SOME BENZO- AND NAPHTHOPYRANS BY NOVEL CYCLISATIONS

a thesis submitted to the

U N I V E R S I T Y O F C A P E T O W N

in fulfilment of the requirements for

the degree of

DOCTOR OF PHILOSOPHY

by

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to my parents

ABSTRACT

It has recently been shown that the naphthalene dimethyl ethers *E*-2-Hydroxymethyl-1,4-dimethoxy-3-pent-1-enylnaphthalene and *E*-2-Hydroxyethyl-1,4-dimethoxy-3-prop-1-enylnaphthalene cyclise to afford naphtho[2,3-*c*]pyrans when treated with two molar equivalents of cerium(IV) ammonium nitrate. It has also been shown that these naphthalenes cyclise readily and in high yield to give naphthopyrans when treated with potassium-*t*-butoxide in dimethylformamide under anaerobic conditions.

In order to determine which structural features present in these compounds are required for each mode of cyclisation, a series of *ortho*-alkenylbenzyl and -naphthyl alcohols, unsubstituted or carrying methoxy or ethyl substituents at appropriate positions on the aromatic ring have been synthesized.

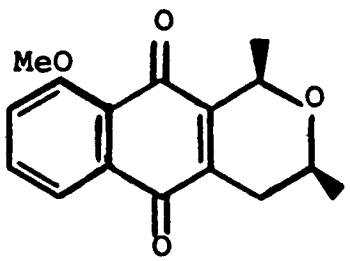
The investigations which were carried out revealed that as far as the cerium(IV) ammonium nitrate reactions were concerned, a methoxy group *ortho* to the alkenyl side chain appeared to be imperative for the success of the reaction. A mechanism for the reaction is proposed.

Although no conclusive general mechanism could be inferred from the results obtained from the base-promoted cyclisations, the explanation for this unusual reaction may involve steric effects, since it was those alcohols in which both the hydroxyalkyl and alkenyl side chains were flanked by bulky groups (forcing the reacting centres into close proximity) which cyclised in high yield.

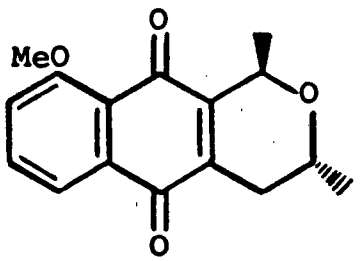
CHAPTER 1

INTRODUCTION

Naphthopyranquinones are widely distributed and well known in nature.[1] Many such compounds have been isolated by various research groups. Examples include the epimeric naphtho[2,3-*c*]-pyran-5,10-quinones eleutherin (1) and isoeleutherin (2) which were first isolated from the tubers of *Eleutherine bulbosa* by Schmid and co-workers.[2]

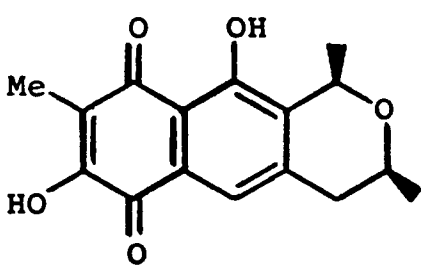


(1)



(2)

Ventilagone (3), being the 6,9 quinone of the naphtho[2,3-*c*]pyran ring system and therefore analagous to the eleutherins, was isolated from the root bark of *Ventilago viminalis* by Cooke and Johnson.[3-5]



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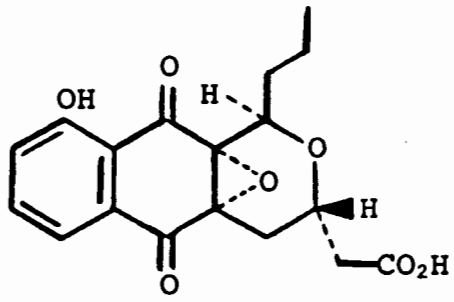
Naphthopyranquinones of microbial origin include frenolicin (4)[6] and granaticin (5),[7] isolated from certain Streptomyces species.



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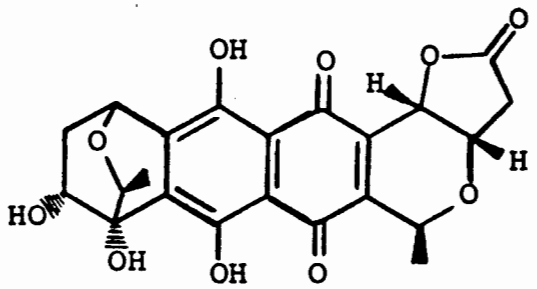
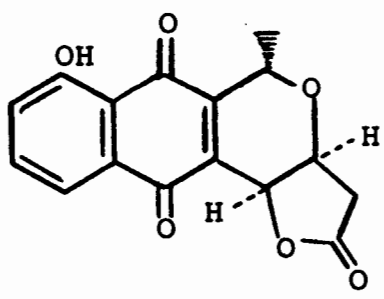


(5)

Nanaomycin D (6)[8] and griseusin A (7)[9] are structurally related by virtue of a pyrano-γ-lactone moiety fused to a 5-hydroxy-naphthoquinone skeleton. Such a combination results in compounds that would be ideally suited to function as dialkylating agents.[10]



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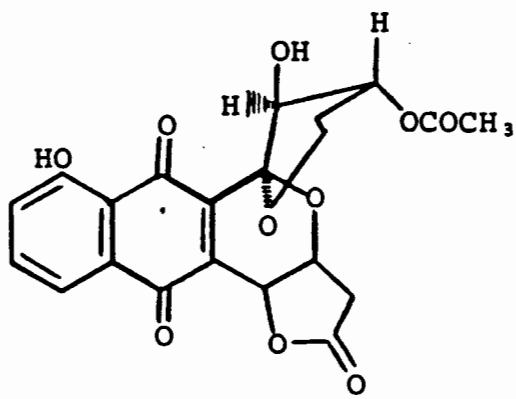

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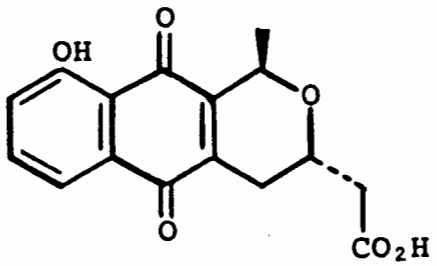
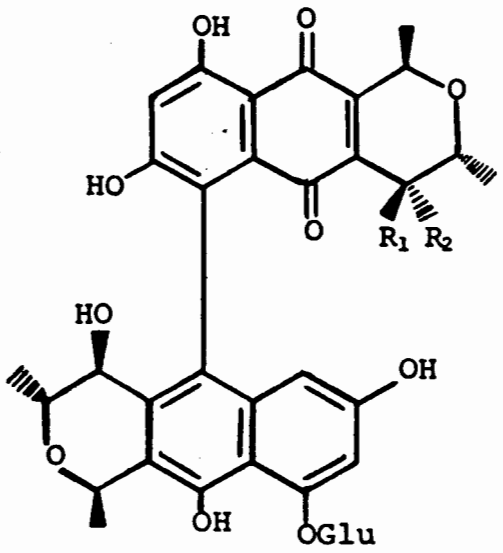
Nanaomycin A (8)[11] is another example of the group of naphtho-quinone antibiotics which is based on the naphthopyran skeleton.



(8)

A milestone in naphthopyranquinone chemistry was reached in 1947 by Lord Todd and his colleagues with their extensive investigation of the aphins, a well known family of aphid pigments,[12] and since a considerable portion of this thesis is related to compounds of this type, they will be discussed in some detail here.

Protoaphins are brownish-yellow, hygroscopic and acidic pigments that are essentially binaphthyl derivatives. They undoubtedly arise from simpler precursors by phenolic coupling, these precursors being natural products in their own right. Protoaphin-*fb* (9) was first isolated from the haemolymph of the broad bean aphid *Aphis fabae* Scop, but has subsequently been found in numerous other species of Aphididae. Protoaphin-*sl* (10), a compound closely structurally related to protoaphin-*fb*, was isolated from *Tuberolachnus salignus* Gmelin. Cameron and Banks[13] isolated deoxyprotoaphin (11) from *Dactynotus cirsii* in 1972, a compound differing from the two epimers above in that it lacked the hydroxy group at their epimeric centre. The relatively weak linkage between the quinone and naphthalenic glucoside moieties was cleaved by mild reduction, using either sodium dithionite[14]

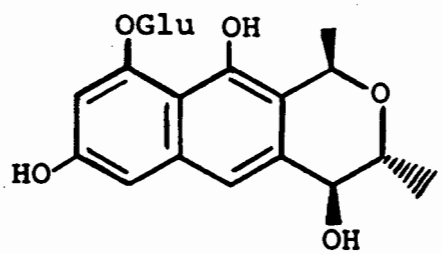


(9) R_1 = OH, R_2 = H

(10) R_1 = H, R_2 = OH

(11) R_1 = R_2 = H

or by catalytic hydrogenation.[15] The systematic simplification brought about by the cleavage of the binaphthyl linkage considerably expedited structure elucidation. Protoaphin-*fb* (9) gave both a glucosidic component, glucoside B (12) and an acidic, orange quinone, *viz*. quinone A (13) after reduction and aerial reoxidation.



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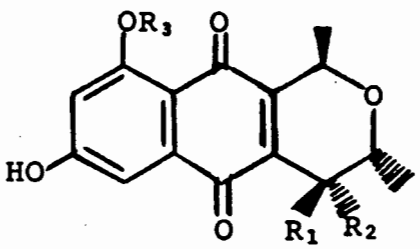


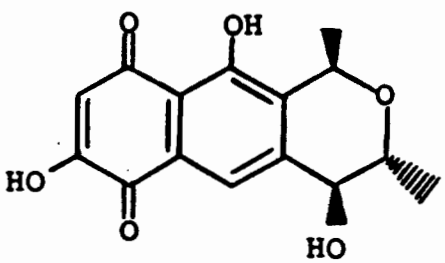
(13) R_1 = OH, R_2 = H, R_3 = H

(14) R_1 = H, R_2 = OH, R_3 = H

(15) R_1 = R_2 = R_3 = H

(16) R_1 = OH, R_2 = H, R_3 = Glucosyl

Protoaphin-*sl* (10), although giving the same glucoside (12), afforded a different quinone, quinone (A)' (14) when subjected to the same treatment. Deoxyprotoaphin (11) similarly gave glucoside B (12), and deoxyquinone A (15). The structures and absolute stereochemistry of these compounds were formulated by comparing the fragments obtained upon various degradations to known compounds of established absolute stereochemistry, e.g. D,D-(+)dilactic acid, as well as through detailed analyses of their n.m.r. spectra.[16] Further proof of the structural relationship between these compounds was obtained by the oxidation of glucoside B (12) with Fremy's salt[14] to quinone A glucoside (16) and an even more acidic quinone, thought to be (17). The β-configuration of the glucosyl moiety was confirmed by its facile



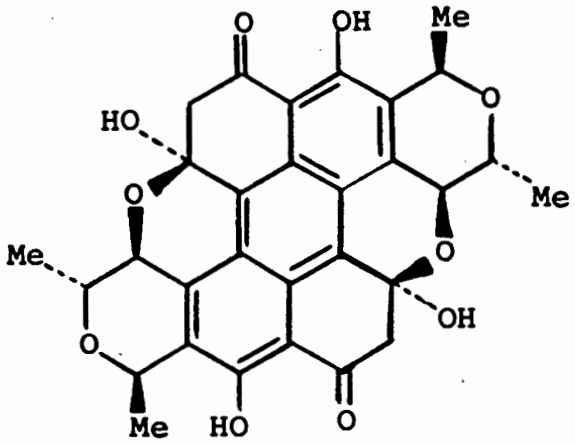
(17)

hydrolysis on treatment with almond emulsin whereas α-glucosidases did not effect this cleavage.[17] The benzylic hydroxy group of quinone A (13) was reductively removed with alkaline sodium stannite to give deoxyquinone A (15).[18]

The *in vitro* linkage of the two halves of the protoaphins can be achieved with remarkable ease,[15] but it seems highly likely

that the *in vivo* formation involves a coupling reaction between them at some stage.

Difficulties were encountered with the initial isolation of the protoaphins because of their lability in biological systems. Their lability stems from the presence of enzymes in many aphid species which are capable of bringing about a series of transformations starting with the hydrolysis of the glucosidic linkage.[19] A highly stable perylenequinone, erythroaphin, is usually obtained as the final product in the series. Careful deactivation of this enzyme system is necessary before the isolation of protoaphins becomes possible. This can be achieved either by use of organic solvents[19] or by heating.[20] A typical series would be protoaphin-*fb* (9) being converted successively to the highly fluorescent xanthoaphin-*fb* (18), chrysoaphin-*fb* (19) and finally erythroaphin-*fb* (20). Erythroaphin-*fb* (20) has been obtained by the epimerisation of erythroaphin-*sl* (21),[22] and *vice versa*. The oxidative coupling of glucoside B (12) with potassium ferricyanide gave the erythroaphin diglucoside (22) which underwent facile hydrolysis to erythroaphin-*fb* (20) in dilute acid. This in effect constitutes a partial synthesis[22] of erythroaphin-*fb* (20) and erythroaphin-*sl* (21).



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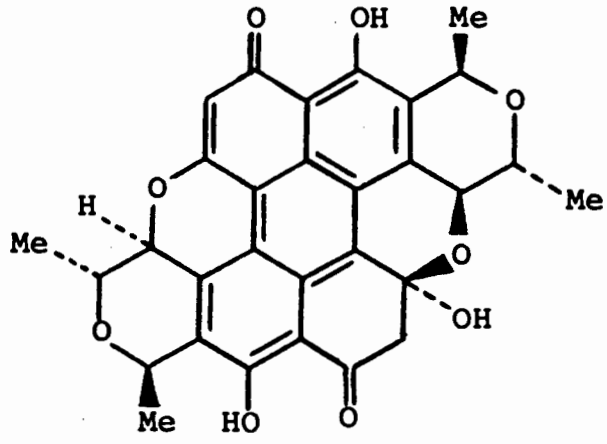

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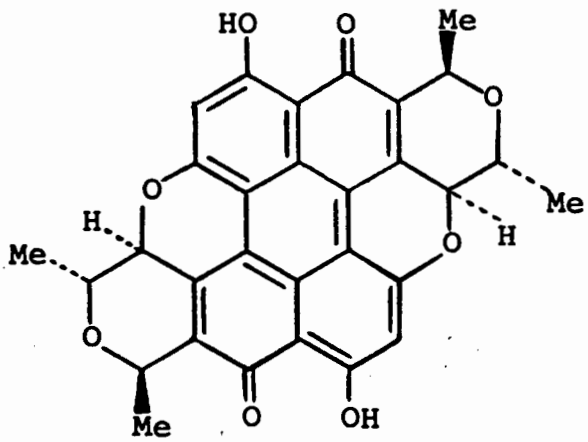

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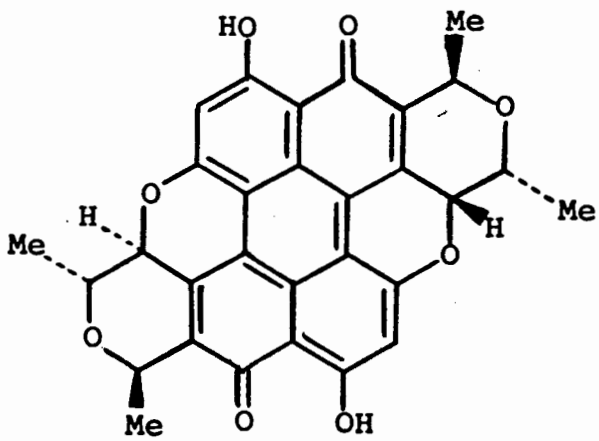

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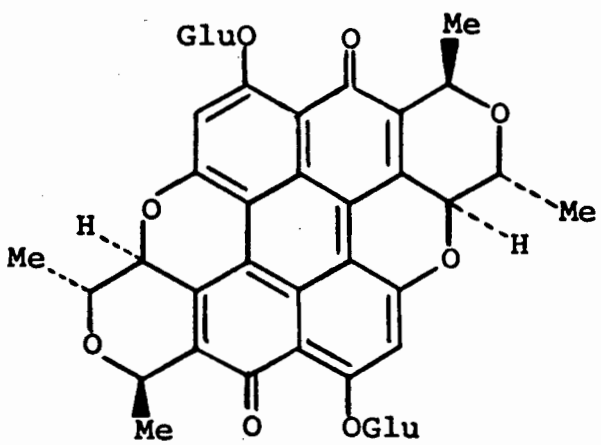

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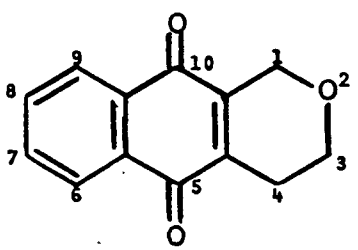
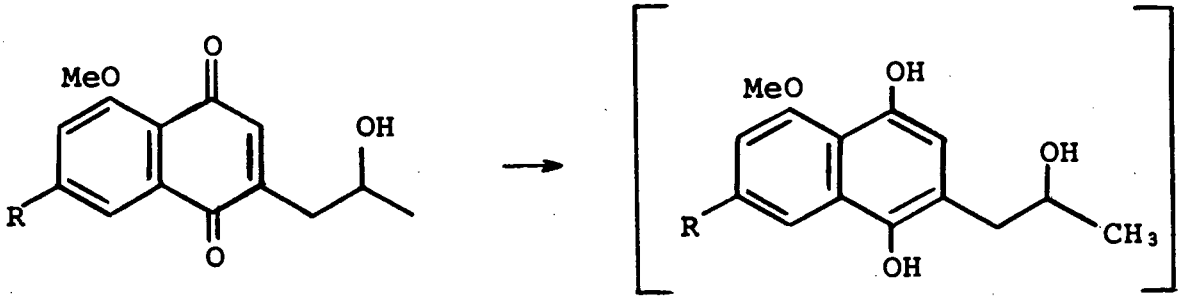
CHAPTER 2

SOME LITERATURE METHODS FOR THE SYNTHESIS OF NAPHTHOPYRANQUINONES

Various methods have been reported for the construction of the naphtho[2,3-*c*]pyran ring system. The synthesis of eleutherin



(1) and isoeleutherin (2) was initially reported by Schmid and Eisenhuth in 1958.[23] The crucial step involved the reduction of the quinone (23) to the quinol (24), which was condensed with

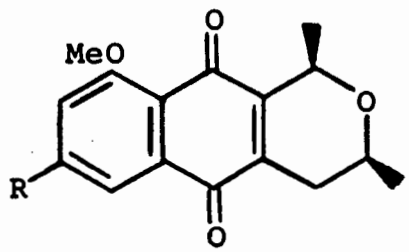


(23) R = H

(25) R = OMe

(24) R = H

(26) R = OMe



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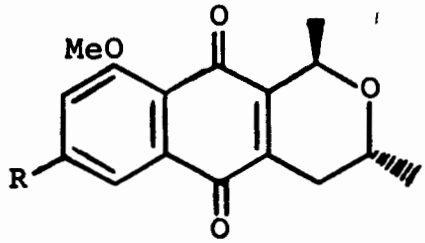


(1) R = H (2) R = H

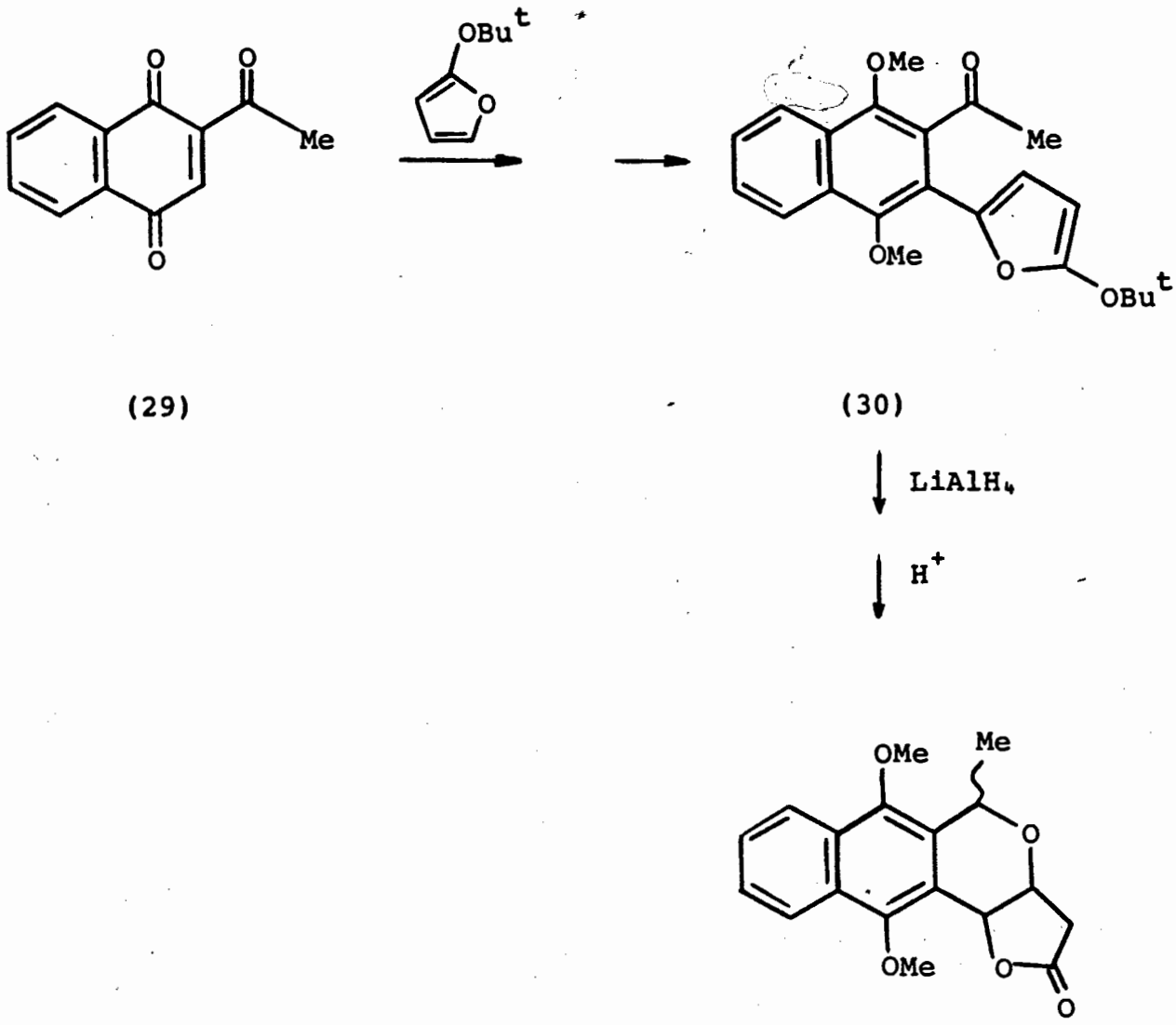
(27) R = OMe (28) R = OMe

acetaldehyde and reoxidised to yield a racemic mixture of the epimers (1) and (2).

A similar approach was recently used by Cameron[24] in his synthesis of the natural products (±)-7-methoxyeleutherin (27)[25] and (±)-deoxyquinone A dimethyl ether (28). In an adaptation of the Schmid synthesis, the dimethoxyquinone (25) was reduced to the quinol (26) with an excess of zinc and hydrochloric acid in tetrahydrofuran and allowed to react with acetaldehyde. A mixture of (±)-7-methoxyeleutherin (27) and (±)-deoxyquinone A dimethyl ether (28) was obtained after atmospheric reoxidation.

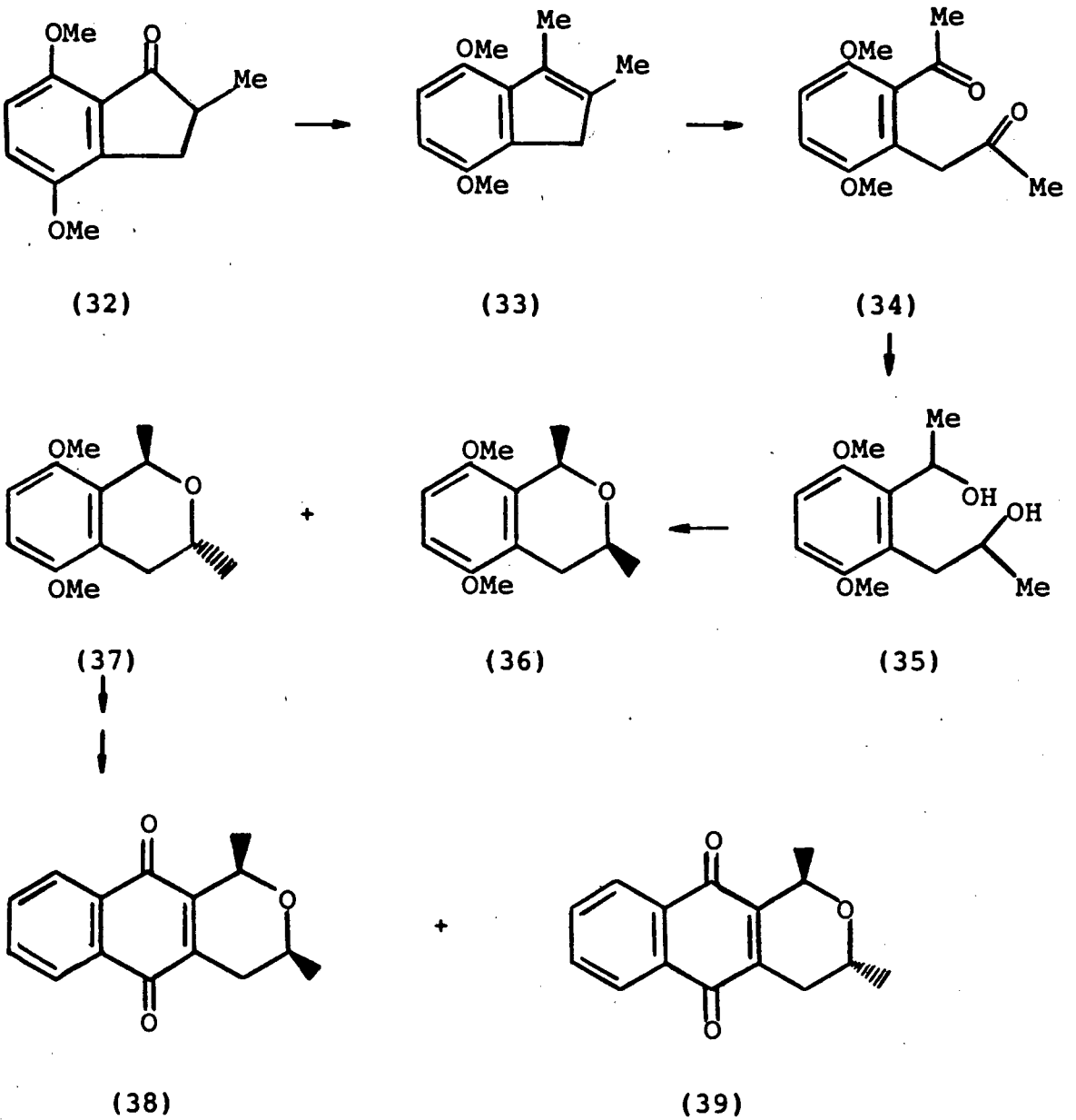
Alternative syntheses of the naphtho[2,3-*c*]pyran ring system have been considered. An approach by Kraus[26] featured the Michael addition of a butenolide anion equivalent, 2-*t*-butoxy-furan, with the acetylnaphthoquinone (29).

The condensation product (30) was then reductively cyclised to give the γ-lactopyran derivatives (31).



(29) (30) (31)

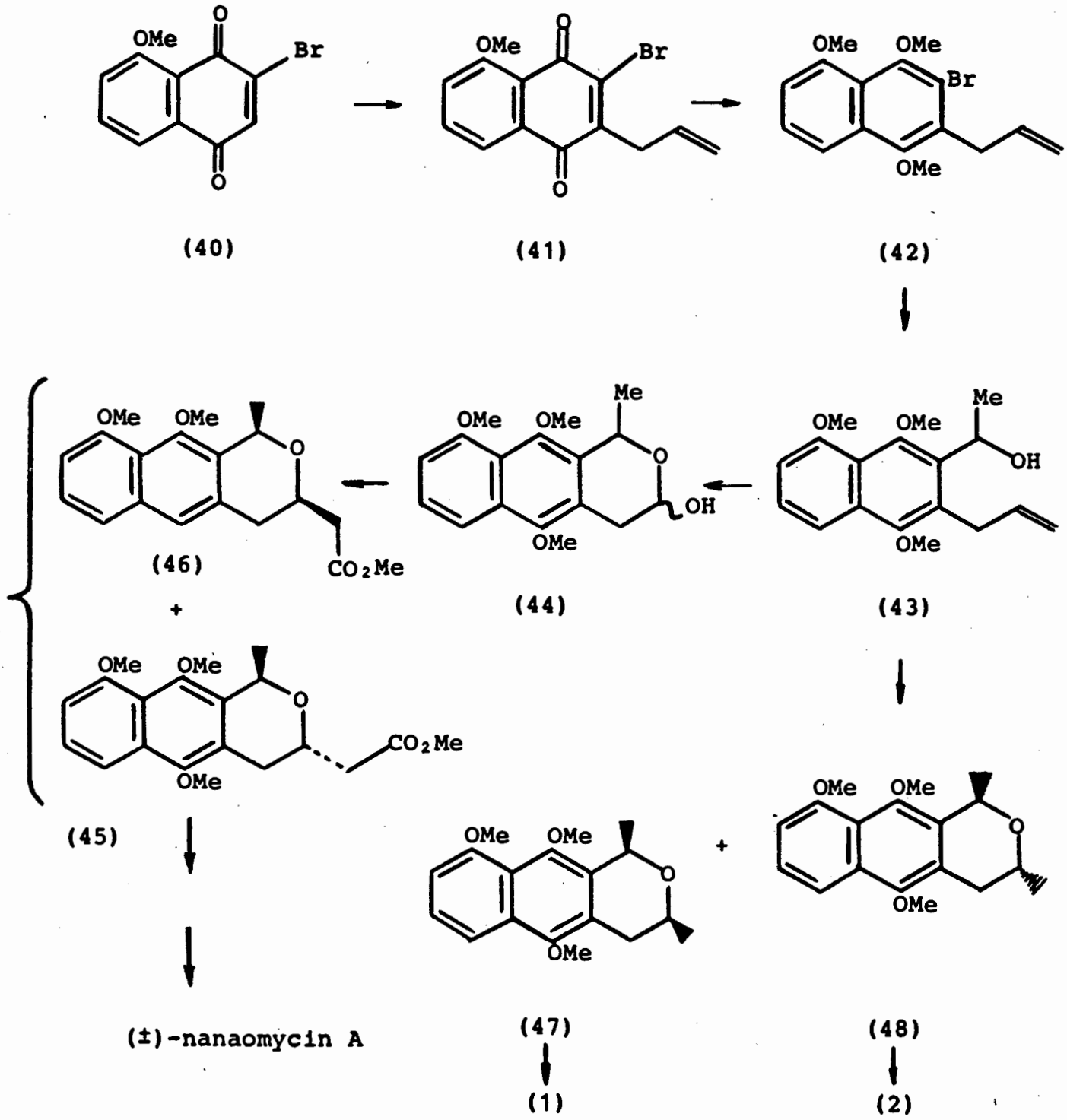
An investigation of the use of readily accessible indanone derivatives as precursors of the pyranonaphthoquinone ring system was undertaken by Yoshii and Kometani in 1981.[27] (See Scheme I). In this fashion the indanone (32) was reacted with methylmagnesium iodide to yield the tertiary alcohol which readily dehydrated to afford the indene (33) upon shaking in ether with dilute hydrochloric acid. Oxidative cleavage of the double bond of the indene produced diketone (34), which was



Scheme I

transformed into the diol (35) with lithium aluminium hydride. The diol (35) gave rise to the isomers (36) and (37) after being subjected to acid-catalysed cyclisation. Individual oxidative demethylation of the isochromans (36) and (37) followed by benzannelation employing 1-acetoxy-buta-1,3-diene ultimately furnished 9-demethoxyeleutherin (38) and 9-demethoxyisoeleutherin (39) respectively.

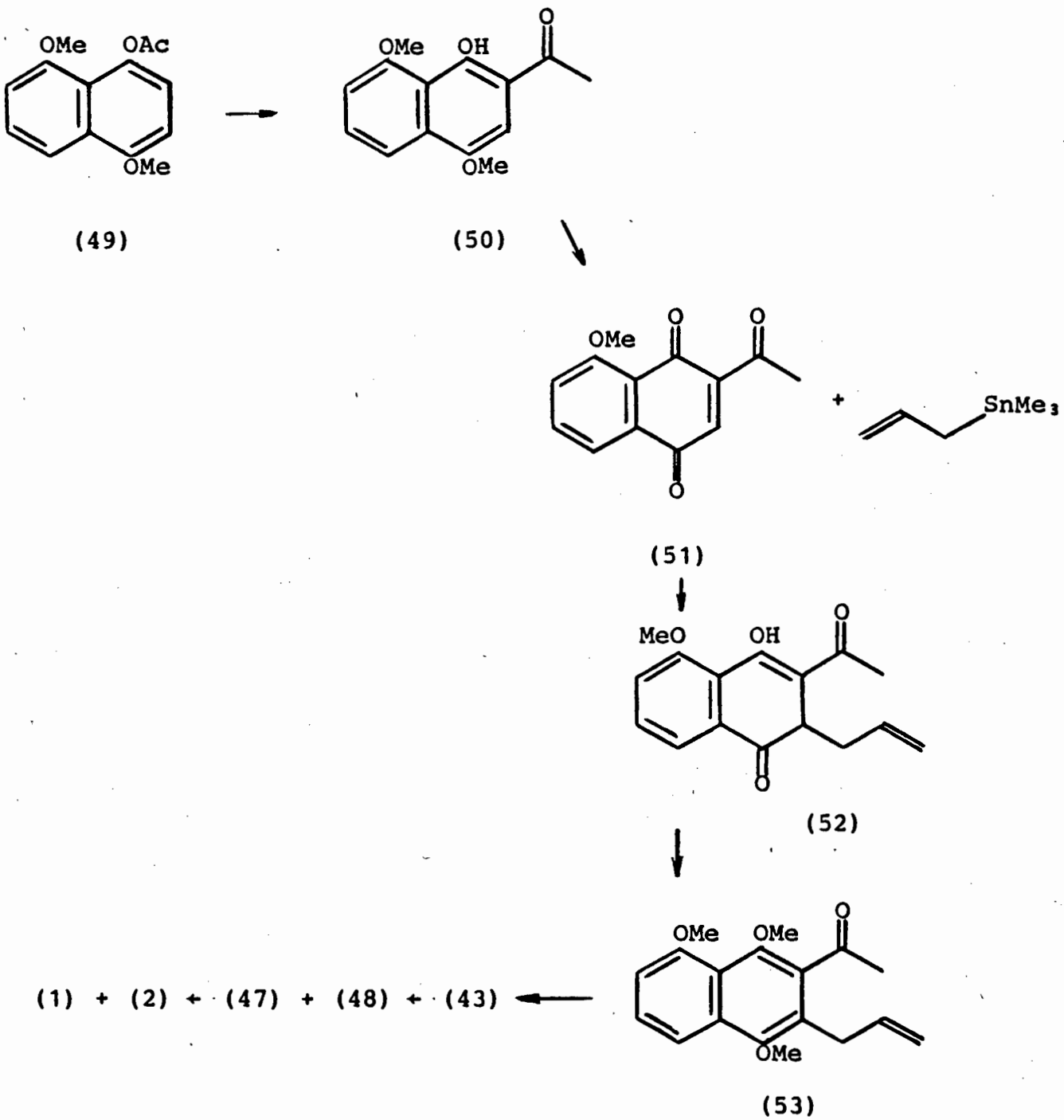
In a concurrent paper Yoshii *et al.*[28] described a different route for the synthesis of nanaomycin A (8), eleutherin (1) and isoeleutherin (2) starting with the oxidative alkylation of 2-bromo-8-methoxy-1,4-naphthoquinone (40) with vinylacetic acid in the presence of persulphate and silver nitrate (see Scheme II).



Scheme II

The 2-allyl derivative (41) obtained was reduced and then methylated to give the trimethoxynaphthalene (42). Treatment of (42) with butyl-lithium and subsequent addition of acetaldehyde resulted in the formation of the key naphthylcarbinol (43). The latter compound could be employed in two ways: (a) Entry to the nanaomycins was gained by oxidation with osmium tetraoxide-sodium metaperiodate to afford the intermediate diastereomeric mixture of lactols (44), which in turn was subjected to Wittig-Horner reaction conditions employing trimethyl phosphonoacetate and sodium hydride to yield the isomeric naphthopyrans (45) and (46), the former compound being a precursor to (±)-nanaomycin A (8), and (b) direct acetoxymercuration-demercuration of the naphthylcarbinol (43) led to the formation of (±)-eleutherin (1) and (±)-isoeleutherin (2) *via* their respective cyclic precursors (47) and (48).

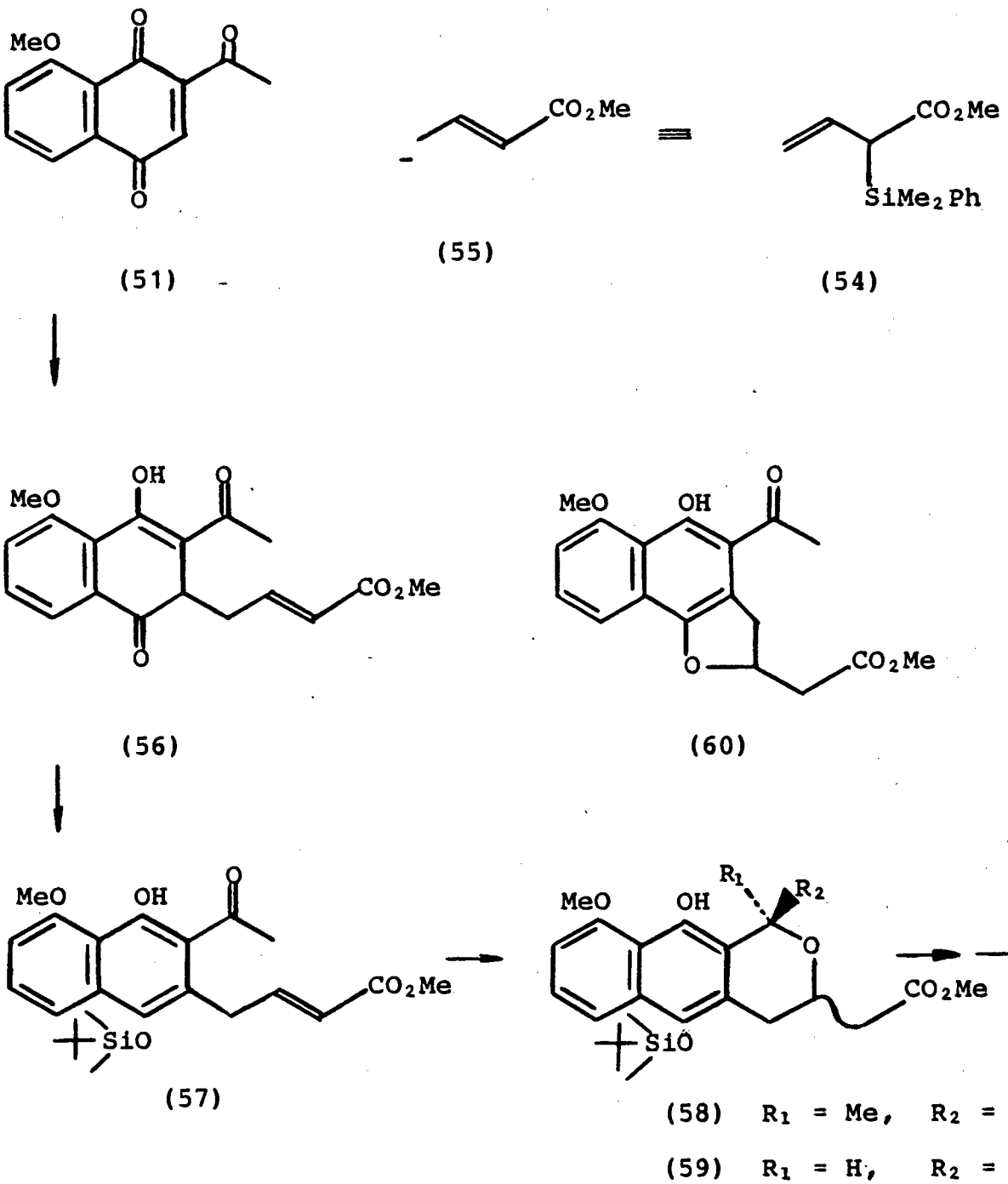
Maruyama and co-workers[29] also managed to prepare the strategic naphthylcarbinol (43) in 1981 by utilizing a different plan. Their synthetic approach required large quantities of 2-acetyl-8-methoxy-1,4-naphthoquinone (51), which they prepared by the Fries rearrangement of 1-acetoxy-4,8-dimethoxy-naphthalene (49) to give naphthol (50), followed by oxidative demethylation with cerium(IV) ammonium nitrate (CAN) (see Scheme III). Nucleophilic addition of allyltrimethylstannane to (51) with boron trifluoride etherate selectively afforded the conjugate adduct (52) after hydrolysis. The allylated product (52) was methylated to the corresponding hydroquinone dimethyl ether (53), the ketone moiety of which was reduced to the benzylic alcohol (43). Cyclisation of (43) was effected as previously described.


