation of the dihydrofuran ring. On this premise, two main approaches were investigated.

Approach A

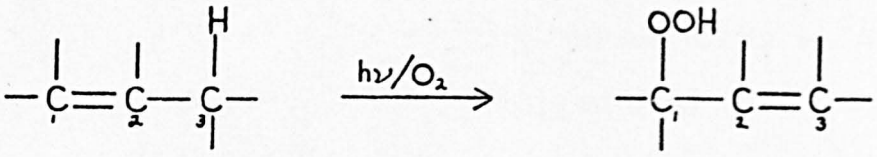
The key compounds in this approach were the allylic alcohols (41) and (42). It was envisaged that these compounds could be converted stereospecifically into vaginol (28) and vaginidiol (27), respectively, by epoxidation and cyclisation as shown in Scheme 1.24. Thus the initial aim was the synthesis of (41) and (42).

A method for synthesizing the cis allylic alcohol (42) was suggested by the work of Polonsky and her co-workers[56]. They found that dye sensitised photo-oxygenation of (43), followed by reduction of the resulting hydroperoxide, gave the cis allylic alcohol (44) (Scheme 1.25). Examination of the n.m.r. signals reported for (44), however, revealed that the resonances for the two olefinic protons on the 3-hydroxy-3-methylbut-1-enyl side chain were accidently equivalent. Thus the assignment of cis stereochemistry to (44) was dubious, since no attempt had been made to shift the signals and thereby determine the coupling constant between these two protons, and hence their relative stereochemistry.

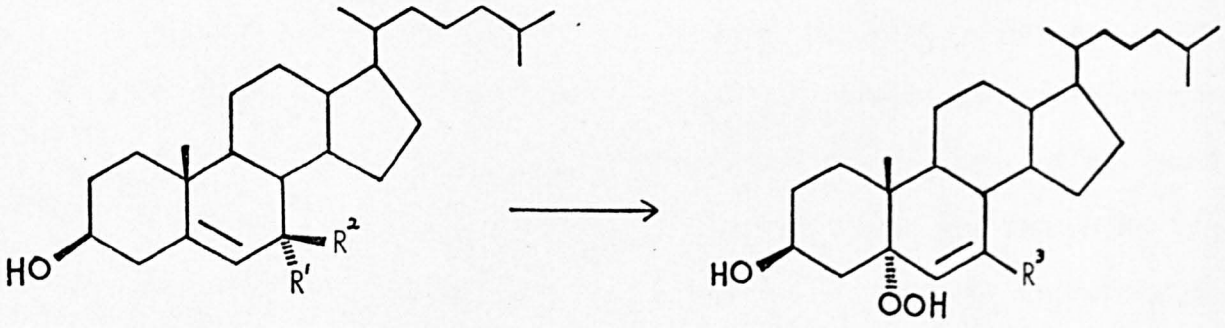
To ascertain whether the stereochemistry of the product(s) from photo-oxygenation of the system (45) could be predicted, the detailed mechanism of this type of reaction was examined.

The dye sensitised photo-oxygenation of olefins, which leads to the formation of allylic hydroperoxides (Scheme 1.26), has been studied by many workers[57], as it represents a convenient method for the introduction of oxygen at a specific site in a molecule. In particular, Nickon and Bagli[58] have shown that dye sensitised photo-oxygenation of cholesterols labelled at

S C H E M E 1.26



S C H E M E 1.27



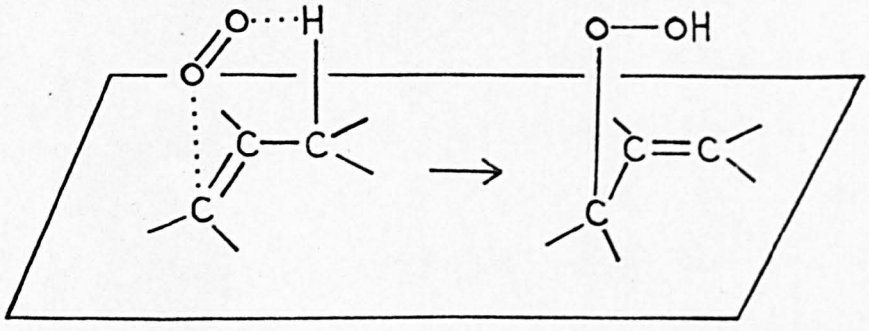
(46) $R' = D$, $R^2 = H$

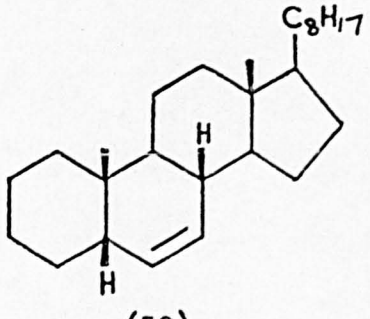
(47) $R' = H$, $R^2 = D$

(48) $R^3 = H$

(49) $R^3 = D$

S C H E M E 1.28





(50)

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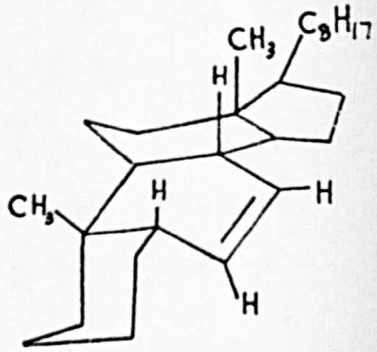
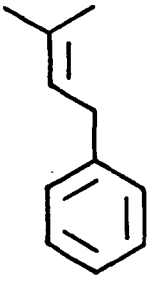


the 7α and 7β positions, (46) and (47), led to the exclusive formation of the 5α hydroperoxides (48) and (49) respectively (Scheme 1.27). From this they deduced that hydrogen abstraction at C-7 occurred on the same side of the molecule as that on which the new carbon-oxygen bond was formed. Consequently , they postulated a cis cyclic 'ene-type' mechanism (Scheme 1.28), in which the most favourable orientation for reaction had an allylic hydrogen atom perpendicular to the olefinic plane. In support of this, they found that (50), which cannot adopt a conformation having an allylic hydrogen atom perpendicular to the olefinic plane, was inert under prolonged photo-oxygenation conditions.

An aromatic 3,3-dimethylallyl group (45) possesses three possible sites at which hydrogen abstraction can occur, namely at the benzylic position or at either of the terminal methyl groups. It would seem reasonable to predict that hydrogen abstraction would be favoured at the doubly activated benzylic position, in agreement with the results of Polonsky (vide supra). Reaction at this benzylic position, however, could lead to both cis and trans allylic hydroperoxides, (51) and (52), dependent on the conformation of the reacting species. Based on the findings of Nickon and Bagli (vide supra) there are two distinct conformations of the 3,3-dimethylallyl group in (45) that could react with singlet oxygen, i.e. the two conformations, (53) and (54), which possess an allylic hydrogen atom perpendicular to the olefinic plane. As shown in Scheme 1.29, reaction of (53) with singlet oxygen would lead stereospecifically to the trans allylic hydroperoxide (51), whereas reaction of (54) with singlet oxygen would lead stereospecifically to the cis allylic hydroperoxide (52). As a result of steric interactions, conformation (53) should be greatly favoured over (54), and thus we predicted that dye sensitised photo-oxygenation of



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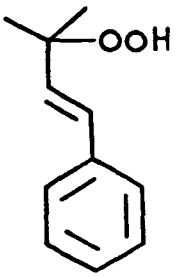

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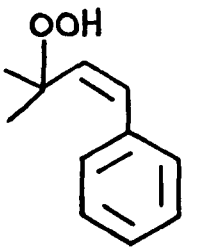
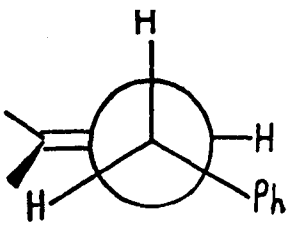


(52)

S C H E M E 1.29



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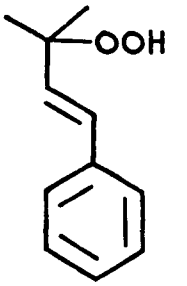

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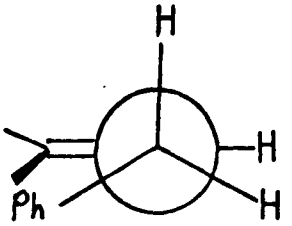
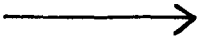
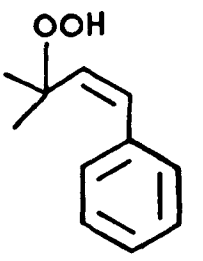


(54)





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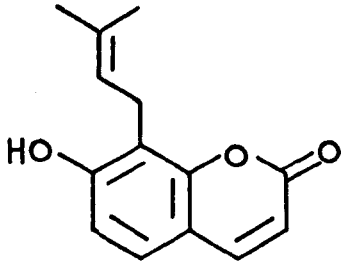

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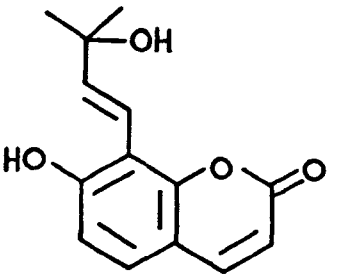
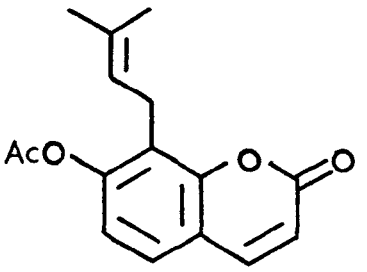
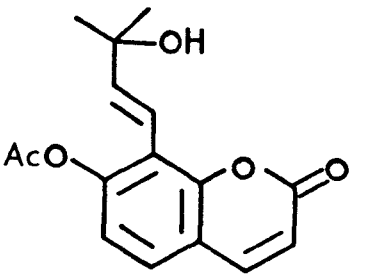


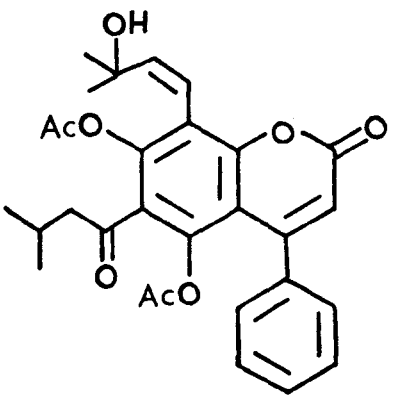
(41)



(55)



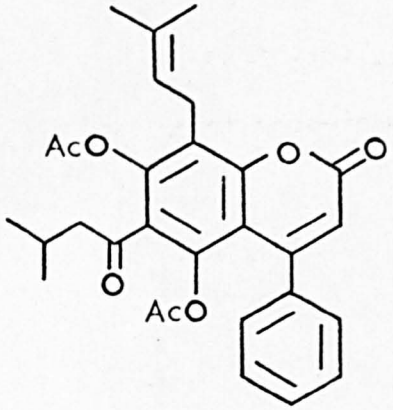
(56)



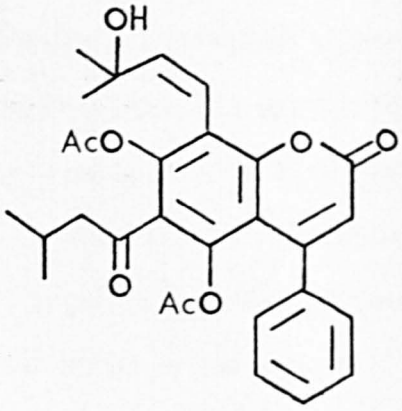
(44)

aromatic compounds possessing the 3,3-dimethylallyl side chain should give stereoselectively, if not stereospecifically, the trans allylic hydroperoxide. Thus the dye sensitised photo-oxygenation of osthenol (21) was investigated as a potential route to the trans allylic alcohol (41).

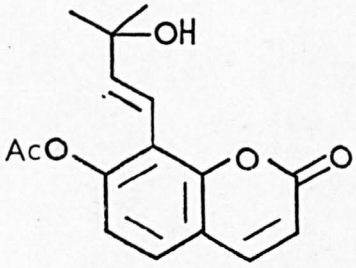
Oxygen was bubbled through a solution of osthenol (21) in pyridine containing a small amount of haematoporphyrin as sensitiser, with irradiation from a 60 watt lamp. Surprisingly, after 48 hours, no reaction had taken place, as indicated by t.l.c. In the possibility that the phenolic group in osthenol (21) was, for some reason, preventing reaction taking place, the reaction was attempted using osthenol acetate (55). When the latter compound was subjected to the above photo-oxygenation conditions, t.l.c. after 18 hours indicated complete conversion to a single, more polar, compound. After removal of pyridine, the assumed hydroperoxide was immediately reduced with triphenylphosphine in chloroform. Unfortunately, the product from this reduction could not be separated completely from the triphenylphosphine oxide, so an alternative method of reduction was employed. Using sodium iodide in ethanol containing a small amount of acetic acid, the reduction was effected smoothly, and the product was easily isolated by using an aqueous work-up. T.l.c. confirmed that a single compound had been formed, and it was identified as the trans allylic alcohol (56), as predicted, on the basis of its n.m.r. spectrum. As Polonsky had observed with (44) (vide supra), the signals for the two olefinic protons on the 3-hydroxy-3-methylbut-1-enyl side chain in (56) were accidently equivalent, but were separated by addition of a small amount of $Eu(fod)_3$, which enabled the coupling constant of 16Hz to be determined, and thus trans stereochemistry to be assigned to (56).



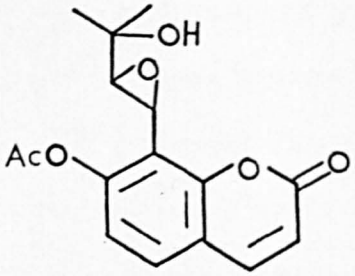
(43)



(44)



(56)



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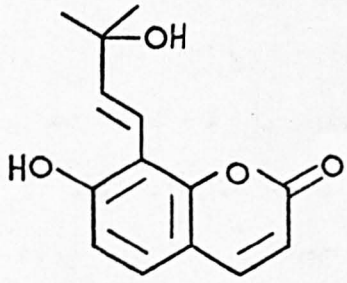
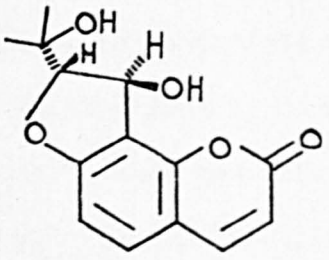


(41)



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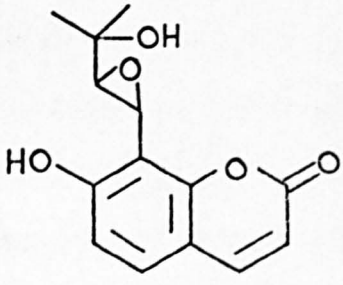


(58)

In the light of the above result, it seems likely that Polonsky *et al*[56] have erroneously assigned *cis* stereochemistry to (44), the product from photo-oxygenation of (43).

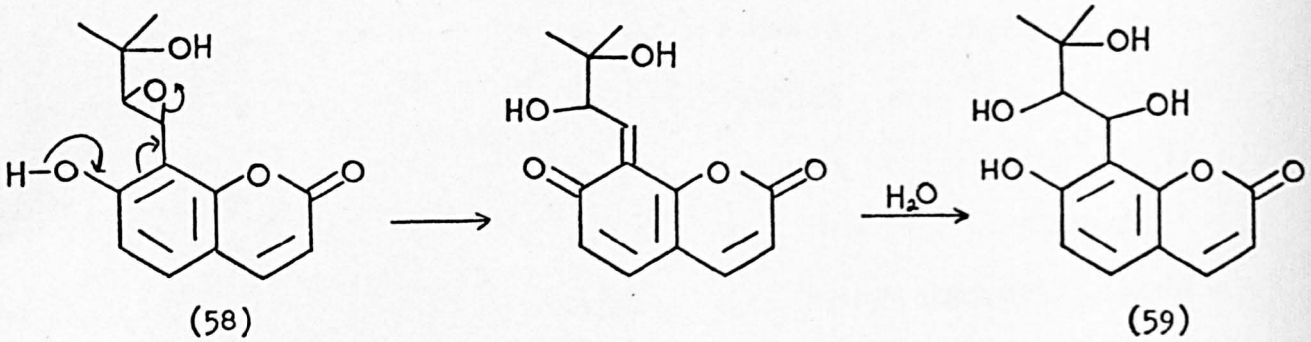
Reaction of (56) with *meta*-chloroperbenzoic acid, in methylene chloride, proceeded smoothly and in high yield to give the epoxide (57). Mild hydrolysis of (57), using 2% aqueous sodium carbonate in methanol, gave, unexpectedly, a very complex mixture of products, separation of which proved impossible. The n.m.r. spectrum of this mixture showed that although no epoxide was present, none of the desired product (28) had been produced.

As an alternative route to (28), the acetate (56) was first hydrolysed to the phenol (41), which was then treated with *meta*-chloroperbenzoic acid, under effectively neutral conditions. In this case, a different but again complex mixture of products was formed.

The absence of any cyclised product (28) from the above two reactions can be rationalised in terms of the stereoelectronic requirements of the transition state for the ring closure process. Examination of molecular models revealed that the *ortho* hydroxyl group in (58) is not favourably positioned for opening the epoxide in the desired manner. This same conclusion was reached using the rules concerning cyclisation reactions, recently published by Baldwin[59]. An alternative mechanism of epoxide opening was then realised, and is shown in Scheme 1.30. The product (59) from this mode of reaction may be present in the two complex mixtures obtained above, as estimated from their n.m.r. spectra. The formation of a complex mixture of products from the mild hydrolysis of (57), and from the epoxidation of (41), remains a mystery.

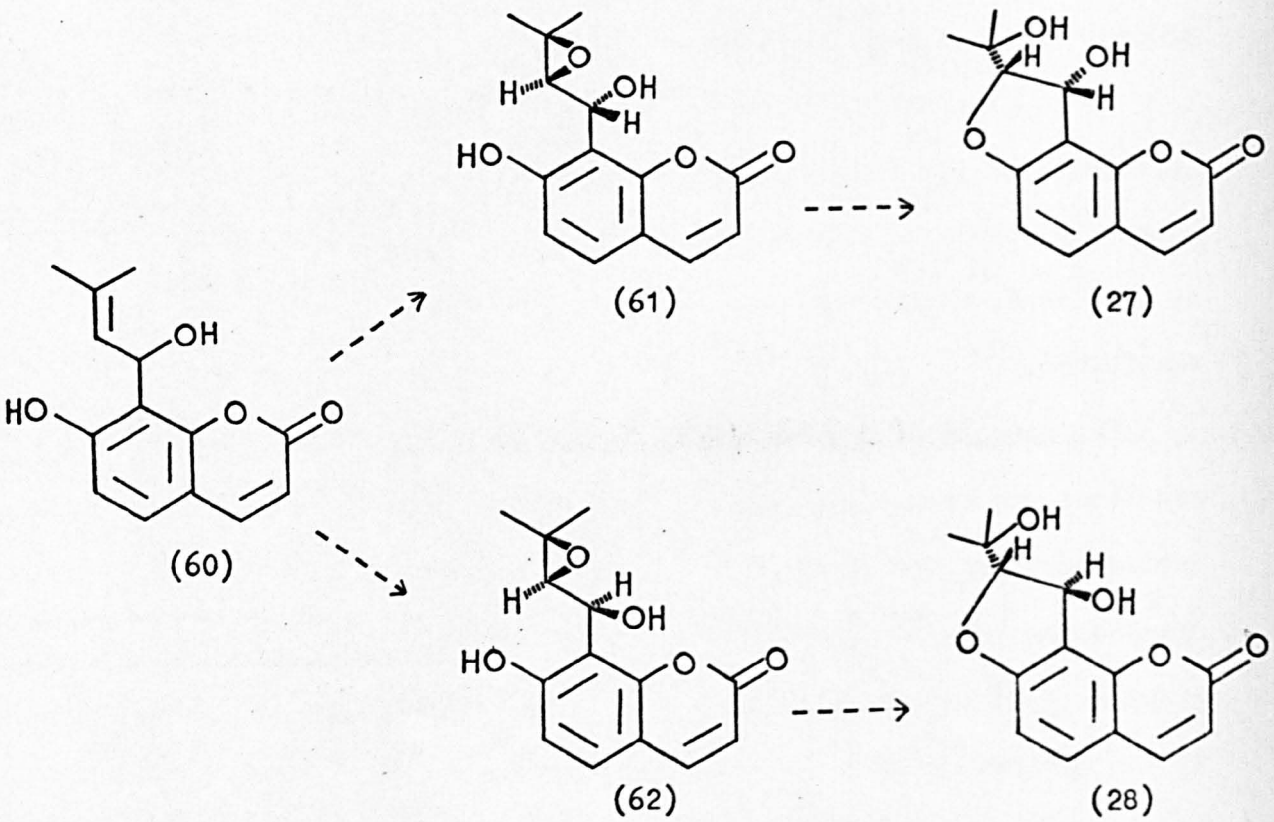
In the light of the above results, this approach to the

SCHEME 1.30

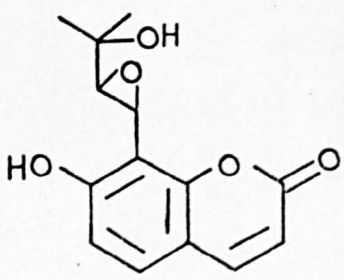


(58) (59)

SCHEME 1.31



(61) (27) (60) (62) (28)



(58)

synthesis of vaginol (28) and vaginidiol (27) was abandoned.

Approach B

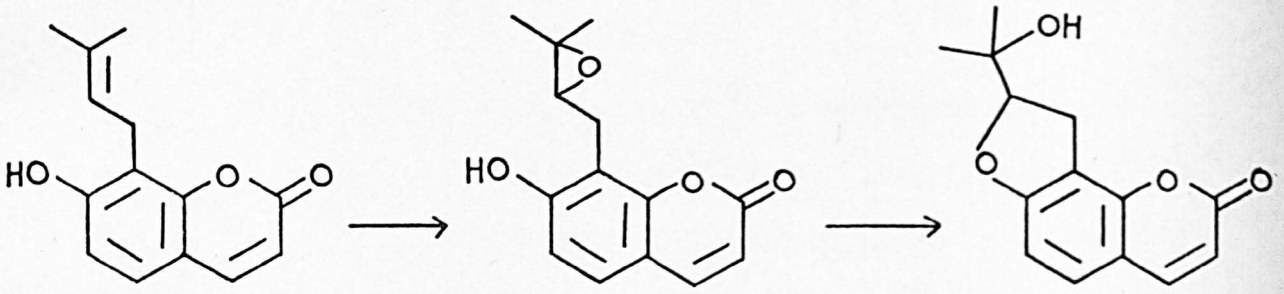
The key intermediate in this approach (Scheme 1.31) was the allylic alcohol (60). In contrast to (58) (see Approach A), examination of molecular models indicated that cyclisation of the epoxy-phenols (61) and (62) should be stereoelectronically favoured, and indeed, a direct analogy with the oxidative cyclisation of osthenol (21) (Scheme 1.32) existed[55]. In this approach, however, a mixture of vaginidiol (27) and vaginol (28) should be produced, the relative amount of each compound depending on the stereochemistry of epoxidation. Various workers have shown[60,61] that the hydroxyl group in allylic alcohols has a directing effect on the stereochemistry of epoxidation of the double bond. In particular, it has been shown[60] that reaction of allylic alcohols of type (63) with a peracid usually results in preferential formation of the threo epoxide (64). Consequently, epoxidation of (60) should lead to a stereoselective formation of the epoxy-phenol (62) and hence to a predominance of vaginol (28).

Thus the initial aim in this approach was the synthesis of the allylic alcohol (60). Since numerous routes to (60) have been investigated, they will be discussed individually, in the appropriate section as follows :

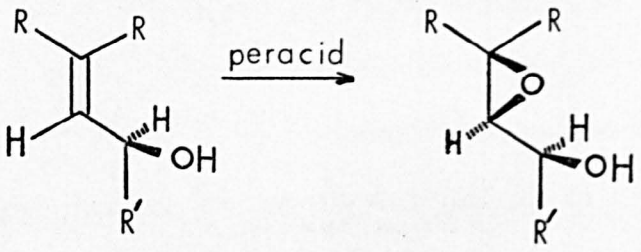
I Direct oxidation of osthenol (21)

One of the most direct routes to the allylic alcohol (60) would simply require a benzylic oxidation of osthenol (21). Although many attempts at the benzylic oxidation of columbianetin (14) were unsuccessful (vide supra), it was thought that oxidation of osthenol (21) would have a greater chance of success, since the benzylic position

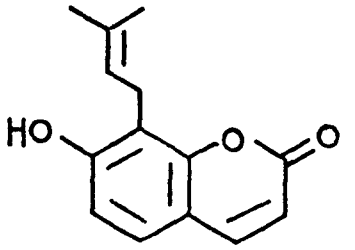
S C H E M E 1.32



(21) (14)



(63) (64)



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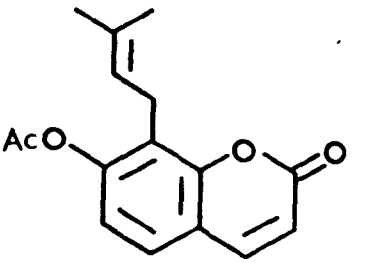

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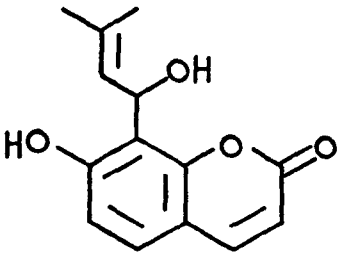
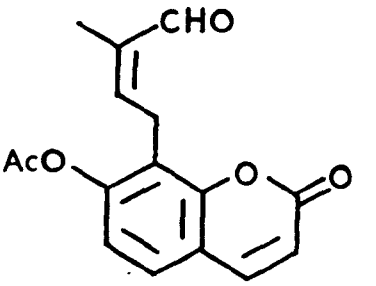
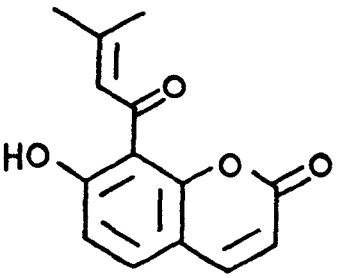


(60)



(65)



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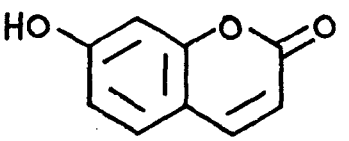
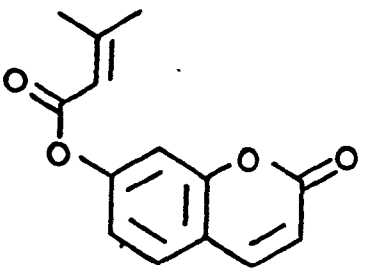
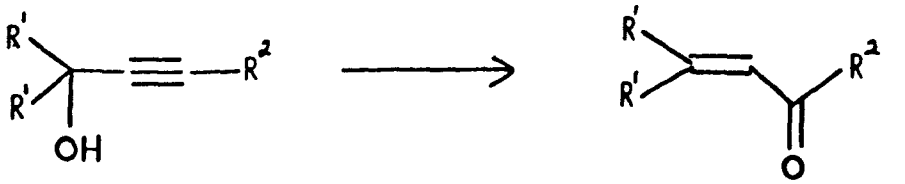


(3)



(67)

SCHEME 1.33



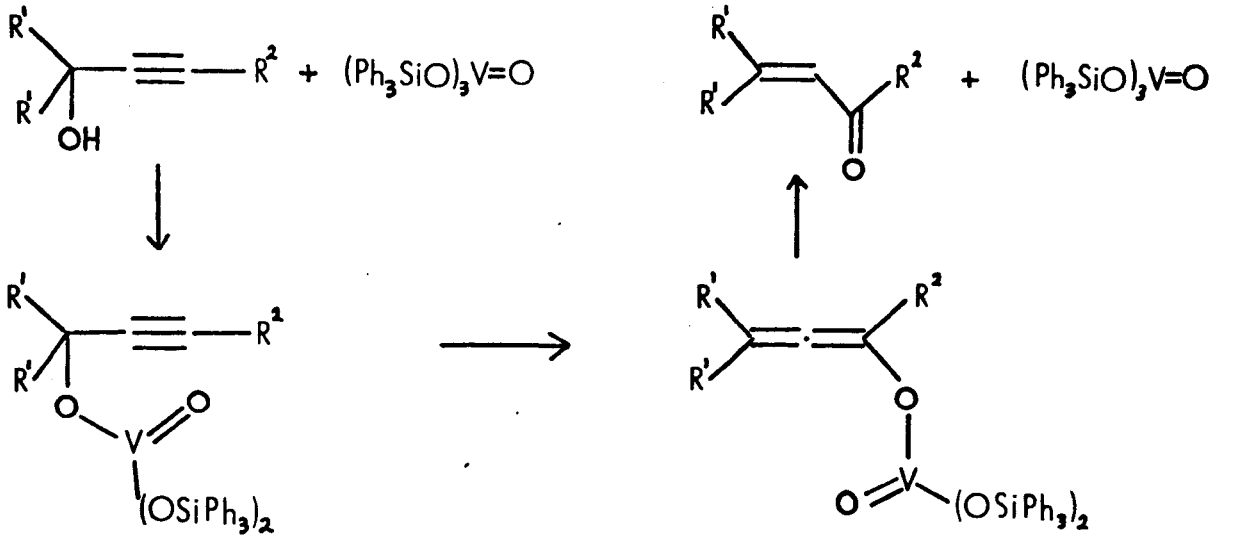
in osthenol (21) is doubly activated, being allylic and benzylic. Repeated attempts, by both Dr. Sutcliffe[55] and the author, to effect the required benzylic oxidation of osthenol (21), or osthenol acetate (55), using the oxidising agents listed in Table 1.1 (vide supra), were totally unsuccessful. The only occasion[55] on which a clean oxidation occurred was with the use of selenium dioxide as oxidant. In this case, oxidation at the 'wrong' position had taken place, giving a good yield of the aldehyde (65). Thus the direct benzylic oxidation of osthenol (21) as a route to (60) was found to be unsuccessful.