OMe
OAc
OMe
(49)
OMe
OH
O
OMe
(50)
OMe
O
O
O
+
SnMe3
(51)
MeO
OH
O
O
(52)
OMe
OMe
O
OMe
(53)
(1) + (2) ← (47) + (48) ← (43)

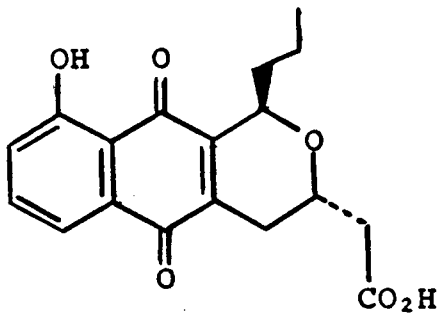
Scheme III

The construction of the required naphthopyranquinone skeleton *via* Michael addition between a benzylic alcohol and an α,β-unsaturated carboxylic acid ester was envisioned by Maruyama in his synthesis of (±)-nanaomycin A.[30] It was noted that the stepwise construction of the required framework lacked efficiency in certain preceeding synthetic efforts. Central to their strategy was the requirement that addition of the 3-alkoxycarbonylallyl group took place at the quinonoid nucleus of the 3-acyl-1,4-naphthoquinone. To satisfy this requirement methyl 2-(dimethylphenylsilyl)-3-butenoate (54) was developed as a new synthetic equivalent of the 3-methoxycarbonylallyl anion (55). Thus, quinone (51) underwent Michael addition when treated with allylsilane (54) in the presence of a Lewis acid [employed to overcome the lack of nucleophilicity of (54) as a Michael donor]. The conjugate adduct (56) was immediately converted to the corresponding monosilyl ether (57) to avoid intramolecular cyclization to the undesirable dihydrofuran derivative (60). Reduction of the silyl ether (57) with sodium borohydride followed by base catalysed intramolecular addition afforded a mixture of stereoisomers (58) and (59), which, in turn, yielded the target molecules after separation, oxidation and demethylation.

Other recent attempts at the formation of the naphthopyran skeleton include a synthesis of deoxyfrenolicin (61) by Semmelhack[31] in which extensive use of organometallic methods was made. It was reasoned that while naphthoquinone precursors were reasonably efficient for the synthesis of frenolicin (4) and nanaomycin A (8), they were less attractive to synthesize the structurally more complex naphthopyranquinones such as


MeO
O
O
O
CO2Me
CO2Me
SiMe2Ph
(51)
(55)
(54)
OH
MeO
O
CO2Me
(56)
MeO
OH
O
O
CO2Me
(60)
MeO
OH
O
SiO
CO2Me
(57)
R1
R2
MeO
OH
O
SiO
CO2Me
(58) R1 = Me, R2 = H
(59) R1 = H, R2 = Me

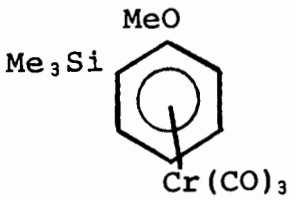
Scheme IV



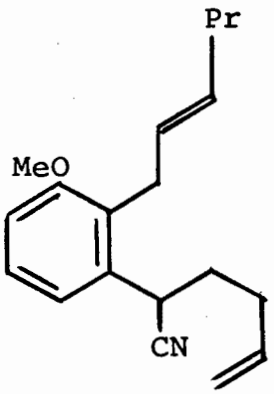
(61)

granaticin (5), for example, where alicycles would have to be added to both rings of the naphthoquinone. A more general procedure was thus envisaged, starting from a simple monocyclic aromatic ring to which the appropriate substituents could be coupled. This method was based on observations that substitutions in anisole derivatives could be achieved with high efficiency and selectivity by the addition/oxidation method for coupling of carbon nucleophiles with η^6-(anisole)tricarbonylchromium complexes.[32]

The relevant η^6-arenetricarbonylchromium complex (62) was no exception and proved to be well suited for the preparation of the multiply substituted aromatic derivative (63) after metallation and condensation with the apposite reactants (*E*)-2-hexenyl bromide and the simple secondary cyano-stabilized anion (64) (see Scheme V). Oxidative decyanation of (63) followed by selective epoxidation of the disubstituted bond gave (65), which could be cyclised to a mixture of isomers (66) and (67) *via* their enol silyl ethers. Pyran ring formation was prompted by the treatment of (66) with a mixture of palladium dichloride and



(62)



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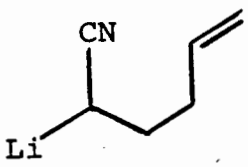
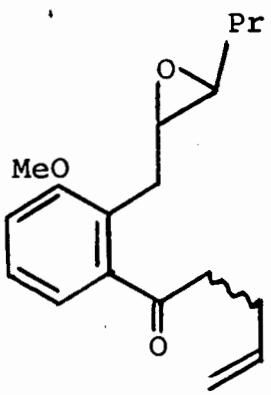


(64)



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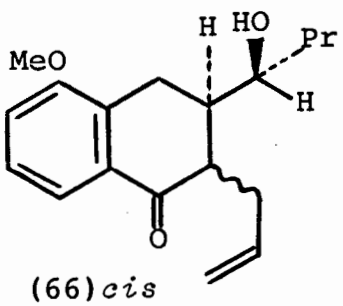
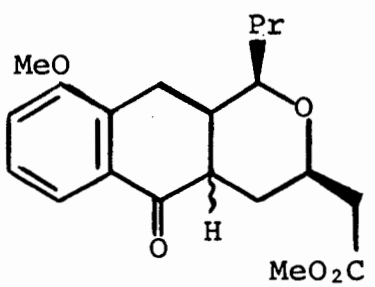
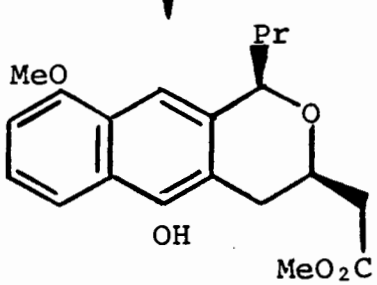


(66) *cis*

(67) *trans*



(68) / (69)



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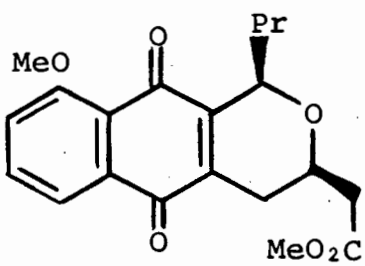


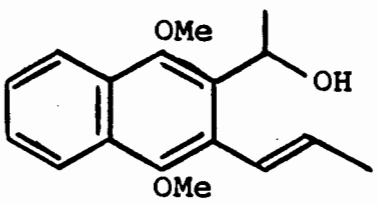
(71)

(61)

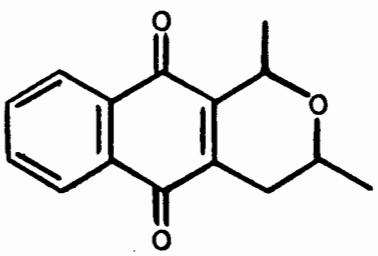
Scheme V

cupric chloride in methanol under carbon monoxide to give the isomeric mixture (68)/(69). Indirect aromatization of this mixture afforded naphthol (70) which in turn was converted by Jones oxidation conditions to naphthoquinone (71); this compound constituted deoxyfrenolicin after demethylation and equilibration of the side chains with concentrated sulphuric acid.

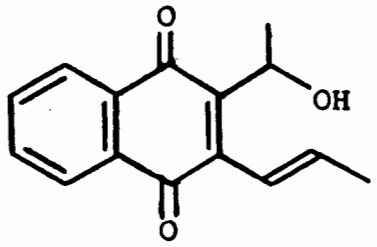
An investigation into the synthesis of naturally occurring quinones of the eleutherin type has also been undertaken at this university, when Professor Giles and his group attempted to cyclise the alcohol (72) to the naphthopyran (73) via the quinone (74) using argentic oxide as oxidant.[33] However, when the oxidative cyclisation of the naphthalene dimethyl ether (72) was undertaken, it was found that this intramolecular Michael-type addition of (74) to (73) did not take place as the reaction provided the quinonoid alcohol (74) as the sole product, which exhibited little proclivity to undergo cyclisation in the required manner (arrows).



(72)



(73)



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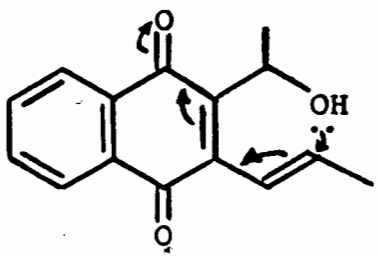
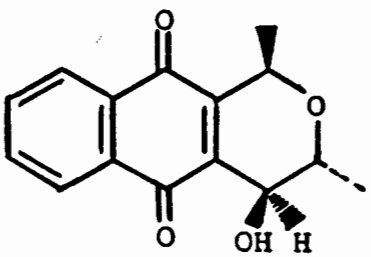
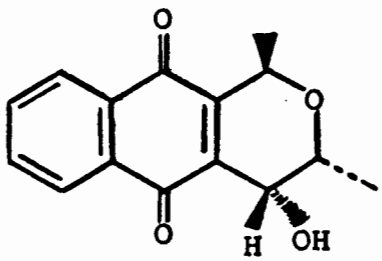


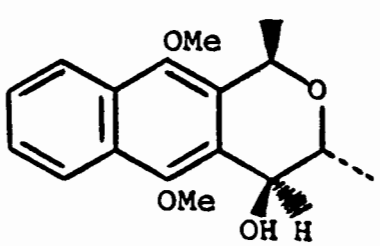


(75)

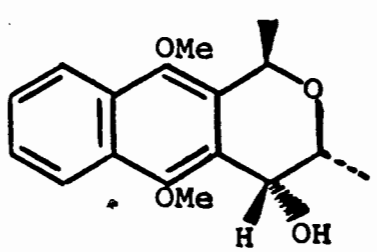


(76)

Oxidation of the same dimethyl ether (72) with cerium(IV)ammonium nitrate afforded a mixture of the two naphthopyranquinones (75) and (76) as their racemates. That cyclisation preceded oxidation in this reaction is patent from the failure of quinone (74) to cyclise with two moles of cerium(IV)ammonium nitrate to (73), whilst the dimethyl ether (72) gave rise to the two naphthopyrans (77) and (78).[34] Compounds (77) and (78) each



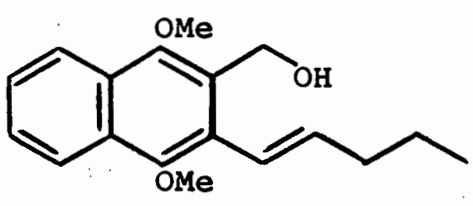
(77)



(78)

separately reacted with two moles of cerium(IV) ammonium nitrate to afford the quinones (75) and (76) respectively. This one-step conversion of the naphthalene dimethyl ether (72) to the naphtho[2,3-*c*]pyran-5,10-quinones (75) and (76) was of considerable value since these products are the 7,9-dideoxy derivatives of quinone A (13) and quinone A' (14) respectively, possessing the correct relative stereochemistries in each case at C-1, C-3, and C-4.

The generality of this unusual cyclisation was supported by the corresponding oxidative cyclisation of the primary alcohol (79) to yield the naphthopyranquinones (80) and (81).[34]



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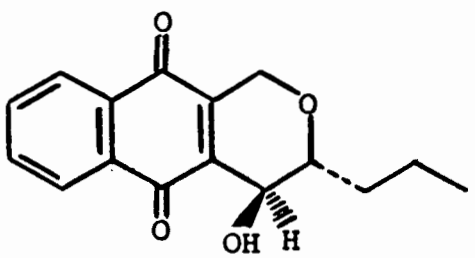
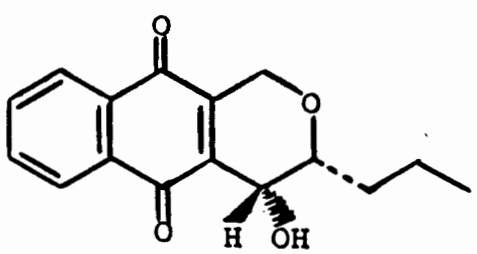


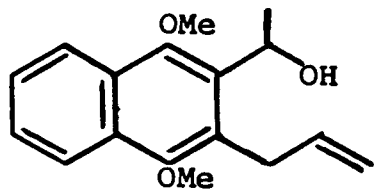
(80)



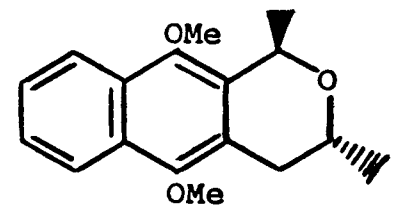
(81)

A further method of synthesizing naphthopyrans was discovered in these laboratories which entailed the base-induced cyclisation of naphthalenes. Examples involved the ring closure of the

unconjugated alkenyl alcohol (82) in remarkably high yield to the pyran (83) when treated with potassium *t*-butoxide in dimethylformamide under nitrogen.[35] The isomeric conjugated compound (72)

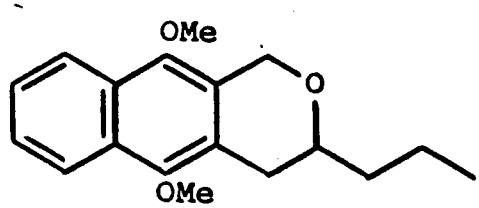


(82)

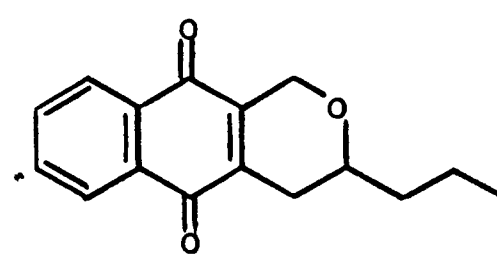


(83)

cyclised equally well under the same conditions. These reactions were of particular importance since they provided the naphthopyran (83) stereoselectively in which the two pyran ring methyl groups could be obtained virtually exclusively *trans*. Cyclisation of (82) and closely related substrates to (83) and its analogues has been observed very recently by other groups,[28,29] but the conditions were non-basic and provided a stereoisomeric mixture of compound (83) and the corresponding *cis*-dimethyl product. Similarly, the *ortho*-pentenyl naphthyl alcohol (79) underwent base-induced cyclisation to the pyran (84), and oxidative demethylation with cerium(IV) ammonium nitrate provided the related quinone (85).[37]



(84)



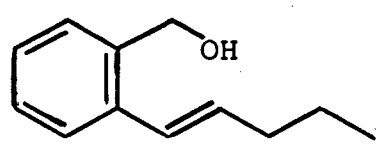
(85)

While the latter oxidative demethylation of hydroquinone dimethyl ethers to quinones with cerium(IV) ammonium nitrate[38] has become routine and is understood mechanistically, the initial cyclisations of the naphthalenes to the naphthopyrans, both with cerium(IV) ammonium nitrate [e.g. (72) to afford (77) and (78)], and with base [e.g. (72) or (82) to yield (83)], were novel and required investigation.

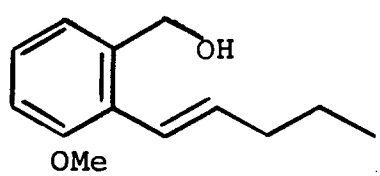
CHAPTER 3

AN INVESTIGATION INTO THE FORMATION OF BENZO- AND NAPHTHOPYRANS BY CYCLISATION OF *ortho*-ALKENYL(HYDROXYALKYL)ARENES USING EITHER CERIUM(IV) AMMONIUM NITRATE OR POTASSIUM *t*-BUTOXIDE IN DIMETHYLFORMAMIDE

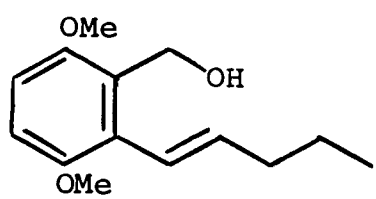
In order to determine which structural features are required in compounds (72) and (79) for each mode of cyclisation, it was decided to synthesize analogues (86), (87), (88) and (89) of compound (79) which lack one or more of the functionalities present in (79). It was hoped that in so doing, greater insight into the scope and limitations of these reactions could be obtained.



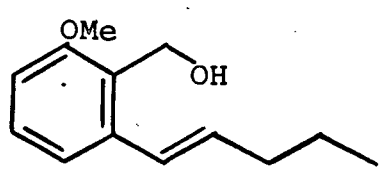
(86)



(87)



(88)



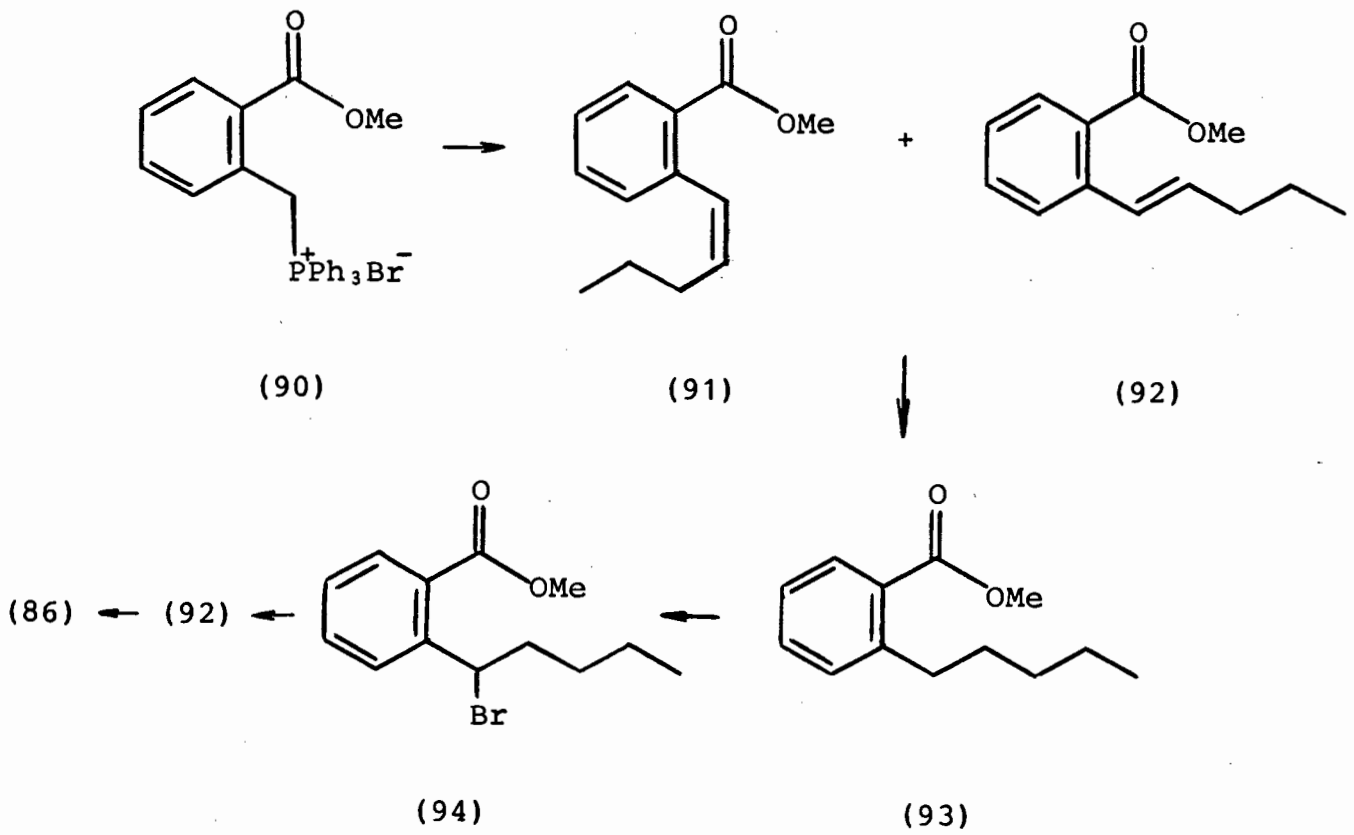
(89)

In formulating syntheses of compounds (86) → (89), two structural requirements had to be met. First, the alkenyl and hydroxyalkyl

substituents were required to be *ortho* to each other, and secondly, it was desirable that the double bond should adopt solely the (*E*)-stereochemistry, as it does in compound (79), to avoid any potential stereochemical differences between the reactants already observed and those in the study to be undertaken. Furthermore, it was more expedient to work with pure isomers.

An initial attempt to synthesize (*E*)-2-pent-1-enylbenzyl alcohol (86) (Scheme VI) involved the establishment of the double bond by a Wittig reaction. The phosphonium salt (90)[39] was boiled with butanal in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene (DBN) to yield a mixture of the (*Z*)-(91) and (*E*)-(92) products in 60% yield after chromatography. That a stereochemical mixture was obtained was borne out by the ^{1}H n.m.r. spectrum of the product which showed a doublet (*J* 11 Hz) at δ6,87 coupled to a doublet of triplets (*J* 7 and 11 Hz) at δ5,73, supporting the presence of the (*Z*)-isomer, together with a doublet (*J* 16 Hz) at δ6,70 coupled to a doublet of triplets (*J* 7 and 16 Hz) at δ6,14 indicating the (*E*)-isomer. Integration of the ^{1}H n.m.r. spectrum signals at δ5,73 and 6,14 showed that the (*E*)- and (*Z*)-isomers were formed in approximately equal proportions. It was hoped that the mixture could be isomerised to afford solely the (*E*)-isomer (92) by the two-step process of hydrogenation to yield the saturated compound (93) followed by benzylic bromination/dehydrobromination since dehydrobromination would be expected to afford only the (*E*)-isomer. This mixture of alkenes was hydrogenated to the alkane (93) using palladium on carbon as catalyst. The ^{1}H n.m.r. spectrum of (93) showed the absence of the olefinic signals observed for the starting compounds

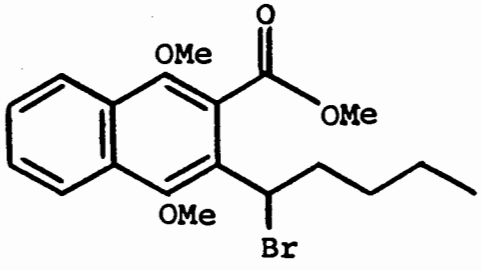
(91) and (92); these were replaced by, *inter alia*, a triplet



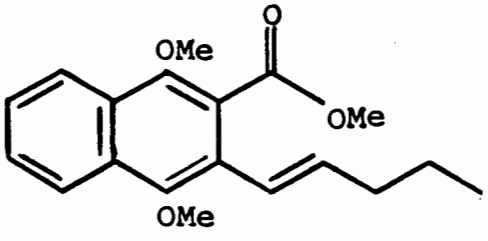
Scheme VI

for the benzylic protons of the product resonating at δ2.96. The saturated ester (93) was brominated with *N*-bromosuccinimide to the benzylic bromide (94), this change being accompanied by the disappearance of the triplet at δ2.96 and the appearance of a new one-proton triplet at δ6.18 due to the benzylic hydrogen on the carbon now bearing bromine. Despite various attempts to dehydrobrominate (94), including the use of boiling 2,6-lutidine, the desired (*E*)-product (92) was not readily obtained. Thus the final step envisaged in Scheme VI, the lithium aluminium hydride

reduction of pure ester (92) to the corresponding alcohol (86), could not be undertaken at this stage. This failure of the bromo ester (94) to undergo the requisite dehydrobromination was in sharp contrast to the smooth dehydrobromination of the bromo ester (95), which afforded the olefin (96) in a yield of at least 93% using 2,6-lutidine under reflux.[34] Other related dehydrobrominations, as in the syntheses of the juglomycins A and B[40] have also been shown to occur readily. The different

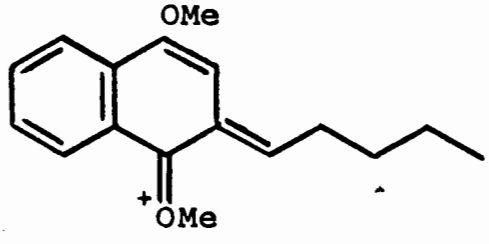


(95)



(96)

behaviour of the bromide (94) now under consideration was ascribed to the fact that it lacked the methoxy group *ortho* to the benzyl bromide present in (95). The presence of the methoxy group might well facilitate the loss of bromide to give an ion such as (97), which would subsequently readily lose a proton to give the observed product. Thus, when bromide (94) was boiled for

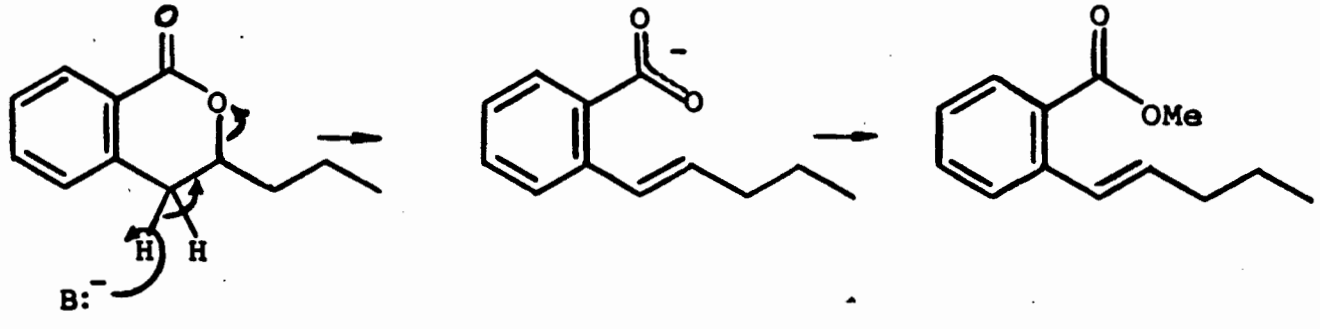


(97)

varying times with lutidine, either no reaction took place, or the bromide was destroyed. When the reaction was attempted at lower temperatures, the starting material (94) was recovered.

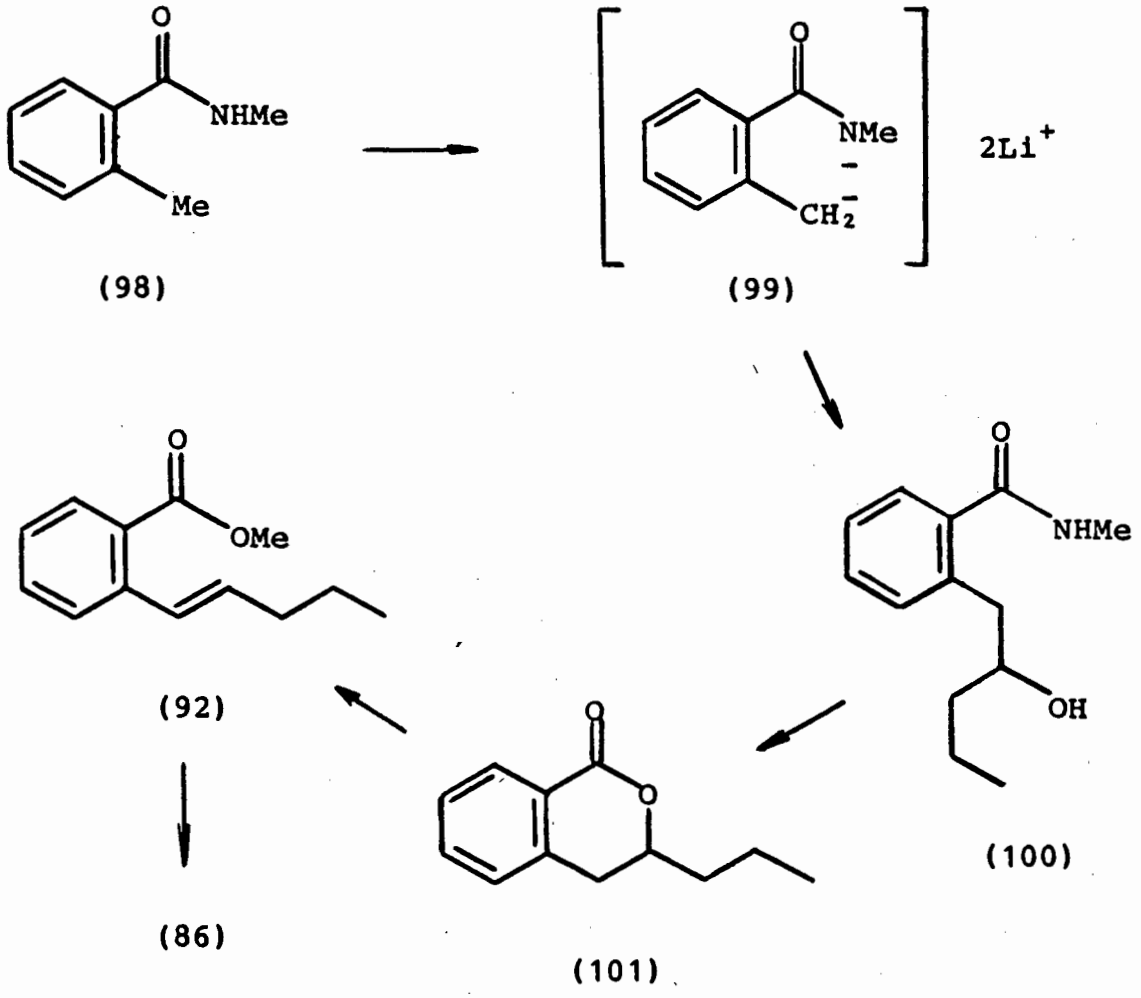
The use of other bases was subsequently investigated. Potassium *t*-butoxide had no effect, the starting material being recovered unchanged. Treatment of (94) with 1,5-diazabicyclo[4.3.0]non-5-ene caused extensive degradation as evidenced by the lack of a significant methoxy signal in the ^1H n.m.r. spectrum of the crude reaction mixture. However, a low-intensity doublet of triplets was present in the olefinic region, suggesting that some elimination might have occurred.

New routes to compound (86) were explored because of diverse difficulties experienced with the dehydrobromination of compound (94). It was envisaged that the δ-lactone (101), possessing the required substitution pattern, would constitute a valid synthetic precursor to compound (92). The plan entailed the ring-opening of the δ-lactone (101) with base, followed by the quenching of the derived carboxylate anion with a methylating agent to form the desired ester. Furthermore, it should be noted



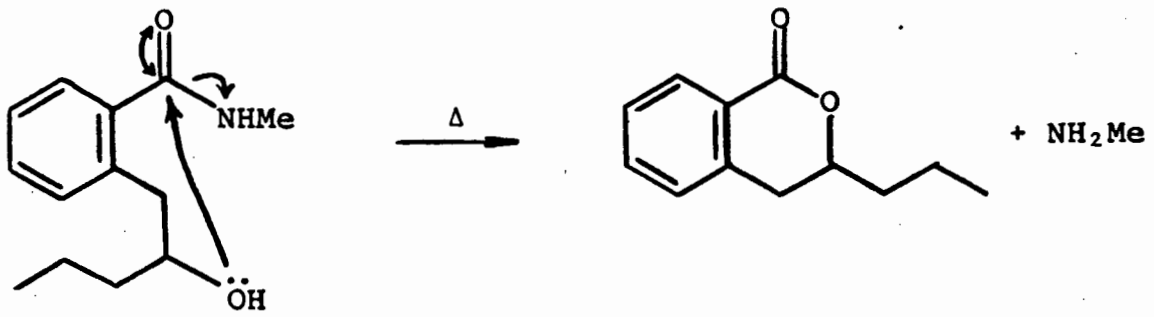
(101) (92)

that this alternative scheme provided the formation of the (*E*)-isomer as the sole product. This occurs because the proton anti-periplanar to the C-O linkage is selectively abstracted by the base. The strategy for the synthesis of the δ-lactone (101) (Scheme VII) was to convert the starting material, *N*-methyl-*o*-toluamide (98) into its dilithio salt (99) with n-butyl-lithium.[41,42] Freshly distilled butanal was then allowed to condense with the salt (99) in solution to give the crude hydroxyamide (100).



Scheme VII

Pyrolysis of this amide afforded the lactone (101) in a yield of 40% from the amide (98) after chromatography. Throughout the course of the reaction methylamine was liberated. The mass

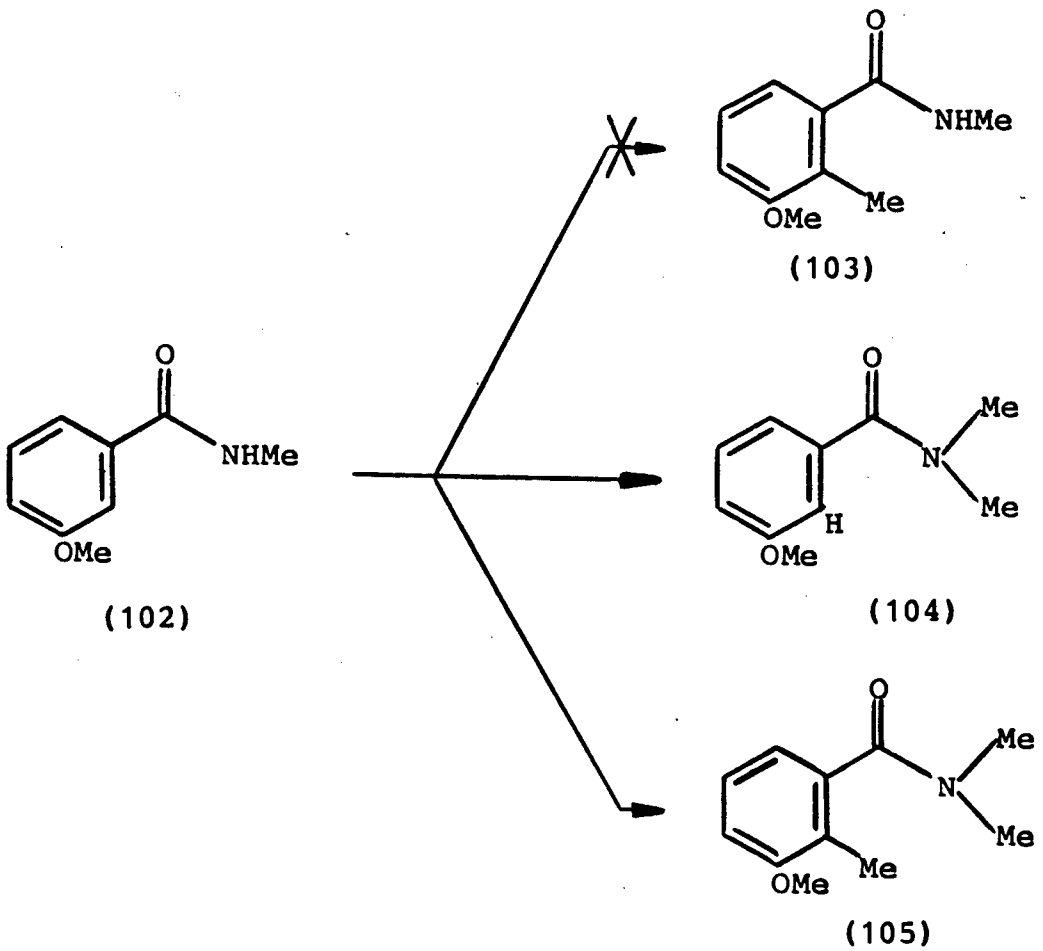


(100) (101)

spectrum of the δ-lactone (101) showed the base peak at m/z 118, consistent with its formulation as a dihydroisocoumarin,[42] which was also evident from the low-field doublet of doublets at δ8.07 (J2 and 7 Hz) due to 8-H in the ^{1}H n.m.r. spectrum,[42] and a strong i.r. absorption at 1710 cm^{-1}. Treatment of the lactone (101) with potassium t-butoxide and dimethyl sulphate in dry dimethylformamide provided the olefinic ester (92) in high yield (85%), in which the double bond had solely the (E)-geometry as planned, the large coupling constant (16 Hz) between the olefinic protons in the ^{1}H n.m.r. spectrum proving conclusive. The oily ester was reduced to the unsaturated alcohol (86) in high yield by lithium aluminium hydride in anhydrous ether, thus completing the reaction sequence for our first target compound.

In the light of the success achieved in the synthesis of the alcohol (86) from the amide (98), the 3-methoxy-2-methyl-amide (103) seemed to be a plausible precursor for the alcohol (87) if

the same reaction sequence was to be applied. It was envisaged that the 3-methoxyamide (102) could be lithiated between the substituents to yield the required compound (103) since there existed ample evidence in the literature for the *ortho*-lithiation of both primary benzamides and anisoles.[43,44] In compound (102) these effects were expected to be additive. The 3-methoxybenzamide was prepared by first methylating 3-hydroxybenzoic acid



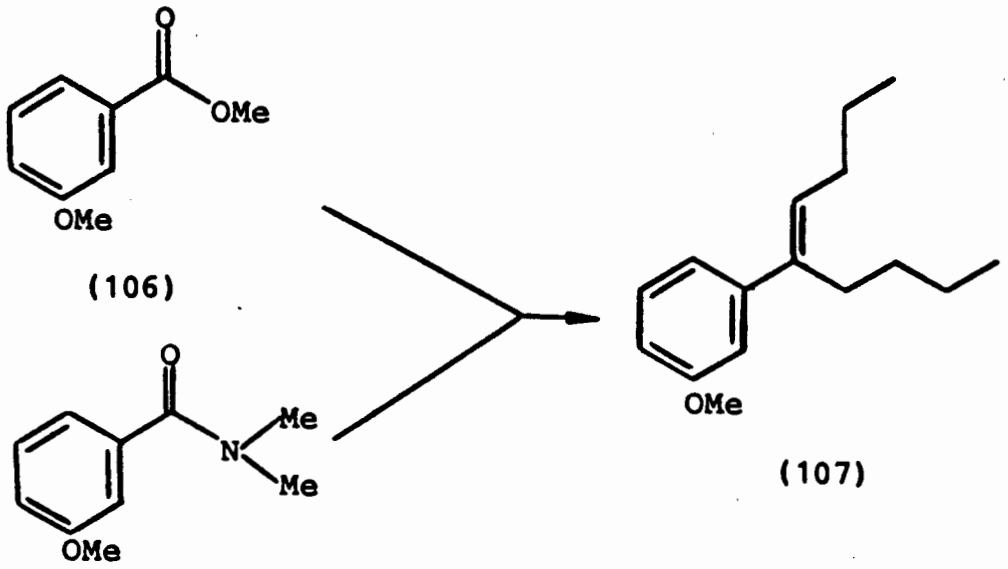
by the method of Graebe [45] to *m*-anisic acid, which was in turn converted *via* the acid chloride to the amide (102) after Brady and Dunn.[46] This was also the general method employed in the synthesis of the analogues of (102) described later.

After treating the amide (102) with 2.2 moles of *n*-butyl-lithium at room temperature and quenching with methyl iodide, the sole product obtained was the *N*-methylated tertiary amide (104) rather than the product (103) of aromatic methylation. A more direct synthesis of the tertiary amide (104) from *m*-anisoyl chloride and dimethylamine proved to have the identical ABX pattern for the three aromatic protons in the ^{1}H n.m.r. spectrum, as well as the broad six-proton signal at δ3.04 and methoxy signal at δ3.81. The fact that the signal due to the two *N*-methyl groups was broad was ascribed to hindrance to rotation about the carbonyl carbon-nitrogen bond through resonance; this bond is known to have some double bond character.[47] The broadness no doubt arose because the spectrum was determined close to the coalescence temperature.

When the temperature of the reaction of amide (102) was lowered under otherwise identical conditions, it was possible to insert a methyl group on the aromatic ring between the two substituents with concomitant *N*-methylation using *n*-butyl-lithium and methyl iodide to yield the 1,2,3-trisubstituted compound (105).[48]

The propensity of tertiary amides to undergo addition reactions with lithium reagents proved to be an impediment to the subsequent formation of the desired anion in the aromatic methylation step. Instead of forming the *C*,*N*-dilithio derivative with *n*-butyl-lithium, either a valerophenone or an alkene derivative were obtained as products depending on the reaction conditions; in this respect their behaviour is not unlike esters. The former reaction to form valerophenones is known,[48] while the latter

reaction to give the alkene has subsequently been reported in an independent observation made by Staunton.[49]



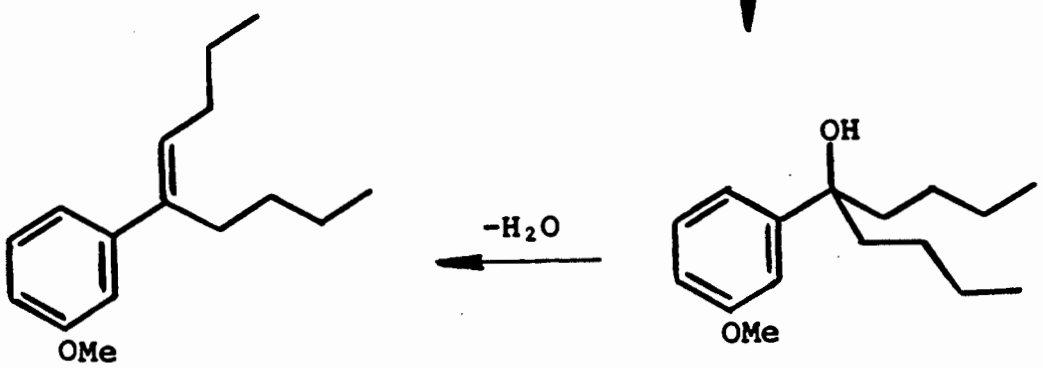
Thus both the ester (106) and the amide (104) react with 2.2 moles of *n*-butyl-lithium to afford the non-4-ene derivative (107) in moderate yield before quenching with the electrophile begins. Spectroscopic evidence for compound (107) includes a molecular ion at *m/z* 232 and a triplet at δ5.66 in the ^{1}H n.m.r. spectrum due to the olefinic proton. The formation of the valerophenone (108) and the nonene (107) can be rationalised in terms of attack of the alkyl anion on the carbonyl carbon of the amide (104) or the ester (106) (with displacement of the dimethylamino- or methoxy-substituents respectively) to initially form the ketone (108). The latter can undergo further attack at its carbonyl group with the same reagent to give the tertiary alcohol (109), which subsequently forms the nonene by dehydration. Different lithiating agents have, however, been reported as succeeding in *ortho*-

lithiating *N*,*N*-disubstituted amides.[64]

(104) X = NMe_2

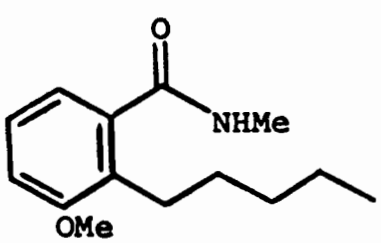
(106) X = OMe

(108)

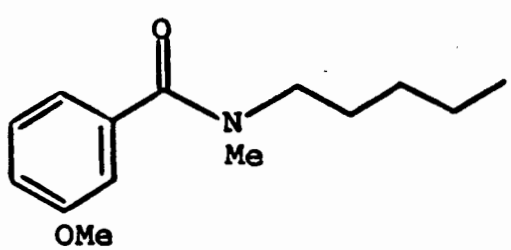


(107) (109)

The possibility of introducing a *C*-pentyl group directly into the amide (102) to give compound (110) was investigated. Whereas both *C*- and *N*-methylation of the amide (102) could be achieved to afford the dimethyl derivative (105) as described above, when alkylation with bromopentane was attempted, only *N*-pentylation took place to give the product (111). The evidence for this was



(110)

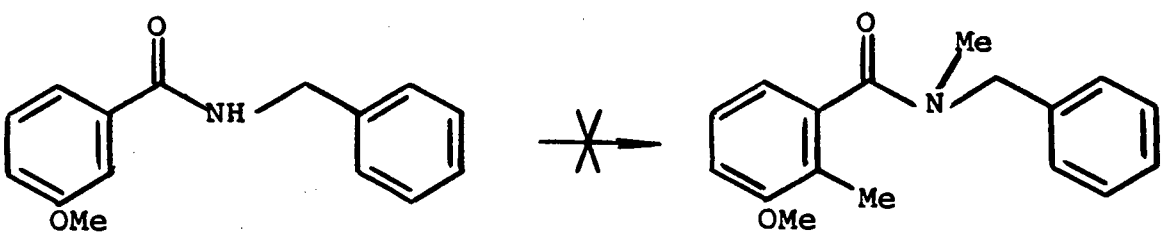


(111)

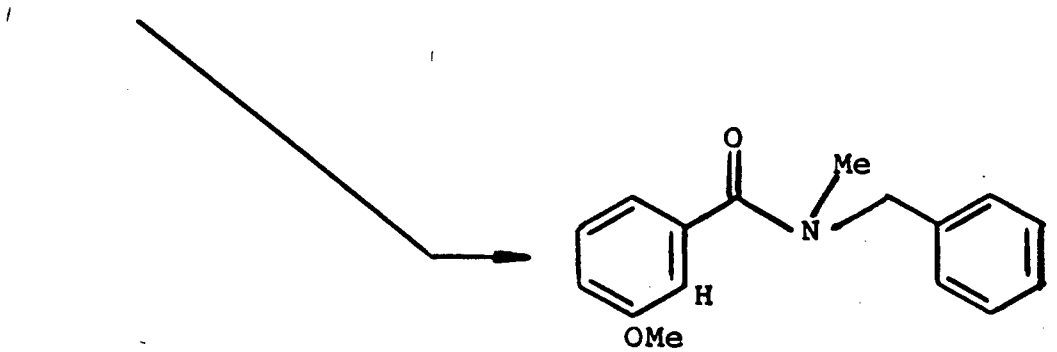
patent from the ^{1}H n.m.r. spectrum of the product in which the *N*-methyl doublet of the starting material had collapsed to a broad singlet at δ3.00, while by contrast the aromatic region still showed a 1,3-disubstitution pattern integrating for four protons.

It soon became obvious that the *N*-methylamides were unsuitable precursors for the formation of the secondary amides from which the dilithio derivatives could be generated. A neat way of obviating this would be to employ a readily removable protecting group in place of the *N*-methyl of compound (102) as a substituent of the initial secondary amides. The secondary amide should be obtained after *N*,*C*-dimethylation followed by replacement of the removable group by hydrogen.

The knowledge that tertiary *N*-benzyl amides can be hydrogenated to secondary amides[50] led us to synthesize the *N*-benzyl amide (112)[46] from *m*-anisoyl chloride and benzylamine. Despite many



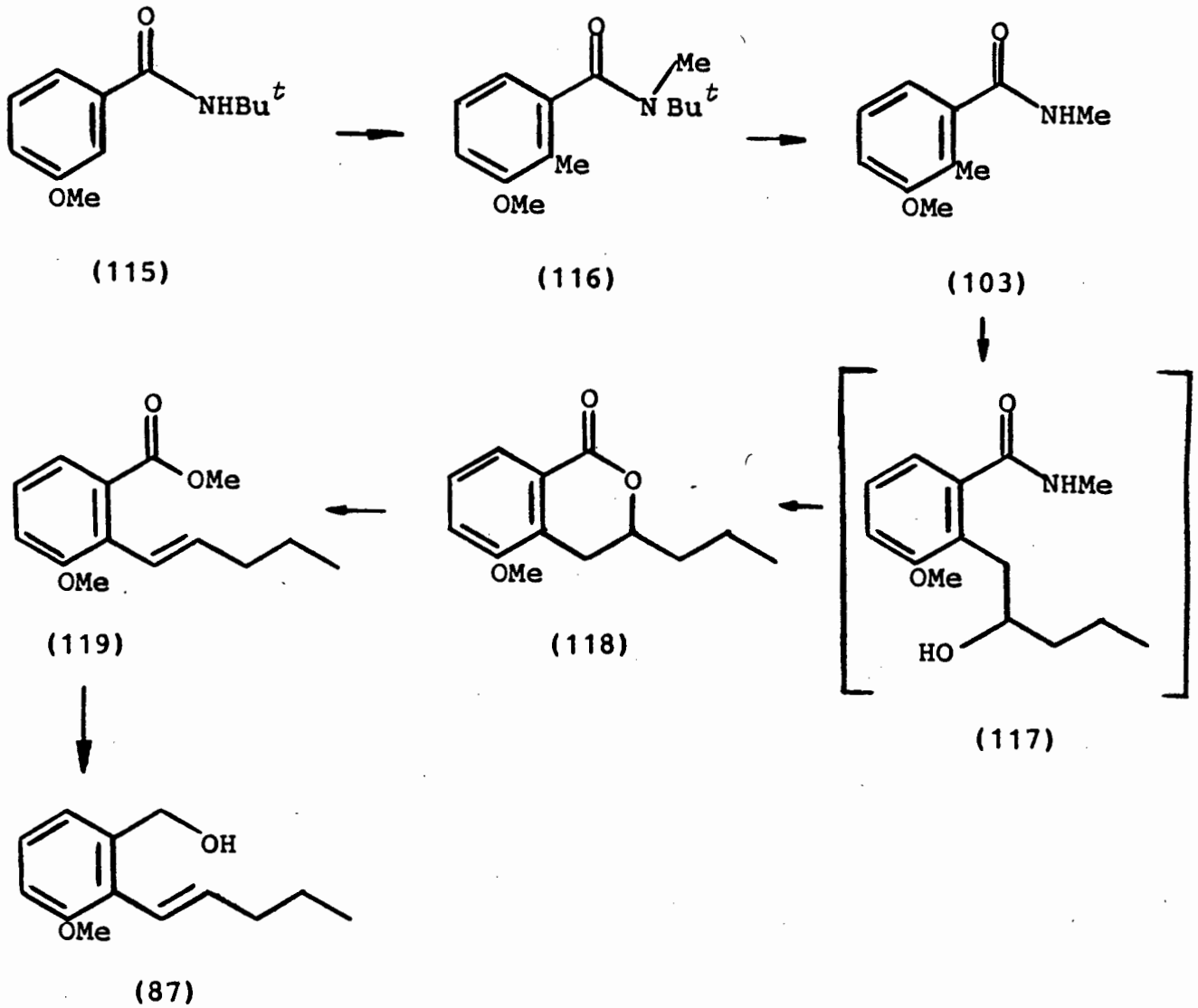
(112) (113)



(114)

attempts under various reaction conditions to subject amide (112) to both *N*- and *C*-methylation, no dimethylated product (113) could be recovered, the *N*-methylated product (114) being obtained preferentially in high yield (typically 92%). No *C*-methyl signal was observed in the ^{1}H n.m.r. spectrum of the product, while the molecular ion obtained by mass spectrometry was consistent with the molecular mass of 255 expected for compound (114).

A second choice was to use *N*-*t*-butylamides as starting materials. This proved to be very useful as the *t*-butyl group could be readily removed by treatment with trifluoroacetic acid.[51] Following this strategy, the known 3-methoxy-*N*-(*t*-butyl)benzamide (115)[52] (see Scheme VIII) was converted *via* its dilithio derivative to the product (116) of both *N*- and *C*-methylation in excellent yield (93%). The *t*-butyl group of compound (116) was most efficiently removed (yield 97%) by stirring at 60 °C in neat trifluoroacetic acid to give the secondary amide (103); a process which could be conveniently monitored kinetically by ^{1}H n.m.r. spectroscopy. The spectrum of the amide (103) in trifluoroacetic acid confirmed the pattern of 1,2,3-trisubstitution with the appearance of three *ortho*-coupled protons in the aromatic region at δ6.88, 7.08 and 7.26 (each *J* 7 Hz). This compound was lithiated and then quenched with butanal to give the intermediate hydroxyamide (117), which was not isolated but pyrolysed to afford the lactone (118). Ring opening of lactone (118) to the ester (119) proceeded as anticipated, in a yield of 53%.



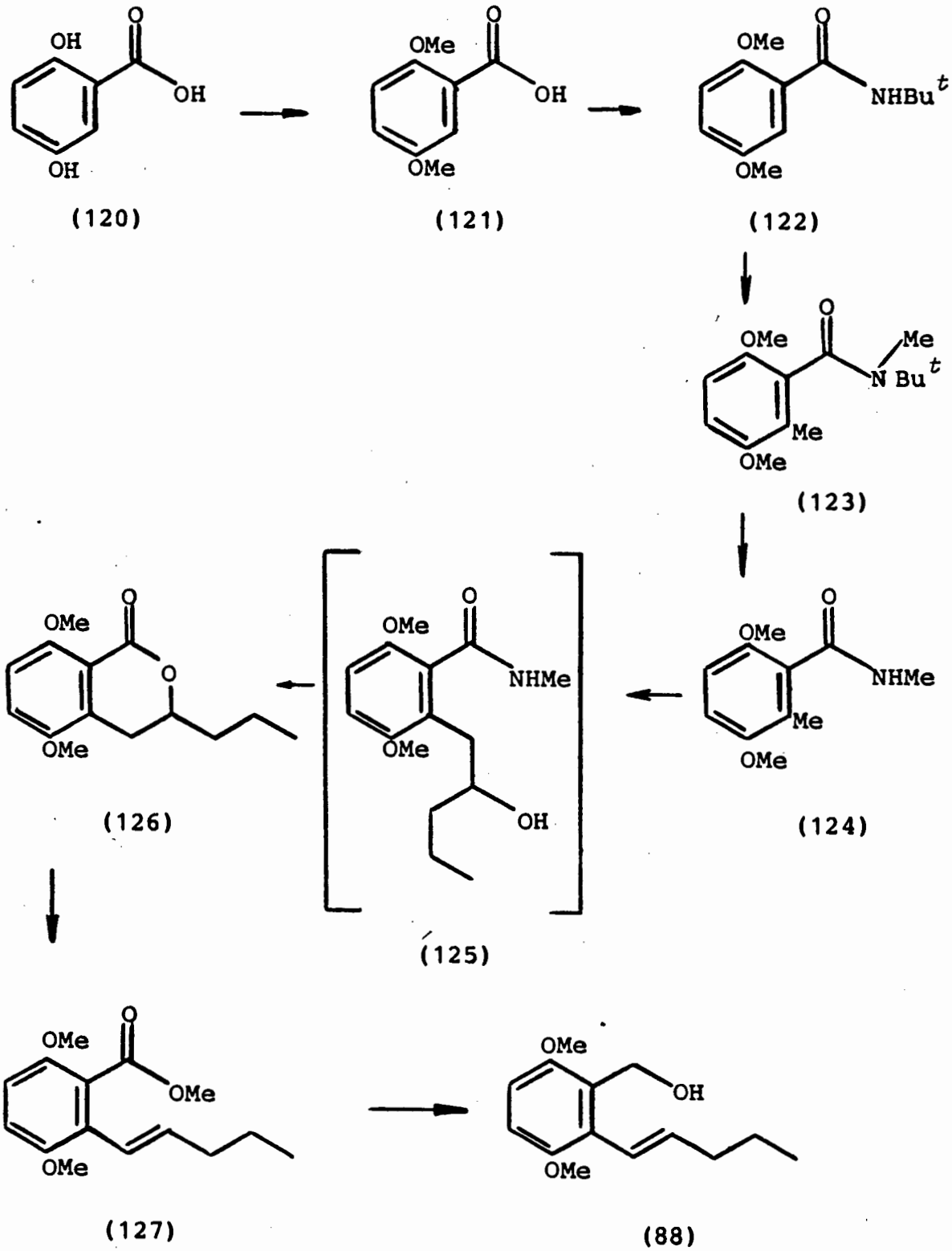
Scheme VIII

The route pioneered (Scheme VIII) to the related compound (87), during which many synthetic obstacles had been surmounted, greatly assisted in the construction of the olefinic alcohol (88) and as a result its synthesis proceeded comparatively smoothly.

Gentisic acid (120) was converted to its dimethyl ether (121) by

the method of Rees and West,[53] which in turn was converted to the previously unknown *N*-*t*-butylamide (122) using the general preparative method of Brady and Dunn[46] (see Scheme IX). ^{1}H n.m.r. spectroscopy showed the tertiary butyl signal at δ1.48. Aromatic lithiation of this compound would be expected to occur at the unsubstituted position between the amide and methoxy groups by analogy with the lithiation of amide (115), where their cumulative *ortho*-directing influences were synergistic. This was observed in practice, the product being compound (123), obtained in a yield of 93%. When the tertiary amide (123) was stirred in neat trifluoroacetic acid at 60 °C, the reaction gave the secondary amide (124), which was converted to the lactone (126) *via* the hydroxyamide intermediate (125). The latter was obtained from compound (124) by lithiation and subsequent reaction with butanal, as described earlier for the conversion of compound (103) to product (117). The opening of the lactone ring of compound (126) proceeded in a yield of 81% to afford the unsaturated ester (127). Alcohol (88) was obtained after the reduction of the olefinic ester (127) with lithium aluminium hydride. The pattern of 1,2,3,4-tetrasubstitution was confirmed not only by the formation of the lactone (126), but also by its ^{1}H n.m.r. spectrum, in which the *ortho*-coupled protons were observed as a doublet of doublets at δ6.87 and 7.07 (*J* 9 Hz).

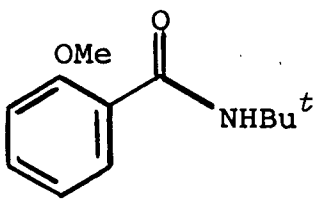
In view of the success achieved with the synthetic pathway to its methoxy analogues, the *N*-*t*-butyl amide (128) was considered to be a reasonable starting material for the acquisition of the olefinic alcohol (89). The initial route investigated to the



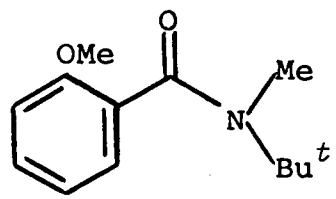
(120) (121) (122) (123) (124) (125) (126) (127) (88)

Scheme IX

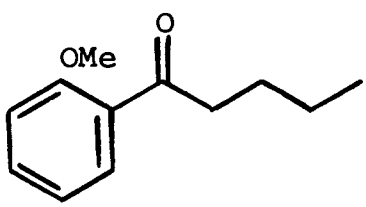
secondary amide (132) (see Scheme X) involved the dilithiation of *o*-methoxy-*N*-*t*-butylbenzamide (128), in which aromatic lithiation would be expected to occur adjacent to the amide function rather than adjacent to the methoxy group in view of the stronger *ortho*-directing influence of the former.[54] However, lower yields



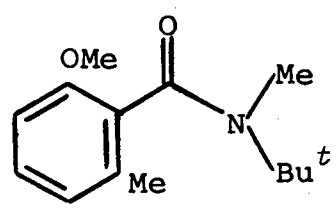
(128)



(129)



(130)

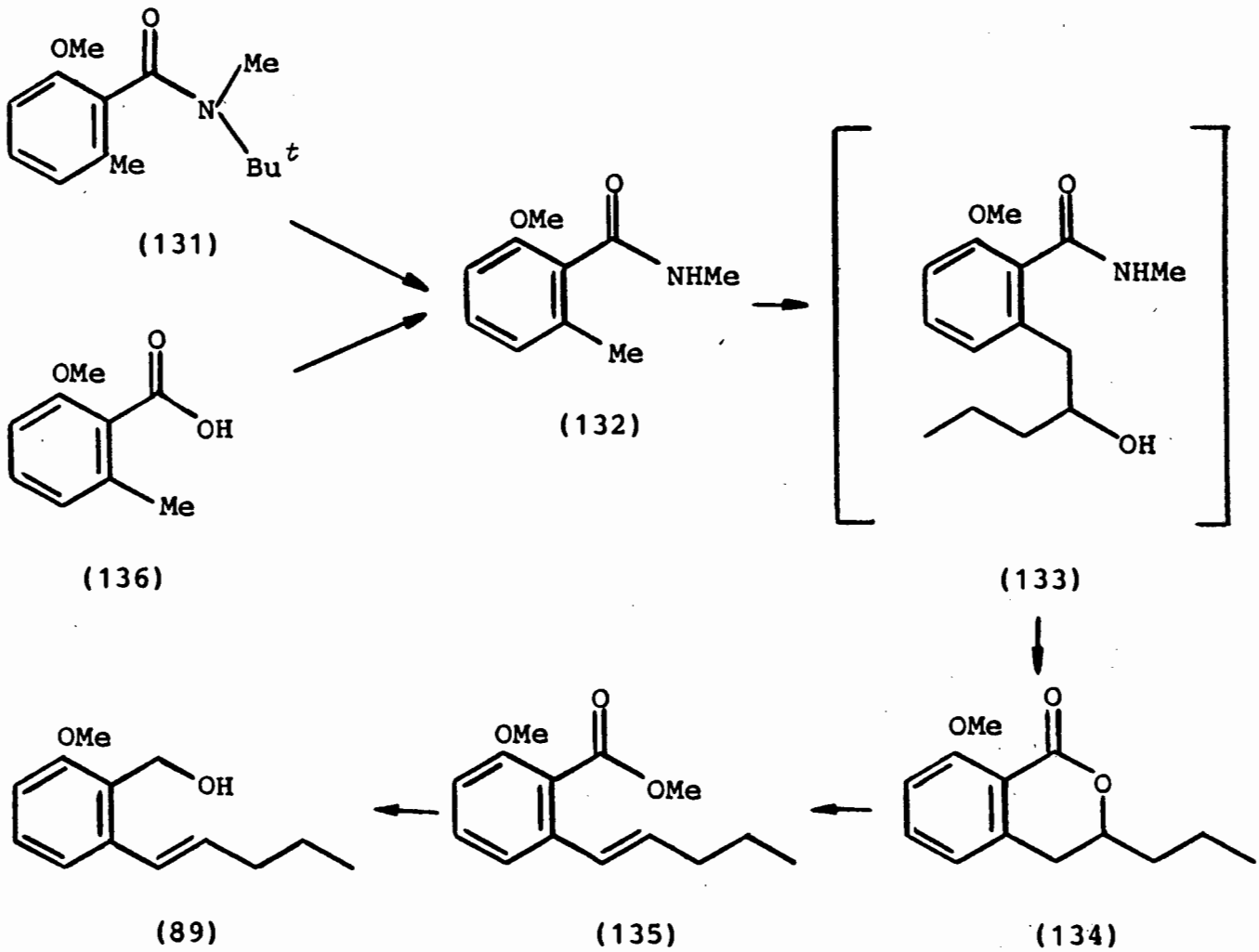


(131)

might be expected than those obtained in the case of the isomeric compound (115) where the directive influences were complementary. This postulate was confirmed in practice. While subsequent aromatic methylation of the dilithio derivative of compound (128) gave the 2,6-disubstituted amide (131) as the exclusive 1,2,3-trisubstituted benzene, difficulties were encountered in obtaining it as the sole product of the reaction. Compound (131) was usually contaminated with the amide (129) (from which it was difficult to separate chromatographically) as well as 2-methoxy valerophenone (130). Yields were variable, as were the

proportions of the by-products (129) and (130).

Although the *N*-*t*-butyl compound (131) was converted to the secondary amide (132) in excellent yield (92%) by stirring in neat trifluoroacetic acid, an alternative pathway had to be pursued to (132) on account of the paucity of material arising out of



Scheme X

the preceeding step. By inspection, it was perceived that the amide (132) could be prepared by standard methods from 2-methoxy-6-methyl benzoic acid (136). Although the acid (136) had been

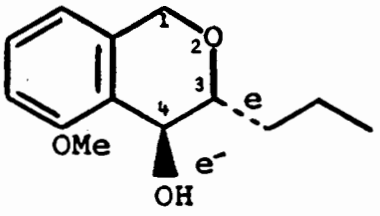
prepared on numerous occasions,[55] the method of Hauser and Pogany[56] was utilised as it was particularly suited to large scale (*ca.* 100 g) preparation. [This synthesis essentially entailed the cyclisation of crotonaldehyde and ethyl acetoacetate. The resulting substituted cyclohexenone was consecutively aromatized with bromine,[57] methylated and hydrolysed to give the 1,2,3-trisubstituted acid (136) by a convenient four-step sequence.]

After our synthesis of alcohol (89) Carter and Wallace[58] reported a two-step synthesis of the acid (136) from commercially available 2,3-dimethyl anisole. This procedure seems suitable for smaller scale production of acid (136).

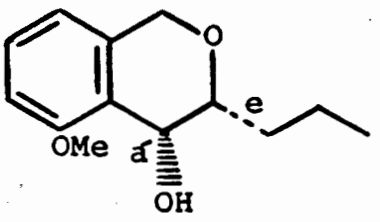
Scheme X depicts that alcohol (89) was prepared in the manner previously described for its related compounds (86) → (88) and underlines both the synthetic utility and generality of the method. Amide (132) was converted *via* the hydroxyamide (133) to the lactone (134), which in turn underwent ring opening in the usual manner with butoxide. Methylation of the resulting carboxylate anion afforded ester (135), which upon reduction by lithium aluminium hydride provided alcohol (89).

Alcohols (86), (87), (88) and (89) are all liquids and appear to be stable at room temperature. Now that their syntheses had been achieved, an investigation into whether or not they possessed suitable structures for the cerium(IV) ammonium nitrate- and butoxide-initiated cyclisations mentioned earlier (Chapter 2, pp. 20 - 22) could be undertaken.

Oxidation of the alcohol (86) with cerium(IV) ammonium nitrate (2 mol equivalents) afforded a complex reaction mixture from which no product could be characterised. However, the similar reaction of the methoxy analogue (87) gave two products which were identified as the hydroxyisochromans (137)(18%) and (138)(48%).

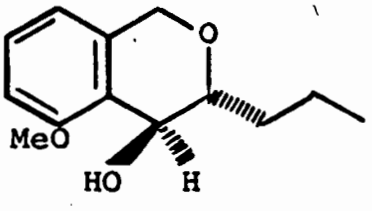


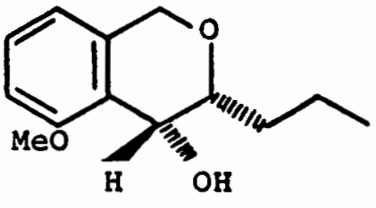
(137)



(138)

The stereochemical assignments were made on the basis of the ^1H n.m.r. spectra of the compounds. The minor isomer (137) had a higher R_F value than the major isomer (138), presumably because the pseudoequatorial hydroxy group of (137), being closer to the *peri*-oxygen, can more effectively intramolecularly hydrogen bond with it.[34] Compound (137) showed the four pyran ring protons as a three proton signal at δ4.71 consisting of a singlet due to



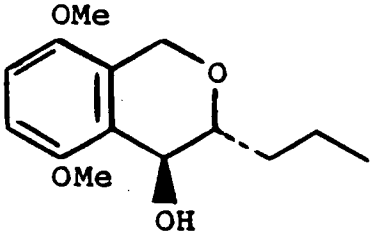


the two methylene protons at C - 1 superimposed on a broadened doublet due to the pseudoaxial proton 4 - H, and a further one proton signal at δ3.58 due to the axial proton 3 - H, which was partially obscured by the resonance of the hydroxy group. Exchange of the hydroxy proton with deuterium oxide simplified the latter signal to a doublet of triplets (*J* 2.5 and 8 Hz). Simultaneous double irradiation of the propyl methylene protons vicinal to 3 - H at δ1.67 collapsed 3 - H to a doublet (*J* 8 Hz), this remaining coupling being with the neighbouring proton 4 - H. The magnitude of the coupling constant indicated that 3 - H was axial and 4 - H pseudoaxial, from which it followed that the C - 3 propyl was equatorial (in keeping with the orientation of bulky groups attached to such ring systems) and the C - 4 hydroxy pseudo-equatorial.

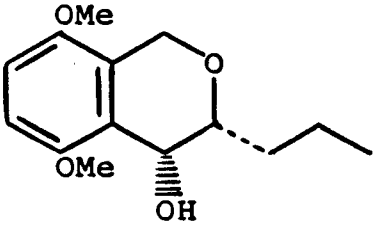
Compound (138) by contrast showed the two methylene protons at C - 1 as two doublets at δ4.67 and 4.87 (*J* 15 Hz). A doublet of triplets at δ3.53 (*J* 2 and 6.5 Hz) was ascribed to the 3 - H proton, as irradiation of the methylene protons vicinal to it at δ1.71 effected its collapse to a doublet with a coupling constant of 2 Hz. This reflected a much smaller dihedral angle between 3 - H and 4 - H, indicating 4 - H to be pseudoequatorial on the reasonable assumption that the C - 3 propyl substituent was equatorial. Alternative double irradiation of 4 - H at δ4.7 simplified the 3 - H signal to a triplet (*J* 6.5 Hz), this coupling arising through interaction with the adjacent propyl methylene protons. A deuterium oxide exchange of the hydroxy proton resulted in 4 - H appearing as a doublet with a coupling constant of 2 Hz. The preponderance of the pseudoaxial hydroxy

epimer was in agreement with the pseudoaxial products (76), (78) and (81) being the major compounds in the formation of the epimeric pairs (75) and (76), (77) and (78), and (80) and (81). This disparity in the relative yields of the products from the reaction can be ascribed to the hydroxy group showing a preference for the pseudoaxial configuration as this would lead to minimal *peri*-interaction with the neighbouring methoxy group. A factor which presumably mitigates against this being the sole orientation is that when the hydroxy group is pseudo-equatorial, it is closer to the *peri*-oxygen, and can therefore be more efficiently intramolecularly hydrogen bonded to it.

Treatment of the dimethoxy alcohol (88) with cerium(IV) ammonium nitrate (2 mol equivalents) similarly afforded the pair of epimeric hydroxyisochromans (139) (21%) and (140) (30%), whose



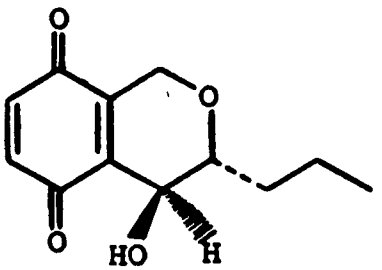
(139)



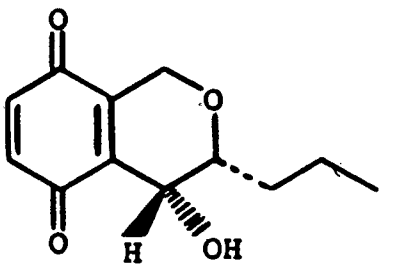
(140)

relative stereochemistries once again followed from their ^1H n.m.r. spectra. The combined yield was somewhat less than that for the oxidation of the monomethoxy compound (87), and this was ascribed to the greater complexity of the reaction, since further oxidation of the products (139) and (140) to the corresponding quinones (141) and (142) was taking place to a minor

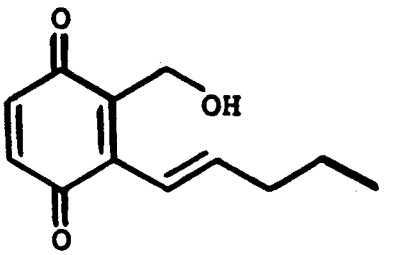
degree, as was the oxidative demethylation of the hydroquinone dimethyl ether (88) to the olefinic quinone (143) (10%).



(141)



(142)



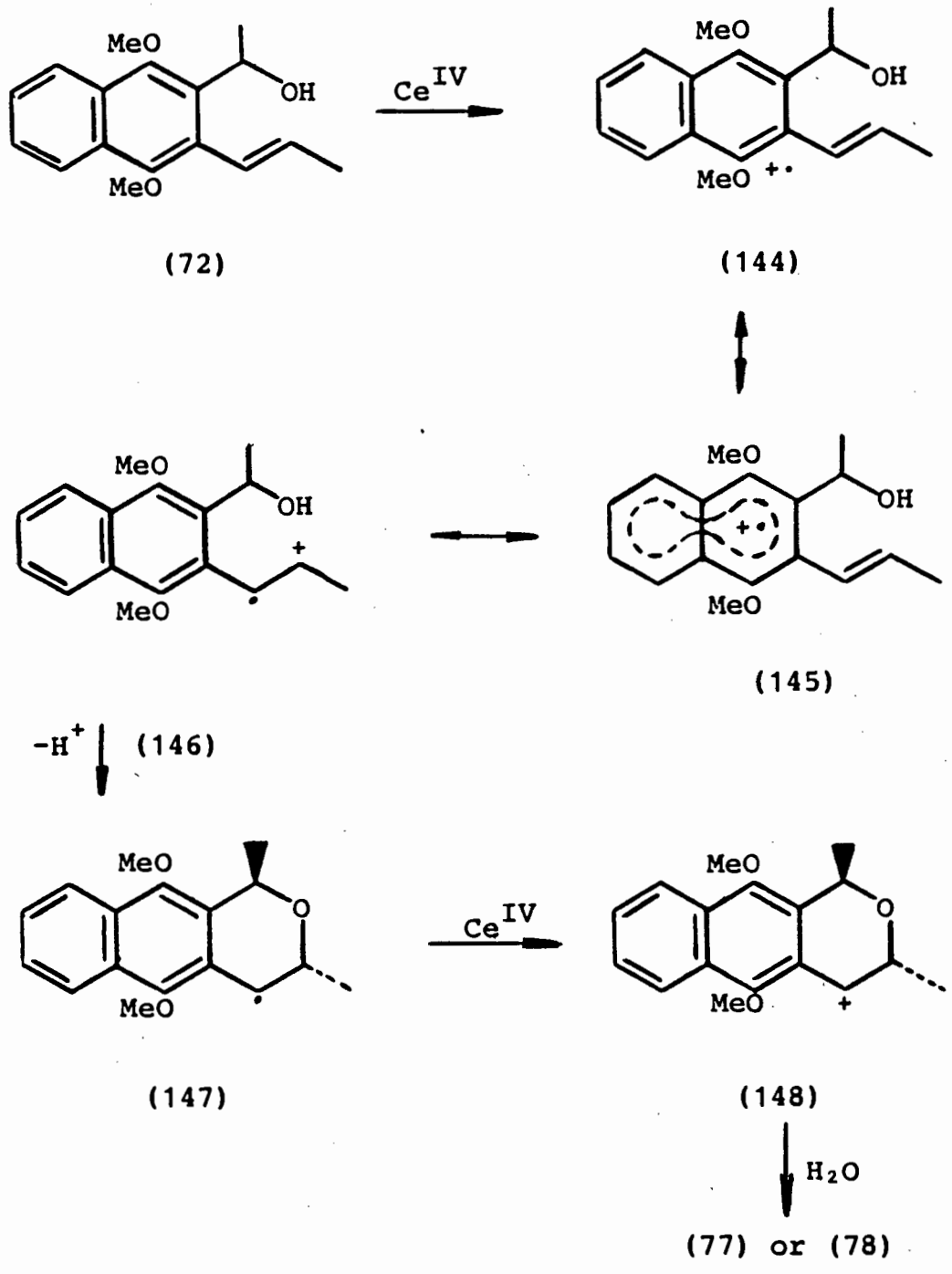
(143)

The latter was identified as having the same R_F as the material obtained by the silver(II)oxide oxidation of compound (88). Silver(II)oxide has been shown in this laboratory to oxidise hydroquinone dimethyl ethers such as (72) and (79) to the corresponding quinones and its mode of action on the compound (88) is therefore different to that of cerium(IV) ammonium nitrate.[33,34] The quinone (143) was somewhat unstable and was not fully characterised. The epimeric quinones (141) and (142) were in turn directly furnished by using four molar equivalents of cerium-(IV) ammonium nitrate to oxidise alcohol (88). Although the pure pseudoaxial quinone (142) was afforded after column chromatography, the pseudoequatorial epimer (141) was contaminated with the olefinic quinone (143) and it was difficult to separate these from each other. The pseudoequatorial hydroxyquinone (141) was best prepared by silver(II)oxide oxidation of the hydroquinone dimethyl ether (139); the epimeric compound (142) was similarly prepared from compound (140). Confirmation of the assignments for compounds (141) and (142) were obtained from

their ^{1}H n.m.r. spectra. Aside from the disappearance of the methoxy signals, the stereochemistry about the pyran rings followed once again from spin-decoupling experiments. Thus, for compound (141), irradiation of the adjacent propyl methylene protons at δ1.70 gave rise to a doublet with a coupling constant of 8 Hz for 3-H, while similar irradiation of compound (142) showed 3-H as a doublet with a coupling constant of 2 Hz. Once again, with H-3 axial, the larger coupling constant for the former compound showed H-4 to be pseudoaxial, while the smaller coupling constant for compound (142) confirmed H-4 as being pseudoequatorial.

Alcohol (89) behaved totally differently to the alcohols (87) and (88) upon treatment with cerium(IV) ammonium nitrate (2 mol equivalents). A mixture of products was obtained from this reaction, none of which was identified as a hydroxyisochroman; it resembled alcohol (86) in this respect.

These results seemed to indicate that in the cerium-promoted oxidative cyclisation of compounds (72) and (79), the methoxy *ortho* to the alkenyl group plays an important role. A mechanism consistent with the experimental observations at this stage is outlined in Scheme XI. This proposal[21] involves the formation of a resonance-stabilised cation (144 ⟷ 145 ⟷ 146) by the oxidation of (72) at the methoxy *ortho* to the alkenyl substituent with cerium(IV) (1 mol equivalent). Ring closure and loss of a proton give rise to a benzylic radical (147) which undergoes oxidation with a second cerium ion to give the benzylic carbonium ion (148); this is then nucleophilically attacked by

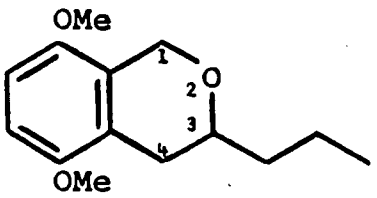


Scheme XI

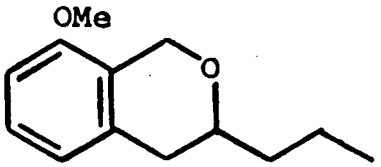
the water present to give the products (77) and (78). Other evidence previously adduced in this laboratory consistent with the formation of a carbonium ion intermediate include its competitive trapping by the nucleophiles water and nitrate.[34]

Thus, in the oxidation of compound (79) with four molar equivalents of cerium(IV) ammonium nitrate, significant quantities of the nitrates [(80) and (81), ONO_2 in place of OH] were obtained when the water content of the reaction mixture was kept to a minimum. This was interpreted as providing conditions in which nitrate, the only nucleophile present other than water, was effectively competing for the carbonium ion intermediate analogous to (148). The formation of these nitrates was mechanistically interesting in the above context; however, they were undesired by-products in the synthesis of the 7,9-dideoxy derivatives of quinones A and A' [(75) and (76) respectively] and their formation could be suppressed to favour the formation of (75) and (76) from (72), and (80) and (81) from (79), by increasing the proportion of water relative to the oxidant. These observations were again consistent with the formation of a carbonium ion such as (148).

The alcohols (86), (87), (88) and (89) also exhibit a varied degree of reactivity as far as the base cyclisations are concerned, and furthermore, as a group they show a differing reactivity to cerium(IV) ammonium nitrate on the one hand and potassium-*t*-butoxide on the other; the individual members which undergo cyclisation with the former reagent do not necessarily undergo reaction with the base and *vice-versa*. Alcohol (86) was recovered unchanged from stirring with potassium *t*-butoxide (4 mol equivalents) in dimethylformamide. Similar immunity was displayed by alcohol (87) despite the temperature being raised and the reaction time being extended in an effort to effect cyclisation. The dimethoxy alcohol (88) by contrast gave the benzopyran (149) in good yield (85%), and its behaviour therefore



(149)

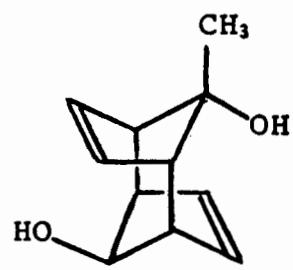


(150)

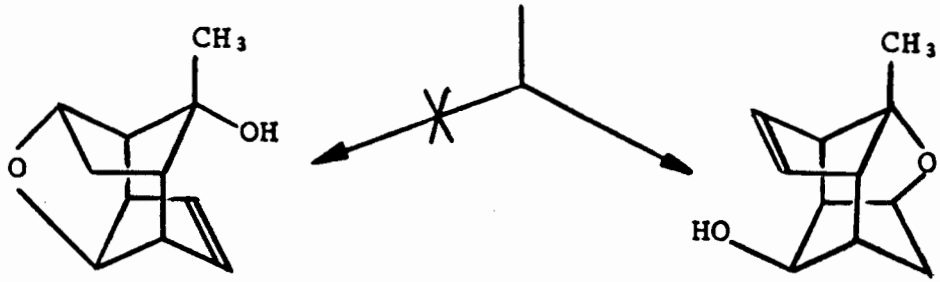
paralleled that of its analogues (72) and (79) under the same conditions which gave the products (83) and (84) in yields of (100%) and (83%) respectively. The reaction of alcohol (88) could readily be monitored by thin layer chromatography as the cyclic ether (149) had a much higher R_F than that of the starting material. Spectroscopic evidence that permitted the assignment of structure (149) to the product included the appearance of a molecular ion at *m/z* 236 in the mass spectrum, as well as a ^1H n.m.r. spectrum which was consistent with the structure. The latter spectrum showed the 3-H proton as a multiplet at δ3.40 - 3.75. The pseudoaxial 4-H resonated as a doublet of doublets (*J* 11 and 17 Hz) at δ2.36, while the 4-H pseudoequatorial proton resonated as a doublet of doublets at δ2.80 (*J* 3.5 and 17 Hz); the smaller coupling constant could in this instance be ascribed to the narrower dihedral angle between the 3-H and pseudoequatorial 4-H proton. Furthermore, the 1-H protons were geminally coupled to each other and resonated at a lower field than the 4-H protons due to their proximity to the electronegative oxygen of the pyran ring. A doublet (*J* 17 Hz) appeared at δ4.58 for the pseudoaxial 1-H while its pseudoequatorial counterpart exhibited the same splitting pattern and coupling constant at δ4.94. A much poorer yield (25%) of the cyclic

ether (150) was obtained from the cyclisation of the alcohol (89).

The explanation for this unusual reaction may involve steric effects, since it is those alcohols in which both the hydroxymethyl and alkenyl substituents are flanked by methoxy groups (forcing the reacting centres into close proximity) that cyclise readily and in high yield. In a recent publication[59] the formation of cyclic ethers from the reaction of an alcohol function with an unactivated double bond when the two are held in close proximity was investigated. It was found that the diol (151),



(151)

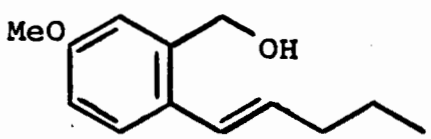


(152) (153)

when subjected to base catalyzed cyclisation in 50% aq. NaOH/ CH_3OH 1:1, gave the cyclic ether (153) as the sole product in quantitative yield. This full regioselectivity (as no trace of the alternative possible product (152) could be found) reflects

the marked difference in reactivity of the two sides of the diol (151), the higher steric compression on the methylated side being the determining factor. This result tends to add weight to the steric argument of the base-induced cyclisations of our compounds; however, further work would have to be undertaken to exclude the involvement of electronic factors. Some efforts aimed at investigating the relative importance of steric *vs.* electronic factors are discussed later in this thesis.