II Reduction of 7-hydroxy-8-(3-methylbut-2-enoyl)coumarin (66)

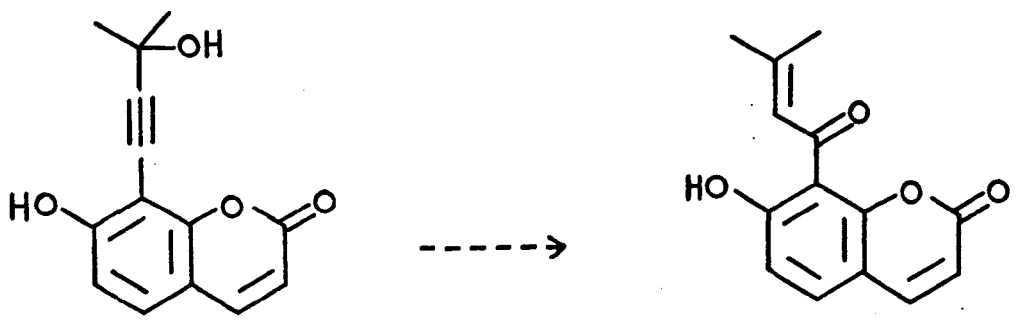
An alternative route to the allylic alcohol (60), which involved reduction of 7-hydroxy-8-(3-methylbut-2-enoyl)coumarin (66), was considered. Consequently, an efficient route to (66) was sought. Two standard methods for the introduction of an acyl group ortho to a phenol had previously been investigated[62] in this department, as a way of synthesizing (66). In the first, umbelliferone (3) was converted to its 3-methylbut-2-enoate (67), but, surprisingly, this compound failed to undergo the expected Fries rearrangement to (66). The second method, based on a Friedel-Crafts reaction between umbelliferone (3) and 3-methylbut-2-enoyl chloride, was equally unsuccessful. Since these two methods for introducing the 3-methylbut-2-enoyl moiety at C-8 in umbelliferone (3) failed, an alternative approach for accomplishing this overall reaction was required.

Recently, a new, mild, catalytic method for the isomerisation of α-acetylenic alcohols to the corresponding α,β-unsaturated ketones (Scheme 1.33) has been reported by Pauling, Andrews and Hindley[63]. This rearrangement, known formally as the Meyer-Schuster

SCHEME 1.34

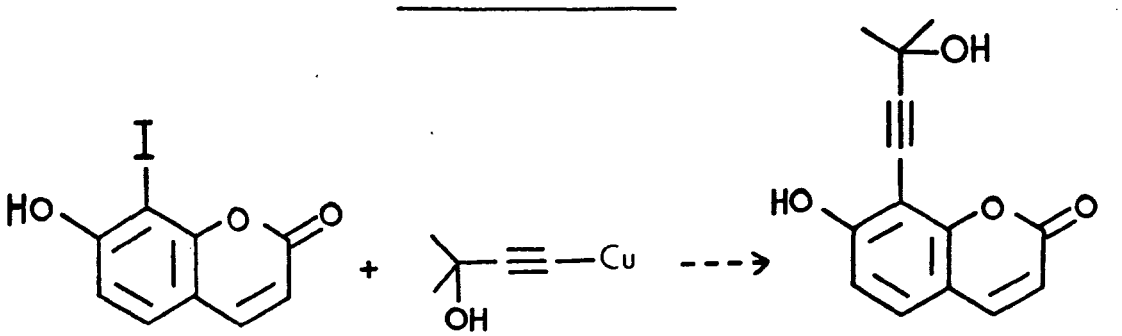


SCHEME 1.35

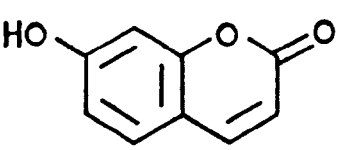


(68) (66)

SCHEME 1.36



(70) (69) (68)



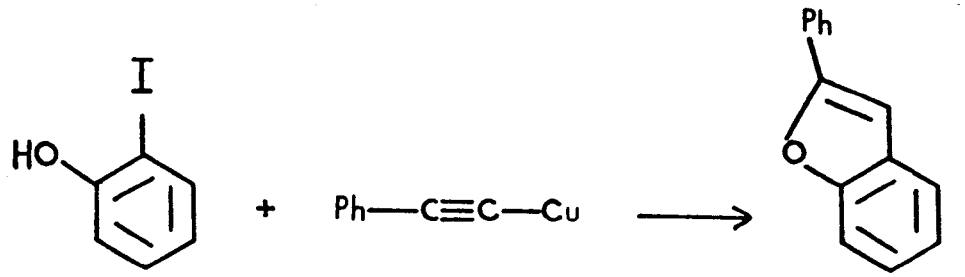
(3)

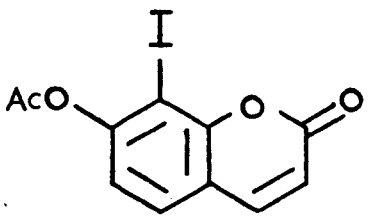
rearrangement, was previously accomplished[64] by heating an α-acetylenic alcohol with an acid catalyst, e.g. formic acid, and consequently, usually resulted in the formation of several products in low yields. The new method, however, involves heating an α-acetylenic alcohol with a catalytic amount of tris(triphenylsilyl) vanadate, in xylene, and generally gives yields of greater than 90%. The mechanism proposed for this reaction[63] is shown in Scheme 1.34. It was realised that rearrangement of the acetylenic alcohol (68), using tris(triphenylsilyl) vanadate as catalyst, should lead to the desired compound (66) (Scheme 1.35). In addition, it was known[65] that arynes could be prepared in reasonable yields by condensation of a copper acetylide with an aryl halide. Consequently, it was decided to investigate the coupling reaction of 3-hydroxy-3-methyl-but-1-yne copper acetylide (69) and 7-hydroxy-8-iodocoumarin (70) (Scheme 1.36) as a potential route to the acetylenic alcohol (68).

7-Hydroxy-8-iodocoumarin (70) was prepared[66] in 90% yield by the regiospecific iodination of umbelliferone (3), using one equivalent of iodine/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 (δ 6.75 and 7.31, each 1H;d;J 8Hz).

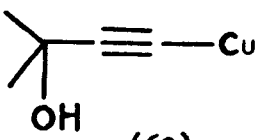
In the coupling reaction of copper acetylides and aryl halides, it is known[65] that aryl halides possessing an ortho hydroxyl group give a furan as sole product, e.g. Scheme 1.37. Consequently, it was necessary to protect the 7-hydroxyl group in 7-hydroxy-8-iodocoumarin (70) before attempting the coupling reaction, and the compound chosen initially for this purpose was 7-acetoxy-8-iodocoumarin (71). The copper acetylide (69) was prepared, but could not be isolated due to its solubility in the

SCHEME 1.37





(71)



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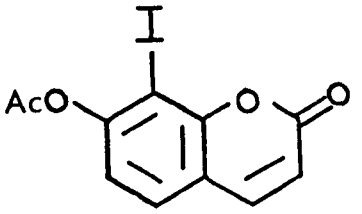

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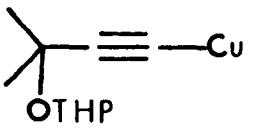

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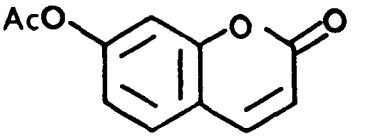

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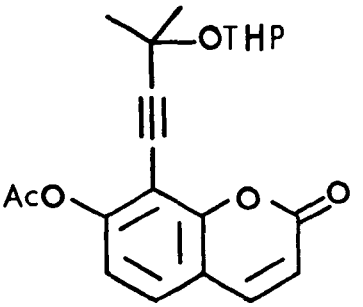

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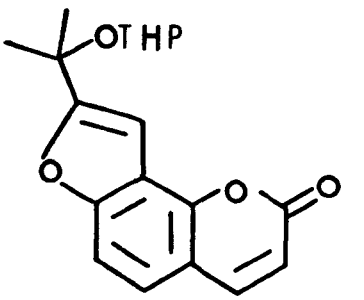
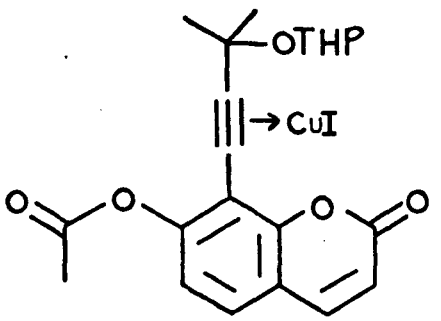
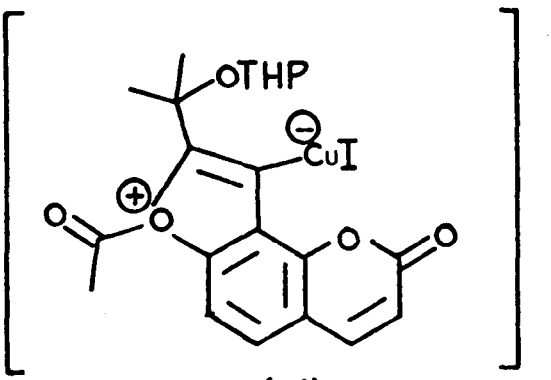


(75)

S C H E M E 1.38



(74)



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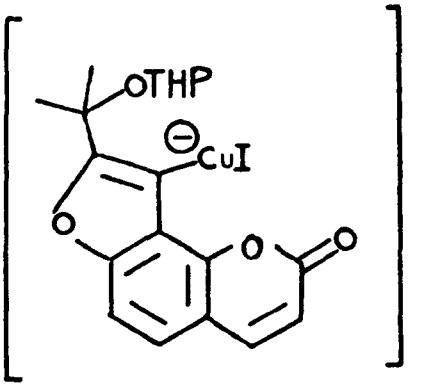

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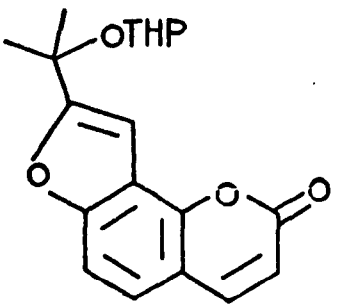
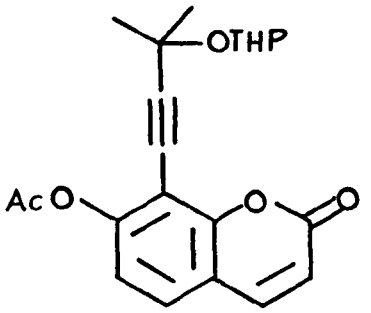


(75)

reaction medium. Consequently, the copper acetylide (72) of the tetrahydropyranyl ether of 3-hydroxy-3-methylbuy-1-yne was used. Thus a solution of (71) and (72) in pyridine was refluxed under argon for 18 hours, when t.l.c. indicated that no starting material remained. The reaction was then worked up, and, after chromatography, furnished two new compounds.

The minor product (21%) was identified as 7-acetoxycoumarin (73) from its spectral data, and comparison with an authentic sample. The formation of (73) was expected, since it is known[67] that in coupling reactions of this type, the main by-product is that resulting from dehalogenation of the starting material. However, the mechanism for this dehalogenation, and the source of the replacement hydrogen atom, are not known[67].

The major product from the reaction was isolated in 55% yield. It was immediately obvious from its spectral data that it was not the expected product (74), since it contained neither acetate nor acetylenic functionality. Significantly, however, the n.m.r. spectrum showed the presence of a new olefinic signal at δ 6.97 (1H ; s.), and this, taken in conjunction with other spectroscopic information, unambiguously determined the structure of this product as the furanocoumarin (75). The formation of (75) was rationalised as follows (Scheme 1.38) : The copper iodide by-product from the coupling reaction may well be co-ordinated with the acetylenic bond in the first formed product (74), thus rendering the triple bond electron deficient. Interaction of the C-7 oxygen atom with this electron deficient triple bond could conceivably lead to an intermediate of type (76). This latter complex would be very susceptible to solvolysis by pyridine, leading to (77), which, on aqueous work-up, would yield the observed product (75). It is



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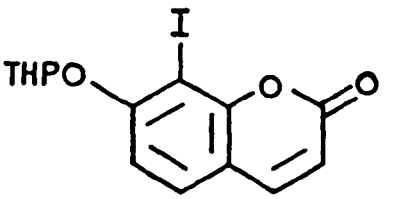
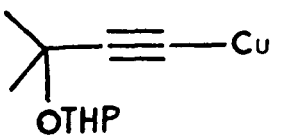


(78)



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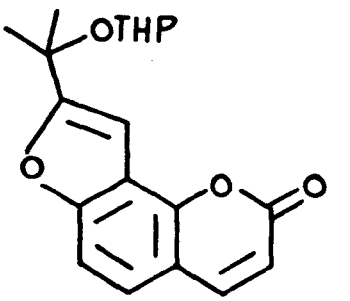
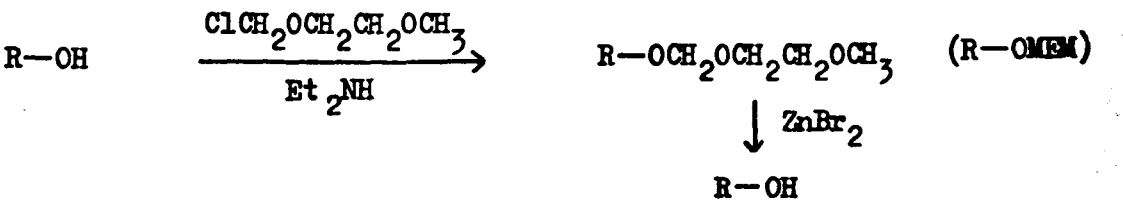
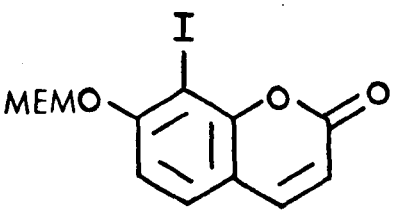


(75)

S C H E M E 1.39





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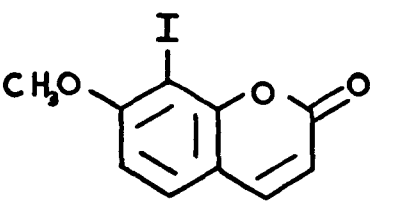

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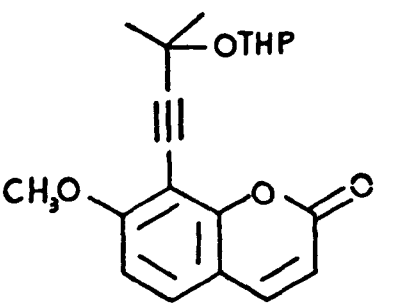


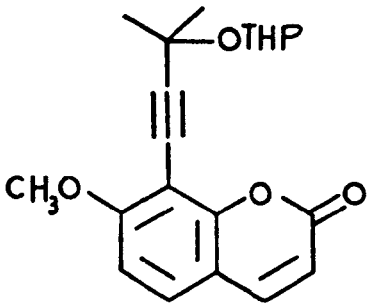
(81)

interesting to note that although the reaction was carefully monitored by analytical t.l.c., no evidence for the assumed intermediate (74) was obtained, indicating that its cyclisation must be very fast.

It was thought that protecting the 7-hydroxyl group in 7-hydroxy-8-iodocoumarin as its tetrahydropyranyl ether (78) might prevent cyclisation of the presumed first formed acetylenic compound. In the event, coupling of (72) and (78) gave, as before, the furanocoumarin (75) as major product, with no trace of any uncyclised product. Since tetrahydropyranyl ethers are normally stable under the conditions used in this coupling reaction, the driving force for formation of the furan ring must be considerable.

Thus it was still necessary to find a suitable protecting group for the 7-hydroxyl group in 7-hydroxy-8-iodocoumarin (70) such that cyclisation of the coupled acetylenic compound would not occur. At that time, Corey and his co-workers[68] reported the use of the β-methoxyethoxymethyl (MEM) group as a protecting group for the hydroxyl function. In general, an MEM ether is formed in high yield by treating an alcohol with β-methoxyethoxymethyl chloride in diethylamine (Scheme 1.39), is stable under a wide variety of conditions, and can be specifically cleaved by treatment with anhydrous zinc bromide in methylene chloride. Thus the MEM ether (79) was prepared, and the coupling reaction with (72) repeated. Once again, the furanocoumarin (75) was the major product from this reaction!

As a last resort, the methyl ether of 7-hydroxy-8-iodocoumarin, (80), was prepared and treated with the copper acetylide (72). On this occasion, the elusive acetylenic compound (81) was the major product (51%) isolated from the reaction, along with small amounts of the de-iodinated compound.



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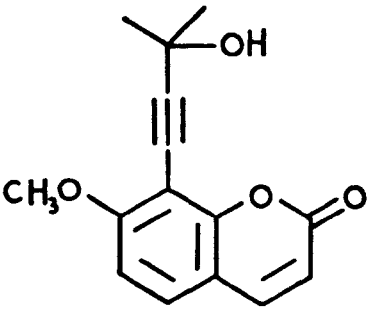

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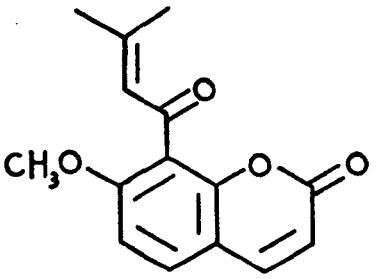
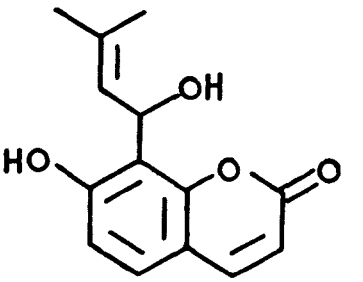


(83)



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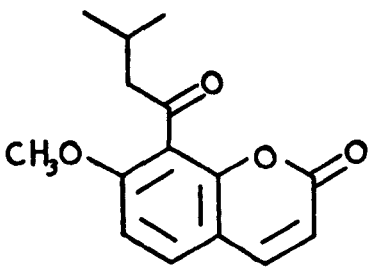
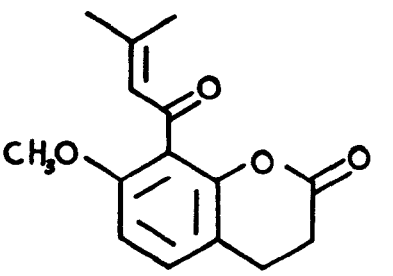


(84)



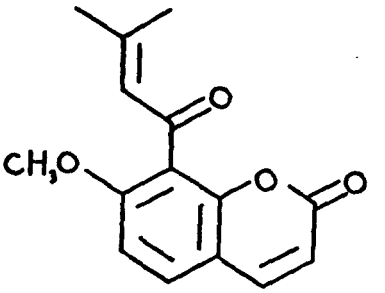
(85)

Treatment of (81) with 70% aqueous acetic acid, at room temperature, furnished the acetylenic alcohol (82) almost quantitatively. Reaction of (82) with a catalytic amount of tris(triphenylsilyl) vanadate in refluxing xylene gave, in 85% yield, the required α,β-unsaturated ketone (83).

Structure (83) has recently been assigned, by Hata et al[69], to a new coumarin isolated from Ligusticum hultenii. The structural proof of this new coumarin was based almost exclusively on spectral evidence; the only chemical reaction quoted being its acid catalysed deacylation to 7-methoxycoumarin. Comparison of the spectral data of synthetic and natural samples has now enabled this assignment (83) to be confirmed.

It remained only to reduce the ketone group in (83), and to cleave the methyl ether protecting the 7-hydroxyl group, to give the desired allylic alcohol (60).

Reaction of (83) with sodium borohydride in ethanol gave a complex mixture of products, which contained, from its n.m.r. spectrum, mainly (84) and (85), resulting from 1,4-reduction of the enone systems in (83). The use of di-isobutylaluminium hydride as a specific reducing agent for the 1,2-reduction of α,β-unsaturated ketones was reported by Masamune et al[70], in 1970. In particular, they found that cyclopent-2-enone, known for its propensity to undergo 1,4-reduction[70], gave exclusively cyclopent-2-enol, on treatment with di-isobutylaluminium hydride. Thus (83) was treated with one equivalent of di-isobutylaluminium hydride at -78°. Again, a complex mixture of reduction products was formed, which, from its n.m.r. spectrum, contained significant amounts of the 1,4-reduction products (84) and (85). A similar result was obtained using lithium tri-t-butoxyaluminium hydride as reductant[71].



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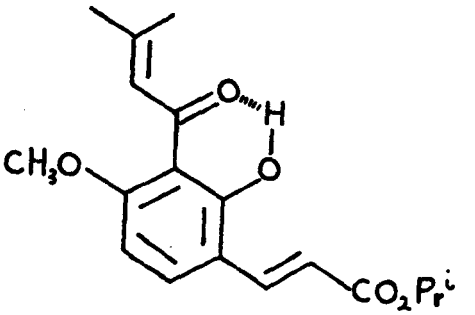
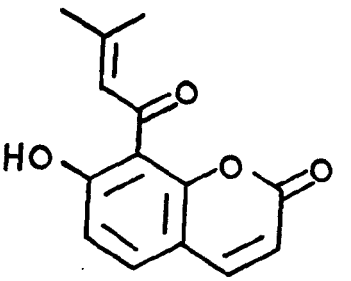


(86)

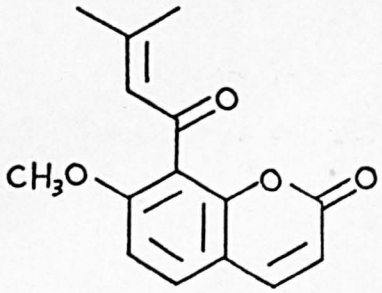


(66)

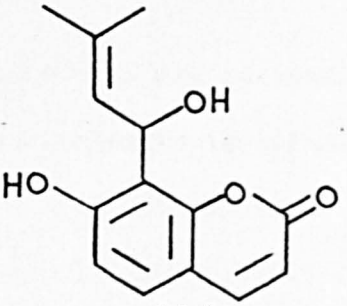
Attention was then directed towards the use of aluminium isopropoxide as a reducing agent. This reagent has been frequently used[72] to reduce α,β-unsaturated ketones to allylic alcohols, since mechanistically there is no pathway by which 1,4-reduction can occur. Reaction of (83) with aluminium isopropoxide led to the clean formation of a new, less polar, compound. The n.m.r. spectrum of this product showed that the characteristic AB quartet for the C-3 and C-4 protons in coumarins was absent; however, new signals arising from a trans disubstituted double bond (δ 5.89 and 7.20; each 1H ; d.; J 13Hz), an isopropyl group attached to oxygen (5.07; 1H ; septet ; J 5Hz and 1.21; 6H ; d.; J 5Hz) and a chelated hydroxyl group (13.80; 1H ; s.) were present. It was apparent that aluminium isopropoxide had opened the lactone ring, and consequently, structure (86) was assigned to this product. Because of the resulting chelation between the phenol group and the adjacent ketone function, reduction of the ketone did not take place, even when an excess of aluminium isopropoxide was used.

In 1975, Krishnamurthy and Brown[73] reported the use of 9-borabicyclo[3.3.1]nonane (9-BBN) as a mild, highly specific, reagent for the reduction of α,β-unsaturated ketones to the corresponding allylic alcohols. In a final attempt to effect the required reduction, (83) was treated with one equivalent of 9-BBN in tetrahydrofuran, according to Brown's procedure. Unfortunately, a complex mixture of products was formed, separation of which proved impossible.

Demethylation of (83) with boron tribromide at -78° gave, in high yield, the corresponding phenol (66). The reduction of (66) was then attempted using, with the exception of aluminium isopropoxide, the above reducing agents, in the hope that the phenolic group



(83)



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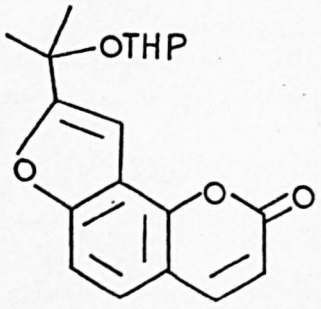
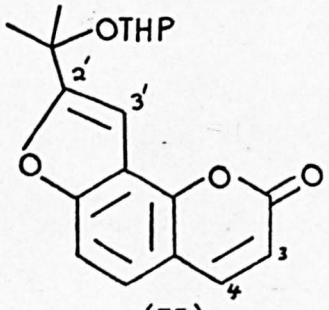
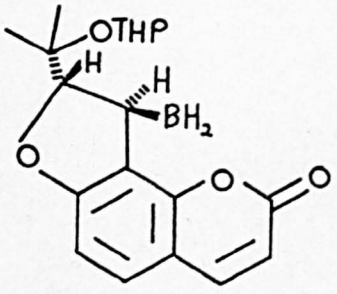


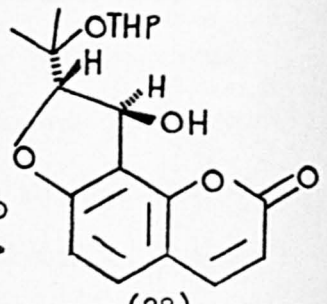
(75)

S C H E M E 1.40



(75)





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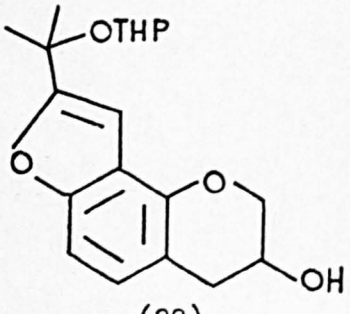
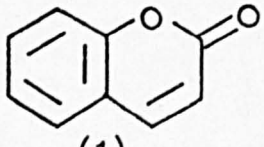
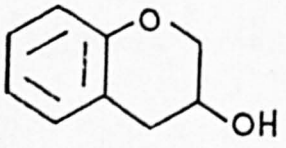


(88)

S C H E M E 1.41



(1)

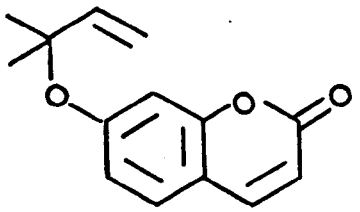


in (66) might have some directing effect on the site of reduction. Unfortunately, similar results to those described above were obtained.

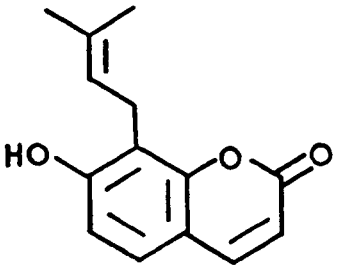
Despite having prepared the enone (83) in good overall yield, this route to the allylic alcohol (60) had to be abandoned because of the inability to reduce (83) regiospecifically.

III Hydroboration of (75)

As a result of work described in the previous section, a considerable quantity of the furanocoumarin (75) was available. In principle, only a simple hydration of the C-2',C-3' double bond would be necessary to convert (75) into vaginol (28). It was envisaged that such a hydration could be effected by a hydroboration-oxidation sequence, as shown in Scheme 1.40. There are, however, two double bonds in (75) which could react with diborane. Nevertheless, it seemed logical to predict that reaction of (75) with the electrophilic diborane should proceed preferentially at the electron rich C-2',C-3' double bond, rather than at the electron deficient C-3,C-4 double bond. In addition, the presence of the furan oxygen atom should direct the cis addition of diborane regiospecifically, as shown, leading to vaginol (28). In the event, reaction of (75) with diborane at 0° in tetrahydrofuran gave one new polar compound, along with unreacted starting material. Examination of the spectral data for the product revealed that the furan ring was still intact, but that the lactone ring was no longer present. Structure (88) was assigned to this product on the basis of its n.m.r. spectrum, and the known[74] reaction of coumarin (1) with diborane (Scheme 1.41).

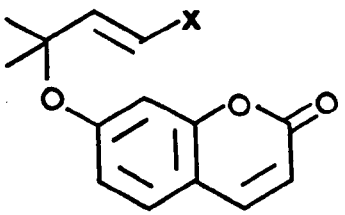


(40)

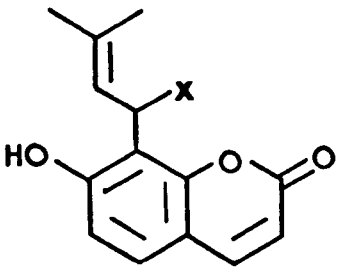


(21)

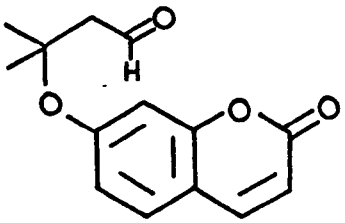
SCHEME 1.42



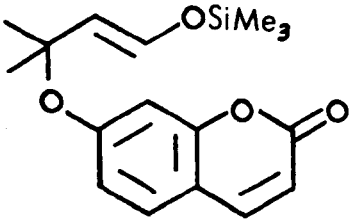
(89)



(60) X = OH



(90)



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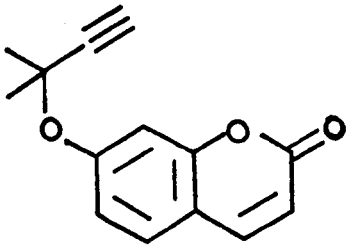

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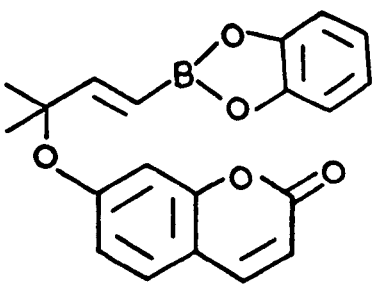

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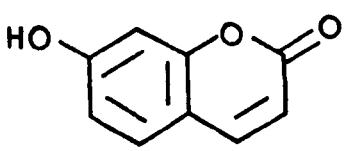

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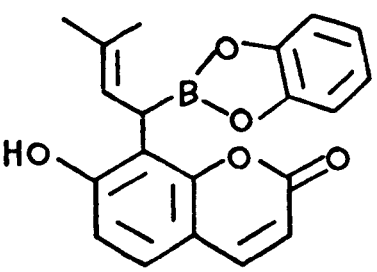


(93)

IV Modified Claisen rearrangement

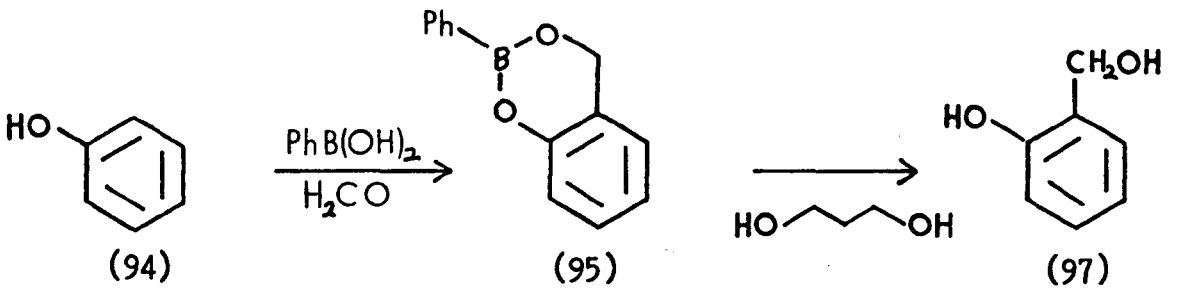
Since the Claisen rearrangement of the 1,1-dimethylallyl ether (40) provided a convenient synthetic route to osthenol (21)[8], we considered the possibility of preparing a functionalised 1,1-dimethylallyl ether (89), such that Claisen rearrangement of (89) would give the required allylic alcohol, or a derivative thereof (Scheme 1.42).