It was decided at this stage that, if the mechanism proposed in Scheme XI were correct, the benzyl alcohol (154), isomeric with the compounds (87) and (89), should also undergo oxidative cyclisation with cerium(IV) ammonium nitrate to the hydroxyisochromans (155) and (156), since the methoxy group was *ortho* to the alkenyl substituent in (87) while *para* to it in structure (154). In the latter case this methoxy group should equally well stabilise a benzylic radical (157) analogous to that proposed in



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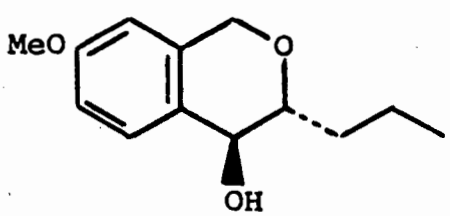

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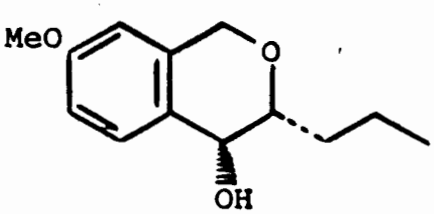

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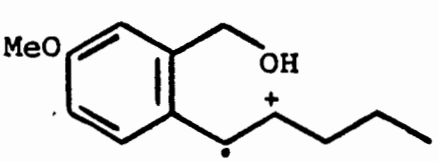
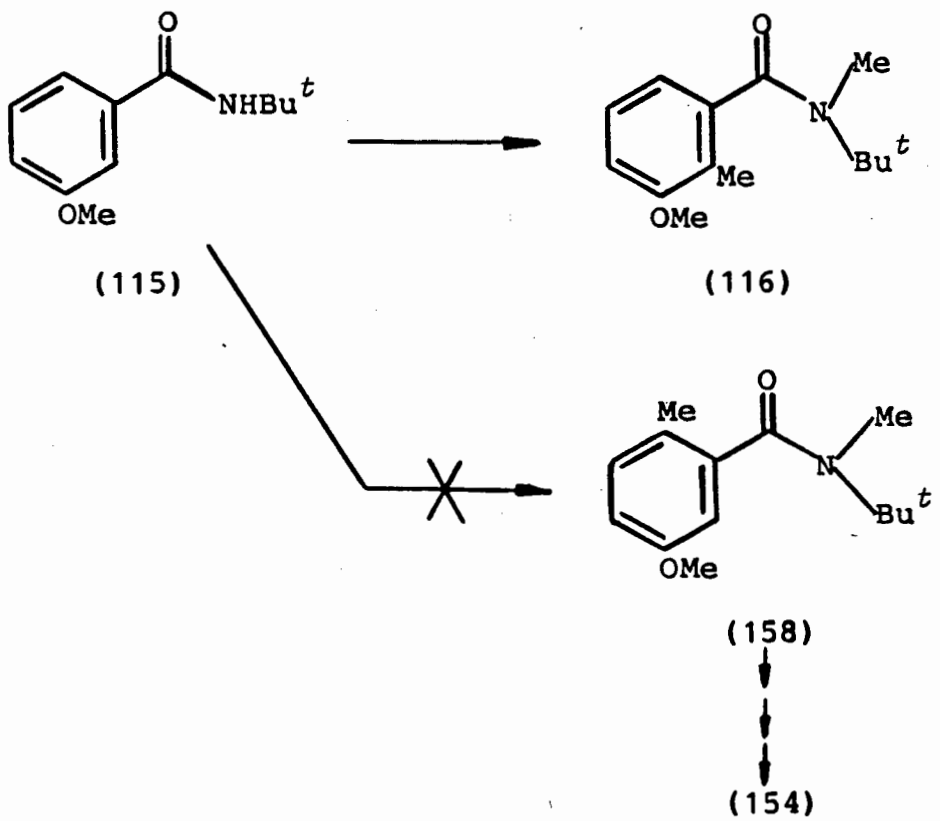


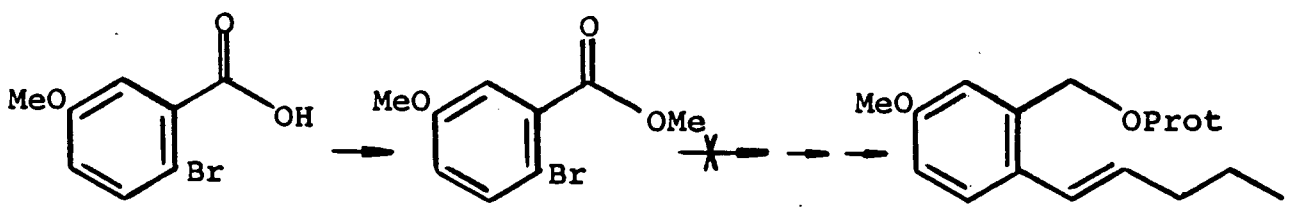
(157)

Scheme XI. It was hoped that more circumspect predictions on the cyclisations of molecules of this type would be substantiated by the synthesis of (154), and many synthetic routes were therefore concurrently considered to it.

When first embarking on its synthesis, it was borne in mind that the trusted method of dimethylating *N*-*t*-butyl amides was unusable from the knowledge that the plausible starting amide (115) gave the 1,2,3-trisubstituted compound (116) and not the desired 1,2,4-trisubstituted compound (158). High premium was therefore placed on the initial establishment of a 1,2,4-trisubstitution pattern.

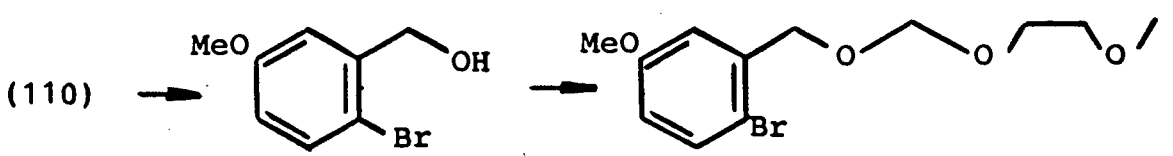


The known bromo acid (159)[60] was esterified to give (160), the strategy being to eventually displace the bromine with a pentyl derivative and then modify the latter to the (*E*)-pent-1-enyl group. Naturally the ester moiety, which deactivates the ring and is itself liable to undergo nucleophilic attack should first be converted to a protected alcohol. It was hoped that the sum effect of these efforts would result in an analogue of (161)



(159) (160) (161)

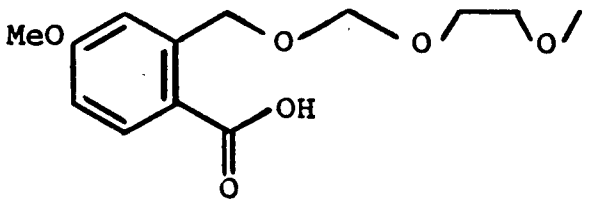
(Prot = protecting group) which after deprotection should yield alcohol (154). The bromo ester (160) was reduced with lithium aluminium hydride to the alcohol (162), which in turn was protected by conversion to compound (163) using sodium hydride as base and methoxyethoxymethyl chloride (MEM chloride), a group quantitatively removable with zinc bromide.[61]



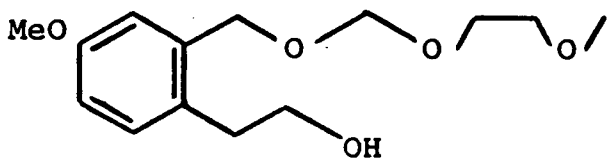
(162) (163)

Numerous attempts were made at attaching various electrophiles to molecule (163) after the displacement of the bromine with

freshly standardised[62] *n*-butyl-lithium in tetrahydrofuran. Of the reagents investigated, the only ones which resulted in any notable success were carbon dioxide and ethylene oxide to give low yields of their respective products (164) (14%) and (165) (23%). In both instances much higher yields of compound (166),

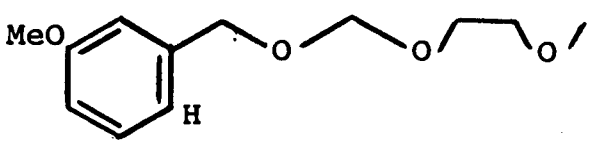


(164)



(165)

in which the bromine had been replaced by hydrogen, were obtained.



(166)

Condensations with other electrophiles such as methyl iodide, butanal and the more relevant pentanal (freshly prepared from the pyridinium dichromate oxidation of pentanol)[63] and 1-pentene oxide also failed, the major product persistently being (166). In the butanal and pentanal experiments, a highly aliphatic, sweet smelling oil of high R_F was always obtained in addition. Although not identified, it is suspected as being a polymer of the aldehydes arising from aldol condensation reactions. Further attempts at using compound (163) as precursor to alcohol (154)

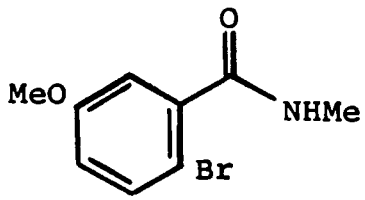
were consequently abandoned as no progress was being made along this route.

A second possibility included the conversion of the acid (159) into various amides of the type (167) (R = H). In such *ortho*-bromoamides, metal-halogen exchange would give rise to an

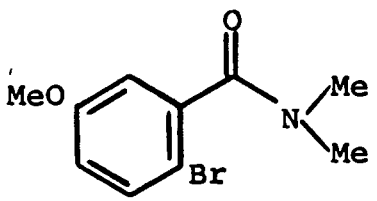
(159) (167)

ortho-lithioamide. It was anticipated that subsequent electrophilic attack on the aromatic ring might well occur at the carbon originally bearing bromine rather than at the carbon between the substituents otherwise favoured in the debromo analogues such as (102) and (115). In effect, the inclination of bromine to undergo metal-halogen exchange was expected to offset the synergism of the combined methoxy and amide *ortho*-directing properties to give the products of 1,2,4-trisubstitution rather than the products of 1,2,3-trisubstitution otherwise obtained.

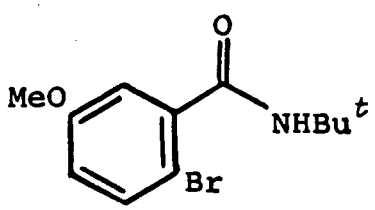
Amides (168), (169) and (170) were prepared by standard methods. Amides (168) and (169) afforded variable yields of their debrominated derivatives after treatment with *n*-butyl-lithium and pentyl bromide in dry tetrahydrofuran at -78°C in an inert atmosphere. Both mass spectrometry and the appearance of a 1,3-disubstitution pattern in the aromatic region of the ^{1}H n.m.r.



(168)

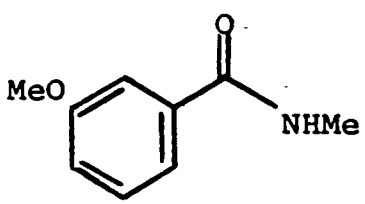


(169)

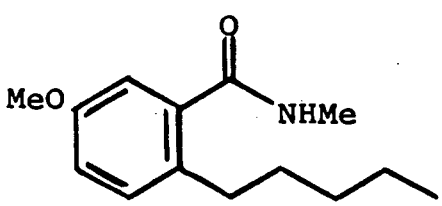


(170)

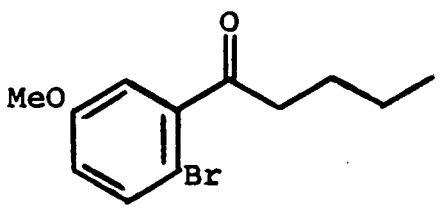
spectrum testified to this. Besides (102), a concomitant low yield of the crystalline pentylated product (171) (15%) was obtained under optimised conditions from compound (168) which could not be improved. Reaction of the tertiary amide (169) also gave the ketone derivative (172) (36%) resulting from butyl anion attack on the carbonyl group. The ^{1}H n.m.r. spectrum of ketone (172) exhibits a triplet at δ2.95 and other signals



(102)



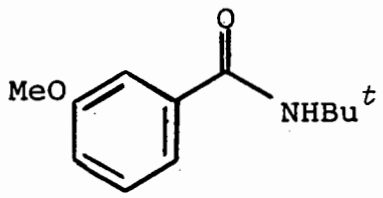
(171)



(172)

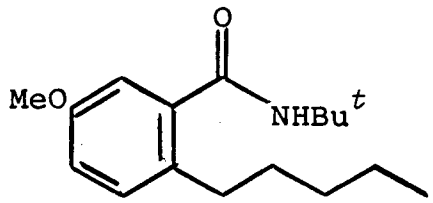
assignable to a butyl group, instead of the two singlets at δ2.90 and 3.16 of the dimethylamide (169).

When the secondary amide (170) was reacted with bromopentane and *n*-butyl-lithium in tetrahydrofuran at -78°C, two products were obtained from the reaction. The band with the lower R_F value had the same ^{1}H n.m.r. spectrum as its previously prepared debromo analogue (115) (18%). The band of higher R_F value on thin layer chromatography seemed to be a mixture; although the ^{1}H n.m.r. spectrum had only one *t*-butyl peak at δ1.47, two methoxy signals at δ3.78



(115)

and 3.81 of roughly the same intensity were present. The duplication of other signals in the ^{1}H n.m.r. spectrum further strengthened this supposition. Although the two compounds were not separable by column chromatography, their primary amides, obtained by boiling the mixture in trifluoroacetic acid for a prolonged period, could readily be resolved by thin layer chromatography. The ^{1}H n.m.r. of the primary amides showed similar signals but for the aromatic regions. One isomer was clearly a 1,2,4-trisubstituted compound as testified by the ABX pattern in the aromatic region, which consisted of an overlapped signal at δ6.95 due to 6-H (structure 175), a doublet of doublets (partly obscured by overlap with the former signal) at δ6.90 (J 3 and 8 Hz) and an *ortho*-coupled doublet at δ7.17 (J 8 Hz). The other product exhibited three *ortho*-coupled aromatic protons at δ6.93, 7.08 and 7.23 not unlike some of the 1,2,3-trisubstituted compounds worked with before. Clearly, these were the isomers (175) and (176) arising from their respective precursors (173) and (174) which were originally obtained as a 1:1 mixture in a yield of 60% in addition to compound (115) from the starting material (170). The results indicate that the electrophile competes for the position favoured by the complementary directive effects of the methoxy and amide substituents and that vacated by the bromine. This discovery was somewhat surprising in view of the finding



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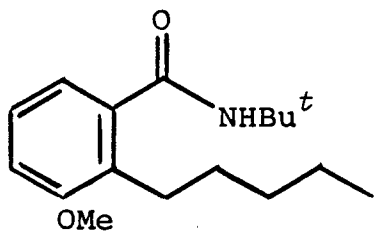
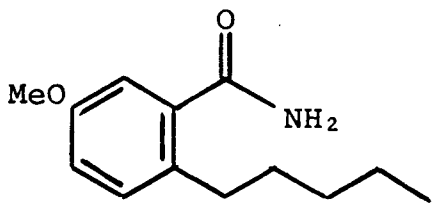


(174)



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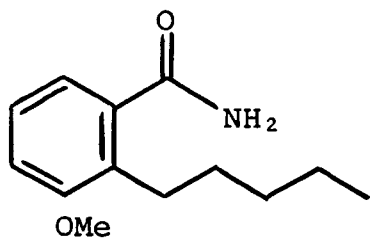
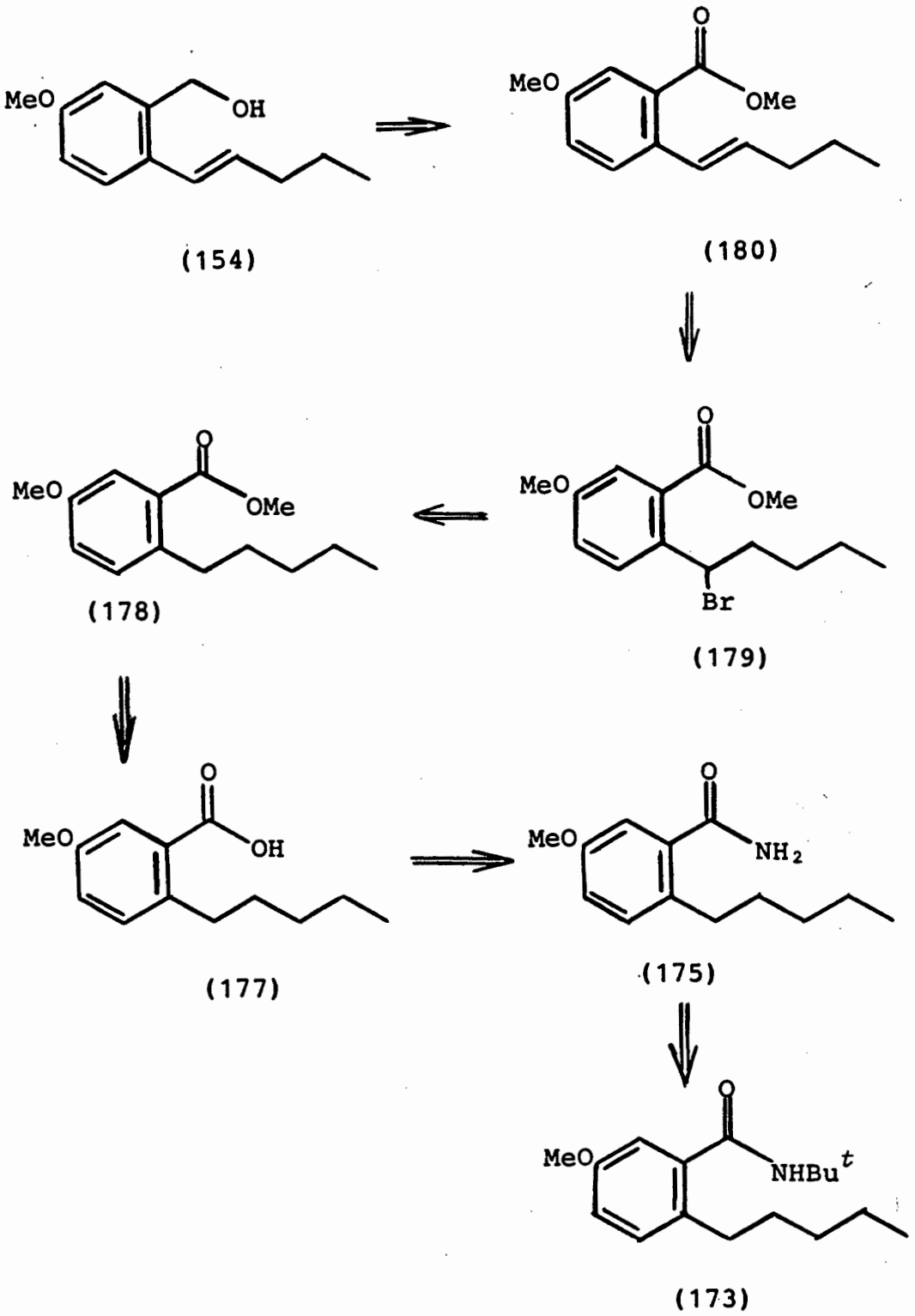


(176)

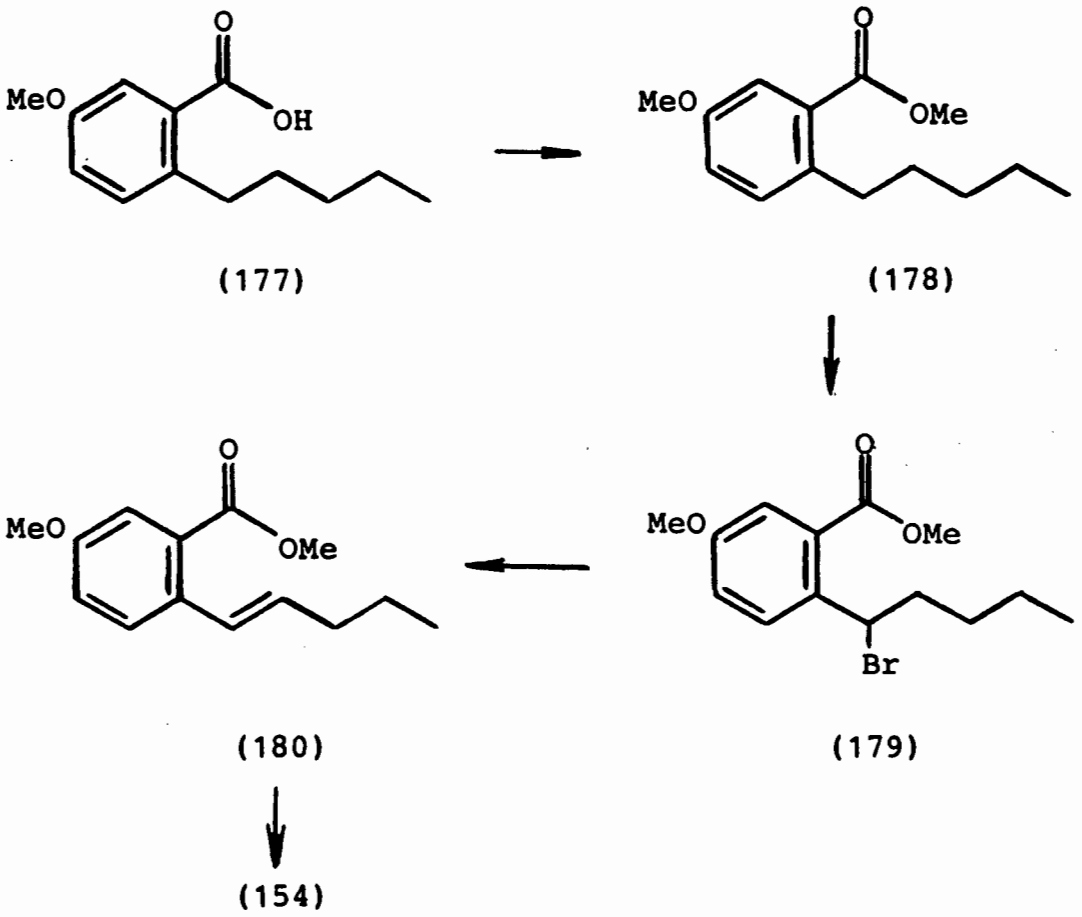
described earlier that when the amide (102) was treated with 2 mol equivalents of *n*-butyl-lithium followed by addition of bromopentane, only the product of *N*-pentylation was observed.

According to the retrosynthetic rationale outlined in Scheme XII, the next step would be to hydrolyze the primary amide (175) to the corresponding acid (177). Benzamides are known to be difficult to hydrolyze[65] and the amide (175) proved to be no exception under conditions of acid or base catalysis. However, this was overcome by first diazotizing[66] the amide (175) before carrying out hydrolysis on the intermediate diazonium salt. This reaction appeared successful on a pilot scale and a band of low R_F value was obtained on t.l.c. which could be construed as being the acid (177) from the crude reaction mixture by ^1H n.m.r. spectroscopy.


MeO
OH
(154)
MeO
OMe
O
(180)
MeO
OMe
Br
(179)
MeO
OMe
(178)
MeO
OH
(177)
MeO
NH2
(175)
MeO
NHBu t
(173)

Scheme XII

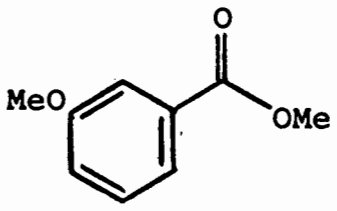
The subsequent synthetic steps in this route to the alcohol (154) (see Scheme XIII) were not attempted since other routes were



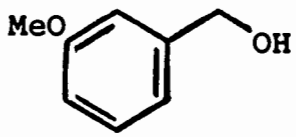
Scheme XIII

showing more promise.

Alternative routes were devised which embraced the idea of directly acylating 1,3-disubstituted compounds to give 1,2,4-trisubstituted ketones as products. The alcohol (181) was prepared by lithium aluminium hydride reduction of the ester (106), which is itself resistant to acylation presumably because of the deactivating influence of the electron-withdrawing ester group. Alcohol (181) gave two products when treated with a



(106)



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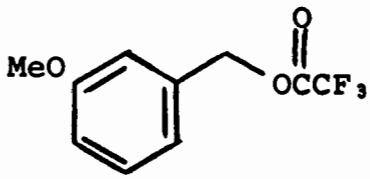
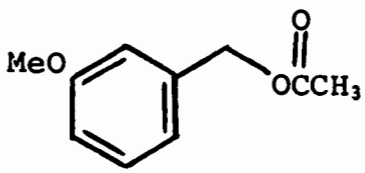
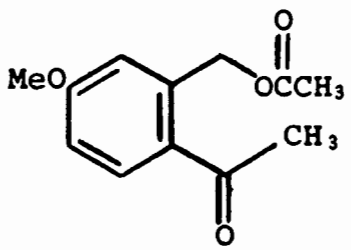


(182)



(183)



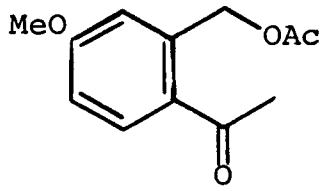
(184)

1.4 : 1 molar mixture of trifluoroacetic anhydride/acetic acid in anhydrous chloroform for 3.5 hours. The compound with the higher R_F value had no acetyl signal in the ^1H n.m.r. spectrum, while the compound with the lower R_F value had an acetyl signal at δ2.11. No trace of the desired trisubstituted product (184) could be isolated. On the basis of their mass spectra, the products obtained from the reaction were assigned the structures (182) and (183), *viz.* the trifluoroacetate and acetate of alcohol (181) respectively. Resubmission of the acetate (183) for five days to the same reaction conditions failed to produce any perceivable alteration whatsoever. However, when acetate (183) was stirred in a neat 1 : 1 trifluoroacetic anhydride/acetic acid mixture,[67] a product with a lower R_F value than starting material gradually increased in prominence on t.l.c. with time. The white crystals isolated after thirty hours had three singlets in the ^1H n.m.r. spectrum; one at δ3.98 due to the methoxy group,

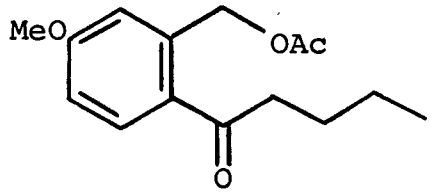
and two singlets at δ2.65 and 2.27 due to the *C*-acetyl and *O*-acetyl groups respectively. A clear ABX pattern was also present in the aromatic region of the spectrum. Mass spectrometry gave the correct molecular ion at *m/z* 222 (16%). These results permitted the assignment of structure (184) to this product. (Further proof is supplied on p. 79, where the assignment of structure (185) for the corresponding valerophenone is made on substitution of the acetic acid by valeric acid in the above reaction.)

Since acetate (183) gave rise to acetophenone (184) by the above method, but was itself formed as one of two products from the alcohol (181), acetate (183) was better prepared cleanly and in high yield from alcohol (181) by acetylation with pyridine and acetic anhydride. This procedure avoided the formation of the trifluoroacetate (182) which was formed in roughly equal quantities to (183) when the alcohol was used as starting material.

As mentioned above, the pentanoyl homologue (185) of acetate (184) was synthesized by substituting valeric acid for acetic acid as the acylating agent. This reaction was more complicated than the two-carbon reaction, possibly because of the steric interference of the bulkier pentanoyl group, although other effects may be involved. The optimum time for this reaction was approximately forty-eight hours - when this period was exceeded, the mixture deteriorated as evidenced by the formation of a yellow streak on thin layer chromatography which increased in quantity with time. It was difficult to purify the products from this contaminant. Moreover, at forty-eight hours starting

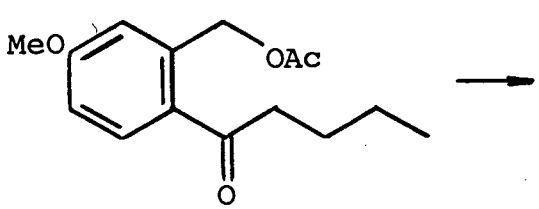


(184)



(185)

material was still present in the reaction mixture. The cumulative effect of these factors contributed to a low yield of (185) (34%) being obtained from unrecovered starting material under optimised conditions. The ^{1}H n.m.r. spectrum differed from that of the acetyl analogue (184) in that a triplet at δ2.92 and the residual signals of a typical *n*-butyl aliphatic splitting pattern were present in place of the *C*-acetyl singlet of the latter. Nonetheless, enough of compound (185) accrued to allow its conversion to the diol (186) with lithium aluminium hydride in preparative yield. Both hydroxy groups converged to give a



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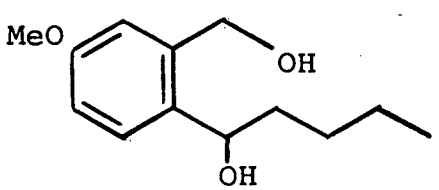
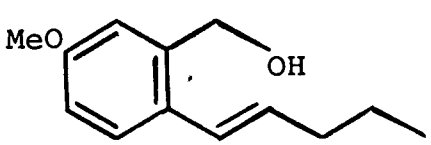


(186)

$-H_2O$



(154)

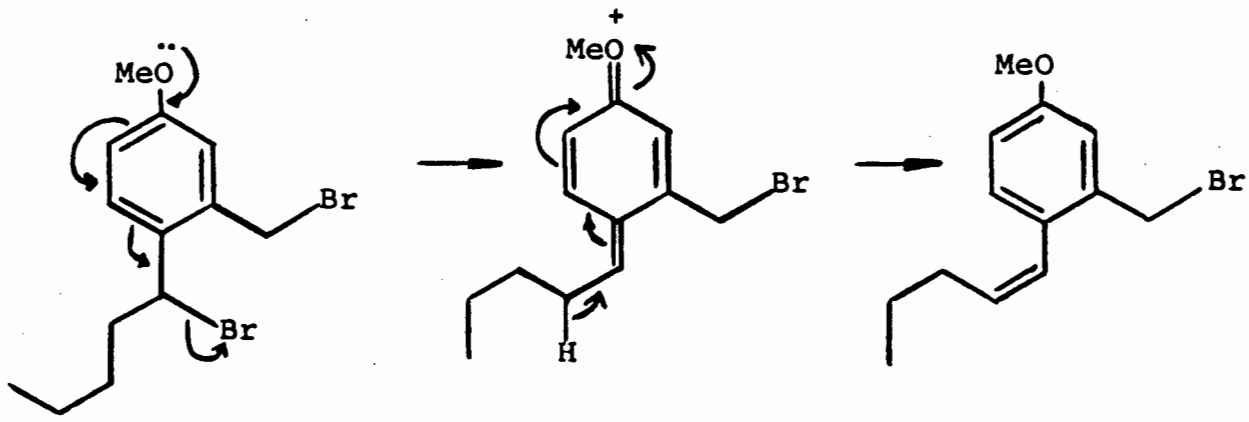
broad singlet integrating for two protons at δ3.30 in the ^1H n.m.r. spectrum. The two methylene protons of the primary hydroxymethyl group gave two doublets at δ4.53 and 4.69 (both *J* 12Hz) probably because of the restricted rotation due to the steric interaction with adjacent pentan-1-ol chain, the benzylic proton of which gave a triplet resonating at δ4.78.

From this strategic position, the final steps of the synthesis would be contingent on the feasibility of the conversion of the diol (186) to the unsaturated alcohol (154). By inspection, this constitutes a simple dehydration involving the secondary alcohol function of the molecule (186). Mechanistically this implied that the secondary hydroxy group of (186) would have to be eliminated in an anti-periplanar fashion to furnish the required *E*-stereochemistry. However, it was clearly understood that this might not be a simple procedure owing to the proximity of the adjacent primary alcohol function. This complexity manifested itself in that, despite many attempts at direct dehydration which included boiling in conc. H_2SO_4 as well as with *p*-toluenesulphonic acid in anhydrous benzene, no product corresponding to alcohol (154) could be isolated. Alternatively, the ketone (185) could also possibly be converted to its hydrazone from which the alkene can be liberated by an excess of methyl-lithium.[68] However, this alternative was not investigated as the following route, which was being attempted concurrently, proved to be successful.

The crux of this method depended upon the practicable transformation of the diol (186) to the dibromo compound (187). (See

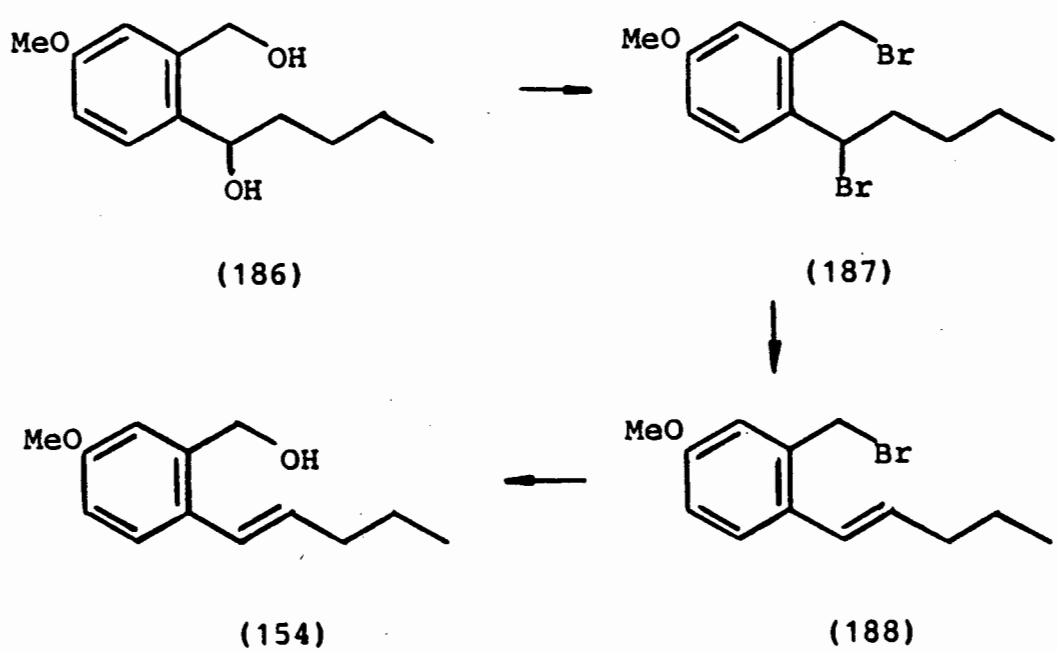
Scheme XIV.) This could conceivably be accomplished by the treatment of the diol with phosphorus tribromide, the expected action of which would be to simultaneously displace both hydroxy groups of the diol by bromine. Elimination of hydrogen bromide from the dibromo compound (187) by the action of a suitable base was predicted to introduce the pent-1-enyl substituent with solely the *E*-stereochemistry.[69] The primary bromide in the molecule would be expected to remain unaffected throughout this treatment because, unlike the secondary bromide on the pentyl side chain, it lacked any protons on the carbon adjacent to the one to which it was attached thus rendering anti-periplanar elimination impossible.

All the above reasoning prompted the stirring of the diol (186) with phosphorus tribromide in anhydrous benzene at room temperature for two hours. The ^{1}H n.m.r. spectrum of the crude product exhibited a quartet at δ4.52 and a triplet resonating at δ5.33 corresponding to the benzylic methylene protons and methine proton of the dibromo compound (187) respectively. Compound (187) is an unstable oil which gave many spots on t.l.c. on standing at room temperature. It can lose bromide as indicated below and seems to be hygroscopic. Its instability is also proven by the disappearance of the triplet at δ5.33 integrating for one proton from the ^{1}H n.m.r. spectrum after standing for a few hours at room temperature.



(187) (188)

The above considerations necessitated the immediate utilisation of the dibromo compound (187) after its formation. Dehydrobromination of compound (187) with lutidine (see Scheme XIV)



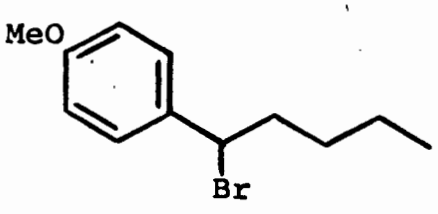
(186) (187)

(154) (188)

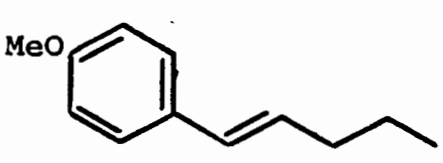
Scheme XIV

afforded a mixture in which the unsaturated bromo compound (188) predominated with some of the alcohol (154) also present. The addition of a drop of water in subsequent trials to the boiling lutidine solution managed to convert the unsaturated bromide (188) of higher R_F value to the unsaturated alcohol (154) as evidenced by thin layer chromatography.

Unfortunately very low overall yields of the alcohol (154) were repetitively obtained in this way. No water was thus added to the boiling lutidine in an effort to overcome this problem. The bromo compound (188) was isolated by chromatography instead and converted to the alcohol by boiling in 40% sodium hydroxide solution containing some toluene. This produced the alcohol in a yield of 60%. It soon became apparent that a method of producing the dibromo compound (187) in higher yield would have to be sought to compensate for the low yielding dehydrobromination step. It should also be noted at this stage that the model



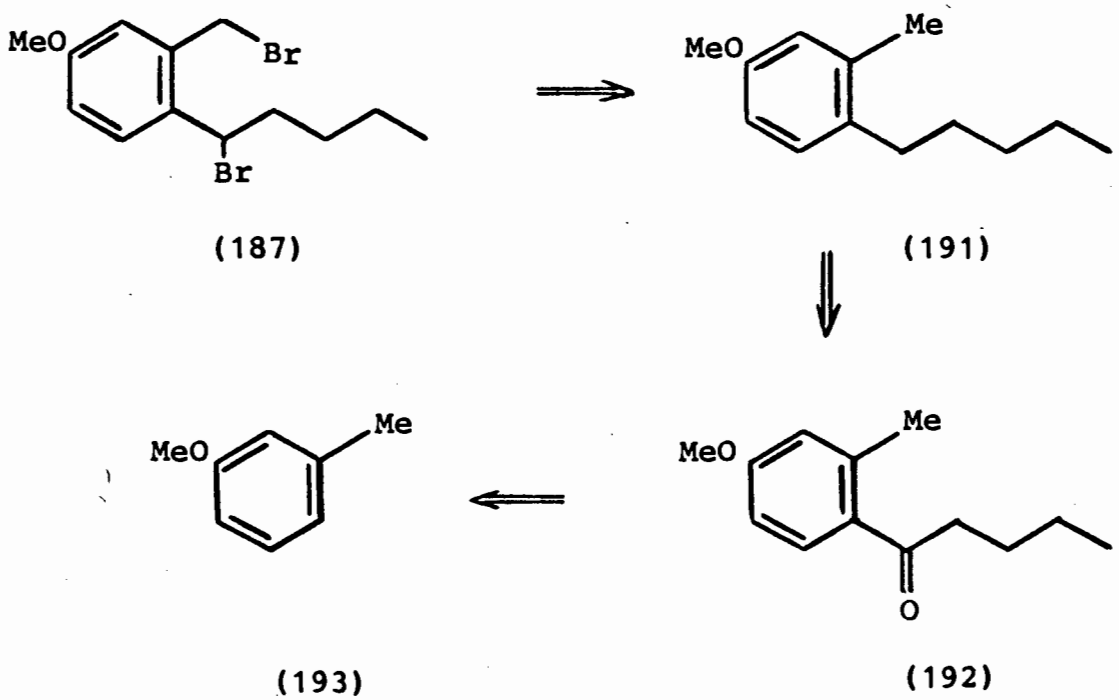
(189)



(190)

compound (189), namely 4-(1-bromopentyl)-anisole, was dehydrobrominated to afford compound (190) in a yield of 92% under identical conditions. Should the dibromo compound (187) be regarded from another perspective, it could be envisaged as the

product of homolytic dibromination of 3-methyl-4-pentyl-anisole (191) (see Scheme XV). Compound (191) was proposed as the



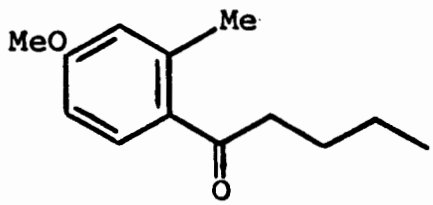
Scheme XV

product of Clemmensen reduction of the ketone (192), which in turn was expected to be constructed by the acylation of *meta*-cresol methyl ether (193), using the mixed anhydride method already described for the conversion of (183) to (185).

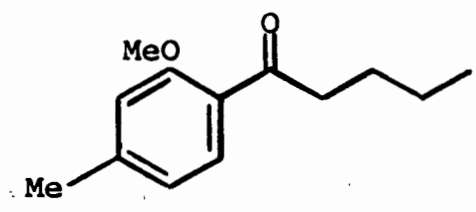
When compound (193) was stirred in premixed valeric acid and trifluoroacetic anhydride (1:1) at room temperature, the reaction yielded an orange liquid which partially crystallised overnight. The liquid gave predominantly one spot on t.l.c. These crystals were filtered off and recrystallised from light petroleum to give colourless cubes. The ^{1}H n.m.r. spectrum of the crystals had

the aryl methyl singlet at δ2.54, a two-proton triplet at δ2.87 and the methoxy signal at δ3.83. The aromatic region showed the *ortho*-coupled doublet at δ7.62 while the other aromatic protons were superimposed and appeared as a multiplet at δ6.82.