Initially, we attempted the preparation of the aldehyde (90), since conversion of this compound to its trimethylsilyl enol ether (91) would provide a suitable compound for Claisen rearrangement. Reaction of the acetylenic ether (39) with one equivalent of catechol borane[75] resulted in formation of (92), as indicated by its n.m.r. spectrum. This compound, without isolation, was treated with basic hydrogen peroxide, conditions which were known[75] to convert vinyl boron compounds to the corresponding carbonyl compound, via its enol form. However, the only product isolated from this reaction was umbelliferone (3). This can be explained if the assumed aldehyde (90) underwent a retro-Michael reaction, under the basic conditions employed.

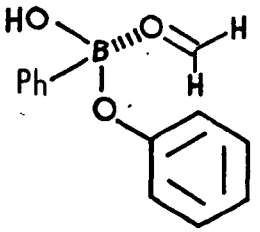
As an alternative, it occurred to us to attempt the Claisen rearrangement of the vinyl boronate (92), since its expected Claisen rearrangement product (93) should be easily converted into the desired allylic alcohol (60). In the event, pyrolysis of (92) at 120° in diglyme gave, unexpectedly, only umbelliferone (3) as product.

V Direct alkylation of umbelliferone (3)

In 1975, Nagata et al[76] reported a new method for the ortho-(α-hydroxy)alkylation of phenols. Faced with the problem

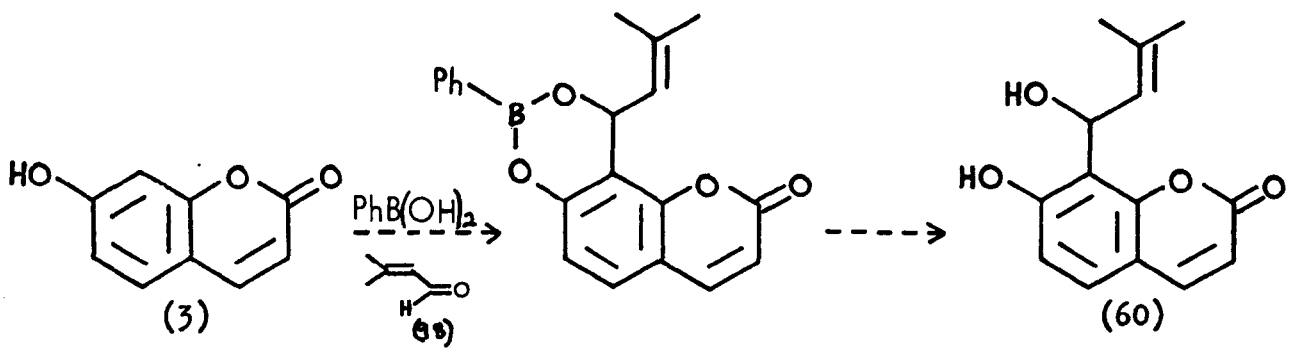


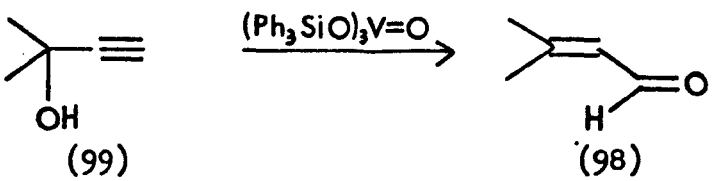
(94) (95) (97)



(96)

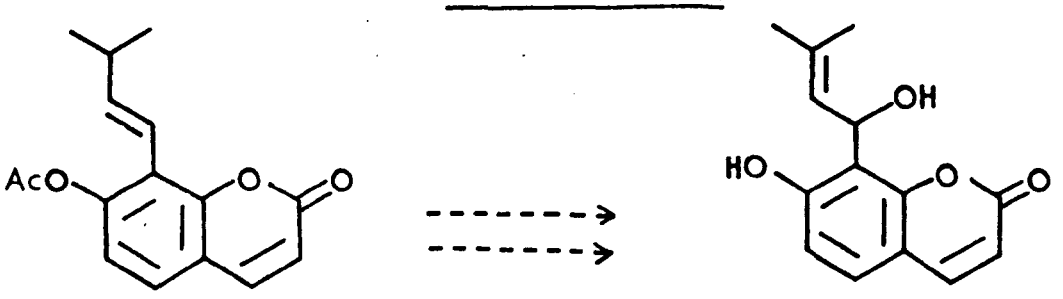
S C H E M E 1.43





(99) (98)

S C H E M E 1.44



(100) (60)

of regiospecifically introducing a hydroxymethyl group ortho to a phenol, they found that reaction of phenol (94) with benzeneboronic acid and formaldehyde in refluxing benzene gave, in high yield, the cyclic boronate (95). The formation of this compound was thought to involve the intermediacy of the chelated species (96). The product (95) was found to be remarkably stable, but could be converted cleanly to ortho-(hydroxymethyl)phenol (97) by an exchange reaction with propylene glycol.

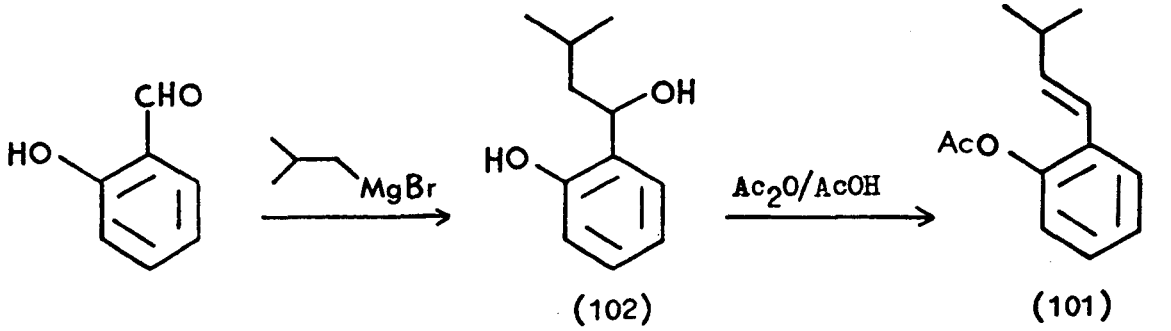
Although no details were given, the authors remarked that the above reaction worked well for a variety of phenols and aldehydes. As a result, it was envisaged that the desired allylic alcohol (60) could be prepared from umbelliferone (3) using this method for the introduction of the C-8 side chain (Scheme 1.43). The requisite aldehyde (98) was conveniently prepared by rearrangement of the readily available 3-hydroxy-3-methylbut-1-yne (99), using tris(triphenylsilyl) vanadate as catalyst. Unfortunately, the required reaction between umbelliferone (3), benzeneboronic acid and the aldehyde (98) did not take place, due to the facile polymerisation of (98) under the reaction conditions.

VI Photo-oxygenation of (100)

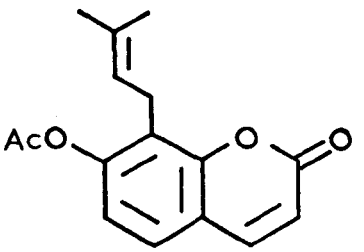
As described earlier, a convenient method for synthesizing allylic alcohols involves dye sensitised photo-oxygenation of the appropriate olefinic compound. Applying this strategy to the synthesis of (60), it was thought that dye sensitised photo-oxygenation of (100) could provide a mild synthetic step to (60) (Scheme 1.44). To realise the potential of this approach, it was decided to investigate the photo-oxygenation of the model compound (101).

(101) was prepared in the following way (Scheme 1.45) : Reaction of ortho-hydroxybenzaldehyde with two equivalents of

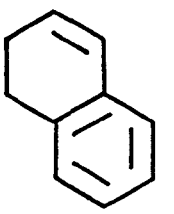
S C H E M E 1.45



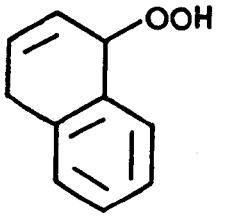
(102) (101)



(55)

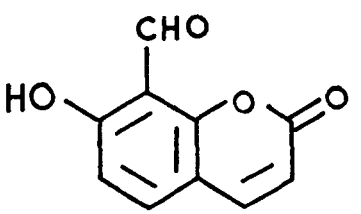


(103)



(104)

S C H E M E 1.46



(107)

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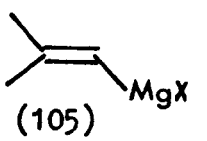
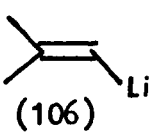
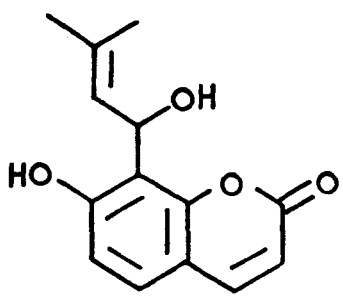


(105)

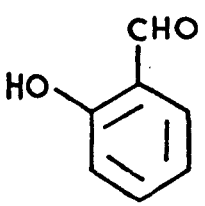
or



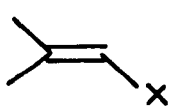
(106)



(60)



(108)



(109) X=Br

(110) X=Cl

the Grignard reagent derived from isobutyl bromide gave, in 89% yield, the required alcohol (102). Treatment of (102) with acetic anhydride in refluxing acetic acid[77] furnished, after chromatography, the desired trans olefin (101) in 50% yield.

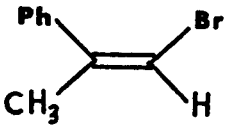
Using the conditions previously established for osthenol acetate (55) (vide supra), the photo-oxygenation of (101) was attempted. Surprisingly, even after 4 days, no trace of reaction was evident. A possible reason for this is the fact that the double bond in (101) is conjugated with the aromatic ring, making it unreactive to photo-oxygenation. This explanation, however, is not completely satisfactory since it has been reported[78] that dye sensitised photo-oxygenation of (103), using standard conditions, gave, in good yield, the allylic hydroperoxide (104).

VII Condensation of (105) or (106) with 7-hydroxy-8-formylcoumarin (107)

This one step approach to the synthesis of the allylic alcohol (60) (Scheme 1.46) involved condensation of either the Grignard reagent (105) or the vinyl-lithium reagent (106) with 7-hydroxy-8-formylcoumarin (107). The feasibility of this route was investigated by using ortho-hydroxybenzaldehyde (108) as a model compound. It was envisaged that (105) and (106) could be conveniently prepared from 1-bromo-2-methylpropene (109). However, only 1-chloro-2-methylpropene (110) is commercially available, and consequently, it was the latter compound which was used in the following reactions.

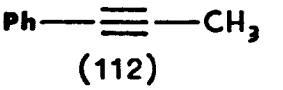
The formation of a Grignard reagent from a vinyl chloride is known to be a difficult process[79]. Normant[79], however, found that using tetrahydrofuran as solvent facilitated the formation of vinyl Grignard reagents. Nevertheless, repeated attempts to form the Grignard reagent from 1-chloro-2-methylpropene (110) were

S C H E M E 1.47



(111)

n-butyl lithium



(112)

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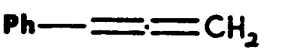
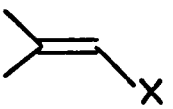
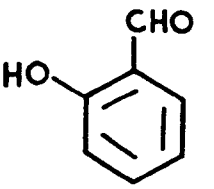


(113)



(109) X=Br

(110) X=Cl



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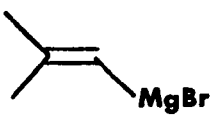

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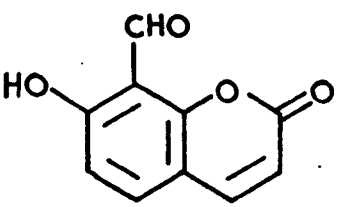
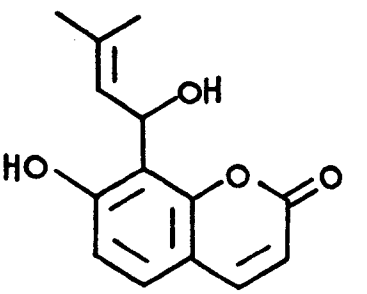
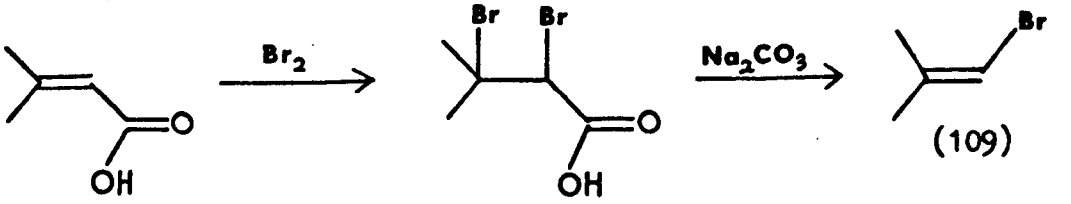


(107)



(60)

S C H E M E 1.48



(109)

singularly unsuccessful.

Attention was then directed to the formation of the vinyl lithium species (106). Two methods are available for converting vinyl halides into the corresponding vinyl-lithium compound. The first requires reaction of the vinyl halide with lithium metal[80] or a 2% sodium-lithium alloy[80]. With both of these procedures, however, (110) failed to react. The second method[80] involves metal-halogen exchange between the vinyl halide and a preformed organo-lithium reagent, e.g. n-butyl-lithium. There are, however, many side reactions that can occur during the preparation of vinyl-lithium compounds[81], e.g. the rearrangement of (111) to (112) and (113) (Scheme 1.47). In the event, reaction of (110) with n-butyl-lithium at -78°, followed by addition of the aldehyde (108), resulted in the formation of a plethora of compounds, from which no useful information could be obtained.

The condensation of the Grignard reagent (114) with 7-hydroxy-8-formylcoumarin (107) was considered to be the most promising route to (60), since it is known[79] that (114) can be formed readily from 1-bromo-2-methylpropene (109).

A survey of the literature revealed that (109) could be prepared[82] from 3,3-dimethylacrylic acid, as shown in Scheme 1.48. By using a modification of the literature procedure, (109) was obtained in 77% yield. Reaction of the Grignard reagent derived from (109) with ortho-hydroxybenzaldehyde (108) gave, unexpectedly, an extremely complex mixture of products, separation of which proved impossible. The explanation for this last result is not known.

General Experimental and Abbreviations.

Melting points, which are uncorrected, were determined on a Kofler hot-stage apparatus. Microanalyses were obtained by Mrs. W. Harkness and her staff. Mass spectra were recorded by Mr. A. Ritchie on an A.E.I.-G.E.C. MS12 instrument. Infra-red spectra were recorded on a Perkin Elmer 225 spectrophotometer by Mrs. F. Lawrie and her staff, or on a Perkin Elmer 257 spectrophotometer. All ultra-violet spectra were recorded for ethanol solutions on a Unicam SP 800 spectrophotometer; λ_{max}(base) refers to the above solutions to which two drops of 5M sodium hydroxide had been added. ^{1}H n.m.r. spectra were recorded on a Varian HA 100 spectrometer by Mr. J. Gall, or on a Varian T-60 spectrometer. ^{13}C n.m.r. spectra were recorded by Dr. D.S. Rycroft on a Varian XL 100 spectrometer. Unless otherwise stated, n.m.r. spectra were recorded using deuteriochloroform as solvent, with tetramethylsilane as internal standard.

Kieselgel GH_{254} 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 and 350nm). Analytical plates were developed by iodine vapour and/or spraying the plates with a solution of ceric ammonium sulphate and then heating the plates at 150°. The solution of ceric ammonium sulphate was prepared by dissolving ceric ammonium nitrate (5g) in concentrated sulphuric acid (50ml) and making the volume up to 500ml with water.

Light petroleum refers to the fraction of b.p. 60-80°. All solutions were dried over anhydrous magnesium sulphate or anhydrous sodium sulphate, and the solvents removed under reduced pressure. The solvents used for chromatography are expressed as a percentage volume, e.g. 30% ethyl acetate-light petroleum is equivalent to ethyl acetate and light petroleum in a volume ratio of 3:7.

The number of elutions required for separation by preparative t.l.c. are indicated after 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)

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.

Work-up (II)

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.

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 solvent.
*	e.g. 6.31* ; this refers to a signal in an n.m.r. spectrum which disappears on addition of deuterium oxide to the solution.

Part 1

Experimental

Attempted photo-oxygenation of osthenol (21).

Oxygen was bubbled, via a glass sinter, upwards through a solution of osthenol (250mg) in pyridine (40ml) containing haematoporphyrin (10mg). This solution was irradiated by a 60 watt lamp, positioned approximately 10cm from the centre of the reaction flask. T.l.c., after 48hours, showed that only starting material was present.

Osthenol acetate (55).

A solution of osthenol (21) (1.0g) in acetic anhydride (5ml) containing pyridine (1ml) was refluxed for 30 mins. Work-up (I) gave crude osthenol acetate (980mg, 82%) which on crystallisation from aqueous ethanol gave colourless needles, m.p. 94-95°. (Found: C,70.65; 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; b.s.), 1.82 (3H; b.s.), 2.35 (3H; s.), 3.48 (2H; b.d.; J 7Hz), 5.15 (1H; b.t.; J 7Hz), 6.37 (1H; d.; J 9.5Hz), 6.98 (1H; d.; J 9Hz), 7.33 (1H; d.; J 9Hz) and 7.63 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 1764, 1735 and 1605cm^{-1}; mass spectral peaks at m/e 272 (M^+, 11%), 230 (87), 229 (27), 215 (32), 201 (18), 187 (43) and 175 (100).

Photo-oxygenation of osthenol acetate (55).

Oxygen was bubbled, via a glass sinter, upwards through a solution of osthenol acetate (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 24 hours. Most of the pyridine was then evaporated, and Work-up (I) gave a brown oil (520mg). This hydroperoxide was immediately reduced, as described below.

Reduction of the hydroperoxide obtained from photo-oxygenation of osthenol acetate

(a) using triphenylphosphine.

The brown oil obtained above (520mg) was dissolved in chloroform (200ml) and triphenylphosphine (450mg) added. The solution was kept at 0° for 15 hours. The chloroform was then evaporated to give a dark brown oil (990mg). Separation of the triphenylphosphine oxide from the reduction product was not possible.

(b) using sodium iodide.

The brown oil obtained above (520mg) was dissolved in absolute ethanol (70ml) containing glacial acetic acid (1.8ml) and sodium iodide (5g). After 18 hours, the ethanol was evaporated and the residue was dissolved in ethyl acetate. The ethyl acetate solution was washed several times with 0.1M sodium thiosulphate solution, brine, dried and evaporated to give a dark brown oil (470mg) which, after purification by preparative t.l.c. (chloroform x1), furnished the allylic alcohol (56) (270mg, 52%) as a colourless oil; n.m.r. signals at δ 1.43 (6H; s.), 2.33 (3H; s.), 2.63* (1H; b.s.), 6.38 (1H; d.; J 9.5Hz), 6.73 (2H; s.), 7.03 (1H; d.; J 9Hz), 7.38 (1H; d.; J 9Hz) and 7.70 (1H; d.; J 9.5Hz). On addition of a small amount of $Eu(fod)_3$ the signal at δ 6.73 separated into 9.15 (1H; d.; J 17Hz) and 9.60 (1H; d.; J 17Hz); $\nu_{max}^{CHCl_3}$ 3500, 1740, 1600, 1114 and 970cm^{-1}; mass spectral peaks at m/e 288 (M^+, 4%), 246 (12), 231 (14), 228 (20) 213 (100) and 149 (74).

Epoxidation of (56).

A solution of (56) (150mg) in chloroform (12ml) and a solution of 76% m-chloroperbenzoic acid (150mg) in chloroform (5ml) were mixed at 0°, and stirred at room temperature for 17 hours. The

solution was then passed through a short column of basic alumina. Evaporation of the chloroform gave the epoxy-acetate (57) (120mg, 77%) as a colourless gum. n.m.r. signals at δ 1.40 (3H; s.), 1.47 (3H; s.), 2.38 (3H; s.), 3.15 (1H; d.; J 2Hz), 4.11 (1H; d.; J 2Hz), 6.40 (1H; d.; J 9.5Hz), 6.97 (1H; d.; J 8Hz), 7.28 (1H; d.; J 8Hz) and 7.67 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 3500, 1745, 1590 and 1117cm^{-1}.

Hydrolysis of the epoxy-acetate (57).

The epoxy-acetate (57) (120mg) in methanol (25ml) was stirred with 2% w./v. aqueous sodium carbonate (2ml) for 15 mins., at room temperature. The solution was then carefully neutralised with 0.1M hydrochloric acid, diluted with water and extracted with ethyl acetate. The ethyl acetate solution was then washed with brine, dried and evaporated to give a yellow oil (100mg). The n.m.r. spectrum of this oil showed that a complex mixture of products had been produced, separation of which proved impossible.

Hydrolysis of (56).

A solution of (56) (220mg) in methanol (8ml) was stirred with 2% w./v. aqueous sodium carbonate (2ml) for 15 mins., at room temperature. The solution was then carefully neutralised with 0.1M hydrochloric acid, diluted with water and extracted with ethyl acetate. The ethyl acetate solution was then washed with brine, dried and evaporated to give the phenol (41) (170mg, 90%) as needles (ethyl acetate-light petroleum), 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 δ 1.32 (6H; s.), 4.64* (1H; b.s.), 6.18 (1H; d.; J 9.5Hz), 6.78 (1H; d.; J 16Hz), 6.94 (1H; d.; J 8.5Hz), 6.96 (1H; d.; J 16Hz), 7.35 (1H; d.; J 8.5Hz), 7.90 (1H; d.; J 9.5Hz) and 10.91* (1H; s.); $\nu_{max}^{CHCl_3}$ 3600,

3500, 2980, 1735, 1620 and 1610cm^{-1} ; λ_{max}^{EtOH} 222, 286 and 328nm (log ϵ 4.43, 4.17 and 4.24); mass spectral peaks at m/e 246 (M^+, 0.13%), 228 (24), 213 (100) and 185 (22).

Epoxidation of (41).

A solution of (41) (150mg) in ethyl acetate (20ml) and a solution of 76% m-chloroperbenzoic acid (160mg) were mixed at 0° and stirred at room temperature for 16 hours. The solution was then washed with 10% w./v. sodium sulphite solution, brine, dried and evaporated to give a yellow oil (150mg). Both t.l.c. and n.m.r. showed that a complex mixture of products had been produced, separation of which proved impossible.

Attempted benzylic oxidation of osthenol acetate (55)

(a) using sodium chromate.

A solution of osthenol acetate (55) (25mg) in acetic acid (2ml) and acetic anhydride (1ml) containing anhydrous sodium chromate (45mg) was kept at 40° for 2 days. Work-up (I) gave a low recovery (6mg, 24%) of a colourless gum containing only starting material (t.l.c.).

(b) using N-bromosuccinimide.

A solution of osthenol acetate (55) (25mg) in carbon tetrachloride (25ml) containing recrystallised N-bromosuccinimide (21mg) and benzoyl peroxide (4mg) was refluxed for 4 hours. T.l.c. of the solution showed the formation of a plethora of compounds, from which no useful information could be obtained.

7-Hydroxy-8-iodocoumarin (70).

This compound was prepared using a modification of the literature method[66].

Umbelliferone (3) (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). Stirring was continued for 5 hours, after which the solution was neutralised with 5M sulphuric acid. The resultant precipitate was filtered, washed with water and dried at 50° to give crude 7-hydroxy-8-iodocoumarin (16.1g, 90%), m.p. 263-266° (lit.[66] m.p. 268°); n.m.r. signals (d_6 dimethylsulphoxide) at δ 6.03 (1H; d.; J 9.5Hz), 6.75 (1H; d.; J 8Hz), 7.31 (1H; d.; J 8Hz) and 7.63 (1H; d.; J 9.5Hz). ν_{max}^{KBr} 3200, 1700, 1610 and 1600cm^{-1}

7-Acetoxy-8-iodocoumarin (71).

A solution of 7-hydroxy-8-iodocoumarin (2g) in acetic anhydride (10ml) and pyridine (1ml) was refluxed for 30 mins. Work-up (I) afforded the acetate (71) as a yellow solid (2.02g, 87%) which on crystallisation from ethyl acetate-light petroleum gave colourless needles, m.p. 143-144°; n.m.r. signals at δ 2.43 (3H; s.), 6.43 (1H; d.; J 9.5Hz), 7.10 (1H; d.; J 8Hz), 7.48 (1H; d.; J 8Hz) and 7.70 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 1740, 1600 and 1120 cm^{-1}; mass spectrum shows M^+ at m/e 330.

Preparation of the copper acetylide (69).

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 (3 x 20ml) 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 (0.6g) in ethanol (30ml). The solution became a bright yellow

colour, indicating formation of the copper acetylide, but the latter could not be isolated due to its high solubility in the reaction medium.

Preparation of the tetrahydropyranyl ether of 3-hydroxy-3-methyl-but-1-yne.

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 30 mins., then potassium carbonate (200mg) added and stirring continued for a further 30 mins. Distillation of the filtered solution gave the required tetrahydropyranyl ether (15.2g, 90%), b.p. 60-65°/8mm (lit[83]. b.p. 64.5-65.5°/8mm); n.m.r. signals at δ 1.50 (3H; s.), 1.57 (3H; s.), 1.70 (6H; b.m.), 2.43 (1H; s.), 3.80 (2H; b.m.) and 5.13 (1H; b.s.).

Preparation of the copper acetylide (72).

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 (3 x 20ml) 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 (1.2g) in ethanol (30ml). Addition of water to the resultant bright yellow solution, precipitated the copper acetylide (72) as a bright yellow solid. This precipitate was filtered on a sintered glass funnel, washed with water, ethanol and ether, and dried in vacuum.

Coupling of 7-acetoxy-8-iodocoumarin (71) and (72).

A solution of 7-acetoxy-8-iodocoumarin (0.580g) and (72) (0.412g) in pyridine (15ml) was refluxed, under argon, for 17 hours. Work-up (I) gave a brown oil (0.602g) which, after purification by preparative t.l.c. (2% methanol-chloroform x 1), furnished:

(i) the furanocoumarin (75) (0.328g, 55%) as pale yellow needles, m.p. 115-117° (ethyl acetate-light petroleum). (Found: C, 69.72; H, 6.25. $C_{19}H_{20}O_5$ requires C, 69.50; H, 6.14%); n.m.r. signals at δ 1.57 (6H; b.m.), 1.67 (3H; s.), 1.73 (3H; s.), 3.67 (2H; b.m.), 4.67 (1H; b.m.), 6.37 (1H; d.; J 9.5Hz), 6.97 (1H; s.), 7.33 (2H; s.) and 7.73 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 1720, 1610 and 1110cm^{-1}; mass spectral peaks at m/e 328 (M^+, 5%), 244 (41), 229 (100), 226 (53), 198 (44) and 187 (50).

(ii) 7-acetoxycoumarin (73) (0.075g, 21%) as pale yellow needles, m.p. 135-137°; n.m.r. signals at δ 2.37 (3H; s.), 6.41 (1H; d.; J 9.5Hz), 7.08 (1H; d.d.; J 8Hz and 2Hz), 7.17 (1H; d.; J 2Hz), 7.53 (1H; d.; J 8Hz), and 7.78 (1H; d.; J 9.5Hz). This compound was identical with an authentic sample.

7-Tetrahydropyranyloxy-8-iodocoumarin (78).

4 Drops of concentrated hydrochloric acid was added to a stirred solution of 7-hydroxy-8-iodocoumarin (2.89g) and dihydropyran (1.68g). Stirring was continued for 1 hour, then potassium carbonate (1g) was added and the solution stirred for a further hour. The solution was then filtered and the product precipitated by addition of light petroleum (100ml). The precipitate was filtered, washed with light petroleum and dried to give the tetrahydropyranyl ether (78) as a white solid (3.45g, 93%); m.p. 129-131°; n.m.r. signals at δ 1.75 (6H; b.m.),

3.67 (2H; b.m.), 5.67 (1H; b.s.), 6.25 (1H; d.; J 9.5Hz), 7.00 (1H; d.; J 8Hz), 7.35 (1H; d.; J 8Hz) and 7.57 (1H; d.; J 9.5Hz). $\nu_{max}^{CHCl_3}$ 1740, 1605 and 1102cm^{-1}; mass spectrum showed M^+ at m/e 372.

Coupling of (78) and (72).

A solution of (78) (0.558g) and (72) (0.577g) in pyridine (20ml) was refluxed under argon for 17 hours. Work-up (I) gave a brown oil (0.680g) which, after purification by preparative t.l.c. (chloroform x1), furnished:

(i) 7-tetrahydropyranyloxycoumarin (0.044g, 12%), m.p. 103-104°; n.m.r. signals at δ 1.70 (6H; b.m.), 3.55 (2H; b.m.), 5.67 (1H; b.s.), 6.34 (1H; d.; J 9.5Hz), 7.12 (1H; d.d.; J 8Hz and 2Hz), 7.23 (1H; d.; J 2Hz), 7.44 (1H; d.; J 8Hz) and 7.67 (1H; d.; J 9.5Hz); mass spectrum showed M^+ at m/e 246.

(ii) the furanocoumarin (75) (0.340g, 68%) (m.p., n.m.r. and t.l.c.).

β-Methoxyethoxymethyl chloride.

This compound was prepared using a modification of Corey's procedure[68]. Dry hydrogen chloride was passed through a solution of trioxane (33g) and β-methoxyethanol (76g) for 30 mins. The solution was then diluted with pentane (450ml), dried and evaporated to give β-methoxyethoxymethyl chloride (102g, 82%). n.m.r. signals at δ 3.37 (3H; s.), 3.67 (4H; m.) and 5.53 (2H; s.).

7-(β-Methoxyethoxymethoxy)-8-iodocoumarin (79).

β-Methoxyethoxymethyl chloride (1.8g) was added to a solution of 7-hydroxy-8-iodocoumarin (1g) and diethylamine (2.5g) in methylene chloride (15ml). After 1 hour, the solution was extracted with ethyl acetate, washed with 5M hydrchloric acid,

brine, dried and evaporated to give (79) (1.15g, 88%), m.p. 112-113°; n.m.r. signals at δ 3.37 (3H; s.), 3.75 (4H; m.), 5.47 (2H; s.), 6.30 (1H; d.; J 9.5Hz), 7.07 (1H; d.; J 8Hz), 7.41 (1H; d.; J 8Hz) and 7.58 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 1740, 1606, 1100 and 1040cm^{-1}; mass spectrum showed M^+ at m/e 376.

Coupling of (79) and (72).

A solution of (79) (0.553g) and (72) (0.453g) in pyridine (20ml) was refluxed for 17 hours, under argon. Work-up (I) gave a brown oil (0.640g) which, after purification by preparative t.l.c. (1% methanol-chloroform x 1), furnished:

(i) 7-(β-methoxyethoxymethoxy)coumarin (0.072g, 20%) as white needles, m.p. 127-129°; n.m.r. signals at δ 3.39 (3H; s.), 3.81 (4H; m.), 5.45 (2H; s.), 6.35 (1H; d.; J 9.5Hz), 6.75 (1H; d.; J 2Hz), 6.87 (1H; d.d.; J 8Hz and 2Hz), 7.37 (1H; d.; J 8Hz) and 7.63 (1H; d.; J 9.5Hz); mass spectrum showed M^+ at m/e 250.

(ii) the furanocoumarin (75) (0.310g, 66%) (m.p., n.m.r. and t.l.c.).

7-Methoxy-8-iodocoumarin (80).

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 1.5 hours. Work-up (II) gave 7-methoxy-8-iodocoumarin (80) as a yellow solid (5.50g, 87%) which, on crystallisation from ethyl acetate-light petroleum gave colourless needles, 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 δ 4.01 (3H; s.), 6.30 (1H; d.; J 9.5Hz), 6.83 (1H; d.; J 8Hz), 7.48 (1H; d.; J 8Hz) and 7.63 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 1750, 1290, 1141 and 1081cm^{-1}; λ_{max}^{EtOH} 213, 265 and 316nm (log ε 4.34, 4.07 and 4.24); mass spectral peaks at m/e 302

(M^+, 100%), 274 (51) and 259 (66).

Coupling of 7-methoxy-8-iodocoumarin (80) and (72).

A solution of (80) (5g) and (72) (4.62g) in pyridine (120ml) was refluxed, under argon, for 18 hours. Work-up (I) gave a brown oil (7.2g) which, after purification by preparative t.l.c. (chloroform x 1), furnished:

(i) 7-methoxycoumarin (0.57g, 21%) as white needles, m.p. 116-118° (lit.[84] m.p. 118°); n.m.r. signals at δ 3.90 (3H; s.), 6.25 (1H; d.; J 9.5Hz), 6.80 (1H; d.; J 2Hz), 6.88 (1H; d.d.; J 8Hz and 2Hz), 7.40 (1H; d.; J 8Hz) and 7.67 (1H; d.; J 9.5Hz). This compound was identical with an authentic sample.

(ii) the acetylene (81) (2.89g, 51%) as a yellow solid, m.p. 99-101°; n.m.r. signals at δ 1.65 (3H; s.), 1.70 (3H; s.), 1.74 (6H; b.m.), 3.73 (2H; b.m.), 3.97 (3H; s.), 5.37 (1H; b.s.), 6.28 (1H; d.; J 9.5Hz), 6.83 (1H; d.; J 8Hz), 7.40 (1H; d.; J 8Hz) and 7.51 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 1750, 1600, 1276 and 1114cm^{-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 (82).

A solution of the tetrahydropyranyl ether (81) (2g) in 60% aqueous acetic acid (120ml) was stirred at room temperature for 2 hours. The solution was then diluted with water, and extracted with ethyl acetate. The ethyl acetate solution was washed with 5% sodium carbonate solution, brine, dried and evaporated to give (82) as a yellow solid (1.36g, 90%), which on crystallisation from ethyl acetate-light petroleum gave colourless needles, 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 δ 1.70 (6H; s.), 4.00 (3H; s.), 6.27 (1H; d.; J 9.5Hz), 6.83 (1H; d.; J 8Hz),

7.21 (1H; d.; J 8Hz) and 7.60 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 3610, 1735, 1604 and 1117cm^{-1}; λ_{max}^{EtOH} 219, 248, 268, 278 and 317nm (log ε 4.22, 3.94, 3.95, 4.05 and 4.06); mass spectral peaks at m/e 258 (M^+, 43%), 243 (87), 227 (29), 215 (26) and 201 (100).

7-Methoxy-8-(3-methylbut-2-enoyl)coumarin (83).

A solution of (83) (0.5g) in xylene (50ml) containing tris(triphenylsilyl) vanadate (0.12g) was refluxed for 5 hours. The xylene was then evaporated and the residue, after preparative t.l.c. (chloroform x1), furnished:

(i) tris(triphenylsilyl) vanadate (0.107g) (t.l.c., i.r.)

(ii) 7-methoxy-8-(3-methylbut-2-enoyl)coumarin (83) as white needles (0.425g, 85%), m.p. 131-132° (ethyl acetate-light petroleum) (lit.[69] m.p. 131-132°); (Found: C, 69.50; H, 5.70; $C_{15}H_{14}O_4$ requires C, 69.76; H, 5.46%); n.m.r. signals at δ 1.96 (3H; b.s.), 2.25 (3H; b.s.), 3.88 (3H; s.), 6.23 (1H; d.; J 9.5Hz), 6.31 (1H; m.), 7.05 (1H; d.; J 9Hz), 7.48 (1H; d.; J 9Hz) and 7.67 (1H; d.; J 9.5Hz); ν_{max}^{nujol} 1720, 1660, 1600 and 1500cm^{-1}; λ_{max}^{EtOH} 220, 252 and 322nm (logε 4.27, 4.31 and 4.28); mass spectral peaks at m/e 258 (M^+, 44%), 227 (100), 203 (62), 199 (43) and 160 (31).

Attempted reduction of (83) using:

(a) Sodium borohydride.

Sodium borohydride (90mg) was added in small portions to a solution of (83) (120mg) in ethanol (10ml), at 0°. After 1 hour, the reaction mixture was acidified with 1M hydrochloric acid and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give a yellow oil (135mg). T.l.c. and n.m.r. of this oil showed that a complex mixture of products had been formed, separation of which proved impossible. (Significant n.m.r. signals at δ 1.30 (d.; J 6Hz) and 7.61 (weak d.; J 9.5Hz); and 1.96 and 2.23 (each b.s.).

(b) Di-isobutylaluminium hydride.

1.41M Di-isobutylaluminium hydride in hexane (0.22ml) was added to a stirred solution of (83) (100mg) in toluene (25ml) at -50°, under nitrogen. After 1 hour, water was added, and the solution extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give a yellow oil (120mg). T.l.c. and n.m.r. showed that a complex mixture of products, similar to that obtained above, had been formed.

(c) Lithium tri-t-butoxyaluminium hydride.

A suspension of lithium tri-t-butoxyaluminium hydride (155mg) in dry tetrahydrofuran (10ml) was added dropwise to a stirred solution of (83) (200mg) in tetrahydrofuran (5ml), at 0°. After 17 hours, the reaction mixture was diluted with water, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give a yellow oil (160mg). T.l.c. and n.m.r. showed that a complex mixture of products had been formed, separation of which was impossible.

(d) Aluminium isopropoxide.

A solution of (83) (100mg) and aluminium isopropoxide (130mg) in isopropanol (5ml) was refluxed for 1.5 hours. The solution was then poured into 1M hydrochloric acid (50ml) and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give (86) as a yellow solid (100mg, 81%), m.p. 107-109°; n.m.r. signals at δ 1.21 (6H; d.; J 5Hz), 1.71 (3H; b.s.), 2.13 (3H; b.s.), 4.03 (3H; s.), 5.07 (1H; septet; J 5Hz), 5.89 (1H; d.; J 13Hz). 6.50 (1H; d.; J 8Hz), 6.83 (1H; m.), 7.20 (1H; d.; J 13Hz), 8.00 (1H; d.; J 8Hz) and 13.80* (1H; s.); $\nu_{max}^{CCl_4}$ at 3300, 1740, 1670, 1602 and 1510cm^{-1}; mass spectrum showed M^+ at m/e 318.

Attempted reduction of (86) with excess aluminium isopropoxide.

A solution of (86) (100mg) and aluminium isopropoxide (300mg) in toluene (5ml) was refluxed for 24 hours. T.l.c. showed that only starting material was present.

(e) 9-Borabicyclo 3.3.1 nonane (9-BBN).

0.45M 9-BBN in tetrahydrofuran (1.1ml) was added to a stirred solution of (83) (167mg) in tetrahydrofuran(5ml) at 0°, under nitrogen. After 4 hours, methanol (0.5ml) was added, and the tetrahydrofuran evaporated. The residue was dissolved in pentane (20ml) and 2-ethanolamine (0.73ml) added. The solution was then filtered and the filtrate evaporated to give a red oil (176mg). T.l.c. and n.m.r. of this oil showed that a very complex mixture of products had been formed.

7-Hydroxy-8-(3-methylbut-2-enoyl)coumarin (66).

7-Methoxy-8-(3-methylbut-2-enoyl)coumarin (83) (0.52g) was dissolved in methylene chloride (40ml) and the solution cooled to -78°. To this cooled solution was added boron tribromide (0.38ml) in one portion. After stirring for 1 hour at -78°, the solution was poured onto iced water (250ml) and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give (66) as yellow needles (0.404g, 82%), m.p. 109-110° (ethyl acetate-light petroleum); (Found: C, 68.79; H, 4.82; $C_{14}H_{12}O_4$ requires C, 68.85; H, 4.95%); n.m.r. signals at δ 2.10 (3H; b.s.), 2.21 (3H; b.s.), 6.20 (1H; d.; J 9.5Hz), 6.80 (1H; d.; J 8Hz), 7.17 (1H; m.), 7.40 (1H; d.; J 8Hz), 7.57 (1H; d.; J 9.5Hz) and 11.17* (1H; s.); $\nu_{max}^{CCl_4}$ 3100, 1745, 1634 and 1600cm^{-1}; λ_{max}^{EtOH} 221, 260(sh), 292 and 320nm (logε 4.57, 4.53, 4.66 and 4.58); λ_{max}^{EtOH} (base) 230, 248, and 384nm; mass spectral peaks at m/e 244 (M^+, 11%), and 229 (100).

Attempted reduction of (66).

The reduction of (66) was attempted using the procedures given in (a), (b), (c) and (e) above. In all cases, similar results to those obtained above were obtained.

Reaction of the furanocoumarin (75) with diborane.

1M Diborane in tetrahydrofuran (0.5ml) was added to a stirred solution of (75) (140mg) in dry tetrahydrofuran (5ml) at 0°, under nitrogen. After 1 hour, water was added (1ml), followed by 3M sodium hydroxide (0.33ml) and 30% hydrogen peroxide (0.33ml). After stirring for 30 mins., the solution was extracted with ethyl acetate, washed with brine, dried and evaporated to give a yellow oil (120mg)which, after preparative t.l.c. (chloroform x1), furnished:

(i) unreacted (75) (70mg, 50%).

(ii) the alcohol (88) as a yellow oil (40mg, 27%); n.m.r. signals at δ 1.54 (8H; b.m.), 1.67 (3H; s.), 1.73 (3H; s.), 3.00* (1H; b.s.), 3.65 (2H; b.m.), 4.30 (3H; b.m.), 4.65 (1H; b.m.), 6.65 (1H; s.) and 7.07 (2H; s.); $\nu_{max}^{CHCl_3}$ 3600, 1600 and 1480cm^{-1}; mass spectrum showed M^+ at m/e 332.

Reaction of (39) with catechol borane.

Catechol borane (0.6ml) was added to a solution of (39) (1.14g) in dry tetrahydrofuran (8ml), under nitrogen. The solution was kept at 40° for 24 hours. An aliquot (0.5ml) was then removed and its n.m.r. spectrum recorded, after evaporation of the tetrahydrofuran. The n.m.r. spectrum showed signals (d_6 dimethyl-sulphoxide) at δ 1.53 (6H; s.) and 6.2-7.5 (11H; m.), which were attributed to the vinyl boronate (92). The above solution was then cooled to 0° , and 3M sodium hydroxide (8.5ml) added, followed by 30% hydrogen peroxide (3.4ml). After 2 hours at room temperature,

the solution was diluted with water, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give a brown solid (0.73g, 90%) which was identified as umbelliferone (3) (t.l.c., n.m.r. and comparison with an authentic sample).

Attempted Claisen rearrangement of (92).

(92) was prepared as above. The nitrogen flow was then increased until all the tetrahydrofuran was removed. Dry diglyme (5ml) was then introduced and the solution heated at 130° for 1 hour. The solution was then treated with sodium hydroxide and hydrogen peroxide, as above, to give a dark brown solid (0.65g, 81%) which was identified as crude umbelliferone (3) (t.l.c., n.m.r. and comparison with an authentic sample).

Preparation of 3-methylbut-2-enal (98) .

A solution of 3-hydroxy-3-methylbut-1-yne (12g), tris(triphenylsilyl) vanadate (3.3g) and stearic acid (0.33g) was heated at 140° for 3 hours. Distillation at 138°/760mm yielded the aldehyde (98) (10.5g, 87%) (lit.[85] b.p. 132°/730mm); n.m.r. signals at δ 1.97 (3H; b.s.), 2.15 (3H; b.s.), 5.85 (1H; m.) and 10.00 (1H; d.; J 8Hz).

Attempted alkylation of umbelliferone (3) using benzeneboronic acid and 3-methylbut-2-enal (98).

A solution of umbelliferone (3) (1.62g), benzeneboronic acid (1.23g) and propionic acid (0.08ml) in dry benzene, was refluxed in a three necked flask equipped with a nitrogen inlet, magnetic stirrer bar and a Dean and Stark apparatus. After 2 hours, a further portion of benzeneboronic acid (0.25g) and the aldehyde (98) (1.47g) was added. Heating was continued, but after 30 mins., the reaction mixture becams viscous and dark brown in colour. This was assumed to be the result of polymerisation of the aldehyde. However,

additional aldehyde (98) (2.5g) was added, and heating continued for 17 hours. The benzene solution was then washed with water, dried and evaporated to give a black oil, which, after preparative t.l.c. (1% methanol-chloroform x1), furnished only umbelliferone (3) (1.3g).

Preparation of (102).

Redistilled ortho-hydroxybenzaldehyde (6.1g) in ether (20ml) was added dropwise to the Grignard reagent prepared from magnesium (2.88g) and isobutyl bromide (17g) in ether (40ml). When the addition was completed, the mixture was stirred for 15 hours, at room temperature, then decomposed with saturated ammonium chloride solution. The mixture was then extracted with ether, dried and evaporated to give (102) as a colourless liquid (8.03g, 89%); (This compound was stable at room temperature, but decomposed on attempted distillation); n.m.r. signals at δ 0.95 (6H; b.d.; J 4Hz), 1.70 (3H; m.), 3.00* (1H; b.s.), 4.83 (1H; b.t.; J 4Hz), 7.00 (4H; m.) and 8.00* (1H; b.s.); $\nu_{max}^{thin\ film}$ 3340, 1600, 1490 1240 and 755cm^{-1}; mass spectral peaks at m/e 180 (M^+, 14%), 162 (63), 147 (79) and 107 (100).

Dehydration of (102).

A solution of (102) (4.2g) in acetic anhydride (40ml) and acetic acid (40ml) was refluxed for 24 hours. The solution was then poured onto water, and extracted with ethyl acetate. The ethyl acetate solution was washed with 0.5% aqueous potassium carbonate, brine, dried and evaporated to give a yellow oil (6g). Purification by column chromatography (elution with hexane, 1% ethyl acetate-hexane and 5% ethyl acetate-hexane) furnished the trans olefin (101) as a colourless liquid (2.4g, 50%); (This compound was stable at room temperature, but decomposed on

attempteddistillation); n.m.r. signals at δ 1.08 (6H; d.; J 7Hz), 2.31 (3H; s.), 2.50 (1H; m.), 6.08 (1H; d.d.; J 16Hz and 4Hz), 6.45 (1H; d.; J 16Hz) and 7.20 (4H; m.); $\nu_{max}^{thin\ film}$ 1770, 1500, 1200, 1179 and 750cm^{-1}; mass spectral peaks at m/e 204 (M^+, 35%), 162 (88) and 147 (100).

Attempted photo-oxygenation of (101).

Oxygen was bubbled, via a glass sinter, upwards through a solution of (101) (500mg) in pyridine (60ml) containing haematoporphyrin (25mg). This solution was irradiated by a 60 watt lamp, positioned approximately 10cm from the centre of the reaction flask. T.l.c., after 4 days, showed that only starting material was present.

Attempted formation of the Grignard reagent from 1-chloro-2-methylpropene (110).

Repeated attempts to form the Grignard reagent from magnesium (0.486g) and (110) (1.9g) in tetrahydrofuran (10ml) were unsuccessful.

Attempted formation of the vinyl-lithium reagent (106)

(a) Reaction between 1-chloro-2-methylpropene (110) (1.84g) and lithium metal (0.28g) or a 2% sodium-lithium alloy (0.3g) in ether, under argon, did not take place.

(b) 1.58M n-Butyl-lithium in hexane (12.8ml) was added to 1-chloro-2-methylpropene (110) (1.84g) in tetrahydrofuran (25ml), at -78°. After stirring for 2 hours at -78°, ortho-hydroxy-benzaldehyde (1.22g) in tetrahydrofuran (10ml) was added, and the resultant solution was stirred for 4 hours at -78°, and 1 hour at room temperature. Saturated ammonium chloride solution was then added, and the mixture extracted with ether. The ether

solution was then washed with brine, dried and evaporated to give a brown oil (2.3g). T.l.c. and n.m.r. showed that a complex mixture of products had been formed, separation of which proved impossible.

Preparation of 1-bromo-2-methyl propene (109).

This compound was prepared using a modification of the literature procedure[82]. A solution of bromine (160g) in carbon tetrachloride (100ml) was added dropwise to a stirred solution of β,β-dimethylacrylic acid (100g) in carbon tetrachloride (1l.) After 3 hours, the carbon tetrachloride was evaporated, and the residue dissolved in water (600ml) containing sodium carbonate (160g). Steam distillation furnished (109) as a colourless liquid (105g, 77%), b.p. 90-90.5° (lit.[82] b.p. 91-91.5°); n.m.r. signals at δ 1.78 (3H; b.s.), 1.80 (3H; b.s.) and 5.88 (1H; b.s.).

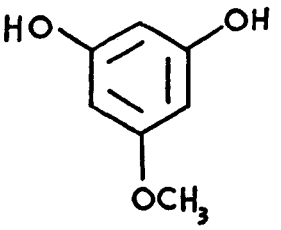
Preparation of the Grignard reagent (114).

A solution of 1-bromo-2-methylpropene (2.7g) in tetrahydrofuran (10ml) was added dropwise to magnesium (0.486g) in tetrahydrofuran (10ml), under nitrogen. Reaction commenced after several minutes, and the rate of addition of the bromide was such to maintain a gentle reflux. After 1 hour, the formation of the Grignard reagent was complete.

Reaction between (114) and ortho-hydroxybenzaldehyde (108).

A solution of (108) (1.22g) in tetrahydrofuran (10ml) was added dropwise to the above solution of (114). After the addition was completed, the reaction mixture was stirred at room temperature for 17hours. Ammonium chloride solution was then added and the resultant mixture extracted with ether. The ether solution was washed with brine, dried and evaporated to give a yellow oil (2.4g). T.l.c. and n.m.r. showed that a complex mixture of products had been formed, separation of which proved impossible.

Introduction to Part 2.



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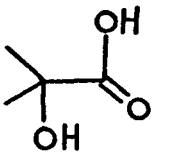

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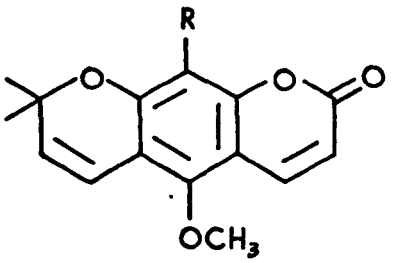

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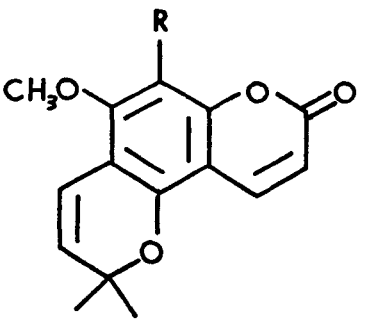

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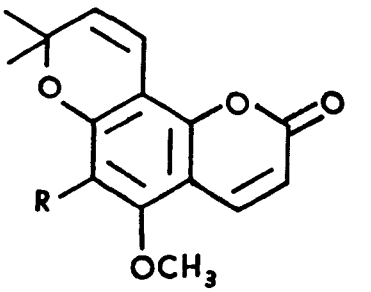


(119)

TABLE 2.1

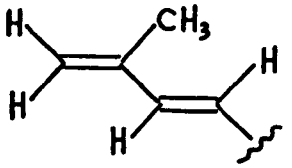
N.M.R. Spectrum of Avicennin

Signal (δ)	Integration	Multiplicity
1.48	6	s.
2.12	3	b.s.
3.26	3	s.
5.15	2	b.s.
5.63	1	d.; J 10Hz
6.23	1	d.; J 10Hz
6.60	1	d.; J 10Hz
6.70	1	d.; J 16Hz
7.42	1	d.; J 16Hz
8.80	1	d.; J 10Hz

In 1960, Arthur and Lee[86] isolated a yellow crystalline compound, from the root-bark of Zanthoxylum avicennae, which they named avicennin. Elemental analysis established the molecular formula of avicennin as $C_{20}H_{22}O_4$, and it was considered to be a coumarin from the characteristic strong i.r. absorption at 1745cm^{-1}, and from its behaviour towards mild base. Degradation to phloroglucinol monomethyl ether (115), by fusion with potassium hydroxide, indicated it to be a 5,7-dioxygenated coumarin, in which one of the two oxygen functions was present as a methyl ether. Since the i.r. spectrum of avicennin showed no hydroxyl absorption, and, apart from the lactone carbonyl, no carbonyl absorption, it was deduced that the other oxygen function was ethereal in nature. Oxidation of avicennin with potassium permanganate led to the formation of α-hydroxyisobutyric acid (116), which suggested the presence of a 2,2-dimethylchromene ring.

From the above information, three alternative structures for avicennin were tentatively considered, namely (117), (118) and (119). The nature of the group R was not established, but the molecular formula required that it be C_5H_9.

Several years later, Arthur and Ollis[87] re-investigated the structure of avicennin, spectroscopically. Examination of the n.m.r. spectrum of avicennin (Table 2.1) indicated the presence of only twenty protons, which implied a molecular formula of $C_{20}H_{20}O_4$ and not $C_{20}H_{22}O_4$ as had been established earlier. The former was confirmed by accurate mass measurement. The n.m.r. spectrum of avicennin showed signals corresponding to the methoxyl group, δ 3.26 (3H; s.), and the 2,2-dimethylchromene ring, 1.48 (6H; s.) and 5.63 and 6.60 (each 1H; d.; J 10Hz), along with the typical AB quartet, 6.23 and 8.80 (each 1H; d.; J 10Hz), for the



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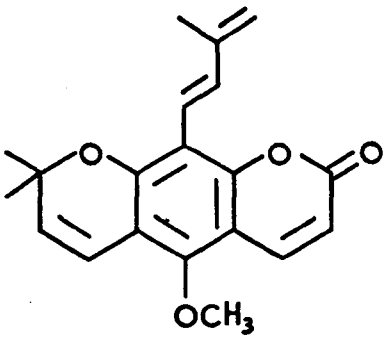
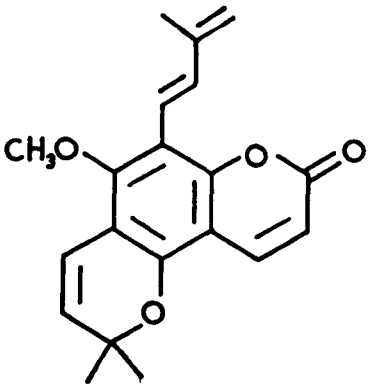


(121)



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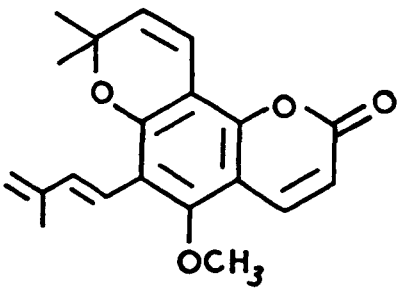


(123)

TABLE 2.2

N.M.R. Spectrum of 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

C-3 and C-4 protons. These data were consistent with each of the three isomeric structures, (117), (118) and (119), previously proposed for avicennin, but the revised molecular formula required that R was C_5H_7. The nature of this group was determined by examination of the remaining proton resonances. An AB system centred at δ 7.42 and 6.70 (each 1H; d.; J 16Hz) suggested the presence of a trans disubstituted double bond, flanked by fully substituted carbon atoms. The spectrum also showed a broad singlet at 5.15 (2H; s.) due to an olefinic methylene group, and a broad singlet at 2.12 (3H; s.) due to a vinyl methyl group. These signals uniquely defined R as a trans-3-methylbuta-1,3-dienyl moiety (120). Distinction between the three possible isomers (121), (122) and (123) was still not achieved, and until very recently, the structure of avicennin remained uncertain.

In 1975, Gray, Waigh and Waterman[88] reported the isolation and structure of a new coumarin, from the root-bark of Zanthoxylum avicennae, which they named avicennol. Its i.r. and u.v. spectra indicated that it was a substituted coumarin having extended conjugation, and the molecular formula was determined as $C_{20}H_{22}O_5$ by elemental analysis and accurate mass measurement. The n.m.r. spectrum of avicennol (Table 2.2) defined all twenty two protons. The C-3 and C-4 protons of the coumarin ring appeared characteristically at δ 6.27 and 8.06 (each 1H; d.; J 10Hz), and a singlet at 3.80 (3H; s.) indicated the presence of a methoxyl group. Another AB quartet at 5.69 and 6.65 (each 1H; d.; J 10Hz) and a six proton singlet at 1.60 (6H; s.) suggested the presence of a 2,2-dimethylchromene ring. This left two trans olefinic protons at 6.81 and 6.95 (each 1H; d.; J 16Hz), a six proton singlet at 1.59 (6H; s.) and a hydroxyl group at 2.58* (1H; s.)

FIGURE 2.1

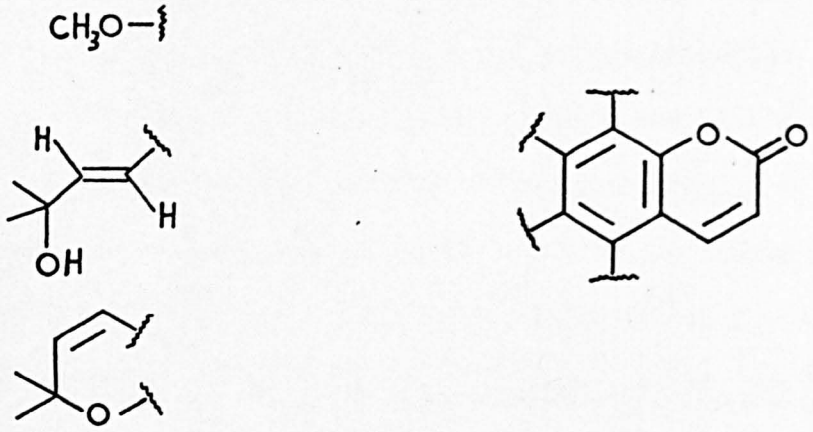
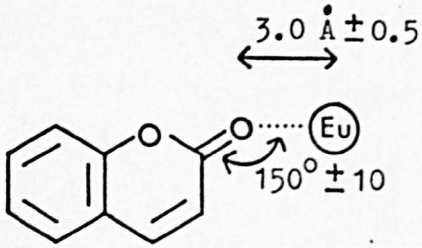


FIGURE 2.2



unassigned. Since there remained only one position on the coumarin nucleus unaccounted for, these signals must arise from a single unit, and were attributed to the trans-3-hydroxy-3-methyl-but-1-enyl group. It is interesting to note that this was only the second reported example of a naturally occurring oxygen heterocycle which possessed the trans-3-hydroxy-3-methylbut-1-enyl side chain, the first[89] being a chromone, isolated from Spathelia sorbifolia by Chan et al in 1967.