A further crop of crystals was obtained from a subsequent re-crystallisation. The residual yellow oil, however, proved to be composed of two products by ^{1}H n.m.r. Two similar sets of signals were present; one set was an exact replica of the spectrum that had been obtained for the previously isolated crystals, while the other set appeared to duplicate the first, i.e. two methoxy and two methyl signals were present. The triplet at δ2.88 appeared as a "quartet", and the *ortho*-coupled doublet now appeared to be a "triplet" because of the superimposition of signals. These observations were consistant with the formation of the *para*- and *ortho*-isomers (192) and (194) respectively. As



(192)

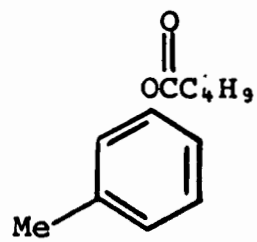


(194)

neither compound had been reported in the literature before, an unambiguous route to either of them had to be devised in order to allow decisive structures to be assigned to each. ^{1}H n.m.r., i.r. and mass spectrometry alone could not provide the correct assignments with a satisfactory degree of confidence. (Nuclear

Overhauser difference spectroscopy was not available at the time.)

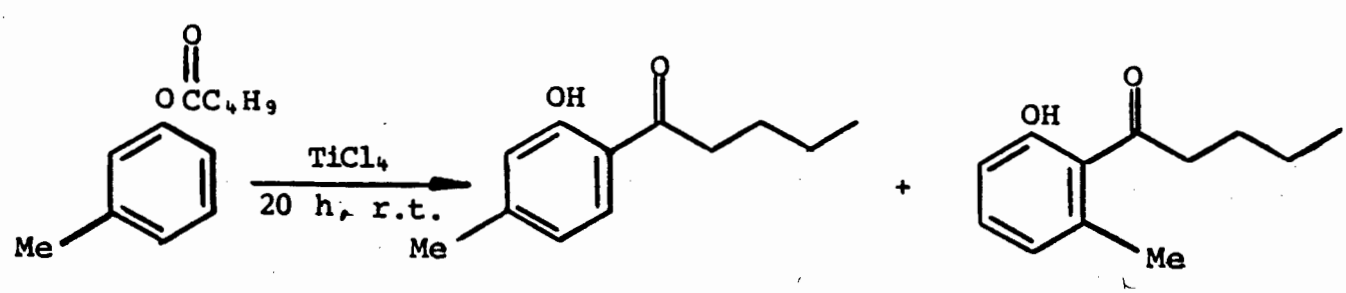
The method employed was to make the valerate ester of *m*-cresol (195) and to allow it to undergo a Fries rearrangement.[70] Titanium



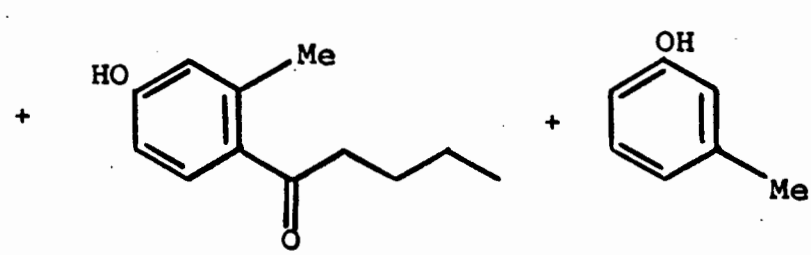
(195)

tetrachloride and boron trifluoride etherate were the two Lewis acids employed.

Compound (195) was stirred for twenty hours in titanium tetrachloride at room temperature under anhydrous conditions. Five compounds were obtained from the reaction. They were carefully separated from one another by column chromatography using light petroleum as eluant. The first fraction isolated was an oil.



(195) (196) (197)



(198)

^{1}H n.m.r. spectroscopy revealed a highly deshielded singlet integrating for one proton at δ12.44. The ABX system in the aromatic region had a deshielded *ortho*-coupled proton at δ7.64, a *meta*-coupled proton at δ6.75 and a doublet of doublets at δ6.70. Other signals were consistent with the pentanoyl chain and aryl methyl. The very high R_F value of this compound was furthermore compatible with the assumption that it was the known[70] compound (196), obtained in 49% yield, where the hydroxy proton is hydrogen-bonded to the adjacent carbonyl group.

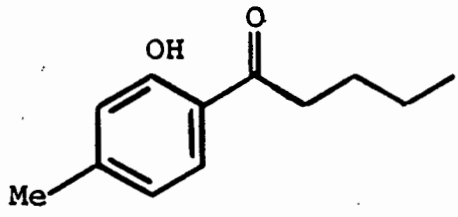
Later fractions were contaminated with starting material, which was regained in a yield of 13%. The next product to elute was a very small fraction which nonetheless gave a clear ^{1}H n.m.r. spectrum. A broad, deshielded signal integrating for one proton resonated at δ11.54. The aromatic protons gave three *ortho*-coupled protons at δ6.72, 6.83 and 7.23, and the usual pentanoyl and methyl signals were also present. This compound is undoubtedly the product of *ortho*-migration between the substituents. Compound (197), an oil, was obtained in a yield of 3%. High resolution mass spectrometry gave the correct mass for the molecular ion.

A rather large fraction was isolated as an oil after the 1,2,3-trisubstituted compound. This was *m*-cresol, probably formed by the cleavage of the ester (195) by the Lewis acid. The large yield of *m*-cresol (25%) militates against the use of titanium tetrachloride as a suitable agent to effect this particular Fries rearrangement. Finally, a small fraction having the lowest R_F value of all was isolated as white crystals. The ^{1}H n.m.r.

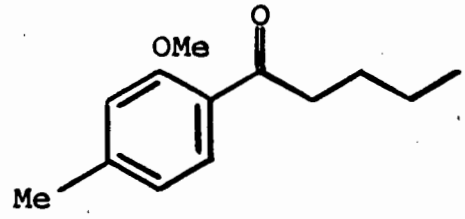
spectrum showed a broad signal integrating for one proton at δ4.32. It also had an *ortho*-coupled signal at δ7.69 and a broad signal integrating for two protons at δ6.73. This was indeed the known[70] compound (198), i.e. the product of *para*-migration which had been produced in very low yield (4%).

A different distribution of products was obtained from the boron trifluoride etherate reaction. When the ester (195) was stirred for 4 hours at 110°C in freshly distilled boron trifluoride etherate only two significant products were isolated. Compound (196) whose yield had risen in prominence from 49% to 85% was by far the major product isolated from the reaction. The product of *para*-migration (198) had somewhat diminished in importance and was obtained in a yield of less than 2%. No starting material, *m*-cresol or the 1,2,3-trisubstituted compound (197) were isolated from the reaction. In conclusion, it can be said that the boron trifluoride etherate mediated Fries rearrangement gave a much cleaner reaction than that catalysed by titanium tetrachloride.

The conversion of the phenols (196) and (198) to their respective methyl ethers (194) and (192) remained to be undertaken in order to correctly identify the individual structures obtained from *meta*-cresol methyl ether on reaction with valeric acid and trifluoroacetic anhydride. This was easily accomplished in high yield using dimethyl sulphate and potassium carbonate in boiling anhydrous acetone.



(196)



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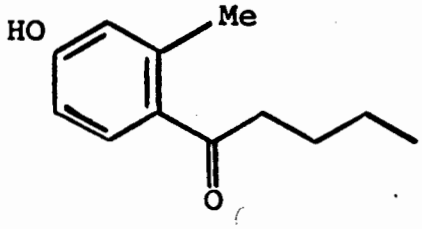
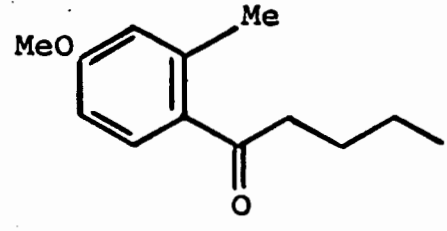


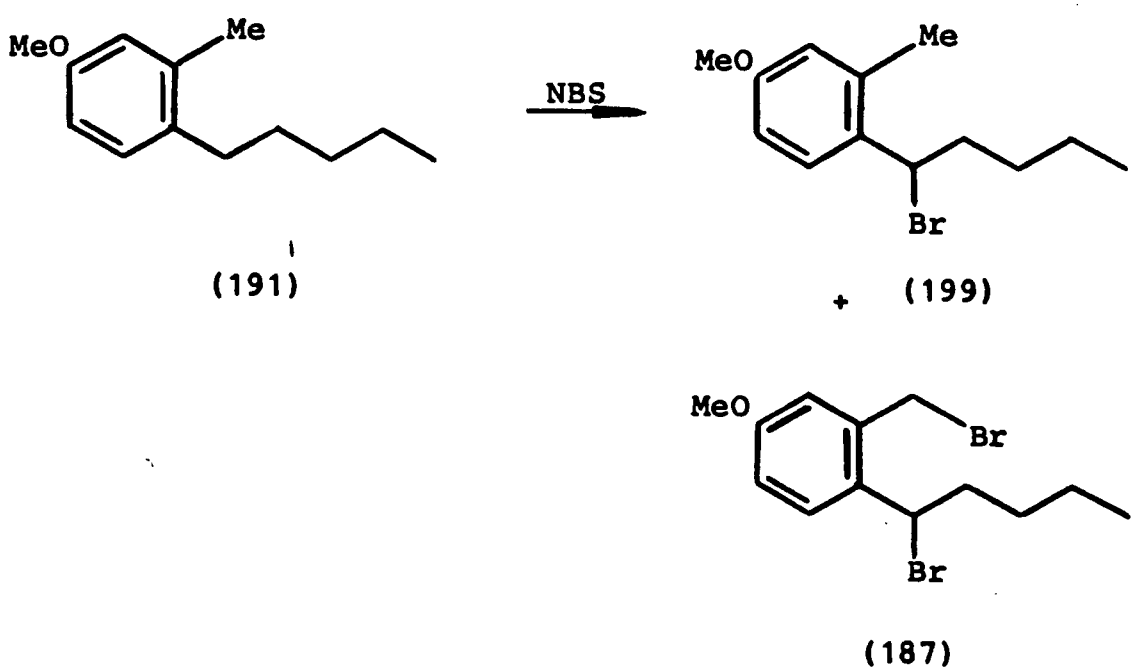
(198)



(192)

Product (194) was isolated as an oil while its isomer (192) gave colourless crystals which had the same ^{1}H n.m.r. and i.r. spectra, melting point and mixed melting point as those crystals obtained from the direct acylation of *meta*-cresol methyl ether (193). Furthermore, the ^{1}H n.m.r. signals of compound (194) correlated perfectly with the extra signals present in the ^{1}H n.m.r. spectrum of the residual mixture obtained after the crystallisation of compound (192). These results therefore indicated that the compounds (192) and (194) had been initially obtained in yields of (73%) and (22%) respectively from the mixed anhydride method. The direct pentanoylation of *meta*-cresol methyl ether was ideally suited for large scale work (*ca.* 10 g) and the high yield of product (192) rendered Scheme XV viable and preferred to the previous route.

Clemmensen reduction of compound (192) proceeded as expected to afford 3-methyl-4-pentyl anisole (191) as an oil. Various conditions were experimented with in the conversion of compound (191) with *N*-bromosuccinimide (NBS) to the dibromo compound (187). This seemingly simple reaction, contrary to expectation, proved to be a very complex reaction indeed. Generally, small scale reactions (*ca.* 100 mg) gave better results than larger. Furthermore, 2.1 mol equivalents of *N*-bromosuccinimide proved to be too little - these trials provided large amounts of the monobromo compound (199). When the number of moles of *N*-bromosuccinimide employed was increased to three, complications set in



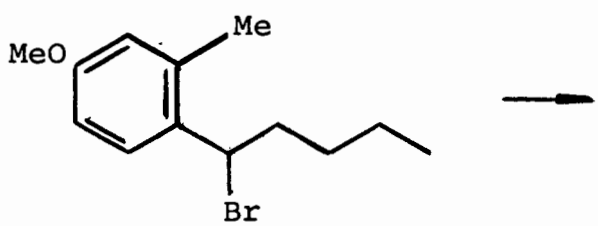
(191) + (199)

(187)

as evidenced by the many spots which were obtained on t.l.c. whilst monitoring the reaction.

Optimum results were obtained when compound (191) was treated with 2.5 mol equivalents of *N*-bromosuccinimide in anhydrous

carbon tetrachloride and heated under reflux for one hour, followed by removal of succinimide and the solvent before boiling in lutidine for thirty minutes. This led to a mixture of the dehydrobrominated compounds (200) and (188) being obtained from their respective precursors (199) and (187). Separation of these two compounds from each other was very difficult as both had high and close R_F values in light petroleum, with the brominated compound (188) having a marginally greater R_F value than compound (200). It was thus decided to postpone separation at



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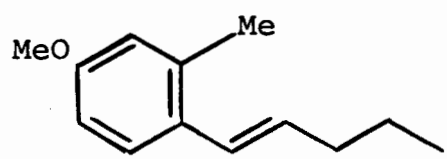
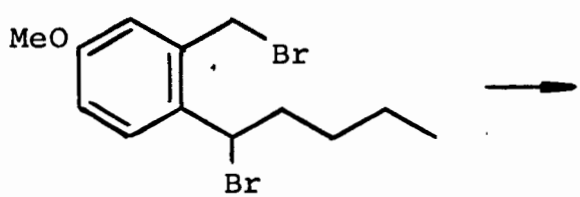
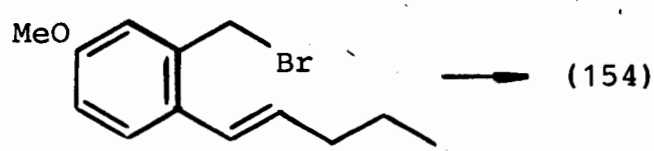


(200)



(187)

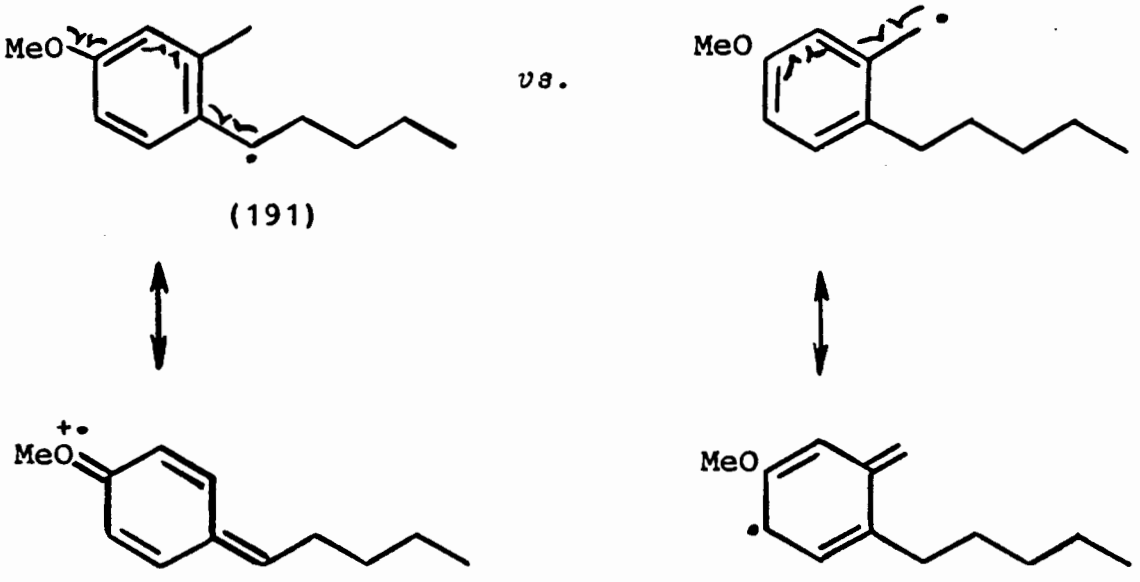


(188)

this stage until after the subsequent conversion of (188) to the alcohol (154) where the difference in R_F was expected to be more pronounced.

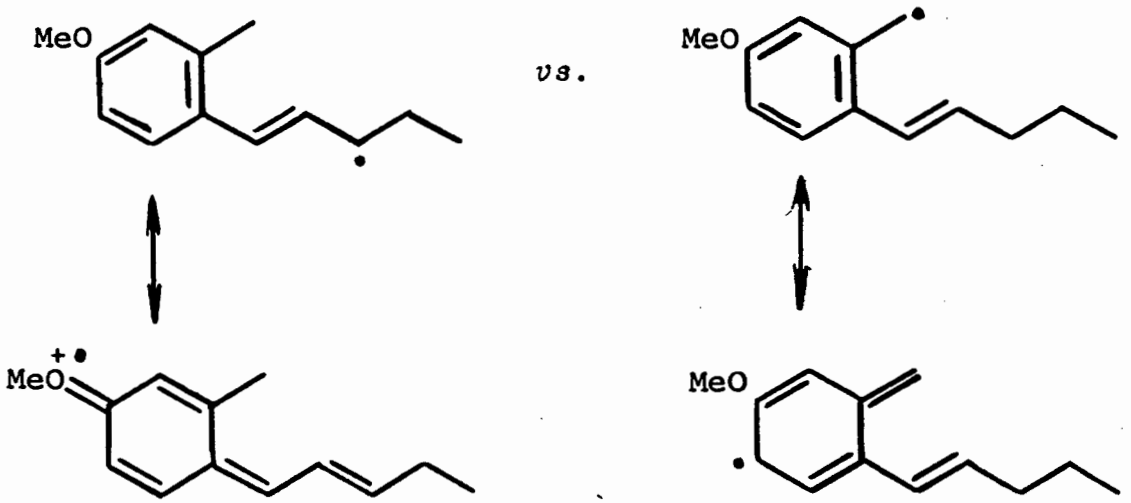
Many efforts were directed at preventing the formation of the ever-present compound (200) which was persistently obtained in higher yield than the functionalised product (188). Compound

(191) gave the product (200) in an overall yield of 92% after dehydrobromination when only one mol of *N*-bromosuccinimide was employed. This selective homolytic bromination is brought



Scheme XVI

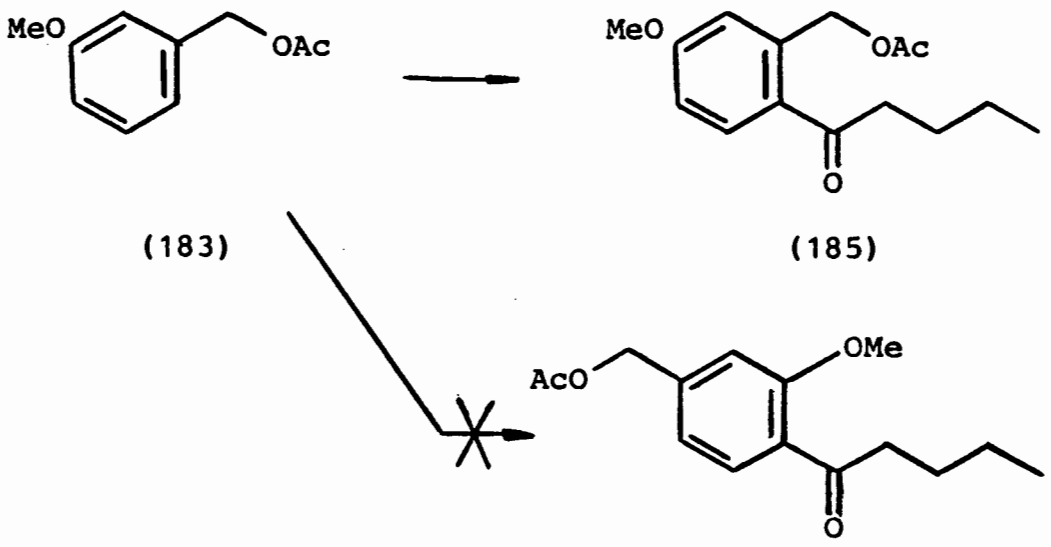
about by the greater stability of the benzylic radical *para* to the methoxy group (see Scheme XVI). A paper on a similar selective bromination has just recently been published.[58] An attempt to recycle product (200) by homolytic bromination afforded a mixture of products as anticipated, none of which corresponded to the compound (188). Once again it can be presumed that the extended stabilised radical *para* to the methoxy group competes favourably with the benzylic radical *meta* to the methoxy group, which does not conjugate onto the methoxy group (see Scheme XVII).



Scheme XVII

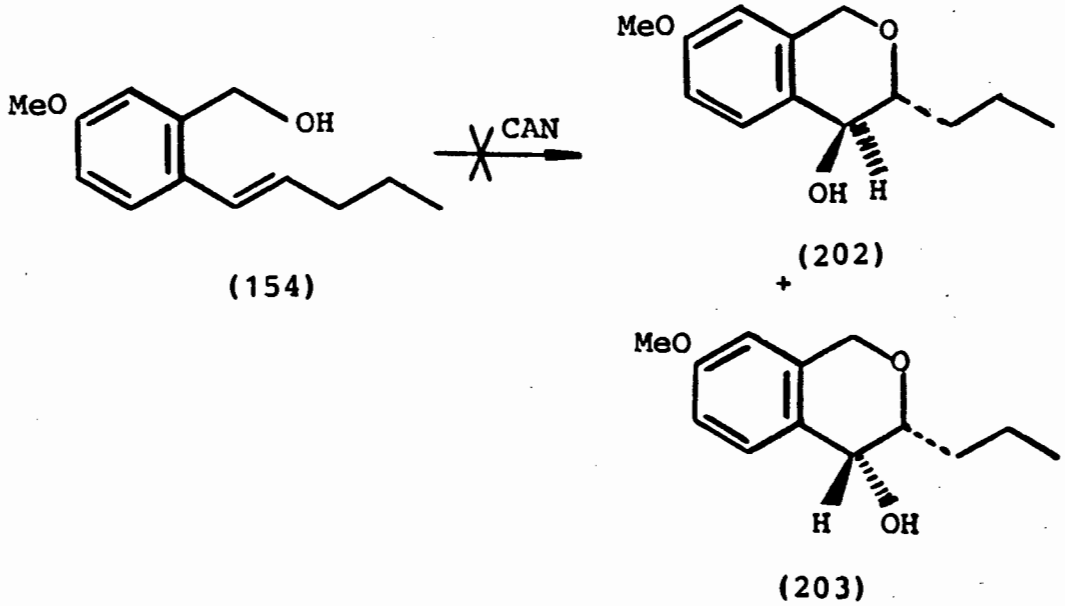
Since it was not possible to entirely avoid compound (200), the mixture of the bromo compound (188) and the less functionalised compound (200) was dissolved in a little toluene and boiled in a 20% sodium hydroxide solution for eighty hours. This afforded alcohol (154), formed by nucleophilic displacement of the bromide by hydroxide in an overall yield of 12% from compound (191). The concomitant side-product (200) was recovered unchanged from the latter treatment in a yield of 28% from the same starting material. Despite the low yield of alcohol (154) obtained from compound (191), this route remains superior to the immediately preceeding one because compound (191) can be prepared more easily, on larger scale, and in higher yield than the diol (186). The route from *meta*-cresol methyl ether was therefore used as the method of choice to prepare alcohol (154).

The alcohol (154) obtained by both routes had identical signals in their ^{1}H n.m.r. spectra. This added further proof that the

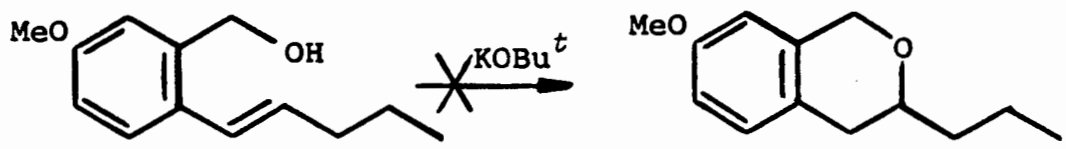


compound isolated from the pentanoylation of (183) was indeed (185), and not its isomer (201) which would also give an ABX system in the aromatic region of the ^{1}H n.m.r. spectrum. By induction, the above mode of acylation can be extended to further validate the structure of the acetyl analogue of compound (185), *viz*, compound (184).

Alcohol (154) gave a crude mixture of products upon treatment with cerium(IV) ammonium nitrate, none of which could be identified as the hydroxyisochromans (202) and (203). Furthermore, compound



(154) was also unaffected by base-induced cyclisation; no evidence could be obtained for the formation of compound (204) upon the treatment of (154) with potassium *t*-butoxide in dimethylformamide under a variety of reaction conditions.

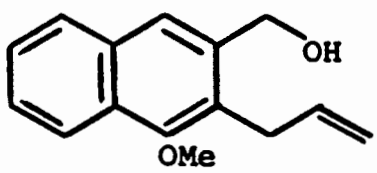


(154) (204)

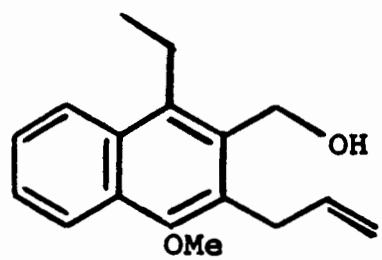
The above results established certain points of considerable importance in this study. First, a methoxy *para* to the alkenyl chain does not support the cerium(IV) ammonium nitrate-promoted cyclisation as does a methoxy in the corresponding *ortho* position. This therefore questioned the authenticity of the mechanism that had earlier been proposed (see p. 48) for this cyclisation prior to the synthesis of compound (154). Secondly, the methoxy *ortho* to the alkenyl side-chain is necessary for the cerium(IV) ammonium nitrate-promoted cyclisations in the examples so far investigated. Thirdly, the hydroxymethyl and alkenyl substituents appear to require to be flanked by groups bulky enough to bring them into close proximity before based-induced cyclisation might occur, since the reaction failed in those cases where these substituents were both flanked by hydrogens. Consequently, substrates had to be devised which would satisfactorily throw more light on some of these intriguing aspects. It was envisaged that the steric dependence of the base-induced cyclisations could be verified by substituting ethyl for methoxy in a new series of *ortho*-alkenyl(hydroxyalkyl)arenes. This elaboration would remove the

electronic influence provided by the methoxy group while retaining a similar steric congestion in these systems, since the only change would be the substitution of an oxygen atom by a methylene group.

The first compounds which were considered were (205) and (206). These naphthalenoid analogues would be closer in structure to the original compounds (72) and (79) whose cyclisations were first observed. An added advantage of the naphthalene ring system was the relative ease of synthesis of these compounds over their benzenoid analogues on account of two positions in the electron-rich ring being blocked, thereby preventing reaction at these two centres. For economy of synthesis, compound (207), the



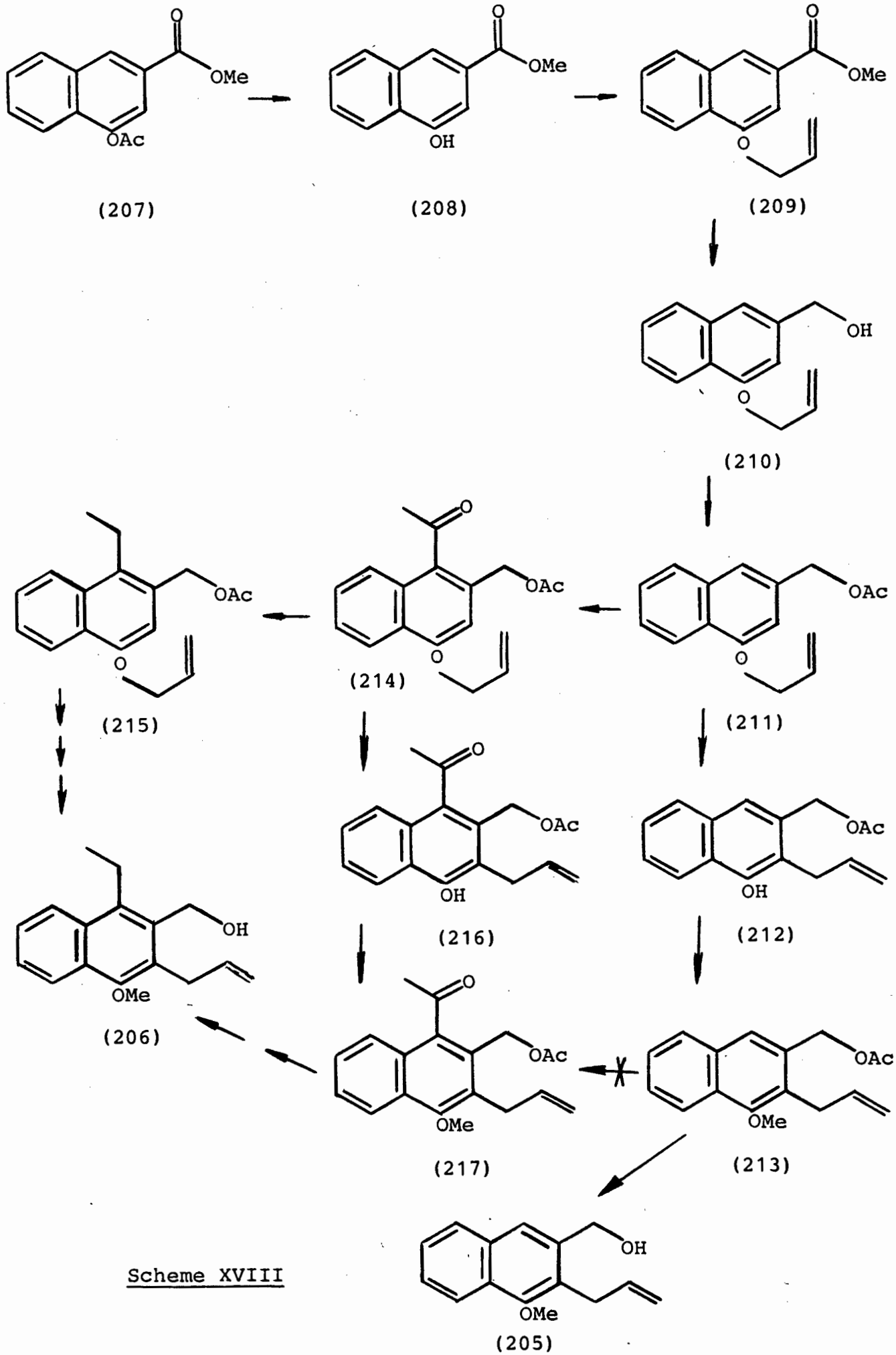
(205)



(206)

product of the Stobbe reaction between benzaldehyde and dimethyl succinate,[71] was initially considered as a starting material leading to both compounds. Their synthetic routes would then follow a common path until a suitable point of divergence was reached (see Scheme XVIII).

The Stobbe product (207) was converted quantitatively to the naphthol (208) by stirring in a 1% sodium hydroxide solution in anhydrous methanol. Without any further purification, compound



Scheme XVIII

(208) was heated under reflux in anhydrous acetone with potassium carbonate and allyl bromide to afford the *O*-allyl ether (209), which had a proton resonating as a signal at δ7.39 for the position between the two substituents and a more deshielded signal at δ8.21 for the *peri*-aromatic proton on the substituted ring. Lithium aluminium hydride reduced ester (209) to the alcohol (210), which was acetylated using acetic anhydride in pyridine to give compound (211). The latter reaction was carried out with the aim of facilitating *C*-acylation in the subsequent step [(211) → (214)] as had been experienced with the conversion of (183) to (184) (see p. 62). Furthermore, the inclusion of a *C*-acylation reaction in the synthetic plan was a supplementary advantage as it made provision for bulkier analogues of (206) to be prepared either by making use of a bulkier acylating agent, or by subsequent modification of the *C*-acetyl group of (214) to the 2-aryl-2-propanol by reaction with methyl magnesium bromide, for example.

Compound (211) furnished the *C*-acylated compound (214) in low yield (27%) upon treatment with premixed trifluoroacetic anhydride/glacial acetic acid (1:1) under optimised conditions. The ^{1}H n.m.r. spectrum of compound (214) showed a singlet at δ2.68 integrating for the protons of the *C*-acetyl group, and the substitution pattern was confirmed by the disappearance of the low field signal at δ7.26 of the starting material (211), the one present in the spectrum being the higher field proton between the substituents at δ6.81. Clemmensen reduction of the benzylic carbonyl of compound (214) also proceeded in low yield (15%) to afford compound (215), from which it was hoped that compound

(206) could be obtained after Claisen rearrangement, methylation and hydrolysis of the acetate. This sequence of reactions was reversed in the hope of obtaining higher yields, but the yield of the tetrasubstituted compound (217) after Claisen rearrangement of (214) to phenol (216) followed by methylation and chromatography was only 19%. Compound (214) proved labile to heat and started to char gradually after being heated for only five minutes at 180°C.

By contrast, the disubstituted compound (211) readily underwent Claisen rearrangement to give the naphthol (212) in high yield (87%) upon heating under nitrogen at 160°C for one hour.[72] Naphthol (212) afforded its methyl ether (213) quantitatively when heated under reflux in the presence of an excess of potassium carbonate and dimethyl sulphate in anhydrous acetone.

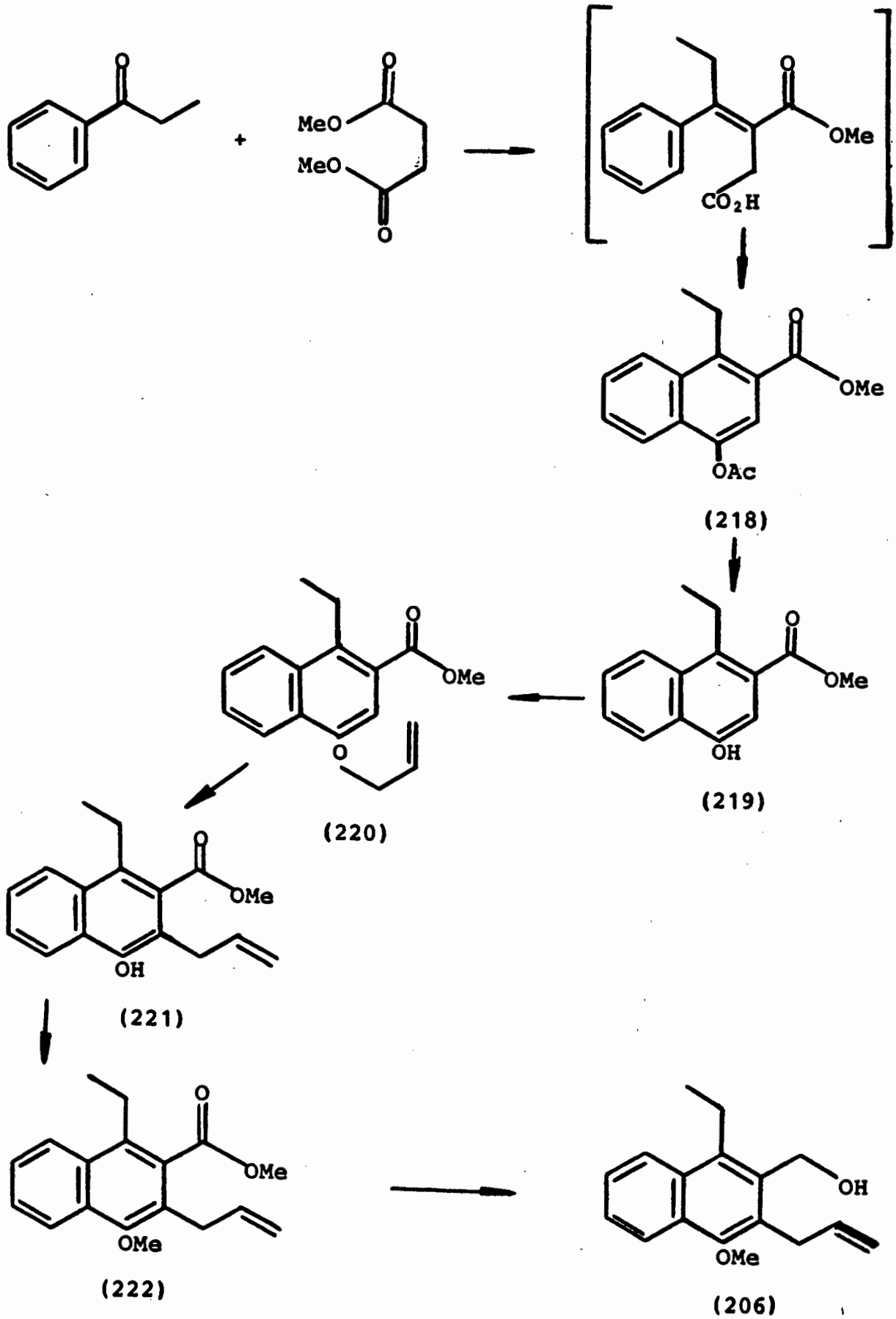
The acetate (213) was conceived as being a second plausible point of entry to the tetrasubstituted compounds (see Scheme XVIII). Unfortunately acylation of compound (213) proved to be extremely difficult as no product (217) could be obtained upon its treatment with trifluoroacetic anhydride and acetic acid under a variety of reaction conditions. However, the *O*-acetyl group of compound (213) was easily removed in high yield (83%) by stirring for 20 minutes in methanolic sodium hydroxide (one molar) to yield the alcohol (205).

The low yields arising from the introduction of an ethyl group by the methods attempted above rendered Scheme XVIII unattractive and necessitated a revision of the synthesis of the target

alcohol (206). This problem was solved by the introduction of the ethyl moiety earlier on in the Stobbe condensation step. Thus, propiophenone was substituted for benzaldehyde in the known[73] Stobbe reaction with dimethyl succinate to afford compound (218) after aromatisation of the intermediate half esters by boiling for five hours in the presence of acetic anhydride and sodium acetate (see Scheme XIX).

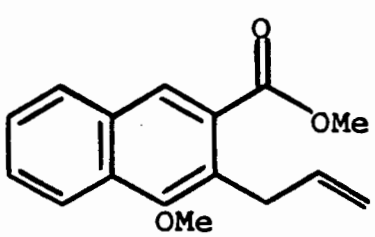
The route from the naphthalene (218) was quite similar to that followed in Scheme XVIII. Treatment of compound (218) with a 1% sodium hydroxide solution in anhydrous methanol cleaved the acetoxy group to afford the naphthol (219) in quantitative yield as witnessed by the disappearance of the acetyl signal at δ2.44 in the ^{1}H n.m.r. spectrum and the appearance of a singlet at δ5.91 due to the hydroxy proton. Naphthol (219) was smoothly allylated by heating under reflux in the presence of allyl bromide and potassium carbonate in anhydrous acetone to give compound (220). The methylene protons of the allyl group of compound (220) resonated as a multiplet at δ4.65 - 4.80 and the aromatic proton of the substituted ring resonated as a singlet at δ7.15.

When compound (220) was heated under nitrogen at 160 - 200°C it underwent a Claisen rearrangement to afford the trisubstituted naphthol (221) in good yield (86%). The only aromatic protons present in the ^{1}H n.m.r. spectrum were those of the unsubstituted ring which appeared as multiplets. The multiplet due to the methylene protons of the allyl group had shifted upfield to δ3.38 - 3.51. Naphthol (221) was very unstable and


MeO
MeO
O
OMe
CO2H
OMe
OAc
(218)
OMe
OH
(219)
OMe
O
(220)
OMe
OH
(221)
OMe
OMe
(222)
OH
OMe
(206)

Scheme XIX

darkened on standing as a neat oil or in solvent (acetone). Both t.l.c. and the ^1H n.m.r. spectrum of naphthol (221) showed that a number of additional compounds had formed after standing at room temperature for twenty-four hours. These observations led to compound (221) being methylated immediately after its formation to afford the methyl ether (222). The overall yield of these two steps was 69%. The reaction sequence was completed by the lithium aluminium hydride reduction of ester (222) to give the alcohol (206) in good yield (86%). It was interesting to note that this reduction required a much longer period of reaction (three hours) than the analogous trisubstituted ester (224) (10 minutes). Presumably, the comparatively longer time of lithium aluminium hydride reduction of ester (222) can be

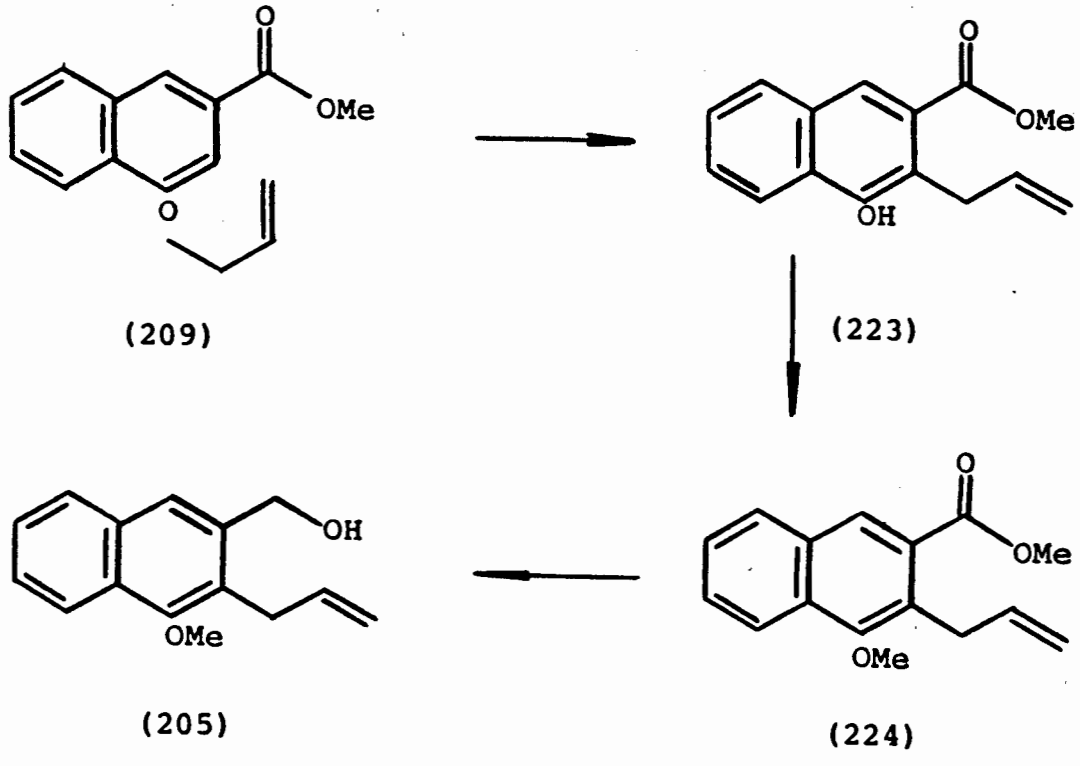


(224)

explained in terms of the greater degree of steric congestion present in ester (222). In compound (224) the ester group is relatively exposed to attack by the reducing agent, while the ester group of the tetrasubstituted compound (222) is embedded between the ethyl and alkenyl side chains making access by the lithium aluminium hydride more difficult.

A shorter route to alcohol (205) was also undertaken at this stage in order to increase the quantity available for the

subsequent cyclisation reaction. This route (see Scheme XX) was two steps shorter than the previous one (Scheme XVIII) as protection/deprotection of the alcohol group was obviated. Compound (209) gave the naphthol (223) in excellent yield (94%)

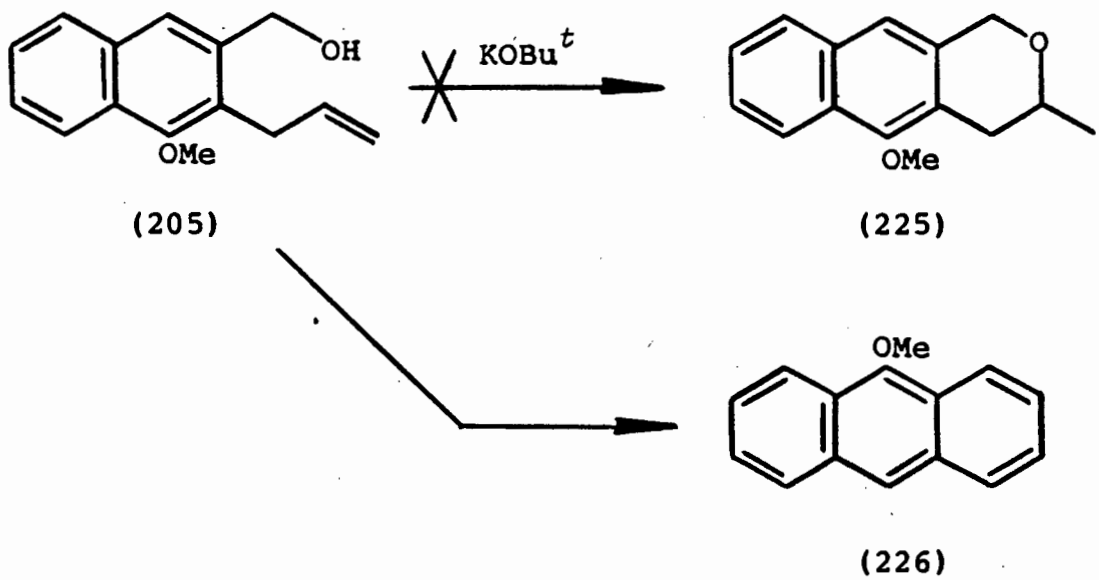


Scheme XX

after chromatography upon heating under nitrogen at 180°C for ninety minutes, which after methylation in the usual way produced the methoxy compound (224). That *ortho*-migration of the allyl group had occurred was obvious from the comparison of the ^{1}H n.m.r. spectra of ethers (209) and (224). Of the two signals resonating at δ7.39 and δ8.21 for the aromatic protons *ortho* and *para* to the allyl ether of compound (209) respectively, it was the more deshielded proton whose chemical shift correlated

very closely with the sole one-proton singlet at δ8.20 in the ^{1}H n.m.r. spectrum of ether (224). Alcohol (205) was readily obtained by the lithium aluminium hydride reduction of ester (224).

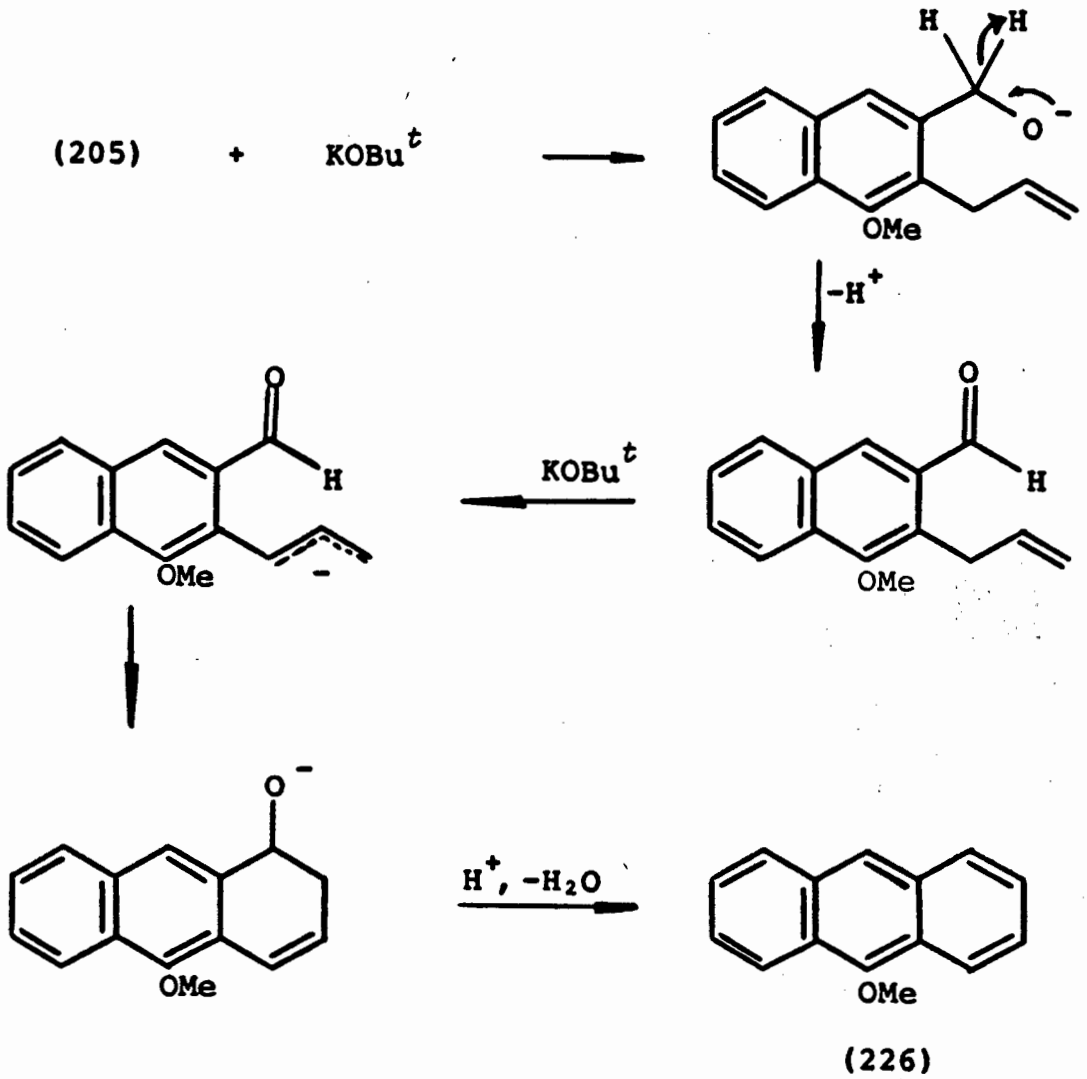
The cyclisation of compounds (205) and (206) using potassium *t*-butoxide in dimethylformamide produced some unusual results. Compound (205), as inferred from the behaviour of alcohol (87),



(205) (225)

(226)

was not expected to give any cyclic ether (225) and this turned out to be the case in practice. However, compound (226), the known[74] 9-methoxyanthracene (see experimental section p. 147) was isolated in a yield of 25%. This latter reaction denotes that a different mode of cyclisation had taken place. A possible mechanism for this unusual reaction is tentatively set out in Scheme XXI. In terms of this proposal, the base initially abstracts the hydroxy proton to produce an alkoxide which eliminates hydride to form an aldehyde. A second butoxide ion then eliminates an acidic benzylic proton to form an allylic

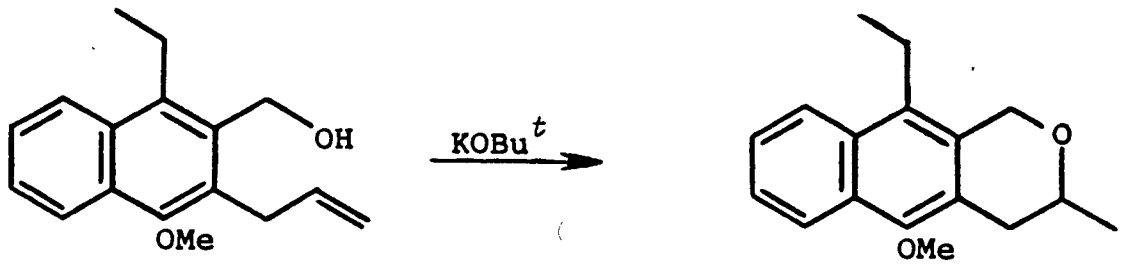


(226)

Scheme XXI

anion, which in turn attacks the aldehyde to give a second alkoxide. This could abstract a proton, for example either from *t*-butyl alcohol formed in an earlier step, or by transfer from the α-methylene group to give the related carbanion, the former eliminating water or the latter hydroxide, to give the observed product (226). The loss of hydride would be more attractive if an obvious hydride acceptor were present. For example, the reaction was not performed under nitrogen, and oxygen may have been involved.

When treated with potassium *t*-butoxide in dimethylformamide compound (206) cyclised to afford the ether (227) in a yield of

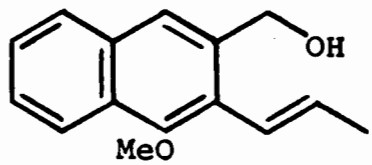


(206) (227)

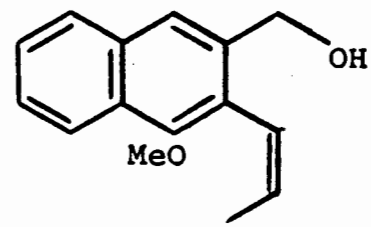
65%. The mass spectrum of compound (227) had the molecular ion as the base peak, and a very prominent (86%) peak at molecular mass 212 corresponding to a fragment arising from a retro-Diels-Alder fragmentation with elimination of acetaldehyde. No vinylic protons were present in the ^{1}H n.m.r. spectrum of compound (227); instead, the pyran methyl appeared as a doublet integrating for three protons at δ1.42, while the benzylic hydroxymethyl protons which resonated as a singlet in the precursor (206), now appeared as two distinct doublets at δ4.89 and 5.18 characteristic of those found in 2-benzopyrans. This splitting is undoubtedly due to the different chemical environments adopted by these protons in the more rigid pyran ring.

It should be noted that when these base-induced reactions of compounds (205) and (206) were interrupted by quenching with water before completion, various side-products were isolated which eventually disappeared in those experiments which were allowed to proceed to completion. These compounds had R_F values quite similar to their respective starting materials

(205) and (206). On the basis of the allylic signals present in their ^1H n.m.r. spectra, they were identified as being the conjugated alkenes (229) and (230), and (231) and (232) isolated as stereoisomeric mixtures from each of their unconjugated



(229)



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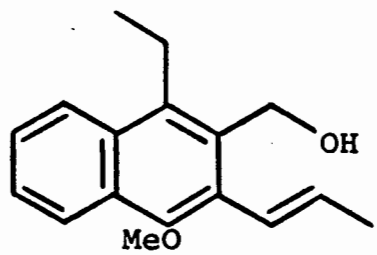

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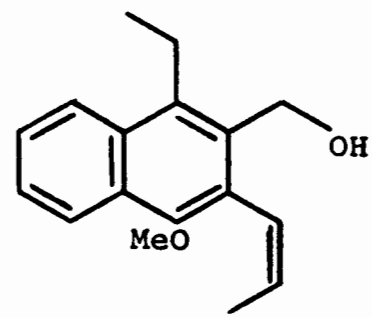
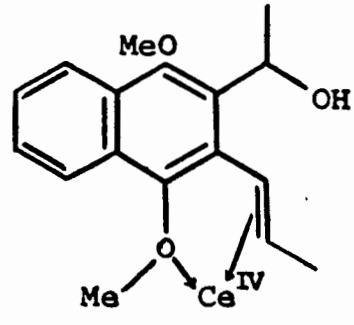


(232)

precursors. Isomerisation of the terminal alkene to the conjugated alkene in similar systems had already been effected in these laboratories using potassium *t*-butoxide in tetrahydrofuran.[36] The base-induced cyclisation of compounds (205) and (206) to their respective products thus in effect also incorporated the cyclisations of their conjugated analogues; implicit in the above is the fact that the reaction proceeds irrespective of the stereochemistry of the allyl group.

Conversely, the position of the double bond extensively influenced the outcome of the cerium(IV) ammonium nitrate reactions of these compounds (Scheme XXII). The following experiment explicitly showed that success of ring closure was contingent on the alkene being conjugated to the aromatic nucleus: In contrast to the reaction of compound (72) with cerium(IV) ammonium nitrate, which gave rise to the two naphthopyranquinones (75) and (76) by initial cyclisation followed by oxidation,[34] identical treatment of the unconjugated isomer (82) with four molar equivalents of the oxidant gave rise to the new quinone (228) in a yield of 70%. Thus, when the double bond is not conjugated with the aromatic system, cyclisation does not occur.

The failure of the alkenylbenzyl alcohol (154) to cyclise to a benzopyran affirmed the necessity of having the methoxy substituent *ortho* to the alkenyl group. Thus a reasonable modification of the mechanism already proposed in Scheme XI might be that the cerium(IV) ion underwent co-ordination to both the methoxy oxygen and the alkenyl substituent simultaneously to form an intermediate such as (233), in which oxidation of the double bond by the metal ion took place to form thereafter the radical cation (146).[76] This in turn would undergo cyclisation to the benzylic radical (147) which would undergo further oxidation as previously described.



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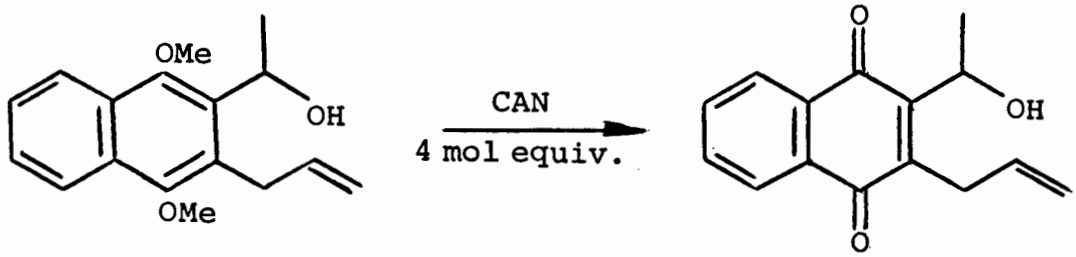
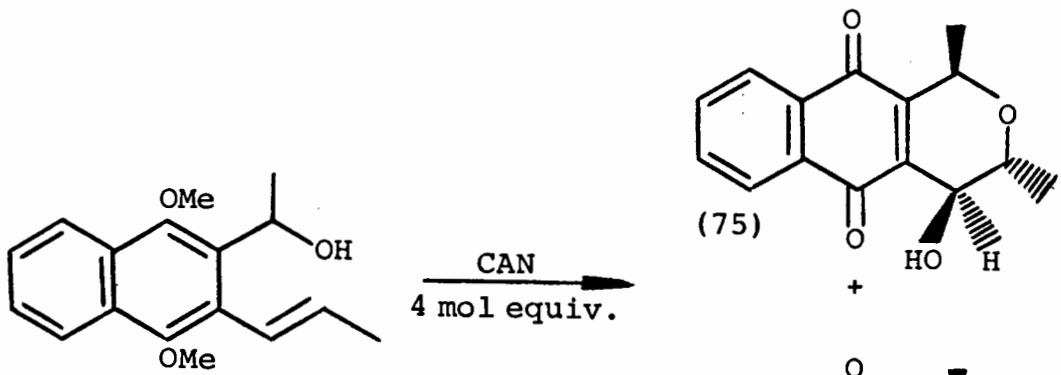
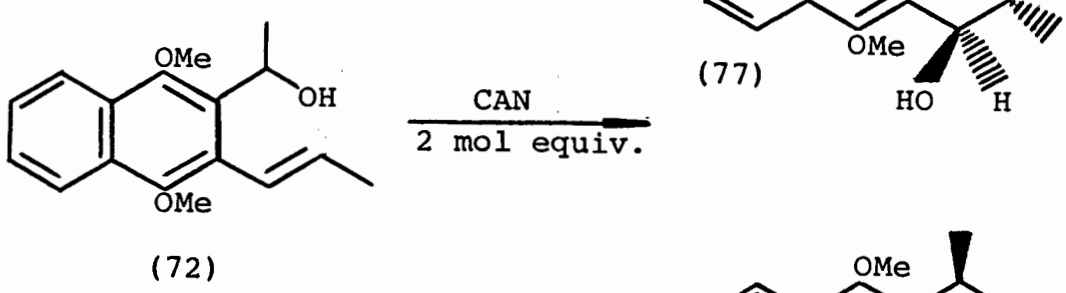


(82) (228)



(72) (75) (76)



(72) (77) (78)

Scheme XXII

In conclusion, it can be stated that the work described in this thesis has answered a number of questions raised at its inception. However, there are areas in which further work may be undertaken, and these are currently being investigated.

E X P E R I M E N T A L

GENERAL

^{1}H n.m.r. spectra were recorded using the following instruments: 60 MHz, Varian EM-360; 90 MHz, Bruker WH-90 and 100 MHz, Varian XL-100. Unless otherwise stated, all ^{1}H n.m.r. spectra were recorded at ambient temperature in deuterochloroform using tetramethylsilane as an internal standard. Mass spectra were recorded on a VG Micromass 16 F mass spectrometer at 70 eV and an ion source temperature between 180 and 220°C. High resolution mass spectra were recorded on a Varian MAT 311 A spectrometer at the University of Stellenbosch. Infrared spectra were measured for Nujol mulls, unless otherwise stated using a Perkin-Elmer 237 spectrophotometer. Melting points are uncorrected and were recorded on a Fisher-Johns apparatus. Elemental analyses were performed on a Heraeus CHN-RAPID analyser.

Column chromatography was carried out on dry columns with Merck Kieselgel 60 (70 - 230 mesh) as adsorbent. Preparative layer chromatography (p.l.c.) was performed on glass plates coated with Merck Kieselgel 60 F_{254}, while thin layer chromatography (t.l.c.) was carried out on aluminium plates coated with the same material.

Light petroleum refers to the fraction of boiling point 60 - 90°C, and ether to diethyl ether. Sodium hydride (Merck) was supplied as a dispersion in paraffin oil. Anhydrous magnesium sulphate was used to dry the organic solvents after extraction procedures, and most organic solvents and liquid reagents were distilled immediately before use.

(E)-2-Pent-1-enylbenzyl alcohol (86)

The ester (92) (0.81 g, 3.95 mmol) was dissolved in dry ether (25 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (300 mg, 7.9 mmol) in dry ether (25 ml) at room temperature. After the mixture had been stirred for 0.5 h, sufficient saturated aqueous ammonium chloride was added to decompose the excess reagent, followed by magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the residue chromatographed (eluant 10% ethyl acetate-light petroleum) to give the product (86) (0.56 g, 81%) as an oil (Found: C, 81.9; H, 9.3. $C_{12}H_{16}O$ requires C, 81.75; H, 9.15%); $\nu_{max.}$ (film) 3310 cm^{-1} (OH); δ0.96 (3H, t, *J* 7 Hz, CH_3), 1.5 (2H, sextet, *J* 7 Hz, 4-CH_2), 1.80 (1H, br s, OH), 2.23 (2H, q, *J* 7 Hz, 3-CH_2), 4.71 (2H, s, ArCH_2), 6.14 (1H, dt, *J* 7 and 16 Hz, 2-CH), 6.70 (1H, d, *J* 16 Hz, 1-CH), and 7.1 - 7.6 (4H, m, ArH).

(E)-3-Methoxy-2-pent-1-enylbenzyl alcohol (87)

The ester (119), (234 mg, 1.00 mmol) was dissolved in dry ether (20 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (76 mg, 2.00 mmol) in dry ether (25 ml) at room temperature. After stirring the mixture for 0.5 h, sufficient saturated aqueous ammonium chloride was added to decompose the excess reagent, followed by magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the residue chromatographed (eluant 15% ethyl acetate - light petroleum) to afford the oily product (87) (197 mg, 95%) (Found: C, 75.55; H, 8.65. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7%); $\nu_{max.}$ (film) 3220 cm^{-1} (OH); δ0.97 (3H, t, *J* 7 Hz, CH_3), 1.43

(2H, sextet, *J* 7 Hz, 4-CH_2), 1.97 (1H, br s, OH), 2.25 (2H, q, *J* 7 Hz, 3-CH_2), 3.81 (3H, s, OCH_3), 4.70 (2H, s, $ArCH_2$), 6.06 (1H, dt, *J* 7 and 16 Hz, 2-CH), 6.43 (1H, d, *J* 16 Hz, 1-CH), 6.83 and 7.03 (each 1H, dd, *J* 1.5 and 8 Hz, 4- and 6-H), and 7.20 (1H, t, *J* 8 Hz, 5-H); *m/z* 206 (M^+, 65%), 159 (100), 135 (35), and 91 (42).

(E)-3,6-Dimethoxy-2-pent-1-enylbenzyl alcohol (88)

The dimethoxy ester (127), (1.06 g, 4.01 mmol) was dissolved in dry ether (50 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (304 mg, 8.02 mmol) in dry ether (25 ml) at room temperature. After the mixture had been stirred for 0.5 h, sufficient saturated aqueous ammonium chloride was added to decompose the excess reagent, followed by magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the residual crude oil chromatographed (eluant 30% ethyl acetate - light petroleum) to afford the product (88) (0.76 g, 80%) as an oil (Found: C, 70.9; H, 8.55. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%); $\nu_{max.}$ 3415 cm^{-1} (OH); δ0.97 (3H, t, *J* 7 Hz, CH_3), 1.54 (2H, sextet, *J* 7 Hz, 4-CH_2), 2.26 (2H, q, *J* 7 Hz, 3-CH_2), 2.50 (1H, t, *J* 6 Hz, OH), 3.78 and 3.84 (each 3H, s, OCH_3), 4.78 (2H, d, *J* 6 Hz, $ArCH_2$), 5.95 (1H, dt, *J* 7 and 17 Hz, 2-CH), 6.49 (1H, d, *J* 17 Hz, 1-CH), and 6.75 (2H, s, 4- and 5-H); *m/z* 236 (M^+, 98%), 189 (100), and 165 (52).

(E)-6-Methoxy-2-pent-1-enylbenzyl alcohol (89)

The ester (135) (0.46 g, 1.97 mmol) was dissolved in dry ether (30 ml) and added dropwise to a stirred suspension of lithium

aluminium hydride (149 mg, 3.94 mmol) in dry ether (30 ml) at room temperature. After the mixture had been stirred for 0.5 h, sufficient saturated aqueous ammonium chloride was added to decompose the excess reagent, followed by magnesium sulphate. After filtration, the solvent was removed under reduced pressure and the residue chromatographed (eluant 30% ethyl acetate - light petroleum) to give the oily product (89) (0.38 g, 94%) (Found: C, 75.55; H, 8.8. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7%); $\nu_{max.}$ 3420 cm^{-1} (OH); δ0.98 (3H, t, *J* 7 Hz, CH_3), 1.50 (2H, m, *J* 7 Hz, 4-CH_2), 2.25 (2H, q, *J* 7 Hz, 3-CH_2), 1.8 - 2.4 (1H, br s, OH), 3.90 (3H, s, OCH_3), 4.48 (2H, s, $ArCH_2$), 6.21 (1H, dt, *J* 7 and 16 Hz, 2-CH), and 6.7 - 7.5 (4H, m, ArH and 1-CH); *m/z* 206 (M^+, 48%), 173 (46), 163 (62), 159 (100), 149 (50), 135 (45), and 91 (59).

(Z)- and (E)-Methyl 2-pent-1-enylbenzoate (91) and (92)

To a mixture of the phosphonium salt[39] of 2-bromomethyl benzoic acid methyl ester (90) (450 mg, 3 mmol) and butanal (0.54 ml, 6 mmol) in acetonitrile (10 ml) was added the base diazabicyclo-[4.3.0]non-5-ene (450 mg, 3.47 mmol). The mixture was heated under reflux for one hour. After cooling, the mixture was thrown into dichloromethane and washed with dilute HCl to remove the base, then with water. The organic layer was separated, dried ($MgSO_4$), filtered and the solvent evaporated under reduced pressure to afford a mixture of the geometric isomers after chromatography (eluant 5% ethyl acetate - light petroleum) (0.511 g, 60%).

(E)-Methyl 2-pent-1-enylbenzoate (92)

The lactone (101) (1.15 g, 6 mmol) was dissolved in dry dimethylformamide (25 ml), and potassium-*t*-butoxide (2.69 g, 24 mmol) was added. The solution was maintained at 90°C for 0.5 h, and dimethyl sulphate (2.27 ml, 24 mmol) was added. The solution was stirred for a further 3 h. After cooling, the mixture was thrown into water, and then extracted exhaustively with ether. The ether layer was washed successively with aqueous ammonia (25%), water, dilute hydrochloric acid and then more water before being separated, dried over magnesium sulphate and filtered. Removal of the organic layer under reduced pressure produced a residue which was chromatographed (eluant 2.5% ethyl acetate - light petroleum) to afford the product (92) (0.81 g, 65% or 85% based on unrecovered starting material) as an oil (Found: C, 76.2; H, 8.05. $C_{13}H_{16}O_2$ requires C, 76.45; H, 7.9%); $\nu_{max.}$ (film) 1712 cm^{-1} (C = O); δ0.96 (3H, t, *J* 7 Hz, CH_3), 1.54 (2H, sextet, *J* 7 Hz, 4'-CH_2), 2.06 (2H, q, *J* 7 Hz, 3'-CH_2), 3.89 (3H, s, OCH_3), 6.14 (1H, dt, *J* 7 and 16 Hz, 2'-CH), 7.14 (1H, d, *J* 16 Hz, 1'-CH), 7.1 - 7.65 (3H, m, 3-, 4-, and 5-H), and 7.84 (1H, dd, *J* 1.5 and 8 Hz, 6-H); *m/z* 204 (M^+, 68%), 172 (38), 161 (100), 157 (58), 144 (74), 115 (78), and 91 (46).

Methyl 2-pentyl-1-benzoate[75] *(93)*

A mixture of the (*Z*)- and (*E*)-methyl 2-pent-1-enylbenzoate (91) and (92) (0.511 g, 2.50 mmol) was dissolved in ethyl acetate (150 ml). Palladium on carbon (0.20 g) was added to this solution. The solution was stirred under hydrogen at a pressure of 3 atmospheres for 5 hours. After this time had elapsed,

the catalyst was filtered off and the solvent removed under reduced pressure to yield the known[75] saturated ester (93), (449 mg, 87%) after chromatography (eluant 2.5% ethyl acetate - light petroleum); (Found: C, 75.7; H, 8.6. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%); $\nu_{max.}$ 1723 cm^{-1} (C = O); δ0.90 (3H, t, *J* 6 Hz, 5-CH_3), 1.11 - 1.80 (6H, m, 4-, 3- and 2-CH_2), 2.96 (2H, t, *J* 7 Hz, ArCH_2), 3.89 (3H, s, OMe), 7.12 - 7.52 (3H, m, 3-, 4- and 5-ArH), and 7.86 (1H, m, 6-H); *m/z* 206 (M^+, 19%), 175 (27), 150 (68), 131 (50), 119 (100), 118 (79), 91 (83), 90 (18), and 65 (21).

Methyl 2-(1-bromopentyl)benzoate (94)

Methyl 2-pentyl benzoate (93), (310 mg, 1.50 mmol), *N*-bromosuccinimide (284 mg, 1.60 mmol) and benzoyl peroxide (94 mg, 0.388 mmol) were heated under reflux in carbon tetrachloride (70 ml) for 3.5 h. After cooling in ice for 30 minutes, the succinimide that had formed during the course of the reaction was filtered off and the solvent removed under reduced pressure to yield the crude bromide (94), (422 mg, 98%); δ0.90 (3H, deformed t, CH_3), 1.39 (4H, m, CH_2CH_2), 2.19 (2H, m, 2-CH_2), 3.90 (3H, s, OMe), 6.17 (1H, t, *J* 7 H, 1-H), and 7.2 - 7.7 (4H, m, ArH).

3,4-Dihydro-3-propyl-1H-2-benzopyran-2-one (101)

N-Methyl-*o*-toluamide (98) (3.70 g, 25 mmol) was dissolved in dry tetrahydrofuran (60 ml) and the reaction flask was flushed with nitrogen. *n*-Butyl-lithium (2.5 mol equiv.) in hexane was added at room temperature, and the resulting red solution was boiled for 15 min. The flask was then cooled on ice, and

butanal (3.6 g, 2 mol equiv.) was added during 30 minutes. The reaction mixture was stirred at room temperature for 45 minutes, and was then poured into hydrochloric acid (100 ml, 2 M) containing half its mass of ice. This was extracted with ethyl acetate (3 x 100 ml), the combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was heated at 200°C for 4 h and chromatographed (eluant 5% ethyl acetate - light petroleum) to give the product (101) (1.75 g, 40%) as an oil (Found: C, 75.6; H, 7.45. $C_{12}H_{14}O_2$ requires C, 75.75; H, 7.4%), $\nu_{max.}$ (film) 1710 cm^{-1} (C = O); δ0.98 (3H, t, *J* 6 Hz, CH_3), 1.2 - 2.0 (4H, m, CH_2CH_2), 2.93 (2H, apparent d, *J* 6.5 Hz, $ArCH_2$), 4.35 - 4.70 (1H, m, 3-H), 7.15 - 7.7 (3H, m, 5-, 6-, and 7-H), and 8.07 (1H, dd, *J* 2 and 7 Hz, 8-H); *m/z* 190 (M^+, 17%), 147 (76), 119 (88), 118 (100), 91 (50), and 90 (61).

3-Methoxy-2,N-dimethylbenzamide (103)

The amide (116) (995 mg, 4.23 mmol) was dissolved in trifluoroacetic acid (10 ml) and the solution was maintained at 60°C. When t.l.c. showed that no more starting material was present (19 h), the solvent was evaporated off and the residue chromatographed (eluant 50% ethyl acetate - light petroleum) to give firstly starting material (103 mg, 10%) followed by the product (103) (656 mg, 87%, or 97% based on unrecovered starting material), m.p. 109 - 110°C (ethanol - water 5:95) (Found: C, 66.7; H, 7.2; N, 7.85. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%); $\nu_{max.}$ 3270 (NH), 1637 cm^{-1} (C = O); δ2.25 (3H, s, CCH_3), 3.95 (3H, d, *J* 5 Hz, NCH_3), 3.84 (3H, s, OCH_3), 5.90 (1H, br s, NH), 6.86

and 6.90 (each 1H, d, *J* 8 Hz, 4- and 6-H), and 7.16 (1H, t, *J* 8 Hz, 5-H); *m/z* 179 (M^+, 71%), 164 (9), 149 (100), 148 (20), and 91 (54).

N-*Methyl-3-methoxy*-N-*pentylbenzamide (111)*

To a stirred solution of *N*-methyl-3-methoxy benzamide (102) (100 mg, 0.6 mmol) in dry tetrahydrofuran (15 ml) under nitrogen at -78°C was added *n*-butyl-lithium (2.2 mol equiv.) in hexane. The solution was stirred for 30 min. before *n*-pentyl-bromide (5 mol equiv.) in dry tetrahydrofuran (3 ml) was added, after which the solution was warmed to -10°C and stirred at this temperature for a further 1 h. This mixture was added to water and exhaustively extracted with ethyl acetate, which was separated from the aqueous phase, dried over magnesium sulphate, filtered and the solvent evaporated to yield a residue which was chromatographed (eluant 5% ethyl acetate - light petroleum) to afford the product (111) (97 mg, 68%) as an oil (Found: C, 71.45; H, 8.95; N, 5.95. $C_{14}H_{21}NO_2$ requires C, 71.49; H, 8.94; N, 5.96%); $\nu_{max.}$ 1627 cm^{-1} (C=O); at 59°C δ0.87 (3H, t, *J* 7 Hz, 5-CH_3), 1.06 - 1.80 (6H, m, 2-, 3-, and 4-CH_2), 2.96 (3H, s, N-CH_3), 3.34 (2H, t, *J* 7 Hz, N-CH_2), 3.78 (3H, s, OMe), 6.78 - 7.02 (3H, m, 2-, 4- and 6-H), and 7.14 - 7.40 (1H, m, 5-H); *m/z* 235 (M^+, 15%), 135 (100), 107 (18), 92 (19), 77 (24), and 64 (39).

N-*Benzyl-3-methoxybenzamide (112)*

3-Methoxy benzoic acid (10.13 g, 66.6 mmol) was dissolved in thionyl chloride (60 ml) and heated under reflux for 3 h. After

the solution had been cooled and the solvent removed under reduced pressure, the residue was poured slowly into a mixture of benzylamine (20 ml), water (50 ml) and 2 N NaOH (60 ml). This mixture was vigorously shaken and cooled in ice for 30 min. Dilute HCl was added to reacidify the mixture before extraction with ethyl acetate began. The organic layer was dried over magnesium sulphate, filtered and evaporated to yield a residue which was recrystallised to afford the product (112) (14.9 g, 93%), m.p. 58-59°C (dichloromethane - light petroleum) as white needles (Found: C, 74.75; H, 6.15; N, 5.85. $C_{15}H_{15}NO_2$ requires C, 74.7; H, 6.2; N, 5.8%); $\nu_{max.}$ 3320 (NH), 1626 cm^{-1} (C = O); δ3.78 (3H, s, OCH_3), 4.58 (2H, d, *J* 6 Hz, $ArCH_2$, collapses to singlet on double irradiation at δ6.75), 6.75 (1H, br s, NH), 6.90 - 7.44 (4H, m, aromatics of disubstituted ring), and 7.31 (5H, s, monosubstituted ring); *m/z* 241 (M^+, 100%), 136 (54), 135 (91), 107 (29), and 77 (27).

N-Benzyl-3-methoxy-N-methylbenzamide (114)

To a stirred solution of amide (112) (250 mg, 1.04 mmol) in dry tetrahydrofuran (20 ml) at -78°C under nitrogen was added *n*-butyl-lithium (2.5 mol equiv.) in hexane. The solution was stirred for a further 20 min before methyl iodide (10 mol equiv.) was added, after which the solution was warmed to -10°C and stirred at this temperature for a further 1 h. This mixture was added to water and exhaustively extracted with ethyl acetate, which was separated from the aqueous phase, dried over magnesium sulphate, filtered and the solvent evaporated to yield a residue which was chromatographed (eluant 30% ethyl acetate - light

petroleum) to give rise to the product (114) (243 mg, 92%) as an oil (Found: C, 74.95; H, 6.65; N, 5.5. $C_{16}H_{17}NO_2$ requires C, 75.25; H, 6.70; N, 5.5%); $\nu_{max.}$ 1636 cm^{-1} (C = O); at 59°C δ2.90 (3H, s, N-CH_3), 3.74 (3H, s, OMe), 4.60 (2H, s, CH_2), 6.78 - 7.08 (3H, m, 2-, 4- and 6-H), 7.08 - 7.44 (1H, m, 5-H), and 7.26 (5H, s, aromatic protons of monosubstituted ring); *m/z* 255 (M^+, 84%), 254 (68), 240 (19), 136 (52), 135 (100), 120 (40), 107 (51), 92 (42), 91 (42), and 77 (49).

*3-Methoxy-2,*N*-dimethyl-*N*-(t-butyl)benzamide (116)*

The amide (115) (100 mg, 0.48 mmol) was dissolved in dry tetrahydrofuran (30 ml) and cooled to -78°C. *n*-Butyl-lithium (2.5 mol equiv.) in hexane was added dropwise, the reaction being performed under nitrogen. The solution was stirred for 20 min, warmed to -10°C, and stirred for a further 30 min. Methyl iodide (3 mol equiv.) was then added and the solution was stirred at this temperature for 1 h and then at room temperature for a further 1 h. The mixture was added to water and extracted with ether. After separation, the combined ether layers were dried over magnesium sulphate, filtered and the organic solvent removed under reduced pressure to give a residue which was chromatographed (eluant 15% ethyl acetate - light petroleum) to give the product (116) (106 mg, 93%), m.p. 106 - 108°C (aqueous ethanol) (Found: C, 71.55; H, 8.95; N, 6.0. $C_{14}H_{21}NO_2$ requires C, 71.5; H, 8.9; N, 6.0%); $\nu_{max.}$ 1620 cm^{-1} (C = O); δ1.53 (9H, s, CCH_3), 2.15 (3H, s, $ArCH_3$), 2.63 (3H, s, NCH_3), 3.80 (3H, s, OCH_3), 6.64 and 6.77 (each 1H, d, *J* 8 Hz, 4- and 6-H), and 7.16 (1H, t, *J* 8 Hz,

5-H); *m/z* 235 (M^+, 45%), 220 (18), 179 (24), 150 (30), 149 (100), 148 (37), and 91 (46).

*3,4-Dihydro-5-methoxy-3-propyl-1*H*-2-benzopyran-1-one (118)*

3-Methoxy-2,*N*-dimethylbenzamide (103) (2.89 g, 16 mmol) was dissolved in dry tetrahydrofuran (20 ml) and the reaction flask flushed with nitrogen. *n*-Butyl-lithium (2.5 mol equiv.) in hexane was added at room temperature, and the resulting red solution was boiled for 20 minutes. The flask was cooled on ice, and butanal (2.3 g, 2 mol equiv.) was added during 30 minutes. The reaction mixture was stirred at room temperature for 45 min, and was then poured into hydrochloric acid (75 ml, 2 M) containing half its mass of ice. This was extracted with ethyl acetate (3 x 50 ml). The organic layers were combined after separation, dried over anhydrous magnesium sulfate, filtered and the solvent removed under reduced pressure. The oily residue was heated under nitrogen at 210°C for 3 h, then chromatographed (eluant 15% ethyl acetate - light petroleum) to afford the product (118) (1.89 g, 53%) as an oil (Found: C, 70.8; H, 7.6. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%); $\nu_{max.}$ (film) 1718 cm^{-1} (C = O); δ0.97 (3H, t, *J* 6.5 Hz, CH_3), 1.3 - 2.0 (4H, m, CH_2CH_2), 2.64 (1H, dd, *J* 12 and 17 Hz, pseudoaxial 4-H), 3.15 (1H, dd, *J* 4 and 17 Hz, pseudoequatorial 4-H), 3.88 (3H, s, OCH_3), 4.3 - 4.65 (1H, m, 3-H), 7.07 (1H, d, *J* 8 Hz, 6-H), 7.33 (1H, t, *J* 8 Hz, 7-H), and 7.71 (1H, d, *J* 8 Hz, 8-H); *m/z* 220 (M^+, 58%) 177 (32), 149 (89), 148 (100), 120 (34), 91 (33), and 90 (26).

(E)-Methyl 3-methoxy-2-pent-1-enylbenzoate (119)

The lactone (118) (530 mg, 2.4 mmol) was dissolved in dry dimethylformamide (35 ml), and potassium-*t*-butoxide (1.07 g, 9.6 mmol) was added. The solution was stirred at 90°C for 2.5 h, and dimethyl sulphate (0.91 ml, 9.6 mmol) was added. This solution was stirred for a further 2 h. After cooling, the mixture was thrown into water, and then extracted exhaustively with ether. The ether layer was washed successively with aqueous ammonia (25%), water, dilute hydrochloric acid and then more water. The ether layer was separated, dried over magnesium sulphate, filtered and the organic solvent removed under reduced pressure to yield a crude oil which was chromatographed (eluant 5% ethyl acetate - light petroleum) to afford the oily ester (119) (300 mg, 53%, yield not optimised) (Found: C, 72.05; H, 7.75. $C_{14}H_{18}O_3$ requires C, 71.85; H, 7.7%); $\nu_{max.}$(film) 1722 cm^{-1}; (C = O); δ0.96 (3H, t, *J* 7 Hz, CH_3), 1.50 (2H, sextet, *J* 7 Hz, 4-CH_2), 2.21 (2H, q, *J* 7 Hz, 3-CH_2), 3.84 (6H, s, OCH_3), 6.00 (1H, dt, *J* 7 and 16 Hz, 2-CH), 6.62 (1H, d, *J* 16 Hz, 1-CH), 6.9 - 7.1 (1H, m, 4-H), and 7.15 - 7.30 (2H, m, 5- and 6-H); *m/z* 234 (M^+, 100%), 202 (72), 191 (87), 179 (99), and 173 (71).