Despite the fact that all the functionality could be assigned, there remained twelve possible isomers for the structure of avicennol, each varying in the position of the substituents on the fully substituted benzenoid ring (Figure 2.1). A large contribution to the determination of the absolute structure of avicennol was made by a novel application of the lanthanide shift reagent tris-(7,7-dimethyl-1,1,1,2,2,3,3-heptafluoro-octene-4,6-dionato)europium III $\left[Eu(fod)_3 \right]$.

Normally, the use of a lanthanide shift reagent to differentiate isomers requires the three dimensional location of the lanthanide atom[90], a procedure usually requiring the use of a computer to achieve a 'best fit' with the observed shifts. However, by regarding the coumarin ring as planar, and assumming co-planarity with the lanthanide atom in the coumarin-shift reagent complex, Gray, Waigh and Waterman reduced the problem to two dimensions. They had previously shown[91] that $Eu(fod)_3$ complexes with the carbonyl oxygen atom of simple coumarins in such a way that all proton shifts could be related to a fixed position of the europium atom, in the plane of the ring (Figure 2.2). By using this position for the europium atom in the avicennol-shift reagent complex, they calculated the expected shifts of the olefinic

EQUATION 2.1

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

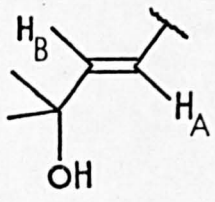
ν = shift

θ = O····Eu····H angle

R = Eu···H distance

TABLE 2.3

	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



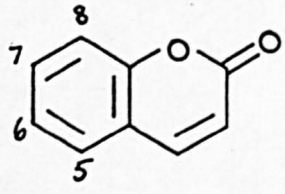
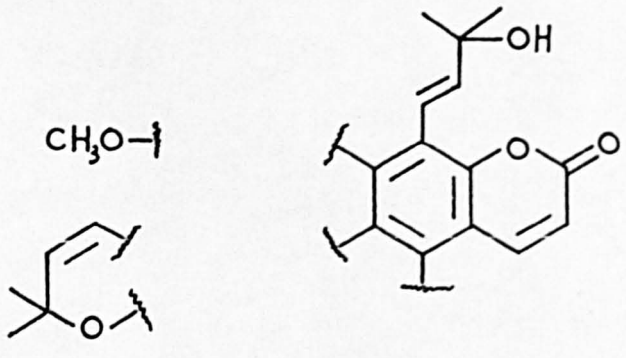


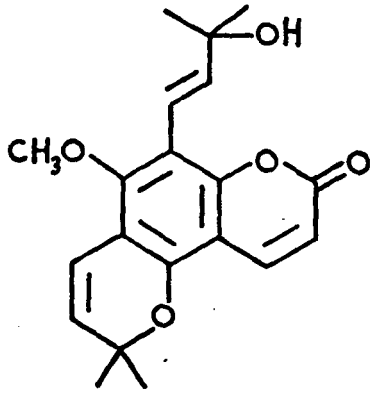
FIGURE 2.3



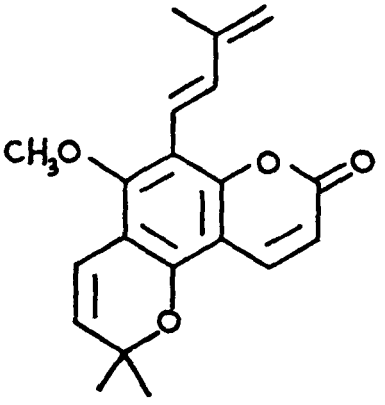
protons of the trans-3-hydroxy-3-methylbut-1-enyl side chain, for the four possible positions of attachment of this group to the benzenoid ring, using the McConnell-Robertson equation[92] (Equation 2.1). Their calculations of these shifts for each possible isomer were based on average values for the Eu···H distance and for the O···Eu···H angle, in the two possible conformations of the side chain double bond in the plane of the ring, and are therefore only approximate, since the actual side chain conformation, in solution, is not known. They then compared these calculated values with the observed shifts of the two olefinic protons under study (Table 2.3). The observed shifts were measured using the trimethylsilyl ether of avicennol, to avoid complexation of the shift reagent with the alcohol function. From the results, they concluded that the trans-3-hydroxy-3-methylbut-1-enyl side chain must be attached to C-8, since only in this position were the calculated shifts in close agreement with the observed shifts. This reduced the number of possible isomers for avicennol from twelve to four (Figure 2.3).

Further distinction between isomers was achieved by measurement of the nuclear Overhauser effect involving the methoxyl group and the olefinic protons. Irradation 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. Since the trans-3-hydroxy-3-methylbut-1-enyl side chain had already been located at C-8 (vide supra), this uniquely determined the structure of avicennol as (124).

Waigh et al also noticed that dehydration of avicennol (124) should produce (122), one of the possible structures for avicennin (vide supra). Initially, all attempts at dehydration failed, but



(124)



(122)

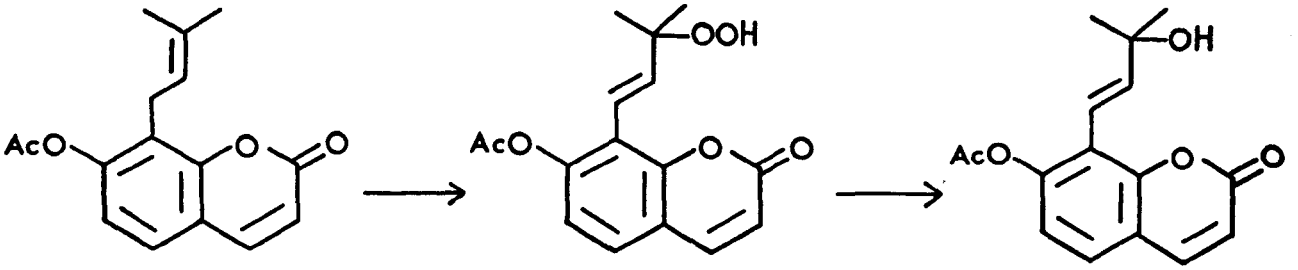
by accident, they found that dehydration could be accomplished rapidly and in high yield by treatment of avicennin with phosgene in chloroform. The diene thus obtained, (122), was found to be identical in all respects with avicennin.

Since the structure of avicennol (124), and hence avicennin (122), was largely based on a novel application of a lanthanide shift reagent, in which several assumptions were made, we felt that confirmation of these structures, as well as support for this method of distinguishing isomers, could be gained if (124) were synthesized by an unambiguous route.

Part 2

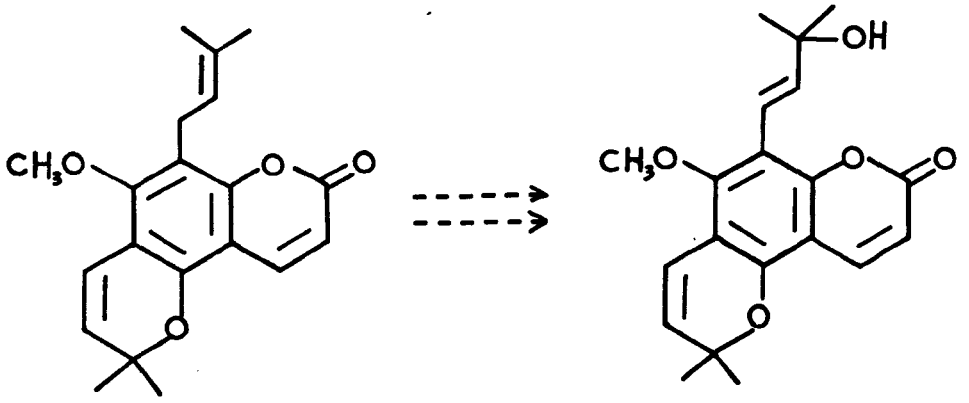
Synthesis of the Coumarins Avicennol, Dipetaline and Dipetalolactone.

SCHEME 2.1



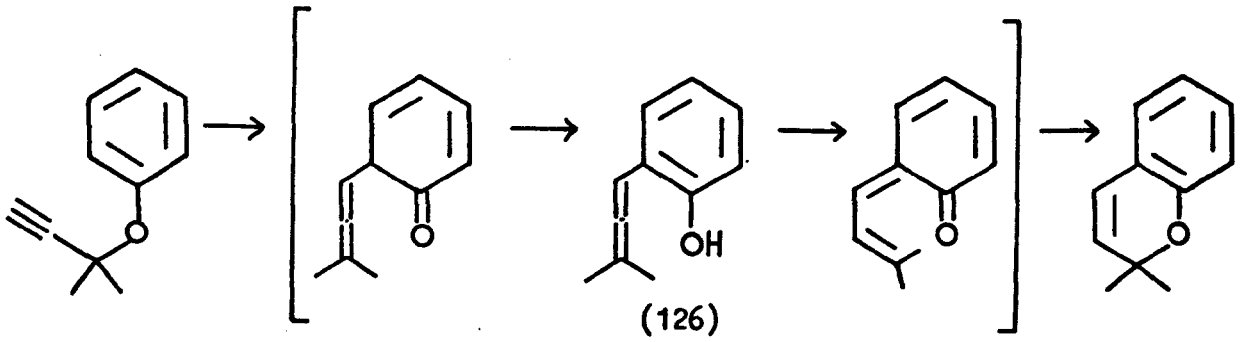
(55)

SCHEME 2.2

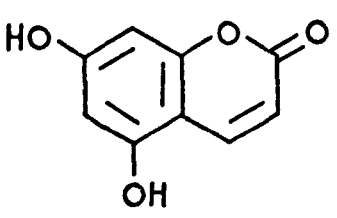


(125) (124)

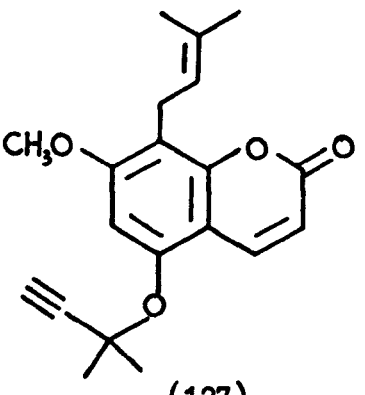
SCHEME 2.3



(126)



(128)



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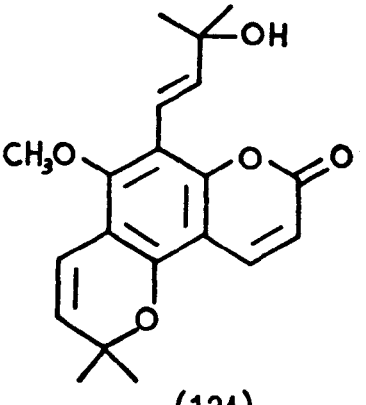


(124)

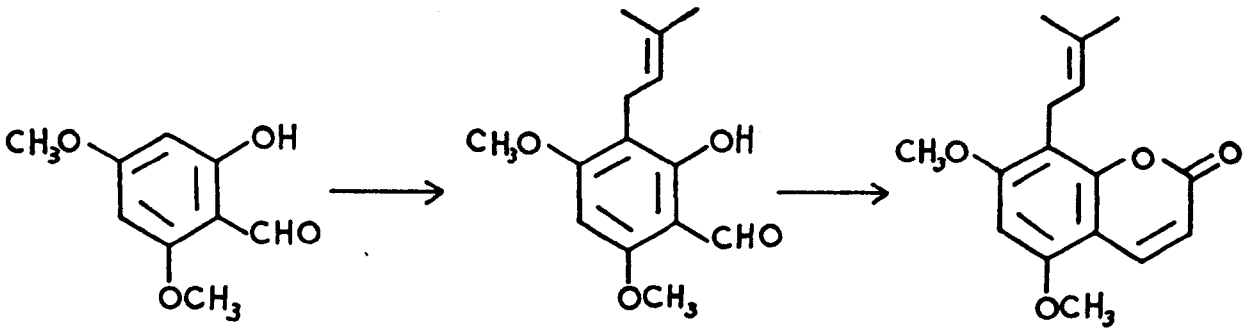
As a result of work described in Part 1 of this thesis, it was known that the trans-3-hydroxy-3-methylbut-1-enyl group could be introduced into an aromatic system by dye sensitised photo-oxygenation of the corresponding 3,3-dimethylallyl (prenyl) compound. Thus the photo-oxygenation of osthenol acetate (55) in pyridine, using haematoporphyrin as sensitiser, gave a single hydroperoxide which, on reduction with sodium iodide in ethanol, gave the trans allylic alcohol only (Scheme 2.1). Consequently, it seemed attractive to consider (125) as a potential synthetic precursor of avicennol (124) (Scheme 2.2).

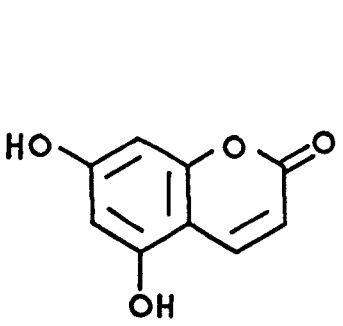
Hlubucek, Ritchie and Taylor[93] have shown that the 2,2-dimethylchromene ring system is formed in high yield by pyrolysis of the corresponding 1,1-dimethylpropargyl ether (Scheme 2.3). The rearrangement proceeds rapidly at 180° and is thought to involve the ortho-allenylphenol (126) as an intermediate. This reaction, taken in conjunction with the photo-oxygenation reaction (vide supra), prompted us to consider the bis ether (127) as the key intermediate in our projected synthesis of avicennol (124).

Any synthetic route to (127) from the ready available 5,7-dihydroxycoumarin (128), would necessitate two regioselective, preferably regiospecific, alkylation processes, C-prenylation at C-8 and O-alkylation at C-5 or C-7.

Direct C-prenylation of an aromatic system has always been difficult, and consequently, has received considerable attention[94]. As a result, two main methods have been developed for the synthesis of ortho-(3,3-dimethylallyl)hydroxycoumarins. The first, developed by Spath[95], involves C-prenylation of a substituted salicylaldehyde, followed by formation of the pyrone ring, as illustrated in Scheme 2.4. This method suffers from the necessity of preparing

SCHEME 2.4





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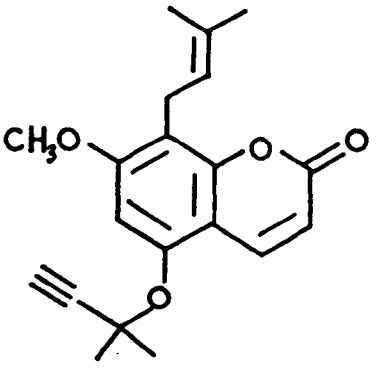

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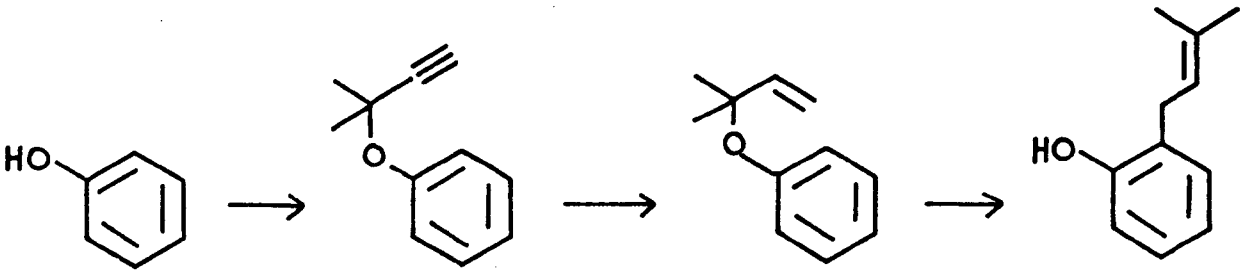
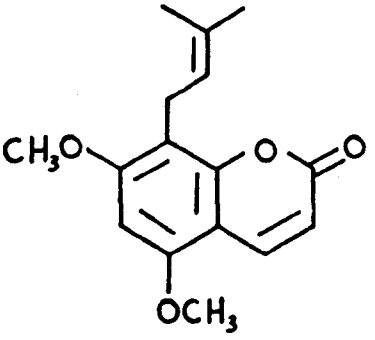
SCHEME 2.5





(129)

the correctly substituted aldehyde. The second general method[96,97] requires C-alkylation of a preformed hydroxycoumarin nucleus. The mode of reaction in both cases involves treatment of the sodium or potassium salt of the appropriate phenol with an allylic halide. Although extensive studies[98,99] have established that the use of non-polar solvents and heterogeneous reaction media favour C-alkylation, these conditions do not provide an efficient synthetic route to ortho-(3,3-dimethylallyl)hydroxycoumarins. Various other methods have been employed in attempts to increase the efficiency of C-prenylation. The use of 2-methylbut-3-ene-2-ol and a Lewis acid, e.g. boron trifluoride-diethyl etherate[100], has provided a mild method for C-prenylation in the synthesis of a number of natural products. However, this method usually results in multiprenylation and poor yields[100,101,102].

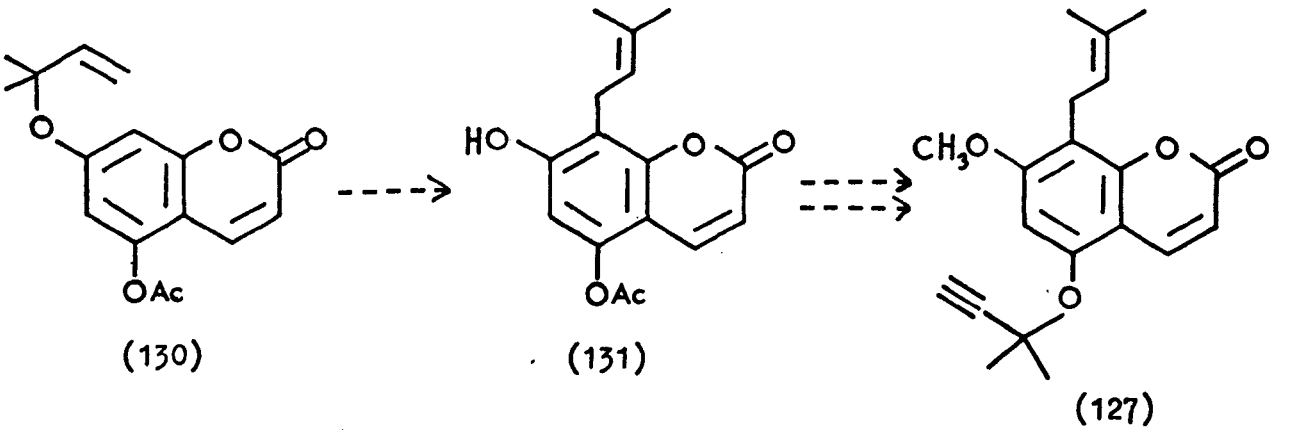
Thus in the light of the above discussion, direct regioselective prenylation of 5,7-dihydroxycoumarin (128) as a synthetic step towards (127) would likely prove to be unfruitful.

As an alternative, Murray et al[103] have developed a mild method for the introduction of a 3,3-dimethylallyl group ortho to a phenol, via Claisen rearrangement of the appropriate 1,1-dimethylallyl ether (Scheme 2.5). Using this method, many natural coumarins have been synthesized, e.g. coumurrayin (129)[103].

In applying this strategy to the synthesis of the key intermediate (127), two possibilities were considered for introducing the 3,3-dimethylallyl (prenyl) group at C-8. Claisen rearrangement of the 7-O-(1,1-dimethylallyl) ether (130) should give predominantly (131) (Scheme 2.6). Alternatively, it was known[104] that pyrolysis of the 5-O-(3,3-dimethylallyl) ether (132) gives exclusively the para Claisen rearrangement product (133) (Scheme 2.7).

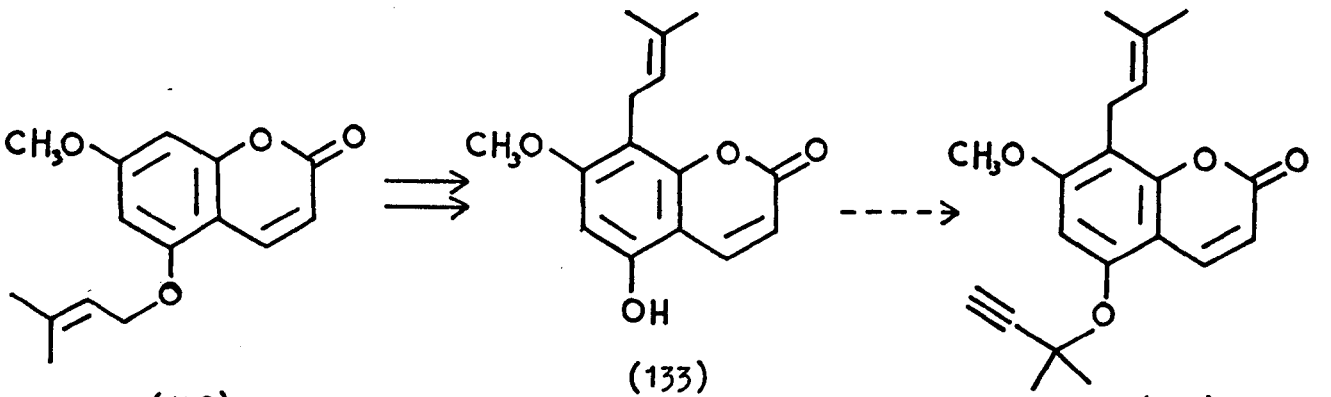
The preparation of either (130) or (132) would necessitate

SCHEME 2.6

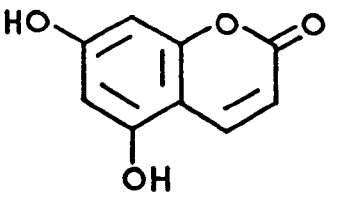


(130) (131) (127)

SCHEME 2.7

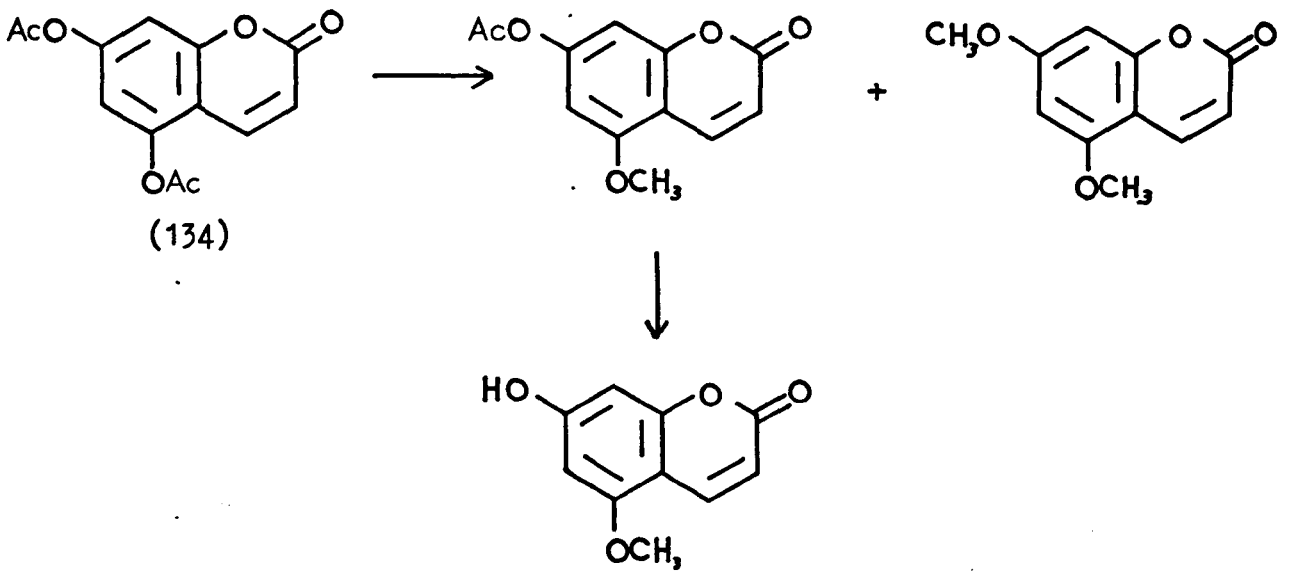


(132) (133) (127)



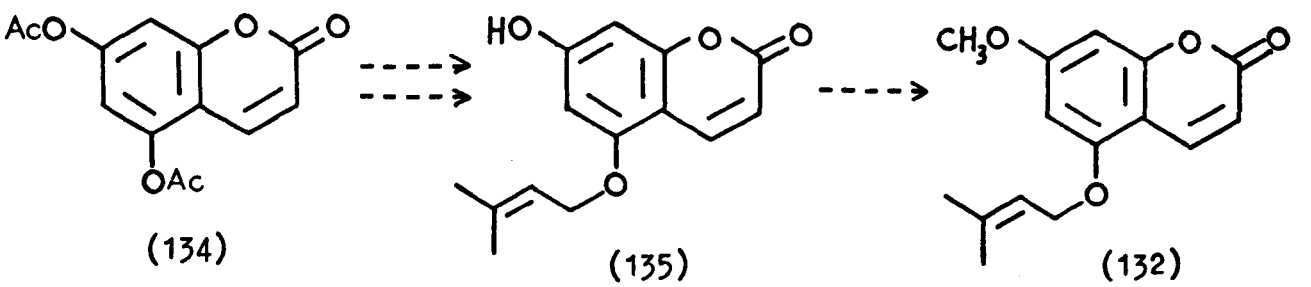
(128)

S C H E M E 2.8



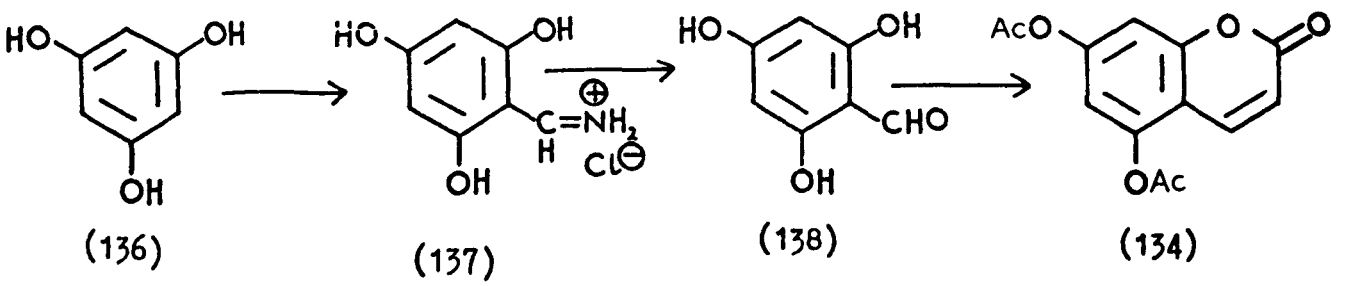
(134)

S C H E M E 2.9



(134) (135) (132)

S C H E M E 2.10



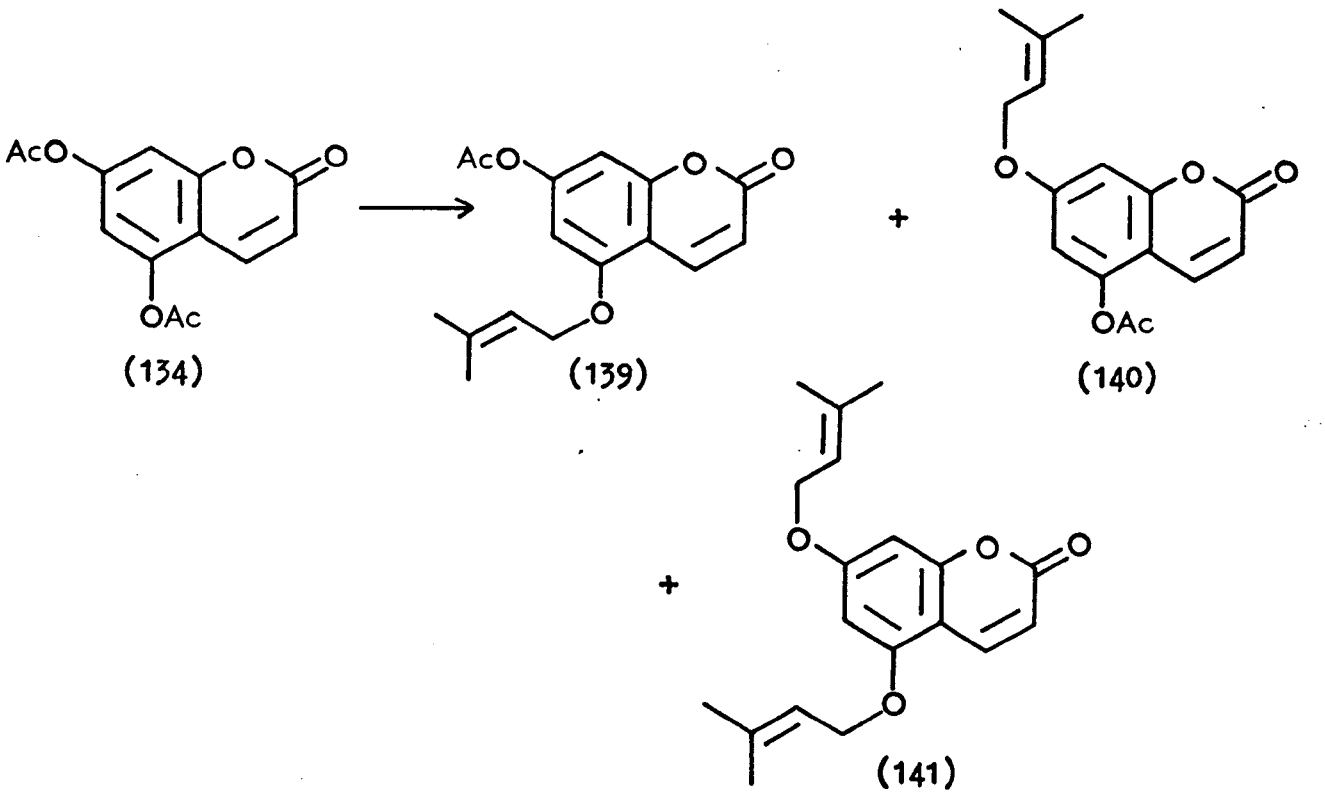
(136) (137) (138) (134)

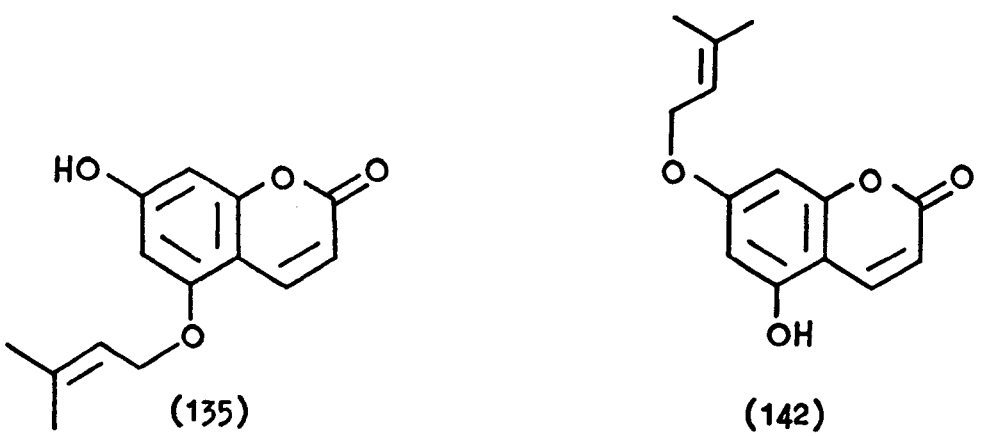
selective functionalisation of the 5- or 7-hydroxyl group of 5,7-dihydroxycoumarin (128). Unfortunately, there is little difference between the reactivities of these two hydroxyl groups, and O-alkylation usually results in a mixture of mono and bis ethers[105]. Seshadri, however, has shown[106] that methylation of 5,7-diacetoxycoumarin (134) using methyl iodide/potassium carbonate proceeds slightly more rapidly at C-5 than at C-7, leading, after hydrolysis, to a mixture of 5-methoxy-7-hydroxycoumarin (55%) and 5,7-dimethoxycoumarin (35%) (Scheme 2.8), which could be easily separated. If prenylation of 5,7-diacetoxycoumarin (134) gave a similar result, then (135) would be obtained, in which the 5-hydroxyl group is protected as a 3,3-dimethylallyl (prenyl) ether, thus leaving the 7-hydroxyl group free for further synthetic manipulation (Scheme 2.9). In particular, if the 7-hydroxyl group in (135) was then methylated, the regiospecific <u>para</u> Claisen rearrangement of (132)[104] could be utilised to insert the prenyl moiety at C-8 (see Scheme 2.7). Thus the initial stage in the projected synthesis of avicennol (124) required preparation of 5-O-(3,3-dimethylallyl)-7-methoxycoumarin (132).