2,5-Dimethoxy-N-(t-butyl)benzamide (122)

2,5-Dimethoxy-benzoic acid (18.5 g, 102 mmol) was dissolved in thionyl chloride (60 ml) and boiled for 3 h. The solvent was evaporated and the residue was added to a solution of sodium hydroxide (5 g) and *t*-butylamine (20 ml, 190 mmol) in water (100 ml). The mixture was shaken vigorously and then cooled in ice for 1 h. The organic material was extracted into ether,

dried over magnesium sulphate, filtered and the organic solvent removed under reduced pressure to give a residue which was chromatographed (eluant 50% ethyl acetate - light petroleum) to afford the amide (122) (18.86 g, 78%), as white rods, m.p. 64 - 65°C (light petroleum) (Found: C, 65.9; H, 8.1; N, 5.9. $C_{13}H_{19}NO_3$ requires C, 65.8; H, 8.0; N, 5.9%); $\nu_{max.}$ 3380 (NH), 1655 cm^{-1} (C = O); δ1.48 (9H, s, CCH_3), 3.82 and 3.90 (each 3H, s, OCH_3), 6.8 - 7.1 (2H, m, 4- and 5-H), 7.66 (1H, d, *J* 3 Hz, 2-H), and 7.98 (1H, br s, NH); *m/z* 237 (M^+, 75%), 181 (24), 165 (100), 163 (33), and 136 (29).

*3,6-Dimethoxy-2,*N*-dimethyl-*N*-(t-butyl)benzamide (123)*

The dimethoxy amide (122) (21.5 g, 91 mmol) was dissolved in tetrahydrofuran (250 ml) and cooled to -78°C. *n*-Butyl-lithium (2.5 mol equiv.) in hexane was added dropwise, the reaction being performed under nitrogen. The solution was stirred for 30 min, warmed to -10°C, and stirred for a further 30 min. Methyl iodide (3 mol equiv.) was then added and the solution was stirred at this temperature for 1 h and then at room temperature for an equal period of time. The mixture was added to water and extracted with ether. The ether layer was dried over magnesium sulphate, filtered and the ether evaporated to give a residue which was chromatographed (eluant 15% ethyl acetate - light petroleum) to give the product (123) (22.36 g, 93%), m.p. 102 - 103°C (light petroleum) (Found: C, 67.8; H, 8.65; N, 5.2. $C_{15}H_{23}NO_3$ requires C, 67.9; H, 8.7; N, 5.3%); $\nu_{max.}$ 1642 cm^{-1} (C = O); δ1.56 (9H, s, CCH_3), 2.12 (3H, s, $ArCH_3$), 2.74 (3H, s, NCH_3), 3.76 and 3.78 (each 3H, s, OCH_3), and 6.69 (2H, s, ArH); *m/z* 265 (M^+, 65%), 209 (22), 180 (32), 179 (100), and 178 (21).

3,6-Dimethoxy-2,N-dimethylbenzamide (124)

The amide (123) (10 g, 37.7 mmol) was dissolved in trifluoroacetic acid (50 ml) and the solution was maintained at 60°C. When t.l.c. showed that no more starting material was present (19 h) the solvent was evaporated and the residue chromatographed (eluant 70% ethyl acetate - light petroleum) to give the product (124) (6.97 g, 88%), m.p. 170 - 171°C (ethanol) (Found: C, 63.05; H, 7.1; N, 6.7. $C_{11}H_{15}NO_3$ requires C, 63.1; H, 7.2; N, 6.7%); $\nu_{max.}$ 3300 (NH), and 1640 cm^{-1} (C = O); δ2.07 (3H, s, CCH_3), 2.98 (3H, d, *J* 5 Hz, NCH_3), 3.76 and 3.78 (each 3H, s, OCH_3), 5.8 (1H, br s, NH), and 6.66 and 6.78 (each 1H, d, *J* 9 Hz, 4- and 5-H); *m/z* 209 (M^+, 74%), and 179 (100).

3,4 Dihydro-5,8-dimethoxy-3-propyl-1H-2-benzopyran-1-one (126)

3,6-Dimethoxy-2,*N*-dimethylbenzamide (124) (5.00 g, 23.9 mmol) was dissolved in dry tetrahydrofuran (300 ml) and the reaction flask kept under nitrogen. *n*-Butyl-lithium (2.5 mol equiv.) in hexane was added at room temperature and the resulting red solution subsequently boiled for 15 minutes, after which the flask was cooled on ice and butanal (3.44 g, 2 mol equiv.) was added during 25 minutes. The mixture was stirred for a further 45 minutes at room temperature before being poured into hydrochloric acid (150 ml, 2 M) containing half its mass of ice. This was extracted with ethyl acetate (3 x 100 ml). The combined organic layers were dried ($MgSO_4$), filtered and the solvent removed under reduced pressure. The residue was heated under nitrogen at 210°C for 4 h followed by chromatography (eluant 50% ethyl acetate - light petroleum) to afford the product (126)

[1.69 g, 28% or 49% based on unrecovered (124) and (125)], m.p. 55.5 - 56°C (Found: C, 66.9; H, 7.3. $C_{14}H_{18}O_4$ requires C, 67.2; H, 7.2%); $\nu_{max.}$ 1732 and 1722 cm^{-1} (C = O); δ0.95 (3H, t, *J* 7 Hz, CH_3), 1.3 - 2.0 (4H, m, CH_2CH_2), 2.54 (1H, dd, *J* 12 and 17 Hz, pseudoaxial 4-H), 3.14 (1H, dd, *J* 3 and 17 Hz, pseudoequatorial 4-H), 3.82 and 3.89 (3H each, s, OCH_3), 4.2 - 4.5 (1H, m, 3-H), and 6.87 and 7.07 (2H, dd, *J* 9 Hz, 6- and 7-H); *m/z* 250 (M^+, 28%), 207 (100), 179 (22), and 150 (28). Later fractions afforded the amide (124) (1.33 g, 27%) followed by the hydroxyamide (125) (1.05 g, 16%).

(E)-Methyl 3,6-dimethoxy-2-pent-1-enylbenzoate (127)

The dimethoxy lactone (126) (1.67 g, 6.7 mmol) was dissolved in dry dimethylformamide (60 ml), and potassium-*t*-butoxide (3.01 g, 26.8 mmol) was added. The solution was stirred at 90°C for 3 h before dimethyl sulphate (2.54 ml, 26.8 mmol) was added. This solution was stirred for a further 1.5 h before being cooled down, thrown into water and extracted exhaustively with ether. After being washed successively with aqueous ammonia (25%), water, dilute hydrochloric acid and then more water, the ether layer was separated, dried over magnesium sulphate, filtered and the ether removed under reduced pressure to give a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum) to afford the product (127) (1.34 g, 76%, or 81% based on unrecovered starting material) (Found: C, 68.25; H, 7.65. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%); $\nu_{max.}$ (film) 1728 cm^{-1} (C = O); δ0.94 (3H, t, *J* 7 Hz, CH_3), 1.47 (2H, sextet, *J* 7 Hz, 4-CH_2), 2.17 (2H, q, *J* 7 Hz, 3-CH_2), 3.78 (6H, s, OCH_3), 3.96 (3H, s,

OCH_3), 6.10 (1H, dt, *J* 7 and 16 Hz, 2-CH), 6.42 (1H, d, *J* 16 Hz, 1-CH), and 6.70 and 6.84 (1H each, *J* 9 Hz, 4- and 5-H); *m/z* 264 (M^+, 100%), 233 (33), 221 (33), and 203 (75).

*2-Methoxy-*N*-(t-butyl)benzamide (128)*

2-Methoxybenzoic acid (24.5 g, 161 mmol) was dissolved in thionyl chloride (70 ml) and boiled for 3 h. The solvent was evaporated off under reduced pressure and the residue was added to a solution of sodium hydroxide (6 g) and *t*-butylamine (25 ml, 238 mmol) in water (110 ml). The mixture was shaken vigorously and then cooled in ice for 1 h. The organic material was extracted into ether and the residue obtained after the ether layer had been dried over magnesium sulphate, filtered and removed under reduced pressure was chromatographed (eluant 25% ethyl acetate - light petroleum) to afford the product (128) (25.1 g, 75%), m.p. 31 - 33°C (Found: C, 69.55; H, 8.3; N, 6.95. $C_{12}H_{17}NO_2$ requires C, 69.6; H, 8.2; N, 6.8%); $\nu_{max.}$ 3380 (NH), 1662 cm^{-1} (C = O); δ1.47 (9H, s, CCH_3), 3.92 (3H, s, OCH_3), 6.94 (1H, d, *J* 8 Hz, 3-H), 7.05 (1H, t, *J* 8 Hz, 5-H), 7.40 (1H, dt, *J* 2 and 8 Hz, 4-H), 7.84 (1H, br s, NH), and 8.19 (1H, dd, *J* 2 and 8 Hz, 6-H); *m/z* 207 (M^+, 46%), 192 (23), and 135 (100).

*2-Methoxy-6,*N*-dimethyl-*N*-(t-butyl)benzamide (131)*

The amide (128) (0.50 g, 2.4 mmol) was dissolved in dry tetrahydrofuran (60 ml) and cooled to -78°C. *n*-Butyl-lithium (2.5 mol equiv.) in hexane was added dropwise, the reaction being performed under nitrogen. The solution was stirred for 20 min,

warmed to -10°C, and stirred for a further 30 min before methyl iodide (3 mol equiv.) was added. This mixture was stirred for a further 1 h at -10°C, then allowed to warm to room temperature at which it was stirred for a further 1 h. Water was added to the reaction flask, the contents transferred to a separatory funnel and the mixture extracted with ether (3 x 60 ml). After separation, the organic layer was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give a residue which was chromatographed (eluant 15% ethyl acetate - light petroleum) to give the product (131) (0,37 g, 65%), m.p. 73.5 - 74.5°C (light petroleum) (Found: C, 71.75; H, 9.2; N, 6.1. $C_{14}H_{21}NO_2$ requires C, 71.5; H, 8.9; N, 6.0%); $\nu_{max.}$ 1642 and 1632 cm^{-1} (C = O); δ1.55 (9H, s, CCH_3), 2.23 (3H, s, $ArCH_3$), 2.74 (3H, s, NCH_3), 3.77 (3H, s, OCH_3), 6.70 and 6.77 (each 1H, d, *J* 8 Hz, 3- and 5-H), and 7.15 (1H, t, *J* 8 Hz, 4-H); *m/z* 235 (M^+, 19%) and 149 (100).

The yield of the amide (131) was variable and it was often, chromatographically, closely followed by the amide (129), δ1.53 (9H, s, CCH_3), 2.78 (3H, s, NCH_3), 3.83 (3H, s, OCH_3), and 6.65 - 7.4 (4H, m, ArH). In addition early fractions gave variable yields of 2-methoxyvalerophenone (130), δ0.92 (3H, t, *J* 6 Hz, CCH_3), 1.2 - 1.9 (4H, m, 3- and 4-CH_2), 2.97 (2H, t, *J* 6 Hz, $COCH_2$), 3.89 (3H, s, OCH_3), 6.96 and 7.04 (each 1H, d, *J* 8 Hz, 3- and 5-H), 7.46 (1H, dt, *J* 2 and 8 Hz, 4-H), and 7.66 (1H, dd, *J* 2 and 8 Hz, 6-H); *m/z* 192 (M^+, 2%), 150 (20) and 135 (100).

*2-Methoxy-6,*N*-dimethylbenzamide (132)*

(a) The amide (131) (220 mg, 0.94 mmol) was dissolved in trifluoroacetic acid (5 ml) and stirred for 36 h at 60°C. The solvent was then removed under reduced pressure and the residue was chromatographed (eluant 50% ethyl acetate - light petroleum) to afford the product (132) (154 mg, 92%), m.p. 165 - 166.5°C (aqueous ethanol) (Found: C, 66.75; H, 7.25; N, 8.0. $C_{10}H_{13}NO_2$ requires C, 67.0; H, 7.3; N, 7.8%); $\nu_{max.}$ 3260 (NH) and 1635 cm^{-1} (C = O); δ2.34 (3H, s, CCH_3), 2.99 (3H, d, *J* 5 Hz, NCH_3), 3.85 (3H, s, OCH_3), 6.32 (1H, br s, NH), 6.89 and 6.98 (each 1H, d, *J* 8 Hz, 3- and 5-H), and 7.37 (1H, t, *J* 8 Hz, 4-H); *m/z* 179 (M^+, 36%), 149 (100), and 91 (22).

(b) 2-Methoxy-6-methylbenzoic acid (136) (14.10 g, 84.9 mmol) was boiled in thionyl chloride (70 ml) under nitrogen for 4 h. The excess of thionyl chloride was removed by evaporation, and the residue was added to an ice-cooled solution of methylamine in water (40%, 50 ml) with stirring, whereupon crystals separated. After 1 h, the mixture was extracted with ether, which was dried over anhydrous magnesium sulphate, filtered and removed under reduced pressure to give a residue which was chromatographed as above to give rise to the product (132) (10.5 g, 68%), identical with the material described in (a) above.

*3,4-Dihydro-8-methoxy-3-propyl-1*H*-2-benzopyran-1-one (134)*

2-Methoxy-6,*N*-dimethylbenzamide (132) (1.92 g, 10.7 mmol) was dissolved in dry tetrahydrofuran (70 ml) and the reaction flask was flushed with nitrogen. *n*-Butyl-lithium (2.5 mol equiv.) in

hexane was added at room temperature, and the red solution was boiled for 20 min. The flask was then cooled on ice, and butanal (1.54 g, 2 mol equiv.) was added during 30 minutes to the cold solution. The reaction mixture was stirred at room temperature for 45 minutes, after which it was poured into hydrochloric acid (150 ml, 2 M) containing half its mass of ice. This was extracted with ethyl acetate (3 x 100 ml), the combined organic layers were dried over magnesium sulfate, filtered and the solvent removed under reduced pressure. The residue was heated in an inert atmosphere (nitrogen) at 190°C for 16 h, after which it was chromatographed (eluant 20% ethyl acetate - light petroleum) to give rise to the product (134) (0.64 g, 27% or 31% based on unrecovered starting material) as an oil (Found: C, 70.9; H, 7.35. $C_{13}H_{16}O_3$ requires C, 70.9; H, 7.3%); $\nu_{max.}$ (film) 1720 cm^{-1} (C = O); δ0.96 (3H, t, *J* 7 Hz, CH_3), 1.2 - 2.0 (4H, m, CH_2CH_2), 2.8 - 3.0 (2H, m, $ArCH_2$), 3.95 (3H, s, OCH_3), 4.4 (1H, m, 3-H), 6.82 and 6.96 (1H each, d, *J* 8.5 Hz, 5- and 7-H), and 7.47 (1H, t, *J* 8.5 Hz, 6-H); *m/z* 220 (M^+, 57%), 149 (100), 148 (84), 146 (38), 91 (45), and 90 (43).

(E)-Methyl 6-methoxy-2-pent-1-enylbenzoate (135)

The lactone (134) (102 mg, 4.6 mmol) was dissolved in dimethylformamide (20 ml), and potassium-*t*-butoxide (2.06 g, 18.4 mmol) was added. The solution was stirred at 90°C for 3 h before dimethyl sulphate (1.74 ml, 18.4 mmol) was added. After stirring for a further 2 h, the solution was cooled off, thrown into water and extracted exhaustively with ether. The ether layer was washed successively with aqueous ammonia (25%), water, dilute

hydrochloric acid and then more water before being separated and dried over magnesium sulphate. Filtration and removal of the ether under reduced pressure produced a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum) to give the oily ester (135) (76 mg, 70%) (Found: C, 71.7; H, 7.9. $C_{14}H_{18}O_3$ requires C, 71.85; H, 7.7%); $\nu_{max.}$ (film) 1730 cm^{-1} (C = O); δ0.94 (3H, t, *J* 7 Hz, CH_3), 1.45 (2H, sextet, *J* 7 Hz, 4-CH_2), 1.8 - 2.3 (2H, m, 3-CH_2), 3.71 and 3.79 (3H each, s, OCH_3), and 6.0 - 7.3 (5H, m, 1- and 2-CH, and 3-, 4-, and 5-H); *m/z* 234 (M^+, 100%), 191 (86), and 174 (98).

(3R,4S)-3,4-Dihydro-4-hydroxy-5-methoxy-3-propyl-1H-2-benzopyran (137) and (3R,4R)-3,4-Dihydro-4-hydroxy-5-methoxy-3-propyl-1H-2-benzopyran (138) and their Enantiomers.

To a stirred solution of the alcohol (87) (148 mg, 0.72 mmol) in acetonitrile (20 ml) and water (20 ml) was added cerium(IV) ammonium nitrate (870 mg, 1.59 mmol) in water (1.5 ml) during 5 min at room temperature. The solution was stirred for a further 30 min and then extracted with dichloromethane, which was separated, dried over magnesium sulphate, filtered and removed under reduced pressure to give a residue which was chromatographed (p.l.c. eluant 15% ethyl acetate - light petroleum) to afford the pyran (137) (29 mg, 18%) as white needles, m.p. 91 - 91.5°C (light petroleum) (Found: C, 69.9; H, 8.15. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.1%); $\nu_{max.}$ 3430 cm^{-1} (OH); δ0.98 (3H, t, *J* 6 Hz, CH_3), 1.4 - 2.1 (4H, m, CH_2CH_2), 3.58 (2H, m, 3-H and OH, collapses to dt, *J* 2.5 and 8 Hz, on D_2O exchange, and further, to d, *J* 8 Hz, on double irradiation at δ1.67), 3.89 (3H, s, OCH_3),

4.71 (2H, s, $ArCH_2$), 4.72 (1H, br d, *J* 8 Hz, 4-H), 6.65 (1H, d, *J* 8 Hz, 6-H), 6.78 (1H, d, *J* 8 Hz, 8-H), and 7.21 (1H, t, *J* 8 Hz, 7-H); *m/z* 204 (M-18, 21%), 150 (100), 149 (66), 133 (86), 132 (54), 117 (38), and 91 (46).

A second band at lower R_F afforded the pyran (138) (77 mg, 48%) as white cubes, m.p. 113 - 114°C (light petroleum) (Found: C, 70.2; H, 8.2. $C_{13}H_{18}O_3$ requires C, 70.25; H, 8.1%); $\nu_{max.}$ 3435 cm^{-1} (OH); δ0.99 (3H, t, *J* 7 Hz, CH_3), 1.15 - 2.05 (4H, m, CH_2CH_2), 2.15 (1H, br s, OH, disappears on D_2O exchange), 3.53 (1H, dt, *J* 2 and 6.5 Hz, 3-H), 3.88 (3H, s, OCH_3), 4.7 (1H, m, 4-H), 4.67 and 4.87 (each 1H, d, *J* 15 Hz, $ArCH_2$), 6.64 (1H, d, *J* 8 Hz, 6-H), 6.78 (1H, d, *J* 8 Hz, 8-H), and 7.25 (1H, t, *J* 8 Hz, 7-H); *m/z* 204 (M-18, 10%), 150 (100), 149 (56), 133 (68), 132 (46), 117 (32), and 91 (38).

(3R,4S),-3,4-Dihydro-5,8-dimethoxy-3-propyl-1H-2-benzopyran (139) and (3R,4R)-3,4-Dihydro-4-hydroxy-5,8-dimethoxy-3-propyl-1H-2-benzopyran (140) and their Enantiomers

To a stirred solution of the alcohol (88) (342 mg, 1.45 mmol) in acetonitrile (25 ml) and water (25 ml) was added cerium(IV) ammonium nitrate (1.55 g, 2.82 mmol) in water (2 ml) during 5 min at room temperature. The solution was stirred for a further 30 min and then extracted with dichloromethane. After the organic layer had been separated and dried over magnesium sulphate it was filtered and the solvent evaporated to yield a residue which was chromatographed (20% ethyl acetate - light petroleum). The early fractions afforded the crude pyran (139) (95 mg, 26%)

which was subjected to p.l.c. (15% ethyl acetate - light petroleum). This gave the pyran (139) (80 mg, 21%). A portion of this material was sublimed and then recrystallised to give white needles, m.p. 74 - 74.5°C (cyclohexane) (Found: C, 66.35, H, 7.95. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.95%); $\nu_{max.}$ 3492 cm^{-1} (OH); δ0.98 (3H, t, *J* 7 Hz, CH_3), 1.2 - 2.0 (4H, m, CH_2CH_2), 3.56 (1H, dt, *J* 2.5 and 8 Hz, 3-H, collapses to d, *J* 8 Hz, on double irradiation at δ1.60), 3.70 (1H, d, *J* 2.5 Hz, OH, disappears on shaking with D_2O), 3.77 and 3.86 (each 3H, s, OCH_3), 4.57 and 4.84 (each 1H, d, *J* 16 Hz, $ArCH_2$), 4.71 (1H, m, 4-H), and 6.71 (2H, s, 6- and 7-H). The middle fractions were a mixture containing the quinone (143). Later fractions gave rise to material which was rechromatographed (eluant 2.5% ethyl acetate - light petroleum) to give the pyran (140) (112 mg, 30%) as white needles, m.p. 132 - 133°C (2.5% ethyl acetate - light petroleum) (Found: C, 66.4; H, 8.0. $C_{14}H_{20}O_4$ requires C, 66.65; H, 7.95%); $\nu_{max.}$ 3507 cm^{-1} (OH); δ0.98 (3H, t, *J* 7 Hz, CH_3), 1.2 - 1.9 (4H, m, CH_2CH_2), 2.4 (1H, br s, OH), 3.46 (1H, dt, *J* 2 and 7 Hz, 3-H), 3.76 and 3.84 (each 3H, s, OCH_3), 4.70 and 4.93 (each 1H, d, *J* 16 Hz, $ArCH_2$), 4.63 (1H, m, 4-H), and 6.73 (2H, s, 6- and 7-H); *m/z* 252 (M^+, 9%), 180 (100), and 165 (30).

(3R,4S)-3,4-Dihydro-4-hydroxy-3-propyl-1H-2-benzopyran-5,8-quinone (141) and its Enantiomer

The alcohol (139) (84 mg, 0.33 mmol) in dioxane (4 ml) containing silver(II)oxide was treated with nitric acid (6 M; 0.4 ml) and the mixture was stirred for 4 min. The reaction was terminated

by the addition of chloroform (8 ml) and water (2 ml). The whole was partitioned between more chloroform and water. The residue obtained after the organic layers had been combined after extraction, dried over magnesium sulphate, filtered and removed under reduced pressure was shown by ^{1}H n.m.r. spectroscopy to be the pure quinone (141) (60 mg, 81%) as an oil. P.l.c. afforded an analytically pure sample (Found: C, 65.1; H, 6.35. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.3%); $\nu_{max.}$ 3460 (OH), and 1663 and 1650 cm^{-1} (C = O); δ0.96 (3H, distorted t, CH_3), 1.2 - 2.05 (4H, m, CH_2CH_2), 3.2 - 3.6 (2H, m, 3-H and OH), 4.2 - 4.75 (3H, m, $ArCH_2$ and 4-H), and 6.76 (2H, s, 6- and 7-H).

(3R,4R)-3,4-Dihydro-4-hydroxy-3-propyl-1H-2-benzopyran-5,8-quinone (142) and its Enantiomer

The alcohol (140) (65 mg, 0.26 mmol) in dioxane (4 ml) containing silver(II) oxide was treated with nitric acid (6 M, 0.4 ml) and the mixture was stirred for 4 min. The reaction was terminated by the addition of chloroform (8 ml) and water (2 ml). The whole was partitioned between more chloroform and water. After extraction and separation the chloroform layer was dried over magnesium sulphate, filtered and the chloroform evaporated to give a residue (56 mg) which was recrystallised from light petroleum to give the product (142) (43 mg, 75%) as yellow rods, m.p. 75 - 76°C (Found: C, 64.7; H, 6.3. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.3%); $\nu_{max.}$ 3450 (OH) and 1654 cm^{-1} (C = O); δ0.98 (3H, t, *J* 7 Hz, CH_3), 1.2 -1.9 (4H, m, CH_2CH_2), 2.38 (1H, br d, *J* 8 Hz, OH, D_2O exchangeable), 3.41 (1H, dt, *J* 2 and 6.5 Hz, 3-H), 4.31 (1H, dd, *J* 1.5 and 20 Hz,

pseudoaxial 1-H), 4.48 (1H, m, pseudoequatorial 4-H), 4.74 (1H, d, *J* 20 Hz, pseudoequatorial 1-H), and 6.80 (2H, s, 6- and 7-H).

*3,4-Dihydro-5,8-dimethoxy-3-propyl-1*H*-2-benzopyran (149)*

The alcohol (88) (157 mg, 0.67 mmol) in dry dimethylformamide (30 ml) was treated with potassium-*t*-butoxide (298 mg, 2.67 mmol), the solution was stirred at 60°C for 25 min, and saturated aqueous ammonium chloride was then added. This was extracted into dichloromethane which was separated, dried over magnesium sulphate, filtered and the organic solvent evaporated to give a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum) to yield the product (149) (134 mg, 85%) as white rods, m.p. 74 - 75°C (light petroleum) (Found: C, 71.25; H, 8.5. $C_{14}H_{20}O_3$ requires C, 71.2; H, 8.5%); δ0.96 (3H, t, *J* 7 Hz, CH_3), 1.3 - 1.85 (4H, m, CH_2CH_2), 2.36 (1H, dd, *J* 11 and 17 Hz, pseudoaxial 4-H), 2.80 (1H, dd, *J* 3.5 and 17 Hz, pseudoequatorial 4-H), 3.4 - 3.75 (1H, m, 3-H), 3.76 and 3.78 (each 3H, s, OCH_3), 4.58 (1H, d, *J* 17 Hz, pseudoaxial 1-H), 4.94 (1H, d, *J* 17 Hz, pseudoequatorial 1-H), and 6.62 (2H, s, 6- and 7-H); *m/z* 236 (M^+, 31%), 165 (32), 163 (100), 146 (63), and 91 (36).

*3,4-Dihydro-8-methoxy-3-propyl-1*H*-2-benzopyran (150)*

The alcohol (89) (104 mg, 0.5 mmol) was treated with potassium-*t*-butoxide (224 mg, 2.0 mmol), the solution was stirred at 60°C for 20 min, and saturated aqueous ammonium chloride was then

added. This was extracted with dichloromethane which was separated, dried over magnesium sulphate, filtered and the organic solvent removed under reduced pressure to give a residue (91 mg) which was chromatographed (p.l.c. 2.5% ethyl acetate - light petroleum). The second of six bands (26 mg, 25%) was the oily product (150) (Found: C, 75.9; H, 8.9. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7%); δ0.97 (3H, distorted t, CH_3), 1.2 - 2.0 (4H, m, CH_2CH_2), 2.64 (2H, apparent d, *J* 7 Hz, 4-CH_2), 3.3 - 3.8 (1H, m, 3-H), 3.78 (3H, s, OCH_3), 4.56 (1H, d, *J* 16 Hz, pseudoaxial 1-H), 4.91 (1H, d, *J* 16 Hz, pseudoequatorial 1-H), 6.62 and 6.67 (each 1H, d, *J* 7.5 Hz, 5- and 7-H), and 7.09 (1H, t, *J* 7.5 Hz, 6-H); *m/z* 206 (M^+, 69%), 163 (25), 148 (39), 135 (100), 134 (100), 105 (53), 104 (93), and 91 (46).

(E)-5-Methoxy-2-pent-1-enylbenzyl alcohol (154)

(a) The bromo compound (188), (102 mg, 0.38 mmol) was dissolved in toluene (3 ml) and added to a 20% sodium hydroxide solution (20 ml). This mixture was refluxed under vigorous stirring for 80 h, after which it was cooled and poured into dilute hydrochloric acid. Dichloromethane was used to extract the organic material. The organic layer was separated after extraction, dried over magnesium sulphate, filtered and the solvent evaporated to yield a residue which was chromatographed (p.l.c. eluant 5% ethyl acetate - light petroleum) to afford the product (154) (47 mg, 60%) as an oil (Found: C, 75.65; H, 9.0. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.7%); $\nu_{max.}$ (neat) 3360 cm^{-1} (OH); δ0.96 (3H, t, *J* 7 Hz, CH_3), 1.49 (2H, m, *J* 7 Hz, 4-CH_2), 1.89 (1H, br s, OH), 1.98 (2H, q, *J* 7 Hz,

3-CH_2), 3.88 (3H, s, OCH_3), 4.68 (2H, s, $ArCH_2$), 6.00 (1H, dt, *J* 7 and 16 Hz, 2-CH), 6.55 (1H, d, *J* 16 Hz, 1-CH), 6.78 (1H, dd, *J* 3 and 8 Hz, 4-H), 6.90 (1H, d, *J* 3 Hz, 6-H), and 7.37 (1H, d, *J* 8 Hz, 3-H); *m/z* 206 (M^+, 78%), 188 (15), 159 (100), 149 (42), 147 (94), 135 (24), and 121 (24).

(b) The diol (186) (128 mg, 0.57 mmol) was dissolved in dry benzene (1 ml) containing phosphorus tribromide (0.67 mol equiv.) and stirred for 100 min at room temperature. The benzene was then evaporated and the fuming residue placed under high vacuum for 10 min. Dry lutidine (10 ml) was then added and the solution boiled for 40 min, after which it was cooled and a few drops of sodium hydroxide solution (5%, ~1 ml) added before boiling was continued for a further 15 min. After cooling, the mixture was thrown into dilute hydrochloric acid, extracted twice with dichloromethane, which was dried over magnesium sulphate, filtered and the organic solvent evaporated to yield a residue which was chromatographed (p.l.c. 30% ethyl acetate - light petroleum). The band of higher R_F gave the bromo compound (188) (26 mg, 16%), while later fractions gave the alcohol (154) (20 mg, 17%) identical with the material described in (a) above.

2-Bromo-5-methoxy-benzyl alcohol (162)

The ester (160), prepared by methylating 2-bromo-5-methoxy-benzoic acid[60] (2.91 g, 11.9 mmol), was dissolved in dry ether (100 ml) and was then added dropwise to a suspension of lithium aluminium hydride (2 mol equiv.) in dry ether (100 ml) at room

temperature. After the mixture had been stirred for 0.5 h, sufficient saturated aqueous ammonium chloride was added to decompose the excess of reagent, followed by anhydrous magnesium sulphate. After filtration, the solvent was removed to give a residue which was chromatographed (eluant 20% ethyl acetate - light petroleum) to give rise to the product (162) (2.37 g, 92%) as white needles, m.p. 45 - 46°C (dichloromethane - light petroleum) (Found: C, 44.25; H, 4.15. $C_8H_9BrO_2$ requires C, 44.25; H, 4.15%); $\nu_{max.}$ 3040 - 3420 cm^{-1} (OH); δ2.33 (1H, br t, OH), 3.82 (3H, s, OCH_3), 4.70 (2H, br d, $ArCH_2$), 6.72 (1H, dd, *J* 3 and 8 Hz, 4-H), 7.1 (1H, d, *J* 3 Hz, 6-H) and 7.45 (1H, d, *J* 8 Hz, 3-H); *m/z* 218 and 216 (M^+ 218, 96%), (M^+ 216, 100%), 137 (33), 109 (59), 108 (49), 94 (40), 77 (41), and 63 (28).

2-Bromo-5-methoxybenzyl methoxyethoxymethyl Ether (163)

The alcohol (162) (5.29 g, 2.44 mmol) was dissolved in dry tetrahydrofuran (50 ml) and cooled to 0°C. Sodium hydride (50% oil emulsion) (1.1 mol equiv.) was added and the mixture was stirred for 15 min under nitrogen. Methoxyethoxymethyl chloride (MEMCl) (2 mol equiv.) was added dropwise in dry tetrahydrofuran (30 ml) over 10 min. After 30 min had elapsed, a further batch of sodium hydride (1.5 mol equiv.) was added followed by more MEMCl (0.5 mol equiv.), and the reaction was stirred for a further 2.5 h. Water was carefully added to the reaction and diethyl ether was used to extract the organic material. The ether layer was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to give

a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum) to afford the product (163) (6.61 g, 89%) as an oil (Found: C, 47.25; H, 5.5. $C_{12}H_{17}BrO_4$ requires C, 47.25; H, 5.6%); δ3.37 (3H, s, OMe), 3.57 (4H, m, OCH_2CH_2O), 3.77 (3H, s, ArOMe), 4.43 (2H, s, OCH_2O), 4.83 (2H, s, $ArCH_2$), 6.67 (1H, dd, *J* 3 and 8 Hz, 4-H), 7.05 (1H, d, *J* 3 Hz, 6-H), and 7.4 (1H, d, *J* 8 Hz, 3-H); *m/z* 306 and 304 (M^+ 306, 9%), (M^+ 304, 9%), 230 (26), 228 (26), 215 (16), 201 (87), 199 (100), 149 (38), 121 (35), 89 (47), 80 (58), and 44 (65).

2-Methoxyethoxymethoxymethyl-4-methoxybenzoic acid (164)

Compound (163) (409 mg, 1.34 mmol) was dissolved in dry ether (30 ml) and cooled to 0°C. *n*-Butyl-lithium (2.1 mol equiv.) in hexane was added dropwise over 2 min under nitrogen. After being stirred at 0°C for 30 min, the solution was poured over dry ice, the flask swirled and allowed to stand for 1 h. The mixture was thrown into ethyl acetate and extracted with a sodium hydroxide solution (1%). The organic layer which remained was dried over magnesium sulphate, filtered and evaporated to yield the product of debromination, 3-methoxy-benzyl methoxyethoxymethyl ether (166), (193 mg, 70%). The basic extract was reacidified with dilute hydrochloric acid and repeatedly extracted with ethyl acetate. After drying over magnesium sulphate, filtering and evaporation of the organic solvent the product (164) (83 mg, 23%) was obtained as white crystals (dichloromethane - light petroleum), m.p. 92 - 94°C (Found: C, 57.30; H, 6.65. $C_{13}H_{18}O_6$ requires C, 57.75, H, 6.70%); $\nu_{max.}$ 1683 cm^{-1} (C = O); δ3.38 (3H, s, MEM OMe),

3.47 - 3.92 (4H, m, OCH_2CH_2O), 3.86 (3H, s, ArOMe), 4.88 (2H, s, OCH_2O), 5.04 (2H, s, $ArCH_2$), 6.82 (1H, dd, *J* 3 and 9 Hz, 4-H), 7.23 (1H, d, *J* 3 Hz, 6-H), 7.30 - 7.96 (1H, br s, OH, disappears on D_2O exchange), and 8.06 (1H, d, *J* 9 Hz, 3-H); *m/z* 181 {M-89, (56%)}, 166 (19), 165 (89), 164 (25), 163 (100), 135 (16), 89 (11), 77 (13), 59 (31), 45 (25), and 31 (9).

2-(2-Hydroxyethyl)-5-methoxybenzyl methoxyethoxymethyl Ether (165)

Compound (163) (1.18 g, 3.87 mmol) was dissolved in dry ether (50 ml) and cooled to 0°C. *n*-Butyl-lithium (2.1 mol equiv.) in hexane was added dropwise under nitrogen. The solution was stirred for 45 min after which an excess of ethylene oxide (5 mol equiv.) was added, and the solution stirred for a further 2 h. The mixture was added to water and extracted with ether, which was dried over magnesium sulphate, filtered and removed under reduced pressure to give a residue which was chromatographed (eluant 20% ethyl acetate - light petroleum). Initial fractions afforded the product of debromination, 3-methoxybenzyl methoxyethoxymethyl ether (166), (417 mg, 48%), while later fractions gave the product (165), (240 mg, 23%) as an oil (Found: C, 61.9; H, 8.2. $C_{14}H_{22}O_5$ requires C, 62.2; H, 8.15%); $\nu_{max.}$ (neat) 3485 cm^{-1} (OH), δ2.30 (1H, br s, OH, disappears on D_2O exchange), 2.84 (2H, t, *J* 7 Hz, collapses to a singlet on double irradiation at δ3.72, CH_2OH), 3.36 (3H, s, MEM OMe), 3.48 - 3,89 (6H, m, OCH_2CH_2O and $ArCH_2CH_2OH$), 3.74 (3H, s, ArOMe), 4.59 (2H, s, OCH_2O), 4.77 (2H, s, $ArCH_2O$), 6.80 (1H, dd, *J* 3 and 8 Hz, 4-H), 6.93 (1H,

d, *J* 3 Hz, 6-H) and 7.23 (1H, d, *J* 8 Hz, 3-H); *m/z* 270 (M^+, 6%), 181 (11), 163 (29), 149 (19), 135 (96), 134 (100), and 59 (58).

2-Bromo-5-methoxy-N-*methylbenzamide (168)*

The acid (159) (5.00 g, 21.6 mmol) was dissolved in thionyl chloride (20 ml) and boiled for 3 h. After cooling, the solvent was evaporated and the residue was added to a solution of water (20 ml) and 40% methylamine solution (20 ml). White crystals immediately formed upon addition. The solution was vigorously shaken and cooled in ice for 1 h. The organic material was extracted into chloroform, which was separated, dried over magnesium sulphate and filtered. Evaporation of the solvent afforded a residue which was recrystallised to give the product (168) (5.27 g, 100%), m.p. 158.5 - 159.5°C as colourless stumps (ethyl acetate) (Found: C, 44.1; H, 4.2; N, 5.7. $C_9H_{10}BrNO_2$ requires C, 44.3; H, 4.10; N, 5.75%); δ2.99 (3H, d, *J* 5 Hz, NCH_3), 3.80 (3H, s, OMe), 6.26 (1H, br s, NH), 6.81 (1H, dd, *J* 3 and 8 Hz, 4-H), 7.07 (1H, d, *J* 3 Hz, 6-H) and 7.43 (1H, d, *J* 8 Hz, 3-H); *m/z* 245 and 243 (M^+ 245, 50%), (M^+ 243, 50%), 215 (68), 213 (69), 187 (15), 185 (15), 172 (16), 170 (16), 78 (40), 63 (100), 58 (29), and 28 (52).

2-Bromo-5-methoxy-N-*(t-butyl)benzamide (170)*

The acid (159) (5.20 g, 22.5 mmol) was dissolved in thionyl chloride (40 ml) and boiled for 4 h, after which it was cooled off, the excess reagent removed under reduced pressure and the

residue added to a (20%) aqueous solution of *t*-butylamine (50 ml). An oil separated immediately upon addition, and the flask was vigorously shaken and cooled in ice for 1 h. The organic material was extracted into dichloromethane, which was dried over magnesium sulphate, filtered and the organic solvent evaporated to afford a residue which was recrystallised to yield the product (170) (4.89 g, 76%), m.p. 93.5 - 95°C (light petroleum) as white rods (Found: C, 50.6; H, 5.65; N, 4.95. $C_{12}H_{16}BrNO_2$ requires C, 50.35; H, 5.60; N, 4.90%); δ1.48 (9H, s, CCH_3), 3.80 (3H, s, OMe), 5.94 (1H, br s, NH), 6.78 (1H, dd, *J* 3 and 8 Hz, 4-H), 7.05 (1H, d, *J* 3 Hz, 6-H), and 7.41 (1H, d, *J* 8 Hz, 3-H); *m/z* 287 and 285 (M^+ 287, 31%), (M^+ 285, 31%), 278 (14), 276 (14), 231 (31), 229 (31), 215 (97), 213 (100), 172 (9), 170 (11), 63 (23), and 57 (22).

5-Methoxy-N-methyl-2-pentylbenzamide (171)

The amide (168) (636 mg, 2.61 mmol) was dissolved in dry tetrahydrofuran (30 ml) and cooled to -78°C. *n*-Butyl-lithium (2.1 mol equiv.) in hexane was added dropwise over 5 min, the reaction being performed under nitrogen. After the solution was stirred at this temperature for 0.5 h, it was warmed to 0°C and stirred for a further 0.5 h. *n*-Pentyl bromide (2.1 mol equiv.) in dry tetrahydrofuran (10 ml) was then added and the solution was stirred at room temperature for a further 2 h. The reaction was quenched with water and extracted into dichloromethane which after being separated, dried over magnesium sulphate, filtered and the organic solvent evaporated, gave a residue which was chromatographed (eluant 40% ethyl acetate -

light petroleum). The third fraction off the column was the crystalline product (171) (92 mg, 15%); $\nu_{max.}$ 3305 cm^{-1} (NH), 1635 (C = O); δ0.90 (3H, t, *J* 7 Hz, 5-CH_3), 1.40 (6H, m, 4-, 3- and 2-CH_2), 2.66 (2H, t, *J* 7 Hz, ArCH_2), 2.90 (3H, d, *J* 5 Hz, NMe), 3.76 (3H, s, OCH_3), 6.24 (1H, br s, OH), 6.83 (1H, d, *J* 3 Hz, 6-H), 6.90 (1H, dd, *J* 3 and 9 Hz, 4-H), and 7.14 (1H, d, *J* 9 Hz, 3-H); *m/z* 235 (M^+, 2%), 221 (73), 206 (9), 192 (100), 191 (35), 190 (32), 179 (29), 178 (64), 161 (71), 149 (39), 135 (40), and 121 (44). The fourth fraction gave *N*-methyl-3-methoxybenzamide (102) (170 mg, 40%).

2-Bromo-5-methoxy-valerophenone (172)

The amide (169) (1.02 g, 3.95 mmol) was dissolved in dry tetrahydrofuran (25 ml) and cooled to -78°C. *n*-Butyl-lithium (1.2 mol equiv.) in hexane was added dropwise, the reaction being performed under nitrogen. The solution was stirred for 20 min, warmed to 0°C, then stirred for a further 30 min. *n*-Pentyl bromide (5 mol equiv.) in dry tetrahydrofuran was added over 10 min. Stirring was allowed to continue for 1.5 h before the mixture was added to water and extracted into dichloromethane. After drying over magnesium sulphate, the organic solvent was filtered and evaporated to yield a residue which was chromatographed (eluant 40% ethyl acetate - light petroleum). Early fractions afforded the product (172) (0,388 g, 36%) as an oil; δ0.95 (3H, t, *J* 7 Hz, 5-CH_3), 1.38 (2H, m, *J* 7 Hz, 4-CH_2), 1.73 (2H, m, *J* 7 Hz, 3-CH_2), 2.93 (2H, t, *J* 7 Hz, 2-CH_2), 3.84 (3H, s, OCH_3), 7.10 (1H, dd, *J* 3 and 8 Hz, 4-H), 7.39 (1H, d, *J* 8 Hz, 3-H) and 7.50 (1H, d, *J* 3 Hz, 6-H); *m/z* 272 and

270 (M^+ 272, 4%), (M^+ 270, 4%), 230 (7), 228 (7), 215 (21), 213 (21), 192 (35), 150 (83), 135 (100), 107 (45), 92 (27), and 77 (34).

5-Methoxy-2-pentyl benzamide (175) and 3-Methoxy-2- pentyl-benzamide (176)

The amide (170) (1.29 g, 4.51 mmol) was dissolved in dry tetrahydrofuran (30 ml) and cooled to -78°C. *n*-Butyl-lithium (2.5 mol equiv.) in hexane was added dropwise over 5 min, the reaction being performed under nitrogen. The solution was stirred for 0.5 h, warmed to 0°C and stirred for a further 45 min. *n*-Pentyl bromide (6 mol equiv.) was then added and the solution was stirred at room temperature for a further 50 min. This mixture was added to water, extracted with dichloromethane which after separation from the aqueous layer was dried over magnesium sulphate, filtered and the solvent removed to yield a residue. This was chromatographed (eluant 20% ethyl acetate - light petroleum) to give 3-methoxy-2-pentyl-*N*-(*t*-butyl)benzamide (174) and 5-methoxy-2-pentyl-*N*-(*t*-butyl)benzamide (173) as an oily inseparable mixture (0,745 g, 60%). A portion of this mixture (56 mg, 0.20 mmol) was dissolved in trifluoroacetic acid (10 ml) and heated under reflux until t.l.c. showed that no more starting material was present (72 h). The solvent was evaporated and chromatography (p.l.c. eluant 30% ethyl acetate - light petroleum) gave two major bands. The band of higher R_F was 3-methoxy-2-pentylbenzamide (176) (13 mg, 29%) isolated as white needles (dichloromethane - light petroleum), m.p. 141 - 142.5°C (Found: C, 70.15; H, 8.35;

N, 6.15; $C_{13}H_{19}NO_2$ requires C, 70.55; H, 8.65; N, 6.35%; $\nu_{max.}$ 3160 and 3350 (NH_2), and 1610-1640 cm^{-1} (C = O); δ0.89 (3H, t, *J* 7 Hz, 5-CH_3), 1.10 - 2.05 (6H, m, 4-CH_2, 3-CH_2, and 2-CH_2), 2.79 (2H, t, *J* 8 Hz, $ArCH_2$), 3.84 (3H, s, OCH_3), 5.75 (2H, br s, NH_2), 6.93 (1H, d, *J* 8 Hz, 4-H), 7.08 (1H, t, *J* 8 Hz, 5-H), and 7.23 (1H, d, *J* 8 Hz, 6-H); *m/z* 221 (M^+, 49%), 204 (21), 178 (62), 165 (100), 164 (68), 161 (28), 148 (17), 121 (18), 91 (26), and 77 (21). The band of lower R_F was identified as being 5-methoxy-2-pentylbenzamide (175) (18 mg, 40%); $\nu_{max.}$ 3360 and 3180 (NH_2), 1645 cm^{-1} (C = O); δ0.91 (3H, t, *J* 7 Hz, 5-CH_3), 1.16 - 1.78 (6H, m, 4-CH_2, 3-CH_2, and 2-CH_2), 2.74 (2H, t, *J* 8 Hz, $ArCH_2$), 3.80 (3H, s, OCH_3), 5.91 (2H, br s, NH_2), 6.90 (1H, dd, *J* 3 and 8 Hz, 4-H), 6.95 (1H, d, 6-H), and 7.17 (1H, d, *J* 8 Hz, 3-H); *m/z* 221 (M^+, 3%), 207 (45), 190 (22), 178 (47), 165 (34), 164 (100), 161 (32), 146 (19), 121 (21), and 77 (14).

2-Acetoxymethyl-4-methoxy-acetophenone (184)

The acetate (183), (390 mg, 2.17 mmol) was added to a prestirred mixture of glacial acetic acid (1.5 mol equiv.) and trifluoroacetic anhydride (1.8 mol equiv.). After stirring for 48 h at room temperature under anhydrous conditions, the mixture was added to dichloromethane and successively washed with sodium bicarbonate (twice) and water. The organic layer was separated, dried over magnesium sulphate, filtered and evaporated to give a residue which was chromatographed (eluant 2.5% ethyl acetate - light petroleum). Early fractions gave starting material (96 mg, 25%), while later fractions gave the product (184) (223 mg, 46%

or 61.5% based on unrecovered starting material) as white needles, m.p. 69.5 - 70.5°C (light petroleum) (Found: C, 64.8; H, 6.3. $C_{12}H_{14}O_4$ requires C, 64.85; H, 6.35%); $\nu_{max.}$ 1733, (acetate), 1652 cm^{-1} (acetyl); δ2.17 (3H, s, OAc), 2.57 (3H, s, Ac), 3.88 (3H, s, OMe), 5.51 (2H, s, $ArCH_2$), 6.88 (1H, dd, *J* 3 and 8 Hz, 5-H), 7.05 (1H, d, *J* 3 Hz, 3-H), and 7.86 (1H, d, *J* 8 Hz, 6-H); *m/z* 222 (M^+, 16%), 180 (33), 179 (100), 165 (65), 161 (55), 77 (16), and 43 (81).

2-Acetoxymethyl-4-methoxy-valerophenone (185)

The acetate (183) (7.43 g, 40.3 mmol) was added to a prestirred mixture of valeric acid (5 mol equiv.) and trifluoroacetic anhydride (5 mol equiv.). The solution was stirred for 72 h at room temperature under anhydrous conditions. Methanol was then added, and after the solution was allowed to stir for a further 1 h, the mixture was poured into dichloromethane. This was successively washed with a saturated sodium bicarbonate solution (twice) and water, after which the organic layer was separated, dried over magnesium sulphate, filtered and the solvent evaporated to yield a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum). Early fractions gave starting material (1.05 g, 14%), while later fractions gave the product (185) (3.05 g, 29% or 34% based on unrecovered starting material) as white crystals, m.p. 42.5 - 43°C (light petroleum) (Found: C, 68.05; H, 7.7. $C_{15}H_{20}O_4$ requires C, 68.2; H, 7.6%); $\nu_{max.}$ 1736 (acetate C=O), 1664 (aromatic C=O), 1611 cm^{-1} (C=C); δ0.95 (3H, t, *J* 7 Hz, 5-CH_3), 1.21 - 1.98 (4H, m, 3- and 4-CH_2), 2.16 (3H, s, OAc), 2.91 (2H, t, *J* 7 Hz, 2-CH_2),

3.88 (3H, s, OMe), 5.49 (2H, s, $ArCH_2$), 6.87 (1H, dd, *J* 3 and 8 Hz, 5-H), 7.06 (1H, d, *J* 3 Hz, 3-H), and 7.84 (1H, d, *J* 8 Hz, 6-H); *m/z* 264 (M^+, 10%), 221 (37), and 165 (100).

2-(1-Hydroxypentyl)-5-methoxybenzyl alcohol (186)

Compound (185) (0.75 g, 2.84 mmol) was dissolved in dry ether and added dropwise to a suspension of lithium aluminium hydride (4 mol equiv.) in dry ether (20 ml) at room temperature. After the mixture had been stirred for 0.5 h, sufficient saturated aqueous ammonium chloride was added to decompose the excess of reagent, followed by anhydrous magnesium sulphate. After filtration, the solvent was removed to give a residue which was chromatographed (eluant 40% ethyl acetate - light petroleum) to afford the product (186) (0.56 g, 88%) as an oil (Found: C, 69.35; H, 9.05. $C_{13}H_{20}O_3$ requires C, 69.65; H, 8.95%); $\nu_{max.}$ (neat) 3430 (OH), and 1611 cm^{-1} (C = C); δ0.89 (3H, deformed t, *J* 6 Hz, CH_3), 1.12 (4H, br m, 3- and 4-CH_2), 1.80 (2H, br m, 2-CH_2), 3.30 (2H, br s, 2 x OH), 3.80 (3H, s, OMe), 4.53 and 4.69 (1H each, d, *J* 12 Hz, $ArCH_2$), 4.78 (1H, t, *J* 7 Hz, 1-H), 7.83 (1H, dd, *J* 3 and 8 Hz, 4-H), 7.89 (1H, br s, 6-H), and 8.32 (1H, d, *J* 8 Hz, 3-H); *m/z* 224 (M^+, 1.4%), 206 (23), 167 (23), 159 (22), 149 (100), 147 (28), 121 (25), 91 (15), and 77 (14).

(E)-5-Methoxy-2-pent-1-enylbenzyl bromide (188)

(a) Compound (191) (501 mg, 2.61 mmol) was dissolved in anhydrous carbon tetrachloride (30 ml). *N*-bromosuccinimide (2.5 mol equiv.) and benzoyl peroxide (50 mg) were subsequently added.

The solution was boiled for 1 h, cooled off and filtered to remove the crystalline succinimide. Evaporation of the solvent produced a residue to which was added lutidine (10 ml) without further delay, and the solution was heated under reflux for 30 min during which it took on a dark appearance. This solution was filtered after cooling to remove the lutidine hydrobromide, and the excess of lutidine evaporated. The residual oil was thrown into dilute acid and extracted with dichloromethane, which was separated, dried over magnesium sulphate, filtered and the organic solvent removed to afford a residue which was chromatographed (p.l.c. eluant light petroleum) to give rise to the oily product (188) (140 mg, 20%) as the band of higher R_F; δ0.97 (3H, t, *J* 7 Hz, 5-CH_3), 1.47 (2H, sextet, *J* 7 Hz, 4-CH_2), 2.20 (2H, q, *J* 7 Hz, 3-CH_2), 3.38 (3H, s, OCH_3), 4.50 (2H, s, $ArCH_2$), 6.06 (1H, dt, *J* 7 and 16 Hz, 2-CH), 6.65 (1H, d, *J* 16 Hz, 1-CH), 6.79 (1H, dd, *J* 3 and 8 Hz, 4-H), 6.86 (1H, d, *J* 3 Hz, 6-H), and 7.41 (1H, d, *J* 8 Hz, 3-H); *m/z* 270 and 268 (M^+ 270, 22%), (M^+ 268, 22%), 241 (8), 239 (7), 189 (51), 160 (35), 159 (76), 147 (100), 115 (77), 91 (50), 77 (27), 63 (24), and 51 (29). A subsequent band of lower R_F proved to be the less functionalised oil, (*E*)-4-methoxy-2-methyl-1-pent-1-enylbenzene (200) (137 mg, 28%); δ0.94 (3H, t, *J* 8 Hz, 5-CH_3), 1.14 - 1.76 (4H, m, 3- and 4-H), 2.29 (3H, s, $ArCH_3$), 3.74 (3H, s, OMe), 5.94 (1H, dt, *J* 7 and 17 Hz, 2-CH), 6.50 (1H, d, *J* 17 Hz, 1-CH), 6.62 - 6,80 (2H, m, 3- and 5-H), and 7.34 (1H, d, *J* 10 Hz, 6-H); *m/z* 190 (M^+, 59%), 161 (100), 146 (15), 134 (58), and 91 (12).

b) For an alternative method of synthesis of compound (188) see experimental section on p. 121 under compound (154).

3-Methyl-4-(1-pentyl)anisole (191)

Compound (192) (5.17 g, 25.1 mmol) was dissolved in toluene (15 ml) and added to a stirred 1:1 mixture of conc. HCl/H_2O which contained amalgamated granular zinc (15 g). The mixture was stirred vigorously under reflux for 72 h to ensure contact of the granular zinc with the organic layer. After cooling, the aqueous and organic layers were decanted into a separatory funnel, water (100 ml) was added and the aqueous layer neutralised with sodium hydrogen carbonate. This was repeatedly extracted with ether, the organic layers separated, dried over magnesium sulphate, filtered and evaporated to give a residue which was chromatographed (eluant - light petroleum). Initial fractions gave the product (191) (2.24 g, 46% or 55% based on unrecovered starting material) as an oil (Found: C, 81.35; H, 10.6. $C_{13}H_{20}O$ requires C, 81.20; H, 10.5%); δ0.96 (3H, t, *J* 6 Hz, CH_3), 1.44 (6H, m, $CH_2CH_2CH_2$), 2.32 (3H, s, $ArCH_3$), 2.58 (2H, t, *J* 8 Hz, $ArCH_2$), 3.82 (3H, s, OMe), 6.7 - 6.8 (2H, m, 2- and 6-H), and 7.10 (1H, d, *J* 9 Hz, 5-H); *m/z* 192 (M^+, 15%), 137 (9), 136 (100), and 120 (28). Later fractions gave starting material (800 mg, 15%).

4-Methoxy-2-methyl-valerophenone (192)

(a) Compound (198) (16.6 mg, 0.086 mmol) was dissolved in anhydrous acetone (30 ml), and potassium carbonate (3 mol equiv.) and dimethyl sulphate (3 mol equiv.) were added and the mixture stirred under reflux for 2 h. The excess potassium carbonate was removed by filtration and the acetone was evaporated to yield a residue which was taken up in ether and washed successively

with ammonia (25%) (twice), water, dilute hydrochloric acid and then more water. After separation, the ether layer was dried over magnesium sulphate, filtered and the ether removed to give a residue which was chromatographed (p.l.c. eluant 10% ethyl acetate - light petroleum) to afford the product (192) (18.7 mg, 97%), m.p. 52 - 53.5°C (light petroleum) as colourless cubes (Found: C, 76.0; H, 8.9. $C_{13}H_{18}O_2$ requires C, 75.70; H, 8.8%); $\nu_{max.}$ 1671 cm^{-1} (C = O); δ0.94 (3H, t, *J* 7 Hz, 5-CH_3), 1.39 (2H, m, *J* 7 Hz, 4-CH_2), 1.69 (2H, m, *J* 7 Hz, 3-CH_2), 2.54 (3H, s, ArCH_3), 2.87 (2H, t, *J* 7 Hz, 2-CH_2), 3.83 (3H, s, OCH_3), 6.68 - 6.84 (2H, m, 3- and 5-H), and 7.74 (1H, d, *J* 8 Hz, 6-H); *m/z* 206 (M^+, 31%), 164 (39), 150 (37), 149 (100), 121 (34), 91 (24), and 77 (17).

b) *m*-Methoxytoluene (193) (5.10 g, 41.8 mmol) was added to a prestirred mixture of trifluoroacetic anhydride (2 mol equiv.) and valeric acid (2 mol equiv.) and stirred for 3.5 h at room temperature. Methanol (100 ml) was then added to the reaction and stirring allowed to continue for a further 1 h, after which the mixture was thrown into saturated sodium hydrogen carbonate and extracted with dichloromethane (4 x 100 ml). The organic layers were combined and backwashed with water before being dried over anhydrous magnesium sulphate, filtered and the dichloromethane was evaporated to yield a crude residue (8.61 g). This was recrystallised twice from light petroleum to give two crops of colourless crystals (4.42 g, 51%) later identified as the product (192) identical with that in (a) above. No further pure crystals could be cleanly recrystallised from the residual yellow mixture (3.81 g) which had the appearance of oily crystals.

^{1}H n.m.r. spectroscopy revealed this to be a 1:1 mixture of the crystals obtained in (a) above and its oily isomer (194) from which it was difficult to separate chromatographically owing to their near-identical R_F-values. The respective yields of the two compounds from the reaction were calculated by apportioning half of the mass of the residual mixture obtained by combining the mother liquors of the two initial recrystallisations to each compound since the ^{1}H n.m.r. spectral integration for the mixture showed that the ratio of (192) to (194) was close to 1:1; on this basis, compound (192) was obtained in a yield of 6.32 g (73%) and compound (194) likewise in a yield of 1.9 g (22%).

2-Methoxy-4-methyl-valerophenone (194)

(a) The phenol (196) (68 mg, 0.35 mmol) was dissolved in anhydrous acetone (30 ml), and potassium carbonate (5 mol equiv.) and dimethyl sulphate (5 mol equiv.) were added. After this mixture was stirred for 10 h under reflux, it was cooled, filtered and the solvent evaporated to give a residue which was taken up in ether and successively washed with ammonia (25%) (twice), water, dilute hydrochloric acid and then more water. The ether layer was separated, dried over magnesium sulphate, filtered and the ether evaporated to give a residue which was chromatographed (p.l.c. 1% ethyl acetate - light petroleum) to afford the product (194) (76 mg, 97%) as an oil (Found: C, 75.75; H, 8.95. $C_{13}H_{18}O_2$ requires C, 75.7; H, 8.8%); $\nu_{max.}$ (film) 1667 (C = O) and 1609 cm^{-1} (C = C); 0.92 (3H, t, *J* 7 Hz, 5-CH_3), 1.17 - 1.87 (4H, m, 3- and 4-CH_2), 2.18 (3H, s,

$ArCH_3$), 2.96 (2H, t, *J* 7 Hz, 2-CH_2), 3.88 (3H, s, OCH_3), 6.6 - 7.0 (2H, m, 3- and 5-H), and 7.61 (1H, d, *J* 8 Hz, 6-H); *m/z* 206 (M^+, 5%), 164 (47), 150 (28), 149 (100), 106 (12), and 91 (33).

(b) For an alternative method of synthesis using the mixed anhydride method, see experimental section on p. 134 under compound (192).

The boron trifluoride etherate Fries rearrangement of the valeric ester of m-cresol

The ester (195) (527 mg, 2.74 mmol) was dissolved in freshly distilled boron trifluoride etherate (3 ml) and heated at 110°C for 4 h. After cooling, the mixture was thrown into water and extracted with ethyl acetate. The organic layer was separated, dried over magnesium sulphate, filtered and the organic solvent evaporated to yield a residue which was chromatographed (eluant 20% ethyl acetate - light petroleum). Two fractions were collected; the first to elute was compound (196), the product of *ortho*-migration (449 mg, 85%), while later fractions yielded compound (198), the product of *para*-migration (12 mg, 2%).

The titanium tetrachloride Fries rearrangement of the valeric acid ester of m-cresol

The ester (195) (530 mg, 2.76 mmol) was dissolved in titanium tetrachloride (3 ml) and stirred for 20 h at room temperature. After this time had elapsed during which the mixture had gradually darkened and appeared black, the mixture was thrown into water

and extracted exhaustively with ethyl acetate. The organic layer was separated, dried over magnesium sulphate, filtered and the organic solvent evaporated to yield a residue which was chromatographed (eluant 2.5% ethyl acetate - light petroleum). Initial fractions afforded compound (196) (225 mg, 49%), i.e. the product of *ortho*-migration, followed by starting material (71 mg, 13%). The third fraction collected with an R_F marginally lower than starting material was the oily product (197), *viz*. 2-hydroxy-6-methyl-valerophenone (Found: M^+ 192.1128, $C_{12}H_{16}O_2$ requires M 192.1150); δ0.94 (3H, t, *J* 7 Hz, CH_3), 1.14 - 1.94 (4H, m, CH_2CH_2), 2.59 (3H, s, $ArCH_3$), 3.95 (2H, t, *J* 7 Hz, 2-CH_2), 6.72 and 6.83 (each 1H, d, *J* 8 Hz, 3- and 5-H), 7.27 (1H, t, *J* 8 Hz, 4-H), and 11.54 (1H, br s, OH); *m/z* 192 (M^+, 10%), 135 (100) and 77 (20). *m*-Cresol (65 mg, 25%) was the next compound to elute, and the final product off the column was compound (198), the product of *para*-Fries migration (17 mg, 4%).

2-Allyl-3-hydroxymethyl-1-methoxy-naphthalene (205)

Method A

Acetate (213) (243 mg, 0.9 mmol) was dissolved in a solution of sodium hydroxide (1 g) in methanol (25 ml). After stirring for 20 min at room temperature, the solution was neutralised with dilute hydrochloric acid and the methanol removed under reduced pressure. Water was added to the residue and this transferred to a separatory funnel and extracted with ether. The ether layer was dried over magnesium sulphate, filtered and the ether removed under reduced pressure to give a residue

which was chromatographed (eluant 30% ethyl acetate - light petroleum) to afford the product (205), (171 mg, 83%) as an oil (Found: C, 78.95; H, 6.9. $C_{15}H_{16}O_2$ requires C, 78.9; H, 7.05%); $\nu_{max.}$ (neat) 3330 cm^{-1} (OH); δ1.97 (1H, br s, OH), 3.68 (2H, m, $ArCH_2C$), 3.92 (3H, s, OMe), 4.80 (2H, s, $ArCH_2O$), 4.80 - 5.12 (2H, m, vinyl CH_2), 5.88 - 6.29 (1H, m, vinyl CH), 7.40 - 7.59 (2H, m, 6- and 7-H), 7.77 (1H, s, 4-H), 7.81 (1H, m, 5-H), and 8.07 (1H, m, 8-H); *m/z* 228 (M^+, 100%), 210 (16), 195 (75), 179 (26), 167 (27), 165 (55), 152 (28), 128 (22), and 115 (21).

Method B

The ester (224) (157 mg, 0.61 mmol) was dissolved in dry ether (20 ml) and added dropwise to a stirred suspension of lithium aluminium hydride (87 mg, 2.28 mmol) in dry ether (20 ml) over 5 min at room temperature. After allowing the mixture to stir for a further 10 min, sufficient saturated ammonium chloride was added to destroy the excess of reagent and magnesium sulphate was then added. The mixture was filtered and the ether removed under reduced pressure to yield a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum) to give the oily product (205) (130 mg, 93%).

2-Allyl-4-ethyl-3-hydroxymethyl-1-methoxy-naphthalene (206)

The ester (222) (1.63 g, 5.74 mmol) was dissolved in anhydrous ether (100 ml) and added dropwise over 15 min to a stirred suspension of lithium aluminium hydride (436 mg, 11.5 mmol) in anhydrous ether (50 ml). After the addition was completed, the

mixture was stirred for 5 h at room temperature, followed by a further 1.5 h of stirring under reflux. The solution was then allowed to cool, and sufficient saturated ammonium chloride solution was cautiously added dropwise to destroy the excess of reagent, followed by magnesium sulphate. This was filtered and the ether removed under reduced pressure to give a residue which was chromatographed (eluant 30% ethyl acetate - light petroleum) to yield the alcohol (206) (1.270 g, 86%) as white crystals, m.p. 85 - 86.5°C (light petroleum) (Found: C, 79.55; H, 7.95. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.85%); $\nu_{max.}$ (neat) 3360 (OH), and 1586 cm^{-1} (C = C); δ1.23 (3H, t, *J* 8 Hz, CH_3), 2.39 (1H, br s, OH), 3.11 (2H, q, *J* 8 Hz, $\underline{CH_2}CH_3$), 3.68 (2H, m, Ar$\underline{CH_2}$CH), 3.84 (3H, s, OMe), 4.71 (2H, s, $ArCH_2O$), 4.71 - 5.14 (2H, m, vinyl CH_2), 5.84 - 6.32 (1H, m, vinyl CH), 7.32 - 7.52 (2H, m, 6- and 7-H), 7.88 (1H, m, 5-H), and 8.15 (1H, m, 8-H); *m/z* 256 (M^+, 100%), 238 (16), 223 (94), and 165 (27).

Methyl 1-allyloxy-3-naphthoate (209)

Compound (208) (1.03 g, 5.1 mmol) was dissolved in dry acetone (90 ml) and potassium carbonate (2.11 g, 15 mmol) and allyl-bromide (1.29 ml, 15 mmol) were added. The mixture was heated under reflux for 4 h, cooled and filtered to remove the excess of potassium carbonate. The acetone was removed under reduced pressure and the residue thrown into water. This was extracted exhaustively with ether, and the combined ether layers dried over anhydrous magnesium sulphate, filtered and the solvent removed under reduced pressure to give the product (209), (1.23 g, ≃ 100%) as an oil (Found: C, 74.45; H, 5.9. $C_{15}H_{14}O_3$

requires C, 74.35; H, 5.8%); $\nu_{max.}$ (neat) 1715 cm^{-1} (C = O); δ3.96 (3H, s, OMe), 4.76 (2H, m, CH_2), 5.26 - 5.66 (2H, m, vinyl CH_2), 6.0 - 6.4 (1H, m, vinyl CH), 7.39 (1H, s, 2-H), 7.48 - 7.66 (2H, m, 6- and 7-H), 7.89 (1H, m, 5-H), 8.21 (1H, s, 4.H), and 8.33 (1H, m, 8-H); *m/z* 242 (M^+, 87%), 202 (17), 201 (100), 164 (17), 162 (11), 171 (17), 143 (53), 142 (15), 116 (28), and 114 (33).

1-Allyloxy-3-hydroxymethyl-naphthalene (210)

Ester (209) (1.40 g, 5.8 mmol) was dissolved in dry ether and added dropwise to a stirred suspension of lithium aluminium hydride (0,440 g, 11.5 mmol) in dry ether (50 ml) over 15 min. Stirring was allowed to continue for a further 10 min before the mixture was slowly quenched with a saturated ammonium chloride solution. Magnesium sulfate was then added and after stirring for a further 10 min the mixture was filtered and the solvent removed under reduced pressure to yield the product (210) (1.24 g, 100%) as an oil (Found: C, 78.25; H, 6.7. $C_{14}H_{14}O_2$ requires C, 78.5; H, 6.6%); $\nu_{max.}$ (film) 3290 (OH), and 1581 cm^{-1} (C = C); δ1.98 (1H, br s, OH, disappears on D_2O wash), 4.71 (2H, m, $ArOCH_2$), 4.77 (2H, s, $ArCH_2$), 5.28 - 5.65 (2H, m, vinyl CH_2), 6.00 - 6.41 (1H, m, vinyl CH), 6.83 (1H, s, 2-H), 7.37 (1H, s, 4-H), 7.42 - 7.60 (2H, m, 6- and 7-H), 7.87 (1H, m, 5-H), and 8.31 (1H, m, 8-H); *m/z* 214 (M^+, 100%), 173 (86), 145 (17), 127 (25), 117 (38), 115 (30), and 91 (15).

3-Acetoxymethyl-1-allyloxy-naphthalene (211)

Alcohol (210) (1.20 g, 5.6 mmol), acetic anhydride (2.5 g, 24 mmol) and pyridine (0,95 g, 12 mmol) were mixed and heated together at 60°C for 1 h. The mixture was thrown into ice, acidified with dilute hydrochloric acid and extracted with dichloromethane. The combined organic layers were dried over magnesium sulphate and filtered. Evaporation of the solvent followed by chromatography (eluant 10% ethyl acetate - light petroleum) yielded the product (211) (1.27 g, 88%) as an oil (Found: C, 74.65; H, 6.25. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%); $\nu_{max.}$ (neat) 1729 cm^{-1} (C = O); δ2.16 (3H, s, CH_3), 4.74 (2H, m, OCH_2CH), 5.23 (2H, s, $ArCH_2$), 5.24 - 5.67 (2H, m, vinyl CH_2), 5.98 - 6.43 (1H, m, vinyl CH), 6.79 (1H, s, 2-H), 7.26 (1H, s, 4-H), 7.38 - 7.60 (2H, m, 6- and 7-H), 7.79 (1H, m, 5-H), and 8.29 (1H, m, 8-H); *m/z* 256 (M^+, 60%), 216 (15), 192 (12), 175 (14), 173 (100), 142 (17), 128 (25), and 115 (13).

3-Acetoxymethyl-2-allyl-1-methoxy-naphthalene (213)

The substituted allyloxynaphthalene (211) (224 mg, 0.87 mmol) was heated for 1 h under nitrogen during which the temperature rose steadily from an initial 180°C to 200°C. The resulting oil, which had somewhat darkened, was dissolved in anhydrous acetone (50 ml), and potassium carbonate (360 mg, 2.6 mmol) and dimethyl sulphate (0.248 ml, 2.6 mmol) were added. This mixture was heated under reflux for 1.5 h, cooled, and then filtered to remove the excess of potassium carbonate. After removing the acetone under reduced pressure, the residue was taken up into ether which was repeatedly washed with ammonia

(25%) to remove the excess of dimethyl sulphate. Dilute hydrochloric acid was then used to wash the ether layer, followed by water (twice), after which the ether layer was separated, dried over magnesium sulphate and filtered. Removal of the ether under reduced pressure afforded a residue which was chromatographed (eluant 20% ethyl acetate - light petroleum) to give the product (213) (205 mg, 87%) as an oil (Found: C, 75.65; H, 7.0. $C_{17}H_{18}O_3$ requires C, 75.55; H, 6.7%); ν_{max} (neat) 1732 cm^{-1} (C = O); δ2.09 (3H, s, CCH_3), 3.66 (2H, m, $ArCH_2C$), 3.90 (3H, s, OCH_3), 4.67 - 5.12 (2H, m, vinyl CH_2), 5.25 (2H, s, OCH_2), 5.94 - 6.16 (1H, m, vinyl CH), 7.29 - 7.55 (m, 2H, 6- and 7-H), 7.65 (1H, s, 4-H), 7.80 (1H, m, 5-H), and 8.06 (1H, m, 8-H); *m/z* 270 (M^+, 19%), 210 (65), 195 (100), 179 (35), 165 (38), 152 (26), 115 (18), and 43 (69).

3-Acetoxymethyl-4-acetyl-1-allyloxy-naphthalene (214)

The disubstituted naphthalene (211) (0.96 g, 3.75 mmol) was added to a premixed solution of glacial acetic acid (0.26 g, 4.3 mmol) and trifluoroacetic anhydride (0.9 g, 4.3 mmol). After stirring at room temperature for 18 h, the mixture was thrown into water, carefully neutralised with saturated sodium bicarbonate and extracted repeatedly with dichloromethane. The organic layers were combined and dried over anhydrous magnesium sulphate, filtered and evaporated to yield an oily residue which was chromatographed (eluant 20% ethyl acetate - light petroleum) to yield the product (214) (0,301 g, 27%) as an oil (Found: C, 72.6; H, 6.05. $C_{18}H_{18}O_4$ requires C, 72.45; H, 6.1%); $\nu_{max.}$ (neat) 1765, 1689 (ArC=O) and 1593 cm^{-1}

(C = C); δ2.11 (3H, s, $OCOCH_3$), 2.68 (3H, s, $CCOCH_3$), 4.76 (2H, m, $O\underline{CH_2}CH$), 5.20 (2H, s, $ArCH_2$), 5.28 - 5.66 (2H, m, vinyl CH_2), 5.97 - 6.38 (1H, m, vinyl CH), 6.81 (1H, s, 2-H), 7.47 - 7.76 (3H, m, 5-, 6- and 7-H), and 8.38 (1H, m, 8-H); *m/z* 298 (M^+, 48%), 255 (18), 241 (21), 238 (23), 216 (28), 215 (97), 197 (27), 169 (35), 141 (25), 115 (20), and 43 (100).

Methyl 4-ethyl-1-hydroxy-3-naphthoate (219)

The acetate (218) (2.37 g, 8.71 mmol), prepared by the method of El-Abbady and Doss[73] was dissolved in a sodium hydroxide solution (0.75%) in methanol (150 ml) and stirred at room temperature for 20 min before the solution was acidified with dilute hydrochloric acid. The methanol was then removed under reduced pressure and more water added to the watery residue. This was extracted repeatedly with ethyl acetate, which after being dried over magnesium sulphate, filtered and evaporated, yielded a crude material which was chromatographed (eluant 30% ethyl acetate - light petroleum) to give the product (219) (2.00 g, ≃100%) as white crystals, m.p. 143 - 144.5°C (isopropyl alcohol) (Found: C, 73.1; H, 6.15. $C_{14}H_{14}O_3$ requires C, 73.05; H, 6.15%); $\nu_{max.}$ 3320 (OH), 1671 cm^{-1} (C = O); δ1.34 (3H, t, *J* 8 Hz, CCH_3), 3.31 (2H, q, *J* 8 Hz, CH_2), 3.92 (3H, s, OMe), 5.91 (1H, s, OH), 7.22 (1H, s, 2-H), 7.52 - 7.64 (2H, m, 6- and 7-H), and 8.08 - 8.37 (2H, m, 5- and 8-H); *m/z* 230 (M^+, 93%), 215 (100), 199 (19), 171 (34), 170 (26), 141 (25), 128 (23), and 115 (36).

Methyl 1-allyloxy-4-ethyl-3-naphthoate (220)

The naphthol (219) (2.0 g, 8.7 mmol) was dissolved in anhydrous acetone (150 ml). Allyl bromide (2.24 ml, 25.9 mmol) and anhydrous potassium carbonate (3.60 g, 26.0 mmol) were added, and the stirred mixture was heated under reflux overnight. After the solution had cooled, it was filtered and the acetone removed under reduced pressure. The residual material was taken up into ether and washed with water (twice). Magnesium sulphate was then added to the separated ether layer; this was filtered and the ether evaporated to give a residue which was chromatographed (eluant 5% ethyl acetate - light petroleum) to yield the product (220) (1.825 g, 78%) as an oil (Found: C, 75.65; H, 6.8. $C_{17}H_{18}O_3$ requires C, 75.55; H, 6.7%); $\nu_{max.}$ (film) 1723 (C = O) and 1595 cm^{-1} (C = C); δ1.34 (3H, t, J 8 Hz, CCH_3), 3.30 (2H, q, J 8 Hz, CH_2CH_3), 3.93 (3H, s, OMe), 4.65 - 4.80 (2H, m, $ArCH_2$), 5.23 - 5.65 (2H, m, vinyl CH_2), 5.95 - 6.42 (1H, m, vinyl CH), 7.15 (1H, s, 2-H), 7.50 - 7.68 (2H, m, 6- and 7-H), 8.16 (1H, m, 5-H), and 8.38 (1H, m, 8-H); *m/z* 270 (M^+, 86%), 229 (69), 197 (100), 169 (68), 142 (32), 141 (46), 115 (24), 105 (26), and 41 (21).

Methyl 2-allyl-4-ethyl-1-hydroxy-3-naphthoate (221)

Compound (220) (786 mg, 2.91 mmol) was heated at 180 - 200°C for 1 h as a neat oil under nitrogen. After this time had elapsed, heat was removed and the oil which had darkened somewhat was chromatographed (eluant 15% ethyl acetate - light petroleum) to yield the naphthol (221) (673 mg, 86%) as an unstable oil (darkens on standing; both the ^1H n.m.r. and

t.l.c. of this naphthol show changes after standing at room temperature for 24 h) (Found: C, 75.5; H, 6.75. $C_{17}H_{18}O_3$ requires C, 75.55; H, 6.7%); $\nu_{max.}$ (film) 3490 (OH), 1732 cm^{-1} (C = O); δ1.29 (3H, t, *J* 8 Hz, CCH_3), 2.94 (2H, q, *J* 8 Hz, $\underline{CH_2}CH_3$), 3.38 - 3.51 (2H, m, $ArCH_2$), 3.93 (3H, s, OMe), 5.09 - 5.36 (2H, m, vinyl CH_2), 5.60 (1H, s, OH), 5.78 - 6.26 (1H, m, vinyl CH), 7.39 - 7.62 (2H, m, 6- and 7-H), 8.00 (1H, m, 5-H), and 8.22 (1H, m, 8-H); *m/z* 270 (M^+, 100%), 255 (89), 239 (15), 223 (26), 195 (27), 181 (16), 165 (17), 152 (14), and 115 (9).

Methyl 2-allyl-4-ethyl-1-methoxy-3-naphthoate (222)

Freshly prepared naphthol (221) (563 mg, 2.09 mmol) was dissolved in anhydrous acetone (100 ml) and dimethyl sulphate (0.606 ml, 6.25 mmol) and potassium carbonate (863 mg, 6.25 mmol) were added. After heating the solution under reflux for 2 h, the mixture was cooled, filtered to remove the excess potassium carbonate and the acetone removed under reduced pressure. The oily residue was partitioned between water and ether, and washed successively with ammonia (25%), water, hydrochloric acid (1 M), then water again before the ether layer was separated and dried over anhydrous magnesium sulphate. Filtration and removal of the ether under reduced pressure gave an oily material which was chromatographed (eluant 2.5% ethyl acetate - light petroleum) to yield the product (222) (516 mg, 87%) as an oil (Found: C, 76.05; H, 7.05. $C_{18}H_{20}O_3$ requires C, 76.05; H, 7.1%); $\nu_{max.}$ (neat) 1726 cm^{-1} (C = O); δ1.31 (3H, t, *J* 8 Hz, CCH_3), 2.97 (2H, q, *J* 8 Hz, $\underline{CH_2}CH_3$), 3.55 - 3.67 (2H, m, $ArCH_2$), 3.92 (6H, s, 2 x OMe), 4.92 - 5.18 (2H, m, vinyl CH_2), 5.78 - 6.23

Anhydrous magnesium sulphate was added to the separated ether layer, which was filtered. Chromatography of the residue which remained after the ether was evaporated (eluant 15% ethyl acetate - light petroleum) yielded the oily ester (224) (691 mg, 94%) (Found: C, 75.05; H, 6.3. $C_{16}H_{16}O_3$ requires C, 75.0; H, 6.3%); $\nu_{max.}$ 1729 cm^{-1} (C = O); δ3.91 (6H, two superimposed s, 2 x OMe), 3.81 - 4.02 (2H, m, $ArCH_2$), 4.19 - 5.07 (2H, m, vinyl CH_2), 5.82 - 6.29 (1H, m, vinyl CH), 7.45 - 7.70 (2H, m, 6- and 7-H), 7.88 (1H, m, 5-H), 8.10 (1H, m, 8-H), and 8.20 (1H, s, 4-H); *m/z* 256 (M^+, 100%), 241 (24), 225 (22), 209 (58), 195 (16), 182 (31), 181 (43), 165 (18), 152 (24), 76 (19), and 36 (30).

9-Methoxyanthracene (226)

Alcohol (205) (93 mg, 0.41 mmol) was dissolved in dry dimethylformamide (10 ml). Potassium *t*-butoxide (184 mg, 1.64 mmol) was added, and the mixture was stirred at 60°C for 120 h. The mixture was thrown into water and the organic material extracted exhaustively with ether, which was separated, dried over anhydrous magnesium sulphate, filtered and the solvent evaporated to afford a residue which was chromatographed (p.l.c. eluant 5% ethyl acetate - light petroleum) to yield needles which were identified as the known 9-methoxyanthracene (21 mg, 25%), m.p. 92°C (lit., 94°C).[74]

3,4-Dihydro-10-ethyl-5-methoxy-3-methyl-1H-naphtho[2,3-c]pyran (227)

Compound (206) (224 mg, 0.82 mmol) was dissolved in dry

dimethylformamide (10 ml) which had been flushed with nitrogen. Potassium *t*-butoxide (369 mg, 3.29 mmol) was added and the reaction mixture, under nitrogen, was immersed in an oil bath and maintained at 60°C for 2 h. The reaction was quenched by the addition of water (20 ml), and the mixture was cooled and extracted with diethyl ether. The extract was backwashed with water, dried over anhydrous magnesium sulphate and the ether evaporated to give a residue which was chromatographed (eluant 15% ethyl acetate - light petroleum) to afford the product (227) (155 mg, 69%) as cubes, m.p. 81 - 82.5°C (aq. methanol) (Found: C, 79.7; H, 7.75. $C_{17}H_{20}O_2$ requires C, 79.65; H, 7.85%); δ1.20 (3H, t, *J* 8 Hz, $CH_2\underline{CH_3}$), 1.42 (3H, d, *J* 7 Hz, $CH\underline{CH_3}$), 2.4 - 3.0 (3H, m, pseudoaxial 4-H and $\underline{CH_2}CH_3$), 3.12 (1H, dd, *J* 3.5 and 17 Hz, pseudoequatorial 4-H), 3.75 - 4.0 (1H, m, 3-H), 3.85 (3H, s, OMe), 4.89 (1H, d, *J* 17 Hz, pseudoaxial 1-H), 5.18 (1H, d, *J* 17 Hz, pseudoequatorial 1-H), 7.39 - 7.60 (2H, m, 7- and 8-H), and 7.94 - 8.22 (2H, m, 6- and 9-H); *m/z* 256 (M^+, 100%), 227 (24), 225 (24), 213 (17), 212 (86), 197 (67), 165 (13), and 115 (10)

2-Allyl-3-hydroxyethyl-naphthoquinone (228)

The unconjugated dimethyl ether (82) (126 mg, 0.463 mmol) was dissolved in a 1:1 mixture of acetonitrile/water (40 ml). Cerium(IV) ammonium nitrate (1.015 g, 1.85 mmol) dissolved in water (2 ml) was added dropwise to the stirred solution at room temperature over 5 min, after which the solution was stirred for a further 1 h. The solution was then thrown into water and extracted with dichloromethane, which after separation from

the aqueous phase was dried over magnesium sulphate, filtered and evaporated to yield a residue which was chromatographed (p.l.c. eluant 20% ethyl acetate - light petroleum) to give product (228) as a yellow oil (79 mg, 70%) (Found: C, 74.35; H, 6.1. $C_{15}H_{14}O_3$ requires C, 74.35; H, 5.85%); $\nu_{max.}$ (film) 3500 (OH), 1662 cm^{-1} (C = O); 1.59 (3H, d, J 8 Hz, CH_3), 3.34 - 3.52 (2H, m, $ArCH_2$), 3.74 - 4.06 (1H, br d, OH), 4.76 - 5.68 (3H, m, $\underline{CH}CH_3$ and vinyl CH_2), 5.58 - 6.06 (1H, m, vinyl H), 7.58 - 7.82 (2H, m, 6- and 7-H), and 7.92 - 8.16 (2H, m, 5- and 8-H); m/z 242 (M^+, 25%), 227 (25), 225 (17), 224 (100), 223 (27), 209 (47), 207 (18), 181 (34), 152 (17), 105 (18), 76 (18), and 43 (23).

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