The starting material for this synthesis was 5,7-diacetoxycoumarin (134), which was easily prepared as shown in Scheme 2.10. Treatment of anhydrous phloroglucinol (136) with hydrogen cyanide/hydrogen chloride according to the Gatterman procedure[107] gave a 90% yield of the imine hydrochloride (137), which was easily hydrolysed under mild conditions to the aldehyde (138). Treatment of (138) with acetic anhydride and sodium acetate at 150° gave 5,7-diacetoxycoumarin (134) almost quantitatively[108].

The prenylation of 5,7-diacetoxycoumarin (134) has already been investigated in this department[8,109]. In particular, it was[109] found that treatment of (134) with 3,3-dimethylallyl bromide (prenyl

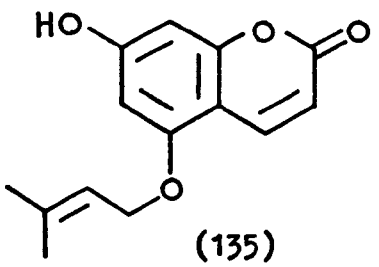
S C H E M E 2.11





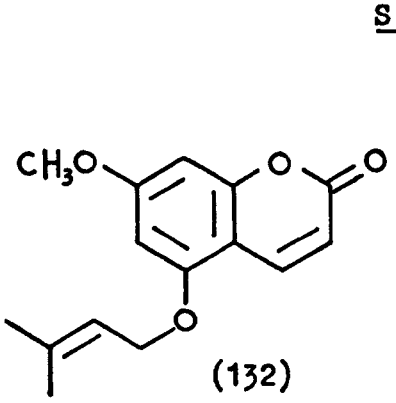
bromide)/ potassium carbonate, in refluxing 1,2-dimethoxyethane, resulted in the formation of a mixture of isomeric acetates, (139) and (140), along with a small amount of the bis ether (141) (Scheme 2.11). The n.m.r. spectrum of the mixture of isomeric acetates, (139) and (140), revealed that the required isomer (139) predominated in a ratio of ~4:1. Separation of these isomeric compounds was found to be impossible, however a small amount of pure (139) was obtained by fractional crystallisation. In order to obviate the difficulty of separating (139) and (140), it was decided to re-investigate the prenylation reaction, with the hope of modifying conditions such that (139) would be the sole product.

Previously, this prenylation reaction had been carried out using a large excess of 3,3-dimethylallyl bromide (prenyl bromide)[109]. By reducing the amount of 3,3-dimethylallyl bromide to only a slight excess, careful monitoring by analytical t.l.c. allowed the reaction to be stopped when no starting material was left, and when the amount of bis ether (141) was a minimum. Fortuitously, it was found that under these conditions only formation of the desired isomer (139) had occurred. In addition, the work-up procedure was such that hydrolysis of the labile acetate function of (139) took place. This was not unexpected, since it is known[110] that 7-acetoxycoumarins can be hydrolysed under very mild conditions (e.g. 2% w./v. sodium carbonate at room temperature) to give the corresponding 7-hydroxycoumarin. Thus, after chromatography to remove the small amount (21%) of bis ether (141), the desired compound (135) was obtained in 60% yield, uncontaminated with its isomer (142). That the sole mono ether from the reaction was (135), and not (142), followed from its u.v. spectrum, which showed the characteristic bathochromic shift of a 7-hydroxycoumarin, on

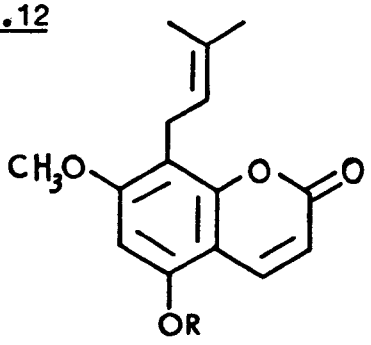


(135)

SCHEME 2.12

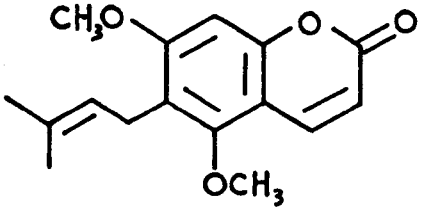


(132)



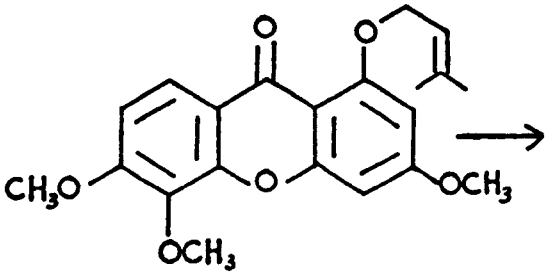
(143) R = $\overset{O}{C}CH_2CH_2CH_3$

(133) R = H

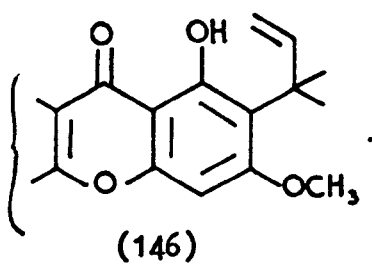


(144)

SCHEME 2.13

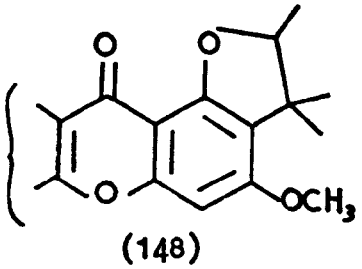


(145)



(146)

+



(148)

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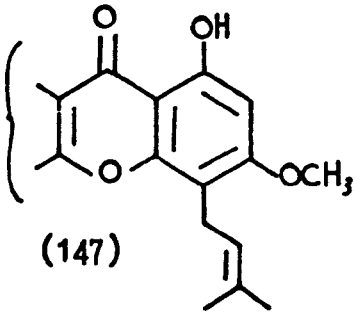
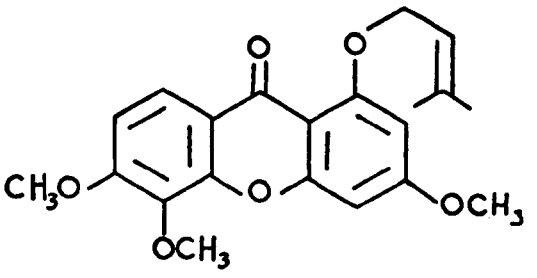


(147)

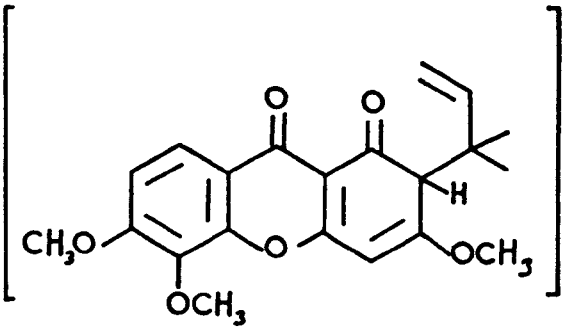
addition of base[4].

Methylation of (135) with methyl iodide/potassium carbonate in refluxing acetone, gave the corresponding methyl ether (132) in 92% yield. This compound was then pyrolysed at 175° in N,N-diethylaniline containing butyric anhydride, conditions which were known[104] to give exclusively the para Claisen rearrangement product (143) (Scheme 2.12). The function of the butyric anhydride in the reaction mixture was to trap the first formed phenol as its butyrate[111,112], thus preventing any acid (phenol) catalysed side reactions. That rearrangement to the para position had occurred, was apparent from the n.m.r. spectrum of the product (143), which showed the presence of a 3,3-dimethylallyl group attached to the aromatic ring. In addition, hydrolysis of the butyrate with 2% aqueous sodium carbonate gave the 5-hydroxycoumarin (133) which showed no intramolecular OH···π hydrogen bonding in its i.r. spectrum, which would be expected if the prenyl moiety was located at C-6.

The formation of the para Claisen rearrangement product (143) from the ether (132), first encountered during the synthesis[104] of toddaculin (144), was anticipated, albeit that it contained a vacant ortho position, since it was meta substituted[113]. Thus Jefferson and Scheinmann[114] had found that pyrolysis of the xanthone (145) in N,N-diethylaniline gave the phenols (146) and (147) along with the cyclised ortho product (148) (Scheme 2.13). The formation of the para product (147) was interpreted[114] in terms of steric compression in the first formed ortho-dienone intermediate (149). As a consequence of the cyclic transition state in the rearrangement of (145) to (149), the 1,1-dimethylallyl substituent will be produced in a pseudo axial orientation. For enolisation to (150) to occur, the ortho hydrogen must become pseudo axial, a conformation in which steric interaction between the bulky 1,1-dimethylallyl



(145)



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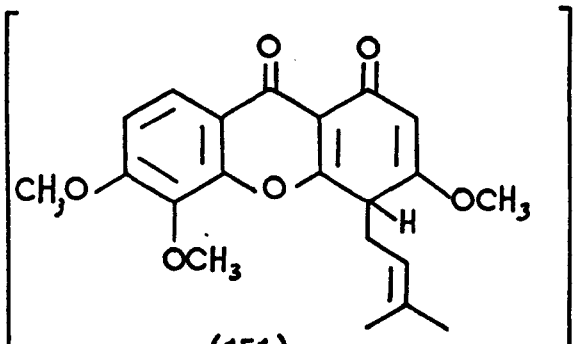

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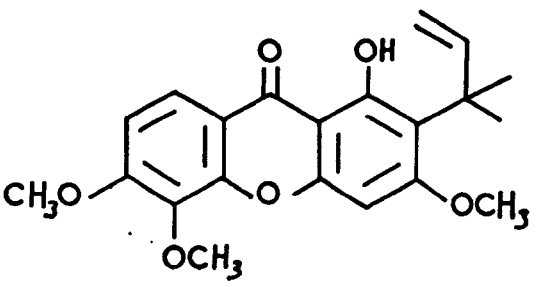

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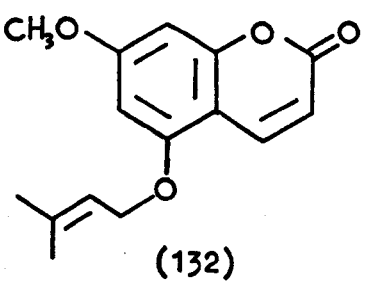
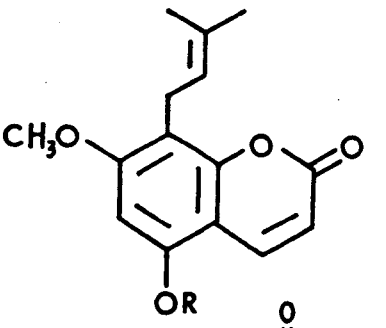
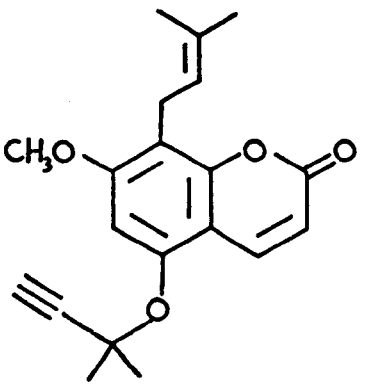


(132)

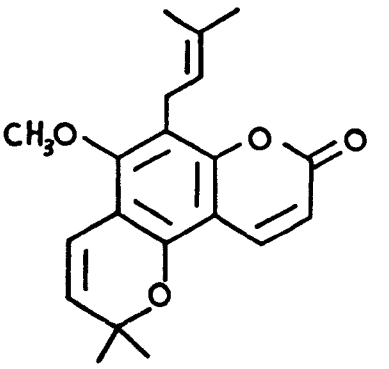


(143) R = $\overset{O}{\overset{\|}{C}}CH_2CH_2CH_3$

(133) R = H



(127)



(125)

group and the neighbouring methoxyl group is increased. Conversely, free rotation of the 1,1-dimethylallyl group in its first formed pseudo axial conformation leads to a geometry conducive for a Cope rearrangement to the para-dienone (151) and thereby to the para product. Thus, in the rearrangement of (132), the complete absence of ortho rearrangement product was synthetically important, but somewhat unexpected.

Hydrolysis of the butyrate (143) with 2% aqueous sodium carbonate in ethanol, at room temperature, proceeded smoothly and in high yield to give the 5-hydroxycoumarin (133). Treatment of this compound (133) with 3-chloro-3-methylbut-1-yne, potassium carbonate and potassium iodide in refluxing 2% aqeous acetone gave the corresponding 1,1-dimethylpropargyl ether (127) in 76% yield. The n.m.r. spectrum of the crude product showed the expected signals for this compound (Figure 2.4). However, signals arising from a small amount of another compound were also apparent. In particular, an 'extra' AB quartet at δ 5.63 and 6.57 (J 10Hz) could be identified. Separation of these two compounds by chromatography proved impossible. It was thought probable that the minor product was the chromene (125) formed by rearrangement of a small amount of the 1,1-dimethylpropargyl ether (127), during its formation. Since the next stage of the synthetic plan involved formation of the chromene (125), purification of the 1,1-dimethylpropargyl ether (127) was unnecessary. As predicted, pyrolysis of the above mixture, at 180°, gave a single compound (88%) which was identified as the chromene (125), on the basis of its n.m.r. spectrum (Figure 2.5). In particular, the signals for the acetylenic proton and the C-6 aromatic proton in (127) were not present, but were replaced by an AB quartet for the two cis olefinic protons of the chromene ring.

FIGURE 2.4

N.M.R. Spectrum of (127)

	Signal (δ)	Integration	Multiplicity
a	1.65	3	b.s.
b	1.72	6	s.
c	1.81	3	b.s.
d	2.73	1	s.
e	3.41	2	b.d.; J 7Hz
f	3.88	3	s.
g	5.20	1	b.t.; J 7Hz
h	6.08	1	d.; J 9.5Hz
i	7.08	1	s.
j	7.83	1	d.; J 9.5Hz

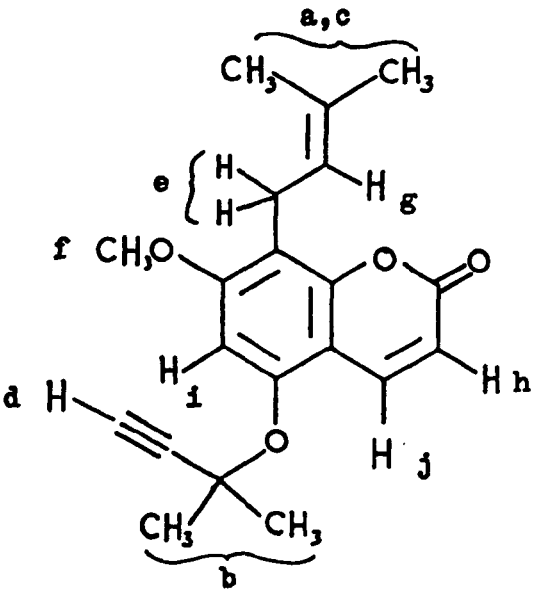
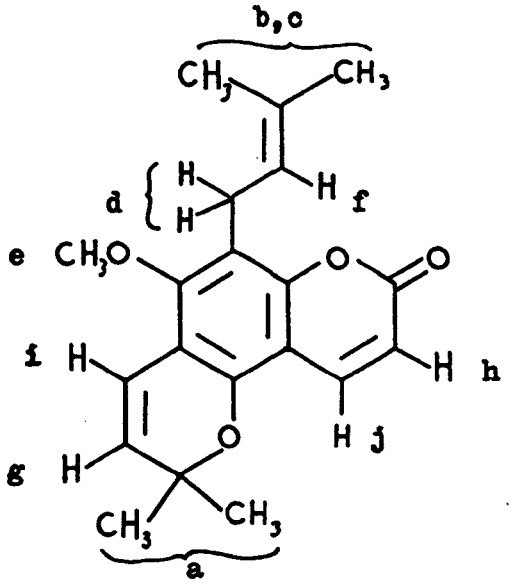
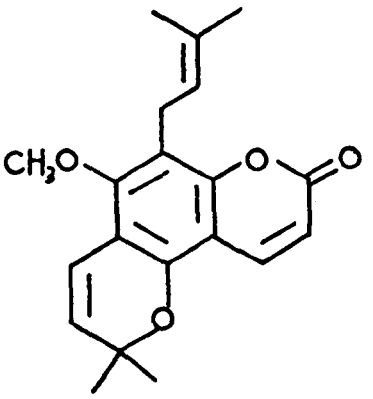


FIGURE 2.5

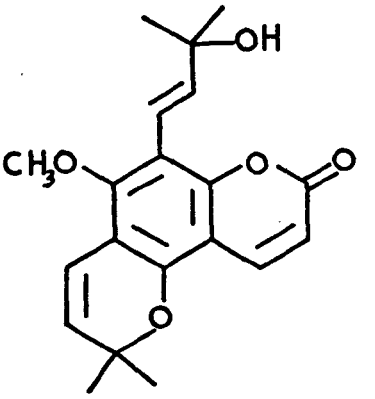
N.M.R. Spectrum of (125)

	Signal (δ)	Integration	Multiplicity
a	1.46	6	s.
b	1.68	3	b.s.
c	1.84	3	b.s.
d	3.45	2	b.d.; J 7Hz
e	3.78	3	s.
f	5.22	1	b.t.; J 7Hz
g	5.63	1	d.; J 10Hz
h	6.23	1	d.; J 9.5Hz
i	6.57	1	d.; J 10Hz
j	8.00	1	d.; J 9.5Hz

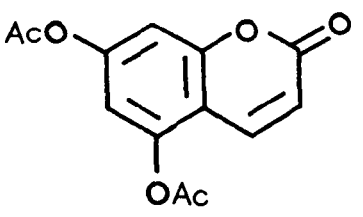




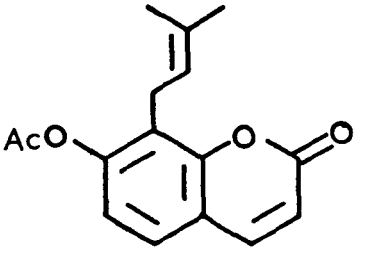
(125)



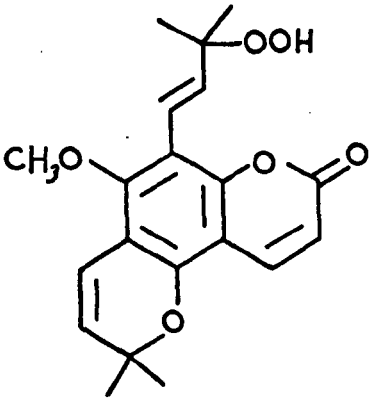
(124)



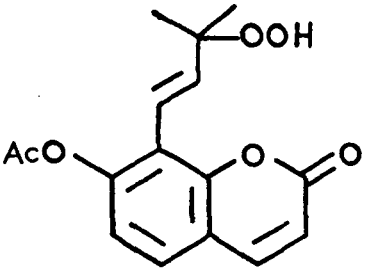
(134)



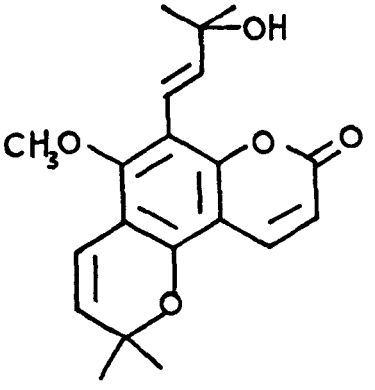
(55)



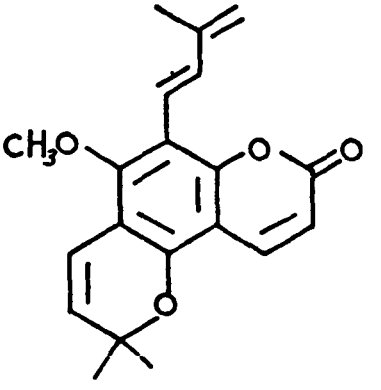
(152)



(153)



(124)



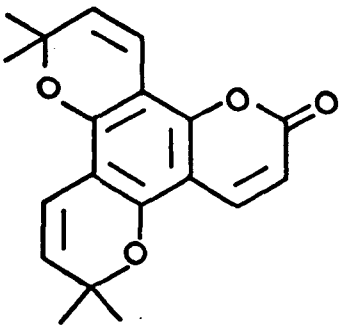
(122)

Thus the chromene (125), the penultimate compound in our projected synthesis of avicennol (124), was prepared in 30% overall yield from 5,7-diacetoxycoumarin (134).

(125) was then subjected to the photo-oxygenation conditions established earlier for osthenol acetate (55). Oxygen was bubbled through a solution of (125) in pyridine, containing haematoporphyrin as sensitiser, with irradiation from a 60 watt lamp. After 19 hours, analytical t.l.c. showed that a new,more polar, compound had been formed. After work-up, attempted reduction of the assumed hydroperoxide (152) with sodium iodide/acetic acid in ethanol resulted in a complex mixture of products. This was surprising, since this reduction procedure had proved successful with the hydroperoxide (153). The reduction was repeated, under effectively neutral conditions, using triphenylphosphine as the reducing agent. This resulted in a clean conversion to the corresponding alcohol, which, owing to difficulty in separation from the triphenylphosphine oxide, was only isolated in 50% yield. As predicted, only the trans allylic alcohol (124) was formed. This was apparent from its n.m.r. spectrum which showed a coupling constant of 16Hz between the two olefinic protons on the C-8 side chain.

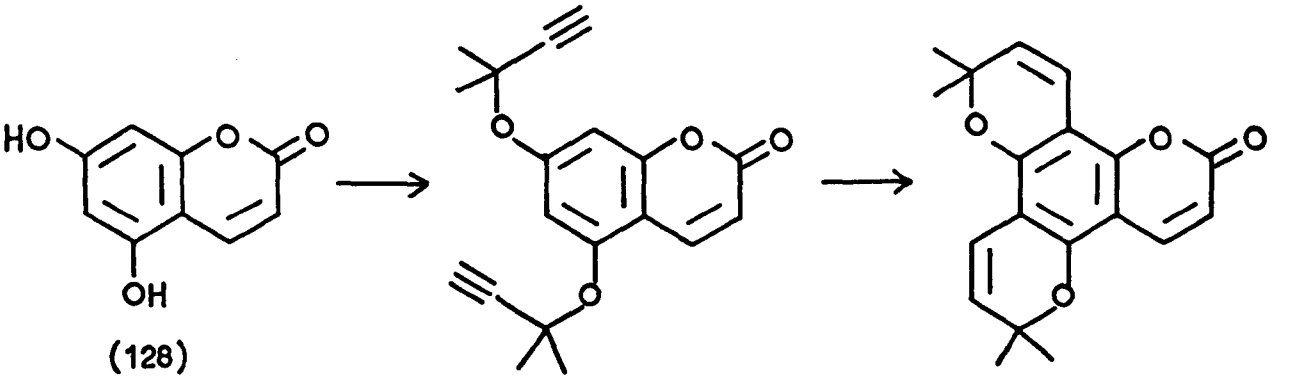
(124) Was found to be identical in all respects with a sample of natural avicennol, kindly provided by Dr. P.G. Waterman. This confirms structure (124) for avicennol and, since avicennol has been converted into avicennin (vide supra), structure (122) for avicennin.

Structure (125) has been tentatively assigned[115] on spectroscopic grounds, to dipetaline, a new coumarin isolated in an impure state from the root-bark of Zanthoxylum dipetalum. Direct comparison of synthetic (vide supra) and natural samples has now enabled this assignment to be confirmed. The presence of



(154)

SCHEME 2.14



(128) (155) (154)

(125) in the plant extract, prevented the crystallisation of another new coumarin, dipetalolactone, which was formulated as (154). The synthesis of this unique dipyranocoumarin was achieved as shown in Scheme 2.14. Treatment of 5,7-dihydroxycoumarin (128) with excess 3-chloro-3-methylbut-1-yne, potassium carbonate and potassium iodide in refluxing 2% aqueous acetone led to the formation (50%) of the bis (1,1-dimethylpropargyl) ether (155). Pyrolysis of this compound at 180^{o} in N,N-diethylaniline gave (154) in 62% yield. Again, the synthetic material and that of natural provenance were found to be identical.

The work described in this section of the thesis has been summarised in a preliminary communication[116].

Part 2

Experimental

2,4,6-Trihydroxybenzaldehyde (138)

Dry hydrogen cyanide and dry hydrogen chloride were bubbled separately through a solution of anhydrous phloroglucinol (36g) in ether (500ml), for 1 hour. The reaction mixture was allowed to stand at room temperature for 24 hours. The supernatant liquid was then decanted off, and the solid imine hydrochloride hydrolysed by boiling with water (200ml) for 1 min. On cooling, 2,4,6-trihydroxybenzaldehyde crystallised out, as orange needles (39.6g, 90%) (lit.[117] no definite m.p.); n.m.r. signals (d_6 acetone) at δ 4.00* (3H; b.s.), 5.93 (2H; s.) and 9.91 (1H; s.).

5,7-Diacetoxycoumarin (134).

A mixture of 2,4,6-trihydroxybenzaldehyde (16g), sodium acetate (16g) and acetic anhydride (80ml) were heated at 190° for 14 hours. The solution was then poured onto iced water, and extracted with ethyl acetate. The ethyl acetate solution was washed with 0.5% aqueous potassium carbonate, brine, dried and evaporated to give crude 5,7-diacetoxycoumarin (24.9g, 92%) as a tan solid, m.p. 139-141° (ethyl acetate-light petroleum) (lit.[118] m.p. 139.5-141°); n.m.r. signals at δ 2.37 (3H; s.), 2.45 (3H; s.), 6.38 (1H; d.; J 9.5Hz), 7.00 (2H; m.) and 7.70 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 1778, 1730 and 1630cm^{-1}; mass spectrum showed M^+ at m/e 262.

Prenylation of 5,7-diacetoxycoumarin.

A mixture of 5,7-diacetoxycoumarin (3.3g), potassium carbonate (5.9g) and 3,3-dimethylallyl bromide (6.88ml) in 1,2-dimethoxyethane (65ml) was refluxed for 18 hours. Work-up II gave a yellow oil which, after purification by preparative t.l.c. (30% ethyl acetate-light petroleum x 1), furnished:

(i) the bis ether (141) (0.83g, 21%) as pale yellow needles, m.p. 78-80° (lit.[8] m.p. 79-81°); n.m.r. signals at δ 1.80 (12H; b.s.),

4.57 (4H; b.d.; J 6.5Hz), 5.50 (2H; b.t.; J 6.5Hz), 6.10 (1H; d.; J 9.5Hz), 6.30 (1H; d.; J 2Hz), 6.40 (1H; d.; J 2Hz) and 7.96 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 1725 and 1608cm^{-1}.

(ii) 5-O-(3,3-dimethylallyl)-7-hydroxycoumarin (135) (1.86g, 60%) as colourless plates, m.p. 142-144° (ether) (lit.[8] 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 at δ 1.73 (3H; b.s.), 1.80 (3H; b.s.), 4.59 (2H; b.d.; J 6.5Hz), 5.47 (1H; b.t.; J 6.5Hz), 6.15 (1H; d.; J 9.5Hz), 6.39 (1H; d.; J 2Hz), 6.63 (1H; d.; J 2Hz), 7.70* (1H; b.s.) and 8.06 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 3600, 3330, 1745 1716 and1705cm^{-1}; λ_{max}^{EtOH} 248, 256 and 330nm (log ε 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-methoxycoumarin (132).

A mixture of (135) (1g), potassium carbonate (1.2g) and methyl iodide (1.7ml) in acetone (40ml) was refluxed for 2 hours. Work-up II gave (132) (0.975g, 92%), m.p. 91-94° (ether-light petrol) (lit.[119] m.p. 90-92°). n.m.r. signals at δ 1.75 (3H; b.s.), 1.80 (3H; b.s.), 3.83 (3H; s.), 4.57 (2H; b.d.; J 6.5Hz), 5.50 (1H; b.t.; J 6.5Hz), 6.08 (1H; d.; J 9.5Hz), 6.25 (1H; d.; J 2Hz), 6.35 (1H; d.; J 2Hz) and 7.95 (1H;d; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 1726, 1611 and 1567cm^{-1}; mass spectral peaks at m/e 260 (M^+, 7%), 192 (80), 164 (40), 149 (13), 135 (9) and 69 (100).

Pyrolysis of 5-O-(3,3-dimethylallyl)-7-methoxycoumarin (132).

A solution of (132) (0.7g) in N,N-diethylaniline (5ml) containing butyric anhydride (2ml) was refluxed for 1 hour at 175°, under nitrogen. The mixture was then diluted with water, and extracted with ethyl acetate. The ethyl acetate solution was washed with 1M hydrochloric acid, 5% w./v. aqueous potassium carbonate,

brine, dried and evaporated to give the butyrate (143) as a yellow solid (0.76g, 85%), m.p. 98-99° (ether) (lit.[109] m.p. 98-100°); (Found: C, 68.90; H, 6.78. $C_{19}H_{22}O_5$ requires C, 69.07; H, 6.71%); n.m.r. signals at δ 1.08 (3H; t.; J 7Hz), 1.68 (3H; b.s.), 1.83 (3H; b.s.), 1.85 (2H; b.m.), 2.65 (2H; t.; J 7Hz), 3.50 (2H; b.d.; J 6.5Hz), 3.92 (3H; s.), 5.22 (1H; b.t.; J 6.5Hz), 6.23 (1H; d.; J 9.5Hz), 6.65 (1H; s.) and 7.60 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 1763, 1740 and 1614cm^{-1}; mass spectral peaks at m/e 330 (M^+, 18), 260 (84), 245 (62), 217 (14), 202 (14) and 189 (18).

5-Hydroxy-7-methoxy-8-(3,3-dimethylallyl)coumarin (133).

The butyrate (143) (300mg) was dissolved in methanol (30ml), and 2% aqueous sodium carbonate (4ml) added. After stirring for 1 hour, the solution was diluted with water, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give (133) as a yellow solid (203mg, 86%), m.p. 195-197° (methanol). (Found: C, 69.17; H, 6.30. $C_{15}H_{16}O_4$ requires C, 69.21; H, 6.20%); n.m.r. signals at (d_6 acetone) δ 1.68 (3H; b.s.), 1.83 (3H; b.s.), 3.47 (2H; d.; J 6.5Hz), 3.88 (3H; s.), 5.20 (1H; b.t.; J 6.5Hz), 6.06 (1H; d.; J 9.5Hz), 6.48 (1H; s.) and 8.02 (1H; d.; J 9.5Hz); $\nu_{max}^{CHCl_3}$ 3599, 1730 and 1616cm^{-1}; λ_{max}^{EtOH} 223 (sh.), 258 (sh.), 263 and 324nm (log ε 4.15, 4.08, 4.12 and 4.14); λ_{max}^{EtOH}(base) 224, 238, 276, 324 and 399nm; mass spectral peaks at m/e 260 (M^+, 66%), 245 (96), 217 (100) 205 (72) and 189(56).

5-O-(1,1-Dimethylpropargyl)-7-methoxy-8-(3,3-dimethylallyl)-coumarin (127).

A mixture of (133) (300mg), potassium carbonate (420mg), potassium iodide (100mg) and 3-chloro-3-methylbut-1-yne (501mg) in 2% aqueous acetone (30ml) was refluxed for 18 hours. Work-up II gave a yellow oil (293mg, 78%) which contained mainly the

propargyl ether (127); n.m.r. signals at δ 1.65 (3H; b.s.), 1.72 (6H; s.), 1.81 (3H; b.s.), 2.73 (1H; s.), 3.41 (2H; b.d.; J 7Hz), 3.88 (3H; s.), 5.20 (1H; b.t.; J 7Hz), 6.08 (1H; d.; J 9.5Hz), 7.08 (1H; s.) and 7.83 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 3303, 1745 and 1605cm^{-1}; mass spectrum showed M^+ at m/e 326. The n.m.r. spectrum also showed signals arising from a small amount of another compound. In particular, an 'extra' AB quartet at δ 5.63 and 6.57 (J 10Hz) was identified. Separation of the above two compounds by chromatography was not possible.

Pyrolysis of (127).

A solution of (127) (300mg) in N,N-diethylaniline (4ml) was heated at 175° for 2 hours, under nitrogen. The solution was then poured onto water, and extracted with ethyl acetate. The ethyl acetate solution was washed with 1M hydrochloric acid, brine, dried and evaporated to give the chromene (125) as a brown solid, which, after crystallisation from ether-light petroleum, gave yellow plates (264mg, 88%), m.p. 113-114.5°. (Found: C, 73.30; H, 6.62. $C_{20}H_{22}O_4$ requires C, 73.60; H, 6.79%); n.m.r. signals at δ 1.46 (6H; s.), 1.68 (3H; b.s.), 1.84 (3H; b.s.), 3.45 (2H; b.d.; J 7Hz), 3.78 (3H; s.), 5.22 (1H; b.t.; J 7Hz), 5.63 (1H; d.; J 10Hz), 6.23 (1H; d.; J 9.5Hz), 6.57 (1H; d.; J 10Hz) and 8.00 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 1745, 1620 and 1590cm^{-1}; λ_{max}^{EtOH} 229, 264, 272, 294 and 315 (sh.) (log ε 4.62, 4.44, 4.30, 4.52 and 4.29); mass spectral peaks at 326 (M^+, 30%), 311 (100), 253 (19) and 241 (13). This compound was identical with a sample of natural dipetaline[115], kindly provided by Dr. P.G. Waterman.

Photo-oxygenation of (125).

Oxygen was bubbled, via a glass sinter, upwards through a solution of (125) (250mg) in pyridine (60ml) containing

haematoporphyrin (25mg). This solution was irradiated by a 60 watt lamp, positioned approximately 10cm from the centre of the reaction flask. After 17 hours, most of the pyridine was evaporated, and Work-up I furnished a brown oil (302mg) which was reduced as follows:

(a) using sodium iodide

The brown oil obtained above was dissolved in absolute ethanol (30ml) containing glacial acetic acid (1ml) and sodium iodide (2.3g). After 18 hours, the ethanol was evaporated and the residue dissolved in ethyl acetate. The ethyl acetate solution was washed with 0.1M sodium thiosulphate solution, brine, dried and evaporated to give a dark brown oil (340mg). T.l.c. and n.m.r. showed that a complex mixture of products had been produced, separation of which proved impossible.

(b) using triphenylphosphine

The brown oil obtained above was dissolved in ether (50ml) and triphenylphosphine (270mg) added. The solution was kept at 0° for 15 hours. The solution was then filtered, and the filtrate evaporated to give a yellow solid (560mg). Purification by preparative t.l.c. (1% methanol-chloroform) furnished the trans allylic alcohol (124) as yellow plates (131mg, 50%), m.p. 123.5-125° (ethyl acetate-light petroleum) (lit.[88] m.p. 123-124.5°) (Found: C, 70.35; H, 6.63. $C_{20}H_{22}O_5$ requires C, 70.20; H, 6.45%); n.m.r. signals at δ 1.59 (6H; s.), 1.60 (6H; s.), 2.58* (1H; s.), 3.80 (3H; s.), 5.69 (1H; d.; J 10Hz), 6.27 (1H; d.; J 10Hz), 6.65 (1H; d.; J 10Hz), 6.81 (1H; d.; J 16Hz), 6.95 (1H; d.; J 16Hz), and 8.06 (1H; d.; J 10Hz); ν_{max}^{KBr} 3470, 1715, 1632, 1612 and 1580cm^{-1}; λ_{max}^{EtOH} 250, 257 and 301nm (log ε 4.50, 4.63 and 4.27); mass spectral peaks at m/e 342 (M^+, 3%), 327 (78), 309 (100) and 277 (14). This compound was identical with a sample of natural

avicennol[88], kindly provided by Dr. P.G. Waterman.

Preparation of (155).

A mixture of 5,7-dihydroxycoumarin (600mg), potassium carbonate (1.68g), potassium iodide (400mg) and 3-chloro-3-methylbut-1-yne (3g) in 2% aqueous acetone (120ml) was refluxed for 22 hours. Work-up II gave the bis ether (155) as a yellow oil (500mg, 43%); n.m.r. signals at δ 1.73 (6H; s.), 1.76 (6H; s.), 2.70 (2H; b.s.), 6.33 (1H; d.; J 9.5Hz), 7.03 (1H; d.; J 2Hz), 7.45 (1H; d.; J 2Hz), and 7.94 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 3300, 1745 and 1605cm^{-1}; mass spectrum showed M^+ at m/e 310.

Pyrolysis of (155).

A solution of the bis ether (155) (500mg) in N,N-diethylaniline (10ml) was heated for 2 hours at 180°, under nitrogen. The reaction mixture was then poured onto water and extracted with ethyl acetate. The ethyl acetate solution was washed with 1M hydrochloric acid, brine, dried and evaporated to give a brown oil, which, after purification by preparative t.l.c. (chloroform x 1), furnished: the dipyranocoumarin (154) (310mg, 62%) as yellow cubes, m.p. 135-136° (ether-light petroleum); (Found: C, 73.22; H, 5.85. $C_{19}H_{18}O_4$ requires C, 73.53; H, 5.85%); n.m.r. signals at δ 1.48 (12H; s.), 5.53 (1H; d.; J 10Hz), 5.57 (1H; d.; J 10Hz), 6.41 (1H; d.; J 9.5Hz), 6.63 (1H; d.; J 10Hz), 6.80 (1H; d.; J 10Hz) and 7.93 (1H; d.; J 9.5Hz); $\nu_{max}^{CCl_4}$ 1744, 1645 and 1600cm^{-1}; λ_{max}^{EtOH} 222, 244(sh.), 250, 297, 308 and 343nm (log ε 4.25, 4.47, 4.53, 4.46, 4.38 and 4.12); mass spectral peaks at m/e 310 (M^+, 30%), 295 (100) and 149 (29). This compound was identical with a sample of natural dipetalolactone[115], kindly provided by Dr. P.G. Waterman.

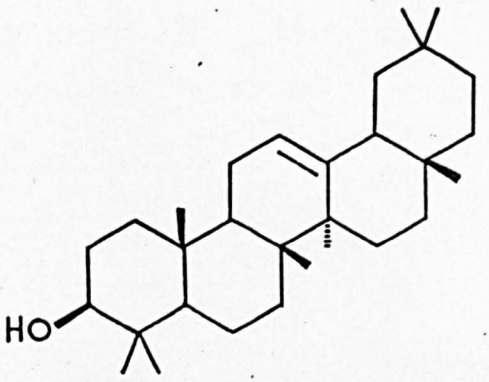
Part 3

Structure Determination of Two New Diterpenoids from Acacia jacqumontii.

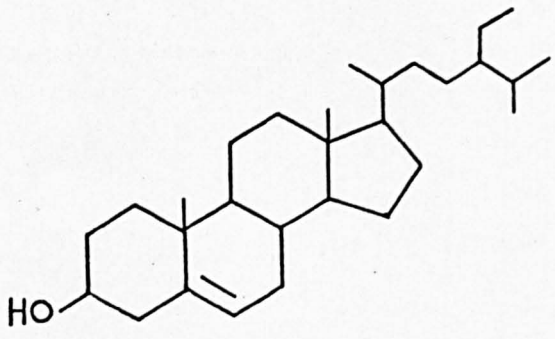
$CH_3(CH_2)_{28}R$

(156) R = CH_2OH

(157) R = CO_2H



(158)



(159)

Acacia jacqumontii is a bushy, thorny, shrub with sweet smelling flowers, and is distributed over various parts of India. Since no phytochemical investigation of this plant had beenreported, Professor Joshi and his co-workers, at the University of Jaipur, Rajasthan, India, undertook an examination of the roots:

The combined light petroleum and benzene extracts of the roots were chromatographed on alumina. Elution with light petroleum furnished n-triacontanol (156) and a new diterpenoid (A). Further elution with mixtures of light petroleum and benzene afforded a second new diterpenoid (B), n-triacontanoic acid (157), β -amyrin (158) and β -sitosterol (159). The Indian workers, however, were not able to make any progress on the structure determination of the two new diterpenoids. Consequently, a sample of each of these compounds was sent, by Professor Joshi, to this Department for investigation. This section of the thesis describes the structure determination of these two new diterpenoids.

Diterpenoid (A)

Elemental analysis and mass measurement established the molecular formula of this diterpenoid as $C_{20}H_{32}O_2$. Its u.v. and i.r. spectra showed that it contained a conjugated diene system (λ_{max}^{EtOH} 239nm; ε 19,00) and a hydroxyl group ($\nu_{max}^{CCl_4}$ 3610cm^{-1}; ε 117) respectively. The ^{1}H n.m.r. spectrum of (A) confirmed that it contained only one hydroxyl group (Figure 3.1, H_f). The absence of any carbonyl absorption in the i.r. spectrum indicated that the other oxygen function was necessarily ethereal in nature. The molecular formula of (A) required that it contained five double bond equivalents. Since no other functionality than that indicated above could be identified, it was concluded that (A) was tricyclic.

FIGURE 3.1

^{1}H NMR Spectrum of Diterpenoid (A)

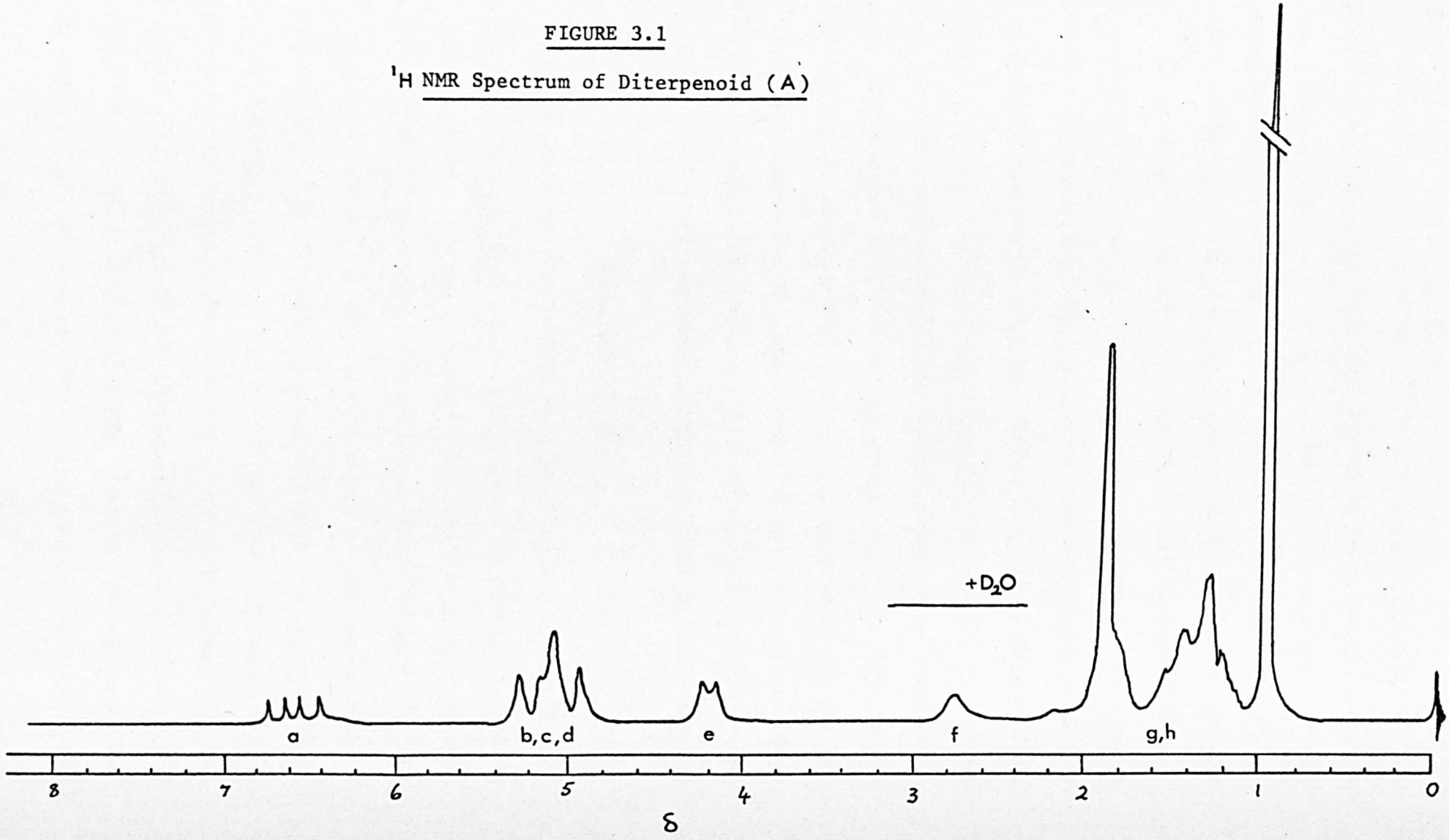
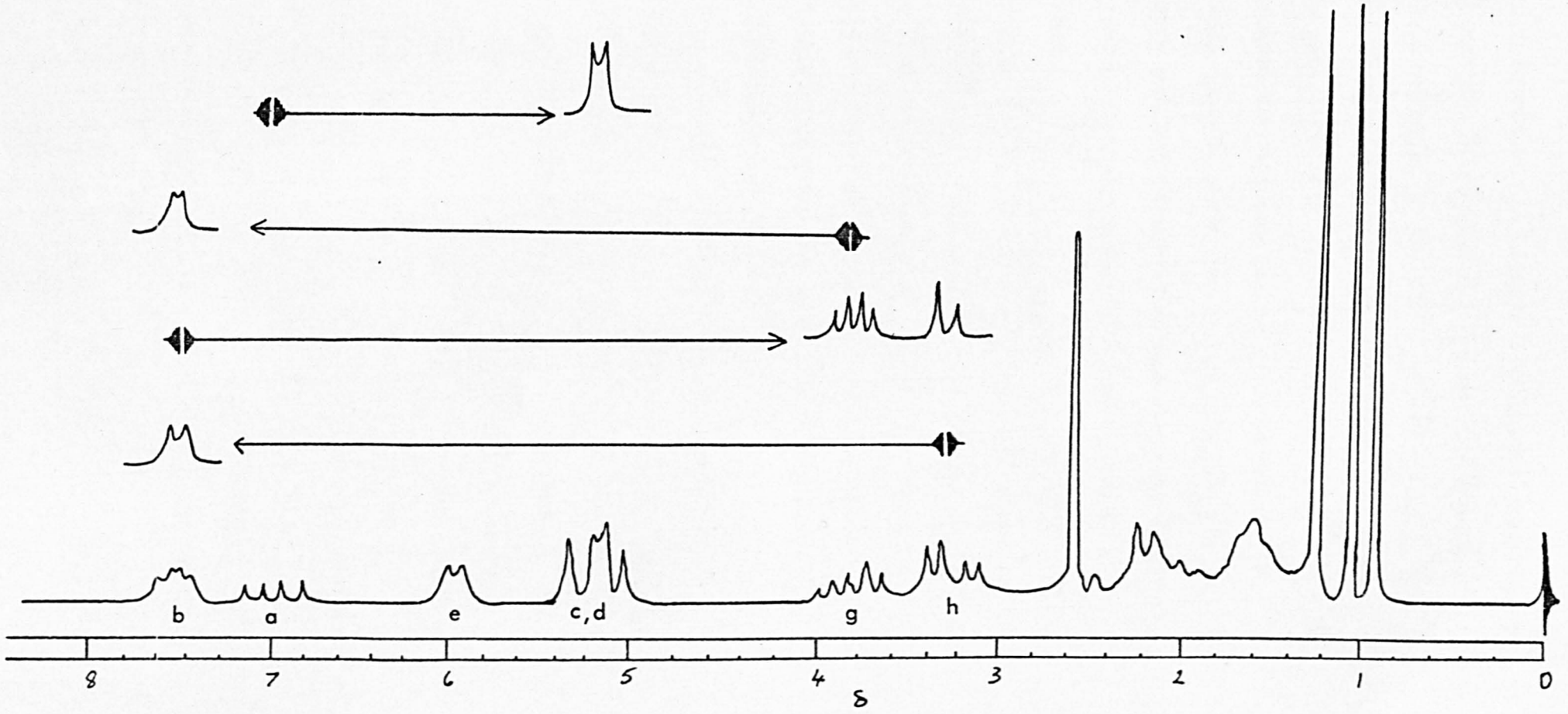
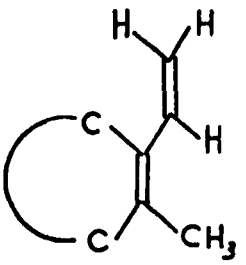


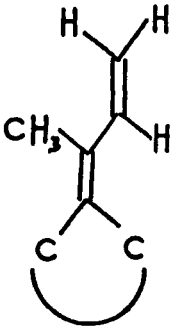
FIGURE 3.2

^1H NMR Spectrum of Diterpenoid (A) + 0.2 M equivalents of $Eu(dpm)_3$

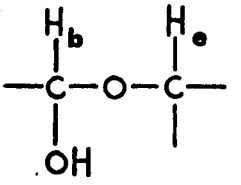




(160)



(161)



(162)

TABLE 3.1

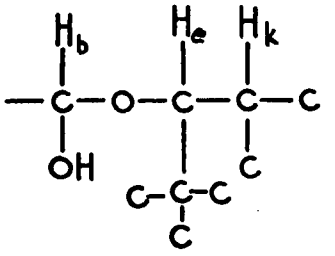
^{13}C NMR Spectrum of (A)

Signal (ppm)	Multiplicity
15.24	q.
16.13	q.
18.71	t.
21.65	t.
22.34	q.
25.71	t.
31.61	t.
33.22	q.
34.42	s.
38.83	s.
40.63	t.
41.83	t.
47.88	s.
55.68	d.
71.69	d.
96.18	d.
112.62	t.
133.01	s.
133.01	s.
135.08	d.

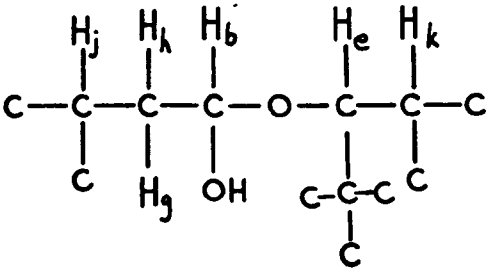
The ^1H n.m.r. spectrum of (A) (Figure 3.1) showed the presence of three olefinic protons, H_a, H_c and H_d. Decoupling experiments on the spectrum after addition of the shift reagent $Eu(dpm)_3$ (Figure 3.2) showed that these protons constituted an AXY system. Consequently, they were attributed to a vinyl group. The ^1H n.m.r. spectrum also indicated the presence of one vinyl methyl group. Thus it seemed likely that the other two carbon substituents on the diene system were saturated ring carbon atoms. From the above information, two partial structures for the diene system in (A) were considered, namely (160) and (161). This was in accord with the ^{13}C n.m.r. spectrum of (A) (Table 3.1) which showed four olefinic resonances (135.08, 112.62 and two superimposed at 133.01ppm). Two of these arose from fully substituted olefinic carbon atoms, one from an olefinic methylene group and one from an olefinic methine group. At this stage, however, distinction between (160) and (161) was not possible.

The ^1H n.m.r. spectrum of (A) showed the presence of two $\underline{H}-\overset{|}{\underset{|}{C}}-O$ protons, one at δ 4.30, H_e, and the other at δ 5.05, H_b. Because of the low field position of the latter signal, it was considered likely that the carbon atom bearing H_b was attached to both oxygen atoms. This was confirmed by the ^{13}C n.m.r. spectrum of (A) (Table 3.1) which showed a signal at 96.18ppm, characteristic of a carbon atom attached to two oxygen atoms. The signal at 71.69ppm was identified as the resonance from a carbon atom attached to one oxygen atom. Thus it was apparent at this stage that (A) contained a hemi-acetal group of type (162). Further information about the environment of the hemi-acetal group was obtained from a detailed examination of the ^1H n.m.r. spectrum:

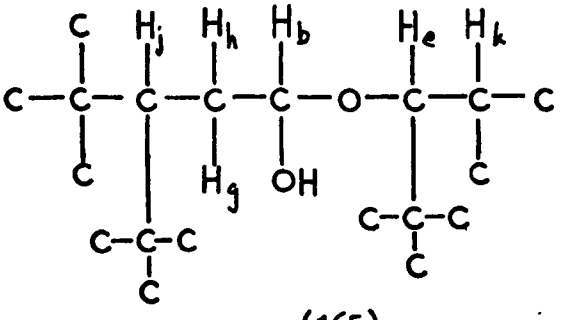
The signal arising from H_e appeared as a doublet (δ 4.30; J 7Hz),



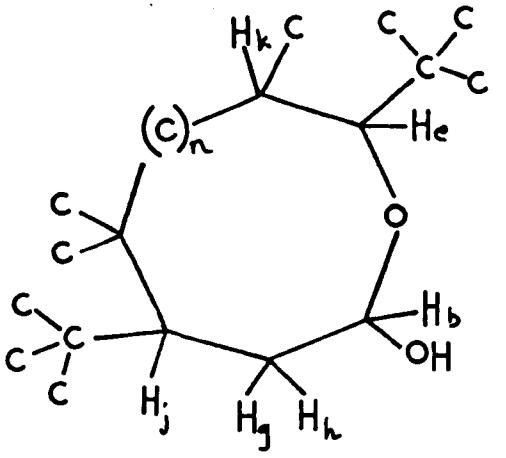
(163)



(164)



(165)



$n \geq 0$

(166)

indicating coupling to one other proton, H_k. It was not possible to see the resonance for H_k, even in the europium shifted spectrum. Thus it seemed likely that H_k was attached to a saturated carbon atom. This now gave the partial structure (163).

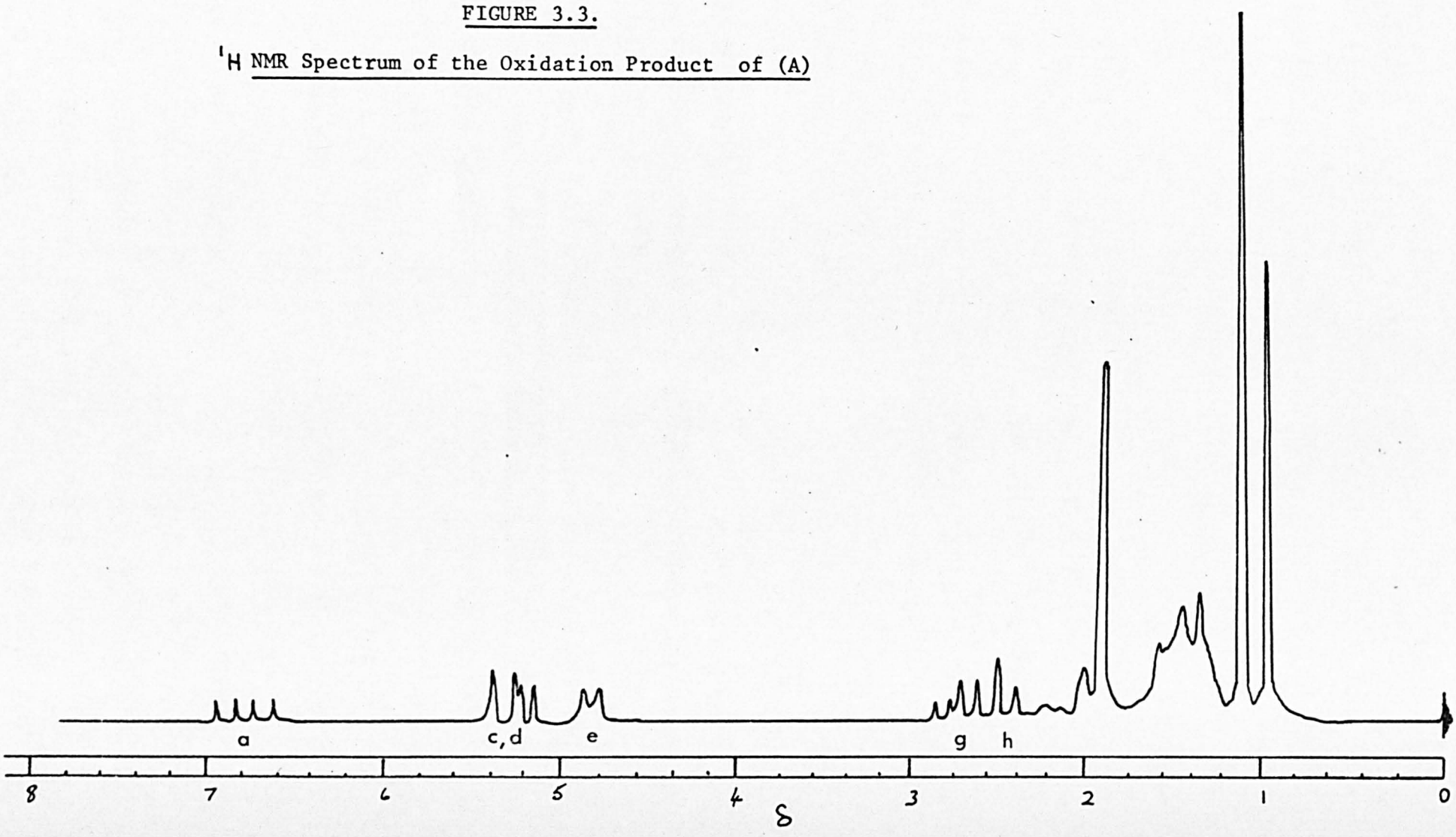
The signal arising from H_b appeared as a double doublet (J 7Hz and 6Hz) in the europium shifted spectrum (Figure 3.2), indicating coupling to two protons, H_g and H_h, on the adjacent carbon atom. The signals for H_g and H_h were found by decoupling experiments on the europium shifted spectrum. A geminal coupling constant of 16Hz between H_g and H_h was identified. It was apparent, however, that H_g was coupled (J 8Hz) to one other proton, H_j, whereas H_h was not. This was taken as indicating a dihedral angle of $\sim 90^\circ$ between H_h and H_j. The partial structure (164) could now be constructed for the hemi-acetal system.

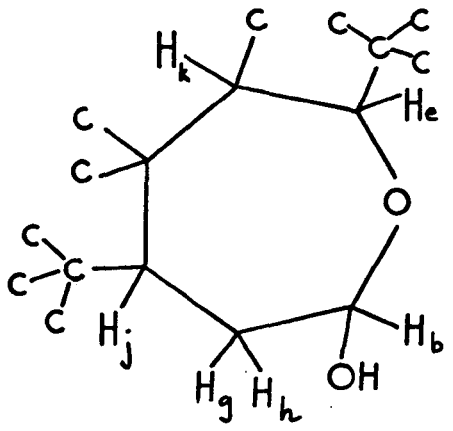
The signal for H_j could be seen in the 0.6M europium shifted spectrum as a doublet (δ 4.20; J 8Hz), i.e. H_j was coupled only to H_g. Thus the carbon atom bearing H_j had to be attached to two fully substituted carbon atoms, as illustrated in (165). It had previously been established that (A) had to be tricyclic. Consequently, it seemed likely that the hemi-acetal group was part of a ring system. So far, a chain of at least seven atoms had been identified (see (165)). Thus, we were led to the conclusion that (A) contained a ring system of type (166), which had to be seven-membered or greater.

Oxidation of (A) with Jones reagent gave a less polar, non-hydroxylic, $C_{20}H_{30}O_2$ compound. The ^1H n.m.r. spectrum of this product (Figure 3.3) showed that the resonance for H_b was no longer present. The signals for H_g and H_h now appeared as a double doublet (δ 2.78; J 16Hz and 8Hz) and a doublet (δ 2.50; J 16Hz)

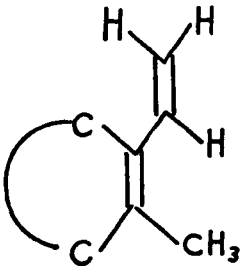
FIGURE 3.3.

^1H NMR Spectrum of the Oxidation Product of (A)

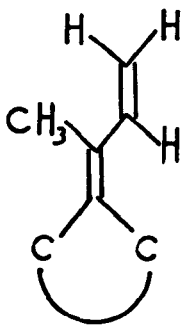




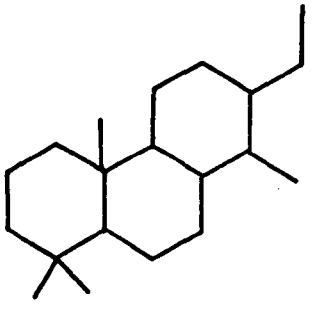
(167)



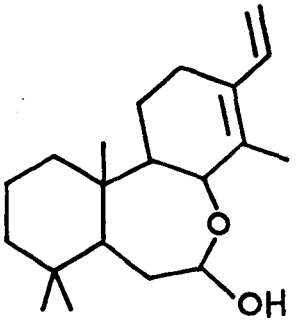
(160)



(161)

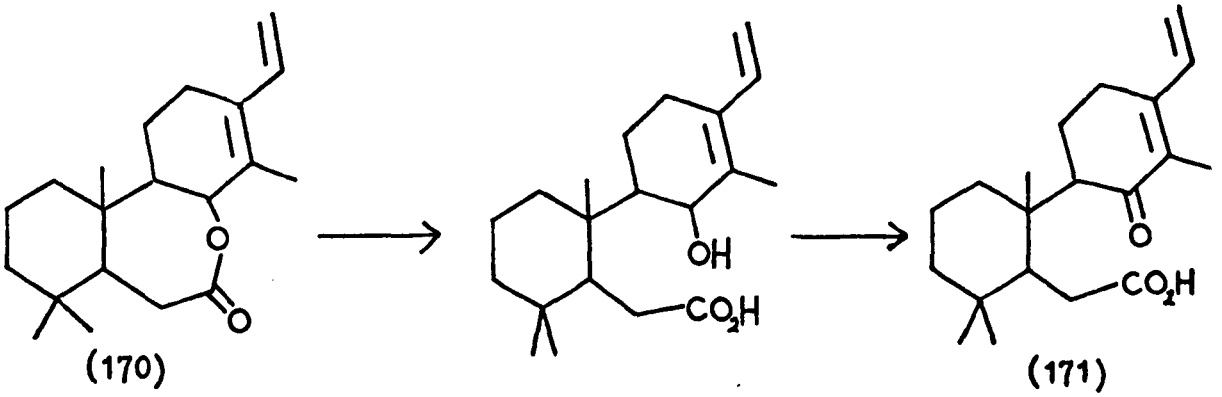


(168)



(169)

SCHEME 3.1



(170) (171)

respectively. The i.r. spectrum showed $\nu_{max}^{CCl_4}$ at 1740cm^{-1}, which indicated that the assumed lactone ring contained at least six atoms. Significantly, the ^{13}C n.m.r. spectrum of this oxidised compound (Table 3.2) showed the carbonyl carbon resonance at 176.4ppm, which is virtually identical with the literature value for the carbonyl carbon resonance of a cyclohexanolide[120] (see Table 3.3). Thus it seemed likely that the oxidation product of (A) contained a cyclohexanolide ring. The formation of a seven-membered ring lactone by mild oxidation required that the hemi-acetal ring in (A) also be seven-membered, i.e. (167).

We had now accounted for all the functionality in (A) by the part structures (167) and (160) or (161). In addition, from the europium shifted ^{1}H n.m.r. spectrum of (A) (Figure 3.2), it was apparent that (A) contained three tertiary methyl groups.

Since (A) was tricyclic, and contained three tertiary methyl groups, one vinyl methyl group and one vinyl group, it seemed likely that (A) might have the carbon skeleton of the cassane group of diterpenoids (168). Thus, we tentatively considered structure (169) for (A). Consequently, we tried to inter-relate the hemi-acetal ether oxygen atom and the diene system. The obvious way to achieve this would require conversion of the oxidation product of (A), assumed to have structure (170), to the hydroxy-acid, followed by its oxidation to the dienone (171) (Scheme 3.1). The lactone, however, was extremely resistant to hydrolysis; an alternative approach was therefore required. (A), for a hemi-acetal, was surprisingly inert to sodium borohydride in ethanol, and lithium aluminium hydride in ether. However, treatment of (A) with lithium aluminium hydride in refluxing tetrahydrofuran afforded, in high yield, a crystalline $C_{20}H_{34}O_2$ diol, which was

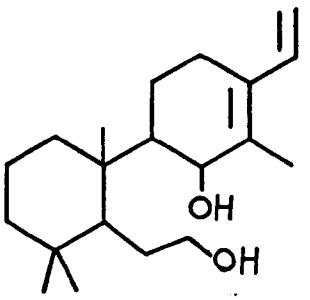
TABLE 3.2

^{13}C NMR Spectrum of the Oxidation Product of (A).

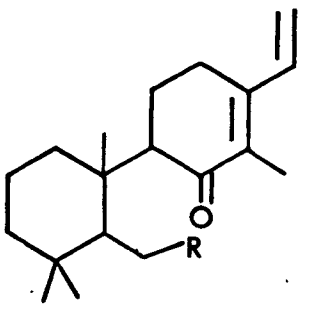
Signal (ppm)	Multiplicity
14.02	q.
16.09	q.
18.59	t.
21.46	q.
21.65	t.
24.50	t.
31.43	t.
33.32	q.
34.98	s.
39.01	t.
39.20	s.
41.40	t.
52.26	s.
54.01	d.
80.23	d.
114.18	t.
129.24	s.
134.35	d.
134.64	s.
176.43	s.

TABLE 3.3

Lactone	^{13}C Carbonyl resonance (ppm)
cyclobutanolide	178.5
cyclopentanolide	167.5
cyclohexanolide	176.5
cycloheptanolide	165.3
cyclooctanolide	173.8
cyclononanolide	172.3



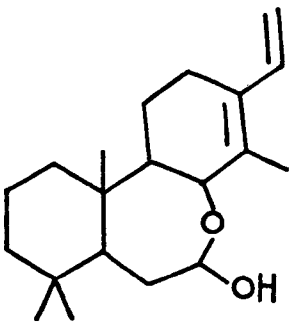
(172)



(173) R = CH_2OH

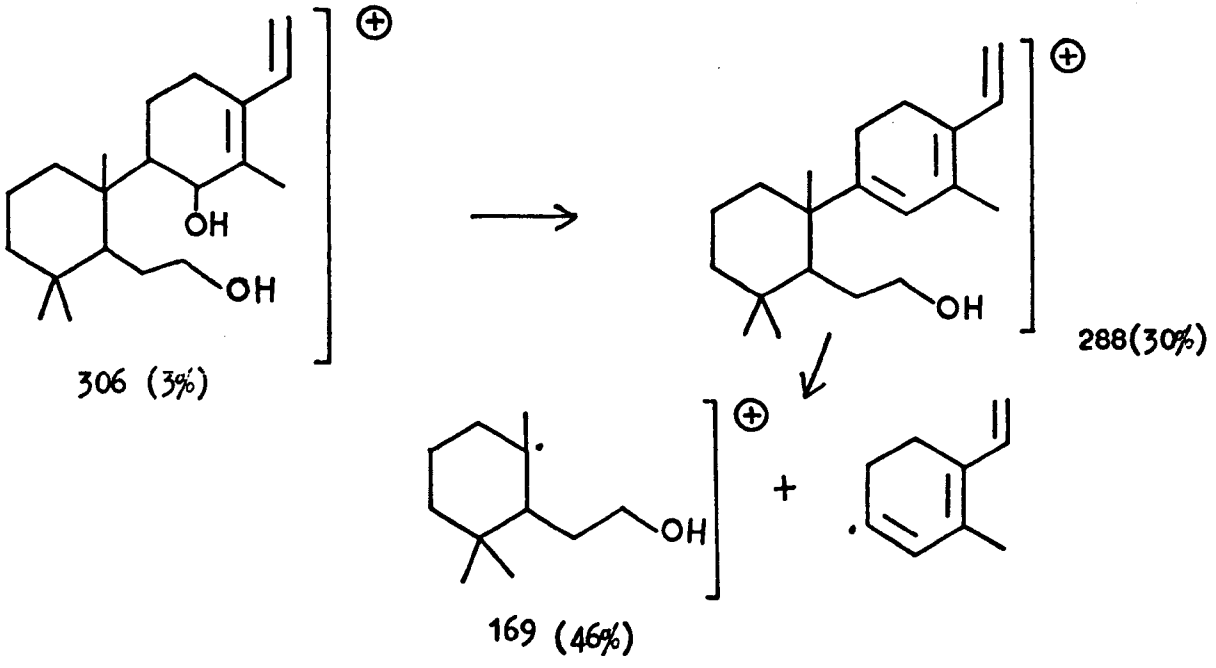
or CHO

or CO_2H



(169)

S C H E M E 3.2



characterised as its diacetate. Repeated attempts, using manganese dioxide, Jones reagent and pyridinium chlorochromate, to effect the oxidation of the diol (172) to the dienone (173) were singularly unsuccessful. In each case, a very complex mixture of products was formed, from which no useful information could be obtained.

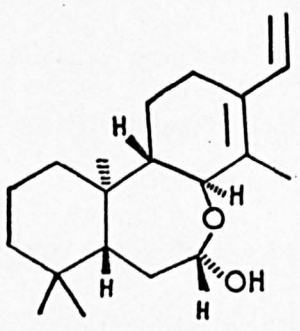
We realised at this point that chemically, it was not going to be easy to relate the hemi-acetal ether oxygen atom to the diene system, with the limited amount of material that we had available. In addition, a literature survey revealed that no other cassane diterpenoid was known having a structure similar to (169), which could be used for structure inter-relation purposes. Thus correlation between (A) and a known compound would not be possible. Consequently, we submitted a sample of (A) for a single crystal X-ray analysis.

There were, however, several spectroscopic features which supported structure (169) for (A). The europium shifted spectrum (Figure 3.2) showed that the vinyl methyl protons were shifted more than H_a, which in turn was shifted more than H_c and H_d. This is precisely the order that would be expected for structure (169), assuming complexation of the shift reagent with the hydroxyl group.

Although the mass spectrum of (A), and its oxidised product, were not very informative, the mass spectrum of the diol produced from the reduction of (A) showed significant peaks at m/e 306 (M^+, 3%), 288 (30) and 169 (46). This fragmentation was interpreted as shown in Scheme 3.2, and provides some evidence for structure (172) for the diol.

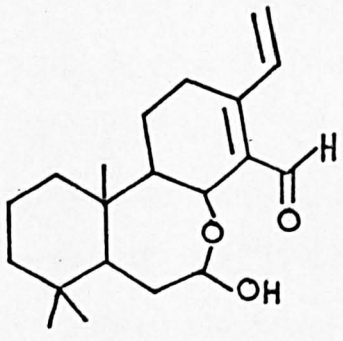
The X-ray analysis [121] (see experimental for details) confirmed structure (169) for (A). In addition, the relative stereochemistry

Diterpenoid (A)



(169)

Diterpenoid (B)



(174)

was determined, and is shown opposite. Figure 3.4 shows a projected view of the molecule, illustrating the solid state conformation.

With the structure of (A) confirmed, all the signals in the ^{13}C n.m.r. spectrum of (A), and its oxidised product, could be assigned, as shown in Table 3.4, by use of known ^{13}C chemical shifts and comparison with literature data for other diterpenoids.

Diterpenoid (B).

This diterpenoid was only present in minor amounts in the roots of the plant. However, it was immediately apparent from its ^{1}H n.m.r. spectrum (Figure 3.5) that it was structurally related to diterpenoid (A), (169). (B) appeared to have the same hemi-acetal system and the same vinyl group of (A), but did not contain a vinyl methyl group. Significantly, a new signal at δ 10.1 was present, which was identified as the resonance from an aldehyde proton. The i.r. spectrum showed $\nu_{max}^{CCl_4}$ at 1675cm^{-1}, characteristic of a conjugated carbonyl group. This was also indicated by its u.v. spectrum (λ_{max}^{EtOH} 273nm, ε 12,000). Thus it was proposed that diterpenoid (B) had the structure (174). In support of this, dilution studies on the i.r. spectrum indicated the presence of intramolecular hydrogen bonding ($\nu_{max}^{CCl_4}$ 3450cm^{-1}) which would be expected for this structure (17_4).

Chemical transformations of (B) were not possible due to the small amount of material which was isolated.

FIGURE 3.4

Projected View of Diterpenoid (A)

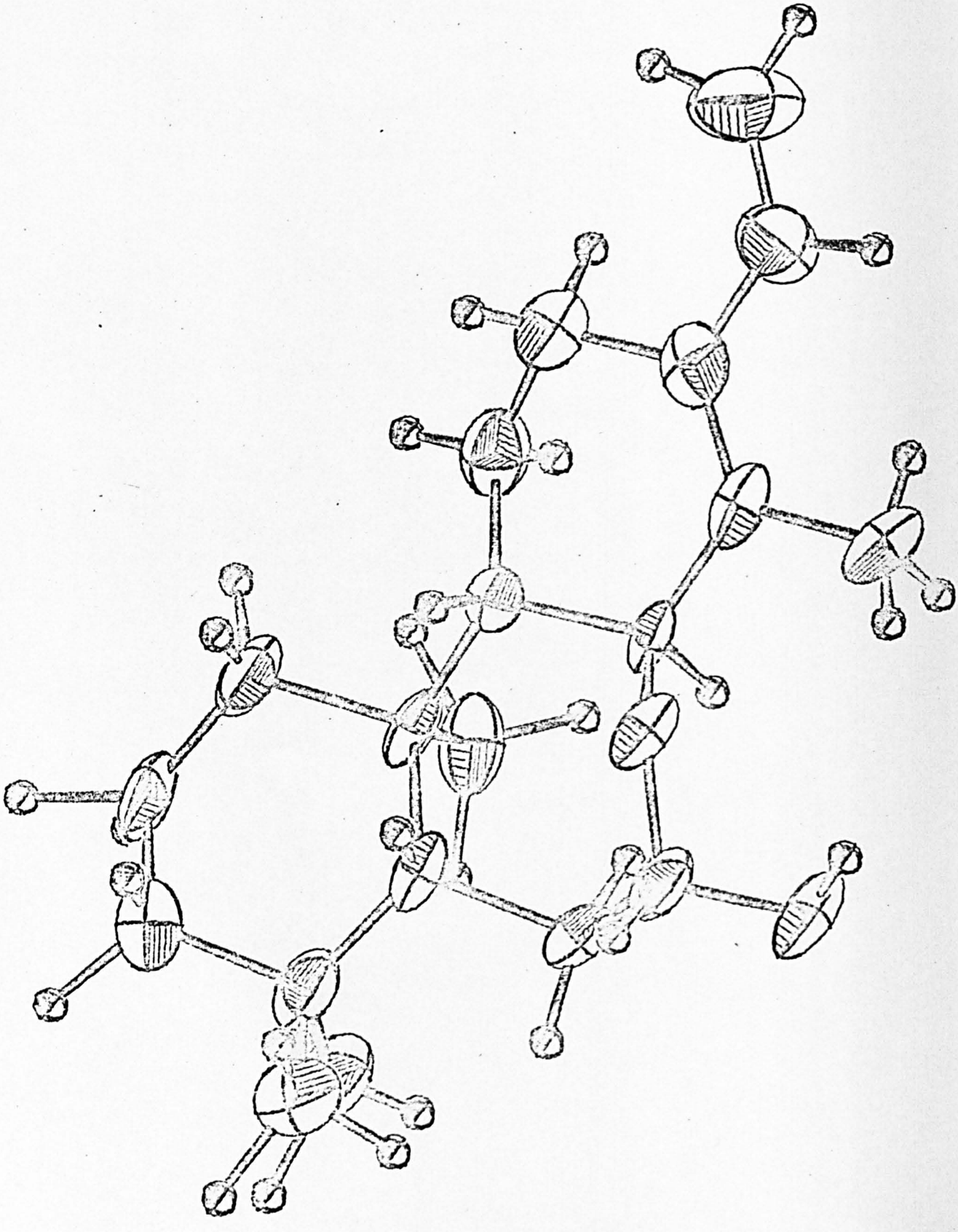
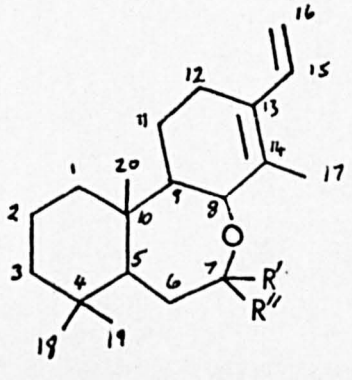


TABLE 3.4

^{13}C NMR Spectrum of Diterpenoid (A) and its Oxidised Product

Carbon No.	Diterpenoid (A)	Oxidised Product
1	40.63[a]	39.01[d]
2	18.71	18.59
3	41.83[a]	41.40[d]
4	34.42[b]	34.98[e]
5	47.88	52.26
6	31.61	31.43
7	96.18	176.43
8	71.69	80.23
9	55.68	54.01
10	38.83[b]	39.20[e]
11	21.65[c]	21.65[f]
12	25.71[c]	24.50
13	133.01	134.64[g]
14	133.01	129.24[g]
15	135.08	134.35
16	112.62	114.18
17	16.13	16.09
18	33.22	33.32
19	22.34	21.66
20	15.24	14.02

a,b,c,d,f,g : These assignments may be reversed, but those given are considered to be the most likely.

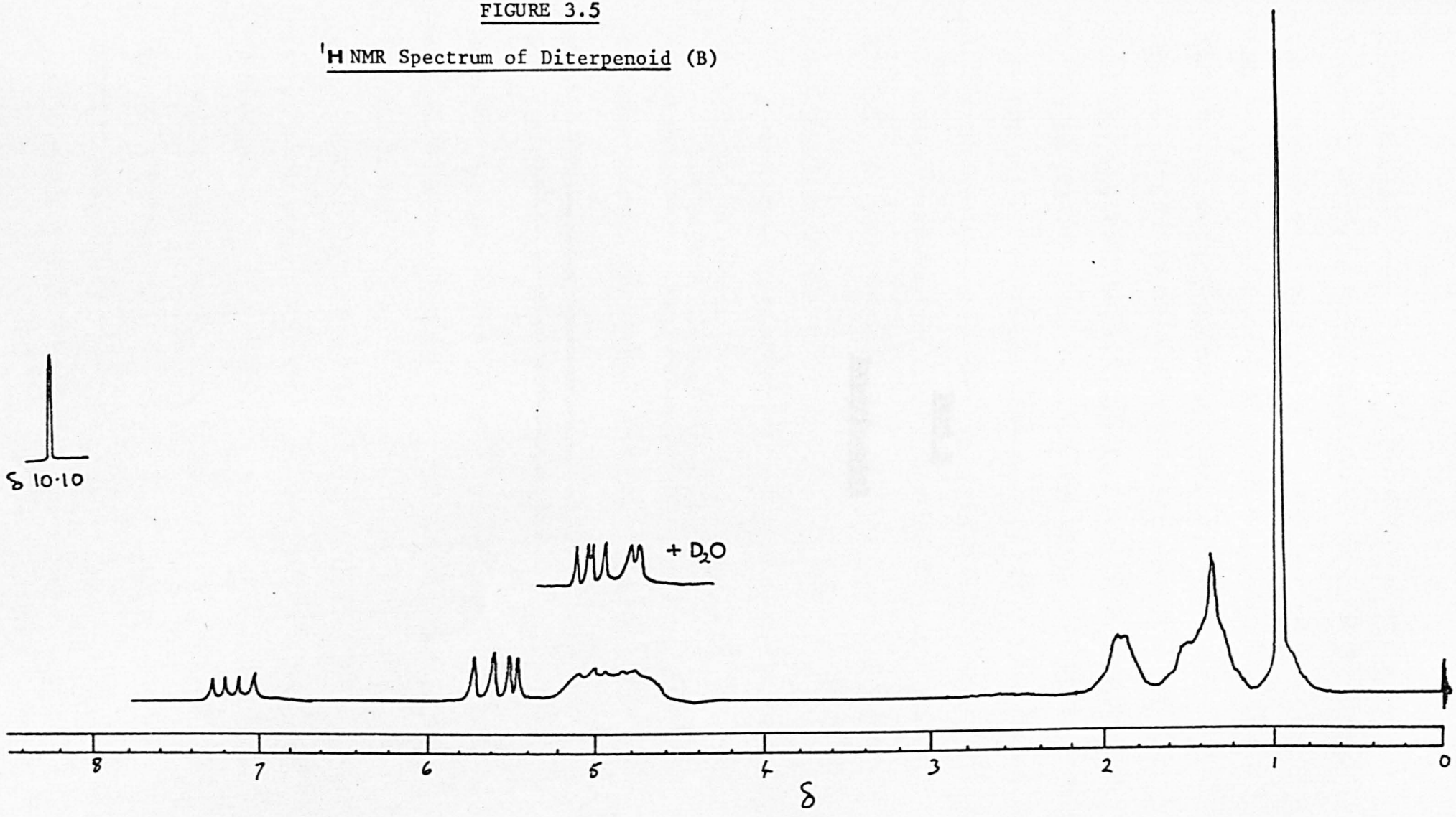


Diterpenoid (A) R' = H
R'' = OH

Oxidised Product R',R'' = O

FIGURE 3.5

^{1}H NMR Spectrum of Diterpenoid (B)



Part 3

Experimental

Diterpenoid (A) : M.p. 210-211° (ethyl acetate-light petroleum) (Found: C, 78.89; H, 10.59. $C_{20}H_{32}O_2$ requires C, 78.95; H, 10.57%); n.m.r. signals at δ 0.94 (9H; s.), 1.02-1.60 (14H; m.), 1.84 (3H; b.s.), 2.72* (1H; b.s.), 4.30 (1H; d.; J 7Hz), 5.05 (3H; m.) and 6.72 (1H; d.d.; J 17.5Hz and 10Hz); n.m.r. signals, after addition of 0.2 M equivalents of $Eu(dpm)_3$, at δ 0.94 (3H; s.), 1.02 (3H; s.), 1.27 (3H; s.), 1.30-2.42 (14H; m.), 3.38 (1H; d.d. J 16Hz and 6Hz), 3.80 (1H; m.), 5.29 (2H; m.), 5.97 (1H; d.; J 7Hz), 6.92 (1H; d.d.; J 17.5Hz and 10Hz) and 7.59 (1H; d.d.; J 8Hz and 6Hz); $\nu_{max}^{CCl_4}$ 3610, 2950, 1640, 1295, 1022, 988 and 900cm^{-1}; λ_{max}^{EtOH} 239nm (ε19,000); mass spectral peaks at m/e 304 (M^+, 49%), 286 (59), 271 (30), 257 (30), 166 (41), 149 (47), 138 (50) and 123 (100).

Jones oxidation of (A).

A solution of Jones reagent was added dropwise to a solution of (A) (60mg) in acetone (10ml) at 0°, until a permanent brown colour was present. The solution was then extracted with ether. The ether solution was washed with brine, dried and evaporated to give the lactone (170) as pale yellow needles (50mg, 80%), m.p. 118-120° (ethyl acetate - light petroleum) (Found: C, 79.31; H, 9.92. $C_{20}H_{30}O_2$ requires C, 79.47; H, 9.93%); n.m.r. signals at δ 0.92 (3H; s.), 1.10 (6H; s.), 1.20-1.80 (12H ; m.), 1.90 (3H; b.s.), 2.50 (1H; d.; J 16Hz), 2.78 (1H; d.d.; J 16Hz and 8Hz), 4.84 (1H; d.; J 7Hz), 5.15 (1H; b.d.; J 10Hz), 5.25 (1H; b.d.; J 18Hz), and 6.75 (1H; d.d.; J 18Hz and 10Hz); $\nu_{max}^{CCl_4}$ 2920, 1740, 1270, 1010 and 900cm ; λ_{max}^{EtOH} 238nm (ε 1700); mass spectral peaks at m/e 302 (M^+, 45%), 287 (25), 165 (50), 164 (100), 137 (70), 136 (75) and 123 (95).

Attempted hydrolysis of (A).

1M Sodium hydroxide solution (3ml) was added to a solution

of (A) (30mg) in methanol (20ml), and the mixture refluxed for 8 hours. T.l.c. indicated only the presence of starting material. Additional sodium hydroxide (70mg) was added, and the solution refluxed for a further 12 hours. T.l.c. still indicated only the presence of starting material.

Reduction of (A).

A suspension of lithium aluminium hydride (50mg) in dry tetrahydrofuran (20ml) containing (A) (50mg) was refluxed for 6 hours. Water was then added and the solution extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give the diol (172) as white needles (48mg,96%), m.p. 155-156° (ethyl acetate-light petroleum); (Found: C, 77.92; H, 11.01. $C_{20}H_{34}O_2$ requires C, 78.31; H, 11.11%); mass spectral peaks at m/e 306 (M^+, 3%), 288 (30), 169 (46), 138 (48), 125 (85) and 95 (100).

Preparation of the diacetate of (172).

A solution of (172) (30mg) in pyridine (3ml) containing acetic anhydride (0.2ml) was stirred at room temperature for 15 hours. The solution was then poured onto water, and extracted with ethyl acetate. The ethyl acetate solution was washed with brine, dried and evaporated to give the diacetate as a yellow oil (25mg,81%); nmr signals at δ 0.95 (3H; s.), 1.10 (6H; s.), 1.20-1.85 (14H; m.), 1.95 (3H; b.s.), 2.19 (6H; s.), 4.65-5.05 (3H; m.), 5.20 (2H; m.) and 6.72 (1H; d.d.; J 17Hz and 10Hz); $\nu_{max}^{CCl_4}$ 2940, 1740, 1230 and 900cm^{-1}; λ_{max}^{EtOH} 239nm; mass spectrum showed M^+ at m/e 390.

Attempted oxidation of the diol (127).

Repeated attempts to effect the required oxidation of (127) using manganese dioxide, Jones reagent and pyridinium chlorochromate were completely unsuccessful.

X-ray analysis of (A).[121]

(A) crystallised from ethyl acetate-light petroleum as orthorhombic crystals; a = 10.3361, b = 24.2304 and c = 7.3077 Å; space group $P2_12_12$; z = 4. A crystal of (A) was exposed to Zr filtered Mo radiation on a Hilger Watts Y290 diffractometer, and the intensities of 1001 independent reflections were measured by the θ,ω scan technique, in the range 2θ = 0-54°. The structure was solved by direct methods and refined by the least squares technique to R = 7.8% .

Diterpenoid (B): M.p. 259-260° (benzene-light petroleum) (Found: C, 75.62; H, 9.66. $C_{20}H_{30}O_4$ requires C, 75.44; H, 9.12%); n.m.r. signals at δ 0.94 (9H; s.), 1.12-1.99 (14H; m.), 4.6-5.2 (3H; m.), 5.52 (1H; d.; J 10Hz), 5.60 (1H; d.; J 16.5Hz), 7.18 (1H; d.d.; J 16.5Hz and 10Hz) and 10.10 (1H; s.); on addition of D_2O, the signal at 4.6-5.2 became 4.84 (1H; d.; J 7Hz) and 5.03 (1H; d.d.; J 8Hz and 6Hz); $\nu_{max}^{CCl_4}$ 3450, 2950, 1675cm^{-1}; λ_{max}^{EtOH} 218 and 273nm (ε 17,000 and 12,100); mass spectral peaks at m/e 318 (M^+, 21%), 149 (73), 134 (90) and 123 (100).

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